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Plasma Amyloid β as a Predictor of Dementia and Cognitive Decline: A Systematic Review and Meta-analysis

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Abstract

Context—Preclinical prediction of Alzheimer's disease is important, critical to effective intervention. Plasma levels of amyloid β-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 in order to determine if plasma amyloid β levels may predict development of dementia, Alzheimer's disease, and cognitive decline.

Data Sources—Prospective studies published between 1995 and 2011 indexed in the PubMed, EMBASE, and PsycInfo databases were searched.

Study Selection—Selected studies included those measuring at least one relevant plasma amyloid β species ($A\beta_{40}$, $A\beta_{42}$, $A\beta_{42}$:$A\beta_{40}$ ratio) and reporting an effect estimate for dementia, Alzheimer's disease, or cognitive change.

Data Extraction—Using a standardized extraction form, appropriate study parameters on subject information, exposure, and outcome were extracted. Random effects models were utilized to generate summary risk ratios and 95% confidence intervals, comparing the bottom versus top quantile for each plasma measure.

Results—Thirteen studies with a total of 10,303 subjects met inclusion criteria for meta-analysis. Lower $A\beta_{42}$:$A\beta_{40}$ ratios were significantly associated with development of Alzheimer's disease (summary RR=1.60, 95% CI=1.04,2.46; p=0.03) and dementia (RR=1.67 95% CI=1.02,2.75; p=0.04). 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 $A\beta_{40}$ and $A\beta_{42}$ alone were not significantly associated with either outcome.

Conclusions—Overall, the literature indicates that plasma $A\beta_{42}$:$A\beta_{40}$ ratios predict development of Alzheimer's disease and dementia. However, significant heterogeneity in the

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meta-analysis underlines the need for substantial further investigation of plasma amyloid β levels as a preclinical biomarker.

Introduction

An enormous public health burden is caused by senile dementia, with Alzheimer's 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's Association and the National Institute on Aging recently established research guidelines for identifying preclinical dementia using neuroimaging and cerebrospinal fluid (CSF) proteins[3], a blood-based biomarker would be less invasive and more cost-effective than CSF or imaging-based methods. Moreover, a blood-based biomarker might also be used in a complementary role to CSF 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-peptides have been a focus of the growing literature on blood-based biomarkers for dementia[4–17], 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 pre-established protocol, a systematic review was conducted by two 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 eFigure 1 were used to search for the exposure and outcomes of interest, as well as to confine our search to epidemiological studies. Studies were limited to those published after 1995, due to the lack of well-developed Aβ assays before this time. The bibliographies of all relevant articles and review papers were also hand-searched; abstracts from major scientific meetings were also examined by the authors, and experts in the field consulted for any further studies.

Inclusion Criteria

Study selection was carried out in two 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 four criteria for study quality: a prospective cohort (including case-cohort or nested case-control designs); measurement of the relevant plasma amyloid β species ($A\beta_{40}$, $A\beta_{42}$, and/or $A\beta_{42}$:$A\beta_{40}$ 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; be adjusted for age at a minimum. All languages were included in the searches.

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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 method; outcomes measured and standard for diagnosis; length of followup; sample size; demographics (mean age at baseline, gender, ethnicity); effect measures, respective *p* values and confidence intervals and/or standard errors; number of cases in each group; 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[18]. For the sake of simplicity, these effect measures will hereafter be referred to as risk ratios (RR). We focused on data regarding $A\beta_{42}$ and $A\beta_{42}$:$A\beta_{40}$, since 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 $A\beta_{40}$ 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 versus the top quantile. These categorical analyses were considered, *a priori*, as our primary analyses for several reasons. First, because absolute measures of Aβ can differ widely between current plasma Aβ assays[19], 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 three or four categories and thus 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 utilized as a continuous measure, but rather that threshold categories will be defined for different risk states. Finally, the majority of 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 four studies reporting cognitive decline as an outcome[4, 10] were not included in the meta-analysis due to large variations in the methods by which cognition was assessed, but are reviewed here qualitatively.

For the dementia outcomes (total dementia and incident AD), both fixed and random effects models were used to generate summary risk ratios across relevant studies. As results were similar using both models, only DerSimonian and Laird random effects estimates are presented[20]. Heterogeneity was assessed using the I^2 statistic, and, if heterogeneity was found, we explored possible explanations using meta-regression models;[21] we tested mean age, gender percentage, year of publication and follow-up time in the meta-regression models. We also conducted meta-analyses excluding certain studies with which were meaningfully different from other investigations in terms of sex. We could not conduct stratified analyses according to follow-up time, since this would have yielded strata with an insufficient number of studies to provide meaningful information in a summary estimate. To assess study quality, since many studies reported results from multiple regression models with minimal and maximal control for potential confounding factors, we conducted two separate meta-analyses of the least and most adjusted risk ratios, 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, since our inclusion criteria (see above) already addressed many primary issues of study quality; that is, given our assessment of study quality as part of inclusion criteria, attempts to further

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stratify studies by quality within the meta-analysis would have resulted in strata with insufficient studies to yield meaningful summary estimates. Publication bias was assessed by means of the Egger test[22], and was found to be nonsignificant for our primary meta-analyses of $A\beta_{42}$ and $A\beta_{42}$:$A\beta_{40}$. All calculations were performed using STATA version 11 (StataCorp 2007, College Station, TX).

Results

Study Selection

After the initial keyword search, there were 424 results from Pubmed, 82 from Embase, and 252 from PSYCInfo, for a total of 758 studies (Figure 1). After compilation of all studies into Endnote version X3 (Thomson Reuters, 2009, New York, NY), removal of duplicates resulted in 726 distinct studies. Two investigators (A.K. and F.G.) independently reviewed the remaining articles and after the first stage of study selection, 25 studies were identified for further consideration. After reviewing the full text of these articles, 14 publications remained which met all of our inclusion criteria.

Description of Studies

Fourteen publications met inclusion criteria for meta-analysis. Of these, two publications were each included as two distinct studies in the meta-analysis rather than as one, because results in each of these publications were presented for two separate subcohorts[9, 23]. In addition, two publications utilized the same cohort, and only the more recent was included as it contained a larger sample[14, 15]. All studies in the meta-analysis were published in 2003 or after. All studies were prospective cohorts, although two were case-cohort studies. The total subject pool was largely female (48–69% across the studies), with one study comprised exclusively of females[4] and another of males[9].

Plasma Amyloid β-Protein and Dementia

1. Plasma *Aβ42* and Ratio of *Aβ42*:*Aβ40*—Six studies reported risk ratios for the association between $A\beta_{42}$ levels and risk of dementia, and all used ordered categories of $A\beta_{42}$ levels (Table 1). Of these, five reported increased risks of developing dementia for lower levels of $A\beta_{42}$ in the least adjusted models, although only two were statistically significant[23]. The pooled risk ratio estimate across the studies was modest, and not statistically significant (summary RR=1.37; 95% CI=0.95,1.98; p=0.10) (Figure 2).

Among the six studies investigating $A\beta_{42}$:$A\beta_{40}$ ratio, five reported an increased risk of developing dementia for the lowest $A\beta_{42}$:$A\beta_{40}$ ratios[5, 12, 23] compared to the highest quantile; four of these found statistically significant increased relative risks. All studies reported the $A\beta_{42}$:$A\beta_{40}$ ratio in quantiles. A pooled analysis yielded a statistically significant RR of 1.67 (95% CI=1.02,2.75; p=0.04).

In all these meta-analyses of plasma Aβ and dementia, the pooled estimate did not change significantly when using results from the most adjusted models, or when excluding the study which only included men. Significant heterogeneity was found in the each of the above meta-analyses, which was not explained by age or gender distribution of the populations studied, or by followup time or year of publication. In a secondary analysis of $A\beta_{42}$ as a continuous measure, results were consistent with those reported here for the quantile comparisons, although as expected, with increased misclassification of Aβ level in the continuous variable, the summary RRs were generally weaker.

2. Plasma *Aβ40*—Four studies reported effect estimates for the association between $A\beta_{40}$ levels and risk of dementia, and all used categorical exposures[5, 9, 12]. A pooled analysis

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indicated no relation between $A\beta_{40}$ and dementia development (RR=1.01; 95% CI: 0.60,1.71; p=0.97).

Plasma Amyloid β-Protein and Cognitive Decline

Four studies reported effect estimates for the association between plasma Aβ levels and cognitive decline[4, 10, 24, 25]. No association between $A\beta_{42}$ levels and cognitive decline was found in two[4, 10] of the studies. One study reported a statistically significant association between decreased baseline $A\beta_{42}$ levels and subsequent cognitive decline[25], while the remaining study also reported a significant association but for increased baseline $A\beta_{42}$ levels[24]. Thus, findings for plasma $A\beta_{42}$ as a predictor of cognitive decline were inconsistent. However, similar to the meta-analysis of dementia, three of four studies reported that lower $A\beta_{42}$:$A\beta_{40}$ ratio at baseline significantly predicted greater cognitive decline[10]. In addition, one of these studies further measured change over ten years of the $A\beta_{42}$:$A\beta_{40}$ ratio, reporting that a decrease in this ratio over time predicted greater subsequent cognitive decline[4]. The most recent study[25] reported an interaction between plasma $A\beta_{42}$:$A\beta_{40}$ and cognitive reserve, such that the relation between $A\beta_{42}$:$A\beta_{40}$ and cognition was strongest in those with the least education. No other studies have examined such an interaction, although the Nurses' Health Study[4] found that $A\beta_{42}$:$A\beta_{40}$ predicted cognitive decline in a well-educated population of women.

Plasma Amyloid β-Protein and Alzheimer's Disease

1. Plasma *Aβ42* and Ratio of *Aβ42*:*Aβ40*—Nine studies reported risk ratios for plasma $A\beta_{42}$ as a predictor of the development of clinically diagnosed AD. Six of these studies employed categorical exposures, and most of the studies were smaller in size than those of total dementia (Table 1). Results for $A\beta_{42}$ were inconsistent: three studies reported risk ratios above 1.0 for lower baseline levels of $A\beta_{42}$ (with 2 achieving statistical significance), while three reported risk ratios below 1.0 (with 2 achieving statistical significance). Reflecting these results, a pooled analysis (Figure 3) showed no relation between levels of $A\beta_{42}$ and risk of developing AD (RR=1.01, 95% CI=0.48,2.11; p=0.99). Of the three studies reporting continuous levels of $A\beta_{42}$, which were thus not included in the meta-analysis, one benefited from a fairly large sample (n=1756; 289 cases), but still observed a null result[12]. The two remaining studies showed a statistically significant decreased risk for lower levels of $A\beta_{42}$[26], although one was no longer significant in the maximally adjusted model[8].

Among eight studies that reported risk ratios for plasma $A\beta_{42}$:$A\beta_{40}$ ratio and risk of developing AD, six employed ordered categories of $A\beta_{42}$ (Table 1). These data were more consistent than for $A\beta_{42}$ alone. Five of the six studies reported an increase in the likelihood of developing AD for the lowest compared to highest quantile of $A\beta_{42}$:$A\beta_{40}$ ratio, and three were statistically significant[5, 6, 10]. In our pooled analysis, there was a significant increase in risk of AD comparing the bottom versus top quantiles of $A\beta_{42}$:$A\beta_{40}$ ratios (RR=1.60, 95% CI=1.04,2.46; p=0.03) (Figure 3). Of the two studies not included in the meta-analysis due to the absence of categorical data on Aβ, one published null results[8] while the other study reported that a lower ratio of $A\beta_{42}$:$A\beta_{40}$ was a significant predictor of a higher rate of AD development[12], 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-male cohort. Heterogeneity was found in the above meta-analyses with an I^2 statistic of 64% for $A\beta_{42}$ and 80% for $A\beta_{42}$:$A\beta_{40}$ ratio; thus, the summary risk ratios must be interpreted cautiously.

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2. Plasma *Aβ40*—Seven studies reported effect estimates for plasma $A\beta_{40}$ as a predictor of AD, of which four presented Aβ levels in ordered categories. Our meta-analysis found an elevated risk of AD with lower $A\beta_{40}$, but the confidence interval was fairly wide and the summary estimate was not statistically significant (RR=1.66; 95% CI=0.98,2.83; p=0.06). Of the three studies not included in the meta-analysis, two reported null results[6, 8], and one showed a statistically significant decreased risk of AD with lower levels of $A\beta_{40}$[12]. Heterogeneity was not significant with an I^2 statistic of 45% for $A\beta_{40}$. Results remained consistent when $A\beta_{40}$ was analyzed as a continuous exposure.

Discussion

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 non-significant risk ratios across studies of both these outcomes. In contrast, the data across studies of $A\beta_{42}$:$A\beta_{40}$ 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 comprised of an all male cohort was excluded. No evidence for publication bias was found. Moreover, four studies reported results for cognitive decline as the outcome, and results from three 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 of 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 risk ratios 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 Aβ. The studies used in this meta-analysis employed varying ELISA assays and multiplex platforms, resulting in a wide distribution of median Aβ levels between studies. The development of a standardized assay is therefore highly important to achieve more comparable results in further research on plasma Aβ. Second, Aβ 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 Aβ 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 pre-clinical AD have only recently been promoted[3]. Thus there was no clear means of evaluating any influence of varying levels of cognitive health at baseline. In two small studies which reported MCI prevalence, estimates ranged from 9.6%[14] to 19.3%[23], 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 time points, as opposed to a single baseline measurement. Some studies have already employed this temporal design and have been relatively consistent in showing significant associations between decreasing levels of $A\beta_{42}$ or $A\beta_{42}$:$A\beta_{40}$ ratio over time and cognitive status[4, 13, 14, 23, 24]. Overall, our results emphasize the need for further research to better understand all of the issues pertaining to

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heterogeneity before plasma Aβ can be of broader predictive utility 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 RR's). Missing data could introduce bias if missingness is related to both the exposure and outcome, which is often likely, although the majority of studies reported reasonable follow-up rates. Additionally, some studies may be inappropriate to pool together. For example, one study[9] included an all male cohort, potentially limiting the generalizability of this study, as women formed the majority 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[27].

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, and 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[28] and 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 non-invasive, 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 $A\beta_{42}$:$A\beta_{40}$ may have value in predicting the risk of later development of dementia or AD and merits further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. 2010 Alzheimer's disease facts and figures. Alzheimers Dement. 2010 Mar; 6(2):158–194. [PubMed: 20298981]
2. Eschweiler GW, Leyhe T, Kloppel S, Hull M. New developments in the diagnosis of dementia. Dtsch Arztebl Int. 2010 Oct; 107(39):677–683. [PubMed: 20963198]
3. Alzheimer's Association NIoA. Recommendations to Update Diagnostic Criteria. http://www.alz.org/research/diagnostic_criteria/.
4. Okereke OI, Xia W, Selkoe DJ, Grodstein F. Ten-year change in plasma amyloid beta levels and late-life cognitive decline. Arch Neurol. 2009 Oct; 66(10):1247–1253. [PubMed: 19822780]
5. Lambert JC, Schraen-Maschke S, Richard F, et al. Association of plasma amyloid beta with risk of dementia: the prospective Three-City Study. Neurology. 2009 Sep 15; 73(11):847–853. [PubMed: 19752451]
6. Abdullah L, Luis C, Paris D, et al. Serum Abeta levels as predictors of conversion to mild cognitive impairment/Alzheimer disease in an ADAPT subcohort. Mol Med. 2009 Nov-Dec;15(11–12):432–437. [PubMed: 19707525]

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7. Schupf N, Tang MX, Fukuyama H, et al. Peripheral Abeta subspecies as risk biomarkers of Alzheimer's disease. Proc Natl Acad Sci U S A. 2008 Sep 16; 105(37):14052–14057. [PubMed: 18779561]
8. Lopez OL, Kuller LH, Mehta PD, et al. Plasma amyloid levels and the risk of AD in normal subjects in the Cardiovascular Health Study. Neurology. 2008 May 6; 70(19):1664–1671. [PubMed: 18401021]
9. Sundelof J, Giedraitis V, Irizarry MC, et al. Plasma beta amyloid and the risk of Alzheimer disease and dementia in elderly men: a prospective, population-based cohort study. Arch Neurol. 2008 Feb; 65(2):256–263. [PubMed: 18268197]
10. Graff-Radford NR, Crook JE, Lucas J, et al. Association of low plasma Abeta42/Abeta40 ratios with increased imminent risk for mild cognitive impairment and Alzheimer disease. Arch Neurol. 2007 Mar; 64(3):354–362. [PubMed: 17353377]
11. Blasko I, Jellinger K, Kemmler G, et al. Conversion from cognitive health to mild cognitive impairment and Alzheimer's disease: prediction by plasma amyloid beta 42, medial temporal lobe atrophy and homocysteine. Neurobiol Aging. 2008 Jan; 29(1):1–11. [PubMed: 17055615]
12. vanOijen M, Hofman A, Soares HD, Koudstaal PJ, Breteler MM. Plasma Abeta(1–40) and Abeta(1–42) and the risk of dementia: a prospective case-cohort study. Lancet Neurol. 2006 Aug; 5(8):655–660. [PubMed: 16857570]
13. Pomara N, Willoughby LM, Sidtis JJ, Mehta PD. Selective reductions in plasma Abeta 1–42 in healthy elderly subjects during longitudinal follow-up: a preliminary report. Am J Geriatr Psychiatry. 2005 Oct; 13(10):914–917. [PubMed: 16223971]
14. Mayeux R, Honig LS, Tang MX, et al. Plasma A[beta]40 and A[beta]42 and Alzheimer's disease: relation to age mortality, and risk. Neurology. 2003 Nov 11; 61(9):1185–1190. [PubMed: 14610118]
15. Mayeux R, Tang MX, Jacobs DM, et al. Plasma amyloid beta-peptide 1–42 and incipient Alzheimer's disease. Ann Neurol. 1999 Sep; 46(3):412–416. [PubMed: 10482274]
16. Seppala TT, Herukka SK, Hanninen T, et al. Plasma A{beta}42 and A{beta}40 as markers of cognitive change in follow-up: a prospective, longitudinal, population-based cohort study. J Neurol Neurosurg Psychiatry. May 16.
17. Viswanathan A, Raj S, Greenberg SM, et al. Plasma Abeta, homocysteine, and cognition: the Vitamin Intervention for Stroke Prevention (VISP) trial. Neurology. 2009 Jan 20; 72(3):268–272. [PubMed: 19153374]
18. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992 Jun 1; 135(11):1301–1309. [PubMed: 1626547]
19. Okereke OI, Xia W, Irizarry MC, et al. Performance characteristics of plasma amyloid-beta 40 and 42 assays. J Alzheimers Dis. 2009 Feb; 16(2):277–285. [PubMed: 19221417]
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep; 7(3):177–188. [PubMed: 3802833]
21. Egger, M.; Smith, GD.; Altman, DG. Systematic reviews in health care: meta-analysis in context. London: BMJ; 2001.
22. Egger M, DaveySmith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13; 315(7109):629–634. [PubMed: 9310563]
23. Seppala TT, Herukka SK, Hanninen T, et al. Plasma A{beta}42 and A{beta}40 as markers of cognitive change in follow-up: a prospective, longitudinal, population-based cohort study. J Neurol Neurosurg Psychiatry. 2010 May 16.
24. Cosentino SA, Stern Y, Sokolov E, et al. Plasma {beta}-Amyloid and Cognitive Decline. Arch Neurol. 2010 Aug 9.
25. Yaffe K, Weston A, Graff-Radford N, et al. Association of Plasma β-Amyloid Level and Cognitive Reserve With Subsequent Cognitive Decline. JAMA. 2011; 305(3):261–266. [PubMed: 21245181]
26. Blasko I, Kemmler G, Jungwirth S, et al. Plasma Amyloid Beta-42 Independently Predicts Both Late-Onset Depression and Alzheimer Disease. Am J Geriatr Psychiatry. 2010 May 7.

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27. Berlin JA. Does blinding of readers affect the results of meta-analyses? University of Pennsylvania Meta-analysis Blinding Study Group. Lancet. 1997 Jul 19; 350(9072):185–186. [PubMed: 9250191]

28. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002 Jul 19; 297(5580):353–356. [PubMed: 12130773]

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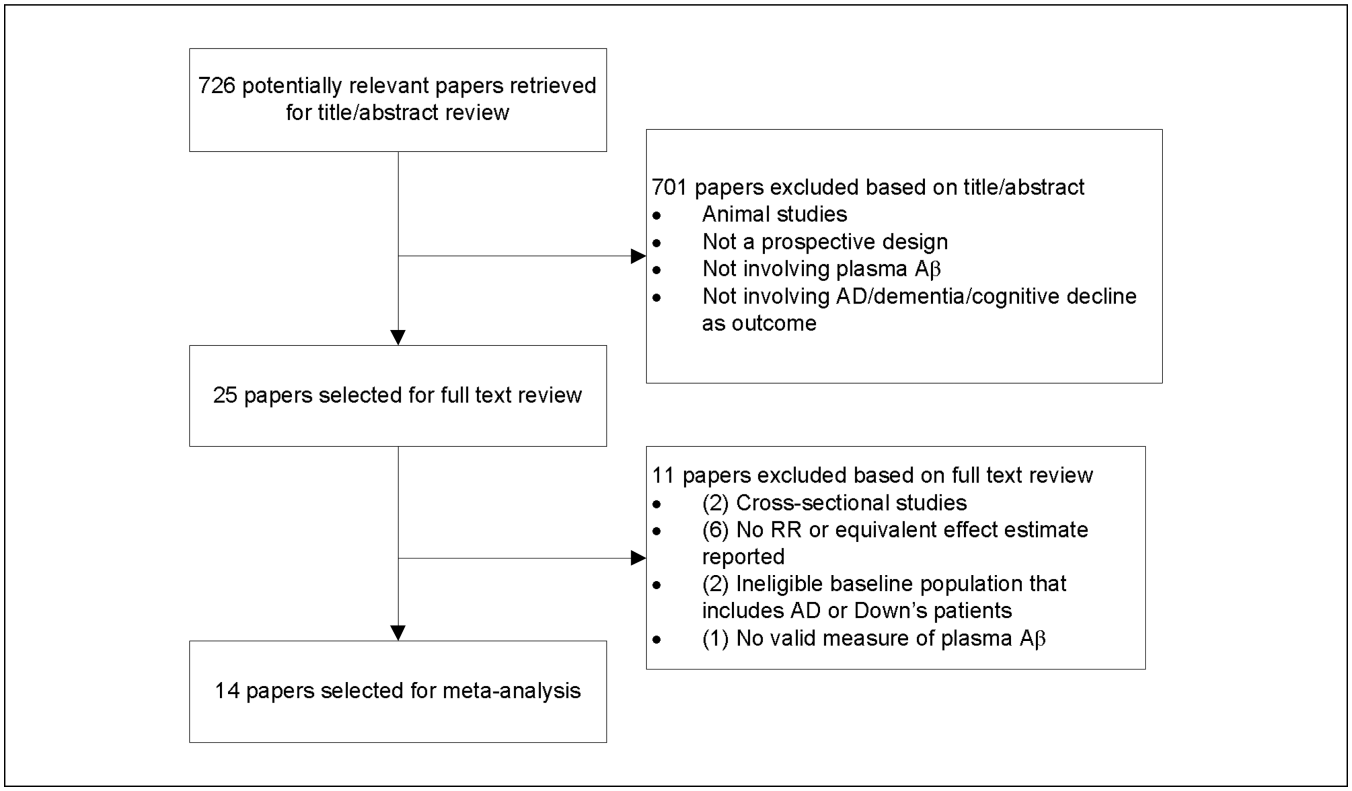

Figure 1.
Study Selection

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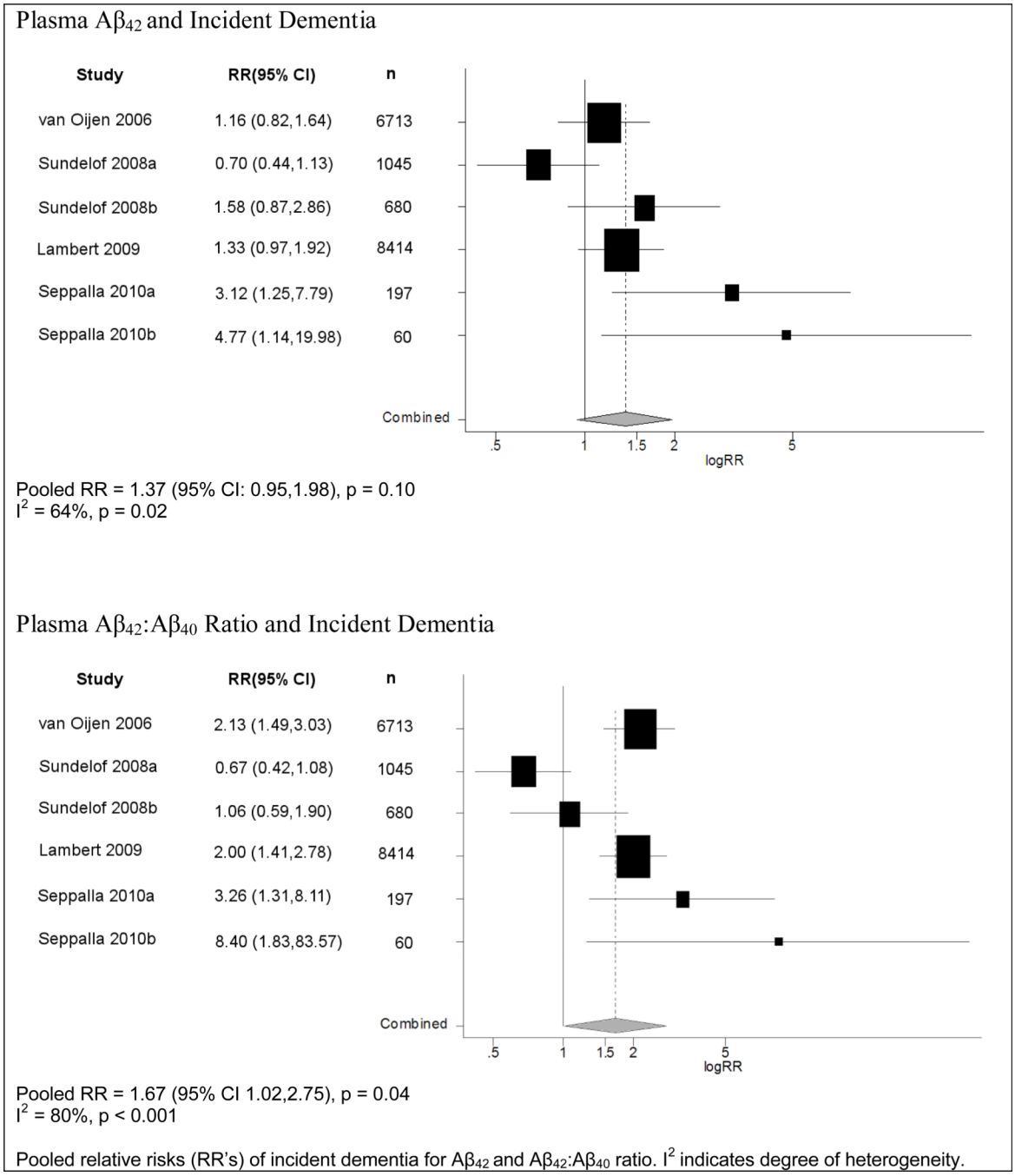

Figure 2.
Meta-Analysis of Plasma Aβ and Incident Dementia

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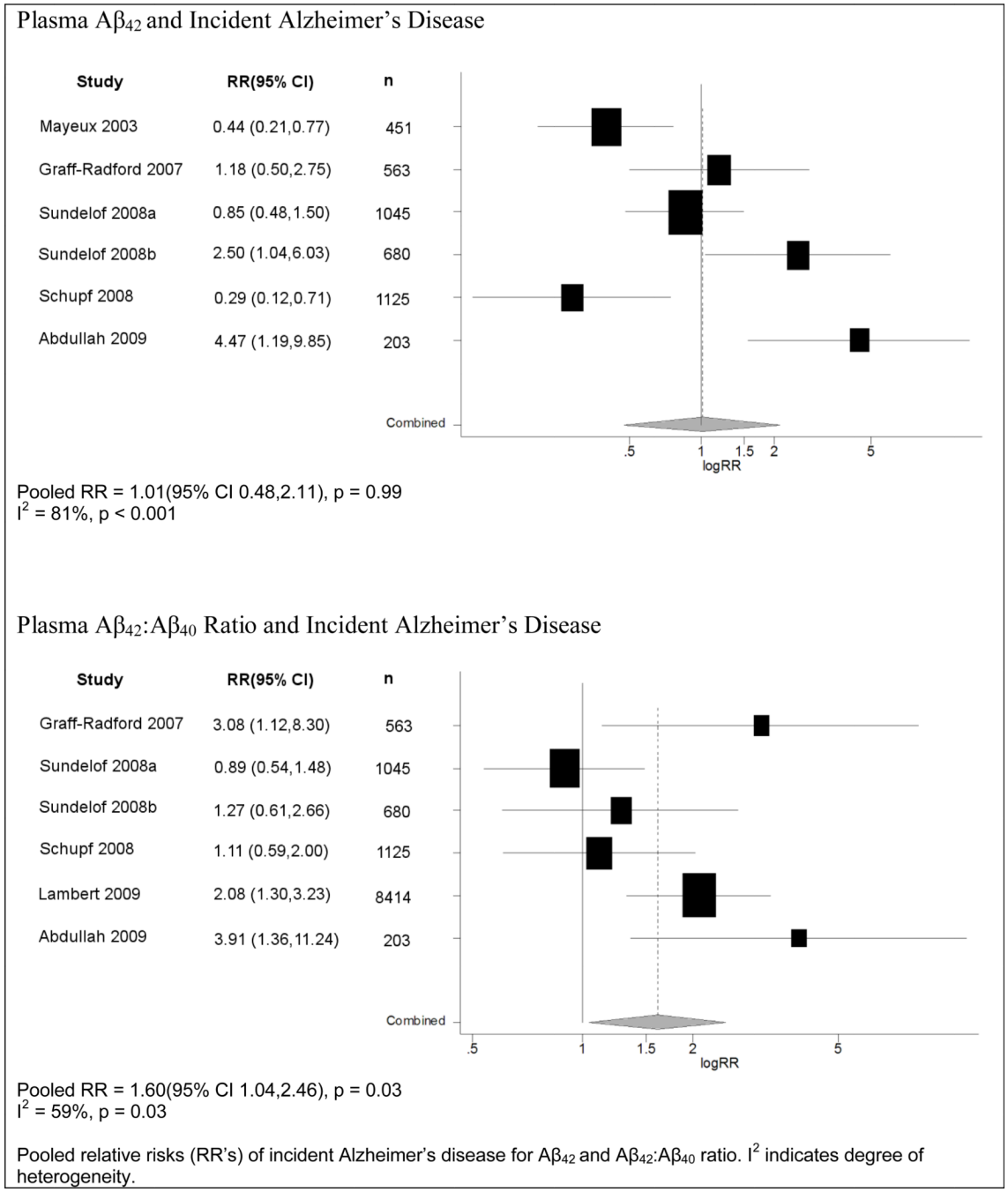

Figure 3.
Meta-Analysis of Plasma Aβ and Incident Alzheimer's Disease

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Table 1

Baseline characteristics of studies

Study	Design	Outcomes	No. at risk	No. of Events		Mean Age	Sex (female)	Follow-up time (yrs)	Adjusted For	Dementia		AD	
				Dem.	AD					RR (Aβ42)	RR ($A\beta_{42}$:$A\beta_{40}$)	RR (Aβ42)	RR ($A\beta_{42}$:$A\beta_{40}$)
Abdullah 2009	cohort	AD	203	--	14	76.8	48.3%	2.1 (median)	age, sex, education	--	--	4.47 (1.19,9.85)	3.91 (1.36,11.24)
Graff-Radford 2007	cohort	AD, cognitive change	563	--	17	78.0 (median)	62.0%	3.7 (median)	age, APOE	--	--	1.18 (0.50,2.75)	3.08 (1.12,8.3)
Lambert 2009	case-cohort	AD, dementia	8414	233	154	74.6	60.4%	4	age, gender, education, site	1.33 (0.97,1.92)	2.00 (1.41,2.78)	--	2.08 (1.30,3.23)
Mayeux 2003	cohort	AD	451	--	86	76.2	68.9%	5	age, education, APOE, Aβ40 level, BMI	--	--	0.4 (0.21,0.77)	--
Schupf 2008	cohort	AD	1125	--	104	76.9	68.3%	4.6 (mean)	age, sex, APOE, education, ethnicity, BMI, cohort membership	--	--	0.29 (0.12,0.71)	1.11 (0.59,2.00)
Seppalla 2010a	cohort	Dementia	197	9[c]	--	70.0[a]	55.0%[a]	3	unknown	3.12 (1.25,7.79)	3.26 (1.31,8.11)	--	--
Seppalla 2010b	cohort	Dementia	60	7[c]	--	70.0[a]	55.0%[a]	6	unknown	4.77 (1.14,19.98)	8.4 (1.83,83.57)	--	--
Sundelof 2008a	cohort	AD, dementia	1045	146	82	71.0	0.0%	11.2 (median)	age, APOE	0.7 (0.44,1.13)	0.67 (0.42,1.08)	0.85 (0.48,1.50)	0.89 (0.54,1.48)
Sundelof 2008b	cohort	AD, dementia	680	74	46	77.6	0.0%	5.3 (median)	AD: age dementia: age, APOE, diabetes	1.58 (0.87,2.86)	1.06 (0.59,1.90)	2.5 (1.04,6.03)	1.27 (0.61,2.66)
van Oijen 2006[b]	case-cohort	AD, dementia	6713	392	289	68.6	61.0%	8.6 (mean)	age, sex	1.16 (0.82,1.64)	2.13 (1.49,3.03)	--	--

Abbreviations: AD = Alzheimer's disease; Aβ = Amyloid beta; APOE = Apolipoprotein E; BMI = Body Mass Index; Dem = Dementia

[a] study population data is for entire cohort

[b] only continuous RR reported for AD outcome

[c] number of events estimated from published data

Note: confidence intervals reflect published results, before random-effects weighting

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Table 2

Baseline characteristics of studies (cont'd)

Study	Design	Outcomes	No. at risk	No. of Events		Mean Age	Sex (female)	Follow-up time (yrs)	Adjusted For	Reason not included
				Dem.	AD					
Blasko 2010	cohort	AD	406	--	33	75.8	56.5%	5	sex, education, creatinine, smoking, stroke/infarction in MRI, sGDS score, interaction between Aβ42 and APOE	only continuous RR reported
Cosentino 2010	cohort	cognitive change	880	--	--	76.1	68.0%	4.5	age, sex, race, BMI, APOE, recruitment wave	cognitive change as outcome
Lopez 2008	cohort	AD	274	--	88	79.3	60.9%	4.5 (mean)	age	only continuous RR reported
Okereke 2009	cohort	cognitive change	481	--	--	63.6	100.0%	10	age, education, BMI, hypertension, dyslipidemia, heart disease, smoking, HT, physical activity, alcohol, depression	cognitive change as outcome
Yaffe 2011	cohort	cognitive change	997	72	--	74.0	55.1%	10	age, race, education, diabetes, smoking, APOE	cognitive change as outcome

Abbreviations: APOE = Apolipoprotein E; BMI = Body Mass Index; HT = postmenopausal hormone therapy; MRI = Magnetic Resonance Imaging; sGDS = short form of the Geriatric Depression Scale

Note: confidence intervals reflect published results, before random-effects weighting

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