JAMA Neurology | Original Investigation

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

Sylvia Villeneuve, PhD; Jacob W. Vogel, BA; Julie Gonneaud, PhD; Alexa Pichet Binette, MSc; Pedro Rosa-Neto, MD, PhD; Serge Gauthier, MD, FRCPC; Randall J. Bateman, MD; Anne M. Fagan, PhD; John C. Morris, MD; Tammie L. S. Benzinger, MD, PhD; Sterling C. Johnson, PhD; John C. S. Breitner, MD, MPH; Judes Poirier, PhD, MD (Hon); for the Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease (PREVENT-AD) Research Group

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 (Aβ) levels in asymptomatic individuals with a parental history of AD dementia.

DESIGN, SETTING, AND PARTICIPANTS This cohort study analyzed Aβ1-42 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 Aβ levels was then assessed using apolipoprotein E ε4 (*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) Aβ 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 Aβ 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 Aβ1-42 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 Aβ biomarker changes in women or *APOE4* carrier asymptomatic individuals with a parental history of sporadic AD.

JAMA Neurol. 2018;75(5):608-619. doi:10.1001/jamaneurol.2017.5135
Published online February 26, 2018.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the PREVENT-AD Research Group are listed at the end of this article.

Corresponding Author: Sylvia Villeneuve, PhD, Department of Psychiatry, McGill University, Faculty of Medicine, Douglas Mental Health University Institute, Perry Pavilion, Room E3417.1, 6875 LaSalle Blvd, Montreal, QC H4H 1R3, Canada (sylvia.villeneuve@mcgill.ca).

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-β1-42 (Aβ1-42) concentrations can be detected 25 years before expected symptom onset and brain Aβ 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 Aβ levels in asymptomatic individuals with a parental history of AD dementia. Given the heterogeneity of AD and because apolipoprotein E ε4 (*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 Aβ levels is influenced by these risk factors. The current study was performed using CSF Aβ1-42 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) cohort[11] using CSF and Pittsburgh compound B carbon 11-labeled positron emission tomography (PIB-PET) Aβ biomarkers.

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.

Methods

Participants and Study Design

All individuals included in the current study had a parental history of AD and Aβ 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 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 Aβ1-42 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 0[12] 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 Aβ1-42 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 Aβ1-42	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: Aβ, 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 Aβ 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).

Aβ Assessments

The CSF from the PREVENT-AD cohort was collected by LP in the morning under fasting conditions. Measurement of Aβ1-42 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 Aβ 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 ε4 alleles) or noncarriers (no ε4 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 Aβ1-42 level (dependent variable) by age while controlling for sex and educational level and CSF Aβ1-42 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 Aβ1-42 level by age while controlling for sex and educational level (model A, step 1, same as previous analysis); CSF Aβ1-42 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 × sex) on CSF Aβ1-42 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 × *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 Aβ1-42 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 Aβ.[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).

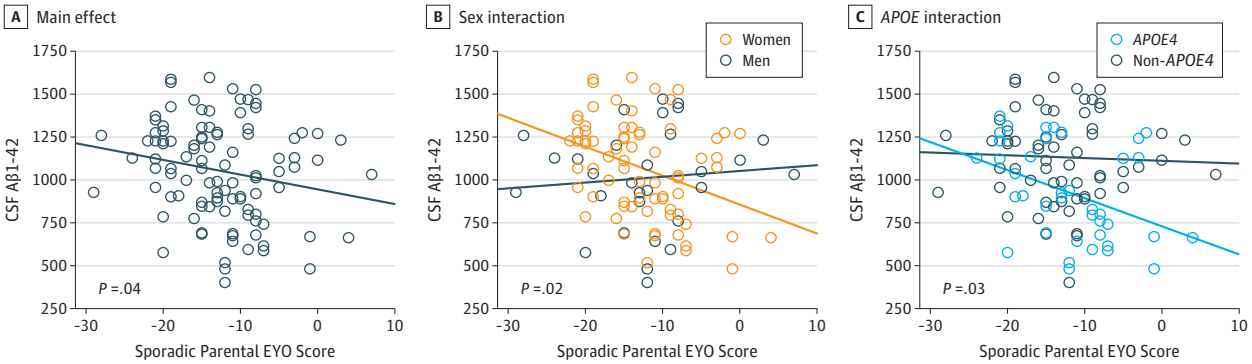
Association Between Sporadic Parental EYO Score and Aβ Burden

Cross-sectional analyses from the PREVENT-AD cohort demonstrated no association between age and CSF Aβ1-42 level or between parent's age at symptom onset and CSF Aβ1-42 level but found a reduction in CSF Aβ1-42 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 Aβ1-42 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 *APOE*4 carriers than in noncarriers.

In the ACS cohort, age was associated with CSF Aβ1-42 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 Aβ burden was replicated in the members of the ACS cohort who underwent PIB-PET, with an increase of brain Aβ 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 Aβ1-42 and PIB-PET data. In addition, longitudinal ACS PIB-PET data further suggest that women tend to accumulate brain Aβ at a faster rate than men as they approach the age at their parent's onset. The sporadic parental EYO score × *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 Aβ1-42 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 (Aβ) 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) × *APOE* status interaction were also controlled for the main effect of *APOE* status. Unadjusted (raw) data are plotted. *APOE4* indicates apolipoprotein E ε4; 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 Aβ accumulation (longitudinal data). The sporadic parental EYO score × *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 × sex interaction for the rate of brain Aβ 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 Aβ 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).

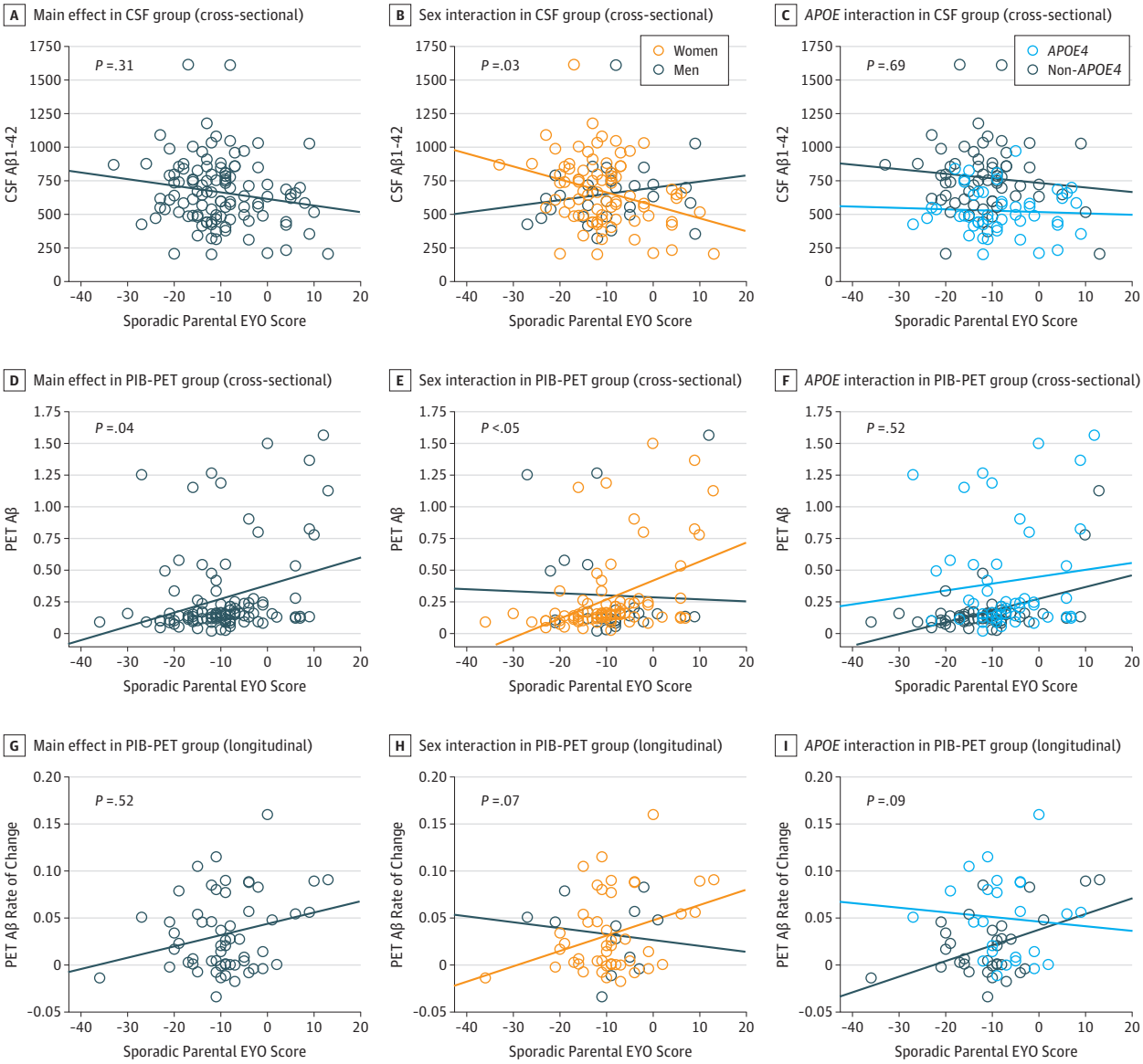
Discussion

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 Aβ 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) Aβ 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 Aβ deposition at a faster rate (WRAP findings) (Figure 3). Of importance, this association seemed to be independent of age-related changes in Aβ burden. Because Aβ burden is known to increase with age[20] 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 Aβ1-42 and age, and adjusting for age did not alter the significant association between sporadic parental EYO score and CSF Aβ1-42 (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 Aβ variability than age. In addition, although increasing age was associated with increasing Aβ 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 Aβ burden in late middle-age individuals, who are less likely to have age-related Aβ, compared with elderly individuals, who have a higher prevalence of Aβ 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 Aβ 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 Aβ1-42 than men as they approach their parent's age at symptom onset

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

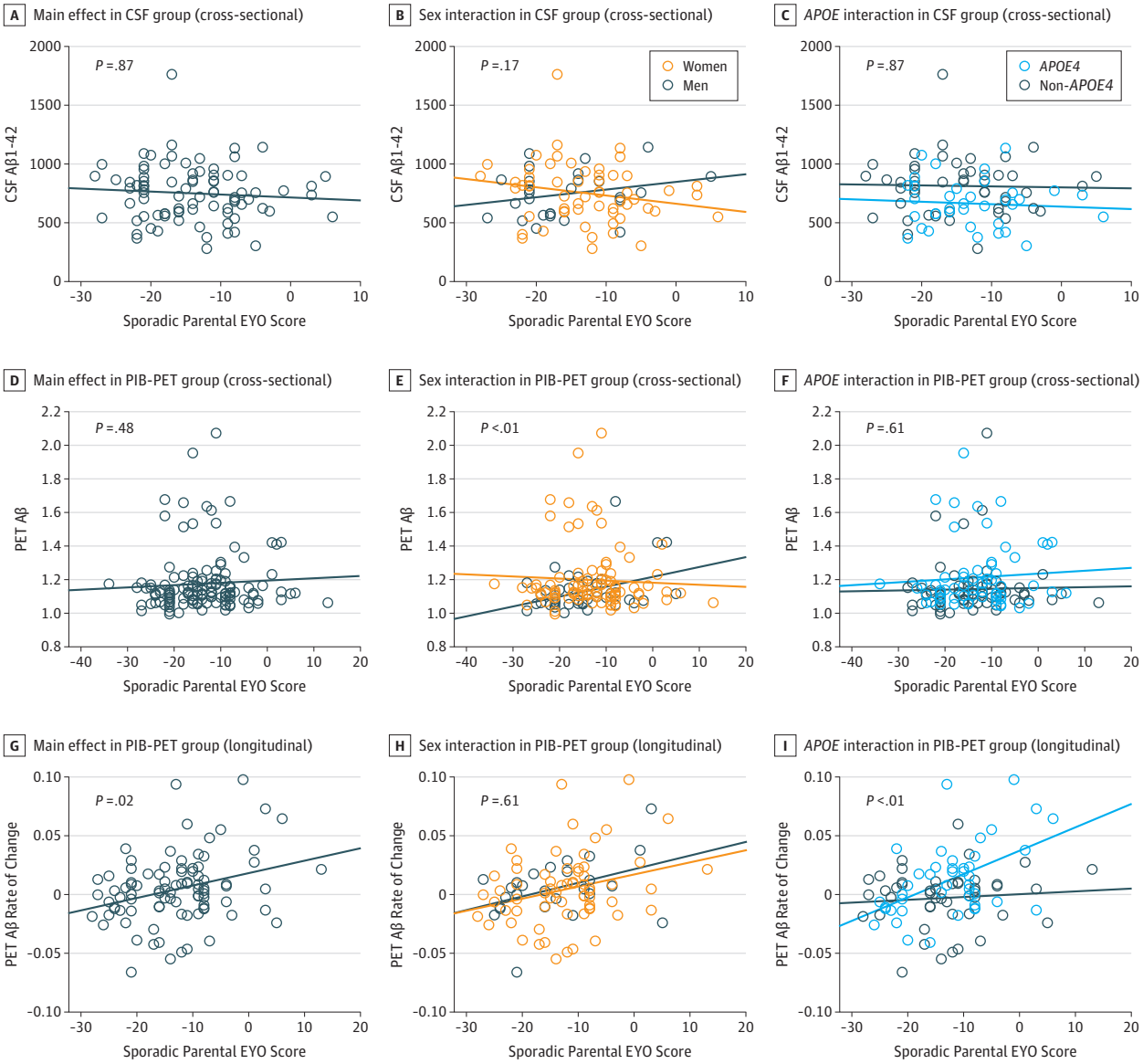


P values were obtained with linear regression models controlled for age, sex, and educational level. Analyses that include the sporadic parental estimated years to symptom onset (EYO) score (calculated as the age of the participant at assessment minus the age of the parent at symptom onset) × *APOE* status interaction were also controlled for the main effect of *APOE* status. Unadjusted (raw) data are plotted. *APOE4* indicates apolipoprotein E ε4; 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 Aβ accumulation, suggesting that women might also present a faster rate of Aβ 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 Aβ1-42 was stronger in *APOE4* carriers (Figure 1). Consistently, *APOE4* carriers in the WRAP cohort accumulated Aβ deposition faster than did the *APOE4* noncarriers (Figure 3). Altogether, these results suggest that the association between sporadic parental EYO score and Aβ burden was increased in individuals with a higher risk of developing AD.

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

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

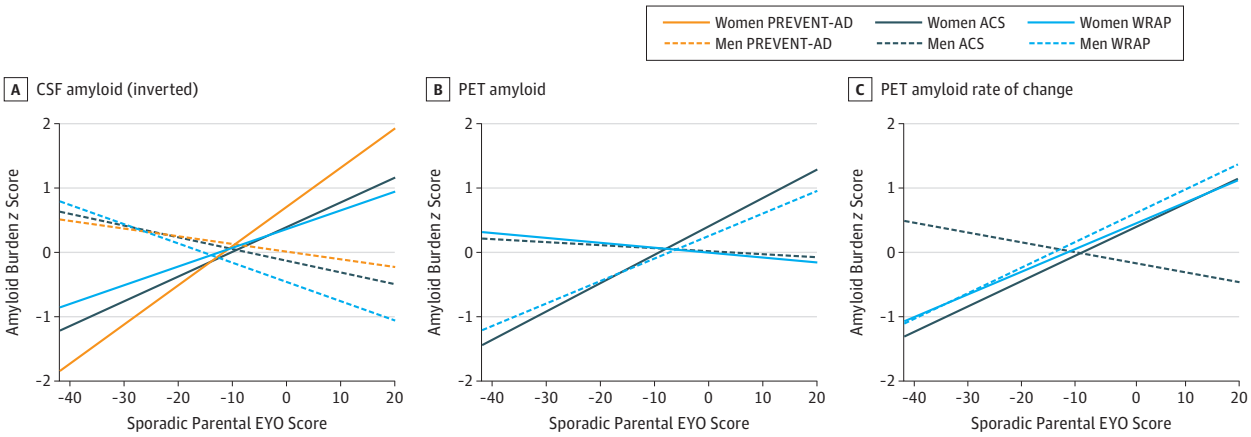


P values were obtained with linear regression models controlled for age, sex, and educational level. Analyses that include the sporadic parental estimated years to symptom onset (EYO) score (calculated as the age of the participant at assessment minus the age of the parent at symptom onset) score × *APOE* status interaction were also controlled for the main effect of *APOE* status. Unadjusted (raw) data are plotted. *APOE4* indicates apolipoprotein E ε4; CSF, cerebrospinal fluid; and PET, positron emission tomography.

limited age groups. The population prevalence of Aβ 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 Aβ1-42 and/or high brain Aβ 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 Aβ 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 Aβ1-42 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 Aβ1-42 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 Aβ levels.

Figure 4. Normalized Amyloid-β (Aβ) 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 Aβ 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 Aβ 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 Aβ levels in the CSF, Aβ 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 Aβ positivity. Although the sporadic parental EYO score will never replace in vivo Aβ 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.

ARTICLE INFORMATION

Accepted for Publication: December 1, 2017.

Published Online: February 26, 2018. doi:10.1001/jamaneurol.2017.5135

Author Affiliations: Department of Psychiatry, McGill University, Montreal, Quebec, Canada (Villeneuve, Gonneaud, Rosa-Neto, Gauthier, Breitner, Poirier); Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada (Villeneuve, Rosa-Neto, Gauthier); Douglas Mental Health University Institute, Studies on Prevention of Alzheimer's Disease (StOP-AD) Centre, Montreal, Quebec, Canada (Villeneuve, Vogel, Gonneaud, Pichet Binette, Rosa-Neto, Gauthier, Breitner, Poirier); McGill Centre for Integrative Neuroscience, McGill University, Montreal, Quebec, Canada (Villeneuve, Vogel, Pichet Binette, Rosa-Neto, Breitner); Department of Neurology, Washington University School of Medicine, St Louis, Missouri (Bateman, Fagan, Morris); Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, Missouri (Bateman, Fagan, Morris, Benzinger); Department of Radiology, Washington University School of Medicine, St Louis, Missouri (Benzinger); Wisconsin Alzheimer's Institute, University of Wisconsin–Madison School of Medicine and Public Health, Madison (Johnson); Alzheimer's Disease Research Center, University of Wisconsin–Madison School of Medicine and Public Health, Madison (Johnson).

Author Contributions: Dr Villeneuve had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Villeneuve, Vogel, Gonneaud, Johnson, Breitner.
Acquisition, analysis, or interpretation of data: Villeneuve, Vogel, Gonneaud, Pichet Binette, Rosa-Neto, Gauthier, Bateman, Fagan, Morris, Benzinger, Breitner, Poirier.
Drafting of the manuscript: Villeneuve, Vogel, Gonneaud.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Villeneuve, Vogel, Gonneaud, Bateman.

Obtained funding: Villeneuve, Bateman, Morris, Benzinger, Johnson, Breitner, Poirier.
Administrative, technical, or material support: Villeneuve, Rosa-Neto, Fagan, Benzinger, Breitner, Poirier.
Supervision: Villeneuve, Bateman, Morris, Breitner.

Conflict of Interest Disclosures: Dr Villeneuve reported having a Canada research chair and receiving research support from the Canadian Institutes of Health Research (CIHR), the Alzheimer's Association, the Alzheimer's Society of Canada, and the Brain Canada Foundation. Mr Vogel reported receiving a Vanier Canada Graduate Doctoral Scholarship. Dr Gonneaud reported having a postdoctoral scholarship from the PREVENT-AD program. Ms Pichet Binette reported having a PhD scholarship from CIHR. Dr Rosa-Neto reported receiving research support from the CIHR, Canadian Consortium on Neurodegeneration in Aging, the Fonds de recherche du Québec–Santé, Chercheur Burcier Junior 2, and the Weston Brain Institute; receiving nonfinancial support from Avid Pharmaceuticals, Enigma Radiopharmaceuticals, Merck & Co, and Roche; and serving as a consultant for Merck & Co, Eli Lilly and Company, Pyramal, and Kalgene. Dr Gauthier reported receiving clinical trial support from Eli Lilly and Company, Roche, TauRx, and Lundbeck; serving as a data and safety monitoring board member for the Alzheimer's Disease Cooperative Study, the Alzheimer's Therapeutic Research Institute, the Alzheimer's Prevention Initiative, and Eisai; and serving as a scientific adviser for AbbVie, ADvantage, Alzheon, Axovant, Boehringer Ingelheim, Firalis, Heptares, IntelGen, Kalgene, Eli Lilly and Company, Lundbeck, Novartis, Otsuka, Servier, Sanofi, Schwabe, Takeda, TauRx, TVM Capital, and Roche. Dr Bateman reported receiving research support from the National Institutes of Health, the Alzheimer's Association, Forest Biometrics Research Institute, BrightFocus Foundation, Cure Alzheimer's Fund, Glenn Foundation for Medical Research, the Metropolitan Life Foundation, Biogen, Abbvie, Eli Lilly and Company, and the Dominantly Inherited Alzheimer Network-Trial Meeting (DIAN-TU) Pharma Consortium (Biogen Idec, Elan Pharmaceuticals, Eli Lilly and Company, Hoffman–La Roche, Genentech, Janssen Alzheimer Immunotherapy, Mithridion, Novartis Pharma AG, Pfizer Biotherapeutics R and D, Sanofi, and Eisai); receiving nonfinancial support from Avid Pharmaceuticals, Cogstate, and Bracket; serving as a consultant for IMI, Sanofi, Global Alzheimer's Platform, Boehringer Ingelheim, and Merck & Co; and serving as an invited speaker for Roche and the Organisation for Economic Co-operation and Development. Dr Fagan reported being on the scientific advisory boards of IBL International and Roche and serving as a consultant for AbbVie, Novartis, and DiamiR. Dr Morris reported currently participating in clinical trials of antidementia drugs from Eli Lilly and Company, Biogen, and Janssen; serving as a consultant for Eli Lilly and Company; receiving research support from Eli Lilly and Company and Avid Radiopharmaceuticals; and receiving funding from grants P01AG003991, P01AG026276, and UF01AG032438 from the National Institutes of Health. Dr Benzinger reported receiving research support from the National Institutes of Health, the Alzheimer's Association, the Barnes-Jewish Hospital Foundation, Avid Radiopharmaceuticals, and the DIAN-TU Pharma Consortium (Biogen Idec, Elan Pharmaceuticals, Eli Lilly and Company, Hoffman–La Roche, Genentech, Janssen Alzheimer Immunotherapy, Mithridion, Novartis Pharma AG, Pfizer Biotherapeutics R and D, Sanofi, and Eisai) and nonfinancial support from Avid Pharmaceuticals. Dr Johnson reported receiving research support from the National Institutes of Health. Dr Breitner reported having a Canada research chair. No other disclosures were reported.

Funding/Support: This work was supported by Canada research chairs (Drs Villeneuve and Breitner), a Canadian Institutes of Health Research foundation grant, a Canada Fund for Innovation, a joint Alzheimer Society of Canada and Brain Canada Research grant (Dr Villeneuve), an Integrative Neuroscience Program recruitment award (Mr Vogel), a postdoctoral fellowship (Dr Gonneaud), and an Alzheimer Society of Canada and Fonds de recherche du Québec–Santé grant (Ms Pichet Binette). PREVENT-AD was funded by a $13.5 million, 7-year public-private partnership using funds provided by McGill University, the Fonds de recherche du Québec–Santé, an unrestricted research grant from Pfizer Canada, the Levesque Foundation, the Douglas Hospital Research Centre and Foundation, the Government of Canada, the Canada Fund for Innovation, and Genome Quebec Innovation Center. The Adult Children Study was supported by grant P01 AG026276 from the National Institute on Aging (Dr Morris), the American Roentgen Ray Scholar Award (Dr Benzinger), and grant P50 AG05681 from the Charles F. and Joanne Knight Alzheimer's Research Initiative of the Washington University Alzheimer's Disease Research Center (Dr Morris). The Wisconsin Registry for Alzheimer Prevention was supported by the National Institutes of Health awards R01 AG027161, R01 AG021155, R01 AG054047, R01 AG037639, P50 AG033514, UL1 TR000427, K23 AG045957, F30AG054115, T32 GM007507, and T32 GM008692, grants from the Alzheimer's Association, Extendicare Foundation, and Northwestern Mutual Life Foundation to the University of Wisconsin–Madison, and donor funds, including the Wisconsin Alzheimer's Institute Lou Holland Fund and contributions from anonymous donors. Portions of this research were supported by resources at the Wisconsin Alzheimer's Institute, the Wisconsin Alzheimer's Disease Research Center, and the Geriatric Research Education and Clinical Center of the William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin.

Role of the Funder/Sponsor: Data used in preparation of this article were obtained from the PREVENT-AD program, data release 3.0 (November 30, 2016). As such, the investigators of the PREVENT-AD program contributed to the design and implementation of PREVENT-AD and/or provided data but did not participate in analysis or writing of this report.

Group Information: The members of the Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer Disease (PREVENT-AD) Research Group are as follows: Alan Barkun, MSc, MD, CM, McGill University, Montreal, Quebec, Canada; Alan Evans, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada,McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Alexa Pichet Binette, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Alyssa Salaciak, BSc, BA, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Angela Tam, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Centre de recherche de l'Institut universitaire de gériatrie de Montreal, Quebec, Canada, and Université de Montréal, Montreal, Quebec, Canada; Anne Labonté, BSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Anne-Marie Faubert, PharmD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Axel Mathieu, PhD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Blandine Courcot, PhD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Bradley T. Hyman, PhD, MD, Massachussets Alzheimer's Disease Research Center, Harvard Medical School, Boston, Massachusetts; Cécile Madjar, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Charles Edouard Carrier, RN, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Christian Dansereau, MEng, Centre Centre de recherche de l'Institut universitaire de gériatrie de Montreal, Quebec, Canada, and Université De Montréal, Montreal, Quebec, Canada; Christina Kazazian, BSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Christine Tardif, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Claude Lepage, PhD, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Claudio Cuello, PhD, McGill University, Montreal, Quebec, Canada; Clément Debacker, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Clifford R. Jack, MD, Mayo Clinic, Rochester, Minnesota; Cynthia Picard, PhD, SToP-AD Centre, Centre for Studies on

Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; David Maillet, PhD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; David Fontaine, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; David S. Knopman, MD, Mayo Clinic, Rochester, Minnesota; Diane Michaud, BSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Doris Couture, RN, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Doris Dea, BSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Eduard Teigner, BSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Elena Anthal, RN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Elsa Yu, BA, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Etienne Vachon-Presseau, PhD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and Northwestern University, Chicago, Illinois; Eunice Farah Saint-Fort, RRT, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Fabiola Ferdinand, RN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Fatiha Benbouhoud, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Galina Pogossova, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Gerhard Maultaup, PhD, McGill University, Montreal, Quebec, Canada; Ginette Mayrand, RN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Guerda Duclair, RN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Gülebru Ayranci, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Guylaine Gagné, RN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Holly Newbold-Fox, MIT, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Illana Leppert, MEng, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Isabelle Vallée, LPN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Jacob Vogel, PhD, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Jamie Near, PhD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Jason Brandt, PhD, The Johns Hopkins University, Baltimore, Maryland; Jean-Robert Maltais, MD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Jeannie-Marie Leoutsakos, PhD, The Johns Hopkins University, Baltimore, Maryland; Jennifer Tremblay-Mercier, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Jens Pruessner, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Joanne Frenette, RN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; John C. Morris, MD, Washington University School of Medicine, St Louis, Missouri; John C. S. Breitner, MPH, MD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; and McGill University, Montreal, Quebec, Canada; Josée Frappier, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Judes Poirier, MD, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Julie Gonneaud, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Justin Kat, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Justin Miron, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Karen Wan, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Laksanun Cheewakriengkrai, MD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Laura Mahar, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Leopoldina Carmo, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Lisa-Marie Münter, PhD, McGill University, Montreal, Quebec, Canada; Louis Collins, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Louise Théroux, BSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Mahsa Dadar, MSc, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Mallar Chakravarty, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Marianne Dufour, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Marie-Elyse

Lafaille-Magnan, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Marina Dauar-Tedeschi, MD,SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre For Studies In Aging, Montreal, Quebec, Canada; Mark A. Sager, MD, Wisconsin Alzheimer's Institute, University of Wisconsin School of Medicine and Public Health, Milwaukee; Mark Eisenberg, MD, McGill University, Montreal, Quebec, Canada; Melissa Appleby, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Mélissa Savard, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Miranda Tuwaig, BSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Mirela Petkova, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Natasha Rajah, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Paul Aisen, MD, University Of Southern California's Alzheimer's Therapeutic Research Institute, San Diego; Paule-Joanne Toussaint, PhD, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Pedro Rosa-Neto, PhD, MD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Penelope Kostopoulos, PhD, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Pierre Bellec, PhD,SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Centre Centre de recherche de l'Institut universitaire de gériatrie de Montreal, Quebec, Canada, and Université De Montréal, Montreal, Quebec, Canada; Pierre Etienne, MD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Pierre N. Tariot, MD, Banner Alzheimer Institute, Phoenix, Arizona; Pierre Orban, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, Centre Centre de recherche de l'Institut universitaire de gériatrie de Montreal, Quebec, Canada, and Université de Montréal, Montreal, Quebec, Canada; Pierre Rioux, MSc, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Pierre-François Meyer, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Rana El-Khoury, LPN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Reisa A. Sperling, MMSc, MD, Center for Alzheimer's Research and Treatment, Harvard Medical School, Boston, Massachusetts; René Desautels, MD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Renee Gordon, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Renuka Giles, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Rick Hoge, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Ronald G. Thomas, PhD, University of California, San Diego, School of Medicine, La Jolla; Samir Das, MSc, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Sander C. J. Verfaillie, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and Alzheimer Center, VU University Amsterdam, Amsterdam, the Netherlands; Sarah Farzin, BSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Seqian Wang, BSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada, McGill University Research Centre For Studies In Aging, Montreal, Quebec, Canada; Serge Gauthier, MD, FRCPC, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre For Studies In Aging, Montreal, Quebec, Canada; Shirin Tabrizi, BA, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Stephanie Tullo, BSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Sulantha Mathotaarachchi, BSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Suzanne Craft, PhD, Wake Forest School of Medicine, Winston-Salem, North Carolina; Sylvia Villeneuve, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Sylvie Dubuc, PharmD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Tanya Lee, MSc, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Tharick A. Pascoal, MD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Thomas J. Montine, PhD, MD, Washington University, Seattle; Thomas Beaudry, BSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Valérie Gervais, LPN, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Vasavan Nair, MD, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and McGill University Research Centre for Studies in Aging, Montreal, Quebec, Canada; Véronique Bohbot, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada, and McGill University, Montreal, Quebec, Canada; Véronique Pagé, MSc, Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Vinod Venugopalan, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal,

Quebec, Canada, and Douglas Mental Health University Institute Research Centre, affiliated with McGill University, Montreal, Quebec, Canada; Vladimir Fonov, PhD, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; Yasser Ituria-Medina, PhD, SToP-AD Centre, Centre for Studies on Prevention of Alzheimer's Disease, Montreal, Quebec, Canada, McGill University, Montreal, Quebec, Canada, and Montreal Neurological Institute and Hospital, Montreal, Quebec, Canada; and Zaven S. Khachaturian, PhD, Khachaturian & Associates Inc, Potomac, Maryland.

Additional Contributions: Cécile Madjar, MSc, SToP-AD Center, Katrina Moulder, PhD, Washington University, Betsy Grant, PhD, Washington University School of Medicine, and Allen Wenzel, BS, Wisconsin Alzheimer's Institute helped with data preparation. They were not compensated beyond their regular salaries. We thank the participants for their time and commitment and the PREVENT-AD, Adult Children Study, and Wisconsin Registry for Alzheimer Prevention research staff.

REFERENCES

1. Bateman RJ, Xiong C, Benzinger TL, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795-804.

2. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer disease. *Arch Gen Psychiatry*. 2006;63(2):168-174.

3. Wingo TS, Lah JJ, Levey AI, Cutler DJ. Autosomal recessive causes likely in early-onset Alzheimer disease. *Arch Neurol*. 2012;69(1):59-64.

4. Corder EH, Saunders AM, Strittmatter WJ, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*. 1993;261(5123):921-923.

5. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet*. 1993;342(8873):697-699.

6. Altmann A, Tian L, Henderson VW, Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators. Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol*. 2014;75(4):563-573.

7. Snyder HM, Asthana S, Bain L, et al. Sex biology contributions to vulnerability to Alzheimer's disease: a think tank convened by the Women's Alzheimer's Research Initiative. *Alzheimers Dement*. 2016;12(11):1186-1196.

8. Breitner JCS, Poirier J, Etienne PE, Leoutsakos JM. Rationale and structure for a new center forStudies on Prevention of Alzheimer's Disease (StoP-AD). *J Prev Alzheimers Dis*. 2016;3(4):236-242.

9. Xiong C, Roe CM, Buckles V, et al. Role of family history for Alzheimer biomarker abnormalities in the adult children study. *Arch Neurol*. 2011;68(10):1313-1319.

10. Coats M, Morris JC. Antecedent biomarkers of Alzheimer's disease: the Adult Children Study. *J Geriatr Psychiatry Neurol*. 2005;18(4):242-244.

11. Sager MA, Hermann B, La Rue A. Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. *J Geriatr Psychiatry Neurol*. 2005;18(4):245-249.

12. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412-2414.

13. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MOCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53(4):695-699.

14. Bendlin BB, Ries ML, Canu E, et al. White matter is altered with parental family history of Alzheimer's disease. *Alzheimers Dement*. 2010;6(5):394-403.

15. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluidtau/β-amyloid$_{42}$ ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol*. 2007;64(3):343-349.

16. Racine AM, Koscik RL, Berman SE, et al. Biomarker clusters are differentially associated with longitudinal cognitive decline in late midlife. *Brain*. 2016;139(pt 8):2261-2274.

17. Gosselin N, De Beaumont L, Gagnon K, et al. BDNFVal^{66}Met polymorphism interacts with sleep consolidation to predict ability to create new declarative memories. *J Neurosci*. 2016;36(32):8390-8398.

18. Villemagne VL, Burnham S, Bourgeat P, et al; Australian Imaging Biomarkers and Lifestyle (AIBL) Research Group. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013;12(4):357-367.

19. Jack CR Jr, Wiste HJ, Lesnick TG, et al. Brain β-amyloid load approaches a plateau. *Neurology*. 2013;80(10):890-896.

20. Jansen WJ, Ossenkoppele R, Knol DL, et al; Amyloid Biomarker Study Group. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313(19):1924-1938.

21. Damoiseaux JS, Seeley WW, Zhou J, et al; Alzheimer's Disease Neuroimaging Initiative. Gender modulates the APOE ε4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. *J Neurosci*. 2012;32(24):8254-8262.

22. Bateman RJ, Aisen PS, De Strooper B, et al. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. *Alzheimers Res Ther*. 2011;3(1):1.

23. Chételat G. Alzheimer disease: Aβ-independent processes-rethinking preclinical AD. *Nat Rev Neurol*. 2013;9(3):123-124.

24. Small SA, Duff K. Linking Aβ and τ in late-onset Alzheimer's disease: a dual pathway hypothesis. *Neuron*. 2008;60(4):534-542.

25. Villeneuve S, Wirth M, La Joie R. Are AD-typical regions the convergence point of multiple pathologies? *Front Aging Neurosci*. 2015;7:42.

26. Craik FI, Bialystok E, Freedman M. Delaying the onset of Alzheimer disease: bilingualism as a form of cognitive reserve. *Neurology*. 2010;75(19):1726-1729.

27. Villeneuve S, Reed BR, Madison CM, et al. Vascular risk and Aβ interact to reduce cortical thickness in AD vulnerable brain regions. *Neurology*. 2014;83(1):40-47.

28. Wirth M, Villeneuve S, La Joie R, Marks SM, Jagust WJ. Gene-environment interactions: lifetime cognitive activity, APOE genotype, and β-amyloid burden. *J Neurosci*. 2014;34(25):8612-8617.