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Blood amyloid levels and risk of dementia in the Ginkgo Evaluation of Memory Study (GEMS): A longitudinal analysis

Oscar L. Lopez^{a,b,*}, Yuefang Chang^{c,d}, Diane G. Ives^d, Beth E. Snitz^a, Annette L. Fitzpatrick^{e,f,g}, Michelle C. Carlson^h, Stephen R. Rappⁱ, Jeffrey D. Williamson^j, Russell P. Tracy^{k,l}, Steven T. DeKosky^{m,n}, Lewis H. Kuller^d

^aDepartment of Neurology, University of Pittsburgh, Pittsburgh, PA, USA

^bDepartment of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

^cDepartment of Neurosurgery, University of Pittsburgh, Pittsburgh, PA, USA

^dDepartment of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA

^eDepartment of Family Medicine, University of Washington, Seattle, WA, USA

^fDepartment of Epidemiology, University of Washington, Seattle, WA, USA

^gDepartment of Global Health, University of Washington, Seattle, WA, USA

^hDepartment of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

ⁱDepartment of Psychiatry and Behavioral Medicine, Wake Forest University, Winston-Salem, NC, USA

^jDepartment of Medicine and the Sticht Center for Healthy Aging and Alzheimer's Prevention, Wake Forest University, Winston-Salem, NC, USA

^kDepartment of Pathology, University of Vermont, Colchester, VT, USA

^lDepartment of Biochemistry, University of Vermont, Colchester, VT, USA

^mDepartment of Neurology, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

ⁿDepartment of Neuroscience, McKnight Brain Institute, University of Florida, Gainesville, FL, USA

Abstract

Introduction—Both high or low plasma amyloid levels have been associated with risk of dementia in nondemented subjects.

*Corresponding author. Tel.: 1412-246-6970; Fax: 1412-246-6873. lopezol@upmc.edu.

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Supplementary data

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Methods—We examined baseline plasma β -amyloid ($A\beta$) levels in relationship to incident dementia during a period of 8.5 years in 2840 subjects age >75 years; 2381 were cognitively normal (CN) and 450 mild cognitive impairment.

Results—Increased plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ levels were associated with gender (women), age, low education, creatinine levels, history of stroke, and hypertension. CN participants who developed dementia had lower levels of $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio compared with those who did not. $A\beta$ levels did not predict dementia in mild cognitive impairment participants.

Discussion—There was an inverse association between $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio to risk of dementia in CN participants. Cerebral and cardiovascular disease and renal function are important determinants of increased $A\beta$ levels and must be considered in evaluations of relationship of plasma $A\beta$ and subsequent risk of dementia.

Keywords

Dementia; Epidemiology; $A\beta_{1-42}$; Apolipoprotein-E; Blood levels

1. Introduction

Aggregation and accumulation of β -amyloid ($A\beta$) proteins as well as the deposition of hyperphosphorylated tau proteins in the brain are the defining pathology associated with neurodegeneration in patients with Alzheimer's disease (AD) [1]. There is growing interest, but limited evidence, that blood biomarkers can predict subsequent risk of AD [2– 12]. Evidence suggests that in monogenic early-onset dementia, increased production of the 42 amino acid peptide $A\beta$ ($A\beta_{1-42}$) in the brain account for increased brain amyloid and high levels of cerebrospinal fluid (CSF) and blood $A\beta_{1-42}$, whereas in late-onset AD, decreased clearance of $A\beta_{1-42}$ from the brain possibly due to damage to the blood-brain barrier or decreased transportation of $A\beta$ across the blood-brain barrier may account for higher brain amyloid deposition and decreased levels of CSF and plasma $A\beta_{1-42}$ [13–15].

Ideally, a blood test based on levels of $A\beta_{1-42}$ in blood, as a reflection of a central nervous system pathological process, could be used to predict the risk of dementia much like levels of serum cholesterol are used to predict risk of coronary heart disease and candidates for drug therapy to lower low-density lipoprotein cholesterol. CSF levels of $A\beta$ are much higher than blood levels of either $A\beta_{1-42}$ or $A\beta_{140}$. Blood levels of $A\beta_{1-40}$ and $1-42$ are highly correlated with each other but blood levels of $A\beta_{1-42}$ and CSF $A\beta_{142}$ are weakly but significantly correlated [16].

There is great variability among existing studies on whether plasma amyloid levels can predict risk of dementia in nondemented individuals, finding that both high or low $A\beta_{1-40}$ or $A\beta_{1-42}$ was associated with incident dementia. Two meta-analyses in 2011 and 2012 of plasma amyloid and risk of dementia came to different conclusions. The first concluded that $A\beta_{1-42}$ in plasma was not a significant predictor of risk of dementia. The $A\beta_{1-42}/A\beta_{1-40}$ ratio was a significant predictor of dementia but with substantial variability across studies [17]. The second study found that the ratio of $A\beta_{1-42}/A\beta_{1-40}$ in plasma was not significantly related to the risk of dementia. Furthermore, they concluded that individuals

who converted from cognitively normal (CN) to AD had higher rather than lower levels of A β 1–42 [4].

The long-term relationship between plasma amyloid levels and incident dementia has been examined in large epidemiological studies. The Framingham Study found that higher A β 1–42 was associated with lower risk of dementia over 7.6 ± 3.0 years, HR 0.80 (0.71–0.90) and a lower ratio of A β 1–42/A β 1–40 with higher risk of dementia [18]. The recent update from the Rotterdam Study over 20 years of follow-up also found that higher levels of A β 1–42 in plasma was associated with decreased to risk of dementia, HR, 0.64 (0.53–0.78) [19]. The Australian Biomarkers and Lifestyles Study reported a lower A β 1–42/A β 1–40 ratio in prevalent AD cases as compared with CN and in participants who converted from CN to mild cognitive impairment (MCI) over 18 months [20].

In the Health, Aging and Body Composition Study lower A β 1–42/A β 1–40 ratio and A β 1–42 were inversely related to decline in global cognition as measured with the Modified Mini-Mental State Examination (3MSE). The Health, Aging and Body Composition Study also reported that low A β 1–42/ A β 1–40 ratio was directly related to lower education, history of diabetes, higher HDL cholesterol, and higher serum creatinine [21,22]. Lower levels of A β 1–42 were significantly related to the presence of the apolipoprotein E4 (*APOE-4*) allele [22].

The purpose of this study was to examine the association between baseline plasma A β 1–40 and A β 1–42 levels and incident dementia in 2840 of the 3070 participants from the Ginkgo Evaluation of Memory Study (GEMS) over an 8.5 year follow-up [23].

2. Methods

A full description of recruitment and screening procedures of GEMS has been reported. Briefly, volunteers were recruited from September 2000 to May 2002 ($n = 3070$) using voter registration and other purchased mailing lists in 4 US communities (Fig. 1). Volunteers were aged 75 years or older. Participants were required to identify a proxy willing to be interviewed at 6-month study visits. Signed informed consent was obtained from participants and their proxies. A list of exclusion criteria from the study has been previous published [23] and included taking warfarin and antidepressants, history of bleeding disorders, hospitalization for depression, history of Parkinson's disease, abnormal liver function, low B₁₂, low platelet count, estimated life expectancy <5 years, abnormal thyroid function, and high serum creatinine >2 mg [23].

Individuals with prevalent dementia were excluded from participation. MCI at the baseline was defined as having impairments at or below the 10th percentile of the Cardiovascular Health Study normative data stratified by age and education on at least two of ten selected neuropsychological test scores from five cognitive domains and a Clinical Dementia Rating global score of 0.5 [23,24].

2.1. Neuropsychological testing

A 3MSE was administered at every six-month visit as was the Alzheimer's Disease Assessment Scale-Cognitive Subscale. The Telephone Interview for Cognitive Status was administered when in-person visits were missed. A comprehensive neuropsychological test battery was administered to all participants annually. The neuropsychological test battery was designed to assess multiple cognitive domains and to be maximally sensitive to detecting cognitive decline associated with preclinical or incident dementia [23,24].

Details of the therapeutic intervention (240 mg of Ginkgo biloba extract [Egb761; Schwabe Pharmaceuticals, Karlsruhe, Germany] or an identical placebo tablet). The study protocol was approved by the Institutional Review Boards of all universities involved in the study as well as the National Institutes of Health. Randomization in the trial was performed separately for each clinical site [23].

The primary outcome of the trial was incident dementia based on the Diagnostic and Statistical Manual of Mental Disorders version IV criteria as determined by an expert consensus panel of clinicians knowledgeable in dementia evaluations [23]. Secondary objectives of GEMS were overall cognitive decline, functional disability, and incidence of cardiovascular disease defined as the combined incidence of confirmed coronary heart disease, angina, stroke, transient ischemic attack, coronary artery bypass surgery, or angioplasty. Incidence was confirmed by review of the participants' medical records after self-report at 6 months and annual visits.

There were 523 (17%) participants with incident dementia over 8.4 years of follow-up; 477 (91%) had AD and 46 (9%) had another type of dementia.

Incident dementia was diagnosed as follows: (1) incident abnormal scores were made on 5 or more tests and at least one of the abnormal scores was on a memory test; (2) incident abnormal scores were made on 4 tests and at least one of the abnormal scores was on a memory test and the participant failed to complete 1 or more of the neuropsychological tests; and (3) incident abnormalities on 2 or more cognitive domains scored below the cutoff for age and education, adjusted norms in both tests of that domain and one of those domains was memory. Participants classified as reaching at this point were then referred for full neurological evaluation, magnetic resonance imaging scan, at the clinic site to confirm that the participant met clinical criteria for dementia and assessed for atypical causes of dementia. The GEMS dementia adjudication panel blinded to treatment assignment reviewed all confirmed cases again to assign a specific dementia classification. This final review incorporated study-related assessments and clinical information. Specific diagnostic criteria were used for designation of dementia classification [23].

There were 3070 randomized in the trial (11 did not have cognitive status in 2000–2002 and 5 did not have a study start date), 1524 to the placebo, 1545 to active therapy, and 1 undetermined. There were 180 in the Ginkgo biloba arm and 198 in the placebo arm who did not contribute longitudinal neuropsychological evaluation. Median follow-up time was 6.1 years with a maximum of 7.3 years. The percentage of participants who were nonadherent at each visit ranged from 3 to about 8.5% throughout the study. Mean age at randomization

was 79.1 years, a range of 72 to 96 years; 54% of participants were men, 95.5% were white, 2.9% African American, 0.9% Asian/Pacific Islanders, and 0.7% other. Education of <12 years was reported by 36% of the participants and 16 years by 38%.

There were 385 deaths before the diagnosis of dementia in which 323 (12.5%) were among 2579 CN participants and 59 (12.3%) among the 480 with MCI and 3 among 11 unknown cognitive status at the baseline in 2000–2002. Families were contacted as well as health care providers and a review of medical records was performed to determine whether dementia had occurred before death for those who died between the 6-month visits. The administration of Ginkgo biloba did not modify the incidence of dementia [23].

2.2. Laboratory tests

All participants had blood tests at the baseline, including complete blood count, thyroid stimulating hormone, and vitamin B12 levels, liver enzymes, creatinine, as well as *APOE* genotyping [25]. The A β proteins were measured using a sandwich ELISA initially developed by Eli Lilly and further implemented at the University of Vermont Laboratory for Clinical Biochemistry. The detailed methodology has been published. Interassay coefficients of variation ranged from 3.1 to 7.9% for A β 1–40 and 12.0–20.0% for A β 1–42 [26].

2.3. Statistical analysis

Continuous variables were evaluated for normality before the analyses, and log-transformations were applied to A β 1–42, A β 1–40, its ratio, and creatinine because of skewed distributions. Plasma amyloid data were also analyzed using quartile groups. Between-group comparisons for categorical variables and for continuous variables were examined by chi-square tests and analysis of variance, respectively. Linear regression models were used to determine the baseline factors that were associated with A β 1–42 and A β 1–40. To study the effect of amyloid marker on the development of dementia, a Cox model with death before dementia as a competing risk was carried out. Time to the event was defined as the duration from the study starting date to the date of dementia diagnosis, date of death, or the end of study. Covariates of the Cox model included study site, intervention group, age, gender, education, history of stroke, creatinine, presence of the *APOE-4* allele, hypertension, and diabetes. Each amyloid marker was examined individually in the Cox model. All the analyses were conducted using SAS 9.4.

3. Results

3.1. Participant characteristics

The GEMS included 3070 participants in 2000–2002 and 523 developed incident dementia over 8 years of follow-up to 2008, including 477 with AD and 24 with other dementia. Mean age at the baseline was 78.5 years for those without dementia and 79.9 for those with incident dementia ($P = .0001$). Risk of dementia was much greater for those with MCI than CN participants and increased with age for both MCI and CN participants (Supplementary Table 1). Among 2579 CN participants, 323 (12.5%) and for the 480 MCI, 199 (41.5%) developed incident dementia between 2000–2002 and 2008.

3.2. Measures of blood A β 1–42 and A β 1–40

Of the 3070 participants, 2840 had determinations of plasma A β 1 in 2000–2002 (Fig. 1). The participants without determinations of plasma A β 1–42 had higher creatinine levels (0.95 vs. 1.00 ng) and had more hypertension (36% vs. 44%), and diabetes mellitus (4.5% vs. 9.5%) than those without. In addition, 45 participants had A β 1–42 measurements at the baseline but had <3 years of follow-up and were alive with no history of dementia at the time of drop out. Among those alive and no history of dementia, about 1/3 (14 of 45) with <3 years of follow-up were diagnosed with MCI at the baseline as compared with 196 (10%) of 1952 with follow-up > 3 years. Baseline A β 1–42 was higher for participants with follow-up > 3 years, mean A β 1–42 15.9 ± 24.2 versus 12.4 ± 13.7 (n = 45) with <3 years of follow-up, $P = .078$ for comparing the differences. Exclusion of these 45 participants from the analysis had no effect on the overall results of the study. There were 133 participants who dropped out after 3 years and were alive and not demented at the time of withdrawal from the study, also in the entire sample, 2452 with and 618 without *APOE* genotyping. There were no differences in blood levels of A β 1–42 between those with and without *APOE* genotype measurements, 15.8 ± 23.7 versus 15.1 ± 19.4 pg/mL (Fig. 1).

Measurement of A β 1–40 and A β 1–42 was carried out at the baseline in 2000 and repeated in 2008, at the end of the study. The Pearson correlation between the two measurements of A β 1–42 (n = 1434) was 0.63 ($P = .0001$) and for A β 1–40 (n = 1659) was 0.53 ($P = .0001$). The levels of A β 1–40 and 1–42 were also moderately correlated at the baseline 0.47 ($P = .0001$), and in 2009, n = 1498, 0.52 ($P = .0001$). There was only a very small change in A β 142 and 1–40 between baseline and 2008. For A β 1–42, the average change in concentration was only 0.84 ± 14.9 pg/ mL and a median of 0.70 pg/mL, 25th percentile of -4.39 pg/mL, and for A β 1–40, concentration was 7.6 ± 71 pg/ mL, 25th percentile -0.38 pg/mL.

Mean time to dementia for participants who were CN at the baseline was 4.7 years (n = 323), and for MCI at the baseline, 3.7 years (n = 196, 3 without study starting date). Mean time to death for CN participants from the year 2000 to 2002 was 3.96 years as compared with 3.20 years for MCI at the baseline. There were no significant associations between time to death and A β 1–40 or A β 1–42 levels or the ratio in the blood.

3.3. A β 1–42 and risk of dementia

Participants who developed dementia during the study were significantly older at the baseline and had lower 3MSE scores and higher Centers for Epidemiologic Studies Depression Scale [3] scores. Levels of A β 1–42 were significantly lower for incident dementia, 13.8 ± 16.1 versus 16.1 ± 24.0 pg/mL ($P = .001$ for those with no dementia). There was no association of A β 1–40 levels and risk of dementia, 190.6 versus 189.2 ($P = .725$) pg/mL. The ratio of A β 1–42/A β 1–40 was lower for incident dementia, 0.07 versus 0.08 (0 = 0.0001), all age-adjusted (not shown).

In analysis restricted to participants who were CN at the baseline (Table 1), levels of A β 1–42 were higher for those who remained CN, 16.0 pg/mL, as compared with those who converted to incident dementia, 13.6 pg/mL (0 = 0.0001). At the baseline, there were no

differences for A β 1–40 levels and significantly lower ratio of A β 1–42/A β 1–40. In addition, age history of stroke, *APOE*-4 allele, and low 3MSE and high Centers for Epidemiologic Studies Depression Scale scores were significantly related to risk of dementia by 2008. There was no significant association of either race or gender with dementia. However, there were only 11 dementia cases among the 84 nonwhite participants.

Outliers were defined as >3 SD from the mean (Table 1) and were excluded from the analysis. The association of A β 1–42 and dementia remained significant (age-adjusted *P* value = .007) after this exclusion (Table 1). There was no association of A β 1–42, 1–40, or ratio of A β 1–42/1–40 and risk of dementia for those who were MCI at the baseline.

A β 1–42 levels were divided into quartiles for the entire sample and for the CN and MCI groups separately. Age-adjusted incidence rates per 1000 person-years (PYs) were then evaluated for total and CN and MCI participants. The HR for the first versus the fourth quartiles of A β 1–42 and the risk of dementia was 1.4 (1.1–1.8) (Table 2) for the total sample, and for CN at the baseline, age-adjusted HR was 1.7 (1.2–2.3) (Table 2, Fig. 2). The association of the A β 1–42/ A β 1–40 ratio to risk of dementia was similar to the risk associated with A β 1–42 (Table 2).

Incidence of dementia among CN participants at the baseline in relationship to quartiles of A β 1–42 concentration was further analyzed separately for men and women. The HR for the first versus the fourth quartiles of A β 1–42 concentration for women was 1.69 (1.08–2.63) and for men, 1.65 (1.03– 2.64) (not shown). There was no association of A β 1–40 and risk of dementia for either men or women.

3.4. Association of blood Ab1–42 levels and other variables

The independent associations of A β 1–42 blood levels in a linear regression model included higher levels of A β 1–42 in older age, among women, hypertension, and higher creatinine levels. Education levels were inversely related to A β 1–42. The association of these variables to A β 1–40 was very similar to 1–42 (Supplementary Tables 2 and 3). There was no association of liver enzymes and A β 1–42 levels.

3.5. APOE-4 allele, Ab1–42, and risk of dementia

The *APOE*-4 was a strong determinant of the risk of dementia. *APOE*-4 carriers had higher incidence of dementia within each of the quartiles of A β 1–42 as compared with noncarriers (Table 3). Age-adjusted incidence rates of dementia went from 42/1000 PYs for those who were in the first quartile of A β 1–42 and were *APOE*-4 carriers to 13.4/ 1000 PYs for those who were noncarriers and in the highest quartile of A β 1–42. The highest quartile of A β 1–42 was also associated with a lower risk of dementia among *APOE*-4 carriers (Table 3).

3.6. Effect of field center and randomization

Blood samples were obtained from the participants before randomization to the placebo or the Ginkgo biloba arm. There was no difference in levels of A β 1–42 at the baseline between the placebo (16.1 pg/mL) and Ginkgo biloba groups (15.4 pg/mL), *P*= .9. There was also no significant difference in the incidence of dementia by level of A β 1–42 at the baseline

between the placebo and Ginkgo biloba arm. The inverse association of A β 1–42 and risk of dementia was significant in the both arms of the study (data not shown).

The four field centers in the GEMS independently randomized their participants. There was a significant difference in the distribution of A β 1–40 or A β 1–42 across the four field centers. The incidence of dementia was significantly higher in one of the four field centers as compared with the other three. There was an inverse relationship between risk of dementia and quartiles of A β 1–42, similar to the total trial, in three of the four sites, and the relationship was significant for two sites. However, in the center with the highest incidence of dementia, average A β 1–42 was higher than the other three centers and there was no relationship of A β 1–42 and risk of dementia (not shown). Exclusion of this center from the analysis had no effect on the relationship of low A β 1–42 in blood and risk of dementia.

3.7. Multivariate models

In Cox proportional hazards analysis, both A β 1–42 and A β 1–42/A β 1–40 ratio were significant predictors of dementia in CN participants at study entry. Other significant predictors of dementia were older age, history of stroke, and *APOE-4* (Table 4). The Cox models were run separately for participants who were *APOE-4* carriers and noncarriers (Supplementary Table 4). Lower levels of A β 1–42 were predictors of risk of dementia, as were age, history of stroke, and women who were *APOE-4* carriers and noncarriers. The lack of significance of the lower quartile of A β 1–42 in *APOE-4* carriers shown in Supplementary Table 4 in the Appendix is likely a function of smaller sample size. Results for the above Cox models were similar when models included death as a competing risk (not shown).

4. Discussion

This study reported an inverse association between low A β 1–42 levels and A β 1–42/A β 1–40 ratio but not A β 1–40 levels to dementia risk, 91% AD, over an approximate 8.5 years of follow-up in CN individuals, but not in those with MCI. This is one of the longest studied and largest samples analyzed, especially with detailed annual evaluations of cognitive status and separation of CN and MCI at the baseline. The results are consistent with those recently reported from both the Rotterdam and Framingham Studies [18,19].

A β 1–40 and 1–42 are cleared from the peripheral circulation primarily by renal excretion, accounting for the higher levels associated with creatinine levels and with factors related to kidney function, such as hypertension, diabetes, age, and markers of brain vascular disease [27,28]. In the Rotterdam Study, A β 1–42 levels increased with age, hypertension, and with lacunar infarcts, microbleeds, and decreased white matter volume in the brain [29]. The liver is the primary organ for peripheral metabolism of A β 1–42. Levels of liver enzymes were not related to A β –142 levels.

Several new methods of measuring A β 1–42 in the periphery have been reported, including one recent study that used gas chromatography mass spectroscopy ratios of A β 1–42 and different molecular species of A β . The authors reported a very high correlation between peripheral plasma A β 1–42 and amyloid precursor protein 669–711 ratios and the extent of

amyloid in the brain [30–32]. In the present study, there was a very high correlation of two samples of A β 1–42 concentration measured approximately 8 years apart, and relatively little change over time in measurements carried out in the same laboratory. Measures of A β 1–42 were therefore repeatable in the laboratory and little variability over the long term within individuals. Accuracy of blood measurements of A β 1–42 or 1–40 cannot be determined without a “gold standard”.

4.1. Limitations

The GEMS sample was a randomized clinical trial and not a population sample. However, inclusion of randomization group and specific field centers did not affect the results. In addition, the GEMS did not have measurements of magnetic resonance imaging at the baseline so that we could not evaluate the relationship of A β 1–42 concentration and brain vascular disease.

Because there was no follow-up after the diagnosis of dementia, the total mortality in relationship to A β 1–42 concentration in the cohort cannot be evaluated. The short period between evaluations and the retrospective review and evaluation of the deaths probably precludes a potential limitation due to selected survival of the cohort.

No measures in the blood of other important biomarkers, such as phosphorylated tau, which has recently been directly related to risk of dementia, were available [33,34]. No follow-up of the total cohort was carried out after 2008 so that measures of change in A β 1–42 concentration between baseline and 8.5 years later cannot be used to evaluate subsequent risk of dementia.

Finally, one major limitation is that we do not know the source of blood A β 1–42. However, we know that A β 1–42 is metabolized in the liver and individuals with chronic liver disease have high levels of A β 1–42 [35]. Only liver enzymes were measured in GEMS and were not related to levels of A β 1–42. A β 1–42 and 1–40 are transported primarily via binding to albumin in plasma. No measures of albumin were available. Studies of plasma exchange of albumin to lower A β 1–42 are ongoing and show a short-term reduction in A β 1–42 [36]. Kidney dialysis is also associated with clearance of A β 1–42 in plasma and decrease in A β 1–42 levels [37,38].

5. Conclusions

Low levels of peripheral A β 1–42 are related to the risk of incident dementia as now reported in three large longitudinal studies. Better measurements of not only A β 1–42 but other species of A β in the blood may improve the use of blood amyloid measurements to predict risk of AD, especially when combined with other measures in the blood, such as tau. A biomarker blood test to predict risk of AD remains an important goal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the published literature (e.g., PubMed) on the relationship between plasma amyloid levels in nondemented individuals and incident dementia.
2. Interpretation: Blood levels of A β 1–42 and A β 1–42/ A β 1–40 ratio were independent predictors of incident dementia, primarily Alzheimer’s disease (AD). The lower levels may be a measure of decreased clearance of A β 1–42 from the brain to periphery. By contrast, age, sex (women), low education level, and multiple age-related pathological processes, especially cerebral and cardiovascular disease, and renal function that are important determinants of increased A β 1–42 and A β 1–40 levels.
3. Future directions: Studies of the prediction of incident AD by plasma Ab levels should be conducted in the context of multiple factors that increase or decrease these levels. The understanding of the contribution of different mechanisms to remove A β 1–42 from the interstitial fluid to the cerebrospinal fluid and peripheral circulation to reduce brain load of A β 1–42 may be an important approach to reducing the extent of AD pathology and the incidence of AD dementia.

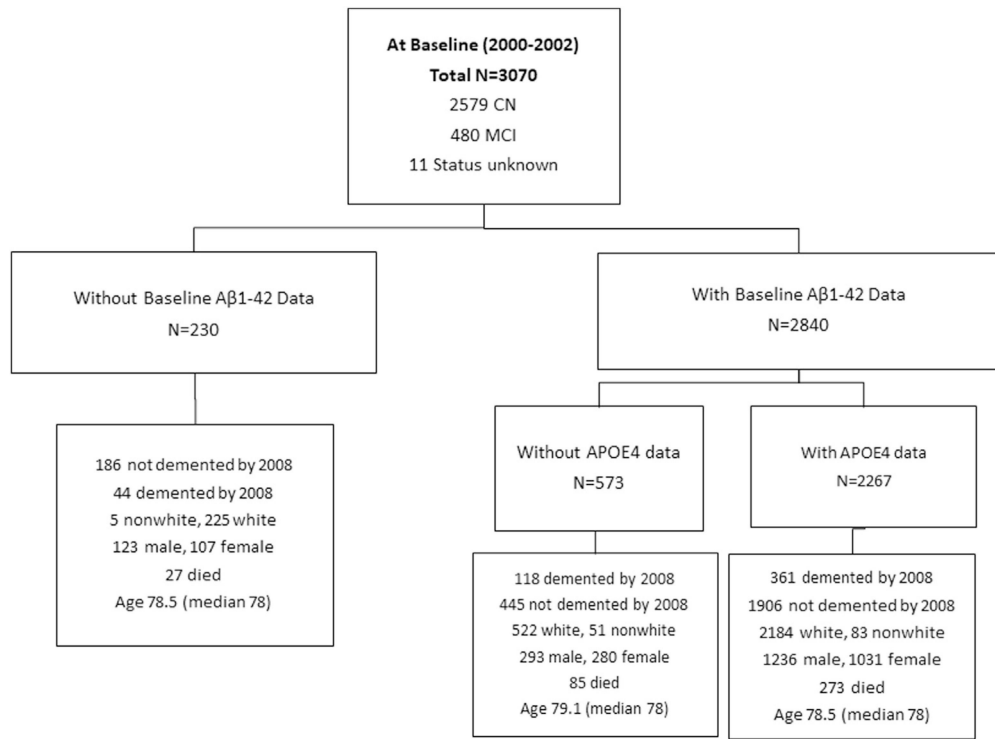


Fig. 1. GEMS participants with and without plasma A β measures stratified by the presence of the *APOE-4* allele.

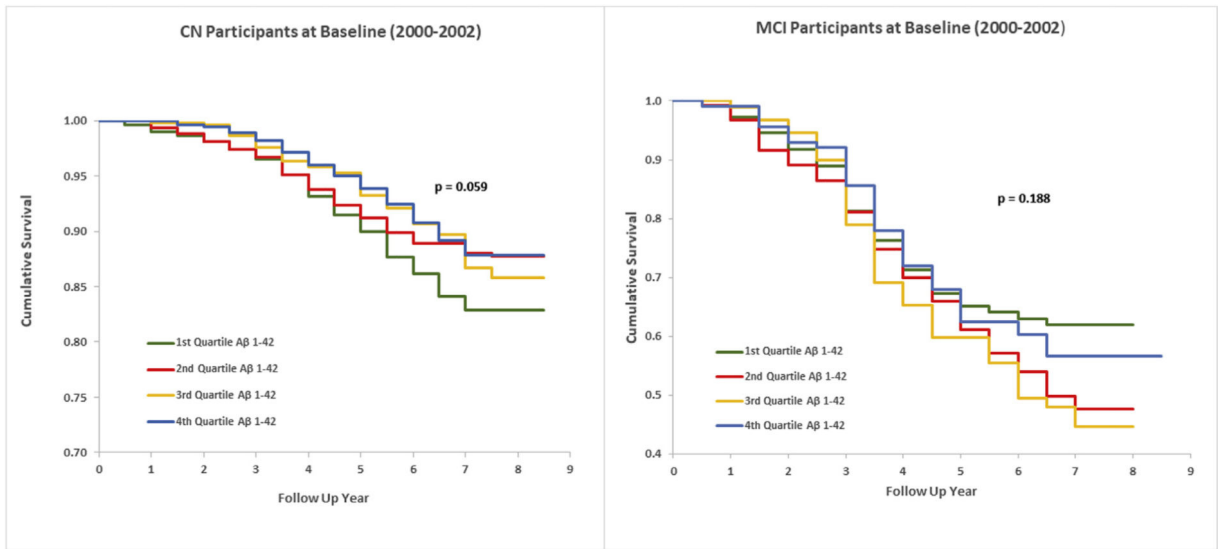


Fig. 2. Kaplan–Meier survival curves for incident dementia by Aβ1–42 quartiles in CN and MCI participants. Abbreviations: CN, cognitively normal; MCI, mild cognitive impairment.

Baseline data by dementia status at 2008 among GEMS participants who were cognitively normal at 2000–2002 (n = 2579)

Table 1

	No dementia (n = 2256)			Dementia (n = 323)			P value	Age adjusted P value
	Mean or N (%)	SD	Median	Mean or N (%)	SD	Median		
Age, years	78.2	3.1	77.0	79.6	3.5	79.0	<.0001	-
Race—White	2183 (97.3)			312 (97.2)			.89	.81
Gender—Women	1021 (45.3)			155 (48.0)			.35	.35
History of stroke	45 (2.0)			20 (6.3)			<.0001	<.0002
Heart disease	202 (9.1)			39 (12.3)			.06	.16
Hypertension	952 (43.2)			143 (45.7)			.40	.44
Diabetes mellitus	196 (8.8)			28 (8.9)			.97	.78
APOE-4 carriers	345 (18.9)			89 (35.3)			<.0001	<.0001
SBP, mm	132.5	17.9	132.0	134.4	17.9	133.0	.07	.25
Creatinine, mg%	1.0	0.2	1.0	1.0	0.3	1.0	.76	.29
GGT, mg%	29.6	16.3	25.0	29.7	16.5	24.0	.95	.68
ALT, mg%	25.6	8.8	24.0	25.7	8.5	25.0	.68	.28
AST, mg%	22.2	6.8	21.0	22.1	6.2	21.0	.98	.99
BMI, kg/m ²	27.3	4.3	26.9	26.8	4.0	26.4	.03	.17
3MSE score	94.3	4.1	95.0	92.1	4.6	92.0	<.0001	<.0001
CES-D	3.3	3.3	2.2	4.4	3.9	3.0	<.0001	<.0001
Aβ1–42, pg/mL	16.0	23.7	11.8	13.6	17.7	11.2	.008	.001
Aβ40, pg/mL	189.0	91.3	180.1	190.1	74.0	183.6	.49	.98
Aβ1–42/Aβ40	0.08	0.07	0.07	0.07	0.06	0.1	.0003	.0001
Aβ1–42*, pg/mL	13.6	9.8	11.7	12.7	9.6	11.1	.02	.007

Abbreviations: GEMS, Ginkgo Evaluation of Memory Study; N, number of participants; 3MSE, Modified Mini-Mental State Examination; CES-D, Center for Epidemiological Studies Depression Scale; BMI, body mass index; SBP, systolic blood pressure; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; AST, aspartate aminotransferase.

* Removed outliers (value 84.31 [i.e. 3SD above the mean; SD and mean were based on the full sample]).

Table 2

Dementia status at 2008 by baseline 2000–2002 A β 1–42 and A β 1–42/A β 1–40 ratio quartile* groups for CN and MCI participants in GEMS

Baseline 2000–2002	N	N dem	Age-adjusted HR	Age-adjusted Rate/1000 PYs	P value for trend
A β 1–42					
All					
1Q	710	131	1.4 (1.1–1.8)	30.9 (23.2–41.3)	.07
2Q	710	122	1.3 (1.0–1.6)	28.5 (21.2–38.5)	
3Q	708	117	1.2 (0.9–1.5)	27.1 (20.0–36.8)	
4Q	708	106	1.0	23.0 (16.7–31.8)	
CN at 2000–2002					
1Q	599	92	1.6 (1.2–2.3)	25.3 (18.0–35.8)	.02
2Q	588	66	1.1 (0.8–1.6)	18.0 (12.0–27.0)	
3Q	609	73	1.2 (0.8–1.7)	19.0 (12.9–28.1)	
4Q	584	62	1.0	16.0 (10.6–24.4)	
MCI at 2000–2002					
1Q	111	39	1.0 (0.6–1.5)	66.8 (38.9–115.4)	.89
2Q	122	56	1.5 (1.0–2.2)	91.4 (58.7–143.2)	
3Q	95	43	1.4 (0.9–2.1)	87.2 (52.1–152.4)	
4Q	119	44	1.0	66.0 (39.3–114.3)	
A β 1–42/A β 1–40 ratio					
All					
1Q	700	136	1.5 (1.2–2.0)	32.1 (24.2–42.7)	.0004
2Q	707	136	1.5 (1.2–2.0)	32.0 (24.2–42.5)	
3Q	720	110	1.1 (0.9–1.5)	24.5 (18.0–33.7)	
4Q	704	94	1.0	21.0 (15.0–29.6)	
CN at 2000–2002					
1Q	579	89	1.8 (1.3–2.5)	24.9 (17.6–35.4)	.0003
2Q	595	85	1.6 (1.1–2.2)	23.2 (16.3–33.1)	
3Q	612	64	1.1 (0.8–1.6)	16.3 (10.8–24.7)	
4Q	589	55	1.0	14.3 (9.2–22.4)	
MCI at 2000–2002					

Baseline 2000–2002	N	N dem	Age-adjusted HR	Age-adjusted Rate/1000 PYs	P value for trend
1Q	121	47	1.1 (0.7–1.7)	72.6 (44.4–120.0)	.53
2Q	111	51	1.6 (1.0–2.4)	93.4 (58.4–150.7)	
3Q	107	46	1.3 (0.9–2.0)	80.2 (49.3–134.8)	
4Q	108	38	-	62.4 (36.1–110.7)	

Abbreviations: A β , amyloid- β ; CN, cognitively normal; MCI, mild cognitive impairment; GEMS, Ginkgo Evaluation of Memory Study; HR, hazards ratio; PY, person-years; Q, quartile; N, number of participants; N with dem, number of participants with incident dementia.

* A β 1–42 quartile: 1Q: 7.8; 3Q: 11.69–16.75; 4Q: >16.75.

Table 3

Baseline A β 1–42 quartile* groups and *APOE*-4 allele among CN participants at 2000–2002 and risk of dementia to 2008 (n = 1921) in GEMS

A β 1–42	<i>APOE</i> -4	N	N Dem (%)	Age adjusted Rate/1000 PYs	Age adjusted HR (95% CI)
1Q	no	391	44 (11.3)	18.7 (11.5–30.6)	1.4 (0.9–2.3)
	yes	106	26 (24.5)	41.6 (21.4–81.5)	3.4 (2.0–5.7)
2Q	no	356	26 (7.3)	11.7 (6.5–22.2)	0.9 (0.5–1.4)
	yes	106	25 (24)	38.0 (19.4–76.6)	3.5 (2.1–5.8)
3Q	no	401	43 (11)	16.7 (10.1–27.9)	1.3 (0.8–2.0)
	yes	88	18 (20.5)	36.1 (16.4–79.3)	2.8 (1.6–5.0)
4Q	no	378	34 (9)	13.4 (7.7–23.9)	1.0
	yes	95	12 (12.6)	19.0 (7.2–52.7)	1.6 (0.8–3.0)

Abbreviations: A β , amyloid- β ; *APOE*-4, apolipoprotein E-4; CN, cognitively normal; GEMS, Ginkgo Evaluation of Memory Study; N, number of participants; N dem, number of participants with incident dementia; PY, person-years; HR, hazards ratio; Q, quartile.

* A β 1–42 quartile: 1Q: 7.8; 3Q: 11.69–16.75; 4Q: >16.75.

Table 4

Predictors of incident dementia (n = 216) in CN participants (n = 1841) in GEMS by A β 1–42 and A β 1–42/A β 1–40 quartiles: Cox model

Variables in the model	Baseline A β 1–42*		Baseline A β 1–42/A β 1–40 ratio [†]	
	HR (95% CI)	P value	HR (95% CI)	P value
Field center				
WFU	1.08 (0.73–1.61)		1.02 (0.69–1.51)	
UCD	1.16 (0.81–1.64)		1.11 (0.78–1.57)	
JHU	1.38 (0.93–2.04)	.44	1.35 (0.91–2.00)	.44
Intervention				
Ginkgo biloba	1.03 (0.79–1.35)	.83	1.02 (0.78–1.34)	.87
Age	1.13 (1.09–1.17)	<.0001	1.13 (1.09–1.17)	<.0001
Gender, Women	1.28 (0.95–1.74)	.10	1.23 (0.91–1.67)	.17
Years of education	1.01 (0.96–1.06)	.84	1.01 (0.96–1.06)	.77
History of stroke	2.69 (1.49–4.86)	.001	2.71 (1.50–4.89)	.001
1Q	1.91 (1.28–2.85)		1.83 (1.23–2.71)	
2Q	1.29 (0.85–1.97)		1.57 (1.05–2.34)	
3Q	1.47 (0.99–2.19)	.01	1.19 (0.79–1.80)	.01
log Creatinine	1.13 (0.58–2.20)	.72	1.00 (0.52–1.91)	.99
APOE-4 allele	2.47 (1.86–3.28)	<.0001	2.41 (1.82–3.21)	<.0001
Hypertension	1.13 (0.86–1.49)	.39	1.13 (0.86–1.49)	.38
Diabetes mellitus	0.97 (0.61–1.55)	.90	0.97 (0.61–1.54)	.88

Abbreviations: CN, cognitively normal; GEMS, Ginkgo Evaluation of Memory Study; A β , amyloid- β ; HR, hazards ratio; WFU, Wake Forest University; UCD, University California, Davis; JHU, Johns Hopkins University; Q, quartile; APOE-4, apolipoprotein E-4.

* A β 1–42 quartile: 1Q: 7.8; 2Q: 7.9–11.68; 3Q: 11.69–16.75.

[†] A β 1–42/A β 1–40 ratio quartile: 1Q: 0.045; 2Q: 0.065–0.087; 3Q: 0.046–0.064.