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# Efficacy and Adverse Effects of *Ginkgo Biloba* for Cognitive Impairment and Dementia: A Systematic Review and Meta-Analysis

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**Abstract**.
**Background:** Research into *Ginkgo biloba* has been ongoing for many years, while the benefit and adverse effects of *Ginkgo biloba* extract EGb761 for cognitive impairment and dementia has been discussed controversially.
**Objective**: To discuss new evidence on the clinical and adverse effects of standardized *Ginkgo biloba* extract EGb761 for cognitive impairment and dementia.
**Methods:** MEDLINE, EMBASE, Cochrane, and other relevant databases were searched in March 2014 for eligible randomized controlled trials of *Ginkgo biloba* EGb761 therapy in patients with cognitive impairment and dementia.
**Results:** Nine trials met our inclusion criteria. Trials were of 22–26 weeks duration and included 2,561 patients in total. In the meta-analysis, the weighted mean differences in change scores for cognition were in favor of EGb761 compared to placebo (−2.86, 95%CI −3.18; −2.54); the standardized mean differences in change scores for activities in daily living (ADLs) were also in favor of EGb761 compared to placebo (−0.36, 95%CI −0.44; −0.28); Peto OR showed a statistically significant difference from placebo for Clinicians' Global Impression of Change (CGIC) scale (1.88, 95%CI 1.54; 2.29). All these benefits are mainly associated with EGb761 at a dose of 240 mg/day. For subgroup analysis in patients with neuropsychiatric symptoms, 240 mg/day EGb761 improved cognitive function, ADLs, CGIC, and also neuropsychiatric symptoms with statistical superiority than for the whole group. For the Alzheimer's disease subgroup, the main outcomes were almost the same as the whole group of patients with no statistical superiority. Finally, safety data revealed no important safety concerns with EGb761.
**Conclusions:** EGb761 at 240 mg/day is able to stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, especially for patients with neuropsychiatric symptoms.

Keywords: Adverse effects, cognitive impairment, dementia, efficacy, *Ginkgo biloba*, meta-analysis, systematic review

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## INTRODUCTION

With an ever growing aging society, senile dementia is gradually turning into a serious social issue [1, 2]. The most common etiologies for dementia are presently attributed to progressive neurodegenerative and vascular diseases, either alone or in combination. And the core syndrome of dementia, which serves as a key diagnostic feature, is cognitive impairment. Therefore, low-risk strategies to stabilize or slow decline in cognitive impairment and dementia are emphasized [3, 4].

*Ginkgo biloba* is one of the oldest living tree species on the planet. The standardized *Ginkgo biloba* extract EGb761, containing 22–27% flavonol glycosides, 5–7% terpene lactones, and less than 5 ppm ginkgolic acids, is one of the most widely used herbal remedies for dementia and cognitive impairment, and remains one of the best evaluated and characterized extracts [5]. Although the detailed molecular basis is not yet fully understood, there is evidence of neuroprotective properties, including the ability to reduce amyloid-β (Aβ) aggregation and Aβ toxicity [6–8]. EGb761 is a polyvalent radical scavenger that improves mitochondrial function [9–11], decreases blood viscosity, and enhances microperfusion [12]. Several studies on rat models also showed that EGb761 improves neurotransmission, in particular glutamatergic [13], dopaminergic, and cholinergic systems [14, 15]. Therefore, standardized *Ginkgo biloba* extract EGb761 could be considered as a multi-target drug.

Most previous reviews of randomized controlled trials (RCTs) have shown inconsistent results and fail to draw firm conclusions whether *Ginkgo biloba* has patient-relevant benefits in people with a diagnosis of cognitive decline or dementia [16, 17]. These trials mainly tested the same standardized preparation of *Ginkgo biloba*, EGb761, at different doses. From our point of view, a major limitation of the available Cochrane Review on the effectiveness of *Ginkgo biloba* is the combined evaluation of the patients of self-reported cognitive complaint with uncertain diagnostic criteria. Nowadays, new studies have been published and point out that EGb761 seem to be particularly useful when dementia is accompanied by neuropsychiatric symptoms (NPS) [18–20]. The similar profile of effects is further found in mild cognitive impairment (MCI) patients with NPS [21]. Therefore, we performed a novel systematic review to evaluate the clinical evidence on the effects and adverse effects of standardized *Ginkgo biloba* extract EGb761 in cognitive impairment as well as dementia covering a variety of outcome domains. Further subgroup analyses were performed in patients with NPS or only in Alzheimer's dementia. Meanwhile, all meta-analyses results for different EGb761 doses were analyzed separately, before combining all doses.

## METHODS

### *Search strategy*

We searched the MEDLINE, EMBASE, PsycINFO, CINAHL, Cochrane Database of Systematic Reviews, and the Cochrane Controlled Trials Register up to March 2014 with the terms Ginkgo* or Gingko* or EGB761 or "EGB 761" or EGB-761. The search terms used to identify relevant controlled trials on dementia, Alzheimer's disease (AD), and cognitive impairment for the Cochrane Controlled Trials Register. Other sources searched were conference proceedings, abstracts, thesis dissertations, poster presentations, and materials from professional society meetings.

### *Selection criteria and data retrieval*

Trials that were included met the following criteria: (1) double-blind, parallel-group, placebo-controlled, with random assignment to a standardized *Ginkgo biloba* extract EGb761; (2) inclusion of patients who have a diagnosis of AD, vascular dementia (VaD), or mixed dementia according to internationally valid diagnostic criteria for the dementia diagnosis, including the International Classification of Diseases (ICD) [22], the Diagnostic and Statistical Manual of Mental Disorders (DSM) [23], the National Institute of Neurological and Communicative Disorders and Stroke, Alzheimer's Disease and related Disorders Association (NINCDS-ADRDA) [24], or the National Institute for Neurological Disorders and Stroke and Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) [25] criteria; inclusion of patients suffering from age-associated memory impairment according to the diagnostic criteria proposed by Crook et al. [26]; inclusion of patients suffering from MCI according to international consensus criteria proposed by Winblad et al. [27]; (3) inclusion of treatments which last 22–26 weeks, contain a number of participants of more than ten per group, and at least one measure reflecting the following: cognition, function, behavior or global assessment of change. Studies with fatal flaws in study design or data analysis were excluded, as were trials whose data were not readily available.

We obtained the following baseline variables from each study: diagnostic criteria, experimental design, medication doses, sample size, age, gender, trial durations, disease severity, baseline cognitive scores (Mini-Mental State Examination), primary and secondary outcomes, adverse events, and all cause dropouts during the trials. We recorded intention-to-treat population results if available, and if not, then extracted observed case or per protocol outcome. Data abstraction was accomplished under the cooperation between two investigators. Any discrepant data were reviewed by discussion with other team members or contact with original investigators.

Measurement scales used in the trials were different from each other. Hence, we recorded measurement scales according to the general domain being assessed: cognition, function, behavior, and global assessment of change. The following rating scales were accepted for clinical outcomes: (1) Cognition: Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) [28], Syndrom- Kurz test (SKT) [29]; (2) Function: GERRI [30], Nürnberger Alters-Alltagsaktivitäten-Skala (NAA) and Nürnberger Alters-Beobachtungsskala (NAB) [31], GBS-ADL (Gottries-Bråne-Steen-Activities of daily living scale) [32], ADL-IS (Alzheimer's Disease Activities-of-Daily-Living International Scale) [33]; (3) Behavior: Neuropsychiatric Inventory (NPI) [34]; (4) Global assessment: Clinical Global Impression (CGI) [35]; Clinical Global Impression of Change (CGIC) [36]. In addition, we recorded the discontinuations from the trials for adverse events to assess the risks of these drugs.

### *Statistical analysis*

The outcomes and the numbers of patients for each trial were statistically combined by use of the fixed effects model by use of Review Manager Version 5.2 software. For continuous data collected using the same measurement scale, we calculated a weighted mean differences (WMD) and its 95% confidence intervals (CIs) for changes from baseline. For continuous data collected using the different measurement scale, we calculated a standardized mean differences (SMD) and its 95% CIs for changes from baseline. For dichotomous clinical outcomes, we conducted an analysis of the odds ratio (OR) with 95% CI and $p$ values to assess the efficacy and safety of the study drug. For binary outcomes, the endpoint itself is of interest and the Peto method of the typical odds ratio is used.

We quantitatively tested the clinical, statistical, and methodological heterogeneity between the trials using the visual inspection, and a $\chi^2$-test combined with the $I^2$ method. $I^2$ approximates the proportion of total variation in the effect size estimates that is due to heterogeneity rather than sampling error. A $\alpha$ error $p < 0.20$ and an $I^2$ statistic greater than 50% was taken as indicators of heterogeneity of outcomes. Subgroup analyses based on medication doses were done for there still were a few differences between groups of varied doses. To establish the robustness of the primary outcome, we used a fixed effects model, and conducted sensitivity analyses. A two-tailed $p$-value <0.05 was considered significant for all the analyses (except for heterogeneity).

## RESULTS

### *Literature search findings*

Our literature search in MEDLINE, EMBASE, PsycINFO, CINAHL, and Cochrane revealed 126 publications that were included in the full-text screening. Only 15 publications reporting nine individual studies, all using the standardized *Ginkgo biloba* extract EGb761 fully met our inclusion criteria.

### *Characteristics of included trials*

In total, 2,561 patients were included and treated. Eight studies included patients with AD. Among them, six studies also included patients with VaD or mixed dementia, and one study included a majority of participants with age-associated memory impairment [37]. Another study only included patients with MCI [21]. In addition, five studies included patients with NPS [18, 19, 21, 38, 39]. Overall, two studies were performed in the US, two in Ukraine, two in Russia or Russian-speaking countries, whereas one study was performed in Germany, Italy, and the Netherlands, respectively. The allocation concealment and randomization methods in all the trials were adequate. Trial durations ranged from 22 weeks to 26 weeks. Two trials were dose ranging [37, 38]; rest of trials used fixed doses. Characteristics of patients and design are summarized in Table 1.

### *Bias risk assessment*

Reporting of allocation concealment and randomization methods was different among trials. Seven reports of studies explicitly mentioned use of placebo and drug pills or capsules that were visually identical for allocation concealment. The randomization was

Table 1
Summary of *Ginkgo biloba* EGb761 trials in patients with dementia and cognitive impairment

| Study | Criteria | Patients | Groups (*n*) | Age, y (SD) | Gender (% men) | Disease severity | Baseline MMSE (SD) | Duration (weeks) | Outcomes | | | | Dropout rate (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Cognition | Function | Behavior | Global | |
| Kanowski et al., [41, 51] | DSM-III-R | AD or VaD | 240 mg daily (106) | 72 (10) | 32 | Mild to moderate | 21.6 (2.6) | 24 | SKT ADAS-cog | NAB | – | CGI | 25.5 |
| | | | Placebo (99) | 72 (10) | 29 | | 21.5 (2.4) | | | | | | 22.2 |
| | | Only AD | 240 mg daily (79) | 72 (10) | 29 | Mild to moderate | 21.5 (2.3) | 24 | SKT ADAS-cog | NAB | – | CGI | – |
| | | | Placebo (79) | 72 (10) | 27 | | 21.6 (2.7) | | | | | | – |
| Le Bars et al., [40] | DSM-III-R ICD-10 | AD or VaD | 120 mg daily (155) | 69 (10) | 49 | Mild to severe | 21.1 (5.8) | 26 | ADAS-cog | GERRI | – | CGIC | 21.3 |
| | | | Placebo (154) | 69 (10) | 44 | | 21.2 (5.5) | | | | | | 20.8 |
| | | Only AD | 120 mg daily (120) | 68 (10) | 46 | Mild to severe | 21.1 (5.9) | 26 | ADAS-cog | GERRI | – | CGIC | – |
| | | | Placebo (116) | 68 (11) | 38 | | 21.3 (5.6) | | | | | | – |
| Mazza et al., [42] | DSM-IV | AD | 160 mg daily (25) | 66.2 (6) | 48 | Mild to moderate | 18.8 (3.6) | 24 | SKT | – | – | CGI | 20.0 |
| | | | Placebo (26) | 69.8 (3) | 39 | | 18.8 (3.6) | | MMSE | | | | 23.1 |
| van Dongen et al., [37] | DSM-III-R ICD-10 | AD or VaD AAMI | 160/240 mg daily (79) | 82.6 (5.1) | 14 | Mild to moderate | 18.0 (4.9) | 24 | SKT | NAA | – | CGI | 16.9 |
| | | | Placebo(44) | 82.5 (5.8) | 18 | | 18.7 (4.6) | | | | | | 8.3 |
| Schneider et al., [38] | DSM-IV NINCDS/ADRDA | AD | 240 mg daily (170) | 78.1 (7.0) | 44 | Mild to moderate | 17.9 (4.0) | 26 | ADAS-cog | GERRI | – | CGIC | 17.6 |
| | | | 120 mg daily (169) | 78.6 (7.0) | 50 | | 18.2 (4.1) | | | | | | 20.1 |
| | | | Placebo (174) | 77.5 (7.4) | 48 | | 18.2 (4.1) | | | | | | 22.4 |
| | | AD with NPS | 240 mg daily (42) | 79.3 (6.6) | 33 | Mild to moderate | 17.4 (3.8) | 26 | ADAS-cog | – | – | CGIC | – |
| | | | 120 mg daily (51) | 79.6 (7.3) | 37 | | 17.9 (4.5) | | | | | | – |
| | | | Placebo (47) | 77.2 (7.8) | 32 | | 17.6 (3.9) | | | | | | – |
| Napryeyenko et al., [39, 45] | NINCDS/ADRDA NINDS/AIREN | AD or VaD with NPS | 240 mg daily (198) | 65 (8) | 28 | Mild to moderate | 14–25 | 22 | SKT | GBS-ADL | NPI | GBS | 2.0 |
| | | | Placebo (197) | 63 (8) | 28 | | 14–25 | | | | | | 2.5 |
| | | Only AD with NPS | 240 mg daily (104) | 66 (8) | 33 | Mild to moderate | 14–25 | 22 | SKT | GBS-ADL | NPI | GBS | 1.9 |
| | | | Placebo (110) | 64 (8) | 29 | | 14–25 | | | | | | 3.6 |
| Ihl et al., [19, 44] | NINCDS/ADRDA NINDS/AIREN | AD or VaD with NPS | 240 mg daily (202) | 65 (10) | 31 | Mild to moderate | 14–25 | 24 | SKT | ADL-IS | NPI | CGIC | 7.9 |
| | | | Placebo (202) | 65 (9) | 34 | | 14–25 | | | | | | 5.9 |
| | | Only AD with NPS | 240 mg daily (163) | 64.9 (9.5) | 33 | Mild to moderate | 14–25 | 24 | SKT | ADL-IS | NPI | CGIC | – |
| | | | Placebo (170) | 64.2 (8.7) | 35 | | 14–25 | | | | | | – |
| Herrschaft et al., [18] | NINCDS/ADRDA NINDS/AIREN | AD or VaD with NPS | 240 mg daily (200) | 65.1 (8.8) | 31 | Mild to moderate | 14–25 | 24 | SKT | ADL-IS | NPI | CGIC | 3.4 |
| | | | Placebo (202) | 64.9 (9.4) | 31 | | 14–25 | | | | | | 2.4 |
| Gavrilova et al., [21] | International consensus criteria* | aMCI with NPS | 240 mg daily (80) | 65 (7) | 28 | Mild | 25.6 (1.3) | 24 | TMT | – | NPI | CGI | 2.5 |
| | | | Placebo (79) | 63 (7) | 16 | | 25.7 (1.5) | | | | | | 3.8 |

AAMI, age-associated memory impairment; AD, Alzheimer's disease; ADAS-cog, Alzheimer's Disease (AD) Assessment Scale, cognitive subscale; ADL-IS, Alzheimer's Disease Activities-of-Daily-Living International Scale; CGI, Clinical Global Impression; CGIC, Clinical Global Impression of Change; GBS-ADL, Gottries-Bråne-Steen-Activities of daily living scale; GERRI, Geriatric Evaluation by Relative's Rating Instrument; MMSE, Mini-Mental State Examination; NAA, Nürnberger Alters-Alltagsaktivitäten-Skala; NAB, Nurnberger-Alters-Beobachtungs-Skala; NPI, Neuropsychiatric Inventory; NPS, neuropsychiatric symptoms; SKT, Syndrom-Kurz test; TMT, Trail-Making Test; VaD, vascular dementia. *Criteria proposed by Winblad et al. [27]. – Not available.

conducted according to a computerized randomization schedule among these trials. Moreover, primary outcomes were analyzed by intention-to-treat data in trials, thus minimizing effects of attrition bias.

*Efficacy*

*Cognitive function:* In all included studies ($n = 9$), cognition was evaluated. Two studies used the ADAS-cog [38, 40], six studies used the SKT [18, 19, 37, 39, 41, 42], and only one study used the Trail-Making Test [21]. In order to facilitate the comparison of the cognitive functioning measured using different scales, we provided an estimation of ADAS-cog scores derived from measured SKT scores. This transformation was performed by using the regression equation ADAS-cog = 5.3 + 1.3* SKT found in a cross-sectional study of Ihl et al. [43], and thus meta-analyses of ADAS-Cog scores in eight trials were performed. There was significant difference in favor of EGb761 for the 240 mg/day (WMD −3.19, 95% CI −3.56 to −2.83, $p < 0.00001$, 6 studies) or 160 mg/day (WMD −3.96, 95% CI −5.13 to −2.80, $p < 0.00001$, 2 studies), and all doses pooled (WMD −2.86, 95% CI −3.18 to −2.54, $p < 0.00001$, 8 studies) (Fig. 1a). However, heterogeneity was substantial ($I^2 = 96\%$). There were quite different treatment effects in Napryeyenko et al. [39] and Mazza et al. [42] compared with all other trials. By removing these two studies from the analysis, the heterogeneity was reduced to 81%; the results still showed significant difference between EGb761 and placebo for the 240 mg/day dose and for all doses pooled.

Four studies with separate analyses of 240 mg/day EGb761 for patients with NPS could be included in the subgroup evaluation. For this subgroup, the change scores of ADAS-cog were greater for ginkgo than for placebo, with WMD = −3.95 (95% CI −4.36 to −3.55, $p < 0.00001$, 4 studies) (Fig. 1b). Also, there was significant heterogeneity in this subgroup ($I^2 = 96\%$), which was reduced to 0% by removing Napryeyenko et al. [39] from the analysis.

A secondary objective of meta-analysis was to examine the results for AD subgroup separately. For AD subgroup, the change scores of ADAS-cog were similar with the whole group, showing a significant effect of EGb761 (Fig. 1c).

*Functional outcome:* We report results from seven studies for activities of daily living (ADLs). Two studies [38, 40] used the GERRI, two studies [18, 19] used the ADL-IS, one study [37] used the NAA, one trial [41] used the NAB, and one study [39] used the GBS-ADL subscale. The results showed benefit for 240 mg/day EGb761 compared with placebo (SMD −0.45, 95%CI −0.55 to −0.36, $p < 0.00001$, 6 studies), and for all doses pooled (SMD −0.36, 95% CI −0.44 to −0.28, $p < 0.00001$, 7 studies) (Fig. 2a). There was significant heterogeneity within the 240 mg/day dose studies ($I^2 = 92\%$), which was reduced to 75% by removing Napryeyenko et al. [39] from the analysis, and then the results also showed significant difference between EGb761 and placebo for the 240 mg/day dose and for all doses pooled.

For patients with NPS subgroup, the standardized change scores were greater for 240 mg/day EGb761 than for placebo, with SMD = −0.67 (95% CI −0.78 to −0.55, $p < 0.00001$, 3 studies) (Fig. 2b). Significant heterogeneity ($I^2 = 91\%$) was reduced to 0% by removing Napryeyenko et al. [39] from the analysis in this subgroup.

For the AD subgroup, the standardized change scores for ADLs outcomes were similar with the whole group, and there is a significant effect of EGb761 for the 240 mg/day dose and all doses pooled (Fig. 2c).

*Global assessment:* For global assessment of change, the CGI or CGIC scale was used in eight trials, and dichotomized between participants who showed clinical global improvement or were unchanged and those who were worse. Because suitable data in 3 trials [21, 37, 42] were not readily available, meta-analyses for global assessment in five trials [18, 19, 38, 40, 41] were performed. There is benefit associated with 240 mg/day EGb761 (565/678 compared with 457/677, OR 2.47, 95% CI 1.91 to 3.20, $p < 0.00001$, 4 studies) or all doses pooled (763/1001 compared with 641/1006, OR 1.88, 95% CI 1.54 to 2.29, $p < 0.00001$, 5 studies), but not for the 120 mg/day dose (Fig. 3a). Heterogeneity was relatively high within the 240 mg/day dose ($I^2 = 80\%$) and all doses pooled studies ($I^2 = 81\%$).

For the patients with NPS subgroup, there are benefits associated with 240 mg/day EGb761 (383/444 compared with 302/451, OR 3.03, 95% CI 2.21 to 4.16, $p < 0.00001$, 3 studies) (Fig. 3b). Heterogeneity was slightly lower in this subgroup ($I^2 = 64\%$).

For the AD subgroup, the Peto OR for global assessment was similar within the whole group, and there were benefits associated with EGb761 for the 240 mg/day dose or all doses pooled (Fig. 3c).

Behavioral symptoms: For behavioral outcome, only four studies in the patients with NPS subgroup used the NPI for analysis [18, 19, 21, 39]; and there was a significant difference in favor of 240 mg/day EGb761 (WMD −4.82, 95% CI −5.44 to −4.20, $p < 0.00001$, 4 studies) (Fig. 4). There was significant heterogeneity

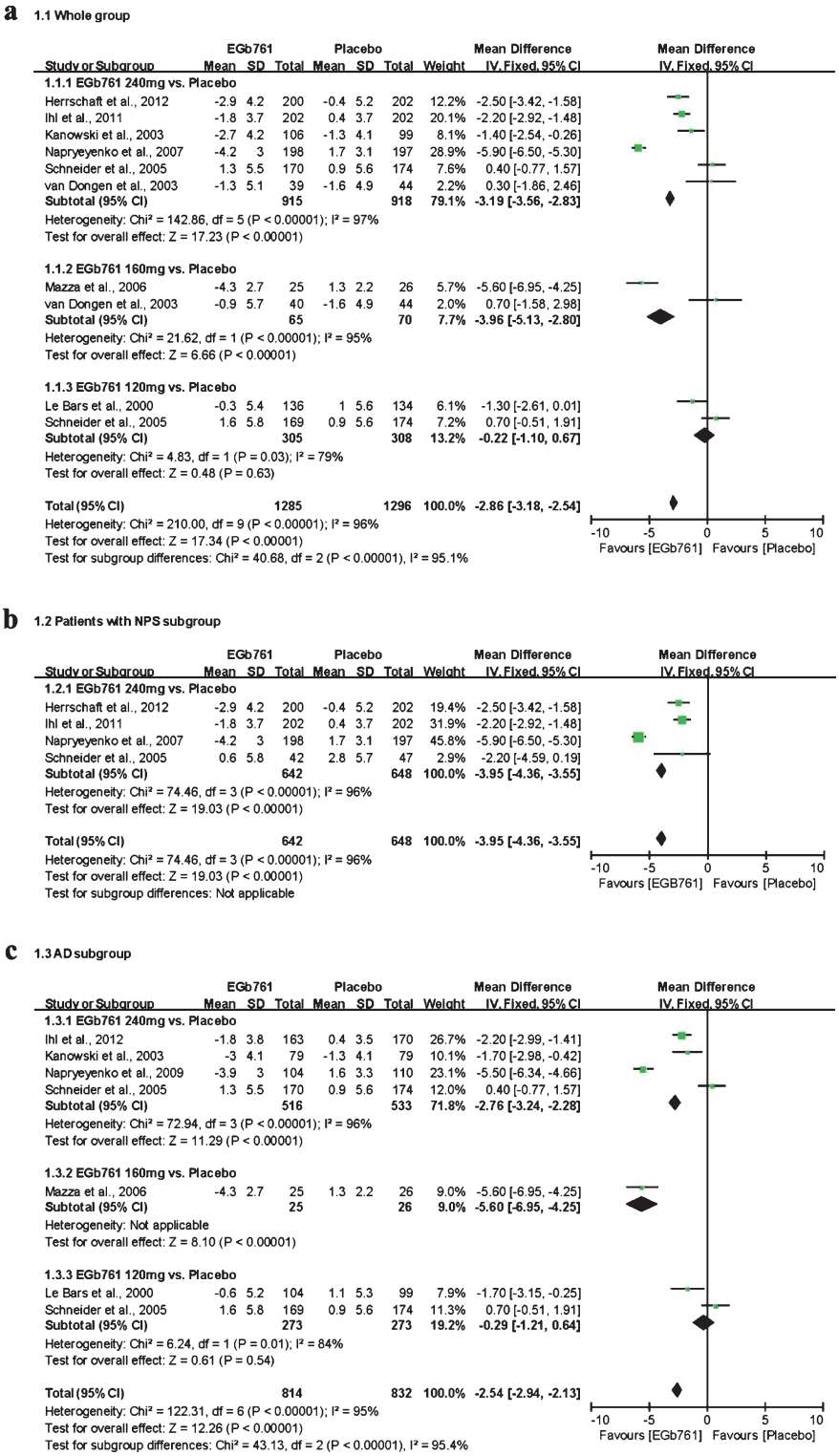



Fig. 1. Comparison EGb761 versus placebo, Cognition outcome, ADAS-Cog (change from baseline after treatment of 22–26 weeks) in whole group (a), in patients with NPS subgroup (b), and in AD subgroup (c). Equation for the derivation of ADAS-cog values from SKT values: ADAS-cog = 5.3 + 1.3* SKT.

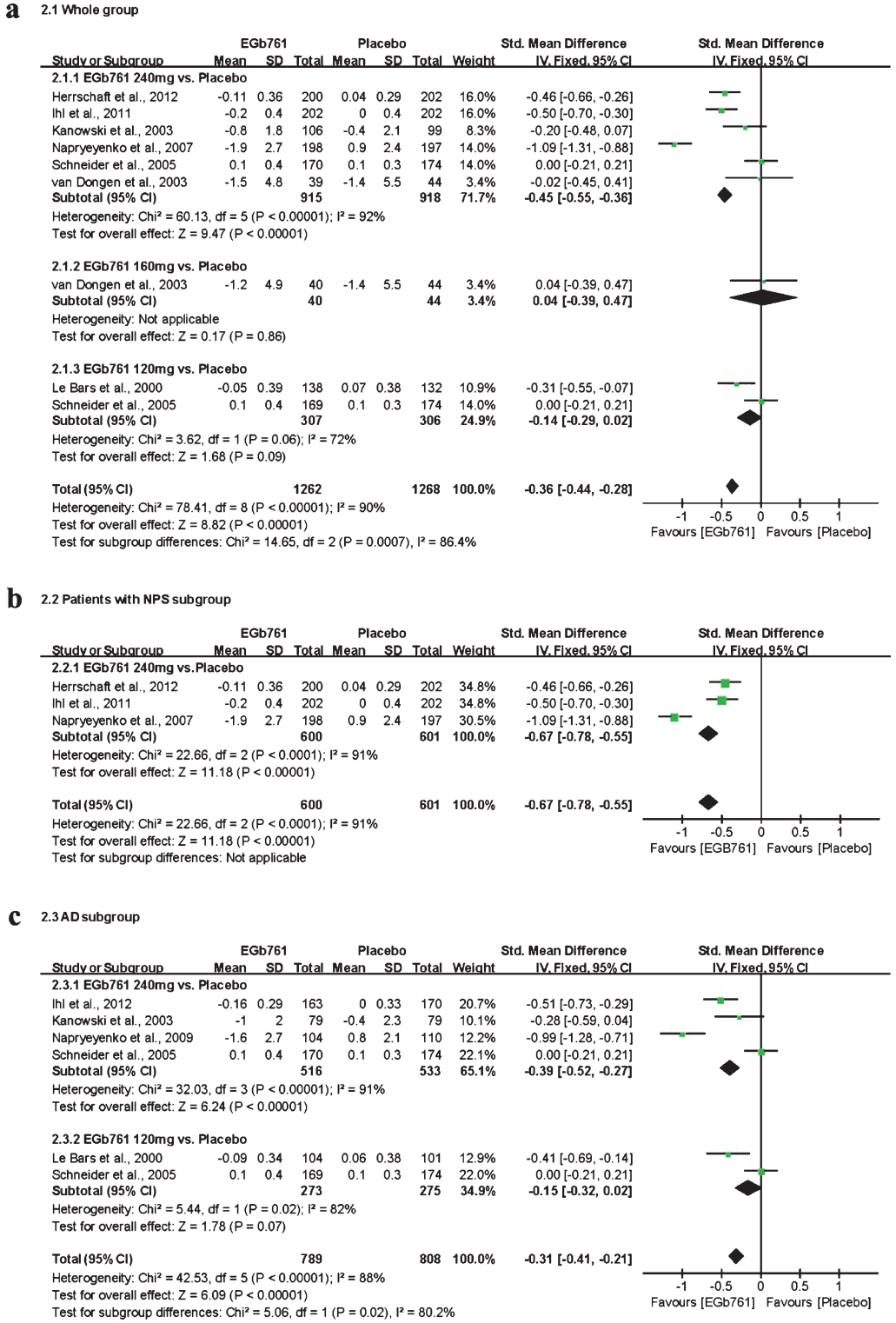



Fig. 2. Comparison EGb761 versus placebo, Outcome of Activities of Daily Living (change from baseline after treatment of 22–26 weeks) in whole group (a), in patients with NPS subgroup (b), and in AD subgroup (c).

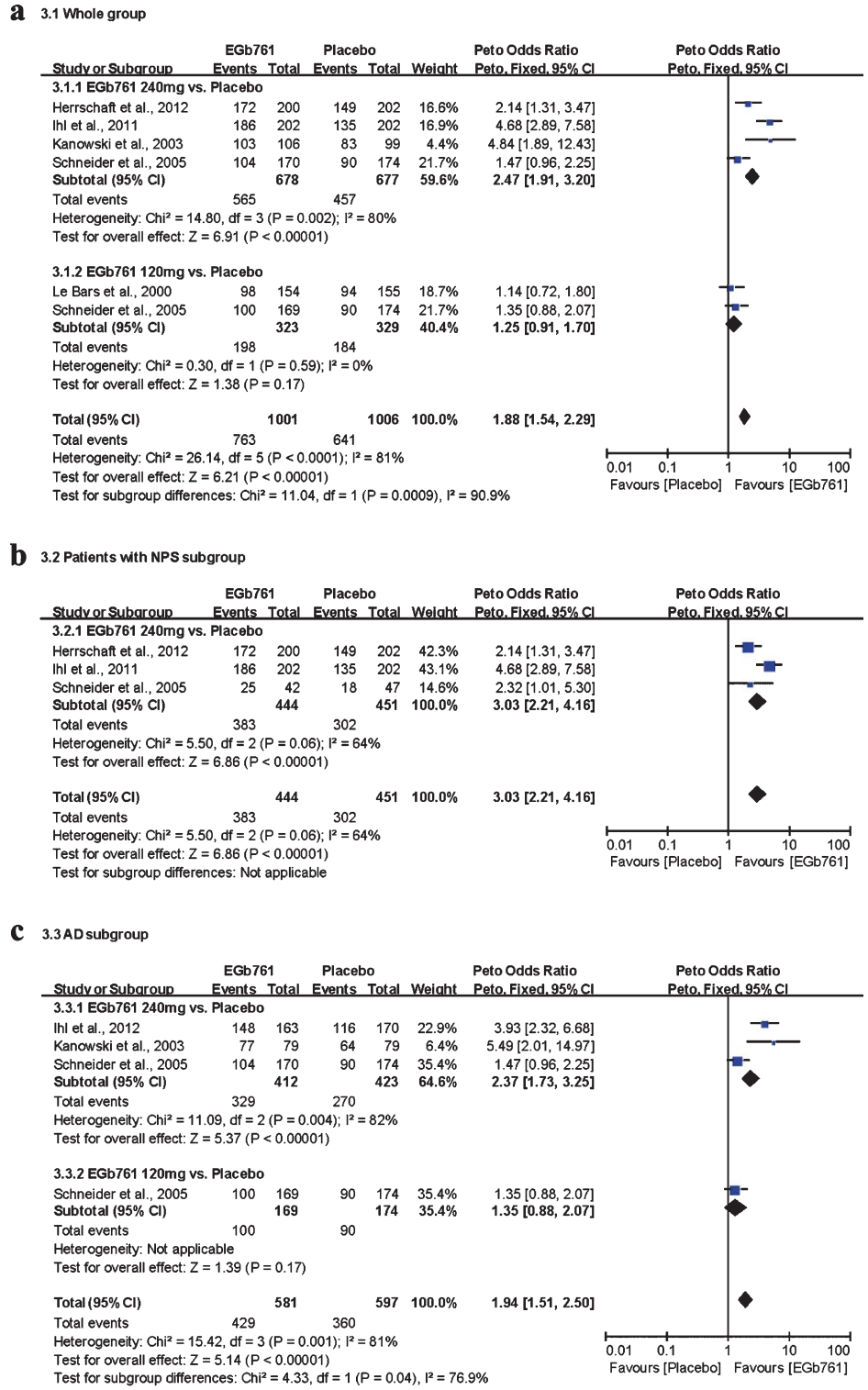



Fig. 3. Comparison EGb761 versus placebo, Global change outcome (CGIC) (numbers improved or unchanged compared with baseline) after treatment of 22–26 weeks in whole group (a), in patients with NPS subgroup (b), and in AD subgroup (c).

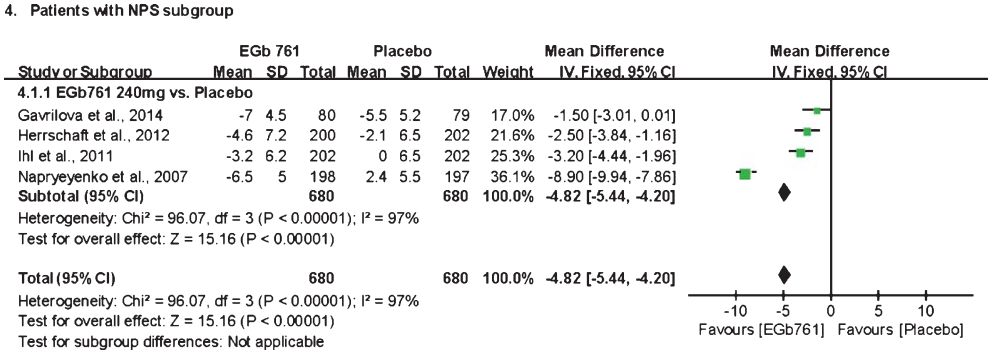



Fig. 4. Comparison EGb761 versus placebo, NPI scale (change from baseline after treatment of 22–24 weeks) in patients with NPS subgroup.

($I^2 = 97\%$), which was reduced to 31% by removing Napryeyenko et al. [39] from the analysis, and then the results also showed significant difference between 240 mg/day EGb761 and placebo (WMD −2.51, 95% CI −3.29 to −1.73, $p < 0.00001$, 3 studies).

*Safety and tolerability*

There were no significant differences between EGb761 and placebo in the proportion of participants experiencing any adverse events or serious adverse events for whole group and subgroup analysis (Figs. 5 and 6). Among them, there was a significant difference, in favor of 240 mg/day EGb761 compared with placebo for participants experiencing the adverse events in AD subgroup (297/443 compared with 340/457) (OR 0.70, 95% CI 0.52 to 0.93, $p = 0.02$, 3 studies [38, 44, 45]) (Fig. 5c). Across all included studies, there were significant differences, in favor of 240 mg/day EGb761 compared with placebo for four causes of adverse events: dizziness (46/781 compared with 86/783) (OR 0.50, 95% CI 0.35 to 0.73, $p = 0.0003$, 4 studies [18, 19, 38, 39]), tinnitus (18/575 compared with 45/578) (OR 0.38, 95% CI 0.22 to 0.67, $p = 0.0008$, 3 studies [19, 38, 39]), headache (120/861 compared with 158/863) (OR 0.70, 95% CI 0.53 to 0.92, $p = 0.009$, 5 studies [18, 19, 21, 38, 39]), and angina pectoris (26/406 compared with 47/404) (OR 0.51, 95% CI 0.31 to 0.85, $p = 0.010$, 2 studies [19, 39]).

## DISCUSSION

We have obtained the treatment effects of 2561 patients with dementia and cognitive impairment from 9 trials. Meta-analyses of these placebo-controlled trials of 22–26 weeks duration show the overall benefits of EGb761 for stabilizing or slowing decline in cognition, function, behavior and clinical global change of patients with dementia and cognitive impairment. In-depth subgroup analyses reveal the differences in effects of different doses, as all these clinical benefits of EGb761 are mainly associated with the 240 mg/day dose. In AD subgroup analysis, the advantage of EGb761 compared to placebo was similar with the whole group with no statistical superiority. More importantly, our results show obvious benefits of EGb761 at a dose of 240 mg/day in the treatment of dementia and cognitive impairment with NPS. The safety and tolerability of EGb761 is excellent. There are only few and minor adverse events that are perfectly balanced between EGb761 and placebo, which is in line with findings from former reviews [16] and long-standing clinical experience.

The duration of RCTs of *Ginkgo biloba* varies from three weeks to 52 weeks, with the majority being of 22–26 weeks. Because the length of treatment as well as methodological factors may be stronger outcome modifiers, our meta-analyses only include the trials ranged from 22 weeks to 26 weeks duration in patients with a validated diagnosis of dementia and cognitive impairment. Our results are consistent with the data of Weinmann et al. [17] and Brondino et al. [20] indicating an advantage for *Ginkgo biloba* compared with placebo in dementia.

Meanwhile, we perform a more comprehensive subgroup analysis covering a variety of outcome domains. Due to our inclusion criteria, the overall methodological quality of studies was relatively higher than in the Cochrane Review [16], which included many older studies without validated diagnoses of dementia and cognitive impairment, less rigorous randomization and allocation schemes and, therefore, a higher risk of bias. Moreover, we identified and included three recently performed trials [18, 19, 21]. These trials showed a considerable superiority of 240 mg/day EGb761 in cognitive impairment or dementia accompanied by

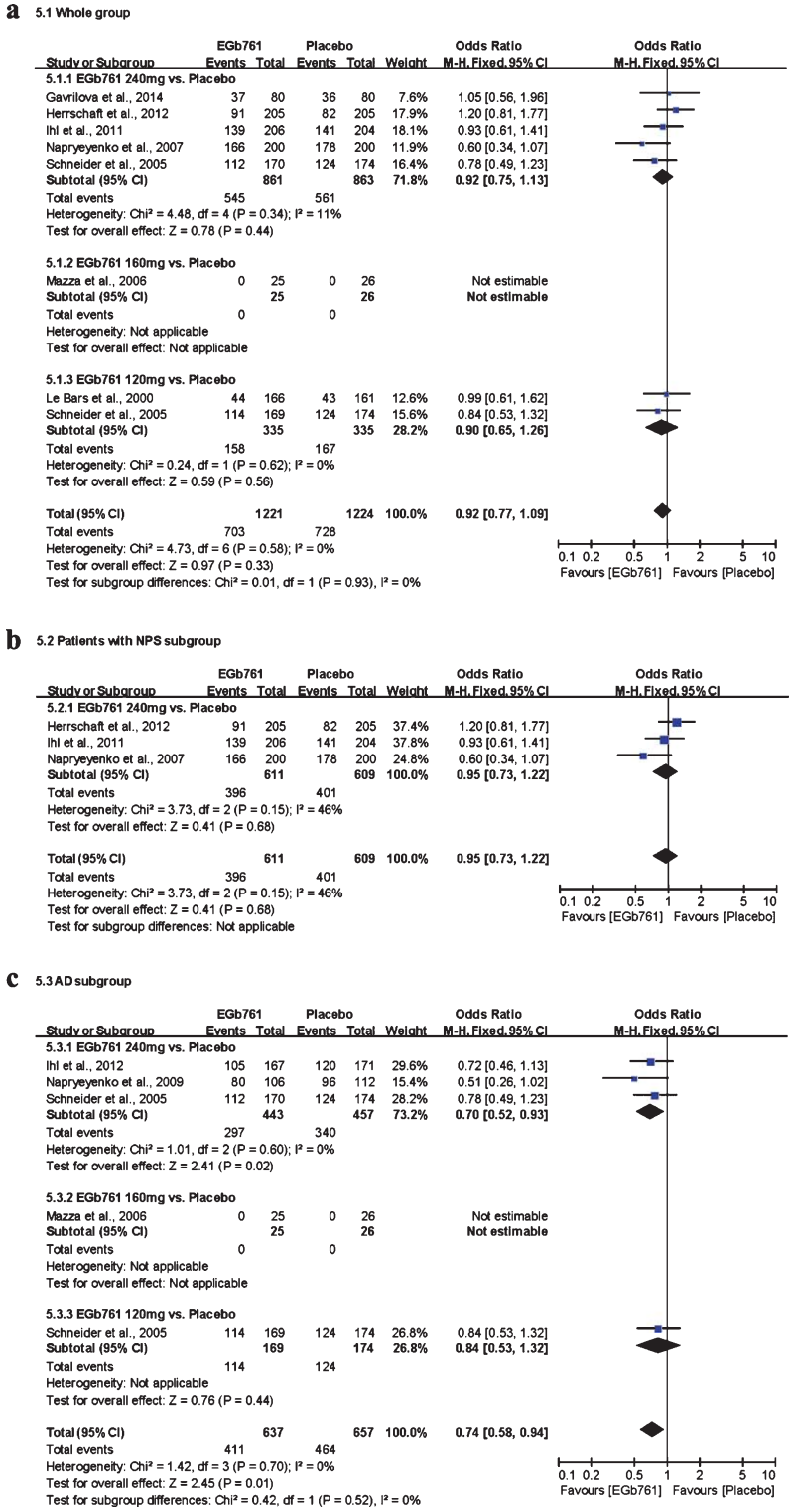
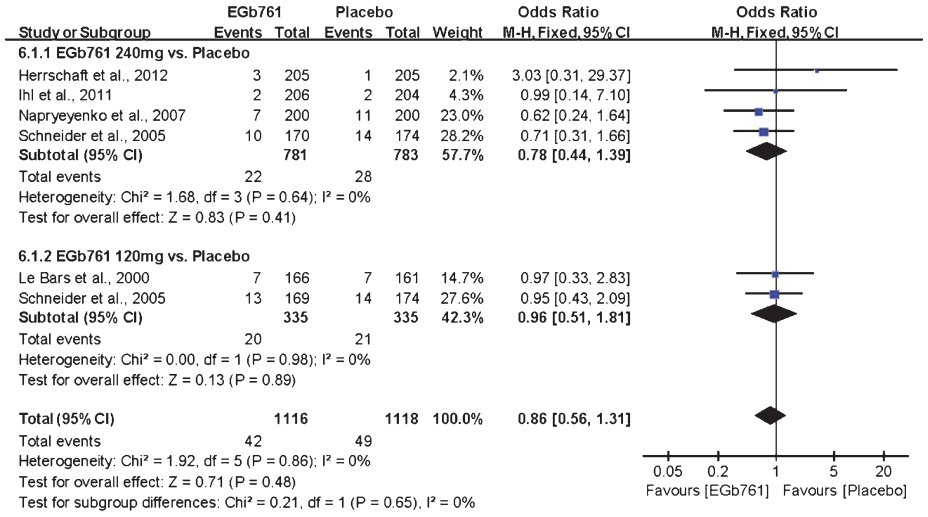
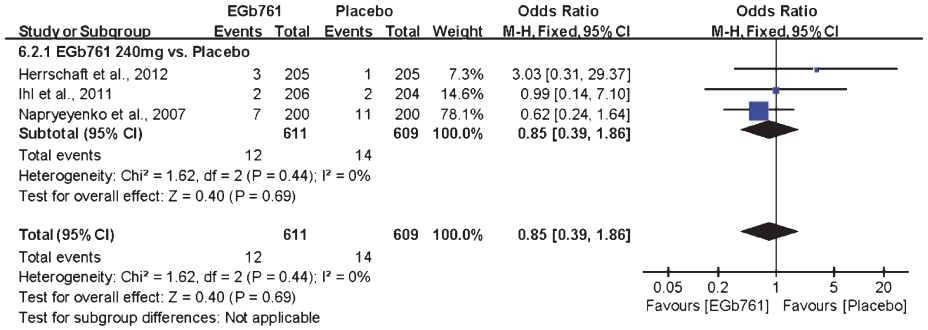



Fig. 5. Comparison EGb761 versus placebo, Number of patients experiencing an adverse event during treatment of 22–26 weeks in whole group (a), in patients with NPS subgroup (b), and AD subgroup (c).

**a** 6.1 Whole group




**b** 6.2 Patients with NPS subgroup




**c** 6.3 AD subgroup

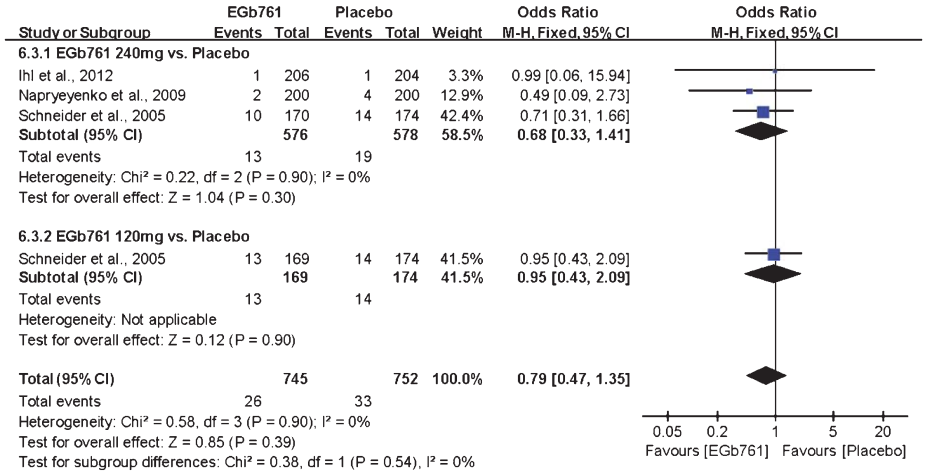



Fig. 6. Comparison EGb761 versus placebo, Number of patients experiencing a serious adverse event during treatment of 22–26 weeks in whole group (a), in patients with NPS subgroup (b), and in AD subgroup (c).

NPS, which may have contributed to the differences between ours and previous reviews, and increase the power of the meta-analysis.

NPS are highly prevalent in patients with dementia (AD and VaD) [46–48], which seem to affect patients' quality of life and to increase the risk for nursing home placement. Such symptoms are also significantly more prevalent in subjects with MCI than in normal cognitive aging [49], and might predict future progression to dementia [50]. Schneider et al. [38] firstly found a significant improvement with EGb761 in a subgroup of patients with NPS. The subsequent studies which specifically enrolled patients with NPS yielded favorable results for EGb761 [18, 19, 39]. A recent study further support EGb761 can alleviate NPS associated with MCI, and the profile of effects is similar to that found in patients with dementia [21]. Therefore, we performed a novel systematic review to evaluate the effects of EGb761 in cognitive impairment as well as dementia, especially in the subgroup of patients with NPS. And 22–26 weeks treatment with EGb761 at a daily dose of 240 mg could largely alleviate NPS and improve cognitive performance, including ADLs and global functioning. It is very essential—for affected patients as well as for health economic reasons—that a treatment for dementia is as effective in patients with pronounced NPS.

Based on the significance of dementia subtyping in routine use of anti-dementia drugs, the secondary objective of our meta-analysis was to examine results for AD subgroup separately. For this subgroup, the cognition, ADLs, and CGIC outcomes were almost the same as the whole group of patients with no statistical superiority. This is partly in line with RCTs findings that shown similar effects of EGb761 treatment in AD and VaD [44, 45, 51]. Taking into account the high prevalence of mixed pathologies [52, 53], the overlap between different types [54], and the difficulties of correct diagnostic classification even in a specialist care setting [52], EGb761 appears to be an appropriate choice given its multi-target approach.

What is worth noting is that the heterogeneity was substantial for the outcomes. Across all included studies, the results of the study by Napryeyenko et al. [39] are strongly in favor of EGb761 and so different statistically from other findings. The much smaller study, Mazza et al. [42] also showed much larger treatment effects and smaller standard deviations than the other studies. These two results regarding the benefit of EGb761 seem to be only applicable to a specific study population in a specific setting. When these studies were removed from the meta-analyses, the very high degree of heterogeneity was much reduced, and any significant treatment effects demonstrated for EGb761 were still present. Additional analysis designed specifically to investigate individual subgroups of patients with NPS have drawn subgroup-specific conclusions with a mild heterogeneity by removing Napryeyenko et al. [39]. However, there is still considerable heterogeneity not fully explained only by dementia type or EGb761 dosage, just as the data of Weinmann et al. [17] and Brondino et al. [20], which possibly have biased our results. Mixed factors including different in- and exclusion criteria and time point of study execution might have an impact on heterogeneity.

In addition, meta-analysis results show that standardized *Ginkgo biloba* extract has a good safety profile. Considering the importance of preventive intervention, some studies aimed to assess efficacy of long-term use of standardized *Ginkgo biloba* extract for preventing cognitive decline or dementia in elderly individuals. The GEM study reported that treatment with standardized *Ginkgo biloba* extract for a median of 6.1 years was not effective for prevention of dementia [55] and cognitive decline [56] in 3069 individuals aged 75 years or older with normal cognition or MCI. Another study [57] reported no effect of use of *Ginkgo biloba* extract for 42 months on the prevention of cognitive decline in the primary analysis of a trial of 185 cognitively intact patients aged 85 years and older. The GuidAge trial [58] assessed with a 5-years follow-up the same preparation and dose of standardized *Ginkgo biloba* extract in a study population aged 70 years and older who had spontaneously complained of memory problems showing no effect in reducing the risk of progression to AD. All these trials did not show evidence for reducing the overall incidence of dementia or AD with *Ginkgo biloba* extract in elderly individuals with or without memory complaints. Due to the particularly long pre-dementia phase, expecting a preventive effect of *Ginkgo biloba* on the incidence of dementia over a period of 3–6 years may be overoptimistic. So, all included patients in this meta-analysis have a validated diagnosis of dementia or cognitive impairment according to internationally diagnostic criteria for only evaluating a clinically therapeutic effect of *Ginkgo biloba*.

In conclusion, a dose of 240 mg/day of standardized *Ginkgo biloba* extract EGb761 appears to be able to stabilize or slow decline in cognition, function, behavior, and global change at 22–26 weeks in cognitive impairment and dementia, with a more pronounced effect in patients with NPS. Good safety profile of EGb761 with greater tolerability further supports its use in patients

with dementia and cognitive impairment. Hopefully, the design of a multicenter study could use currently available level of treatment and care, in order to provide a broader generalizability of the results in the future.

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