

Proximity to Parental Symptom Onset and Amyloid- β Burden in Sporadic Alzheimer Disease

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 Supplemental content

IMPORTANCE Alzheimer disease (AD) develops during several decades. Presymptomatic individuals might be the best candidates for clinical trials, but their identification is challenging because they have no symptoms.

OBJECTIVE To assess whether a sporadic parental estimated years to symptom onset calculation could be used to identify information about amyloid- β ($A\beta$) levels in asymptomatic individuals with a parental history of AD dementia.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed $A\beta_{1-42}$ in cerebrospinal fluid (CSF) specimens from 101 cognitively normal individuals who had a lumbar puncture as part of the Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease (PREVENT-AD) cohort from September 1, 2011, through November 30, 2016 (374 participants were enrolled in the cohort during this period). The study estimated each participant's proximity to his/her parent's symptom onset by subtracting the index relative's onset age from his/her current age. The association between proximity to parental symptom onset and $A\beta$ levels was then assessed using apolipoprotein E $\epsilon 4$ (*APOE4*) status and sex as interactive terms. These analyses were performed again in 2 independent cohorts using CSF and Pittsburgh compound B carbon 11-labeled positron emission tomography (PIB-PET) $A\beta$ biomarkers: the Adult Children Study (ACS) and the Wisconsin Registry for Alzheimer Prevention (WRAP) cohorts.

MAIN OUTCOMES AND MEASURES The association between proximity to parental symptom onset and $A\beta$ burden in asymptomatic individuals with a parental history of sporadic AD.

RESULTS The present analysis included a subset of 101 PREVENT-AD individuals (mean [SD] age, 61.8 [5.1] years; 30 [29.7%] male), 128 ACS participants (112 participants underwent CSF measurement: mean [SD] age, 63.4 [5.1] years; 31 [27.7%] male; and 107 underwent PIB-PET: mean [SD] age, 64.6 [5.3] years; 27 [25.2%] male), and 135 WRAP participants (85 participants underwent CSF measurement: mean [SD] age, 59.9 [6.0] years; 27 [31.8%] male; and 135 underwent PIB-PET: mean [SD] age, 59.6 [6.1] years; 43 [31.9%] male). In the PREVENT-AD cohort, individuals approaching their parent's onset age had lower CSF $A\beta_{1-42}$ levels (range, 402-1597; $B = -9.09$, $P = .04$). This association was stronger in *APOE4* carriers ($B = -17.9$, $P = .03$) and women ($B = -19.8$, $P = .02$). In the ACS cohort, the main association was replicated using PIB-PET data, and the sex interaction was replicated using CSF and PIB-PET data. In the WRAP cohort, the results were not replicated using cross-sectional data, but the main association and the *APOE* interaction were replicated using PIB-PET longitudinal data.

CONCLUSIONS AND RELEVANCE These results suggest that proximity to parental symptom onset may help estimate $A\beta$ biomarker changes in women or *APOE4* carrier asymptomatic individuals with a parental history of sporadic AD.

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No treatment currently exists to stop or prevent Alzheimer disease (AD). The best time window to prevent AD is likely when individuals are still asymptomatic, before extensive neuronal degeneration has occurred. Identifying asymptomatic individuals is challenging and expensive, posing significant difficulties for the current generation of clinical trials.

In autosomal dominant AD (ADAD), symptom onset is determinable across generations. It is therefore possible to calculate the estimated years to symptom onset (EYO) score in individuals with ADAD by subtracting their parent's onset age from their current age.¹ With this approach, ADAD findings suggest that a decrease in cerebrospinal fluid (CSF) amyloid- β 1-42 (A β 1-42) concentrations can be detected 25 years before expected symptom onset and brain A β aggregation can be detected 15 years before expected symptom onset.¹ The EYO score can therefore be used in ADAD to estimate AD biomarker abnormalities and potentially guide the optimal timing of treatments.

The heritability of sporadic AD dementia is estimated at approximately 70%,^{2,3} with age at onset heritability being 67% to 87% in early-onset AD.³ Whether the parent's age at onset can help determine biomarker abnormalities in AD is not known. The aim of the current study was to test whether a sporadic parental EYO calculation could be used to identify information about A β levels in asymptomatic individuals with a parental history of AD dementia. Given the heterogeneity of AD and because apolipoprotein E ϵ 4 (APOE4)^{4,5} and female sex^{6,7} increase the risk of AD, we further assessed whether the association between sporadic parental EYO score and A β levels is influenced by these risk factors. The current study was performed using CSF A β 1-42 data from the Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease (PREVENT-AD) cohort.⁸ We repeated the analysis in the Adult Children Study (ACS)^{9,10} and the Wisconsin Registry for Alzheimer Prevention (WRAP) cohort¹¹ using CSF and Pittsburgh compound B carbon 11-labeled positron emission tomography (PIB-PET) A β biomarkers.

Methods

Participants and Study Design

All individuals included in the current study had a parental history of AD and A β quantification (CSF and/or PIB-PET). The **Table** gives the participants' characteristics. All specified procedures were approved by the local ethics committees of each respective cohort (institutional review board of McGill University Faculty of Medicine, Washington University Human Research Protection Office, and University of Wisconsin Institutional Review Board), and all participants provided signed informed consent forms before participation. Data were deidentified.

PREVENT-AD Cohort

Recruitment for the PREVENT-AD cohort was begun in 2011 with enrollment of individuals from the greater Montreal metropolitan area (details in the eMethods in the [Supplement](#)). The

Key Points

Question Can proximity to parental symptom onset be used to help estimate amyloid- β burden in preclinical sporadic Alzheimer disease?

Findings In this study of 101 cognitively normal individuals with a parental history of sporadic Alzheimer disease, amyloid- β burden increased as individuals approached their parent's age at symptom onset.

Meaning This study indicates that, as in autosomal dominant Alzheimer disease, an individual's proximity to parent's age at symptom onset may help estimate the advancement of preclinical disease.

PREVENT-AD study participants must satisfy the following conditions: (1) a family history of AD-like dementia, (2) 60 years or older at study entry or 55 to 59 but less than 15 years from their siblings' or parents' age at symptom onset, and (3) normal cognition and no other major neurologic disease.⁸ Data from 374 individuals were collected from September 1, 2011, through November 30, 2016, and archived in the PREVENT-AD internal data release 3.0. The present analysis included a subset of 101 PREVENT-AD individuals with a parental history of AD who underwent lumbar puncture (LP) to assess CSF A β 1-42 concentration. Four individuals included in the current study were suspected to have mild cognitive impairment based on an extensive neuropsychological battery. All 101 individuals had a Clinical Dementia Rating (CDR) of 0¹² and a score above 23 on the Montreal Cognitive Assessment.¹³

To assess the robustness of our results, we conducted similar analyses in 2 independent cohorts of individuals with a parental history of AD: the ACS^{9,10} and WRAP.¹¹ Because these 2 studies included PIB-PET and CSF A β 1-42 assessments, we included the participants who had either or both of these assessments. Longitudinal PIB-PET data were available for both cohorts; thus, we also explored the association between sporadic parental EYO score and annual rate of change in PIB-PET indexes.

ACS Cohort

The ACS is a longitudinal study enrolling cognitively normal individuals that was conducted at the Knight Alzheimer Disease Research Center at Washington University School of Medicine in St Louis, Missouri.^{9,10} The ACS eligibility criteria include age at entry between 45 and 75 years and normal cognition, defined as a CDR of 0. A total of 128 participants 55 years and older were included in the study, among whom 112 underwent LP and 107 underwent PIB-PET. Fifty-nine individuals underwent PIB-PET a second time. The mean (SD) delay between the 2 scans was 3 years (mean [SD], 36.1 [17.3] months; median, 36 months; range, 13.0-106.3 months).

WRAP Cohort

WRAP is a longitudinal study conducted by the Wisconsin Alzheimer Institute at the University of Wisconsin School of Medicine and Public Health that enrolls individuals free of dementia.^{11,14} Participants are aged 40 to 65 years at entry and

Table. Demographic Characteristics of the Study Participants^a

Characteristic	PREVENT-AD (n = 101)	ACS (n = 128)	WRAP (n = 135)	Main Effects P Value
Age, y				
CSF	61.8 (5.1) [55 to 78]	63.4 (5.1) [55 to 76]	59.9 (6.0) [48 to 70]	<.001 ^{b,c,d}
PIB-PET	NA	64.6 (5.3) [55 to 76]	59.6 (6.1) [46 to 71]	<.001
Male, No. (%)				
CSF	30 (29.7)	31 (27.7) ^b	27 (31.8)	.82
PIB-PET	NA	27 (25.2) ^c	43 (31.9)	.26
Educational level				
CSF	15.0 (3.0) [10 to 27]	15.9 (2.3) [11 to 20]	16.5 (2.5) [12 to 25]	.002 ^{b,c}
PIB-PET	NA	16.0 (2.2) [11 to 20]	16.3 (2.6) [12 to 25]	.32
APOE4, No. (%)				
CSF	39 (38.6)	49 (43.8) ^b	36 (42.4)	.70
PIB-PET	NA	50 (46.7) ^c	63 (46.7)	.99
CDR of 0, No. (%)				
CSF	101 (100)	128 (100)	49 (71.0) ^e	NA
PIB-PET	NA	100	82 (75.3) ^f	NA
MMSE score				
CSF	NA	29.0 (1.3) [24 to 30]	29.2 (1.2) [24 to 30]	.30
PIB-PET	NA	29.0 (1.3) [24 to 30]	29.2 (1.2) [23 to 30]	.25
MOCA for the CSF group	27.9 (1.5) [24 to 30]	NA	NA	NA
Age of parent at disease onset, y				
CSF	74.3 (7.4) [55 to 90]	73.6 (7.6) [51 to 93]	73.8 (8.0) [55 to 91]	.80
PIB-PET	NA	74.1 (7.6) [51 to 93]	73.2 (8.3) [45 to 91]	.41
Sporadic parental EYO score ^g				
CSF	-12.5 (6.7) [-29 to 7]	-10.2 (8.7) [-33 to 13]	-13.9 (7.4) [-28 to 6]	.004 ^{b,d}
PIB-PET	NA	-9.5 (9.2) [-36 to 13]	-13.6 (8.0) [-34 to 13]	<.001 ^d
CSF A β 1-42	1056 (284) [402 to 1597]	665 (252) [202 to 1615]	750 (235) [280 to 1763]	NA ^h
PIB-PET index ⁱ	NA	0.28 (0.34) [0.02 to 1.57]	1.18 (-0.18)[1.00 to 2.07]	NA ^h
PIB-PET rate of change	NA	0.033 (0.041) [-0.03 to 0.16]	0.005 (0.029) [-0.07 to 0.10]	NA ^h

Abbreviations: A β , amyloid- β ; ACS, Adult Children Study; APOE, apolipoprotein E; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; EYO, estimated years to symptom onset; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; NA, not applicable; PIB-PET, Pittsburgh compound B carbon 11-labeled positron emission tomography; PREVENT-AD, Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease; WRAP, Wisconsin Registry for Alzheimer Prevention.

^a Data are expressed as mean (SD) [range] unless otherwise indicated. In the ACS cohort, n = 112 in the CSF group and n = 107 in the PIB-PET group. In the WRAP cohort, n = 85 in the CSF group and n = 135 in the PIB-PET group.

^b Difference between PREVENT-AD and ACS is significant.

^c Difference between PREVENT-AD and WRAP is significant.

^d Difference between ACS and WRAP is significant.

^e Information missing for 16 individuals.

^f Information missing for 26 individuals.

^g Calculated as the age of the participant at assessment minus the age of the parent at symptom onset.

^h Distribution of A β values (CSF and PIB-PET) cannot be statistically compared among the 3 cohorts because of differences in quantification methods.

ⁱ Mean cortical potential binding was computed for the ACS cohort, whereas distributed volume ratios were computed for the WRAP cohort (eMethods in the Supplement).

were free of dementia based on a neuropsychological evaluation with expert review. The cohort therefore included cognitively normal individuals (CDR, 0) and individuals with mild cognitive impairment (CDR, 0.5). A total of 135 participants 48 years and older were included in the study. The PIB-PET scans were available for all participants. Among them, 85 also underwent LP. An overlapping 92 participants had undergone PIB-PET a second time after an interval of approximately 2 years (mean [SD], 26.7 [3.5] months; median, 26.2 months; range, 20.5-40.7 months).

A β Assessments

The CSF from the PREVENT-AD cohort was collected by LP in the morning under fasting conditions. Measurement of A β 1-42

was determined by enzyme-linked immunosorbent assay (INNOTEST; Fujirebio, formerly Innogenetics). In the ACS and WRAP cohorts, the CSF samples were acquired and assayed using previously published procedures (details are provided in the eMethods in the Supplement).^{15,16}

In the ACS and WRAP cohorts, PIB-PET acquisition and processing were performed using in-house procedures that have been described previously.^{9,16} Accordingly, mean cortical binding potential values corrected for regional spread function are presented for the ACS cohort, and distribution to volume ratio data are presented for the WRAP cohort (eMethods in the Supplement).

Additional analyses were performed to assess whether proximity to parental onset was associated with the annual rate

of brain A β accumulation in the ACS (n = 59) and WRAP (n = 92) cohorts. To do so, the PIB-PET annual rate of change was calculated as follows: amyloid scores at follow-up minus amyloid scores at baseline divided by the interval (in years) between the 2 scans.

Sporadic Parental EYO Score Calculation

The sporadic parental EYO score was calculated as the age of the participant at assessment minus the age of the parent at symptom onset.¹ 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 sporadic parental EYO score. The age of the parent at symptom onset corresponds to the age at which the family observed significant cognitive or memory changes in the PREVENT-AD and WRAP cohorts, whereas it corresponds to the age at which dementia symptoms began in the ACS cohort (eMethods in the [Supplement](#)).

APOE Genotype

APOE genotype in the PREVENT-AD cohort has previously been described (eMethods in [Supplement](#)).¹⁷ For statistical analysis, participants were classified as APOE4 carriers (1 or 2 ϵ 4 alleles) or noncarriers (no ϵ 4 allele). A similar approach was used in the 2 other cohorts.

Statistical Analysis

We examined differences among the 3 cohorts using linear regression analyses for continuous variables and Pearson χ^2 tests for categorical variables. In the PREVENT-AD cohort, independent linear regression analyses were first used to determine CSF A β 1-42 level (dependent variable) by age while controlling for sex and educational level and CSF A β 1-42 level (dependent variable) by parent's age at symptom onset while controlling for sex and educational level. A step-by-step hierarchical linear regression analysis was then used to determine CSF A β 1-42 level by age while controlling for sex and educational level (model A, step 1, same as previous analysis); CSF A β 1-42 level by sporadic parental EYO score while controlling for age, sex, and educational level (model A, step 2); and the interaction between sporadic parental EYO score and sex (sporadic parental EYO score \times sex) on CSF A β 1-42 level while including age, sex, educational level, and sporadic parental EYO score as covariates (model A, step 3). A similar hierarchical analysis (model B) was used to assess the interaction between sporadic parental EYO score and APOE (sporadic parental EYO score \times APOE status). APOE status was included in this second and independent model. Exploratory analyses also assessed parental sex as a possible interactive term.

Models A and B were replicated in the 2 validation cohorts (ACS and WRAP) using baseline CSF A β 1-42 values and PIB-PET values. Annual rate of change in PIB-PET binding was also investigated in the ACS and WRAP cohorts. One ACS participant and 1 WRAP participant with high baseline PIB-PET uptake were removed from the longitudinal analysis because they had a decrease in PIB-PET binding over time, which suggests that they could no longer accumulate additional brain A β .^{18,19}

All analyses were completed using SPSS software, version 20 (IBM Inc). A 2-sided $P < .05$ was considered to be significant.

Results

The present analysis included a subset of 101 PREVENT-AD individuals (mean [SD] age, 61.8 [5.1] years; 30 [29.7%] male), 128 ACS participants (112 participants underwent CSF measurement: mean [SD] age, 63.4 [5.1] years; 31 [27.7%] male; and 107 underwent PIB-PET: mean [SD] age, 64.6 [5.3] years; 27 [25.2%] male), and 135 WRAP participants (85 participants underwent CSF measurement: mean [SD] age, 59.9 [6.0] years; 27 [31.8%] male; and 135 underwent PIB-PET: mean [SD] age, 59.6 [6.1] years; 43 [31.9%] male).

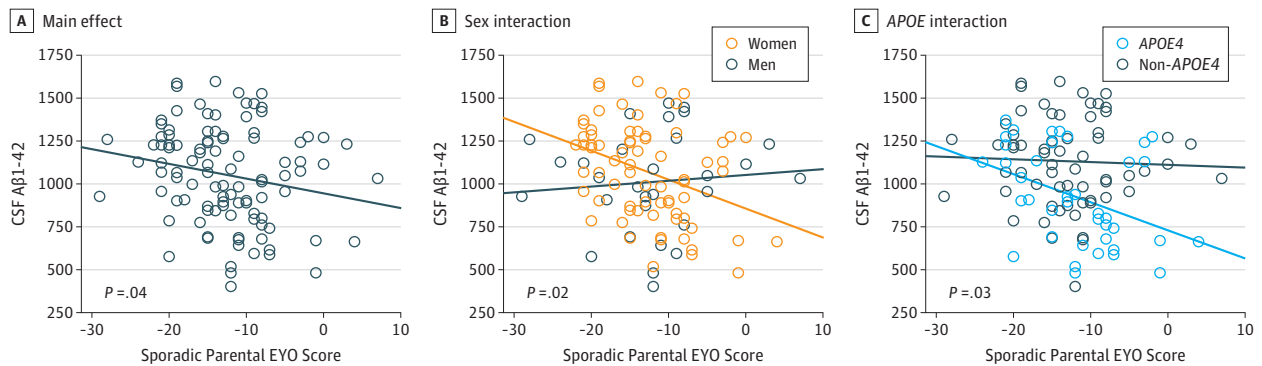
Association Between Sporadic Parental EYO Score and A β Burden

Cross-sectional analyses from the PREVENT-AD cohort demonstrated no association between age and CSF A β 1-42 level or between parent's age at symptom onset and CSF A β 1-42 level but found a reduction in CSF A β 1-42 levels as participants approached the parent's age at onset (eFigure in the [Supplement](#)). Adding sporadic parental EYO score as a covariate into the model that already included age increased the explained variance (step 1 with age: $r^2 = 0.034$, F change = 1.135; step 2 with age and sporadic parental EYO score: $r^2 = 0.077$, F change = 4.441; difference between step 1 and step 2: $P = .04$; effect of sporadic parental EYO: $B = -9.09$, $P = .04$). An interaction was found between sporadic parental EYO score and sex ($B = -19.8$, $P = .02$), suggesting that the association between sporadic parental EYO score and A β 1-42 level was stronger among women than among men ([Figure 1](#) and eTable 1 in the [Supplement](#)). An interaction was also found between sporadic parental EYO score and APOE status ($B = -17.9$, $P = .03$), revealing a stronger association in APOE4 carriers than in noncarriers.

In the ACS cohort, age was associated with CSF A β 1-42 and PIB-PET data, but these associations were no longer significant when sporadic parental EYO score was included in the models (eTable 2 in the [Supplement](#)). The association between sporadic parental EYO score and A β burden was replicated in the members of the ACS cohort who underwent PIB-PET, with an increase of brain A β deposition as individuals approached their parent's age at symptom onset ([Figure 2](#) and eTable 2 in the [Supplement](#)). The interaction between sporadic parental EYO score and sex was also replicated using CSF A β 1-42 and PIB-PET data. In addition, longitudinal ACS PIB-PET data further suggest that women tend to accumulate brain A β at a faster rate than men as they approach the age at their parent's onset. The sporadic parental EYO score \times APOE interaction was not replicated in the ACS cohort using cross-sectional or longitudinal data. No other association reached significance.

In the WRAP cohort, age alone was associated with cross-sectional CSF A β 1-42 and PIB-PET data, and the association between age and PIB-PET was still significant when including spo-

Figure 1. Proximity to Parental Symptom Onset and Amyloid- β Burden in the Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease (PREVENT-AD) Cohort



P values were obtained with linear regression models controlled for age, sex, and educational level. Analyses that include the sporadic parental estimated years to symptom onset (EYO) score (calculated as the age of the participant at assessment minus the age of the parent at symptom onset) \times *APOE* status

interaction were also controlled for the main effect of *APOE* status. Unadjusted (raw) data are plotted. *APOE4* indicates apolipoprotein E ϵ 4; CSF, cerebrospinal fluid.

radic parental EYO score in the model (eTable 3 in the Supplement). We did not replicate the PREVENT-AD cross-sectional findings (Figure 3 and eTable 3 in the Supplement). However, as individuals approached their parent's age at symptom onset, they demonstrated a faster rate of brain A β accumulation (longitudinal data). The sporadic parental EYO score \times *APOE* interaction further suggests that this association was stronger in *APOE4* carriers than in *APOE4* noncarriers. We did not find a sporadic parental EYO score \times sex interaction for the rate of brain A β accumulation. Significant results from the main analyses are summarized in Figure 4 and eTable 4 in the Supplement.

Exploratory Analysis on Parental Sex

The association between A β accumulation and sporadic parental EYO score was not associated with parental sex in any of the cohorts ($B = -10.7$, $P = 0.45$ for the PREVENT-AD; $B = 4.2$, $P = .49$ for the ACS individuals with CSF; $B = 0.01$, $P = .41$ for the ACS individuals with PIB-PET; $B = -0.001$, $P = .49$ for the ACS individuals with longitudinal PIB-PET; $B = 13.2$, $P = .13$ for the WRAP individuals with CSF; $B = -0.002$, $P = .62$ for the WRAP individuals with PIB-PET; $B = 0.0003$, $P = .78$ for the WRAP individuals with longitudinal PIB-PET).

Discussion

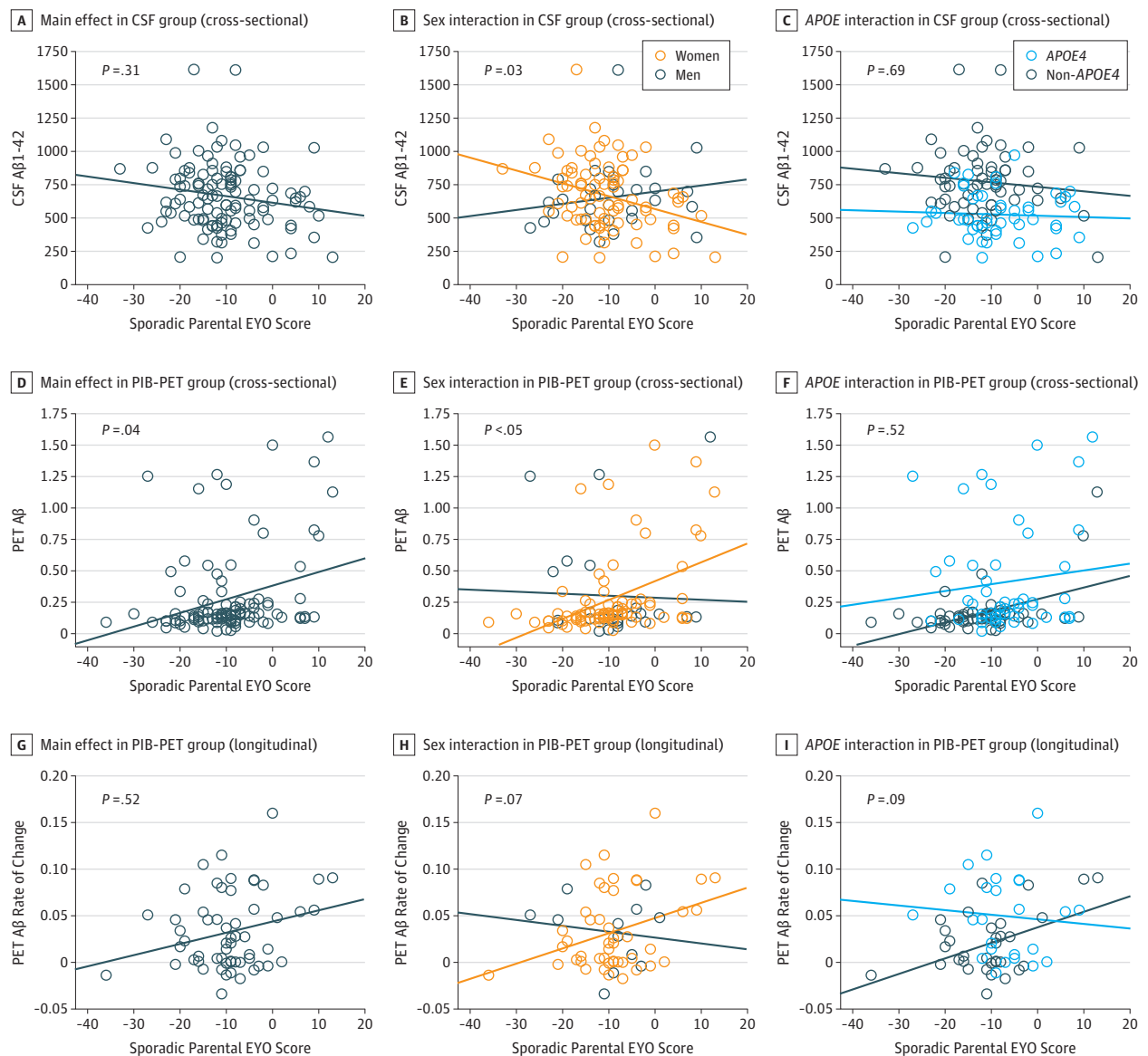
Disappointing outcomes from clinical trials performed in individuals with AD dementia and increasing experimental research performed in the preclinical phase of AD suggest that asymptomatic individuals in the preclinical stages of AD might be the best candidates for disease modification therapies. An important challenge facing AD prevention trials is the identification of asymptomatic individuals who could benefit from such therapies.

Our results suggest that proximity to parental symptom onset (or sporadic parental EYO score)² might help estimate A β

biomarker advancement in individuals with a parental history of AD. Specifically, asymptomatic individuals with such a family history were more likely to demonstrate abnormal CSF (PREVENT-AD findings) (Figure 1) and brain (ACS findings) (Figure 2) A β biomarkers as they approached their parent's age at onset irrespective of their own age. Individuals who were closer to their parent's age at onset also accumulated brain A β deposition at a faster rate (WRAP findings) (Figure 3). Of importance, this association seemed to be independent of age-related changes in A β burden. Because A β burden is known to increase with age²⁰ and sporadic parental EYO score is based (in part) on individuals' age, it is reasonable to hypothesize that age itself could have driven our results. However, in the PREVENT-AD, we did not find any association between CSF A β 1-42 and age, and adjusting for age did not alter the significant association between sporadic parental EYO score and CSF A β 1-42 (model A, step 1) (eTable 1 in the Supplement). Thus, in our sample, the sporadic parental EYO score appeared to be a better indicator of A β variability than age. In addition, although increasing age was associated with increasing A β burden in the 2 replication cohorts, this association with sporadic parental EYO score was still present after age adjustment (eTable 2 and eTable 3 in the Supplement). The relatively low mean age of the 3 cohorts (approximately 62 years) might partially explain this age-independent finding. The sporadic parental EYO score may be a better predictor of A β burden in late middle-age individuals, who are less likely to have age-related A β , compared with elderly individuals, who have a higher prevalence of A β deposition.²⁰

Not all individuals with a parental history of AD will develop the disease within their lifespan; thus, we assessed whether the association between sporadic parental EYO score and A β pathologic findings is influenced by sex or *APOE4* status, 2 important risk factors for AD.⁴⁻⁷ Of interest, findings from the PREVENT-AD cohort indicated that asymptomatic women had a stronger decrease in concentration of CSF A β 1-42 than men as they approach their parent's age at symptom onset

Figure 2. Proximity to Parental Symptom Onset and Amyloid- β (A β) Burden in the Adult Children Study (ACS) Cohort



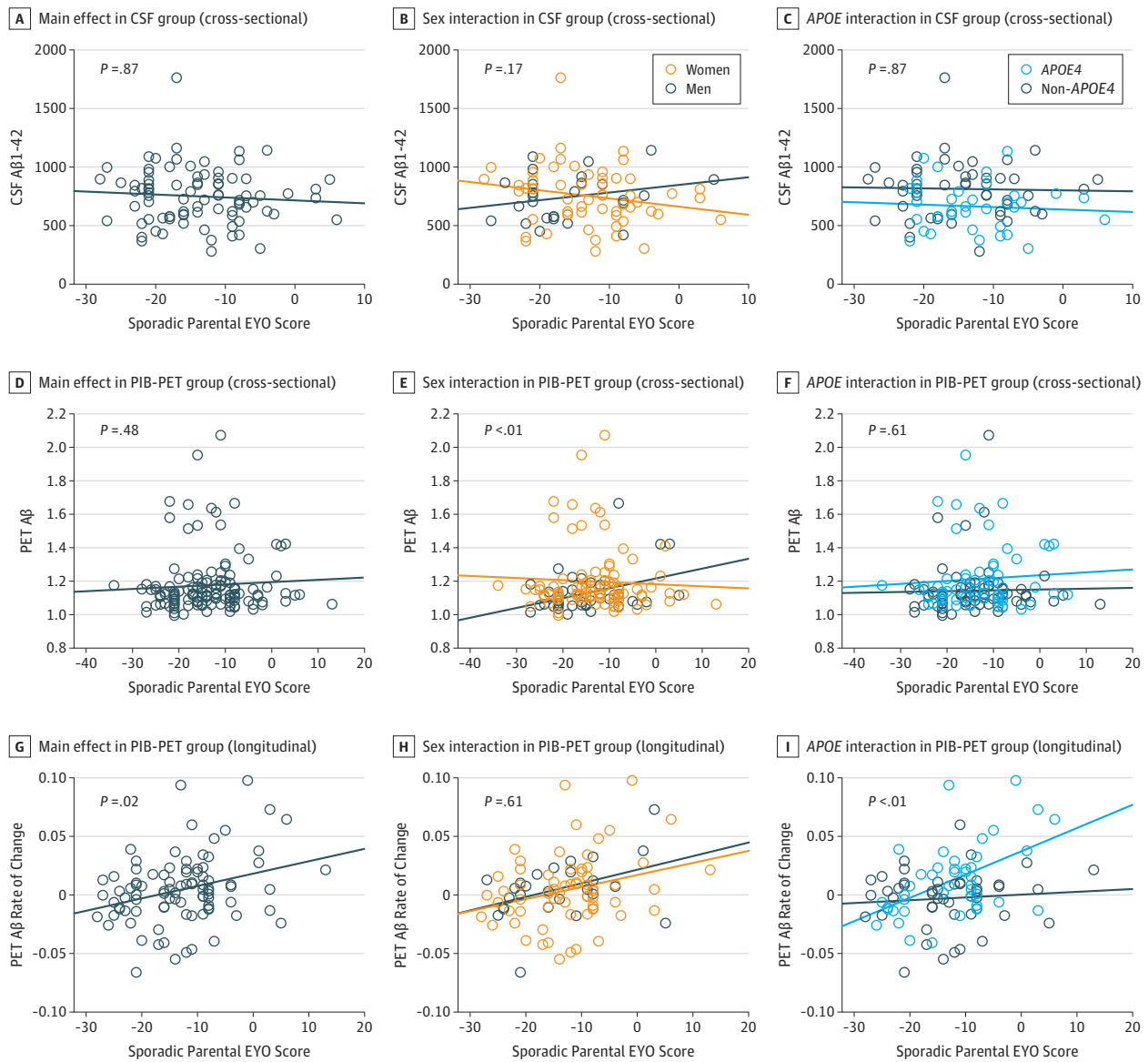
P values were obtained with linear regression models controlled for age, sex, and educational level. Analyses that include the sporadic parental estimated years to symptom onset (EYO) score (calculated as the age of the participant at assessment minus the age of the parent at symptom onset) \times APOE status

interaction were also controlled for the main effect of APOE status. Unadjusted (raw) data are plotted. APOE4 indicates apolipoprotein E ϵ 4; CSF, cerebrospinal fluid; and PIB-PET, Pittsburgh compound B carbon 11-labeled positron emission tomography.

(Figure 1 and Figure 4). This interaction of sporadic parental EYO score with sex was replicated in the ACS cohort members with CSF data, where it was additionally supported by PIB-PET imaging findings comparing women and men (Figure 2 and Figure 4). In the ACS cohort members with PIB-PET data, we further found a marginal interaction with sex while looking at the annual rate of A β accumulation, suggesting that women might also present a faster rate of A β accumulation when approaching their parent's age at onset. In addition, analyses in the PREVENT-AD cohort highlighted that the association between sporadic parental EYO score and CSF A β 1-42 was stronger in APOE4 carriers (Figure 1). Consistently, APOE4

carriers in the WRAP cohort accumulated A β deposition faster than did the APOE4 noncarriers (Figure 3). Altogether, these results suggest that the association between sporadic parental EYO score and A β burden was increased in individuals with a higher risk of developing AD.

These latter results regarding the sporadic parental EYO score \times APOE4 status interaction do not make clear whether APOE4 status directly influences the association between A β burden and sporadic parental EYO score or whether we found a stronger association between sporadic parental EYO score and A β burden in APOE4 carriers only because most noncarriers did not have significant A β deposition in these

Figure 3. Proximity to Parental Symptom Onset and Amyloid- β Burden in the Wisconsin Registry for Alzheimer Prevention (WRAP) Cohort

P values were obtained with linear regression models controlled for age, sex, and educational level. Analyses that include the sporadic parental estimated years to symptom onset (EYO) score (calculated as the age of the participant at assessment minus the age of the parent at symptom onset) score \times APOE

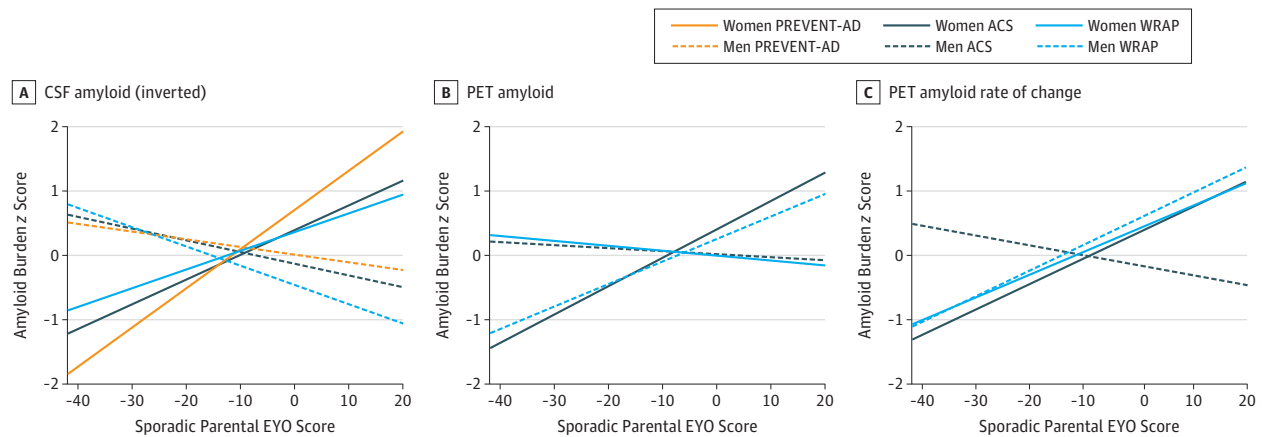
status interaction were also controlled for the main effect of APOE status. Unadjusted (raw) data are plotted. APOE4 indicates apolipoprotein E ϵ 4; CSF, cerebrospinal fluid; and PET, positron emission tomography.

limited age groups. The population prevalence of A β positivity in APOE4 noncarriers without dementia at approximately 60 years of age has been found to be only approximately 10%.²⁰ An increasing literature suggests that the effect of APOE4 on AD risk is stronger in women than in men.^{6,21} Although our data did not permit us to directly test this 3-way interaction, most APOE4 carriers with low A β 1-42 and/or high brain A β burden were women in the PREVENT-AD and the ACS and WRAP cohorts.

Our finding of an association between proximity to parental symptom onset and A β in 3 independent cohorts at approximately 50 to 70 years of age supports the well-accepted

idea that brain changes start many years before clinical symptoms. This finding also supports the perspective that AD shares common pathophysiologic features with ADAD,²² emphasizing that AD is a strongly heritable disorder. In the PREVENT-AD cohort, for instance, we found no association between the age of a person and CSF A β 1-42 concentration when the age of the parent at symptom onset was not subtracted from the age of the person. We also did not find an association between the parent's age at symptom onset and CSF A β 1-42 concentration, which implies that, in the PREVENT-AD cohort, it was really the proximity to the parent's age at onset that provided information about A β levels.

Figure 4. Normalized Amyloid- β ($A\beta$) Burden Levels as a Function of Sporadic Parental Estimated Years to Symptom Onset (EYO) Score in Men and Women in the Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease (PREVENT-AD), Adult Children Study (ACS), Wisconsin Registry for Alzheimer Prevention (WRAP) Cohorts



Regression lines were obtained by calculating z scores in each cohort and $A\beta$ measurement. Values were inverted for cerebrospinal fluid (CSF) so that higher z scores correspond to an increased level of pathologic findings PET indicates positron emission tomography.

Strengths and Limitations

Considering the relatively small sample size of each cohort and that not all individuals with a family history of AD will develop dementia, the sporadic parental EYO score was associated with $A\beta$ burden in all 3 cohorts. Each association was replicated in at least 1 cohort despite the 3 cohorts differing in inclusion criteria (ie, the WRAP cohort included individuals with mild cognitive impairment), the participants being recruited in different regions and countries, and different amyloidosis mechanisms being assessed (ie, decrease of $A\beta$ levels in the CSF, $A\beta$ deposition detection and accumulation over time using in vivo PET) (Figure 4 and eTable 4 in the Supplement).

In this article, we used the proposed term *sporadic parental EYO score*.¹ We acknowledge, however, that this term might not be appropriate for sporadic AD because not all individuals with a family history of sporadic AD will develop AD dementia. Furthermore, although the heritability of age at onset has been estimated to be 67% to 87% in AD,^{2,3} longitudinal studies will be needed to test whether a score of -10 means that a person is truly 10 years away from symptom onset of AD. That some individuals (particularly in the ACS cohort) passed

the age at onset of their parents, even when exhibiting abnormal biomarkers, might suggest that some individuals have an age at onset that is delayed with regard to their parent's age at onset. Compared with ADAD, sporadic AD is hypothesized to be multifactorial,²³⁻²⁵ and better lifestyle habits and increased cognitive and brain reserve could play a role in delaying symptom onset.²⁶⁻²⁸

Conclusions

Overall, the sporadic parental EYO score may help the identification of asymptomatic candidates for clinical trials. For instance, the sporadic parental EYO score could be applied as an inexpensive prescreening method that could enrich trial candidate populations for $A\beta$ positivity. Although the sporadic parental EYO score will never replace in vivo $A\beta$ assessment, limiting PET or CSF screening to individuals who are within a 10-year time window of their parent's symptom onset could significantly reduce the number of LP or PET procedures performed.

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