Prospective associations between plasma amyloid-beta 42/40 and frailty in community-dwelling older adults

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Abstract

BACKGROUND—Brain amyloid-beta (Aβ) plaques, a hallmark of the pathophysiology of Alzheimer's disease, have been associated with frailty. Whether the plasma Aβ markers show similar relationship with frailty is unknown.

OBJECTIVES—To investigate the prospective associations between plasma Aβ42/40 ratio and overtime frailty in community-dwelling older adults.

METHODS—From the 5-year Multidomain Alzheimer Preventive Trial (MAPT), we included 477 adults 70 years with available data on plasma Aβ42/40 ratio (lower is worse). Fried frailty phenotype (robust, pre-frail and frail) was assessed at the same time-point of plasma Aβ measures and after until the end of follow-up. The outcomes of interest were the change in the frailty phenotype over time (examined by mixed-effect ordinal logistic regressions) and incident frailty (examined by Cox proportional hazard models).

RESULTS—Plasma Aβ42/40 did not show significant associations with incident frailty; however, after adjusting for Apolipoprotein E (APOE) ε4 genotype, people in the lower quartile of plasma Aβ42/40 (0.103) had higher risk of incident frailty (HR=2.63; 95% CI, 1.00 to 6.89), compared to those in the upper quartile (>0.123). Exploratory analysis found a significant association between the lower quartile of plasma Aβ42/40 and incident frailty among APOE ε4 non-carriers (HR=3.48; 95% CI, 1.19 to 10.16), but not among carriers. No associations between plasma Aβ42/40 and evolution of frailty were observed.

CONCLUSION—No significant associations between plasma Aβ42/40 and frailty were found when APOE ε4 status was not accounted into the model. Nevertheless, APOE ε4 non-carriers with high Aβ burden might be more susceptible to develop frailty.

Keywords

INTRODUCTION

Frailty is a common geriatric syndrome characterized by reduced physiological reserve and increased vulnerability, which leads to an increased risk of adverse health outcomes in older adults(1). Frailty was also found to be associated with cognitive decline(2), leading researchers to propose these two conditions would share similar biological pathways(3) and brain pathology.

Previous studies had shown that brain amyloid-beta (Aβ) deposition, a well-known marker of cognitive decline involved in Alzheimer's disease (AD) pathology(4,5), was associated

with frailty severity(6) and its components(7–10) over time in non-demented older adults. However, to the best of the authors' knowledge, no investigation has examined the associations of plasma Aβ levels with frailty severity and its incidence in older people. Plasma Aβ has several advantages: it is a simple test, highly correlated to Aβ burden in the brain(11,12), less expensive than positron emission tomography (PET) and less invasive than cerebrospinal fluid test and, then, has a potential to be used in large populations for measuring amyloid load(13).

The objective of the present study was to evaluate the prospective associations of plasma Aβ42/40 with frailty severity and incidence in community-dwelling older adults.

METHODS

Study source

This is a secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT), whose detailed methods and main results had been described in previous publications(14,15). In brief, the MAPT study was a multicenter, randomized controlled trial which aimed to investigate the effect of a three-year multidomain intervention, omega-3 fatty acids supplementation, or their combination, in cognitive function among community-dwelling older adults. The multidomain intervention consisted of physical activity counselling, cognitive training and nutritional advice. Participants were recruited from May 2008 to February 2011 and randomized into four groups (the three above-mentioned interventions, and a placebo control group). After the three-year period, two additional years of observational follow-up were conducted, without any intervention. The five-year follow-up ended in April 2016. The MAPT study protocol was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and was authorized by the French Health Authority. All participants signed an informed consent.

Study population

A total of 1,679 community-dwelling adults older than 70 years, with either spontaneous memory complaint, limitations in one instrumental activity of daily living or slow gait speed, were enrolled into the MAPT study. Among them, 478 subjects with prospective frailty measurements had their plasma Aβ concentrations assessed – either at the study 12-month visit, for 442 people (92.7%), or at the 24-month visit, for the rest of the sample. One subject with extremely high plasma Aβ value (>4 standard deviations (SD) above the mean value) was excluded; finally, a total of 477 participants were included in this study. Among them, 377 individuals who were robust or pre-frail (definition described in below section) at the same timepoint of plasma Aβ measurement and who had at least one repeated frailty assessment over the follow-up period were included in the investigation of frailty incidence (Supplementary Figure S1).

Main outcome measures

Frailty status was assessed at the same timepoint as for plasma Aβ, and then every one year until the end of the five-year follow-up period; frailty assessments performed before the plasma Aβ measurements were not taken into account in this study. The timepoint of

plasma Aβ measures (either at 12-month or 24-month visit) was defined as the start point of follow-up (hereafter called "baseline").

Frailty was assessed according to the Fried frailty phenotype, which is based on five components(1): (1) weakness (poor handgrip strength measured by a handheld dynamometer with sex- and body mass index (BMI)–specific cutoffs); (2) slowness (4-m usual gait speed with cutoffs established for men and women, according to height); (3) involuntary weight loss (self-reporting >4.5 kg of weight loss in the prior year); (4) exhaustion (according to two items of the Center for Epidemiologic Studies depression scale(16)); (5) low physical activity (<383 kcal/week in men and <270 kcal/week in women during the prior 2 weeks by using Minnesota Leisure Time Activity 15-item questionnaire). Frailty condition was defined as meeting three or more frailty criteria; pre-frail met 1 or 2 criteria; and robust met no criterion. Participants were identified as having incident frailty if they were initially robust or pre-frail and met frailty definition during the follow-up period.

Two main outcomes of frailty were explored in this study. We first evaluated the evolution of frailty among the overall study population (477 individuals) by using the changes in the frailty phenotype as our outcome; the median (interquartile range – IQR) follow-up time was 1408 (731) days. We further focused on 377 non-frail individuals and identified the incident frailty over the follow-up period as our second outcome; the median number of days between baseline and last frailty assessment among this subgroup was 1425 days (ranging from 286 to 1798 days).

Plasma Aβ measurement

The plasma Aβ assay methods had been described elsewhere(12). Briefly, targeted Aβ isoforms (Aβ38, Aβ40, and Aβ42) were simultaneously immunoprecipitated from 0.45 mL of plasma via a monoclonal anti-Aβ mid-domain antibody (HJ5.1, anti-Aβ13–28) conjugated to M-270 Epoxy Dynabeads (Invitrogen). Prior to immunoprecipitation, samples were spiked with a known quantity of 12C15N-Aβ38, 12C15N-Aβ40 and 12C15N-Aβ42 for use as analytical internal standards. Proteins were digested into peptides using LysN endoprotease (Pierce). Liquid chromatography-mass spectrometry was performed as previously illustrated(12). Plasma analyses were performed as targeted parallel reaction monitoring (PRM) on an Orbitrap Fusion Lumos Tribrid mass spectrometer (Thermo Fisher) interfaced with an M-class nanoAcquity chromatography system (Waters). The precursor and product ion pairs utilized for analysis of Aβ species were chosen as previously illustrated(11,17). The derived integrated peak areas were analyzed using the Skyline software package(18). The Aβ42 and Aβ40 amounts were calculated by integrated peak area ratios to known concentrations of the internal standards. The value of Aβ42/40 ratio (dividing plasma Aβ42 by Aβ40) was then calculated and their normalized values were used.

The plasma Aβ42/40 was classified based on the cut-off value from receiver operating characteristic (ROC) curve analysis; a plasma Aβ42/40 ≤0.107 with the maximum Youden's Index was considered the best cut-off value for correlating to PET Aβ positive among MAPT participants. Subjects with plasma Aβ42/40 ≤0.107 were then defined as low plasma Aβ42/40 (Aβ42/40 >0.107 as reference group). Because there is no consensus yet on the

cutoff defining plasma Aβ status in the literature, we also categorized the plasma Aβ42/40 based on the lower quartile (0.103) of study population, considering plasma Aβ42/40 higher than upper quartile (>0.123) as the reference group.

Confounders

Confounding variables were selected based on data availability and on the literature on frailty and plasma Aβ(6,12,19): age, sex, MAPT group allocation, educational level, BMI, cognitive status evaluated by the 30-item Mini-Mental State Examination (MMSE)(20) and Apolipoprotein E (APOE) ε4 genotype (carriers defined as having at least one ε4 allele). BMI and MMSE score were assessed at the same timepoint as plasma Aβ measures (either 12-month or 24-month visit).

Statistical analysis

Descriptive statistics were presented as mean and SD, median and IQR, or frequencies and percentages. Student's t-test and Chi-square/Fisher exact test were used to compare baseline characteristics according to plasma Aβ42/40 status. We applied mixed-effect ordinal logistic regressions (with random effect on participant level and time), adjusted for all confounders mentioned above, to examine the prospective associations between plasma Aβ42/40 and evolution of the frailty phenotype; proportional odds assumption was checked. The plasma Aβ42/40 was further examined as a continuous variable, transforming from the original value multiplied with 100 for easier interpretation, and provided in Supplementary Table S2. Cox proportional hazard models with discrete time variable (ie, the clinical visits) were performed in non-frail subjects (n=377) to explore associations between plasma Aβ42/40 and incident frailty. Time-to-event was defined as the time interval between the plasma Aβ42/40 measures and the first time the participant was classified as frail; participants without the event were censored at their last frailty assessment visit. Proportional hazard assumption was tested using the Kolmogorov-type supremum test (p >0.05 was considered as non-violation of the assumption).

For mixed-effect ordinal logistic regressions and Cox regressions, we first performed an adjusted model without including APOE ε4 genotype as a confounder. Considering that the addition of APOE ε4 genotype in analyses led to a reduction in the sample size (less 42 participants (8.8%) in the mixed-effect models presented in Table 2, and 30 participants (8.0%) in the Cox models presented in Table 3), a second model with adjustment for APOE ε4 status was conducted; sensitivity analyses restricted to participants with available data of APOE ε4 status, but not including this variable in the model, are presented in Supplementary Tables S3 and S4, to explore the possibility of selection bias. If the association was significant, an interaction term between plasma Aβ42/40 and APOE ε4 genotype was introduced and the stratified results according to APOE ε4 genotype were provided (Supplementary Table S5). Statistical significance was defined as p-value <0.05. All data were analyzed by using SAS, version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Baseline characteristics (obtained at the same time-point as Aβ measurements) of the 477 participants are presented in Table 1. The mean age of participants was 76.8 ± 4.5 years, with a majority of women (59.3%). About 33% of the study population had plasma Aβ42/40 0.107 at baseline. Characteristics of the 377 participants included in incident frailty investigation were similar to the overall study population (Supplementary Table S1).

Results of the associations between plasma Aβ42/40 and the evolution of frailty phenotype over time are displayed in Table 2. No significant associations were found in either unadjusted models or models with adjustment for confounders. Sensitivity analysis using plasma Aβ42/40 as a continuous variable in the mixed-effect model (Supplementary Table S2) provided similar results.

Among 377 participants who were initially robust or pre-frail, 49 (13.0%) became frail over the follow-up. In adjusted Cox models, participants with low plasma Aβ42/40 did not show a higher risk of incident frailty, compared to those with high plasma Aβ42/40 (Table 3). However, when APOE ε4 genotype was accounted into the model, participants in the lower quartile of plasma Aβ42/40 (0.103) had 2.6 times more risk of incident frailty compared to those in the upper quartile (>0.123) (HR=2.63; 95% CI, 1.00 to 6.89; p=0.049) (Table 3). We explored if this positive result remained without introducing APOE ε4 status in the model among the same population with available data of APOE ε4 genotype (n=343); this sensitivity analysis found that plasma Aβ42/40 was not significantly associated with incident frailty (HR=2.12; 95% CI, 0.83 to 5.45; p=0.118) (Supplementary Table S4), suggesting that there was no selection bias of the population and that APOE ε4 was playing a role in the plasma Aβ42/40-incident frailty association. We further performed the Cox analysis introducing the interaction between APOE ε4 genotype and plasma Aβ42/40. Although the interaction did not reach significance (p=0.090), a significant association between the lower quartile of plasma Aβ42/40 and incident frailty was found among APOE ε4 non-carriers (HR=3.48; 95% CI, 1.19 to 10.16), but not among carriers (Supplementary Table S5).

DISCUSSION

To our knowledge, this is the first work to investigate prospective associations between plasma Aβ and frailty among older adults. Neither the overtime evolution of frailty phenotypes nor incident frailty was significantly associated with plasma Aβ42/40 when APOE ε4 status was not accounted into the model. Nevertheless, once adjusting for APOE ε4 genotype, people with low plasma Aβ42/40 (as defined by the lower quartile) showed higher risk of incident frailty over the follow-up, comparing to those with high plasma Aβ42/40 (the upper quartile); this association seems to be dependent of the APOE ε4 genotype, having been found only among non-carriers in an exploratory analysis.

To the best of our knowledge, only one study had investigated the prospective associations between brain Aβ and incident frailty before(6). In that study, also performed with MAPT participants and adjusted for APOE ε4 genotype, Maltais et al. did not discover relationships between brain Aβ load and incidence of frailty (defined as frailty index (FI) 0.25)(6).

Our study, which analyzed the associations between low plasma Aβ and incident frailty, differed from Maltais et al.(6) in the classifications for frailty, in the measurement of Aβ, and consequently, in the study population. Incident frailty measured by FI represents a general vulnerable status in older adults, including having depressive symptoms or uncontrolled hypertension; in contrast, the Fried frailty phenotype applied in the present work is more related to physical elements and performance. Previous studies working on physical performance had demonstrated cross-sectional and longitudinal associations between cerebral Aβ deposition and slow gait speed in older adults free of dementia (8–10). Inverse associations between physical activity level and brain Aβ had also been observed(21), although not in all studies(22). In addition, our study examined Aβ levels in blood rather than the Aβ plaques in brain. The imbalance of plasma Aβ42/40 could be detected before brain amyloidosis(12); therefore, it is plausible that plasma Aβ could be more sensitive to early preclinical impairments in cognitive performance, which further was shown to predict the elevated risk of onset of frailty(23,24). Again, our findings must be interpreted with caution, since the significant association was only found in the analysis including APOE ɛ4 genotype as a confounder. Whether plasma Aβ42/40 could properly predict future frailty requires further investigation.

Complex mechanisms linking plasma Aβ and frailty might also exist, since the relationship between plasma Aβ and the progression of frailty is mediated by other covariates. Our exploratory analysis considering the interaction between APOE ɛ4 status and plasma Aβ provided significant association with incident frailty only among APOE ɛ4 non-carriers. While APOE ɛ4 genotype is a strong genetic risk factor of AD and ɛ4 positive showed increased brain Aβ deposition in both preclinical AD patients and cognitively normal individuals(25,26), its association with frailty is controversial(27,28). Additional studies exploring the relationship between frailty, plasma Aβ and APOE ɛ4 genotype, as well as the potential mechanism behind it, would shed light on this topic in the future.

The lack of associations between plasma Aβ42/40 and change in the frailty phenotype may be potentially explained by the unexpected large proportion of frail people with higher plasma Aβ42/40 at baseline. It is also possible that the change of plasma Aβ42/40 over time, rather than a single point value of plasma Aβ42/40, would be better associated with frailty progression. Alternatively, it could be that frailty is not strongly affected by the presence of amyloid plaques, but interact with this marker of Alzheimer's disease pathology to develop further adverse outcomes including dementia(29). Further studies to explore the long-term associations between changes in plasma Aβ and frailty evolution, and their interaction effect on cognitive decline are encouraged.

This study has important strengths: it is the first to investigate the associations between the plasma Aβ marker and frailty in older adults. The plasma Aβ42/40 applied in our work was assessed by a recently improved technique, which provided a sensitive and reliable measure for predicting brain amyloidosis(11,13). Moreover, we applied a longitudinal design and explored different kinds of frailty outcome (phenotype evolution and incidence). Nonetheless, some limitations are worth mentioning. First, as usual in longitudinal studies, some measures of frailty were missing during the follow-up period, which might have, on one hand, underestimated the time of incident frailty for cases (individuals developing

the event) and, on the other hand, misclassified some individuals as non-cases (individuals without the event). In addition, this is a secondary analysis of a randomized controlled trial in which three-quarters of the population received interventions, even though interventions did not affect physical function(15) nor frailty incidence as measured by Fried frailty phenotype(30); all analyses were adjusted by allocation to intervention groups in an attempt to minimize the impact of this bias.

To conclude, our study did not demonstrate significant associations between plasma Aβ42/40 and frailty over time when APOE ε4 status is not taken into consideration. However, APOE ε4 non-carriers in the lower quartile of plasma Aβ42/40 might have an increased risk of developing frailty. Further longitudinal studies investigating the relationship between frailty, plasma Aβ and APOE ε4 genotypes should be encouraged.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Baseline characteristics of the study population according to plasma amyloid-β status.

Variables	Total	High plasma Aβ42/40 (>0.107)	Low plasma Aβ42/40 (0.107)
N (%)	477	318 (66.7)	159 (33.3)
Age (years)	76.8 (4.5)	76.5 (4.5)	77.5 (4.6) [*]
Sex (female)	283 (59.3)	203 (63.8)	80 (50.3)†
MAPT groups			
Multidomain intervention + omega-3	128 (26.8)	93 (29.3)	35 (22.0)
Omega-3	111 (23.3)	72 (22.6)	39 (24.5)
Multidomain intervention	118 (24.7)	81 (25.5)	37 (23.3)
Placebo	120 (25.2)	72 (22.6)	48 (30.2)
Education			
No diploma or primary school certificate	121 (25.7)	76 (24.3)	45 (28.7)
Secondary education	155 (33.0)	95 (30.3)	60 (38.2)
High school diploma	67 (14.3)	52 (16.6)	15 (9.5)
University level	127 (27.0)	90 (28.8)	37 (23.6)
Fried frailty phenotype			
Robust (0/5)	220 (52.5)	138 (49.1)	82 (59.4)
Pre-frail (1–2/5)	183 (43.7)	130 (46.3)	53 (38.4)
Frail (3/5)	16 (3.8)	13 (4.6)	3 (2.2)
CDR			
Score 0	209 (43.8)	147 (46.2)	62 (39.0)
Score 0.5 or 1	268 (56.2)	171 (53.8)	97 (61.0)
MMSE	27.9 (1.9)	27.9 (1.9)	27.7 (1.9)
Body mass index (kg/m²)	26.5 (4.0)	26.6 (4.2)	26.3 (3.6)
APOE ε4 carriers	121 (27.9)	61 (21.4)	60 (40.5)†
Plasma Aβ42/40, median (IQR)	0.103 (0.113, 0.123)	0.120 (0.110, 0.130)	0.100 (0.090, 0.100) [†]

Values presented in number (%) for categorical variables or mean (standard deviation) for continuous variables, unless otherwise indicated.

Aβ, amyloid-beta; APOE, Apolipoprotein E; AD, Alzheimer's disease; CDR, Clinical Dementia Rating scale; IQR, interquartile range; MAPT, Multidomain Alzheimer Preventive Trial; MMSE, Mini-Mental State Examination (0–30, 0 is worse).

[*] p<0.05

[†] p<0.01 between two groups determined by Student's t-test or by Chi-square/Fisher exact test.

Table 2.

Mixed-effect ordinal logistic regressions examining associations between plasma amyloid-β 42/40 and frailty evolution over time.

Plasma Aβ42/40	Unadjusted model* (N=477)			Adjusted model 1† (N=466)			Adjusted model 2‡ (N=424)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Threshold 1: cutoff									
High (>0.107)	ref.	-	-	ref.	-	-	ref.	-	-
Low (≤ 0.107)	1.19	0.95 – 1.48	0.123	1.20	0.97 – 1.50	0.097	1.14	0.90 – 1.45	0.266
Threshold 2: quartile									
25th percentile (≤ 0.103)	1.16	0.87 – 1.56	0.316	1.23	0.91 – 1.65	0.175	1.18	0.86 – 1.62	0.302
>25th–50th percentile (>0.103, ≤0.113)	0.98	0.73 – 1.31	0.888	0.99	0.74 – 1.32	0.950	0.96	0.70 – 1.31	0.795
>50th–75th percentile (>0.113, ≤0.123)	0.99	0.74 – 1.31	0.916	1.04	0.78 – 1.38	0.779	1.07	0.79 – 1.44	0.685
>75th percentile (>0.123)	ref.	-	-	ref.	-	-	ref.	-	-

OR, odds ratio of increasing frailty severity over time compared to reference group

Aβ, amyloid-beta; CI, confidence interval; ref, reference group

*
Random slope on time and on participants only

†
Adjustments for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, body mass index, Mini-Mental State Examination (MMSE) score, time and interaction between plasma Aβ42/40 group and time; excluding participants without data of education, body mass index or MMSE score

‡
Adjustments for age, sex, MAPT groups, education, body mass index, MMSE score, APOE ε4 genotype, time and interaction between plasma Aβ42/40 group and time; excluding participants without data of education, body mass index, MMSE score or APOE ε4 genotype.

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Table 3.

Cox proportional hazard models for incident frailty over the follow-up.

Plasma Aβ42/40	Unadjusted model (N=377)			Adjusted model 1 [*] (N=373)			Adjusted model 2 [†] (N=343)		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Threshold 1: cutoff									
High (>0.107)	ref.	-	-	ref.	-	-	ref.	-	-
Low (≤0.107)	1.18	0.66 – 2.11	0.580	1.35	0.73 – 2.50	0.332	1.71	0.87 – 3.35	0.122
Threshold 2: quartile									
25th percentile (≤0.103)	1.69	0.77 – 3.73	0.193	1.85	0.78 – 4.40	0.163	2.63	1.00 – 6.89	0.049
>25th–50th percentile (>0.103, ≤0.113)	0.77	0.30 – 1.95	0.581	0.71	0.27 – 1.89	0.490	0.91	0.31 – 2.72	0.872
>50th–75th percentile (>0.113, ≤0.123)	1.42	0.64 – 3.16	0.391	1.30	0.56 – 3.04	0.542	1.36	0.53 – 3.50	0.530
>75th percentile (>0.123)	ref.	-	-	ref.	-	-	ref.	-	-

Aβ, amyloid-beta; CI, confidence interval; HR, hazard ratio; ref, reference group;

[*] Adjustments for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) groups, education, body mass index and Mini-Mental State Examination (MMSE) score; excluding participants without data of education, body mass index or MMSE score

[†] Adjustments for age, sex, MAPT groups, education, body mass index, MMSE score and APOE ε4 genotype; excluding participants without data of education, body mass index, MMSE score or APOE ε4 genotype.