# Evaluation of Plasma A beta as Predictor of Alzheimer's Disease in Older Individuals Without Dementia: A Population-Based Study

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# Evaluation of Plasma Aβ as Predictor of Alzheimer's Disease in Older Individuals without Dementia: a Population-based Study

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## Abstract

Amyloid-β (Aβ) pathology is a major component in the mechanisms behind Alzheimer's disease (AD). Measurement of $A\beta_{42}$ in cerebrospinal fluid predicts cognitive decline in patients with mild cognitive impairment and identifies AD in patients with dementia. However, studies on Aβ in plasma are contradictory. In this prospective population-based study, plasma $A\beta_{42}$ and $A\beta_{40}$ were measured at baseline in 730 adults aged 70 years or older and without dementia. After five years, plasma levels were analyzed again and participants were assessed for development of dementia. During follow-up, 53 individuals (7 %) developed dementia of which 37 (5 %) were classified as AD. No difference in baseline plasma $A\beta_{42}$, $A\beta_{40}$ or $A\beta_{42}/A\beta_{40}$ ratio levels were observed between converters to dementia or AD compared to the cognitively stable individuals. However, individuals with plasma $A\beta_{40}$ levels above the median level for the group at baseline had an increased risk of developing dementia and AD during the follow-up, even after adjustment for age, sex, *APOE* genotype and educational level (odds ratio=2.2, 95% confidence interval=1.0-4.7, $p < 0.05$). Neither plasma $A\beta_{42}$ nor the $A\beta_{42}/A\beta_{40}$ ratio influenced the risk of developing dementia or AD. Moreover, $A\beta_{42}$ and $A\beta_{40}$ levels increased over the 5 years, whereas the $A\beta_{42}/A\beta_{40}$ ratio decreased ($p < 0.001$). In conclusion, this study suggests that measurement of plasma Aβ should not be used clinically to predict dementia or AD. However, plasma $A\beta_{40}$ may possibly be regarded as a moderate risk marker comparable to other risk markers for AD such as first-degree family history of dementia.

Keywords: Amyloid beta 40, Amyloid beta 42, Biological Markers, Plasma, Alzheimer Disease, Dementia, Cohort Studies.

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia and is associated with large cost for the health care system. Development of disease-arresting or -modifying drugs for AD is currently ongoing. To be effective and prevent development of dementia, these novel therapeutic agents must be administered before extensive, irreversible neuropathologic damage has occurred. Hence, early or preclinical detection of individuals with ongoing neurodegenerative processes will be important in the future. For this purpose, biological markers must be identified, since changes in cognition are relatively late symptoms of these processes [1].

One of the hallmark neuropathologic changes in AD is the occurrence of senile plaques. The major component in these plaques is amyloid-β (Aβ). This is a product of a proteolytic cleavage of the cell-membrane bound amyloid precursor protein (APP) by a specific set of secretases. Depending on the cleavage site, different isoforms of Aβ are produced. The most studied Aβ isoforms contain 40 amino acids ($A\beta_{40}$) or 42 amino acids ($A\beta_{42}$). $A\beta_{40}$ is most abundant whereas $A\beta_{42}$ is more prone to aggregate into oligomerers, fibrils and eventually into plaques. $A\beta_{40}$ is also found in plaques but is believed to aggregate first after the core of the plaque consisting primarily of $A\beta_{42}$ has developed [2, 3].

As a biomarker for AD, the levels of $A\beta_{42}$ in the cerebrospinal fluid (CSF) discriminate and predict AD with high accuracy in patients with mild cognitive impairment (MCI) [4, 5]. CSF $A\beta_{42}$ levels have even correlated with future cognitive decline in cognitively unimpaired healthy individuals [6-8]. In contrast, CSF $A\beta_{40}$ levels have not shown the same high accuracy [2]. Measurement of Aβ in plasma instead of in CSF would be of value, because plasma is more easily obtained than CSF in the clinical practice. However, reports on the ability of plasma $A\beta_{40}$ and $A\beta_{42}$ levels to discriminate and predict AD in cohorts with MCI

have been contradictory [2, 9-11]. Similarly, mixed results have been reported in the ability of plasma Aβ levels to predict cognitive decline and AD development in older individuals without dementia [2, 9-11].

In the present study we investigated whether plasma Aβ levels predicted development of dementia and AD in a population-based cohort of adults aged 70 years and older and without dementia. Plasma was analyzed for $A\beta_{40}$ and $A\beta_{42}$ in 730 healthy elderly who were subsequently followed for five years related to development of any type of dementia disorder.

## Materials and Methods

The study sample was derived from the Prospective Population Study of Women (PPSW) and from the Gerontological and Geriatric Population Studies (H70) in Gothenburg, Sweden [12-14]. Population samples were obtained from the Swedish Population Register, based on birth date, and included both persons living in private households and in institutions. The PPSW had its baseline examination in 1968-69 on a representative sample of women born in 1908, 1914, 1918, 1922, and 1930. One of the follow-up examinations was conducted in 2000, when participants were at least 70 years old. The H70 Study is a study of birth cohorts with baseline examinations at age 70 years. A new cohort of men and women born in 1930 was examined for the first time in 2000. In total, an effective sample of 1479 individuals from PPSW and H70 was invited for examination in 2000, and 1018 accepted a neuropsychiatric examination (response rate 68.8%, men 64%, women 71%; $p<0.05$). The participants were included in the present study if they: (1) had $A\beta_{40}$ and/or $A\beta_{42}$ measurements and (2) were without dementia at baseline (i.e. year 2000). Among the examined 1018 participants, 760 had $A\beta_{40}$ and/or $A\beta_{42}$ measurements, and of those, 30 were excluded because of dementia, leaving 730 individuals for inclusion in the study (202 men, 528 women).

In 2005-06, a 5-year follow-up of the included participants was conducted. Between baseline and follow-up, 64 participants had died leaving an effective sample of 666 individuals. Among these, 99 were lost due to other reasons (mainly refusal), leaving 567 (response rate 85%) for follow-up examination. Those not attending the follow-up examination (n=163), were traced in medical records for a diagnosis of dementia.

Compared to non-participants (n=461), those who participated (n=1018) in the study were less likely to die before January 2006 (13.4% vs. 20.4%, $p<0.05$), and were less often registered with a psychiatric diagnosis (9.6% vs. 16.7%, $p<0.001$) in the Swedish Hospital

Discharge register. In women, there were no significant differences in age (p=0.597) or hospital discharge diagnoses of dementia (3.3% vs. 5.0%, p=0.112). All men were 70 years old.

Informed consent was obtained from all participants and/or their relatives. The study was approved by the Ethics Committee for Medical Research at the University of Gothenburg.

*Study examinations*

Most participants were investigated at the geriatric outpatient clinic of Vasa Hospital in Gothenburg. Home visits were offered when needed. Examinations included comprehensive social, functional, somatic, neuropsychiatric and neuropsychological examinations, and close informant interviews. Neuropsychiatric examinations and close informant interviews were performed by experienced psychiatric research nurses. The examinations and interviews were semi-structured and included psychiatric symptoms and signs, mental and cognitive functioning, behaviour, and activities of daily living, as described previously [15]. Episodic memory was estimated with a ten word immediate and delayed recall test with an intermediate distraction task.

The somatic examinations included systolic and diastolic blood pressure (SBP/DBP) in the seated position after 5 minutes rest, body height (nearest cm) and weight (nearest 0.1 kg), body-mass-index (BMI) determination ($kg/m^2$), electrocardiogram (ECG) and fasting blood samples analyzed for determination of Aβ levels, *APOE* genotype, glucose, and cholesterol. The participants were additionally surveyed regarding educational level (less or more than basic = 6-7 years), medication use, and history of myocardial infarction, diabetes mellitus and stroke/TIA. Antiplateletes treatment was categorized as use of acetylsalicylic acid or clopidogrel.

*Dementia diagnoses*

Dementia at the examinations was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Third edition, revised (DSM-III-R) criteria [16] by neuropsychiatrists at consensus meetings using information from neuropsychiatric examinations and close informant interviews. AD was diagnosed according to NINCDS-ADRDA-criteria [17] and Vascular dementia (VaD) according to NINDS-AIREN criteria [18].

For those who were lost to follow-up in 2005-06, psychiatrists examined hospital medical records, the Swedish Hospital Discharge Register, and death certificates for information regarding dementia diagnoses. Information regarding dementia diagnoses was available for all participants since almost all people in Sweden have access to public health services and therefore have equal chances to have medical records, or being in the hospital discharge register.

*Analysis of plasma*

At baseline and follow-up blood samples were drawn by venipuncture in the morning after an overnight fast. For plasma collection, blood was drawn into tubes containing EDTA as anticoagulant. After centrifugation, plasma was aliquoted into polypropylene tubes and stored at −80 °C pending biochemical analyses, without being thawn and re-frozen. Quantification of $A\beta_{40}$ and $A\beta_{42}$ in plasma was performed using Luminex xMAP technology and the INNO-BIA plasma Aβ forms assays (Innogenetics, Ghent, Belgium) as previously described [19]. Plasma Aβ levels are presented as ng/L.

Serum cholesterol levels were measured at the Clinical Chemistry Laboratory at Sahlgrenska University Hospital according to clinical practice and measured in mmol/l.

*Statistical analyses*

Two primary analysis strategies were pursued: 1) baseline, cross-sectional among all study participants; and 2) prospective analyses predicting the odds of dementia from baseline Aβ measures.

Baseline, cross-sectional analyses: Means and standard deviations were calculated for all quantitative variables (e.g., age, MMSE score, Aβ levels, BMI, etc. Table 1); and frequencies and percentages for categorical variables (e.g., percentage *APOE*-ε4, presence of antihypertensive treatment, etc. Table 1). Correlational analyses with Aβ levels were assessed using non-parametric Mann-Whitney U-test (follow-up diagnosis, sex, antiplateletes treatment and presence of *APOE*-ε4), Kruskal-Wallis test (follow-up cognitive status) and Spearman's rank correlation coefficient (age, MMSE score and delayed word recall score).

Prospective analyses: Logistic regression models were used to estimate the odds of dementia and of AD by plasma Aβ levels. Four regression models were used. Model 1 was unadjusted. Model 2 was adjusted for age. Model 3 was adjusted for age, sex, *APOE* genotype, MMSE score, and education level. Model 4 was adjusted for age, sex, *APOE* genotype, MMSE score, education level, history of stroke, history of myocardial infarction, history of diabetes, use of antihypertensive treatment, cholesterol level, body-mass-index (BMI), and systolic and diastolic blood pressure. All model covariates are from the baseline examination. Plasma Aβ levels were analyzed as continuous variables (Z-scores), as well as dichotomized based on the median. Tertiles of Aβ levels were also considered and the lowest tertile was used as

reference. Logistic regression was performed using all participants as well as using only the subgroup with follow-up neuropsychiatric exam in year 2005-06. Moreover, longitudinal change in plasma Aβ levels on a group level was analyzed with Wilcoxon Signed Ranks Test.

Statistical analyses were performed using all available data. Missing data were treated as missing and no data were imputed, thus the number of participants varies slightly between analyses. The significant level was set to $p < 0.05$. SPSS for Windows®, version 19.0 was used for the statistical analyses.

## Results

Of 730 participants without dementia at baseline, 53 (7 %) developed dementia during the 5-year follow-up period (AD in 37 (5%) individuals, VaD in 11 (2%) individuals and other dementias (OD) in 5 (1%) individuals) (Figure 1). Of the 567 participants with a follow-up neuropsychiatric exam in 2005-6, 46 (8%) had dementia at follow-up (Figure 1). Baseline demographic data for the participants divided by clinical follow-up diagnosis are presented in table 1. At baseline, higher $A\beta_{40}$ and $A\beta_{42}$ was associated with higher age ($p< 0.05$), whereas no association was seen with sex, presence of *APOE*-ε4 allele, follow-up MMSE score or antiplateletes treatment (n = 130). However, *APOE*-ε4 allele positive participants had a tendency for lower $A\beta_{42}/A\beta_{40}$ ratio compared to those without an ε4 allele ($p<0.07$).

Participants who developed dementia during follow-up did not differ in baseline plasma $A\beta_{40}$ or $A\beta_{42}$ levels compared to those remaining without dementia (Table 1). This was also observed in analyses by dementia subtype (Table 1). However, as shown in table 2, individuals with $A\beta_{40}$ levels above the median baseline level for the entire group had an increased risk for developing dementia in general and AD dementia in particular. The increased risk of incident AD remained even after adjustment for age, sex, *APOE* genotype, MMSE score and educational level (Table 2). No increased risk was observed for $A\beta_{40}$ tertile or z-values or for any of the variables of $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio. However, if only including participants in the neuropsychiatric exam in 2005 (n=567), the association between $A\beta_{40}$ concentration and future dementia and AD became stronger (Table 3). In this group, $A\beta_{40}$ levels within the middle tertile level for the entire group increased the risk of development of AD compared to those within the lowest tertile. No increased risk was seen for those within the highest tertile. $A\beta_{42}$ levels and $A\beta_{42}/A\beta_{40}$ ratio remained non-significant.

In 324 individuals, plasma collection was performed both at baseline and at follow-up. In this group, $A\beta_{40}$ and $A\beta_{42}$ levels increased over the 5 years ($p < 0.001$), whereas the $A\beta_{42}/A\beta_{40}$ ratio levels decreased ($p < 0.001$). Sub-analysis of the individuals that remained non-demented ($n = 295$) at follow-up, showed the same significant increase in $A\beta_{40}$ and $A\beta_{42}$ levels, and decrease in $A\beta_{42}/A\beta_{40}$ ratio levels ($p < 0.001$). The same tendencies could be seen in the demented group ($n = 29$) and the AD group ($n = 21$) at follow-up, however these were not significant.

Sub-analysis revealed that the non-demented individuals with high MMSE scores at follow-up ($\geq 27$, $n = 431$) did not differ from those with lower MMSE scores at follow-up ($<27$, $n = 87$) when it comes to baseline plasma $A\beta_{40}$ levels, $A\beta_{42}$ levels, or $A\beta_{42}/A\beta_{40}$ ratio. Similarly, no difference was observed between those in the non-demented group who performed well or poorer on the delayed word recall test at follow-up, regardless of the cut-off score used on the memory test.

## Discussion

In this study we found that individuals without dementia and with plasma $A\beta_{40}$ levels above the median level for the population had a slightly increased risk to develop dementia and AD dementia over a 5-year period. However, the plasma levels of $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$ ratio were not found to be associated with future development of dementia.

The ability of plasma $A\beta_{40}$ and $A\beta_{42}$ levels in population-based samples of older adults to predict dementia has been studied previously, and the results are conflicting. Most of the population-based studies align with our findings suggesting that higher plasma $A\beta_{40}$ levels are related to an increased risk of developing AD dementia, and in some cases, an increased risk of VaD [20-23]. However, several other population-based studies report no relationship between plasma $A\beta_{40}$ and AD dementia [24-26] or between plasma $A\beta_{40}$ and cognitive decline [27] or that *decreased* plasma $A\beta_{40}$ levels are related to an increased risk of AD [28]. Similarly, studies investigating the utility of plasma $A\beta_{40}$ to discriminate individuals with AD dementia from other dementia subtypes report conflicting findings, where both higher levels [21] and lower levels [28, 29] of plasma $A\beta_{40}$ levels have been associated with AD dementia, as well as no difference in $A\beta_{40}$ levels from other dementia subtypes [19, 30-32]. Conflicting patterns are also observed for plasma $A\beta_{42}$ [19, 22, 24-28, 31] and plasma $A\beta_{42}/A\beta_{40}$ ratio, [21, 22, 25, 26, 30, 32] which in our study did not affect the risk for development of dementia or AD dementia. Additionally, it is evident in all studies that there is substantial overlap in plasma $A\beta_{40}$ and $A\beta_{42}$ levels between diagnostic groups [9, 11, 32]. The contradictory results and the substantial overlap between diagnostic groups together with the moderately increased odds ratio found in the present study strongly suggest that plasma $A\beta_{40}$ and $A\beta_{42}$ are not diagnostic or predictive markers for AD that can be used in a clinical setting. Instead, $A\beta_{40}$ could possibly be regarded as a rather weak risk marker, which has also been proposed by

others [10, 11, 20]. The odds ratio of plasma $A\beta_{40}$ for future AD is similar to that reported for first-degree family history of dementia [33, 34].

Several studies have shown that plasma Aβ levels do not correlate to amount of cerebral amyloid depositions [35-37]. Thus, plasma Aβ differs from CSF $A\beta_{42}$ because there are studies showing a correlation between CSF amyloid and brain amyloid load [36, 38]. Similarly, the association between $A\beta_{42}$ in CSF and future development of AD is stronger than that presented for plasma Aβs [2, 4, 9]. A possible explanation is that plasma Aβ is produced by many different cells types outside the central nervous system [2, 11, 39] and several studies have shown that plasma levels of Aβ do not correlate to the levels found in CSF [19, 35-37]. It has been proposed that plasma Aβ levels reflect Aβ clearance rather than cerebral Aβ load and might associate more strongly with microvascular dysfunction than CSF concentrations [11]. Additional support for this hypothesis are observed relationships between plasma Aβ levels and amount of both lacunar infarcts and white matter lesions as well as with atherosclerotic vessels. This could also explain observations that plasma $A\beta_{40}$ levels are associated with future development of VaD in addition to AD [21, 39-41].

While there are numerous strengths of this study, there are also limitations. First, participants in this study were all without dementia at baseline and re-evaluated after 5 years. This follow-up period is short, and there is a risk that some of the cases in the cognitively stable group are indeed affected by *prodromal* dementia disorders and will develop dementia after more than 5 years. Hence, the OR presented could be underestimated, given the assumption that plasma $A\beta_{40}$ is also changed in this asymptomatic subgroup. Clinical follow-up periods of more than five years are needed to answer this question. Second, no evaluation in regard to MCI diagnosis was available for the individuals, which could further increase the risk of underestimating the prevalence of *prodromal* dementia disorders. However, no relationship between MMSE score or episodic memory performance at follow-up and the studied plasma

Aβ levels could be observed in the group who did not develop dementia. Third, not all participants (22 %) were clinically evaluated at follow-up. For these individuals the follow-up dementia diagnosis was based on a medical record review and information from the Swedish Hospital Discharge Register. The risk of misclassification is greater in this subgroup without neuropsychiatric examination at follow-up. However, conducting the analyses separately for those participating in the neuropsychiatric examination (78 %) shows similar results, as those obtained using all participants in the study. Nevertheless, in comparison to the other plasma amyloid studies using community dwelling population [20-22, 24-28, 30], this study could include a relatively high percentage (49 %) of individuals from the original cohort. Moreover, quite few individuals were lost during follow-up as journal records were used in addition to the clinical evaluation within the study.

## Conclusions

Our data suggest that measurement of plasma Aβ is not clinically useful to predict AD or dementia. However, plasma $A\beta_{40}$ may possibly be regarded as a moderate risk marker comparable to other risk markers for AD such as first degree family history of dementia.

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# Tables

**Table 1**. Demographic data and baseline plasma Aβ levels according to 5-year follow-up diagnosis.

| | Remained normal | Normal to dementia | Normal to AD | Normal to VaD | Normal to OD |
|---|---|---|---|---|---|
| Number | 677 | 53 | 37 | 11 | 5 |
| Sex (F/M) | 483 / 194 | 45 / 8* | 32 / 5 | 9 / 2 | 4 / 1 |
| Age, baseline | 73.1 ± 4.8 | 77.8 ± 6.2*** | 77.3 ± 6.1*** | 78.9 ± 7.0*** | 78.8 ± 5.9* |
| Post compulsory education | 263 (39 %) | 17 (33 %) | 11 (30 %) | 4 (40 %) | 2 (40 %) |
| *APOE*-ε4 allele | 176 (27 %) | 19 (40 %) | 13 (38 %) | 4 (40 %) | 2 (50 %) |
| MMSE | 27.9 ± 2.4 | 26.7 ± 2.7*** | 26.8 ± 2.7*** | 26.3 ± 3.3** | 27.2 ± 1.5 |
| | | | | | |
| Myocardial infarction | 57 (8 %) | 8 (15 %) | 5 (14 %) | 1 (9 %) | 2 (40 %) |
| Diabetes mellitus | 51 (7 %) | 6 (11 %) | 4 (11 %) | 2 (18 %) | 0 (0 %) |
| Antihypertensive treatment | 181 (27 %) | 15 (29 %) | 11 (30 %) | 3 (30 %) | 1 (20 %) |
| Cerebrovascular insult | 94 (14 %) | 18 (34 %)*** | 8 (22 %) | 9 (82%)*** | 1 (20 %) |
| Cholesterol level (mmol/L) | 6.0 ± 1.1 | 6.2 ± 0.9 | 6.4 ± 0.9* | 6.0 ± 0.9 | 5.9 ± 0.8 |
| BMI | 26.8 ± 4.2 | 25.2 ± 3.8** | 25.2 ± 3.7* | 23.9 ± 4.1 | 28.1 ± 2.9 |
| Blood pressure (mmHg) | 156/85 ± 22/11 | 157/84 ± 20/10 | 158/85 ± 19/9 | 145/80 ± 19/13 | 170/89 ± 18/11 |
| | | | | | |
| **Plasma Aβ (ng/L)** | | | | | |
| Plasma $A\beta_{40}$ | 155.2 ± 39.4 | 160.6 ± 35.1 | 160.3 ± 34.9 | 163.6 ± 36.4 | 154.8 ± 42.8 |
| Plasma $A\beta_{42}$ | 37.9 ± 10.6 | 39.1 ± 10.6 | 39.0 ± 11.5 | 41.3 ± 7.9 | 35.6 ± 9.8 |
| Plasma $A\beta_{42}/A\beta_{40}$ ratio | 0.26 ± 0.10 | 0.26 ± 0.10 | 0.26 ± 0.11 | 0.26 ± 0.07 | 0.26 ± 0.09 |
| | | | | | |

Data are presented as number (%) or mean ± SD. Each subgroup was compared to those who remained normal: * p <0.05, ** p <0.01, *** p <0.001. AD = Alzheimer's disease, VaD = vascular dementia, OD = other dementias, F = female, M =male, MMSE = mini-mental state examination, BMI = body-mass-index, Aβ = Amyloid β.

Missing data: Remained normal - post compulsory education (7), *APOE* (31), MMSE (1), heart disease (1), diabetes mellitus (1), antihypertensive treatment (13), cholesterol (1), BMI (9), systolic blood pressure (1), diastolic blood pressure (30), $A\beta_{40}$ (7), $A\beta_{42}$ (1), $A\beta_{42}/A\beta_{40}$ ratio (8); To dementia - post compulsory education (1), *APOE* (5), antihypertensive treatment (1), systolic blood pressure (1), diastolic blood pressure (2), $A\beta_{40}$ (1), $A\beta_{42}/A\beta_{40}$ ratio (1); To AD - *APOE* (3), diastolic blood pressure (1); To VaD - post compulsory education (1), *APOE* (1), antihypertensive treatment (1), blood pressure (1); To OD - *APOE* (1), $A\beta_{40}$ (1), $A\beta_{42}/A\beta_{40}$ ratio (1).

**Table 2**. Associations between baseline Aβ plasma levels and development of dementia or AD over 5 years for all participants.

| **All participants** | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | 95 % C.I. | Odds ratio | 95 % C.I. | Odds ratio | 95 % C.I. | Odds ratio | 95 % C.I. |
| **Dementia*** | | | | | | | | |
| $A\beta_{40}$ median | 2.0 | 1.1-3.5 | 1.8 | 1.0-3.4 | ns | | ns | |
| $A\beta_{40}$ tertile | ns | | ns | | ns | | ns | |
| $A\beta_{40}$ z-value | ns | | ns | | ns | | ns | |
| $A\beta_{42}$ median | ns | | ns | | ns | | ns | |
| $A\beta_{42}$ tertile | ns | | ns | | ns | | ns | |
| $A\beta_{42}$ z-values | ns | | ns | | ns | | ns | |
| $A\beta_{42}/A\beta_{40}$ median | ns | | ns | | ns | | ns | |
| $A\beta_{42}/A\beta_{40}$ tertile | ns | | ns | | ns | | ns | |
| $A\beta_{42}/A\beta_{40}$ z-value | ns | | ns | | ns | | ns | |
| | *(n=729)* | | *(n=729)* | | *(n=685)* | | *(n=631)* | |
| **Alzheimer's dementia**** | | | | | | | | |
| $A\beta_{40}$ median | 2.5 | 1.2-5.0 | 2.3 | 1.1-4.8 | 2.2 | 1.0-4.7 | ns | |
| $A\beta_{40}$ tertile | ns | | ns | | ns | | ns | |
| $A\beta_{40}$ z-values | ns | | ns | | ns | | ns | |
| $A\beta_{42}$ median | ns | | ns | | ns | | ns | |
| $A\beta_{42}$ tertile | ns | | ns | | ns | | ns | |
| $A\beta_{42}$ z-value | ns | | ns | | ns | | ns | |
| $A\beta_{42}/A\beta_{40}$ median | ns | | ns | | ns | | ns | |
| $A\beta_{42}/A\beta_{40}$ tertile | ns | | ns | | ns | | ns | |
| $A\beta_{42}/A\beta_{40}$ z-value | ns | | ns | | ns | | ns | |
| | *(n=713)* | | *(n=713)* | | *(n=672)* | | *(n=631)* | |

Model 1: unadjusted; Model 2: adjusted for age; Model 3: adjusted for age, *APOE*, sex, MMSE score, education level; Model 4: adjusted for age, *APOE*, sex, MMSE score, education level, record of cerebrovascular insult, myocardial infarction and diabetes, any antihypertensive treatment, cholesterol level, body-mass-index, systolic and diastolic blood pressure. All significant odds ratios had p-value <0.05. * Seven participants had no $A\beta_{40}$ values and eight participants had no $A\beta_{42}/A\beta_{40}$ ratio values. ** Six participants had no $A\beta_{40}$ values and seven participants had no $A\beta_{42}/A\beta_{40}$ ratio values. N = number (in each model), Aβ = Amyloid β, C.I. = confidence interval, ns = non-significant.

**Table 3**. Associations between baseline plasma Aβ levels and development of dementia or AD over 5 years for participants with follow-up neuropsychiatric examination.

| With follow-up neuropsychiatric examination | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|
| | Odds ratio | 95 % C.I. | Odds ratio | 95 % C.I. | Odds ratio | 95 % C.I. | Odds ratio | 95 % C.I. |
| **Dementia** | | | | | | | | |
| $A\beta_{40}$ median | 2.3 | 1.2-4.5 | 2.2 | 1.1-4.3 | 2.1 | 1.0-4.3 | 2.4 | 1.1-5.4 |
| $A\beta_{40}$ tertile* | ns | | ns | | ns | | ns | |
| $A\beta_{40}$ z-value | ns | | ns | | ns | | ns | |
| | *(n=562)* | | *(n=562)* | | *(n=541)* | | *(n=497)* | |
| **Alzheimer's dementia** | | | | | | | | |
| $A\beta_{40}$ median | 2.8 | 1.3-6.2 | 2.7 | 1.2-5.9 | 2.7 | 1.1-6.4 | Ns | |
| $A\beta_{40}$ tertile (middle)* | 2.8 | 1.1-7.4 | 2.7 | 1.0-7.4 | 3.2 | 1.1-9.4 | 3.3 | 1.0-10.3 |
| $A\beta_{40}$ z-value | ns | | ns | | ns | | ns | |
| | *(n=550)* | | *(n=550)* | | *(n=530)* | | *(n=488)* | |

Model 1: unadjusted; Model 2: adjusted for age; Model 3: adjusted for age, *APOE*, sex, MMSE score, education level; Model 4: adjusted for age, *APOE*, sex, MMSE score, education level, record of cerebrovascular insult, myocardial infarction and diabetes, any antihypertensive treatment, cholesterol level, body-mass-index, systolic and diastolic blood pressure. All significant odds ratios had p-value <0.05. * Compared to the lowest tertile. N = number (in each model), Aβ = Amyloid β, C.I. = confidence interval, ns = non-significant.

## Figure Legends

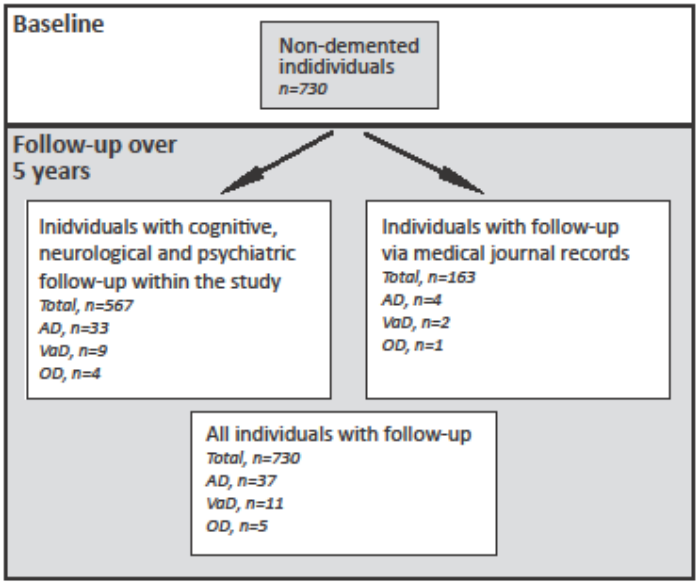


**Figure 1**

Participant flow-chart with follow-up diagnosis presented for the entire group as well as specified for the individuals with full cognitive follow-up evaluation and for the individuals with only medical journal record follow-up.