Plasma Amyloid-β as a Predictor of Dementia and Cognitive Decline

A Systematic Review and Meta-analysis

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Background: Preclinical prediction of Alzheimer disease (AD) is important and critical to effective intervention. Plasma levels of amyloid-β (Aβ) peptides have been a principal focus of the growing literature on blood-based biomarkers, but studies to date have varied in design, assay methods, and sample size, making it difficult to readily interpret the overall data.

Objective: To conduct a systematic review and meta-analysis of relevant prospective studies to determine whether plasma amyloid-β levels may predict development of dementia, AD, and cognitive decline.

Design: We searched prospective studies published between 1995 and 2011 indexed in the MEDLINE, EMBASE, and PsycINFO databases. Selected studies included those measuring at least 1 relevant plasma amyloid-β species (Aβ40, Aβ42, or Aβ42:Aβ40 ratio) and reporting an effect estimate for dementia, AD, or cognitive change.

Main Outcome Measures: Using a standardized extraction form, appropriate study parameters on subject information, exposure, and outcome were extracted. Random effects models were used to generate summary risk ratios and 95% confidence intervals comparing the bottom vs top quantiles for each plasma measure.

Results: Thirteen studies with a total of 10 303 subjects met inclusion criteria for meta-analysis. Lower Aβ42:Aβ40 ratios were significantly associated with development of AD (summary risk ratio, 1.60; 95% CI, 1.04-2.46; P = .03) and dementia (risk ratio, 1.67; 95% CI, 1.02-2.75; P = .04). Significant heterogeneity was found for both summary estimates, which could not be explained by participants’ age, sex distribution, the study’s follow-up time, or year of publication. Plasma levels of Aβ40 and Aβ42 alone were not significantly associated with either outcome.

Conclusions: Overall, the literature indicates that plasma Aβ42:Aβ40 ratios predict development of AD and dementia. However, significant heterogeneity in the meta-analysis underlines the need for substantial further investigation of plasma amyloid-β levels as a preclinical biomarker.


A enormous public health burden is caused by senile dementia, with Alzheimer disease (AD) alone being the seventh-leading cause of death in the United States and costing an estimated $172 billion annually.1 Current therapies to treat AD are minimally effective and do not alter the disease process. It is widely believed that novel therapeutic agents expected to be developed in the coming years will be optimally administered preclinically before patients develop full dementia. Thus, preclinical prediction of dementia through biomarkers is an important field, critical to effective intervention and disease modification.2 Although the Alzheimer Association and the National Institute on Aging recently established research guidelines for identifying preclinical dementia using neuroimaging and cerebrospinal fluid proteins,3 a blood-based biomarker would be less invasive and more cost-effective than cerebrospinal fluid or imaging-based methods. Moreover, a blood-based biomarker...
might also be used in a complementary role to cerebrospinal fluid and imaging as a first-step screen for high-risk individuals who would maximally benefit from these more invasive and expensive modalities.

Plasma levels of amyloid-β (Aβ) peptides have been a focus of the growing literature on blood-based biomarkers for dementia but studies to date have varied substantially in their design, assay methods, and sample size, making it difficult to interpret the overall data. Therefore, we performed a systematic review and meta-analysis to evaluate the scientific literature, asking whether plasma Aβ levels predict development of dementia, including AD, and cognitive decline.

**METHODS**

**SEARCH STRATEGY**

Following a preestablished protocol, a systematic review was conducted by 2 investigators with methodological expertise (A.K. and F.G.) using a Boolean search strategy on the electronic databases MEDLINE, EMBASE, and PsycINFO. Keywords shown in the eFigure (www.archneur.com) were used to search for the exposure and outcomes of interest, as well as to refine our search to epidemiologic studies. Studies were limited to those published after 1993 owing to the lack of well-developed Aβ assays before this time. The bibliographies of all relevant articles and review papers were also hand-searched; we also examined abstracts from major scientific meetings and consulted experts in the field for any further studies.

**INCLUSION CRITERIA**

Study selection was carried out in 2 stages using the same inclusion criteria. The first stage involved reviewing only the title and abstract of each article and the second stage involved reviewing the full text. For an article to be included in either stage, it had to fulfill 4 criteria for study quality: a prospective cohort (including case-cohort or nested case-control designs); measurement of the relevant plasma amyloid-β species (Aβ40, Aβ42, and/or Aβ42/Aβ40 ratio); report of the relative risk or equivalent effect estimates for incident AD, total dementia, and/or mean differences in cognitive decline for studies of that outcome; and be adjusted for age at a minimum. All languages were included in the searches.

**DATA EXTRACTION**

Data extraction was performed using a standardized extraction form. We extracted the following variables from each study: year of publication; study design; country of study population; name of cohort, exposures measured, and variable coding methods; outcomes measured and standard for diagnosis; length of follow-up; sample size; demographics (mean age at baseline, sex, and ethnicity); effect measures, respective P values and confidence intervals, and/or standard errors; number of cases in each group; and covariates used in modeling.

**DATA SYNTHESIS**

For the analyses, odds ratios, incidence rate ratios, hazard ratios, or risk ratios for dichotomous outcomes were considered as equivalent effect measures. For the sake of simplicity, these effect measures will herein be referred to as risk ratios (RRs). We focused on data regarding Aβ40 and Aβ42:

"Äβ⁴₀ ratio because these likely provide the most relevant information for risk prediction based on the existing literature. In addition, there is less biological rationale supporting the measurement of Aβ⁴₀ alone as a predictor of dementia; therefore, we evaluated those studies secondarily. In studies reporting plasma amyloid-β protein as a categorical variable, we considered the highest quantile as the reference group for our meta-analysis and generated a summary effect estimate for the comparison of the bottom vs the top quantile. These categorical analyses were considered a priori as our primary analyses for several reasons. Some reasons are because absolute measures of Aβ can differ widely between current plasma Aβ assays"⁴⁰ and the categorical classification of Aβ is subject to less misclassification than a continuous variable. That is, while a continuous measure requires that each unit is appropriately estimated, an ordered categorical variable only requires that subjects are generally ranked correctly across 3 or 4 categories, thus it yields less misclassification. Additionally, ordered categories are less susceptible to outliers of high levels of Aβ as well as very low levels that approach the detection limit of the assay, again resulting in less misclassification when using quantiles. Most importantly, in eventual clinical practice, it is most likely that Aβ will not be used as a continuous measure but rather that threshold categories will be defined for different risk states. Finally, most studies presented analyses of Aβ as a categorical variable. However, secondary analyses were also performed to derive a summary effect estimate from the incremental dose-response RR for each study, when available. The 4 studies reporting cognitive decline as an outcome were not included in the meta-analysis owing to large variations in the methods by which cognition was assessed, but they are reviewed here qualitatively.

For the dementia outcomes (total dementia and incident AD), both fixed and random-effects models were used to generate summary RRs across relevant studies. Because results were similar using both models, only DerSimonian and Laird random-effects estimates are presented. Heterogeneity was assessed using the I² statistic, and, if heterogeneity was found, we explored possible explanations using meta-regression models; we tested mean age, sex percentage, year of publication, and follow-up time in the meta-regression models. We also conducted meta-analyses excluding certain studies that were meaningfully different from other investigations in terms of sex. We could not conduct stratified analyses according to follow-up time because this would have yielded strata with an insufficient number of studies to provide meaningful information in...
a summary estimate. To assess study quality, because many studies reported results from multiple regression models with minimal and maximal control for potential confounding factors, we conducted 2 separate meta-analyses of the least and most adjusted RRs, and the pooled estimates for each were compared for significant differences. Besides evaluating maximal control of confounding factors, we did not conduct additional analyses examining study quality because our inclusion criteria already addressed many primary issues of study quality; that is, given our assessment of study quality as part of inclusion criteria, attempts to further stratify studies by quality within the meta-analysis would have resulted in strata with insufficient studies. The total subject pool was largely female (48%-69% female). 

Table 1. Baseline Characteristics of Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients at Risk, No.</th>
<th>No. of Events</th>
<th>Mean Age, y</th>
<th>Female, %</th>
<th>Follow-up Time, y</th>
<th>Variables Adjusted for</th>
<th>Dementia RR (95% CI)</th>
<th>AD RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdullah et al, 2009b,c</td>
<td>203</td>
<td>14</td>
<td>76.8</td>
<td>48.3</td>
<td>2.1e</td>
<td>Age, sex, education</td>
<td>4.47</td>
<td>3.91</td>
</tr>
<tr>
<td>Graff-Radford et al, 2007b,c,d</td>
<td>563</td>
<td>17</td>
<td>78.0e</td>
<td>62.0</td>
<td>3.7e</td>
<td>Age, APOE</td>
<td>(1.19-9.85)</td>
<td>(1.36-11.24)</td>
</tr>
<tr>
<td>Lambert et al, 2009c,f,g</td>
<td>8414</td>
<td>233</td>
<td>154</td>
<td>74.6</td>
<td>60.4</td>
<td>Age, sex, education, site</td>
<td>1.33 (0.97-1.92)</td>
<td>2.00 (1.41-2.78)</td>
</tr>
<tr>
<td>Mayeux et al, 2003b,c</td>
<td>451</td>
<td>86</td>
<td>76.2</td>
<td>68.9</td>
<td>5</td>
<td>Age, education, APOE, APOE level, BMI</td>
<td>0.40 (0.21-0.77)</td>
<td></td>
</tr>
<tr>
<td>Schupf et al, 2008b,c</td>
<td>1125</td>
<td>104</td>
<td>76.9</td>
<td>68.3</td>
<td>4.6</td>
<td>Age, sex, APOE, education, race/ethnicity, BMI, cohort</td>
<td>0.29 (0.12-0.71)</td>
<td>1.11 (0.59-2.00)</td>
</tr>
<tr>
<td>Seppalla et al, 2010a,b,g</td>
<td>197</td>
<td>9h</td>
<td>70.0i</td>
<td>55.0i</td>
<td>3</td>
<td>Unknown</td>
<td>3.12 (1.25-7.79)</td>
<td>3.26 (1.31-8.11)</td>
</tr>
<tr>
<td>Seppalla et al, 2010a,b,g</td>
<td>60</td>
<td>7h</td>
<td>70.0i</td>
<td>55.0i</td>
<td>6</td>
<td>Unknown</td>
<td>4.77 (1.14-19.98)</td>
<td>8.40 (1.83-3.57)</td>
</tr>
<tr>
<td>Sundelöf et al, 2008b,c,g</td>
<td>1045</td>
<td>146</td>
<td>82</td>
<td>71.0</td>
<td>0.0</td>
<td>Age, APOE</td>
<td>0.70 (0.44-1.13)</td>
<td>0.67 (0.42-1.08)</td>
</tr>
<tr>
<td>Sundelöf et al, 2008b,c,g</td>
<td>680</td>
<td>74</td>
<td>46</td>
<td>77.6</td>
<td>0.0</td>
<td>AD: age, dementia: age, APOE, diabetes</td>
<td>1.58 (0.87-2.86)</td>
<td>1.06 (0.59-1.90)</td>
</tr>
<tr>
<td>van Dijen et al, 2006c,f,g,i</td>
<td>6713</td>
<td>392</td>
<td>289</td>
<td>68.6</td>
<td>61.0</td>
<td>Age, sex</td>
<td>1.16 (0.82-1.64)</td>
<td>2.13 (1.49-3.03)</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, amyloid-β; AD, Alzheimer disease; APOE, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); RR, risk ratio.

DESCRIPTION OF STUDIES

Fourteen publications met inclusion criteria for meta-analysis (Table 1 and Table 2). Of these, 2 publications were each included as 2 distinct studies in the meta-analysis rather than as 1 because results in each of these publications were presented for 2 separate subcohorts.9,16 In addition, 2 publications used the same cohort, and only the more recent was included because it contained a larger sample.14,15 All studies in the meta-analysis were published in 2003 or later. All studies were prospective cohorts, although 2 were case-cohort studies. The total subject pool was largely female (48%-69% female).
across the studies), with 1 study comprising women exclusively\(^4\) and another comprising only men.\(^9\)

**PLASMA AMYLOID-\(\beta\) PROTEIN AND DEMENTIA**

**Plasma \(\text{A}\beta_{12}\) and Ratio of \(\text{A}\beta_{12}:\text{A}\beta_{40}\)**

Six studies reported RRs for the association between \(\text{A}\beta_{12}\) levels and risk for dementia, and they all used ordered categories of \(\text{A}\beta_{12}\) levels (Table 1). Of these, 5 reported increased risks for developing dementia for lower levels of \(\text{A}\beta_{12}\) in the least adjusted models, although only 2 were statistically significant.\(^10\) The pooled RR estimate across the studies was modest and not statistically significant (summary RR, 1.37; 95% CI, 0.95-1.98; \(P = .10\)) (Figure 2).

Among the 6 studies investigating \(\text{A}\beta_{12}:\text{A}\beta_{40}\) ratio, 5 reported an increased risk for developing dementia for the lowest \(\text{A}\beta_{12}:\text{A}\beta_{40}\) ratios\(^5,12,16\) compared with the highest quantile; 4 of these found statistically significant increased relative risks. All studies reported the \(\text{A}\beta_{12}:\text{A}\beta_{40}\) ratio in quartiles. A pooled analysis yielded a statistically significant RR of 1.67 (95% CI, 1.02-2.75; \(P = .04\)).

In all these meta-analyses of plasma \(\text{A}\beta\) and dementia, the pooled estimate did not change significantly when using results from the most adjusted models or when excluding the study that only included men. Significant heterogeneity was found in each of the meta-analyses, which was not explained by age or sex distribution of the populations studied or by follow-up time or year of publication. In a secondary analysis of \(\text{A}\beta_{12}\) as a continuous measure, results were consistent with those reported here for the quantile comparisons, although as expected with increased misclassification of \(\text{A}\beta\) level in the continuous variable, the summary RRs were generally weaker.

**Plasma \(\text{A}\beta_{40}\)**

Four studies reported effect estimates for the association between \(\text{A}\beta_{40}\) levels and risk for dementia, and they all used categorical exposures.\(^5,9,12\) A pooled analysis indicated no relation between \(\text{A}\beta_{40}\) and dementia development (RR, 1.01; 95% CI, 0.60-1.71; \(P = .97\)).

**PLASMA AMYLOID-\(\beta\) PROTEIN AND COGNITIVE DECLINE**

Four studies reported effect estimates for the association between \(\text{A}\beta_{40}\) levels and cognitive decline.\(^4,10,23,24\) No association between \(\text{A}\beta_{42}\) levels and cognitive decline was found in 2\(^1,10\) of the studies. One study reported a statistically significant association between decreased baseline \(\text{A}\beta_{42}\) levels and subsequent cognitive decline.\(^24\) while the remaining study also reported a significant association but for increased baseline \(\text{A}\beta_{42}\) levels.\(^23\) Thus, findings for plasma \(\text{A}\beta_{42}\) as a predictor of cognitive decline were inconsistent. However, similar to the meta-analysis of dementia, 3 of 4 studies reported that lower \(\text{A}\beta_{42}:\text{A}\beta_{40}\) ratio at baseline significantly predicted greater cognitive decline.\(^10\) In addition, 1 of these studies further measured change over 10 years of the \(\text{A}\beta_{42}:\text{A}\beta_{40}\) ratio, reporting that a decrease in this ratio over time predicted greater subsequent cognitive decline.\(^4\) The most recent study\(^24\) reported an interaction between plasma \(\text{A}\beta_{42}:\text{A}\beta_{40}\) ratio and cognitive reserve such that the relation between \(\text{A}\beta_{42}:\text{A}\beta_{40}\) ratio and cognition was strongest in those with the least education. No other studies have examined such an interaction, although the Nurses’ Health Study\(^1\) found that \(\text{A}\beta_{42}:\text{A}\beta_{40}\) ratio predicted cognitive decline in a well-educated population of women.

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**Table 2. Baseline Characteristics of Additional Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcomes</th>
<th>Patients at Risk, No.</th>
<th>No. of Events</th>
<th>Mean Age, y</th>
<th>Female, %</th>
<th>Follow-up Time, y</th>
<th>Variables Adjusted For</th>
<th>Reason Not Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blasko et al, 2010(^23)</td>
<td>Cohort</td>
<td>AD</td>
<td>406</td>
<td>33</td>
<td>75.8</td>
<td>56.5</td>
<td>5</td>
<td>Sex, education, creatinine, smoking, stroke/infection in MRI, GDS score, interaction between ApoE and ApoE, recruitment wave</td>
<td>Only continuous RR reported</td>
</tr>
<tr>
<td>Cosentino et al, 2010(^23)</td>
<td>Cohort</td>
<td>Cognitive change</td>
<td>880</td>
<td></td>
<td>76.1</td>
<td>68.0</td>
<td>4.5</td>
<td>Age, sex, race, BMI, ApoE, recruitment wave</td>
<td>Cognitive change as outcome</td>
</tr>
<tr>
<td>Lopez et al, 2008(^2)</td>
<td>Cohort</td>
<td>AD</td>
<td>274</td>
<td>88</td>
<td>79.3</td>
<td>60.9</td>
<td>4.5 (mean)</td>
<td>Age</td>
<td>Only continuous RR reported</td>
</tr>
<tr>
<td>Ökerke et al, 2009(^4)</td>
<td>Cohort</td>
<td>Cognitive change</td>
<td>481</td>
<td></td>
<td>63.6</td>
<td>100.0</td>
<td>10</td>
<td>Age, education, BMI, hypertension, dyslipidemia, heart disease, smoking, PHT, physical activity, alcohol, depression</td>
<td>Cognitive change as outcome</td>
</tr>
<tr>
<td>Yaffe et al, 2011(^14)</td>
<td>Cohort</td>
<td>Cognitive change</td>
<td>997</td>
<td>72</td>
<td>74.0</td>
<td>55.1</td>
<td>10</td>
<td>Age, race, education, diabetes, smoking, ApoE</td>
<td>Cognitive change as outcome</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; ApoE, Apolipoprotein E; BMI, body mass index; GDS, Geriatric Depression Scale; MRI, magnetic resonance imaging; PHT, postmenopausal hormone therapy; RR, risk ratio.
PLASMA AMYLOID-ß PROTEIN AND ALZHEIMER DISEASE

Plasma Aβ_{42} and Ratio of Aβ_{42}:Aβ_{40}

Nine studies reported RRs for plasma Aβ_{42} as a predictor of the development of clinically diagnosed AD. Six of these studies used categorical exposures, and most of the studies were smaller in size than those of total dementia (Table 1). Results for Aβ_{42} were inconsistent: 3 studies reported RRs greater than 1.0 for lower baseline levels of Aβ_{42} (with 2 achieving statistical significance), while 3 reported RRs less than 1.0 (with 2 achieving statistical significance). Reflecting these results, a pooled analysis (Figure 3) showed no relation between levels of Aβ_{42} and risk for developing AD (RR, 1.01; 95% CI, 0.48-2.11; P = .99). Of the 3 studies reporting continuous levels of Aβ_{42}, which were not included in the meta-analysis, 1 published null results, while the other study reported that a lower ratio of Aβ_{42}:Aβ_{40} was a significant predictor of a higher rate of AD development, consistent with the findings of our meta-analysis.

In all meta-analyses of plasma Aβ species and AD, the pooled estimate did not significantly change when using results from the most adjusted models or when excluding the all-men cohort. Heterogeneity was found in the above meta-analyses with an I^2 statistic of 64% for Aβ_{42} and 80% for Aβ_{42}:Aβ_{40} ratio; thus, the summary RRs must be interpreted cautiously.

Plasma Aβ_{40}

Seven studies reported effect estimates for plasma Aβ_{40} as a predictor of AD, of which 4 presented Aβ levels in ordered categories. Our meta-analysis found an elevated risk for AD with lower Aβ_{40}, but the confidence interval was fairly wide and the summary estimate was not statistically significant (RR, 1.66; 95% CI, 1.04-2.46; P = .03) (Figure 3). Of the 2 studies not included in the meta-analysis owing to the absence of categorical data on Aβ, 1 published null results, while the other study reported that a lower ratio of Aβ_{42}:Aβ_{40} was a significant predictor of a higher rate of AD development, consistent with the findings of our meta-analysis.
In this systematic review, we examined the literature regarding plasma $A\beta_{42}$ as well as the ratio of $A\beta_{42}:A\beta_{40}$ as predictors of dementia and AD. We found that plasma levels of $A\beta_{42}$ alone were not strong predictors of dementia or AD risk, with nonsignificant RRs across studies of both these outcomes. In contrast, the data across studies of $A\beta_{42}:A\beta_{40}$ ratio were more promising; we found a significant elevated risk for developing dementia or AD in subjects with lower $A\beta_{42}:A\beta_{40}$ ratios, with most studies reporting fairly similar findings. These results were robust to sensitivity analyses when using data from the most adjusted models reported, when analyzed as continuous levels rather than as ordered categories, and when the single study comprising an all-male cohort was excluded. No evidence for publication bias was found. Moreover, 4 studies reported results for cognitive decline as the outcome, and results from 3 of these were consistent with our meta-analysis in observing that a lower ratio of $A\beta_{42}:A\beta_{40}$ predicted worse cognitive decline. Collectively, the existing research offers cautious support for the hypothesis that lower levels of the plasma $A\beta_{42}:A\beta_{40}$ ratio reflect a process of selective deposition of $A\beta_{42}$ in the brain as insoluble amyloid plaques, thus predictive of dementia development.

While we calculated summary RRs across studies to produce a quantitative estimate of effect from the existing data, a key limitation of our findings was the significant heterogeneity in each pooled estimate, necessitating caution in our interpretation of findings. We could not formally identify the source of heterogeneity; however, we can hypothesize as to its causes. First, we suspect that much of the heterogeneity was likely the consequence of known measurement issues for plasma $A\beta$. The studies used in this meta-analysis used varying enzyme-linked immunosorbent assays and multiplex platforms, resulting in a wide distribution of median $A\beta$ levels between studies. Therefore, the development of a standardized assay is highly important to achieve more comparable results in further research on plasma $A\beta$. Second, $A\beta$ levels likely have differing implications at different stages in the pathogenesis of dementia, and the follow-up time varied considerably among studies; although meta-regression did not show this to significantly contribute to heterogeneity. Yet, variation of baseline $A\beta$ levels and the subjects' degree of underlying preclinical dementia at baseline may have been important contributors to heterogeneity, regardless of follow-up time. Most studies in the meta-analysis did not assess baseline levels of mild cognitive impairment in participants, and criteria for preclinical AD have only recently been promoted. Thus, there were no clear means of evaluating any influence of varying levels of cognitive health at baseline. In 2 small studies that reported mild cognitive impairment prevalence, estimates ranged from 9.6% to 19.3%, indicating there is likely wide variation in the level of early or underlying dementia across studies. Future research will be informed by more standard assessment of preclinical dementia both at baseline and during follow-up. These
issues can be addressed in part by measuring the relative change of Aβ levels at multiple points, as opposed to a single baseline measurement. Some studies have already used this temporal design and have been relatively consistent in showing significant associations between decreasing levels of Aβ42 or Aβ42/Aβ40 ratio over time and cognitive status. Overall, our results emphasize the need for further research to better understand all of the issues pertaining to heterogeneity before plasma Aβ can be of broader predictive use as a biomarker of impending dementia.

Other limitations of our meta-analysis should be considered. Results from individual studies are subject to potential unmeasured confounding and bias, and a meta-analysis cannot eliminate these issues (although we found similar results when using both minimally and maximally adjusted RRs). Missing data could introduce bias if missingness is related to both the exposure and outcome, which is often likely, although most studies reported reasonable follow-up rates. Additionally, some studies may be inappropriate to pool together. For example, 1 study included an all-male cohort, potentially limiting the generalizability of this study because women formed most of the other cohorts. However, excluding this study did not alter findings of our meta-analysis. Lastly, data extraction was not blinded, which may also be a source of bias, although this issue is debatable.

There are numerous reasons why plasma Aβ is a particularly appealing biomarker: (1) most interventions currently under investigation for AD focus on manipulating Aβ levels, thus an Aβ-based biomarker may be especially relevant for identifying those who will benefit if such treatments become available; (2) Aβ accumulation appears to be the initial step in AD pathogenesis, thus an Aβ-based biomarker should be especially suitable for identifying patients at the earliest stages of the disease process when intervention will likely be most effective; and (3) a plasma-based biomarker is simple, inexpensive, and noninvasive, all of which are important qualities for population-based screening tools.

In conclusion, despite the limitations of existing research and heterogeneity across the studies considered, this systematic review and meta-analysis suggests that the ratio of plasma Aβ42/Aβ40 may have value in predicting the risk for later development of dementia or AD and merits further investigation.

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