Ginkgo biloba for Preventing Cognitive Decline in Older Adults

A Randomized Trial

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Context The herbal product *Ginkgo biloba* is taken frequently with the intention of improving cognitive health in aging. However, evidence from adequately powered clinical trials is lacking regarding its effect on long-term cognitive functioning.

Objective To determine whether *G biloba* slows the rates of global or domain-specific cognitive decline in older adults.

Design, Setting, and Participants The Ginkgo Evaluation of Memory (GEM) study, a randomized, double-blind, placebo-controlled clinical trial of 3069 community-dwelling participants aged 72 to 96 years, conducted in 6 academic medical centers in the United States between 2000 and 2008, with a median follow-up of 6.1 years.

Intervention Twice-daily dose of 120-mg extract of *G biloba* (n=1545) or identical-appearing placebo (n=1524).

Main Outcome Measures Rates of change over time in the Modified Mini-Mental State Examination (3MSE), in the cognitive subscale of the Alzheimer Disease Assessment Scale (ADAS-Cog), and in neuropsychological domains of memory, attention, visual-spatial construction, language, and executive functions, based on sums of *z* scores of individual tests.

Results Annual rates of decline in *z* scores did not differ between *G biloba* and placebo groups in any domains, including memory (0.043; 95% confidence interval [CI], 0.034-0.051 vs 0.041; 95% CI, 0.032-0.050), attention (0.043; 95% CI, 0.037-0.050 vs 0.048; 95% CI, 0.041-0.054), visuospatial abilities (0.107; 95% CI, 0.097-0.117 vs 0.118; 95% CI, 0.108-0.128), language (0.045; 95% CI, 0.037-0.054 vs 0.041; 95% CI, 0.033-0.048), and executive functions (0.092; 95% CI, 0.086-0.099 vs 0.089; 95% CI, 0.082-0.096). For the 3MSE and ADAS-Cog, rates of change varied by baseline cognitive status (mild cognitive impairment), but there were no differences in rates of change between treatment groups (for 3MSE, $P=.71$; for ADAS-Cog, $P=.97$). There was no significant effect modification of treatment on rate of decline by age, sex, race, education, *APOE*E4* allele, or baseline mild cognitive impairment ($P>.05$).

Conclusion Compared with placebo, the use of *G biloba,* 120 mg twice daily, did not result in less cognitive decline in older adults with normal cognition or with mild cognitive impairment.

Trial Registration clinicaltrials.gov Identifier: NCT00010803

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GINKGO BILOBA IS MARKETED widely and used with the hope of improving, preventing, or delaying cognitive impairment associated with aging and neurodegenerative disorders such as Alzheimer disease. The primary outcome analysis from the Ginkgo Evaluation of Memory (GEM) study, the largest completed randomized, double-blind, placebo-controlled dementia prevention trial to date,[1] found that *G biloba*, 120 mg twice daily, was not effective in reducing the incidence of Alzheimer dementia or dementia overall.

Beyond consideration of a clinical dementia outcome, however, it is possible that *G biloba* may have had more subtle, therapeutic effects on the rate of cognitive change. Specifically, *G biloba* may have prevented or delayed age-related changes in individuals with nor-

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mal cognition, or *G biloba* may have slowed the rate of decline in those characterized as having mild cognitive impairment (MCI). Indeed, in the United States and particularly in Europe, *G biloba* is perhaps the most widely used herbal treatment consumed specifically to prevent age-related cognitive decline.[2] Putative mechanisms of action on brain functioning include vascular effects such as cerebral vasorelaxation and reduction of blood viscosity,[3,4] reduction of oxygen free radicals,[5] and neurotransmitter system effects.[6,7] Moreover, some in vitro studies indicate that *G biloba* may inhibit amyloid aggregation, suggesting another mechanism of preventing or delaying cognitive decline associated with Alzheimer disease.[8]

To date, adequately powered, longer-duration clinical trials testing the effect of *G biloba* on the rate of cognitive decline in aging have been lacking. Most reported human studies of the cognitive effects of *G biloba* in individuals without dementia have been restricted by very small samples and limiting design features[9] such as acute administration,[10-12] short-term treatment intervals,[13] combinations of agents,[14] or study of younger healthy volunteers.[11,14]

The present study reports on cognitive decline as an a priori secondary outcome of the GEM study.[15] The aims were to (1) determine if *G biloba* affected the rate of global cognitive change; (2) determine if *G biloba* had differential effects in specific cognitive domains; ie, memory, language, visuospatial construction, attention, and executive functions; and (3) examine whether baseline cognitive status, presence of *APOE*E4* allele, age, sex, race, or education modified any effects of *G biloba* treatment on cognitive change.

METHODS

Participants

A full description of recruitment and screening procedures has been reported previously.[1,15,16] Briefly, participants were recruited from September 2000 to May 2002 from 4 US communities: Hagerstown, Maryland; Pittsburgh, Pennsylvania; Sacramento, California; and Winston-Salem and Greensboro, North Carolina. Participants were required to identify a proxy willing to be interviewed at 6-month study visits. Written informed consent was obtained from participants and their proxies.

Individuals with prevalent dementia meeting *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition)[17] criteria for dementia or a score greater than 0.5 on the Clinical Dementia Rating (CDR) scale[18] were excluded from participation. Also excluded were individuals meeting any of the following criteria: (1) currently taking warfarin; (2) taking cholinesterase inhibitors for cognitive problems or dementia (memantine had not been approved for use in the United States when the study began); (3) unwilling to discontinue over-the-counter *G biloba* for the duration of the study; (4) current treatment with tricyclic antidepressants, antipsychotics, or other medications with significant psychotropic or central cholinergic effects; (5) daily use of more than 400 IU of vitamin E or unwillingness to reduce intake to this level; (6) history of bleeding disorders; (7) hospitalization for depression within the last year or electroconvulsive therapy within the last 10 years; (8) diagnosis of Parkinson disease or taking anti-Parkinson medications; (9) abnormal thyroid, serum creatinine, or liver function test results; (10) low baseline vitamin B_{12} levels; (11) low hematocrit level; (12) low platelet count; (13) disease-limited life expectancy of less than 5 years; or (14) known allergy to *G biloba*.

Participants with MCI at baseline were not excluded. Criteria for MCI at baseline were based on published consensus guidelines.[19] In brief, participants were defined as having MCI if they had: (1) impairments at or below the 10th percentile of Cardiovascular Health Study normative data, stratified by age and education, on at least 2 of 10 selected neuropsychological test scores from 5 cognitive domains; and (2) a CDR global score of 0.5.[20]

Study Intervention and Randomization

Participants were randomized to twice-daily doses of *G biloba* extract, 120 mg (EGb 761; Schwabe Pharmaceuticals, Karlsruhe, Germany), or an identical-appearing placebo, in a blister-pack format. Selection of the *G biloba* preparation for the study was made via an independent procurement procedure by the National Center for Complementary and Alternative Medicine (NCCAM) and required specific standards of exact chemical content and consistency. The formulation EGb 761 is an extract standardized in its major constituents, approximately 24% ginkgo-specific flavone glycosides and 6% terpene lactones.[15] The 120-mg twice-daily dose of EGb 761 was chosen based on information from prior clinical studies suggesting a dose-response relationship up to 240 mg.[1]

Assignment to *G biloba* or placebo was determined by permuted-block design by site to ensure balanced allocation between treatment groups. All clinical and coordinating personnel and participants were blinded to treatment assignment for the duration of the study, with the exception of specific data coordinating center personnel responsible for monitoring serious adverse events and reporting to the study's data and safety monitoring board. Only these individuals and the study pharmacist, who allocated the medication into batches, knew which medication was active, but all of these personnel were unaware of participant information and had no contact with participants. Further details of intervention, quality assurance, and randomization procedures have been reported.[1,15]

The study protocol was approved by the institutional review boards of all universities involved in the study as well as by the National Institutes of Health.

Neuropsychological Test Administration

The Modified Mini-Mental State Examination (3MSE)[21] was administered at every 6-month visit, as was the cognitive subscale of the Alzheimer Dis-

ease Assessment Scale (ADAS-Cog)[22] through August 1, 2004; thereafter, the ADAS-Cog was administered annually in alternation with the all-study annual neuropsychological evaluations, as described below. The Telephone Interview for Cognitive Status[23] was administered when in-person visits were missed.

A comprehensive neuropsychological test battery was administered to all participants at study screening and at annual intervals beginning in 2004 (approximately 3-4 years after randomization). In addition to these regularly administered (all-study) neuropsychological evaluations to all participants, diagnostic neuropsychological evaluations (consisting of the same neuropsychological tests) were administered to participants with potential cognitive changes as part of the mechanism for diagnosing dementia, the primary GEM study outcome. Diagnostic neuropsychological evaluations were administered at any visit during the study for the following reasons: (1) specified point decline on 2 of the 3 cognitive screening tests (3MSE, CDR, or ADAS-Cog); (2) onset of a new memory or other cognitive problem reported by the participant or family; (3) new dementia diagnosis by a nonstudy physician; or (4) initiation of a medication with a cognitive indication, such as donepezil, rivastigmine, galantamine, or memantine.

The neuropsychological test battery was designed to assess multiple cognitive domains and be maximally sensitive to detecting cognitive decline associated with preclinical or incident dementia. Memory tests included the California Verbal Learning Test[24] and recall conditions of the modified Rey Osterrieth Figure Test.[25] Tests of visual-spatial construction included the copy condition of the Rey Osterrieth Figure Test and the modified Wechsler Adult Intelligence Scale–Revised (WAIS-R) Block Design.[26] Language tests included a 30-item Boston Naming Test[27] and semantic verbal fluency.[28] Tests of attention and psychomotor speed included the WAIS-R Digit Span and the Trail Making Test Part A.[29] Tests of executive functions included the Trail Making Test Part B[29] and Stroop Color/Word Test.[30]

Statistical Analysis

The primary analysis compared rates of change in cognitive scores by treatment group using an intention-to-treat approach. Each of the aforementioned 5 cognitive domains was represented by 2 tests from the neuropsychological battery. Scores were scaled so that higher values consistently indicated worse performance and skewed measures were log-transformed for use in regression models. The transformed scores were standardized into *z* scores based on their means and standard deviations at baseline. Each domain was represented by the mean of the 2 component *z* scores. A global score was calculated as the mean of the 5 domain scores.

Linear mixed models were used to analyze cognitive decline through the end of follow-up, death, or dementia diagnosis. All 3069 eligible randomized participants were included. The 378 participants who had only a baseline neuropsychological evaluation contributed to estimation of intercepts in the models and were retained. Participants completed up to 9 neuropsychological test batteries (median, 5), 15 3MSE or Telephone Interview for Cognitive Status tests (median, 13), and 12 ADAS-Cog tests (median, 9). Review of a sample of trajectories supported the decision to model the change in neuropsychological test scores as linear; the more frequently measured ADAS and 3MSE supported a quadratic fit. To improve precision, models were adjusted for age at randomization in years, sex, nonwhite race, years of education, MCI, and depression at baseline. Race was determined by self-report and was included in the study because of reported associations with risk of cognitive decline.[31] To assess effect modification with treatment on the rate of change, we examined the significance of 3-way interaction terms among treatment, time, and each covariate of interest. Analyses were performed using Stata software, release 10 (StataCorp, College Station, Texas). Statistical tests were 2-sided.

Because of concerns that we might not adequately capture cognitive decline in all participants, the primary analysis of the neuropsychological test scores used imputed outcome data. Final scores were imputed for participants who did not have a neuropsychological examination during the year before death or dropout or during the month before censoring for dementia. Imputed scores were assigned as of the censoring date. Missing scores for intervening tests were not imputed. Scores were imputed for 234 (61%) of the 385 participants who died, 154 (79%) of the 195 who dropped out, and 70 (13%) of the 523 who were diagnosed as having dementia. Factors in the imputation model were treatment group, age, sex, race, years of education, study site, smoking status, *APOE*E4* status, MCI at baseline, cancer or diabetes in the 5 years before baseline, marital status, body mass index, history of coronary heart disease, history of stroke, self-rated health, depression, upper extremity strength, mobility, activities of daily living and instrumental activities of daily living scores, 3MSE scores, ADAS-Cog scores, CDR sum of boxes, time since randomization, time from the previous visit to the final actual or imputed visit, and reason for censoring. Results did not differ importantly when using only observed data. Multiple imputation was performed in Stata, release 10, using ICE; estimates were combined across 5 sets of imputed data using MIM.

In an alternative analysis of 2564 participants, the analysis time started at the first visit during or after August 2004 (3-4 years after randomization), when the neuropsychological battery was given annually to all participants, thus omitting the period during which the battery was given only for suspected cognitive problems. In support of this approach, the number of participants censored from the analysis before August 2004 and reasons for censoring were similar by treatment group. Because this analysis omits

the potentially important early treatment period, however, we regard it as secondary. Models were adjusted for baseline *z* scores (from the time of randomization) and the covariates used in the main analysis; results were similar when omitting the baseline score.

When the GEM study was planned, a sample size of 3000 was calculated to provide adequate power to detect the primary end point of incident dementia. We expected that 2820 participants would have at least 2 neuropsychological examinations. Assuming 5 years of follow-up with annual rates in the placebo group of 4% for dementia incidence and 6% for death or loss to follow-up and a 2-sided significance level of .05, we estimated 95% power to detect a difference in mean 3MSE slopes between the *G biloba* and placebo groups of –0.675 points per year. This represented about 40% of the observed decline in Cardiovascular Health Study participants aged 75 years or older.

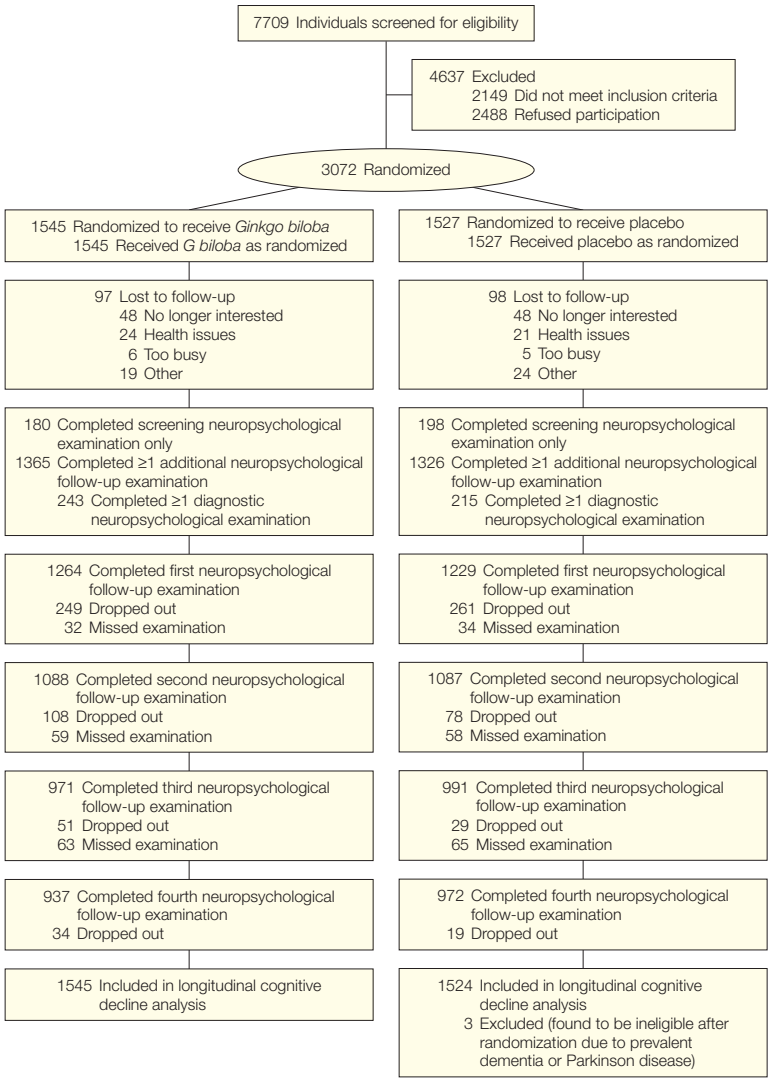
RESULTS

The flow diagram for all participants randomized to either placebo (n=1524) or *G biloba* (n=1545) is shown in the FIGURE. There was no difference between treatment groups in the number of participants who did not contribute longitudinal neuropsychological data (180 *G biloba* and 198 placebo participants; *P*=.25). Median follow-up time was 6.1 years (maximum, 7.3 years). Cumulative study drug adherence did not differ between assigned treatments, with 60.3% of all active participants taking their assigned study medications at the end of the trial. The percentage of participants who were nonadherent at each visit ranged from 3% to 8.5% throughout the study. Participants were considered nonadherent at the time of a scheduled visit if any of the following criteria were met: (1) they refused further participation in the study; (2) they took less than 50% of the study pills for 2 consecutive visits; or (3) they missed 2 consecutive visits or consecutively missed 1 visit and took less than 50% of pills at 1 visit.

The mean age at randomization was 79.1 years (range, 72-96 years), and 54% of participants were men (TABLE 1). Self-reported race was 95.5% white (n=2930), 2.9% African American (n=90), 0.9% Asian/Pacific Islander (n=28), and 0.7% other (n=21). Education was reported as 12 or fewer years by 36.0% of participants (n=1104) and 16 years or more by 38.0% (n=1190). The treatment groups did not differ with respect to age, sex, years of education, MCI status at baseline, or *APOE*E4* status. The placebo group performed better than the *G biloba* group on the California Verbal Learning Test delayed recall (*P*=.04), WAIS-R Block Design (*P*=.007), and Stroop interference (*P*=.02) tests at baseline; scores on the other 7 neuropsychological tests and the 3MSE and ADAS-Cog did not differ by treatment group. Although relatively few were enrolled, the placebo group had more African Americans than the *G biloba* group (3.5% vs 2.3%; *P*=.05).

TABLE 2 shows the primary results of the analysis for cognitive decline. On average, test performance was worse with increasing time since randomization.

Figure. Flow of Participants Through the Ginkgo Evaluation of Memory Study and Longitudinal Cognitive Decline Analysis



Average scores did not differ by treatment group. The *G biloba* and placebo groups did not differ in rates of cognitive change for the global cognition score or any of the cognitive domains, as indicated by the treatment × time coefficient, which represents the average annual difference in slopes between treatment groups. We found no significant effect modification by age, sex, race, *APOE*E4* status, education, or MCI status at baseline ($P > .05$). The eTable (available at http://www.jama.com) presents full model estimates. TABLE 3 shows estimated annual rates of change for all individual neuropsychological test scores in their original scales. Mean scores for representative neuropsychological tests in their original scales are shown in eFigure 1. While the actual values reflect the different reasons for administering the tests (for diagnostic purposes to year 4, then routinely), the lack of differences between treatment groups is apparent.

Neuropsychological tests were given only for diagnostic reasons up to approximately year 4. However, the 3MSE and ADAS-Cog were administered throughout the study, so these results were analyzed as well. Estimated annual rates of 3MSE change among participants without MCI at baseline were –0.25 (95% confidence interval [CI], –0.31 to –0.20) and –0.27 (95% CI, –0.32 to –0.22) points per year in the placebo and *G biloba* groups, respectively ($P = .71$ for difference by treatment). Those with MCI at baseline scored lower initially and declined more quickly, with annual rates of change of –0.44 (95% CI, –0.57 to –0.31) and –0.59 (95% CI, –0.71 to –0.47) in the placebo and *G biloba* groups, respectively. Observed 3MSE mean scores are shown in eFigure 2. A test for modification of the association of treatment with decline by MCI status was suggestive ($P = .06$), but stratified analyses found no effect of treatment on rate of change in either those with ($P = .48$) or without ($P = .96$) MCI at baseline. Similar analyses of ADAS-Cog data showed no association of treatment with rate of change ($P = .97$). The annual rate of ADAS-Cog change was 0.13 (95% CI, 0.10-0.16) for participants without MCI at baseline and 0.32 (95% CI, 0.27-0.38) for those with MCI at baseline regardless of treatment group. Observed ADAS-Cog mean scores are shown in eFigure 3.

In a secondary analysis, the baseline was shifted to study year 6, thereby excluding the period when neuropsychological evaluations were administered only as part of diagnosis (to participants who had positive results on the screening tests). Results of this secondary analysis were consistent with the primary analysis results; rates of cognitive change for all domains and for the global score did not differ by treatment group (all $P > .50$).

The adverse event profiles for the *G biloba* and placebo groups were similar and the rates of serious adverse events, including mortality and incidence of coronary heart disease, stroke of any type, and major bleeding, did not differ significantly. Complete rates of adverse and serious adverse events were published previously.[1]

COMMENT

This study examined whether a twice-daily 120-mg dose of *G biloba* affected the rate of cognitive change over time

Table 1. Baseline Characteristics of Study Participants by Study Drug Assignment

Characteristics	Study Group: Placebo (n = 1524)	Study Group: *Ginkgo biloba* (n = 1545)	*P* Value[a]
Age, mean (SD), y	79.1 (3.3)	79.1 (3.3)	.88
Male, No. (%)	808 (53)	843 (55)	.39
Nonwhite, No. (%)	76 (5.0)	63 (4.1)	.23
Education, mean (SD), y	14.4 (3.0)	14.3 (3.0)	.12
Depression score, mean (SD)[b]	3.6 (3.4)	3.6 (3.6)	.70
Mild cognitive impairment, No. (%)	226 (14.8)	256 (16.6)	.19
Presence of *APOE*E4* allele, No. (%)[c]	281 (23.0)	297 (24.1)	.52
Modified Mini-Mental State Examination total score, mean (SD)	93.3 (4.7)	93.4 (4.7)	.76
Alzheimer Disease Assessment Scale total score, cognitive subscale, mean (SD)[d]	6.4 (2.7)	6.5 (2.8)	.16
Neuropsychological domains, mean (SD), original scale for each test			
Memory			
CVLT delayed recall (range, 0-16)	8.9 (3.2)	8.7 (3.2)	.04
Rey-Osterrieth Figure Test delayed recall, % retained	72 (19)	71 (21)	.18
Attention			
WAIS-R Digit Span, forward (range, 2-14)	7.8 (2.1)	7.7 (2.1)	.17
Trail Making Test Part A, seconds to complete (sample range, 17-240)[d]	43.3 (15.8)	44.4 (16.1)	.06
Visuospatial abilities			
Rey-Osterrieth Figure Test copy (range, 0-24)	22.1 (2.4)	22.0 (2.4)	.61
WAIS-R Block Design (range, 0-24)	12.0 (4.4)	11.5 (4.3)	.007
Language			
Animal fluency, No. of words generated in 60 seconds	15.8 (4.3)	16.0 (4.4)	.35
Boston Naming Test (range, 0-30)	26.6 (2.9)	26.6 (3.0)	.89
Executive functions			
Trail Making Test Part B, seconds to complete (sample range, 16-240)[d]	107 (39)	107 (39)	.95
Stroop Color/Word Test interference (sample range, 3-157)	77.0 (21.8)	75.0 (22.7)	.02

Abbreviations: CVLT, California Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised.
[a] *P* values were computed using χ^2 (discrete variables) or *t* test (continuous variables).
[b] Centers for Epidemiologic Studies Depression total score; 30-point scale.
[c] *APOE* genotype data were available for 2452 participants.
[d] Higher score indicates worse performance.

Table 2. Results of Linear Mixed Models for Each Cognitive Domain and Global Cognition[a]

	Treatment (*G biloba*) Effect: Overall Difference in *z* Scores vs Placebo, Mean (95% CI)	Annual Rate of Change in *z* Scores, Mean (95% CI)		Treatment × Time Interaction: Annual Difference in Rates of Change Between *G biloba* and Placebo, Mean (95% CI)
		Placebo	*G biloba*	
Memory	0.034 (–0.019 to 0.086)	0.041 (0.032 to 0.050)	0.043 (0.034 to 0.051)	0.002 (–0.010 to 0.013)
P value	.21	<.001	<.001	.79
Attention	0.037 (–0.012 to 0.086)	0.048 (0.041 to 0.054)	0.043 (0.037 to 0.050)	–0.004 (–0.013 to 0.005)
P value	.14	<.001	<.001	.37
Visuospatial abilities	0.038 (–0.017 to 0.093)	0.118 (0.108 to 0.128)	0.107 (0.097 to 0.117)	–0.011 (–0.022 to 0.001)
P value	.17	<.001	<.001	.08
Language	–0.041 (–0.093 to 0.011)	0.041 (0.033 to 0.048)	0.045 (0.037 to 0.054)	0.005 (–0.005 to 0.014)
P value	.13	<.001	<.001	.33
Executive functions	0.013 (–0.042 to 0.069)	0.089 (0.082 to 0.096)	0.092 (0.086 to 0.099)	0.003 (–0.006 to 0.013)
P value	.64	<.001	<.001	.49
Global cognition	0.015 (–0.018 to 0.047)	0.071 (0.065 to 0.076)	0.069 (0.064 to 0.074)	–0.002 (–0.009 to 0.005)
P value	.38	<.001	<.001	.65

Abbreviations: CI, confidence interval; *G biloba*, *Ginkgo biloba*.
[a]Higher coefficients indicate worse test performance. Adjusted for age, sex, nonwhite race, years of education, mild cognitive impairment, and depression score at baseline. Scores are derived from the mean of 2 tests for each cognitive domain, with global cognition representing the mean of the 5 cognitive domain scores. (See Table 3 for estimated annual rates of change for each individual test.) As described in the Methods, test scores were transformed so that higher scores were worse and skewed measures were log-transformed. Scores were then standardized into *z* scores. Annual rates of change in each cognitive domain are presented. Results of the other components of the model are shown in the eTable.

Table 3. Annual Rates of Change for Individual Neuropsychological Test Scores by Study Drug Assignment[a]

Neuropsychological Domain/Test	Annual Rate of Change in Original Scores, Mean (95% CI)		*P* Value[b]
	Placebo	*Ginkgo biloba*	
Memory			
CVLT delayed recall (range, 0-16)	–0.15 (–0.18 to –0.12)	–0.14 (–0.17 to –0.11)	.71
P value	<.001	<.001	
Rey-Osterrieth Figure Test delayed recall, % retained	–0.002 (–0.004 to 0.0003)	–0.004 (–0.006 to –0.002)	.14
P value	.09	<.001	
Attention			
WAIS-R Digit Span forward (range, 0-14)	–0.03 (–0.04 to –0.01)	–0.02 (–0.04 to –0.01)	.68
P value	<.001	.006	
Trail Making Test Part A, seconds to complete (range, 12-240)[c]	1.55 (1.34 to 1.77)	1.45 (1.23 to 1.66)	.50
P value	<.001	<.001	
Visuospatial abilities			
Rey-Osterrieth Figure Test copy (range, 0-24)	–0.41 (–0.44 to –0.38)	–0.38 (–0.41 to –0.35)	.28
P value	<.001	<.001	
WAIS-R Block Design (range, 0-24)	–0.19 (–0.22 to –0.15)	–0.14 (–0.17 to –0.11)	.06
P value	<.001	<.001	
Language			
Animal fluency, No. of words generated in 60 seconds	–0.22 (–0.26 to –0.19)	–0.26 (–0.30 to –0.22)	.17
P value	<.001	<.001	
Boston Naming Test (range, 0-30)	–0.04 (–0.07 to –0.02)	–0.06 (–0.08 to –0.04)	.31
P value	<.001	<.001	
Executive functions			
Trail Making Test Part B, seconds to complete (range, 16-240)[c]	3.27 (2.90 to 3.64)	3.47 (3.10 to 3.84)	.44
P value	<.001	<.001	
Stroop Color/Word Test interference (range, 0-161)	–2.08 (–2.26 to –1.90)	–2.04 (–2.21 to –1.86)	.75
P value	<.001	<.001	

Abbreviations: CI, confidence interval; CVLT, California Verbal Learning Test; WAIS-R, Wechsler Adult Intelligence Scale–Revised.
[a]These values were transformed as described in the "Methods" section of the text and in Table 2 to derive the *z* scores used to compare cognitive domains.
[b]*P* values from treatment-by-time interaction term: average annual difference in rates of change between *G. biloba* and placebo groups.
[c]Higher values (times to completion of task) indicate worse test performance.

in older adults. We found no evidence for an effect of *G biloba* on global cognitive change and no evidence of effect on specific cognitive domains of memory, visual-spatial construction, language, attention and psychomotor speed, and executive functions. We found also no evidence for differences in treatment effects by age, sex, race, education, *APOE*E4* allele status, or baseline cognitive status (MCI vs normal cognition).

The observation of no significant effect modification by baseline cognitive status suggests that *G biloba* affected neither subtle preclinical cognitive changes associated with dementia prodrome nor cognitive changes associated with normal aging. Consistent with this conclusion is the alternative analysis in which the baseline was shifted to study year 6. By censoring the early period of the study, participants with early dementia or dementia prodrome who had reached a study end point were excluded. Results of this analysis indicate that 3 to 4 years of prior *G biloba* treatment had no significant effect on cognitive decline over the subsequent 2 to 3 years in older adults who were most likely not in a dementia prodrome at the beginning of the trial.

The present results are consistent with smaller trials. Solomon et al[32] reported that in a 6-week, placebo-controlled, double-blind clinical trial among 219 older adults, *G biloba* (120-mg daily dose) did not facilitate performance on standard neuropsychological tests of memory, attention, or language. A feasibility trial by Dodge et al[33] randomized 118 older adults (mean age, 87 years) to 240 mg/d of *G biloba* vs placebo and reported no difference in episodic memory decline during an average follow-up of 3.5 years in an intention-to-treat analysis. However, the statistical significance of the treatment effect was borderline ($P=.05$), and a secondary adherence analysis suggested a smaller decline in memory scores in the *G biloba* group ($P=.04$). Memory was the only cognitive domain evaluated by Dodge et al.

The GEM study is the largest randomized controlled trial of *G biloba* to report on outcomes to date. Strengths of this study include the large number of randomized participants (n=3069), long duration of follow-up (median of 6 years), and breadth of the neuropsychological evaluation, including measurement of multiple cognitive domains. The estimated power to detect a reliable difference in the rates of cognitive decline was high, as reflected by the 95% CIs reported in Table 2. For example, with regard to global cognition, we had sufficient power to rule out a difference of more than 0.009 SDs per year favoring the treatment group relative to the placebo group at the 95% confidence level. With regard to memory, a difference of more than 0.010 SDs per year favoring the treatment group relative to the placebo group can be confidently ruled out.

A final point to consider is the clinical meaning of decline in this study. A 4-point change in the ADAS-Cog score is considered clinically significant within the context of treatment trials in Alzheimer disease. By comparison, the annual change in ADAS-Cog scores in this study was observed to be 0.32 points within participants characterized as having MCI, a much slower rate of decline. The rates of change we observed in the 3MSE also were small and not clinically significant, though they are consistent with other studies of generally healthy older adults.[34,35]

The study also had several limitations. The full neuropsychological assessment schedule was not ideally designed for the purposes of these analyses, as the first several years of treatment were not captured by detailed cognitive evaluations. We have attempted to address this challenge by conducting secondary analyses which reset the baseline to the time in the study when regular annual assessments for all participants began. These secondary analyses were consistent with those of the primary analyses using all available assessments. We also assessed the 3MSE and ADAS-Cog outcomes throughout the study and found no significant difference by treatment group. Another point of consideration is the observed baseline differences in 3 neuropsychological tests favoring the placebo group; however, the magnitudes of these differences were small and clinically nonsignificant, and analyses were adjusted for baseline scores with regard to treatment comparisons. Finally, we note constraints on the generalizability of the present results due to underrepresentation in the cohort of individuals with divergent ethnic/cultural backgrounds and relatively few participants with lower education levels.

In sum, we find no evidence that *G biloba* slows the rate of cognitive decline in older adults. These findings are consistent with previous smaller studies examining prevention of decline[33] and facilitation of cognitive performance[32] and with the 2009 Cochrane review of *G biloba* for dementia and cognitive impairment.[36]

Author Contributions: Dr Snitz had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: O'Meara, Arnold.
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