Title: Association of years to parent's sporadic onset and risk factors with neural integrity and Alzheimer's biomarkers

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ABSTRACT

Objective: To evaluate the hypothesis that proximity to parental age at onset (AAO) in sporadic Alzheimer's disease (AD) is associated with greater AD and neural injury biomarker alterations during midlife and to assess the role of non-modifiable and modifiable factors.

Methods: This observational study included 290 cognitively unimpaired (CU) participants with family history (FH) of clinically-diagnosed sporadic AD (aged 49-73) from the ALFA study. [18F]Flutemetamol-PET SUVRs, CSF Aβ42/40 ratio and p-tau were used as AD biomarkers. Hippocampal volumes and CSF t-tau were used as neural injury biomarkers. Mental and vascular health proxies were calculated. In multiple regression models, we assessed the effect of proximity to parental AAO and its interaction with age on AD and neural injury biomarkers. Then, we evaluated the effects of FH load (number of parents affected), sex, APOE-ε4, education, vascular and mental health.

Results: Proximity to parental AAO was associated with β-amyloid, but not with neural injury biomarkers, and interacted with sex and age, showing women and older participants increased β-amyloid. FH load and APOE-ε4 showed independent contributions to β-amyloid load. Education, vascular and mental health proxies were not associated with AD biomarkers. However, lower mental health proxies were associated with decreased hippocampal volumes with age.

Conclusions: The identification of the earliest biomarker changes and modifiable factors to be targeted in early interventions is crucial for AD prevention. Proximity to parental AAO may offer a timeline for detection of incipient β-amyloid changes in women. In risk-enriched middle-aged cohorts, mental health may be a target for early interventions.

Classification of evidence: This study provides Class II evidence that in CU adults with FH of sporadic AD proximity to parental AAO was associated with β-amyloid but not with neural injury biomarkers.

INTRODUCTION

The optimal time window to prevent Alzheimer's disease (AD) dementia is probably before substantial neuronal loss occurs when individuals are still asymptomatic. Recent evidence suggests a *very early* window for therapeutic treatment on participants showing subthreshold amyloid increases.[1,2] Indeed, even incipient increases of AD pathology have deleterious effects on brain and cognition. Identification of individuals showing the *earliest* detectable biomarker changes is thus crucial for clinical trials to succeed.

Midlife is a critical period of divergence between normal and pathological aging.[3] While the prevalence of AD pathologic changes in cognitively unimpaired (CU) adults during midlife is low (10%),[4] the estimates are 3 to 4 times higher in middle-aged CU adults with a genetic predisposition. Moreover, middle-aged CU with family history of *sporadic* AD start showing AD-related pathologic changes during midlife.[5] Interestingly, a recent study showed that proximity to parental age at onset (AAO) may help capture incipient amyloid changes during midlife in CU participants with family history (FH) of sporadic AD.[6] This approach may be especially useful to detect amyloid burden during this period when age-related amyloid is less likely to appear,[6] however, proximity to parental AAO may also result in an acceleration of age-related effects.

An important addition to previous research using the proximity to parental AAO approach would be: first, to evaluate whether it is also useful to estimate alterations in biomarkers of neural injury during midlife (cerebrospinal [CSF] t-tau and hippocampal volume), and second, to examine the role of AD? risk and protective factors as potential modifiers. This is important because middle-aged adults with FH of sporadic AD are at increased risk of developing dementia[7] and thus represent a candidate population for risk reduction strategies through lifestyle interventions. Effect modification would imply that the association between proximity to parental AAO and AD or neural injury biomarkers differs by

the exposure to AD risk factors. Identifying potentially modifiable factors represents an important step towards identification of at "higher risk" individuals, as well as targetable modifiable factors that may play a role in the development of the disease. Recent research suggest that risk factors for neural injury and amyloid are different.[8] Since the presence of both neural injury and AD pathologies best predict cognitive impairment, understanding the role that risk and protective factors play in increasing resistance to AD pathologies (amyloid and tau) and brain resilience (brain structure and function) is fundamental.[9] Yet, few studies focused on understanding the role of these factors on imaging and CSF biomarkers in midlife.[10,11] Sex, *APOE-ε4* status and FH load (number of affected parents) are amongst the non-modifiable factors associated with greater alteration of AD biomarkers.[4,12,13] Further, modifiable factors such as years of formal education, or vascular and mental health may be associated with AD pathologies or neural injury biomarkers.[14–18]

The present study focuses on CU middle-aged adults with FH of AD dementia, with the following objectives*:* (i) to evaluate the association between proximity to AAO and AD pathologies (measured using core AD CSF biomarkers and amyloid PET), (ii) to test the association between AAO and biomarkers of neuronal injury (hippocampal volume and CSF t-tau) and (iii) to provide a comprehensive evaluation the potential effect modification by non-modifiable (sex, FH load, *APOE-ε4*) and modifiable (years of education, mental and vascular health) factors. We hypothesized that proximity to parental AAO will be associated with AD pathologic changes and to a lesser extent to neural injury markers. Further, we hypothesized that we would be able to identify modifiable and non-modifiable factors differently associated with AD *versus* neural injury biomarkers.

METHODS

Participants

Two hundred ninety one participants of the ALFA+ (for ALzheimer's and FAmilies) study were included in this investigation (See Table 1). ALFA+ is a nested longitudinal long-term study of the ALFA parent cohort. In brief, the ALFA cohort was established as a research platform to characterize preclinical AD and is composed of 2,743 cognitively preserved individuals, aged between 45 and 75 years old with increased risk for AD. [19] In the nested ALFA+ study, participants underwent advanced protocols of magnetic resonance imaging (MRI), amyloid PET imaging with [18F]flutemetamol and CSF core AD biomarkers. The participants included here represented the first consecutive cases with FH and available biomarker data. As described below, from the initial sample with self-reported FH (n=332), only 291 fulfilled our criteria to be considered in the study. From these, 275 had available CSF biomarker data and 260 amyloid-PET data.

Family history of AD

Family history of AD was evaluated using self-reports. Forty seven percent of the participants brought the clinical diagnosis on paper. When this report was not available, a neurologist performed a retrospective diagnosis through a structured interview. In brief, FH of AD was only considered when (i) a self-report, and (ii) a clinical diagnosis, or (iii) a retrospective diagnosis consistent with AD dementia existed. This is an on-going study and these data are updated during follow-up visits. For the present study, we used a conservative approach (only participants with strong evidence for FH were considered) and thus FH updates could only affect the family history load variable (1 *versus* 2 parents). However, taking into account the age of the participants and their parents, significant changes in FH are not expected.

AD biomarkers

Cerebrospinal fluid biomarkers. Fresh CSF samples were collected in 15-mL polypropylene tubes (Sarstedt catalog #62.554), the supernatant aliquoted into 0.5-mL polypropylene tubes (Sarstedt catalog #72.730.005), and frozen within 2 h after lumbar puncture. Aliquots were placed into long-term storage boxes and stored at − 80 °C until shipment on dry ice for analysis. CSF Aβ42 and Aβ40 were measured using the NeuroToolKit (Roche) on an Elecsys cobas e 411 instrument. The Elecsys® phosphotau (181P) and Elecsys® total-tau immunoassays for CSF on a cobas e 601 analyzer (software version 05.02) at the Clinical Neurochemistry Laboratory, University of Gothenburg, Sweden (ALFA+) or at the Biomarker Research Laboratory, University of Pennsylvania, USA (ADNI), according to the kit manufacturer's instructions and as described in previous studies.[20] The CSF Aβ42/40 ratio was used the biomarker for cerebral amyloid plaque pathology.[21]

Structural MRI. The T1-weighted 3D-TFE sequence was acquired in a Philips 3 T Ingenia CX scanner with a voxel size of 0.75 × 0.75 × 0.75 mm3, FOV 240 × 240 × 180 mm3, sagittal acquisition, flip angle 8°, TR = 9 .9ms, TE = 4 .6ms, TI = 900 ms.

Amyloid-PET. PET imaging was conducted in a Siemens Biograph mCT, following a cranial CT scan for attenuation correction. Participants were injected with 185 MBq (range 166.5–203.5 MBq) of [18F]flutemetamol, and 4 frames of 5 min each were acquired 90 min post-injection. Images were reconstructed with an OSEM3D algorithm using 8 iterations and 21 subsets and with point spread function (PSF) and time of flight (TOF) corrections into a matrix size of 1.02 × 1.02 × 2.03 mm.

Proximity to parental AAO calculation. The parental AAO corresponds to the age at which the participant observed significant cognitive decline (age at symptom onset). The proximity to parental AAO variable was calculated as the age of the participant at assessment minus the age of the parent at symptom onset. If an individual had 2 parents with a history of AD dementia, the age of the parent with the earliest onset was used to calculate the proximity to parental AAO score. The study sample was within an average of -8.32 years before parental AAO ranging from -21.7 to 15.9 years. Thus,

12% of the sample surpassed the parental AAO. This group was at an average of 3.9 years above (from 0.13 to 15.9). Here, we present the analyses with the full group, but we conducted sensitivity analysis excluding participants that passed the parental AAO.

Vascular and mental health. A proxy of systemic vascular health was calculated based on the number of self-reported vascular comorbidities (diabetes, obesity, and hypertension). Of the study sample 37.1% reported 0 vascular comorbidities, 38,4% 1, 16.5% 2 and 10.4% more than 2 (up to 5). Given the data distribution, we created a factor with 3 levels: 0- no reported comorbidities, 1- one comorbidity, 2- more than 1 reported comorbidities (up to 5).

A mental health indicator was created based on self-reported history of anxiety and depression (including generalized anxiety disorder and major depression). Of the study sample, 74.2% did not have history of mental disorders, 19.4% 1, and 6.5% between 2 and 3. Given the distribution of the data we created a dichotomous variable: 0- no history of mental disorders, 1- history of mental disorders. The group with history of mental disorders also showed higher levels of anxiety and depression during the ALFA+ visit as measured by the Hospital Anxiety and Depression Scale (HADS[22]) (t=4.152, p=0.001).

APOE Genotype. Total DNA was obtained from blood cellular fraction by proteinase K digestion followed by alcohol precipitation. Samples were genotyped for two single nucleotide polymorphisms (SNPs), rs429358 and rs7412, determining the possible *APOE* alleles: ε1, rs429358 (C) + rs7412 (T); ε2, rs429358 (T) + rs7412 (T); ε3, rs429358 (T) + rs7412 (C); and ε4, rs429358 (C) + rs7412 (C).

Imaging preprocessing and statistical analyses

MRI processing. Hippocampal volumes and total intracranial volumes (TIV) were calculated using FreeSurfer V. (6.0).[23] FreeSufer segmentations as well as hippocampal volumes values' distribution were visually inspected. We averaged right and left hippocampal volumes and adjusted them from TIV by calculating the residual from a linear regression (hippocampal volume *versus* intracranial volume) among the subjects included in the study. Adjusted hippocampal volumes reflect the deviation in participants' hippocampal volumes from what is expected given their TIV.

Flutemetamol-PET. Images were preprocessed using SPM12. In brief, average PET images were co-registered to the corresponding MRI scans and normalized to MNI space. We calculated the SUVr in MNI space using the whole cerebellum as reference region (for details see [24]).

Statistical models

We performed two sets of complementary multiple regression analyses with AD (amyloid as measured by CSF Aβ42/40 ratio and PET, and p-tau) or neural injury biomarkers (t-tau and hippocampal volumes) as outcome measurements. The statistical analyses were performed with IBM SPSS software (version? Reference?).

In the first set of analyses, the measure of interest was the main effect of proximity to parental AAO on AD and neural injury biomarkers. The models included age, sex and years of education as covariates. The secondary measurements of interests were the 2-way interactions between proximity to parental AAO, age, sex and years of education. These interaction terms were thus included in the model. In follow-up analyses, we tested whether the effects were still significant when *APOE-ε4* status and FH load (1 or two parents affected) were introduced in the model.

In secondary analyses, we assessed whether vascular and mental health modified the significant effects of age and proximity to parental AAO on AD and neural injury biomarkers.

Taking into account the number of dependent variables and statistical models, we considered significant results when p≤0.01 (0.05/5), p values between 0.05-0.01 were interpreted as trends.

RESULTS

Table 1

Associations between proximity to parental AAO and biomarkers of AD pathology and neural injury

Regarding AD biomarker models, those considering amyloid as dependent variable showed significant associations with proximity to parental AAO (Table 2?), while those considering p-tau did not (table?).

Thus, both age and proximity to parental AAO showed a main effect and an interaction on Flutemetamol-PET SUVRs (Figure 1?). The association of proximity to parental AAO with increased Flutemetamol-PET SUVRs was stronger at older ages: xxx (Figure 1, Figure 2). Sex showed a significant main effect and an interaction with proximity to parental AAO; the association between proximity to parental AAO and amyloid-PET was stronger in women: xxx (compare effect sizes for both groups, and state p for interaction) (See Table 2). Finally, years of education did not show neither a significant main effect nor a significant interaction (table/figure?).

In follow-up analyses, when *APOE-ε4* and FH (1 *versus* 2 parents affected) status were included in the amyloid-PET model, the main effect of proximity to parental AAO (β=-3.33, p=0.001) and its interaction with age remained significant (β=2.25, p=0.002), suggesting an independent effect. Furthermore, both *APOE-ε4* status (β=0.148, p=0.009), and FH load (β=0.148, p=0.008) showed significant main effects on amyloid-PET, but they did not interact with proximity to parental AAO (Figure 1).

In the Aβ42/40 ratio model, the main effect of proximity to parental AAO and its interaction with age only showed trends towards significance. Age, sex and years of education did not show any main effects or interactions with proximity to parental AAO. In follow-up analyses, *APOE-ε4* status (β=-0.411, p<0.001), and FH load (1 or two parents affected, β=-0.176, p=0.001) showed significant effects (Figure 1).

In supplemental analyses, we tested for quadratic relationships between proximity to parental AAO and amyloid biomarkers. The associations were not significant (data not shown).

Finally, no significant effects (nor trends) of proximity to parental AAO were found in the model including p-tau as dependent variable (table/figure?). However, there was a trend towards a significant correlation with age (β= 0.27, p=0.035). This effect was significant when the non-significant interaction terms were removed from the model (β =0.31; p=0.001)

Neural injury biomarkers models (including t-tau or hippocampal volumes as dependent variables), did not show any significant association with proximity to parental AAO (figure 3?). Thus, only age showed trends towards significant associations with both t-tau and hippocampal volumes (β =0.26, p=0.041, β=0.27, p=0.035). The association between increasing age, t-tau and hippocampal volumes was significant when the non-significant interactions were removed from the model (t-tau: β=0.31, p<0.001, hippocampal volumes: β=-0.182, p=0.006) (Figure 3).

Effects of mental and vascular health

We tested the effect modification by mental and vascular health on the significant relationships mentioned above, by including the 2-way interactions between proximity to parental AAO and mental or vascular health. Since there were no associations between neural injury markers and proximity to parental AAO or family history variables, in neural injury models we only evaluated whether vascular and mental health modified the associations with age. We did not find any interaction between mental and vascular health on amyloid models (figure 3?). However, we found a trend towards a significant interaction of vascular health and age (β =-1.633, p=0.044), and a significant interaction of mental health with age (β =-2.042, p=0.007) on hippocampal volumes. Since participants with history of anxiety and depression also showed higher scores in the HADS, we conducted additional analysis including these variables. However, no significant effect or interaction was found (supplementary material? Data not shown?).

DISCUSSION

The present study assessed incipient biomarker changes in CU middle-aged adults with FH of AD dementia. The main results of the study were: (1) proximity to parental AAO was linearly associated with amyloid burden as measured by amyloid PET, and to a lesser extent with the Aβ42/40 ratio, (2) the association was stronger at older ages and was driven by women; (3) proximity to parental AAO, *APOE-ε4* and FH load independently contributed to amyloid burden; (4) neural injury biomarkers did not change as a function of proximity to parental AAO, but they showed greater alterations with age in participants with lower mental and vascular health indicators.

Our findings suggest that middle-aged adults with FH of sporadic AD showed greater amyloid deposition as they approached parental age at symptom onset. Both age and proximity to parental AAO were linearly associated with greater amyloid deposition and their contribution was independent and additive. When age, proximity to parental AAO and their interaction was considered in the statistical models, they all contributed to explain variability on amyloid measurements. However, proximity to parental AAO showed the strongest effect. The effects using Aβ42-40 ratios were in the same direction but less statistically significant. While CSF amyloid is thought to change earlier in the AD continuum ,[25] the non-linear nature of the amyloid CSF measurement together with the cross-sectional design of the study could have prevented us from detecting greater effects on CSF amyloid.

The present results reinforce findings from a previous study showing greater amyloid burden as a function of proximity to parental AAO in 3 independent cohorts of middle-aged older adults.[6] While the reported effects are moderate, altogether, the results support the need for further research using this approach with longitudinal follow-up data and powered statistical models. The inclusion of the proximity to parental AAO may help detect incipient and/or accelerated rates of amyloid accumulation during midlife in risk-enriched populations. The success of clinical trials may depend partly on the ability to discriminate the earliest stages of AD. Amyloid is accumulated, approximately, over a 15-year interval and follows a sigmoidal curve. [26] Initial linear increases in individuals with overall low

amyloid burden predict tau levels[2] and cognitive decline. Therefore detecting the earliest amyloid changes is highly relevant.[1] Future studies are guaranteed to assess whether the therapeutic window for preventive interventions starts earlier and/or is narrower in people with FH of sporadic AD dementia.

Proximity to parental AAO, *APOE-ε4* status and FH load variables provided independent contributions to explain variability on amyloid-PET measurements. We hypothesized that we would observe changes in neural injury biomarkers as proximity to parental AAO. However, proximity to parental AAO, *APOE-ε4* status and FH load were not significantly associated with greater alterations of p-tau or neural injury biomarkers (hippocampal volumes or t-tau), but increased with age. Both *APOE-ε4* and the number of parents have been associated with amyloid load and to a lesser extent to neural injury biomarkers, notably hippocampal volumes.[13,27] The results are in line with the idea that *APOE-ε4* and FH load act mainly through amyloid-dependent pathways. Importantly, proximity to parental AAO offers a continuous measure and thus a timeline for detection of incipient biomarker changes in risk-enriched population with FH.

As previously reported,[6] our findings support the usefulness of this approach in women. Indeed, only women showed increased amyloid as they approached parental AAO. In contrast with what was previously described, the interaction in our data was present using amyloid-PET as outcome measurement and not CSF amyloid. While the prevalence of AD is higher in women, whether women show earlier AD pathological changes is a matter of debate.[28] The sex-specific findings could be interpreted in different ways: since we focused on CU older adults, our results could reflect a survival effect where only women close to the parental AAO and high amyloid burden remain cognitively unimpaired. Thus, women may be more resilient to AD pathologies.[29] In line with this idea, men usually show more co-pathologies[30] which may lower brain resilience and result in a faster expression of cognitive impairment. Finally, under the assumption that proximity to parental AAO provides a disease-timeline, our results may also imply that women show increase amyloid deposition than men.

However, previous studies in CU older adults did not show differences in amyloid burden between men and women[31,32] and, although controversial reports exist,[33,34] a meta-analysis showed no differences.[4]

The present study sample is a risk-enriched cohort (47% *APOE-ε4* carriers) of middle-age older adults with FH of sporadic AD, thus, a candidate population for risk reduction through lifestyle interventions. The clinical expression of the disease may occur sooner in participants with risk-enhancing exposures and lower brain resilience and resistance to AD pathologies.[9] Thus we investigated the effect of modifiable factors on AD and neural injury biomarkers to further understand factors that may increase resilience and resistance to AD.[9] Recent research has shown that mental (for example, stress, depression and loneliness[16,17]) and vascular health (references here?) may be associated with AD pathologies and neural injury biomarkers. Education and early cognitive engagement has also been associated with amyloid deposition.[14,35] In this study, we did not find any factors associated with resistance to amyloid since the association between education, mental and vascular health and amyloid burden were not significant. Further, these factors did not modify the association of increasing amyloid with proximity to parental AAO. The effects of education and lifestyle factors on amyloid pathologies have been controversial across studies and may therefore be sample-dependent. Nevertheless, we may not have been able to capture effects due to the cross-sectional nature of the study and the incipient biomarkers changes in our cohort. Therefore, this question deserves further assessment using longitudinal approaches.

Likewise, assessing the effects of modifiable factors on neural injury biomarkers on this population is of high relevance. Our results suggest that history of mental health and to a lesser extent history of vascular comorbidities were associated with age-effects on hippocampal volumes. Thus, middle-aged CU participants with history of anxiety/depression and those reporting more than 2 comorbidities showed lower hippocampal volumes with age. Interestingly, the age-effects were not present in participants with absence of history of mental illnesses and vascular conditions. In complementary

analyses, we showed that history of anxiety rather than current anxiety levels was associated with hippocampal volumes suggesting that the cumulative effect of mental health conditions, rather than the current anxiety/depressive levels are relevant to predict lower hippocampal volumes. Previous studies suggest that mental-health related indicators may be early signs of the disease rather than modifiers or accelerators,[18,36] . However, our results support the idea that these factors act to increase AD dementia risk[37] by lowering brain resilience.

The present study is not free of limitations. The effect sizes of the main measurements of interest were weak to moderate. However, we are investigating incipient changes and thus strong effect sizes were not expected. Further, the results survived conservative p values. While the sample size is relatively small, this is a well-characterized, risk-enriched sample derived from a large registry of participants with an extensive and careful assessment of FH. This allows a solid addition to previous research. Finally, twelve percent of the sample passed the parental AAO, however, our results were consistent when we excluded those participants.

Conclusions

In a risk-enriched sample of CU middle-aged participants with FH of AD, proximity to parental AAO may offer a timeline for detection of incipient biomarker alterations notably in women. Age-related effects on hippocampal volumes were present with worst mental and vascular health indicators. These factors may be thus candidate targets for early interventions in CU adults with FH of AD and should be taken into account for designing future trials.

AUTHOR CONTRIBUTIONS

Dr. Arenaza-Urquijo: study concept and design, data analysis and interpretation, writing the manuscript, Ms. Salvadó: acquisition of data and analysis, Dr. Operto: acquisition of data and analysis, Dr. Minguillón: study design, critical revision of the manuscript, Dr. Sanchéz-Benavides, data acquisition, interpretation, critical revision of the manuscript, Dr. Crous-Bou: interpretation, critical revision of the manuscript, Dr. Grau: data acquisition, interpretation, critical revision of the manuscript, Dr. Falcón: acquisition and data analysis, Dr. Suárez-Calvez: data acquisition, interpretation, critical revision of the manuscript, Dr. Zetterberg: interpretation, critical revision of the manuscript, Dr. Blennow: interpretation, critical revision of the manuscript, Dr. Gispert: study design, interpretation, critical revision of the manuscript, study supervision. Dr. Molinuevo: study design, interpretation, critical revision of the manuscript, study supervision.

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Table 1. Demographics of the study sample.

	Mean (SD)/n (%)	Range
Age	60.82 (4.82)	49-73
Education (years)	13.48 (3.56)	6-18
Sex (females)	184 (63.7%)	-
APOE-ε4 carriers	137 (47%)	-

able 2. Results from the multiple regression analyses with Flutemetamol-PET SUVR as dependent variable.

Non standardized beta coefficients, 2- standardized beta coefficients, PPAAO: proximity to parental age at onset.

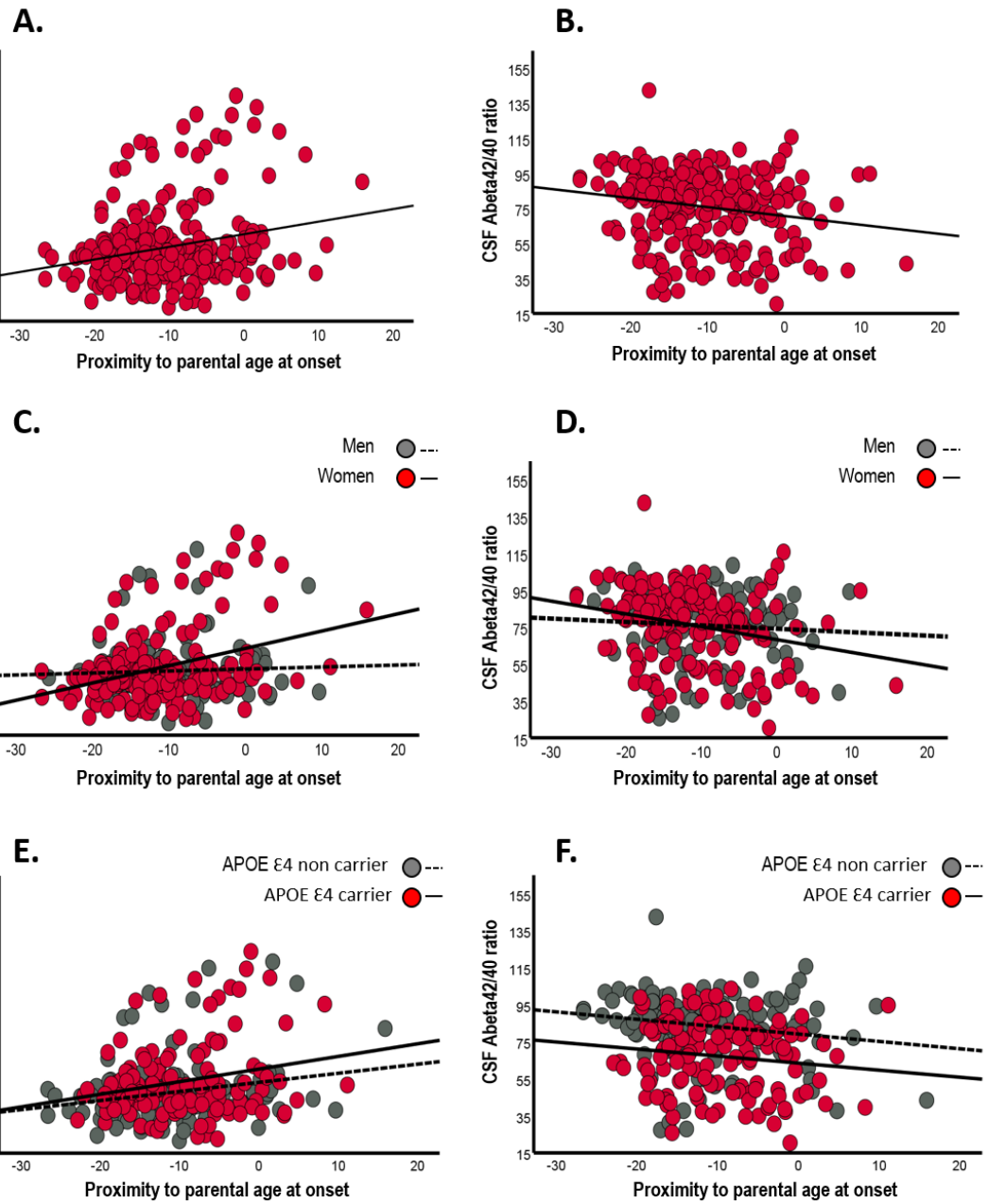
	βeta[1]	βeta[2]	95% CI	T statistic	P value
Proximity to parental AAO	-0.063	-3.108	-0.11 to -0.30	-3.05	0.003
Age	0.017	0.564	0.01 to 0.03	4.58	<0.001
Sex	0.084	2.684	0.02 to 0.15	2.68	<0.001
Years of education	-0.001	-0.02	-0.01 to 0.01	-0.17	0.86
PPAAO*Age	0.001	2.8462	0.00 to 0.001	3.06	<0.001
PPAAO*sex	0.007	0.621	0.002 to 0.012	2.55	0.01
PPAAO*years of education	<0.001	0.141	-0.001 to 0.001	0.53	0.594

able 3. Results from the multiple regression analyses with Abeta40/42 ratio as dependent variable.

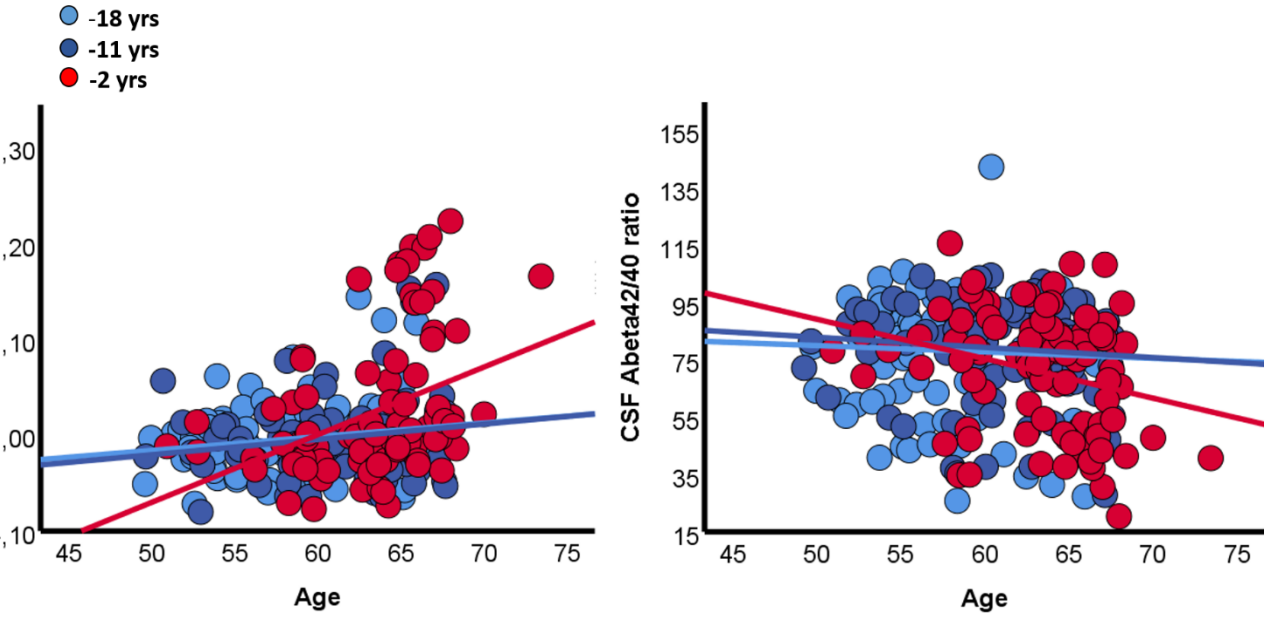
Non standardized beta coefficients, 2- standardized beta coefficients, PPAAO: proximity to parental age at onset

	βeta[1]	βeta[2]	95% CI[3]	T statistic	P value
Proximity to parental AAO	5.631	2.001	0.074 to 11.187	1.995	0.047
Age	-1.449	-0.350	-2.485 to -0.414	-2.755	0.006
Sex	-6.418	-0.153	-15.083 to 2.247	-1.458	0.146
Years of education	-0.191	-0.034	-1.454 to 1.072	-0.297	0.766
PPAAO*Age	-0.080	-1.677	-0.155 to -0.004	-2.080	0.039
PPAAO*sex	-0.550	-0.376	-1.267 to 0.167	-1.509	0.132
PPAAO*years of education	-0.013	-0.065	-0.112 to 0.087	-0.248	0.804

e 1. Plots showing the association between proximity to parental age at onset and PET and CSF amyloid measurements. Association
en proximity to parental AAO and PET and CSF amyloid measurements (A, B), the interaction with sex (C,D) and the non-significant interaction
-*ε4* status.



e 2. Plots showing the association between amyloid-PET and age in groups at different proximity to parental age at onset. The groups w
d based on tertiles. The years to proximity to parental AAO of each group reflects the group average.



3. Plots showing the interaction of age with mental (A) and vascular health (B) on hippocampal volumes. Presence refers to more than
on for mental health (red), and 1 (dark blue) or more than 1 (red) for vascular health.