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Health Technology Assessment (HTA)

**HTA Report**

# Ginkgo biloba in patients with decreasing mental performance, peripheral arterial occlusive disease, vertigo, or tinnitus

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| Title | Ginkgo biloba in patients with decreasing mental performance, peripheral arterial occlusive disease, vertigo, or tinnitus |
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**Conflict of Interest:**

All authors are employed by a healthcare consulting company that was contracted to complete this review. The authors have no financial, academic, personal, or any other conflicts of interest to declare in relation to this project.

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Cover image: Simplified representation of a fictional probabilistic sensitivity analysis on a cost-effectiveness plane with the diagonal willingness-to-pay line.

## Executive Summary

### BACKGROUND

The herbal drug preparation ginkgo biloba is thought to reduce inflammation and improve cerebral blood flow; it is also thought to have antioxidant and neuroprotective effects. In Switzerland, ginkgo-based medicinal products (doses 120 mg to 240 mg) have been approved and are reimbursed for adults with mental performance deficits (MPD), peripheral arterial occlusive disease (PAOD), vertigo, and tinnitus. However, some studies have reported conflicting results regarding the effectiveness of this therapy. Within the context of the Federal Office of Public Health (FOPH) Health Technology Assessment (HTA) Program, the evidence for these coverage decisions is to be re-evaluated.

### OBJECTIVE

This HTA report assesses the efficacy, safety, cost-effectiveness, and budget impact, as well as ethical, legal, social, and organisational (ELSO) benefits and harms of ginkgo biloba for the indications as described above in Switzerland.

### METHODS

Two systematic literature reviews (SLRs) were conducted to identify the clinical and economic evidence on formulations of ginkgo biloba approved and reimbursed in Switzerland for use in adults with MPD, PAOD, vertigo, and tinnitus. A single, combined search strategy for each database (MEDLINE, Embase, EconLit, CENTRAL, Cochrane Database of Systematic Reviews [CDSR], National Health Service [NHS] Economic Evaluation Database [EED]) was utilised for both SLRs. Screening of the literature was performed by 2 independent reviewers. Data were extracted by one reviewer with full data validation by a second reviewer.

For the clinical SLR, eligible studies were randomised controlled trials (RCTs) comparing ginkgo biloba with placebo or active comparators. Where possible, studies were pooled and summary effect estimates calculated by meta-analyses. To assess whether differences were clinically meaningful, minimum clinically important differences (MCIDs) were identified; where MCIDs were unavailable, standardised mean differences (SMDs) were used to categorize effect sizes as trivial/no effect, small, moderate, or large. When pooling results was not possible, results for individual studies are reported. The overall quality of evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

For the economic SLR, eligible studies were cost analyses or any type of economic evaluation of ginkgo biloba. Evidence from available health economic evaluations was synthesised narratively and presented as tabular summaries.

To assess the total costs and budget impact of ginkgo biloba, a budget impact model (BIM) was developed in accordance with appropriate guidelines.

For the evaluation of ELSO domains, the publications included in the SLR were reviewed and were supplemented by targeted literature searches in MEDLINE, Embase, and the grey literature.

**RESULTS**

A total of 42 RCTs were included in the clinical SLR on the efficacy and safety of ginkgo biloba in MPD (k=28), PAOD (k=8), vertigo (k=2), and tinnitus (k=4). All results are reported as mean difference (MD) or relative risk (RR) with 95% confidence intervals (CIs).

**Efficacy and safety**

*Mental performance deficits*

In patients with MPD, there was a statistically significant and clinically meaningful difference between 24 weeks of treatment with either 240 mg ginkgo biloba or placebo in cognitive function assessed with Syndrom-Kurz-Test (SKT) scores (MD -2.32 [95% CI -3.82 to -0.83]; 4 RCTs; 1'406 patients; moderate certainty evidence; MCID 2 points). After 24 weeks of treatment with 240 mg ginkgo biloba or placebo, there was a statistically significant and clinically meaningful difference in favour of ginkgo biloba in the Neuropsychiatric Inventory (NPI) Composite Total Score (MD -4.03 [95% CI -7.32 to -0.74]; 4 RCTs; 1'360 patients; moderate certainty evidence; MCID 4 points). In addition, 24 weeks of treatment with 240 mg ginkgo biloba was statistically significantly better than placebo in functioning assessed using the Alzheimer's Disease Activities of Daily Living International Scale (ADL-IS) score (MD -0.17 [95% CI -0.22 to -0.12]; 2 RCTs; 806 patients; high certainty evidence; MCID not identified; SMD -0.50 [95% CI -0.64 to -0.36]); and health-related quality of life (HRQoL) on the Dementia-Related Quality of Life (DEMQOL)-proxy (MD 2.00 [95% CI 0.85 to 3.15]; 2 RCTs; 806 patients; moderate certainty evidence; MCID not identified; SMD 0.24 [95% CI 0.10 to 0.38]).

Comparing 240 mg ginkgo biloba and placebo for 24 weeks, there was no statistically significant difference in the risk of experiencing either any adverse event (AE) (RR 0.97 [95% CI 0.90 to 1.05]; 5 RCTs; 1'716 patients; moderate certainty evidence) or any serious adverse event (SAEs) (RR 0.98 [95% CI 0.53 to 1.83]; 3 RCTs; 1'143 patients; moderate certainty evidence).

*Peripheral arterial occlusive disease*

In patients with PAOD, 24 weeks of treatment with 160 mg ginkgo biloba was associated with statistically significantly better pain-free walking distance (PFWD) than placebo (MD 36.0 m [95% CI 15.4 to 56.6]; 2 RCTs; 73 patients; very low certainty evidence; MCID 20 m). Similarly, 120 mg ginkgo biloba was associated with statistically significantly better PFWD than placebo after 24 weeks (MD 24.4 m [95% CI 4.9 to 43.9]; 3 RCTs; 225 patients; low certainty evidence; MCID 20 m). A daily dose of 120 mg ginkgo biloba for 24 weeks is associated with a statistically significant improvement in pain measured on a visual analogue scale (VAS; range 0 to 100 mm) compared with placebo, but it is unclear whether the difference is clinically meaningful due to

substantial variability in the MCID reported in the literature (MD -13.4 mm [95% CI -19.7 to -7.1]; 2 RCTs; 116 patients; low certainty evidence; MCID median 23 mm [interquartile range 12 to 39]). The available findings do not support any conclusions regarding other measures of mobility, peripheral blood circulation, or safety (all very low certainty evidence). No studies were identified that reported HRQoL in patients with PAOD.

*Vertigo*

Based on 2 RCTs in patients with vertigo, there were no statistically significant differences in vestibular symptoms after 12 weeks comparing either 240 mg ginkgo biloba (multiple outcome measures; 1 RCT; 160 patients; low certainty evidence) or 160 mg ginkgo biloba (multiple outcome measures; 1 RCT; 31 patients; very low certainty evidence) with 32 mg betahistine. However, patients treated with 240 mg ginkgo biloba for 12 weeks were statistically significantly less likely to experience any AEs, compared to 32 mg betahistine (RR 0.61 [95% CI 0.38 to 0.99]; 1 RCT; 160 patients; moderate certainty evidence). No studies were identified that reported HRQoL in patients with vertigo.

*Tinnitus*

Evidence regarding the use of ginkgo biloba in tinnitus was heterogeneous in terms of both dosage of ginkgo biloba and comparator treatment, resulting in no possible meta-analyses and low or very low certainty regarding the treatment effect in all efficacy and safety outcomes. No statistically significant differences were found between treatment with ginkgo biloba (120 mg or 150 mg) and placebo in patients' subjective assessment of tinnitus severity over 12 weeks, measured with a variety of categorical and continuous scales (2 RCTs; 815 patients; low certainty evidence). In the trial investigating 150 mg ginkgo biloba vs. placebo for the condition of tinnitus, there was no statistically significant difference in the number of people with ≥1 AE during 12 weeks of treatment (RR 1.06 [95% CI 0.74 to 1.52]; 1 RCT; 978 patients; low certainty evidence). No studies were identified that reported HRQoL in patients with tinnitus.

*Safety across indications*

To supplement the findings regarding the safety of ginkgo biloba in each indication, meta-analyses were conducted to assess the number of patients experiencing ≥1 AE when treated with ginkgo biloba compared with placebo across indications (i.e. MPD, PAOD, vertigo, and tinnitus studies were analysed together). Among patients treated with either 120 mg ginkgo biloba or placebo for 24 weeks, there was no statistically significant difference in the occurrence of AEs across indications (RR 0.91 [95% CI 0.70 to 1.18]; 7 RCTs; 1133 patients). Similarly, there was no statistically significant difference in the proportion of patients experiencing ≥1 AE comparing 24 weeks of treatment with any dose of ginkgo biloba (120 mg, 150 mg, 160 mg, or 240 mg) vs. placebo (RR 0.96 [95% CI 0.89 to 1.04]; 12 RCTs; 2728 patients). Note that 2 additional trials (total of 14 RCTs and 2'801 patients) did not contribute to the meta-analysis because they reported zero AEs in both treatment groups.

**Costs, cost-effectiveness, and budget impact**

The economic SLR identified a total of 3 eligible studies. All 3 were cost-comparison economic analyses that used data collected from RCTs to model the direct costs of ginkgo biloba, from a public payer perspective, in patients with Alzheimer's disease (AD) or dementia. Two studies conducted in Austria included the costs of ginkgo biloba, as well as estimated costs of patient care (i.e. physician visits, nursing care) modelled using efficacy data from an RCT comparing ginkgo biloba to placebo. Both analyses found that ginkgo biloba was cost-saving compared to placebo due to estimated delays in symptom progression when patients received ginkgo biloba. The third study, conducted in Germany, included the drug costs of ginkgo biloba and galantamine; they also used data from 6 RCTs comparing galantamine to placebo and 1 RCT comparing ginkgo biloba to placebo to estimate costs of patient care (i.e. physician visits, long-term care insurance, and caregiver time). In this study, ginkgo biloba was found to be more costly than galantamine for mild-to-moderate AD from the payer perspective. The most recent study was published in 2015, so these findings may not be representative of current clinical practice or current costs.

Results from the present Swiss customized budget impact analysis show that the reimbursement of ginkgo biloba resulted in a 5-year total spending of CHF 167'154'958. Indication-specific costs were CHF 56'912'066 (MPD), CHF 29'956'227 (PAOD), CHF 20'325'738 (vertigo), and CHF 59'960'927 (tinnitus). Scenario analysis showed that when patients with dementia switched from ginkgo biloba to an alternative treatment, the total budget impact was higher, resulting in excess costs regardless of the treatment: rivastigmine (CHF 12'180'648), donepezil (CHF 23'302'095), galantamine (CHF 9'514'923), memantine (CHF 21'713'115), and a weighted average of these treatments (CHF 16'757'340).

**Ethical, legal, social, and organisational issues**

A total of 23 studies on ELSO domains were included; identified study designs were systematic and narrative reviews (k=12), governmental guidance documents (k=2), pharmacovigilance studies (k=2), pharmacologic studies (k=2), expert interviews (k=2), discrete choice experiment (k=1), retrospective analysis of RCT data (k=1), and clinical guidelines (k=1). Study quality was not assessed. This review did not identify any serious ethical or social issues specific to ginkgo biloba. The identified ELSO issues were generally related to effective communication of benefits and risks in vulnerable populations and equitable access to care, which are broadly applicable to the patients in these populations.

**CONCLUSIONS**

The present HTA identified 42 RCTs evaluating the efficacy of ginkgo biloba. Based on these studies, 240 mg ginkgo biloba showed benefits in patients with MPD after 24 weeks of treatment, specifically in cognitive functioning, neuropsychiatric symptoms, functional status, and HRQoL. For PAOD, vertigo, and tinnitus, the available findings do not support any conclusions of benefit

compared with placebo for most outcomes. The findings do not indicate increased risks of AEs or SAEs associated with ginkgo biloba.

The BIM provides information on the estimated costs (i.e. reimbursement costs) of ginkgo biloba over 5 years, as well as scenario analyses that assess the economic impact of treatment switching. However, the scenario analyses are based in part on expert opinion due to gaps in the scientific literature and should be interpreted with caution.

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# Abbreviations and acronyms

| | |
|---|---|
| ABI | Ankle-Brachial Index |
| AChEIs | acetylcholinesterase inhibitors |
| AD | Alzheimer's disease |
| ADAS-Cog | Alzheimer's Disease Assessment Scale-Cognitive |
| ADCS | Alzheimer's Disease Cooperative Study |
| ADCS-ADL-MCI-24 | Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment – 24-item |
| ADCS-CGIC | Alzheimer's Disease Cooperative Study Clinical Global Impression of Change |
| ADDTC | Alzheimer's Disease Diagnostic and Treatment Centers |
| ADL | activities of daily living |
| ADL-IS | Alzheimer's Disease Activities of Daily Living International Scale |
| AE | adverse event |
| AMIPB-DSR | Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall |
| AR | adverse reaction |
| BCRS | Brief Cognitive Rating Scale |
| BfS | Mental Balance Scale (Befindlichkeitsskala) |
| BIM | budget impact model |
| BMI | body mass index |
| BPPV | benign paroxysmal positional vertigo |
| CDR | Clinical Dementia Rating |
| CDSR | Cochrane Database of Systematic Reviews |
| CDT | Clock-Drawing Test |
| CGIC | Clinical Global Impression of Change |
| CGIS | Clinical Global Impression of Severity |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CHF | Swiss Franc |
| CI | confidence interval |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| CVD | cerebrovascular disease |
| DEMQOL-proxy | Dementia-Related Quality of Life-proxy |
| DLB | diffuse Lewy body disease |
| DSM-5 | Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition |
| DSM-III | Diagnostic and Statistical Manual of Mental Disorders, Third Edition |

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|---|---|
| DSM-III-R | Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition |
| EED | Economic Evaluation Database |
| ELSO | ethical, legal, social or organisational |
| EMA | European Medicines Agency |
| ESC | European Society of Cardiology |
| EU | European Union |
| EUR | Euros |
| FAERS | FDA Adverse Event Reporting System |
| FDA | Food and Drug Administration |
| FOPH | Swiss Federal Office of Public Health |
| FTD | frontotemporal dementia |
| FTLD | frontotemporal lobar degeneration |
| GBS | Gottfries-Bråne-Steen Scale |
| GDS | Geriatric Depression Scale |
| GERRI | Geriatric Evaluation by Relative's Rating Instrument |
| GI | gastrointestinal |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HA | hearing aid |
| HADS | Hospital Anxiety and Depression Scale |
| HAMD | Hamilton Depression Rating Scale |
| HMPC | Committee on Herbal Medicinal Products |
| HR | hazard ratio |
| HRQoL | health-related quality of life |
| HTA | health technology assessment |
| IC | intermittent claudication |
| ICD-10 | International Classification of Diseases, Tenth Revision |
| ICD-9 | International Classification of Diseases, Ninth Revision |
| ICER | incremental cost-effectiveness ratio |
| INAHTA | International Network of Agencies for Health Technology Assessment |
| IQ | intelligence quotient |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen |
| LY | life-year |
| MADRS | Montgomery- Åsberg Depression Rating Scale |
| MCI | mild cognitive impairment |
| MCID | minimum clinically important difference |
| MCRT | Multiple Choice Reaction Test |
| MD | mean difference |

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|---|---|
| MDBF | Mehrdimensionaler Befindlichkeitsbogen |
| MDRS | Mattis Dementia Rating Scale |
| MID | multi-infarct dementia |
| MMSE | Mini-Mental State Examination |
| MPD | mental performance deficit |
| MRI | magnetic resonance imaging |
| MWD | maximum walking distance |
| MWT IQ | Multiple Choice Vocabulary Intelligence Test |
| NA | not applicable |
| NAA-ADL | Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living |
| NAB | Nuremberg Gerontopsychological Observation Scale |
| NAI | Nuremberg Age Inventory |
| NAI-ZN-G | Nuremberg Age Inventory-ZahlennachsprechenTest G (Digit Memory Span G) |
| NAI-ZVT-G | Nuremberg Age Inventory-Zahlen-Verbindungs-Test G |
| NAI-WL-tot | Nuremberg Age Inventory-Wortliste (Word List) total |
| NAR | Nuremberg Age Rating |
| NAS | numeric analogue scale |
| NE | not estimable |
| NHS | National Health Service |
| NICE | National Institute for Health and Care Excellence |
| NINCDS-ADRDA | National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association |
| NINDS-AIREN | National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences |
| NMDA | N-methyl-D-aspartate |
| NPI | Neuropsychiatric Inventory |
| NR | not reported |
| NS | not significant |
| NSL | Nuremberg Self-Assessment List |
| PAD | peripheral arterial disease |
| PAOD | peripheral arterial occlusive disease |
| PDD | Parkinson’s disease dementia |
| PDS | Progressive Deterioration Scale |
| PFWD | pain-free walking distance |
| PICO | population, intervention, comparator, and outcomes |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PRMQ | Prospective and Retrospective Memory Questionnaire |
| PY | person-years |

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|---|---|
| QALY | quality-adjusted life-year |
| QoL-AD | Quality of Life-Alzheimer's Disease |
| RCT | randomised controlled trial |
| RR | relative risk |
| SAE | serious adverse event |
| SCAG | Sandoz Clinical Assessment Geriatric Scale |
| SD | standard deviation |
| SDS | Sheehan Disability Scale |
| SF-36 | 36-Item Short Form Health Survey |
| SKT | Syndrom-Kurz-Test |
| SLR | systematic literature review |
| SMD | standardised mean difference |
| SMT | Seven Minute Test |
| STAI-X1 | State-Trait Anxiety Inventory-state subscale |
| TE4D | Test for the Early Detection of Dementia from Depression |
| THI | Tinnitus Handicap Inventory |
| TIA | transient ischaemic attack |
| TMT | Trail-Making Test |
| TQ | Tinnitus Questionnaire |
| TSST | Trier Social Stress Test |
| TT | Termine Test |
| UK | United Kingdom |
| USA | United States of America |
| VAS | Visual Analogue Scale |
| WMS III | Wechsler Memory Scale III |
| WTS-ALS | Vienna Test System—Work Performance Series |
| WTS-DT | Vienna Test System—Determination Test |
| VSS-A | Vertigo Symptom Scale autonomic-anxiety |
| VSS-SF | Vertigo Symptom Scale short-form |
| VSS-V | Vertigo Symptom Scale vertigo-balance |

## Objective of the HTA report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology, their execution, and the results are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical effectiveness and safety, costs, cost-effectiveness and budget impact, ethical, legal, social and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable, and high-quality health system.

# 1. Policy question and context

The HTA topic entails a policy question that will be informed by addressing HTA research questions (see ***Section 5***).

In healthcare, a policy question is a request to regulate a reimbursement policy and is aimed at securing financing for health technologies. Such a request, related to a particular health technology, typically addresses uncertainty around a technology. This HTA report addresses the following policy question:

**Does the existing evidence on efficacy, safety, and economic efficiency justify the coverage of ginkgo biloba for adults with mental performance deficits (MPD), peripheral arterial occlusive disease (PAOD), vertigo, and/or tinnitus?**

In Switzerland, ginkgo biloba is currently covered by the mandatory health insurance in a variety of formulations for the treatment of patients with MPD, PAOD, vertigo, and tinnitus.[1] However, some studies have reported conflicting results regarding the effectiveness of this therapy. The Swiss Federal Office of Public Health (FOPH) is summoned to re-evaluate the evidence on ginkgo biloba. This HTA report, conducted following the review protocol published on the FOPH website[2] presents all available evidence meeting prespecified eligibility criteria on the use of ginkgo biloba as a standalone therapy or as adjunctive treatment for MPD, PAOD, vertigo, and tinnitus.

# 2. Medical background

## 2.1 Mental performance deficits

Depending on the severity and type of MPD, daily activities may be affected. Dementia—now referred to as major neurocognitive disorder in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*—is an acquired disorder of cognitive functions (e.g. learning and memory, complex attention, executive functions, social cognition, language, or perceptual-motor skills) due to brain dysfunction that consistently affects an individual's ability to perform daily activities. Dementia can result from different causes, such as Alzheimer's disease (AD) and vascular diseases. Worldwide, almost 10 million people per year are diagnosed with dementia.[3] Clinically, dementia is characterised by a significant deterioration in one or more cognitive ability domains, namely learning and memory, social cognition, language, complex attention, executive functions, and perceptual-motor function. Before receiving a dementia diagnosis due to a neurodegenerative disease such as AD, patients often experience a period of mild cognitive impairment (MCI), where the symptoms are present but daily life is not substantially affected, now referred to as minor neurocognitive disorder in the *DSM-5*. In addition to clinical examination by a neurologist, diagnostic

tools for MPD range from neuroimaging, cerebrospinal fluid (CSF) and/or blood biomarkers (e.g. neurofilament light chain, plasma phosphorylated tau), to genetic markers.[4]

Although AD is the most common condition leading to MPD, different types of brain pathology are found, such as tau and amyloid pathology in AD; tau-, FUS- or TDP43-pathology in frontotemporal lobar degeneration (FTLD), and synuclein pathology in Parkinson's disease dementia (PDD) or diffuse Lewy body disease (DLB). Vascular pathology is the hallmark of vascular dementia but may also represent a co-factor in any other form of dementia. MPD may also be caused by other brain pathologies, such as traumatic brain injury, brain infections, or (non-progressive) stroke. Risk factors for MPD include older age, smoking, arterial hypertension, and type 2 diabetes,[4] as well as low socioeconomic status, hearing loss, and depression.[5]

The clinical course of dementia due to neurodegeneration is progressive in nature. Although some dementia risk factors are modifiable, there is currently no cure for any dementia with neurodegenerative causes. Treatment options focus on lifestyle intervention, psychosocial support, and symptomatic management that aim to slow the decrease of cognitive performance. With regard to AD dementia, pharmacological therapies include acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists. In AD and PDD, AChEIs improve the functioning of cholinergic neurons and may stabilise memory functions but may also improve mood and behavioural changes. However, there are rarely cardiovascular adverse effects, and there are frequently gastrointestinal adverse effects.[6] The NMDA receptor antagonist memantine is meant to achieve a neuroprotective effect against further nerve cell death in the brain, and may improve mood and behaviour in people with dementia due to AD.[7,8] However, patients may be likely to discontinue these treatments, with only about 40% (rivastigmine and galantamine) to 50% (donepezil and memantine) of patients continuing treatment for longer than 12 months.[9] Recent developments in pharmacotherapies for MCI due to AD and AD dementia show that lecanemab and other anti-amyloid monoclonal antibodies may slow the progression of cognitive decline compared to placebo.[4] These anti-amyloid antibodies clear the cerebral amyloid plaques, which are thought to play an important role in the pathogenesis of AD, and therefore may be able to target underlying causes rather than focusing on symptomatic management. However, these medications are not currently approved for use in Switzerland, and the data that are currently available from clinical trials indicate that there is a considerable risk of adverse events (AEs) with lecanemab and other anti-amyloid antibodies, particularly the so-called 'amyloid-related imaging abnormalities'.[10] In addition, a recent Cochrane review found that the benefits of anti-amyloid antibodies may be small at best.[10] Therefore, the possible risks of such therapies must be carefully balanced against the possible benefits.[4] Furthermore, uncertainties around pricing and the cost-effectiveness of lecanemab and other anti-amyloid antibodies mean that their role in treating AD remains unclear.[11,12]

In addition to these approved pharmacological therapies, patients with MPD of whatever cause may be treated with herbal medicinal products such as ginkgo biloba[13] or non-pharmacologic

interventions such as cognitive stimulation[14] to help treat the symptoms of cognitive decline. Ginkgo biloba is believed to help treat symptoms of MPD primarily through its antioxidant effects,[15] but some preclinical evidence suggests that it also inhibits amyloid-β aggregation.[16]

## 2.2 Peripheral arterial occlusive disease

PAOD is a type of cardiovascular disease that affects the blood vessels in the limbs. It is typically caused by atherosclerosis, whereby blood flow to the extremities is restricted due to fatty deposits in the arteries.[17,18] Several factors are associated with a higher prevalence of PAOD, including smoking, diabetes, body mass index (BMI) over 30, hypertension, dyslipidaemia, Black ethnicity, and family history of cerebrovascular disease (CVD).[19] The global prevalence of PAOD was estimated to be 6% in 2015.[20]

The most common symptom of PAOD is intermittent claudication (IC) – cramping and pain in the lower limbs during physical activity. Other symptoms include numbness in the legs, changes to the appearance of the skin, wounds and sores that do not heal, and brittle toenails.[21] In addition to physical examination of the lower limbs, the Ankle-Brachial Index (ABI) test is used to diagnose PAOD by comparing blood pressure measurements from different parts of the body. Computed tomography or magnetic resonance imaging scans may also be required to establish a diagnosis of PAOD.[18] Improvement in either patient-reported symptoms, such as IC, or assessments by physicians, such as ABI, may be an indicator of treatment efficacy.

Without treatment, the progression of atherosclerosis in people with PAOD leads to a higher risk of coronary heart disease, stroke, and angina. Treatment is focused primarily on lowering cardiovascular risk factors through lifestyle changes, such as physical activity and giving up smoking, and secondary prevention through medical therapy (e.g. aspirin, statins, and anti-hypertension medication).[22] However, introducing or increasing physical activity may be challenging due to the pain patients experience in PAOD. To address this, patients may benefit from specialised exercise interventions that account for IC.[23] Patients may also receive herbal medicinal products such as ginkgo biloba, which may both treat the symptoms of PAOD and IC, as well as facilitate physical activity to help reduce cardiovascular risk factors.[24] Ginkgo biloba may treat PAOD symptoms through a variety of mechanisms, including antioxidant effects, vasodilation, and suppression of platelet activation.[25,26] Where symptoms are severe, patients may be treated with angioplasty or stenting, bypass surgery, or limb amputation.[27]

## 2.3 Vertigo

Vertigo is a symptom that an individual experiences as a sensation of motion – most often a feeling of rotation or spinning – when they are not in motion. Other symptoms such as nausea, vomiting, and perspiration may also accompany the feeling of motion. It is estimated that approximately 3% to 10% of the population is affected by vertigo at some point during their lifetime.[28] In addition to

having a negative impact on an individual's daily activities, vertigo increases the risk of falls, which may translate to a higher risk of injury in certain groups, such as elderly people.[29,30]

The aetiology of vertigo differentiates between peripheral and central vertigo. Diagnosing both types of vertigo entails a thorough physical examination, electrophysiological examination of the peripheral vestibular function, and, eventually, imaging studies of the brain undertaken in the case of suspected central vertigo.[31,32] The causes of central vertigo include stroke, tumours, and other pathologies affecting the brainstem or cerebellum.[33] Peripheral vertigo is the more common type and usually stems from vestibular disorders, whereby the sensory system that controls balance and coordination does not function properly. Benign paroxysmal positional vertigo (BPPV), Ménière's disease, and acute unilateral vestibulopathy (formerly called 'vestibular neuronitis') are among the underlying causes of peripheral vertigo.[34,35]

Treatment of vertigo depends on the identified underlying cause. Patients with central vertigo resulting from acute ischaemic stroke affecting the brainstem or cerebellum may receive thrombolytic agents to dissolve blood clots, and, in some cases, surgery may be necessary to relieve pressure on the brain.[36] Pharmacotherapy with 4-aminopyridine may also be beneficial for individuals with central vertigo.[37] Peripheral vertigo resulting from vestibular dysfunction can be treated with physical therapy and vestibular rehabilitation exercises, while pharmacological treatments such as antiemetics to combat nausea, anti-hypertension medication, antihistamines, and benzodiazepines can help to manage vertigo symptoms.[37,38] Although the specific mechanism through which ginkgo biloba may affect vertigo is not well understood, preclinical studies reported that ginkgo biloba may impact vestibular compensation, as demonstrated by an increase in both the new formation of synapses and protein synthesis in the vestibular nuclei.[39-41]

## 2.4 Tinnitus

Tinnitus is the symptom of hearing persistent sounds in the absence of an external auditory source. People with tinnitus compare the sounds that they hear to a variety of noises, such as ringing, buzzing, insects, winds, running water, grating metals, and running engines.[42] Based on a global SLR of 83 studies, the pooled prevalence of tinnitus among adults was 14.4% (range: 4.1% to 37.2%), and approximately 2.3% (range: 0.5% to 12.6%) of adults have severe tinnitus.[43] The underlying causes are extremely varied and include conditions related to the ear (e.g. sudden deafness, otitis, Ménière's disease, presbycusis, noise trauma), head and neck function (e.g. temporomandibular dysfunction, whiplash, cervicalgia),[44] neurologic causes (e.g. head injury), psychologic factors, and side effects of medications; in many cases, there is an interplay of various aetiologic factors, and sometimes no clear underlying cause can be discerned.[42]

A diagnosis of tinnitus involves a comprehensive evaluation of the individual's perception of the problem, possible sources of tinnitus-related distress, and comorbidities such as anxiety, insomnia, and head or neck pain, in addition to an audiological assessment.[45] A wide range of treatments to improve tinnitus symptoms have been studied, including ginkgo biloba, zinc, and transcranial

stimulation.[45] Both animal and human studies indicate that ginkgo biloba acts through a variety of mechanisms, including antioxidant effects, suppression of platelet activation, and antiapoptotic activity.[39] For people with hearing loss and tinnitus, amplification devices or cochlear implants may be considered.[45] Psychological interventions, including tinnitus counselling, cognitive behavioural therapy, and mindfulness-based therapy, may help reduce tinnitus-related distress and reduce its impact on an individual's well-being by promoting effective coping strategies and adjustment to living with the condition.[46] Cognitive behavioural therapy is the most well-researched treatment for tinnitus and is recommended by clinical practice guidelines, particularly for those with bothersome or severe tinnitus.[47-49]

For many further treatments, the evidence base about their effectiveness remains largely uncertain. Among these treatment options are antidepressants and betahistine (usually used in patients for whom tinnitus is a symptom of Meniere's disease). Although the precise mechanism has not been determined, these effects may work to help prevent free-radical damage to the cochlea, increase blood flow to the inner ear, and/or affect auditory processing.

# 3. Technology

## 3.1 Technology description

The herbal drug preparation ginkgo biloba consists of leaf extracts from the ginkgo biloba tree (also known as the maidenhair tree), most commonly found in eastern Asia. The main active ingredients from the leaf — terpene lactones and flavone glycosides — are used to create the standardised ginkgo extract EGb 761,[50] one of the most commonly used herbal drug preparations in the world.[51] The mechanism of action of ginkgo extract involves reducing inflammation and improving cerebral blood flow; it is also thought to have antioxidant and neuroprotective effects.[52]

The European Medicines Agency Committee on Herbal Medicinal Products (HMPC) developed an assessment report on the use of ginkgo biloba dry extract (drug-extract ratio: 35-67:1),[53] as well as a European Union herbal monograph.[54] The HMPC monograph reports that the dry extract (drug-extract ratio 35-67:1) is appropriate for the improvement of age-associated cognitive impairment in daily dosages of 120 to 240 mg. Treatment should last at least 8 weeks; if symptoms have not improved within 3 months, clinicians should evaluate whether continued use is warranted. Although the HMPC report and monograph have not been updated since 2015, current clinical practice guidelines support the use of ginkgo biloba herbal medicinal products in patients with mild to moderate dementia.[55,56] In Switzerland, ginkgo-based products are approved and reimbursed either as a standalone therapy or as an adjunct treatment for patients with decreasing mental performance (after ruling out certain psychiatric or organic brain disorders requiring specific treatment), PAOD, vertigo, and tinnitus. The various formulations of ginkgo biloba that are reimbursed in Switzerland are detailed in ***Table 1***.

Ginkgo biloba is taken orally, either via capsules or tablets, in dosages of 120 to 240 mg per day.[1] The recommended duration of treatment is typically at least 8 weeks, with an assessment at 3 months to consider whether treatment continuation is appropriate. It should not be used in people with galactose intolerance or hypersensitivity to any of the ingredients. In some cases, ginkgo biloba lowers blood sugar levels, and in people with epilepsy, there is some risk of seizures being triggered by ginkgo extract.[1] There may be an interaction between ginkgo-based products and oral theophylline, efavirenz, medicines that inhibit blood clotting, and calcium antagonists.[1] Additionally, the efficacy of medications that involve cytochromes P450, 3A4, 1A2, 2E1, and 2C9 may be affected by ginkgo extract. Due to a lack of available efficacy and safety evidence, ginkgo biloba is not currently recommended for use in children and adolescents. In addition, because it is unknown whether the ingredients of ginkgo-based products pass into breast milk, ginkgo biloba should be avoided while breastfeeding. Although there is no evidence of reproductive toxicity, ginkgo-based products may impact bleeding and are therefore not recommended for use during pregnancy.[1]

**Table 1: Formulations of ginkgo biloba approved and reimbursed in Switzerland**

| Formulation | Indication(s) | Route of administration | Dosing |
|---|---|---|---|
| SimiMed® Ginkgo | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC, vertigo, and tinnitus | Tablet | 2 x 120 mg or 1 x 240 mg per day |
| Ginkgo-Mepha | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC, vertigo, and tinnitus | Tablet | 120 to 240 mg per day divided into 2 or 3 doses |
| Ginkgo Sandoz® | • Symptomatic treatment of MPD<br>• Dizziness of unknown cause<br>• Adjuvant treatment of tinnitus | Tablet | 240 mg per day in 2 or 3 doses |
| Ginkgo Spirig HC® | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC and tinnitus<br>• Vertigo of unknown cause | Tablet | 1 x 240 mg or 2 x half 240 mg tablet |
| Rezirkane® | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC and tinnitus<br>• Vertigo of unknown cause | Tablet | 120 to 240 mg daily in 1 to 2 doses |
| Symfona® 120 mg | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC<br>• Vertigo and tinnitus | Capsule | 2 x 120 mg per day |
| Symfona® 240 mg | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC and tinnitus<br>• Vertigo of unknown cause | Tablet | 1 x 240 mg per day |

| Formulation | Indication(s) | Route of administration | Dosing |
|---|---|---|---|
| Tebokan® 120 | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC<br>• Vertigo and tinnitus | Tablet | 2 x 120 mg per day |
| Tebokan® 240 | • Symptomatic treatment of MPD<br>• Adjuvant treatment of IC<br>• Vertigo and tinnitus | Tablet | 1 x 240 mg per day |

*Abbreviations*

IC = intermittent claudication, MPD = mental performance deficits.

*Notes*

**Source:** Medicinal product information search platform (AIPS) (Drug Information Publication System FI/PI)[1]

## 3.2 Alternative technologies

There are several medications approved in Switzerland for the conditions in this report, detailed in ***Table 2***. In addition, non-pharmacological treatments, such as cognitive stimulation, tinnitus retraining therapy, or physical exercise programs, may be used alone or in conjunction with pharmacological interventions.[14,23,57]

Although these treatments are approved in Switzerland, they are not all consistently recommended by clinical practice guidelines, and some populations under study lack any approved treatments. Generally, AChEIs (i.e. donepezil, galantamine, and rivastigmine) are recommended as first-line treatment for the symptoms of mild-to-moderate dementia due to AD, with rivastigmine also recommended for use in PDD.[56,58,59] Memantine is approved for symptomatic treatment of moderate-to-severe AD.[56,58,59] However, there are no alternative treatments currently approved in Switzerland for either other types of dementia (e.g. vascular dementia) or MCI. For the remaining conditions, there are limited pharmacologic treatment options, and many are not recommended by clinical practice guidelines. Guidelines for the treatment of PAOD typically focus on lifestyle changes, such as diet, exercise, and smoking cessation, rather than pharmacologic treatments.[60,61] For patients with vertigo, guidelines prioritise identifying and treating the underlying cause.[62] Although there are medications approved for the treatment of tinnitus, clinical practice guidelines recommend cognitive behavioural therapy rather than pharmacologic treatments.[47-49] Alternatives to ginkgo biloba are further described in ***Section 9.1***.

**Table 2: Alternative treatment options**

| Treatment | Formulations/brands | Indication(s) | Route of administration | Dosing |
|---|---|---|---|---|
| **Donepezil** | Aricept®/Evess; Donepezil-Mepha 5/10 Lactab®; Donepezil NOBEL lingual; Donepezil Sandoz® 5/10; Donepezil Spirig HC® | Symptomatic treatment of mild to moderate AD dementia | Film-coated tablet; orodispersible tablet; Lactab | Starting dose 5 mg per day, can be increased to maximum daily dose of 10 mg after 1 month |
| **Galantamine** | Galantamine SR Zentiva®; Reminyl® Prolonged Release | Symptomatic treatment of mild to moderate AD dementia | Extended-release capsules | Starting dose 8 mg per day, can be increased to 16 mg per day for 4 weeks; increasing to maximum dose of 24 mg per day is recommended only after careful clinical assessment of benefit and tolerability |
| **Rivastigmine** | Exelon® | Symptomatic treatment of patients with mild to moderate AD dementia or PDD | Hard capsule; oral solution | Starting dose 3 mg per day, can be increased at intervals of ≥2 weeks up to maximum daily dose of 12 mg |
| | Exelon® Patch; Rivastigmine-Mepha Patch, transdermal patch; Rivastigmine Patch Sandoz®; Rivastigmine Zentiva® Patch | Symptomatic treatment of mild to moderate AD dementia | Transdermal patch | Starting *in vivo* release dose of 4.6 mg per day, can be increased to 9.5 mg per day after 4 weeks; if well-tolerated, patients with significant cognitive and functional decline can increase to 13.3 mg per day after ≥6 months |
| **Memantine** | Axura®; Axura® solution; Ebixa®; Memantine-Mepha Teva, film-coated tablets; Memantine- | Symptomatic treatment of patients with moderate to severe AD dementia (MMSE scores from 3 to 19) | Film-coated tablet; oral solution; Lactab | Starting dose 5 mg per day, increased 5 mg per week up to maximum daily dose of 20 mg |

| Treatment | Formulations/brands | Indication(s) | Route of administration | Dosing |
|---|---|---|---|---|
| | Mepha, Lactab®; Memantine Sandoz®; Memantine Zentiva® | | | |
| **Pentoxifylline** | Pentoxi-Mepha® extended-release tablets | PAOD of arteriosclerotic or diabetic origin (e.g. with IC) | Extended-release tablet | 1200 mg per day, divided into 3 doses; can be reduced to 800 mg per day after improvement |
| **Betahistine** | Betahistine-Mepha Tablets; Betaserc® | Dizziness due to circulatory disorders of the inner ear; Ménière's syndrome and Ménière-like syndromes (dizziness, ringing in the ears, hearing loss) | Tablet | 24 to 48 mg per day, divided into 2 or 3 doses |
| **Cinnarizine** | Cinnageron®; Stugeron® | Cochlear and vestibular disorders: tinnitus, dizziness, nystagmus and related nausea, sweating and vomiting; Ménière's disease | Tablet; capsule | 75 mg per day |
| **Vitamin E** | Burgerstein Vitamin E; Ephynal® | Adjuvant treatment of IC | Capsule; softgel | 400 IU or 300-600 mg per day |
| **Lidocaine** | Xyloneural | Adjuvant treatment of migraine, dizzy spells, tinnitus | Injection (10 mg/mL) | For most indications, 5-10 mL is sufficient; maximum dose of 20 mL per 70 kg |

*Abbreviations*

AD = Alzheimer's disease, IC = intermittent claudication, MMSE = Mini-Mental State Examination, PAOD = peripheral arterial occlusive disease, PDD = Parkinson's disease dementia.

*Notes*

Source: Medicinal product information search platform (AIPS) (Drug Information Publication System FI/PI).[1]

### 3.3 Regulatory status / provider

The specific formulations of ginkgo biloba reimbursed in Switzerland, as well as their indications, are presented in ***Table 1***. Briefly, ginkgo-based products are approved and reimbursed as part of the mandatory health insurance for patients with decreasing mental performance (after ruling out certain psychiatric or organic brain disorders requiring specific treatment), PAOD, vertigo, and tinnitus. All ginkgo biloba products approved in Switzerland are oral medications, taken as either capsules or tablets, and do not require professional administration or storage.

## 4. Population, Intervention, Comparator, Outcomes (PICO)

The PICO criteria for this HTA are shown below in ***Table 3***.

**Table 3: PICO**

| | | | | |
|---|---|---|---|---|
| **P:** | Adults with MPD. MPD can be caused by varying aetiologies, including but not limited to neurodegenerative AD, PDD, DLB, FTLD, and vascular disease. | Adults with PAOD, also known as PAD. | Adults with vertigo/dizziness (peripheral or central vestibular system dysfunction). This includes acute vestibular syndrome (i.e. usually manifests with a single episode, such as vestibular neuritis), episodic vestibular syndrome (i.e. recurrent by nature, such as Ménière's disease or vestibular migraine), and chronic vestibular syndrome (i.e. persistent symptoms over an extended period of time, such as cerebellar degeneration). | Adults with tinnitus, including acute tinnitus (duration <3 months), chronic tinnitus (duration >3 months), and sub-acute tinnitus (although this term is rarely used, for completeness, studies describing patients with sub-acute tinnitus are eligible). |
| **I:** | Ginkgo biloba 120 mg to 240 mg<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | | | |
| **C:** | • Placebo<br>• No treatment<br>• Active comparators approved for treatment of MPD, PAOD, vertigo, and/or tinnitus in Switzerland | | | |
| **O:** | • Cognitive function<br>• Behavioural changes<br>• Functional status<br>• HRQoL | • Mobility<br>• Pain<br>• Peripheral blood circulation<br>• HRQoL | • Timing and intensity of vestibular symptoms, including patient-perceived handicap<br>• HRQoL | • Tinnitus severity<br>• Tinnitus loudness<br>• Level of hearing loss<br>• HRQoL |

| | | | |
|---|---|---|---|
| • All AEs/SAEs<br>• Economic outcomes | • All AEs/SAEs<br>• Economic outcomes | • All AEs/SAEs<br>• Economic outcomes | • All AEs/SAEs<br>• Economic outcomes |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, C = comparator, DLB = diffuse Lewy body disease, FTD = frontotemporal dementia, HRQoL = health-related quality of life, I = intervention, MCI = mild cognitive impairment, MPD = mental performance deficits, O = outcome, p = population, PAD = peripheral arterial disease, PAOD = peripheral arterial occlusive disease, PDD = Parkinson's disease dementia, SAE = serious adverse event.

# 5. HTA research questions

For the evaluation of the technology, the following research questions are addressed:

1. Is the technology effective/efficacious compared to the comparator technology?
2. Is the technology safe compared to the comparator technology?
3. What is the budget impact of the technology?
4. What is the cost-effectiveness of the technology?
5. Are there ethical, legal, social or organisational (ELSO) issues related to the technology?

# 6. Efficacy and safety

***Summary statement efficacy and safety***

A total of 42 randomised controlled trials (RCTs) were included in the clinical systematic literature review (SLR) on MPD (k=28), PAOD (k=8), vertigo (k=2), and tinnitus (k=4). All results are reported as mean difference (MD) or relative risk (RR) with 95% confidence intervals (CIs). Minimum clinically important differences (MCIDs) or standardised mean differences (SMDs) were used to determine whether results were clinically meaningful.

**MPD**

In patients with AD dementia or vascular dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with statistically significantly improved cognitive function as measured by both Syndrom-Kurz-Test (SKT) scores (MD -2.32 [95% CI -3.82 to -0.83]; 4 RCTs; 1'406 patients; moderate certainty evidence; MCID 2 points) and verbal fluency (MD 1.27 [95% CI 0.25 to 2.30]; 3 RCTs; 1'201 patients; low certainty evidence; MCID not identified; SMD 0.77 [95% CI 0.02 to 1.52]). In patients with MCI, AD, or dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, there was statistically significantly more improvement in the Neuropsychiatric Inventory (NPI) Composite Total Score in patients treated with ginkgo biloba (MD -4.03 [95% CI -7.32 to -0.74]; 4 RCTs; 1'360 patients; moderate certainty evidence; MCID 4 points). Compared with placebo, 24 weeks of treatment with 240 mg ginkgo biloba was associated with statistically significantly better functioning assessed using the Alzheimer's Disease Activities of Daily Living International Scale (ADL-IS) score (MD -0.17 [95% CI -0.22 to -0.12]; 2 RCTs; 806 patients; high certainty evidence; MCID not identified; SMD -0.50 [95% CI -0.64 to -0.36]). After 24 weeks of treatment, patients with AD dementia or vascular dementia receiving 240 mg ginkgo biloba had statistically significantly better health-related quality of life (HRQoL) on the Dementia-Related Quality of Life (DEMQOL)-proxy compared to placebo MD

2.00 [95% CI 0.85 to 3.15]; 2 RCTs; 806 patients; moderate certainty evidence; MCID not identified; SMD 0.24 [95% CI 0.10 to 0.38]).

Over 24 weeks of treatment there was no statistically significant difference between 240 mg ginkgo biloba or placebo in the occurrence of AEs (RR 0.97 [95% CI 0.90 to 1.05]; 5 RCTs; 1'716 patients; moderate certainty evidence) or serious AEs (SAEs) (RR 0.98 [95% CI 0.53 to 1.83]; 3 RCTs; 1'143 patients; moderate certainty evidence) in patients with MPD. Comparing patients with AD or probable AD who received 120 mg ginkgo biloba, 240 mg ginkgo biloba, or placebo over 26 weeks, no statistically significant differences in the overall occurrence of bleeding AEs were identified between any of the 3 treatment arms (p = 0.61). The GuidAge trial reported the risk of specific AEs in 2'820 patients who had consulted a physician for memory problems and were randomised to receive either 240 mg ginkgo biloba or placebo for 5 years. There was no statistically significant difference in any of the specific AEs over the course of the trial, including haemorrhagic events. No other trials reported on bleeding AEs.

**PAOD**

Two trials reported pain in people with PAOD treated with either 120 mg ginkgo biloba or placebo for 24 weeks; both trials measured pain on a 0 to 100 mm visual analogue scale (VAS). There was a statistically significant difference in favour of ginkgo biloba after 24 weeks of treatment (MD -13.4 mm [95% CI -19.7 to -7.1]; 2 RCTs; 116 patients; low certainty evidence). However, the difference reported may or may not be clinically meaningful since estimates of the MCID in the 0 to 100 mm VAS vary substantially (median 23 mm, IQR 12 to 39). Twenty-four weeks of treatment with 160 mg ginkgo biloba was associated with statistically significantly better pain-free walking distance (PFWD) than placebo, and this difference is likely to be clinically meaningful, although the certainty is very low (MD 36.0 m [95% CI 15.4 to 56.6]; 2 RCTs; 73 patients; very low certainty evidence; MCID 20 m). Total PFWD after 24 weeks of treatment was statistically significantly higher in patients receiving 120 mg ginkgo biloba than in those receiving placebo (MD 24.4 m [4.9 to 43.9]; 3 RCTs; 225 patients; low certainty evidence; MCID 20 m). The available findings do not support any additional conclusions regarding other measures of mobility, peripheral blood circulation, or safety (all very low certainty evidence). No data were reported on HRQoL.

**Vertigo**

There is no evidence to suggest that ginkgo biloba differs statistically significantly from betahistine dihydrochloride in vestibular symptoms, but the evidence base is sparse, and the overall certainty of evidence is low. One trial compared 12 weeks of treatment with 240 mg ginkgo biloba vs. 32 mg betahistine dihydrochloride using a range of patient-reported outcome measures to assess vestibular symptoms (11-point scale, Romberg test subscales, Unterberger's stepping test, Vertigo Symptom Scale subscales). None of the results showed any statistically significant differences between treatment groups (1 RCT; 160 patients; low certainty evidence). Another

trial compared 160 mg ginkgo biloba with 32 mg betahistine dihydrochloride over 12 weeks and reported no statistically significant differences in any measures of vestibular symptoms (1 RCT; 31 patients; very low certainty evidence). In the trial comparing 240 mg ginkgo biloba vs. 32 mg betahistine, patients treated with 240 mg ginkgo biloba were statistically significantly less likely to experience ≥1 AE during 12 weeks of treatment (RR 0.61 [95% CI 0.38 to 0.99]; 1 RCT; 160 patients; moderate certainty evidence). No data were reported on HRQoL.

**Tinnitus**

No statistically significant differences were found between treatment with ginkgo biloba (120 mg or 150 mg) and placebo in patients' subjective assessment of tinnitus severity over 12 weeks, measured with a variety of categorical and continuous scales (2 RCTs; 815 patients; low certainty evidence). One trial found that tinnitus loudness, measured in decibels, was statistically significantly lower with 120 mg ginkgo biloba than with placebo after 12 weeks of treatment (MD -6.1 decibels [95% CI -10.9 to -1.3]; 1 RCT; 73 patients; low certainty evidence; MCID 5 decibels). However, another trial found no statistically significant difference between 150 mg ginkgo biloba and placebo on tinnitus loudness measured by trial-specific questionnaires after 12 weeks of treatment or 2 weeks after stopping treatment. The available findings do not support any conclusions regarding the efficacy of ginkgo biloba on the level of hearing loss (1 RCT; 22 patients; very low certainty evidence). In the trial investigating 150 mg ginkgo biloba vs. placebo for the condition of tinnitus, there was no statistically significant difference in the number of people with ≥1 AE during 12 weeks of treatment (RR 1.06 [95% CI 0.74 to 1.52]; 1 RCT; 978 patients; low certainty evidence). In the trial investigating 12 weeks of 120 mg ginkgo biloba vs. placebo for patients with tonally definable chronic tinnitus lasting at least 2 months, there were no AEs in either group (1 RCT; 99 patients; low certainty evidence). No data were reported on HRQoL.

**Safety across indications**

To supplement the findings regarding the safety of ginkgo biloba in each indication, meta-analyses were conducted to assess the number of patients experiencing ≥1 AE when treated with ginkgo biloba compared with placebo across indications. Among patients treated with either 120 mg ginkgo biloba or placebo for 24 weeks, there was no statistically significant difference in the occurrence of AEs across indications (RR 0.91 [95% CI 0.70 to 1.18]; 7 RCTs; 1'133 patients). A meta-analysis was also conducted on the proportion of patients with any eligible indication (MPD, PAOD, vertigo, or tinnitus), comparing 24 weeks of treatment with any dose of ginkgo biloba (120 mg, 150 mg, 160 mg, 240 mg) vs. placebo. Overall, there was no statistically significant difference between ginkgo biloba and placebo (RR 0.96 [95% CI 0.89 to 1.04]; 12 RCTs; 2'728 patients). Note that 2 additional trials (total of 14 RCTs and 2'801 patients) did not contribute to the meta-analysis because they reported zero AEs in both treatment groups.

## 6.1 Methodology efficacy and safety

### 6.1.1 Databases and search strategy

The SLR was conducted in accordance with guidance from the Cochrane Handbook for Systematic Reviews of Interventions[63] and the reporting considered all items from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[64] The search parameters for the identification of relevant literature are detailed in ***Table 4***. The search strategies were developed based on the PICO framework, in cooperation with an information specialist and taking the European Union herbal monograph on Ginkgo biloba L., folium into account.[54] The search strategies used Medical Subject Headings and Emtree terms, as well as free-text words specific to the research questions being addressed. Because MPD can have varying aetiologies and are described using many different terms in the literature, the search strategy did not include population terms. Instead, the search strategy aimed to identify all records reporting on any clinical outcomes from observational or interventional studies. The full search strategies are presented in ***Appendix A***. To gain insight into ongoing RCTs with study characteristics aligned with the PICO of this HTA, supplementary searches were conducted on the websites ClinicalTrials.gov (https://clinicaltrials.gov) and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu). Where trial registrations could be matched to published trials, the registration was utilised to assess selective outcome reporting. In addition to controlled studies, uncontrolled observational studies were identified through published SLRs and monographs.

**Table 4: Search parameters for clinical systematic literature review**

| | |
|---|---|
| **Electronic databases** | MEDLINE, Embase, EconLit, CENTRAL, CDSR, and NHS EED (all via OvidSP); INAHTA |
| **Other sources** | • ClinicalTrials.gov (https://clinicaltrials.gov)<br>• European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu) https://www.clinicaltrialsregister.eu<br>• Reference lists of relevant published SLRs/meta-analyses identified in the database search |
| **Publication type** | Journal articles only |
| **Search dates** | No restriction |
| **Language** | No restriction[a] |
| **Geography** | No restriction |

*Abbreviations*

CDSR = Cochrane Database of Systematic Reviews, EED = Economic Evaluation Database, INAHTA = International Network of Agencies for Health Technology Assessment, NHS = National Health Service, SLR = systematic literature review.

*Notes*

a = Although the search strategy was not restricted by language, publications in languages other than English, German, Italian, and French were excluded during title/abstract screening.

### 6.1.2 Study selection

The electronic records of the articles retrieved by the database searches were exported into an EndNote library (Clarivate Analytics, United States of America [USA]); and after deduplication, they were imported into DistillerSR for study selection. DistillerSR is an online tool that allows for blinded title/abstract and full-text screening of citations between independent reviewers and resolution of study inclusion conflicts. Screening was performed to include studies that meet the pre-defined study selection criteria (***Table 5***, ***Table 6***, ***Table 7***, and ***Table 8***), as well as to provide an exclusion reason for each publication/study that did not meet at least one of the pre-defined criteria. Screening was conducted in 2 levels: first, the title and abstract of each publication were assessed for relevance to the objectives of the SLR; second, articles that seemed to contain relevant data underwent full-text screening.

The identified title/abstracts and full-text publications were screened by 2 independent reviewers, and conflicts were resolved via discussion. If a consensus could not be reached, a third reviewer was consulted. SLRs/meta-analyses of relevant populations identified via the database search were flagged during the screening process and utilised to identify any additional studies. The studies included in such SLRs/meta-analyses were compared with the final list of included studies in this SLR to determine if any additional studies were eligible.

**Table 5: Eligibility criteria: Clinical evidence for MPD**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with MPD. MPD can be caused by varying aetiologies, including but not limited to neuro-degenerative AD, PDD, DLB, FTLD, or vascular disease | • Studies in which not all patients have MPD and data are not stratified[a]<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both MPD and hypertension)[b] |
| **Interventions** | Ginkgo biloba 120 mg to 240 mg *(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions approved in Switzerland, including herbal supplements[c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Active comparators approved for treatment of MPD in Switzerland | Other comparators[c] |
| **Outcomes** | • Cognitive function<br>• Behavioural changes/mood<br>• Functional status<br>• HRQoL<br>• Global assessment of health status[d]<br>• Symptoms of other conditions in this review (i.e. dizziness or tinnitus)[d]<br>• AEs/SAEs | Other outcomes |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f] | • Observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews |
| **Geography** | Any | Not applicable |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, DLB = diffuse Lewy body disease, FTLD = frontotemporal lobar degeneration, HRQoL = health-related quality of life, MPD = mental performance deficit, PDD = Parkinson's disease dementia, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review.

*Notes*

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

a = Studies in which only a subset of patients met the relevant eligibility criteria (e.g. some do not have MPD or are younger than 18 years of age) were not excluded during title/abstract screening, in case stratified data were reported in the full text.

b = This review sought to identify the best available evidence. If there were not sufficient data on MPD alone, studies of patients required to have a comorbid condition would have been included, but this was not necessary.

c = Studies in which ginkgo biloba was evaluated together with another intervention were eligible, as long as these co-interventions were identical across treatment arms.

d = The list of outcomes in the protocol was based on a preliminary search. This efficacy outcome was identified during full-text screening and was determined to be relevant to supporting the decision-making process.

e = The search strategy was not restricted by language; this criterion was applied during screening.

f = This review sought to identify the best available evidence. RCTs provided sufficient evidence (i.e. ≥2 studies) to inform the ***Efficacy*** HTA report chapter. Therefore, the eligibility criteria did not need to be expanded by descending the hierarchical evidence pyramid for study designs[65] to provide additional evidence.

g = SLRs and meta-analyses were included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses were reviewed to identify additional publications not picked up by database searches.

**Table 6: Eligibility criteria: Clinical evidence for PAOD**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with PAOD, also known as PAD | • Studies in which not all patients have PAOD and data are not stratified[a]<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study that only includes patients with both PAOD and acute myocardial infarction)[b] |
| **Interventions** | Ginkgo biloba 120 mg to 240 mg<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions approved in Switzerland, including herbal supplements[c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Active comparators approved for treatment of PAOD in Switzerland | Other comparators[c] |
| **Outcomes** | • Mobility<br>• Pain<br>• Peripheral blood circulation<br>• HRQoL<br>• Global assessment of health status[d]<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f] | • Observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews |
| **Geography** | Any | Not applicable |

*Abbreviations*

AE = adverse event, HRQoL = health-related quality of life, PAD = peripheral arterial disease, PAOD = peripheral arterial occlusive disease, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review.

*Notes*

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

a = Studies in which only a subset of patients met the relevant eligibility criteria (e.g. some do not have PAOD or are younger than 18 years of age) were not excluded during title/abstract screening, in case stratified data were reported in the full text.

b = This review sought to identify the best available evidence. If there were not sufficient data on PAOD alone, studies of patients required to have a comorbid condition would have been included, but this was not necessary.

c = Studies in which ginkgo biloba was evaluated together with another intervention were eligible as long as these co-interventions were identical across treatment arms.

d = The list of outcomes in the protocol was based on a preliminary search. This efficacy outcome was identified during full-text screening and was determined to be relevant to supporting the decision-making process.

e = The search strategy was not restricted by language; this criterion was applied during screening.

f = This review sought to identify the best available evidence. RCTs provided sufficient evidence (i.e. ≥2 studies) to inform the ***Efficacy*** HTA report. Therefore, the eligibility criteria did not need to be expanded by descending the hierarchical evidence pyramid for study designs[65] to provide additional evidence.

g = SLRs and meta-analyses were included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses were reviewed to identify additional publications not picked up by database searches.

**Table 7: Eligibility criteria: Clinical evidence for vertigo**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with vertigo/dizziness (peripheral or central vestibular system dysfunction). This includes acute vestibular syndrome (i.e. usually manifests with a single episode, such as vestibular neuritis), episodic vestibular syndrome (i.e. recurrent by nature, such as Ménière's disease or vestibular migraine), and chronic vestibular syndrome (i.e. persistent symptoms over an extended period of time, such as cerebellar degeneration). Studies of subtypes of vertigo are eligible. | • Studies in which not all patients have vertigo and data are not stratified[a]<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study of patients with vertigo and hypertension)[b] |
| **Interventions** | Ginkgo biloba 120 mg to 240 mg<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions approved in Switzerland, including herbal supplements[c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Active comparators approved for treatment of vertigo/dizziness in Switzerland | Other comparators[c] |
| **Outcomes** | • Timing and intensity of vestibular symptoms, including patient-perceived handicap<br>• HRQoL<br>• Global assessment of health status[d]<br>• Functional status[d]<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f] | • Observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews |
| **Geography** | Any | Not applicable |

*Abbreviations*

AE = adverse event, HRQoL = health-related quality of life, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review.

*Notes*

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

a = Studies in which only a subset of patients met the relevant eligibility criteria (e.g. some do not have vertigo or are younger than 18 years of age) were not excluded during title/abstract screening, in case stratified data were reported in the full text.

b = This review sought to identify the best available evidence. If there were not sufficient data on vertigo alone, studies of patients required to have a comorbid condition would have been included, but this was not necessary.

c = Studies in which ginkgo biloba was evaluated together with another intervention were eligible as long as these co-interventions were identical across treatment arms.

d = The list of outcomes in the protocol was based on a preliminary search. This efficacy outcome was identified during full-text screening and was determined to be relevant to supporting the decision-making process.

e = The search strategy was not restricted by language; this criterion was applied during screening.

f = This review sought to identify the best available evidence. RCTs provided sufficient evidence (i.e. ≥2 studies) to inform the ***Efficacy*** HTA report chapter. Therefore, the eligibility criteria did not need to be expanded by descending the hierarchical evidence pyramid for study designs[65] to provide additional evidence.

g = SLRs and meta-analyses were included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses were reviewed to identify additional publications not picked up by database searches.

**Table 8: Eligibility criteria: Clinical evidence for tinnitus**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | Adults with tinnitus. This includes acute tinnitus (duration <3 months), chronic tinnitus (duration >3 months), and sub-acute tinnitus (although this term is rarely used, studies describing patients with sub-acute tinnitus will be included for completeness). Studies of subtypes of tinnitus are eligible. | • Studies in which not all patients have tinnitus and data are not stratified<br>• Studies in which some patients are <18 years old and data are not stratified[a]<br>• Studies in which a comorbid condition is required as part of the patient eligibility criteria (e.g. a study of patients with tinnitus and depression)[b] |
| **Interventions** | Ginkgo biloba 120 mg to 240 mg<br>*(including all herbal medicinal products approved and reimbursed in Switzerland)* | Other interventions approved in Switzerland, including herbal supplements[c] |
| **Comparators** | • Placebo<br>• No treatment<br>• Active comparators approved for treatment of MPD in Switzerland | Other comparators[c] |
| **Outcomes** | • Tinnitus severity<br>• Tinnitus loudness<br>• Level of hearing loss<br>• HRQoL<br>• Functional status[d]<br>• Mood[d]<br>• AEs/SAEs | Other outcomes[d] |
| **Language** | English, German, Italian, and French[e] | Other languages |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • RCTs[f] | • Observational studies[f]<br>• SLRs[g]<br>• Case reports/studies<br>• Letters to the editor<br>• Expert opinions<br>• Editorials<br>• Narrative reviews<br><br>**Economic evidence:**<br>• Divergent study design |
| **Geography** | Any | Not applicable |

*Abbreviations*

AE = adverse event, HRQoL = health-related quality of life, RCT = randomised controlled trial, SAE = serious adverse event, SLR = systematic literature review.

*Notes*

Please note that the interventions, comparators, language, time horizon, study design, and geography are the same across all 4 indications; only the population and outcomes differ.

a = Studies in which only a subset of patients met the relevant eligibility criteria (e.g. some do not have tinnitus or are younger than 18 years of age) were excluded during title/abstract screening, in case stratified data were reported in the full text.

b = This review sought to identify the best available evidence. If there were not sufficient data on tinnitus alone, studies of patients required to have a comorbid condition would have been included, but this was not necessary.

c = Studies in which ginkgo biloba was evaluated together with another intervention were eligible as long as these co-interventions were identical across treatment arms.

d = The list of outcomes in the protocol was based on a preliminary search. This efficacy outcome was identified during full-text screening and was determined to be relevant to supporting the decision-making process.

e = The search strategy was not restricted by language; this criterion was applied during screening.

f = This review sought to identify the best available evidence. RCTs provided sufficient evidence (i.e. ≥2 studies) to inform the ***Efficacy*** HTA report chapter. Therefore, the eligibility criteria did not need to be expanded by descending the hierarchical evidence pyramid for study designs[65] to provide additional evidence.

g = SLRs and meta-analyses were included and flagged during title and abstract screening and excluded during full-text screening; the bibliographies of relevant SLRs or meta-analyses were reviewed to identify additional publications not picked up by database searches.

### 6.1.3 Assessment of quality of evidence

For each included trial, detailed information about trial methodology was collected (see ***Section 6.1.4.1***) and used to inform risk of bias assessment for each study. The risk of bias for each study was completed by one researcher and fully reviewed by a second researcher. For each of the following domains, risk of bias was assessed as high (reported methods are likely to lead to a biased estimate of the treatment effect), low (reported methods are unlikely lead to a biased estimate of the treatment effect), or unclear (there is not enough information available to determine the risk): random sequence generation; allocation concealment; blinding of participants, study personnel, and outcome assessors; and attrition bias. The results of the risk of bias assessments are displayed in figures with colour-coded ratings for each domain. Where multiple publications on a trial were available, all publications were used in an effort to limit the number of ‘unclear' ratings.

The overall quality of evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. The 5 domains (imprecision, inconsistency, indirectness, risk of bias, and publication bias) of the GRADE framework were scored (high, moderate, low, very low). The overall certainty of the evidence on the outcome level was appraised by one researcher and fully verified by a second researcher. Differences were resolved by discussion, and in case of discrepancy, a third researcher was consulted to reach a consensus. GRADE assessments were not completed for outcomes that were not prespecified in the protocol, as these were considered supplementary results (see ***Appendix C*** for a complete list of outcomes collected that were not prespecified). GRADE assessments were also not completed for earlier timepoints of identical outcomes (e.g. if a trial reported results for the same questionnaire at both 12 weeks and 24 weeks, both results are included in this report, but GRADE assessment was only completed for the 24-week results). For all outcomes in which the SMD was used to categorize the clinical relevance of the effect size (see ***Section 6.1.4.2*** for additional details), the SMD and its 95% CI were also used to assess uncertainty related to imprecision. Outcomes were downgraded one level for imprecision if the 95% CI included the threshold between small effects and trivial/no effects (0.2) and two levels if the 95% CI also included zero. The overall certainty of the evidence was summarised in GRADE summary of findings tables using the GRADEpro GDT software (Evidence Prime Inc., Canada).

### 6.1.4 Methodology data extraction, analysis, and synthesis of domain efficacy and safety

#### 6.1.4.1 Data extraction

Data were extracted from included publications by one reviewer, and complete confirmation of the data extracted was conducted by a second reviewer. A third reviewer was consulted if agreement was not reached between reviewers. Data extraction was completed in a Microsoft Excel spreadsheet. Where multiple publications (including trial registration records) were available for the same trial, all publications were utilised to complete data extraction.

A list of data elements extracted from each included publication is provided below:

- **Trial information:** author, publication date, study identifier, study objective, source of funding, country, number of patients randomised, enrolment dates, randomisation technique, allocation concealment details, blinding, maximal follow-up duration, inclusion and exclusion criteria, statistical methods (i.e. methods for handling missing data, type of statistical test utilised), primary and secondary outcomes of interest as described by trial authors, patient attrition (per outcome where available).
- **Demographic information and baseline clinical characteristics (per treatment arm):** number of participants with available data, age, sex, BMI, definition of disease, concomitant medications, geography, and race/ethnicity.
- **Intervention and comparator details:** dose, route, formulation, duration of intervention, and any co-interventions administered alongside the intervention and comparator(s).
- **Outcomes of interest:** measurement tool, timepoint of follow-up, and results for outcomes detailed in ***Section 4.***
- **Others:** limitations of the study that do not fall clearly under standard quality assessment (e.g. the trial was stopped early, unexpected changes to prespecified trial methodology).

#### 6.1.4.2 Statistical analysis and synthesis methods

For all 4 conditions, the following have been performed by the authors of this report:

- All timepoints have been transformed to weeks to facilitate comparison across studies.
- For all categorical outcomes, where either numerators or percentages were not reported by the original study authors, they were calculated by the authors of this report.
- For all continuous outcomes, where 95% CIs were not reported by the original study authors, but another measure of precision (e.g. standard deviation) was, 95% CIs were calculated by the authors of this report.

For each efficacy and safety outcome with sufficient reported data, studies with similar study design characteristics, intervention-comparator characteristics, and outcomes/endpoint characteristics were included in meta-analyses. Random effects models (restricted maximum-likelihood estimator)

were utilised for all meta-analyses; fixed-effect estimates are also reported in the forest plots. Dichotomous outcomes (e.g. AEs) were reported using RRs[a] with 95% CIs.[b] Continuous outcomes were reported as MDs[c] with 95% CIs. Meta-analysis results were illustrated using forest plots, as they provide a visual representation of the reported effect sizes and uncertainty across the included studies. To assess whether differences were clinically meaningful, MCIDs were identified; where MCIDs were unavailable, SMDs were used to categorize effect sizes as trivial/no effect (-0.2 to 0.2), small (0.2 to 0.5 or -0.5 to -0.2), moderate (0.5 to 0.8 or -0.8 to -0.5), or large (≥0.8 or ≤-0.8). Heterogeneity was assessed using both the $I^2$ statistic and the $\tau^2$ statistic. An $I^2$ of 0% to 40% is low heterogeneity (i.e. may not be important), 30% to 60% is moderate, 50% to 90% is substantial, and 75% to 100% is considerable heterogeneity.[63] Separate analyses were conducted for each dosage of ginkgo biloba. Where sufficient data were available, subgroup analyses were conducted based on the specific condition at baseline (e.g. AD was analysed separately from vascular dementia). The following timepoints were grouped for meta-analyses:

- 12 weeks: described in original studies as 90 days, 12 weeks, or 3 months
- 24 weeks: described in original studies as 180 days, 22 to 26 weeks, or 6 months
- 52 weeks: described in original studies as 52 weeks, 12 months, or 1 year

All statistical analyses were conducted using R version 4.4.1.[66] In cases where a meta-analysis was not possible, ranges of effect estimates were reported and narratively synthesised.

## 6.2 Results efficacy and safety

### 6.2.1 PRISMA flow diagram

The results of the systematic literature search are summarised in ***Figure 1***.

[a] Statistical analyses were conducted using log(RR) but were reported as RR for interpretability. The protocol stated that meta-analyses would be conducted using odds ratios (ORs), but included studies consistently reported RRs, so RRs were used for consistency with the original study reporting.

[b] Studies in which both treatment arms had zero events were excluded from meta-analyses. This only occurred for 2 outcomes. Excluding these studies resulted in meta-analysis not being possible (i.e. only zero or one remaining trial after excluding these studies from analysis).

[c] For all continuous outcomes, supplementary meta-analyses were conducted using SMDs.

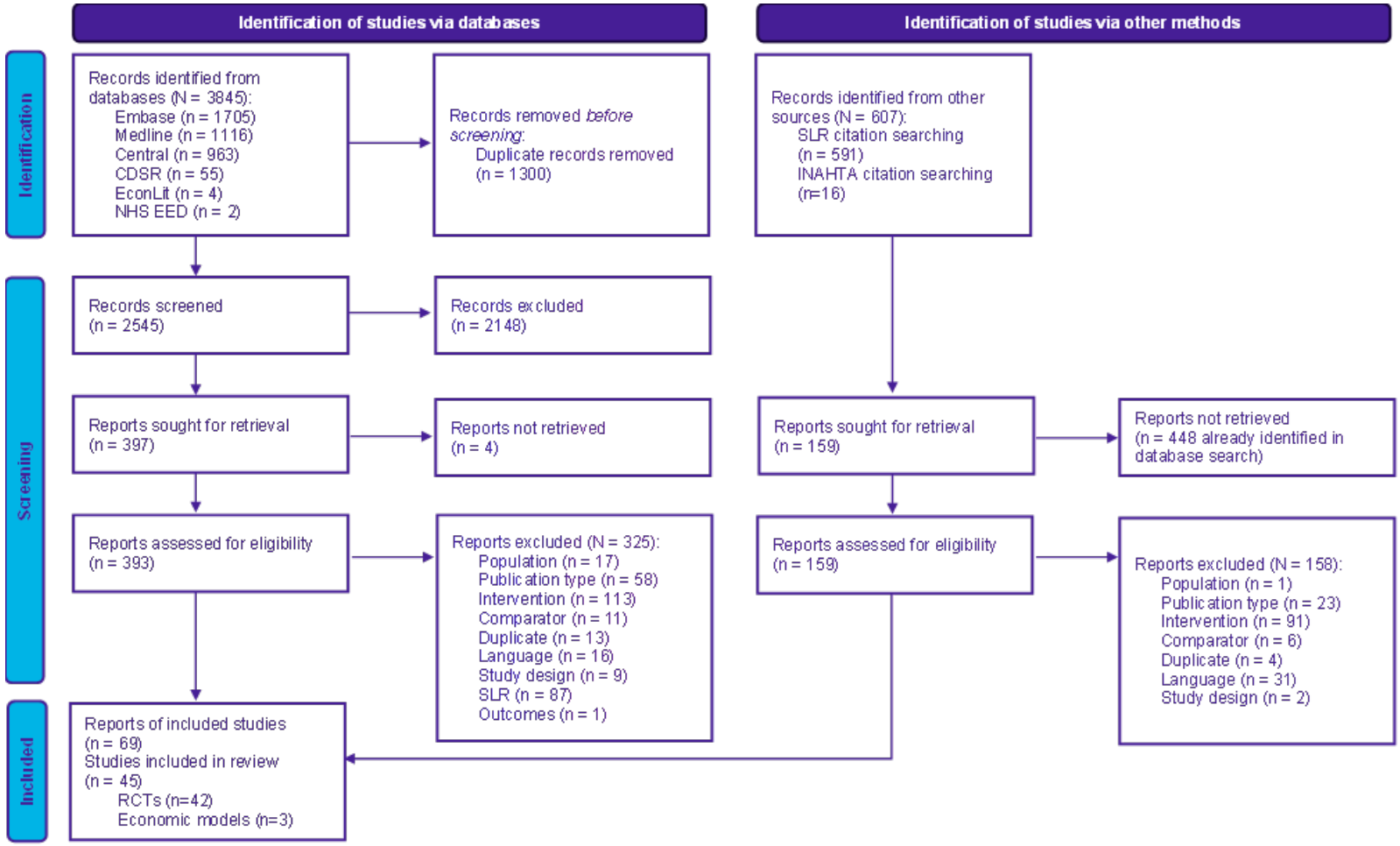


**Figure 1: PRISMA 2020 flow diagram for clinical and economic SLRs**

*Abbreviations*

CDSR = Cochrane Database of Systematic Reviews, EconLit = economic literature, INAHTA = International Network of Agencies for Health Technology Assessment, NHS EED = National Health Service Economic Evaluation Database, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomised controlled trial, SLR = systematic literature review.

### 6.2.2 Study characteristics and quality assessment of included studies

The study characteristics of the included RCTs for each of the 4 conditions of interest are reported in subsequent sections: MPD (***Section 6.2.2.1***), PAOD (***Section 6.2.2.2***), vertigo (***Section 6.2.2.3***), and tinnitus (***Section 6.2.2.4***).

#### **6.2.2.1** Mental performance deficits

A total of 28 included RCTs in 46 publications reported on the efficacy of ginkgo biloba in patients with MPD (***Table 9***). These trials were quite heterogeneous in terms of patient population, intervention and comparator, treatment duration, country, and study quality. These 28 studies, published between 1985 and 2019, included a total of 8'060 patients with MPD (sample size range: 20 to 2854). The identified studies reported on a variety of patient populations, including dementia, organic brain syndrome, cerebral insufficiency, MCI, and memory impairment. Although studies on dementia were the most common (14/28, 50%), these studies included different types of dementia (e.g. AD dementia, vascular dementia, multi-infarct dementia) and utilised a variety of clinical criteria. In addition, populations were defined in varying levels of detail (e.g. criteria unspecified, with or without imaging, etc.), and most studies were conducted before relevant biomarkers were utilised for diagnosis. Most (23/28, 82%) were conducted in Europe,[d] with the remaining RCTs conducted in the USA (3), China (1), and Iran (1). Most studies compared either 120 mg ginkgo biloba (8 RCTs) or 240 mg ginkgo biloba (10 RCTs) with placebo, with one additional study comparing 120 mg ginkgo biloba, 240 mg ginkgo biloba, and placebo. In addition, 2 studies each compared 150 mg ginkgo biloba or 160 mg ginkgo biloba to placebo. Two trials compared ginkgo biloba with active comparators: 4.5 mg rivastigmine or 10 mg donepezil. Finally, in 2 RCTs, some patients were allocated to change treatments during the course of the study. In the first, patients were randomised to receive either 240 mg ginkgo biloba or placebo for the first 6 months; then, all patients received 240 mg ginkgo biloba open-label for the second 6 months.[67] In the second, patients were randomised to 5 treatment arms: 240 mg ginkgo biloba for all 24 weeks of the study, 160 mg ginkgo biloba for all 24 weeks of the study, 240 mg ginkgo biloba for 12 weeks followed by placebo for 12 weeks, 160 mg ginkgo biloba for 12 weeks followed by placebo for 12 weeks, or placebo for all 24 weeks of the study.[68,69]

Overall, most included RCTs had a low risk of bias for random sequence generation, allocation concealment, and blinding, although several trials, particularly those that were published earlier, lacked details regarding methodology (***Figure 2***). The primary source of potential bias arose from study attrition (i.e. patients dropping out of the study). Although this is not unexpected given the older age and cognitive difficulties of this population, it does raise concerns regarding the reliability and validity of these studies. Eight studies were rated as unclear risk of bias because either patient attrition was not reported or was not reported per treatment arm.[70-79] Four studies were rated as

[d] Note that included here are 1 study conducted in Russia and 1 study conducted in the Republic of Belarus, the Republic of Moldova, and the Russian Federation.

high risk of bias because of high rates of attrition that were relatively similar across all treatment groups (range: 19% to 37%).[80-86] Finally, treatment arms had differential patient withdrawal across treatment arms in Rai 1991 (25% vs. 13%),[87] DRKS00000423 (40% vs. 7%),[88] NCT01046292 (28% vs. 4%),[67] and the Maastricht Ginkgo Trial (23%, 13%, 13%, 10%, and 9%).[68,69]

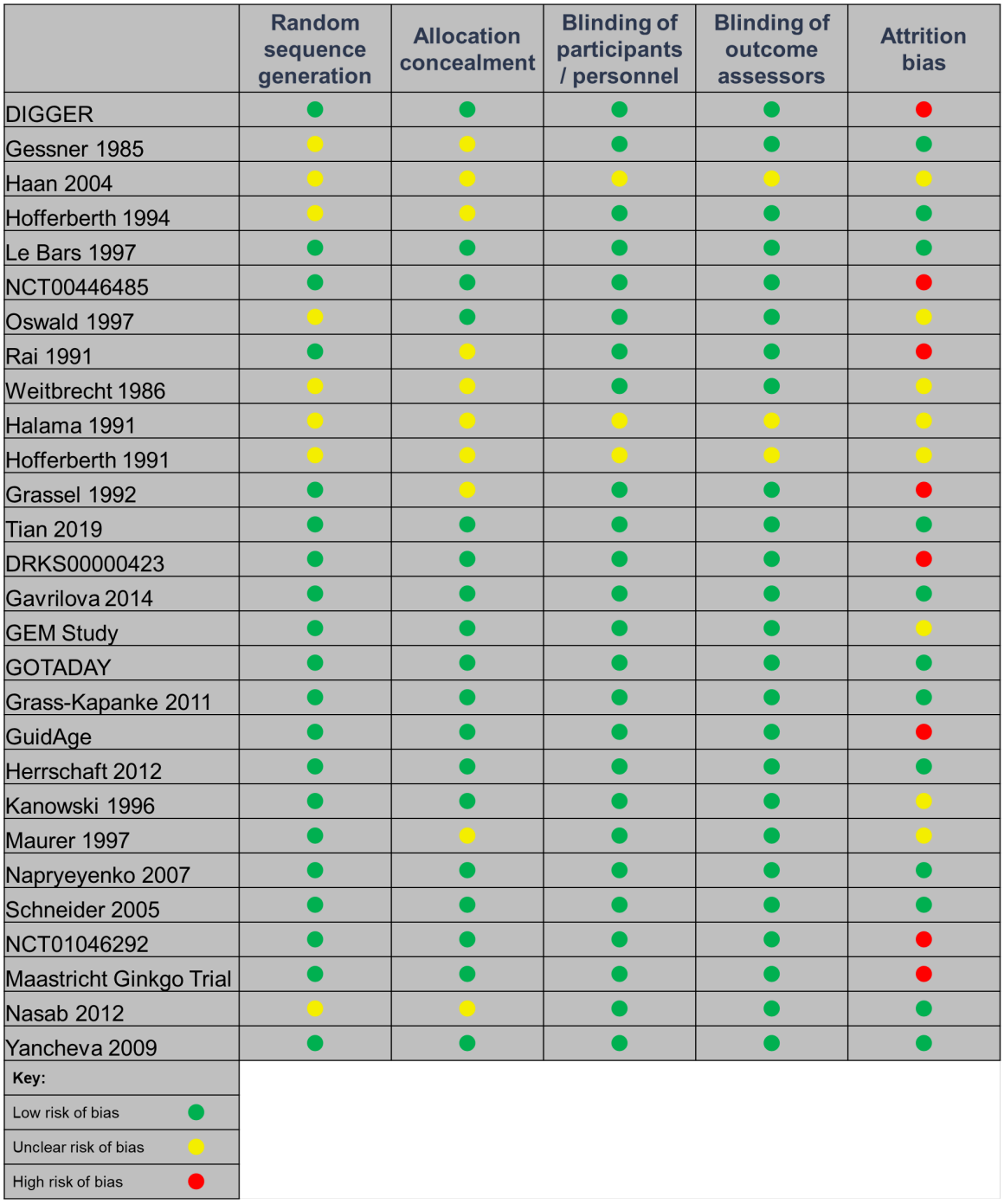


**Figure 2: Quality assessment – MPD**

### 6.2.2.2 Peripheral arterial occlusive disease

Eight included RCTs in 12 publications reported on the efficacy of ginkgo biloba in patients with PAOD (***Table 10***). These trials were generally older and included relatively few patients; they were

published between 1984 and 2007 and included a total of 474 people with PAOD (sample size range: 22 to 109). Most were conducted in Europe (6 in Germany, 1 in the UK), with one study conducted in Australia. All 8 RCTs lasted approximately 24 weeks, and 7 compared various doses of ginkgo biloba (120 mg, 160 mg, or 240 mg) with placebo, while the last study compared 2 doses of ginkgo biloba (120 mg vs. 240 mg).

Overall, most studies lacked methodological details regarding random sequence generation, allocation concealment, and blinding (most stating only that the study was 'double-blind'), possibly due to the fact that nearly all were published before the establishment of RCT reporting standards (***Figure 3***). In addition, 2 RCTs had a high risk of bias related to attrition, with patient withdrawal ranging from 18% to 30% across treatment arms.[89,90]


**Figure 3: Quality assessment – PAOD**

### 6.2.2.3 Vertigo

Two included RCTs reported on the efficacy of ginkgo biloba in patients with vertigo (***Table 11***). These trials, published in 1998 and 2014, included a total of 204 randomised patients with vertigo (44 and 160). Both were conducted in Europe (Italy and Ukraine). Both RCTs lasted approximately 12 weeks and compared ginkgo biloba with 32 mg betahistine dihydrochloride, although different doses of ginkgo biloba were utilised (160 mg and 240 mg).

ISRCTN02262139 was considered low risk of bias in all domains (***Figure 4***), using a computer-generated randomisation sequence, sequentially numbered complete drug packages, and a double-dummy technique, wherein each patient received a placebo version of the other treatment.[91] In addition, very few patients withdrew from the study, and the numbers were similar across treatment arms (3/80 in the ginkgo biloba treatment arm, 2/80 in the betahistine dihydrochloride treatment arm). In contrast, Cesarani 1998 was an open-label study in which all outcomes were patient-

reported.[92] Study authors did not clearly report methods for random sequence generation or allocation concealment, and there was limited information about patient withdrawal, which was not described per treatment arm (7/44 [16%] randomised patients were excluded from analyses).

| | Random sequence generation | Allocation concealment | Blinding of participants / personnel | Blinding of outcome assessors | Attrition bias |
|---|---|---|---|---|---|
| Cesarani 1998 | 🟡 | 🟡 | 🔴 | 🔴 | 🟡 |
| ISRCTN02262139 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 |
| **Key:** | | | | | |
| Low risk of bias 🟢 | | | | | |
| Unclear risk of bias 🟡 | | | | | |
| High risk of bias 🔴 | | | | | |

**Figure 4: Quality assessment – vertigo**

#### 6.2.2.4 Tinnitus

Four included RCTs in 5 publications reported on the efficacy of ginkgo biloba in patients with tinnitus (***Table 12***). These trials, published between 1990 and 2020, included a total of 1'310 people with tinnitus (sample size range: 33 to 978). Three trials were conducted in Europe (Czech Republic, Germany, UK), and the fourth was conducted in Brazil. All 4 RCTs lasted approximately 12 weeks, but each assessed a different intervention and comparator. Doses of ginkgo biloba ranged from 120 mg to 240 mg, and comparators included placebo, 600 mg of pentoxifylline, and a hearing aid.

Overall, most domains were rated as low risk of bias, although some studies lacked clear methodological details, particularly regarding allocation concealment (***Figure 5***). In addition, Drew 1999 was rated as high risk of bias related to the random sequence generation and allocation concealment.[93,94] Rather than patients being sequentially assigned based on a randomly generated list of numbers, patients were matched in pairs based on specific patient characteristics. Then, one patient in each pair was randomly assigned to receive ginkgo biloba, while the other received placebo. This method of allocating patients does not sufficiently address concerns regarding unmeasured confounding. Finally, in trial RBR2SN8XV (Brazilian trial registry number), it was not feasible to blind patients or study personnel to treatment, because the comparator treatment was a hearing aid.[95] Although study personnel administering questionnaires, the person outside the research team completing data entry, and those analysing the data were blinded to the intervention, all the outcomes reported were self-assessed (e.g. tinnitus annoyance, tinnitus discomfort), and therefore were likely to be influenced by the participants' knowledge of their treatment.

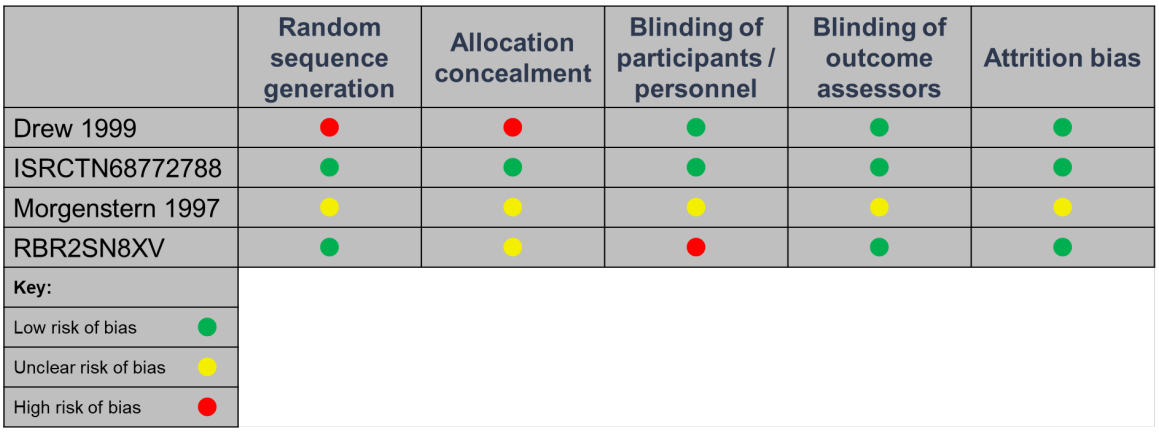


**Figure 5: Quality assessment – tinnitus**

### 6.2.3 Evidence table

**Table 9: Evidence table – MPD**

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| DIGGER (2008)[83,84] | UK<br>Non-industry funding | 2003-2005<br>6 months | Dementia: Clinical diagnosis by referring clinician | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>HRQoL<br>Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 120 mg (EGb 761, BID) | 88 | 79.3 ± 7.77 | 58 | 3 years[a] | |
| | | | Placebo | 88 | 79.7 ± 7.53 | 63.6 | 3 years[a] | |
| Gessner 1985[96] | France; Germany<br>Bio-Data GmbH | NR<br>12 weeks | Cerebral insufficiency: Symptoms of cerebral deterioration | | | | | Cognitive function |
| | | | Ginkgo biloba 120 mg (EGb 761, TID) | 20 | 65.5 ± 25.6 | NR | NR | |
| | | | Placebo | 20 | 65.5 ± 25.6 | NR | NR | |
| Haan 2004[71] | Germany<br>NR[b] | NR<br>12 months | AD/dementia: Mild to moderate AD or MID | | | | | Cognitive function<br>Functional status |
| | | | Ginkgo biloba 120 mg (EGb 761, NR) | -- | NR | NR | NR | |
| | | | Placebo | -- | NR | NR | NR | |
| Hofferberth 1994[97] | Germany<br>Non-industry funding | NR<br>3 months | AD: (1) Blessed Dementia Scale: sum Part A: 0-16, sum Part B: 9.5-30.5, (2) Hachinski Ischemic Score <4, and (3) normal or diffuse and possible asymmetrically atrophic CT findings | | | | | Cognitive function<br>Behavioural changes/mood |
| | | | Ginkgo biloba 120 mg (EGb 761, TID) | 21 | NR | 33.3 | NR | |
| | | | Placebo | 19 | NR | 36.8 | NR | |
| Le Bars 1997[98-101] | USA | NR | AD/dementia: Outpatients with AD or MID, without other significant medical conditions | | | | | Cognitive function<br>Functional status |

| RCT identifier | Country<br><br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | Dr. Willmar Schwabe GmbH & Co. KG | 52 weeks | Ginkgo biloba 120 mg (EGb 761, TID) | 166 | 69 ± 10 | 51 | 4.6 ± 4.3 years | Global assessment of health status<br>AEs |
| | | | Placebo | 161 | 69 ± 10 | 56 | 3.9 ± 3 years | |
| NCT00446485 (2017)[81] | Croatia | 2007-2010 | Cerebral insufficiency: (1) Cerebrovascular insufficiency, and (2) MMSE score of >20 and ≤28 | | | | | Cognitive function<br>Behavioural changes/mood |
| | Milsing d.o.o. | 6 months | Ginkgo biloba 120 mg (EGb 761, QD) | 30 | 66.7 ± 7.7[c] | 63.8[c] | NR | Global assessment of health status |
| | | | Placebo | 30 | | | NR | AEs |
| Oswald 1997[78] | Germany | 1989-1994 | Organic brain syndrome: (1) mild to moderate cognitive disorders of old age (DSM-III, Cat. 1 or ICD-9 No. 290), (2) SCAG between 40 and 90, and (3) average score of ≥3.5 in items 2, 3, 6, and 8, and a total score of 24 in items 1 to 8, with none of these items having a score of 7 | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>HRQoL |
| | NR | 12 weeks | Ginkgo biloba 120 mg (EGb 761, TID) | 103 | 70.5 ± 7.8 | 65 | 2.7 ± 1.2 years[c] | Global assessment of health status |
| | | | Placebo | 92 | 71.4 ± 7.9 | 53 | | |
| Rai 1991[87] | UK | NR | Memory impairment: mild to moderate memory impairment of organic origin as classified by NINCDS-ADRDA for ≥3 months. | | | | | Cognitive function<br>Functional status |
| | Non-industry funding | 6 months | Ginkgo biloba 120 mg (EGb 761, TID) | 12 | 73.42 ± 7.25 | 66.7 | NR | |
| | | | Placebo | 15 | 78.3 ± 5.93 | 80.0 | NR | |
| Weitbrecht 1986[79] | Germany | NR | Dementia: primary degenerative dementia using the Hachinski Ischemic Scale, excluding patients with scores >7 (MID) | | | | | Cognitive function<br>Behavioural changes/mood |
| | | 12 weeks | Ginkgo biloba 120 mg (EGb 761, TID) | 20 | 71.9 ± 5.8 | 65.0 | 8.9 ± 2.5 years | Global assessment of health status |
| | | | Placebo | 20 | 71.5 ± 4.4 | 65.0 | 8.8 ± 3 years | |
| Halama 1991[72] | Germany | NR | Dementia: Outpatients from a neurology specialist practice with a diagnosis of pre-senile, simple senile, or arteriosclerotic dementia | | | | | Cognitive function<br>Global assessment of health status |
| | NR | 12 months | Ginkgo biloba 150 mg (LI1370, TID) | 20 | 61 (46 to 83)[d] | 75.0 | NR | |

| RCT identifier | Country<br><br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | Placebo | 22 | 61 (35 to 85)[d] | 54.5 | NR | |
| Hofferberth 1991[73] | Germany | NR | Organic brain syndrome: Inpatients from a neurological specialty department with organic brain syndrome | | | | | Cognitive function<br>Global assessment of health status |
| | NR | 6 weeks | Ginkgo biloba 150 mg (LI1370, TID) | 25 | 65 ± 5[c] | 42.0[c] | NR | |
| | | | Placebo | 25 | | | NR | |
| Grassel 1992[82] | Germany | NR | Cerebral insufficiency: (1) 'cerebral insufficiency', based on anamnesis data (indications of a stenosing vascular process in the cranial area, e.g. TIA or previous infarct), verified using Doppler ultrasound when in doubt; and (2) IQ value of short-term memory capacity less than MWT IQ | | | | | Cognitive function<br>AEs |
| | NR[e] | 24 weeks | Ginkgo biloba 160 mg (EGb 761, BID) | 36 | 65.4 ± 7.3 | 48.3 | NR | |
| | | | Placebo | 36 | 64.7 ± 9 | 50.0 | NR | |
| Tian 2019[102] | China | 2015-2017 | Amnestic MCI: (1) memory complaints, (2) Chinese version of the AMIPB-DSR age-adjusted subtest score of <15.5 (aged 50-64 years <15.5, 65-74 years <12.5, and over 75 years <10); (3) normal general cognitive function as determined by a clinician's judgment based on a structured interview with the patients, MMSE score of 24 to 30, and CDR score of 0.5, with the memory domain 0.5 or 1, and no other domain greater than 1; (4) score of 38-52 on ADCS-ADL-MCI-24 | | | | | Cognitive function<br>Functional status<br>AEs |
| | | 52 weeks | Ginkgo biloba 160 mg (EGb 761, BID) | 105 | 64.43 ± 7.72 | 57.7 | NR | |
| | | | Placebo | 70 | 64.15 ± 7.25 | 47.1 | NR | |
| DRKS 00000423 (2016)[88] | Germany<br><br>Dr. Willmar Schwabe GmbH & Co. KG | 2010-2012<br>2 months | Memory impairment: ≥1 item answered with 'rather often' or 'very often', or ≥5 questions answered 'sometimes' in the PRMQ | | | | | Cognitive function<br>Behavioural changes/mood<br>AEs |
| | | | Ginkgo biloba 240 mg (EGb 761, QD) | 31 | 57.5 ± 4.6 | 48.4 | NR | |
| | | | Placebo | 30 | 57.1 ± 4.4 | 60.0 | NR | |

| RCT identifier | Country<br><br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Gavrilova 2014[103,104] | Russia<br>Dr. Willmar Schwabe GmbH & Co. KG | NR<br>24 weeks | Amnestic MCI: International consensus criteria | | | | | Cognitive function<br>Behavioural changes/mood<br>Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 240 mg (EGb 761, QD) | 80 | 65 ± 7 | 73 | 42 ± 31 months | |
| | | | Placebo | 80 | 63 ± 7 | 84 | 36 ± 26 months | |
| GEM Study (2008)[70] | USA<br><br>Non-industry funding; medications provided by Dr. Willmar Schwabe GmbH & Co. KG | 2000-2002<br><br>6.1 years | MCI: (1) ≤10th percentile of Cardiovascular Health Study normative data, stratified by age and education, on ≥2 of 10 selected neuropsychological test scores from each cognitive domain, including memory, language, Visuospatial abilities, attention, and executive function; and (2) CDR global score of 0.5 | | | | | Cognitive function |
| | | | Ginkgo biloba 240 mg (EGb 761, BID) | 256 | NR | NR | NR | |
| | | | Placebo | 226 | NR | NR | NR | |
| GOTADAY (2011)[105-109] | Ukraine<br><br>Dr. Willmar Schwabe GmbH & Co. KG | 2006-2007<br><br>24 weeks | AD/dementia: score ≥5 on the NPI, with at least one item score ≥3, as well as 1 of the following: (1) probable AD in accordance with the NINCDS-ADRDA criteria, (2) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (3) probable vascular dementia according to NINDS-AIREN | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>HRQoL<br>Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 240 mg (EGb 761, QD) | 206 | 65 ± 10 | 69 | 4.9 ± 4.2 years | |
| | | | Placebo | 204 | 65 ± 10 | 66 | 4.8 ± 3.5 years | |
| Grass-Kapanke 2011[110] | Latvia | NR | Very MCI: (1) subjective complaints of impairment in ≥1 of the following: memory, attention/concentration, speed of functioning, efforts required to complete complex tasks, general performance/efficiency; (2) low functioning (≥1 SD below the mean) in ≥1 of WMS III Faces I + II, WTS-ALS (S1), WTS-DT (S16), TT; (3) duration ≥3 months; (4) >23 in the MMSE; (5) intact ADL; and (6) no indication of dementia | | | | | Cognitive function<br>HRQoL<br>AEs |

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | Non-industry funding | 12 weeks | Ginkgo biloba 240 mg (EGb 761, QD) | 150 | 55.3 ± 5.7 | 81.2 | NR | |
| | | | Placebo | 150 | 54.5 ± 6.1 | 83.7 | NR | |
| GuidAge (2012)[80,85,86] | France | 2002-2004 | Memory impairment: (1) Consulted a healthcare professional regarding memory problems, (2) MMSE score >25, (3) Covi anxiety score <6, and (4) Geriatric depression scale score <15 | | | | | Cognitive function<br>AEs |
| | Ipsen International | 5 years | Ginkgo biloba 240 mg (EGb 761, BID) | 1406 | 76.3 ± 4.4 | 66 | 39.7 months[a] | |
| | | | Placebo | 1414 | 76.3 ± 4.4 | 67 | 39 months[a] | |
| Herrschaft 2012[106,111,112] | Republic of Belarus, Republic of Moldova, and Russian Federation | 2008-2009 | AD/dementia: Duration ≥6 months and 1 of the following: (1) probable AD in accordance with the NINCDS-ADRDA criteria, (2) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (3) probable vascular dementia according to NINDS-AIREN | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>HRQoL<br>Global assessment of health status |
| | Dr. Willmar Schwabe GmbH & Co. KG | 24 weeks | Ginkgo biloba 240 mg (EGb 761, QD) | 205 | 65.1 ± 8.8 | 69.5 | 3.2 ± 2.2 years | AEs |
| | | | Placebo | 205 | 64.9 ± 9.4 | 69.3 | 3.4 ± 2.8 years | |
| Kanowski 1996[74,75] | Germany | 1990-1991 | AD/dementia: AD or MID according to DSM-III-R | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>Global assessment of health status |
| | NR[f] | 24 weeks | Ginkgo biloba 240 mg (EGb 761, BID) | 106 | 72 ± 10 | 68 | NR | |
| | | | Placebo | 99 | 72 ± 10 | 71 | NR | |
| Maurer 1997[76,77] | Germany<br>Non-industry funding | NR<br>3 months | AD: Mild to moderate AD (mean BCRS score 3-5) | | | | | Cognitive function<br>Global assessment of health status |
| | | | Ginkgo biloba 240 mg (EGb 761, TID) | 10 | 68.5 ± 6 | 55.6 | NR | |
| | | | Placebo | 10 | 60.6 ± 8.82 | 44.4 | NR | |
| Napryeyenko | Ukraine | 2003-2004 | AD/dementia: Total score 9-23 (both inclusive) on the SKT test battery, and a score ≥5 on the NPI, with at least one item score ≥3, as well as one of the | | | | | Cognitive function<br>Behavioural changes/mood |

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| 2007[106,113-115] | | | following: (1) probable AD in accordance with the NINCDS-ADRDA criteria, (2) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (3) probable vascular dementia according to NINDS-AIREN | | | | | Functional status<br>AEs |
| | Dr. Willmar Schwabe GmbH & Co. KG | 22 weeks | Ginkgo biloba 240 mg (EGb 761, BID) | 200 | 65 ± 8 | 72 | 2.2 ± 2.1 years | |
| | | | Placebo | 200 | 63 ± 8 | 72 | 2 ± 1.9 years | |
| Schneider 2005[116,117] | USA | 1999-2000 | AD: (1) diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA), (2) duration of dementia symptoms ≥6 months, (3) Modified Hachinski Ischemic Score <4, and (4) MMSE score of 10 to 24; no more than one-third of the subjects enrolled at each site could have an MMSE score of ≥20 | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>Global assessment of health status<br>AEs |
| | Dr. Willmar Schwabe GmbH & Co. KG | 26 weeks | Ginkgo biloba 120 mg (EGb 761, BID) | 169 | 78.6 ± 7 | 50 | 4.6 ± 2.7 years | |
| | | | Ginkgo biloba 240 mg (EGb 761, BID) | 170 | 78.1 ± 7 | 56 | 4.1 ± 3 years | |
| | | | Placebo | 174 | 77.5 ± 7.4 | 52 | 4.6 ± 3.4 years | |
| NCT01046292 (2017)[67] | Switzerland | 2010-2014 | MCI: (1) reduction in gait velocity of ≥10% during dual-task compared to single-task walking, (2) MCI according to Winblad et al. 2004, and (3) no dementia according to ICD-10 and DSM-IV | | | | | Cognitive function<br>AEs |
| | Non-industry funding and Vifor SA | 12 months | Ginkgo biloba 240 mg (blinded) → 240 mg Ginkgo biloba (open label) (LI1370, BID) | 25 | 67.8 ± 8.3 | 60 | NR | |
| | | | Placebo (blinded) → Ginkgo biloba 240 mg (open label) (LI1370, BID) | 25 | 69.2 ± 8.6 | 40 | NR | |
| Maastricht Ginkgo Trial (2000)[68,69] | The Netherlands | 1994-1996 | Memory impairment or dementia: (1) Dementia according to DSM-III-R and ICD-10 criteria, or (2) nondemented patients with age-associated memory impairment | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status |

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | Dr. Willmar Schwabe GmbH & Co. KG | 24 weeks | Ginkgo biloba 160 mg → Ginkgo biloba 160 mg (EGb 761, BID) | 40 | 82.8 ± 4.9[c] | 85[c] | NR | Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 160 mg → Placebo (EGb 761, BID) | 40 | | | NR | |
| | | | Ginkgo biloba 240 mg → Ginkgo biloba 240 mg (EGb 761, BID) | 39 | 83.3 ± 5.3[c] | 85[c] | NR | |
| | | | Ginkgo biloba 240 mg → Placebo (EGb 761, BID) | 38 | | | NR | |
| | | | Placebo | 44 | 82.6 ± 5.7 | 81 | NR | |
| Nasab 2012[118] | Iran<br>Non-industry funding | 2008-2009<br>24 weeks | AD: Probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as an MMSE score of 10-24 | | | | | Cognitive function |
| | | | Ginkgo biloba 120 mg (EGb 761, QD) | 25 | 65.72 ± 4.69 | 52 | NR | |
| | | | Rivastigmine 4.5 mg | 26 | 66.03 ± 4.64 | 57.7 | NR | |
| Yancheva 2009[119] | Bulgaria | 2003-2004 | AD: (1) probable AD according to the DSM-IV and the NINCDS-ADRDA criteria; (2) mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test; and (2) CT or MRI scan <1 year old consistent with the diagnosis | | | | | Cognitive function<br>Behavioural changes/mood<br>Functional status<br>AEs |
| | Dr. Willmar Schwabe GmbH & Co. KG | 22 weeks | Donepezil 10 mg | 33 | 66 ± 8 | 84.4 | 4 ± 1.8 years | |
| | | | Ginkgo biloba 240 mg (EGb 761, BID) | 31 | 69 ± 8 | 54.8 | 4.7 ± 3.1 years | |
| | | | Ginkgo biloba 240 mg + Donepezil 10 mg (EGb 761, BID) | 32 | 68 ± 9 | 67.7 | 4.6 ± 2.7 years | |

*Abbreviations*

AD = Alzheimer’s disease, ADCS-ADL-MCI-24 = Alzheimer’s Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment – 24-item, ADL = activities of daily living, AE = adverse event, AMIPB-DSR = Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall, BID = twice daily, CDR = Clinical Dementia Rating, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, HRQoL = health-related quality of life, ICD-10 = International Classification of Diseases, Tenth Revision, ICD-9 = International Classification of Diseases, Ninth Revision, IQ = intelligence quotient, MCI = mild cognitive impairment, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, MRI = magnetic resonance imaging, MWT IQ = Multiple Choice Vocabulary Intelligence Test, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NR = not reported, NPI = Neuropsychiatric Inventory, PRMQ = Prospective and Retrospective Memory Questionnaire, QD = once daily, RCT = randomised controlled trial, SCAG = Sandoz Clinical Assessment Geriatric Scale, SD = standard deviation, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression, TIA = transient ischaemic attack, TID = three times daily, TT = Termine Test, UK = United Kingdom, WMS III = Wechsler Memory Scale III, WTS-ALS = Vienna Test System—Work Performance Series, WTS-DT = Vienna Test System—Determination Test.

*Notes*

a = Reported as median.

b = Funding not reported, but second author is an employee of Dr. Willmar Schwabe GmbH & Co.

c = Not reported by treatment arm.

d = Values were reported but type of value was not labelled (e.g. may be mean, median, range, etc.).

e = Manufacturer of ginkgo biloba was Intersan GmbH, but it is not clear whether the treatments were provided to the study by the manufacturer.

f = Funding not reported, but randomisation sequence generation was completed by Dr. Willmar Schwabe GmbH & Co., and some authors are employees of Dr. Willmar Schwabe GmbH & Co. and Parexel GmbH.

**Table 10: Evidence table – PAOD**

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Bauer 1984[120-124] | Germany<br>NR | NR<br>24 weeks | PAOD: PFWD <300 m; occlusions were unilaterally dominant and had been present for ≥1 year | | | | | Mobility<br>Pain<br>Peripheral blood circulation<br>Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 120 mg (EGb 761, TID) | 44 | 60.6 ± 7.2 | 22.7 | NR | |
| | | | Placebo | 35 | 61.1 ± 6.5 | 22.9 | NR | |
| Blume 1996[125] | Germany<br>NR[a] | 1990<br>24 weeks | Fontaine's stage IIb PAOD: Angiographically confirmed within prior 8 months; IC duration >6 months | | | | | Mobility<br>Peripheral blood circulation<br>Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 120 mg (EGb 761, TID) | 30 | 71 (65.2 to 74.8)[b] | 40 | NR | |
| | | | Placebo | 30 | 68.6 (65.5 to 73.2)[b] | 20 | NR | |
| Blume 1998[126] | Germany<br>NR[a] | NR<br>24 weeks | Fontaine's stage IIb PAOD: Confirmed via angiography or Doppler-sonography | | | | | Mobility<br>Peripheral blood circulation<br>AEs |
| | | | Ginkgo biloba 160 mg (EGb 761, BID) | 21 | 66.4 ± NR | 33.3 | NR | |
| | | | Placebo | 20 | 68.2 ± NR | 21.1 | NR | |
| Bulling 1991[127] | Germany<br>NR[a] | 1987-1989<br>24 weeks | Fontaine's stage IIb PAOD: PFWD 50-200 m | | | | | Mobility<br>Peripheral blood circulation<br>AEs |
| | | | Ginkgo biloba 160 mg (EGb 761, BID) | 17 | 62.8 ± 8.5 | 29.4 | NR | |

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | | | Placebo | 16 | 63.3 ± 9.3 | 25.0 | NR | |
| Peters 1998[128] | Germany<br>NR | NR<br>24 weeks | Fontaine's stage IIb PAOD: IC duration >6 months<br>Ginkgo biloba 120 mg (EGb 761, TID) | 52 | 62.8 ± NR | 44 | NR | Mobility<br>Peripheral blood circulation<br>Global assessment of health status |
| | | | Placebo | 57 | 61.2 ± NR | 40 | NR | AEs |
| Schweizer 1999[129] | Germany<br>NR | 1994-1996<br>24 weeks | Fontaine's stage IIb PAOD: Occlusion of the superficial femoral artery on one leg and without occlusion of the deep femoral artery; PFWD <200 m and MWD 100-300 m<br>Ginkgo biloba 120 mg (EGb 761, BID) | 38 | 63.4 ± 7.1 | 21 | NR | Mobility<br>Pain<br>Peripheral blood circulation<br>Global assessment of health status<br>AEs |
| | | | Ginkgo biloba 240 mg (EGb 761, BID) | 36 | 62.9 ± 7.8 | 28 | NR | |
| Thomson 1990[90] | UK<br>Ipsen International | NR<br>24 weeks | Fontaine's stage II PAOD: Affecting the iliac or femoral arteries and involving predominantly one leg<br>Ginkgo biloba 120 mg (EGb 761, TID) | 25 | NR | NR | NR | Mobility<br>Pain<br>Peripheral blood circulation |
| | | | Placebo | 24 | NR | NR | NR | |
| Wang 2007[89] | Australia | NR | PAOD: ABI <0.90 at rest and <0.80 after treadmill walking test; stable IC for ≥6 months | | | | | Mobility<br>Peripheral blood circulation |

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | NR; medications provided by Mayne Health Consumer Products | 24 weeks | Ginkgo biloba 240 mg (EGb 761, BID) | 11 | 71.6 ± 8 | 18.2 | NR | |
| | | | Placebo | 11 | 71.2 ± 6.3 | 0.0 | NR | |

*Abbreviations*

ABI = Ankle-Brachial Index, AE = adverse event, BID = twice daily, IC = intermittent claudication, MWD = maximum walking distance, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RCT = randomised controlled trial, SD = standard deviation, TID = three times daily.

*Notes*

a = Manufacturer of ginkgo biloba was Intersan GmbH, but it is not clear whether the treatments were provided to the study by the manufacturer.

b = Reported as median (range).

**Table 11: Evidence table – vertigo**

| RCT identifier | Country | Enrolment period | Population | | | | | Outcomes |
|---|---|---|---|---|---|---|---|---|
| | Funding | Follow-up | Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD unless otherwise specified) | |
| Cesarani 1998[92] | Italy | NR | Vertigo, dizziness, or both, due to vascular vestibular disorders | | | | | Vestibular symptoms<br>AEs |
| | NR | 90 days | Ginkgo biloba 160 mg (EGb 761, BID) | 20 | 64.55 ± 5.07 | 75.0 | <1 month: 5%<br>1-6 months: 25%<br>6-12 months: 25%<br>>12 months: 45% | |
| | | | Betahistine dihydrochloride 32 mg | 17 | 63.59 ± 4.78 | 70.6 | <1 month: 5.9%<br>1-6 months: 11.8%<br>6-12 months: 35.3%<br>>12 months: 47.1% | |
| ISRCTN 02262139 (2014)[91] | Ukraine | NR | Peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10; symptoms ≥3 months; ≥3 on NAS (1-10) at screening | | | | | Vestibular symptoms<br>Global assessment of health status<br>Functional status<br>AEs |
| | Dr. Willmar Schwabe GmbH & Co. KG | 12 weeks | Ginkgo biloba 240 mg (EGb 761, BID) | 80 | 57.5 ± 9.2 | 69 | 25.1 ± 37.3 months | |
| | | | Betahistine dihydrochloride 32 mg | 80 | 57.9 ± 8.4 | 73 | 22.5 ± 31.2 months | |

*Abbreviations*

AE = adverse event, BID = twice daily, ICD-10 = International Classification of Diseases, Tenth Revision, NAS = numeric analogue scale, NR = not reported, RCT = randomised controlled trial, SD = standard deviation.

**Table 12: Evidence table – tinnitus**

| RCT identifier | Country<br>Funding | Enrolment period<br>Follow-up | Population<br>Study arm, total daily dose (formulation, schedule) | N | Age, y (Mean ± SD) | Sex (% female) | Duration of condition (Mean ± SD) | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Drew 1999[93,94] | UK<br>Non-industry funding | NR<br>14 weeks | Self-reported tinnitus | | | | | Tinnitus severity<br>AEs |
| | | | Ginkgo biloba 150 mg (LI1370, TID) | 489 | 52.9 ± 9.3 | 31 | 10 ± 8.3 years | |
| | | | Placebo | 489 | 53 ± 9.3 | 31 | 10.1 ± 8.3 years | |
| ISRCTN 68772788 (2018)[130] | Czech Republic<br><br><br><br>None | 2012-2014<br><br><br><br>12 weeks | (1) Unilateral or bilateral chronic or sub-chronic tinnitus, (2) duration ≥3 months, (3) maskable by noise masking, (4) the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale at screening and baseline visits, and (5) ≥5 on the Mini-TQ at baseline | | | | | Tinnitus severity<br>Tinnitus loudness<br>Functional status<br>Behaviour/mood<br>AEs |
| | | | Ginkgo biloba 120 mg (EGb 761, QD) | 100 | 55.4 ± 10.5 | 58.6 | 79.6 ± 77.9 months | |
| | | | Pentoxifylline 600 mg | 100 | 53.1 ± 10.9 | 60.2 | 84.6 ± 94.5 months | |
| Morgenstern 1997[131] | Germany<br><br>NR[a] | NR<br><br>12 weeks | (1) Tonally definable chronic tinnitus, (2) duration ≥2 months, and (3) maskable tinnitus | | | | | Tinnitus severity<br>Tinnitus loudness<br>Hearing loss<br>AEs |
| | | | Ginkgo biloba 120 mg (EGb 761, TID) | 49 | NR | NR | 4.5 years[b] | |
| | | | Placebo | 50 | NR | NR | | |
| RBR2SN8XV (2020)[95] | Brazil<br><br>Non-industry funding; medications provided by Momenta Farmacêutica Ltda | 2015-2015<br><br>90 days | Unilateral or bilateral tinnitus and sensorineural or mixed hearing loss, as evaluated by otolaryngologists | | | | | Tinnitus severity |
| | | | Ginkgo biloba 240 mg (EGb 761, NR) | 11 | 56.3 ± 16.8 | 54.5 | 58.9 ± 17.7 months | |
| | | | Ginkgo biloba 240 mg + hearing aid (EGb 761, NR) | 11 | | | | |
| | | | Hearing aid | 11 | | | | |

*Abbreviations*

AE = adverse event, NR = not reported, QD = once daily, RCT = randomised controlled trial, SD = standard deviation, TID = three times daily, TQ = tinnitus questionnaire, UK = United Kingdom.

*Notes*

a = Manufacturer of ginkgo biloba was Dr. Willmar Schwabe GmbH & Co, but it is not clear whether the treatments were provided to the study by the manufacturer.

b = Not reported by treatment arm.

### 6.2.4 Findings: Efficacy

The findings for the efficacy outcomes for each of the 4 conditions of interest are reported in subsequent sections: MPD (***Section 6.2.4.1***), PAOD (***Section 6.2.4.2***), vertigo (***Section 6.2.4.3***), and tinnitus (***Section 6.2.4.4***). For all meta-analysed continuous outcomes presented in these sections, supplementary meta-analyses conducted using SMDs are available in ***Appendix E***.

#### **6.2.4.1** Mental performance deficits

A summary of the overall certainty of the body of evidence relating to ginkgo biloba for MPD is presented in ***Table 85***. The rest of this section presents detailed outcome data relating to the efficacy of various doses of ginkgo biloba vs. placebo, rivastigmine, or donepezil for the treatment of MPD.

Because of the abundance of data regarding the efficacy of ginkgo biloba in MPD, the following results are available in ***Appendix F***:

- Studies in which some patients changed treatment assignments during the course of the trial (e.g. patients received placebo for the first half of the trial and ginkgo biloba for the second half of the trial); these trials either did not report data at the end of each treatment period or did not report results stratified by treatment arm and therefore could not be synthesised with other studies.
- Doses of ginkgo biloba not currently approved in Switzerland (i.e. 150 mg or 160 mg)[e]
- Results used to supplement meta-analyses (e.g. cognitive function results comparing 240 mg ginkgo biloba vs. placebo for any questionnaires, other than those that could be meta-analysed).

##### 6.2.4.1.1 Cognitive function

Studies of patients with MPD included various measures of cognitive function, doses of ginkgo biloba, and durations of treatment. An overview of meta-analysis results is available in ***Table 13.***

**Table 13: Summary of meta-analysis results for cognitive function in patients with MPD**

| Outcome | Analysis metric | Dose (mg) | Timepoint (weeks) | Statistically significant | Clinically meaningful |
|---|---|---|---|---|---|
| ADAS-Cog | Continuous | 120 | 24 | Yes | Yes |
| SKT | Improve ≥3 points | 240 | 24 | Yes | NA[a] |
| | Continuous | 240 | 12 | Yes | No |
| | | | 24 | Yes | Yes |
| Verbal fluency | Continuous | 240 | 24 | Yes | Yes |

*Abbreviations*

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive, NA = not applicable, SKT = Syndrom-Kurz-Test.

*Notes*

[e] Please note that studies on these dosages of ginkgo biloba are reported in the main body of the report for the other 3 conditions due to the relative sparsity of data for those conditions.

a = Dichotomous outcome, no determination for whether result is clinically meaningful.

In patients with AD dementia or other dementia treated with 120 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with statistically significantly improved cognitive function as measured by the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) score (MD -1.03 [95% CI -1.66 to -0.39]; 3 RCTs; 789 patients; moderate certainty evidence) (***Figure 6***).[f] A systematic review identified published articles on the MCID of cognitive assessment tools.[132] That review identified one study that derived a new MCID for ADAS-cog in patients with mild AD and 2 studies that validated previously developed MCID thresholds for the ADAS-cog in patients with mild to moderate AD. Based on these studies, which all used anchor-based methods, the MCID is 3 points on the ADAS-Cog. The identified effect estimate of 120 mg ginkgo biloba (1.03-point difference) may therefore not be clinically meaningful. This was also reflected in the SMD analysis (SMD -0.21 [95% CI -0.35 to -0.07]), in which the 95% CI showed a statistically significant effect but crossed the threshold of 0.2 between small effects and trivial/no effects (***Figure 50***), There was no statistical evidence of heterogeneity across these 3 trials.

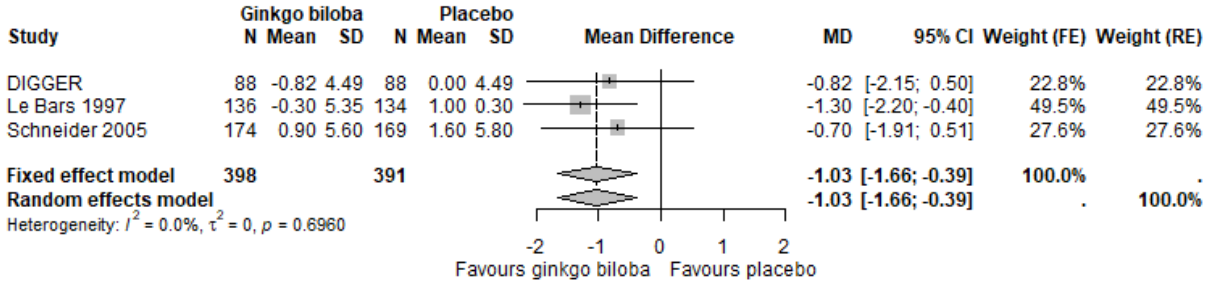


**Figure 6: ADAS-Cog: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. ADAS-Cog scores range from 0 to 70, with lower scores indicating better cognitive functioning.[133,134]

In patients with AD dementia or vascular dementia (including MID) treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with statistically significantly improved cognitive function as measured by the proportion of patients whose SKT score improved by ≥3 points (RR 2.94 [95% CI 1.30 to 6.65]; 4 RCTs; 1'406 patients; moderate certainty evidence)

[f] ADAS-Cog scores range from 0 to 70, with lower scores indicating better cognitive functioning.

(***Figure 7***). Two of these trials also reported results stratified by baseline condition (AD dementia vs. vascular dementia) (***Figure 8***). In the subgroup of patients with AD dementia, 240 mg ginkgo biloba was associated with statistically significantly higher rates of improvement in SKT score (RR 4.68 [95% CI 1.10 to 19.96]; 2 RCTs; 547 patients). In the subgroup of patients with vascular dementia, 240 mg ginkgo biloba was associated with non-significantly higher rates of improvement in SKT score (RR 4.20 [95% CI 0.56 to 31.22]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2$ = 0.01, p = 0.9306).

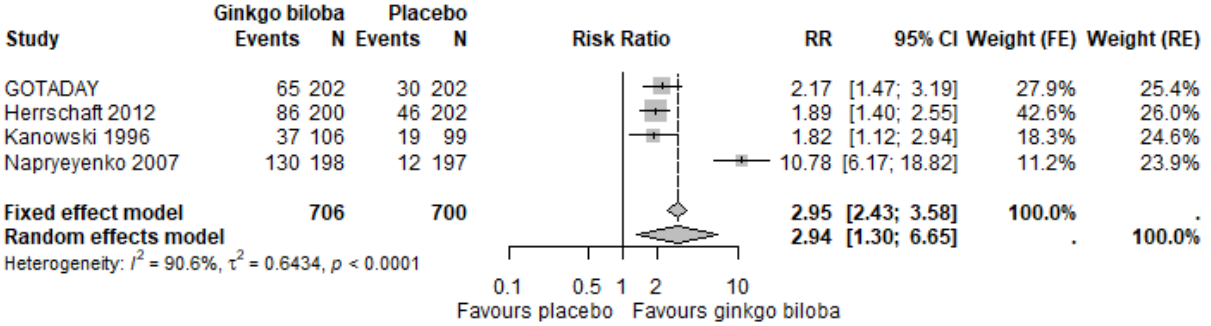


**Figure 7: SKT improved by ≥3 points: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, RR = relative risk.

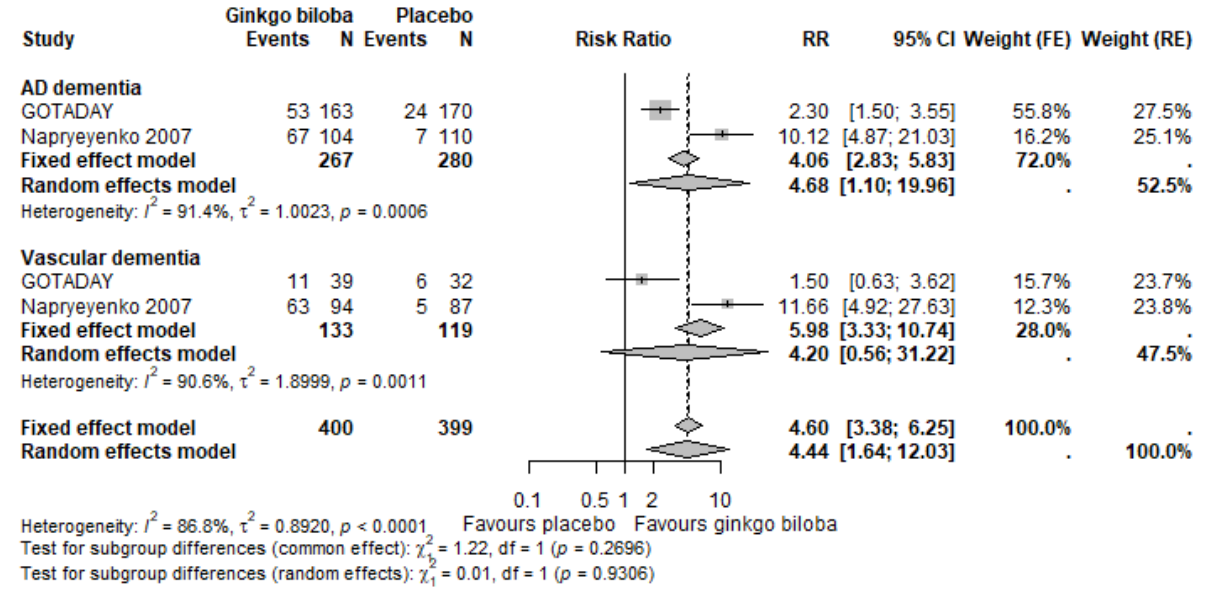


**Figure 8: SKT improved by ≥3 points: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, RE = random effects, RR = relative risk.

In patients with AD dementia or vascular dementia treated with 240 mg ginkgo biloba or placebo for 12 weeks, ginkgo biloba was associated with statistically significantly improved cognitive function as measured by the SKT total score (MD -1.69 [95% CI -2.55 to -0.82; 4 RCTs; 1'233 patients)

(***Figure 9***).[9] The meta-analysis identified substantial heterogeneity across studies, but taken together, these studies show a statistically significant positive effect of ginkgo biloba compared with placebo. There is not a well-established MCID in the SKT total score in the literature, but both Napryeyenko 2007[106,113-115] and the GOTADAY study[105-109] used the SKT total score as one of their primary outcomes and based power calculations on an MCID of 2 points. Using this MCID, the observed effect estimate of a 1.69-point improvement after 12 weeks of treatment with ginkgo biloba may not be clinically meaningful. However, based on the SMD meta-analysis, the data suggest that 12 weeks of treatment with 240 mg ginkgo biloba is associated with at least a small improvement in cognitive function (SMD -0.82 [95% CI -1.3 to -0.33]) (***Figure 51***).

Two of these trials also reported results stratified by baseline condition (AD dementia vs. vascular dementia) (***Figure 10***; SMD analysis available in ***Figure 52***). In the subgroup of patients with AD dementia, 240 mg ginkgo biloba was associated with statistically significantly improved SKT score (MD -1.64 [95% CI -2.72 to -0.56; 2 RCTs; 547 patients). In the subgroup of patients with vascular dementia, 240 mg ginkgo biloba was associated with a non-significantly improved SKT score (MD -1.74 [95% CI -3.20 to -0.28]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2 = 0.01$, $p = 0.9147$).

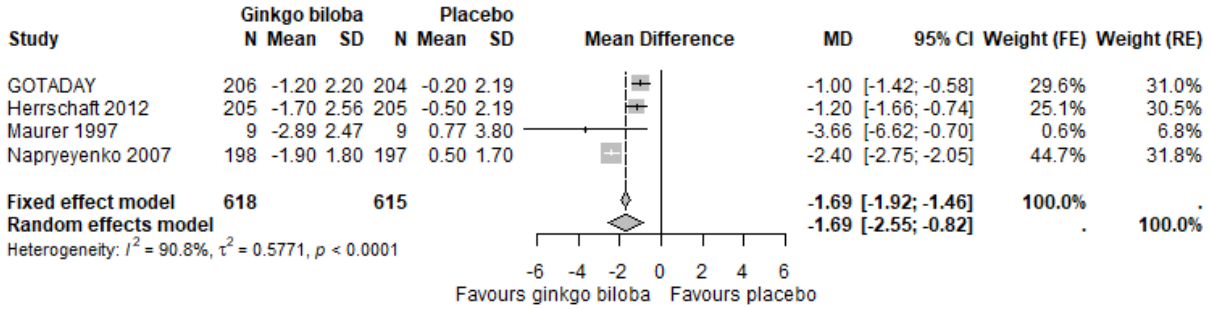


**Figure 9: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation, SKT = Syndrom-Kurz-Test.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

[9] SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

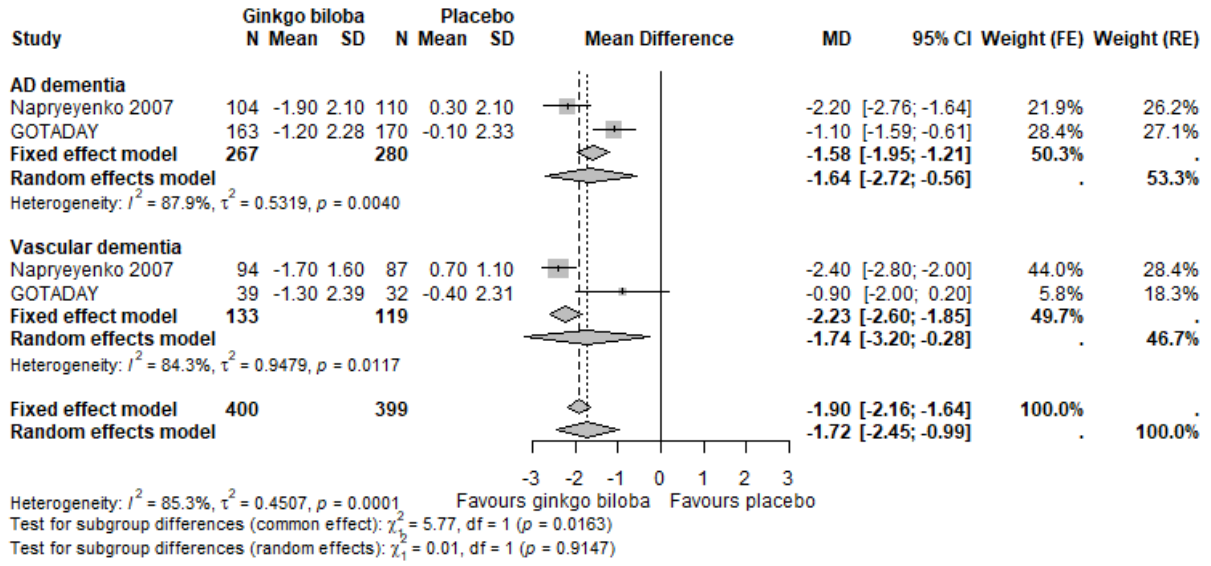


**Figure 10: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation, SKT = Syndrom-Kurz-Test.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

Similar results were seen regarding the effect of 240 mg ginkgo biloba on SKT total score at 24 weeks, although the additional treatment time appears to be associated with a stronger effect of ginkgo biloba (***Figure 11***). In patients with AD dementia or vascular dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with statistically significantly improved SKT scores (MD -2.32 [95% CI -3.82 to -0.83]; 4 RCTs; 1'406 patients; moderate certainty evidence). Although substantial statistical heterogeneity across studies introduces some uncertainty regarding the true magnitude of effect, AD dementia and vascular dementia are degenerative diseases, and all 4 RCTs demonstrated that patients treated with 240 mg ginkgo biloba for 24 weeks saw small improvements in cognitive function (mean change from baseline ranging from -1.40 points to -3.20 points among patients treated with 240 mg ginkgo biloba). There is not a well-established minimal clinically important difference in the SKT total score in the literature, although some original study authors used an MCID of 2 points to complete power calculations. Given this cutoff, an improvement of 2.32 points would be clinically meaningful. The SMD analysis indicates a large effect of ginkgo on the SKT total score at 24 weeks, although the 95% CI spans the threshold of trivial/no effect (SMD -0.84 [95% CI -1.54 to -0.13]) (***Figure 53***).

Three of these trials also reported subgroup data for patients with AD dementia and 2 reported subgroup data for vascular dementia (***Figure 12***; SMD analysis available in ***Figure 54***). For the

subgroup of patients with AD dementia, treatment with 240 mg ginkgo biloba for 24 weeks was associated with statistically significantly improved SKT score compared with placebo (MD -2.42 [95% CI -4.21 to -0.63]; 3 RCTs; 705 patients). For the subgroup of patients with vascular dementia, treatment with 240 mg ginkgo biloba for 24 weeks was associated with a non-significantly improved SKT score compared with placebo (MD -3.20 [95% CI –6.63 to 0.23]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups (χ2 = 0.16, p = 0.6933).

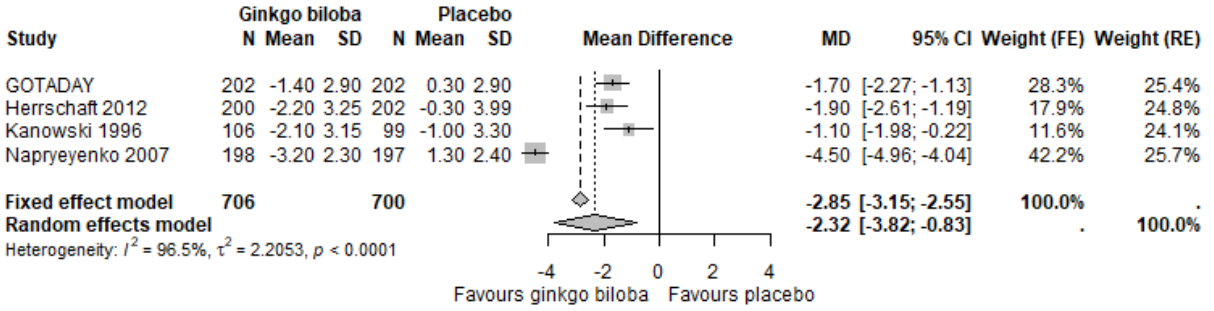


**Figure 11: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

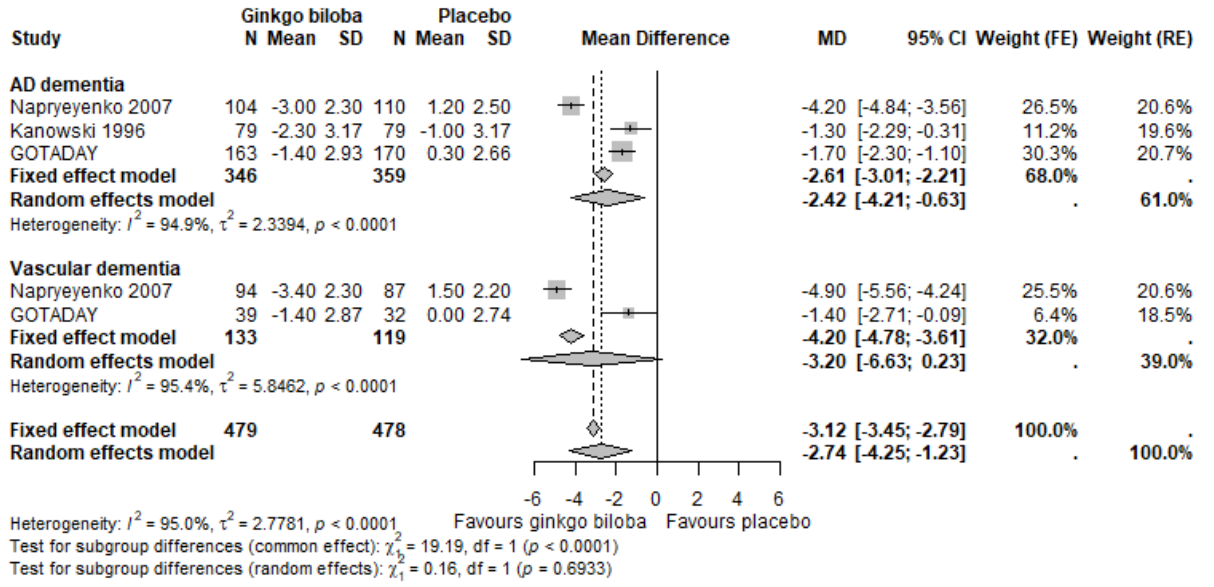


**Figure 12: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

Verbal fluency is a task in which patients are asked to name as many items in a particular category as possible within a specified time limit.[135,136] In patients with AD dementia or vascular dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with a statistically significantly larger improvement in verbal fluency (MD 1.27 [95% CI 0.25 to 2.30]; 3 RCTs; 1'201 patients; low certainty evidence) (***Figure 13***). No MCID for verbal fluency was reported in any of the included trials, nor could one be identified in the literature. The SMD analysis showed that there was a moderate effect on verbal fluency, but the 95% CI spans the threshold of trivial/no effect (SMD 0.77 [95% CI 0.02 to 1.52]) (***Figure 55***). There was substantial heterogeneity, introducing uncertainty regarding the true magnitude of effect, which may be related to the specific verbal fluency test used. Both Herrschaft 2012[106,111,112] and the GOTADAY study[105-109] stated that they utilised the verbal fluency test as adapted by Mahoney 2005,[135] which asks participants to name as many animals as possible in one minute. In this adaptation, the maximum score is 10, even when the participant specifies more than 10 different animals. In contrast, Napryeyenko 2007 referenced Rosen 1980,[136] which presents multiple versions of the verbal fluency test (e.g. naming animals, naming words that start with the letters 'C', 'F', or 'L') with several different time limits and does not appear to limit the maximum score. Similar results were seen in both the AD dementia and vascular dementia subgroup analyses, each reported in 2 studies (***Figure 14***; SMD analysis available in ***Figure 56***). In the subgroup of patients with AD dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with statistically significantly improved verbal fluency compared with placebo (MD 1.55 [95% CI 0.08 to 3.02]; 2 RCTs; 547 patients). In the subgroup of patients with vascular dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with statistically significantly improved verbal fluency compared with placebo (MD 1.74 [95% CI 0.57 to 2.92]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2 = 0.04$, p = 0.8365).

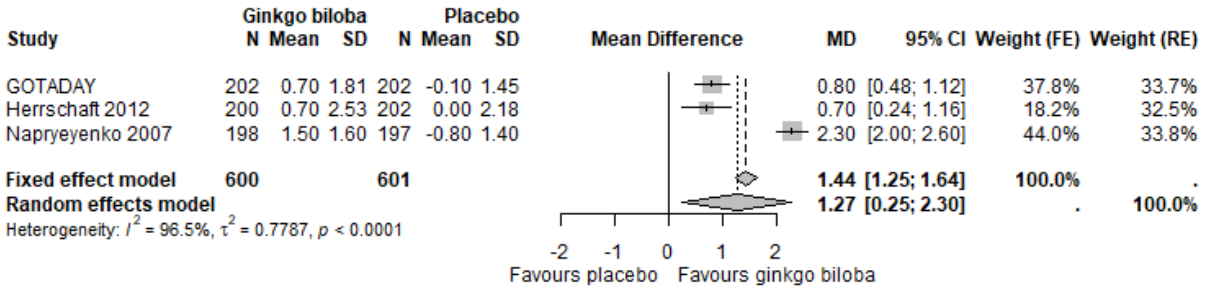


**Figure 13: Verbal Fluency Test: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline.

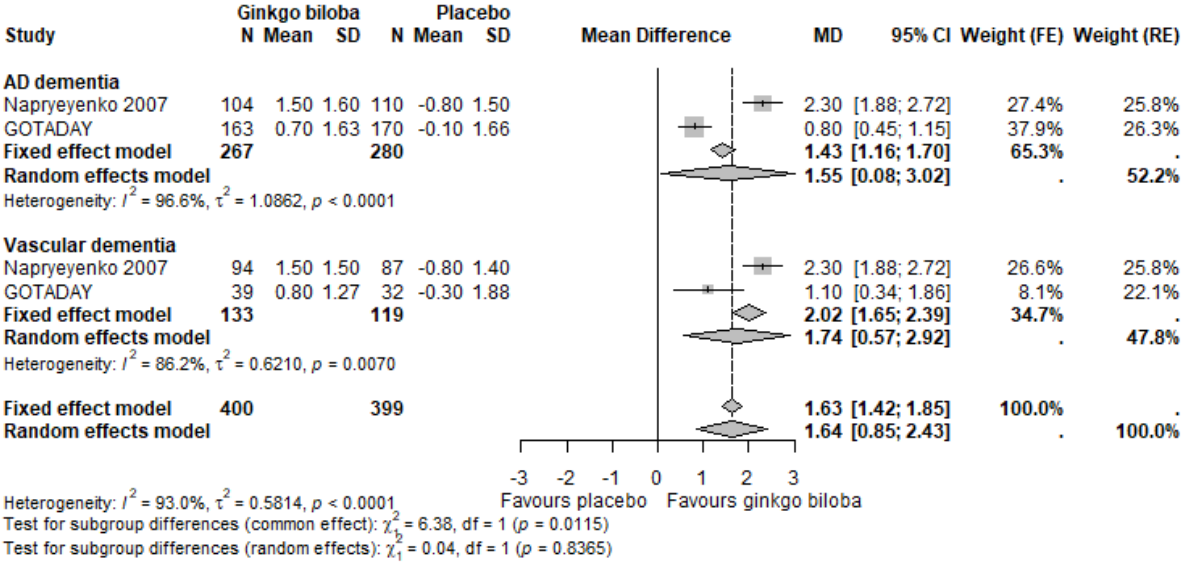


**Figure 14: Verbal Fluency Test: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline.

Two RCTs reported on the effect of 240 mg ginkgo biloba on the incidence of AD and/or vascular dementia among people with existing MCI or memory impairment (***Table 14***).[70,80,85,86] In adults who had consulted a physician for memory problems treated with 240 mg ginkgo biloba or placebo for a median of 5.0 years (interquartile range 2.9 to 5.1 years), there was no statistically significant difference in the cumulative incidence of AD (hazard ratio [HR] 0.84 [95% CI 0.60 to 1.18]; 2'820 patients; p = 0.306). However, study authors noted that there was a statistically significant treatment by time interaction, indicating that the proportional hazards assumption was violated and the relationship between ginkgo biloba and incidence of AD is not constant over time.[80,85,86] Study authors therefore reported the incidence of AD for each year of follow-up. For years 1 to 4, there were no statistically significant differences between ginkgo biloba and placebo. However, in year 5,[h] the incidence of AD was statistically significantly lower among adults treated with 240 mg ginkgo biloba compared to placebo (HR 0.49 [95% CI 0.25 to 0.96]; 1'834 patients; p = 0.034). Among adults with MCI[i] treated with 240 mg ginkgo biloba or placebo for a median of 6.1 years, there was no statistically significant difference in the cumulative incidence of AD or vascular dementia (HR 1.13 [95%

[h] Includes diagnoses up to 63 months because the final assessment could be within 3 months of 5 years of follow-up.
[i] MCI was defined as meeting both of the following criteria: (1) impaired at or below the 10th percentile of the Cardiovascular Health Study normative data on at least 2 of 10 neuropsychological test scores from each cognitive domain (memory, language, visuospatial abilities, attention, executive function), and (2) CDR global score of 0.5.

CI 0.85 to 1.50]; 482 patients; p = 0.39).[70] Although both studies had low risk of bias in most domains, the long follow-up time and nature of the population under study did result in a high risk of bias due to attrition for one study,[80,85,86] while the other did not report patient dropout by treatment arm for the subgroup of patients with MCI.[j70] Taken together, these studies provide low certainty evidence that 240 mg of ginkgo biloba is not statistically significantly different from placebo in preventing incident cases of dementia in people with existing MCI or memory impairment.

[j] The GEM study included both cognitively healthy adults and those with MCI. Studies of cognitively healthy adults were not eligible for this review, so only data reported specifically for patients with MCI at baseline have been included here.

**Table 14: Efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – incidence of dementia**

| Outcome | Study | Timepoint (years) | Ginkgo biloba n/N (%) | Placebo n/N (%) | Ginkgo biloba Incidence per 100 PY | Placebo Incidence per 100 PY | p-value | Effect HR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| **Probable AD[a]** | Guid-Age[80,85,86b] | 5 (cumulative) | 61/1'406 (4.3) | 73/1'414 (5.2) | 1.20 | 1.40 | 0.306 | 0.84 (0.60 to 1.18)[c] |
| | | 1 | 10/1'406 (0.7) | 14/1'414 (1.0) | 0.80 | 1.12 | 0.416 | 0.72 (0.32 to 1.61) |
| | | 2 | 20/1'201 (1.7) | 12/1'195 (1.0) | 1.78 | 1.07 | 0.159 | 1.66 (0.81 to 3.40) |
| | | 3 | 13/1'071 (1.2) | 12/1'095 (1.1) | 1.27 | 1.15 | 0.796 | 1.11 (0.51 to 2.43) |
| | | 4 | 5/984 (0.5) | 9/1'011 (0.9) | 0.53 | 0.94 | 0.302 | 0.57 (0.19 to 1.69) |
| | | ≥5 | 13/911 (1.4) | 26/923 (2.8) | 1.51 | 3.01 | 0.034 | 0.49 (0.25 to 0.96) |
| **Pure AD or AD with vascular dementia[a]** | | 5 | 70/1'406 (5.0) | 84/1'414 (5.9) | 1.40 | 1.60 | 0.267 | NR[c] |
| **Any AD and/or vascular dementia[d]** | GEM Study[70e] | 6.1 | 112/256 (43.8) | 87/226 (38.5) | 9.82 | 8.68 | 0.39 | 1.13 (0.85 to 1.50) |
| **Any AD[d,f]** | | | 104/256 (40.6) | 83/226 (36.7) | 9.12 | 8.28 | 0.51 | 1.10 (0.83 to 1.47) |
| **AD with vascular dementia[d,f]** | | | 24/256 (9.4) | 22/226 (9.7) | 2.10 | 2.20 | 0.89 | 0.96 (0.54 to 1.71) |
| **AD without vascular dementia[d,f]** | | | 80/256 (31.3) | 61/226 (27) | 7.02 | 6.09 | 0.40 | 1.15 (0.83 to 1.61) |
| **Vascular dementia without AD[d,f]** | | | 2/256 (0.8) | 3/226 (1.3) | 0.18 | 0.30 | 0.56 | 0.59 (0.10 to 3.51) |

*Abbreviations*

AD = Alzheimer's disease, ADDTC = Alzheimer's Disease Diagnostic and Treatment Centers, CDR = Clinical Dementia Rating, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, HR = hazard ratio, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, PY = person-years.

*Notes*

a = According to DSM-IV and NINCDS-ADRDA criteria.

b = Included patients were those who had consulted a healthcare professional for memory problems and had an MMSE score >25, a Covi anxiety score <6, and a geriatric depression scale score <15.

c = Authors of the original study reported that the proportional hazards assumption was not met for analyses at 5 years. The tests for proportional hazards were not reported for any other analyses.

d = Defined as incident abnormalities in any of the 3 following categories: abnormal scores on ≥5 tests, including ≥1 memory test; abnormal scores on ≥4 tests, including ≥1 memory test, and failure to complete ≥1 neuropsychological test; or abnormalities in ≥2 cognitive domains (scored below age- and education-adjusted cutoffs in both tests of that domain), including ≥1 memory domain.

e = Included patients were those who met both of the following criteria: (1) ≤10th percentile of Cardiovascular Health Study normative data, stratified by age and education, on ≥2 of 10 selected neuropsychological test scores from each cognitive domain, including memory, language, visuospatial abilities, attention, and executive function; and (2) CDR global score of 0.5.

f = Patients were categorised by whether their dementia was (1) possible/probable AD (according to NINCDS-ADRDA criteria) and/or (2) vascular dementia (according to ADDTC criteria).

One trial reported that there was no statistically significant difference in the mean change from baseline in the total score on the ADAS-Cog after 26 weeks comparing patients with AD or probable AD receiving 120 mg ginkgo biloba and those receiving 240 mg ginkgo biloba (***Table 15***).[116,117]

**Table 15: Continuous efficacy results comparing 120 mg vs. 240 mg ginkgo biloba in patients with MPD – cognitive function**

| Outcome[a] | Ginkgo biloba 120 mg Mean (95% CI)[b] | Ginkgo biloba 240 mg Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **ADAS-Cog** | 1.6 (0.7 to 2.5) | 1.3 (0.5 to 2.1) | 0.32 | 0.3 (-0.9 to 1.5) |

*Abbreviations*

AD = Alzheimer's disease, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MD = mean difference, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association.

*Notes*

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with placebo; other dose comparisons are reported in relevant sections.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

One RCT randomised 56 patients with mild-to-moderate AD dementia to receive either 120 mg ginkgo biloba or 4.5 mg rivastigmine for 24 weeks. Cognitive function was measured using scores on the Mini-Mental State Examination (MMSE) and Seven Minute Test (SMT) (***Table 16***).[118] The original study authors reported that rivastigmine was statistically significantly better than ginkgo biloba ($p<0.05$); they stated that all statistical analyses utilised an analysis of variance (ANOVA) model including age, gender, and severity of cognitive impairment at baseline as factors. However, the original study authors reported only the resulting p-value for this comparison, rather than an estimate of the treatment effect and measure of precision. The mean difference and 95% CI were therefore calculated by the authors of this report using group-level data; the unadjusted differences did not appear to be statistically significant (very low evidence).

**Table 16: Continuous efficacy results comparing 120 mg ginkgo biloba vs. 4.5 mg rivastigmine in patients with MPD – cognitive function**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Rivastigmine Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **MMSE** | 16.8 (15.1 to 18.5) | 17.5 (15.6 to 19.5) | 0.05[d] | -0.8 (-3.4 to 1.9) |

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Rivastigmine Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **SMT** | 213.0 (172.3 to 253.6) | 201.2 (161.7 to 240.7) | 0.05[d] | 11.8 (-46.3 to 69.8) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MD = mean difference, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, SMT = Seven Minute Test.

*Notes*

a = All results in this table are from the same trial (Nasab 2012[118]) and at the same timepoint (24 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as an MMSE score of 10 to 24 at screening.

b = Mean value at timepoint.

c = Calculated by the authors of this report.

d = These p-values were reported by the authors of the original study. They were based on analysis of variance models that included age, sex, and severity of cognitive impairment at baseline. Original study authors did not report an estimate of the difference between treatment groups for any outcome.

A single 3-arm trial randomised patients with probable AD of mild to moderate severity to receive 240 mg ginkgo biloba alone, 10 mg donepezil alone, or 240 mg ginkgo biloba combined with 10 mg donepezil for 22 weeks. There was no statistically significant difference across treatment arms in the proportion of patients whose SKT score improved by at least 4 points (1 RCT; 93 patients; p = 0.40; very low evidence) (***Table 17***).[119]

**Table 17: Categorical efficacy results comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD – cognitive function**

| Outcome[a] | Ginkgo biloba + donepezil n/N (%) | Donepezil alone n/N (%) | Ginkgo biloba alone n/N (%) | p-value | Effect RR (95% CI)[b] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **SKT improved by ≥4 points** | 14/31 (45) | 12/32 (38) | 11/30 (36) | 0.40 | 1.20 (0.67 to 2.18) | 0.98 (0.51 to 1.87) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MPD = mental performance deficits, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, RR = relative risk, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Calculated by the authors of this report.

Among patients with probable AD of mild to moderate severity treated for 22 weeks, there was no statistically significant difference between 240 mg ginkgo biloba alone, 10 mg donepezil alone, or 240 mg ginkgo biloba combined with 10 mg donepezil in terms of cognitive function as measured by the Clock-Drawing Test (p = 0.30), SKT total score (p = 0.08), or verbal fluency test (p = 0.47) (***Table 18***).[119]

**Table 18: Continuous efficacy results comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD – cognitive function**

| Outcome[a] | Ginkgo bi-loba + donepezil Mean (95% CI)[b] | Donepezil alone Mean (95% CI)[b] | Ginkgo biloba alone Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo bi-loba + donepezil vs. donepezil alone | Ginkgo bi-loba alone vs. donepezil alone |
| **CDT** | 0.8 (0.3 to 1.3) | 0.7 (0.2 to 1.2) | 1.4 (0.6 to 2.2) | 0.30 | 0.1 (-0.6 to 0.8) | 0.7 (-0.3 to 1.7) |
| **SKT total score** | -3.5 (-4.7 to -2.3) | -2.5 (-3.7 to -1.3) | -1.8 (-3.4 to -0.2) | 0.08 | -1.0 (-2.7 to 0.7) | 0.7 (-1.3 to 2.7) |
| **Verbal Fluency Test** | 1.8 (0.7 to 2.9) | 0.8 (-0.2 to 1.8) | 1.4 (0.4 to 2.4) | 0.47 | 1.0 (-0.5 to 2.5) | 0.6 (-0.8 to 2.0) |

*Abbreviations*

AD = Alzheimer's disease, CDT = Clock-Drawing Test, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MD = mean difference, MPD = mental performance deficits, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

#### 6.2.4.1.2 Behavioural changes/mood

Studies of patients with MPD reporting on behavioural changes/mood included various analysis methods and timepoints. An overview of meta-analysis results is available in ***Table 19.***

**Table 19: Summary of meta-analysis results for behavioural changes/mood in patients with MPD**

| Outcome | Analysis metric | Dose (mg) | Timepoint (weeks) | Statistically significant | Clinically meaningful |
|---|---|---|---|---|---|
| NPI total score | Improve ≥4 points | 240 | 24 | Borderline | NA[a] |
| | Continuous | 240 | 12 | Yes | No |
| | | | 24 | Yes | Yes |

*Abbreviations*

NA = not applicable, NPI = Neuropsychiatric Inventory.

*Notes*

a = Dichotomous outcome, no determination for whether result is clinically meaningful.

In patients with MCI, AD dementia, or vascular dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, ginkgo biloba was associated with a non-significantly larger proportion of patients showing improvement of at least 4 points on the NPI Composite Total Score (RR 2.50 [95% CI 0.99 to 6.32]; 4 RCTs; 1'369 patients; moderate certainty evidence) (***Figure 15***).[k] When restricting the analysis to patients with AD dementia or vascular dementia, those treated with 240 mg ginkgo biloba were statistically significantly more likely to improve by at least 4 points on the NPI Composite Total Score (RR 4.25 [95% CI 1.55 to 11.63]; 2 RCTs; 799 patients) (***Figure 16***). Both trials also reported results stratified by type of dementia (AD dementia vs. vascular dementia) (***Figure 16***). Among the subgroup of patients with AD dementia, 240 mg ginkgo biloba was associated with a non-significantly larger proportion of patients showing improvement of at least 4 points on the NPI Composite Total Score (RR 4.87 [95% CI 0.74 to 32.20]; 2 RCTs; 547 patients). Similarly, in patients with vascular dementia, 240 mg ginkgo biloba was associated with a non-significantly larger proportion of patients showing improvement of at least 4 points on the NPI Composite Total Score (RR 3.81 [95% CI 0.79 to 18.33]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi 2 = 0.04$, $p = 0.8448$).

Across all meta-analyses of NPI, Napryeyenko 2007[106,113-115] showed a much stronger effect of ginkgo biloba on neuropsychiatric symptoms; the reasons behind this are uncertain, particularly given the similarities in population with the GOTADAY study.[105-109] Both studies included patients at least 50 years of age with one of the following diagnoses: probable AD (NINCDS-ADRDA criteria); possible AD with cerebrovascular disease (NINDS-AIREN criteria); or probable vascular dementia (NINDS-AIREN criteria). Both studies also required that patients have a SKT total score

[k] NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.

from 9 to 23 (both inclusive), as well as a score of at least 5 on the NPI, with at least one item score of at least 3 (excluding delusion or hallucination). However, patients in the GOTADAY study had slightly lower mean NPI Composite Total Score at baseline (ginkgo biloba: 16.4 [SD 8.1]; placebo: 17.0 [SD 8.2]) compared with patients in Napryeyenko 2007 (ginkgo biloba: 21.3 [SD 9.5]; placebo: 21.6 [SD 9.9]). A secondary analysis of the GOTADAY study found that, among patients treated with placebo, those with higher NPI scores (>18 points) at baseline had faster deterioration than those with lower NPI scores (<12 points) at baseline.[137] This faster deterioration was not seen among patients treated with ginkgo biloba, so the net benefit of ginkgo biloba was larger among patients with higher NPI scores at baseline. Although there is insufficient published data to be certain, it is possible that the higher NPI baseline scores in Napryeyenko 2007 explain some of the difference in treatment effects between Napryeyenko 2007 and the GOTADAY study.

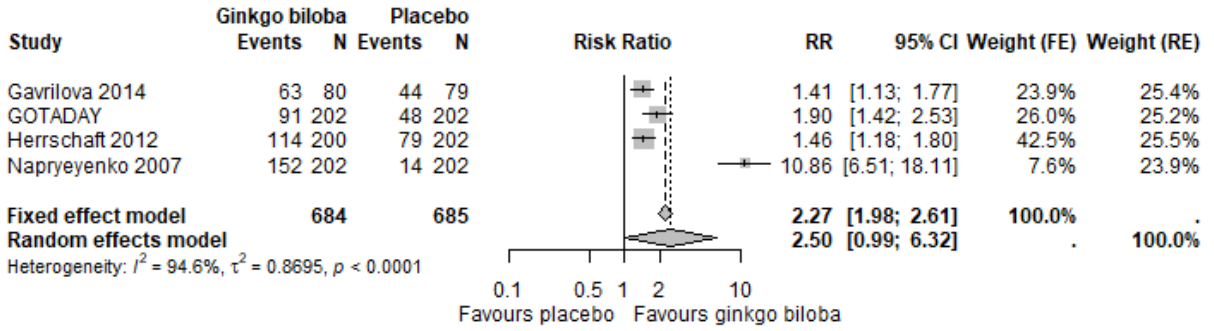


**Figure 15: NPI Composite Total Score improved by ≥4 points: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, NPI = Neuropsychiatric Inventory, RE = random effects, RR = relative risk.

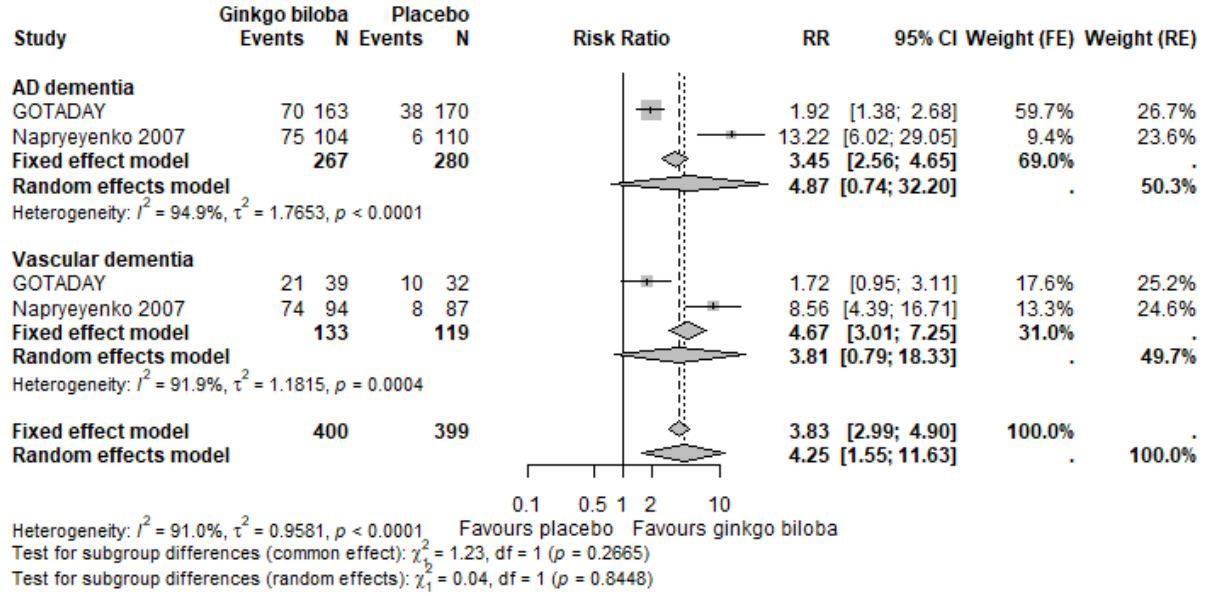

**Figure 16: NPI Composite Total Score improved by ≥4 points: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, NPI = Neuropsychiatric Inventory, RE = random effects, RR = relative risk.

In patients with MCI, AD, or dementia, treatment with 240 mg ginkgo biloba or placebo for 12 weeks was associated with statistically significant improvement in neuropsychiatric symptoms as measured by the NPI Composite Total Score (MD -2.18 [95% CI -4.02 to -0.34]; 4 RCTs; 1'374 patients) (***Figure 17***). Three of these trials defined clinical response on the NPI as a difference of at least 4 points, although only Gavrilova 2014 provided a reference for this MCID.[105-109,113-115,138] Based on this cutoff, the estimated effect of ginkgo biloba (a 2.18-point improvement) may not be clinically meaningful after 12 weeks (see following paragraphs for analysis after 24 weeks of treatment). This is similarly reflected in the SMD analysis, where the 95% CI spans the threshold of trivial/no effect (SMD -0.54 [95% CI -1.08 to -0.01]) (***Figure 57***).

Two of these trials reported subgroup data for patients with AD and vascular dementia (***Figure 18***; SMD analysis available in ***Figure 58***). In patients with AD dementia, 240 mg ginkgo biloba was associated with non-significantly larger improvement NPI Composite Total Score (MD -2.95 [95% CI -6.58 to 0.68]; 2 RCTs; 547 patients). Similarly, in patients with vascular dementia, 240 mg ginkgo biloba was associated with non-significantly larger improvement NPI Composite Total Score (MD -3.22 [95% CI -7.33 to 0.89]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2 = 0.01$, p = 0.9219).

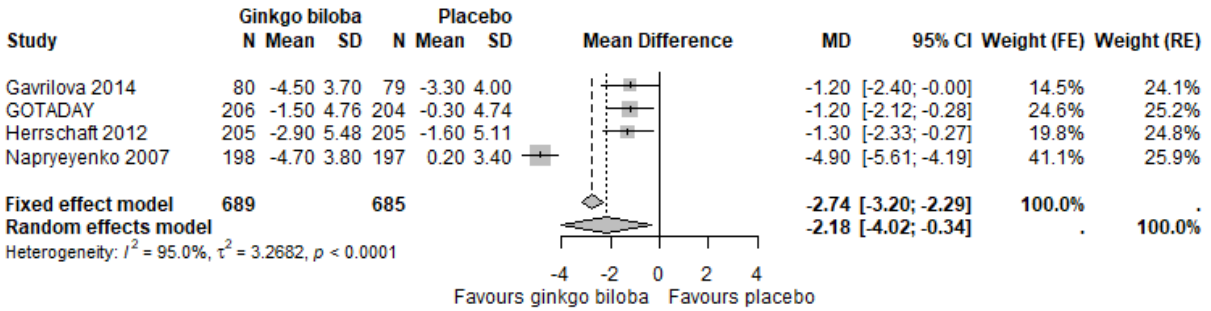


**Figure 17: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, NPI = Neuropsychiatric Inventory, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

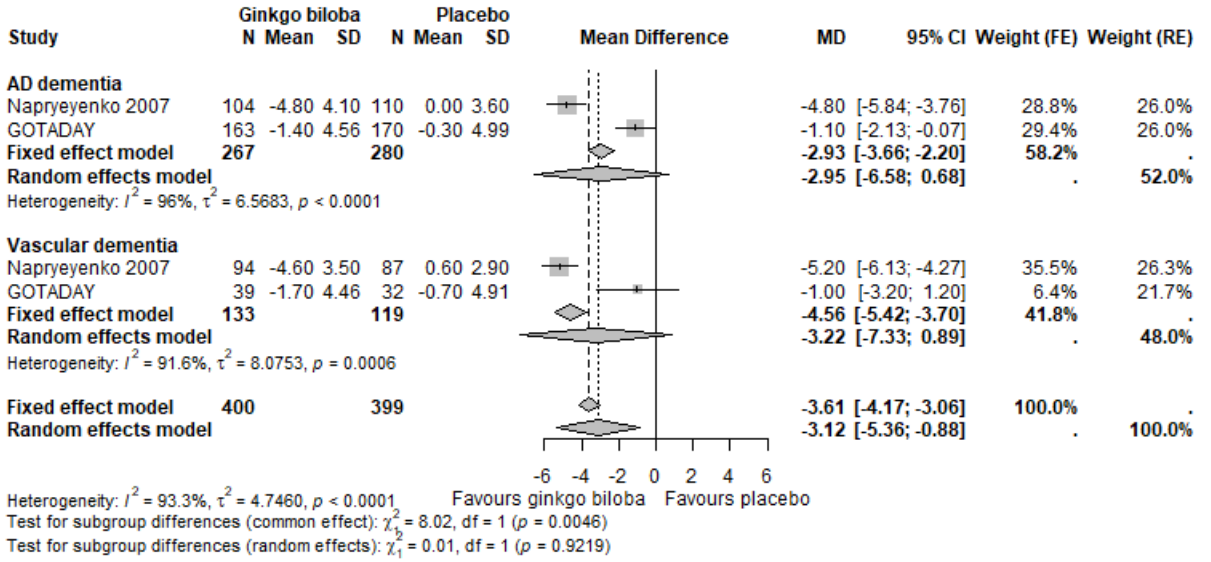


**Figure 18: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

The results for the NPI Composite Total Score at 24 weeks were largely similar to those at 12 weeks. In patients with MCI, AD, or dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, there was statistically significantly more improvement in the NPI Composite Total Score in patients treated with 240 mg ginkgo biloba (MD -4.03 [95% CI -7.32 to -0.74]; 4 RCTs; 1'360 patients; moderate certainty evidence) (***Figure 19***). As seen in previous analyses, Napryeyenko 2007[106,113-115] showed a much stronger effect of ginkgo biloba, which may be related to the severity of neuropsychiatric symptoms at baseline. As noted in the previous paragraph, 3 of these trials defined clinical response on the NPI as a difference of at least 4 points, although the methods for determining this MCID were not reported.[105-109,113-115,138] Based on this MCID, the estimated treatment effect of 240 mg ginkgo biloba seen at 24 weeks (a 4.03-point improvement) represents a clinically meaningful response. In another trial conducted in patients with AD, authors determined the MCID by calculating 0.4 of the SD of the change from baseline over one year; based on that analysis, the MCID for NPI was 8 points.[140] However, this MCID analysis used a distribution-based approach to determining the MCID and therefore cannot capture what difference is actually meaningful to patients or their caregivers. Based on the SMD analysis, treatment with 240 mg ginkgo biloba was associated with a moderate effect on the NPI Composite Total Score, but the 95% CI includes the threshold for trivial/no effect (SMD -0.72 [95% CI -1.36 to -0.08]) (***Figure 59***).

Two of these trials reported subgroup data for patients with AD and vascular dementia (***Figure 20***; SMD analysis available in ***Figure 60***). Compared with placebo, treatment with 240 mg ginkgo biloba for 24 weeks was associated with statistically significantly larger improvement NPI Composite Total Score for patients with either AD dementia (MD -5.75 [95% CI -10.94 to -0.55]; 2 RCTs; 547 patients) or vascular dementia (MD -6.63 [95% CI -13.09 to -0.17]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2 = 0.04$, p = 0.8350).

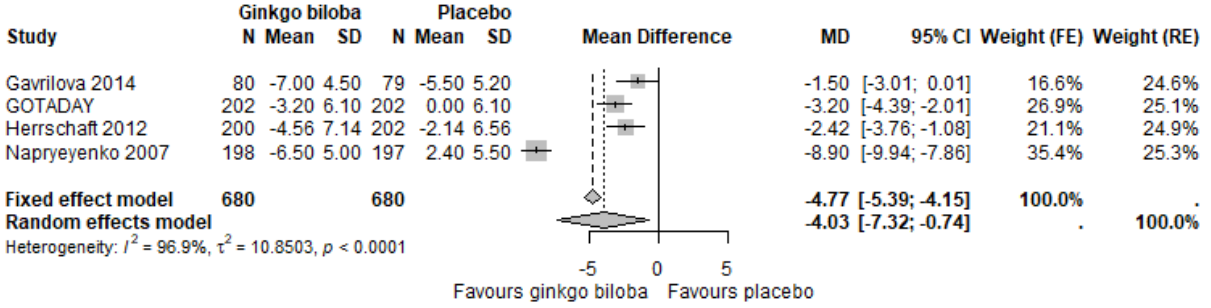


**Figure 19: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, NPI = Neuropsychiatric Inventory, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

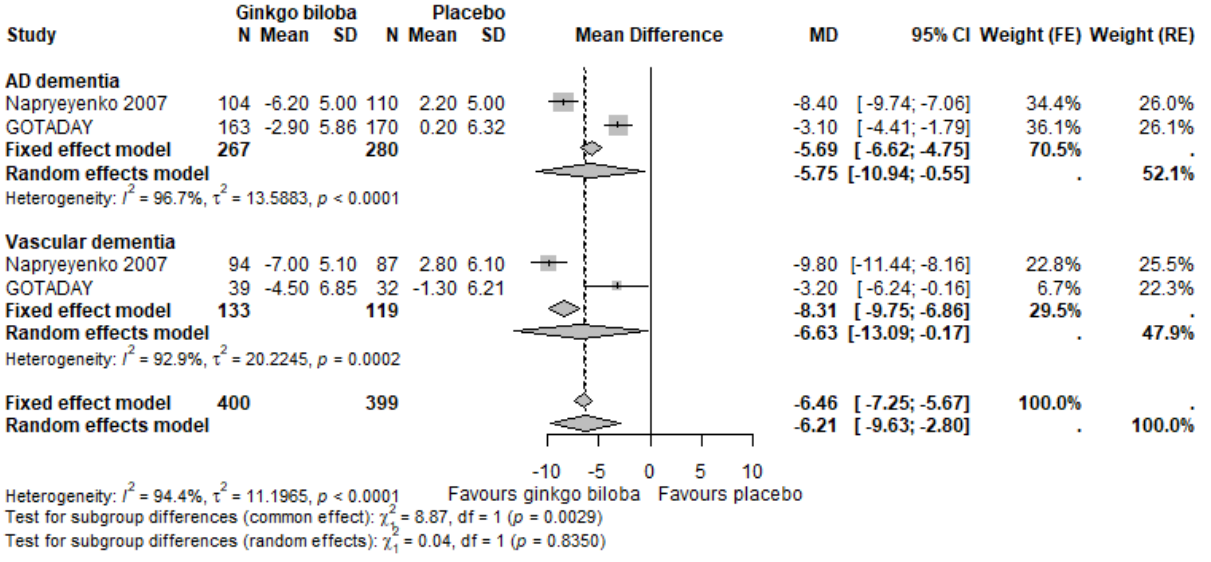


**Figure 20: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, MD = mean difference, NPI = Neuropsychiatric Inventory, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

A single RCT of 195 patients with mild to moderate cognitive impairment reported on the effect of 12 weeks of treatment with either 120 mg ginkgo biloba compared with placebo on the Nürnberger-Alters-Rating [Nuremberg Age Rating] (NAR), a subscale of the Nürnberger-Alters-Inventar [Nuremberg Age Inventory] (NAI) (***Table 20***). Although there was no statistically significant difference in the proportion of patients who improved on either the NAR Total Score or the NAR Mood Score, statistically significantly more patients treated with 120 mg ginkgo biloba showed improvement in the NAR Performance Score (RR 1.16 [95% CI 1.00 to 1.34]; 1 RCT; 195 patients).[78]

**Table 20: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – behavioural changes/mood**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Improvement in NAR Total** | 83/103 (80.6) | 68/92 (73.9) | 0.133 | 1.09 (0.93 to 1.27) |
| **Improvement in NAR Performance** | 88/103 (85.4) | 68/92 (73.9) | 0.022 | 1.16 (1.00 to 1.34) |
| **Improvement in NAR Mood** | 82/103 (79.6) | 69/92 (75.0) | 0.221 | 1.06 (0.91 to 1.24) |

*Abbreviations*

CI = confidence interval, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, ICD-9 = International Classification of Diseases, Ninth Revision, NAR = Nuremberg Age Rating, RR = relative risk, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = All results in this table are from the same trial (Oswald 1997[78]) and at the same timepoint (12 weeks). Included patients were those with mild to moderate cognitive disorders of old age (DSM-III, Cat. 1 or ICD-9 No. 290), whose cognitive performance according to SCAG was between 40 and 90, and who also achieved an average score of at least 3.5 in items 2 to 3 to 6, and 8, and a total score of 24 in items 1 to 8, with none of these items having a score of 7.

b = Calculated by the authors of this report.

Two additional trials reported on neuropsychiatric symptoms in patients receiving either 120 mg ginkgo biloba or placebo (very low certainty evidence) (***Table 21***). In patients with vascular cognitive impairment, 12 weeks of treatment with 120 mg ginkgo biloba was associated with borderline significant improvement in the Sandoz Clinical Assessment Geriatric Scale (SCAG) total score (MD 6.6 [95% CI 0.0 to 13.2]; 1 RCT; 39 patients).[81] Similar results were seen after 24 weeks of

treatment with either 120 mg ginkgo biloba or placebo (MD 6.9 [95% CI -0.3 to 13.2]; 1 RCT; 39 patients). The DIGGER trial reported a borderline significant effect of 120 mg ginkgo biloba on the NPI Composite Total Score (MD -4.512 [95% CI -9.176 to 0.152]; 1 RCT; 88 patients).[83,84]

**Table 21: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – behavioural changes/mood**

| Out-come | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI) |
|---|---|---|---|---|---|---|
| **SCAG** | 12 | NCT 00446485[81b] | 45.7 (40.1 to 51.3) | 39.1 (36.0 to 42.2) | NR | 6.6 (0.0 to 13.2)[c] |
| | 24 | NCT 00446485[81b] | 43.6 (37.2 to 50.0) | 36.7 (34.0 to 39.4) | 0.676[d] | 6.9 (-0.3 to 14.1)[c] |
| **NPI Compo-site - to-tal score** | 24 | DIG-GER[83,84e] | NR | NR | 0.061 | -4.512 (-9.176 to 0.152) |

*Abbreviations*

CI = confidence interval, MD = mean difference, MMSE = Mini-Mental State Examination, MPD = mental performance deficit, NPI = Neuropsychiatric Inventory, NR = not reported, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = Mean value at timepoint.

b = Included patients were those with vascular cognitive impairment based on cerebrovascular insufficiency and a Folstein MMSE score of >20 and ≤28.

c = Calculated by the authors of this report.

d = This study included a third treatment arm that is not approved in Switzerland and is therefore ineligible for this review. This p-value is a comparison across all 3 treatment groups.

e = Included patients were those with a clinical diagnosis of dementia made by the referring clinician.

f = Reported by study authors. Adjusted estimate.

Based on a single trial in 96 patients with probable AD treated with 240 mg ginkgo biloba alone, 10 mg donepezil alone, or 240 mg ginkgo biloba combined with 10 mg donepezil for 22 weeks, there was no statistically significant difference in either depression (p = 0.98 across 3 treatment groups) or neuropsychiatric symptoms more broadly (p = 0.75 across 3 treatment groups) (***Table 22***). Depression was measured using the Hamilton Depression Rating Scale (HAMD), while neuropsychiatric symptoms were assessed using the NPI Composite Total Score. There was no statistically significant difference between 240 mg ginkgo biloba and 10 mg donepezil, nor any additive effect of ginkgo biloba when combined with donepezil vs. donepezil alone.

**Table 22: Continuous efficacy results comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD – behavioural changes/mood**

| Outcome[a] | Ginkgo biloba + donepezil Mean (95% CI)[b] | Donepezil alone Mean (95% CI)[b] | Ginkgo biloba alone Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **HAMD** | -2.3 (-3.6 to -1.0) | -1.9 (-3.1, -0.7) | -1.9 (-2.9 to -0.9) | 0.98 | -0.4 (-2.2 to 1.4) | 0.0 (-1.6 to 1.6) |
| **NPI Composite Total Score** | -8.2 (-11.3 to -5.1) | -7.6 (-10.3 to -4.9) | -6.4 (-9.0 to -3.8) | 0.75 | -0.6 (-4.8 to 3.6) | 1.2 (-2.7 to 5.1) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, HAMD = Hamilton Depression Rating Scale, MD = mean difference, MPD = mental performance deficit, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NPI = Neuropsychiatric Inventory, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

#### 6.2.4.1.3 Functional status

Multiple meta-analyses of functional status in patients with MPD were conducted based on the available data. An overview of meta-analysis results is available in ***Table 23.***

**Table 23: Summary of meta-analysis results for functional status in patients with MPD**

| Outcome | Analysis metric | Dose (mg) | Timepoint (weeks) | Statistically significant | Clinically meaningful |
|---|---|---|---|---|---|
| GERRI | Continuous | 120 | 24 | Borderline | Unknown[a] |
| ADL-IS | Continuous | 240 | 24 | Yes | Yes |

*Abbreviations*

ADL-IS = Activities of Daily Living International Scale, GERRI = Geriatric Evaluation by Relative's Rating Instrument, MCID = minimal clinically important difference, SMD = standardised mean difference.

*Notes*

a = No MCID was identified for GERRI, so the SMD analysis was utilized to assess whether the result was clinically meaningful. The SMD estimate indicates a small but clinically meaningful effect, but this effect was not statistically significant.

A meta-analysis was conducted in 3 RCTs (789 patients) that reported functional status as measured by the Geriatric Evaluation by Relative's Rating Instrument (GERRI) in patients with AD dementia or other dementia treated with 120 mg ginkgo biloba or placebo for 24 weeks (***Figure 21***). There was a borderline statistically significant effect of 120 mg ginkgo biloba on GERRI scores (MD -0.08 [95% CI -0.16 to 0.00]; 3 RCTs; 789 patients; low certainty evidence). There was moderate heterogeneity across the 3 studies, largely driven by the lack of effect of 120 mg ginkgo biloba in Schneider 2005.[116,117] In contrast, both the DIGGER trial[83,84] and Le Bars 1997[98-101] reported a statistically significantly larger improvement in GERRI scores compared with placebo. Because no MCID could be identified in the literature, the SMD analysis was used to determine clinical relevance. The SMD estimate indicates a small effect of 120 mg ginkgo biloba on GERRI total score, but this effect was not statistically significant (SMD -0.22 [95% CI -0.47 to 0.02]) (***Figure 61***).

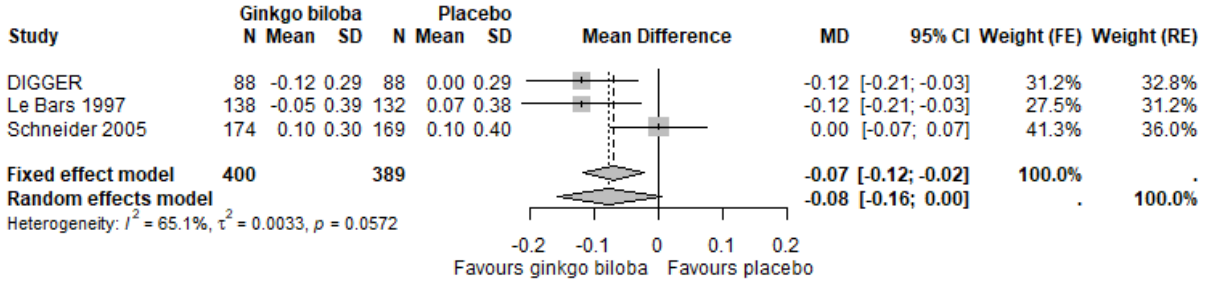


**Figure 21: GERRI: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, GERRI = Geriatric Evaluation of Relative's Rating Instrument, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. The GERRI consists of 49 items to assess the frequency of complaints related to functioning, with higher scores indicating more severe functional impairment.[141]

Two RCTs assessed the impact of 240 mg ginkgo biloba vs. placebo on functional status in patients with AD dementia or vascular dementia, measured using the ADL-IS. Compared with placebo, 24 weeks of treatment with 240 mg ginkgo biloba was associated with statistically significantly larger improvements in ADL-IS score (MD -0.17 [95% CI -0.22 to -0.12]; 2 RCTs; 806 patients; high certainty evidence) (***Figure 22***). There was little to no heterogeneity across studies. However, neither of these RCTs defined an MCID for the ADL-IS, nor could one be identified in a search of the literature. The SMD analysis indicated that this represents a moderate treatment effect, and the

95% CI provides evidence that 240 mg ginkgo biloba is likely to result in at least a small effect on functional status (SMD -0.5 [95% CI -0.64 to -0.36]) (***Figure 62***).

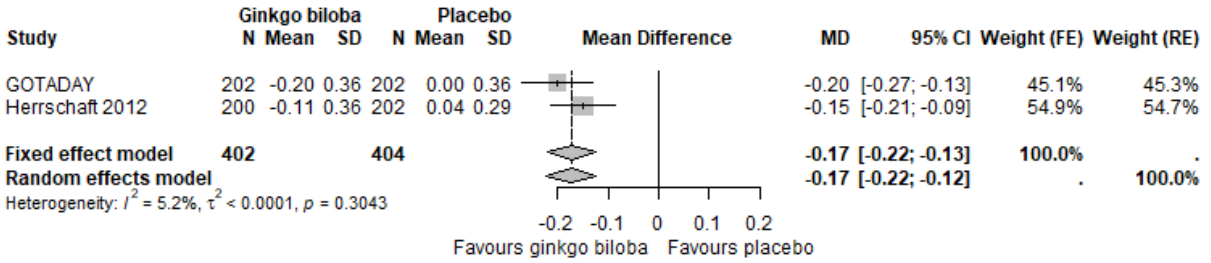


**Figure 22: ADL-IS: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

ADL-IS = Activities of Daily Living International Scale, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. The ADL-IS score is the average of up to 40 items, each scored from 0 to 4, with higher scores indicating more severe functional impairment.[142]

A single trial compared functional status for patients with AD or probable AD treated with 120 mg ginkgo biloba, 240 mg ginkgo biloba, and placebo for 26 weeks (***Table 24***).[l] There was no evidence of a statistically significant difference between 120 mg and 240 mg ginkgo biloba in either the GERRI (MD 0.0 [95% CI -0.1 to 0.1]; 1 RCT; 339 patients) or the Progressive Deterioration Scale (PDS) (MD -1.0 [95% CI -3.0 to 1.0]; 1 RCT; 339 patients).

**Table 24: Continuous efficacy results comparing 120 mg vs. 240 mg ginkgo biloba in patients with MPD – functional status**

| Outcome[a] | Ginkgo biloba 120 mg Mean (95% CI)[b] | Ginkgo biloba 240 mg Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **GERRI** | 0.1 (0.0 to 0.2) | 0.1 (0.0 to 0.2) | 0.42 | 0.0 (-0.1 to 0.1) |
| **PDS** | -5.6 (-6.9 to -4.3) | -4.6 (-6.1 to -3.1) | 0.70 | -1.0 (-3.0 to 1.0) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, GERRI = Geriatric Evaluation by Relative's Rating Instrument, MD = mean difference, MMSE = Mini-Mental State Examination, MPD = mental performance deficit, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, PDS = Progressive Deterioration Scale.

*Notes*

[l] Note that comparisons of 120 mg ginkgo biloba vs. placebo and 240 mg vs. placebo are reported in the relevant sections.

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with placebo; other dose comparisons are reported in relevant sections.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

An RCT compared the effect of 22 weeks of treatment with 240 mg ginkgo biloba with or without 10 mg donepezil vs. donepezil alone on the functional status of patients with probable AD. Authors of the original study reported the proportion of patients with improvement on Gottfries-Bråne-Steen Scale (GBS) total score and ADL subscale (***Table 25***), as well as the mean change from baseline on the GBS total score and GBS-ADL subscale (***Table 26***). For all analyses, there was no evidence of a statistically significant difference between treatment groups after 22 weeks.

**Table 25: Categorical efficacy results comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD – functional status**

| Outcome[a] | Ginkgo biloba + donepezil n/N (%) | Donepezil alone n/N (%) | Ginkgo biloba alone n/N (%) | p-value | Effect RR (95% CI)[b] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **GBS-ADL, Improvement** | 12/31 (39) | 11/32 (34) | 11/30 (36) | 0.70 | 1.13 (0.59 to 2.16) | 1.07 (0.55 to 2.09) |
| **GBS total, Improvement** | 24/31 (77) | 20/32 (63) | 21/30 (68) | 0.19 | 1.24 (0.89 to 1.72) | 1.12 (0.78 to 1.60) |

*Abbreviations*

AD = Alzheimer's disease, ADL = activities of daily living, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, GBS = Gottfries-Bråne-Steen Scale, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, RR = relative risk, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined

as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Calculated by the authors of this report.

**Table 26: Continuous efficacy results comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD – functional status**

| Outcome[a] | Ginkgo biloba + donepezil Mean (95% CI)[b] | Donepezil alone Mean (95% CI)[b] | Ginkgo biloba alone Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **GBS-ADL** | -0.5 (-1.8 to 0.8) | -0.1 (-1.0 to 0.8) | -0.8 (-1.7 to 0.1) | 0.68 | -0.4 (-2.0 to 1.2) | -0.7 (-1.9 to 0.5) |
| **GBS total score** | -5.9 (-8.5 to -3.3) | -4.5 (-7.7 to -1.3) | -3.7 (-6.7 to -0.7) | 0.62 | -1.4 (-5.5 to 2.7) | 0.8 (-3.7 to 5.3) |

*Abbreviations*

AD = Alzheimer's disease, ADL = activities of daily living, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, GBS = Gottfries-Bråne-Steen Scale, MD = mean difference, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

#### 6.2.4.1.4 Health-related quality of life

Based on a meta-analysis of 2 RCTs including 806 patients with AD dementia or vascular dementia, 240 mg ginkgo biloba for 24 weeks is associated with statistically significantly improved HRQoL compared with placebo, as measured by the DEMQOL-proxy total score at 24 weeks (MD 2.00 [95% CI 0.85 to 3.15]; 2 RCTs; 806 patients; moderate certainty evidence) (***Figure 23***). There was minimal heterogeneity across studies. However, it is uncertain whether the mean difference of 2.00 points between ginkgo biloba and placebo is clinically meaningful; neither included trial reported an MCID for the DEMQOL-proxy, and only an MCID for the original DEMQOL could be identified in the literature. The MCID for the DEMQOL is 5 to 6 points,[143] but the DEMQOL and the DEMQOL-proxy have different score ranges, and the DEMQOL is not appropriate for use in patients with

severe dementia.[144] Based on the SMD analysis, there is probably a small treatment effect, but it is possible that the treatment effect is trivial (SMD 0.24 [95% CI 0.10 to 0.38]) (***Figure 63***).

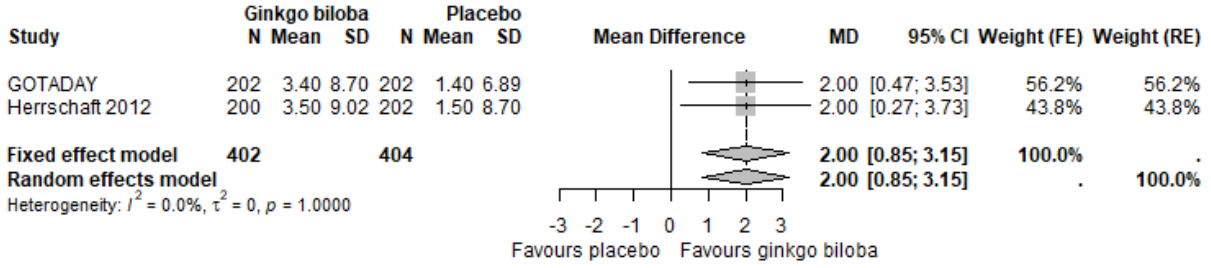


**Figure 23: DEMQOL-proxy total score: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, DEMQOL-proxy = Dementia-Related Quality of Life-proxy, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. DEMQOL-proxy total scores range from 31 to 124, with higher scores indicating better quality of life.[145]

Although a meta-analysis was not possible, neither of the 2 RCTs reporting HRQoL results comparing 120 mg ginkgo biloba with placebo showed an effect of ginkgo biloba. In one trial, patients with mild to moderate cognitive impairment were treated with 120 mg ginkgo biloba or placebo for 12 weeks, and there was no statistically significant difference in the proportion of patients who improved on the Nuremberg Self-Assessment Scale, a subscale of the NAI (***Table 27***).[78] In the DIGGER trial, there was no statistically significant difference between 120 mg ginkgo biloba and placebo in either the carer-rated Quality of Life-Alzheimer's Disease (QoL-AD) (p = 0.222; 176 patients) or participant-rated QoL-AD (p = 0.787; 176 patients) after 24 weeks of treatment (***Table 28***).[83,84]

**Table 27: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – HRQoL**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Improvement in Nuremberg Aging Self-Assessment Scale** | 50/103 (48.5) | 43/92 (46.7) | 0.401 | 1.04 (0.77 to 1.40) |

*Abbreviations*

CI = confidence interval, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, ICD-9 = International Classification of Diseases, Ninth Revision, RR = relative risk, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = All results in this table are from the same trial (Oswald 1997[78]) and at the same timepoint (12 weeks). Included patients were those with mild to moderate cognitive disorders of old age (DSM-III, Cat. 1 or ICD-9 No. 290), whose cognitive performance according to SCAG was between 40 and 90, and who also achieved an average score of at least 3.5 in items 2 to 3 to 6, and 8, and a total score of 24 in items 1 to 8, with none of these items having a score of 7.

b = Calculated by the authors of this report.

**Table 28: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – HRQoL**

| Outcome[a] | p-value | Effect<br>MD (95% CI)[b] |
|---|---|---|
| **Carer-rated QoL-AD** | 0.222 | -0.981 (-2.551 to 0.589) |
| **Participant-rated QoL-AD** | 0.787 | -0.187 (-1.542 to 1.168) |

*Abbreviations*

CI = confidence interval, MD = mean difference, QoL-AD = Quality of Life-Alzheimer's Disease.

*Notes*

a = All results in this table are from the same trial (DIGGER[83,84]) and at the same timepoint (24 weeks). Included patients were those with a clinical diagnosis of dementia made by the referring clinician.

b = Reported by study authors; adjusted estimate.

#### 6.2.4.1.5 Global assessment of health status

Two RCTs compared scores on the Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (ADCS-CGIC) for patients with AD dementia or vascular dementia who received either 240 mg ginkgo biloba or placebo.[105-109,111,112] The ADCS-CGIC is an adaptation of the general CGIC, specifically for use in patients with AD or dementia. It includes a semi-structured interview with the patient and carer conducted at both baseline and follow-up, designed to elucidate the patient's cognitive, behavioural, social, and daily functioning. These interviews are then utilised by the clinician to categorise the patient's change in overall health status from 1 (marked improvement) to 7 (marked worsening).[146,147] In a meta-analysis of patients with AD dementia or vascular dementia, patients treated with 240 mg ginkgo biloba for 24 weeks had a statistically significantly better score on the ADCS-CGIC than those treated with placebo (MD -0.70 [95% CI -0.85 to -0.55]; 2 RCTs; 806 patients) (***Figure 24***). There was no evidence of heterogeneity across studies. The ADCS-CGIC is designed to identify only meaningful changes in patient health status (i.e. if the clinician selects any answer other than 'no change', the change is, by definition, considered clinically meaningful).[146,147] Based on this, the estimated effect of 0.70 points may or may not be clinically meaningful. In contrast, the SMD analysis indicates that this is a moderately sized treatment effect, and the 95% CI shows that there is likely to be at least a small treatment effect (SMD -0.65 [95% CI -0.86 to -0.44]) (***Figure 64***).

Although often treated as a continuous measurement, the ADCS-CGIC may also be reported categorically as the number and percentage of patients in each change category (marked improvement, moderate improvement, minimal improvement, no change, minimal worsening, moderate worsening, marked worsening) (***Figure 25***). Although formal testing has not been conducted, a larger proportion of patients treated with ginkgo biloba appear to have improved over the course of the study for both trials, as well as for the subgroups of patients with either AD or vascular dementia.

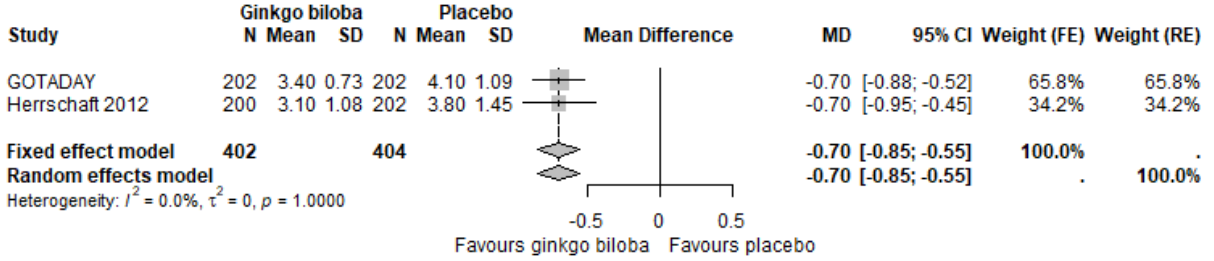


**Figure 24: ADCS-CGIC Score: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Scores on the ADCS-CGIC range from 1 (Marked Improvement) to 7 (Marked Worsening), with 4 representing no change in overall health status since baseline.[146,147]


**Figure 25: ADCS-CGIC categories: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

AD = Alzheimer's disease, ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, VaD = vascular dementia.

Unlike the higher dose, there is no evidence that 120 mg ginkgo biloba is superior to placebo in terms of categorical measures of health status (***Table 29***). One trial found no statistically significant effect of ginkgo biloba on the proportion of patients who were overall responders or showed an improvement in the Nuremberg Self-Assessment List (NSL), a subscale of the NAI, after 12 weeks.[78] Similarly, the DIGGER trial found no statistically significant difference in the proportion of carers who reported they would continue with treatment after 26 weeks,[83,84] while Schneider 2005 reported no statistically significant difference in the proportion of patients who improved on the ADCS-CGIC.[116,117]

**Table 29: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – global assessment of health status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Overall well-being responder[b]** | 12 | Oswald 1997[78c] | 48/103 (46.6) | 42/92 (45.7) | 0.447 | 1.02 (0.75 to 1.38) |
| **Improvement in NSL** | 12 | Oswald 1997[78c] | 53/103 (51.5) | 50/92 (54.3) | 0.657 | 0.95 (0.73 to 1.23) |
| **Carer would continue with treatment** | 26 | DIGGER[83,84d] | 36/88 (51) | 29/88 (43) | 0.340 | 1.24 (0.84 to 1.83) |
| **ADCS-CGIC, Improvement or No Change** | 26 | Schneider 2005[116,117e] | 100/169 (61) | 90/174 (55) | 0.20 | 1.14 (0.95 to 1.38) |
| **ADCS-CGIC, Worsening** | | | 65/169 (39) | 75/174 (45) | | 0.89 (0.69 to 1.15) |

*Abbreviations*

AD = Alzheimer's disease, ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, CI = confidence interval, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, ICD-9 = International Classification of Diseases, Ninth Revision, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NSL = Nuremberg Self-Assessment List, RR = relative risk, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = Calculated by the authors of this report.

b = Favourable rating in at ≥2 of the following: Nuremberg Aging Self-Assessment Scale, Nuremberg Aging Daily Activities Scale, and Nuremberg Self-Assessment List.

c = Included patients were those with mild to moderate cognitive disorders of old age (DSM-III, Cat. 1 or ICD-9 No. 290), whose cognitive performance according to SCAG was between 40 and 90, and who also achieved an average score of at least 3.5 in items 2 to 3 to 6, and 8, and a total score of 24 in items 1 to 8, with none of these items having a score of 7.

d = Included patients were those with a clinical diagnosis of dementia made by the referring clinician.

e = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 240 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

Similar results were seen in continuous measures of global health status comparing 120 mg ginkgo biloba with placebo (***Table 30***). Only Weitbrecht 1986 reported a statistically significant effect of ginkgo biloba, with statistically significantly improved scores on the physician assessment of health status after 12 weeks; score range and tool were not reported in the original study, but authors did specify that a decrease in score indicated improvement.[79] Neither NCT00446485[81] nor Le Bars 1997[98-101] found any statistically significant difference between 120 mg ginkgo biloba and placebo in the Clinical Global Impression of Severity (CGIS) or CGIC.

**Table 30: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – global assessment of health status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **Physician assessment of health status** | 12 | Weitbrecht 1986[79c] | 2.4 (2.0 to 2.8) | 3.1 (2.7 to 3.5) | <0.01[d] | -0.7 (-1.2 to -0.2) |
| **CGIS** | 12 | NCT00446485[81e] | 2.6 (2.2 to 3.0) | 2.7 (2.4 to 3.0) | NR | -0.1 (-0.6 to 0.4) |
| | 24 | | 2.6 (2.2 to 3.0) | 2.8 (2.5 to 3.1) | 0.038[f] | -0.2 (-0.7 to 0.3) |
| **CGIC** | 26 | Le Bars 1997[98-101g] | 4.2 (4.1 to 4.3) | 4.2 (4.1 to 4.3) | 0.51 | 0.0 (-0.1 to 0.1)[h] |
| | 52 | | 4.2 (4.1 to 4.4) | 4.2 (4.1 to 4.3) | 0.77 | 0.0 (-0.1 to 0.1)[h] |

*Abbreviations*

AD = Alzheimer's disease, CGIC = Clinical Global Impression of Change, CGIS = Clinical Global Impression of Severity, CI = confidence interval, MD = mean difference, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination.

*Notes*

a = Mean value at timepoint.

b = Calculated by the authors of this report unless otherwise specified.

c = Included patients were those with primary degenerative dementia, diagnosed using the Hachinski Ischemic Scale, and excluding those with MID.

d = Although reported values are the mean value at 12 weeks, the p-value is for the change from baseline.

e = Included patients were those with vascular cognitive impairment based on cerebrovascular insufficiency and a Folstein MMSE score of >20 and ≤28.

f = This study included a third treatment arm that is not approved in Switzerland and is therefore ineligible for this review. This p-value is a comparison across all 3 treatment groups.

g = Included patients were outpatients with AD or MID, without other significant medical conditions.

h = Reported by study authors.

Based on the results from one trial, there is no statistically significant difference between 120 mg ginkgo biloba and 240 mg ginkgo biloba in the proportion of patients with AD (according to the DSM-IV) or probable AD (based on NINCDS-ADRDA criteria) who improved on the ADCS-CGIC after 26 weeks of treatment (***Table 31***).[116,117]

**Table 31: Categorical efficacy results comparing 120 mg vs. 240 mg ginkgo biloba in patients with MPD – global assessment of health status**

| Outcome[a] | Ginkgo biloba 120 mg n/N (%) | Ginkgo biloba 240 mg n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **ADCS-CGIC, Improvement or No Change** | 100/169 (61) | 104/170 (62) | 0.20 | 0.97 (0.81 to 1.15) |
| **ADCS-CGIC, Worsening** | 65/169 (39) | 65/170 (39) | | 1.01 (0.77 to 1.32) |

*Abbreviations*

AD = Alzheimer's disease, ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an

MMSE score of ≥20. Note that this study also included a group treated with placebo; other dose comparisons are reported in relevant sections.

b = Calculated by the authors of this report.

#### 6.2.4.1.6 Symptoms of other conditions in this review (i.e. dizziness or tinnitus)

In addition to symptoms and outcomes specific to MPD, 3 trials reported on how 24 weeks of treatment with 240 mg ginkgo biloba and placebo impacted symptoms of dizziness and tinnitus in patients with AD dementia or vascular dementia. Both dizziness and tinnitus were measured using an 11-point box scale, a form of numeric analogue scale, in which patients are asked to rate the severity of symptoms. All 3 trials and the random effect meta-analysis indicate that symptoms of dizziness were improved statistically significantly more in patients treated with 240 mg ginkgo biloba (MD -0.76 [95% CI -1.38 to -0.14]; 3 RCTs; 1'201 patients) (***Figure 26***; SMD analysis available in ***Figure 65***). There was substantial heterogeneity, however, leading to uncertainty in the magnitude of effect. In contrast, the meta-analysis showed no statistically significant effect of ginkgo biloba on tinnitus symptoms in patients with AD dementia or vascular dementia (MD -0.53 [95% CI -1.10 to 0.05]; 3 RCTs; 1'201 patients) (***Figure 27***; SMD analysis available in ***Figure 66***).

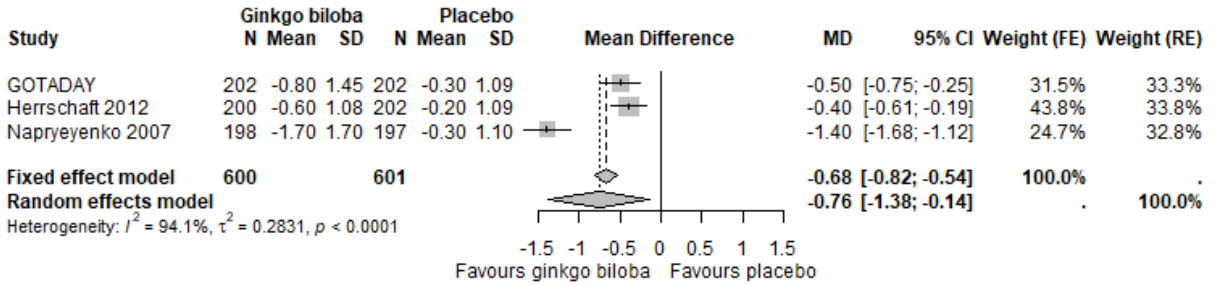


**Figure 26: 11-point box scale dizziness: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

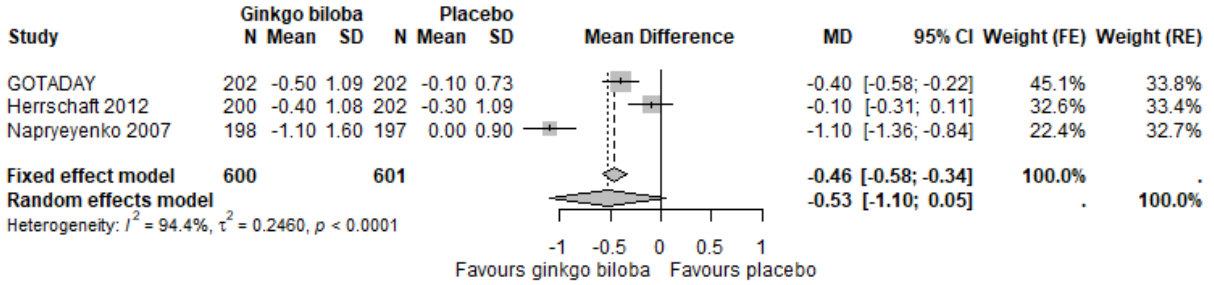


**Figure 27: 11-point box scale tinnitus: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

Based on data from one trial conducted in 96 patients, there is no statistically significant difference between 240 mg ginkgo biloba alone, 10 mg donepezil alone, and a combination of 240 mg ginkgo biloba and 10 mg donepezil in either symptoms of dizziness (p = 0.28 across all treatment groups) or tinnitus (p = 0.97 across all treatment groups) as measured by an 11-point box scale (***Table 32***).

**Table 32: Continuous efficacy results comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD – other measures of efficacy**

| Outcome[a] | Ginkgo biloba + donepezil Mean (95% CI)[b] | Donepezil alone Mean (95% CI)[b] | Ginkgo biloba alone Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **11-point box scale dizziness** | -0.6 (-1.1 to -0.1) | -0.2 (-0.6 to 0.2) | -0.4 (-0.9 to 0.1) | 0.28 | -0.4 (-1.0 to 0.2) | -0.2 (-0.8 to 0.4) |
| **11-point box scale tinnitus** | -0.3 (-0.6 to 0.0) | -0.3 (-0.7 to 0.1) | -0.4 (-0.9 to 0.1) | 0.97 | 0.0 (-0.5 to 0.5) | -0.1 (-0.7 to 0.5) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MD = mean difference, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

#### 6.2.4.2 Peripheral arterial occlusive disease

A summary of the overall certainty of the body of evidence relating to ginkgo biloba for PAOD is presented in ***Table 86***. The rest of this section presents detailed outcome data relating to the efficacy of various doses of ginkgo biloba vs. placebo.

#### 6.2.4.2.1 Mobility

Mobility in patients with PAOD was reported using various measures, doses of ginkgo biloba, and durations of treatment. An overview of meta-analysis results is available in ***Table 33.***

**Table 33: Summary of meta-analysis results for mobility in patients with PAOD**

| Outcome | Analysis metric | Dose (mg) | Timepoint (weeks) | Statistically significant | Clinically meaningful |
|---|---|---|---|---|---|
| MWD | Continuous | 160 | 16 | Yes | Yes |
| | | | 24 | No | NA[a] |
| PFWD | Continuous | 120 | 24 | Yes | Yes |
| | | 160 | 16 | Yes | Yes |
| | | | 24 | Yes | Yes |

*Abbreviations*

MWD = maximum walking distance, NA = not applicable, PFWD = pain-free walking distance.

*Notes*

a = Result is not statistically significant.

In patients with Fontaine's stage IIb PAOD treated with 160 mg ginkgo biloba or placebo for 16 weeks, ginkgo biloba was associated with a statistically significant improvement in maximum walking distance (MD 31.4 m [95% CI 13.1 to 49.6]; 2 RCTs; 73 patients) (***Figure 28***; SMD analysis available in ***Figure 67***).[126,127] This difference is likely to be clinically meaningful, given the anchor-based MCID of 20 m reported in the literature.[148] However, this should be interpreted with the context that values for one trial were digitized from a figure displaying the maximum walking distance at each timepoint, necessitating the digitization of multiple timepoints to calculate the change from baseline.[127] In addition, certainty of evidence was not assessed for this timepoint (see following paragraph for the results after 24 weeks of treatment).

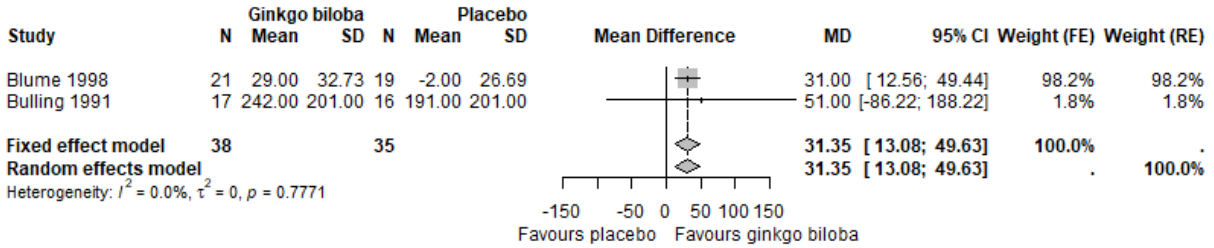


**Figure 28: Maximum walking distance: 160 mg ginkgo biloba vs. placebo at 16 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that data from Bulling 1991 were reported only in a figure as raw values at each timepoint.[127] The means and standard deviations at baseline and 16 weeks were digitized,

rounded to the nearest meter, and used to calculate the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

In contrast to the results at 16 weeks of follow-up, 24 weeks of treatment with 160 mg ginkgo biloba showed no statistically significant effect on maximum walking distance compared to placebo (MD 80.2 m [95% CI -36.4, 196.7]; 2 RCTs; 73 patients; very low certainty evidence) (***Figure 29***; SMD analysis available in ***Figure 68***).[126,127] As above, values for one trial were digitized from a figure displaying the maximum walking distance at each timepoint, necessitating the digitization of multiple timepoints to calculate the change from baseline.[127]

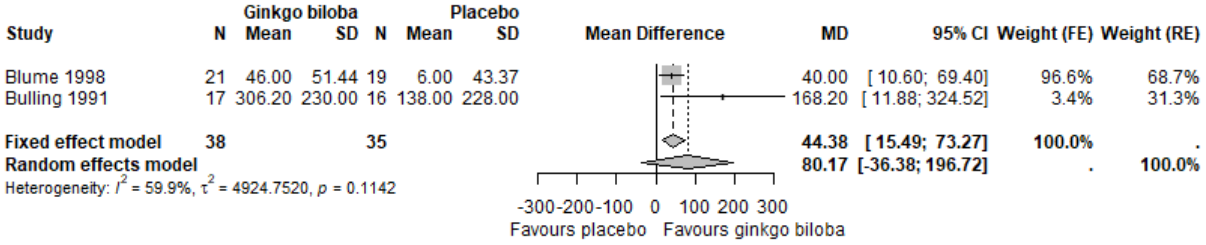


**Figure 29: Maximum walking distance: 160 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that although the mean change from baseline was reported in the text for Bulling 1991, the standard deviations were reported only in a figure and were for the values at each timepoint.[127] Standard deviations at baseline and 24 weeks were digitized, rounded to the nearest meter, and used to calculate the standard deviation for the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. To assess the accuracy of the digitization process, the means were also digitized and used to calculate the mean change from baseline. The values reported in the text were 306.2 (ginkgo biloba) and 138.0 (placebo) meters; the digitized values were 303 (ginkgo biloba) and 136 (placebo) meters. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

Total PFWD after 24 weeks of treatment was statistically significantly higher in patients receiving 120 mg ginkgo biloba than in those receiving placebo (MD 24.4 m [4.9 to 43.9]; 3 RCTs; 225 patients; low certainty evidence) (***Figure 30***; SMD analysis available in ***Figure 69***).[90,120-124,128] The difference of 24.4 m is likely to be clinically meaningful given the anchor-based MCID of 20 m reported in the literature.[148]

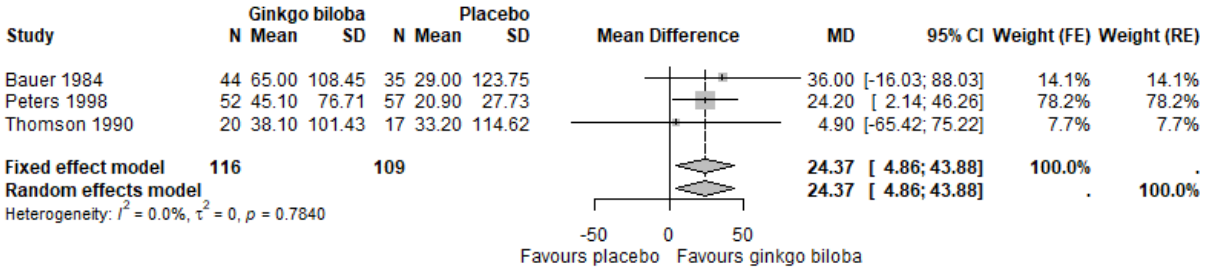


**Figure 30: PFWD: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, PFWD = pain-free walking distance, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. Thomson 1990 reported the mean and standard deviation at baseline and 24 weeks, and these were used to calculate the mean change from baseline and corresponding standard deviation.[90] Data for Bauer 1984 were extracted from a secondary publication for that trial.[121] Data were available only in a figure, although the standard deviations were labelled for each timepoint. The labelled standard deviations for baseline and 24 weeks were used to calculate the standard deviation for the mean change from baseline. The mean values at baseline and 24 weeks were digitized, rounded to the nearest meter, and used to calculate the mean change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other.

After 16 weeks of treatment, patients treated with 160 mg ginkgo biloba showed statistically significantly better PFWD than patients treated with placebo (MD 25.8 m [95% CI 9.0 to 42.7; 2 RCTs; 73 patients) (***Figure 31***; SMD analysis available in ***Figure 70***). As above, this difference is likely to be clinically meaningful, given the anchor-based MCID of 20 m reported in the literature.[148] As above, values for one trial were digitized from a figure displaying the maximum walking distance at each timepoint, necessitating the digitization of multiple timepoints to calculate the change from baseline.[127] In addition, certainty of evidence was not assessed for this timepoint (see following paragraph for the results after 24 weeks of treatment).

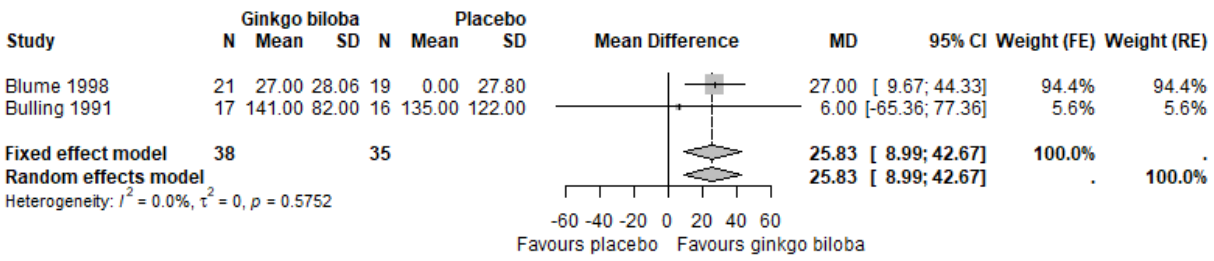


**Figure 31: PFWD: 160 mg ginkgo biloba vs. placebo at 16 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, PFWD = pain-free walking distance, RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that data from Bulling 1991 were reported only in a figure as raw values at each timepoint.[127] The means and standard deviations at baseline and 16 weeks were digitized, rounded to the nearest meter, and used to calculate the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

After 24 weeks, the difference between 160 mg ginkgo biloba and placebo seen at 16 weeks was maintained. Patients with Fontaine's stage IIb PAOD had statistically significantly better PFWD when treated with ginkgo biloba compared to placebo (MD 36.0 m [95% CI 15.4 to 56.6]; 2 RCTs; 73 patients; very low certainty evidence) (***Figure 32***; SMD analysis available in ***Figure 71***).[126 127] Based on the anchor-based MCID of 20 m, this is likely to be a clinically meaningful difference, but the evidence is very uncertain about the true treatment effect.

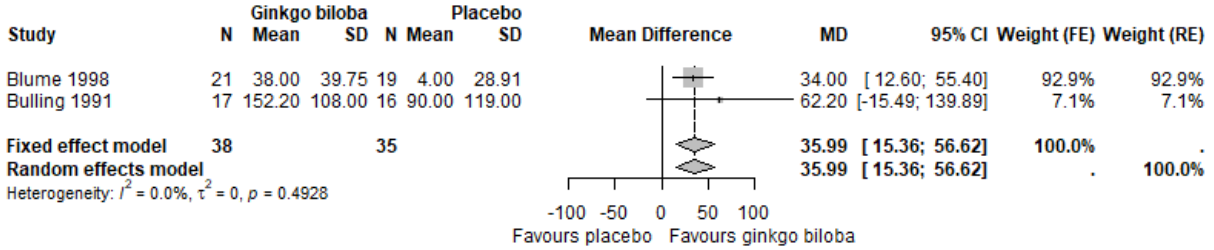


**Figure 32: PFWD: 160 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, PFWD = pain-free walking distance; RE = random effects, SD = standard deviation.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that although the mean change from baseline was reported in the text for Bulling 1991, the standard deviations were reported only in a figure and were for the values at each timepoint.[127] Standard deviations at baseline and 24 weeks were digitized, rounded to the nearest meter, and used to calculate the standard deviation for the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. To assess the accuracy of the digitization process, the means were also digitized and used to calculate the mean change from baseline. The values reported in the text were 152.2 (ginkgo biloba) and 90.0 (placebo) meters; the digitized values were 152 (ginkgo biloba) and 91 (placebo) meters. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

One trial used various categorical outcome measures to assess mobility in people with PAOD treated with 120 mg ginkgo biloba or placebo (***Table 34***).[120-124] Regarding maximum walking distance, there were no statistically significant differences between groups in the proportions of individuals reaching 0-100 m, 100-200 m, >300 m, or ≥600 m after 24 weeks of treatment. At the same timepoint, statistically significant results were found showing that people treated with 120 mg ginkgo biloba were 3, 5, and 6 times more likely, relative to placebo, to have an increase of ≥30%, ≥75%, and ≥100% in maximum walking distance, respectively.

Regarding PFWD, people treated with 120 mg ginkgo biloba were 3 times more likely to have an increase of ≥75% after 24 weeks of treatment, relative to placebo.

**Table 34: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with PAOD – mobility**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **MWD** | | | | | | |
| **0 to 100 m** | 12 | Bauer 1984[120-124b] | 14/44 (31.8) | 14/35 (40) | NR | 0.80 (0.44 to 1.44) |
| | 24 | Bauer 1984[120-124b] | 12/44 (27.2) | 14/35 (40) | NR | 0.68 (0.36 to 1.28) |
| **100 to 200 m** | 12 | Bauer 1984[120-124b] | 16/44 (36.4) | 11/35 (31.4) | NR | 1.16 (0.62 to 2.16) |
| | 24 | Bauer 1984[120-124b] | 14/44 (31.8) | 11/35 (31.4) | NR | 1.01 (0.53 to 1.95) |
| **200 to 300 m** | 12 | Bauer 1984[120-124b] | 9/44 (20.5) | 7/35 (20) | NR | 1.02 (0.42 to 2.47) |
| | 24 | Bauer 1984[120-124b] | 9/44 (20.5) | 6/35 (17.1) | NR | 1.19 (0.47 to 3.03) |
| **>300 m** | 12 | Bauer 1984[120-124b] | 5/44 (11.4) | 3/35 (8.6) | NR | 1.33 (0.34 to 5.17) |
| | 24 | Bauer 1984[120-124b] | 9/44 (20.5) | 4/35 (11.4) | NR | 1.79 (0.60 to 5.33) |
| **≥600 m** | 24 | Bauer 1984[120-124b] | 7/44 (15.9) | 2/35 (5.7) | NR | 2.78 (0.62 to 12.6) |
| **0% to 10% increase** | 24 | Bauer 1984[120-124b] | 3/37 (8.1) | 7/31 (22.6) | NR | 0.36 (0.10 to 1.27) |
| **10% to 30% increase** | 24 | Bauer 1984[120-124b] | 6/37 (16.2) | 7/31 (22.6) | NR | 0.72 (0.27 to 1.91) |

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥30% increase** | 24 | Bauer 1984[120-124b] | 31/44 (70.5) | 8/35 (22.9) | NR | 3.08 (1.63 to 5.83) |
| **30% to 50% increase** | 24 | Bauer 1984[120-124b] | 9/37 (24.3) | 2/31 (6.5) | NR | 3.77 (0.88 to 16.2) |
| **50% to 100% increase** | 24 | Bauer 1984[120-124b] | 7/37 (18.9) | 4/31 (12.9) | NR | 1.47 (0.47 to 4.55) |
| **≥75% increase** | 24 | Bauer 1984[120-124b] | 20/44 (45.5) | 3/35 (8.6) | NR | 5.30 (1.71 to 16.4) |
| **≥100% increase** | 24 | Bauer 1984[120-124b] | 15/44 (34.1) | 2/35 (5.7) | NR | 5.97 (1.46 to 24.4) |
| **100% to 200% increase** | 24 | Bauer 1984[120-124b] | 5/37 (13.5) | 0/31 (0) | NR | 9.26 (0.53 to 161.21) |
| **200% to 400% increase** | 24 | Bauer 1984[120-124b] | 3/37 (8.1) | 0/31 (0) | NR | 5.89 (0.32 to 109.92) |
| **0% to 10% decrease** | 24 | Bauer 1984[120-124b] | 2/37 (5.4) | 3/31 (9.7) | NR | 0.56 (0.10 to 3.13) |
| **10% to 20% decrease** | 24 | Bauer 1984[120-124b] | 1/37 (2.7) | 5/31 (16.1) | NR | 0.17 (0.02 to 1.36) |
| **>20% decrease** | 24 | Bauer 1984[120-124b] | 1/37 (2.7) | 3/31 (9.7) | NR | 0.28 (0.03 to 2.55) |
| **PFWD (meters)** | | | | | | |
| **≥75% increase** | 24 | Bauer 1984[120-124b] | 21/44 (47.7) | 5/35 (14.3) | NR | 3.34 (1.40 to 7.96) |
| **Any decrease** | 24 | Blume 1996[125c] | 0/28 (0) | 9/26 (33) | NR | 0.05 (0.00 to 0.80) |

*Abbreviations*

CI = confidence interval, MWD = maximum walking distance, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = Calculated by the authors of this report, using 0.5 continuity correction where necessary.

b = Included patients were those with chronic PAOD and a PFWD <300 meters. Occlusions were unilaterally dominant and had been present for ≥1 year.

c = Included patients were those with angiographically confirmed (within the prior 8 months) Fontaine's stage IIb PAOD with intermittent claudication for >6 months.

In addition to the categorial outcome measures described above, the same trial also reported mobility using the continuous variables maximum walking distance and PFWD.[120-124] After 24 weeks of treatment, there was no statistically significant difference between 120 mg ginkgo biloba and placebo in maximum walking distance; however, for PFWD, measured at 16 weeks, the ginkgo biloba group could walk 15 m more than the placebo group (MD 15.0 [95% CI 8.9 to 21.1]; 1 RCT; 109 patients) (***Table 35***). However, this is unlikely to be clinically meaningful, given the MCID of ≥20 m reported in the literature.[148]

**Table 35: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with PAOD – mobility**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **MWD (meters)** | 12 | Bauer 1984[120-124c] | 201 (152.2 to 249.8) | 175 (131.1 to 218.9) | NR | 26 (-40.7 to 92.7) |
| | 24 | | 225 (171.0 to 279.0) | 178 (134.3 to 221.7) | NR | 47 (-23.6 to 117.6) |
| **PFWD (meters)** | 12 | Bauer 1984[120-124c] | 107 (78 to 136) | 95.0 (75 to 115) | NR | 12 (-23.8 to 47.8) |
| | 16 | Peters 1998[128d] | 138 (127 to 150)[e] | 121 (112 to 130)[e] | NR | 17 (9.4 to 24.6) |
| | | | 31.5 (21.0 to 42.0)[f] | 16.5 (10.7 to 22.3)[f] | 0.007 | 15.0 (8.9 to 21.1) |

*Abbreviations*

CI = confidence interval, MWD = maximum walking distance, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = Mean value at timepoint unless otherwise specified.

b = Calculated by the authors of this report.

c = Included patients were those with chronic PAOD and a PFWD <300 meters. Occlusions were unilaterally dominant and had been present for ≥1 year. Means for all outcomes were reported only in figures; they were digitised and rounded to the closest whole number. Standard deviations were reported in the figure labels and extracted directly.

d = Included patients were those with Fontaine's stage IIb PAOD with intermittent claudication for >6 months.

e = Means and 95% CIs were reported only in figures; they were digitised and rounded to the closest whole number.

f = Mean absolute change from baseline.

One trial reported mobility measured as the maximum number of toe stands and pain-free toe stands after 24 weeks of treatment with either 160 mg ginkgo biloba or placebo.[127] There were no statistically significant differences between the groups using either measure of mobility (***Table 36***).

**Table 36: Continuous efficacy results comparing 160 mg ginkgo biloba vs. placebo in patients with PAOD – mobility**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **Maximum number of toe stands** | 37 (24 to 51) | 32 (18 to 45) | NR | 5 (-5 to 15) |
| **Pain-free toe stands** | 57 (34 to 81) | 56 (11 to 102) | NR | 1 (-26 to 28) |

*Abbreviations*

CI = confidence interval, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance; RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Bulling 1991[127]) and at the same timepoint (24 weeks). Included patients were those with Fontaine's stage IIb PAOD. Patients had a PFWD between 50 and 200 meters.

b = Mean value at timepoint. Means and 95% CIs were reported only in figures; they were digitised and rounded to the closest whole number.

c = Calculated by the authors of this report.

For 240 mg ginkgo biloba vs. placebo, there was no statistically significant difference between groups in maximum walking time or pain-free walking time, measured at either 12 weeks or 24 weeks of treatment (***Table 37***).[89]

**Table 37: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with PAOD – mobility**

| Outcome[a] | Timepoint (weeks) | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|---|
| **Maximum walking time (seconds)** | 12 | 236 (16 to 456) | 384 (139 to 629) | <0.05 | -148 (-498 to 202) |
| | 24 | 557 (302 to 812) | 820 (534 to 1'106) | <0.01 | -263 (-671 to 145) |
| | 12 | 118 (16 to 220) | 155 (-8 to 318) | NS | -37.0 (-241 to 167) |

| Outcome[a] | Timepoint (weeks) | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|---|
| **Pain-free walking time (seconds)** | 24 | 268 (9 to 527) | 484 (-124 to 1’092) | NS | -216 (-919 to 487) |

*Abbreviations*

ABI, Ankle-Brachial Index, CI = confidence interval, MD = mean difference, NS = not significant, PAOD = peripheral arterial occlusive disease.

*Notes*

a = All results in this table are from the same trial (Wang 2007[89]). Included patients were those with PAOD, defined by ABI <0.90 at rest and <0.80 after treadmill walking test, as well as a history of stable intermittent claudication for ≥6 months. During the second 12 weeks of the study, all patients in both groups received an exercise training intervention.

b = Mean value at timepoint.

c = Calculated by the authors of this report.

#### 6.2.4.2.2 Pain

Two trials reported pain in people with PAOD treated with either 120 mg ginkgo biloba or placebo for 24 weeks; both trials measured pain on a 0 to 100 mm Visual Analogue Scale (VAS). There was a statistically significant difference in favour of ginkgo biloba after 24 weeks of treatment (MD -13.4 mm [95% CI -19.7 to -7.1]; 2 RCTs; 116 patients; low certainty evidence) (***Figure 33***).[90,120-124] However, the difference reported may or may not be clinically meaningful since estimates of the MCID in the 0 to 100 mm VAS vary substantially (median 23 mm, IQR 12-39).[149] The variability is thought to be due to a range of clinical and methodological factors, including baseline pain and differences in statistical methods used to determine MCID when used to measure chronic pain. In the SMD analysis, the estimate represents a clinically meaningful (moderate) treatment effect, but the effect is not statistically significant (SMD -0.58 [95% CI -1.29 to 0.12]) (***Figure 72***).

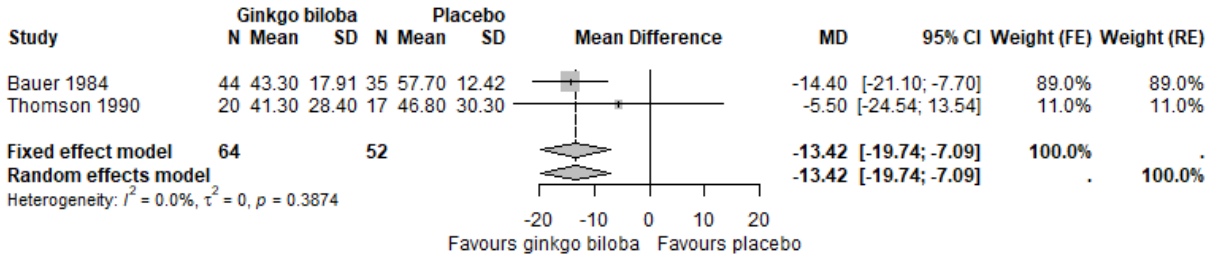


**Figure 33: Pain: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

6.2.4.2.3 Peripheral blood circulation

Two trials used resting ankle pressure to assess peripheral blood circulation in people with PAOD treated with either 120 mg ginkgo biloba or placebo. There was no statistically significant difference between the groups after 24 weeks of treatment (MD -1.72 [95% CI -23.07 to 19.63]; 2 RCTs; 116 patients; very low certainty evidence) (***Figure 34***; SMD analysis available in ***Figure 73***).[90,120-124]

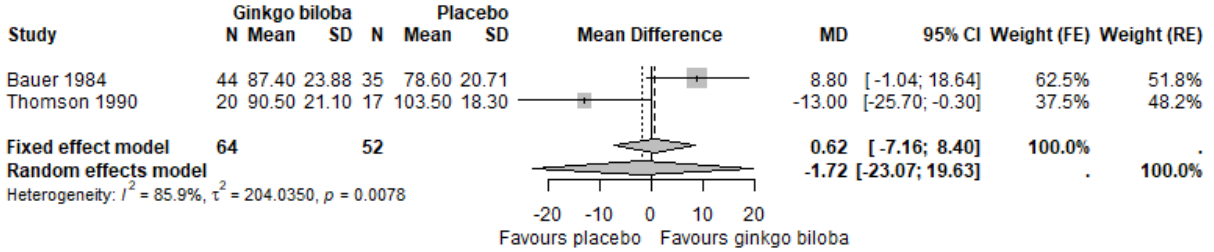


**Figure 34: Resting ankle pressure: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

The same 2 trials also measured post-exercise ankle pressure after 24 weeks of either 160 mg ginkgo biloba or placebo, and a meta-analysis again found no statistically significant difference between the treatment groups (MD 4.36 [95% CI -7.19 to 15.91]; 2 RCTs; 116 patients; very low certainty evidence) (***Figure 35***; SMD analysis available in ***Figure 74***).

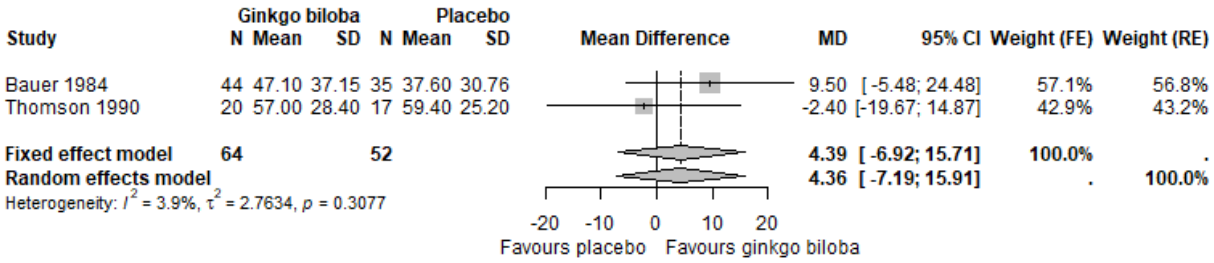


**Figure 35: Post-exercise ankle pressure: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MD = mean difference, RE = random effects, SD = standard deviation.

Two trials investigating the lower dose of 120 mg ginkgo biloba vs. placebo reported a range of continuous outcome measures used to assess peripheral blood circulation.[90,120-124] None of the results showed any statistically significant differences after either 12 or 24 weeks of treatment (***Table 38***).

**Table 38: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with PAOD – peripheral blood circulation**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **Peak flow[c]** | 12 | Bauer 1984[120-124d] | 5.1 (4.3 to 5.9) | 5.0 (4.0 to 6.0) | NR | 0.1 (-1.2 to 1.4) |
| | 24 | | 5.9 (4.9 to 6.9) | 5.3 (4.1 to 6.5) | NR | 0.6 (-1.0 to 2.2) |
| **Rate flow[c]** | 12 | Bauer 1984[120-124d] | 2.4 (2.0 to 2.8) | 2.0 (1.8 to 2.2) | NR | 0.4 (0.0 to 0.8) |
| | 24 | | 2.5 (2.1 to 2.9) | 2.0 (1.6 to 2.4) | NR | 0.5 (-0.1 to 1.1) |
| **Time to peak flow[c]** | 12 | Bauer 1984[120-124d] | 4.5 (3.3 to 5.7) | 5.1 (3.7 to 6.5) | NR | -0.6 (-2.4 to 1.2) |
| | 24 | | 4.0 (3.0 to 5.0) | 4.8 (3.4 to 6.2) | NR | -0.8 (-2.5 to 0.9) |
| **Post-exercise ankle arterial pressure** | 12 | Bauer 1984[120-124d] | 46.3 (35.5 to 57.1) | 39.0 (29.0 to 49.0) | NR | 7.3 (-7.6 to 22.2) |
| **Resting ankle arterial pressure** | 12 | Bauer 1984[120-124d] | 88.4 (81.1 to 95.7) | 81.3 (74.8 to 87.8) | NR | 7.1 (-2.8 to 17.0) |
| **Recovery time[e]** | 24 | Thomson 1990[90f] | 6.1 (3.9 to 8.3) | 6.7 (4.3 to 9.1) | NS | -0.6 (-4.0 to 2.8) |

*Abbreviations*

CI = confidence interval, MD = mean difference, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = Mean value at timepoint.

b = Calculated by the authors of this report.

c = Measured using plethysmography on affected side.

d = Included patients were those with chronic PAOD and a PFWD <300 meters. Occlusions were unilaterally dominant and had been present for ≥1 year. Means for all outcomes were reported only in figures; they were digitised and rounded to the closest whole number. Standard deviations were reported in the Figure labels and extracted directly.

e = Time for Doppler pressure to return to pre-exercise level.

f = Included patients were those with Fontaine's stage II PAOD affecting the iliac or femoral arteries and involving predominantly one leg.

Similarly, after 24 weeks of treatment with the higher dosage of 160 mg ginkgo biloba vs. placebo, no statistically significant differences were found between the 2 groups for peripheral blood circulation measured using either arterial pressure in dorsalis pedis or arterial pressure in tibialis posterior (***Table 39***).[127]

**Table 39: Continuous efficacy results comparing 160 mg ginkgo biloba vs. placebo in patients with PAOD – peripheral blood circulation**

| Outcome[a] | Timepoint (weeks) | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|---|
| **Arterial pressure in dorsalis pedis** | 12 | 78.8 (71.1 to 86.5) | 100.0 (84.0 to 116.0) | NR | -21.2 (-39.7 to -2.7) |
| | 24 | 77.2 (68.5 to 85.9) | 93.3 (79.6 to 107.0) | NR | -16.1 (-33.0 to 0.8) |
| **Arterial pressure in tibialis posterior** | 12 | 80.6 (70.6 to 90.6) | 102.5 (88.0 to 117.0) | NR | -21.9 (-40.3 to -3.5) |
| | 24 | 79.7 (69.3 to 90.1) | 97.3 (82.5 to 112.1) | NR | -17.6 (-36.4 to 1.2) |

*Abbreviations*

CI = confidence interval, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Bulling 1991[127]). Included patients were those with Fontaine's stage IIb PAOD. Patients had a PFWD between 50 and 200 meters.

b = Mean value at timepoint.

c = Calculated by the authors of this report.

Consistent with the results for 120 mg and 160 mg ginkgo biloba vs. placebo in various assessments of peripheral blood circulation, there were no statistically significant differences between 240 mg ginkgo biloba and placebo in post-exercise ABI or resting ABI after 12 or 24 weeks of treatment (***Table 40***).[89]

**Table 40: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with PAOD – peripheral blood circulation**

| Outcome[a] | Timepoint (weeks) | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|---|
| **Post-exercise ABI** | 12 | 0.4 (-0.2 to 0.9) | 0.5 (0.0 to 1.1) | NS | -0.2 (-1.0 to 0.7) |
| | 24 | 0.5 (0.0 to 0.9) | 0.5 (0.1 to 0.9) | NS | 0.0 (-0.7 to 0.6) |
| **Resting ABI** | 12 | 0.6 (0.3 to 0.9) | 0.7 (0.3 to 1.0) | NS | -0.1 (-0.6 to 0.5) |
| | 24 | 0.6 (0.3 to 0.9) | 0.7 (0.2 to 1.2) | NS | -0.1 (-0.7 to 0.5) |

*Abbreviations*

ABI = Ankle-Brachial Index, CI = confidence interval, MD = mean difference, NS = not significant, PAOD = peripheral arterial occlusive disease.

*Notes*

a = All results in this table are from the same trial (Wang 2007[89]). Included patients were those with PAOD, defined by ABI <0.90 at rest and <0.80 after treadmill walking test, as well as a history of stable intermittent claudication for ≥6 months. During the second 12 weeks of the study, all patients in both groups received an exercise training intervention.

b = Mean value at timepoint.

c = Calculated by the authors of this report.

#### 6.2.4.2.4 Health-related quality of life

No HRQoL outcomes were identified for the condition of PAOD.

#### 6.2.4.2.5 Global assessment of health status

One trial investigating 24 weeks of 120 mg ginkgo biloba vs. placebo measured functional status with both investigator-reported and patient-reported global assessment of health status, rated as poor, moderate, good or very good.[120-124] According to both investigators and patients, an assessment of 'good' health was more likely with 120 mg ginkgo biloba than with placebo (***Table 41***). For the highest-rated category, patients taking 120 mg ginkgo biloba were almost 10 times more likely to assess their health as 'very good' (RR 9.55 [95% CI 1.30 to 69.9]; 1 RCT; 79 patients) relative to placebo. In the 'very good' category as assessed by investigators, the difference between ginkgo biloba and placebo was not statistically significant (RR 10.40 [95% CI 0.61 to 178.52; 1 RCT; 79 patients).

**Table 41: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with PAOD – global assessment of health status**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Investigator assessment of therapy: Poor** | 4/44 (9.1) | 30/35 (85.7) | NR | 0.11 (0.04 to 0.27) |
| **Investigator assessment of therapy: Moderate** | 13/44 (29.5) | 3/35 (8.6) | NR | 3.45 (1.07 to 11.2) |
| **Investigator assessment of therapy: Good** | 21/44 (47.7) | 2/35 (5.7) | NR | 8.35 (2.10 to 33.2) |
| **Investigator assessment of therapy: Very good** | 6/44 (13.6) | 0/35 (0) | NR | 10.40 (0.61 to 178.52) |
| **Patient assessment of therapy: Poor** | 5/44 (11.4) | 22/35 (62.9) | NR | 0.18 (0.08 to 0.43) |

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Patient assessment of therapy: Moderate** | 10/44 (22.7) | 6/35 (17.1) | NR | 1.33 (0.53 to 3.29) |
| **Patient assessment of therapy: Good** | 17/44 (38.6) | 6/35 (17.1) | NR | 2.25 (0.99 to 5.11) |
| **Patient assessment of therapy: Very good** | 12/44 (27.3) | 1/35 (2.9) | NR | 9.55 (1.30 to 69.9) |

*Abbreviations*

CI = confidence interval, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Bauer 1984[120-124]) and at the same timepoint (24 weeks). Included patients were those with chronic PAOD and a PFWD <300 meters. Occlusions were unilaterally dominant and had been present for ≥1 year.

b = Calculated by the authors of this report.

A second trial also investigated both investigator-reported and patient-reported global assessment of health status, but compared 120 mg vs. 240 mg ginkgo biloba.[129] There were no statistically significant differences between the groups after 24 weeks of treatment (***Table 42***).

**Table 42: Categorical efficacy results comparing 120 mg vs. 240 mg ginkgo biloba in patients with PAOD – global assessment of health status**

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Placebo n/N (%)[b] | p-value | Effect RR (95% CI)[c] |
|---|---|---|---|---|
| **Investigator assessment of therapy: Poor** | 7/35 (18.4) | 5/33 (13.9) | NR | 1.32 (0.46 to 3.75) |
| **Investigator assessment of therapy: Moderate** | 8/35 (21.1) | 5/33 (13.9) | NR | 1.51 (0.55 to 4.15) |
| **Investigator assessment of therapy: Good** | 10/35 (26.3) | 12/33 (33.3) | NR | 0.79 (0.39 to 1.57) |
| **Investigator assessment of therapy: Very good** | 10/35 (26.3) | 11/33 (30.6) | NR | 0.86 (0.42 to 1.75) |
| **Patient assessment of therapy: Poor** | 4/35 (10.5) | 3/32 (8.3) | NR | 1.22 (0.30 to 5.03) |
| **Patient assessment of therapy: Moderate** | 7/35 (18.4) | 5/32 (13.9) | NR | 1.28 (0.45 to 3.63) |
| **Patient assessment of therapy: Good** | 10/35 (26.3) | 9/32 (25) | NR | 1.02 (0.47 to 2.18) |

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Placebo n/N (%)[b] | p-value | Effect RR (95% CI)[c] |
|---|---|---|---|---|
| **Patient assessment of therapy: Very good** | 14/35 (36.8) | 15/32 (41.7) | NR | 0.85 (0.49 to 1.48) |

*Abbreviations*

CI = confidence interval, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Schweizer 1999[129]) and at the same timepoint (24 weeks). Included patients were those with Fontaine's stage IIb PAOD with occlusion of the superficial femoral artery on one leg and without occlusion of the deep femoral artery. Patients had a PFWD <200 meters and maximum walking distance between 100 and 300 meters.

b = Percentages here are as they were reported in the original trial publication. The percentages use the total study population as the denominator. The denominators reported in this report are those with data reported.

c = Calculated by the authors of this report.

#### **6.2.4.3** Vertigo

A summary of the overall certainty of the body of evidence relating to ginkgo biloba for vertigo is presented in ***Table 87***. The rest of this section presents detailed outcome data relating to the efficacy of various doses of ginkgo biloba vs. 32 mg betahistine for treating vertigo.

##### 6.2.4.3.1 Timing and intensity of vestibular symptoms, including patient-perceived handicap

One trial used a range of categorical measures to assess the effect of 240 mg ginkgo biloba on vestibular symptoms compared with 32 mg betahistine after 12 weeks of treatment (***Table 43***).[91] All of the results suggested little to no difference between groups (1 RCT; 160 patients; low certainty evidence).

**Table 43: Categorical efficacy results comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo – vestibular symptoms**

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Betahistine n/N (%)[b] | p-value | Effect RR (95% CI)[c] |
|---|---|---|---|---|
| 50% improvement in 11-point NAS | 63/80 (79) | 60/80 (75) | NR | 1.05 (0.89 to 1.24) |
| Romberg test: No swaying | 39/80 (49) | 39/80 (49) | NR | 1.00 (0.73 to 1.37) |
| Romberg test: Slight swaying | 41/80 (51) | 40/80 (50) | NR | 1.03 (0.75 to 1.39) |
| Romberg test: Swaying with foot movement | 0/80 (0) | 1/80 (1) | NR | 0.33 (0.01 to 8.06) |
| Romberg test: Tendency to fall | 0/80 (0) | 0/80 (0) | NR | NE |

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Betahistine n/N (%)[b] | p-value | Effect RR (95% CI)[c] |
|---|---|---|---|---|
| Unterberger's stepping test: rotation <30 degrees | 74/80 (93) | 72/80 (90) | NR | 1.03 (0.93 to 1.13) |
| Unterberger's stepping test: rotation >60 degrees | 0/80 (0) | 0/80 (0) | NR | NE |
| Unterberger's stepping test: rotation 30 to 60 degrees | 6/80 (7) | 8/80 (10) | NR | 0.75 (0.27 to 2.06) |

*Abbreviations*

CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, NAS = numeric analogue scale, NE = not estimable, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Percentages for all outcomes were reported only in figures; they were digitised and rounded to the closest percentage.

c = Calculated by the authors of this report, using 0.5 continuity correction where necessary.

Similar to the results seen in the categorical outcome measures, when vestibular symptoms were assessed using a range of continuous scales, there were no statistically significant differences between the 240 mg ginkgo biloba and 32 mg betahistine groups after 12 weeks of treatment (1 RCT; 160 patients; low certainty evidence) (***Table 44***).[91]

**Table 44: Continuous efficacy results comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo – vestibular symptoms**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Betahistine Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **11-point box scale vertigo** | -3.5 (-3.9 to -3.1) | -3.3 (-3.7 to -2.9) | 0.704 | -0.2 (-0.7 to 0.3) |
| **VSS-A** | -7.1 (-8.0 to -6.2) | -6.4 (-7.4 to -5.4) | 0.446 | -0.7 (-2.1 to 0.7) |
| **VSS-SF** | -14.7 (-16.4 to -13.0) | -13.4 (-15.3 to -11.5) | 0.319 | -1.3 (-3.8 to 1.2) |
| **VSS-V** | -7.6 (-8.7 to -6.5) | -7.0 (-8.1 to -5.9) | 0.432 | -0.6 (-2.2 to 1.0) |

*Abbreviations*

CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference, NR = not reported, RR = relative risk, VSS-A = Vertigo Symptom Scale autonomic-anxiety, VSS-SF = Vertigo Symptom Scale short-form; VSS-V = Vertigo Symptom Scale vertigo-balance.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

There were no statistically significant differences between the lower dose of 160 mg ginkgo biloba and 32 mg betahistine in terms of efficacy assessed with various categorical outcome measures after 12 weeks of treatment (1 RCT; 31 patients; very low certainty evidence) (***Table 45***).[92]

**Table 45: Categorical efficacy results comparing 160 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo – vestibular symptoms**

| Outcome[a] | Ginkgo biloba n/N (%) | Betahistine n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Patient assessment: vertigo disappeared** | 8/18 (44.4) | 6/13 (46.1) | NS | 0.96 (0.44 to 2.10) |
| **Patient assessment: vertigo improved** | 4/18 (22.2) | 6/13 (46.1) | | 0.48 (0.17 to 1.37) |
| **Patient assessment: vertigo unchanged** | 2/18 (11.1) | 1/13 (7.6) | | 1.44 (0.15 to 14.3) |
| **Patient assessment: vertigo worsened** | 4/18 (22.2) | 0/13 (0) | | 6.63 (0.39 to 113.40) |
| **Babinsky-Weil test no longer positive** | 6/20 (30.0) | 4/17 (23.5) | NR | 1.28 (0.43 to 3.78) |
| **Romberg test no longer positive** | 4/20 (20.0) | 3/17 (17.6) | NR | 1.13 (0.29 to 4.37) |

*Abbreviations*

CI = confidence interval, NR = not reported, NS = not significant, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Cesarani 1998[92]) and at the same timepoint (12 weeks). Included patients were those with vertigo, dizziness, or both, due to vascular vestibular disorders.

b = Calculated by the authors of this report, using 0.5 continuity correction where necessary.

#### 6.2.4.3.2 Health-related quality of life

No HRQoL outcomes were identified for the condition of vertigo.

#### 6.2.4.3.3 Global assessment of health status

There was no statistically significant difference in the proportion of patients who perceived their vertigo symptoms to be improved after 12 weeks of treatment with 240 mg ginkgo biloba or 32 mg betahistine (RR 1.13 [95% CI 0.94 to 1.35]; 1 RCT; 160 patients) (***Table 46***).[91]

**Table 46: Categorical efficacy results comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo – global assessment of health status**

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Betahistine n/N (%)[b] | p-value | Effect RR (95% CI)[c] |
|---|---|---|---|---|
| **CGIC, much improved or very much improved** | 63/80 (79) | 56/80 (70) | NR | 1.13 (0.94 to 1.35) |

*Abbreviations*

CGIC = clinical global impression of change; CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Percentages were reported only in figures; they were digitised and rounded to the closest percentage.

c = Calculated by the authors of this report.

One trial measured change from baseline in the Clinical Global Impression of Change Scale used for quantifying global health status after 12 weeks of treatment with 240 mg ginkgo biloba or 32 mg betahistine.[91] There was no statistically significant difference between the 2 groups (MD -0.2 [95% CI -0.5 to 0.1]; 1 RCT; 160 patients) (***Table 47***).

**Table 47: Continuous efficacy results comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo – global assessment of health status**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Betahistine Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **CGIC** | 1.9 (1.7 to 2.1) | 2.1 (1.9 to 2.3) | 0.237 | -0.2 (-0.5 to 0.1) |

*Abbreviations*

CGIC = clinical global impression of change; CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified

(H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Mean value at timepoint.

c = Calculated by the authors of this report.

#### 6.2.4.3.4 Functional status

One trial measured functional status using the Sheehan Disability Scale (SDS) (possible range: 0-30; higher score = more severe impairment).[91] There was no statistically significant difference in change in mean scores from baseline after 12 weeks of treatment with either 240 mg ginkgo biloba or 32 mg betahistine (MD -1.1 [95% CI -2.9 to 0.7]; 1 RCT; 160 patients) (***Table 48***).

**Table 48: Continuous efficacy results comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo – functional status**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Betahistine Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **SDS total score** | -9.4 (-10.6 to -8.2) | -8.3 (-9.5 to -7.1) | 0.260 | -1.1 (-2.9 to 0.7) |

*Abbreviations*

CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, NR = not reported, RR = relative risk, SDS = Sheehan Disability Scale.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

### **6.2.4.4** Tinnitus

A summary of the overall certainty of the body of evidence relating to ginkgo biloba for tinnitus is presented in ***Table 88***. The rest of this section presents detailed outcome data relating to the efficacy of ginkgo biloba vs. either placebo, hearing aid, or pentoxifylline for treating tinnitus.

#### 6.2.4.4.1 Tinnitus severity

One trial found no statistically significant difference between 120 mg ginkgo biloba and placebo in patients' subjective impression of improvement of tinnitus (RR 2.19 [95% CI 0.98 to 4.90]; 1 RCT; 99 patients; low certainty evidence) (***Table 49***).[131] The outcome was measured after 12 weeks of treatment using a scale of -5 (significant deterioration) to +5 (no tinnitus).

**Table 49: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with tinnitus – tinnitus severity**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Patient subjective impression: tinnitus improved** | 15/49 (30.6) | 7/50 (14) | NR | 2.19 (0.98 to 4.90) |

*Abbreviations*

CI = confidence interval, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Morgenstern 1997[131]) and at the same timepoint (12 weeks). Included patients were those with tonally definable chronic tinnitus that could be masked and had persisted for ≥2 months.

b = Calculated by the authors of this report.

One trial matched patients on age, sex, and duration of tinnitus, and randomised one person in each pair to receive 150 mg ginkgo biloba, while the other person received placebo.[93,94] There were no statistically significant differences between 150 mg ginkgo biloba and placebo in patients' subjective assessment of tinnitus severity (***Table 50***). Patients were asked after 12 weeks of treatment if their condition had improved, and then they were asked 2 weeks after stopping treatment if their condition had worsened.

**Table 50: Categorical efficacy results comparing 150 mg ginkgo biloba vs. placebo in patients with tinnitus – tinnitus severity**

| Outcome[a] | Timepoint (weeks) | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|---|
| **Patient-reported improvement in troublesome nature of tinnitus since beginning treatment** | 12 | 34/360 (9.4) | 35/360 (9.7) | NS | 0.97 (0.62 to 1.52) |
| **Patient-reported worsening troublesome nature of tinnitus since stopping treatment 2 weeks before** | 14 | 47/354 (13.3) | 39/354 (11.0) | NS | 1.21 (0.81 to 1.79) |

*Abbreviations*

CI = confidence interval, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Drew 1999[93,94]). Included patients were those with self-reported tinnitus.

b = Calculated by the authors of this report.

The same trial found no statistically significant differences between 150 mg ginkgo biloba and placebo across various continuous measures designed to measure patients' assessment of tinnitus severity after 12 weeks of treatment and again 2 weeks after stopping treatment (***Table 51***).[93,94]

**Table 51: Continuous efficacy results comparing 150 mg ginkgo biloba vs. placebo in patients with tinnitus – tinnitus severity**

| Outcome[a] | Timepoint (weeks) | Outcome metric | Effect MD (95% CI)[b] |
|---|---|---|---|
| **Awareness of or ability to ignore tinnitus, range 0 to 22** | 12 | Score at timepoint | -0.70 (-0.43 to 0.30)[c] |
| | | Change from baseline | -0.15 (-0.52 to 0.22) |
| | 14 | Score at timepoint | 0.16 (-0.22 to 0.54) |
| **Tinnitus impact, range 0 to 39** | 12 | Score at timepoint | -1.09 (-2.24 to 0.05) |
| | | Change from baseline | -0.15 (-0.76 to 0.46) |
| | 14 | Score at timepoint | -0.56 (-1.80 to 0.68) |
| **Tinnitus severity, range 0 to 73** | 12 | Score at timepoint | -1.32 (-2.85 to 0.21) |
| | | Change from baseline | -0.22 (-1.11 to 0.67) |
| | 14 | Score at timepoint | -0.10 (-1.78 to 1.58) |
| **Variability of tinnitus, range 0 to 6** | 12 | Score at timepoint | -0.22 (-0.48 to 0.04) |
| | | Change from baseline | -0.08 (-0.27 to 0.11) |
| | 14 | Score at timepoint | -0.26 (-0.52 to -0.01)[d] |
| **Treatment impact on troublesome nature of tinnitus, range -4 to 4** | 12 | Score at timepoint | 0.03 (-0.17 to 0.17) |
| | 14 | Score at timepoint | -0.10 (-0.24 to 0.04) |

*Abbreviations*

CI = confidence interval, MD = mean difference.

*Notes*

a = All results in this table are from the same trial (Drew 1999[93,94]). Included patients were those with self-reported tinnitus. All outcomes were ascertained using trial-designed questionnaires. Content and score ranges are reported for each outcome.

b = Ginkgo biloba vs. placebo. Note that this is the mean difference between matched pairs (i.e. a pair of patients were matched, and one was randomly assigned to ginkgo biloba, while the other patient received placebo). Results not reported by treatment.

c = The mean difference presented here does not fall within the 95% CI; however, this is how the data were reported in the original study publication. Because results were not reported by treatment, the correct values could not be ascertained.

d = p = 0.045.

One trial found no statistically significant differences between 120 mg ginkgo biloba and 600 mg pentoxifylline in tinnitus severity measured after 12 weeks of treatment using either the abridged Tinnitus Questionnaire (MD 0.4 [95% CI -0.1 to 0.9]; 1 RCT; 198 patients; low certainty evidence) or an 11-point numeric analogue scale (MD 0.0 [95% CI -0.2 to 0.2]; 1 RCT; 198 patients; low certainty evidence) (***Table 52***).[130]

**Table 52: Continuous efficacy results comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus – tinnitus severity**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Pentoxifylline Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **11-point box scale tinnitus annoyance** | -0.6 (-0.8 to -0.3)[d] | -0.5 (-0.8 to -0.3)[e] | 0.938 | 0.0 (-0.2 to 0.2) |
| **Mini-TQ** | -1.6 (-2.3 to -0.9)[f] | -1.9 (-2.6 to -1.3)[f] | 0.4514 | 0.4 (-0.1 to 0.9) |

*Abbreviations*

CI = confidence interval, MD = mean difference, Mini-TQ = abridged tinnitus questionnaire.

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

d = p = 0.0002 vs. baseline.

e = p = 0.0003 vs. baseline.

f = p <0.0001 vs. baseline.

One trial reported tinnitus severity outcomes in patients with unilateral or bilateral tinnitus and sensorineural or mixed hearing loss, as evaluated by otolaryngologists after 12 weeks of treatment for 3 different treatment groups: 240 mg ginkgo biloba alone, 240 mg ginkgo biloba with a hearing aid, and a hearing aid alone (***Table 53***).[95] Adding ginkgo biloba to a hearing aid resulted in statistically significantly worse severity outcomes compared to a hearing aid alone, measured with the Tinnitus Handicap Inventory (THI) (possible score: 0 to 100; higher score = greater tinnitus severity) and a 0 to 10 VAS (higher score = greater tinnitus severity) (1 RCT; 33 patients; very low certainty evidence). In contrast, there was little to no difference in THI scores between ginkgo biloba alone and a hearing aid alone, but there were slightly worse tinnitus severity VAS scores in the ginkgo biloba group than in the hearing aid group (1 RCT; 33 patients; very low certainty evidence).

**Table 53: Continuous efficacy results comparing 240 mg ginkgo biloba with or without a hearing aid vs. hearing aid alone in patients with tinnitus – tinnitus severity**

| Outcome[a] | Ginkgo biloba + HA Mean (95% CI)[b] | HA alone Mean (95% CI)[b] | Ginkgo biloba alone Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + HA vs. HA alone | Ginkgo biloba alone vs. HA alone |
| **THI** | 27 (22.9 to 31.1) | 14 (12.2 to 15.8) | 16 (13.0 to 19.0) | NR | 13 (8.2 to 17.8) | 2 (-1.7 to 5.7) |
| **VAS (0 to 10) tinnitus discomfort** | 3.7 (3.3 to 4.1) | 2.3 (2.0 to 2.6) | 3.0 (2.6 to 3.4) | NR | 1.4 (0.9 to 1.9) | 0.7 (0.2 to 1.2) |

*Abbreviations*

CI = confidence interval, HA = hearing aid, MD = mean difference, NR = not reported, THI = Tinnitus Handicap Inventory, VAS = Visual Analogue Scale.

*Notes*

a = All results in this table are from the same trial (RBR2SN8XV[95]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral tinnitus and sensorineural or mixed hearing loss, as evaluated by otolaryngologists.

b = Mean value at timepoint. Means and standard deviations for all outcomes were reported only in figures; they were digitised and rounded to the closest whole number (for THI) or tenth (for VAS), depending on the range of the Y-axis.

c = Calculated by the authors of this report.

#### 6.2.4.4.2 Tinnitus loudness

One trial found that tinnitus loudness, measured in decibels, was statistically significantly lower with 120 mg ginkgo biloba than with placebo after 12 weeks of treatment (MD -6.1 decibels [95% CI -10.9 to -1.3]; 1 RCT; 73 patients; low certainty evidence) (***Table 54***).[131] The difference of -6.1 decibels is considered to be clinically meaningful according to the trial authors, who used an MCID of 5 decibels.[131]

**Table 54: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with tinnitus – tinnitus loudness**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **Loudness in the more affected ear (decibels)** | 39.0 (31.9 to 46.1) | 45.1 (39.1 to 51.2) | <0.05 | -6.1 (-10.9 to -1.3) |

*Abbreviations*

CI = confidence interval, MD = mean difference.

*Notes*

a = All results in this table are from the same trial (Morgenstern 1997[131]) and at the same timepoint (12 weeks). Included patients were those with tonally definable chronic tinnitus that could be masked and had persisted for ≥2 months.

b = Mean value at timepoint.

c = Calculated by the authors of this report.

One trial matched patients on age, sex, and duration of tinnitus, and randomised one person in each pair to receive 150 mg ginkgo biloba, while the other person received placebo.[93,94] This study found no statistically significant differences between matched pairs in tinnitus loudness measured after 12 weeks of treatment and 2 weeks after stopping treatment (***Table 55***).[93,94] Tinnitus loudness was measured with a trial-specific questionnaire (possible score: 0 to 12; higher score = louder tinnitus) and with a scale measuring the extent to which the treatment affects the patient's tinnitus (range: -4 to 6; higher score = greater improvement in tinnitus loudness).

**Table 55: Continuous efficacy results comparing 150 mg ginkgo biloba vs. placebo in patients with tinnitus – tinnitus loudness**

| Outcome[a] | Timepoint (weeks) | Outcome metric | Effect MD (95% CI)[b] |
|---|---|---|---|
| **Tinnitus loudness, range 0 to 12** | 12 | Score at timepoint | -0.07 (-0.35 to 0.21) |
| | | Change from baseline | -0.08 (-0.27 to 0.11) |
| | 14 | Score at timepoint | 0.06 (-0.23 to 0.34) |
| **Treatment impact on tinnitus loudness, range -4 to 6** | 12 | Score at timepoint | 0.01 (-0.16 to 0.19) |
| | 14 | Score at timepoint | -0.05 (-2.00 to 0.11) |

*Abbreviations*

CI = confidence interval, MD = mean difference.

*Notes*

a = All results in this table are from the same trial (Drew 1999[93,94]). Included patients were those with self-reported tinnitus. All outcomes were ascertained using trial-designed questionnaires. Content and score ranges are reported for each outcome.

b = Ginkgo biloba vs. placebo. Note that this is the mean difference between matched pairs (i.e. a pair of patients were matched and one was randomly assigned to ginkgo biloba, while the other patient received placebo). Results not reported by treatment.

One trial found little to no difference between 12 weeks of treatment with either 120 mg ginkgo biloba or 600 mg pentoxifylline in tinnitus loudness measured on an 11-point box scale (MD 0.0 [95% CI -0.2 to 0.2]; 1 RCT; 197 patients) (***Table 56***).[130]

**Table 56: Continuous efficacy results comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus – tinnitus loudness**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Pentoxifylline Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **11-point box scale tinnitus loudness** | -0.4 (-0.7 to -0.2)[d] | -0.4 (-0.7 to -0.2)[e] | 0.9284 | 0.0 (-0.2 to 0.2) |

*Abbreviations*

CI = confidence interval, MD = mean difference

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

d = p = 0.0021 vs. baseline.

e = p = 0.0015 vs. baseline.

#### 6.2.4.4.3 Level of hearing loss

One trial reported no statistically significant difference between groups in the level of hearing loss after 12 weeks of treatment with 120 mg ginkgo biloba or placebo.[131] Hearing loss was assessed with tonal audiometric measurement. The trial authors did not report any data per treatment group; the only information available was the statement, 'In the tonal audiometric measurement of hearing loss, there was no difference between the two groups' (1 RCT; 73 patients; very low certainty evidence).

#### 6.2.4.4.4 Health-related quality of life

No HRQoL outcomes were identified for the condition of tinnitus.

#### 6.2.4.4.5 Functional status

One trial measured functional status treatment using the Sheehan Disability Scale after 12 weeks of treatment with either 120 mg ginkgo biloba or 600 mg pentoxifylline.[130] No statistically significant difference was found between the groups in the mean change in score from baseline (MD 0.0 [95% CI -0.2 to 0.2]; 1 RCT; 197 patients) (***Table 57***).

**Table 57: Continuous efficacy results comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus – functional status**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Pentoxifylline Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **SDS total score** | -0.6 (-0.9 to -0.3) | -0.6 (-0.9 to -0.3) | 0.9485 | 0.0 (-0.2 to 0.2) |

*Abbreviations*

CI = confidence interval, MD = mean difference, SDS = Sheehan Disability Scale.

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

#### 6.2.4.4.6 Mood

One trial used the Hospital Anxiety and Depression Scale (HADS) to measure mood after 12 weeks of either 120 mg ginkgo biloba or 600 mg pentoxifylline.[130] There was little to no difference between groups in the number of people with a HADS score indicating clinical anxiety (RR 0.91 [95% CI 0.54 to 1.51]; 1 RCT; 197 patients) (***Table 58***).

**Table 58: Categorical efficacy results comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus – behaviour/mood**

| Outcome[a] | Ginkgo biloba n/N (%) | Pentoxifylline n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Abnormal HADS anxiety (≥11)** | 22/95 (23)[c] | 23/90 (26)[d] | NR | 0.91 (0.54 to 1.51) |

*Abbreviations*

CI = confidence interval, HADS = hospital anxiety and depression scale, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Calculated by the authors of this report.

c = p = 0.005 vs. baseline.

d = p = 0.105 vs. baseline.

One trial used the HADS instrument to measure anxiety and depression after 12 weeks of treatment with either 120 mg ginkgo biloba or 600 mg pentoxifylline.[130] There was no statistically significant difference in mean change from baseline between the 2 groups in either anxiety (MD -0.2 [95% CI -0.6 to 0.2]; 1 RCT; 197 patients) or depression (MD 0.1 [95% CI -0.3 to 0.5]; 1 RCT; 197 patients) (***Table 59***).

**Table 59: Continuous efficacy results comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus – behaviour/mood**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Pentoxifylline Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|
| **HADS anxiety** | -1.3 (-1.8 to -0.9) | -1.1 (-1.6 to -0.6) | 0.2523 | -0.2 (-0.6 to 0.2) |
| **HADS depression** | -0.4 (-0.9 to 0.2) | -0.5 (-0.9 to 0.0) | 0.5753 | 0.1 (-0.3 to 0.5) |

*Abbreviations*

CI = confidence interval, HADS = Hospital Anxiety and Depression Scale, MD = mean difference.

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

### 6.2.5 Findings: Safety

The findings for the safety outcomes for each of the 4 conditions of interest are reported in subsequent sections: MPD (***Section 6.2.5.1***), PAOD (***Section 6.2.5.2***), vertigo (***Section 6.2.5.3***), and tinnitus (***Section 6.2.5.4***).

#### **6.2.5.1** Mental performance deficits

Because of the abundance of data regarding the safety of ginkgo biloba in MPD, the following results are available in ***Appendix F***:

- Studies in which some patients changed treatment assignments during the course of the trial (e.g. patients received placebo for the first half of the trial and ginkgo biloba for the second half of the trial); these trials cannot be synthesised with other studies.
- Doses of ginkgo biloba not currently approved in Switzerland (i.e. 150 mg or 160 mg).[m]

[m] Please note that studies on these dosages of ginkgo biloba are reported in the main body of the report for the other 3 conditions due to the relative sparsity of data for those conditions.

#### 6.2.5.1.1 Adverse events

Most trials reported on the proportion of patients who experience ≥1 AE. Overall, although AEs were relatively common, which is expected given the elderly population, there was no evidence to suggest that patients with MPD receiving ginkgo biloba were at elevated risk of experiencing an AE compared to placebo. In a meta-analysis of 4 RCTs comparing 120 mg ginkgo biloba to placebo, there was no statistically significant difference in the proportion of patients experiencing an AE over 24 weeks of treatment (RR 0.91 [95% CI 0.69 to 1.19]; 4 RCTs; 885 patients; low certainty evidence) (***Figure 36***). There was moderate heterogeneity across the 4 studies. In a sensitivity analysis excluding NCT00446485, which had a small sample size and reported a statistically significantly higher rate of AEs among patients treated with placebo, there was minimal heterogeneity (RR 1.04 [95% CI 0.92 to 1.18]; 3 RCTs; 846 patients) (***Figure 37***).[81]

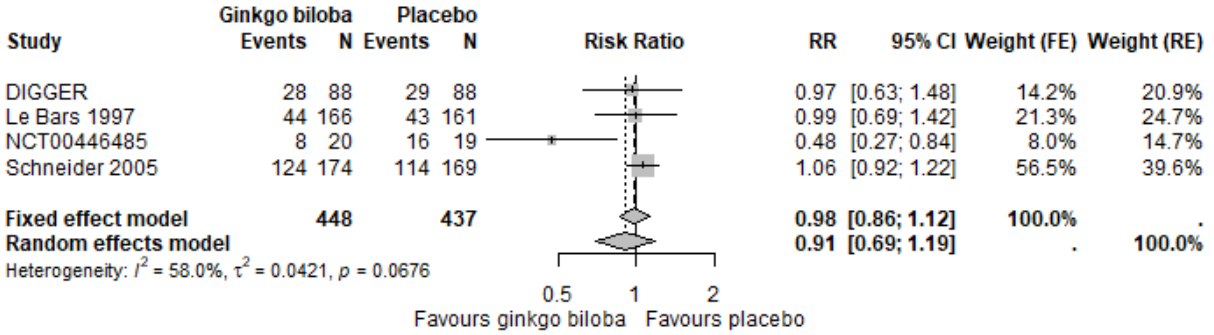


**Figure 36: At least one AE in patients with MPD: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, MPD = mental performance deficits, RE = random effects, RR = relative risk.

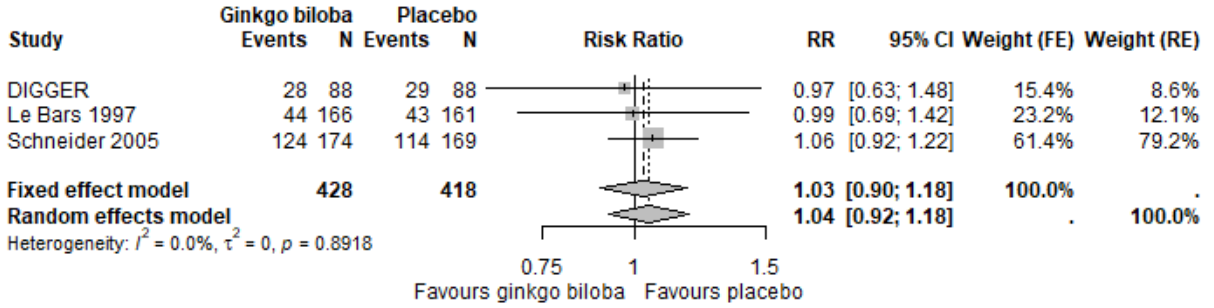


**Figure 37: At least one AE in patients with MPD: 120 mg ginkgo biloba vs. placebo at 24 weeks sensitivity analysis**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, MPD = mental performance deficits, RE = random effects, RR = relative risk.

Based on a meta-analysis of 5 RCTs conducted in patients with MCI, AD dementia, or vascular dementia, there was no statistically significant difference between 240 mg ginkgo biloba or placebo in the occurrence of AEs over 24 weeks (RR 0.97 [95% CI 0.90 to 1.05]; 5 RCTs; 1'716 patients; moderate certainty evidence) (***Figure 38***). There was low to moderate heterogeneity across studies, which appeared to be primarily driven by Gavrilova 2014, which reported numerically fewer AEs in the ginkgo biloba treatment group.[103,104]

Two of these trials also reported AE results for subgroups with AD dementia or vascular dementia (***Figure 39***). In the subgroup of patients with AD dementia, patients receiving 240 mg ginkgo biloba were statistically significantly less likely to experience ≥1 AE over 24 weeks than those treated with placebo (RR 0.89 [95% CI 0.81 to 0.99]; 2 RCTs; 547 patients). There was no evidence of statistical heterogeneity across studies. In contrast, there was substantial heterogeneity in the subgroup meta-analysis of vascular dementia, which showed no statistically significant effect of ginkgo biloba (RR 1.10 [95% CI 0.82 to 1.49]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2 = 1.67$, p = 0.1957).

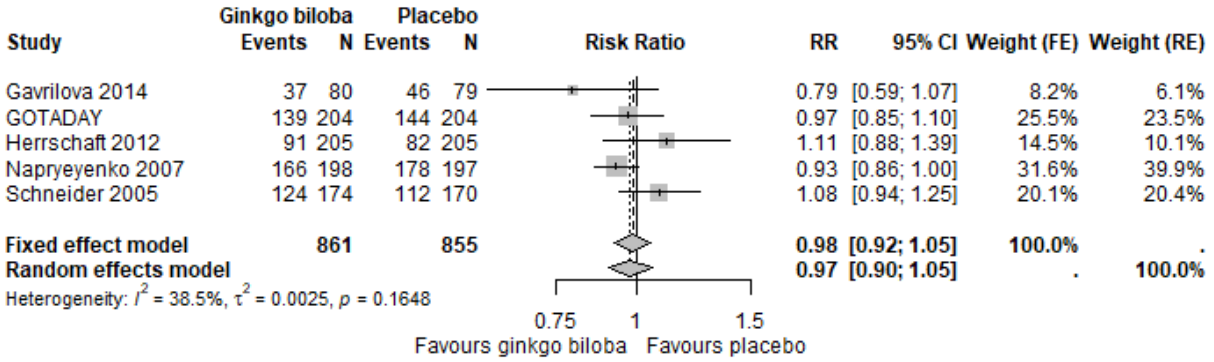


**Figure 38: At least one AE in patients with MPD: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, MPD = mental performance deficits, RE = random effects, RR = relative risk.

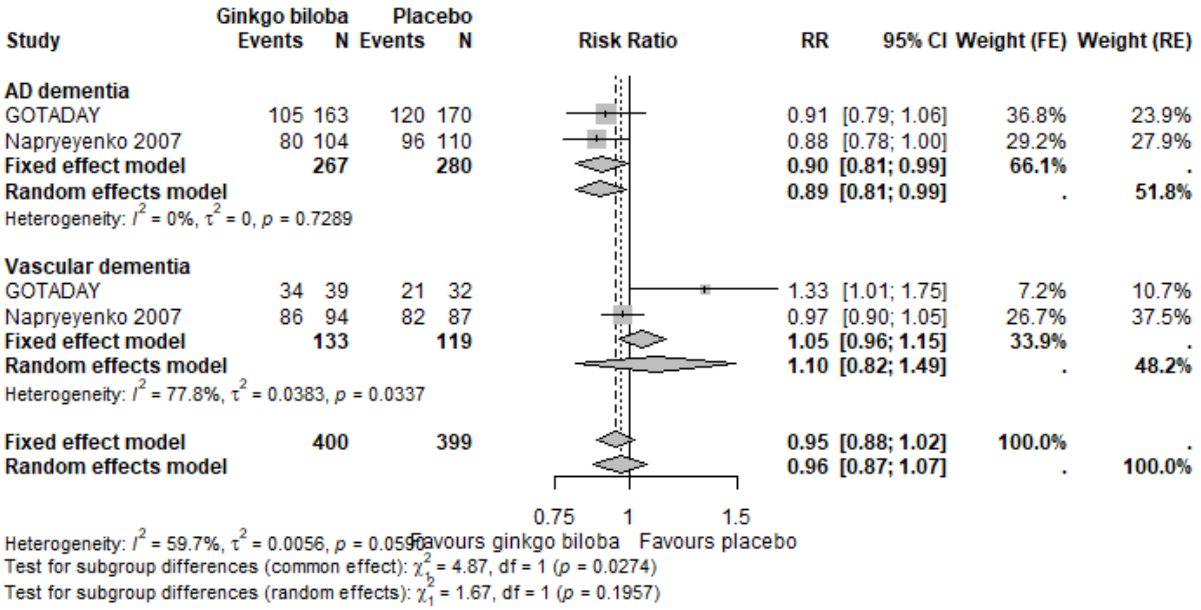


**Figure 39: At least one AE in patients with MPD: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, MPD = mental performance deficits, RE = random effects, RR = relative risk.

Similar to the results of the meta-analyses reported above, none of the other trials reporting the proportion of patients experiencing ≥1 AE or ≥1 AE potentially related to treatment found any statistically significant difference between 120 mg ginkgo biloba and placebo at any timepoint (***Table 60***).

**Table 60: At least one AE comparing 120 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 AE potentially related to treatment** | 26 | Schneider 2005[116,117b] | 26/169 (15) | 33/174 (19) | NR | 0.81 (0.51 to 1.30) |
| **≥1 AE during follow-up** | 52 | Le Bars 1997[98-101c] | 49/166 (30) | 50/161 (31) | NR | 0.95 (0.68 to 1.32) |
| **≥1 AE possibly related to treatment** | 52 | Le Bars 1997[98-101c] | 27/166 (16) | 19/161 (12) | NR | 1.38 (0.80 to 2.38) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, AR = adverse reaction, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 240 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

c = Included patients were outpatients with AD or MID, without other significant medical conditions.

Results from other timepoints were consistent with those that could be meta-analysed. Comparing 240 mg ginkgo biloba and placebo, there was no evidence of a statistically significant difference in the proportion of patients experiencing ≥1 AE after either 8[88] or 12[110] weeks of treatment (***Table 61***).

**Table 61: At least one AE comparing 240 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 AE during follow-up** | 8 | DRKS 00000423[88b] | 19/31 (59.4) | 12/30 (40) | NR | 1.53 (0.91 to 2.58) |
| | 12 | Grass-Kapanke 2011[110c] | 23/149 (15.4) | 23/147 (15.6) | NR | 0.99 (0.58 to 1.68) |
| **≥1 AE potentially related to treatment** | 26 | Schneider 2005[116,117][d] | 32/170 (19) | 33/174 (19) | NR | 0.99 (0.64 to 1.54) |

*Abbreviations*

AD = Alzheimer's disease, ADL = activities of daily living, AE = adverse event, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NR = not reported, PRMQ = Prospective and Retrospective Memory Questionnaire, RR = relative risk, SAE = serious adverse event, TT = Termine

Test, WMS III = Wechsler Memory Scale III, WTS-ALS = Vienna Test System—Work Performance Series, WTS-DT = Vienna Test System—Determination Test.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with subjective memory impairment, defined as ≥1 item answered with 'rather often' or 'very often', or at least 5 questions answered 'sometimes' in the PRMQ.

c = Included patients were those with very MCI, as defined by the diagnostic criteria: a) subjective complaints of impairment, perceived as a decline from former level of functioning in at least one of the following: memory, attention/concentration, speed of functioning, efforts required to complete complex tasks, general performance/efficiency; b) low functioning (≥1 standard deviation worse than the mean of the most appropriate normative group) in at least one of the cognitive tests administered at screening and baseline (WMS III Faces I + II, WTS-ALS (S1), WTS-DT (S16), TT; c) perceived impairment present for at least 3 months; d) widely preserved general cognitive function, as evidenced by a total score above 23 in the MMSE; e) intact ADL, as evidenced by inquiry (subtle difficulties, in particular slowing or increased efforts, in complex tasks is acceptable); f) no indication of dementia.

d = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 120 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

One trial found that although the majority of patients receiving either 120 or 240 mg ginkgo biloba experienced ≥1 AE during the 26 weeks of the study, there was no statistically significant difference between the 2 groups (RR 1.02 [95% CI 0.88 to 1.19]; 1 RCT; 339 patients) (***Table 62***). Similarly, there was no statistically significant difference in the proportion of patients who experienced ≥1 AE potentially related to treatment (RR 0.82 [95% CI 0.51 to 1.31]; 1 RCT; 339 patients).

**Table 62: At least one AE comparing 120 mg vs. 240 mg ginkgo biloba in patients with MPD**

| Outcome[a] | Ginkgo biloba 120 mg n/N (%) | Ginkgo biloba 240 mg n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | 114/169 (68) | 112/170 (66) | NR | 1.02 (0.88 to 1.19) |
| **≥1 AE potentially related to treatment** | 26/169 (15) | 32/170 (19) | NR | 0.82 (0.51 to 1.31) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with placebo; other dose comparisons are reported in relevant sections.

b = Calculated by the authors of this report.

One trial compared 240 mg ginkgo biloba alone, 10 mg donepezil alone, or a combination of 240 mg ginkgo biloba and 10 mg donepezil in patients with probable AD.[119] Comparing the combination treatment arm and the donepezil alone treatment arm (i.e. the additive effect of 240 mg ginkgo biloba), there was no statistically significant difference in the proportion of patients with ≥1 AE over 22 weeks (RR 0.77 [95% CI 0.54 to 1.11] 1 RCT; 63 patients; very low certainty evidence) (***Table 63***). However, patients receiving donepezil alone were approximately twice as likely to experience an AE compared to those receiving ginkgo biloba alone (RR 0.44 [95% CI 0.26 to 0.77] 1 RCT; 62 patients; very low certainty evidence).

**Table 63: At least one AE comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD**

| Outcome[a] | Ginkgo biloba + donepezil n/N (%) | Donepezil alone n/N (%) | Ginkgo biloba alone n/N (%) | p-value | Effect RR (95% CI)[b] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **≥1 AE during follow-up** | 18/31 (56) | 24/32 (73) | 10/30 (32) | NR | 0.77 (0.54 to 1.11) | 0.44 (0.26 to 0.77) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MPD = mental performance deficits, MRI = magnetic resonance imaging, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Calculated by the authors of this report.

#### 6.2.5.1.2 Serious adverse events

Among patients with AD dementia or vascular dementia treated with 240 mg ginkgo biloba or placebo for 24 weeks, there was no statistically significant difference in the occurrence of SAEs (RR 0.98 [95% CI 0.53 to 1.83]; 3 RCTs; 1'143 patients; moderate certainty evidence) (***Figure 40***). In addition to the 3 RCTs included in the meta-analysis, Gavrilova 2014 reported that among patients with MCI treated for 24 weeks, 0/80 patients treated with 240 mg ginkgo biloba and 0/79 patients treated with placebo experienced SAEs.[103,104] Because there were no events in either treatment group, this study was not included from the meta-analysis.

Two RCTs reported subgroup data for patients with AD dementia or vascular dementia (***Figure 41***). There was no statistically significant difference between 240 mg ginkgo biloba and placebo for either patients with AD dementia (RR 0.63 [95% CI 0.15 to 1.66]; 2 RCTs; 547 patients) or patients with vascular dementia (RR 0.68 [95% CI 0.24 to 1.913]; 2 RCTs; 252 patients). There was no statistically significant difference between subgroups ($\chi^2 = 0.01$, p = 0.9370).

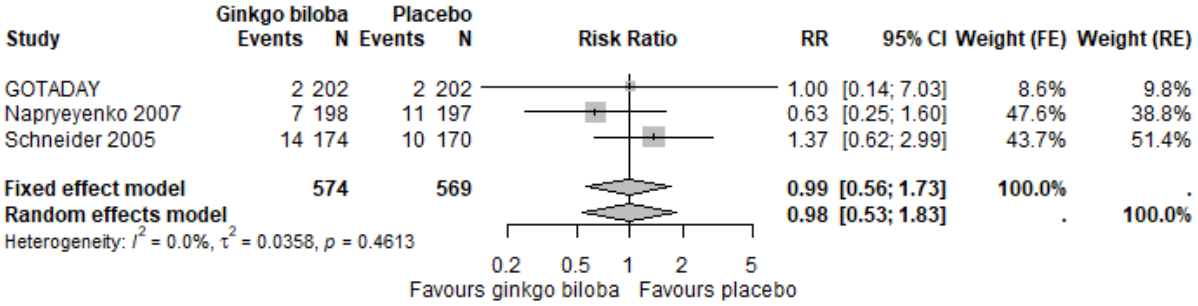


**Figure 40: At least one SAE in patients with MPD: 240 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

CI = confidence interval, FE = fixed effect, MPD = mental performance deficits, RE = random effects, RR = relative risk, SAE = serious adverse event.

*Notes*

Gavrilova 2014[103,104] reported that after 24 weeks, 0/80 patients treated with 240 mg ginkgo biloba and 0/79 patients treated with placebo experienced SAEs. This trial was therefore excluded from the meta-analysis.

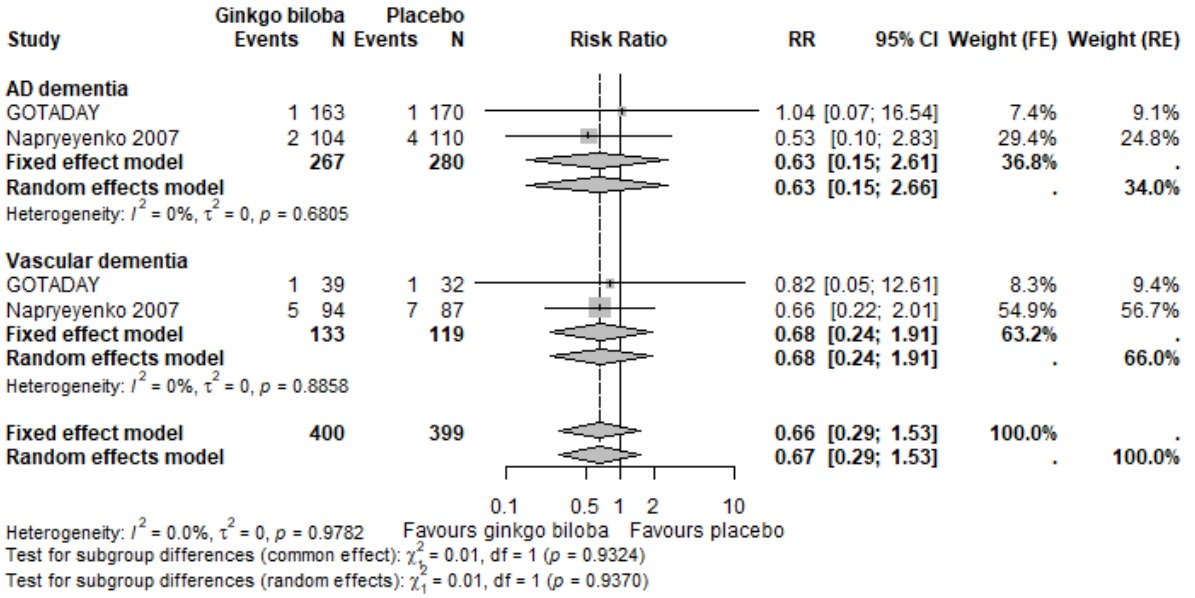


**Figure 41: At least one SAE in patients with MPD: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, MPD = mental performance deficits, RE = random effects, RR = relative risk, SAE = serious adverse event.

Similar to the meta-analyses displayed above, across additional results for all doses of ginkgo biloba, comparators, and timepoints, the percentage of patients experiencing ≥1 SAE was consistently low (***Table 64***, ***Table 65***, ***Table 66***, and ***Table 67***). Frequently, the relative difference between treatment groups could not be calculated because zero events occurred in one or both treatment arms. When a relative effect could be calculated, there were no statistically significant differences identified.

**Table 64: At least one SAE comparing 120 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 SAE during follow-up** | 26 | Schneider 2005[116,117b] | 13/169 (8) | 14/174 (8) | NR | 0.96 (0.46 to 1.97) |
| **≥1 SAE during follow-up (excluding definitely unrelated)** | 26 | Schneider 2005[116,117b] | 1/169 (1) | 0/174 (0) | NR | NE |

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 SAE during follow-up** | 52 | Le Bars 1997[98-101c] | 3/166 (1.8) | 2/161 (1.2) | NR | 1.45 (0.25 to 8.59) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NE = not estimable, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 240 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

c = Included patients were outpatients with AD or MID, without other significant medical conditions.

**Table 65: At least one SAE comparing 240 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 SAE during follow-up** | 12 | Grass-Kapanke 2011[110b] | 0/149 (0) | 0/147 (0) | NR | NE |
| **≥1 SAE during follow-up (excluding definitely unrelated)** | 26 | Schneider 2005[116,117d] | 3/170 (2) | 0/174 (0) | NR | NE |

*Abbreviations*

AD = Alzheimer's disease, ADL = activities of daily living, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NE = not estimable, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NR = not reported, PRMQ = Prospective and Retrospective Memory Questionnaire, RR = relative risk, SAE = serious adverse event, TT = Termine

Test, WMS III = Wechsler Memory Scale III, WTS-ALS = Vienna Test System—Work Performance Series, WTS-DT = Vienna Test System—Determination Test.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with very MCI, as defined by the diagnostic criteria: a) subjective complaints of impairment, perceived as a decline from former level of functioning in at least one of the following: memory, attention/concentration, speed of functioning, efforts required to complete complex tasks, general performance/efficiency; b) low functioning (≥1 standard deviation worse than the mean of the most appropriate normative group) in at least one of the cognitive tests administered at screening and baseline (WMS III Faces I + II, WTS-ALS (S1), WTS-DT (S16), TT; c) perceived impairment present for at least 3 months; d) widely preserved general cognitive function, as evidenced by a total score above 23 in the MMSE; e) intact ADL, as evidenced by inquiry (subtle difficulties, in particular slowing or increased efforts, in complex tasks is acceptable); f) no indication of dementia.

c = Included patients were those diagnosed with amnestic MCI in accordance with international consensus criteria.

d = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 120 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

**Table 66: At least one SAE comparing 120 mg vs. 240 mg ginkgo biloba in patients with MPD**

| Outcome[a] | Ginkgo biloba 120 mg n/N (%) | Ginkgo biloba 240 mg n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 SAE during follow-up** | 13/169 (8) | 10/170 (6) | NR | 1.31 (0.59 to 2.90) |
| **≥1 SAE during follow-up (excluding definitely unrelated)** | 1/169 (1) | 3/170 (2) | NR | 0.34 (0.04 to 3.19) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with placebo; other dose comparisons are reported in relevant sections.

b = Calculated by the authors of this report.

**Table 67: At least one SAE comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD**

| Out-come[a] | Ginkgo biloba + donepezil n/N (%) | Donepezil alone n/N (%) | Ginkgo biloba alone n/N (%) | p-value | Effect RR (95% CI)[b] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **≥1 SAE during follow-up** | 0/31 (0) | 0/32 (0) | 1/30 (3.3) | NR | NE | NE |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MPD = mental performance deficits, MRI = magnetic resonance imaging, NE = not estimable, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Calculated by the authors of this report.

#### 6.2.5.1.3 Bleeding adverse events

Only one trial reported on the overall occurrence of bleeding AEs in patients with MPD.[116,117] Comparing patients with AD or probable AD who received 120 mg ginkgo biloba, 240 mg ginkgo biloba, or placebo over 26 weeks, no statistically significant differences were identified between any of the 3 treatment arms (p = 0.61) (***Table 68***). Please note that one additional trial reported on specific AEs that included bleeding-related events (reported in ***Section 6.2.5.1.4***).

**Table 68: Bleeding AEs comparing 120 mg ginkgo biloba, 240 mg ginkgo biloba, and placebo in patients with MPD**

| Out-come[a] | Ginkgo biloba 120 mg n/N (%) | Ginkgo biloba 240 mg n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] | | |
|---|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba 120 mg vs. placebo | Ginkgo biloba 240 mg vs. placebo | Ginkgo biloba 120 mg vs. 240 mg |
| **Any bleeding AE** | 8/169 (4.7) | 12/170 (7.1) | 10/174 (5.7) | 0.61 | 0.82 (0.33 to 2.04) | 1.23 (0.55 to 2.77) | 0.67 (0.28 to 1.60) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20.

b = Calculated by the authors of this report.

#### 6.2.5.1.4 Other specific adverse events

Two RCTs reported on the occurrence of various specific AEs in patients treated with either 120 mg ginkgo biloba or placebo (***Table 69***).[81,116,117] AEs were generally rare, although placebo-treated patients in one trial had relatively high rates of nausea (21%), vertigo (16%), and vomiting (16%);[81] p-values were not reported in either trial; after calculating effect estimates, the authors of this review did not identify any statistically significant differences between treatment groups.

**Table 69: Other AEs comparing 120 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Abdominal pain** | 26 | NCT00446485[81b] | 0/20 (0) | 0/19 (0) | NR | NE |
| **Agitation/agitation aggravated** | 26 | Schneider 2005[116,117c] | 10/169 (5.9) | 8/174 (4.6) | NR | 1.29 (0.52 to 3.18) |
| **Arterial hypertension** | 26 | NCT00446485[81b] | 1/20 (5) | 0/19 (0) | NR | NE |
| **Concentration impairment** | 26 | NCT00446485[81b] | 0/20 (0) | 1/19 (5.3) | NR | NE |
| **Dizziness** | 26 | Schneider 2005[116,117c] | 17/169 (10.1) | 12/174 (6.9) | NR | 1.46 (0.72 to 2.96) |
| **Feeling generally unwell** | 26 | NCT00446485[81b] | 0/20 (0) | 1/19 (5.3) | NR | NE |
| **Headache** | 26 | NCT00446485[81b] | 2/20 (10) | 0/19 (0) | NR | NE |

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| | | Schneider 2005[116,117c] | 4/169 (2.4) | 9/174 (5.2) | NR | 0.46 (0.14 to 1.46) |
| **Insomnia** | 26 | NCT00446485[81b] | 0/20 (0) | 1/19 (5.3) | NR | NE |
| **Nausea** | 26 | NCT00446485[81b] | 0/20 (0) | 4/19 (21.1) | NR | NE |
| **Nausea/vomiting** | 26 | Schneider 2005[116,117c] | 5/169 (3) | 8/174 (4.6) | NR | 0.64 (0.21 to 1.93) |
| **Rash** | 26 | NCT00446485[81b] | 1/20 (5) | 2/19 (10.5) | NR | 0.48 (0.05 to 4.82) |
| **Retching** | 26 | NCT00446485[81b] | 0/20 (0) | 0/19 (0) | NR | NE |
| **Tachycardia** | 26 | NCT00446485[81b] | 0/20 (0) | 1/19 (5.3) | NR | NE |
| **Tinnitus** | 26 | NCT00446485[81b] | 1/20 (5) | 0/19 (0) | NR | NE |
| **Tinnitus/tinnitus aggravated** | 26 | Schneider 2005[116,117c] | 5/169 (3) | 12/174 (6.9) | NR | 0.43 (0.15 to 1.19) |
| **Upper respiratory tract infection** | 26 | Schneider 2005[116,117c] | 19/169 (11.2) | 18/174 (10.3) | NR | 1.09 (0.59 to 2.00) |
| **Varicose veins on legs** | 26 | NCT00446485[81b] | 2/20 (10) | 0/19 (0) | NR | NE |
| **Vertigo** | 26 | NCT00446485[81b] | 1/20 (5) | 3/19 (15.8) | NR | 0.32 (0.04 to 2.79) |
| **Vomiting** | 26 | NCT00446485[81b] | 0/20 (0) | 3/19 (15.8) | NR | NE |
| **Weight loss** | 26 | Schneider 2005[116,117c] | 4/169 (2.4) | 10/174 (5.7) | NR | 0.41 (0.13 to 1.29) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, AR = adverse reaction, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NE = not estimable, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with vascular cognitive impairment based on cerebrovascular insufficiency and a Folstein MMSE score of >20 and ≤28.

c = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 240 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

Four RCTs reported on the occurrence of various specific AEs in patients treated with either 240 mg ginkgo biloba or placebo (***Table 70***). All specific AEs occurred in fewer than 15% of patients except for headache, which was reported in 21% of patients treated with 240 mg ginkgo biloba and 19% of patients treated with placebo[105-109]; p-values were not reported in any of the trials, although Herrschaft 2012 reported the risk difference and 95% CI between treatment groups.[106,111,112] The only statistically significant differences identified by either the original study authors or the authors of this review were in the occurrence of other symptoms for which ginkgo biloba is approved in Switzerland. In Herrschaft 2012, patients in the ginkgo biloba group were statistically significantly less likely to experience dizziness than placebo patients.[106,111,112] Similarly, in the GOTADAY study, patients receiving ginkgo biloba were statistically significantly less likely to experience tinnitus.[105-109]

**Table 70: Other AEs comparing 240 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Agitation/agitation aggravated** | 26 | Schneider 2005[116,117b] | 5/170 (2.9) | 8/174 (4.6) | NR | 0.64 (0.21 to 1.92) |
| **Angina pectoris** | 24 | GOTADAY[105-109c] | 6/206 (2.9) | 12/204 (5.9) | NR | 0.50 (0.19 to 1.29) |
| **Blood pressure increased, hypertension** | 24 | GOTADAY[105-109c] | 22/206 (10.7) | 21/204 (10.3) | NR | 1.04 (0.59 to 1.83) |
| **Diarrhoea** | 24 | GOTADAY[105-109c] | 9/206 (4.4) | 13/204 (6.4) | NR | 0.69 (0.30 to 1.57) |
| **Dizziness** | 24 | GOTADAY[105-109c] | 19/206 (9.2) | 23/204 (11.3) | NR | 0.82 (0.46 to 1.46) |

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| | 24 | Herrschaft 2012[106,111,112d] | 4/205 (2) | 15/205 (7.3) | NR | 0.27 (0.09 to 0.79)<br>-5.4 (-9.9 to -1.3)[f] |
| | 26 | Schneider 2005[116,117b] | 11/170 (6.5) | 12/174 (6.9) | NR | 0.94 (0.43 to 2.07) |
| **Dyspepsia/epigastric discomfort** | 24 | Gavrilova 2014[103,104e] | 4/80 (5) | 1/79 (1.3) | NR | 3.95 (0.45 to 34.6) |
| **Headache** | 24 | Gavrilova 2014[103,104e] | 6/80 (7.5) | 9/79 (11.4) | NR | 0.66 (0.25 to 1.76) |
| | 24 | GOTA-DAY[105-109c] | 43/206 (20.9) | 38/204 (18.6) | NR | 1.12 (0.76 to 1.66) |
| | 24 | Herrschaft 2012[106,111,112d] | 15/205 (7.3) | 17/205 (8.3) | NR | 0.88 (0.45 to 1.72)<br>-1.0 (-6.4 to 4.4)[f] |
| | 26 | Schneider 2005[116,117b] | 7/170 (4.1) | 9/174 (5.2) | NR | 0.80 (0.30 to 2.09) |
| **Hypertension** | 24 | Herrschaft 2012[106,111,112d] | 5/205 (2.4) | 8/205 (3.9) | NR | 0.63 (0.21 to 1.88)<br>-1.5 (-5.3 to 2.2)[f] |
| **Increased blood pressure** | 24 | Gavrilova 2014[103,104e] | 6/80 (7.5) | 7/79 (8.9) | NR | 0.85 (0.30 to 2.41) |
| **Nausea/vomiting** | 26 | Schneider 2005[116,117b] | 11/170 (6.5) | 8/174 (4.6) | NR | 1.41 (0.58 to 3.41) |
| **Respiratory tract infection** | 24 | GOTA-DAY[105-109c] | 27/206 (13.1) | 20/204 (9.8) | NR | 1.34 (0.78 to 2.31) |

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| | 24 | Gavrilova 2014[103,104e] | 7/80 (8.8) | 3/79 (3.8) | NR | 2.30 (0.62 to 8.59) |
| **Somnolence** | 24 | Herrschaft 2012[106,111,112d] | 8/205 (3.9) | 4/205 (2) | NR | 2.00 (0.61 to 6.54)<br>2.0 (-1.6 to 5.8)[f] |
| **Tinnitus** | 24 | GOTA-DAY[105-109c] | 2/206 (1) | 15/204 (7.4) | NR | 0.13 (0.03 to 0.57) |
| **Tinnitus/tinnitus aggravated** | 26 | Schneider 2005[116,117b] | 7/170 (4.1) | 12/174 (6.9) | NR | 0.60 (0.24 to 1.48) |
| **Upper abdominal pain** | 24 | Herrschaft 2012[106,111,112d] | 5/205 (2.4) | 7/205 (3.4) | NR | 0.71 (0.23 to 2.21)<br>-1.0 (-4.7 to 2.6)[f] |
| **Upper respiratory tract infection** | 26 | Schneider 2005[116,117b] | 11/170 (6.5) | 18/174 (10.3) | NR | 0.63 (0.30 to 1.28) |
| **Viral respiratory tract infection** | 24 | Herrschaft 2012[106,111,112d] | 8/205 (3.9) | 6/205 (2.9) | NR | 1.33 (0.47 to 3.77)<br>1.0 (-2.9 to 4.9)[f] |
| **Weight loss** | 26 | Schneider 2005[116,117b] | 8/170 (4.7) | 10/174 (5.7) | NR | 0.82 (0.33 to 2.02) |

*Abbreviations*

AD = Alzheimer's disease, ADL = activities of daily living, AE = adverse event, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NR = not reported, PRMQ = Prospective and Retrospective Memory Questionnaire, RR = relative risk, SAE = serious adverse event, TT = Termine Test, WMS III = Wechsler Memory Scale III, WTS-ALS = Vienna Test System—Work Performance Series, WTS-DT = Vienna Test System—Determination Test.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 120 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

c = Included patients were those with (a) probable AD in accordance with the NINCDS-ADRDA criteria, (b) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (c) probable vascular dementia according to NINDS-AIREN.

d = Included patients were those with (a) probable AD in accordance with the NINCDS-ADRDA criteria, (b) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (c) probable vascular dementia according to NINDS-AIREN. Dementia symptoms were present for ≥6 months.

e = Included patients were those diagnosed with amnestic MCI in accordance with international consensus criteria.

f = Absolute difference in percentage of patients with AE and 95% CI. Reported by original study authors.

The GuidAge trial reported the risk of specific AEs in 2'820 patients who had consulted a physician for memory problems and were randomised to receive either 240 mg ginkgo biloba or placebo for 5 years (***Table 71***).[80,85,86] There was no statistically significant difference in any of the specific AEs over the course of the trial, including haemorrhagic events.

**Table 71: Long-term safety results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome[a] | p-value | Effect<br>HR (95% CI)[b] |
|---|---|---|
| **Angina pectoris** | 0.99 | 1.00 (0.59 to 1.71) |
| **Cardiac disorders** | 0.93 | 0.99 (0.82 to 1.20) |
| **Cardiac failure** | 0.76 | 0.93 (0.58 to 1.48) |
| **Death** | 0.68 | 0.94 (0.69 to 1.28) |
| **Gastrointestinal** | 0.81 | 0.93 (0.54 to 1.62) |
| **Haemorrhagic events, overall** | 0.55 | 0.93 (0.73 to 1.18) |
| **Haemorrhagic stroke** | 0.46 | 1.72 (0.41 to 7.22) |
| **Ischaemic (TIA and ischaemic stroke)** | 0.90 | 1.03 (0.64 to 1.65) |
| **Myocardial infarction** | 0.43 | 0.74 (0.36 to 1.55) |
| **Nervous system (including haemorrhagic stroke)** | 0.27 | 1.85 (0.62 to 5.56) |
| **Stroke, other** | 0.59 | 1.19 (0.64 to 2.19) |
| **Stroke, overall** | 0.57 | 1.12 (0.77 to 1.63) |
| **Vascular** | 0.19 | 0.70 (0.42 to 1.18) |

*Abbreviations*

CI = confidence interval, HR = hazard ratio, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, TIA = transient ischaemic attack.

*Notes*

a = All results in this table are from the same trial (GuidAge[80,85,86]) and at the same timepoint (5 years). Included patients were those who had consulted a healthcare professional regarding memory problems and had an MMSE score >25, a Covi anxiety score <6, and a geriatric depression scale score <15.

b = Reported by original study authors.

After 26 weeks of treatment with either 120 or 240 mg ginkgo biloba, there was no evidence of a statistically significant difference in the occurrence of specific AEs among patients with AD or probable AD (***Table 72***).

**Table 72: Other AEs comparing 120 mg vs. 240 mg ginkgo biloba in patients with MPD**

| Outcome[a] | Ginkgo biloba 120 mg n/N (%) | Ginkgo biloba 240 mg n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Agitation/agitation aggravated** | 10/169 (5.9) | 5/170 (2.9) | NR | 2.01 (0.70 to 5.76) |
| **Dizziness** | 17/169 (10.1) | 11/170 (6.5) | NR | 1.55 (0.75 to 3.22) |
| **Headache** | 4/169 (2.4) | 7/170 (4.1) | NR | 0.57 (0.17 to 1.93) |
| **Nausea/vomiting** | 5/169 (3) | 11/170 (6.5) | NR | 0.46 (0.16 to 1.29) |
| **Tinnitus/tinnitus aggravated** | 5/169 (3) | 7/170 (4.1) | NR | 0.72 (0.23 to 2.22) |
| **Upper respiratory tract infection** | 19/169 (11.2) | 11/170 (6.5) | NR | 1.74 (0.85 to 3.54) |
| **Weight loss** | 4/169 (2.4) | 8/170 (4.7) | NR | 0.50 (0.15 to 1.64) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MMSE = Mini-Mental State Examination, MPD = mental performance deficits, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = All results in this table are from the same trial (Schneider 2005[116,117]) and at the same timepoint (26 weeks). Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with placebo; other dose comparisons are reported in relevant sections.

b = Calculated by the authors of this report.

After 22 weeks of treatment with 240 mg ginkgo biloba, 10 mg donepezil, or a combination of the 2, there were no statistically significant differences in any of the reported specific AEs across

treatment groups (***Table 73***). However, there were a relatively small number of patients in each treatment group, leading to a higher level of imprecision around the effect estimates.

**Table 73: Other AEs comparing 240 mg ginkgo biloba with or without 10 mg donepezil vs. 10 mg donepezil alone in patients with MPD**

| Out-come[a] | Ginkgo biloba + donepezil n/N (%) | Donepezil alone n/N (%) | Ginkgo bi-loba alone n/N (%) | p-valu e | Effect RR (95% CI)[b] | |
|---|---|---|---|---|---|---|
| | | | | | Ginkgo biloba + donepezil vs. donepezil alone | Ginkgo biloba alone vs. donepezil alone |
| **Diar-rhoea** | 0/31 (0) | 5/32 (15.6) | 1/30 (3.3) | NR | NE | 0.21 (0.03 to 1.72) |
| **Fatigue** | 2/31 (6.5) | 3/32 (9.4) | 1/30 (3.3) | NR | 0.69 (0.12 to 3.84) | 0.36 (0.04 to 3.23) |
| **Head-ache** | 3/31 (9.7) | 6/32 (18.8) | 2/30 (6.7) | NR | 0.52 (0.14 to 1.88) | 0.36 (0.08 to 1.63) |
| **Insomnia** | 2/31 (6.5) | 4/32 (12.5) | 4/30 (13.3) | NR | 0.52 (0.10 to 2.62) | 1.07 (0.29 to 3.89) |

*Abbreviations*

AD = Alzheimer's disease, AE = adverse event, CI = confidence interval, CT = computed tomography, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MPD = mental performance deficits, MRI = magnetic resonance imaging, NE = not estimable, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, RR = relative risk, SAE = serious adverse event, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression.

*Notes*

a = All results in this table are from the same trial (Yancheva 2009[119]) and at the same timepoint (22 weeks). Included patients were those with probable AD (according to the DSM-IV and the NINCDS-ADRDA criteria) of mild to moderate severity, defined as a score <36 on the cognitive part of the TE4D, between 9 and 23 on the SKT test battery, and <6 on the Clock-Drawing Test. A CT or MRI scan no more than one year old had to be consistent with the diagnosis of probable AD.

b = Calculated by the authors of this report.

### **6.2.5.2** Peripheral arterial occlusive disease

#### 6.2.5.2.1 Adverse events

Three trials reported the number of participants experiencing ≥1 AEs after 24 weeks of treatment with either 120 mg ginkgo biloba or placebo for PAOD.[120-125,128] Overall, there were 3 events in each group and no statistically significant difference between the groups (RR 0.80 [95% CI 0.16 to 3.98]; 3 RCTs; 248 patients; very low certainty evidence) (***Figure 42***).

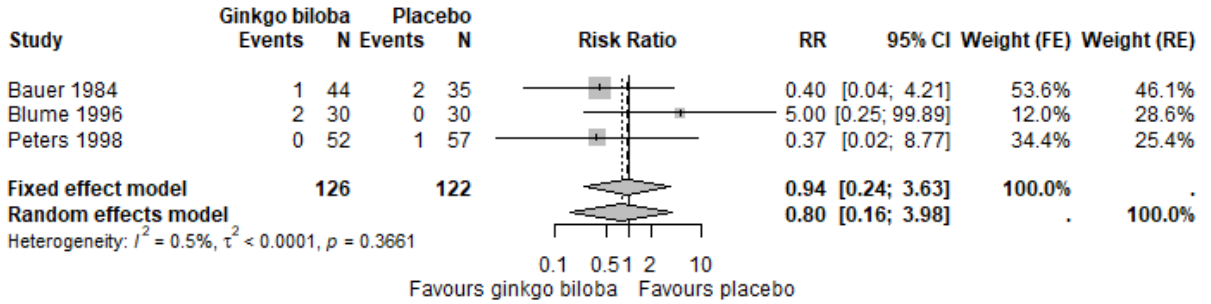


**Figure 42: At least one AE in patients with PAOD: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, RE = random effects, RR = relative risk.

In 2 trials investigating 160 mg ginkgo vs. placebo for PAOD, there were no AEs in either arm after 24 weeks of treatment (2 RCTs; 73 patients; very low certainty evidence) (***Table 74***).[126,127]

**Table 74: At least one AE comparing 160 mg ginkgo biloba vs. placebo in patients with PAOD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 AE during follow-up** | 24 | Bulling 1991[127b] | 0/17 (0) | 0/16 (0) | NR | NE |
| | 24 | Blume 1998[126c] | 0/21 (0) | 0/19 (0) | NR | NE |

*Abbreviations*

AE = adverse event, CI = confidence interval, NE = not estimable, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with Fontaine's stage IIb PAOD. Patients had a PFWD between 50 and 200 meters.

c = Included patients were those with angiographically or Doppler sonography confirmed Fontaine's stage IIb PAOD.

In the trial investigating 24 weeks of treatment with 120 mg vs. 240 mg ginkgo biloba for PAOD, there were no AEs in the placebo group compared to one person with ≥1 AE in the 120 mg ginkgo biloba group (***Table 75***).[129]

**Table 75: At least one AE comparing 120 mg vs. 240 mg ginkgo biloba in patients with PAOD**

| Outcome[a] | Ginkgo biloba 120 mg n/N (%) | Ginkgo biloba 240 mg n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | 1/38 (2.6) | 0/36 (0) | NR | NE |

*Abbreviations*

AE = adverse event, CI = confidence interval, NE = not estimable, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Schweizer 1999[129]) and at the same timepoint (24 weeks). Included patients were those with Fontaine's stage IIb PAOD with occlusion of the superficial femoral artery on one leg and without occlusion of the deep femoral artery. Patients had a PFWD <200 meters and maximum walking distance between 100 and 300 meters.

b = Calculated by the authors of this report.

#### 6.2.5.2.2 Serious adverse events

No SAEs were identified for the condition of PAOD.

#### 6.2.5.2.3 Bleeding adverse events

No bleeding AEs were identified for the condition of PAOD.

#### 6.2.5.2.4 Other specific adverse events

Two trials investigating 120 mg ginkgo biloba vs. placebo for PAOD reported rates of specific AEs after 24 weeks of treatment.[120-125] Each specific AE occurred in only one patient; because there were zero events in the other arm, the relative effect could not be calculated (***Table 76***).

**Table 76: Other AEs comparing 120 mg ginkgo biloba vs. placebo in patients with PAOD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Blood in urine** | 24 | Bauer 1984[120-124b] | 1/44 (2.3) | 0/35 (0) | NR | NE |
| **Nausea** | 24 | Bauer 1984[120-124b] | 1/44 (2.3) | 0/35 (0) | NR | NE |
| | 24 | Blume 1996[125c] | 1/30 (3.3) | 0/30 (0) | NR | NE |
| **Stomach disorder** | 24 | Bauer 1984[120-124b] | 0/44 (0) | 1/35 (2.9) | NR | NE |
| **Stomach pain** | 24 | Blume 1996[125c] | 1/30 (3.3) | 0/30 (0) | NR | NE |
| **Weakness** | 24 | Bauer 1984[120-124b] | 0/44 (0) | 1/35 (2.9) | NR | NE |

*Abbreviations*

CI = confidence interval, NE = not estimable, NR = not reported, PAOD = peripheral arterial occlusive disease, PFWD = pain-free walking distance, RR = relative risk.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with chronic PAOD and a PFWD <300 meters. Occlusions were unilaterally dominant and had been present for ≥1 year.

c = Included patients were those with angiographically confirmed (within the prior 8 months) Fontaine's stage IIb PAOD with intermittent claudication for >6 months.

### 6.2.5.3 Vertigo

#### 6.2.5.3.1 Adverse events

In the trial comparing 240 mg ginkgo biloba vs. 32 mg betahistine, patients treated with 240 mg ginkgo biloba were statistically significantly less likely to experience ≥1 AE during 12 weeks of treatment (RR 0.61 [95% CI 0.38 to 0.99]; 1 RCT; 160 patients; moderate certainty evidence) (***Table 73***).[91]

**Table 77: At least one AE comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo**

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Betahistine n/N (%)[b] | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | **19/80 (24)** | **31/80 (39)** | **NR** | 0.61 (0.38 to 0.99) |

*Abbreviations*

AE = adverse event, CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Calculated by the authors of this report.

In the trial comparing the lower dose of 160 mg ginkgo biloba vs. 32 mg betahistine, there was no statistically significant difference in the number of people experiencing ≥1 AE during 12 weeks of treatment (RR 1.70 [95% CI 0.17 to 17.2]; 1 RCT; 37 patients; very low certainty evidence) (***Table 78***).[92] One person in the ginkgo biloba group had an AE that led to treatment discontinuation vs. none in the betahistine group.[92]

**Table 78: At least one AE comparing 160 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo**

| Outcome[a] | Ginkgo biloba n/N (%) | Betahistine n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | 2/20 (10) | 1/17 (5.9) | NR | 1.70 (0.17 to 17.2) |
| **AE leading to treatment discontinuation** | 1/20 (5) | 0/17 (0) | NR | NE |

*Abbreviations*

AE = adverse event, CI = confidence interval, NE = not estimable, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Cesarani 1998[92]) and at the same timepoint (12 weeks). Included patients were those with vertigo, dizziness, or both, due to vascular vestibular disorders.

b = Calculated by the authors of this report.

#### 6.2.5.3.2 Serious adverse events

In the trial comparing 240 mg ginkgo biloba vs. 32 mg betahistine, one person in the betahistine group (1/80, 1.3%) had an SAE compared to none in the ginkgo biloba group (0/80, 0%).[91] In the trial comparing the lower dose of 160 mg ginkgo biloba vs. 32 mg betahistine, the occurrence of SAEs was not reported.[92]

#### 6.2.5.3.3 Bleeding adverse events

No bleeding AEs were identified for the condition of vertigo.

#### 6.2.5.3.4 Other specific adverse events

A trial comparing 240 mg ginkgo biloba vs. 32 mg betahistine reported rates for a range of specific AEs and found no statistically significant differences between groups for any of them (***Table 79***).[91]

**Table 79: Other AEs comparing 240 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo**

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Betahistine n/N (%)[b] | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Diarrhoea, frequent bowel movements** | 1/80 (1) | 3/80 (4) | NR | 0.33 (0.04 to 3.14) |
| **Dyspepsia and abdominal discomfort/pain** | 2/80 (3) | 5/80 (6) | NR | 0.40 (0.08 to 2.00) |
| **Headache** | 3/80 (4) | 5/80 (6) | NR | 0.60 (0.15 to 2.43) |
| **Nausea and vomiting** | 3/80 (4) | 1/80 (1) | NR | 3.00 (0.32 to 28.2) |
| **Respiratory tract infections** | 5/80 (6) | 9/80 (11) | NR | 0.56 (0.19 to 1.59) |

*Abbreviations*

AE = adverse event, CI = confidence interval, ICD-10 = International Classification of Diseases, Tenth Revision, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 02262139[91]) and at the same timepoint (12 weeks). Included patients were those with peripheral vertigo not otherwise specified (H81.3) or vertiginous syndrome not otherwise specified (H81.9) as classified by ICD-10, with symptoms of vertigo for at least 3 months, who scored ≥3 on a numeric analogue scale (1 to 10) at screening.

b = Calculated by the authors of this report.

In the trial comparing the lower dose of 160 mg ginkgo biloba vs. 32 mg betahistine, few AEs were reported (***Table 80***).[92] Headache and gastric pyrosis were reported in the ginkgo biloba group but not in the betahistine group; in contrast, cyanosis of nails and lips was reported in the betahistine group but not in the ginkgo biloba group. Because of the low number of events, it was not possible to calculate effect estimates for these specific AEs.

**Table 80: Other AEs comparing 160 mg ginkgo biloba vs. 32 mg betahistine in patients with vertigo**

| Outcome[a] | Ginkgo biloba n/N (%) | Betahistine n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Headache** | 1/20 (5) | 0/17 (0) | NR | NE |
| **Cyanosis of nails and lips** | 0/20 (0) | 1/17 (5.9) | NR | NE |
| **Gastric pyrosis** | 1/20 (5) | 0/17 (0) | NR | NE |

*Abbreviations*

AE = adverse event, CI = confidence interval, NE = not estimable, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Cesarani 1998[92]) and at the same timepoint (12 weeks). Included patients were those with vertigo, dizziness, or both, due to vascular vestibular disorders.

b = Calculated by the authors of this report.

### **6.2.5.4** Tinnitus

#### 6.2.5.4.1 Adverse events

In the trial investigating 12 weeks of 120 mg ginkgo biloba vs. placebo for patients with tonally definable chronic tinnitus lasting at least 2 months, there were no AEs in either group (1 RCT; 99 patients; low certainty evidence).[131]

In the trial investigating 150 mg ginkgo biloba vs. placebo for the condition of tinnitus, there was no statistically significant difference in the number of people with ≥1 AE during 12 weeks of treatment (RR 1.06 [95% CI 0.74 to 1.52]; 1 RCT; 978 patients; low certainty evidence) (***Table 81***).[93,94]

**Table 81: At least one AE comparing 150 mg ginkgo biloba vs. placebo in patients with tinnitus**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | 54/489 (11) | 51/489 (10.4) | NR | 1.06 (0.74 to 1.52) |

*Abbreviations*

AE = adverse event, CI = confidence interval, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Drew 1999[93,94]) and at the same timepoint (12 weeks). Included patients were those with self-reported tinnitus.

b = Calculated by the authors of this report.

In the trial investigating 120 mg ginkgo biloba vs. 600 mg pentoxifylline for the condition of tinnitus, there was no statistically significant difference in the number of people with ≥1 AE during 12 weeks of treatment (RR 0.70 [95% CI 0.42 to 1.18]; 1 RCT; 200 patients; moderate certainty evidence) (***Table 82***).[130]

**Table 82: At least one AE comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus**

| Outcome[a] | Ginkgo biloba n/N (%) | Pentoxifylline n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | 19/100 (19) | 27/100 (27) | NR | 0.70 (0.42 to 1.18) |

*Abbreviations*

AE = adverse event, CI = confidence interval, Mini-TQ = abridged Tinnitus Questionnaire, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Calculated by the authors of this report.

#### 6.2.5.4.2 Serious adverse events

In the trial investigating 120 mg ginkgo biloba vs. 600 mg pentoxifylline for unilateral or bilateral chronic or sub-chronic tinnitus, there were no SAEs in either group after 12 weeks.[130] No other included trials reported on the occurrence of SAEs in patients with tinnitus.

#### 6.2.5.4.3 Bleeding adverse events

No bleeding AEs were identified for the condition of tinnitus.

#### 6.2.5.4.4 Other specific adverse events

A trial investigating 12 weeks of treatment with 150 mg ginkgo biloba or placebo for the condition of tinnitus reported the rates of a range of specific AEs and found no statistically significant differences between groups for any of them (***Table 83***).[93,94]

**Table 83: Other AEs comparing 150 mg ginkgo biloba vs. placebo in patients with tinnitus**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Awareness of heartbeat** | 3/489 (0.6) | 3/489 (0.6) | NR | 1.00 (0.20 to 4.93) |
| **Dizziness, light-headedness, or nausea** | 6/489 (1.2) | 7/489 (1.4) | NR | 0.86 (0.29 to 2.53) |

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Flushing or redness of the face** | 1/489 (0.2) | 4/489 (0.8) | NR | 0.25 (0.03 to 2.23) |
| **Gastrointestinal upset** | 15/489 (3.1) | 15/489 (3.1) | NR | 1.00 (0.49 to 2.02) |
| **Headache** | 4/489 (0.8) | 4/489 (0.8[c]) | NR | 1.00 (0.25 to 3.98) |
| **Hearing worse** | 3/489 (0.6) | 1/489 (0.2) | NR | 3.00 (0.31 to 28.7) |
| **Hyperacusis** | 0/489 (0) | 2/489 (0.4) | NR | NE |
| **Mouth ulcer, dryness, bad taste** | 3/489 (0.6) | 6/489 (1.2) | NR | 0.50 (0.13 to 1.99) |
| **Skin worse (dry, itchy, spots)** | 2/489 (0.4) | 3/489 (0.6) | NR | 0.67 (0.11 to 3.97) |
| **Sleep or dreams worse** | 4/489 (0.8) | 3/489 (0.6) | NR | 1.33 (0.30 to 5.93) |
| **Worsening of blocking or pressure in ear** | 10/489 (2.1) | 4/489 (0.8) | NR | 2.50 (0.79 to 7.92) |

*Abbreviations*

AE = adverse event, CI = confidence interval, NE = not estimable, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Drew 1999[93,94]) and at the same timepoint (12 weeks). Included patients were those with self-reported tinnitus.

b = Calculated by the authors of this report.

c = Percentage reported as 0.2% in Table 5 of the original study. This does not correspond to the calculated value based on the reported numerator and denominator. Preference was given to the numerator and denominator, based on the results of McNemar's test, also reported in Table 5 of the original study.

A trial investigating 120 mg ginkgo biloba vs. 600 mg pentoxifylline for the condition of tinnitus reported the rates of a range of specific AEs and found no statistically significant differences between groups for any of them (***Table 84***).[130]

**Table 84: Other AEs comparing 120 mg ginkgo biloba vs. 600 mg pentoxifylline in patients with tinnitus**

| Outcome[a] | Ginkgo biloba n/N (%) | Pentoxifylline n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Abdominal discomfort** | 0/100 (0) | 1/100 (1) | NR | NE |
| **Abdominal distension** | 0/100 (0) | 2/100 (2) | NR | NE |
| **Bronchitis** | 1/100 (1) | 1/100 (1) | NR | 1.00 (0.06 to 15.8) |

| Outcome[a] | Ginkgo biloba n/N (%) | Pentoxifylline n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **Diarrhoea** | 2/100 (2) | 0/100 (0) | NR | NE |
| **Dyspepsia** | 0/100 (0) | 1/100 (1) | NR | NE |
| **Ear discomfort** | 1/100 (1) | 0/100 (0) | NR | NE |
| **Gastroenteritis** | 0/100 (0) | 1/100 (1) | NR | NE |
| **Nasopharyngitis** | 1/100 (1) | 2/100 (2) | NR | 0.50 (0.05 to 5.43) |
| **Nausea** | 0/100 (0) | 2/100 (2) | NR | NE |
| **Pertussis** | 0/100 (0) | 1/100 (1) | NR | NE |
| **Unspecified gastrointestinal symptom** | 0/100 (0) | 1/100 (1) | NR | NE |
| **Upper abdominal pain** | 0/100 (0) | 4/100 (4) | NR | NE |
| **Vertigo** | 0/100 (0) | 1/100 (1) | NR | NE |
| **Worsening of tinnitus** | 5/100 (5) | 3/100 (3) | NR | 1.67 (0.41 to 6.79) |

*Abbreviations*

AE = adverse event, CI = confidence interval, Mini-TQ = abridged Tinnitus Questionnaire, NE = not estimable, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (ISRCTN 68772788[130]) and at the same timepoint (12 weeks). Included patients were those with unilateral or bilateral chronic or sub-chronic tinnitus of ≥3 months' duration. Tinnitus was maskable (by noise masking), the degree of annoyance by tinnitus was rated ≥3 on an 11-Point Box Scale (type of numeric analogue scale) at screening and baseline visits, and they scored ≥5 on the Mini-TQ at baseline.

b = Calculated by the authors of this report.

#### 6.2.5.5 Safety analysis across indications

To supplement the findings regarding the safety of ginkgo biloba in each indication, meta-analyses were conducted to assess the safety of ginkgo biloba across indications. However, for most dose comparisons, results were only reported for a single eligible indication. Comparing 240 mg of ginkgo biloba vs. placebo, only studies on patients with MPD reported on the number of patients with ≥1 AE, so those results are shown in ***Section 6.2.5.1.1***. Similarly, only one tinnitus trial reported the proportion of AEs comparing 150 mg ginkgo biloba vs. placebo (***Section 6.2.5.3.1***). Although 2 PAOD trials and one MPD trial reported AE data for 160 mg ginkgo biloba vs. placebo, both PAOD trials reported zero events in both treatment groups (***Section 6.2.5.2.1***). Among patients treated with either 120 mg ginkgo biloba or placebo for 24 weeks, there was no statistically significant difference in the occurrence of AEs (RR 0.91 [95% CI 0.70 to 1.18]; 7 RCTs; 1'133 patients) (***Figure 43***).

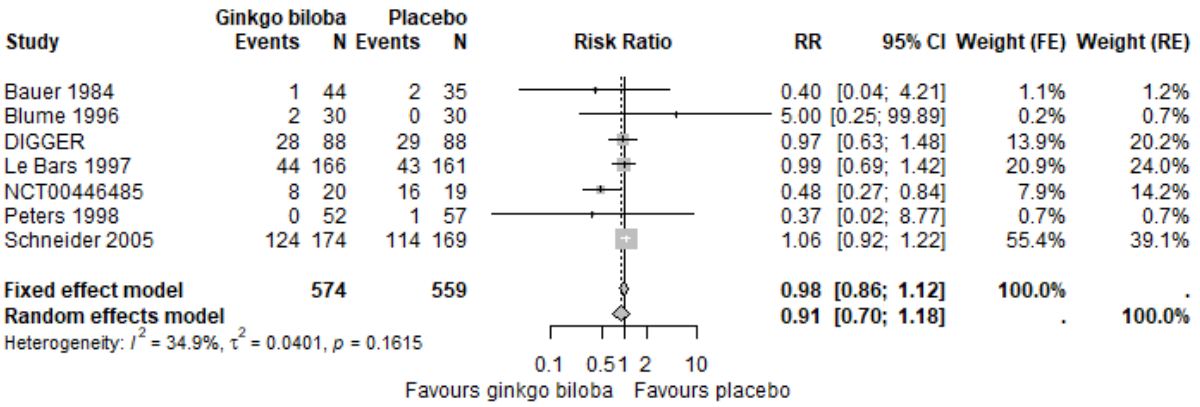


**Figure 43: At least one AE in patients with any indication of interest: 120 mg ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, RE = random effects, RR = relative risk.

Finally, a meta-analysis was conducted on the proportion of patients with any eligible indication (MPD, PAOD, vertigo, or tinnitus), comparing 24 weeks of treatment with any dose of ginkgo biloba or placebo (***Figure 44***). Overall, there was no statistically significant difference between ginkgo biloba and placebo (RR 0.96 [95% CI 0.89 to 1.04]; 12 RCTs; 2'728 patients). Note that 2 additional trials are displayed in the forest plot but did not contribute to the meta-analysis because there were no AEs reported in either treatment group.

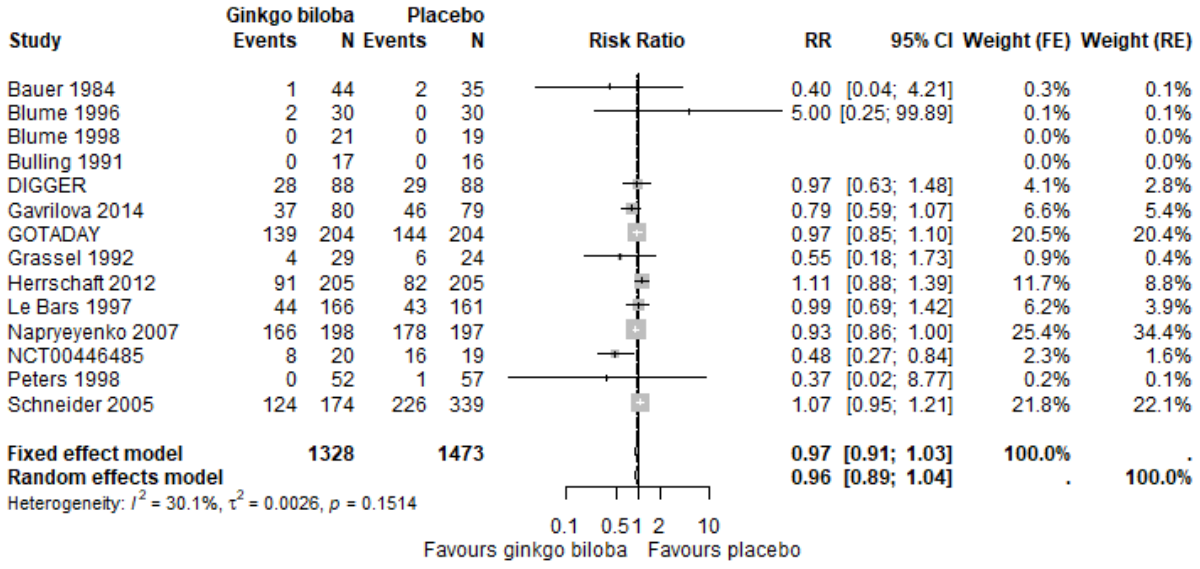


**Figure 44: At least one AE in patients with any indication of interest: any dose of ginkgo biloba vs. placebo at 24 weeks**

*Abbreviations*

AE = adverse event, CI = confidence interval, FE = fixed effect, RE = random effects, RR = relative risk.

### 6.2.6 GRADE summary of findings tables

The overall certainty of evidence for up to 7 outcomes for each of the 4 conditions of interest are reported in subsequent sections: MPD (***Section 6.2.6.1***), PAOD (***Section 6.2.6.2***), vertigo (***Section 6.2.6.3***), and tinnitus (***Section 6.2.6.4***). The certainty of evidence for additional outcomes is available in ***Appendix G.***

### 6.2.6.1 Mental performance deficits

**Table 85: Summary of findings table – MPD**

**240 mg ginkgo biloba compared to placebo for mental performance deficits**

**Patient or population:** Mental performance deficits
**Setting:** Outpatient clinics and/or residential care
**Intervention:** 240 mg ginkgo biloba
**Comparison:** placebo

| Outcome<br>№ of participants (studies) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **240 mg ginkgo biloba** | **Difference** | | |
| Cognitive function assessed with: SKT score<br>follow-up: 24 weeks<br>№ of participants: 1’406 (4 RCTs) | Four studies measured change in SKT total score and found statistically significantly greater change from baseline with 240 mg ginkgo biloba (MD -2.32, 95% CI -3.82 to -0.83). These studies also measured proportions of participants with improvement in SKT score by ≥3 points (RR 2.94, 95% CI 1.30 to 6.65) | | | | ⊕⊕⊕◯<br>Moderate[a] | 240 mg ginkgo biloba probably results in a slight improvement in cognitive function, measured with SKT score. The difference of 2.32 points is higher than the MCID of 2 points. |

**240 mg ginkgo biloba compared to placebo for mental performance deficits**

**Patient or population:** Mental performance deficits
**Setting:** Outpatient clinics and/or residential care
**Intervention:** 240 mg ginkgo biloba
**Comparison:** placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **240 mg ginkgo biloba** | **Difference** | | |
| Cognitive function<br>assessed with: Change in verbal fluency test score<br>follow-up: 24 weeks<br>№ of participants: 1’201<br>(3 RCTs) | - | The mean change in verbal fluency test score with placebo was **0.8 to 0** | - | MD **1.27 higher** (0.25 higher to 2.3 higher)<br>SMD **0.77 higher** (0.02 higher to 1.52 higher) | ⨁⨁◯◯<br>Low[a,b] | 240 mg ginkgo biloba may result in a moderate improvement in cognitive function, measured with the verbal fluency test. |
| Cognitive function<br>assessed with: Incidence of dementia<br>follow-up: 5 years<br>№ of participants: 3’302<br>(2 RCTs) | Two studies measured incident cases of probable Alzheimer's disease (HR 0.84 [95% CI 0.60 to 1.18]), any dementia (HR 1.10 [95% CI 0.83 to 1.47]), Alzheimer's disease with vascular dementia (HR 0.96 [95% CI 0.54 to 1.71]), and Alzheimer's disease without vascular dementia (HR 1.15 [95% CI 0.83 to 1.61)]. There were no statistically significant differences between 240 mg ginkgo biloba and placebo in incident cases of any of these conditions. | | | | ⨁⨁◯◯<br>Low[c] | 240 mg ginkgo biloba may result in little to no difference in cognitive function, assessed as number of incident cases of dementia in people with existing mild cognitive impairment or memory impairment. |

**240 mg ginkgo biloba compared to placebo for mental performance deficits**

**Patient or population:** Mental performance deficits
**Setting:** Outpatient clinics and/or residential care
**Intervention:** 240 mg ginkgo biloba
**Comparison:** placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **240 mg ginkgo biloba** | **Difference** | | |
| Behavioural changes assessed with: Neuropsychiatric Inventory score<br>follow-up: 24 weeks<br>№ of participants: 1’360<br>(4 RCTs) | Four studies measured mean change in total NPI score and found a greater difference in change from baseline with 240 mg ginkgo biloba (MD -4.03, 95% CI -7.32 to -0.74), compared to placebo. These four studies also measured the proportion of individuals achieving a change in NPI score of ≥4 points (RR 2.50, 95% CI 0.99 to 6.32). | | | | ⊕⊕⊕◯<br>Moderate[a] | 240 mg ginkgo biloba may result in a slight improvement in behavioural changes and neuropsychiatric symptoms, measured with NPI score. The difference of 4.03 points is higher than the MCID of 4 points. |
| Functional status assessed with: Change in ADL-IS score<br>follow-up: 24 weeks<br>№ of participants: 806<br>(2 RCTs) | - | The mean change in ADL score with placebo was **0 to 0.04** | - | MD **0.17 lower** (0.22 lower to 0.12 lower)<br>SMD **0.5 lower** (0.64 lower to 0.36 lower) | ⊕⊕⊕⊕<br>High | 240 mg ginkgo biloba results in a moderate improvement in functional status, measured with ADL-IS score. |

**240 mg ginkgo biloba compared to placebo for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 240 mg ginkgo biloba

**Comparison:** placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **240 mg ginkgo biloba** | **Difference** | | |
| HRQoL<br>assessed with: DEMQOL-proxy<br>follow-up: 24 weeks<br>№ of participants: 806<br>(2 RCTs) | - | The mean DEMQOL-proxy score with placebo was **1.4 to 1.5** | - | MD **2 higher** (0.85 higher to 3.15 higher)<br>SMD **0.24 higher** (0.10 higher to 0.38 higher) | ⨁⨁⨁◯<br>Moderate[b] | 240 mg ginkgo biloba probably results in a slight improvement in HRQoL, measured with DEMQOL-proxy score. |
| Adverse events<br>follow-up: 24 weeks<br>№ of participants: 1’716<br>(5 RCTs) | **RR 0.97**<br>(0.90 to 1.05) | 65.7% | **63.8%**<br>(69 to 59.2) | **2.0% fewer**<br>(6.6 fewer to 3.3 more) | ⨁⨁⨁◯<br>Moderate[d] | 240 mg ginkgo biloba probably results in little to no difference in adverse events. |

**240 mg ginkgo biloba compared to placebo for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 240 mg ginkgo biloba

**Comparison:** placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo** | **240 mg ginkgo biloba** | **Difference** | | |
| Serious adverse events<br>follow-up: 24 weeks<br>№ of participants: 1'143<br>(3 RCTs) | **RR 0.98**<br>(0.53 to 1.83) | 4.0% | **4.0%**<br>(7.4 to 5.1) | **0.1% fewer**<br>(1.9 fewer to 3.4 more) | ⊕⊕⊕◯<br>Moderate[d] | 240 mg ginkgo biloba probably results in little to no difference in SAEs. |

**Note: The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

ADL-IS = Activities of Daily Living International Scale, CI = confidence interval, DEMQOL = Dementia-Related Quality of Life, MD = mean difference, NPI = Neuropsychiatric Inventory, RCT = randomised controlled trial, RR = risk ratio, SKT = Syndrom-Kurz-Test, SMD = standardised mean difference.

*Explanations*

a = Downgraded one level for inconsistency due to high degree of statistical heterogeneity and variability in size of effect.

b = Downgraded one level for imprecision due to 95% CI spanning the threshold between small and trivial/no effect (0.2 using SMD).

c = Downgraded two levels for imprecision due to 95% CIs spanning appreciably different effect estimates.

d = Downgraded one level for imprecision due to 95% CIs spanning different directions of effect.

### 6.2.6.2 Peripheral arterial occlusive disease

**Table 86: Summary of findings table – PAOD**

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease
**Setting:** Outpatient clinics
**Intervention:** 120-240 mg ginkgo biloba
**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Mobility: 120 mg ginkgo biloba<br>assessed with: PFWD<br>follow-up: 24 weeks<br>№ of participants: 225<br>(3 RCTs) | - | The mean PFWD with placebo was **20.9 to 33.2** m | - | MD **24.37 m higher**<br>(4.86 higher to 43.88 higher) | ⨁⨁◯◯<br>Low[a,b] | 120 mg ginkgo biloba may increase PFWD, compared to placebo. The difference of 24.37 m is higher than the MCID of 20 m. |
| Mobility: 160 mg ginkgo biloba<br>assessed with: PFWD<br>follow-up: 24 weeks<br>№ of participants: 73<br>(2 RCTs) | - | The mean PFWD with placebo was **4 to 90** meters | - | MD **35.99 m higher**<br>(15.36 higher to 56.62 higher) | ⨁◯◯◯<br>Very low[c,d] | 160 mg ginkgo biloba may increase PFWD, compared to placebo, but the evidence is very uncertain.<br>The difference of 35.99 m is higher than the MCID of 20 m. |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Mobility: 160 mg ginkgo biloba<br>assessed with: MWD<br>follow-up: 24 weeks<br>№ of participants: 73<br>(2 RCTs) | - | The mean MWD with placebo was **6 to 138** meters | - | MD **80.17 m higher**<br>(36.38 lower to 196.72 higher) | ⊕◯◯◯<br>Very low[c,e] | 160 mg ginkgo biloba may increase maximum walking distance, compared to placebo, but the evidence is very uncertain. The difference of 80.17 m is higher than the MCID of 20 m. |
| Pain: 120 mg ginkgo biloba<br>assessed with: 0-100 mm VAS<br>follow-up: 24 weeks<br>№ of participants: 116<br>(2 RCTs) | - | The mean pain score with placebo was **47 to 58** | - | MD **14.37 lower**<br>(15.43 lower to 13.32 lower) | ⊕⊕◯◯<br>Low[a,b] | 120 mg ginkgo biloba may reduce pain slightly. |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Peripheral blood circulation: 120 mg ginkgo biloba assessed with: resting ankle pressure<br>follow-up: 24 weeks<br>№ of participants: 116<br>(2 RCTs) | - | The mean peripheral blood circulation with placebo was **79 to 104** mmHg | - | MD **1.72 mmHg lower**<br>(23.07 lower to 19.63 higher) | ⊕◯◯◯<br>Very low[a,f] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on resting ankle pressure, compared to placebo. |
| Peripheral blood circulation: 120 mg ginkgo biloba assessed with: post-exercise ankle pressure<br>follow-up: 24 weeks<br>№ of participants: 116<br>(2 RCTs) | - | The mean peripheral blood circulation: with placebo was **38-49** mmHg | - | MD **4.36 mmHg higher**<br>(7.19 lower to 15.91 higher) | ⊕◯◯◯<br>Very low[a,f] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on post-exercise ankle pressure compared to placebo. |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Adverse events: 120 mg ginkgo biloba<br>follow-up: 24 weeks<br>№ of participants: 248<br>(3 RCTs) | **RR 0.80**<br>(0.16 to 3.98) | 2.5% | **2.0%**<br>(9.8 to 0.4) | **0.5% fewer**<br>(2.1 fewer to 7.3 more) | ⊕◯◯◯<br>Very low[a,f] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on the risk of adverse events compared to placebo. |
| Adverse events: 160 mg ginkgo biloba<br>follow-up: 24 weeks<br>№ of participants: 73<br>(2 RCTs) | No participants had any adverse events with either 160 mg ginkgo biloba or placebo. | | | | ⊕◯◯◯<br>Very low[c,f] | The evidence is very uncertain about the effect of 160 mg ginkgo biloba on the risk of adverse events compared to placebo. |

**Note: The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

CI = confidence interval, MCID = minimum clinically important difference, MD = mean difference, MWD = maximum walking distance, PFWD = pain-free walking distance, RCT = randomised controlled trial, RR = risk ratio, SAE = serious adverse event, VAS = visual analogue scale.

*Explanations*

a = Downgraded one level for risk of bias due to unclear reporting of randomisation and allocation concealment procedures.

b = Downgraded one level for imprecision due to low numbers of participants.

c = Downgraded two levels for risk of bias due to absence of reporting of randomisation and allocation concealment and unclear reporting of who was blinded to treatment allocation.

d = Downgraded two levels for imprecision due to low numbers of participants (<100).

e = Downgraded three levels for imprecision due to low numbers of participants (<100) and 95% CI spanning appreciably different effects.

f = Downgraded one level for imprecision due to low numbers of participants and 95% CI spanning appreciably different effects.

### 6.2.6.3 Vertigo

**Table 87: Summary of findings table – vertigo**

**160-240 mg ginkgo biloba compared to 32 mg betahistine dihydrochloride for vertigo**

**Patient or population:** Vertigo
**Setting:** Outpatient clinics
**Intervention:** 160-240 mg ginkgo biloba
**Comparison:** 32 mg betahistine

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **32 mg betahistine dihydrochloride** | **160-240 mg ginkgo biloba** | **Difference** | | |
| Vestibular symptoms: 240 mg ginkgo biloba assessed with: Patient-reported instruments<br>follow-up: 12 weeks<br>№ of participants: 160<br>(1 RCT) | One trial used a range of patient-reported outcome measures to assess vestibular symptoms (11-point scale, Romberg test subscales, Unterberger's stepping test, Vertigo Symptom Scale subscales). None of the results showed any statistically significant differences compared to 32 mg betahistine dihydrochloride. | | | | ⊕⊕◯◯<br>Low[a] | 240 mg ginkgo biloba may result in little to no difference in vestibular symptoms. |
| Vestibular symptoms: 160 mg ginkgo biloba assessed with: Patient-reported assessment<br>follow-up: 12 weeks<br>№ of participants: 31<br>(1 RCT) | One trial reported no statistically significant differences in the proportion of participants with improvement in (RR 0.48 [95% CI 0.17 to 1.37]) or disappearance of vertigo symptoms (RR 0.96 [05% CI 0.44 to 2.10]). There were also no statistically significant differences in the proportion of participants with Babinsky Weil and Romberg tests that were no longer positive (RR 1.28 [95% CI 0.43 to 3.78] and RR 1.13 [95% CI 0.29 to 4.37], respectively). | | | | ⊕◯◯◯<br>Very low[b,c] | The evidence is very uncertain about the effect of 160 mg ginkgo biloba on vestibular symptoms. |

**160-240 mg ginkgo biloba compared to 32 mg betahistine dihydrochloride for vertigo**

**Patient or population:** Vertigo
**Setting:** Outpatient clinics
**Intervention:** 160-240 mg ginkgo biloba
**Comparison:** 32 mg betahistine

| Outcome<br>№ of participants (studies) | Relative effect (95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **32 mg betahistine dihydrochloride** | **160-240 mg ginkgo biloba** | **Difference** | | |
| Functional status: 240 mg ginkgo biloba assessed with: SDS<br>follow-up: 12 weeks<br>№ of participants: 160 (1 RCT) | - | The mean SDS score with betahistine was **-8.3** | - | MD **1.1 lower** (2.9 lower to 0.7 higher) | ⨁◯◯◯<br>Very low[a,d] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba on functional status. |
| HRQoL - not reported | - | - | - | - | - | |
| Adverse events: 240 mg ginkgo biloba<br>follow-up: 12 weeks<br>№ of participants: 160 (1 RCT) | **RR 0.61** (0.38 to 0.99) | 23.8% | **14.5%** (23.5 to 9) | **9.3% fewer** (14.7 fewer to 0.2 fewer) | ⨁⨁⨁◯<br>Moderate[e] | There are probably slightly fewer adverse events with 240 mg ginkgo biloba than with 32 mg betahistine |
| Adverse events: 160 mg ginkgo biloba<br>follow-up: 12 weeks<br>№ of participants: 37 (1 RCT) | **RR 1.70** (0.17 to 17.20) | 5.9% | **10.0%** (100 to 1) | **4.1% more** (4.9 fewer to 95.3 more) | ⨁◯◯◯<br>Very low[c] | The evidence is very uncertain about the effect of 160 mg ginkgo biloba on adverse events compared to 32 mg betahistine |
| SAEs: 160 mg ginkgo biloba - not reported | - | - | - | - | - | |

**160-240 mg ginkgo biloba compared to 32 mg betahistine dihydrochloride for vertigo**

**Patient or population:** Vertigo
**Setting:** Outpatient clinics
**Intervention:** 160-240 mg ginkgo biloba
**Comparison:** 32 mg betahistine

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **32 mg betahistine dihydrochloride** | **160-240 mg ginkgo biloba** | **Difference** | | |
| SAEs: 240 mg ginkgo biloba<br>follow-up: 12 weeks<br>№ of participants: 160<br>(1 RCT) | There were no SAEs with 240 mg ginkgo biloba and 1/80 participants had a SAE with betahistine. | | | | ⨁⨁◯◯<br>Low[f] | 240 mg ginkgo biloba may result in little to no difference in SAEs compared to 32 mg betahistine |

**Note: The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

CI = confidence interval, HRQoL = health-related quality of life, RCT = randomised controlled trial, RR = relative risk, SAE = serious adverse event, SDS = Sheehan Disability Scale.

*Explanations*

a = Downgraded two levels for imprecision due to low numbers of participants and 95% CIs spanning appreciably different effects.

b = Downgraded two levels for risk of bias due to lack of information on randomisation and allocation concealment and lack of blinding

c = Downgraded three levels for imprecision due to very low numbers of participants (<100) and 95% CIs spanning appreciably different effects.

d = Downgraded one level for indirectness due to the lack of established minimum clinically important difference for the outcome measure in this population.

e = Downgraded one level for imprecision due to low numbers of participants.

f. Downgraded two levels for imprecision due to low numbers of participants and low event rate.

### 6.2.6.4 Tinnitus

**Table 88: Summary of findings table – tinnitus**

| **Ginkgo biloba compared to placebo or pentoxifylline or a hearing aid for tinnitus** | | |
|---|---|---|
| **Patient or population:** Tinnitus<br>**Setting:** Outpatient clinics<br>**Intervention:** 120-240 mg ginkgo biloba<br>**Comparison:** Control (placebo or pentoxifylline or a hearing aid) | | |
| Outcome<br>№ of participants<br>(studies) | **Impact** | Certainty |
| Tinnitus severity: 120 to 150 mg ginkgo biloba<br>assessed with: patient-reported subjective assessment<br>Follow-up: 12 weeks<br>№ of participants: 1’013<br>(3 RCTs) | No statistically significant differences were found between ginkgo biloba (120 mg or 150 mg) and either placebo or pentoxifylline in patients’ subjective assessment of tinnitus severity, measured with a variety of categorical and continuous scales. | ⊕⊕◯◯<br>Low[a] |
| Tinnitus severity: 240 mg ginkgo biloba<br>assessed with: THI and 0 to 10 VAS<br>Follow-up: 12 weeks<br>№ of participants: 22<br>(1 RCT) | No statistically significant difference was found between the 240 mg ginkgo biloba group and the hearing aid group in tinnitus severity measured with the THI, but when measured with 0 to 10 VAS, tinnitus severity was slightly worse in the 240 mg ginkgo biloba group than in the hearing aid group. | ⊕◯◯◯<br>Very low[b,c] |

**Ginkgo biloba compared to placebo or pentoxifylline or a hearing aid for tinnitus**

**Patient or population:** Tinnitus
**Setting:** Outpatient clinics
**Intervention:** 120-240 mg ginkgo biloba
**Comparison:** Control (placebo or pentoxifylline or a hearing aid)

| Outcome<br>№ of participants<br>(studies) | **Impact** | Certainty |
|---|---|---|
| Tinnitus severity: 240 mg ginkgo biloba plus hearing aid assessed with: THI and 0 to 10 VAS<br>Follow-up: 12 weeks<br>№ of participants: 22<br>(1 RCT) | Tinnitus severity was worse in the 240 mg ginkgo biloba plus hearing aid group compared to a hearing aid alone, measured with THI and 0 to 10 VAS. | ⊕◯◯◯<br>Very low[b,c] |
| Tinnitus loudness assessed with: patient-reported subjective assessment<br>Follow-up: 12 weeks<br>№ of participants: 996<br>(3 RCTs) | Two studies (923 participants) found no statistically significant differences between ginkgo biloba and placebo or pentoxifylline, respectively, in patient-reported assessment of tinnitus loudness measured with a variety of ordinal scales. One of these studies compared 150 mg ginkgo vs. placebo, and the other compared 120 mg ginkgo biloba vs. 600 mg pentoxifylline.<br>A third study (73 participants) found that 120 mg ginkgo biloba reduced tinnitus loudness more than in the placebo group. | ⊕⊕◯◯<br>Low[d,e] |
| Adverse events: ginkgo biloba 120 mg<br>Follow-up: 12 weeks<br>№ of participants: 200<br>(1 RCT) | At least one AE occurred in 19/100 (19%) of people treated with ginkgo biloba 120 mg compared with 27/100 (27%) of those treated with pentoxifylline 600 mg daily (RR 0.70, 95% CI 0.42 to 1.18).<br>No SAEs occurred in either of the groups. | ⊕⊕⊕◯<br>Moder-ate[f] |
| Adverse events: ginkgo biloba 120 mg<br>Follow-up: 12 weeks<br>№ of participants: 99<br>(1 RCT) | No AEs occurred in either the ginkgo biloba 120 mg group or the placebo group (1 study, 99 partici-pants).<br>SAEs were not reported. | ⊕⊕◯◯<br>Low[d,f] |

**Ginkgo biloba compared to placebo or pentoxifylline or a hearing aid for tinnitus**

**Patient or population:** Tinnitus
**Setting:** Outpatient clinics
**Intervention:** 120-240 mg ginkgo biloba
**Comparison:** Control (placebo or pentoxifylline or a hearing aid)

| Outcome<br>№ of participants<br>(studies) | **Impact** | Certainty |
|---|---|---|
| Adverse events: ginkgo biloba 150 mg<br>Follow-up: 12 weeks<br>№ of participants: 978<br>(1 RCT) | At least one AE occurred in 54/489 (11%) of participants in the ginkgo biloba 150 mg group compared to 51/489 (10.4%) in the placebo group (RR 1.06, 95% CI 0.74 to 1.52).<br>SAEs were not reported. | ⊕⊕◯◯<br>Low[a] |

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

AE = adverse event; HRQoL = health-related quality of life, RCT = randomised controlled trial, RR = relative risk, SAE = serious adverse event, THI = Tinnitus Handicap Inventory, VAS = Visual Analogue Scale.

*Explanations*

a = Downgraded 2 levels for risk of bias due to lack of robust random sequence generation and unclear reporting of allocation concealment and blinding procedures.

b = Downgraded one level for risk of bias due to unclear reporting of allocation concealment procedures and due to lack of blinding of the participants, which could have an impact on subjectively reported outcomes.

c = Downgraded 2 levels for imprecision due to low numbers of participants (<100).

d = Downgraded one level for risk of bias due to unclear reporting of allocation concealment and blinding procedures.

e = Downgraded one level for inconsistency due to differing directions of effect.

f = Downgraded one level for imprecision due to low numbers of participants.

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# 7. Costs, cost-effectiveness and budget impact

***Summary statement costs, cost-effectiveness and budget impact***

An SLR was conducted to identify studies reporting economic analyses and costs associated with ginkgo biloba for managing MPD, PAOD, vertigo, or tinnitus. The SLR did not identify any studies reporting primary data on the costs associated with ginkgo biloba (e.g. costs of treatment, doctor's visits, AEs associated with ginkgo biloba, changes in necessary care following ginkgo biloba, etc.). Three cost-comparison economic analysis studies were identified, which modelled the costs and benefits of ginkgo biloba over different disease progression scenarios. All 3 studies investigated the direct costs of ginkgo biloba, from a public payer perspective, in patients with AD or dementia. In 2 studies conducted in Austria, ginkgo biloba was found to be cost-saving compared to placebo, while a study in Germany reported that ginkgo biloba is more costly than galantamine for AD. The findings are based on data collected more than 15 years ago, so these findings may not be representative of current clinical practice or current costs. Reporting quality was varied, with key information missing on model rationale, assumptions, and economic analysis plans.

The present BIM estimated the budget impact of ginkgo biloba reimbursement through the mandatory health insurance. The analysis compared costs in patients with MPD, PAOD, vertigo, and tinnitus. The model adopts a Swiss healthcare perspective over a 5-year time horizon. The structure of the model was based solely on the costs of the ginkgo biloba formulation, as the SLR did not identify cost offsets that would have an impact on the budget. Ginkgo biloba costs were based on the Spezialitätenliste. Prescription data was used to calculate the overall utilisation of ginkgo biloba; however, prescription data were not available per indication, so the prevalence rates of MPD, PAOD, vertigo, and tinnitus in the Swiss population were identified from the literature and used to estimate the utilisation of ginkgo biloba per indication. The results of this budget impact analysis indicate that the reimbursement of ginkgo biloba resulted in a 5-year total spending of CHF 167'154'958.

## 7.1 Methodology costs, cost-effectiveness and budget impact

### 7.1.1 Databases and search strategy

The SLR of economic evidence was conducted in accordance with guidance from the Cochrane Handbook for Systematic Reviews of Interventions[63] and the reporting considered all items from the PRISMA checklist.[64] The search parameters for the identification of relevant literature are detailed in ***Table 89***. Because there was likely to be substantial overlap with the references identified

in the SLR of clinical evidence, a single, combined search strategy for each database was utilised (***Appendix A***).

**Table 89: Search parameters for economic systematic literature review**

| | |
|---|---|
| **Electronic databases** | MEDLINE, Embase, EconLit, CENTRAL, CDSR, and NHS EED (all via OvidSP); INAHTA |
| **Other sources** | Reference lists of relevant published SLRs/meta-analyses identified in the database search |
| **Publication type** | Journal articles only |
| **Search dates** | No restriction |
| **Language** | No restriction[a] |
| **Geography** | No restriction |

*Abbreviations*

CDSR = Cochrane Database of Systematic Reviews, EED = Economic Evaluation Database, INAHTA = International Network of Agencies for Health Technology Assessment, NHS = National Health Service, SLR = systematic literature review

*Notes*

a = Although the search strategy will not be restricted by language, publications in languages other than English, German, Italian, and French will be excluded during title/abstract screening.

### 7.1.2 Study selection

The electronic records of the articles retrieved by the database searches were exported into an EndNote library (Clarivate Analytics, USA), and after deduplication, they were imported into DistillerSR for study selection. Screening was performed to include studies that met the pre-defined study selection criteria (***Table 90***), as well as to provide an exclusion reason for each publication/study that did not meet at least one of the pre-defined criteria. Screening was conducted in 2 levels: first, the title and abstract of each publication were assessed for relevance to the objectives of the SLR; and second, articles that seemed to contain relevant data underwent full-text screening.

The identified title/abstracts and full-text publications were screened by 2 independent reviewers, and conflicts were resolved via discussion. If a consensus could not be reached, a third reviewer was consulted. SLRs/meta-analyses of relevant populations identified via the database search were flagged during the screening process and utilised to identify any additional studies. The studies included in such SLRs/meta-analyses were compared with the final list of included studies in this SLR to determine if any additional studies were eligible.

**Table 90: Eligibility criteria for economic evidence**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | As for ***Table 5***, ***Table 6***, ***Table 7***, and ***Table 8*** | |
| **Interventions** | As for ***Table 5***, ***Table 6***, ***Table 7***, and ***Table 8*** | |
| **Comparators** | As for ***Table 5***, ***Table 6***, ***Table 7***, and ***Table 8*** | |
| **Outcomes** | • All-cause healthcare costs<br>• Disease-related healthcare costs<br>• ICERs<br>• Incremental and total costs<br>• Incremental and total effects, including QALYs and LYs | Other outcomes |
| **Language** | As for ***Table 5***, ***Table 6***, ***Table 7***, and ***Table 8*** | |
| **Time horizon** | Any | None |
| **Study design/ publication type** | • Cost-effectiveness analyses<br>• BIMs<br>• Cost analyses<br>• Cost-utility analyses<br>• Cost-consequence analyses<br>• Cost-minimisation analyses<br>• Cost-benefit analyses | • SLRs |

*Abbreviations*

BIM = budget impact model, ICER = incremental cost-effectiveness ratio, LY = life-year, QALY = quality-adjusted life-year, SLR = systematic literature review.

### 7.1.3 Assessment of quality of evidence

The reporting quality of health economic evaluations was assessed using the CHEERS statement.[150] The reporting quality of each health economic evaluation was assessed by one researcher and fully reviewed by a second researcher. Differences were resolved by discussion, and in case of discrepancy, a third researcher was consulted to reach consensus.

### 7.1.4 Methodology data extraction, analysis and synthesis of health economic data

#### 7.1.4.1 Data extraction

Data were extracted from included publications by one reviewer and complete confirmation of the data extracted was conducted by a second reviewer. A third reviewer was consulted if agreement was not reached between reviewers. Data extraction was completed in a Microsoft Excel spreadsheet.

A list of data elements to be extracted from each included publication is provided below. Please note that although the list below is comprehensive, additional items could be added if unanticipated data were available:

- **Study information:** author, publication date, study identifier, study objective, source of funding, country, type of economic evaluation, model structure, key assumptions, source(s) of model inputs, discount rate, perspective, and time horizon.
- **Population characteristics:** definition of disease, number of participants with available data, age, sex, BMI, concomitant medications, geography, and race/ethnicity.
- **Intervention and comparator details:** dose, route, formulation, duration of intervention, and any co-interventions administered alongside the intervention and comparator(s).
- **Outcomes of interest:** measurement methods, timepoint of follow-up, and results for economic outcomes, as well as the results of any sensitivity analyses.

#### 7.1.4.2 Synthesis

Evidence from available health economic evaluations was synthesised narratively, and tabular summaries were provided. Study characteristics and outcomes were grouped by patient population, sub-population (e.g. underlying pathology of vertigo), study type, and geography. Economic outcomes were also used to provide information for the BIM described in ***Section 7.2.6***.

### 7.1.5 Budget impact model

#### 7.1.5.1 Model overview

Model structure

Ginkgo biloba is currently reimbursed through mandatory health insurance and is associated with substantial costs. As part of the reassessment of ginkgo biloba coverage, a model was developed to estimate the budget impact of ginkgo biloba for the treatment of patients with MPD, PAOD, vertigo, or tinnitus from the perspective of a Swiss healthcare payer. The prescription costs of all formulations of ginkgo biloba currently reimbursed through mandatory health insurance were considered. Based on both the SLR results (reported in ***Section 7.2.4*** and ***Section 7.2.5***) and supplemental targeted searches, no evidence was identified on how the reimbursement of ginkgo biloba may impact other costs. Therefore, only drug costs of ginkgo biloba were included in the base case analysis.

***Figure 45*** provides a schematic presentation of the model structure.

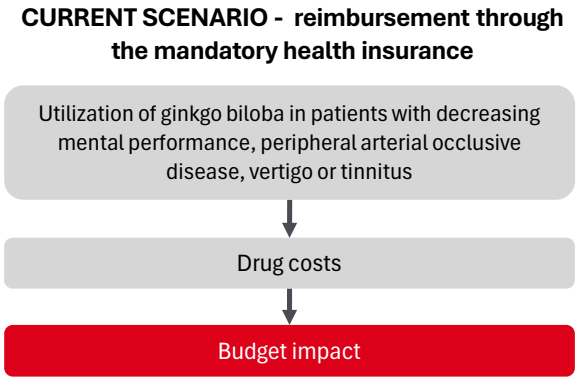

**Figure 45: Model structure**

Patient population

Utilisation data from 2024 were used to estimate the costs of ginkgo biloba treatment in patients with MPD, PAOD, vertigo, or tinnitus. These utilisation data are available per prescription, rather than per person, so it is currently unknown how many patients are treated with ginkgo biloba through the mandatory health insurance.

Model perspective

The model was developed from a Swiss healthcare payer perspective. Costs of healthcare services covered by the Swiss mandatory health insurance were analysed, irrespective of the actual payer (mandatory health insurance, other social insurance, government, out-of-pocket). The analysis did not include indirect costs due to productivity losses and additional non-medical costs for patients, such as travel costs.

Time horizon

A 5-year time horizon was used to estimate the budget impact for ginkgo biloba treatment in patients with MPD, PAOD, vertigo, or tinnitus.

Intervention

Ginkgo biloba may be used either as a standalone therapy (typically when other treatments are unavailable or contraindicated) or as adjunctive treatment (e.g. some formulations of ginkgo biloba are approved only for adjuvant treatment of intermittent claudication or tinnitus), as shown in ***Table 1***. Additionally, there are some types of MPD for which no other treatments are approved (e.g. MCI, vascular dementia, etc.; see ***Section 3.2*** for additional details on alternative treatments and their approved indications), while ginkgo biloba is approved for use in the symptomatic treatment of MPD more broadly. The current clinical practice guidelines (described in more detail in ***Section 9.1***) do not clearly describe how or when ginkgo biloba should be used as a replacement for other treatments vs. as an adjunctive treatment. Rather, guidelines focus on the uses of each treatment option separately.

The Swiss Memory Clinics guidelines for therapy of dementia describe the use of AChEIs, memantine, and ginkgo biloba as symptomatic treatment for MPD. Ginkgo biloba treatment may be considered for patients with subjective cognitive decline and MCI. However, it should always be combined with thorough counseling on dementia preventive measures. In addition, both the Swiss Memory Clinics guidelines and the German S3 Dementia guideline recommend ginkgo biloba for mild to moderate AD or vascular dementia with non-psychotic behavioural symptoms. However, the recommendation level for improving cognition is lower than that for AChEIs.[56,58]

In Switzerland, ginkgo biloba is approved for adjunctive treatment of intermittent claudication (the primary symptom of PAOD), rather than for use as a standalone therapy (see ***Table 1***). However, current guidelines from the European Society of Cardiology (ESC) did not describe the use of

ginkgo biloba in recommendations for patients with PAOD, focusing instead on lifestyle changes aimed at lowering cardiovascular risk factors.[60]

The interdisciplinary guidance paper for clinical practice describes that in patients with acute unilateral vestibulopathy, ginkgo biloba may be considered to support central adaptation.[62] However, the primary goal in the treatment of vertigo should be to identify and treat the underlying cause, rather than treating symptoms.

Tinnitus guidelines do not recommend pharmacologic treatments, ginkgo biloba, or other herbal medicinal products.[49]

Costs

All ginkgo biloba-related costs with an impact on the budget were considered. However, the model was solely based on the costs of the ginkgo biloba formulation, as the SLR did not identify evidence on cost offsets that would have an impact on the budget. Because the clinical practice guidelines do not describe when or how to use ginkgo biloba as a replacement for other treatments and no evidence on real-world treatment patterns of standardised formulations of ginkgo biloba could be identified in the literature, substitution costs were not included in the base case analysis.

To supplement the literature gap regarding the use of ginkgo biloba in real-world practice, 4 medical specialists were consulted to determine which drug treatments would be used if ginkgo biloba were no longer reimbursed. For PAOD, vertigo, or tinnitus, ginkgo biloba was assumed to remain the first-choice treatment, regardless of reimbursement, as it is available over the counter. Decisions regarding switching treatments for patients with MPD in AD dementia depend on the severity and progression of the condition, the patient's age, and their overall medical condition. Possible alternative treatments include rivastigmine, donepezil, galantamine, and memantine. Scenario analysis was conducted to assess the impact of dementia patients switching to alternative treatments on the total costs.

The BIM does not include indirect costs, as the focus is on costs that would directly affect the Swiss healthcare payer. Costs in the model reflect 2025 CHF prices.

Model outcomes

The budget impact analysis estimates the total costs over a 5-year time horizon. Budget impact and disaggregated budget impact results are reported.

#### **7.1.5.2** Model inputs

Data for the model were obtained from a variety of sources, including published studies, available databases, clinical experts, and assumptions as necessary. The following sections describe the inputs and data sources used in the model.

Prescription inputs

The model includes the total number of packages (units) per ginkgo biloba formulation, which was used to estimate the costs. Prevalence data for MPD, PAOD, vertigo, and tinnitus were used to estimate the utilisation per indication.

Prevalence of MPD was based on a study of Börsch-Supran et al. 2025, which used survey data of 47'773 individuals aged 65 years and older in Europe. MPD prevalence among those aged 65 years and older (22.4%) was calculated using the sum of MCI (17.8%) and dementia (4.6%).[151]

Prevalence of PAOD was based on the PANDORA study conducted by Cimminiello et al. 2011, which evaluated 9'816 patients.[152] The prevalence among patients aged 45 and older (men) and 55 and older (women) with ≥1 cardiovascular risk factor was 12.2%.

Prevalence of vertigo was based on a study of Neuhauser et al. 2005. They conducted a neurotologic survey with a random sample of 4'869 participants in Germany followed by detailed interviews (n = 1'003). The prevalence of vestibular vertigo was 7.2% among people aged 60-69 years and 8.8% among people aged 70 years and older.[153]

Prevalence of tinnitus was based on a systematic review and meta-analysis of Jarach et al. 2022. Among 767 publications, 113 eligible articles published between 1972 and 2021 were identified, and prevalence estimates from 83 articles were extracted. The pooled prevalence of any tinnitus among people aged 65 and older was 23.6% (95% CI 19.4% to 28.5%).[43]

The number of units per ginkgo biloba formulation per indication was calculated by multiplying the number of units (***Table 91***) by the weighted (sum to 100%) utilisation per indication (***Table 1*** and ***Table 92***). Utilisation data were evaluated by 4 clinical reviewers.

Historical data (average number of prescriptions 349'824 [2020] and 406'772 [2024]) were used to forecast the annual growth rate of 3.26% (SASIS Tarifpool 2020-2024 dataset).

**Table 91: Ginkgo biloba units and costs in 2025**

| Ginkgo biloba formulation | Units | Costs | Source |
|---|---|---|---|
| **Ginkgo-Mepha** | | | SASIS Tarifpool 2024 and BAG Spezialitäten-liste |
| Filmtablets 80 mg 60s | 793 | CHF 39.30 | |
| Filmtablets 80 mg 120s | 1'663 | CHF 56.65 | |
| Filmtablets 120 mg 60s | 3'922 | CHF 47.65 | |
| Filmtablets 120 mg 120s | 15'449 | CHF 71.35 | |
| **Ginkgo Sandoz** | | | |
| Filmtablets 120 mg 30s | 837 | CHF 32.85 | |
| Filmtablets 120 mg 100s | 12'884 | CHF 63.00 | |

| Ginkgo biloba formulation | Units | Costs | Source |
|---|---|---|---|
| **Ginkgo Spirig HC** | | | |
| Filmtablets 240 mg Blist 30s | 841 | CHF 48.00 | |
| Filmtablets 240 mg Blist 90s | 6’366 | CHF 96.95 | |
| **Rezirkane** | | | |
| Filmtablets 120 mg 60s | 2’543 | CHF 50.85 | |
| Filmtablets 240 mg 30s | 3’496 | CHF 48.45 | |
| Filmtablets 240 mg 60s | 16’036 | CHF 72.85 | |
| Filmtablets 240 mg 90s | 7’495 | CHF 98.15 | |
| **SimiMed Ginkgo** | | | |
| Filmtablets 120 mg 60s | 92 | CHF 47.90 | |
| Filmtablets 120 mg 90s | 46 | CHF 59.55 | |
| Filmtablets 120 mg 120s | 93 | CHF 71.80 | |
| Filmtablets 240 mg 60s | 142 | CHF 68.00 | |
| Filmtablets 240 mg 90s | 481 | CHF 89.15 | |
| **Symfona 120** | | | |
| Capsules 120 mg 60s | 7’926 | CHF 50.80 | |
| Capsules 120 mg 120s | 35’206 | CHF 76.95 | |
| **Symfona 240** | | | |
| Filmtablets 240 mg 30s | 6’458 | CHF 50.80 | |
| Filmtablets 240 mg 60s | 126’912 | CHF 76.95 | |
| **Tebokan 120** | | | |
| Filmtablets 120 mg 90s | 9’511 | CHF 72.95 | |
| Filmtablets 120 mg 120s | 43’458 | CHF 87.20 | |
| **Tebokan 240** | | | |
| Filmtablets 240 mg Blist 30s | 7’472 | CHF 30.89 | |
| Filmtablets 240 mg Blist 60s | 10’411 | CHF 54.36 | |
| Filmtablets 240 mg Blist 90s | 86’181 | CHF 78.79 | |

**Table 92: Utilisation of ginkgo biloba across indications**

| Utilisation across indications | Value | Weighted | Source |
|---|---|---|---|
| **Symptomatic treatment of MPD[a]** | 22.4% sum of mild cognitive impairment (17.8%) and dementia (4.6%) | 33.84%, sum of mild cognitive impairment (26.89%) and dementia (6.95%) | Börsch-Supan 2025[151] |
| **PAOD[b]** | 12.2% | 18.43% | Cimminiello 2011[152] |
| **Vertigo[c]** | 8.0% | 12.08% | Neuhauser 2005[153] |
| **Tinnitus[a]** | 23.6% | 35.65% | Jarach 2022[43] |

*Abbreviations*

MPD = mental performance deficits, PAOD = peripheral arterial occlusive disease.

*Notes*

a = Prevalence among people aged 65 and older.

b = Prevalence among people with ≥1 cardiovascular risk factor aged 45 and older (men) or 55 and older (women).

c = Average of prevalence among people aged 60 to 69 (7.2%) and people aged 70 and older (8.0%).

Costs inputs

Drug costs were calculated by multiplying the units (***Table 91***) by the weighted utilisation (***Table 92***) per indication (***Table 1***) and the costs (***Table 91***). There are no substitution costs (see "Costs" in ***Section 7.1.5.1***).

Sensitivity analysis inputs

The model incorporates a one-way sensitivity analysis for key model parameters. One-way sensitivity analyses were conducted to test how varying each of the model parameters over a range of ±10% of the base case value affected the model results. The costs were recorded at the upper and lower limits to produce a tornado diagram.

Scenario analyses inputs

Scenario analyses were conducted to evaluate the impact of using rivastigmine, donepezil, galantamine, and memantine in patients with dementia.[n] The impact on the total cost was assessed by replacing ginkgo biloba drug costs fully with the drug costs of each other intervention (i.e. rivastigmine, donepezil, galantamine, and memantine) in these patients. Additionally, the impact on the total cost was analysed by replacing ginkgo biloba drug costs with a weighted average of

[n] Note that although these treatments are only approved for use in AD dementia and/or PDD, that level of granularity is not available in the data. To provide an estimate of the maximum impact, it was assumed that all patients with dementia would switch to one of these treatments.

rivastigmine, donepezil, galantamine, and memantine. The number of units, weighted percentages and costs are shown in ***Table 93***.

**Table 93: Rivastigmine, donepezil, galantamine, and memantine percentage and costs**

| Drug | Units[a] | Percentage | Costs[b] | Source |
|---|---|---|---|---|
| **Rivastigmine** | 61,807 | 46.35% | 78.52 CHF | SASIS Tarifpool 2024 and BAG Spezialitätenliste |
| **Donepezil** | 33,270 | 24.95% | 150.20 CHF | |
| **Galantamine** | 10,205 | 7.65% | 61.33 CHF | |
| **Memantine** | 28.055 | 21.04% | 139.96HF | |

*Notes*

a = Units represent the total sum per formulation of rivastigmine, donepezil, galantamine, and memantine.

b = Costs are calculated as weighted averages based on the utilisation and prices per package for each formulation of rivastigmine, donepezil, galantamine, and memantine.

Scenario analyses were conducted to evaluate the impact of the annual growth rate (3.26%) of the number of units. The impact on the budget was assessed using a low growth rate 2% and a high growth rate 4%.

#### **7.1.5.3** Key assumptions and limitations

While a deliberate effort has been made to employ methodologically sound modelling techniques, the inputs and assumptions used in this model may not align with the whole population served by the Swiss healthcare payer. The following limitations are noted.

First, drug strength and package sizes are not indication-specific. The SASIS Tarifpool data only describe the utilisation of ginkgo biloba in Switzerland as a whole and do not provide information specific to individual indications. Prevalence rates of symptomatic treatment of MPD, PAOD, vertigo, and tinnitus were therefore used to calculate the treatment utilisation. This approach, while necessary to estimate indication-specific budget impact, assumes that the different indications are equally likely to use ginkgo biloba (i.e. it assumes that the per-indication utilisation is driven only by the total number of people with the indication, without accounting for the possibility that different conditions may have a different likelihood of receiving ginkgo biloba). These prevalence rates are based on multiple sources, some of which may not fully reflect the Swiss population. Additionally, prevalence rates are assumed to be constant over time. The prevalence of symptomatic MPD used here may also be an underestimate of the true prevalence because only MCI and dementia were considered. Although these are understood to be the largest segment of the MPD population, MPD is used to broadly identify patients with deteriorating cognitive functioning, some of whom may not be fully captured under the diagnoses of MCI and dementia.[151] Similarly, the estimated vertigo

prevalence (5.2%) is assumed to correspond to vertigo of unknown cause and dizziness of unknown cause, as described in the prescription information (***Table 1***).

Finally, there are no substitution costs included, as guidelines do not describe the use of ginkgo biloba as a replacement for other treatments and no evidence on real-world treatment patterns could be identified from the literature.

## 7.2 Results costs, cost-effectiveness and budget impact

### 7.2.1 PRISMA flow diagram

The results of the systematic literature search are summarised in ***Figure 1***.

### 7.2.2 Study characteristics and quality assessment of included studies

Three studies were identified that reported health economic outcomes associated with ginkgo biloba (***Table 94***). All 3 studies were cost-comparison analyses and used data collected from RCTs to model the costs and benefits associated with ginkgo biloba treatment over the course of different disease progression scenarios. The only outcomes reported were direct costs of ginkgo biloba from a public payer perspective. None of the studies reported outcomes in terms of cost per QALY or incremental cost-effectiveness ratios.

The study population in all 3 studies was MPD, specifically people with dementia in 2 studies, both conducted in Austria,[154,155] and people with AD in the other study, which was conducted in Germany.[156] No studies reporting economic data were identified for PAOD, vertigo, or tinnitus. The comparator in both of the dementia studies was placebo,[154,155] while the comparator in the AD study was galantamine.[156] The time horizon was 10 years in the AD study and varied from 3 years to 9 years in the 2 dementia studies, according to different disease progression scenarios.

The 2 dementia studies reported similar modelling methods. Horr et al 2002[154] extrapolated clinical trial data indicating that 6 months' treatment with 120 mg ginkgo biloba resulted in a 10.3-month delay in symptom progression vs. placebo. This served as the basis for modelling longer-term scenarios. The model included direct costs of ginkgo biloba (€213.27 per person per year [PPPY]), doctor visits (€22.40 PPPY), and the federal care allowance (€145.35 to €1'531.51 per person per month, depending on the level of care). Since the cost year was not reported, it is assumed that the costs related to no later than the year of publication of the study (2002). Klement et al 2015[155,157] took a similar approach to modelling the costs and benefits of a higher dose of ginkgo biloba. The delay in symptom progression with 22 or 24 weeks of ginkgo biloba 240 mg was estimated to be 23.3 weeks, extrapolated from 3 RCTs. The costs included in the model, in 2011 EUR, were €288.35 PPPY for ginkgo biloba, €37.62 PPPY for doctor visits, as well as the federal care allowance (no further details on the cost of federal care were reported by the study authors). Neither of the models took into account costs associated with caregivers (i.e. relatives of the patients).

Compared to the 2 dementia studies, the study focusing on patients with AD reported more details on their modelling methods. The study authors described conducting a discrete event simulation model to predict the rate of disease progression based on RCT data showing the change in ADAS-cog scores with either ginkgo biloba 240 mg or galantamine vs. placebo. Costs included in the model, in 2009 EUR, were daily drug costs (€2.20 for ginkgo biloba 240 mg; and €4.11 and €4.55 for galantamine 16 mg and 24 mg, respectively), doctor visits per quarter (€31.40), and monthly costs of home or institutional care (ranging from €384 to €1'432). The cost of caregiver time was also incorporated into the model, based on data from one primary study.

Reporting quality across the 3 studies, assessed by CHEERS, was varied (***Figure 46***). The AD study investigating ginkgo biloba vs. galantamine[156] reported details for most of the items specified by CHEERS but lacked information on setting and approach to engagement with patients. None of the studies reported fully the rationale and assumptions underlying the models. Details on health economic analysis plans and full descriptions of the study population were also missing; for instance, details of the clinical characteristics of the target population were absent. Selection and measurement of outcomes were also unclear, and no discounting rate for costs and benefits was described in 2 of the 3 studies. One study reported the methods and results of sensitivity analysis, but no attempt was made in the other 2 studies to characterise uncertainty in their models.[156] Finally, pharmaceutical funding and conflicts of interest were reported in one study[156] but not described in the other 2.[154,155]

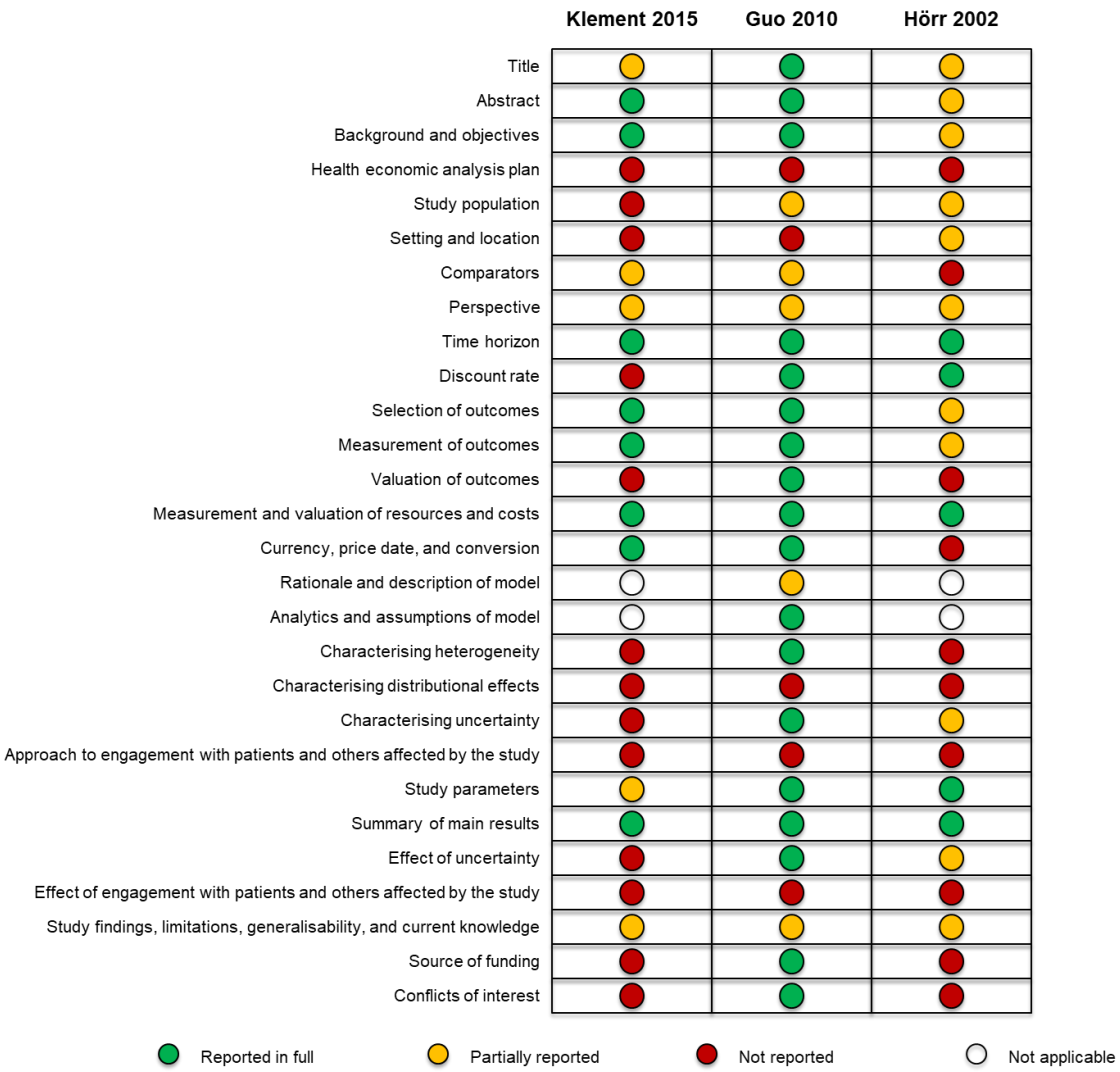


**Figure 46: Results of the assessment of reporting quality of studies reporting economic data**

### 7.2.3 Evidence table

In 7 different scenarios in 2 studies comparing direct costs of ginkgo biloba for dementia in Austria, ginkgo biloba was found to be cost-saving compared to placebo at both 120 mg/day and 240 mg/day dosages.[154,155] Both studies found that ginkgo biloba led to a delay in symptom progression, resulting in a longer time living independently and less need for cost-intensive care, compared to placebo. However, ginkgo biloba 240 mg/day was found to be more costly than galantamine for AD since there was less benefit seen with ginkgo biloba in terms of delay in disease progression and time in institutional care (***Table 94***).[156] Probabilistic sensitivity analysis suggested that this result could vary from an incremental cost of -807 EUR to 9'654 EUR per patient.[156]

The findings are based on data from clinical trials published from 1997 to 2012 and on costs from 2009 to 2011. The findings may not be representative of clinical practice or costs in 2026 and are likely to have limited applicability outside the German and Austrian contexts of the study settings. Various factors could have changed in the intervening period since the studies were conducted that could affect cost comparisons of ginkgo biloba to other treatments; for instance, life expectancy,

the cost of home or institutional care, and the size of the target population may be different in the present day compared to when these data were collected and reported. With this in mind, the conclusions drawn from these economic analyses should be considered with appropriate caution.

**Table 94: Summary of cost-comparison analyses investigating ginkgo biloba for MPD, PAOD, vertigo, or tinnitus**

| Study ID | Study population | Country | Intervention | Comparator | Time horizon | Perspective | Discounting | Cost year and currency | Outcomes: Costs per person |
|---|---|---|---|---|---|---|---|---|---|
| **Klement 2015**[155,157] | Dementia | Austria | EGb 761 240 mg | Placebo | 9 years[a] | Public payer | NR | 2011 EUR | EUR 29’577 cost savings with ginkgo biloba |
| **Klement 2015**[155,157] | Dementia | Austria | EGb 761 240 mg | Placebo | 7 years[b] | Public payer | NR | 2011 EUR | EUR 26’099 cost savings with ginkgo biloba |
| **Klement 2015**[155,157] | Dementia | Austria | EGb 761 240 mg | Placebo | 9 years[c] | Public payer | NR | 2011 EUR | EUR 17’841 cost savings with ginkgo biloba |
| **Klement 2015**[155,157] | Dementia | Austria | EGb 761 240 mg | Placebo | 3 years[d] | Public payer | NR | 2011 EUR | EUR 3’692 cost savings with ginkgo biloba |
| **Hörr 2002**[154] | Dementia | Austria | EGb 761 120 mg | Placebo | 9 years[a] | Public payer | None[e] | NR | EUR 12’153 cost savings with ginkgo biloba |
| **Hörr 2002**[154] | Dementia | Austria | EGb 761 120 mg | Placebo | 7 years[b] | Public payer | None | NR | EUR 12’484 cost savings with ginkgo biloba |
| **Hörr 2002**[154] | Dementia | Austria | EGb 761 120 mg | Placebo | 9 years[c] | Public payer | None | NR | EUR 7’425 cost savings with ginkgo biloba |

| Study ID | Study population | Country | Intervention | Comparator | Time horizon | Perspective | Discounting | Cost year and currency | Outcomes: Costs per person |
|---|---|---|---|---|---|---|---|---|---|
| **Hörr 2002[154]** | Dementia | Austria | EGb 761 120 mg | Placebo | 3 years[d] | Public payer | None | NR | EUR 910 cost savings with ginkgo biloba |
| **Hörr 2002[154]** | Dementia | Austria | EGb 761 240 mg | Placebo | 9 years[f] | Public payer | None | NR | EUR 10'660 cost savings with ginkgo biloba |
| **Hörr 2002[154]** | AD | Austria | EGb 761 240 mg | Placebo | 9 years[g] | Public payer | None | NR | EUR 18'299 cost savings with ginkgo biloba |
| **Guo 2010[156]** | AD | Germany | EGb 761 240 mg[h] | Galantamine | 10 years | Public payer | 5% | 2009 EUR | Incremental cost of ginkgo biloba: EUR 3'972 |

*Abbreviations*

AD = Alzheimer's disease, EUR = euros, MPD = mental performance deficits, NR = not reported; RCT = randomised controlled trial; PAOD = peripheral arterial occlusive disease.

*Notes*

a = Scenario 1: Best possible realism: disease progression 9 years from onset, 2 years full independence, 7 years increasing need for care.

b = Scenario 2: Shorter course of illness: course of illness 7 years from onset, 2 years of full independence, 5 years of additional independence increasing need for care.

c = Scenarios 3: Late onset of treatment: course of illness 9 years from onset, 2 years full independence, 7 years to increasing need for care.

d = Scenario 4: Early death.

e = Study authors reported that discounting was omitted in light of the resulting ratios of treatment costs to savings.

f = Scenario 5: Higher dose: as in Scenario 1, but treatment with Ginkgo special extract EGb 761 at a higher dosage of 240 mg/day.

g = Scenario 6: Alzheimer's type dementia: as in Scenario 5 but focused only on AD.

h = Reported in the published study as ‘Ginkgo biloba 240 mg’; it is assumed to be EGb 761 240 mg because the trial data used in the economic model are from one of the studies included in the review of efficacy data (see ***Section 6.2.4***).

### 7.2.4 Findings: Costs

None of the studies identified in the economic SLR reported primary cost data for patients using ginkgo biloba. See ***Section 7.1.5.2*** for cost inputs for the BIM.

### 7.2.5 Findings: Cost-effectiveness

None of the studies identified in the economic SLR reported cost-effectiveness data.

### 7.2.6 Findings: Budget impact

The budget impact analysis is based on 406'711 ginkgo biloba prescriptions in Year 1 for patients with MPD, PAOD, vertigo, or tinnitus. The budget impact results over a 5-year time horizon (2025-2029) are shown in the tables and figure below (***Table 95***, ***Table 96***, ***Figure 47***).

The reimbursement of ginkgo biloba resulted in a 5-year total spending of CHF 167'154'958.

**Table 95: Annual and cumulative budget impact of ginkgo biloba reimbursement over 5 years**

| | Year 1 (2025) | Year 2 (2026) | Year 3 (2027) | Year 4 (2028) | Year 5 (2029) | Total (5 years) |
|---|---|---|---|---|---|---|
| **Budget impact** | CHF 31'447'694 | CHF 32'439'343 | CHF 33'430'992 | CHF 34'422'641 | CHF 35'414'289 | CHF 167'154'958 |

**Table 96: Annual and cumulative budget impact of ginkgo biloba reimbursement over 5 years per indication**

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Total (5 years) |
|---|---|---|---|---|---|---|
| **Costs MPD** | CHF 10'707'150 | CHF 11'044'782 | CHF 11'382'413 | CHF 11'720'045 | CHF 12'057'676 | CHF 56'912'066 |
| **Costs PAOD** | CHF 5'635'814 | CHF 5'813'530 | CHF 5'991'245 | CHF 6'168'961 | CHF 6'346'677 | CHF 29'956'227 |
| **Costs vertigo** | CHF 3'823'982 | CHF 3'944'565 | CHF 4'065'148 | CHF 4'185'730 | CHF 4'306'313 | CHF 20'325'738 |
| **Costs tinnitus** | CHF 11'280'748 | CHF 11'636'466 | CHF 11'992'185 | CHF 12'347'904 | CHF 12'703'623 | CHF 59'960'927 |

*Abbreviations*

MPD = mental performance deficits, PAOD = peripheral arterial occlusive disease.

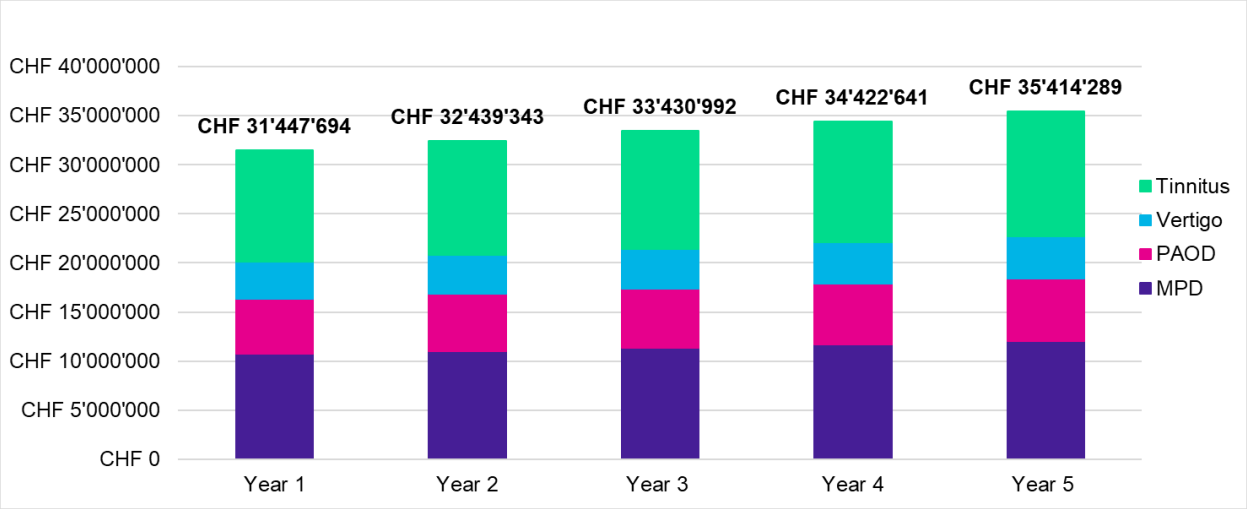


**Figure 47: Annual budget impact of ginkgo biloba reimbursement over 5 years**

*Abbreviations*

MPD = mental performance deficits, PAOD = peripheral arterial occlusive disease.

### 7.2.6.1 Sensitivity analysis

One-way sensitivity analyses were conducted to test the sensitivity of the model to variation in the model parameters by varying the key model parameters over a range of ±10% of the base case value. The output for the one-way sensitivity analysis is the 5-year budget impact with a base case value of CHF 167’154’958. The width of the bars represents the variation in the budget impact over the range of tested parameter values.

The results of the sensitivity analysis are shown in ***Figure 48***.

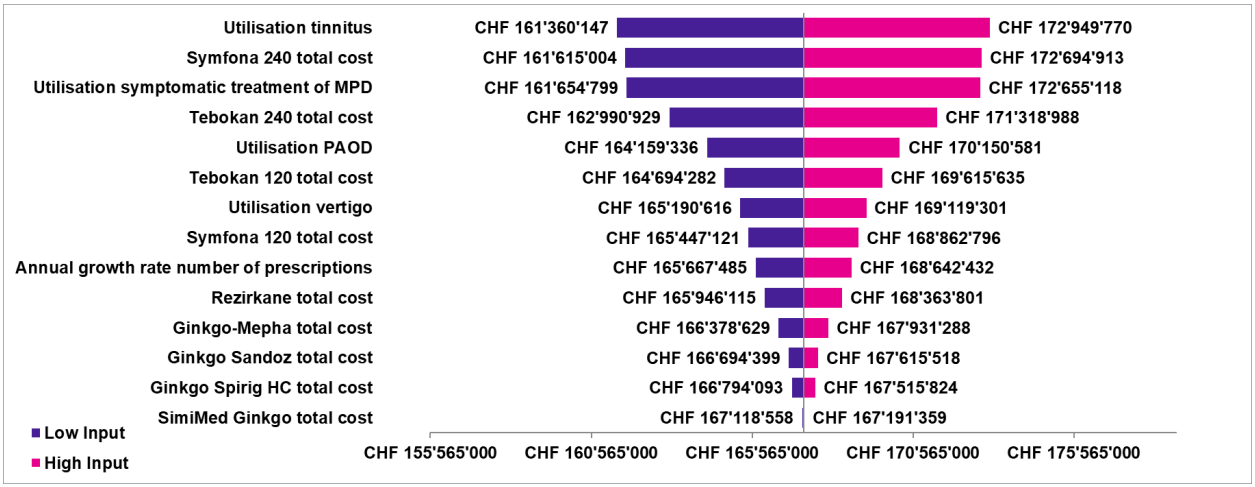


**Figure 48: Tornado diagram sensitivity analysis**

*Abbreviations*

MPD = mental performance deficits, PAOD = peripheral arterial occlusive disease.

The model results were most sensitive to the utilisation of tinnitus, Symfona 240 total cost, and the utilisation of symptomatic treatment of MPD. The sensitivity analysis showed a maximum expected

budget impact of CHF 172’949’770 when the utilisation of tinnitus was increased by 10% and a minimum expected budget impact of CHF 161’360’147 when the utilisation of tinnitus was reduced by 10%.

#### 7.2.6.2 Scenario analyses

In the scenario where ginkgo biloba is not reimbursed, patients with AD dementia or PDD may switch to alternative treatments rivastigmine, donepezil, galantamine, and memantine. Scenario analyses were conducted to assess the impact of treatment switching on the budget. The scenario analyses assumed that all dementia patients receiving ginkgo biloba (6.95% of all ginkgo biloba units) would switch to a new treatment if ginkgo biloba was no longer reimbursed. The analyses indicate additional treatment costs over 5 years if all dementia patients currently receiving ginkgo biloba switch to either rivastigmine (CHF 12’180’648), donepezil (CHF 23’302’095), galantamine (CHF 9’514’923), or memantine CHF (21’713’115). Furthermore, if dementia patients currently receiving ginkgo biloba switched to a treatment based on a weighted percentage calculated from the current utilisation of rivastigmine, donepezil, galantamine, and memantine, treatment switching would result in additional costs of CHF 16’757’340 over 5 years.

Additional scenario analyses were conducted to evaluate the impact of differing annual growth rates (base case annual growth rate: 3.26%) of the number of units of ginkgo biloba. The impact on the budget is CHF 161'417’039 and CHF 170’553’853 using a low and high growth rate of 2% and 4%, respectively, compared to the base case budget impact of CHF 167’154’958 over a 5-year time horizon.

The results of the scenario analyses are shown in ***Table 97***.

**Table 97. Scenario analyses results**

| Scenario | Budget impact | Difference |
|---|---|---|
| Dementia patients all on ginkgo biloba (base case) | CHF 167’154’958 | - |
| Dementia patients all on rivastigmine | CHF 179’335’606 | CHF 12’180’648 |
| Dementia patients all on donepezil | CHF 190’457’053 | CHF 23’302’095 |
| Dementia patients all on galantamine | CHF 176’669’881 | CHF 9’514’923 |
| Dementia patients all on memantine | CHF 188’868’073 | CHF 21’713’115 |
| Dementia patients receiving treatment based on weighted percentage, calculated using current utilisation of rivastigmine (46.34%), donepezil (24.97%), galantamine (7.65%), and memantine (21.03%) | CHF 183’912’299 | CHF 16’757’340 |

| | | |
|---|---|---|
| Low annual growth rate of 2% | CHF 161’417’039 | CHF -5’737’919 |
| High annual growth rate of 4% | CHF 170’553’853 | CHF 3’398’895 |

# 8. Ethical, legal, social and organisational issues

***Summary statement ethical, legal, social and organisational issues***

The literature review identified 23 studies highlighting important ethical, legal, social and organisational (ELSO) issues associated with the use of ginkgo biloba in the treatment of MPD, PAOD, vertigo, and tinnitus. There was no eligibility restriction on study design; studies identified included systematic and narrative reviews (k=12), governmental guidance documents (k=2), pharmacovigilance studies (k=2), pharmacologic studies (k=2), expert interviews (k=2), discrete choice experiment (k=1), retrospective analysis of RCT data (k=1), and clinical guidelines (k=1), Study quality was not assessed. Ethical concerns primarily revolved around the principles of respecting patient autonomy, promoting beneficence, and ensuring non-maleficence, especially in vulnerable populations like the elderly and those with cognitive impairments. In these groups, the potential for herb-drug interactions and the risks posed by non-standardised supplements are particularly pronounced. Legal issues highlighted regulatory inconsistencies across countries, which contribute to inadequate pharmacovigilance and potential gaps in product labelling. Social disparities in access to high-quality products and the societal burden of these conditions could further exacerbate healthcare inequities. Organisational challenges involved integrating ginkgo biloba into evidence-based treatment pathways, improving pharmacovigilance systems, and addressing patient adherence through education and multidisciplinary collaboration. Such measures are essential to ensure the safety and efficacy of ginkgo biloba.

## 8.1 Methodology: ethical, legal, social and organisational issues

### 8.1.1 Databases and search strategy

To address the ELSO issues, all publications included in the SLRs described in ***Section 6*** and ***Section 7*** were reviewed for any relevant information. Subsequently, a targeted literature search in Embase and MEDLINE (see ***Appendix B*** for the detailed search strategy) was conducted to supplement the findings.

### 8.1.2 Other sources

Complementary hand searches were performed on relevant websites such as the European Medicines Agency (EMA) and Swissmedic.

### 8.1.3 Study selection

Inclusion and exclusion criteria are presented in ***Table 98*** and were developed in accordance with those of the clinical and economic evidence search, with the limitation of including only those articles published since 2015. However, there were no restrictions on study design, as discussions on ELSO outcomes were considered likely to encompass a range of study methodologies. A single researcher screened and reviewed the literature to identify studies pertinent to ELSO domains.

**Table 98: Eligibility criteria for ELSO issues**

| | Inclusion criteria | Exclusion criteria |
|---|---|---|
| **Population** | As for ***Table 5***, ***Table 6***, ***Table 7***, ***Table 8*** | |
| **Interventions** | As for ***Table 5***, ***Table 6***, ***Table 7***, ***Table 8*** | |
| **Comparators** | As for ***Table 5***, ***Table 6***, ***Table 7***, ***Table 8*** | |
| **Outcomes** | Discussion of ethical, legal, social, or organisational aspects | No discussion of ethical, legal, social, or organisational aspects |
| **Language** | As for ***Table 5***, ***Table 6***, ***Table 7***, ***Table 8*** | |
| **Time horizon** | 2015 to present | |
| **Study design/ publication type** | Journal articles<br>No restrictions on study design | Conference abstracts |

*Abbreviations*

ELSO = ethical, legal, social, and organisational

### 8.1.4 Data extraction and synthesis

It is important to note that a formal data extraction and an assessment of the quality of evidence were not conducted for ELSO outcomes. The primary ELSO aspects identified through this targeted search are presented descriptively, as this review did not follow a systematic methodology. This approach was deemed appropriate, as the main goal is to highlight key aspects relevant to ELSO rather than to provide an exhaustive or systematic review of the literature on these domains.

## 8.2 Results: ethical, legal, social and organisational issues

### 8.2.1 PRISMA flow diagram

The results of the targeted literature search are summarised in ***Figure 49***.

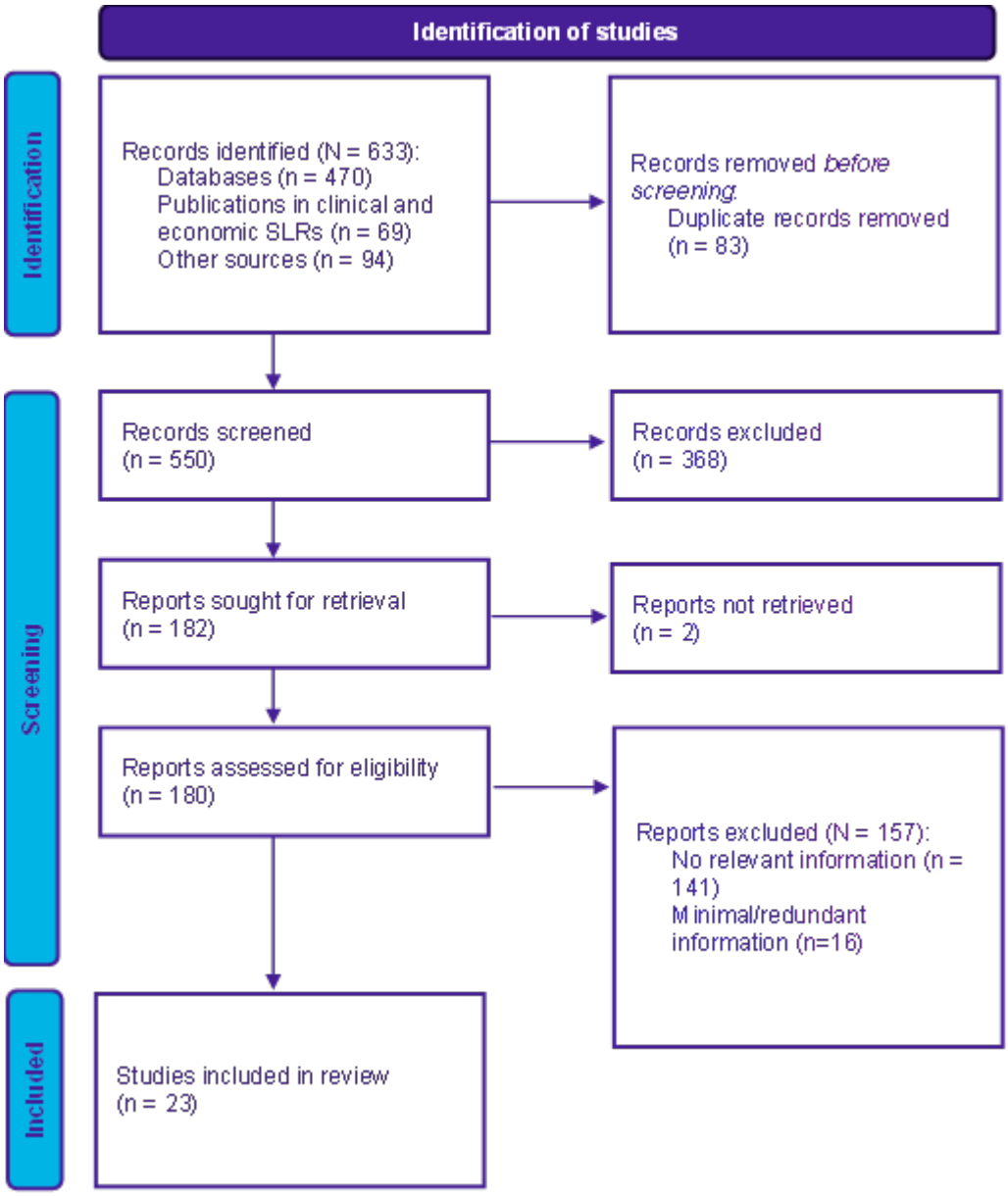


**Figure 49: PRISMA 2020 flow diagram for ELSO targeted literature review**

### 8.2.2 Study characteristics and risk of bias of included studies

The characteristics of the studies identified for the ELSO domains are displayed in ***Table 99***. Risk of bias assessment for these studies was not performed.

**Table 99: Study characteristics table – ethical, legal, social, and organisational issues**

| Study | Study design | Population | Ginkgo biloba-specific data reported | Outcomes reported | | | |
|---|---|---|---|---|---|---|---|
| | | | | Ethics | Legal | Social | Organi-sational |
| **Agbabiaka 2017**[158] | SLR | Across conditions (age ≥65) | Yes | X | | | |
| **Alghamdi 2023**[159] | Pharmacovigilance study | Across conditions | Yes | X | X | | X |
| **Booker 2016**[160] | Pharmacologic study | Not conducted in humans | Yes | X | X | X | X |
| **Callahan 2015**[161] | Retrospective analysis of RCT data | MCI | No | X | | X | |
| **Chugh 2018**[162] | Review | Across conditions | Yes | | X | | |
| **Dy 2025**[163] | Review | Vertigo | No | | | X | |
| **Ekhart 2025**[164] | Semi-structured interviews of ex-perts | Experts in herbal pharmacovigi-lance | Yes | | X | | |
| **EMA 2015**[54] | HMPC monograph | Across conditions | Yes | | X | | X |
| **Gupta 2018**[165] | Review | Across conditions | Yes | | X | | |
| **Hundal 2022**[166] | Semi-structured interviews of ex-perts | Experts in the use of Western herbal medicine for brain health | No | | | X | |
| **Husni 2020**[167] | Review | Cardiovascular diseases | Yes | | | X | |
| **Lamb 2023**[168] | Review | Across conditions | Yes | | | | X |
| **Lorca 2023**[169] | SLR | Tinnitus, cognitive impairment | Yes | | | | X |
| **Mahmoudian-Sani 2017**[170] | Review | Tinnitus | Yes | X | | X | |
| **Nicolaï 2009**[171] | SLR | PAOD | Yes | X | | X | |
| **Rademaker 2021**[172] | Discrete choice experiment | Tinnitus | No | X | | X | |
| **Raposo 2021**[173] | Review | PAOD | Yes | X | | | X |

| Study | Study design | Population | Ginkgo biloba-specific data reported | Outcomes reported | | | |
|---|---|---|---|---|---|---|---|
| | | | | Ethics | Legal | Social | Organi-sational |
| **Smolderen 2022**[174] | Guideline | PAOD | No | | | X | |
| **Swissmedic 2025**[175] | Guidance document | Across conditions | Yes | | X | | X |
| **Trabert 2024**[176] | Pharmacologic study | Not conducted in humans | Yes | X | X | X | X |
| **Varkey 2021**[177] | Review | Across conditions | No | X | | | |
| **Watt 2024**[178] | SLR of guidelines | Dementia | Yes | X | | | |
| **Yao 2025**[179] | Pharmacovigilance study | Across conditions | Yes | | X | | |

*Abbreviations*

HMPC = Committee on Herbal Medicinal Products, MCI = mild cognitive impairment, PAOD = peripheral arterial occlusive disease, RCT = randomised controlled trial, SLR = systematic literature review.

### 8.2.3 Evidence table

The findings of the ELSO domains are described narratively in ***Section 8.2.4*** (ethical issues), ***Section 8.2.5*** (legal issues), ***Section 8.2.6*** (social issues), and ***Section 8.2.7*** (organisational issues).

### 8.2.4 Findings: Ethical issues

#### 8.2.4.1 General use of ginkgo biloba

The ethical principles of beneficence, non-maleficence, autonomy and justice form the foundation of clinical decision-making and should be central to the use of ginkgo biloba. Healthcare providers must act in the best interests of patients (beneficence) by promoting their welfare while minimising harm.[177] Although this review focused on approved standard formulations, the widespread availability of non-standardised ginkgo biloba supplements is concerning. Such products have been found to contain toxic levels of ginkgolic acids or adulterants, which pose risks to consumers and violate the principle of avoiding harm (non-maleficence).[160,176] Particularly, increases in costs may cause lower-income populations to face barriers to accessing safe and effective standardised ginkgo biloba products, further complicating ethical considerations of fairness and equitable treatment (justice).[160,176]

Autonomy, another core ethical principle, requires that patients be fully informed about the risks and benefits of ginkgo biloba so they can make decisions aligned with their values and preferences. However, many patients are unaware of the potential herb-drug interactions associated with ginkgo biloba, including its antiplatelet activity, which may potentially increase the risk of bleeding when combined with anticoagulants or nonsteroidal anti-inflammatory drugs.[159,173] Healthcare providers must ensure that patients receive accurate and transparent information to make informed decisions, particularly in vulnerable populations such as elderly patients or those with multimorbidity and polypharmacy.[158]

#### 8.2.4.2 Mental performance deficits

The use of any treatment, including ginkgo biloba, for cognitive decline and dementia raises specific ethical concerns, particularly in elderly patients who may have impaired decision-making capacity. Obtaining informed consent in such cases can be challenging and may require surrogate or shared decision-making processes to respect patients' autonomy.[178,180] Healthcare providers must carefully balance the principles of beneficence and non-maleficence when considering the risks of herb-drug interactions and the potential for adverse effects. For example, the concurrent use of ginkgo biloba with prescription drugs in elderly patients has the potential to increase the risk of bleeding, further complicating ethical decision-making.[158] Treatments must align with the patients' values and preferences while minimising harm.

#### 8.2.4.3 Peripheral arterial occlusive disease

Management strategies for PAOD aim to achieve 2 distinct goals: lowering cardiovascular risk and improving walking ability. The largest potential ethical concern regarding the use of ginkgo biloba for PAOD is ensuring that patients understand the risks of herb-drug interactions. This is especially relevant for older adults taking anticoagulants or other cardiovascular medications. Additionally, the limited evidence supporting ginkgo biloba's clinical significance in improving walking distance for patients with intermittent claudication underscores the need for clear communication with patients about its potential benefits and risks.[24]

#### 8.2.4.4 Vertigo

For patients with vertigo, respecting autonomy requires healthcare providers to communicate clearly about the condition, prognosis, and available treatment options. Ethical considerations focus on ensuring accurate diagnosis and timely treatment to prevent complications, particularly for central causes of vertigo, which may result in severe neurological outcomes if not addressed promptly.[177]

#### 8.2.4.5 Tinnitus

Ethical concerns in the treatment of tinnitus include prioritising patient preferences in treatment outcomes, such as the reduction of tinnitus loudness, which is considered the most desirable outcome by patients.[172] However, the heterogeneity of tinnitus symptoms complicates treatment planning, highlighting the importance of shared decision-making to address individual patient needs.[170]

### 8.2.5 Findings: Legal issues

#### 8.2.5.1 General use of ginkgo biloba

The regulatory status of ginkgo biloba varies across countries, creating challenges in ensuring product quality and safety. In Switzerland, all herbal medicinal products must meet stringent safety and quality standards, including pharmacovigilance plans,[175] and both Swissmedic and the EMA have released guidelines to improve herbal pharmacovigilance.[54,175] However, the inconsistent implementation of legal frameworks across different regions results in gaps in adverse event reporting and risk assessment.[159,181] For example, in the United States, it is marketed as a dietary supplement, while in Germany and France, it is regulated as a prescription drug.[182] Dietary supplements often lack rigorous pre-marketing and post-marketing surveillance, increasing the risk of adulteration and toxicity.[160,176] In fact, over 700 adverse event reports related to ginkgo biloba supplements were identified in the United States FDA Adverse Event Reporting System (FAERS) database.[179] Because of the differences in legal requirements for herbal medicinal products and dietary supplements, changes in the availability of standardised forms of ginkgo biloba require careful consideration of possible ramifications.

#### 8.2.5.1 Regulatory standards for safety and labelling

Legal issues for patients with all included conditions include the need for appropriate labelling to warn about herb-drug interactions, particularly with anticoagulants, due to the potentially increased risk of bleeding. Pharmacovigilance systems must monitor AEs to ensure patient safety.[175]

#### 8.2.5.2 Mental performance deficits

In Switzerland, products intended for dementia treatment must demonstrate compliance with Good Clinical Practice and provide sufficient documentation to substantiate safety claims.[175] Additionally, while the European Union requires herbal medicines to meet pharmacopoeia standards, dietary supplements are not subject to the same stringent requirements, creating potential risks for consumers.[54,162]

### 8.2.6 Findings: Social issues

#### 8.2.6.1 Burden of disease

The collective societal burden of MPD, PAOD, vertigo, and tinnitus highlight the need for equitable access to effective treatments and comprehensive support systems.

- Cognitive decline and dementia, which often manifest as decreasing mental performance, are associated with high healthcare costs, caregiver burden, and reduced quality of life, particularly in aging populations.[166,180]
- PAOD, characterised by intermittent claudication, limits mobility and independence, leading to reduced productivity and increased healthcare utilisation, particularly in lower socioeconomic groups.[24,174]
- Vertigo, a common symptom in primary care, results in frequent emergency visits, work absenteeism, and long-term disability, especially when misdiagnosed or untreated.[163]
- Tinnitus, often associated with depression and anxiety, significantly impacts psychological well-being, social functioning, and productivity, further compounding its societal burden.[170,172]

#### 8.2.6.2 Disparities in access

Social disparities in access to ginkgo biloba are reported across geographic and socioeconomic lines. High-quality products like EGb 761® are often expensive and inaccessible to lower-income populations, while adulterated or substandard products are widely available and promoted, exacerbating inequities in healthcare delivery.[160,167,176]

#### 8.2.6.3 Cultural and behavioural factors

Cultural distrust of healthcare providers and established lifestyle habits among elderly patients can affect adherence to ginkgo biloba treatment. Practitioners often face challenges in managing

patient expectations and compliance, particularly when herbal treatments are perceived as less potent than conventional drugs.[166]

### 8.2.7 Findings: Organisational issues

#### 8.2.7.1 Pharmacovigilance and quality control

Organisational challenges include the need for standardised treatment protocols and robust regulatory oversight of pharmacovigilance systems to monitor AEs and ensure consistent quality control.[160,176]

#### 8.2.7.2 Integration into treatment pathways

The integration of ginkgo biloba into treatment pathways for cognitive decline, PAOD, vertigo, and tinnitus requires a multidisciplinary approach.[54,175] Many healthcare providers lack adequate training to assess the efficacy, safety, and herb-drug interactions. This knowledge gap limits their ability to integrate ginkgo biloba into treatment pathways effectively and safely. Developing standardised educational programmes is essential to address this challenge.[159]

#### 8.2.7.3 Adherence to therapy

Adherence to ginkgo biloba therapy is influenced by patient perception and education. Studies indicate that patients may discontinue treatment prematurely due to misconceptions about efficacy or fear of adverse effects.[168,169] Developing standardised educational programmes and counselling is essential to address this knowledge gap to improve adherence and reduce risks.[173]

# 9. Additional issues

## 9.1 Clinical practice guidelines

Rather than targeting the underlying disease pathology, currently approved drug treatments for dementia aim to either improve or reduce deterioration of symptoms, specifically cognitive impairment, daily functioning, and neuropsychiatric symptoms. Based on both the German guidelines and National Institute for Health and Care Excellence (NICE) guidelines on dementia treatment, as well as those developed by the Swiss Memory Clinics, the AChEIs donepezil, galantamine, and rivastigmine are recommended for the symptomatic treatment of mild-to-moderate dementia due to AD.[56,58,59] Rivastigmine is also recommended for use in PDD.[56,58,59] Memantine is recommended for use in moderate-to-severe AD dementia, although the NICE guidelines specify that it should be used as second-line treatment to AChEIs in patients with moderate AD.[56,58,59] The German guidelines and recommendations from the Swiss Memory Clinics both note that ginkgo biloba is efficacious in improving cognitive function and daily functioning, although heterogeneity across published studies introduce some uncertainty.[56,58] In general, both indicate that it is appropriate to use standardised extracts of ginkgo biloba for the treatment of mild-to-moderate AD, noting that it might be more effective in patients who have non-psychotic neuropsychiatric symptoms.[56,58] The Swiss

Memory Clinics recommendations also state that ginkgo biloba preparations are the only substances approved for MCI in Switzerland,[58] while the German guidelines reported that AChEIs have been shown to be ineffective in patients with MCI.[56] Finally, the Asian Clinical Expert Group on Neurocognitive Disorders recommends that EGb 761 should be considered among the current best practice treatments for patients with both AD and neuropsychiatric symptoms (Class of recommendation I; level of evidence A) and may be considered for use in patients with MCI (Class of recommendation IIb; level of evidence A).[55]

The NICE guidelines on PAOD, as well as those developed by the European Society of Cardiology (ESC), recommend lifestyle changes, such as diet, exercise, and treating tobacco dependence.[60,61] In terms of pharmacologic treatment, both also recommend aspirin or rivaroxaban plus aspirin for preventing later cardiac events in people with symptomatic PAOD. Clopidogrel may also be appropriate in some cases. The ESC guidelines do not recommend oral anticoagulant monotherapy, long-term dual antiplatelet therapy, or routine use of ticagrelor in patients with PAOD.[60] For the treatment of IC among patients with PAOD, both NICE and the ESC state that naftidrofuryl oxalate can be considered.[60,61] The NICE guidelines state that cilostazol, pentoxifylline, and inositol nicotinate are not recommended for the treatment of IC in patients with PAOD, while the ESC guidelines did not recommend prostanoids, pentoxifylline, L-arginine, buflomedil, or ginkgo biloba because of inconsistent evidence of effect.[60,61]

Following a survey of Swiss primary care physicians, recommendations for the diagnosis and treatment of vertigo and dizziness have been created by an interdisciplinary working group, including neurologists, ear-nose-throat specialists, and a general practitioner from Switzerland, as well as a representative from Germany.[62] In general, the guidelines emphasise the importance of identifying and treating the underlying cause of vertigo and dizziness, particularly acute causes that may be imminently dangerous or include accompanying neurological symptoms (e.g. double vision, ataxia) or cardiovascular symptoms (e.g. palpitations, chest pain). For BPPV, repositioning manoeuvres may be appropriate, including the Epley manoeuvre or the Semont-plus manoeuvre for posterior canal BPPV, as well as the Gufoni manoeuvre or 360-degree barbecue manoeuvre for lateral canal BPPV. If necessary, antiemetics and/or sedatives may be used before conducting repositioning manoeuvres. For acute unilateral vestibulopathy, doctors should consider steroids, ensuring that they account for patients' comorbidities. They can also consider antiemetics (i.e. domperidone, metoclopramide, ondansetron) and/or antivertiginous drugs (i.e. cinnarizine) for no more than 2 to 3 days, as well as standardised ginkgo biloba extract EGb 761. For many causes of vertigo or dizziness, multimodal treatment is required, and may include physical therapy, psychotherapy, auditory rehabilitation, or other lifestyle modifications.

The majority of tinnitus guidelines either do not recommend pharmacologic treatment or recommend strongly against pharmacologic treatment; some also recommend against treatment with dietary supplements or herbal medicinal products.[47-49] Instead, most guidelines recommend the use of cognitive behavioural therapy, while some also offer options including sound therapy or tinnitus

retraining therapy, although they generally note that the evidence is inconsistent. For patients who also experience some level of hearing loss, assessment for a hearing aid may also be appropriate. However, pharmacologic treatment can be indicated for the treatment of tinnitus co-morbidities.

## 9.2 Existing HTA reports

Although ginkgo biloba has been widely studied, the only HTA report available for comparison was that conducted by the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) and published in 2008.[183] The IQWiG HTA report included patients with mild, moderate, or severe AD, including mixed forms of AD such as vascular dementia, diagnosed using generally accepted criteria. Based on an SLR with searches conducted in 2007, the IQWiG HTA report concluded that there is some evidence of the effect of 240 mg ginkgo biloba on cognitive function, ADLs, psychopathological symptoms, and caregiver burden, but that due to the heterogeneity across studies, there is uncertainty regarding the magnitude of effect. There was also no evidence of harm from ginkgo biloba in terms of AEs or SAEs, although there was some evidence that patients taking ginkgo biloba were more likely to withdraw from the study. Because of extensive heterogeneity, they did not draw any definitive conclusions regarding the potential benefits of 120 mg ginkgo biloba. Finally, they stated the need for long-term data regarding any potential side effects of long-term treatment with ginkgo biloba.

## 9.3 Ongoing randomised clinical trials

On 8 April 2025, a search was completed of ClinicalTrials.gov and the EU Clinical Trials Register. After removing duplicate records, a total of 122 records from ClinicalTrials.gov and 16 records from the EU Clinical Trials Register were screened for eligibility. No relevant ongoing trials were identified in either platform. Of the 8 potentially relevant trial records on ClinicalTrials.gov, 3 correspond to trial publications identified in this review, 3 were completed with no posted results or information about available publications, 1 was terminated due to an inability to recruit a sufficient number of patients, and 1 has an unknown status. Of the 4 potentially relevant trial records on the EU Clinical Trials Register, 2 correspond to trial publications identified in this review, 1 did not provide results, and 1 included both cognitively healthy adults and those with MCI but did not report stratified results for patients with MCI at baseline.

Although it was not identified in the search of ongoing trials, a relevant trial has been published since the conduct of the search.[184] This study compared 120 mg ginkgo biloba with 36 mg betahistine over 12 weeks in 86 adults with dizziness/vertigo without an identified aetiology. Although this study was not formally included in the present review, the results appear generally consistent with the identified studies: there were no significant differences between ginkgo biloba and betahistine in dizziness/vertigo severity. One additional relevant trial has been identified but not included.[185] Although this trial appears to be eligible, it could not be identified through any of the methods utilised in the present review (see ***Section 6.1.1***). The journal is not indexed in any of the prespecified bibliographic databases searched, nor in any of the databases recommended by the Cochrane

Handbook for Systematic Reviews of Interventions.[63] It was also not included in any of the SLRs identified during the search and screening process, nor in the searches of clinical trial registries. Because a key characteristic of an SLR is that it is reproducible, it would be methodologically inappropriate to include this study. The study included 36 adults with permanent or recurrent central vestibular vertigo due to ischaemic lesions of the brainstem or cerebellum. Patients were randomised to receive either 240 mg ginkgo biloba or placebo for 180 days; all patients were instructed to complete daily vestibular exercises. After 180 days, the VAS rating of vertigo severity (range: 0 to 100) had decreased statistically significantly more in the patients receiving ginkgo biloba (mean -20.4 [95% CI -30.7 to -10.1]) than those receiving placebo (mean -6.8 [95% CI -18.0 to -4.4], p = 0.04). This is the only identified trial in patients with vertigo that compared ginkgo biloba and placebo. Because it included only 36 patients, results would need to be replicated in larger studies to provide confidence in the findings.

# 10. Discussion

## 10.1 Summary of results

Overall, the present HTA report identified 42 RCTs evaluating the efficacy of ginkgo biloba. Based on these studies, the higher approved daily dose of ginkgo biloba (240 mg) showed benefits in patients with MPD after 24 weeks of treatment, specifically in cognitive functioning (4 RCTs; moderate certainty evidence), neuropsychiatric symptoms (4 RCTs; moderate certainty evidence), functional status (2 RCTs; high certainty evidence), and HRQoL (2 RCTs; moderate certainty evidence). For the other indications, the results for all efficacy outcomes were based on low or very low certainty evidence, meaning that the true effect estimates may be substantially different from those presented here. Although no studies of the higher daily dose of ginkgo evaluated pain in patients with PAOD, 120 mg ginkgo biloba may result in a small reduction in pain among patients with PAOD compared with placebo (2 RCTs; low certainty evidence). In patients with vertigo, there were no differences in vestibular symptoms between high-dose ginkgo biloba and betahistine (1 RCT; low certainty evidence). For PAOD, vertigo, and tinnitus, the available findings do not support any conclusions of benefit compared with placebo for the remaining outcomes (all very low certainty evidence). Despite this, there is long-standing traditional use of ginkgo biloba in herbal medicine.[54]

Based on the results of both per-indication analyses and analyses across indications and doses, taking ginkgo biloba for 24 weeks is not associated with an increased risk of AEs or SAEs. Although some have raised concerns regarding the effect of ginkgo biloba on the risk of bleeding due to its antiplatelet activity,[1,159,173] only 2 trials (durations 26 weeks and 5 years) reported data on bleeding AEs in patients taking ginkgo biloba (dosages 120 mg to 240 mg). Neither trial found any statistically significant differences between ginkgo biloba and placebo in the occurrence of bleeding AEs, but these results have not been replicated in other studies.

To estimate the budget impact of ginkgo biloba treatment for patients with MPD, PAOD, vertigo or tinnitus reimbursed through mandatory health insurance, a BIM was developed. The results indicate that the budget impact of reimbursing ginkgo biloba over a 5-year period amounted to CHF 167'154'958. Scenario analysis showed additional costs when patients with dementia switched from ginkgo biloba to alternative treatment rivastigmine (CHF 12'180'648), donepezil (CHF 23'302'095), galantamine (CHF 9'514'923), memantine CHF (21'713'115), and a weighted average of these treatments (CHF 16'757'340). Sensitivity analyses showed the budget impact results were most sensitive to the utilisation of tinnitus, Symfona 240 total cost, and the utilisation of symptomatic treatment of MPD.

To identify any ELSO issues associated with the use of ginkgo biloba, a targeted search was conducted. The ethical and social issues identified were not typically unique to ginkgo biloba. Primarily, concerns revolve around adequate communication of potential benefits and harms, particularly among vulnerable populations such as those with MPD; improving pharmacovigilance systems to capture potential risks specific to standardised formulations; and ensuring equitable access to high-quality treatments. Although there is uncertainty regarding the magnitude of effect in patients with MPD, ginkgo biloba is currently the only pharmacologic therapy approved in Switzerland to treat MCI, non-specific memory problems, and types of dementia other than AD dementia and PDD.

## 10.2 Comparison with existing HTA reports

An IQWiG HTA report published in 2008 included an SLR with searches covering up through September 2007.[183] The authors included patients with mild, moderate, or severe AD, including mixed forms of AD such as vascular dementia, diagnosed using generally accepted criteria. Although the current HTA report is broader in scope, both in terms of the types of eligible MPD conditions and in the inclusion of PAOD, vertigo, and tinnitus, the methodology used was generally similar. In the IQWiG review, eligible trials compared ginkgo biloba in any formulation approved for use in Germany with either placebo or pharmacological or non-pharmacological treatments approved for AD in Germany. One notable difference is that the IQWiG review restricted eligibility to trials lasting at least 16 weeks, while the current review did not have a minimum required treatment duration or follow-up time. In general, similar endpoints were included in both reviews (cognitive function, ADL/functional status, HRQoL, other disease-related symptoms such as neuropsychiatric changes, and AEs), although the IQWiG review also included caregiver-related outcomes. In addition, the IQWiG report does not include GRADE assessments of the certainty of evidence.

All 6 published trials identified in the IQWiG report were included in the present review; the IQWiG report also included one unpublished study obtained from the manufacturer. Despite the large number of studies that have been published since the IQWiG review was conducted, our conclusions are largely very similar. Both the IQWiG HTA report and the present HTA identified serious heterogeneity across studies in terms of effect estimates, particularly in the 120 mg dose studies, which limited the ability to make definitive statements on the magnitude of treatment effects. Due to this

heterogeneity, both the IQWiG and present HTA report performed separate analyses by dose of ginkgo biloba. Although the evidence on the lower dose (120 mg) is generally of very low certainty, both the IQWiG report and this HTA review identified evidence that 240 mg ginkgo biloba is beneficial for cognitive function (low certainty evidence), functional status (moderate certainty evidence), and overall neuropsychiatric symptoms (low certainty evidence). The IQWiG report also noted that only a single study reported HRQoL for 240 mg ginkgo biloba; although a statistically significant result in favour of ginkgo biloba was observed, it was not considered enough evidence to form strong conclusions. The present HTA review could not include that study as it was unpublished; however, 2 studies with relevant HRQoL data have been published since the conduct of the IQWiG review and were included. Based on the new evidence, the present review additionally reports that there is moderate certainty evidence that 240 mg ginkgo biloba improved HRQoL compared to placebo.

Although the IQWiG HTA report did not describe MCIDs (all meta-analyses used SMDs rather than mean difference in scores), their recent general methods document provides guidance on determining clinically meaningful differences.[186] MCIDs may vary depending on a variety of factors, including both the methodology used to determine the MCID and characteristics of the patients being assessed. To address this uncertainty, IQWiG outlines the following approach for the assessment of primary studies:

1. For responder analyses based on a pre-specified MCID of a continuous scale (i.e. proportion of participants whose score changed by at least the pre-specified MCID), analyses for which the MCID is at least 15% of the scale range will be accepted without further investigation and responder analyses will be preferred over analyses of continuous data for assessment.
2. If the MCID is not pre-specified or the pre-specified MCID is less than 15% of the scale range, the responder analysis will generally not be used for assessment. If analyses of continuous data are available, SMDs will be used. An irrelevance threshold of 0.2 will be used for assessment. If the confidence interval of the effect estimate is completely above this threshold, the effect will be considered at least “small” (i.e. the effect is not within a range that is certainly irrelevant). If continuous data are not available, post hoc analyses with a response criterion of exactly 15% will be considered for assessment.

## 10.3 Comparison with published systematic literature reviews (SLRs)

There have been many SLRs published on the use of ginkgo biloba in MPD, PAOD, vertigo, and tinnitus, including Cochrane reviews.[13,24,50,57,187] However, the majority of identified SLRs do not specify the formulation of ginkgo biloba. In countries such as the United States, where there are no clear regulations regarding the contents of herbal supplements, the ginkgo biloba intervention may include a wide range of specific formulations. It is inappropriate to generalise results from dietary

supplements to standardised formulations such as those included in the current review,[188-191] so those SLR results are not discussed here.

A few SLRs specific to the efficacy of the standardised ginkgo biloba extract EGb 761 in dementia have been conducted.[192-194] Although these 3 SLRs were somewhat narrower in scope than the present review, the studies included in those reviews overlapped substantially with the studies included in the meta-analyses conducted in this review, and the conclusions were therefore largely similar. All 3 SLRs were restricted to studies of patients with AD, vascular dementia, and/or mixed dementia. For all 3 SLRs, doses of 120 mg to 240 mg of ginkgo biloba were eligible; however, at least one treatment group received 240 mg ginkgo biloba in most or all trials included in each SLR (6/7,[o192] 7/9,[p193] and 4/4[194] included trials). Two SLRs included only studies that were at least 20 to 22 weeks in duration;[192,194] the third did not restrict based on study duration, although they required that studies have "similar…duration of administration".[193] One SLR also required patients in the included studies to have behavioural and psychological symptoms.[194] All 3 SLRs demonstrated efficacy of EGb 761 in cognitive function;[192-194] ginkgo biloba was also found to improve daily functioning,[192] global assessment of health status,[192] and neuropsychiatric symptoms.[194] Two of these SLRs conducted subgroup analyses by dose of ginkgo biloba and found that 240 mg was more effective in improving cognitive function than 120 mg[192] or 160 mg[193] doses.

## 10.4 Evidence gaps

The clinical and economic SLRs identified several evidence gaps. There was extensive efficacy and safety data on MPD, although heterogeneity across studies led to uncertainty. In addition, the comparator was a placebo in nearly all trials, limiting understanding regarding the relative efficacy and safety of ginkgo biloba compared with other active treatments. Trials conducted in PAOD also showed substantial heterogeneity. Coupled with the generally small number of patients in these trials, the heterogeneity resulted in low or very low certainty evidence to determine the efficacy of ginkgo biloba in PAOD. In addition, the majority of the data focused on mobility outcomes, with only a few trials reporting data on pain, peripheral blood circulation, and overall assessment of health status. None of the PAOD trials reported HRQoL data. There were also limited recent data available, with only the most recent PAOD trial published after 2000 (Wang 2007).[89] The overall evidence base for both vertigo and tinnitus was limited, with only 2 and 4 trials identified, respectively. In addition, none of the RCTs for either vertigo or tinnitus reported any HRQoL data. Finally, economic evidence was sparse; all 3 identified studies were cost-comparison analyses focused on MPD, and the most recent data were published in 2015. No primary studies were identified that reported direct or indirect costs of formulations of ginkgo biloba that are reimbursed in Switzerland, nor were any cost-effectiveness analyses identified.

[o] One trial included in the SLR had 3 treatment arms: placebo, 120 mg ginkgo biloba, and 240 mg ginkgo biloba.
[p] One trial included in the SLR had 3 treatment arms: placebo, 160 mg ginkgo biloba, and 240 mg ginkgo biloba.

## 10.5 Strengths and limitations of this review

This review was conducted using rigorous methodology in line with international standards. It comprehensively identified and synthesised the available evidence on the efficacy and safety of ginkgo biloba in MPD, PAOD, vertigo, and tinnitus. No publication date limit was applied in the systematic literature search. Although this allowed the review to incorporate all available evidence, older studies often lack methodological detail, do not report all outcomes, and are less likely to use validated outcome measures. The body of evidence presented in this HTA was in part restricted, as only studies that evaluated formulations of ginkgo biloba approved and reimbursed in Switzerland were included. Although this is necessary because it is inappropriate to combine dietary supplements with standardised herbal medicinal products,[188-191] it also resulted in some substantial evidence gaps. In contrast, the body of evidence in this review was less restricted than other identified HTA reports or SLRs in terms of the eligible indications. While other identified reviews typically limited studies to those with AD dementia or dementia more broadly, the present HTA review included the entire spectrum of deteriorating mental performance. Although the heterogeneity of MPD populations (e.g. varying severity of cognitive function, presence or absence of neuropsychiatric symptoms, underlying cause of disease, etc.) is likely one of the drivers behind the heterogeneity of effect estimates, the broader eligibility criteria allowed for the assessment of ginkgo biloba in conditions without other approved treatment options (e.g. vascular dementia, MCI). Finally, studies that reported zero events in both treatment arms were excluded from meta-analyses, which could result in biased meta-analysis results or the omission of relevant data. However, this affected only 2 per-indication safety outcomes—where excluding these studies resulted in a meta-analysis not being possible (i.e. only zero or one remaining trial after excluding these studies from analysis) —and the supplemental meta-analysis of AEs conducted across indications and doses of ginkgo biloba.

It should be noted that the model inputs for the BIM were based on a variety of underlying assumptions, especially regarding the prevalence rates which may not fully reflect the Swiss population, drug strength and packages sizes which are not indication specific, symptomatic treatment of MPD which is assumed to be equivalent to the sum of mild cognitive impairment and dementia, and vertigo prevalence which is assumed to correspond to vertigo of unknown cause and dizziness of unknown cause. The model was also limited by the inability to include cost offsets of clinical outcomes such as AEs, delayed requirement of nursing care in dementia patients, or costs of palliative treatments. Although these are all costs that could potentially be impacted by the reimbursement of ginkgo biloba, there was insufficient evidence in the literature to support including them.

# 11. Conclusions

The body of evidence evaluating the efficacy of ginkgo biloba for the indications MPD and PAOD was substantial, while the body of evidence for the indications vertigo and tinnitus was sparse. For MPD, the findings of this HTA review align with those in the IQWiG HTA report: available evidence

suggests that, compared with placebo, 240 mg ginkgo biloba improves cognitive function, neuropsychiatric symptoms, HRQoL, and functional status, although heterogeneity across studies introduces uncertainty regarding the magnitude of effect. In contrast, based on the available evidence, the efficacy of ginkgo biloba for treating PAOD, vertigo, and tinnitus remains largely unclear. However, as described in ***Section 6.2.4***, there is low certainty evidence that ginkgo biloba may improve pain in patients with PAOD compared with placebo, as well as low certainty evidence that there is no statistically significant difference between ginkgo biloba and betahistine dihydrochloride in vestibular symptoms among patients with vertigo.

Across all conditions of interest, AEs and SAEs were generally rare, and this review did not identify any evidence of elevated risk of AEs for any dose of ginkgo biloba when compared with placebo, either per indication or across indications and doses. There was also some evidence that ginkgo biloba was associated with fewer safety concerns than other active treatments, such as donepezil (low certainty) and betahistine (moderate certainty).

The budget impact analysis is based on the costs of ginkgo biloba treatment for patients with MPD, PAOD, vertigo, or tinnitus. The reimbursement of ginkgo biloba resulted in a 5-year total spending of CHF 167’154’958. In the scenario where ginkgo biloba is not reimbursed, there is uncertainty regarding which treatments, if any, patients will utilise instead. Although the scenario analyses presented here provide the estimated budget impact of alternative treatments, they are based on expert consensus and assumptions and should be interpreted with caution.

No serious ethical and social issues unique to ginkgo biloba were found. The concerns that were identified primarily stem from factors such as effective communication of benefits and risks in vulnerable populations and equitable access to care, which are broadly applicable to the patients in these populations.

Taken together, the evidence from this review suggests that only patients with MPD may benefit from a daily dose of 240 mg ginkgo biloba, although this benefit may vary due to underlying patient characteristics, such as severity of cognitive impairment and presence of neuropsychiatric symptoms. However, these results must be interpreted in the context of the overall uncertainty of evidence, the present treatment landscape for these conditions, and the uncertainty regarding economic evidence.

# 12. References


1. AIPS (Drug Information Publication System FI/PI). 2025. [Available from: https://swissmedicinfo.ch/].
2. Fusco N, Fi Stewart, Gomez-Espinosa E, et al. Ginkgo biloba in patients with decreasing mental performance, peripheral arterial occlusive disease, vertigo or tinnitus. HTA Protocol, FOPH. 2025. [Available from: https://www.bag.admin.ch/en/ginkgo-biloba-in-patients-with-decreasing-mental-performance-peripheral-arterial-occlusive-disease-vertigo-or-tinnitus].
3. World Health Organization. Dementia fact sheet. 2025. Accessed 5 February 2026. [Available from: https://www.who.int/news-room/fact-sheets/detail/dementia].
4. Hafiz R, Alajlani L, Ali A, et al. The latest advances in the diagnosis and treatment of dementia. *Cureus* 2023;15(12):e50522. doi: 10.7759/cureus.50522
5. Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *The Lancet* 2024;404(10452):572-628. doi: 10.1016/S0140-6736(24)01296-0
6. Ruangritchankul S, Chantharit P, Srisuma S, et al. Adverse drug reactions of acetylcholinesterase inhibitors in older people living with dementia: a comprehensive literature review. *Therapeutics and Clinical Risk Management* 2021:927-49.
7. Jain KK. Evaluation of memantine for neuroprotection in dementia. *Expert Opinion on Investigational Drugs* 2000;9(6):1397-406.
8. Wu H-M, Tzeng N-S, Qian L, et al. Novel neuroprotective mechanisms of memantine: increase in neurotrophic factor release from astroglia and anti-inflammation by preventing microglial activation. *Neuropsychopharmacology* 2009;34(10):2344-57.
9. Byun J, Lee DY, Jeong C-W, et al. Analysis of treatment pattern of anti-dementia medications in newly diagnosed Alzheimer's dementia using OMOP CDM. *Scientific Reports* 2022;12(1):4451.
10. Nonino F, Minozzi S, Sambati L, et al. Amyloid-beta-targeting monoclonal antibodies for people with mild cognitive impairment or mild dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2026(4) doi: 10.1002/14651858.CD016297
11. Nguyen HV, Mital S, Knopman DS, et al. Cost-effectiveness of Lecanemab for individuals with early-stage Alzheimer Disease. *Neurology* 2024;102(7):e209218.
12. Tahami Monfared AA, Tafazzoli A, Chavan A, et al. The potential economic value of lecanemab in patients with early Alzheimer's disease using simulation modeling. *Neurology and Therapy* 2022;11(3):1285-307.
13. Denton DA, Rutjes AW, Chong LY, et al. Vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild cognitive impairment. *Cochrane Database of Systematic Reviews* 2018(11)
14. Woods B, Rai HK, Elliott E, et al. Cognitive stimulation to improve cognitive functioning in people with dementia. *Cochrane Database of Systematic Reviews* 2023;1(1):CD005562. doi: 10.1002/14651858.CD005562.pub3
15. Pietri S, Maurelli E, Drieu K, et al. Cardioprotective and antioxidant effects of the Terpenoid Constituents of ginkgo biloba extract (EGb 761). *Journal of Molecular and Cellular Cardiology* 1997;29(2):733-42.
16. Luo Y, Smith JV, Paramasivam V, et al. Inhibition of amyloid-β aggregation and caspase-3 activation by the Ginkgo biloba extract EGb761. *Proceedings of the National Academy of Sciences* 2002;99(19):12197-202.
17. Krishna SM, Moxon JV, Golledge J. A review of the pathophysiology and potential biomarkers for peripheral artery disease. *International Journal of Molecular Sciences* 2015;16(5):11294-322.
18. Swedish Council on Health Technology Assessment (SBU) Stockholm. Peripheral Arterial Disease–Diagnosis and Treatment: A Systematic Review. Published 2008. [Available from: https://www.ncbi.nlm.nih.gov/books/NBK448000/].
19. Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). *Journal of Vascular Surgery* 2007;45(1):S5-S67.
20. Song P, Rudan D, Zhu Y, et al. Global, regional, and national prevalence and risk factors for peripheral artery disease in 2015: an updated systematic review and analysis. *The Lancet Global Health* 2019;7(8):e1020-e30.
21. Watson K, Anderson S. Peripheral Arterial Disease. In: DiPiro JT, Yee GC, Haines ST, et al., eds. DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12th Edition. New York, NY: McGraw Hill 2023.

22. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135(12):e686-e725.
23. Jansen SC, Abaraogu UO, Lauret GJ, et al. Modes of exercise training for intermittent claudication. *Cochrane Database of Systematic Reviews* 2020(8):CD009638. doi: 10.1002/14651858.CD009638.pub3
24. Nicolai PAS, Kruidenier LM, Bendermacher LWB, et al. Ginkgo biloba for intermittent claudication. *Cochrane Database of Systematic Reviews* 2013(12)
25. Zhou W, Chai H, Lin PH, et al. Clinical use and molecular mechanisms of action of extract of Ginkgo biloba leaves in cardiovascular diseases. *Cardiovascular Drug Reviews* 2004;22(4):309-19.
26. Tian J, Liu Y, Chen K. Ginkgo biloba extract in vascular protection: molecular mechanisms and clinical applications. *Current Vascular Pharmacology* 2017;15(6):532-48.
27. National Institute for Health Care and Excellence. Peripheral arterial disease: Diagnosis and management. NICE clinical guideline CG147. Published 2012. Last updated 11 December 2020. [Available from: https://www.nice.org.uk/guidance/cg147].
28. Murdin L, Schilder AG. Epidemiology of balance symptoms and disorders in the community: a systematic review. *Otology & Neurotology* 2015;36(3):387-92.
29. Hyland S, Hawke LJ, Taylor NF. Benign paroxysmal positional vertigo without dizziness is common in people presenting to falls clinics. *Disability and Rehabilitation* 2024:1-6.
30. Shao L, Shi Y, Xie X-Y, et al. Incidence and risk factors of falls among older people in nursing homes: systematic review and meta-analysis. *Journal of the American Medical Directors Association* 2023;24(11):1708-17.
31. Herdman D. Advances in the diagnosis and management of acute vertigo. *The Journal of Laryngology & Otology* 2024;138(S2):S8-S13.
32. Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. *The Neurologist* 2008;14(6):355-64.
33. Dommaraju S, Perera E. An approach to vertigo in general practice. *Australian Family Physician* 2016;45(4):190-94.
34. Lee A. Diagnosing the cause of vertigo: a practical approach. *Hong Kong Med J* 2012;18(4):327-32.
35. Strupp M, Bisdorff A, Furman J, et al. Acute unilateral vestibulopathy/vestibular neuritis: Diagnostic criteria: Consensus document of the committee for the classification of vestibular disorders of the Bárány Society. *Journal of Vestibular Research* 2022;32(5):389-406.
36. Lui F, Foris LA, Tadi P. Central vertigo. StatPearls [Internet]: StatPearls Publishing 2024.
37. Dyhrfjeld-Johnsen J, Attali P. Management of peripheral vertigo with antihistamines: New options on the horizon. *British Journal of Clinical Pharmacology* 2019;85(10):2255-63.
38. Raymond MJ, Vivas EX. Current and emerging medical therapies for dizziness. *Otolaryngologic Clinics of North America* 2021;54(5):1037-56.
39. Hallak B, Schneider A, Güntensperger D, et al. Standardized Ginkgo biloba Extract in the Treatment of Vertigo and/or Tinnitus: A Review of the Literature. *Advances in Aging Research* 2021;10(02):31.
40. Lindner M, Gosewisch A, Eilles E, et al. Ginkgo biloba extract EGb 761 improves vestibular compensation and modulates cerebral vestibular networks in the rat. *Frontiers in Neurology* 2019;10:147.
41. Hamann K-F. Ginkgo-Spezialextrakt bei Schwindel. *HNO* 2007;55(4):258-63.
42. Han BI, Lee HW, Kim TY, et al. Tinnitus: characteristics, causes, mechanisms, and treatments. *Journal of Clinical Neurology* 2009;5(1):11-19.
43. Jarach CM, Lugo A, Scala M, et al. Global prevalence and incidence of tinnitus: A systematic review and meta-analysis. *JAMA Neurol* 2022;79(9):888-900. doi: 10.1001/jamaneurol.2022.2189
44. Michiels S. Somatosensory tinnitus: Recent developments in diagnosis and treatment. *Journal of the Association for Research in Otolaryngology: JARO* 2023;24(5):465-72. doi: 10.1007/s10162-023-00912-3 [published Online First: 20231004]
45. Kleinjung T, Peter N, Schecklmann M, et al. The current state of tinnitus diagnosis and treatment: a multidisciplinary expert perspective. *Journal of the Association for Research in Otolaryngology* 2024;5:413-25. doi: 10.1007/s10162-024-00960-3
46. Lopez-Escamez JA, Perez-Carpena P. Technological advances in the diagnosis and management of tinnitus. *Journal of Clinical Medicine* 2022;11(15):4597.
47. Tunkel DE, Bauer CA, Sun GH, et al. Clinical practice guideline: tinnitus. *Otolaryngology–Head and Neck Surgery* 2014;151(2_suppl):S1-S40.

48. Meijers S, Stegeman I, van der Leun JA, et al. Analysis and comparison of clinical practice guidelines regarding treatment recommendations for chronic tinnitus in adults: a systematic review. *BMJ Open* 2023;13(9):e072754.
49. Langguth B, Kleinjung T, Schlee W, et al. Tinnitus guidelines and their evidence base. *Journal of Clinical Medicine* 2023;12(9):3087.
50. Birks J, Evans JG. Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database of Systematic Reviews* 2009(1):CD003120. doi: 10.1002/14651858.CD003120.pub3
51. Wachtel-Galor S, Benzie IF. Herbal medicine: An introduction to its history, usage, regulation, current trends, and research needs. In: Benzie IFF W-GS, ed. *Herbal Medicine: Biomolecular and Clinical Aspects* 2nd ed. Boca Raton, Florida: CRC Press/Taylor & Francis; 2011. Chapter 1, 2012.
52. Diamond BJ, Bailey MR. Ginkgo biloba: indications, mechanisms, and safety. *The Psychiatric clinics of North America* 2013;36(1):73-83.
53. European Medicines Agency-Committee on Herbal Medicinal Products. Assessment report on Ginkgo biloba L., folium: European Medicines Agency London, 2014.
54. European Medicines Agency-Committee on Herbal Medicinal Products. European Union herbal monograph on Ginkgo biloba L., folium: European Medicines Agency London, 2015.
55. Kandiah N, Ong PA, Yuda T, et al. Treatment of dementia and mild cognitive impairment with or without cerebrovascular disease: Expert consensus on the use of Ginkgo biloba extract, EGb 761®. *CNS Neuroscience & Therapeutics* 2019;25(2):288-98.
56. Deutsche Gesellschaft für Neurologie e. V. (DGN), Deutsche Gesellschaft für Psychiatrie und Psychotherapie Psychosomatik und Nervenheilkunde e. V. (DGPPN). S3-Leitlinie: Demenzen Leitlinienreport AWMF-Reg.-Nr.: 038-013;S3 Guideline: Dementia Guideline Report AWMF-Reg.-Nr.: 038-013, 2023.
57. Sereda M, Xia J, Scutt P, et al. Ginkgo biloba for tinnitus. *Cochrane Database of Systematic Reviews* 2022;11(11):CD013514. doi: https://doi.org/10.1002/14651858.CD013514.pub2
58. Klöppel S, Meyer-Heim T, Ehrensperger M, et al. Die empfehlungen der Swiss Memory Clinics für die therapie der demenzerkrankungen [The Swiss Memory Clinic's recommendations for the treatment of dementia]. *PRAXIS* 2024;113(8):113-30.
59. National Institute for Health and Clinical Excellence. Dementia: assessment, management and support for people living with dementia and their carers. NICE Guideline NG197. 2018. [Available from: https://www.nice.org.uk/guidance/ng97].
60. Mazzolai L, Teixido-Tura G, Lanzi S, et al. 2024 ESC Guidelines for the management of peripheral arterial and aortic diseases: Developed by the task force on the management of peripheral arterial and aortic diseases of the European Society of Cardiology (ESC) Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS), the European Reference Network on Rare Multisystemic Vascular Diseases (VASCERN), and the European Society of Vascular Medicine (ESVM). *European Heart Journal* 2024;45(36):3538-700. doi: 10.1093/eurheartj/ehae179
61. National Institute for Health Care and Excellence. Peripheral arterial disease: diagnosis and management 2012.
62. Tarnutzer AA, Kerkeni H, Diener S, et al. Diagnosis and treatment of vertigo and dizziness: Interdisciplinary guidance paper for clinical practice. *HNO* 2025:1-13.
63. Cochrane Handbook for Systematic Reviews of Interventions (Version 6.4). 2023. [Available from: www.training.cochrane.org/handbook].
64. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71
65. Murad MH, Asi N, Alsawas M, et al. New evidence pyramid. *BMJ Evidence-Based Medicine* 2016;21(4):125-27.
66. Team RC. R: A Language and Environment for Statistical Computing. Vienna, Austria. 2024
67. Gschwind YJ, Bridenbaugh SA, Reinhard S, et al. Ginkgo biloba special extract LI 1370 improves dual-task walking in patients with MCI: a randomised, double-blind, placebo-controlled exploratory study. *Aging Clinical and Experimental Research* 2017;29(4):609-19. doi: https://dx.doi.org/10.1007/s40520-016-0699-y
68. Van Dongen M, Van Rossum E, Kessels A, et al. Ginkgo for elderly people with dementia and age-associated memory impairment: A randomized clinical trial. *Journal of Clinical Epidemiology* 2003;56(4):367-76. doi: https://dx.doi.org/10.1016/S0895-4356%2803%2900003-9
69. Van Dongen MCJM, Van Rossum E, Kessels AGH, et al. The efficacy of ginkgo for elderly people with dementia and age-associated memory impairment: New results of a randomized clinical

trial. *Journal of the American Geriatrics Society* 2000;48(10):1183-94. doi: https://dx.doi.org/10.1111/j.1532-5415.2000.tb02589.x
70. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: A randomized controlled trial. *JAMA* 2008;300(19):2253-62. doi: https://dx.doi.org/10.1001/jama.2008.683
71. Haan J, Horr R. Delay in progression of dependency and need of care of dementia patients treated with Ginkgo special extract EGb 761. *Wiener Medizinische Wochenschrift* 2004;154(21-22):511-14. doi: https://dx.doi.org/10.1007/s10354-004-0116-6
72. Halama P. Judgement of well-being and psychometric tests in patients from a neurological practice treated with Ginkgo. *Befindlichkeitsbeurteilung und Psychometrie testung der Ginkgo-biloba-Wirkung bei Patienten einer Neurologischen Fachpraxis* 1991;133(Suppl 1):S19.
73. Hofferberth B. Ginkgo Biloba Special Extract Treatment in Patients with Cerebro-Organic Syndrome Study on the Efficacy and Psychometrical Methods. *Munchener medizinische Wochenschrift (1950)* 1991;133(Suppl):30.
74. Kanowski S, Herrmann WM, Stephan K, et al. Proof of efficacy of the ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of the Alzheimer type or multi-infarct dementia. *Pharmacopsychiatry* 1996;29(2):47-56. doi: https://dx.doi.org/10.1055/s-2007-979544
75. Kanowski S, Hoerr R. Ginkgo biloba extract EGb 761 in dementia: Intent-to-treat analyses of a 24-week, multi-center, double-blind, placebo-controlled, randomized trial. *Pharmacopsychiatry* 2003;36(6):297-303. doi: https://dx.doi.org/10.1055/s-2003-45117
76. Maurer K, Ihl R, Dierks T, et al. Clinical efficacy of ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. *Journal of Psychiatric Research* 1997;31(6):645-55. doi: https://dx.doi.org/10.1016/S0022-3956%2897%2900022-8
77. Maurer K, Ihl R, Dierks T, et al. Clinical efficacy of Ginkgo biloba special extract EGb 761 in dementia of the Alzheimer type. *Phytomedicine: International Journal of Phytotherapy and Phytopharmacology* 1998;5(6):417-24. doi: https://dx.doi.org/10.1016/S0944-7113(98)80037-8
78. Oswald WD, Horr R, Oswald B, et al. Increase of fluid cognitive factors with Ginkgo biloba special extract EGb 761 Reg. in elderly patients with mild to moderate organic brain syndrome. *Zeitschrift fur Gerontopsychologie & Psychiatrie* 1997;10(3):133.
79. Weitbrecht WU, Jansen W. Primary degenerative dementia: therapy with Ginkgo biloba extract. Placebo-controlled double-blind and comparative study [Primar degenerative Demenz: Therapie mit Ginkgo-biloba-Extrakt. Plazebo-kontrollierte Doppelblind- und Vergleichsstudie]. *Fortschr Med* 1986;104(9):199-202.
80. Dardenne S, Delrieu J, Sourdet S, et al. Memory complaints and cognitive decline: Data from the GUIDAGE Study. *Journal of Alzheimer's Disease* 2017;60(4):1567-78. doi: https://dx.doi.org/10.3233/JAD-170229
81. Demarin V, Kes VB, Trkanjec Z, et al. Efficacy and safety of Ginkgo biloba standardized extract in the treatment of vascular cognitive impairment: A randomized, double-blind, placebo-controlled clinical trial. *Neuropsychiatric Disease and Treatment* 2017;13:483-90. doi: https://dx.doi.org/10.2147/NDT.S120790
82. Grassel E. The influence of ginkgo biloba extract on mental performance. *Einfluss von ginkgo-biloba-extrakt auf die geistige leistungsfahigkeit* 1992;110:73.
83. McCarney R, Fisher P, Iliffe S, et al. Ginkgo biloba for mild to moderate dementia in a community setting: A pragmatic, randomised, parallel-group, double-blind, placebo-controlled trial. *International Journal of Geriatric Psychiatry* 2008;23(12):1222-30. doi: https://dx.doi.org/10.1002/gps.2055
84. McCarney R, Warner J, Iliffe S, et al. The Hawthorne Effect: A randomised, controlled trial. *BMC Medical Research Methodology* 2007;7:30. doi: https://dx.doi.org/10.1186/1471-2288-7-30
85. Scherrer B, Andrieu S, Ousset PJ, et al. Analysing time to event data in dementia prevention trials: the example of the guidage study of EGB761. *Journal of nutrition, health & aging* 2015;19(10):1009. doi: https://doi.org/10.1007/s12603-015-0661-2
86. Vellas B, Coley N, Ousset PJ, et al. Long-term use of standardised ginkgo biloba extract for the prevention of Alzheimer's disease (GuidAge): A randomised placebo-controlled trial. *The Lancet Neurology* 2012;11(10):851-59. doi: https://dx.doi.org/10.1016/S1474-4422%2812%2970206-5
87. Rai GS, Shovlin C, Wesnes KA. A double-blind, placebo controlled study of Ginkgo biloba extract ('Tanakan') in elderly outpatients with mild to moderate memory impairment. *Current Medical Research and Opinion* 1991;12(6):350-55.

88. Beck SM, Ruge H, Schindler C, et al. Effects of Ginkgo biloba extract EGb 761 on cognitive control functions, mental activity of the prefrontal cortex and stress reactivity in elderly adults with subjective memory impairment - A randomized double-blind placebo-controlled trial. *Human Psychopharmacology* 2016;31(3):227-42. doi: https://dx.doi.org/10.1002/hup.2534
89. Wang J, Zhou S, Bronks R, et al. Supervised exercise training combined with ginkgo biloba treatment for patients with peripheral arterial disease. *Clinical Rehabilitation* 2007;21(7):579-86. doi: https://dx.doi.org/10.1177/0269215507075205
90. Thomson GJ, Vohra RK, Carr MH, et al. A clinical trial of ginkgo biloba extract in patients with intermittent claudication. *International Angiology: A Journal of the International Union of Angiology* 1990;9(2):75-78.
91. Sokolova L, Hoerr R, Mishchenko T. Treatment of Vertigo: A Randomized, Double-Blind Trial Comparing Efficacy and Safety of Ginkgo biloba Extract EGb 761 and Betahistine. *International journal of otolaryngology* 2014;2014:682439. doi: https://dx.doi.org/10.1155/2014/682439
92. Cesarani A. Ginkgo biloba (EGb 761) in the treatment of equilibrium disorders. *Advances in Therapy* 1998;15(5):291-304.
93. Drew S, Davies W. Ginkgo biloba in the treatment of tinnitus: preliminary results of a match-paired, double-blinded placebo-controlled trial involving 1115 subjects. *Proceedings of the Sixth International Tinnitus Seminar* 1999:261.
94. Drew S, Davies E. Effectiveness of Ginkgo biloba in treating tinnitus: Double blind, placebo controlled trial. *British Medical Journal* 2001;322(7278):73-75.
95. Radunz CL, Okuyama CE, Branco-Barreiro FCA, et al. Clinical randomized trial study of hearing aids effectiveness in association with Ginkgo biloba extract (EGb 761) on tinnitus improvement. *Brazilian Journal of Otorhinolaryngology* 2020;86(6):734-42. doi: https://dx.doi.org/10.1016/j.bjorl.2019.05.003
96. Gessner B, Voelp A, Klasser M. Study of the long-term action of a ginkgo biloba extract on vigilance and mental performance as determined by means of quantitative pharmaco-EEG and psychometric measurements. *Arzneimittel-Forschung/Drug Research* 1985;35(9):1459-65.
97. Hofferberth B. The efficacy of EGb 761 in patients with senile dementia of the Alzheimer type, a double-blind, placebo-controlled study on different levels of investigation. *Human Psychopharmacology* 1994;9(3):215-22.
98. Le Bars PL, Katz MM, Berman N, et al. A placebo-controlled, double-blind, randomized trial of an extract of ginkgo biloba for dementia. *JAMA* 1997;278(16):1327-32. doi: https://dx.doi.org/10.1001/jama.278.16.1327
99. Le Bars PL, Velasco FM, Ferguson JM, et al. Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGb 761 in Alzheimer's disease. *Neuropsychobiology* 2002;45(1):19 - 26. doi: https://dx.doi.org/10.1159/000048668
100. Le Bars PL, Kieser M, Itil KZ. A 26-week analysis of a double-blind, placebo-controlled trial of the Ginkgo biloba extract EGb 761 in dementia. *Dementia and Geriatric Cognitive Disorders* 2000;11(4):230-37. doi: https://dx.doi.org/10.1159/000017242
101. Le Bars PL. Response patterns of EGb 761 in Alzheimer's disease: influence of neuropsychological profiles. *Pharmacopsychiatry* 2003;36 Suppl 1:S50-S55. doi: https://dx.doi.org/10.1055/s-2003-40456
102. Tian J, Shi J, Wei M, et al. Chinese herbal medicine Qinggongshoutao for the treatment of amnestic mild cognitive impairment: A 52-week randomized controlled trial. *Alzheimer's and Dementia: Translational Research and Clinical Interventions* 2019;5:441-49. doi: https://dx.doi.org/10.1016/j.trci.2019.03.001
103. Cummings JL, Tribanek M, Hoerr R. Sensitivity to change of composite and frequency scores of the neuropsychiatric inventory in mild cognitive impairment. *International Psychogeriatrics* 2014;26(11):1871-74. doi: https://dx.doi.org/10.1017/S1041610214001185
104. Gavrilova SI, Preuss UW, Wong JWM, et al. Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. *International Journal of Geriatric Psychiatry* 2014;29(10):1087-95. doi: https://dx.doi.org/10.1002/gps.4103
105. Ihl R, Bachinskaya N, Korczyn AD, et al. Efficacy and safety of a once-daily formulation of Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: a randomized controlled trial. *International Journal of Geriatric Psychiatry* 2011;26(11):1186-94. doi: https://dx.doi.org/10.1002/gps.2662
106. Bruggemann P, Grando Soria M, Brandes-Schramm J, et al. The influence of depression, anxiety and cognition on the treatment effects of ginkgo biloba extract egb 761 in patients with tinnitus

and dementia: a mediation analysis. *Journal of Clinical Medicine* 2021;10(14):3151. doi: https://doi.org/10.3390/jcm10143151
107. Bachinskaya N, Hoerr R, Ihl R. Alleviating neuropsychiatric symptoms in dementia: The effects of Ginkgo biloba extract EGb 761. Findings from a randomized controlled trial. *Neuropsychiatric Disease and Treatment* 2011;7(1):209-15. doi: https://dx.doi.org/10.2147/NDT.S18741
108. Ihl R, Tribanek M, Bachinskaya N. Baseline neuropsychiatric symptoms are effect modifiers in ginkgo biloba extract (EGb 761) treatment of dementia with neuropsychiatric features. Retrospective data analyses of a randomized controlled trial. *Journal of the Neurological Sciences* 2010;299(1-2):184-87. doi: https://dx.doi.org/10.1016/j.jns.2010.08.033
109. Ihl R, Tribanek M, Bachinskaya N. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761 R in Alzheimer's disease and vascular dementia: results from a randomised controlled trial. *Pharmacopsychiatry* 2012;45(2):41-46. doi: https://dx.doi.org/10.1055/s-0031-1291217
110. Grass-Kapanke B, Busmane A, Lasmanis A, et al. Effects of ginkgo biloba special extract EGb 761® in very mild cognitive impairment (vMCI). *Neuroscience & Medicine* 2011;2(1):48-56. doi: 10.4236/nm.2011.21007
111. Herrschaft H, Nacu A, Likhachev S, et al. Ginkgo biloba extract EGb 761 in dementia with neuropsychiatric features: A randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. *Journal of Psychiatric Research* 2012;46(6):716-23. doi: https://dx.doi.org/10.1016/j.jpsychires.2012.03.003
112. Nacu A, Hoerr R. Neuropsychiatric symptoms in dementia and the effects of Ginkgo biloba extract EGb 761® treatment: Additional results from a 24-week randomized, placebo-controlled trial. *Open Access Journal of Clinical Trials* 2016;8:1-6. doi: https://doi.org/10.2147/OAJCT.S93531
113. Napryeyenko O, Sonnik G, Tartakovsky I. Efficacy and tolerability of Ginkgo biloba extract EGb 761 by type of dementia: Analyses of a randomised controlled trial. *Journal of the Neurological Sciences* 2009;283(1-2):224-29. doi: https://dx.doi.org/10.1016/j.jns.2009.02.353
114. Napryeyenko O, Borzenko I. Ginkgo biloba special extract in dementia with neuropsychiatric features: A randomised, placebo-controlled, double-blind clinical trial. *Arzneimittel-Forschung/Drug Research* 2007;57(1):4-11. doi: https://dx.doi.org/10.1055/s-0031-1296579
115. Scripnikov A, Khomenko A, Napryeyenko O. Effects of Ginkgo biloba extract EGb 761 on neuropsychiatric symptoms of dementia: Findings from a randomised controlled trial. *Wiener Medizinische Wochenschrift* 2007;157(13-14):295-300. doi: https://dx.doi.org/10.1007/s10354-007-0427-5
116. Schneider LS, DeKosky ST, Farlow MR, et al. A randomized, double-blind, placebo-controlled trial of two doses of Ginkgo biloba extract in dementia of the Alzheimer's type. *Current Alzheimer Research* 2005;2(5):541-51. doi: https://dx.doi.org/10.2174/156720505774932287
117. Kloft C, Hoerr R. EGb 761 does not affect blood coagulation and bleeding time in patients with probable Alzheimer's dementia-secondary analysis of a randomized, double-blind placebo-controlled trial. *Healthcare (Basel, Switzerland)* 2021;9(12):1678. doi: https://doi.org/10.3390/healthcare9121678
118. Nasab NM, Bahrammi MA, Nikpour MR, et al. Efficacy of rivastigmine in comparison to ginkgo for treating Alzheimer's dementia. *JPMA The Journal of the Pakistan Medical Association* 2012;62(7):677 - 80.
119. Yancheva S, Ihl R, Nikolova G, et al. Ginkgo biloba extract EGb 761, donepezil or both combined in the treatment of Alzheimer's disease with neuropsychiatric features: A randomised, double-blind, exploratory trial. *Aging and Mental Health* 2009;13(2):183-90. doi: https://dx.doi.org/10.1080/13607860902749057
120. Bauer U. 6-Month double-blind randomised clinical trial of Ginkgo biloba extract versus placebo in two parallel groups in patients suffering from peripheral arterial insufficiency. *Arzneimittel-Forschung/Drug Research* 1984;34(6):716-20.
121. Bauer, U. Ginkgo biloba extract, EGb 761, and its effects on the arteries of the leg. In: *Advances in Ginkgo Biloba Extract Research. Cardiovascular Effects of Ginkgo Biloba Extract (EGb 761)*. Clostre F, Defeudis FV (eds). Elsevier, 1994:3:121-133. [
122. Bauer U. A two-year study of ginkgo biloba extract in the treatment of peripheral arterial disease (Fontaine stage IIb). *What is new in angiology? Trends and controversies* 1986:531.
123. Schlitter K. Treatment of peripheral occlusive arteriopathy with Ginkgo extract EGb 761. *Munchener Medizinische Wochenschrift* 1989;131(20 SUPPL.):2-3.

124. Bauer U. Ginkgo biloba extract in the treatment of arteriopathy of the lower extremities. A 65-week trial. *L'extrait de Ginkgo biloba dans le traitement de l'arteriopathie des membres inferieurs Etude sur 65 semaines* 1986;15(31):1546-49.
125. Blume J, Kieser M, Holscher U. Placebo-controlled double-blind study of the effectiveness of Ginkgo biloba special extract EGb 761 in trained patients with intermittent claudication. *Placebokontrollierte Doppelblindstudie zur Wirksamkeit von Ginkgo-biloba-Spezialextrakt EGb 761 bei austrainierten Patienten mit Claudicatio intermittens* 1996;25(3):265-74.
126. Blume J, Kieser M, Holscher U. Ginkgo-special-extract EGb 761 in peripheral arterial occlusive diseases stage IIb according to Fontaine. *Ginkgo-Spezialextrakt EGb 761 bei pAVK Plazebokontrollierte Doppelblindstudie bei Patienten mit pAVK im Stadium IIb nach Fontaine* 1998;116(35-36):36-7.
127. Bulling B, Von Bary S. Treatment of chronic peripheral occlusive disease with physical training and ginkgo biloba extract 761. *Medizinische Welt* 1991;42(8):702-08.
128. Peters H, Kieser M, Holscher U. Demonstration of the efficacy of ginkgo biloba special extract EGb 761 on intermittent claudication - A placebo-controlled, double-blind multicenter trial. *Vasa - Journal of Vascular Diseases* 1998;27(2):106 - 10.
129. Schweizer J, Hautmann C. Comparison of two dosages of Ginkgo biloba extract EGb 761 in patients with peripheral arterial occlusive disease Fontaine's stage IIb: A randomised, double-blind, multicentric clinical trial. *Arzneimittel-Forschung/Drug Research* 1999;49(11):900-04. doi: https://dx.doi.org/10.1055/s-0031-1300524
130. Prochazkova K, Sejna I, Skutil J, et al. Ginkgo biloba extract EGb 761 versus pentoxifylline in chronic tinnitus: a randomized, double-blind clinical trial. *International journal of clinical pharmacy* 2018;40(5):1335. doi: https://doi.org/10.1007/s11096-018-0654-4
131. Morgenstern C, Biermann EFdM. Long term therapy of tinnitus with Gingko biloba extract EGb 761. *Tinnitus-Langzeittherapiemit Ginkgo-spezialextrakt EGb 761* 1997;115(29):57.
132. Muir RT, Hill MD, Black SE, et al. Minimal clinically important difference in Alzheimer's disease: Rapid review. *Alzheimers Dement* 2024;20(5):3352-63. doi: 10.1002/alz.13770 [published Online First: 20240401]
133. Balsis S, Benge JF, Lowe DA, et al. How do scores on the ADAS-Cog, MMSE, and CDR-SOB correspond? *The Clinical Neuropsychologist* 2015;29(7):1002-09.
134. Grochowalski JH, Liu Y, Siedlecki KL. Examining the reliability of ADAS-Cog change scores. *Aging, Neuropsychology, and Cognition* 2016;23(5):513-29.
135. Mahoney R, Johnston K, Katona C, et al. The TE4D-Cog: a new test for detecting early dementia in English-speaking populations. *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences* 2005;20(12):1172-79.
136. Rosen WG. Verbal fluency in aging and dementia. *Journal of clinical and experimental neuropsychology* 1980;2(2):135-46.
137. Ihl R, Tribanek M, Bachinskaya N. Baseline neuropsychiatric symptoms are effect modifiers in Ginkgo biloba extract (EGb 761) treatment of dementia with neuropsychiatric features. Retrospective data analyses of a randomized controlled trial. *J Neurol Sci* 2010;299(1-2):184 - 87. doi: https://dx.doi.org/10.1016/j.jns.2010.08.033
138. Gavrilova SI, Preuss UW, Wong JWM, et al. Efficacy and safety of Ginkgo biloba extract EGb 761 in mild cognitive impairment with neuropsychiatric symptoms: a randomized, placebo-controlled, double-blind, multi-center trial. *Int J Geriatr Psychiatry* 2014;29(10):1087-95. doi: https://dx.doi.org/10.1002/gps.4103
139. Saari T, Koivisto A, Hintsa T, et al. Psychometric properties of the neuropsychiatric inventory: a review. *Journal of Alzheimer's Disease* 2022;86(4):1485-99.
140. Howard R, Phillips P, Johnson T, et al. Determining the minimum clinically important differences for outcomes in the DOMINO trial. *International journal of geriatric psychiatry* 2011;26(8):812-17.
141. Schwartz GE. Geriatric evaluation by relative's rating instrument (GERRI). *Psychopharmacol Bull* 1988;24:713-16.
142. Reisberg B, Finkel S, Overall J, et al. The Alzheimer's disease activities of daily living international scale (ADL-IS). *International Psychogeriatrics* 2001;13(2):163-81.
143. Lee EC, Wright J, Walters SJ, et al. Estimating the minimum important difference in the DEMQOL instrument in people with dementia. *Quality of Life Research* 2021;30(10):2995-3005.
144. Smith SC, Lamping DL, Banerjee S, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess* 2005;9(10):1-93, iii-iv. doi: 10.3310/hta9100

145. Mulhern B, Rowen D, Brazier J, et al. Development of DEMQOL-U and DEMQOL-PROXY-U: generation of preference-based indices from DEMQOL and DEMQOL-PROXY for use in economic evaluation. *Health Technology Assessment (Winchester, England)* 2013;17(5):v.
146. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord* 1997;11 Suppl 2:S22-S32. doi: 10.1097/00002093-199700112-00004
147. Schneider LS, Olin JT. Clinical Global Impression of Change Clinical Global Impressions in Alzheimer's Clinical Trials. *International Psychogeriatrics* 1996;8(2):277-90. doi: https://doi.org/10.1017/S1041610296002645
148. Perera S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures in older adults. *Journal of the American Geriatrics Society* 2006;54(5):743-49. doi: 10.1111/j.1532-5415.2006.00701.x
149. Olsen MF, Bjerre E, Hansen MD, et al. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. *J Clin Epidemiol* 2018;101:87-106.e2. doi: 10.1016/j.jclinepi.2018.05.007 [published Online First: 20180521]
150. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *International Journal of Technology Assessment in Health Care* 2013;29(2):117-22.
151. Borsch-Supan A, Douhou S, Otero MC, et al. Harmonized prevalence estimates of dementia in Europe vary strongly with childhood education. *Sci Rep* 2025;15(1):14024. doi: 10.1038/s41598-025-97691-z [published Online First: 20250423]
152. Cimminiello C, Kownator S, Wautrecht J-C, et al. The PANDORA study: peripheral arterial disease in patients with non-high cardiovascular risk. *Internal and Emergency Medicine* 2011;6(6):509-19. doi: 10.1007/s11739-011-0511-0
153. Neuhauser HK, von Brevern M, Radtke A, et al. Epidemiology of vestibular vertigo: a neurotologic survey of the general population. *Neurology* 2005;65(6):898-904. doi: 10.1212/01.wnl.0000175987.59991.3d
154. Horr R, Kieser M. Pharmaco-economic evaluation of Ginkgo special extract EGb 761 for dementias in Austria. *Pharmakookonomische Bewertung von Ginkgo-Spezialextrakt EGb 761 im Indikationsgebiet dementielle Erkrankungen bezogen auf Osterreich* 2002;152(15-16):427-31. doi: https://dx.doi.org/10.1046/j.1563-258x.2002.02067.x
155. Klement S. Ginkgo biloba extract EGb 761 in the treatment of dementia: A pharmacoeconomic analysis of the Austrian setting. *Zeitschrift fur Phytotherapie* 2015;36(2):48-52. doi: https://dx.doi.org/10.1055/s-0041-101221
156. Guo S, Hernandez L, Wasiak R, et al. Modelling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany. *Journal of Medical Economics* 2010;13(4):641-54.
157. Rainer M, Mucke H, Schlaefke S. Ginkgo biloba extract EGb 761 in the treatment of dementia: A pharmacoeconomic analysis of the Austrian setting. *Wiener Klinische Wochenschrift* 2013;125(1-2):8 - 15. doi: https://dx.doi.org/10.1007/s00508-012-0307-x
158. Agbabiaka TB, Wider B, Watson LK, et al. Concurrent use of prescription drugs and herbal medicinal products in older adults: A systematic review. *Drugs Aging* 2017;34(12):891-905. doi: 10.1007/s40266-017-0501-7
159. Alghamdi W, Al-Fadel N, Alghamdi EA, et al. Signal Detection and Assessment of Herb-Drug Interactions: Saudi Food and Drug Authority Experience. *Drugs Real World Outcomes* 2023;10(4):577-85. doi: 10.1007/s40801-023-00388-w [published Online First: 20231019]
160. Booker A, Frommenwiler D, Reich E, et al. Adulteration and poor quality of Ginkgo biloba supplements. *Journal of Herbal Medicine* 2016;6(2):79-87. doi: https://dx.doi.org/10.1016/j.hermed.2016.04.003
161. Callahan KE, Lovato JF, Miller ME, et al. Associations between mild cognitive impairment and hospitalization and readmission. *J Am Geriatr Soc* 2015;63(9):1880-5. doi: 10.1111/jgs.13593 [published Online First: 20150827]
162. Chugh NA, Bali S, Koul A. Integration of botanicals in contemporary medicine: road blocks, checkpoints and go-ahead signals. *Integr Med Res* 2018;7(2):109-25. doi: 10.1016/j.imr.2018.03.005 [published Online First: 20180328]

163. Dy JS, Freeman AM. Vertigo in clinical practice: Evidence-based diagnosis and treatment. 2025. StatPearls [Internet]. Treasure Island (FL): StatPearls. [Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK482356/].
164. Ekhart C, Wiarda SHP, van de Koppel S, et al. Qualitative interviews with stakeholders in herbal pharmacovigilance and recommendations for best practices to be applied worldwide. *Drug Saf* 2025;48(1):75-86. doi: 10.1007/s40264-024-01480-y [published Online First: 20240912]
165. Gupta RC, Srivastava A, Lall R. Toxicity potential of nutraceuticals. *Methods Mol Biol* 2018;1800:367-94. doi: 10.1007/978-1-4939-7899-1_18
166. Hundal S, Green J. Experience of Western Herbal Medicine practitioners in supporting brain health in mid-life and older patients: A qualitative research study. *Journal of Herbal Medicine* 2022;32:100547. doi: 10.1016/j.hermed.2022.100547
167. Husni HS. The emerging risk of interaction between complementary alternative medicines and cardiovascular medicines. *Indian Journal of Public Health Research & Development* 2020;11(1):1155-60. doi: 10.37506/v11/i1/2020/ijphrd/193995
168. Lamb LWB, Rodrigues GZP, Saraiva TES, et al. Permitted daily exposure from preclinical studies of Ginkgo biloba L. dry extract. *Brazilian Journal of Pharmaceutical Sciences* 2023;59:e23037. doi: https://dx.doi.org/10.1590/s2175-97902023e23037
169. Lorca C, Mulet M, Arevalo-Caro C, et al. Plant-derived nootropics and human cognition: A systematic review. *Crit Rev Food Sci Nutr* 2023;63(22):5521-45. doi: 10.1080/10408398.2021.2021137 [published Online First: 20220103]
170. Mahmoudian-Sani MR, Hashemzadeh-Chaleshtori M, Asadi-Samani M, et al. Ginkgo biloba in the treatment of tinnitus: An updated literature review. *Int Tinnitus J* 2017;21(1):58-62. doi: 10.5935/0946-5448.20170011 [published Online First: 20170601]
171. Nicolaï SP, Kruidenier LM, Bendermacher BL, et al. Ginkgo biloba for intermittent claudication. *Cochrane Database of Systematic Reviews* 2009(2)
172. Rademaker MM, Essers BAB, Stokroos RJ, et al. What tinnitus therapy outcome measures are important for patients? A discrete choice experiment. *Frontiers in Neurology* 2021;12:668880. doi: 10.3389/fneur.2021.668880 [published Online First: 20210525]
173. Raposo A, Saraiva A, Ramos F, et al. The role of food supplementation in microcirculation - a comprehensive review. *Biology (Basel)* 2021;10(7) doi: 10.3390/biology10070616 [published Online First: 20210702]
174. Smolderen KG, Alabi O, Collins TC, et al. Advancing Peripheral Artery Disease Quality of Care and Outcomes Through Patient-Reported Health Status Assessment: A Scientific Statement From the American Heart Association. *Circulation* 2022;146(20):e286-e97. doi: 10.1161/CIR.0000000000001105
175. Swissmedic. Guidance document. Authorisation of herbal medicinal products, 2025.
176. Trabert M, Seifert R. Critical analysis of ginkgo preparations: comparison of approved drugs and dietary supplements marketed in Germany. *Naunyn Schmiedebergs Arch Pharmacol* 2024;397(1):451-61. doi: 10.1007/s00210-023-02602-6 [published Online First: 20230720]
177. Varkey B. Principles of clinical ethics and their application to practice. *Med Princ Pract* 2021;30(1):17-28. doi: 10.1159/000509119 [published Online First: 20200604]
178. Watt JA, Porter J, Tavilsup P, et al. Guideline Recommendations on Behavioral and Psychological Symptoms of Dementia: A Systematic Review. *J Am Med Dir Assoc* 2024;25(5):837-46 e21. doi: 10.1016/j.jamda.2024.03.007 [published Online First: 20240417]
179. Yao Y, Zhao J, Li C, et al. Ginkgo biloba extract safety: Insights from a real-world pharmacovigilance study of FDA adverse event reporting system (FAERS) events. *J Ethnopharmacol* 2025;337(Pt 3):119010. doi: 10.1016/j.jep.2024.119010 [published Online First: 20241029]
180. Callahan KE, Lovato JF, Miller ME, et al. Associations between mild cognitive impairment and hospitalization and readmission. *Journal of the American Geriatrics Society* 2015;63(9):1880-85. doi: 10.1111/jgs.13593 [published Online First: 20150827]
181. Ekhart C, Wiarda SHP, van de Koppel S, et al. Qualitative interviews with stakeholders in herbal pharmacovigilance and recommendations for best practices to be applied worldwide. *Drug Safety* 2025;48(1):75-86. doi: 10.1007/s40264-024-01480-y [published Online First: 20240912]
182. Gupta RC, Srivastava A, Lall R. Toxicity potential of nutraceuticals. *Methods in Molecular Biology* 2018;1800:367-94. doi: 10.1007/978-1-4939-7899-1_18
183. IQWiG. Ginkgohaltige Präparate bei Alzheimer Demenz: Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) Köln, 2008:103.
184. Jianbunjongkit N, Nattarangsi W, Teeravanittrakul P. Efficacy of EGb 761(®) and Betahistine in Treatment of Dizziness/Vertigo: A Randomized Double-Blind Controlled Trial. *J Otolaryngol*

*Head Neck Surg* 2026;55:19160216251407927. doi: 10.1177/19160216251407927 [published Online First: 20260105]
185. Heide W, Adlung B, Körtke C, et al. Ginkgo biloba extract EGb 761® improves central vestibular vertigo in patients undergoing vestibular exercises: a randomised placebo-controlled trial. *Neuroscience and Medicine* 2022;13(3):91-102.
186. IQWiG. General Methods Version 6.1 of 24 January 2022. [Available from: https://www.iqwig.de/methoden/general-methods_version-6-1.pdf].
187. Webster KE, Galbraith K, Harrington-Benton NA, et al. Pharmacological interventions for acute attacks of vestibular migraine. *Cochrane Database of Systematic Reviews* 2023;4(4):CD015322. doi: 10.1002/14651858.CD015322.pub2
188. Cohen M, Hunter J. Complementary medicine products: interpreting the evidence base. *Internal Medicine Journal* 2017;47(9):992-98.
189. Hunter J. Applying evidence-based-medicine when prescribing herbal products. *OA Alternative Med* 2013;1:21-25.
190. Kulić Ž, Lehner MD, Dietz GP. Ginkgo biloba leaf extract EGb 761® as a paragon of the product by process concept. *Frontiers in pharmacology* 2022;13:1007746.
191. Wohlmuth H, Savage K, Dowell A, et al. Adulteration of Ginkgo biloba products and a simple method to improve its detection. *Phytomedicine* 2014;21(6):912-18.
192. Gauthier S, Schlaefke S. Efficacy and tolerability of Ginkgo biloba extract EGb 761 in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Clinical interventions in aging* 2014;9:2065 - 77. doi: https://dx.doi.org/10.2147/CIA.S72728
193. Hashiguchi M, Ohta Y, Shimizu M, et al. Meta-analysis of the efficacy and safety of Ginkgo biloba extract for the treatment of dementia. *Journal of pharmaceutical health care and sciences* 2015;1:14. doi: https://dx.doi.org/10.1186/s40780-015-0014-7
194. von Gunten A, Schlaefke S, Uberla K. Efficacy of Ginkgo biloba extract EGb 761 in dementia with behavioural and psychological symptoms: A systematic review. *World Journal of Biological Psychiatry* 2016;17(8):622-33. doi: https://dx.doi.org/10.3109/15622975.2015.1066513

# 13. Appendices

# A. Search strategies for clinical and economic evidence

**Table 100: Search strategy for Embase (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | Ginkgo biloba extract/ |
| | 3 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |
| | 4 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 5 | ((drug-extract ratio or DER or DEV) adj1 35-67).tw. |
| | 6 | or/1-5 |
| Observational studies | 7 | Clinical study/ |
| | 8 | Case control study/ |
| | 9 | Family study/ |
| | 10 | Longitudinal study/ |
| | 11 | Retrospective study/ |
| | 12 | Prospective study/ |
| | 13 | Randomized controlled trials/ |
| | 14 | 12 not 13 |
| | 15 | Cohort analysis/ |
| | 16 | (Cohort adj (study or studies)).mp. |
| | 17 | (Case control adj (study or studies)).tw. |
| | 18 | (follow up adj (study or studies)).tw. |
| | 19 | (observational adj (study or studies)).tw. |
| | 20 | (epidemiologic$ adj (study or studies)).tw. |
| | 21 | (cross sectional adj (study or studies)).tw. |
| | 22 | or/7-11,14-21 |
| RCTs | 23 | Clinical Trial/ |
| | 24 | Randomized Controlled Trial/ |
| | 25 | controlled clinical trial/ |
| | 26 | multicenter study/ |
| | 27 | Phase 3 clinical trial/ |
| | 28 | Phase 4 clinical trial/ |
| | 29 | exp RANDOMIZATION/ |
| | 30 | Single Blind Procedure/ |
| | 31 | Double Blind Procedure/ |
| | 32 | Crossover Procedure/ |
| | 33 | PLACEBO/ |
| | 34 | randomi?ed controlled trial$.tw. |
| | 35 | rct.tw. |
| | 36 | (random$ adj2 allocat$).tw. |
| | 37 | single blind$.tw. |
| | 38 | double blind$.tw. |
| | 39 | ((treble or triple) adj blind$).tw. |
| | 40 | placebo$.tw. |
| | 41 | Prospective Study/ |
| | 42 | or/23-41 |
| Economic/cost outcomes | 43 | Economics/ |
| | 44 | Cost analysis/ |
| | 45 | Cost allocation/ |
| | 46 | Cost control/ |
| | 47 | Cost savings/ |

| Search facet | # | Search strings |
|---|---|---|
| | 48 | Cost of illness/ |
| | 49 | Health care costs/ |
| | 50 | Direct service costs/ |
| | 51 | Drug costs/ |
| | 52 | Hospital costs/ |
| | 53 | Health expenditures/ |
| | 54 | Capital expenditures/ |
| | 55 | Economics, hospital/ |
| | 56 | Economics, medical/ |
| | 57 | Economics, nursing/ |
| | 58 | Economics, pharmaceutical/ |
| | 59 | ((health?care or unit) adj cost$).mp. |
| | 60 | (fiscal or funding or financial or finance).tw. |
| | 61 | (cost adj (estimate$ or variable$)).mp. |
| | 62 | (economic$ or pharmacoeconomic$ or price$ or pricing or fiscal or financial or finance or funding).tw. |
| | 63 | Socioeconomics/ |
| | 64 | Economic aspect/ |
| | 65 | Financial management/ |
| | 66 | Health care cost/ |
| | 67 | Health care financing/ |
| | 68 | Health economics/ |
| | 69 | Hospital cost/ |
| | 70 | resource allocation/ |
| | 71 | resource management/ |
| | 72 | (health care utili?ation or hospitali?ation$ or resource utili?ation or resource$ or cost$).mp. |
| | 73 | health care utilization/ |
| | 74 | hospitalization/ |
| | 75 | Cost/ |
| | 76 | exp Health Economics/ |
| | 77 | Budget/ |
| | 78 | budget*.ti,ab,kf. |
| | 79 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. |
| | 80 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 |
| | 81 | (value adj2 (money or monetary)).mp. |
| | 82 | or/43-81 |
| Economic evaluations | 83 | economic evaluation*.ti,ab,kf. or economic evaluation/ |
| | 84 | ((cost* or economic) adj2 (effective* or assess* or utilit* or benefit* or minimi* or analy* or outcome or outcomes or model)).ab,kf. |
| | 85 | (value adj2 (money or monetary)).ti,ab,kf. |
| | 86 | statistical model/ |
| | 87 | exp economic model/ |
| | 88 | probability/ |
| | 89 | economic model*.ab,kf. |
| | 90 | markov.ti,ab,kf. |
| | 91 | monte carlo method/ |
| | 92 | monte carlo.ti,ab,kf. |
| | 93 | decision theory/ |
| | 94 | decision tree/ |
| | 95 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. |
| | 96 | Quality-Adjusted Life Year/ |
| | 97 | quality adjusted life.ti,ab,kf. |

| Search facet | # | Search strings |
|---|---|---|
| | 98 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. |
| | 99 | disability adjusted life year*.ti,ab,kf. |
| | 100 | disability-adjusted life year/ |
| | 101 | (daly* or disability free life expectanc* or haly* or health* life expectanc*).ti,ab,kf. |
| | 102 | healthy life expectancy/ |
| | 103 | cost benefit analysis/ or 'cost effectiveness analysis'/ or 'cost utility analysis'/ |
| | 104 | (cost effectiveness or cost-effectiveness).ti,ab,kf. |
| | 105 | (cost benefit or cost-benefit).ti,ab,kf. |
| | 106 | (cost utility or cost-utility).ti,ab,kf. |
| | 107 | (incremental* adj2 cost*).tw. |
| | 108 | ICER.tw. |
| | 109 | utilities.tw. |
| | 110 | or/83-109 |
| Combine all relevant outcomes/study designs | 111 | 22 or 42 or 82 or 110 |
| Combine with intervention terms | 112 | 6 and 111 |
| Exclude animal studies and ineligible publication types | 113 | exp animal/ not exp human/ |
| | 114 | (rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw. |
| | 115 | letter/ or editorial/ or note/ or case report/ |
| | 116 | (letter or editorial or note or case reports).pt. |
| | 117 | anonymous.au. |
| | 118 | or/113-117 |
| | 119 | 112 not 118 |
| | 120 | review.pt. not (systematic adj2 review).pt,ti,ab. |
| | 121 | 119 not 120 |
| Exclude conference abstracts | 122 | conference$.pt,st. |
| | 123 | 121 not 122 |

**Table 101: Search strategy for MEDLINE (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |
| | 3 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 4 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 5 | or/1-4 |
| Observational studies | 6 | Epidemiologic studies/ |
| | 7 | exp case control studies/ |
| | 8 | exp cohort studies/ |
| | 9 | Case control.tw. |
| | 10 | (cohort adj (study or studies)).tw. |
| | 11 | Cohort analy$.tw. |
| | 12 | (Follow up adj (study or studies)).tw. |
| | 13 | (observational adj (study or studies)).tw. |
| | 14 | Longitudinal.tw. |
| | 15 | Retrospective.tw. |
| | 16 | Cross sectional.tw. |
| | 17 | Cross-sectional studies/ |
| | 18 | or/6-17 |
| RCTs | 19 | Randomized Controlled Trials as Topic/ |
| | 20 | randomized controlled trial/ |
| | 21 | Random Allocation/ |
| | 22 | Double Blind Method/ |
| | 23 | Single Blind Method/ |
| | 24 | clinical trial/ |
| | 25 | clinical trial, phase i.pt. |
| | 26 | clinical trial, phase ii.pt. |

| Search facet | # | Search strings |
|---|---|---|
| | 27 | clinical trial, phase iii.pt. |
| | 28 | clinical trial, phase iv.pt. |
| | 29 | controlled clinical trial.pt. |
| | 30 | randomized controlled trial.pt. |
| | 31 | multicenter study.pt. |
| | 32 | clinical trial.pt. |
| | 33 | exp Clinical Trials as topic/ |
| | 34 | (clinical adj trial$).tw. |
| | 35 | ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. |
| | 36 | PLACEBOS/ |
| | 37 | placebo$.tw. |
| | 38 | randomly allocated.tw. |
| | 39 | (allocated adj2 random$).tw. |
| | 40 | or/19-39 |
| Economic/cost outcomes | 41 | Economics/ |
| | 42 | Cost analysis/ |
| | 43 | Cost allocation/ |
| | 44 | Cost control/ |
| | 45 | Cost savings/ |
| | 46 | Cost of illness/ |
| | 47 | Health care costs/ |
| | 48 | Direct service costs/ |
| | 49 | Drug costs/ |
| | 50 | Hospital costs/ |
| | 51 | Health expenditures/ |
| | 52 | Capital expenditures/ |
| | 53 | Economics, hospital/ |
| | 54 | Economics, medical/ |
| | 55 | Economics, nursing/ |
| | 56 | Economics, pharmaceutical/ |
| | 57 | ((health?care or unit) adj cost$).mp. |
| | 58 | (fiscal or funding or financial or finance).tw. |
| | 59 | (cost adj (estimate$ or variable$)).mp. |
| | 60 | (economic$ or pharmacoeconomic$ or price$ or pricing or fiscal or financial or finance or funding).tw. |
| | 61 | Socioeconomic Factors/ |
| | 62 | Economic Status/ |
| | 63 | Financial management/ |
| | 64 | Health care cost/ |
| | 65 | Health economics/ |
| | 66 | Hospital cost/ |
| | 67 | resource allocation/ |
| | 68 | (health care utili?ation or hospitali?ation$ or resource utili?ation or resource$ or cost$).mp. |
| | 69 | health care utilization/ |
| | 70 | hospitalization/ |
| | 71 | Cost/ |
| | 72 | exp Health Economics/ |
| | 73 | Budget/ |
| | 74 | budget*.ti,ab,kf. |
| | 75 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. |
| | 76 | (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 |
| | 77 | (value adj2 (money or monetary)).mp. |
| | 78 | or/41-77 |
| Health economic models | 79 | ((cost* or economic) adj2 (effective* or assess* or utilit* or benefit* or minimi* or analy* or outcome or outcomes or model)).ab,kf. |
| | 80 | (value adj2 (money or monetary)).ti,ab,kf. |
| | 81 | exp models, economic/ |

| Search facet | # | Search strings |
|---|---|---|
| | 82 | economic model*.ab,kf. |
| | 83 | markov chains/ |
| | 84 | markov.ti,ab,kf. |
| | 85 | monte carlo method/ |
| | 86 | monte carlo.ti,ab,kf. |
| | 87 | exp Decision Theory/ |
| | 88 | (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. |
| | 89 | (cost effectiveness or cost-effectiveness).ti,ab,kf. |
| | 90 | (cost benefit or cost-benefit).ti,ab,kf. |
| | 91 | (cost utility or cost-utility).ti,ab,kf. |
| | 92 | (incremental* adj2 cost*).tw. |
| | 93 | ICER.tw. |
| | 94 | utilities.tw. |
| | 95 | Quality-Adjusted Life Years/ |
| | 96 | quality adjusted life.ti,ab,kf. |
| | 97 | (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf. |
| | 98 | disability adjusted life year*.ti,ab,kf. |
| | 99 | disability-adjusted life years/ |
| | 100 | (daly* or disability free life expectanc* or haly* or health* life expectanc*).ti,ab,kf. |
| | 101 | healthy life expectancy/ |
| | 102 | Cost-Effectiveness Analysis/ or Cost-Benefit Analysis/ |
| | 103 | or/79-102 |
| Combine all relevant outcomes/study designs | 104 | 18 or 40 or 78 or 103 |
| Combine with intervention terms | 105 | 5 and 104 |
| Exclude animal studies and ineligible publication types | 106 | exp animal/ not exp human/ |
| | 107 | (rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw. |
| | 108 | letter/ or editorial/ or note/ or case report/ |
| | 109 | (letter or editorial or note or case reports).pt. |
| | 110 | anonymous.au. |
| | 111 | or/106-110 |
| | 112 | 105 not 111 |
| | 113 | review.pt. not (systematic adj2 review).pt,ti,ab. |
| | 114 | 112 not 113 |

**Table 102: Search strategy for Cochrane Central Register of Controlled Trials (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |
| | 3 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 4 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 5 | or/1-4 |
| Exclude animal studies and ineligible publication types | 6 | exp animals/ not exp humans/ |
| | 7 | (rat or rats or mouse or mice or murine).ti. or (nonhuman or in vitro study or in vivo study).hw. |
| | 8 | (letter or editorial or comment$ or note or study guide or protocol).pt. |
| | 9 | case study/ or letter/ or editorial/ or case report/ or news/ or note/ or study guide/ |
| | 10 | anonymous.au. |
| | 11 | or/6-10 |
| | 12 | 5 not 11 |
| Exclude conference abstracts | 13 | (conference$ or Trial registry record).pt,st. |
| | 14 | 12 not 13 |

**Table 103: Search strategy for Cochrane Database of Systematic Reviews (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |

| | | |
|---|---|---|
| | 2 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 3 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 4 | or/1-3 |
| Exclude ineligible publication types | 5 | (letter or editorial or comment$ or note or study guide or protocol).pt. |
| | 6 | 4 not 5 |

**Table 104: Search strategy for EconLit (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |
| | 2 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 3 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 4 | or/1-3 |

**Table 105: Search strategy for NHS Economic Evaluation Database (via OvidSP)**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |
| | 2 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 3 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 4 | or/1-3 |

**Table 106: Search strategy for European Union Clinical Trials Register**

| Search facet | Search strings |
|---|---|
| Intervention | Ginkgo OR Ginkgo OR Ginkgo OR Maidenhair OR 'Egb 761' OR Egb761 OR EGb-761 OR tebokan OR rezirkane OR symfona |

**Table 107: Search strategy for ClinicalTrials.gov**

| Search facet | Search strings |
|---|---|
| Intervention | Ginkgo |
| | Ginkgo |
| | Ginkgo |
| | Maidenhair |
| | rezirkane |
| | symfona |
| | tebokan |
| | Egb 761 |
| | Egb761 |
| | EGb-761 |

*Notes:*

ClinicalTrials.gov does not allow for more complex searching syntax, so each item listed in this table will be searched individually in the 'Intervention/treatment' category and all results will be reviewed for each search.

**Table 108: Search strategy for International Network of Agencies for Health Technology Assessment database**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ [MeSH search] |
| | 2 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair) [All] |
| | 3 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761). [All] |
| | 4 | or/1-3 |

# B. Search strategy for ELSO issues

**Table 109: Search strategy for ELSO issues**

| Search facet | # | Search strings |
|---|---|---|
| Intervention | 1 | Ginkgo biloba/ |
| | 2 | Ginkgo biloba extract/ |
| | 3 | (Ginkgo* or Ginkgo* or Ginkgo* or Maidenhair).tw. |
| | 4 | (rezirkane or symfona or tebokan or Egb 761 or Egb761 or EGb-761).tw. |
| | 5 | ((drug-extract ratio or DER or DEV) adj1 35#67).tw. |
| | 6 | or/1-5 |
| Ethical, social, and legal items | 7 | exp Ethics, Clinical/ |
| | 8 | exp Ethical Analysis/ |
| | 9 | Legislation, Drug/ |
| | 10 | Social Change/ |
| | 11 | medical ethics/ |
| | 12 | drug legislation/ |
| | 13 | 'social aspects and related phenomena'/ |
| | 14 | social aspect/ |
| | 15 | Social Responsibility/ |
| | 16 | Social Welfare/ |
| | 17 | Social Factors/ |
| | 18 | exp social structure/ |
| | 19 | (ethics or legal or law or social).ti,ab. |
| | 20 | or/7-19 |
| Organizational items | 21 | 'Organisation and Administration'/ |
| | 22 | exp Health Facility Administration/ |
| | 23 | Policy/ |
| | 24 | Policy Making/ |
| | 25 | Organizational Policy/ |
| | 26 | Insurance, Health/ |
| | 27 | exp Insurance Coverage/ |
| | 28 | exp Drug Approval/ |
| | 29 | exp Health Services Accessibility/ |
| | 30 | health care organization/ |
| | 31 | exp health care system/ |
| | 32 | exp hospital organization/ |
| | 33 | exp health insurance/ |
| | 34 | (organization or organisation or policy or approval or coverage or reimburse* or access or disinvestment or drug dispensing or ((regulation or regulatory) adj3 (agency or agencies or medicine* or medication* or drug* or approval*))).ti,ab. |
| | 35 | or/21-34 |
| Combine terms | 36 | 6 and 20 |
| | 37 | 6 and 35 |
| | 38 | 36 or 37 |
| Exclude conference abstracts | 39 | conference$.pt,st. |
| | 40 | 38 not 39 |
| Remove duplicates | 41 | remove duplicates from 40 |
| Limit to last 10 years | 42 | limit 41 to yr='2015 -Current' |

# C. Deviations from protocol

All deviations from the protocol published on the FOPH website are described in the table below (***Table 110***).

**Table 110: Description of deviations from methodology prespecified in the published protocol**

| Protocol methodology | Review conduct | Justification for change |
|---|---|---|
| Outcomes of interest were prespecified for each condition | In addition to the outcomes prespecified in the protocol, the following outcomes were collected:<br>• MPD: global assessment of health status; symptoms of other conditions in this review (i.e. dizziness and tinnitus)<br>• PAOD: global assessment of health status<br>• Vertigo: global assessment of health status; functional status<br>• Tinnitus: functional status; mood | These measures of efficacy were not anticipated during protocol development. However, they were determined to provide valuable information regarding the patient experience, so data were systematically extracted on each outcome. In addition to these outcomes, imaging in patients with MPD was identified as a potential efficacy outcome and determined not to be of interest. |
| Meta-analyses of dichotomous outcomes will be conducted using ORs | Meta-analyses of dichotomous outcomes were conducted using RRs. | Included studies reporting comparative effect estimates for dichotomous outcomes all used RRs. Meta-analyses were conducted using RRs for consistency with the original study reporting and interpretability. |
| Comparative longitudinal observational studies are eligible for inclusion. | After the completion of full-text screening, observational studies were not included. | Three eligible observational studies were identified during full-text screening; all were conducted in patients with MPD and none included follow-up longer than 12 months. Because of the large number of RCTs in patients with MPD, including several with ≥1 year of follow-up, evidence for this review was limited to RCTs. |

*Abbreviations*

MPD = mental performance deficits, RCT = randomised controlled trial, RR = relative risk, OR = odds ratio, PAOD = peripheral arterial occlusive disease.

# D. Excludes during full-text selection clinical and economic systematic reviews

**Table 111: Excluded studies identified through the systematic literature searches**

| Reference | Reason for exclusion |
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| Franco, L., Cuny, G., Nancy, F. M. A Multi-Centre Study on the Efficacy of Ginkgo Biloba Extract (e.g.b 761) in the Treatment of Age Associated Memory Problems. Revue de geriatrie. 1991. | Comparator/backbone therapy |
| Nayak, L., Dehury, S., Rautray, S., Sahu, L., Sahu, D. Comparative analysis of efficacy, safety, and cost-effectiveness of betahistine alone, caroverine alone, and caroverine plus ginkgo biloba in moderate tinnitus. Indian J Pharmacol. 2024;56(6):379-385. doi:10.4103/ijp.ijp_695_24 | Comparator/backbone therapy |
| Han, S. S., Nam, E. C., Won, J. Y., Lee, K. U., Chun, W., Choi, H. K., Levine, R. A. Clonazepam quiets tinnitus: A randomised crossover study with Ginkgo biloba. J Neurol Neurosurg Psychiatry. 2012;83(8):821 - 827. doi:10.1136/jnnp-2012-302273 | Comparator/backbone therapy |
| Zhang, S. J., Xue, Z. Y. Effect of Western medicine therapy assisted by Ginkgo biloba tablet on vascular cognitive impairment of none dementia. Asian Pac J Trop Med. 2012;5(8):661 - 664. doi:10.1016/S1995-7645%2812%2960135-7 | Comparator/backbone therapy |
| Issing, W., Klein, P., Weiser, M. The homeopathic preparation Vertigoheel vs. Ginkgo biloba in the treatment of vertigo in an elderly population: A double-blinded, randomized, controlled clinical trial. Journal of Alternative and Complementary Medicine. 2005;11(1):155 - 160. doi:10.1089/acm.2005.11.155 | Comparator/backbone therapy |
| Morgenstern, C., Biermann, E. The efficacy of Ginkgo special extract EGb 761 in patients with tinnitus. Int J Clin Pharmacol Ther. 2002;40(5):188 - 197. doi:10.5414/CPP40188 | Comparator/backbone therapy |
| Burschka, M. A., Hassan, H. A. H., Reineke, T., Van Bebber, L., Caird, D. M., Mosges, R. Effect of treatment with Ginkgo biloba extract EGb 761 (oral) on unilateral idiopathic sudden hearing loss in a prospective randomized double-blind study of 106 outpatients. Eur Arch Otrhinolaryngol. 2001;258(5):213 - 219. doi:10.1007/s004050100343 | Comparator/backbone therapy |
| Wettstein, V. A. Cholinesterase inhibitors and Ginkgo extracts, are they comparable in the treatment of dementia?. Fortschr Med. 1999;117(SUPPL. 1):11 - 18. doi: | Comparator/backbone therapy |
| Canevelli, Marco, Adali, Nawal, Kelaiditi, Eirini, Cantet, Christelle, Ousset, Pierre-Jean, Cesari, Matteo. Effects of Ginkgo biloba supplementation in Alzheimer's disease patients receiving cholinesterase inhibitors: data from the ICTUS study. Phytomedicine. 2014;21(6):888-92. doi:10.1016/j.phymed.2014.01.003 | Comparator/backbone therapy |
| Itil, T. M., Eralp, E., Ahmed, I., Kunitz, A., Itil, K. Z. The pharmacological effects of ginkgo biloba, a plant extract, on the brain of dementia patients in comparison with tacrine. Psychopharmacol Bull. 1998;34(3):391-7. doi: | Comparator/backbone therapy |
| Dubreuil, C. [Therapeutic trial in acute cochlear deafness. A comparative study of Ginkgo biloba extract and nicergoline]. Essai therapeutique dans les surdites cochleaires aigues. Etude comparative de l'extrait de Ginkgo biloba et de la nicergoline. 1986;15(31):1559-61. doi: | Comparator/backbone therapy |
| Chartres, J. P., Bonnan, P., Martin, G. Dosage reduction in psychotropic medications administered to aged institutionalized patients: a double-blind study with Ginkgo Biloba extract 761 and placebo. Psychol Med (Paris). 1987. | Duplicate |
| Centre for, Reviews, Dissemination. Modelling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany (Structured abstract). | Duplicate |

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| Modelling the clinical and economic implications of galantamine in the treatment of mild-to-moderate Alzheimer's disease in Germany. 2010;(Issue 2). | |
| Morgenstern, C., Biermann, E. Long-term treatment of tinnitus with the special ginkgo extract, EGb 761. Fortschr Med. 1997;115(29):57 - 58. | Duplicate |
| Drabaek, H., Petersen, J. R., Wiinberg, N., Winther Hansen, K. F., Mehlsen, J. Effect of Ginkgo biloba extract on lower limb symptoms and cognitive function in patients with intermittent claudication. Ugeskr Laeger. 1996;158(27):3928 - 3931. | Duplicate |
| Stocksmeier, U., Eberlein, M. Depressive emotional deterioration in case of brain function disorders. TW Neurologie Psychiatrie. 1992;6(1-2):74 - 76. | Duplicate |
| Halama, P., Bartsch, G., Meng, G. Disorders of brain performance of vascular origin. Randomized double-blind study of the effectiveness of Ginkgo biloba extract. Fortschr Med. 1988;106(19):408 - 412. | Duplicate |
| Weitbrecht, W. U., Jansen, W. Ginkgo-biloba extract in the treatment of primary degenerative dementia. Placebo-controlled, double-blind and comparative study. Fortschr Med. 1986;104(9):199 - 202. | Duplicate |
| Salz, H. Efficacy of a Ginkgo biloba preparation in arterial circulatory disturbances in the lower extremities. Ther Ggw. 1980;119(11):1345 - 1356. | Duplicate |
| Herrschaft, Horst, Nacu, Anatol, Likhachev, Sergey, Sholomov, Ilya, Hoerr, Robert, Schlaefke, Sandra. Ginkgo biloba extract EGb 761 R in dementia with neuropsychiatric features: a randomised, placebo-controlled trial to confirm the efficacy and safety of a daily dose of 240 mg. J Psychiatr Res. 2012;46(6):716-23. doi:10.1016/j.jpsychires.2012.03.003 | Duplicate |
| Gasser, U. S., Gasser, T. [Alzheimer dementia. Comparison of the effectiveness of cholinesterase inhibitors and ginkgo]. Alzheimer-Demenz. Vergleich der Wirksamkeit von Cholinesterasehemmern und Ginkgo. 2001;143(51-52):40-1. | Duplicate |
| Drabaek, H., Petersen, J. R., Winberg, N., Hansen, K. F., Mehlsen, J. [The effect of Ginkgo biloba extract in patients with intermittent claudication]. Effekten af Ginkgo biloba-ekstrakt hos patienter med claudicatio intermittens. 1996;158(27):3928-31. | Duplicate |
| Taillandier, J., Ammar, A., Rabourdin, J. P., Ribeyre, J. P., Pichon, J., Niddam, S., Pierart, H. [Treatment of cerebral aging disorders with Ginkgo biloba extract. A longitudinal multicenter double-blind drug vs. placebo study]. Traitement des troubles du vieillissement cerebral par l'extrait de Ginkgo biloba. Etude longitudinale multicentrique a double insu face au placebo. 1986;15(31):1583-7. | Duplicate |
| Haguenauer, J. P., Cantenot, F., Koskas, H., Pierart, H. [Treatment of equilibrium disorders with Ginkgo biloba extract. A multicenter double-blind drug vs. placebo study]. Traitement des troubles de l'equilibre par l'extrait de Ginkgo biloba. Etude multicentrique a double insu face au placebo. 1986;15(31):1569-72. | Duplicate |
| Chartres, J. P., Bonnan, P., Martin, G. Reduction of the dosage of psychotropic drugs in elderly institutionalised people. Double-blind study in patients taking either Ginkgo biloba 761 extract or placebo. REDUCTION DE POSOLOGIE DE MEDICAMENTS PSYCHOTROPES CHEZ DES PERSONNES AGEES VIVANT EN INSTITUTION. ETUDE A DOUBLE-INSU CHEZ DES PATIENTS PRENANT SOIT DE L'EXTRAIT DE GINKGO BILOBA 761 SOIT DU PLACEBO. 1987;19(8):1365. | Intervention |
| Salz, H. The effectiveness of a Ginkgo biloba preparation in arterial ischemic diseases of the leg. Controlled double-blind cross-over study. ZUR WIRKSAMKEIT EINEES GINKGO-BILOBA-PRAPARATS BEI ARTERIELLEN DURCHBLUTUNGS-STORUNGEN DER UNTEREN EXTREMITATEN. 1980;119(11):1345. | Intervention |

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|---|---|
| Haguenauer, J. P., Cantenot, F., Koskas, H., Pierart, H. Treatment of disturbances of equilibrium with Ginkgo biloba extract. A multicentre, double-blind, drug versus placebo study. TRAITEMENT DES TROUBLES DE L'EQUILIBRE PAR L'EXTRAIT DE GINKGO BILOBA. ETUDE MULTICENTRIQUE A DOUBLE INSU FACE AU PLACEBO. 1986;15(31):1569. | Intervention |
| Taillandier, J., Ammar, A., Rabourdin, J. P. Ginkgo biloba extract in the treatment of cerebral disorders due to aging. A longitudinal, multicentre, double-blind, drug versus placebo study. TRAITEMENT DES TROUBLES DU VIEILLISSEMENT CEREBRAL PAR L'EXTRAIT DE GINKGO BILOBA. ETUDE LONGITUDINALE MULTICENTRIQUE A DOUBLE INSU FACE AU PLACEBO. 1986;15(31):1583. | Intervention |
| Hartmann, A., Frick, M. Effectiveness of a Ginkgo Special Extract on Psychometric Parameters in Patients with Vascular Dementia. Munch Med Wochenschr. 1991;133(Suppl):23. | Intervention |
| Chen, Y., Xiong, Z., Chen, H., Hu, Y., Dong, Y., Wang, Y. Effects of ginkgo biloba leaf combined with hyperbaric oxygen on coagulation function, hemorheology and serum SVCAM-1, HMGB1 and ENA-78 in patients with sudden deafness. Acta medica mediterranea. 2021;37(3):1411. doi: https://doi.org/10.19193/0393-638420213225 | Intervention |
| Walger, M., von Wedel, H., Calero, L., Hoenen, S., Rutwalt, D. Ergegnisse einer studie zur effektivitat einer kombinierten low-power-laser und ginkgo-therapie auf den chronischen tinnitus. HNO - Informationen. 1993;4():35. doi: | Intervention |
| Panhoca, V. H., de Aquino Junior, A. E., de Souza, V. B., Ferreira, S. A., Ferreira, L. T., de Oliveira Souza, K. J., Tamae, P. E., Saito Nogueira, M., Bagnato, V. S. Effects of Red and Infrared Laser Therapy in Patients with Tinnitus: a Double-Blind, Clinical, Randomized Controlled Study Combining Light with Ultrasound, Drugs and Vacuum Therapy. J Pers Med. 2023;13(4). doi: https://doi.org/10.3390/jpm13040581 | Intervention |
| Kim, T. S., Lee, H. S., Chung, J. W. The Effect of Korean Red Ginseng on Symptoms and Quality of Life in Chronic Tinnitus: a Randomized, Open-Label Pilot Study. Journal of audiology & otology. 2015;19(2):85. doi: https://doi.org/10.7874/jao.2015.19.2.85 | Intervention |
| Saudreau, F., Serise, J. M., Pillet, J., Maiza, D., Mercier, V., Kretz, J. G., Thibert, A. Efficiency of Ginkgo-biloba extract in treatment of stages III (fontaine classification) chronic occlusive arterial diseases of the lower limbs. J Mal Vasc. 1989;14(3):177. doi: | Intervention |
| Garzya, G., Picar, M. Treatment of peripheral vasculopathies with Ginkgo biloba extract. Trattamento delle vasculopatie periferiche con una nuova sostanza estrattiva: il tanakan. 1981;20(5):936. doi: | Intervention |
| Bohmer, D., Kalinski, S., Michaelis, P., Szogy, A. Efficacy and tolerance of Ginkgo biloba extract compared to that of pentoxifylline in the treatment of patients suffering from peripheral chronic arterial occlusive disease. Hers kreislauf. 1988;20(1):5. doi: | Intervention |
| Kwiecinski, H., Lusakowska, A., Mieszkowski, J. Improvement in concentration following treatment with Ginseng/Ginkgo biloba combination in patients with chronic cerebrovascular disorders: a double-blind, placebo-controlled study. European journal of clinical research. 1997;9():59. doi: | Intervention |
| Arrigo, A., Cattaneo, S. Clinical and psychometric evaluation of Ginkgo biloba extract in chronic cerebro-vascular diseases. Effects of ginkgo biloba extract on organic cerebral impairment. 1985. | Intervention |
| McDonnell, Michelle N., Hillier, Susan L. Vestibular rehabilitation for unilateral peripheral vestibular dysfunction. | Intervention |
| Hobson, Jonathan, Chisholm, Edward, El Refaie, Amr. Sound therapy (masking) in the management of tinnitus in adults. | Intervention |

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|---|---|
| MartinezDevesa, Pablo, Perera, Rafael, Theodoulou, Megan, Waddell, Angus. Cognitive behavioural therapy for tinnitus. | Intervention |
| Wakawa, I. A., Musami, U. B., Kwairanga, S. H., Ogualili, P. N., Mahmood, M. Y., Fugu, M. A., Gimba, M. M., Allamin, M. M., Abbas, Z. U., Sunkani, M. K., Yaganami, Z. B., Kadau, F. M., Sani, N. M., Danmallam, P., Nanjul, L., Babazau, L., Muhammad, Z., Goni, B. W., Machina, B. K., Karch, C. M., Udeh-Momoh, C., Karikari, T. K., Onyike, C. U., Maina, M. B. Management of Dementia in a Resource-Constrained Sub-Saharan African Setting: Outcome of a Retrospective Survey of Clinical Practice in the Only Neuropsychiatric Facility in Northeastern Nigeria. medRxiv. 2024.10.1101/2024.09.09.24313311 | Intervention |
| Bohlken, J., Hajek, A., Burkart, M., Kostev, K. Ginkgo biloba Extract Prescriptions Are Associated with Slower Progression of Dementia Severity-Analysis of Longitudinal Real-World Data. Brain Sci. 2025;15(1):12. doi:10.3390/brainsci15010012 | Intervention |
| Liu, L., Zhang, C. S., Zhang, A. L., Cai, Y., Xue, C. C. Oral Chinese herbal medicine combined with donepezil for mild cognitive impairment: A systematic review and meta-analysis. J Am Geriatr Soc. 2024;72(12):3890 - 3902. doi:10.1111/jgs.19125 | Intervention |
| Langguth, B., Reineke, T., Burkart, M., Kostev, K. Ginkgo biloba extract prescriptions are associated with less frequent repeat visits to ENT doctors due to tinnitus: a retrospective cohort study. Front Neurol. 2024;15():1402978. doi:10.3389/fneur.2024.1402978 | Intervention |
| Zhang, L., Sun, H., Han, Z. The impact of nimodipine combined with Ginkgo biloba extract on cognitive function and ADL scores in patients with Parkinson's disease: A retrospective study. Medicine (United States). 2024;103(29):e38720. doi:10.1097/MD.0000000000038720 | Intervention |
| Lee, W., Kim, M. Comparative study of choline alfoscerate as a combination therapy with donepezil: A mixed double-blind randomized controlled and open-label observation trial. Medicine (United States). 2024;103(24):e38067. doi:10.1097/MD.0000000000038067 | Intervention |
| Adam, C. E., Fitzpatrick, A. L., Leary, C. S., Hajat, A., Ilango, S. D., Park, C., Phelan, E. A., Semmens, E. O. Change in gait speed and fall risk among community-dwelling older adults with and without mild cognitive impairment: a retrospective cohort analysis. BMC Geriatr. 2023;23(1):328. doi:10.1186/s12877-023-03890-6 | Intervention |
| Yan, J., Bao, S., Liu, L., Zhang, Y. Q., Ming, J., Wei, Y., Chen, Y. Reporting quality of economic evaluations of the negotiated Traditional Chinese Medicines in national reimbursement drug list of China: A systematic review. Integrative Medicine Research. 2023;12(1):100915. doi:10.1016/j.imr.2022.100915 | Intervention |
| Lu, H., Dang, M., Chen, K., Shang, H., Wang, B., Zhao, S., Li, X., Zhang, Z., Zhang, J., Chen, Y. Naoxin'an capsules protect brain function and structure in patients with vascular cognitive impairment. Front Pharmacol. 2023;14():1129125. doi:10.3389/fphar.2023.1129125 | Intervention |
| Huang, Y., Du, B., Zhu, S., Mu, Y., Geng, D. Effect of ginkgo leaf tablets combined with compound carbidopa on patients with Parkinson's disease. Tropical Journal of Pharmaceutical Research. 2023;22(8):1675 - 1681. doi:10.4314/TJPR.V22I8.19 | Intervention |
| Aslam, M. M., Fan, K. H., Lawrence, E., Bedison, M. A., Snitz, B. E., DeKosky, S. T., Lopez, O. L., Feingold, E., Kamboh, M. I. Genome-wide analysis identifies novel loci influencing plasma apolipoprotein E concentration and Alzheimer's disease risk. Mol Psychiatry. 2023;28(10):4451 - 4462. doi:10.1038/s41380-023-02170-4 | Intervention |
| Ozge, A., Ghouri, R., Oksuz, N., Tasdelen, B. Early intervention and adding effective doses of EGb761 like Ginkgo extract slow down dementia progression: insights to the neurovascular unit. Front Neurol. 2023;14():1240655. doi:10.3389/fneur.2023.1240655 | Intervention |

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|---|---|
| Wu, H., Wan, W., Jiang, H., Xiong, Y. Prognosis of Idiopathic Sudden Sensorineural Hearing Loss: The Nomogram Perspective. Ann Otol Rhinol Laryngol. 2023;132(1):5 - 12. doi:10.1177/00034894221075114 | Intervention |
| Zhao, M., Luo, Y., Wang, H., Cao, Y., Ma, L., Pei, H., Li, H. Guilingji capsule for Alzheimer's disease: secondary analysis of a randomized non-inferiority controlled trial. J Tradit Chin Med. 2023;43(5):1019 - 1025. doi:10.19852/j.cnki.jtcm.20230404.006 | Intervention |
| Mura, T., Coley, N., Amieva, H., Berr, C., Gabelle, A., Ousset, P. J., Vellas, B., Andrieu, S. Cognitive decline as an outcome and marker of progression toward dementia, in early preventive trials. Alzheimer's and Dementia. 2022;18(4):676 - 687. doi:10.1002/alz.12431 | Intervention |
| Bohlken, J., Peters, O., Kostev, K. Association Between Ginkgo Biloba Extract Prescriptions and Dementia Incidence in Outpatients with Mild Cognitive Impairment in Germany: A Retrospective Cohort Study. J Alzheimers Dis. 2022;86(2):703 - 709. doi:10.3233/JAD-215348 | Intervention |
| Gelardi, M., Marano, P. G., Giancaspro, R., Cassano, M., Alonzi, L., Bava, G., Biamonte, P., Bocciolini, C., Bucci, A., Di Cosola, M., Floro, M. D., Florridia, A., Freccia, R., Giannattasio, L., Gramellini, G., Malfa, F. L., Luperto, P., Maffezzoni, E., Maffezzoni, F., Maira, S., Malisardi, G., Miconi, A., Misale, M., Monserrino, S., Notargiacomo, M., Piccininni, K., Piccolo, M., Pirri, S., Porro, G., Raffaeli, M., Ragone, M., Romeo, M., Santoro, F., Sorbo, A., Sorrentino, G., Stabile, C., Sulis, G., Tofeily, A. The effect of dietary supplements-based alpha-lipoic acid, acetyl l-carnitine and vitamin B complex in patients with tinnitus. J Biol Regul Homeost Agents. 2022;36(1 S2):25 - 33. doi:10.23812/j.biol.regul.homeost.agents.202236.1S2.4 | Intervention |
| Zhang, H., Chen, H., Pei, H., Wang, H., Ma, L., Li, H. The Effect of Guilingji Capsules on Vascular Mild Cognitive Impairment: A Randomized, Double-Blind, Controlled Trial. Evidence-based Complementary and Alternative Medicine. 2022;2022():4778163. doi:10.1155/2022/4778163 | Intervention |
| Zhang, Y., Wei, C., Sun, Z., Wu, Y., Chen, Z., Liu, B. Hearing Benefits of Clinical Management for Meniere's Disease. J Clin Med. 2022;11(11):3131. doi:10.3390/jcm11113131 | Intervention |
| Slawsky, E. D., Hajat, A., Rhew, I. C., Russette, H., Semmens, E. O., Kaufman, J. D., Leary, C. S., Fitzpatrick, A. L. Neighborhood greenspace exposure as a protective factor in dementia risk among U.S. adults 75 years or older: a cohort study. Environmental Health: A Global Access Science Source. 2022;21(1):14. doi:10.1186/s12940-022-00830-6 | Intervention |
| Mathai, P., Chandran, A., Das, S. Effectiveness and safety of ginkgo biloba, vinpocetine and piracetam as a single agent and fixed dose combination in patients with subjective tinnitus. Journal of Clinical and Diagnostic Research. 2021;15(2):MC01 - MC05. doi:10.7860/JCDR/2021/48182.14589 | Intervention |
| Zhou, E., Xiao, X. P., Liu, B., Tan, Z. Q., Miao, G. Y., Liu, X. B., Bu, M. X., Cao, X., Zhong, J. Y. Earfullness characteristics and prognosis in patients with all-frequency sudden sensorineural hearing loss. J Laryngol Otol. 2021;135(10):926 - 931. doi:10.1017/S0022215121002206 | Intervention |
| Zheng, Y., Xie, Y., Qi, M., Zhang, L., Wang, W., Zhang, W., Sha, L., Wu, J., Li, W., Wu, T. Ginkgo Biloba Extract Is Comparable With Donepezil in Improving Functional Recovery in Alzheimer's Disease: Results From a Multilevel Characterized Study Based on Clinical Features and Resting-State Functional Magnetic Resonance Imaging. Front Pharmacol. 2021;12():721216. doi:10.3389/fphar.2021.721216 | Intervention |
| Koch, M., Furtado, J. D., Cronje, H. T., DeKosky, S. T., Fitzpatrick, A. L., Lopez, O. L., Kuller, L. H., Mukamal, K. J., Jensen, M. K. Plasma antioxidants and risk of dementia in older adults. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2021;7(1):e12208. doi:10.1002/trc2.12208 | Intervention |

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|---|---|
| Gutierrez, L., Folch, A., Rojas, M., Cantero, J. L., Atienza, M., Folch, J., Camins, A., Ruiz, A., Papandreou, C., Bullo, M. Effects of nutrition on cognitive function in adults with or without cognitive impairment: A systematic review of randomized controlled clinical trials. Nutrients. 2021;13(11):3728. doi:10.3390/nu13113728 | Intervention |
| Gupta, S., Shenoy, A., Chaudhari, V., Buttar, H. S., Chintamaneni, M., Kaur, G. THERAPEUTIC ROLES OF ANTIOXIDANT AND NUTRACEUTICALS IN THE PREVENTION AND MANAGEMENT OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW. Biomedical Reviews. 2021;32():1 - 29. doi:10.14748/bmr.v32.8496 | Intervention |
| Koch, M., Furtado, J. D., Dekosky, S. T., Fitzpatrick, A. L., Lopez, O. L., Kuller, L. H., Mukamal, K. J., Jensen, M. K. Case-cohort study of plasma phospholipid fatty acid profiles, cognitive function, and risk of dementia: A secondary analysis in the Ginkgo Evaluation of Memory Study. Am J Clin Nutr. 2021;114(1):154 - 162. doi:10.1093/ajcn/nqab087 | Intervention |
| Park, E., Song, I., Jeong, Y. J., Im, G. J., Jung, H. H., Choi, J., Rah, Y. C. Evidence of Cochlear Synaptopathy and the Effect of Systemic Steroid in Acute Idiopathic Tinnitus With Normal Hearing. Otol Neurotol. 2021;42(7):978 - 984. doi:10.1097/MAO.0000000000003189 | Intervention |
| Koch, M., DeKosky, S. T., Goodman, M., Sun, J., Furtado, J. D., Fitzpatrick, A. L., Mackey, R. H., Cai, T., Lopez, O. L., Kuller, L. H., Mukamal, K. J., Jensen, M. K. High density lipoprotein and its apolipoprotein-defined subspecies and risk of dementia. J Lipid Res. 2020;61(3):445 - 454. doi:10.1194/jlr.P119000473 | Intervention |
| Lai, X., Wen, H., Li, Y., Lu, L., Tang, C. The comparative efficacy of multiple interventions for mild cognitive impairment in alzheimer's disease: A bayesian network meta-analysis. Front Aging Neurosci. 2020;12():121. doi:10.3389/fnagi.2020.00121 | Intervention |
| Bustin, J., Rojas, G., O'Neill, S., Sarasola, D., Triskier, F., Urtasun, M., Canas, M., Mastai, R., Demey, I. What is happening with not recommended drugs for dementia in Argentina? Prescription patterns and direct costs analysis. Int J Geriatr Psychiatry. 2020;35(3):270 - 275. doi:10.1002/gps.5242 | Intervention |
| Koch, M., Costanzo, S., Fitzpatrick, A. L., Lopez, O. L., Dekosky, S., Kuller, L. H., Price, J., MacKey, R. H., Jensen, M. K., Mukamal, K. J. Alcohol Consumption, Brain Amyloid-beta Deposition, and Brain Structural Integrity among Older Adults Free of Dementia. J Alzheimers Dis. 2020;74(2):509 - 519. doi:10.3233/JAD-190834 | Intervention |
| Koch, M., Dekosky, S. T., Goodman, M., Sun, J., Furtado, J. D., Fitzpatrick, A. L., Mackey, R. H., Cai, T., Lopez, O. L., Kuller, L. H., Mukamal, K. J., Jensen, M. K. Association of Apolipoprotein e in Lipoprotein Subspecies with Risk of Dementia. JAMA Network Open. 2020;3(7):e209250. doi:10.1001/jamanetworkopen.2020.9250 | Intervention |
| Li, S., Cao, G., Deng, Q., Zhu, D., Yan, F. Effect of Pushen capsule for treating vascular mild cognitive impairment: a pilot observational study. J Int Med Res. 2019;47(11):5483 - 5496. doi:10.1177/0300060519859766 | Intervention |
| Qiao, X. F., Li, X., Wang, G. P., Bai, Y. H., Zheng, W., Li, T. L. Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Patients with Sudden Sensorineural Hearing Loss. Med Princ Pract. 2019;28(1):23 - 27. doi:10.1159/000494556 | Intervention |
| Lopez, O. L., Chang, Y., Ives, D. G., Snitz, B. E., Fitzpatrick, A. L., Carlson, M. C., Rapp, S. R., Williamson, J. D., Tracy, R. P., DeKosky, S. T., Kuller, L. H. Blood amyloid levels and risk of dementia in the Ginkgo Evaluation of Memory Study (GEMS): A longitudinal analysis. Alzheimer's and Dementia. 2019;15(8):1029 - 1038. doi:10.1016/j.jalz.2019.04.008 | Intervention |

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|---|---|
| Koch, M., Fitzpatrick, A. L., Rapp, S. R., Nahin, R. L., Williamson, J. D., Lopez, O. L., Dekosky, S. T., Kuller, L. H., Mackey, R. H., Mukamal, K. J., Jensen, M. K., Sink, K. M. Alcohol Consumption and Risk of Dementia and Cognitive Decline among Older Adults with or Without Mild Cognitive Impairment. JAMA Network Open. 2019;2(9):e1910319. doi:10.1001/jamanetworkopen.2019.10319 | Intervention |
| Chen, X. H., Zeng, C. J., Fang, Z. M., Zhang, R., Cheng, J. M., Lin, C. The Natural History of Labyrinthine Hemorrhage in Patients With Sudden Sensorineural Hearing Loss. Ear, Nose and Throat Journal. 2019;98(5):E13 - E20. doi:10.1177/0145561319834862 | Intervention |
| Zhao, Y., Tudorascu, D. L., Lopez, O. L., Cohen, A. D., Mathis, C. A., Aizenstein, H. J., Price, J. C., Kuller, L. H., Kamboh, M. I., DeKosky, S. T., Klunk, W. E., Snitz, B. E. Amyloid beta deposition and suspected non-Alzheimer pathophysiology and cognitive decline patterns for 12 years in oldest old participants without dementia. JAMA Neurol. 2018;75(1):88 - 96. doi:10.1001/jamaneurol.2017.3029 | Intervention |
| Koch, M., DeKosky, S. T., Fitzpatrick, A. L., Furtado, J. D., Lopez, O. L., Kuller, L. H., Mackey, R. H., Hughes, T. M., Mukamal, K. J., Jensen, M. K. Apolipoproteins and Alzheimer's pathophysiology. Alzheimer's and Dementia: Diagnosis, Assessment and Disease Monitoring. 2018;10():545 - 553. doi:10.1016/j.dadm.2018.07.001 | Intervention |
| Palta, P., Carlson, M. C., Crum, R. M., Colantuoni, E., Sharrett, A. R., Yasar, S., Nahin, R. L., DeKosky, S. T., Snitz, B., Lopez, O., Williamson, J. D., Furberg, C. D., Rapp, S. R., Golden, S. H. Diabetes and Cognitive Decline in Older Adults: The Ginkgo Evaluation of Memory Study. J Gerontol A Biol Sci Med Sci. 2017;73(1):123 - 130. doi:10.1093/gerona/glx076 | Intervention |
| Chi, G. C., Fitzpatrick, A. L., Sharma, M., Jenny, N. S., Lopez, O. L., DeKosky, S. T. Inflammatory Biomarkers Predict Domain-Specific Cognitive Decline in Older Adults. J Gerontol A Biol Sci Med Sci. 2017;72(6):796 - 803. doi:10.1093/gerona/glw155 | Intervention |
| Polanski, J. F., Soares, A. D., de Mendonca Cruz, O. L. Antioxidant therapy in the elderly with tinnitus. Braz J Otorhinolaryngol. 2016;82(3):269 - 274. doi:10.1016/j.bjorl.2015.04.016 | Intervention |
| Zhang, Q. J. A study on the combinational effect of cholinesterase inhibitors and NDMA receptor antagonist with herbal therapy among Alzheimer's disease patients. Latin American Journal of Pharmacy. 2016;35(8):1850 - 1854. doi: | Intervention |
| Callahan, K. E., Lovato, J. F., Miller, M. E., Easterling, D., Snitz, B., Williamson, J. D. Associations between mild cognitive impairment and hospitalization and readmission. J Am Geriatr Soc. 2015;63(9):1880 - 1885. doi:10.1111/jgs.13593 | Intervention |
| Acar, B., Karasen, R. M., Buran, Y. Efficacy of medical therapy in the prevention of residual dizziness after successful repositioning maneuvers for Benign Paroxysmal Positional Vertigo (BPPV). B-ENT. 2015;11(2):117 - 121. doi: | Intervention |
| Agus, S., Benecke, H., Thum, C., Strupp, M. Clinical and demographic features of vertigo: Findings from the REVERT registry. Front Neurol. 2013;4 MAY():48. doi:10.3389/fneur.2013.00048 | Intervention |
| Polanski, J. F., Cruz, O. L. Evaluation of antioxidant treatment in presbyacusis: Prospective, placebo-controlled, double-blind, randomised trial. J Laryngol Otol. 2013;127(2):134 - 141. doi:10.1017/S0022215112003118 | Intervention |
| Snitz, B. E., Weissfeld, L. A., Lopez, O. L., Kuller, L. H., Saxton, J., Singhabahu, D. M., Klunk, W. E., Mathis, C. A., Price, J. C., Ives, D. G., Cohen, A. D., McDade, E., DeKosky, S. T. Cognitive trajectories associated with beta-amyloid deposition in the oldest-old without dementia. Neurology. 2013;80(15):1378 - 1384. doi:10.1212/WNL.0b013e31828c2fc8 | Intervention |
| Park, I. S., Kim, Y. B., Choi, S. H., Hong, S. M. Clinical analysis of recurrent sudden sensorineural hearing loss. ORL. 2013;75(4):245 - 249. doi:10.1159/000353552 | Intervention |

| | |
|---|---|
| Su, C. X., Yan, L. J., Lewith, G., Liu, J. P. Chinese herbal medicine for idiopathic sudden sensorineural hearing loss: A systematic review of randomised clinical trials. Clinical Otolaryngology. 2013;38(6):455 - 473. doi:10.1111/coa.12198 | Intervention |
| Rent, N. H., Bhojwani, K. M., Bhat, J. S., Unnikrishnan, B. Tinnitus: Characterization of associated hearing loss and modalities of treatment. Indian Journal of Otology. 2013;19(4):182 - 185. doi:10.4103/0971-7749.124513 | Intervention |
| Yasar, S., Xia, J., Yao, W., Furberg, C. D., Xue, Q. L., Mercado, C. I., Fitzpatrick, A. L., Fried, L. P., Kawas, C. H., Sink, K. M., Williamson, J. D., DeKosky, S. T., Carlson, M. C. Antihypertensive drugs decrease risk of Alzheimer disease Ginkgo Evaluation of Memory Study. Neurology. 2013;81(10):896 - 903. doi:10.1212/WNL.0b013e3182a35228 | Intervention |
| Bach, J. P., Riedel, O., Klotsche, J., Spottke, A., Dodel, R., Wittchen, H. U. Impact of complications and comorbidities on treatment costs and health-related quality of life of patients with Parkinson's disease. J Neurol Sci. 2012;314(1-2):41 - 47. doi:10.1016/j.jns.2011.11.002 | Intervention |
| Bettermann, K., Arnold, A. M., Williamson, J., Rapp, S., Sink, K., Toole, J. F., Carlson, M. C., Yasar, S., Dekosky, S., Burke, G. L. Statins, risk of dementia, and cognitive function: Secondary analysis of the ginkgo evaluation of memory study. Journal of Stroke and Cerebrovascular Diseases. 2012;21(6):436 - 444. doi:10.1016/j.jstrokecerebrovasdis.2010.11.002 | Intervention |
| Canis, M., Olzowy, B., Welz, C., Suckfull, M., Stelter, K. Simvastatin and Ginkgo biloba in the treatment of subacute tinnitus: A retrospective study of 94 patients. American Journal of Otolaryngology - Head and Neck Medicine and Surgery. 2011;32(1):19 - 23. doi:10.1016/j.amjoto.2009.09.004 | Intervention |
| Pandey, S., Mahato, N. K., Navale, R. Role of self-induced sound therapy: Bhramari Pranayama in Tinnitus. Audiol Med. 2010;8(3):137 - 141. doi:10.3109/1651386X.2010.489694 | Intervention |
| Brinkley, T. E., Lovato, J. F., Arnold, A. M., Furberg, C. D., Kuller, L. H., Burke, G. L., Nahin, R. L., Lopez, O. L., Yasar, S., Williamson, J. D. Effect of Ginkgo biloba on Blood Pressure and Incidence of Hypertension in Elderly Men and Women. Am J Hypertens. 2010.10.1038/ajh.2010.14 | Intervention |
| Wang, G., Cheng, Q., Zhang, S., Bai, L., Zeng, J., Cui, P. J., Zhang, T., Sun, Z. K., Ren, R. J., Deng, Y. L., Xu, W., Wang, Y., Chen, S. D. Economic impact of dementia in developing countries: An evaluation of Alzheimer-type dementia in Shanghai, China. J Alzheimers Dis. 2008;15(1):109 - 115. doi:10.3233/JAD-2008-15109 | Intervention |
| Mazza, M., Capuano, A., Bria, P., Mazza, S. Ginkgo biloba and donepezil: A comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. European Journal of Neurology. 2006;13(9):981 - 985. doi:10.1111/j.1468-1331.2006.01409.x | Intervention[q] |
| Dietrich, E. S., Jopp, R., Schreier, U., Gilge, R., Bartmann, P., Berthold, H. Drug expenditures resulting from the implementation of clinical practice guidelines in Germany. Gesundheitsokonomie und Qualitatsmanagement. 2005;10(1):35 - 43. doi:10.1055/s-2004-813943 | Intervention |
| Heinen-Kammerer, T., Motzkat, K., Daniel, D., Gertz, H. J., Koller, M., Lorenz, W., Pilartz, H., Zimmer, B., Habs, M., von den Driesch, V., Rychlik, R. The situation of patients with dementia may be rectified by Ginkgo biloba. Results of a health services research study concerning the ability of patients with dementia, quality of life of the nursing family members and total treatment costs. MMW Fortschr Med. 2005;147 Suppl 3():127 - 133. doi: | Intervention |
| Maelicke, A. Critical assessment and results: Long-term treatment of dementia of the Alzheimer type (AD 2000 Study). PsychoNeuro. 2004;30(9):514 - 516. doi:10.1055/s-2004-835167 | Intervention |

[q] Although this article states that the ginkgo biloba intervention used was EGb761, the IQWiG report stated that, upon communication with the original study authors, it is not clear that a standardised ginkgo biloba extract was used. The study was therefore excluded from this review.

| | |
|---|---|
| Andrieu, S., Gillette, S., Amouyal, K., Nourhashemi, F., Reynish, E., Ousset, P. J., Albarede, J. L., Vellas, B., Grandjean, H. Association of Alzheimer's disease onset with Ginkgo biloba and other symptomatic cognitive treatments in a population of women aged 75 years and older from the EPIDOS study. Journals of Gerontology - Series A Biological Sciences and Medical Sciences. 2003;58(4):372 - 377. doi:10.1093/gerona/58.4.m372 | Intervention |
| Reisser, Ch, Weidauer, H. Ginkgo biloba extract EGb 761 or pentoxifylline for the treatment of sudden deafness: A randomized, reference-controlled, double-blind study. Acta Otolaryngol. 2001;121(5):579 - 584. doi:10.1080/000164801316878854 | Intervention |
| Hesse, G., Rienhoff, N. K., Nelting, M., Brehmer, D. Medicine costs in patients with chronic complex tinnitus. HNO. 1999;47(7):658 - 660. doi:10.1007/s001060050442 | Intervention |
| Winther, K., Randlov, C., Rein, E., Mehlsen, J. Effects of Ginkgo biloba extract on cognitive function and blood pressure in elderly subjects. Current Therapeutic Research - Clinical and Experimental. 1998;59(12):881 - 888. doi:10.1016/S0011-393X%2898%2985053-4 | Intervention |
| Kiesewetter, H., Birk, A., Ihme, N., Jung, F. Association between vasoactive substances and the incidence of cardiovascular events. Clin Hemorheol. 1995;15(4):681 - 686. doi: | Intervention |
| Pelc, A., Montron, A., Westerloppe, J. Cost of follow-up of patients treated with peripheral vasodilators in general medicine. Journal d'Economie Medicale. 1995;13(5):259 - 271. doi: | Intervention |
| Funfgeld, E. W. Statistical reliability of the cerebral action of Nootropics with the computerized 20-frequency-band analysis of the EEG in case of presenile/senile Alzheimer disease (AD/SDAT). The first report: Methodology, observations after medication with Ginkgo biloba extract. Geriatrie Forschung. 1995;5(1):41 - 54. doi: | Intervention |
| Semlitsch, H. V., Anderer, P., Saletu, B., Binder, G. A., Decker, K. A. Cognitive psychophysiology in nootropic drug research: Effects of Ginkgo biloba on event-related potentials (P300) in age-associated memory impairment. Pharmacopsychiatry. 1995;28(4):134 - 142. doi:10.1055/s-2007-979605 | Intervention |
| von Wedel, H., Calero, L., Walger, M., Hoenen, S., Rutwalt, D. Soft-laser/Ginkgo therapy in chronic tinnitus. A placebo-controlled study. Adv Otorhinolaryngol. 1995;49():105 - 108. doi: | Intervention |
| Holgers, K. M., Axelsson, A., Pringle, I. Ginkgo biloba extract for the treatment of tinnitus. Audiology. 1994;33(2):85 - 92. doi: | Intervention |
| Mancini, M., Agozzino, B., Bompani, R. Clinical and therapeutic effects of biloba Ginkgo extract (e.g.b) compared to placebo in the treatment of patients affected by senile psychorganic dementia on an arteriosclerotic basic. Gazzetta Medica Italiana Archivio per le Scienze Mediche. 1993;152(3):69 - 80. doi: | Intervention |
| Gerhardt, G., Rogalla, K., Jaeger, J. Drug therapy of disorders of cerebral performance. Randomized comparative study of dihydroergotoxine and Ginkgo biloba extract. Fortschr Med. 1990;108(19):384 - 388. doi: | Intervention |
| Hamann, K. F. Vestibular vertigo treated by physical therapy in association with Ginkgo biloba extract. Therapiewoche. 1985. 35:4586 - 4590 | Intervention |
| Boger, J., Braun, M. Demonstration of cerebral efficacy of a Ginkgo biloba preparation. A clinical report. Therapiewoche. 1982;32(35):4086 - 4090. doi: | Intervention |
| Schwerdtfeger, F. Results of Rokan treatment of vertiginous symptoms verified electronystagmographically and clinically. Therapiewoche. 1981;31(52):8658 - 8667. doi: | Intervention |
| Courbier, R., Jausseran, J. M., Reggi, M. Double blind crossover trial of Ginkgo biloba extract in arteriopathies of the lower limbs. Mediterr Med. 1977;5(126):61 - 64. doi: | Intervention |

| | |
|---|---|
| Ambrosi, C., Bourde, C. A new treatment in arteriopathy of the lower limbs: Ginkgo biloba extract. Clinical trial and study by the method of liquid crystals. Gaz Med Fr. 1975;82(6):628 - 632. doi: | Intervention |
| Wal, Ankita, Verma, Neha, Balakrishnan, Senthil Kumar, Gahlot, Vinod, Dwivedi, Sumeet, Sahu, Pankaj Kumar, Tabish, Mohammad, Wal, Pranay. A Systematic Review of Herbal Interventions for the Management of Cardiovascular Diseases. Curr Cardiol Rev. 2024;20(5):e030524229664. doi:10.2174/011573403X286573240422104647 | Intervention |
| Chauhan, Bhushan, Arya, Shantanu, Chauhan, Komal. Ginkgo biloba Administered Singly and Combined With Antioxidants in Tinnitus Patients. Journal of audiology & otology. 2023;27(1):37-44. doi:10.7874/jao.2022.00395 | Intervention |
| Lopez, Oscar L., Klunk, William E., Mathis, Chester A., Snitz, Beth E., Chang, Yuefang, Tracy, Russell P., Kuller, Lewis H. Relationship of amyloid-beta1-42 in blood and brain amyloid: Ginkgo Evaluation of Memory Study. Brain communications. 2020;2(1):fcz038. doi:10.1093/braincomms/fcz038 | Intervention |
| Hajat, Anjum, Park, Christina, Adam, Claire, Fitzpatrick, Annette L., Ilango, Sindana D., Leary, Cindy, Libby, Tanya, Lopez, Oscar, Semmens, Erin O., Kaufman, Joel D. Air pollution and plasma amyloid beta in a cohort of older adults: Evidence from the Ginkgo Evaluation of Memory study. Environ Int. 2023;172():107800. doi:10.1016/j.envint.2023.107800 | Intervention |
| Si, Xia, Yu, Zhiying, Ren, Xiaolei, Huang, Lin, Feng, Yufei. Efficacy and safety of standardized Ginkgo biloba L. leaves extract as an adjuvant therapy for sudden sensorineural hearing loss: A systematic review and meta-analysis. J Ethnopharmacol. 2022;282():114587. doi:10.1016/j.jep.2021.114587 | Intervention |
| Snitz, Beth E., Chang, Yuefang, Tudorascu, Dana L., Lopez, Oscar L., Lopresti, Brian J., DeKosky, Steven T., Carlson, Michelle C., Cohen, Ann D., Kamboh, M. Ilyas, Aizenstein, Howard J., Klunk, William E., Kuller, Lewis H. Predicting resistance to amyloid-beta deposition and cognitive resilience in the oldest-old. Neurology. 2020;95(8):e984-e994. doi:10.1212/WNL.0000000000010239 | Intervention |
| Stoehr, Gary P., Jacobsen, Erin, Jia, Yichen, Snitz, Beth E., Ganguli, Mary. Trends in the Use of Medications and Supplements to Treat or Prevent Dementia: A Population-based Study. Alzheimer Dis Assoc Disord. 2020;34(2):148-155. doi:10.1097/WAD.0000000000000357 | Intervention |
| Nishad, Rajeev Kumar, Jain, Anil Kumar, Singh, Mangal, Verma, Reetu, Jain, Sanyogita. Randomised Controlled Clinical Study of Injection Caroverine and Ginkgo Biloba Extract in Cochlear Synaptic Tinnitus. Indian J Otolaryngol Head Neck Surg. 2019;71(Suppl 2):1523-1528. doi:10.1007/s12070-019-01655-5 | Intervention |
| Mathis, Chester A., Kuller, Lewis H., Klunk, William E., Snitz, Beth E., Price, Julie C., Weissfeld, Lisa A., Rosario, Bedda L., Lopresti, Brian J., Saxton, Judith A., Aizenstein, Howard J., McDade, Eric M., Kamboh, M. Ilyas, DeKosky, Steven T., Lopez, Oscar L. In vivo assessment of amyloid-beta deposition in nondemented very elderly subjects. Ann Neurol. 2013;73(6):751-61. doi:10.1002/ana.23797 | Intervention |
| Yasar, Sevil, Lin, Fu-Mei, Fried, Linda P., Kawas, Claudia H., Sink, Kaycee M., DeKosky, Steven T., Carlson, Michelle C. Diuretic use is associated with better learning and memory in older adults in the Ginkgo Evaluation of Memory Study. Alzheimers Dement. 2012;8(3):188-95. doi:10.1016/j.jalz.2011.03.010 | Intervention |
| Frank, Wilhelm, Konta, Brigitte, Seiler, Gerda. Therapy of unspecific tinnitus without organic cause. GMS Health Technol Assess. 2006;2():Doc17. doi: | Intervention |
| Saxton, J., Snitz, B. E., Lopez, O. L., Ives, D. G., Dunn, L. O., Fitzpatrick, A., Carlson, M. C., Dekosky, S. T. Functional and cognitive criteria produce different rates of mild cognitive impairment | Intervention |

| | |
|---|---|
| and conversion to dementia. J Neurol Neurosurg Psychiatry. 2009;80(7):737-43. doi:10.1136/jnnp.2008.160705 | |
| Belle, Steven H., Zhang, Song, Czaja, Sara J., Burns, Robert, Schulz, Richard. Use of cognitive enhancement medication in persons with Alzheimer disease who have a family caregiver: results from the Resources for Enhancing Alzheimer's Caregiver Health (REACH) project. Am J Geriatr Psychiatry. 2004;12(3):250-7. doi: | Intervention |
| Brautigam, M. R., Blommaert, F. A., Verleye, G., Castermans, J., Jansen Steur, E. N., Kleijnen, J. Treatment of age-related memory complaints with Ginkgo biloba extract: a randomized double blind placebo-controlled study. Phytomedicine. 1998;5(6):425-34. doi:10.1016/S0944-7113(98)80038-X | Intervention |
| Meyer, B. [A multicenter study of tinnitus. Epidemiology and therapy]. Etude multicentrique des acouphenes. Epidemiologie et therapeutique. 1986;103(3):185-8. doi: | Intervention |
| Meyer, B. [Multicenter randomized double-blind drug vs. placebo study of the treatment of tinnitus with Ginkgo biloba extract]. Etude multicentrique randomisee a double insu face au placebo du traitement des acouphenes par l'extrait de Ginkgo biloba. 1986;15(31):1562-4. doi: | Intervention |
| Liu, P., Luo, H. C., Shen, Y. C., Guo, H., Zhao, X. Y., Yu, J., Yin, J. L., Liu, G. Z., Zhong, H. W., Zhang, B., Lu, L. L., Yang, F. S., Zhang, S. Q., Ma, Q. M., Yan, X. X., Zhu, L. C., Zhu, S. M., Nie, X. W. Combined use of ginkgo biloba extracts on the efficacy and adverse reactions of various antipsychotics. The Chinese journal of clinical pharmacology. 1997;13(4):193. doi: | Language |
| Dai, C. F., Chui, Y., Zhao, Y. L., and Wang, Z. M. The curative effect of standardized Ginkgo Bilobaete extract (e.g.b 761) on peripheral vestibular vertigo. Chinese journal of ophthalmology and otolaryngology. 2002;2(1):14. doi: | Language |
| Drabaek, H., Petersen, J. R., Wiinberg, N., Hansen, K. F. W., Mehlsen, J. Effect of ginkgo biloba extraction patients with intermittent claudication. Effekten af ginkgo biloba-ekstrakt hos patienter med claudicatio intermittens. 1996;158(27):3928. doi: | Language |
| Wen-juan, M. The effect of ginkgo biloba extract combined with piracetam in treatment of vascular dementia and its affection on cognitive dysfunction. Modern preventive medicine. 2010;2():081. doi: | Language |
| Cekkayan, S., Ozl, uuml, gbreve, lu, L., Yolo, gbreve, lu, S., ouml, ylemezo, gbreve, lu, S., Erpek, G. Comparison of the efficiency of betahistine hydrochloride and ginkgo biloba extract in tinnitus patients. Tinnituslu hastalarda betahistin ve ginkgo biloba ekstresinin etkinliginin karsilastirilmasi. 1996;4():19. doi: | Language |
| Yarmoammadi, M. E., Naseri, M., Nabavi, nbsp, Sm, Zanganeh, nbsp, Zayeri, nbsp. The efficacy of Ginkgo-TD on amelioration of subjective tinnitus. Bimonthly Scientific Research Journal of Shahed University. 2007;14(67):67. doi: | Language |
| Liao, H. W., Ji, J. N., Wu, C. F. Effect of scalp acupuncture plus real-time cognitive training on cerebral blood flow in Alzheimer disease patients. Shanghai journal of acupuncture and moxibustion [shang hai zhen jiu za zhi]. 2015;34(11):1031. doi: | Language |
| Cao, T., Teng, Y., Yao, X., Shi, J., Ni, J., Tian, J. Efficacy and safety of butylphthalide soft capsule in the treatment of vascular dementia: A meta-analysis. Chinese Journal of Evidence-Based Medicine. 2020;20(4):444 - 452. doi:10.7507/1672-2531.201907060 | Language |
| Teng, Y., Shi, J., Cao, T., Yao, X., Ni, J., Tian, J. Efficacy and safety of butylphthalide soft capsule in the treatment of Alzheimer's disease: A meta-analysis. Chinese Journal of Evidence-Based Medicine. 2019;19(12):1446 - 1452. doi:10.7507/1672-2531.201904115 | Language |

| | |
|---|---|
| Zhao, M. X., Dong, Z. H., Yu, Z. H., Xiao, S. Y., Li, Y. M. Effects of Ginkgo biloba extract in improving episodic memory of patients with mild cognitive impairment: A randomized controlled trial. Journal of Chinese Integrative Medicine. 2012;10(6):628 - 634. doi:10.3736/jcim20120605 | Language |
| Orendorz-Fraczkowska, K., Pospiech, L., Gawron, W. Results of combined treatment for vestibular receptor impairment with physical therapy and Ginkgo biloba extract (e.g.b 761). Otolaryngol Pol. 2002;56(1):83 - 88. doi: | Language |
| Van der Kuy, A. A pharmacoeconomic finger exercise. Costs and benefits of phytotherapeutic compounds. Pharm Weekbl. 2001;136(18):659 - 661. doi: | Language |
| Novotny, M. Ginkgo biloba in the treatment of tinnitus. Prakt Lek. 1999;79(11):641 - 642. doi: | Language |
| Enrique Gomez, A. Multicenter study with standardized extract of ginko-biloba EGb 761 in the treatment of memory alteration, vertigo and tinnitus. Invest Med Int. 1997;24(2):31 - 39. doi: | Language |
| Halama, P., Bartsch, G., Meng, G. Disturbances of cerebral performance of vascular origin. Randomized, double-blind study on the efficacy of Ginkgo biloba extract. Revista Brasileira de Neurologia. 1991;27(2):73 - 78. doi: | Language |
| Roland, Pal-Didrik Hoff, Nergard, Cecilie Sogn. [Ginkgo biloba--effect, adverse events and drug interaction]. Ginkgo biloba--effekt, bivirkninger og interaksjoner. 2012;132(8):956-9. doi:10.4045/tidsskr.11.0780 | Language |
| Holstein, N. Ginkgo special extract EGb 761 in tinnitus therapy. An overview of results of completed clinical trials. Ginkgo-Spezialextrakt EGb 761 in der Tinnitus-Therapie. Eine Ubersicht über die Ergebnisse der durchgeführten klinischen Prüfungen. 2001;118(4):157. doi: | Otherwise eligible SLR |
| Hilton, Malcolm P., Zimmermann, Eleanor F., Hunt, William T. Ginkgo biloba for tinnitus. | Otherwise eligible SLR |
| Nicolai, P. A. Saskia, Kruidenier, Lotte M., Bendermacher, L. W. Bianca, Prins, Martin H., Stokmans, Rutger A., Broos, P. H. L. Pieter, Teijink, A. W. Joep. Ginkgo biloba for intermittent claudication. | Otherwise eligible SLR |
| Birks, Jacqueline, Grimley Evans, John. Ginkgo biloba for cognitive impairment and dementia. | Otherwise eligible SLR |
| Riepe, M., Hoerr, R., Schlaefke, S. Ginkgo biloba extract EGb 761 is safe and effective in the treatment of mild dementia meta-analysis of patient subgroups in randomised controlled trials. World J Biol Psychiatry. 2025.10.1080/15622975.2024.2446830 | Otherwise eligible SLR |
| Deng, X., Li, D. Effect of long-term pharmacological treatments on Alzheimer disease A systematic review and network meta-analysis. Medicine (United States). 2024;103(38):e39753. doi:10.1097/MD.0000000000039753 | Otherwise eligible SLR |
| Alshammari, M. K., Hussain, K. H., Alshammari, M. R., Alshammari, H. H., Althagafi, H. S., Bajunaid, H. R., Alanzi, B. A., Alshammari, A. A., Alshammari, A. K., Aljasim, M. A. J., Alanizi, Y. S., Al-Sulais, W. M., Albaqami, A. A. A. N. D. Effectiveness of Complementary and Alternative Medicine and Physical Therapies in Peripheral Arterial Disease with Intermittent Claudication: A Systematic Review. Indian Journal of Pharmaceutical Education and Research. 2024;58(2 Supplement):s340 - s353. doi:10.5530/ijper.58.2s.37 | Otherwise eligible SLR |
| Nimmons, D., Aker, N., Burnand, A., Jordan, K. P., Cooper, C., Davies, N., Manthorpe, J., Chew-Graham, C. A., Kingstone, T., Petersen, I., Walters, K. Clinical effectiveness of pharmacological and non-pharmacological treatments for the management of anxiety in community dwelling people living with dementia: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2024;157():105507. doi:10.1016/j.neubiorev.2023.105507 | Otherwise eligible SLR |

| | |
|---|---|
| Ahmad, S., Ahmed, S. B., Khan, A., Wasim, M., Tabassum, S., Haider, S., Ahmed, F., Batool, Z., Khaliq, S., Rafiq, H., Tikmani, P., Gilani, A. U. H. Natural remedies for Alzheimer's disease: A systematic review of randomized controlled trials. Metab Brain Dis. 2023;38(1):17 - 44. doi:10.1007/s11011-022-01063-9 | Otherwise eligible SLR |
| Hort, J., Duning, T., Hoerr, R. Ginkgo biloba Extract EGb 761 in the Treatment of Patients with Mild Neurocognitive Impairment: A Systematic Review. Neuropsychiatr Dis Treat. 2023;19():647 - 660. doi:10.2147/NDT.S401231 | Otherwise eligible SLR |
| Gao, X., Cheng, Y., Liu, F., Han, X., Liu, C. The clinical efficacy and safety of Ginkgo biloba in vertigo patients: A meta-analysis. Advances in Integrative Medicine. 2023;10(4):158 - 166. doi:10.1016/j.aimed.2023.10.001 | Otherwise eligible SLR |
| Cave, A. E., Chang, D. H., Munch, G. W., Steiner-Lim, G. Z. A systematic review of the safety and efficacy on cognitive function of herbal and nutritional medicines in older adults with and without subjective cognitive impairment. Syst Rev. 2023;12(1):143. doi:10.1186/s13643-023-02301-6 | Otherwise eligible SLR |
| Li, D., Ma, J., Wei, B., Gao, S., Lang, Y., Wan, X. Effectiveness and safety of ginkgo biloba preparations in the treatment of Alzheimer's disease: A systematic review and meta-analysis. Front Aging Neurosci. 2023;15():1124710. doi:10.3389/fnagi.2023.1124710 | Otherwise eligible SLR |
| Theleritis, C., Siarkos, K., Politis, A., Smyrnis, N., Papageorgiou, C., Politis, A. M. A Systematic Review of Pharmacological Interventions for Apathy in Aging Neurocognitive Disorders. Brain Sci. 2023;13(7):1061. doi:10.3390/brainsci13071061 | Otherwise eligible SLR |
| Knorz, A. L., Quante, A. Alzheimer's Disease: Efficacy of Mono- and Combination Therapy. A Systematic Review. J Geriatr Psychiatry Neurol. 2022;35(4):475 - 486. doi:10.1177/08919887211044746 | Otherwise eligible SLR |
| Cheng, N., Bell, L., Lamport, D. J., Williams, C. M. Dietary Flavonoids and Human Cognition: A Meta-Analysis. Mol Nutr Food Res. 2022;66(21):e2100976. doi:10.1002/mnfr.202100976 | Otherwise eligible SLR |
| Lee, J., Kwon, S., Jin, C., Cho, S. Y., Park, S. U., Jung, W. S., Moon, S. K., Park, J. M., Ko, C. N., Cho, K. H. Traditional East Asian Herbal Medicine Treatment for Alzheimer's Disease: A Systematic Review and Meta-Analysis. Pharmaceuticals. 2022;15(2):174. doi:10.3390/ph15020174 | Otherwise eligible SLR |
| Liang, N., Chen, Y., Yang, S., Liang, C., Gao, L., Wang, S., Wang, Y., Zhang, Z., Shi, N. Chinese Herbal Medicine for Mild Cognitive Impairment: A Systematic Review of Randomized Controlled Trials. Front Neurol. 2022;13():903224. doi:10.3389/fneur.2022.903224 | Otherwise eligible SLR |
| Sereda, M., Xia, J., Scutt, P., Hilton, M. P., El Refaie, A., Hoare, D. J. Ginkgo biloba for tinnitus. Cochrane Database of Systematic Reviews. 2022;2022(11):CD013514. doi:10.1002/14651858.CD013514.pub2 | Otherwise eligible SLR |
| Roheger, M., Hennersdorf, X. S., Riemann, S., Floel, A., Meinzer, M. A systematic review and network meta-analysis of interventions for subjective cognitive decline. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2021;7(1):e12180. doi:10.1002/trc2.12180 | Otherwise eligible SLR |
| Zhan, M., Sun, L., Liu, J., Zeng, Z., Shen, W., Li, H., Wang, Y., Han, F., Shi, J., Zeng, X., Lu, X., Zhang, Y., Liao, X. EGb in the Treatment for Patients with VCI: A Systematic Review and Meta-Analysis. Oxid Med Cell Longev. 2021;2021():8787684. doi:10.1155/2021/8787684 | Otherwise eligible SLR |
| Fink, H. A., Linskens, E. J., MacDonald, R., Silverman, P. C., McCarten, J. R., Talley, K. M. C., Forte, M. L., Desai, P. J., Nelson, V. A., Miller, M. A., Hemmy, L. S., Brasure, M., Taylor, B. C., Ng, W., Ouellette, J. M., Sheets, K. M., Wilt, T. J., Butler, M. Benefits and harms of prescription drugs and supplements for treatment of clinical Alzheimer-type dementia: A systematic review and meta-analysis. Ann Intern Med. 2020;172(10):656 - 668. doi:10.7326/M19-3887 | Otherwise eligible SLR |

| | |
|---|---|
| Cocchiara, R. A., de Lucia, F., Koci, L., Lisanti, E., Petruccini, G., la Torre, G. Management of the early stage of Alzheimer's disease: A systematic review of literature over the past 10 years. Clin Ter. 2020;171(4):E357 - E368. doi:10.7417/CT.2020.2239 | Otherwise eligible SLR |
| Thancharoen, O., Limwattananon, C., Waleekhachonloet, O., Rattanachotphanit, T., Limwattananon, P., Limpawattana, P. Ginkgo biloba Extract (e.g.b761), Cholinesterase Inhibitors, and Memantine for the Treatment of Mild-to-Moderate Alzheimer's Disease: A Network Meta-Analysis. Drugs Aging. 2019;36(5):435 - 452. doi:10.1007/s40266-019-00648-x | Otherwise eligible SLR |
| Mathie, R. T., Fok, Y. Y. Y., Viksveen, P., To, A. K. L., Davidson, J. R. T. Systematic Review and Meta-Analysis of Randomised, Other-than-Placebo Controlled, Trials of Non-Individualised Homeopathic Treatment. Homeopathy. 2019;108(2):88 - 101. doi:10.1055/s-0038-1677481 | Otherwise eligible SLR |
| McGrattan, A. M., McEvoy, C. T., McGuinness, B., McKinley, M. C., Woodside, J. V. Effect of dietary interventions in mild cognitive impairment: A systematic review. Br J Nutr. 2018;120(12):1388 - 1405. doi:10.1017/S0007114518002945 | Otherwise eligible SLR |
| Bhome, R., Berry, A. J., Huntley, J. D., Howard, R. J. Interventions for subjective cognitive decline: Systematic review and meta-analysis. BMJ Open. 2018;8(7):e021610. doi:10.1136/bmjopen-2018-021610 | Otherwise eligible SLR |
| D'Cunha, N. M., Georgousopoulou, E. N., Dadigamuwage, L., Kellett, J., Panagiotakos, D. B., Thomas, J., McKune, A. J., Mellor, D. D., Naumovski, N. Effect of long-term nutraceutical and dietary supplement use on cognition in the elderly: A 10-year systematic review of randomised controlled trials. Br J Nutr. 2018;119(3):280 - 298. doi:10.1017/S0007114517003452 | Otherwise eligible SLR |
| Zenner, H. P., Delb, W., Kroner-Herwig, B., Jager, B., Peroz, I., Hesse, G., Mazurek, B., Goebel, G., Gerloff, C., Trollmann, R., Biesinger, E., Seidler, H., Langguth, B. A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. Eur Arch Otrhinolaryngol. 2017;274(5):2079 - 2091. doi:10.1007/s00405-016-4401-y | Otherwise eligible SLR |
| Hyde, A. J., May, B. H., Dong, L., Feng, M., Liu, S., Guo, X., Zhang, A. L., Lu, C., Xue, C. C. Herbal medicine for management of the behavioural and psychological symptoms of dementia (BPSD): A systematic review and meta-analysis. J Psychopharmacol. 2017;31(2):169 - 183. doi:10.1177/0269881116675515 | Otherwise eligible SLR |
| Yang, G., Wang, Y., Sun, J., Zhang, K., Liu, J. Ginkgo biloba for mild cognitive impairment and alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. Curr Top Med Chem. 2016;16(5):520 - 528. doi:10.2174/1568026615666150813143520 | Otherwise eligible SLR |
| von Gunten, A., Schlaefke, S., Uberla, K. Efficacy of Ginkgo biloba extract EGb 761 in dementia with behavioural and psychological symptoms: A systematic review. World J Biol Psychiatry. 2016;17(8):622 - 633. doi:10.3109/15622975.2015.1066513 | Otherwise eligible SLR |
| Strohle, A., Schmidt, D. K., Schultz, F., Fricke, N., Staden, T., Hellweg, R., Priller, J., Rapp, M. A., Rieckmann, N. Drug and Exercise Treatment of Alzheimer Disease and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis of Effects on Cognition in Randomized Controlled Trials. American Journal of Geriatric Psychiatry. 2015;23(12):1234 - 1249. doi:10.1016/j.jagp.2015.07.007 | Otherwise eligible SLR |
| Tan, M. S., Yu, J. T., Tan, C. C., Wang, H. F., Meng, X. F., Wang, C., Jiang, T., Zhu, X. C., Tan, L. Efficacy and adverse effects of Ginkgo Biloba for cognitive impairment and dementia: A systematic review and meta-analysis. J Alzheimers Dis. 2015;43(2):589 - 603. doi:10.3233/JAD-140837 | Otherwise eligible SLR |
| Yang, M., Xu, D. D., Zhang, Y., Liu, X., Hoeven, R., Cho, W. C. S. A systematic review on natural medicines for the prevention and treatment of Alzheimer's disease with meta-analyses of intervention effect of ginkgo. Am J Chin Med. 2014;42(3):505 - 521. doi:10.1142/S0192415X14500335 | Otherwise eligible SLR |

| | |
|---|---|
| Gauthier, S., Schlaefke, S. Efficacy and tolerability of Ginkgo biloba extract EGb 761 in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. Clin Interv Aging. 2014;9():2065 - 2077. doi:10.2147/CIA.S72728 | Otherwise eligible SLR |
| Cooper, C., Mukadam, N., Katona, C., Lyketsos, C. G., Blazer, D., Ames, D., Rabins, P., Brodaty, H., De Mendonca Lima, C., Livingston, G. Systematic review of the effectiveness of pharmacologic interventions to improve quality of life and well-being in people with dementia. American Journal of Geriatric Psychiatry. 2013;21(2):173 - 183. doi:10.1016/j.jagp.2012.10.018 | Otherwise eligible SLR |
| Cooper, C., Li, R., Lyketsos, C., Livingston, G. Treatment for mild cognitive impairment: Systematic review. Br J Psychiatry. 2013;203(4):255 - 264. doi:10.1192/bjp.bp.113.127811 | Otherwise eligible SLR |
| Butler, R., Radhakrishnan, R. Dementia. BMJ clinical evidence. 2012;2012. | Otherwise eligible SLR |
| Kellermann, A. J., Kloft, C. Is there a risk of bleeding associated with standardized Ginkgo biloba extract therapy? A systematic review and meta-analysis. Pharmacotherapy. 2011;31(5):490 - 502. doi:10.1592/phco.31.5.490 | Otherwise eligible SLR |
| Yang, Z., Li, W. J., Huang, T., Chen, J. M., Zhang, X. Meta-analysis of Ginkgo biloba extract for the treatment of Alzheimer's disease. Neural Regeneration Research. 2011;6(15):1125 - 1129. doi:10.3969/j.issn.1673-5374.2011.15.001 | Otherwise eligible SLR |
| Fu, L. M., Li, J. T. A systematic review of single Chinese herbs for Alzheimer's disease treatment. Evidence-based Complementary and Alternative Medicine. 2011;2011():640284. doi:10.1093/ecam/nep136 | Otherwise eligible SLR |
| von Boetticher, A. Ginkgo biloba extract in the treatment of tinnitus: A systematic review. Neuropsychiatr Dis Treat. 2011;7(1):441 - 447. doi:10.2147/ndt.s22793 | Otherwise eligible SLR |
| Nicolai, S. P., Gerardu, V. C., Kruidenier, L. M., Prins, M. H., Teijink, J. A. From the Cochrane library: Ginkgo biloba for intermittent claudication. Vasa - Journal of Vascular Diseases. 2010;39(2):153 - 158. doi:10.1024/0301-1526/a000021 | Otherwise eligible SLR |
| Wang, H., Song, Y. Y., Qi, H., Rong, Z. X., Wang, B. S., Zhang, L., Chen, H. Z. Effectiveness of standardized ginkgo biloba extract on cognitive symptoms of dementia with a six-month treatment: A bivariate random effect meta-analysis. Pharmacopsychiatry. 2010;43(3):86 - 91. doi:10.1055/s-0029-1242817 | Otherwise eligible SLR |
| Janssen, I. M., Sturtz, S., Skipka, G., Zentner, A., Garrido, M. V., Busse, R. Ginkgo biloba in Alzheimer's disease: A systematic review. Wiener Medizinische Wochenschrift. 2010;160(21-22):539 - 546. doi:10.1007/s10354-010-0844-8 | Otherwise eligible SLR |
| Drijgers, R. L., Aalten, P., Winogrodzka, A., Verhey, F. R. J., Leentjens, A. F. G. Pharmacological treatment of apathy in neurodegenerative diseases: A systematic review. Dement Geriatr Cogn Disord. 2009;28(1):13 - 22. doi:10.1159/000228840 | Otherwise eligible SLR |
| Weinmann, S., Roll, S., Schwarzbach, C., Vauth, C., Willich, S. N. Effects of Ginkgo biloba in dementia: systematic review and meta-analysis. BMC Geriatr. 2010;10():14. doi: | Otherwise eligible SLR |
| Warner, J. P., Butler, R., Gupta, S. Dementia. BMJ clinical evidence. 2010;2010. | Otherwise eligible SLR |
| Man, S. C., Durairajan, S. S. K., Kum, W. F., Lu, J. H., Huang, J. D., Cheng, C. F., Chung, V., Xu, M., Li, M. Systematic review on the efficacy and safety of herbal medicines for Alzheimer's disease. J Alzheimers Dis. 2008;14(2):209 - 223. doi:10.3233/JAD-2008-14209 | Otherwise eligible SLR |

| | |
|---|---|
| Conlin, A. E., Parnes, L. S. Treatment of sudden sensorineural hearing loss I. A systematic review. Archives of Otolaryngology - Head and Neck Surgery. 2007;133(6):573 - 581. doi:10.1001/archotol.133.6.573 | Otherwise eligible SLR |
| Conlin, A. E., Parnes, L. S. Treatment of sudden sensorineural hearing loss II. A meta-analysis. Archives of Otolaryngology - Head and Neck Surgery. 2007;133(6):582 - 586. doi:10.1001/archotol.133.6.582 | Otherwise eligible SLR |
| Savage, J., Cook, S., Wadell, A. Tinnitus. BMJ clinical evidence. 2007;2007. | Otherwise eligible SLR |
| Hamann, K. F. Special ginkgo extract in cases of vertigo. A systematic review of randomised, double-blind, placebo controlled clinical examinations. HNO. 2007;55(4):258 - 263. doi:10.1007/s00106-006-1440-5 | Otherwise eligible SLR |
| Maxion-Bergemann, S., Wolf, M., Bornhoft, G., Matthiessen, P. F., Wolf, U. Complementary and alternative medicine costs - A systematic literature review. Forsch Komplementarmed. 2006;13(2):42 - 45. doi:10.1159/000093313 | Otherwise eligible SLR |
| Savovic, J., Wider, B., Ernst, E. Effects of Ginkgo biloba on blood coagulation parameters: A systematic review of randomised clinical trials. Evidence-Based Integrative Medicine. 2005;2(3):167 - 176. doi:10.2165/01197065-200502030-00007 | Otherwise eligible SLR |
| Pittler, M. H., Ernst, E. Complementary therapies for peripheral arterial disease: Systematic review. Atherosclerosis. 2005;181(1):1 - 7. doi:10.1016/j.atherosclerosis.2005.02.021 | Otherwise eligible SLR |
| Langa, K. M., Foster, N. L., Larson, E. B. Mixed dementia: Emerging concepts and therapeutic implications. JAMA. 2004;292(23):2901 - 2908. doi:10.1001/jama.292.23.2901 | Otherwise eligible SLR |
| Mills, E. J., Chow, T. W. Randomized controlled trials in long-term care residents with dementia: A systematic review. J Am Med Dir Assoc. 2003;4(6):302 - 307. doi:10.1016/S1525-8610%2804%2970388-6 | Otherwise eligible SLR |
| Pittler, M. H. Complementary therapies for peripheral arterial disease. Focus on Alternative and Complementary Therapies. 2004;9(2):93 - 95. doi: | Otherwise eligible SLR |
| Rejali, D., Sivakumar, A., Balaji, N. Ginkgo biloba does not benefit patients with tinnitus: A randomized placebo-controlled double-blind trial and meta-analysis of randomized trials. Clin Otolaryngol Allied Sci. 2004;29(3):226 - 231. doi:10.1111/j.1365-2273.2004.00814.x | Otherwise eligible SLR |
| Wettstein, A. Cholinesterase inhibitors and Ginkgo extracts--are they comparable in the treatment of dementia? Comparison of published placebo-controlled efficacy studies of at least six months' duration. Phytomedicine. 2000;6(6):393 - 401. doi:10.1016/S0944-7113%2800%2980066-5 | Otherwise eligible SLR |
| Pittler, M. H., Ernst, E. Ginkgo Biloba extract for the treatment of intermittent claudication: A meta-analysis of randomized trials. Am J Med. 2000;108(4):276 - 281. doi:10.1016/S0002-9343%2899%2900454-4 | Otherwise eligible SLR |
| Daly, M. P. Diagnosis and management of Alzheimer disease. J Am Board Fam Pract. 1999;12(5):375 - 385. doi:10.3122/jabfm.12.5.375 | Otherwise eligible SLR |
| Dobie, R. A. A review of randomized clinical trials in tinnitus. Laryngoscope. 1999;109(8):1202 - 1211. doi:10.1097/00005537-199908000-00004 | Otherwise eligible SLR |
| Ernst, E., Pittler, M. H. Ginkgo biloba for dementia. A systematic review of double-blind, placebo-controlled trials. Clin Drug Investig. 1999;17(4):301 - 308. doi: | Otherwise eligible SLR |
| Ernst, E., Stevinson, C. Ginkgo biloba for tinnitus: A review. Clin Otolaryngol Allied Sci. 1999;24(3):164 - 167. doi:10.1046/j.1365-2273.1999.00243.x | Otherwise eligible SLR |

| | |
|---|---|
| Ernst, E. Ginkgo biloba in treatment of intermittent claudication. A systematic research based on controlled studies in the literature. Fortschr Med. 1996;114(8):85 - 87. doi: | Otherwise eligible SLR |
| Letzel, H., Schoop, W. Ginkgo-biloba EGb 761 is comparable to the efficacy of pentoxifylline in peripheral occlusive arterial disease with intermittent claudication. Vasa - Journal of Vascular Diseases. 1992;21(4):403 - 410. doi: | Otherwise eligible SLR |
| Schneider, B. Ginkgo biloba extract in peripheral arterial disease: Meta-analysis of controlled clinical trials. Arzneimittel-Forschung/Drug Research. 1992;42(4):428 - 436. doi: | Otherwise eligible SLR |
| Boustani, Malaz, Peterson, Britt, Harris, Russell, Lux, Linda J., Krasnov, Carol, Sutton, Sonya F., Hanson, Laura, Lohr, Kathleen N. Screening for Dementia. .2003. | Otherwise eligible SLR |
| Pagotto, Guilherme Lopes de Oliveira, Santos, Livia Maria Oliveira Dos, Osman, Najwa, Lamas, Caroline Barbalho, Laurindo, Lucas Fornari, Pomini, Karina Torres, Guissoni, Leila M., Lima, Enzo Pereira de, Goulart, Ricardo de Alvares, Catharin, Virginia M. C. Strozze, Direito, Rosa, Tanaka, Masaru, Barbalho, Sandra Maria. Ginkgo biloba: A Leaf of Hope in the Fight against Alzheimer's Dementia: Clinical Trial Systematic Review. Antioxidants (Basel, Switzerland). 2024;13(6). doi:10.3390/antiox13060651 | Otherwise eligible SLR |
| Jiang, Lijuan, Su, Lijie, Cui, Huiru, Ren, Juanjuan, Li, Chunbo. Ginkgo biloba extract for dementia: a systematic review. Shanghai archives of psychiatry. 2013;25(1):10-21. doi:10.3969/j.issn.1002-0829.2013.01.005 | Otherwise eligible SLR |
| de Vries, Karin, Medawar, Evelyn, Korosi, Aniko, Witte, A. Veronica. The Effect of Polyphenols on Working and Episodic Memory in Non-pathological and Pathological Aging: A Systematic Review and Meta-Analysis. Frontiers in nutrition. 2021;8():720756. doi:10.3389/fnut.2021.720756 | Otherwise eligible SLR |
| Zhang, Tingting, Liu, Nanyang, Cao, Hongfu, Wei, Wei, Ma, Lina, Li, Hao. Different Doses of Pharmacological Treatments for Mild to Moderate Alzheimer's Disease: A Bayesian Network Meta-Analysis. Front Pharmacol. 2020;11():778. doi:10.3389/fphar.2020.00778 | Otherwise eligible SLR |
| Yuan, Chao, Zhang, Huan, Sun, Cuicui, Zhang, Kai. Efficacy and safety of Ginkgo biloba extract as an adjuvant in the treatment of Chinese patients with sudden hearing loss: a meta-analysis. Pharm Biol. 2023;61(1):610-620. doi:10.1080/13880209.2023.2190782 | Otherwise eligible SLR |
| Broderick, Cathryn, Forster, Rachel, Abdel-Hadi, Mohammed, Salhiyyah, Kareem. Pentoxifylline for intermittent claudication. Cochrane Database Syst Rev. 2020;10():CD005262. doi:10.1002/14651858.CD005262.pub4 | Otherwise eligible SLR |
| Liao, Ziwei, Cheng, Liping, Li, Xiaoxue, Zhang, Miaomiao, Wang, Sha, Huo, Ruimin. Meta-analysis of Ginkgo biloba Preparation for the Treatment of Alzheimer's Disease. Clin Neuropharmacol. 2020;43(4):93-99. doi:10.1097/WNF.0000000000000394 | Otherwise eligible SLR |
| Chan, Edwin Sy, Bautista, Dianne T., Zhu, Yanan, You, Yong, Long, Jian Ting, Li, Wenyun, Chen, Christopher. Traditional Chinese herbal medicine for vascular dementia. Cochrane Database Syst Rev. 2018;12():CD010284. doi:10.1002/14651858.CD010284.pub2 | Otherwise eligible SLR |
| Ghorani-Azam, Adel, Sepahi, Samaneh, Khodaverdi, Elham, Mohajeri, Seyed Ahmad. Herbal medicine as a promising therapeutic approach for the management of vascular dementia: A systematic literature review. Phytother Res. 2018;32(9):1720-1728. doi:10.1002/ptr.6120 | Otherwise eligible SLR |
| Perng, Cheng-Hwang, Chang, Yue-Cune, Tzang, Ruu-Fen. The treatment of cognitive dysfunction in dementia: a multiple treatments meta-analysis. Psychopharmacology (Berl). 2018;235(5):1571-1580. doi:10.1007/s00213-018-4867-y | Otherwise eligible SLR |
| Butler, Mary, Nelson, Victoria A., Davila, Heather, Ratner, Edward, Fink, Howard A., Hemmy, Laura S., McCarten, J. Riley, Barclay, Terry R., Brasure, Michelle, Kane, Robert L. Over-the-Counter | Otherwise eligible SLR |

| | |
|---|---|
| Supplement Interventions to Prevent Cognitive Decline, Mild Cognitive Impairment, and Clinical Alzheimer-Type Dementia: A Systematic Review. Ann Intern Med. 2018;168(1):52-62. doi:10.7326/M17-1530 | |
| de Souza Silva, Jose Edson, Santos Souza, Carlos Adriano, da Silva, Tamara Bispo, Gomes, Isla Alcantara, Brito, Giselle de Carvalho, de Souza Araujo, Adriano Antunes, de Lyra-Junior, Divaldo Pereira, da Silva, Wellington Barros, da Silva, Francilene Amaral. Use of herbal medicines by elderly patients: A systematic review. Arch Gerontol Geriatr. 2014;59(2):227-33. doi:10.1016/j.archger.2014.06.002 | Otherwise eligible SLR |
| Hashiguchi, Masayuki, Ohta, Yuriko, Shimizu, Mikiko, Maruyama, Junya, Mochizuki, Mayumi. Meta-analysis of the efficacy and safety of Ginkgo biloba extract for the treatment of dementia. Journal of pharmaceutical health care and sciences. 2015;1():14. doi:10.1186/s40780-015-0014-7 | Otherwise eligible SLR |
| Savage, Julian, Waddell, Angus. Tinnitus. BMJ Clinical Evidence. 2012;2012. doi: | Otherwise eligible SLR |
| Savage, Julian, Cook, Stephanie, Waddell, Angus. Tinnitus. BMJ clinical evidence. 2009;2009. doi: | Otherwise eligible SLR |
| Moher, D., Pham, B., Ausejo, M., Saenz, A., Hood, S., Barber, G. G. Pharmacological management of intermittent claudication: a meta-analysis of randomised trials. Drugs. 2000;59(5):1057-70. doi:10.2165/00003495-200059050-00003 | Otherwise eligible SLR |
| Warner, J., McCarney, R., Griffin, M., Hill, K., Fisher, P. Participation in dementia research: Rates and correlates of capacity to give informed consent. J Med Ethics. 2008;34(3):167 - 170. doi:10.1136/jme.2006.019786 | Outcomes |
| Maier, P., Atilde, para, sl, M., Atilde, para, ppel, E. Ginkgo - Wundermittel fÃ¼r Ã¤ltere Golfspieler?. Leistungssport. 2003;4():57. doi: | Population |
| Maillet, P., Bazex, J., d'Arbigny, P., et al. Ginkgo biloba extract, EGb 761 and trophic disorders of the lower limbs: contribution of EGb 761's anti-ischemic action associated with local treatment. In: advances in ginkgo biloba extract research. Cardiovascular effects of ginkgo biloba extract (e.g.b 761). Clostre F, defeudis FV (eds). Elsevier, Paris. 1994;3():151. doi: | Population |
| Halama, P., Bartsch, G., Meng, G. Cerebrovascular insufficiency. A placebo-controlled randomized double-blind trial on the effect of Ginkgo biloba extract. Fortschr Med. 1988;106():408. doi: | Population |
| Stocksmeier, U., Eberlein, M. Depressive mood in patients with brain disorders: a double-blind assessment of the effect of Ginkgo biloba extract. Depressive Verstimmung bei Hirnleistungsstoerungen Wirkung eines GinkgobilobaExtraktes in DoppelblindStudie ueberprueft. 1992;6(1-2):74. doi: | Population |
| Dong, H., Liu, M., Rong, L., Yang, S., Wang, J. Efficacy and Hemorheology of Ginkgo biloba Extract (e.g.b 761) in the Treatment of Sudden Sensorineural Hearing Loss: A Retrospective Study. Noise Health. 2024;26(122):383 - 389. doi:10.4103/nah.nah_73_24 | Population |
| Ilango, S. D., Leary, C. S., Ritchie, E., Semmens, E. O., Park, C., Fitzpatrick, A. L., Kaufman, J. D., Hajat, A. An Examination of the Joint Effect of the Social Environment and Air Pollution on Dementia among USA Older Adults. Environmental Epidemiology. 2023;7(3):E250. doi:10.1097/EE9.0000000000000250 | Population |
| Sharma, P., Kumar, R., Sinha, V. Role of Ginkgo Biloba Extract in Sensorineural Hearing Loss: A Randomised Prospective Clinical Study. International Journal of Pharmaceutical and Clinical Research. 2021;13(6):160 - 162. doi: | Population |

| | |
|---|---|
| Choi, S., Oh, D. S., Jerng, U. M. A systematic review of the pharmacokinetic and pharmacodynamic interactions of herbal medicine with warfarin. PLoS One. 2017;12(8):e0182794. doi:10.1371/journal.pone.0182794 | Population |
| Amieva, H., Meillon, C., Helmer, C., Barberger-Gateau, P., Dartigues, J. F. Ginkgo Biloba Extract and Long-Term Cognitive Decline: A 20-Year Follow-Up Population-Based Study. PLoS One. 2013;8(1):e52755. doi:10.1371/journal.pone.0052755 | Population |
| Jerant, A., Chapman, B., Duberstein, P., Robbins, J., Franks, . Personality and medication non-adherence among older adults enrolled in a six-year trial. Br J Health Psychol. 2011;16(Pt 1):151 - 169. doi: | Population |
| Kuller, L. H., Ives, D. G., Fitzpatrick, A. L., Carlson, M. C., Mercado, C., Lopez, O. L., Burke, G. L., Furberg, C. D., DeKosky, S. T. Does ginkgo biloba reduce the risk of cardiovascular events? Circulation: Cardiovascular Quality and Outcomes. 2010;3(1):41 - 47. doi:10.1161/CIRCOUTCOMES.109.871640 | Population |
| Dartigues, J. F., Carcaillon, L., Helmer, C., Lechevallier, N., Lafuma, A., Khoshnood, B. Vasodilators and nootropics as predictors of dementia and mortality in the PAQUID cohort. J Am Geriatr Soc. 2007;55(3):395 - 399. doi:10.1111/j.1532-5415.2007.01084.x | Population |
| Gaus, W., Westendorf, J., Diebow, R., Kieser, M. Identification of adverse drug reactions by evaluation of a prescription database, demonstrated for 'risk of bleeding'. Methods Inf Med. 2005;44(5):697 - 703. doi:10.1055/s-0038-1634027 | Population |
| Mills, E., Wu, P., Johnston, B. C., Gallicano, K., Clarke, M., Guyatt, G. Natural health product-drug interactions: A systematic review of clinical trials. Ther Drug Monit. 2005;27(5):549 - 557. doi:10.1097/01.ftd.0000170880.95267.90 | Population |
| Garg, R. K., Nag, D., Agrawal, A. A double blind placebo controlled trial of ginkgo biloba extract in acute cerebral ischaemia. J Assoc Physicians India. 1995;43(11):760 - 763. doi: | Population |
| Hofferberth, B. Effect of Ginkgo biloba extract on neurophysiological and psychometric measurement results in patients with cerebro-organic syndrome. A double-blind study vs. placebo. Arzneimittel-Forschung/Drug Research. 1989;39(8):918 - 922. doi: | Population |
| Hoffmann, F., Beck, C., Schutz, A., Offermann, P. [Ginkgo extract EGb 761 (tenobin)/HAES vs. naftidrofuryl (Dusodril)/HAES. A randomized study of therapy of sudden deafness]. Ginkgoextrakt EGb 761 (Tebonin)/HAES vs. Naftidrofuryl (Dusodril)/HAES. Eine randomisierte Studie zur Horsturztherapie. 1994;73(3):149-52. doi:10.1055/s-2007-997099 | Population |
| Thuro, H. The future of dementia therapy with Ginkgo-Specialextract EGb 761. Beilage für nervenzerzte. 1997. | Publication not retrievable |
| Napreyenko, A. Ginkgo biloba Extract EGb 761Â in Dementia with Neuropsychiatric Features: a Randomised, Placebo-controlled Double-blind Trial. Wilmar schabe. 2006. | Publication not retrievable |
| Diehm, C., Heinrich, F., ouml, rl, H. Placebo-controlled, multicentre, randomised, double-blind pilot study examining the effectiveness of Ginkgo biloba extract EGb 761 in patients with Fontaine stage IIb peripheral aterial disease. Placebokontrollierte, multizentrische, randomisierte, doppelblinde Pilotstudie zur Prüfung der Wirksamkeit des Ginkgo-biloba-Extraktes EGb 761® bei Patienten mit peripherer arterieller Verschlusskrankheit im Stadium IIb nach Fontaine. 1990. | Publication not retrievable |
| Van Dongen, M. C., Van Rossum, E., Kessels, A., Sielhorst, B. J., Knipschild, P. G. Effectiveness of ginkgo biloba in elderly people with beginning dementia and memory loss: results of a randomised experiment. Tijdschrift voor sociale gezondheidszorg. 1998. | Publication not retrievable |

| | |
|---|---|
| Vellas, B. Ginkgo biloba extract did not reduce risk for alzheimer disease in elderly patients with memory complaints. Ann Intern Med. 2013;158(2):JC7. doi: https://doi.org/10.7326/0003-4819-158-2-201301150-02007 | Publication type |
| Snitz, B. E., O'Meara, E. S., Carlson, M. C., Arnold, A. M., Ives, D. G., Saxton, J., Lopez, O. L., Dunn, L. O., Sink, K. M., DeKosky, S. T. Negative results from the secondary outcomes analysis of the Ginkgo Evaluation of Memory Study of Ginkgo biloba. Focus on alternative and complementary therapies. 2010;15(2):111. doi: https://doi.org/10.1211/fact.15.2.0008 | Publication type |
| Liu, H., Ye, M., Guo, H. An Updated Review of Randomized Clinical Trials Testing the Improvement of Cognitive Function of Ginkgo biloba Extract in Healthy People and Alzheimer's Patients. Front Pharmacol. 2019;10():1688. doi: https://doi.org/10.3389/fphar.2019.01688 | Publication type |
| Ernst, E. Ginkgo extract inhibits Alzheimer symptoms. Fortschr Med. 1998;116(11):4. doi: | Publication type |
| Kennedy, D., Scholey, A. B., Wesnes, K. Enhancement of cognitive performance by single doses of Ginkgo Biloba. J Psychopharmacol. 2000;14(Suppl 3):A45. doi: | Publication type |
| Heinen Kammerer, T., Motzkat, K., Daniel, D., Gertz, H. J., Koller, M., Lorenz, W., Pilartz, H., Zimmer, B., Habs, M., Von Den Driesch, V., Rychlik, R. The care situation of patients with dementia may be rectified by ginkgo biloba. MMW Fortschr Med. 2005;147(42):51. doi: | Publication type |
| Kalra, L. Antihypertensive drugs decrease risk of Alzheimer disease: ginkgo Evaluation of Memory Study. Neurology. 2014;82(13):1192. doi: https://doi.org/10.1212/WNL.0000000000000231 | Publication type |
| Stevinson, C. Negative trial of ginkgo for tinnitus. Focus on alternative and complementary therapies. 2001;6(2):121. doi: | Publication type |
| Kaye, J. Ginkgo biloba prevention trials: more than an ounce of prevention learned. Arch Neurol. 2009;66(5):652. doi: https://doi.org/10.1001/archneurol.2009.47 | Publication type |
| Claussen, C. F., Claussen, E., Bocking, H. H., Patil, N. P. Extractum Ginkgo Biloba in the combined treatment of vertigo, nausea and tinnitus. Vertigo, nausea, tinnitus and hypoacusia in metabolic disorders. 1988;791():583. doi: | Publication type |
| Plath, P., Olivier, J. Results of combined low-power laser therapy and extracts of Ginkgo biloba in cases of sensorineural hearing loss and tinnitus. Adv Otorhinolaryngol. 1995;49():101. doi: https://doi.org/10.1159/000424348 | Publication type |
| Beaubrun, G., Gray, G. E. A review of herbal medicines for psychiatric disorders. Psychiatr Serv. 2000;51(9):1130. doi: https://doi.org/10.1176/appi.ps.51.9.1130 | Publication type |
| Hoerr, R., Napryeyenko, O., and Borzenko, I. Effects of ginkgo biloba extract EGb 761 on dizziness and tinnitus in patients with dementia. FACT: focus on alternative and complementary therapies. 2007;12():26. doi: | Publication type |
| Barry, H. Is ginkgo biloba effective in managing memory problems in the elderly?. Evidence based practice. 2001. | Publication type |
| Rejali, D., Kumar, S., and Natarajan, B. A randomized placebo-controlled trial of Ginkgo biloba and its effect on tinnitus and associated hearing loss. Abstracts for the otolaryngological research society (ORS), April. 2004;29(4):389. doi: | Publication type |
| Hoerr, R. Ginkgo biloba does not reduce incidence of dementia in elderly people. Evid Based Ment Health. 2009;12(3):85. doi: | Publication type |
| Rogowski, M., Bartnik, G., Fabijanska, A. Randomized double-blind drug/retraining vs. placebo/retraining study of the treatment of tinnitus with Ginkgo biloba extract (e.g.b 761). Eur Arch Otrhinolaryngol. 2001;258(8):422. doi: | Publication type |

| | |
|---|---|
| Schoop, W., Breddin, K., Diehm, C., Grub, J., Held, K., Horsch, S., Rieger, H., Rudofsky, G., Salzmann, G., Trubestein, G., Wuppermann, T. Clinical test with ginkgo biloba EGb 761 extract for patients with peripheral arterial occlusive disease stage IIb fontaine in comparison with placebo. Klinische prufung mit ginkgo biloba-spezialextrakt EGb 761 bei patienten mit peripherer arterieller verschlusskrankheit im stadium IIb nach fontaine im vergleich zu placebo. 1997;26():160. doi: | Publication type |
| Winther, K., Randlov, C., Rein, E., Mehisen, J. Ginkgo biloba enhances the ability to concentrate and remember in elderly volunteers with moderately reduced cognitive function. European journal of neurology. 1996;3(Suppl 5):25. doi: | Publication type |
| Hoffmann, E., Beck, C., Schutz, A., and Offermann, P. Naftidrofuryl + HAES vs. ginko extract EGb 761 + HAES - a randomised study on the therapy of acute hearing loss. Naftidrofuryl + HAES vs. Ginkgoextrakt EGb 761 + HAES - Eine randomisierte Studie zur Horsturztherapie. 1993;Suppl II():256. doi: | Publication type |
| Cockle, S. M., Kimber, S., Hindmarch, I. Ginkgo biloba extract (LI 1370) supplementation and activities of daily living: a questionnaire survey in older volunteers. International journal of neuropsychopharmacology. 2000. | Publication type |
| Hazzard Mary, E. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. Alternative health practitioner. 1999;5(2):178. doi: | Publication type |
| Stevermer, J. J., Lindbloom, E. J. Clinical question: does an extract of Ginkgo biloba safely alter cognitive and functional outcomes in patients with dementia?. J Fam Pract. 1998. | Publication type |
| Van Dongen, M. C. J., Van Rossum, E., Kessels, A. G. H., Sielhorst, B. J. G., Knipschild, P. G. Efficacy of Ginkgo Biloba in elderly people with dementia and cognitive decline. Gerontologist. 2000;40(Suppl 1):218. doi: | Publication type |
| Centre for, Reviews, Dissemination. Ginkgo biloba extract EGb 761 in the treatment of dementia: a pharmacoeconomic analysis of the Austrian setting (Provisional abstract). Ginkgo biloba extract EGb 761 in the treatment of dementia: a pharmacoeconomic analysis of the Austrian setting. 2013;(2015 Issue 2). doi: | Publication type |
| Zhang, H. F., Huang, L. B., Zhong, Y. B., Zhou, Q. H., Wang, H. L., Zheng, G. Q., Lin, Y. An overview of systematic reviews of Ginkgo biloba extracts for mild cognitive impairment and dementia. Front Aging Neurosci. 2016;8(DEC):276. doi:10.3389/fnagi.2016.00276 | Publication type |
| Levine, D. A., Langa, K. M. Vascular Cognitive Impairment: Disease Mechanisms and Therapeutic Implications. Neurotherapeutics. 2011;8(3):361 - 373. doi:10.1007/s13311-011-0047-z | Publication type |
| Bloom, M. Z. Ginkgo biloba does not appear to prevent dementia. Consultant Pharmacist. 2009;24(1):11 - 14. doi:10.4140/TCP.n.2009.11 | Publication type |
| Canter, P. H. Ginkgo evaluation of memory study of Ginkgo biloba for prevention of dementia returns negative result. Focus on Alternative and Complementary Therapies. 2009;14(1):15 - 16. doi:10.1111/j.2042-7166.2009.tb01857.x | Publication type |
| Schulz, V. IQWiG final report 2008 on Ginkgo biloba extract: Patients with dementia can cope better with their daily lives. Zeitschrift fur Phytotherapie. 2009;30(1):27 - 28. doi:10.1055/s-0029-1215603 | Publication type |
| Gold, M. Study design factors and patient demographics and their effect on the decline of placebo-treated subjects in randomized clinical trials in Alzheimer's disease. J Clin Psychiatry. 2007;68(3):430 - 438. doi:10.4088/JCP.v68n0313 | Publication type |
| Schneider, B., Klein, P., Weiser, M. Treatment of vertigo with a homeopathic complex remedy compared with usual treatments: A meta-analysis of clinical trials. Arzneimittel-Forschung/Drug Research. 2005;55(1):23 - 29. doi:10.1055/s-0031-1296821 | Publication type |

| | |
|---|---|
| Heinen-Kammerer, T., Motzkat, K., Daniel, D., Gertz, H. J., Koller, M., Lorenz, W., Pilartz, H., Zimmer, B., Habs, M., Von Den Driesch, V., Rychlik, R. The situation of patients with dementia may be rectified by ginkgo biloba. MMW-Fortschritte der Medizin. 2005;147(42):51. doi: | Publication type |
| Jonas, W. B., Crawford, C. C. Vertigoheel is non-inferior to Ginkgo biloba in the treatment of vertigo in an elderly population. Focus on Alternative and Complementary Therapies. 2005;10(4):297 - 298. doi:10.1211/fact.10.4.0015 | Publication type |
| Ernst, E. Should we dismiss complementary medicine if evidence tells us to?. Pharmaceutical Journal. 2004;273(7325):722. doi: | Publication type |
| Gasser, U. S., Gasser, T. Comparison of cholinesterase inhibitors and ginkgo extract in the treatment of Alzheimer's dementia. MMW-Fortschritte der Medizin. 2001;143(51-52):40 - 41. doi: | Publication type |
| Juretzek, W., Muller, W. E. Application of phytopharmaceutics in dementia therapy: Quality and efficacy of ginkgo biloba extract. Pharm Unserer Zeit. 2002;31(4):370 - 375. doi:10.1002/1615-1003%28200207%2931:4%3C370::AID-PAUZ370%3E3.0.CO;2-E | Publication type |
| Schreiter Gasser, U., Gasser, T. A comparison of cholinesterase inhibitors and ginkgo extract in treatment of Alzheimer dementia. Fortschr Med Orig. 2001;119(3-4):135 - 138. doi: | Publication type |
| Bakal, C., Becker, G., Clement, D. L., Cronenwett, J., Durand-Zaleski, I., Diehm, C., Harris, K., Hiatt, W. R., Hunink, M., Isner, J., Lammer, J., Norgren, L., Novo, S., Ricco, J. B., Verstraete, M., White, J. Management of Peripheral Arterial Disease (PAD). European Journal of Vascular and Endovascular Surgery. 2000;19(SUPPL. A):S1 - S243. doi: | Publication type |
| Reust, C. E., Stevermer, J. J. Is ginkgo biloba more effective than placebo for the treatment of intermittent claudication?. J Fam Pract. 2000;49(7):657. doi: | Publication type |
| Bornkessel, B. The diagnosis and treatment of Alzheimer's disease. Med Monatsschr Pharm. 1998;21(8):244 - 247. doi: | Publication type |
| Wincor, M. Z. Ginkgo biloba for dementia: a reasonable alternative?. J Am Pharm Assoc (Wash). 1999;39(3):415 - 416. doi:10.1016/S1086-5802%2816%2930449-1 | Publication type |
| Stevermer, J. J., Lindbloom, E. J. Ginkgo biloba for dementia. J Fam Pract. 1998;46(1):20. doi: | Publication type |
| Horr, R., Keiser, M. The Ginkgo biloba special extract EGb 761 - An antidementia agent. Also effective in more severe cases. Fortschr Med. 1998;116(3):39 - 40. doi: | Publication type |
| Choo Pin, Por, Evans, M. F. Does ginkgo help delay dementia?. Canadian Family Physician. 1998;44(MAY.):997 - 999. doi: | Publication type |
| Hamann, K. F. Treatment of vertigo. HNO. 1993;41(5):278 - 285. doi: | Publication type |
| Woelk, H. Recent results with Ginkgo biloba. Revista Brasileira de Neurologia. 1994;30(SUPPL. 1):26S - 29S. doi: | Publication type |
| Muller, D. Rokan (Ginkgo biloba extract) in the treatment of brain function disorders. Praxis Magazin Med. 1992; (5):10 - 11. doi: | Publication type |
| Schonweiler, R. Causes, assessment and therapy of tinnitus. DMW. 1986;111(39):1489 - 1494. doi:10.1055/s-2008-1068659 | Publication type |
| Karkos, P. D., Leong, S. C., Arya, A. K., Papouliakos, S. M., Apostolidou, M. T., Issing, W. J. 'Complementary ENT': a systematic review of commonly used supplements. J Laryngol Otol. 2007;121(8):779-82. doi:10.1017/S002221510600449X | Publication type |
| DeBisschop, Michael. Ginkgo ineffective for tinnitus. J Fam Pract. 2003;52(10):766-769. doi: | Publication type |

| | |
|---|---|
| Hesse, G., Schaaf, H. [Ginkgo biloba: ineffective against tinnitus?]. Ginkgo biloba: Unwirksam gegen Tinnitus? 2001;49(6):434-6. doi:10.1007/s001060170092 | Publication type |
| Holstein, N. [Ginkgo extract helps patients suffering from tinnitus. Review of the literature shows: tinnitus decreases]. Ginkgo-Extrakt hilft Tinnitus-Geplagten. Literaturrecherche zeigt: Ohrgerausche nehmen ab. 2000;142(47):46. doi: | Publication type |
| Wettstein, A. [Cholinesterase inhibitor and ginkgo extracts in therapy of dementia. A comparison of effectiveness based on controlled studies]. Cholinesterasehemmer und Ginkgoextrakte in der Demenztherapie. Ein Vergleich der Wirksamkeit anhand kontrollierter Studien. 1999;117(5):48-9. doi: | Publication type |
| Claussen, C. F. [Diagnostic and practical value of craniocorpography in vertiginous syndromes]. Interet diagnostique et pratique de la craniocorpographie dans les syndromes vertigineux. 1986;15(31):1565-8. doi: | Publication type |
| Sorbini, E. [Ginkgo-biloba in the therapy of vascular diseases]. La ginkgo-biloba nella terapia vascolare. 1973;64(79 Suppl):4201-8. doi: | Publication type |
| De Amicis, E. [Activity of ginkgo-biloba in ear diseases due to arteriosclerosis]. Attivita della ginkgo-biloba nelle otopatie da arteriosclerosi. 1973;64(79 Suppl):4193-4. doi: | Publication type |
| Bartolo, M. [Clinical results in therapy of peripheral vascular diseases with ginkgo-biloba]. Risultati clinici della terapia con ginkgo-biloba nelle vasculopatie periferiche. 1973;64(79 Suppl):4187-93. doi: | Publication type |
| Garcia-Alberca, J. M., Mendoza, S., Gris, E. Benefits of Treatment with Ginkgo Biloba Extract EGb 761 Alone or Combined with Acetylcholinesterase Inhibitors in Vascular Dementia. Clin Drug Investig. 2022;42(5):391 - 402. doi:10.1007/s40261-022-01136-8 | Study design |
| Garcia-Alberca, J. M., Gris, E., Mendoza, S. Combined treatment with Ginkgo biloba extract EGb 761 plus acetylcholinesterase inhibitors improved cognitive function and neuropsychiatric symptoms in patients with mild cognitive impairment. Alzheimer's and Dementia: Translational Research and Clinical Interventions. 2022;8(1):e12338. doi:10.1002/trc2.12338 | Study design |
| Rapp, M., Burkart, M., Kohlmann, T., Bohlken, J. Similar treatment outcomes with Ginkgo biloba extract EGb 761 and donepezil in Alzheimer's dementia in very old age: A retrospective observational study. Int J Clin Pharmacol Ther. 2018;56(3):130 - 133. doi:10.5414/CP203103 | Study design |
| Cummings, J. L., Ihl, R., Herrschaft, H., Hoerr, R., Tribanek, M. Sensitivity to change of composite and frequency scores of the Neuropsychiatric Inventory in mild to moderate dementia. Int Psychogeriatr. 2013;25(3):431 - 438. doi:10.1017/S1041610212001974 | Study design |
| Czeche, S., Schussel, K., Franzmann, A., Burkart, M., Schulz, M. Dosage strength is associated with medication persistence with Ginkgo biloba drug products: A cohort study of ambulatory drug claims data in Germany. BMC Complement Altern Med. 2013;13():278. doi:10.1186/1472-6882-13-278 | Study design |
| Santos-Neto, L. L. D., De Vilhena Toledo, M. A., Medeiros-Souza, P., De Souza, G. A. The use of herbal medicine in Alzheimer's disease - A systematic review. Evidence-based Complementary and Alternative Medicine. 2006;3(4):441 - 445. doi:10.1093/ecam/nel071 | Study design |
| Kleijnen, J., Knipschild, P. The comprehensiveness of medline and embase computer searches. Searches for controlled trials of homoe pathy, asocorbic acid for common cold and ginkgo biloba for cerebral insufficiency and intermittent claudication. Pharmaceutisch Weekblad - Scientific Edition. 1992;14(5):316 - 320. doi:10.1007/BF01977620 | Study design |
| Lauliac, M., Bernasconi, P. Clinical study of Tanakan (chloroquine) in peripheral vascular disorders. Lille Medical. 1976;21(7 sup.3):620 - 622. doi: | Study design |

| | |
|---|---|
| Linde, K., ter Riet, G., Hondras, M., Vickers, A., Saller, R., Melchart, D. Systematic reviews of herbal medicines--an annotated bibliography. Forsch Komplementarmed Klass Naturheilkd. 2003;10 Suppl 1():17-27. doi:10.1159/000071688 | Study design |

# E. Meta-analyses conducted using standardised mean differences

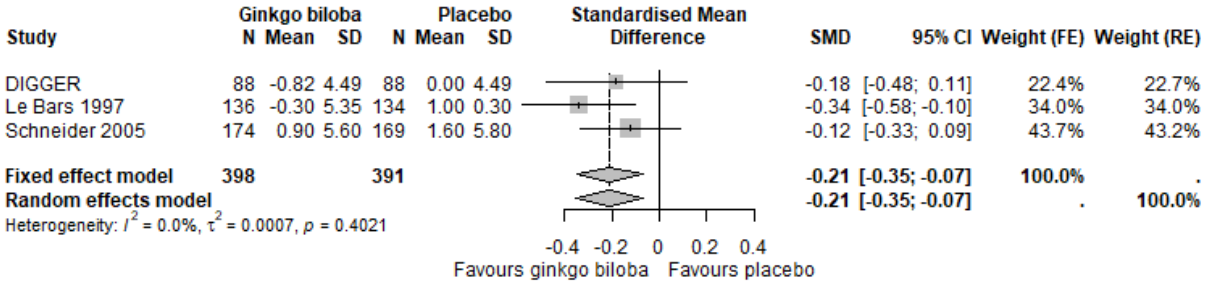


**Figure 50: ADAS-Cog: 120 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. ADAS-Cog scores range from 0 to 70, with lower scores indicating better cognitive functioning.[133,134]

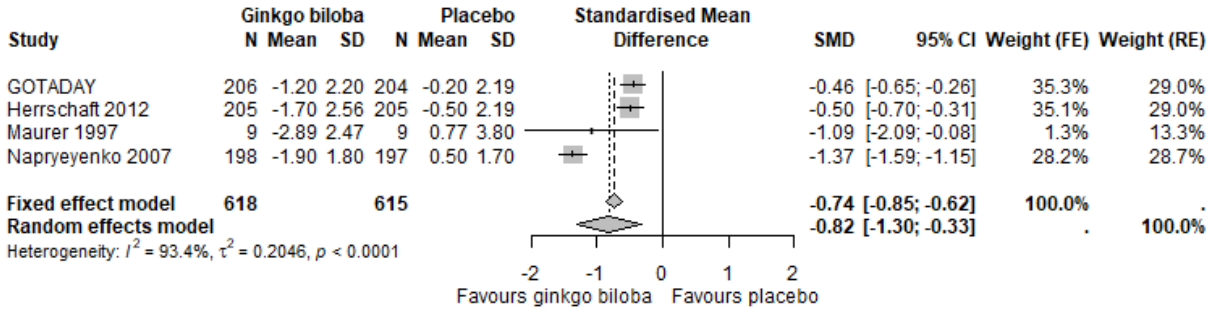


**Figure 51: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SKT = Syndrom-Kurz-Test, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

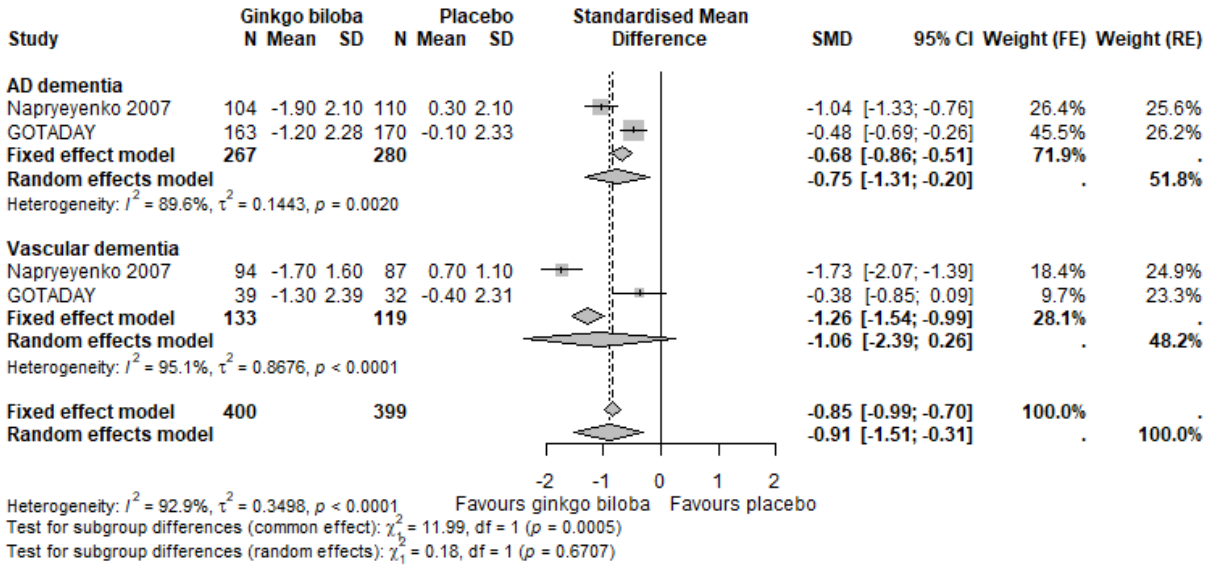


**Figure 52: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks subgroup analysis, standardised mean difference**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SKT = Syndrom-Kurz-Test, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

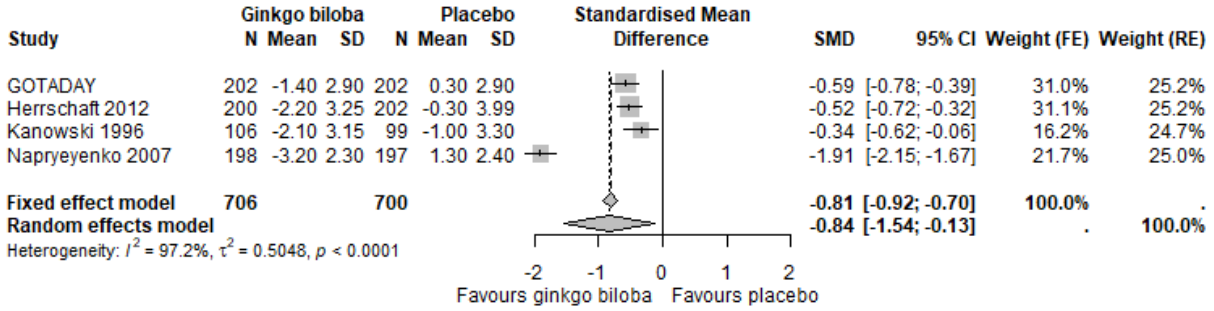


**Figure 53: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SKT = Syndrom-Kurz-Test, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

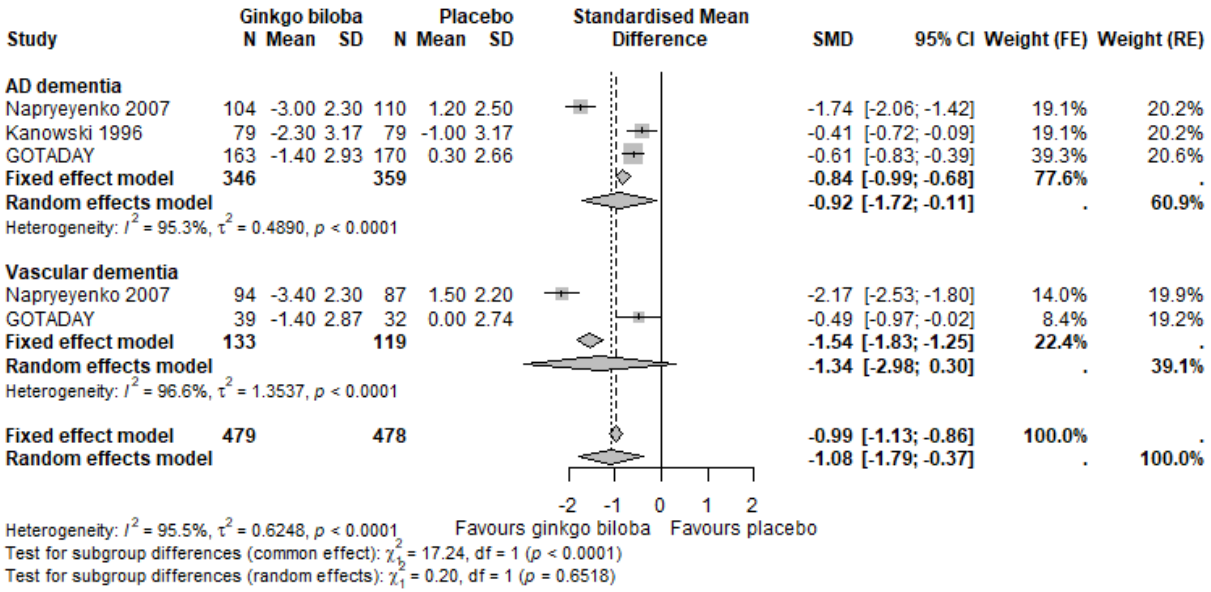


**Figure 54: SKT Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis, standardised mean difference**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SKT = Syndrom-Kurz-Test, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. SKT scores range from 0 to 27, with lower scores indicating better cognitive functioning.

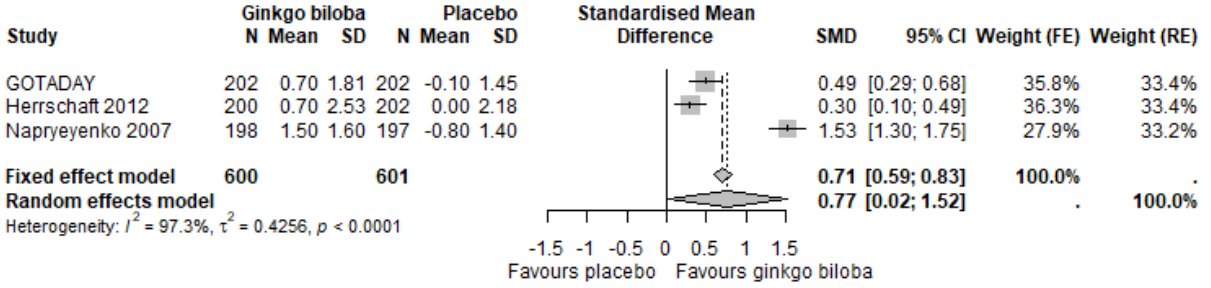


**Figure 55: Verbal Fluency Test: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline.

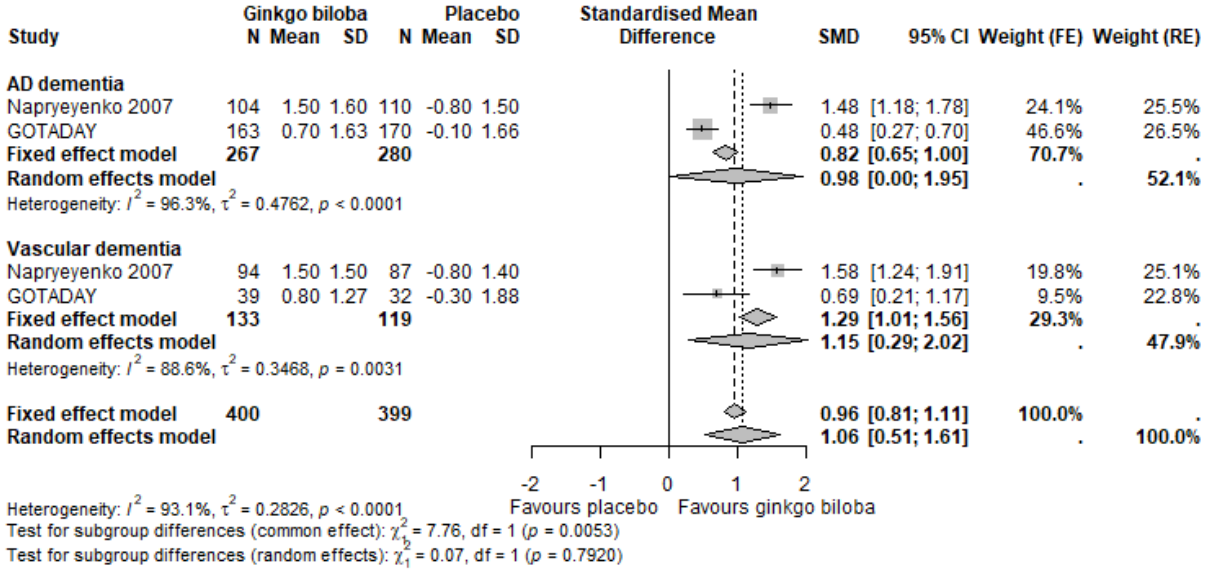


**Figure 56: Verbal Fluency Test: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis, standardised mean difference**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline.

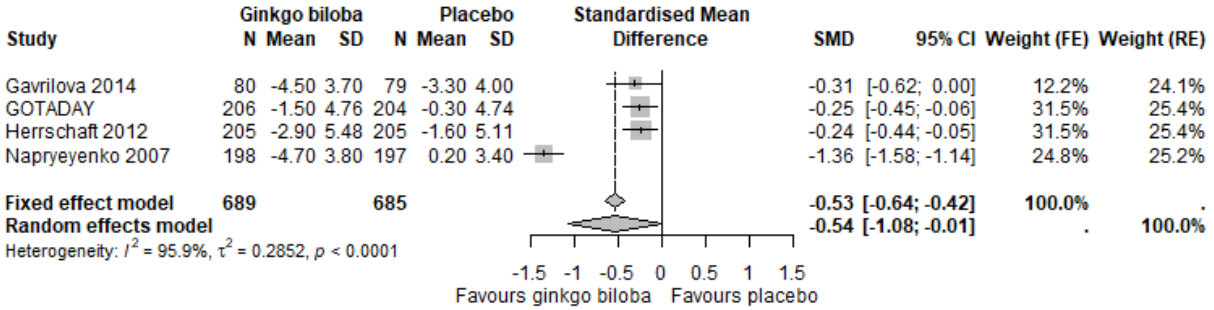


**Figure 57: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, NPI = Neuropsychiatric Inventory, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

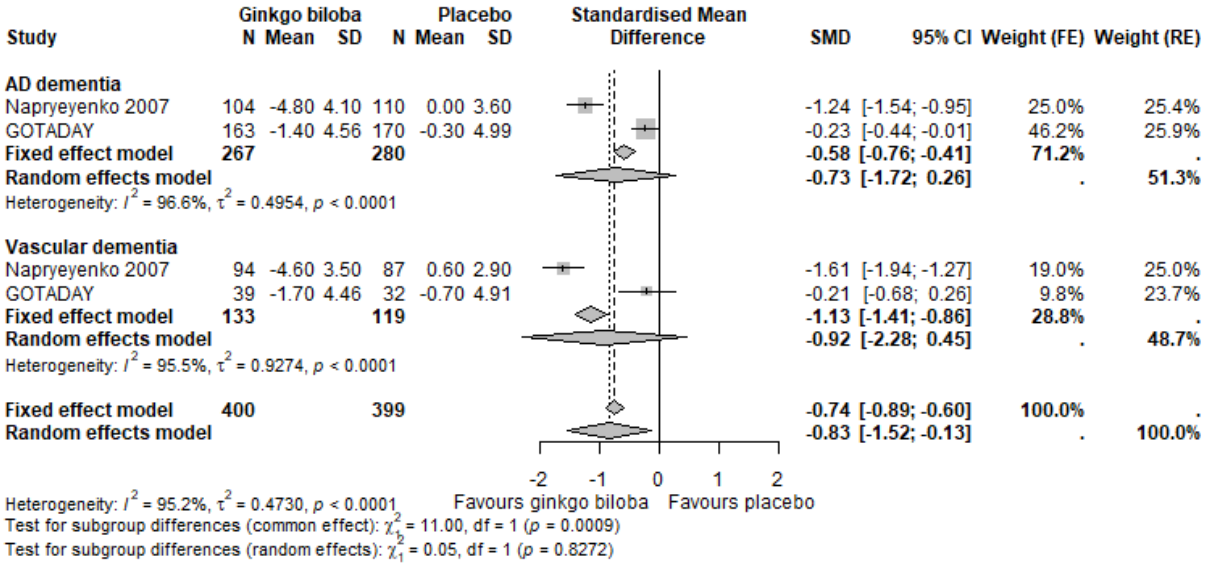


**Figure 58: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 12 weeks subgroup analysis, standardised mean difference**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

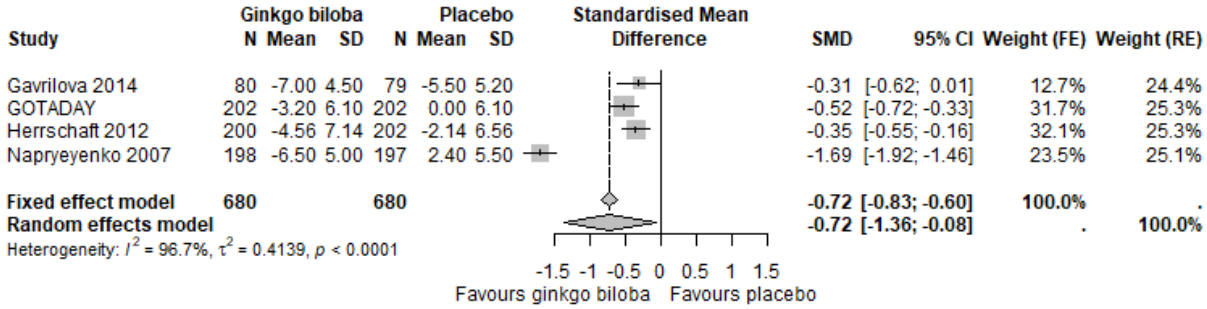


**Figure 59: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, NPI = Neuropsychiatric Inventory, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

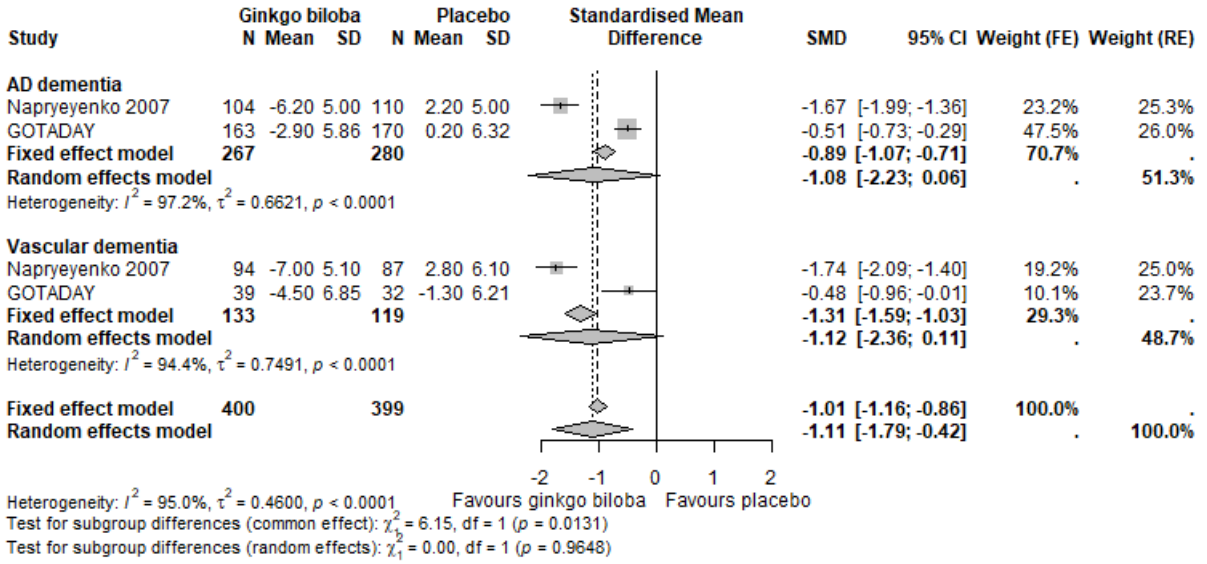


**Figure 60: NPI Composite Total Score: 240 mg ginkgo biloba vs. placebo at 24 weeks subgroup analysis, standardised mean difference**

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, FE = fixed effect, NPI = Neuropsychiatric Inventory, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. NPI Composite Total Score ranges from 0 to either 120 (10 domains) or 144 (12 domains), with higher scores indicating more intense psychiatric symptoms.[139]

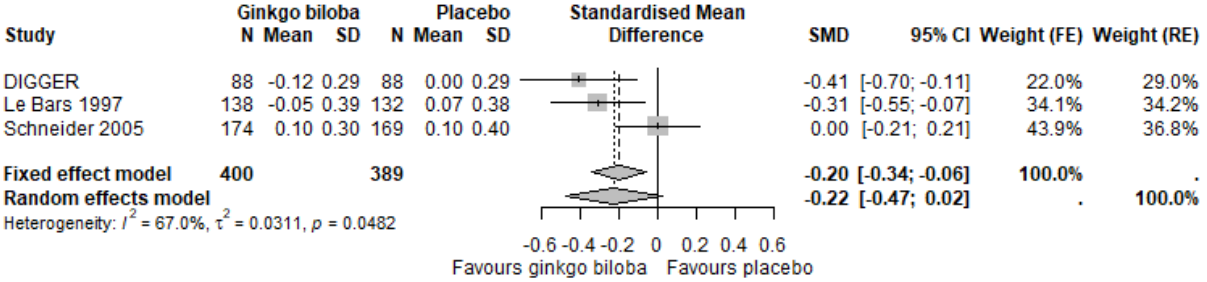


**Figure 61: GERRI: 120 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, GERRI = Geriatric Evaluation of Relative's Rating Instrument, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. The GERRI consists of 49 items to assess the frequency of complaints related to functioning, with higher scores indicating more severe functional impairment.[141]

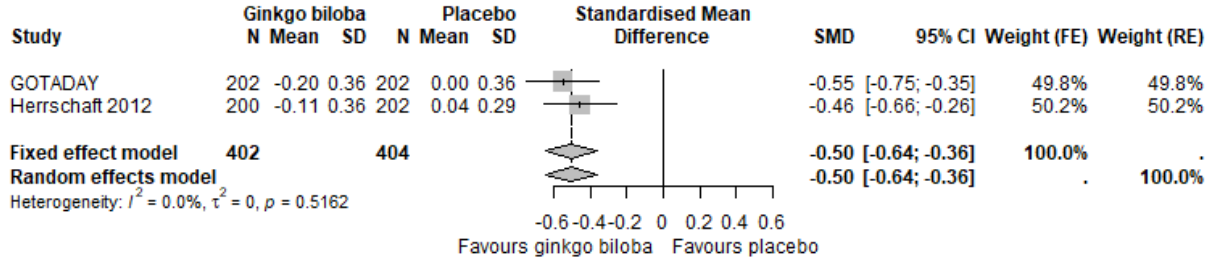


**Figure 62: ADL-IS: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

ADL-IS = Activities of Daily Living International Scale, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. The ADL-IS score is the average of up to 40 items, each scored from 0 to 4, with higher scores indicating more severe functional impairment.[142]

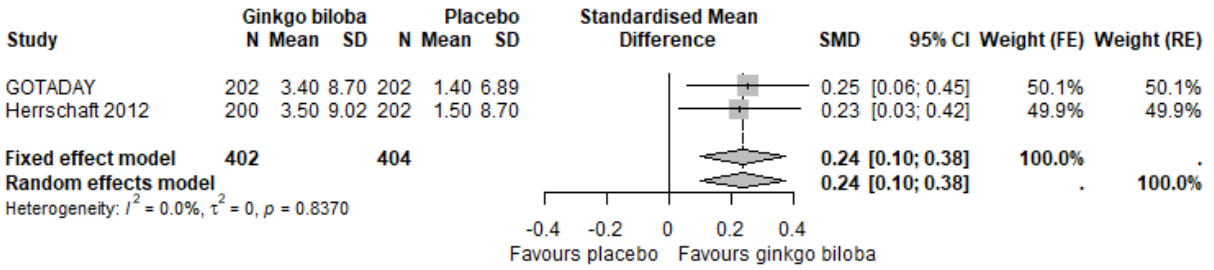


**Figure 63: DEMQOL-proxy total score: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, DEMQOL-proxy = Dementia-Related Quality of Life-proxy, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. DEMQOL-proxy total scores range from 31 to 124, with higher scores indicating better quality of life.[145]

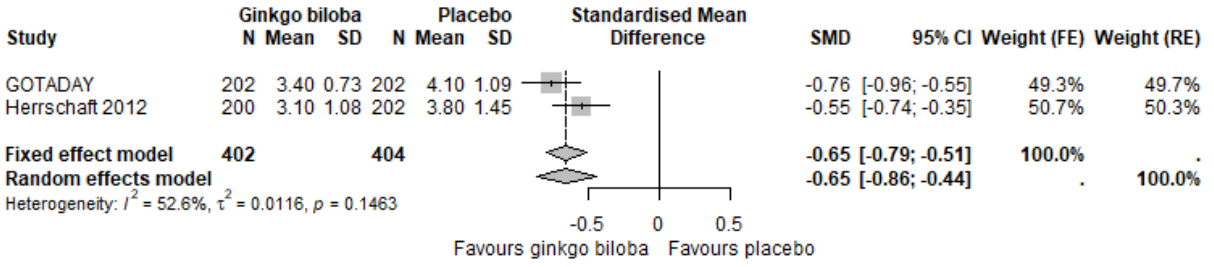


**Figure 64: ADCS-CGIC Score: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Scores on the ADCS-CGIC range from 1 (Marked Improvement) to 7 (Marked Worsening), with 4 representing no change in overall health status since baseline.[146,147]

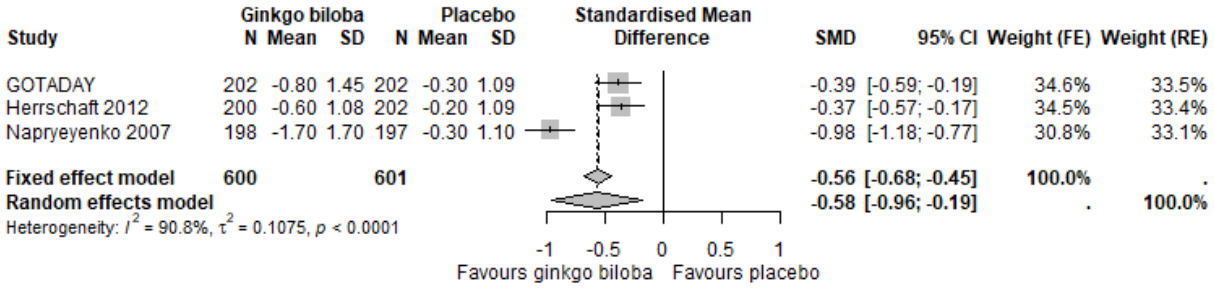


**Figure 65: 11-point box scale dizziness: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

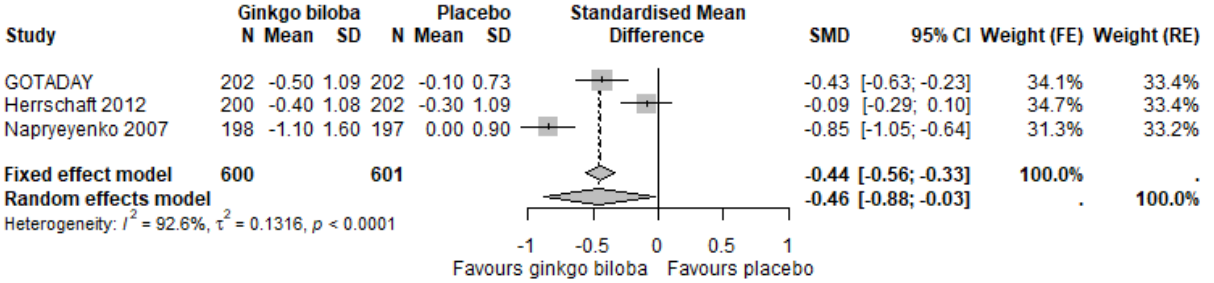


**Figure 66: 11-point box scale tinnitus: 240 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

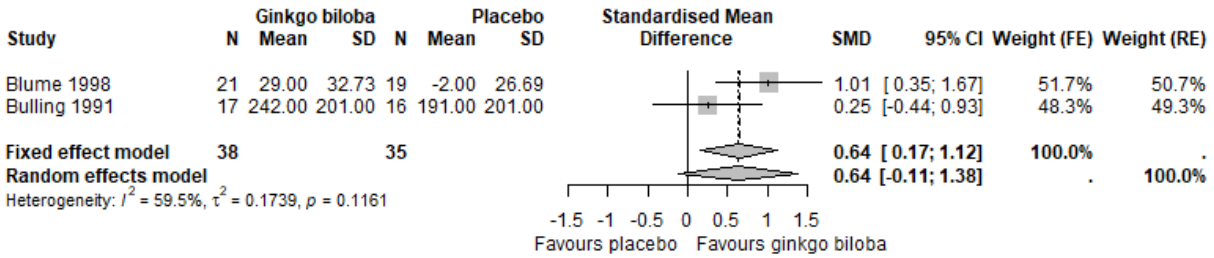


**Figure 67: Maximum walking distance: 160 mg ginkgo biloba vs. placebo at 16 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that data from Bulling 1991 were reported only in a figure as raw values at each timepoint.[127] The means and standard deviations at baseline and 16 weeks were digitized, rounded to the nearest meter, and used to calculate the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

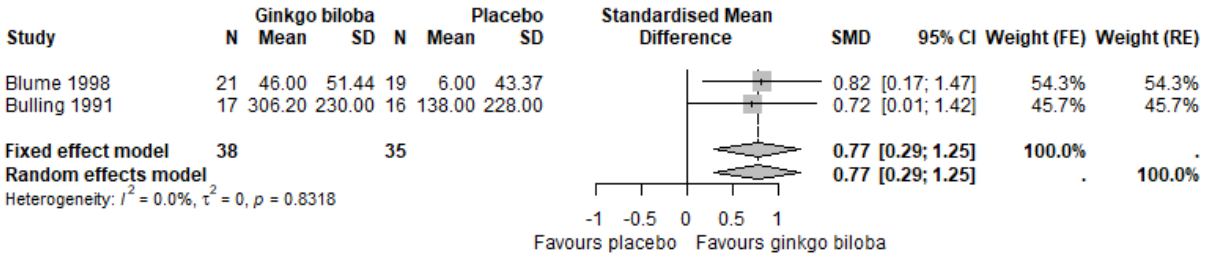


**Figure 68: Maximum walking distance: 160 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that although the mean change from baseline was reported in the text for Bulling 1991, the standard deviations were reported only in a figure and were for the values at each timepoint.[127] Standard deviations at baseline and 24 weeks were digitized, rounded to the nearest meter, and used to calculate the standard deviation for the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. To assess the accuracy of the digitization process, the means were also digitized and used to calculate the mean change from baseline. The values reported in the text were 306.2 (ginkgo biloba) and 138.0 (placebo) meters; the digitized values were 303 (ginkgo biloba) and 136 (placebo) meters. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

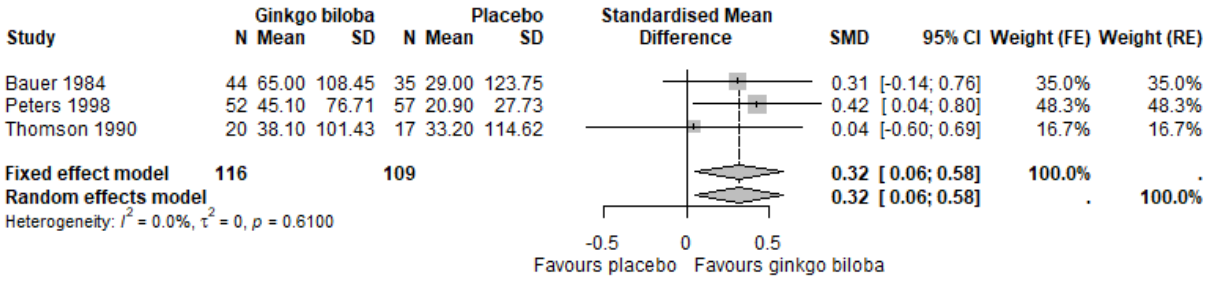


**Figure 69: PFWD: 120 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, PFWD = pain-free walking distance, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. Thomson 1990 reported the mean and standard deviation at baseline and 24 weeks, and these were used to calculate the mean change from baseline and corresponding standard deviation.[90] Data for Bauer 1984 were extracted from a secondary publication for that trial.[121] Data were available only in a figure, although the standard deviations were labelled for each timepoint. The labelled standard deviations for baseline and 24 weeks were used to calculate the standard deviation for the mean change from baseline. The mean values at baseline and 24 weeks were digitized, rounded to the nearest meter, and used to calculate the mean change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other.

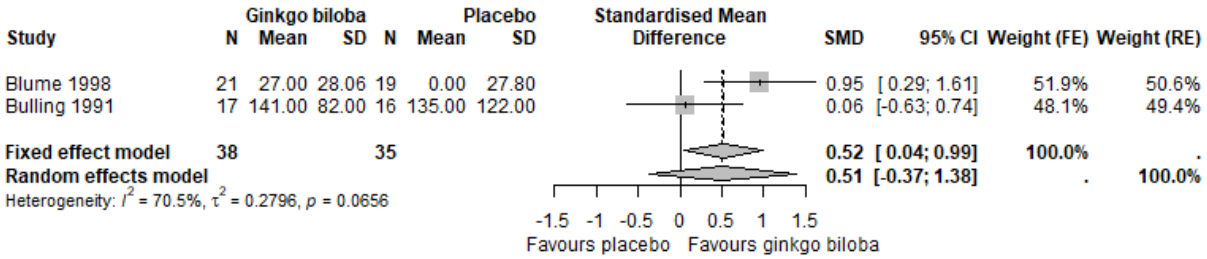


**Figure 70: PFWD: 160 mg ginkgo biloba vs. placebo at 16 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, PFWD = pain-free walking distance, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that data from Bulling 1991 were reported only in a figure as raw values at each timepoint.[127] The means and standard deviations at baseline and 16 weeks were digitized, rounded to the nearest meter, and used to calculate the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

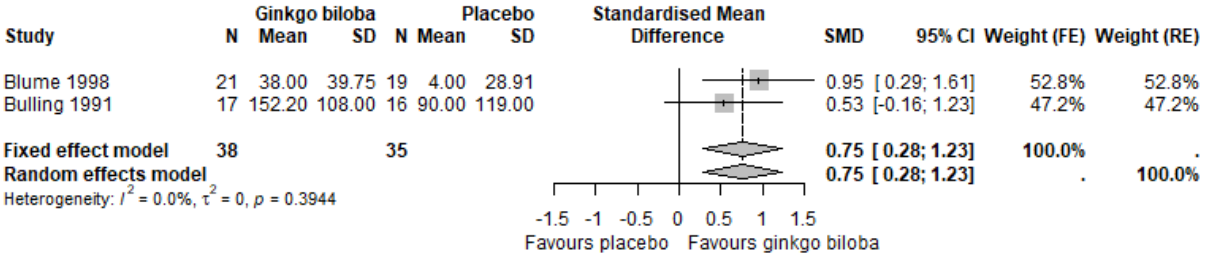


**Figure 71: PFWD: 160 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, PFWD = pain-free walking distance; RE = random effects, SD = standard deviation, SMD = standardised mean difference.

*Notes*

Values per treatment arm are reported as mean change from baseline. Please note that although the mean change from baseline was reported in the text for Bulling 1991, the standard deviations were reported only in a figure and were for the values at

each timepoint.[127] Standard deviations at baseline and 24 weeks were digitized, rounded to the nearest meter, and used to calculate the standard deviation for the change from baseline. To minimize the potential for error, each value was digitized 3 times, and the median estimate was used. All estimates for each value were within 2 meters of each other. To assess the accuracy of the digitization process, the means were also digitized and used to calculate the mean change from baseline. The values reported in the text were 152.2 (ginkgo biloba) and 90.0 (placebo) meters; the digitized values were 152 (ginkgo biloba) and 91 (placebo) meters. Because multiple values were digitized for each estimate, these data should be interpreted with caution.

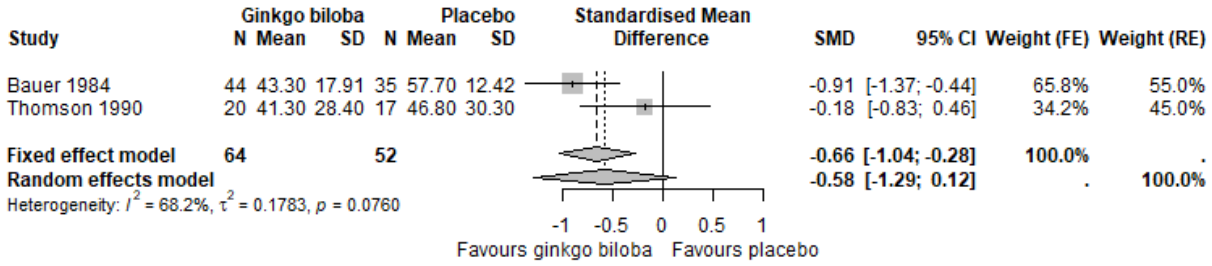


**Figure 72: Pain: 120 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

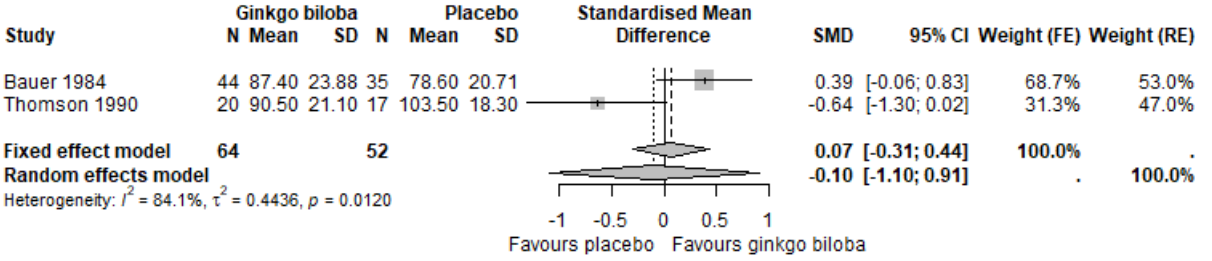


**Figure 73: Resting ankle pressure: 120 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

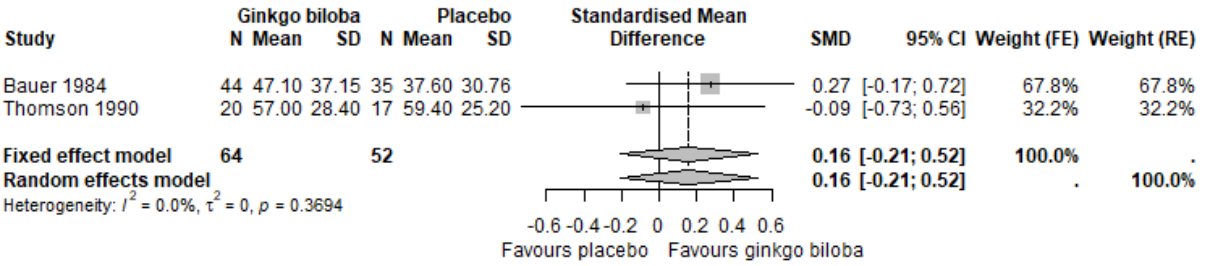


**Figure 74: Post-exercise ankle pressure: 120 mg ginkgo biloba vs. placebo at 24 weeks, standardised mean difference**

*Abbreviations*

CI = confidence interval, FE = fixed effect, RE = random effects, SD = standard deviation, SMD = standardised mean difference.

# F. Supplemental efficacy and safety tables

## Studies in which patients may have changed treatment

**Table 112: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo followed by 120 mg ginkgo biloba in patients with MPD – cognitive function**

| Outcome[a] | Timepoint (weeks) | Ginkgo biloba Mean (95% CI)[b,d] | Placebo then ginkgo biloba Mean (95% CI)[c,d] | p-value | Effect MD (95% CI)[e] |
|---|---|---|---|---|---|
| **Semantic memory dual-task** | | | | | |
| **Base of support** | 12 | 9.2 (8.0 to 10.4) | 10.0 (8.1 to 11.9) | NR | -0.8 (-3.1 to 1.5) |
| | 24 | 9.5 (8.6 to 10.4) | 10.5 (8.7 to 12.3) | 0.51 | -1.0 (-3.1 to 1.1) |
| | 52 | 8.9 (7.8 to 10.0) | 10.5 (8.3 to 12.7) | NR | -1.6 (-4.1 to 0.9) |
| **Cadence** | 12 | 91.2 (82.4 to 100.0) | 87.7 (78.5 to 96.9) | NR | 3.5 (-9.6 to 16.6) |
| | 24 | 91.5 (81.9 to 101.1) | 85.0 (79.6 to 90.4) | 0.373 | 6.5 (-4.8 to 17.8) |
| | 52 | 93.8 (85.6 to 102.0) | 83.2 (73.5 to 92.9) | NR | 10.6 (-2.5 to 23.7) |
| **Stride time variability** | 12 | 14.3 (0.1 to 28.5) | 13.0 (1.2 to 24.8) | NR | 1.3 (-17.7 to 20.3) |
| | 24 | 10.0 (3.1 to 16.9) | 10.1 (3.0 to 17.2) | 0.962 | -0.1 (-10.3 to 10.1) |
| | 52 | 11.5 (3.6 to 19.4) | 10.8 (0.3 to 21.3) | NR | 0.7 (-12.9 to 14.3) |
| **Velocity** | 12 | 93.2 (81.2 to 105.2) | 92.1 (78.4 to 105.8) | NR | 1.1 (-17.7 to 19.9) |
| | 24 | 93.8 (80.5 to 107.1) | 86.6 (78.2 to 95.0) | 0.564 | 7.2 (-9.0 to 23.4) |
| | 52 | 98.6 (85.6 to 111.6) | 86.5 (73.8 to 99.2) | NR | 12.1 (-6.6 to 30.8) |
| **Working memory dual-task** | | | | | |
| **Base of support** | 12 | 8.7 (7.5 to 9.9) | 9.3 (7.9 to 10.7) | NR | -0.6 (-2.6 to 1.4) |
| | 24 | 9.1 (8.0 to 10.2) | 9.4 (7.7 to 11.1) | 0.79 | -0.3 (-2.4 to 1.8) |
| | 52 | 8.4 (7.3 to 9.5) | 10.0 (8.5 to 11.5) | NR | -1.6 (-3.6 to 0.4) |

| | | | | | |
|---|---|---|---|---|---|
| **Cadence** | 12 | 100.1 (91.1 to 109.1) | 97.7 (92.7 to 102.7) | NR | 2.4 (-8.2 to 13.0) |
| | 24 | 103.2 (96.2 to 110.2) | 91.2 (83.9 to 98.5) | 0.019 | 12.0 (1.6 to 22.4) |
| | 52 | 101.3 (93.3 to 109.3) | 94.0 (85.6 to 102.4) | NR | 7.3 (-4.6 to 19.2) |
| **Stride time variability** | 12 | 7.9 (-0.3 to 16.1) | 4.8 (3.0 to 6.6) | NR | 3.1 (-5.6 to 11.8) |
| | 24 | 6.5 (2.6 to 10.4) | 8.4 (2.1 to 14.7) | 0.212 | -1.9 (-9.5 to 5.7) |
| | 52 | 10.0 (-2.2 to 22.2) | 5.4 (1.1 to 9.7) | NR | 4.6 (-8.8 to 18.0) |
| **Velocity** | 12 | 109.9 (95.7 to 124.1) | 107.4 (97.7 to 117.1) | NR | 2.5 (-15.2 to 20.2) |
| | 24 | 111.2 (99.4 to 123.0) | 99.5 (88.9 to 110.1) | 0.186 | 11.7 (-4.6 to 28.0) |
| | 52 | 111.9 (98.7 to 125.1) | 104.1 (90.7 to 117.5) | NR | 7.8 (-11.6 to 27.2) |

*Abbreviations*

CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, ICD-10 = International Classification of Diseases, Tenth Revision, MCI = mild cognitive impairment, MD = mean difference, NR = not reported.

*Notes*

a = All results in this table are from the same trial (NCT01046292[67]). Included patients were those with impaired executive functions defined as a reduction in gait velocity of ≥10% during dual-task compared to single-task walking, MCI according to Winblad et al. 2004, and no dementia according to ICD-10 and DSM-IV.

b = Patients received 120 mg ginkgo biloba in a blinded fashion for 6 months, followed by 120 mg ginkgo biloba in an unblinded fashion for an additional 6 months.

c = Patients received placebo in a blinded fashion for 6 months, followed by 120 mg ginkgo biloba in an unblinded fashion for 6 months.

d = Mean value at timepoint.

e = Calculated by the authors of this report.

**Table 113: Safety results comparing 120 mg ginkgo biloba vs. placebo followed by 120 mg ginkgo biloba in patients with MPD**

| Outcome[a] | Ginkgo biloba n/N (%)[b] | Placebo then ginkgo biloba n/N (%)[c] | p-value | Effect RR (95% CI)[d] |
|---|---|---|---|---|
| **≥1 AE during follow-up** | 23/25 (92) | 19/25 (76) | 0.468 | 1.21 (0.94 to 1.55) |
| **≥1 SAE during follow-up** | 4/25 (16) | 5/25 (20) | 0.358 | 0.80 (0.24 to 2.64) |

*Abbreviations*

AE = adverse event, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, ICD-10 = International Classification of Diseases, Tenth Revision, MCI = mild cognitive impairment, NR = not reported, RR = relative risk, SAE = serious adverse event.

*Notes*

a = All results in this table are from the same trial (NCT01046292[67]) and at the same timepoint (52 weeks). Included patients were those with impaired executive functions defined as a reduction in gait velocity of ≥10% during dual-task compared to single-task walking, MCI according to Winblad et al. 2004, and no dementia according to ICD-10 and DSM-IV.

b = Patients received 120 mg ginkgo biloba in a blinded fashion for 6 months, followed by 120 mg ginkgo biloba in an unblinded fashion for an additional 6 months.

c = Patients received placebo in a blinded fashion for 6 months, followed by 120 mg ginkgo biloba in an unblinded fashion for 6 months.

d = Calculated by the authors of this report.

**Table 114: Efficacy results from the Maastricht Ginkgo Trial – cognitive function**

| Outcome[a] | Timepoint (weeks) | Group 1 Mean (95% CI)[b] | Group 2 Mean (95% CI)[b] | Effect MD (90% CI)[c] |
|---|---|---|---|---|
| **Any ginkgo biloba (first 12 weeks) vs. Placebo (first 12 weeks)** | | | | |
| 11-point box scale memory status | 12 | -0.09 (-0.28 to 0.10) | 0.28 (0.00 to 0.56) | -0.25 (-0.55 to 0.05) |
| NAI-ZN-G | 12 | -0.01 (-0.25 to 0.23) | 0.05 (-0.28 to 0.38) | -0.03 (-0.43 to 0.37) |
| NAI-ZVT-G | 12 | 6.00 (-2.87 to 14.87) | -14.60 (-31.32 to 2.12) | 14.5 (-2.1 to 31.1) |
| NAI-WL-tot | 12 | -0.29 (-0.74 to 0.16) | -0.14 (-0.95 to 0.67) | -0.02 (-0.88 to 0.84) |
| **Any ginkgo biloba (all 24 weeks) vs. Placebo (all 24 weeks)** | | | | |

| Outcome[a] | Timepoint (weeks) | Group 1 Mean (95% CI)[b] | Group 2 Mean (95% CI)[b] | Effect MD (90% CI)[c] |
|---|---|---|---|---|
| 11-point box scale memory status | 24 | -0.03 (-0.29 to 0.23) | 0.25 (-0.09 to 0.59) | -0.15 (-0.51 to 0.27) |
| NAI-ZN-G | 24 | -0.28 (-0.64 to 0.08) | -0.20 (-0.70 to 0.30) | -0.01 (-0.54 to 0.52) |
| NAI-ZVT-G | 24 | 11.00 (-2.32 to 24.32) | -12.50 (-29.11 to 4.11) | 18.4 (-0.7 to 37.5) |
| NAI-WL-tot | 24 | -0.60 (-1.24 to 0.04) | -1.00 (-1.85 to -0.15) | 0.12 (-0.69 to 0.93) |
| SKT total score | 24 | -0.8 (-1.7 to 0.1) | -1.2 (-2.3 to -0.1) | 0.40 (-0.9 to 1.7) |
| **Ginkgo biloba 240 mg (all 24 weeks) vs. Ginkgo biloba 160 mg (all 24 weeks)** | | | | |
| 11-point box scale memory status | 24 | 0.13 (-0.29 to 0.55) | -0.18 (-0.50 to 0.14) | 0.23 (-0.26 to 0.72) |
| NAI-ZN-G | 24 | -0.39 (-0.87 to 0.09) | -0.18 (-0.73 to 0.37) | -0.01 (-0.70 to 0.68) |
| NAI-ZVT-G | 24 | 7.45 (-10.80 to 25.70) | 14.24 (-5.68 to 34.16) | -2.2 (-27.0 to 22.6) |
| NAI-WL-tot | 24 | -1.26 (-2.22 to -0.30) | 0.03 (-0.79 to 0.85) | -1.37 (-2.78 to 0.04) |
| SKT total score | 24 | -1.0 (-2.2 to 0.2) | -0.7 (-2.1 to 0.7) | -0.3 (-1.9 to 1.3) |
| **Any ginkgo biloba (all 24 weeks) vs. Any ginkgo biloba (first 12 weeks) followed by placebo (second 12 weeks)** | | | | |
| 11-point box scale memory status | 24 | -0.03 (-0.29 to 0.23) | -0.12 (-0.44 to 0.20) | 0.09 (-0.22 to 0.40) |
| NAI-ZN-G | 24 | -0.28 (-0.64 to 0.08) | -0.07 (-0.44 to 0.30) | -0.06 (-0.48 to 0.36) |
| NAI-ZVT-G | 24 | 11.00 (-2.32 to 24.32) | 2.60 (-9.77 to 14.97) | 10.70 (-4.30 to 25.70) |
| NAI-WL-tot | 24 | -0.60 (-1.24 to 0.04) | -1.25 (-1.85 to -0.65) | 0.70 (-0.21 to 1.61) |
| SKT total score | 24 | -0.8 (-1.7 to 0.1) | -1.1 (-1.9 to -0.3) | 0.2 (-0.8 to 1.2) |

*Abbreviations*

CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference, NAI-ZN-G = Nuremberg Age Inventory-ZahlennachsprechenTest G (Digit Memory Span G), NAI-ZVT-G = Nuremberg Age Inventory-Zahlen-Verbindungs-Test G, NAI-WL-tot = Nuremberg Age Inventory-Wortliste (Word List) total, SKT = Syndrom-Kurz-Test.

*Notes*

a = All results in this table are from the same trial (Maastricht Ginkgo Trial[68,69]). Patients received 240 mg ginkgo biloba, 160 mg ginkgo biloba, or placebo for the first 12 weeks. Patients receiving ginkgo biloba were then randomised to continue their dose of ginkgo biloba or switch to placebo. Authors of the original study reported varying comparisons across groups and timepoints. Included patients were those with dementia according to DSM-III-R and ICD-10 criteria or nondemented patients with age-associated memory impairment.

b = Mean absolute change from baseline.

c = Reported by study authors. Adjusted estimate.

**Table 115: Efficacy results from the Maastricht Ginkgo Trial – behaviour/mood**

| Outcome[a] | Timepoint (weeks) | Group 1 Mean (95% CI)[b] | Group 2 Mean (95% CI)[b] | Effect MD (90% CI)[c] |
|---|---|---|---|---|
| **Any ginkgo biloba (first 12 weeks) vs. Placebo (first 12 weeks)** | | | | |
| SCAG | 12 | 0.18 (0.06 to 0.30) | 0.04 (-0.13 to 0.21) | 0.12 (-0.08 to 0.32) |
| GDS | 12 | -0.62 (-1.05 to -0.19) | -1.20 (-2.23 to -0.17) | 0.60 (-0.31 to 1.51) |
| **Any ginkgo biloba (all 24 weeks) vs. Placebo (all 24 weeks)** | | | | |
| SCAG | 24 | 0.07 (-0.11 to 0.25) | 0.03 (-0.19 to 0.25) | 0.01 (-0.22 to 0.24) |
| GDS | 24 | -0.58 (-1.20 to 0.04) | -1.14 (-2.07 to -0.21) | 0.54 (-0.46 to 1.54) |
| **Ginkgo biloba 240 mg (all 24 weeks) vs. Ginkgo biloba 160 mg (all 24 weeks)** | | | | |
| SCAG | 24 | 0.02 (-0.20 to 0.24) | 0.13 (-0.15 to 0.41) | -0.23 (-0.54 to 0.08) |
| GDS | 24 | -0.59 (-1.47 to 0.29) | -0.57 (-1.48 to 0.34) | -0.10 (-1.32 to 1.12) |
| **Any ginkgo biloba (all 24 weeks) vs. Any ginkgo biloba (first 12 weeks) followed by placebo (second 12 weeks)** | | | | |
| SCAG | 24 | 0.07 (-0.11 to 0.25) | 0.12 (-0.05 to 0.29) | -0.02 (-0.22 to 0.17) |
| GDS | 24 | -0.58 (-1.20 to 0.04) | -0.69 (-1.35 to -0.03) | 0.15 (-0.62 to 0.92) |

*Abbreviations*

CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, GDS = Geriatric Depression Scale, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = All results in this table are from the same trial (Maastricht Ginkgo Trial[68,69]). Patients received 240 mg ginkgo biloba, 160 mg ginkgo biloba, or placebo for the first 12 weeks. Patients receiving ginkgo biloba were then randomised to continue their dose of ginkgo biloba or switch to placebo. Authors of the original study reported varying comparisons across groups and timepoints. Included patients were those with dementia according to DSM-III-R and ICD-10 criteria or nondemented patients with age-associated memory impairment.

b = Mean absolute change from baseline.

c = Reported by study authors. Adjusted estimate.

**Table 116: Efficacy results from the Maastricht Ginkgo Trial – functional status**

| Outcome[a] | Timepoint (weeks) | Group 1 Mean (95% CI)[b] | Group 2 Mean (95% CI)[b] | Effect MD (90% CI)[c] |
|---|---|---|---|---|
| **Any ginkgo biloba (first 12 weeks) vs. Placebo (first 12 weeks)** | | | | |
| **NAA-ADL** | 12 | -0.42 (-1.00 to 0.16) | -1.77 (-3.19 to -0.35) | 1.35 (0.22 to 2.49) |
| **Any ginkgo biloba (all 24 weeks) vs. Placebo (all 24 weeks)** | | | | |
| **NAA-ADL** | 24 | -0.92 (-1.94 to 0.10) | -2.57 (-3.93 to -1.21) | 1.32 (-0.13 to 2.77) |
| **Ginkgo biloba 240 mg (all 24 weeks) vs. Ginkgo biloba 160 mg (all 24 weeks)** | | | | |
| **NAA-ADL** | 24 | -1.45 (-2.99 to 0.09) | -0.43 (-1.80 to 0.94) | -1.43 (-3.21 to 0.35) |
| **Any ginkgo biloba (all 24 weeks) vs. Any ginkgo biloba (first 12 weeks) followed by placebo (second 12 weeks)** | | | | |
| **NAA-ADL** | 24 | -0.92 (-1.94 to 0.10) | -1.18 (-2.15 to -0.21) | -0.02 (-1.17 to 1.13) |

*Abbreviations*

CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference, NAA-ADL = Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living.

*Notes*

a = All results in this table are from the same trial (Maastricht Ginkgo Trial) and at the same timepoint (24 weeks). Patients received 240 mg ginkgo biloba, 160 mg ginkgo biloba, or placebo for the first 12 weeks. Patients receiving ginkgo biloba were then randomised to continue their dose of ginkgo biloba or switch to placebo. Authors of the original study reported varying comparisons across groups and timepoints. Included patients were those with dementia according to DSM-III-R and ICD-10 criteria or nondemented patients with age-associated memory impairment.

b = Mean absolute change from baseline.

c = Reported by study authors. Adjusted estimate.

**Table 117: Efficacy results from the Maastricht Ginkgo Trial – global assessment of health status**

| Outcome[a] | Timepoint (weeks) | Group 1 Mean (95% CI) | Group 2 Mean (95% CI) | Effect MD (90% CI)[b] |
|---|---|---|---|---|
| **Any ginkgo biloba (first 12 weeks) vs. Placebo (first 12 weeks)** | | | | |
| 11-point box scale health status[c] | 12 | -0.24 (-0.46 to -0.02) | 0.04 (-0.42 to 0.50) | -0.38 (-0.73 to -0.04) |
| **Any ginkgo biloba (all 24 weeks) vs. Placebo (all 24 weeks)** | | | | |
| 11-point box scale health status[c] | 24 | -0.16 (-0.49 to 0.17) | 0.16 (-0.22 to 0.54) | 0.41 (-0.15 to 0.97) |
| CGIC[d] | 24 | 4.3 (4.0 to 4.6) | 4.3 (4.0 to 4.6) | 0.0 (-0.3 to 0.4) |
| **Ginkgo biloba 240 mg (all 24 weeks) vs. Ginkgo biloba 160 mg (all 24 weeks)** | | | | |
| 11-point box scale health status[c] | 24 | 0.21 (-0.30 to 0.72) | -0.53 (-0.91 to -0.15) | -0.15 (-0.56 to 0.26) |
| CGIC[d] | 24 | 4.4 (4.0 to 4.8) | 4.2 (3.9 to 4.5) | -0.3 (-0.7 to 0.2) |
| **Any ginkgo biloba (all 24 weeks) vs. Any ginkgo biloba (first 12 weeks) followed by placebo (second 12 weeks)** | | | | |
| 11-point box scale health status[c] | 24 | -0.16 (-0.49 to 0.17) | -0.17 (-0.49 to 0.15) | 0.10 (-0.25 to 0.46) |
| CGIC[d] | 24 | 4.3 (4.0 to 4.6) | 4.4 (4.2 to 4.6) | -0.1 (-0.4 to 0.2)[e] |

*Abbreviations*

CGIC = Clinical Global Impression of Change, CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference.

*Notes*

a = All results in this table are from the same trial (Maastricht Ginkgo Trial[68,69]). Patients received 240 mg ginkgo biloba, 160 mg ginkgo biloba, or placebo for the first 12 weeks. Patients receiving ginkgo biloba were then randomised to continue their dose of ginkgo biloba or switch to placebo. Authors of the original study reported varying comparisons across groups and timepoints. Included patients were those with dementia according to DSM-III-R and ICD-10 criteria or nondemented patients with age-associated memory impairment.

b = Reported by study authors. Adjusted estimate.

c = Mean absolute change from baseline.

d = Mean value at timepoint.

e = Original publication reported a mean difference (95% CI) of 0.1 (-0.2 to 0.4) for a comparison of ginkgo followed by placebo vs. ginkgo for all 24 weeks; this was transformed by the authors of this report to align with the other reported comparisons.

**Table 118: Safety results from the Maastricht Ginkgo Trial**

| Out-come[a] | Timepoint (weeks) | Group 1 n/N (%) | Group 2 n/N (%) | Group 3 n/N (%) | Group 1 vs. Group 2 RR (95% CI)[b] | Group 2 vs. Group 3 RR (95% CI)[b] | Group 1 vs. Group 3 RR (95% CI)[b] |
|---|---|---|---|---|---|---|---|
| **≥1 AE during follow-up** | | Ginkgo biloba 240 mg (first 12 weeks) | Ginkgo biloba 160 mg (first 12 weeks) | Placebo (first 12 weeks) | | | |
| | 12 | 46/82 (56) | 44/84 (52) | 21/48 (44) | 1.07 (0.81 to 1.42) | 1.20 (0.82 to 1.75) | 1.28 (0.88 to 1.86) |
| | | Ginkgo biloba 240 mg (24 weeks) | Ginkgo biloba 160 mg (24 weeks) | Placebo at any time[c] | | | |
| | 24 | 18/39 (46) | 16/40 (40) | 79/122 (65) | 1.15 (0.69 to 1.92) | 0.62 (0.41 to 0.92) | 0.71 (0.50 to 1.03) |
| **≥1 SAE during follow-up** | | Any ginkgo biloba[d] | Placebo (24 weeks) | NA | | | |
| | 24 | 26/166 (16) | 9/48 (19) | NA | 0.84 (0.42 to 1.66) | NA | NA |

*Abbreviations*

AE = adverse event, CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, ICD-10 = International Classification of Diseases, Tenth Revision, MD = mean difference, NA = not applicable, SAE = serious adverse event.

*Notes*

a = All results in this table are from the same trial (Maastricht Ginkgo Trial[68,69]). Patients received 240 mg ginkgo biloba, 160 mg ginkgo biloba, or placebo for the first 12 weeks. Patients receiving ginkgo biloba were then randomised to continue their dose of ginkgo biloba or switch to placebo. Authors of the original study reported varying comparisons across groups and timepoints. Included patients were those with dementia according to DSM-III-R and ICD-10 criteria or nondemented patients with age-associated memory impairment.

b = Calculated by the authors of this report.

c = Includes patients who received either 240 mg or 160 mg of ginkgo biloba for 12 weeks, followed by placebo for 12 weeks, as well as patients who received placebo for all 24 weeks.

d = Includes patients who received either 240 mg or 160 mg of ginkgo biloba for 12 weeks, followed by either continued ginkgo biloba or placebo for 12 weeks.

## Results for unapproved doses of ginkgo biloba in patients with mental performance deficits

**Table 119: Categorical efficacy results comparing 160 mg ginkgo biloba vs. placebo in patients with MPD – cognitive function**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **ADAS-Cog improved by ≥4 points** | 29/104 (27.84) | 4/70 (5.8) | <0.001 | 4.88 (1.79 to 13.3) |
| **Progression to AD (CDR >1)** | 1/104 (0.96) | 7/70 (10) | NR | 0.10 (0.01 to 0.76) |

*Abbreviations*

AD = Alzheimer's disease, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL-MCI-24 = Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment – 24-item, AMIPB-DSR = Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall, CDR = Clinical Dementia Rating, CI = confidence interval, MCI = mild cognitive impairment, MMSE = Mini-Mental State Examination, NR = not reported, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Tian 2019[102]) and at the same timepoint (52 weeks). Included patients were those with amnestic MCI, defined as: (1) memory complaints; (2) Chinese version of the AMIPB-DSR age-adjusted subtest score of <15.5 (aged 50 to 64 years <15.5 to 65 to 74 years <12.5, and over 75 years <10); (3) normal general cognitive function as determined by a clinician's judgment based on a structured interview with the patients, MMSE score of 24 to 30, and CDR score of 0.5, with the memory domain 0.5 or 1, and no other domain greater than 1; (4) score of 38 to 52 on ADCS-ADL-MCI-24 items.

b = Calculated by the authors of this report.

**Table 120: Continuous efficacy results comparing 160 mg ginkgo biloba vs. placebo in patients with MPD – cognitive function**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI) | Placebo Mean (95% CI) | p-value | Effect MD (95% CI)[a] |
|---|---|---|---|---|---|---|
| **IQ Values of Short-Term** | 12 | Grassel | 101.9 (95.1 to 108.7) | 96.3 (89.6 to 103.0) | NS | 5.6 (-4.2 to 15.4) |
| **Memory Capacity** | 24 | 1992[82b] | 107.5 (101.0 to 114.0) | 95.8 (89.3 to 102.3) | 0.018 | 11.7 (2.3 to 21.1) |
| **MWT IQ** | 12 | Grassel | 105.5 (99.2 to 111.8) | 111.3 (103.4 to 119.2) | NS | -5.8 (-16.1 to 4.5) |
| | 24 | 1992[82b] | 110.8 (105.4 to 116.2) | 106.4 (99.1 to 113.7) | NS | 4.4 (-4.9 to 13.7) |
| **ADAS-Cog** | 52 | Tian | 2.4 (1.8 to 3.1) | -1.3 (-2.0 to -0.5) | NR | 3.7 (2.7 to 4.7) |
| **AMIPB-DSR** | | 2019[102c] | -3.0 (-4.0 to -2.0) | -1.4 (-2.5 to -0.2) | NR | -1.6 (-3.2 to -0.1) |
| **CDR sum of boxes** | | | 0.3 (0.0 to 0.5) | 0.0 (-0.3 to 0.3) | NR | 0.3 (-0.1 to 0.7) |
| **MMSE** | | | -0.9 (-1.2 to -0.5) | 0.3 (-0.2 to 0.7) | NR | -1.1 (-1.7 to -0.5) |

*Abbreviations*

ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, ADCS-ADL-MCI-24 = Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment – 24-item, AMIPB-DSR = Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall, CDR = Clinical Dementia Rating, CI = confidence interval, IQ = intelligence quotient, MCI = mild cognitive impairment, MD = mean difference, MMSE = Mini-Mental State Examination, MWT IQ = Multiple Choice Vocabulary Intelligence Test, NR = not reported, NS = not significant, TIA = transient ischaemic attack.

*Notes*

a = Calculated by the authors of this report.

b = All outcomes for this study are reported as the mean value at timepoint. Included patients were those diagnosed with 'cerebral insufficiency', made based on anamnesis data (indications of a stenosing vascular process in the cranial area, e.g. TIA or previous infarct) while considering internal medical risk factors (e.g. arterial hypertension). In case of doubt, the findings were verified using Doppler ultrasound. Additionally, the psychometric inclusion criterion 'IQ value of short-term memory capacity is less than MWT IQ' had to be met.

c = All outcomes for this study are reported as the mean absolute change from baseline. Included patients were those with amnestic MCI, defined as: (1) memory complaints; (2) Chinese version of the AMIPB-DSR age-adjusted subtest score of <15.5 (aged 50 to 64 years <15.5 to 65 to 74 years <12.5, and over 75 years <10); (3) normal general cognitive function as determined by a clinician's

judgment based on a structured interview with the patients, MMSE score of 24 to 30, and CDR score of 0.5, with the memory domain 0.5 or 1, and no other domain greater than 1; (4) score of 38 to 52 on ADCS-ADL-MCI-24 items.

**Table 121: Continuous efficacy results comparing 160 mg ginkgo biloba vs. placebo in patients with MPD – functional status**

| Outcome[a] | Ginkgo biloba Mean (95% CI) | Placebo Mean (95% CI) | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|
| **ADCS-ADL-MCI-24** | -3.0 (-4.0 to -2.0) | -1.4 (-2.5 to -0.2) | NR | -1.6 (-3.2 to -0.1) |

*Abbreviations*

ADCS-ADL-MCI-24 = Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment – 24-item, AMIPB-DSR = Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall, CDR = Clinical Dementia Rating, CI = confidence interval, MCI = mild cognitive impairment, MD = mean difference, MMSE = Mini-Mental State Examination, NR = not reported.

*Notes*

a = All results in this table are from the same trial (Tian 2019[102]) and at the same timepoint (52 weeks). Included patients were those with amnestic MCI, defined as: (1) memory complaints; (2) Chinese version of the AMIPB-DSR age-adjusted subtest score of <15.5 (aged 50 to 64 years <15.5 to 65 to 74 years <12.5, and over 75 years <10); (3) normal general cognitive function as determined by a clinician's judgment based on a structured interview with the patients, MMSE score of 24 to 30, and CDR score of 0.5, with the memory domain 0.5 or 1, and no other domain greater than 1; (4) score of 38 to 52 on ADCS-ADL-MCI-24 items.

b = Calculated by the authors of this report.

**Table 122: Safety results comparing 160 mg ginkgo biloba vs. placebo in patients with MPD**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **≥1 AE during follow-up** | 24 | Grassel 1992[82b] | 4/29 (13.8)[c] | 6/24 (25)[c] | NR | 0.55 (0.18 to 1.73) |
| | 52 | Tian 2019[102d] | 43/104 (41.4) | 30/70 (42.9) | NS | 0.96 (0.68 to 1.38) |

*Abbreviations*

ADCS-ADL-MCI-24 = Alzheimer's Disease Cooperative Study – Activities of Daily Living for Mild Cognitive Impairment – 24-item, AE = adverse event, AMIPB-DSR = Adult Memory and Information Processing Battery Logical Memory Delayed Story Recall, CDR = Clinical Dementia Rating, CI = confidence interval, IQ = intelligence quotient, MMSE = Mini-Mental State Examination, MWT IQ = Multiple Choice Vocabulary Intelligence Test, NR = not reported, NS = not significant, RR = relative risk, TIA = transient ischaemic attack.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those diagnosed with 'cerebral insufficiency', made based on anamnesis data (indications of a stenosing vascular process in the cranial area, e.g. TIA or previous infarct) while considering internal medical risk factors (e.g. arterial hypertension). In case of doubt, the findings were verified using Doppler ultrasound. Additionally, the psychometric inclusion criterion 'IQ value of short-term memory capacity is less than MWT IQ' had to be met.

c = Percentages were calculated by the authors of this report.

d = Included patients were those with amnestic MCI, defined as: (1) memory complaints; (2) Chinese version of the AMIPB-DSR age-adjusted subtest score of <15.5 (aged 50 to 64 years <15.5 to 65 to 74 years <12.5, and over 75 years <10); (3) normal general cognitive function as determined by a clinician's judgment based on a structured interview with the patients, MMSE score of 24 to 30, and CDR score of 0.5, with the memory domain 0.5 or 1, and no other domain greater than 1; (4) score of 38 to 52 on ADCS-ADL-MCI-24 items.

**Table 123: Categorical efficacy results comparing 150 mg ginkgo biloba vs. placebo in patients with MPD – global assessment of health status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Physician's assessment of therapy** | | | | | | |
| **Good** | 6 | Hofferberth | 19/25 (76) | 0/25 (0) | <0.001 | NE |
| **Moderate** | | 1991[73b] | 4/25 (16) | 11/25 (44) | | 0.36 (0.13 to 0.99) |
| **Unsatisfactory** | | | 2/25 (8) | 14/25 (56) | | 0.14 (0.04 to 0.56) |
| **Good** | 12 | Halama | 12/20 (60) | 2/22 (9.1) | <0.001 | 6.60 (1.68 to 26.0) |
| **Moderate** | | 1991[72c] | 4/20 (20) | 3/22 (13.6) | | 1.47 (0.37 to 5.77) |
| **Unsatisfactory** | | | 4/20 (20) | 17/22 (77.3) | | 0.26 (0.10 to 0.64) |

*Abbreviations*

CI = confidence interval, NE = not estimable, RR = relative risk.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were inpatients from a neurological specialty department with organic brain syndrome. Numerators for all outcomes were reported only in figures; they were digitised and rounded to the closest whole number. The percentage was calculated from percentage and denominator.

c = Included patients were outpatients from a neurology specialist practice with a diagnosis of pre-senile, simple senile, or arteriosclerotic dementia.

## Results to supplement the conducted meta-analyses in patients with mental performance deficits

**Table 124: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – cognitive function**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Cognitive performance responder[b]** | 12 | Oswald 1997[78c] | 61/103 (59.2) | 45/92 (48.9) | 0.074 | 1.21 (0.93 to 1.58) |
| **Improvement in Digit-Symbol Test** | | | 46/103 (44.7) | 35/92 (38) | 0.174 | 1.17 (0.84 to 1.65) |
| **Improvement in Maze Test** | | | 67/103 (65) | 49/92 (53.3) | 0.047 | 1.22 (0.96 to 1.55) |
| **Improvement in Number Connection Test** | | | 56/103 (54.4) | 49/92 (53.3) | 0.438 | 1.02 (0.79 to 1.32) |
| **ADAS-Cog improved by ≥2 points** | 26 | Le Bars 1997[98-101d] | 60/136 (44) | 44/134 (33) | 0.04 | 1.34 (0.99 to 1.83) |
| **ADAS-Cog improved by ≥4 points** | | | 36/136 (26) | 23/134 (17) | | 1.54 (0.97 to 2.46) |
| **ADAS-Cog worsened by ≥2 points** | | | 42/136 (31) | 54/134 (41) | | 0.77 (0.55 to 1.06) |
| **ADAS-Cog worsened by ≥4 points** | | | 31/136 (23) | 40/134 (30) | | 0.76 (0.51 to 1.14) |

*Abbreviations*

AD = Alzheimer's disease, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CI = confidence interval, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, ICD-9 = International Classification of Diseases, Ninth Revision, MID = multi-infarct dementia, RR = relative risk, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = Calculated by the authors of this report.

b = Improved in ≥2 of the following: Digit-Symbol Test, Maze Test, Number Connection Test.

c = Included patients were those with mild to moderate cognitive disorders of old age (DSM-III, Cat. 1 or ICD-9 No. 290), whose cognitive performance according to SCAG was between 40 and 90, and who also achieved an average score of at least 3.5 in items 2 to 3, 6, and 8, and a total score of 24 in items 1 to 8, with none of these items having a score of 7.

d = Included patients were outpatients with AD or MID, without other significant medical conditions.

**Table 125: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – cognitive function**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **Reaction time** | 12 | Weitbrecht 1986[79c] | 1.6 (1.5 to 1.8) | 1.8 (1.7 to 1.9) | <0.01[d] | -0.2 (-0.4 to 0.0) |
| **Flicker frequency** | 12 | Weitbrecht 1986[79c] | 41.4 (40.3 to 42.5) | 38.5 (37.7 to 39.3) | <0.0001[d] | 2.9 (1.5 to 4.3) |
| **MCRT, stimulus interval** | 12 | Gessner 1985[96e] | 111 (101 to 121) | 105 (93 to 117) | NS | 6 (-10 to 22) |
| **MDRS** | 12 | NCT00446485[81f] | 126.2 (120.0 to 132.4) | 125.9 (120.2 to 131.6) | NR | 0.3 (-8.4 to 9.0) |
| | 24 | NCT00446485[81f] | 128.4 (122.4 to 134.4) | 127.2 (121.6 to 132.8) | 0.749[g] | 1.2 (-7.3 to 9.7) |
| **MMSE** | 12 | NCT00446485[81f] | 27.4 (26.5 to 28.3) | 27.8 (26.8 to 28.8) | NR | -0.4 (-1.8 to 1.0) |
| | 24 | NCT00446485[81f] | 27.9 (26.8 to 29.0) | 28.1 (26.8 to 29.4) | 0.766[g] | -0.2 (-1.9 to 1.5) |
| **ADAS-Cog** | 52 | Le Bars 1997[98-101h] | 0.1 (-0.8 to 1.0)[i] | 1.5 (0.4 to 2.5)[j] | 0.04 | -1.4 (-2.7 to 0.0)[k] |

*Abbreviations*

AD = Alzheimer's disease, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CI = confidence interval, MCRT = Multiple Choice Reaction Test, MD = mean difference, MDRS = Mattis Dementia Rating Scale, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, NR = not reported, NS = not significant.

*Notes*

a = Mean value at timepoint unless otherwise specified.

b = Calculated by the authors of this report unless otherwise specified.

c = Included patients were those with primary degenerative dementia, diagnosed using the Hachinski Ischemic Scale, and excluding those with MID.

d = Although reported values are the mean value at 12 weeks, the *p-value* is for the change from baseline.

e = Included patients were those with symptoms of cerebral deterioration. Means and standard deviations were reported only in figures; they were digitised and rounded to the closest whole number.

f = Included patients were those with vascular cognitive impairment based on cerebrovascular insufficiency and a Folstein MMSE score of >20 and ≤28.

g = This study included a third treatment arm that is not approved in Switzerland and is therefore ineligible for this review. This *p-value* is a comparison across all 3 treatment groups.

h = Included patients were outpatients with AD or MID, without other significant medical conditions.

i = Mean absolute change from baseline. Not significant.

j = Mean absolute change from baseline. *P*=0.006 (significant worsening since baseline).

k = Reported by study authors.

**Table 126: Categorical efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – cognitive function**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **SKT improved by ≥4 points** | 24 | Kanowski 1996[74,75b] | 30/79 (38)[c] | 14/77 (18)[d] | <0.05[d] | 2.09 (1.20 to 3.62)<br>20.0 (6.0 to 34.0)[d] |
| **ADAS-Cog improved by ≥4 points[e]** | 24 | Kanowski 1996[74,75b] | 37/106 (35) | 19/99 (19) | 0.01 | 1.82 (1.12 to 2.94) |
| **ADAS-Cog did not improve by ≥4 points[e]** | | | 69/106 (65) | 80/99 (81) | | 0.81 (0.68 to 0.95) |
| **ADAS-Cog improved by ≥2 points[e]** | 24 | Kanowski 1996[74,75b] | 65/106 (61) | 37/99 (37) | <0.001 | 1.64 (1.22 to 2.21) |
| **ADAS-Cog did not improve by ≥2 points[e]** | | | 41/106 (39) | 62/99 (63) | | 0.62 (0.46 to 0.82) |

*Abbreviations*

AD = Alzheimer's disease, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, MID = multi-infarct dementia, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, RR = relative risk, SKT = Syndrom-Kurz-Test.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with AD or MID according to DSM-III-R.

c = This analysis was conducted in the per protocol population rather than the intent-to-treat population.

d = Absolute difference in percentage of patients with event and 95% CI. Reported by original study authors.

e = ADAS-Cog score was not measured directly. Authors of the original study transformed SKT scores to ADAS-Cog scores and reported ADAS-Cog results separately.

**Table 127: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – cognitive function**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **Delayed response task Error rate, repeat mode** | 8 | DRKS 00000423[88c] | 26.3 (22.5 to 30.1)[d] | 28.3 (24.4 to 32.2)[d] | NR | -2.0 (-7.5 to 3.5) |
| **Delayed response task Reaction time, repeat mode** | 8 | DRKS 00000423[88c] | 1380 (1294 to 1466)[d] | 1380 (1307 to 1453)[d] | NR | 0.0 (-115 to 115) |
| **Delayed response task Error rate, switch mode** | 8 | DRKS 00000423[88c] | 23.4 (19.7 to 27.1)[d] | 28.5 (23.9 to 33.1)[d] | NR | -5.1 (-11.2 to 1.0) |
| **Delayed response task Reaction time, switch mode** | 8 | DRKS 00000423[88c] | 1358 (1270 to 1446)[d] | 1356 (1285 to 1427)[d] | NR | 2 (-114 to 118) |
| **Go-NoGo-task False alarm rate** | 8 | DRKS 00000423[88c] | 12.9 (9.9 to 15.9)[d] | 19.2 (13.1 to 25.3)[d] | NR | -6.3 (-13.2 to 0.6) |
| **Go-NoGo-task Reaction time** | 8 | DRKS 00000423[88c] | 429 (410 to 448)[d] | 432 (418 to 446)[d] | NR | -3 (-27 to 21) |
| **Prospective memory task Error rate** | 8 | DRKS 00000423[88c] | 0.3 (0.0 to 0.6)[d] | 0.4 (0.0 to 0.8)[d] | NR | -0.1 (-0.6 to 0.4) |
| **Prospective memory task Reaction time** | 8 | DRKS 00000423[88c] | 643 (608 to 678)[d] | 642 (612 to 672)[d] | NR | 1.0 (-46 to 48) |
| **BfS** | 12 | Grass-Kapanke 2011[110e] | -2.3 (-4.1 to -0.6) | -4.1 (-5.9 to -2.3) | 0.92 | 1.8 (-0.7 to 4.3) |
| **TT - Delayed Recall** | 12 | Grass-Kapanke 2011[110e] | 5.5 (4.5 to 6.4) | 4.3 (3.4 to 5.1) | 0.03 | 1.2 (-0.1 to 2.4) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **TT - Immediate Recall** | 12 | Grass-Kapanke 2011[110e] | 5.6 (4.8 to 6.5) | 4.7 (3.8 to 5.5) | 0.06 | 0.9 (-0.3 to 2.2) |
| **WMS III - Faces I** | 12 | Grass-Kapanke 2011[110e] | 4.1 (3.3 to 5.0) | 3.1 (2.3 to 3.8) | 0.04 | 1.1 (-0.1 to 2.2) |
| **WMS III - Faces II** | 12 | Grass-Kapanke 2011[110e] | 4.8 (3.8 to 5.8) | 4.4 (3.6 to 5.2) | 0.27 | 0.4 (-0.9 to 1.7) |
| **WTS-ALS - Answered Stimuli** | 12 | Grass-Kapanke 2011[110e] | 44.2 (24.8 to 63.5) | 17.8 (3.9 to 31.7) | 0.01 | 26.4 (2.5 to 50.3) |
| **WTS-DT - Correct Reactions** | 12 | Grass-Kapanke 2011[110e] | 8.9 (2.0 to 15.8) | 5.1 (-0.9 to 11.2) | 0.21 | 3.8 (-5.4 to 12.9) |
| **ADAS-Cog** | 12 | Maurer 1997[76,77f] | 30.3 (20.7 to 40.0)[d] | 36.1 (26.0 to 46.3)[d] | NR | -5.8 (-21.0 to 9.4) |
| **ADAS-Cog** | 26 | Schneider 2005[116,117g] | 1.3 (0.5 to 2.1) | 0.9 (0.1 to 1.7) | 0.32 | 0.4 (-0.8 to 1.6) |
| **CDT** | 22 | Napryeyenko 2007[106,113-115h] | 1.1 (0.9 to 1.3) | 0.0 (-0.1 to 0.1) | <0.001 | 1.2 (1.0 to 1.4)[i] |
| **TE4D cognitive score** | 24 | Herrschaft 2012[106,111,112j] | 2.9 (2.2 to 3.6) | 0.7 (0.2 to 1.3) | <0.001 | 2.2 (1.3 to 3.1) |
| **TMT-A** | 24 | Gavrilova 2014[103,104k] | -22.4 (-27.4 to -17.4) | -18.1 (-23.7 to -12.5) | 0.04 | -4.3 (-11.9 to 3.3) |
| **TMT-B** | 24 | Gavrilova 2014**[103,104k]** | -44.7 (-52.8 to -36.6) | -32.2 (-40.8 to -23.6) | 0.0112 | -12.5 (-24.4 to -0.6) |

*Abbreviations*

AD = Alzheimer's disease, ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, BCRS = Brief Cognitive Rating Scale, BfS = Mental Balance Scale (Befindlichkeitsskala), CDT = Clock-Drawing Test, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MCI = mild cognitive impairment, MD = mean difference, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NR = not reported, PRMQ = Prospective and Retrospective Memory Questionnaire, SKT = Syndrom-Kurz-Test, TE4D = Test for the Early Detection of Dementia from Depression, TMT = Trail-Making Test, TT = Termine Test, WMS III = Wechsler Memory Scale III, WTS-ALS = Vienna Test System—Work Performance Series, WTS-DT = Vienna Test System—Determination Test.

*Notes*

a = Mean absolute change from baseline unless otherwise specified.

b = Calculated by the authors of this report unless otherwise specified.

c = Included patients were those with subjective memory impairment, defined as ≥1 item answered with 'rather often' or 'very often', or at least 5 questions answered 'sometimes' in the PRMQ.

d = Mean value at timepoint.

e = Included patients were those with very MCI, as defined by the diagnostic criteria: a) subjective complaints of impairment, perceived as a decline from former level of functioning in at least one of the following: memory, attention/concentration, speed of functioning, efforts required to complete complex tasks, general performance/efficiency; b) low functioning (≥1 standard deviation worse than the mean of the most appropriate normative group) in at least one of the cognitive tests administered at screening and baseline (WMS III Faces I + II, WTS-ALS (S1), WTS-DT (S16), TT; c) perceived impairment present for at least 3 months; d) widely preserved general cognitive function, as evidenced by a total score above 23 in the MMSE; e) intact ADL, as evidenced by inquiry (subtle difficulties, in particular slowing or increased efforts, in complex tasks is acceptable); f) no indication of dementia.

f = Included patients were those with mild to moderate Alzheimer-type senile dementia (mean BCRS score 3 to 5).

g = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 120 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

h = Included patients were those with (a) probable AD in accordance with the NINCDS-ADRDA criteria, (b) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (c) probable vascular dementia according to NINDS-AIREN. Patients had to have mild to moderate dementia, as evidenced by a total score from 9 to 23 (both inclusive) on the SKT test battery.

i = Reported by study authors. Adjusted estimate.

j = Included patients were those with (a) probable AD in accordance with the NINCDS-ADRDA criteria, (b) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (c) probable vascular dementia according to NINDS-AIREN. Dementia symptoms were present for ≥6 months.

k = Included patients were those diagnosed with amnestic MCI in accordance with international consensus criteria.

**Table 128: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – behavioural changes/mood**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **MDBF alertness/fatigue after TSST** | 8 | DRKS 00000423[88c] | 11.3 (10.7 to 11.9) | 10.3 (9.6 to 11.0) | NR | 1.0 (0.0 to 2.0) |
| **MDBF alertness/fatigue before TSST** | 8 | DRKS 00000423[88c] | 11.1 (10.6 to 11.6) | 10.6 (10.1 to 11.1) | NR | 0.5 (-0.2 to 1.2) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **MDBF calmness/restlessness after TSST** | 8 | DRKS 00000423[88c] | 11.8 (11.0 to 12.6) | 10.8 (10.1 to 11.5) | NR | 1.0 (-0.1 to 2.1) |
| **MDBF calmness/restlessness before TSST** | 8 | DRKS 00000423[88c] | 11.0 (10.3 to 11.7) | 11.4 (10.7 to 12.1) | NR | -0.4 (-1.5 to 0.7) |
| **MDBF good/bad mood after TSST** | 8 | DRKS 00000423[88c] | 10.8 (10.3 to 11.3) | 10.6 (10.1 to 11.1) | NR | 0.2 (-0.5 to 0.9) |
| **MDBF good/bad mood before TSST** | 8 | DRKS 00000423[88c] | 10.8 (10.3 to 11.3) | 10.9 (10.3 to 11.5) | NR | -0.1 (-0.9 to 0.7) |
| **NPI frequency score** | 12 | Gavrilova 2014[103,104d] | -2.0 (-2.4 to -1.6)[e] | -1.5 (-1.9 to -1.1)[e] | <0.05 | -0.5 (-1.1 to 0.1) |
| | 24 | Gavrilova 2014[103,104d] | -3.7 (-4.3 to -3.1)[e] | -2.7 (-3.3 to -2.1)[e] | <0.01 | -1.0 (-1.9 to -0.1) |
| **NPI severity score** | 12 | Gavrilova 2014[103,104d] | -1.8 (-2.2 to -1.4)[e] | -1.2 (-1.6 to -0.8)[e] | <0.01 | -0.6 (-1.1 to -0.1) |
| | 24 | Gavrilova 2014[103,104d] | -2.9 (-3.4 to -2.4)[e] | -2.3 (-2.8 to -1.8)[e] | <0.01 | -0.6 (-1.3 to 0.1) |
| **GDS** | 24 | Gavrilova 2014[103,104d] | -3.0 (-3.6 to -2.4)[e] | -2.3 (-3.0 to -1.6)[e] | 0.0658 | -0.7 (-1.6 to 0.2) |
| **STAI-X1 state score** | 24 | Gavrilova 2014[103,104d] | -6.6 (-8.3 to -4.9)[e] | -3.8 (-5.4 to -2.2)[e] | 0.0271 | -2.8 (-5.2 to -0.4) |
| **HAMD** | 22 | Napryeyenko 2007[106,113-115f] | -3.3 (-3.6 to -3.0)[e] | 0.9 (0.6 to 1.2)[e] | <0.001 | -4.3 (-4.8 to -3.8)[g] |
| **MADRS** | 24 | Kanowski 1996[**74,75**h] | 13.2 (11.8 to 14.6) | 13.6 (12.0 to 15.2) | NR | -0.4 (-2.6 to 1.8) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, GDS = Geriatric Depression Scale, HAMD = Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MCI = mild cognitive impairment, MD = mean difference, MDBF = Mehrdimensionaler Befindlichkeitsbogen, MID = multi-infarct dementia, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NPI = Neuropsychiatric Inventory, NR = not reported, PRMQ = Prospective and Retrospective Memory Questionnaire, SKT = Syndrom-Kurz-Test, STAI-X1 = State-Trait Anxiety Inventory-state subscale, TSST = Trier Social Stress Test.

*Notes*

a = Mean value at timepoint unless otherwise specified.

b = Calculated by the authors of this report unless otherwise specified.

c = Included patients were those with subjective memory impairment, defined as ≥1 item answered with ‘rather often’ or ‘very often’, or at least 5 questions answered ‘sometimes’ in the PRMQ.

d = Included patients were those diagnosed with amnestic MCI in accordance with international consensus criteria.

e = Mean absolute change from baseline.

f = Included patients were those with (a) probable AD in accordance with the NINCDS-ADRDA criteria, (b) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (c) probable vascular dementia according to NINDS-AIREN. Patients had to have mild to moderate dementia, as evidenced by a total score from 9 to 23 (both inclusive) on the SKT test battery.

g = Original publication reported a mean difference (95% CI) of 4.3 (3.8 to 4.8) for a comparison of placebo vs. ginkgo; this was transformed by the authors of this report to align with the other comparisons.

h = Included patients were those with AD or MID according to DSM-III-R.

**Table 129: Categorical efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – functional status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **Improvement in NAA-ADL** | 12 | Oswald 1997[78b] | 36/103 (35) | 35/92 (38) | 0.673 | 0.92 (0.63 to 1.33) |
| **GERRI improved** | 26 | Le Bars 1997[98-101c] | 41/138 (30) | 33/132 (25) | 0.006 | 1.19 (0.80 to 1.76) |
| **GERRI worsened** | | | 23/138 (17) | 49/132 (37) | | 0.45 (0.29 to 0.69) |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, GERRI = Geriatric Evaluation by Relative's Rating Instrument, ICD-9 = International Classification of Diseases, Ninth Revision, MID = multi-infarct dementia, NAA-ADL = Nuremberg Gerontopsychological Rating Scale for Activities of Daily Living, RR = relative risk, SCAG = Sandoz Clinical Assessment Geriatric Scale.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with mild to moderate cognitive disorders of old age (DSM-III, Cat. 1 or ICD-9 No. 290), whose cognitive performance according to SCAG was between 40 and 90, and who also achieved an average score of at least 3.5 in items 2 to 3, 6, and 8, and a total score of 24 in items 1 to 8, with none of these items having a score of 7.

c = Included patients were outpatients with AD or MID, without other significant medical conditions.

**Table 130: Continuous efficacy results comparing 120 mg ginkgo biloba vs. placebo in patients with MPD – functional status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI) |
|---|---|---|---|---|---|---|
| **PDS** | 26 | Schneider 2005[116,117b] | -5.6 (-6.9 to -4.3) | -4.7 (-6.2 to -3.2) | 0.70 | -0.9 (-2.9 to 1.1)[c] |
| **GERRI** | 24 | Haan 2004[71d] | NR | NR | <0.05 | -0.12 (NR)[e] |
| | 52 | | NR | NR | <0.05 | -0.16 (NR)[e] |
| | 52 | Le Bars 1997[98-101f] | -0.1 (-0.1 to 0.0) | 0.1 (0.0 to 0.1) | 0.004 | -0.14 (-0.23 to -0.04)[e] |

*Abbreviations*

AD = Alzheimer's disease, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, GERRI = Geriatric Evaluation by Relative's Rating Instrument, MD = mean difference, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NR = not reported, PDS = Progressive Deterioration Scale.

*Notes*

a = Mean absolute change from baseline.

b = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 240 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

c = Calculated by the authors of this report.

d = Included patients were those with mild to moderate AD or MID.

e = Reported by study authors. Adjusted estimate.

f = Included patients were outpatients with AD or MID, without other significant medical conditions.

**Table 131: Categorical efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – functional status**

| Outcome[a] | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[b] |
|---|---|---|---|---|
| **NAB improved by ≥2 points** | 26/79 (33) | 18/77 (23) | <0.095[c] | 1.41 (0.84 to 2.35) |

| | |
|---|---|
| | 10.0 (-5.0 to 24.0)[c] |

*Abbreviations*

AD = Alzheimer's disease, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, MID = multi-infarct dementia, NAB = Nuremberg Gerontopsychological Observation Scale, RR = relative risk.

*Notes*

a = All results in this table are from the same trial (Kanowski 1996[74,75]) and at the same timepoint (24 weeks). Included patients are those with AD or MID according to DSM-III-R.

b = Calculated by the authors of this report.

c = Absolute difference in percentage of patients with event and 95% CI. Reported by original study authors.

**Table 132: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – functional status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba Mean (95% CI)[a] | Placebo Mean (95% CI)[a] | p-value | Effect MD (95% CI)[b] |
|---|---|---|---|---|---|---|
| **GBS-ADL** | 12 | Napryeyenko 2007[106,113-115c] | -1.1 (-1.3 to -0.9)[d] | 0.6 (0.4 to 0.8)[d] | NR | -1.7 (-2.0 to -1.4) |
| | 22 | Napryeyenko 2007[106,113-115c] | -1.9 (-2.3 to -1.5) | 0.9 (0.6 to 1.2) | NR | -2.8 (-3.3 to -2.3)[e] |
| **GBS total score** | 22 | Napryeyenko 2007[106,113-115c] | -9.9 (-11.1 to -8.7) | 4.1 (3.0 to 5.2) | NR | -14.0 (-15.7 to -12.4)[e] |
| **NAB** | 24 | Kanowski 1996[74,75f] | -0.8 (-1.2 to -0.1) | -0.4 (-0.8 to 0.0) | 0.12 | -0.4 (-1.0 to -0.1)[g] |
| **GERRI** | 26 | Schneider 2005[116,117h] | 0.1 (0.0 to 0.2) | 0.1 (0.1 to 0.1) | 0.42 | 0.0 (-0.1 to 0.1) |
| **PDS** | 26 | Schneider 2005[116,117h] | -4.6 (-6.1 to -3.1) | -4.7 (-6.2 to -3.2) | 0.70 | 0.1 (-2.0 to 2.2) |

*Abbreviations*

AD = Alzheimer's disease, ADL = activities of daily living, CI = confidence interval, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, GBS = Gottfries-Bråne-Steen Scale, GERRI = Geriatric Evaluation by Relative's Rating Instrument, MD = mean difference, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, NAB = Nuremberg Gerontopsychological Observation Scale, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, NINDS-AIREN = National Institute of Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences, NR = not reported, PDS = Progressive Deterioration Scale, SKT = Syndrom-Kurz-Test.

*Notes*

a = Mean absolute change from baseline.

b = Calculated by the authors of this report unless otherwise specified.

c = Included patients were those with (a) probable AD in accordance with the NINCDS-ADRDA criteria, (b) possible AD with cerebrovascular disease, as defined by the NINDS-AIREN criteria, or (c) probable vascular dementia according to NINDS-AIREN. Patients had to have mild to moderate dementia, as evidenced by a total score from 9 to 23 (both inclusive) on the SKT test battery.

d = Means and standard deviations were reported only in figures; they were digitised and rounded to the closest tenth.

e = Original publication reported mean differences (95% CI) of 2.8 (2.3 to 3.3) and 14.0 (12.4 to 15.7), for GBS-ADL and GBS total score, respectively, for a comparison of placebo vs. ginkgo; this was transformed by the authors of this report to align with the other comparisons

f = Included patients were those with AD or MID according to DSM-III-R.

g = Reported by study authors. Adjusted estimate.

h = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 120 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

**Table 133: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – HRQoL**

| Outcome[a] | Ginkgo biloba<br>Mean (95% CI)[b] | Placebo<br>Mean (95% CI)[b] | p-value | Effect<br>MD (95% CI)[c] |
|---|---|---|---|---|
| **SF36 Mental health** | 11.1 (8.2 to 13.9) | 9.0 (6.3 to 11.7) | 0.15 | 2.1 (0.1 to 4.1) |
| **SF36 Physical health** | 9.0 (6.4 to 11.6) | 5.7 (3.0 to 8.4) | 0.04 | 3.3 (1.5 to 5.2) |

*Abbreviations*

ADL = activities of daily living, CI = confidence interval, MCI = mild cognitive impairment, MD = mean difference, MMSE = Mini-Mental State Examination, TT = Termine Test, WMS III = Wechsler Memory Scale III, WTS-ALS = Vienna Test System—Work Performance Series, WTS-DT = Vienna Test System—Determination Test.

*Notes*

a = All results in this table are from the same trial (Grass-Kapanke 2011[110]) and at the same timepoint (12 weeks). Included patients were those with very MCI, as defined by the diagnostic criteria: a) subjective complaints of impairment, perceived as a decline from former level of functioning in at least one of the following: memory, attention/concentration, speed of functioning, efforts required to complete complex tasks, general performance/efficiency; b) low functioning (≥1 standard deviation worse than the mean of the most appropriate normative group) in at least one of the cognitive tests administered at screening and baseline (WMS III Faces I + II, WTS-ALS (S1), WTS-DT (S16), TT; c) perceived impairment present for at least 3 months; d) widely preserved general cognitive function, as evidenced by a total score above 23 in the MMSE; e) intact ADL, as evidenced by inquiry (subtle difficulties, in particular slowing or increased efforts, in complex tasks is acceptable); f) no indication of dementia.

b = Mean absolute change from baseline.

c = Calculated by the authors of this report.

**Table 134: Categorical efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – global assessment of health status**

| Outcome | Timepoint (weeks) | Study | Ginkgo biloba n/N (%) | Placebo n/N (%) | p-value | Effect RR (95% CI)[a] |
|---|---|---|---|---|---|---|
| **CGIC** | | | | | | |
| **Very Much Improved** | 12 | Maurer 1997[76,77b] | 0/9 (0) | 0/9 (0) | NR | NE |
| **Much Improved** | | | 3/9 (33) | 1/9 (11) | NR | 3.00 (0.38 to 23.7) |
| **Slightly Improved** | | | 2/9 (22) | 0/9 (0) | NR | NE |
| **No Change** | | | 3/9 (33) | 5/9 (56) | NR | 0.60 (0.20 to 1.79) |
| **Slightly Worse** | | | 1/9 (11) | 2/9 (22) | NR | 0.50 (0.05 to 4.58) |
| **Much Worse** | | | 0/9 (0) | 1/9 (11) | NR | NE |
| **Very Much Worse** | | | 0/9 (0) | 0/9 (0) | NR | NE |
| **Much Improved or Very Much Improved (reported by informant/carer)** | 24 | Gavrilova 2014[103,104c] | 49/80 (61.3) | 33/79 (41.8) | 0.0140 | 1.47 (1.07 to 2.01) |
| **Much Improved or Very Much Improved (reported by patient)** | | | 48/80 (60.1) | 37/79 (46.8) | 0.0961 | 1.28 (0.95 to 1.72) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Much Improved or Very Much Improved** | 24 | Kanowski | 29/106 (27) | 15/99 (15) | 0.003 | 1.81 (1.03 to 3.16) |
| **Slightly Improved** | | 1996[74,75d] | 41/106 (39) | 39/99 (39) | | 0.98 (0.70 to 1.38) |
| **No Change** | | | 33/106 (31) | 29/99 (29) | | 1.06 (0.70 to 1.61) |
| **Worsened or Much Worsened** | | | 3/106 (3) | 16/99 (16) | | 0.18 (0.05 to 0.58) |
| **ADCS-CGIC** | | | | | | |
| **Improvement or No Change** | 26 | Schneider | 104/170 (62) | 90/174 (55) | 0.20 | 1.18 (0.98 to 1.43) |
| **Worsening** | | 2005[116,117e] | 65/170 (39) | 75/174 (45) | | 0.89 (0.69 to 1.15) |

*Abbreviations*

AD = Alzheimer's disease, ADCS-CGIC = Alzheimer's Disease Cooperative Study Clinical Global Impression of Change, BCRS = Brief Cognitive Rating Scale, CGIC = Clinical Global Impression of Change, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, MCI = mild cognitive impairment, MID = multi-infarct dementia, MMSE = Mini-Mental State Examination, NE = not estimable, NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke - Alzheimer's Disease and Related Disorders Association, RR = relative risk.

*Notes*

a = Calculated by the authors of this report.

b = Included patients were those with mild to moderate Alzheimer-type senile dementia (mean BCRS score 3 to 5).

c = Included patients were those diagnosed with amnestic MCI in accordance with international consensus criteria.

d = Included patients were those with AD or MID according to DSM-III-R.

e = Included patients were those with a diagnosis of AD (DSM-IV) or probable AD (NINCDS-ADRDA) with a duration of dementia symptoms ≥6 months. Patients had a Modified Hachinski Ischemic Score <4 and an MMSE score of 10 to 24. In order to avoid an over-representation of very mildly impaired subjects, no more than one-third of the subjects enrolled at each site were allowed to have an MMSE score of ≥20. Note that this study also included a group treated with 120 mg ginkgo biloba; other dose comparisons are reported in relevant sections.

**Table 135: Continuous efficacy results comparing 240 mg ginkgo biloba vs. placebo in patients with MPD – global assessment of health status**

| Outcome[a] | Ginkgo biloba Mean (95% CI)[b] | Placebo Mean (95% CI)[b] | p-value | Effect MD (95% CI)[c] |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **CGIC** | 4.1 (3.9 to 4.3) | 4.5 (4.3 to 4.7) | 0.007 | -0.4 (-0.5 to -0.3) |

*Abbreviations*

AD = Alzheimer's disease, CGIC = Clinical Global Impression of Change, CI = confidence interval, DSM-III-R = Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised, MD = mean difference, MID = multi-infarct dementia.

*Notes*

a = All results in this table are from the same trial (Kanowski 1996[74,75]) and at the same timepoint (24 weeks). Included patients are those with AD or MID according to DSM-III-R.

b = Mean value at timepoint.

c = Reported by study authors. Adjusted estimate.

# G. Supplemental GRADE summary of findings tables

**Table 136. Supplemental summary of findings table: Mental performance deficits**

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits
**Setting:** Outpatient clinics and/or residential care
**Intervention:** 120-240 mg ginkgo biloba
**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Cognitive function 120 mg ginkgo biloba<br>assessed with: Change in ADAS-cog score<br>follow-up: 24 weeks<br>№ of participants: 789<br>(3 RCTs) | - | The mean change in ADAS-cog score in the placebo group ranged from **0 to 1.6** | - | MD **1.03 lower**<br>(1.66 lower to 0.39 lower) | ⨁⨁⨁◯<br>Moder-ate[a] | 120 mg ginkgo biloba may result in a slight improvement in cognitive func-tion, assessed with ADAS-cog score, compared to placebo. However, it is unlikely to be clinically meaningful given the MCID of 3 points. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Cognitive function: 120 mg ginkgo biloba assessed with: MMSE<br>follow-up: 24 weeks<br>№ of participants: 51<br>(1 RCT) | One trial reported cognitive function assessed with MMSE (MD -0.8 [95% CI -3.4 to 1.9]) and Seven Minute Test (MD 11.8 [95% CI -46.3 to 69.8]). There were no statistically significant differences between 240 mg ginkgo biloba and 4.5 mg rivastigmine. | | | | ⨁◯◯◯<br>Very low[a,d] | The evidence is very uncertain about the effect of 120 ginkgo biloba on cog-nitive function compared to 4.5 mg ri-vastigmine. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Cognitive function: 240 mg ginkgo biloba + 10 mg donepezil<br>follow-up: 22 weeks<br>№ of participants: 93<br>(1 RCT) | One trial reported no statistically significant differences in cognitive function assessed with the Clock-Drawing Test, SKT and verbal fluency test in the groups treated with 240 mg ginkgo biloba alone, 10 mg donepezil alone, or 240 mg ginkgo biloba combined with 10 mg donepezil.<br>240 mg Ginkgo biloba + 10 mg donepezil vs. 10 mg donepezil alone: CDT MD 0.1 (95% CI -0.6 to 0.8); SKT MD -1.0 (95% CI -2.7 to 0.7); Verbal fluency test MD 1.0 (95% CI -0.5 to 2.5).<br>240 mg Ginkgo biloba alone vs. 10 mg donepezil alone: CDT MD 0.7 (95% CI -0.3 to 1.7); SKT MD 0.7 (95% CI -1.3 to 2.7); Verbal fluency test MD 0.6 (95% CI -0.8 to 2.0) | | | | ⊕◯◯◯<br>Very low[d] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba + 10 mg donepezil on cognitive function compared to either ginkgo biloba or donepezil alone. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Behavioural changes: 120 mg ginkgo biloba assessed with: SCAG and NPI<br>follow-up: 24 weeks<br>№ of participants: 215<br>(2 RCTs) | One trial assessed behavioural changes with the SCAG Scale (MD 6.9 [95% CI -0.3 to 14.1]) and another study used NPI score (MD -4.512 [95% CI -9.176 to 0.152]). There were no statistically significant differences between 120 mg ginkgo biloba and placebo. | | | | ⨁◯◯◯<br>Very low[d] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on behavioural changes measured with SCAG and NPI, compared to placebo. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Behavioural changes: 240 mg ginkgo biloba + 10 mg donepezil<br>assessed with: Hamilton Depression Rating Scale and NPI<br>follow-up: 22 weeks<br>№ of participants: 93<br>(1 RCT) | One trial reported no statistically significant differences in behavioural changes, assessed with the Hamilton Depression Rating Scale and NPI score, in the groups treated with 240 mg ginkgo biloba alone, 10 mg donepezil alone, or 240 mg ginkgo biloba combined with 10 mg donepezil.<br>240 mg ginkgo biloba + 10 mg donepezil vs. 10 mg donepezil alone: HAMD MD -0.4 (95% CI -2.2 to 1.4); NPI MD -0.6 (95% CI -4.8 to 3.6).<br>240 mg ginkgo biloba alone vs. 10 mg donepezil alone: HAMD MD 0.0 (95% CI -1.6 to 1.6); NPI MD 1.2 (95% CI -2.7 to 5.1). | | | | ⊕◯◯◯<br>Very low[d] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba + 10 mg donepezil on behavioural changes compared to either ginkgo biloba alone or donepezil alone. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Functional status: 120 mg ginkgo biloba<br>assessed with: Change in GERRI score<br>follow-up: 24 weeks<br>№ of participants: 789<br>(3 RCTs) | - | The mean change in GERRI score in the placebo group ranged from **0 to 0.1** | - | MD **0.08 lower**<br>(0.16 lower to 0.0)<br>SMD **0.22 lower**<br>(0.47 lower to 0.02 higher) | ⨁⨁◯◯<br>Low[e] | 120 mg ginkgo biloba may result in a slight improvement in functional status assessed with GERRI score, com-pared to placebo. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Functional status: 240 mg ginkgo biloba + 10 mg donepezil<br>assessed with: Improve-ment in GBS-ADL and GBS total scores<br>follow-up: 22 weeks<br>№ of participants: 93<br>(1 RCT) | One trial reported no statistically significant differences in the propor-tions of participants with improvement in functional status, assessed with GBS-ADL and GBS total scores, in the groups treated with 240 mg ginkgo biloba alone, 10 mg donepezil alone, or 240 mg ginkgo biloba combined with 10 mg donepezil.<br>240 mg ginkgo biloba + 10 mg donepezil vs. 10 mg donepezil alone: GBS-ADL RR 1.13 (95% CI 0.59 to 2.16); GBS total RR 1.24 (95% CI 0.89 to 1.72).<br>240 mg ginkgo biloba alone vs. 10 mg donepezil alone: GBS-ADL RR 1.07 (95% CI 0.55 to 2.09); GBS total RR 1.12 (95% CI 0.78 to 1.60). | | | | ⊕◯◯◯<br>Very low[d] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba + 10 mg donepezil on functional status compared to either ginkgo biloba alone or donepezil alone. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | **Anticipated absolute effects (95% CI)** | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| HRQoL: 120 mg ginkgo biloba<br>assessed with: Nurem-berg Self-Assessment Scale and Quality of Life-Alzheimer's Disease score<br>follow-up: 12 to 24 weeks<br>№ of participants: 371<br>(2 RCTs) | Two trials found no statistically significant differences between 120 mg ginkgo biloba and placebo in HRQoL measured with different instru-ments.<br>One trial reported the proportion of participants with improvement in Nu-remberg Self-Assessment Scale after 12 weeks (RR 1.04 [95% CI 0.77 to 1.40]). The other trial reported change in carer-rated Quality of Life-Alzheimer's Disease score (MD -0.981 [95% CI-2.551 to 0.589]) and participant-rated QoL-AD at 24 weeks (MD -0.187 [95% CI -1.542 to 1.168]). | | | | ⊕◯◯◯<br>Very low[a,f] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on HRQoL, compared to placebo. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Adverse events: 120 mg ginkgo biloba<br>follow-up: 24 weeks<br>№ of participants: 885<br>(4 RCTs) | **RR 0.91**<br>(0.69 to 1.19) | 46.2% | **42.1%**<br>(55 to 31.9) | **4.2% fewer**<br>(14.3 fewer to 8.8 more) | ⨁⨁◯◯<br>Low[f] | There may be little to no difference in the risk of adverse events with 120 mg ginkgo biloba compared to pla-cebo but there is uncertainty due to the 95% confidence interval spanning appreciable benefit and appreciable harm. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Adverse events: 240 mg ginkgo biloba + 10 mg donepezil<br>follow-up: 22 weeks<br>№ of participants: 93<br>(1 RCT) | 10/30 (32%) of the 240 mg ginkgo biloba group had ≥1 adverse event, compared to 18/31 (56%) of the group taking 240 mg ginkgo biloba + 10 mg donepezil, and 24/32 (73%) of the 10 mg donepezil group. None of these differences are statistically significant. | | | | ⨁◯◯◯<br>Very low[d] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba + 10 mg donepezil on the risk of adverse events compared to either ginkgo biloba or donepezil alone. |
| Serious adverse events:<br>120 mg ginkgo biloba<br>follow-up: 52 weeks<br>№ of participants: 327<br>(1 RCT) | **RR 1.45**<br>(0.25 to 8.59) | 1.2% | **1.8%**<br>(10.7 to 0.3) | **0.6% more**<br>(0.9 fewer to 9.4 more) | ⨁◯◯◯<br>Very low[a,g] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on the risk of serious adverse events compared to placebo. |

**120-240 mg ginkgo biloba compared to Placebo or 4.5 mg rivastigmine or 10 mg donepezil for mental performance deficits**

**Patient or population:** Mental performance deficits

**Setting:** Outpatient clinics and/or residential care

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo or 4.5 mg rivastigmine or 10 mg donepezil

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **Placebo or 4.5 mg rivastig-mine or 10 mg donepezil** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Serious adverse events:<br>240 mg ginkgo biloba + 10 mg donepezil<br>follow-up: 22 weeks<br>№ of participants: 93<br>(1 RCT) | There were no serious adverse events with either 240 mg ginkgo biloba + 10 mg donepezil or ginkgo biloba or donepezil alone | | | | ⨁⨁◯◯<br>Low[g] | There may be little to no difference in serious adverse events with 240 mg ginkgo biloba + 10 mg donepezil compared to either ginkgo biloba or donepezil alone. |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive, CI = confidence interval, GBS-ADL = Gottfries-Bråne-Steen Scale, GERRI = Geriatric Evaluation by Relative's Rating Instrument, MD = mean difference, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatry Inventory, RCT = randomised controlled trial, RR = risk ratio, SCAG = Sandoz Clinical Assessment Geriatric, SKT = Syndrom-Kurz-Test

*Explanations*

a = Downgraded one level for risk of bias due to lack of reporting of randomisation and allocation concealment procedures.

b = Downgraded one level for imprecision due to 95% CI spanning the threshold between small and trivial/no effect (0.2 using SMD).

c = Downgraded one level for inconsistency due to high impact of heterogeneity leading to substantial differences in effect size.

d = Downgraded three levels for imprecision due to small numbers of participants and 95% CIs that span appreciably different effect estimates.

e = Downgraded two levels for imprecision due to 95% CI spanning the threshold between small and trivial/no effect (0.2 using SMD), as well as the threshold of no effect.

f = Downgraded two levels for imprecision due to the 95% CIs spanning appreciably different effect estimates.

g = Downgraded two levels for imprecision due to low event rate and 95% CIs spanning appreciably different effect estimates.

**Table 137. Supplemental summary of findings table: Peripheral arterial occlusive disease**

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Mobility: 120 mg ginkgo biloba<br>assessed with: MWD<br>follow-up: 24 weeks<br>№ of participants: 79<br>(1 RCT) | - | The mean mobility: 120 mg ginkgo biloba was **178** meters | - | MD **47 meters higher**<br>(23.6 lower to 117.6 higher) | ⊕◯◯◯<br>Very low[a,c] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on maximum walking distance compared to placebo. |
| Mobility: 240 mg ginkgo biloba<br>assessed with: MWT<br>follow-up: 24 weeks<br>№ of participants: 22<br>(1 RCT) | - | The mean mobility: 240 mg ginkgo biloba was **820** seconds | - | MD **263 seconds lower**<br>(671 lower to 145 higher) | ⊕◯◯◯<br>Very low[a,c] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba on MWT time compared to placebo |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Mobility: 240 mg ginkgo biloba<br>assessed with: PFWT<br>follow-up: 24 weeks<br>№ of participants: 22<br>(1 RCT) | - | The mean mobility: 240 mg ginkgo biloba was **484** seconds | - | MD **216 seconds fewer**<br>(919 fewer to 487 more) | ⊕◯◯◯<br>Very low[a,c] | The evidence is very uncertain about the effect of 240 mg ginkgo biloba on PFWD compared to placebo. |
| Peripheral blood circulation: 160 mg ginkgo biloba<br>assessed with: arterial pressure in Dorsalis Pedis<br>follow-up: 24 weeks<br>№ of participants: 33<br>(1 RCT) | - | The mean peripheral blood circulation: 160 mg ginkgo biloba was **93.3** mmHg | - | MD **16.1 mmHg lower**<br>(33 lower to 0.8 higher) | ⊕◯◯◯<br>Very low[b,c] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on arterial pressure in dorsalis pedis, compared to placebo. |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Peripheral blood circulation: 160 mg ginkgo biloba assessed with: arterial pressure in Tibialis Posterior<br>follow-up: 24 weeks<br>№ of participants: 33<br>(1 RCT) | - | The mean peripheral blood circulation: 160 mg ginkgo biloba was **97.3** mmHG | - | MD **17.6 mmHG lower**<br>(36.4 lower to 1.2 higher) | ⨁◯◯◯<br>Very low[b,c] | The evidence is very uncertain about the effect of 120 mg ginkgo biloba on arterial pressure in tibialis posterior, compared to placebo. |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| Peripheral blood circulation: 240 mg ginkgo biloba assessed with: post-exercise ABI<br>follow-up: 24 weeks<br>№ of participants: 22<br>(1 RCT) | - | The mean peripheral blood circulation: 240 mg ginkgo biloba was **0.5** | - | **0**<br>(0.7 lower to 0.6 higher) | ⨁◯◯◯<br>Very low[a,c] | 240 mg ginkgo biloba may have little to no effect on post-exercise ABI compared to placebo but the evidence is very uncertain. |
| Peripheral blood circulation: 240 mg ginkgo biloba assessed with: resting ABI<br>follow-up: 24 weeks<br>№ of participants: 22<br>(1 RCT) | - | The mean peripheral blood circulation: 240 mg ginkgo biloba was **0.7** | - | MD **0.1 lower**<br>(0.7 lower to 0.5 higher) | ⨁◯◯◯<br>Very low[a,c] | 240 mg ginkgo biloba may have little to no effect on resting ABI, compared to placebo, but the evidence is very uncertain. |

**120-240 mg ginkgo biloba compared to placebo for peripheral arterial occlusive disease**

**Patient or population:** Peripheral arterial occlusive disease

**Setting:** Outpatient clinics

**Intervention:** 120-240 mg ginkgo biloba

**Comparison:** Placebo

| Outcome<br>№ of participants<br>(studies) | Relative effect<br>(95% CI) | Anticipated absolute effects (95% CI) | | | Certainty | What happens |
|---|---|---|---|---|---|---|
| | | **placebo** | **120-240 mg ginkgo biloba** | **Difference** | | |
| HRQoL - not reported | - | - | - | - | - | |

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

ABI – ankle-brachial index, CI = confidence interval, MD = mean difference, MWD = maximum walking distance, MWT = maximum walking time, PFWD = pain-free walking distance, PFWT = pain-free walking distance time, RCT – randomised controlled trial, RR = risk ratio

*Explanations*

a = Downgraded one level for risk of bias due to unclear reporting of randomisation and allocation concealment procedures.

b = Downgraded two levels for risk of bias due to absence of reporting of randomisation and allocation concealment and unclear reporting of who was blinded to treatment allocation.

c = Downgraded three levels for imprecision due to low numbers of participants (<100) and a wide 95% CI that spans appreciable benefit and appreciable harm.

**Table 138. Supplemental summary of findings table: Tinnitus**

**Ginkgo biloba compared to placebo or pentoxifylline or a hearing aid for tinnitus**

**Patient or population:** Tinnitus
**Setting:** Outpatient clinics
**Intervention:** 120 mg ginkgo biloba
**Comparison: P**lacebo

| Outcome<br>№ of participants<br>(studies) | **Impact** | Certainty |
|---|---|---|
| Level of hearing loss assessed with: tonal audiometric measurement<br>Follow-up: 12 weeks<br>№ of participants: 73<br>(1 RCT) | One study (73 participants) reported no statistically significant difference between 120 mg ginkgo biloba and placebo in the level of hearing loss at 3 months' follow-up. | ⊕◯◯◯<br>Very low[a,b] |
| HRQoL - not reported | | - |

**GRADE Working Group grades of evidence**
**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

*Abbreviations*

HRQoL = health-related quality of life, RCT = randomised controlled trial.

*Explanations*

a = Downgraded two levels for imprecision due to low numbers of participants (<100).

b = Downgraded two levels for risk of bias due to unclear reporting of randomisation, allocation concealment, and blinding procedures.