Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Participants, Study Design, and Parental Age at Onset Assessment

Presymptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease (PREVENT-AD) cohort

The primary goal of PREVENT-AD is to test whether serial determination of multi-modal biomarkers of AD may be measured and used in pre-symptomatic persons at high risk of subsequent AD dementia to trace the progression of the disease process and to measure effects of any potentially preventive treatment interventions. The PREVENT-AD work is intended to provide preliminary data regarding the probable efficacy and safety of potential new treatments for prevention of AD dementia. Only individuals free of treatment were included in the current study. Parental history and age at onset were self-reported. The parental age at onset corresponded to the age at which the family observed changes sufficient to warrant a consultation resulting in a diagnosis consistent with AD dementia.

Adult Children Study (ACS) cohort

Only data for individuals aged 55-year-old and older were available for the current study. Family history and parental age at onset were self-reported by the participants. Parental age at onset corresponds to the age at which dementia symptoms began.

Wisconsin Registry for Alzheimer's Prevention (WRAP) cohort

Participants from Data Freeze 12 were included in the current study. Only including individuals aged 55 years and older in the analysis (to be consistent with the PREVENT-AD and the ACS cohorts) did not change the main results, but significantly reduced the sample size. Parental history of AD was determined by a multidisciplinary diagnostic consensus panel, as previously described.[1] Age of parental symptom onset was defined by onset of memory loss symptoms.

Aβ assessments

Cerebrospinal Fluid assessment (CSF) in the PREVENT-AD cohort

CSF samples were stored in polypropylene tubes at −80°C. Collection, storage, and assay techniques were performed as standardized by the European project BIOMARKAPD that was created to harmonize assays used to measure biological markers in neurodegenerative diseases.[2,3]

CSF in the ACS cohort

CSF samples were collected and analyzed using a similar procedure and assay as the one used in the PREVENT-AD and are fully described elsewhere.[4] Briefly, CSF (20-30 mL) was collected via gravity drip by lumbar puncture (LP) at 8:00am after an overnight fasting period. Samples were centrifuged, aliquoted (0.5mL) and stored at −84°C in polypropylene tubes. Levels of $A\beta_{1-42}$ were then analyzed after a single thaw following initial freezing and determined by ELISA (INNOTEST; Fujirebio [formerly Innogenetics], Ghent, Belgium).

CSF in the WRAP cohort

CSF samples were collected with a similar procedure as the one used in the PREVENT-AD and the ACS and are fully described elsewhere.[5,6] Briefly, CSF (22mL) samples were collected by LP in the morning after an overnight fasting period (i.e. 12 hours). They were then centrifuged within 10 minutes, aliquoted (0.5 mL) and stored at −80°C in polypropylene tubes. Levels of $A\beta_{1-42}$ CSF were quantified by electrochemiluminescence using an Aβ triplex assay (MSD Human Aβ peptide Ultra-Sensitive Kit, Meso Scale Discovery).

PIB Positron Emission Tomography (PET) acquisition and analysis in the ACS

PIB-PET acquisition and processing are fully described elsewhere.[7] Briefly, all participants were scanned on either a Siemens 961 HR ECAT PET scanner or a Siemens 962 HR ECAT PET scanner (Control Technology, Inc, Knoxville, Kentucky). A 60-minute 3D PET-scan was acquired after intravenous administration of approximately 12mCi of ^{11}C-PIB. Binding potentials were calculated for multiple regions of interest (ROIs) derived from Freesurfer, using the cerebellum as a reference region. Binding potential was calculated by subtracting 1 from the distribution to volume ratio (DVR), obtained through Logan analysis and corrected for regional spread function.[8] Finally the mean cortical binding potential (MCBP) was obtained by averaging left and right lateral orbitofrontal, interior parietal, precuneus, rostral middle frontal, superior frontal, superior temporal, and middle temporal ROIs. Standardized uptake value ratio (SUVR) and MCBP data not corrected for regional spread function were also available and gave similar results. All analyses presented used MCBP values as a continuous variable. Individuals above the threshold of 0.37 are considered Aβ-positive based on the ACS dictionary guidelines (unpublished data, see[9] for threshold derivation methods).

PIB-PET acquisition and analysis in the WRAP

PIB-PET acquisition and processing for the WRAP data are fully described elsewhere.[6] With the exception of the partial volume effect correction, the processing of the WRAP data are very similar to that performed on the ACS PIB-PET data. Briefly, all participants were scanned on a Siemens HR+ scanner. A 70-minute dynamic PET scan was performed after an intravenous injection of approximatively 15mCi of ^{11}C-PIB. Data were transformed into voxel-wise DVR maps, through Logan analysis, and scaled using the cerebellum as reference region. Mean cortical Aβ burden was calculated by averaging the mean DVR within eight bilateral ROIs, including the angular gyrus, anterior cingulate gyrus, posterior cingulate gyrus, frontal medial orbital gyrus, precuneus, supramarginal gyrus, middle temporal gyrus, and superior temporal gyrus. All analyses used DVR values as a continuous variable. Individuals above the threshold of 1.18 are considered Aβ-positive based on a previous publication.[10]

PIB-PET annual rate of change

Additional analyses were performed to assess whether proximity to parental onset (sporadic parental EYO) influences the annual rate of brain Aβ accumulation in the ACS (n = 59) and the WRAP (n = 92) cohorts. To do so, 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 two scans’.

APOE genotype

APOE genotype in the PREVENT-AD was determined using the PyroMark Q96 pyrosequencer (Qiagen, Toronto, ON, Canada) and the following primers: rs429358_amplification_forward 5'-ACGGCTGTCCAAGGAGCT G-3', rs429358_amplification_reverse_biotinylated 5'-CACCTCGCCGCGGTACTG-3', rs429358_sequencing 5'-CGGACATGGAGGACG-3', rs7412_amplification_forward 5'-CTCCGCGATGCCGATGAC-3', rs7412_amplification_reverse_biotinylated 5'-CCCCGGCCTGGTACACTG-3' and rs7412_sequencing 5’-CGATGACCTGCAGAAG-3’.

eTable 1. Proximity to Parental Symptom Onset and Amyloid Burden in the PREVENT-AD Cohort

			Prevent-AD CSF (n = 101) Cross-sectional data			
Models		Independent Variables	Unst. B Value	Std. Error	Std. Beta Value	P value
Model A.	Step 1	Sex	59.67	61.89	.096	.337
		Education	12.86	9.56	.134	.182
		Age	-3.95	5.57	-.071	.480
	Step2	Sex	57.23	60.83	.092	.349
		Education	14.82	9.44	.155	.120
		Age	-1.14	5.63	-.020	.840
		spEYO	-9.09	4.31	-.214	**.038**
	Step3	Sex	-188.68	120.05	-.305	.119
		Education	11.91	9.31	.124	.204
		Age	-2.67	5.54	-.048	.631
		spEYO	22.63	14.10	.532	.112
		spEYO*Sex	-19.79	8.40	-.878	**.020**
Model B.	Step3[a]	Sex	88.31	58.36	.143	.134
		Education	11.04	8.72	.115	.209
		Age	-4.74	5.24	-.085	.368
		APOE	-426.21	114.76	-.734	<.001
		spEYO	-.018	5.22	<.001	.997
		spEYO*_APOE_	-17.88	8.23	-.451	**.032**

Shown are the unstandardized regression coefficients (B values), the standard error, standardized regression coefficient (Beta values) and the p values related to Figure 1, main text.

[a] Steps 1 and 2 are the same one as Model A.

APOE = Apolipoprotein E; CSF: cerebrospinal fluid; Prevent-AD = Pre-symptomatic Evaluation of Novel or Experimental Treatments for Alzheimer's Disease; spEYO = Sporadic Parental Estimated Years to Symptom Onset (calculated as the age of the participant at assessment minus the age of the parent at symptom onset).

eTable 2. Proximity to Parental Symptom Onset and Amyloid Burden in the ACS Cohort

			ACS CSF (n = 112) Cross-sectional data				ACS PIB-PET (n = 107) Cross-sectional data				ACS PIB-PET (n = 58) Longitudinal data			
Models		Independent Variables	Unstd B value	Std. Error	Std. Beta Value	P value	Unstd B value	Std. Error	Std. Beta Value	P value	Unstd B value	Std. Error	Std. Beta Value	P value
Model A.	Step 1	Sex	-27.79	53.58	-.050	.605	.004	.076	.005	.955	.008	.013	.078	.554
		Education	-21.88	10.23	-.193	.044	.002	.015	.013	.892	.003	.002	.152	.249
		Age	-11.17	4.66	-.225	**.018**	.015	.006	.235	**.019**	.002	.001	.33	**.015**
	Step2	Sex	-27.79	53.57	-.050	.605	-.007	.075	-.009	.929	.006	.013	.062	.645
		Education	-21.77	10.26	-.201	.036	.004	.014	.025	.797	.003	.002	.153	.247
		Age	-8.52	5.32	-.172	.112	.006	.008	.096	.412	.002	.001	.261	.130
		spEYO	-3.17	3.08	-.110	.306	.009	.004	.243	**.037**	.001	.001	.108	.519
	Step3	Sex	-145.46	74.65	-.26	.054	.136	.102	.176	.185	.035	.020	.348	.093
		Education	-20.00	10.11	-.185	.050	.003	.014	.023	.806	.003	.002	.175	.178
		Age	-7.07	5.27	-.143	.183	.005	.007	.074	.524	.002	.001	.310	.070
		EYO	17.34	9.71	.599	.077	-.019	.014	-.508	.194	-.05	.003	-1.01	.114
		spEYO*Sex	-12.52	5.64	-.793	**.028**	.016	.008	.815	**.046**	.003	.002	1.14	.071
Model B.	Step3[a]	Sex	-28.17	47.85	-.050	.557	-.001	.073	-.001	.988	.011	.013	.113	.387
		Education	-17.08	9.25	-.158	.068	.001	.014	.004	.968	.002	.002	.117	.345
		Age	-9.48	4.80	-.191	.051	.006	.007	.097	.391	.002	.001	.252	.117
		APOE	-216.45	66.12	-.429	.001	.186	.092	.275	.046	.008	.015	.097	.592
		spEYO	-1.13	3.85	-.039	.771	.007	.006	.181	.232	.001	.001	.208	.268
		spEYO*_APOE_	2.03	5.03	.058	.687	-.003	.007	-.053	.717	-.002	.001	-.331	.092

Shown are the unstandardized regression coefficients (B values), the standard error, standardized regression coefficient (Beta values) and the p values related to Figure 2, main text.

[a] Steps 1 and 2 are the same one as Model A.

ACS = Adult Children Study; *APOE* = Apolipoprotein E; CSF: cerebrospinal fluid; PET = Positron Emission Tomography; spEYO = Sporadic Parental Estimated Years to Symptom Onset (calculated as the age of the participant at assessment minus the age of the parent at symptom onset).

eTable 3. Proximity to Parental Symptom Onset and Amyloid Burden in the WRAP Cohort

			WRAP CSF (n = 85) Cross-sectional data				Wrap PIB-PET (n = 135) Cross-sectional data				Wrap PIB-PET (n = 91) Longitudinal data			
Models		Independent Variables	Unstd B value	Std. Error	Std. Beta Value	P value	Unstd B value	Std. Error	Std. Beta Value	P value	Unstd B value	Std. Error	Std. Beta Value	P value
Model A.	Step 1	Sex	-.89	54.62	-.002	.987	.082	.031	.217	.010	.001	.007	.013	.903
		Education	-9.41	10.21	-.100	.359	.008	.006	.111	.186	.001	.001	.100	.341
		Age	-8.73	4.26	-.222	**.044**	.008	.002	.285	**.001**	.001	<.001	.275	**.010**
	Step2	Sex	.89	56.08	.002	.987	.085	.032	.225	.008	-.001	.006	-.017	.865
		Education	-9.41	10.27	-.101	.361	.008	.006	.111	.184	.001	.001	.090	.380
		Age	-8.50	4.52	-.217	.064	.009	.003	.307	.001	.001	.001	.192	.078
		spEYO	-.59	3.71	-.018	.874	-.001	.002	-.062	.480	.001	<.001	.248	**.023**
	Step3[a]	Sex	-158.01	126.60	-.314	.216	-.063	.064	-.166	.328	-.006	.012	-.098	.611
		Education	-9.13	10.21	-.098	.374	.007	.006	.102	.211	.001	.001	.092	.374
		Age	-6.99	4.62	-.178	.134	.010	.003	.358	<.001	.001	.001	.201	.070
		spEYO	17.17	13.23	.539	.198	.016	.007	.722	.021	.001	.001	.430	.264
		spEYO*Sex	-10.80	7.72	-.621	.166	-.011	.004	-.883	**.009**	<.001	.001	-.201	.621
Model B.	Step3[b]	Sex	27.94	55.01	.056	.613	.081	.031	.215	.011	.002	.006	.024	.803
		Education	-6.02	10.07	-.064	.551	.007	.006	.104	.214	.001	.001	.105	.274
		APOE	-7.45	4.38	-.190	.093	.009	.003	.312	<.001	.001	<.001	.212	.037
		Age	-158.63	106.83	-.335	.142	.091	.056	.260	.108	.038	.010	.668	<.001
		spEYO	0.51	4.44	.016	.909	-.003	.003	-.115	.316	<.001	<.001	-.009	.945
		spEYO*_APOE_	-1.14	6.98	-.038	.871	.002	.004	.089	.609	.002	.001	.523	**.007**

Shown are the unstandardized regression coefficients (B values), the standard error, standardized regression coefficient (Beta values) and the p values related to Figure 3, main text.

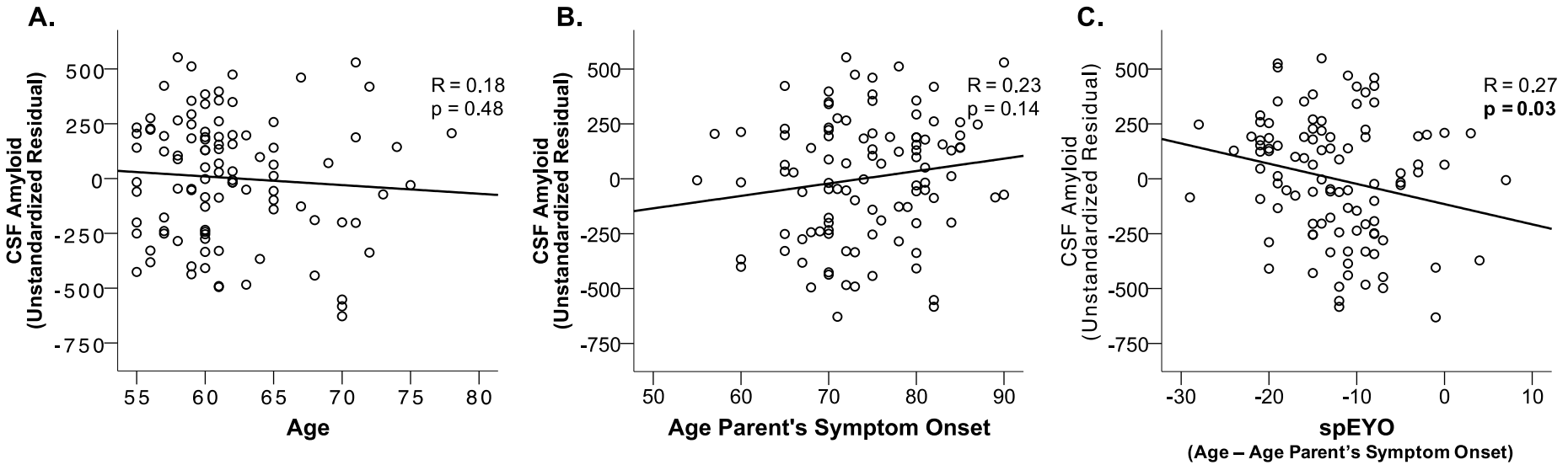
[a] Steps 1 and 2 are the same one as Model A.

APOE = Apolipoprotein E; CSF: cerebrospinal fluid; PET = Positron Emission Tomography; WRAP = Wisconsin Registry for Alzheimer's Prevention; spEYO = Sporadic Parental Estimated Years to Symptom Onset (calculated as the age of the participant at assessment minus the age of the parent at symptom onset)

eTable 4. Association Between Sporadic Parental Estimated Years to Symptom Onset (EYO) and Amyloid-β (Aβ) Burden Across Cohort and Aβ Assessment Methods

	CSF $A\beta_{1-42}$			PET Aβ		PET Aβ Rate of Change	
	PREVENT-AD	ACS	WRAP	ACS	WRAP	ACS	WRAP
spEYO	●			●			●
spEYO × sex	●	●		●	☒	○	
spEYO × *APOE*	●						●

Full dots indicate a significant effect of sporadic parental Estimated Years to Symptom Onset (spEYO) score (calculated as the age of the participant at assessment minus the age of the parent at symptom onset) on Aβ burden (●: $P < .05$); open dots indicate marginal effects (○: $P < .10$); and crossed squares indicate a significant or marginal effect in the unexpected direction (☒: $P < .10$).



eFigure. Cross-sectional Analyses of Cognitively Normal Individuals From the PREVENT-AD Cohort Demonstrated No Relationship Between Age and CSF $A\beta_{1\text{-}42}$ (A) or Between Age of Parent's Symptom Onset and CSF $A\beta_{1\text{-}42}$ (B), but Individuals Showed Reductions in CSF $A\beta_{1\text{-}42}$ Levels as They Approached the Age of Their Parent at Onset (C)
Analyses are controlled for sex and education.
spEYO = Sporadic Parental Estimated Years to Symptom Onset (calculated as the age of the participant at assessment minus the age of the parent at symptom onset).

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