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Maternal dementia age at onset in relation to amyloid burden in non-demented elderly offspring

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Abstract

Family history of dementia (FH) is a major risk factor for Alzheimer's disease (AD), particularly when the FH is maternal and when the age of dementia onset (AO) is younger. This study tested whether brain amyloid-beta (A β) deposition, measured in vivo with ¹¹C-Pittsburgh compound B (PiB), was associated with parental dementia and/or younger parental AO. Detailed FH and positron emission tomography (PiB-PET) data were acquired in 147 non-demented aging individuals (mean age 75 $\pm$ 8). No participant had both positive maternal and paternal FH. A series of analyses revealed that those with maternal, but not paternal, FH had greater levels of PiB retention in a global cortical region than those without FH. PiB retention in maternal FH was not significantly greater than paternal FH. Younger maternal dementia AO was related to greater PiB retention in offspring, while younger paternal dementia AO was not. Overall, results suggest that not only is A β burden greater in individuals with maternal FH, but also that the burden is greater in association with younger maternal AO.

Keywords

PET; Family History; PiB; amyloid-beta

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1. Introduction

While the genetics of early-onset Alzheimer's disease (AD) is known to include the autosomal dominant inheritance of specific mutations, the genetics of more typical, late-onset AD has been much more difficult to elucidate (Mayeux, 2003). In addition to age as a prominent risk factor for AD (Mayeux, 2003), another major factor that confers additional risk is family history (FH), particularly when it involves the parents (Jarvik and Blazer, 2005; Jarvik et al., 2008; Silverman et al., 2003, 2005), and much of the FH risk has been attributed to the e4 allele of the apolipoprotein E (APOE) genotype (Mayeux, 2010). An interaction of APOE ϵ 4 effects and gender is widely recognized (Miech et al., 2002), and evidence for a maternal transmission factor for AD has been reported (Duara et al., 1993; Edland et al., 1996); however, controlling for age and female longevity, the data have been inconsistent (Heggeli et al., 2012; Ehrenkrantz et al., 1999). To explore the biological basis of these risk factors, investigators have evaluated AD imaging endophenotypes, with specific focus on maternal FH. Thus, AD-like changes in regional brain volume (Honea et al., 2010; Berti et al., 2011), FDG metabolism (Mosconi et al., 2007), and amyloid-beta ($A\beta$) deposition (Mosconi et al., 2010; Honea et al., 2012) have been reported in non-demented subjects with maternal FH in excess of what is seen in groups of subjects with no FH or in those with a paternal FH. Importantly, these changes have been detected even when controlling for APOE ϵ 4 carrier status.

To further explore this phenomenon, we collected FH and PET data for 147 non-impaired older adults. We hypothesized that younger parental age of onset (AO) of dementia would relate to greater $A\beta$ burden and that the effect would be greater in those with a maternal history of dementia. A complicating factor in the analysis was that age of onset of dementia was not available for mothers who did not experience onset of dementia; i.e., it is right-censored by the age at which the mother was last known to be alive without dementia. We handled this feature through special treatment in linear regression of $A\beta$ in offspring on maternal AO and through reverse proportional hazards regression models of maternal AO on offspring $A\beta$.

2. Methods

2.1. Sample

Participants (N=147) were enrolled in longitudinal studies of aging and dementia at Massachusetts General and Brigham and Women's Hospitals, which were approved by the Partners Human Research Committee. All participants were evaluated with subject and informant interviews as well as cognitive testing and had a Clinical Dementia Rating (CDR) global score of 0 or 0.5, which included cognitively normal participants, participants who would be best characterized as having subjective cognitive concerns, and non-demented participants who met mild cognitive impairment (MCI) criteria. None of the participants had any neurological or medical illness or any history of alcoholism, drug abuse, or head trauma. All scored 11 or lower on the 30-item Geriatric Depression Scale (GDS) (Yesavage et al., 1983), 22 or higher on the Mini Mental State Examination (MMSE) (Folstein et al., 1975), and 93 or higher on the American National Adult Reading Test (AMNART) (Ryan and Paolo, 1992).

A parental history questionnaire, described below, yielded information about 279 biological parents of participants. 15 of the 147 participants were able to provide family history information about only one parent, as information about the other parent was unknown; these 15 were excluded from analyses in which we required definitive parental family history from both parents, but were included in others.

2.2. Parental History Questionnaire

Participants were classified into offspring groups according to parental history of dementia, using a family history questionnaire administered in person or by telephone. Each was asked whether either parent had a progressive dementia syndrome and whether it was physician-diagnosed. No formal distinction was made between subjective reports of dementia and actual diagnosis of dementia or AD in a parent, since we did not have access to parents' medical records, and furthermore AD was rarely diagnosed when these parents were elderly. Participants who could not recall a diagnosis of dementia in their parents were read a short list of typical dementia symptoms, to assist in determining whether dementia was present. They were also queried as to parents' major medical illnesses, causes of death, ages at death, and ages at dementia symptom onset.

2.3. PiB PET Imaging in Offspring

Carbon-11 PiB was synthesized and PET data were acquired and processed as described previously (Becker et al., 2011; Rentz et al., 2010). Briefly, following a transmission scan, 8.5–15mCi ¹¹C-PiB was injected as a bolus, followed immediately by a 60-minute dynamic acquisition. Each frame was evaluated to verify adequate count statistics and absence of head motion. PiB retention was expressed as the distribution volume ratio (DVR) using cerebellar cortex as a reference tissue (Logan, 1990). Regions of interest (ROIs) were defined using the Automated Anatomic Labeling method (Tzourio-Mazoyer et al., 2002). An aggregate of cortical regions that have historically displayed elevated PiB burden in AD dementia (frontal, lateral parietal, lateral temporal, and retrosplenial cortices; FLR) was used for analysis, as described previously (Gomperts et al., 2008).

2.4. Statistical Analysis: Models Relating FH to PiB Retention

Fisher's exact test was used for tests of FH association of categorical variables and Wilcoxon rank sum tests or Kruskal-Wallis tests were used for continuous variables. Exact Wilcoxon tests were used when sample sizes were small enough to permit the computational burden. Models included terms for age of the offspring (coded as categorical according to the tertiles of its distribution: <70, 70–81, >81), CDR (0 vs. 0.5), gender of subject, and years of education.

The reader is referred to Table 1 to serve as a guide to analyses and associated comparison groups below. Linear regression models were fit for PiB retention and treated family history as a binary variable in several different forms, described in detail below. All models were fit with and without APOE due to high numbers with missing APOE (42 missing/147 participants), to confirm results in the larger sample. The models also included years of education, gender, age of offspring and CDR. Histograms of residuals from the models were examined and appeared to be sufficiently unimodal and symmetric.

Initial linear regression analyses (Analysis #1; Table 3 Demographics) were strictly limited to families in which both parents could be definitively classified with regard to their dementia status as of age 75. That is, both parents either had to have onset of dementia at any age, or be known to be free of dementia up to age 75. 65 individuals were included in this analysis (43 when APOE was included as a covariate). This thresholding dealt with the problem of censored AO; only parents whose dementia status was known relative to age 75 were included. Any parent who was censored for dementia prior to age 75 was not included as his/her dementia status at age 75 could not be inferred. Age 75 was selected arbitrarily as likely to be a reasonable thresholding value for onset of dementia. Parents who had onset of dementia prior to age 75 conferred either positive maternal or paternal history status on their adult offspring, the participants in this study. Mother-father dyads in which neither parent experienced dementia onset by age 75 conferred negative family history on their adult offspring, even if dementia onset occurred after age 75. An additional model included an interaction term between family history and age of onset, to allow for refined association between PiB retention in offspring and age of onset in parents who experienced onset by age 75.

A second set of linear regression models (Analysis #2; Table 2 Demographics) was more lenient with inclusion criteria and included participants if parent dementia status was known for at least one parent at parent age 75. In those with available maternal dementia status at parent age 75, those with positive maternal history were compared to those with negative maternal history, regardless of whether paternal history was known. Similarly, those with positive paternal history were compared to those with negative paternal history, regardless of whether maternal history was known. 106 individuals were included in the maternal history models (74 when APOE was included), and 91 were included in the paternal history models (63 when APOE was included). These models were also fit with an interaction term between family history and age of onset.

A third set of linear regression models (Analysis #3; Table 2 Demographics) were fit to determine the association between parent AO and PiB retention in offspring participants after adjusting for potential confounders. A complete case approach to dealing with missing covariates in regression models simply deleted all subjects with missing covariates. For this analysis, this involved using only subjects for whom either parent's AO was known; it is valid when the censoring of AO is independent of offspring PiB retention given the unobserved AO. A drawback of this approach is that it does not make any use of subjects whose parents did not have dementia. An initial model included parent AO of all subjects with positive parental dementia history as the predictor variable, and subsequent models were run separately for those with maternal history and those with paternal history. Offspring PiB retention was the dependent variable, and models were adjusted for gender, CDR, education, and age of the offspring at the time of PiB scan. Again, models were fit with and without APOE due to high numbers with missing APOE, to confirm results in the larger sample.

2.5. Statistical Analysis: Relationship of Parental AO to Offspring PiB Retention: Hazard Regression Models

As an alternative analysis for the association between parental AO and offspring PIB retention, a proportional hazards model was fit for parental AO (Analysis #4; Table 2 Demographics), stratified by age of offspring (<70, 70–81, >81: the 25th, 50th, and 75th percentiles of the age distribution), with adjustment for gender, CDR, education, mother versus father, offspring PIB retention, and interaction between mother vs. father and PIB retention. This analysis considered all offspring of participants and all parents, including all parents who had not experienced onset of dementia, and thus provided a considerably larger sample size (N=147) than the thresholding analysis. The analysis treated parental AO as potentially right censored, rather than as binary as in the linear regression analysis. Parents who did not have dementia were treated as censored observations at their ages at death or ages at which offspring could no longer provide dementia information. Interaction terms (between age of offspring and mother versus father, age and PIB retention) were examined, but none added significantly to the model. While the hazard ratio that was estimated by the model was not itself interpretable, it did provide for a valid hypothesis test for association between offspring PIB retention and parental AO (Atem et al., 2015). This approach also has the advantage of not requiring choice of an arbitrary threshold. In the analysis, we adjusted for clustering due to two contributions from each son/daughter (i.e., one for mother, one for father) using Wei-Lin-Weissfeld robust variance. APOE was initially included, but did not add to the model, plus many subjects lacked APOE data, so APOE was not included in the final analyses. This approach enabled us to include 279 parents of the 147 offspring (no information was available for 15 parents), and 197 parents with offspring APOE were included in the model (42 offspring, and thus 84 parents, were missing offspring APOE).

3. Results

3.1 Sample

Using a dementia cutoff of age 75, 106 mothers of 147 total participants could be definitively classified with respect to dementia (positive/negative), as could 91 of the fathers (Table 2). Of the 106 mothers, 13 had onset of dementia by age 75 and 93 did not. Of the 91 fathers, 12 had onset of dementia by age 75 and 79 did not.

Only 65 of 147 participants could be included in initial regression analyses (Analysis #1; Table 3 Demographics), which required having had two parents with definitive dementia status (positive/negative) as of parent age 75. In this subset of 65, 7 had a positive maternal dementia history coupled with a negative paternal history, 7 had a positive paternal history coupled with a negative maternal history, and none had both maternal and paternal dementia histories.

The mean age among the 147 participants was 75.0 (min=58.8, max=89.9, SD=7.6). Among the 65 subjects with knowledge of parental dementia status, the mean age was 73.4 (min=58.8, max=88.4, SD=8.0). Subject age was not significantly associated with parental history ($p=0.34$ overall, $p=0.99$ for maternal vs. negative history, $p=0.17$ for paternal vs. negative history, $p=0.17$ for maternal vs. paternal, $p=0.72$ for any parental dementia history).

(either maternal or paternal) vs. negative history. CDR was not significantly associated with family history ($p=0.71$ overall, $p=0.41$ for maternal vs. negative, $p=1.00$ for paternal vs. negative, $p=1.00$ for maternal vs. paternal, $p=0.30$ for any parental dementia history (either maternal or paternal) vs. negative history).

105 of the 147 subjects had APOE results: 28 were positive and 77 were negative. Of the 105, 43 had two parents with definitive dementia status (7 maternal, 4 paternal, 32 negative; see Table 3) and an additional 10 subjects had either positive maternal or paternal history but lacked determinate history for the other parent. Together, 21 (7+4+10) subjects with APOE results had positive family history and 32 had determinate negative family history. APOE was significantly associated with family history [maternal vs. paternal vs. negative) ($p=0.02$); 19% (6/32) with negative history were positive for APOE vs. 75% (3/4) with paternal history, vs. 57% (4/7) with maternal history. APOE was marginally significantly associated with any family history (either maternal or paternal versus negative) ($p=0.07$); 43% (9/21) with any history were positive vs. 19% (6/32) with negative history. APOE was not significantly associated with maternal history vs. paternal history ($p=1.00$), though the numbers are sparse (4/7 versus 3/4).

3.2. Maternal history of dementia is associated with increased PiB retention

Analyses #1 and #2 (See Table 1 for reference)—In regression analysis #1 in which participants were included only if parental dementia status was known for both parents at age 75 ($N=65$), global PiB retention significantly differed according to FH status (mean increase in PiB retention of 0.17; $p=0.004$ overall) and was significantly higher in those with maternal history of dementia versus those without (difference in PiB retention of 0.23; $p=0.0002$) and not in those with a paternal history versus those without (difference in PiB retention of 0.06; $p=0.41$). In addition, earlier AO among mothers of those with maternal history was significantly associated with increased PiB retention (increase of 0.06 units for every year of earlier onset; $p=0.05$). With APOE status and the interaction with age of onset included ($N=43$), the results were nearly identical. PiB retention was also significantly associated with the covariates of CDR, (retention lower on average by 0.13 units for CDR 0 versus 0.5, $p=0.01$), scan age (retention higher on average by 0.16 units for age range 70–81 versus age >81, $p=0.03$), and APOE carrier status (non-carriers had an average of 0.16 units less PiB retention than carriers, $p=0.007$). Wilcoxon rank sum tests showed that those with maternal history had significantly more PiB retention than those with definitively negative family history ($p=0.007$), but no significant differences existed between those with paternal history vs. negative history ($p=0.38$), or those with maternal history vs. paternal history ($p=0.09$). A marginally significant difference existed between positive parental dementia history overall (either maternal or paternal, $n=25$; Table 2 Demographics) and negative history ($n=51$; Table 3 Demographics), ($p=0.06$).

Linear regression models (Analysis #2; Table 2 Demographics) with less stringent criteria included participants with knowledge of the definitive dementia status of at least one, but not necessarily both, parents at parent age 75 (inclusive of participants in Analysis #1). Those with positive maternal dementia history had higher PiB retention (higher on average by 0.20 units, $p<0.001$; $N=106$) than those without maternal history. In a model that

included an interaction between maternal AO and maternal history, maternal AO was associated with an increase in PiB retention of 0.01 for every additional year of earlier onset ($p=0.002$). PiB retention did not differ between those with and without paternal dementia history ($p=0.34$; $N=91$).

Overall results from Analyses # 1 and 2 suggest that maternal dementia history, but not paternal history, is associated with greater amyloid burden, as measured by PiB. Furthermore, among those with positive family history as defined to age 75, there is an additional association between PiB retention and earlier age of onset. Alternate versions of these analyses were run using parent age 70 instead of 75 to determine sensitivity to age cutoff and the results (not shown) were similar.

3.3. Younger parental AO of dementia is associated with greater PiB retention in offspring participants. The parental AO association with PiB retention is greater in adult children with maternal FH

Analysis #3—In AO-PiB linear regression models with covariates that delete all subjects without parental dementia onset, results were similar when including only parents whose onset was definitely known relative to age 75 ($N=25$) and a complete-case analysis ($N=62$) that included all parents whose age at onset was known, irrespective of its relation to age 75. Greater PiB retention in participants with parental dementia history (either maternal or paternal) was associated with earlier parental AO (0.01 units per earlier year of age of onset) ($p=0.04$). Subsequent analyses suggested that the association was driven by the maternal history group. No significant interaction was detected between mother versus father and AO ($p=0.67$). Nonetheless, given the finding of an interaction in earlier analyses, separate models were fit for subjects with maternal history and for subjects with paternal history. Greater PiB retention was associated with a younger AO of mother (every additional year in maternal age of onset decreased PiB by 0.01 units; $p<0.05$), while PiB retention in paternal history positive subjects was not significantly related to father's AO ($p=0.10$).

Analysis #4—Additionally, proportional hazards models that included all 147 participants through their natural accommodation of censoring (Demographics Table 2), showed that increased global PiB retention, e.g., of 0.25 units, in participants (offspring) was associated with younger AO of dementia in their mothers ($p<0.0001$). In contrast, increased PIB retention at any level in participants was not significantly associated with dementia AO in fathers ($p=0.25$). As expected, mothers had an earlier age of onset of dementia than fathers at a given level of PIB retention for the participant (e.g., $p=0.04$ at $\text{PiB}=1.25$; $p=0.009$ at $\text{PiB}=1.5$).

4. Discussion

Previous studies have shown that subjects with a maternal family history of dementia have greater A β burden than either those with no family history or only a paternal history of dementia (Mosconi et al., 2010; Honea et al., 2012). We also observed this relationship, but in addition related A β load measured with PiB-PET to maternal age of dementia onset. We found that mothers had an earlier age of dementia onset than fathers at a given level of PIB retention for the subject.

The ideal statistical analysis to address this question would have required that all parents had experienced onset of dementia. As this was not the case, regression models had to accommodate right-censored ages of onset of dementia. Three approaches were considered: (1) thresholding of age of onset into a binary history variable and deletion of some subjects who could not be definitively identified as positive or negative; (2) complete case analysis in which only offspring whose parents had onset of dementia were included; and (3) reverse modeling via a proportional hazards regression model that naturally accommodates censoring. None of these approaches is optimal. The first two lose information through deletion of subjects. The first additionally loses information through dichotomizing of age of onset on the basis of an arbitrary threshold. The third suffers from non-interpretability of the effect estimates from the model as it involves a reversal in time and models risk of dementia in the parent given A β level in the offspring. It does, however, provide a valid test of association. Nonetheless, this paper demonstrated consistency of the main finding across all three of these approaches.

Family history is a known risk factor for AD dementia, and A β is a defining neuropathologic feature of AD. A positive FH of dementia has previously been associated with A β burden, especially when the affected parent was the mother (Mosconi et al., 2010; Honea et al., 2012). We chose to test our hypotheses in primarily cognitively normal subjects (approximately 70% CDR0 and 30% CDR0.5), rather than AD dementia patients because it reduced the bias that the vast majority of them would already have significant A β accumulation. Our findings strengthen the connection between maternal history and AD risk by linking one of the pathologic features of AD with an earlier dementia AO in mothers.

This research is important because evidence is mounting that AD processes begin decades before clinical symptoms are expressed, and if this is true, it may be possible to identify those at risk and intervene long before symptoms appear. Cognitive and brain reserve are thought to be protective against cognitive decline and to complicate the clinical phenotype; therefore, additional expressions of AD risk, such as FH, parental AO, and A β burden, may be useful. The combination of FH and parent AO as linked to A β accumulation may provide predictive information that is useful for refining the profile of AD risk. Although A β load significantly relates to ApoE e4 carrier status in a dose-dependent way (Reiman et al., 2009; Kantarci et al., 2012), our results persisted after covarying APOE and thus were observed independently of genetic risk. A limitation of this observation is that APOE status was unknown for a substantial number of participants in this study.

Related studies have found evidence of reduced gray matter volume in cognitively normal maternal FH participants relative to those with no parental dementia history (Honea et al., 2010; Berti et al., 2011). Mosconi and colleagues (2007) have also reported FDG hypometabolism in maternal FH offspring, which they later (2013) reported co-occurs with increased PiB retention in AD-related brain regions. More recently, in line with reports that two-parent AD history confers greater AD risk than single-parent AD history (Lautenschlager et al., 1996; Jayadev et al., 2008; Bird et al., 1993), Mosconi and colleagues (2014) reported that cognitively normal adults with two-parent AD history display more severe FDG hypometabolism, grey matter volume reductions, and PiB retention in AD-related brain regions, although only marginally significantly more than maternal FH adults

in PiB retention. In addition to greater PiB retention in maternal FH cognitively normal and MCI participants, Honea et al. (2012) found greater evidence of AD cerebrospinal biomarkers (e.g. decreased A β levels and increased tau/ A β ratio) in MCI maternal FH individuals when compared to those with no parental history of dementia.

The mechanisms that underlie maternal-specific trends in these studies and ours remain a mystery. Although both parents contribute to a person's AD risk (Katzman, 1986), it has been suggested that mothers affect AD risk more than fathers because mtDNA, which greatly affects mitochondrial durability over time, is solely inherited from the mother (Swerdlow et al., 2010). Declining mitochondrial function with age, moderated by genetic and environmental factors, may be partly responsible for brain changes observed in AD, such as A β plaques, neurofibrillary tangles, and other manifestations of neurodegeneration (Swerdlow et al., 2004; 2009; Navarro and Boveris, 2007; Trifunovic, 2004). AD pathology could be accelerated as a result of cellular energy depletion due to this mitochondrial aging (Swerdlow et al., 2010; Coskun et al., 2012). Alternative explanatory mechanisms include the rare phenomenon of genomic imprinting, in which particular genes are expressed in a parent-of-origin-specific manner (Constancia et al., 2004) or chromosome X-mediated transmission (Carrasquillo et al., 2009).

This study's AO findings suggest that maternal AO plays a role in AD-like brain pathology in offspring. We are unaware of any previous study that investigated relationships between demented parent AO and PiB retention in their aged offspring. However, other neuroimaging studies have investigated FH relationships. For example, Bassett (2006) found that non-demented offspring of AD individuals show enhanced activation in the frontal and temporal lobes (including the hippocampus) during memory encoding, and decreased activation in the thalamus and cingulum during recall, up to 10 years before their parent's AO.

Among AD-affected individuals, investigation of A β burden and AO has yielded inconsistent results. For example, Choo (2011) found that among a group of AD dementia patients, early-onset AD was related to greater A β burden relative to late-onset AD. Marshall (2007) found that early-onset AD was associated with more neuritic plaques and neurofibrillary tangles than late-onset AD. Ho (2002) found that compared to late onset AD, early onset AD subjects had greater cognitive impairment, declined more rapidly, and at autopsy had more neuritic plaques and neurofibrillary tangles and more neocortical cholinergic loss. Rabinovici (2010), however, did not find any AD AO differences in A β burden visualized by PiB PET. Early-onset AD has also been associated with faster cortical atrophy and white matter changes relative to late-onset AD (Chan et al., 2003; Caso et al., 2015).

One of the acknowledged difficulties in evaluating AO phenomena in dementing disorders is this concept of greater overall female survival. Previous studies have found that between 65% and 75% of single-parent history of dementia is from the mother (Basset et al., 2002; Andrawis et al., 2010; Honea et al., 2011). The results of this study are consistent with previous reports that females are up to three times as likely as males to develop AD (Baum, 2005), likely due, in part, to longer female survival. As suggested by Heggeli and colleagues

(2012), it is possible that maternal dementia history in AD patients results in earlier AO and rate of disease progression without specifically implicating maternal inheritance of the disease. Similarly, this report's observation of greater A β burden in non-demented participants with maternal FH, particularly in those with younger maternal AO, could reflect a relationship between rate of A β accumulation and maternal FH, but not necessarily a maternal-based causal link for disease transmission.

Studies of the relationship between AO and risk of dementia in family members have yielded conflicting results. Silverman (2003, 2005) suggested that elevated AD risk due to AD history in relatives decreases as the AO of that relative increases. Another study found that younger AO in AD does not increase AD risk for the individual's relatives (Farrer et al., 1989). Gomez-Tortosa (2007) found that 80% of AD dementia subjects had a younger AO than their parent, and concluded that a person's risk of dementia decreases after reaching the parent's AO.

In this study, parental history of dementia, rather than parental history of Alzheimer's disease, was used to classify subjects because medical records of our subjects' parents were largely unavailable, and AD was not always widely diagnosed when the parents were elderly. Ideally, we would have preferred AD confirmation for all subjects who reported history of dementia in a parent. An additional limitation was that FH group classification was based on offspring's own reports of parental dementia or AD in older age, so recall uncertainty or bias may have affected results. Moreover, positive family history may be over-represented because memory problems within a family often drive participants to studies such as ours.

An analytical challenge of this study emerged from the many subjects who did not report parental onset of dementia; this presented the authors with a "censored covariate" in the desired regression model of PiB retention on parental age of onset. The authors dealt with this by constructing a binary variable of family history, which is defined as the definitive onset of dementia by age 75 versus onset after age 75 or simply no known onset prior to age 75. This method is a simple and valid way to deal with those parents who do not present ages of onset. That is, onsets of dementia before age 75 were counted as dementia, and onsets of dementia and ages last known to be dementia-free greater than 75 as non-dementia. While information was lost with respect to the precise ages of onset after age 75 for those for whom they were available, the advantage was the ability to include subjects whose parental onset is unknown after age 75. A final, related, limitation was the small sample size of certain comparison groups. This was difficult to avoid, as some research questions could only be explored within strict subsets of the study's 147 participants (e.g. fewer than ten participants in each of two Analysis 1 conditions). Results should be confirmed in larger samples in the future.

On the whole, this study supports the previously reported relationship between greater A β burden in those with a maternal FH of dementia relative to those with paternal FH and no FH. Our findings also suggest that A β burden, as measured by PiB, is associated with younger parent AO when the demented parent is the mother, but not when the demented parent is the father. In the future, PET should be acquired to determine longitudinal within-

subject A β changes. Another longitudinal and prospective study could involve studying the relation of maternal FH and AO to progression to MCI/AD.

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References

- Andrawis JP, Hwang KS, Green AE, Kotlerman J, Elashoff D, Morra JH, Cummings JL, Toga AW, Thompson PM, Apostolova LG. Effects of ApoE4 and maternal history of dementia on hippocampal atrophy. *Neurobiol Aging*. 2012; 33:856–866. [PubMed: 20833446]
- Atem FD, Qian J, Maye JE, Johnson KA, Betensky RA. Linear Regression with a Randomly Censored Covariate: Application to an Alzheimer's Study. 2015 Available at: <http://www.hsph.harvard.edu/rebecca-betensky/software/>.
- Bassett SS, Avramopoulos D, Fallin D. Evidence for parent of origin effect in late-onset Alzheimer disease. *Am J Med Genet*. 2002; 114:679–686. [PubMed: 12210287]
- Bassett SS, Yousem DM, Cristinzio C, Kusevic I, Yassa MA, Caffo BS, Zeger SL. Familial risk for Alzheimer's disease alters fMRI activation patterns. *Brain*. 2006; 129:1229–1239. [PubMed: 16627465]
- Baum LW. Sex, Hormones, and Alzheimer's Disease. *J Gerontol A Biol Sci Med Sci*. 2005; 60:736–743. [PubMed: 15983176]
- Becker JA, Hedden T, Carmasin J, Maye J, Rentz DM, Putcha D, Fischl B, Greve DN, Marshall GA, Salloway S, Marks D, Buckner RL, Sperling RA, Johnson KA. Amyloid- β associated cortical thinning in clinically normal elderly. *Ann Neurol*. 2011; 69:1032–1042. [PubMed: 21437929]
- Berti V, Mosconi L, Glodzik L, Li Y, Murray J, De Santi S, Pupi A, Tsui W, de Leon MJ. Structural brain changes in normal individuals with a maternal history of Alzheimer's. *Neurobiol Aging*. 2011; 32:2325.e17–2325.e26. [PubMed: 21316814]
- Bird TD, Nemens EJ, Kukull WA. Conjugal Alzheimer's disease: is there an increased risk in offspring? *Ann Neurol*. 1993; 65:396–399. [PubMed: 8363356]
- Carrasquillo MM, Zou F, Pankratz VS, Wilcox SL, Younkin SG, Younkin CS, Younkin LH, Bisceglia GD, Ertekin-Taner N, Crook JE, Dickson DW, Petersen RC, Graff-Radford NR, Younkin SG. Genetic variation in PCDH11X is associated with susceptibility to late-onset Alzheimer's disease'. *Nat. Genet*. 41:192–198.
- Caso F, Agosta F, Mattavelli D, Migliaccio R, Canu E, Magnani G, Marcone A, Copetti M, Falautano M, Comi M, Comi G, Falini A, Filippi M. White matter degeneration in atypical Alzheimer's disease. *Radiology*. 2015 [Epub ahead of print].
- Chan D, Janssen JC, Whitwell JL, Watt HC, Jenkins R, Frost C, Rossor MN, Fox NC. Change in rates of cerebral atrophy over time in early-onset Alzheimer's disease: longitudinal MRI study. *The Lancet*. 2003; 362:1121–1122.
- Choo IH, Lee DY, Kim JW, Seo EH, Lee DS, Kim YK, Kim SG, Park SY, Woo JI, Yoon EJ. Relationship of Amyloid-Beta Burden With Age-At-Onset in Alzheimer Disease. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2011; 19:627–634. [PubMed: 21709608]
- Constancia M, Kelsey G, Relk W. Resourceful imprinting. *Nature*. 2004; 432:53–57. [PubMed: 15525980]
- Coskun P, Wyrembak J, Schriener SE, Chen HW, Marciniack C, Laferla F, Wallace DC. A mitochondrial etiology of Alzheimer and Parkinson disease. *Biochim. Biophys. Acta*. 2012; 1820:553–564. [PubMed: 21871538]

- Duara R, Lopex-Alberola RF, Barker WW, Loewenstein DA, Zatinsky M, Eisdorfer CE, Weinberg GB. A comparison of familial and sporadic Alzheimer's disease. *Neurology*. 1993; 43:1377–1384. [PubMed: 8327141]
- Edland SD, Silverman JM, Peskind ER, Tsuang D, Wijsman E, Morris JC. Increased risk of dementia in mothers of Alzheimer's disease cases: evidence for maternal inheritance. *Neurology*. 1996; 47:254–256. [PubMed: 8710088]
- Ehrenkrantz D, Silverman JM, Smith CJ, Birstein S, Marin D, Mohs RC, Davis KL. Genetic epidemiological study of maternal and paternal transmission of Alzheimer's disease. *Am J Med Genet*. 1999; 88:378–382. [PubMed: 10402505]
- Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. *Ann Neurol*. 1989; 25:485–493. [PubMed: 2774490]
- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state" A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 1975; 12:189–198. [PubMed: 1202204]
- Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE, Mathis CA, Elmaleh DR, Shoup T, Fischman AJ, Hyman BT, Growdon JH, Johnson KA. Imaging amyloid deposition in Lewy body diseases. *Neurology*. 2008; 71:903–910. [PubMed: 18794492]
- Gómez-Tortosa E, Barquero MS, Barón M, Sainz MJ, Manzano S, Payno M, Ros R, Almaraz C, Gómez-Garré P, Jiménez-Escrig A. Variability of age at onset in siblings with familial Alzheimer disease. *Arch Neurol*. 2007; 64:1743–1748. [PubMed: 18071037]
- Heggeli KA, Crook J, Thomas C, Graff-Radford N. Maternal transmission of Alzheimer disease. Alzheimer disease and associated disorders. 2012; 26:364–366. [PubMed: 22273801]
- Ho GJ, Hansen LA, Alford MF, Foster K, Salmon DP, Galasko D, Thal LJ, Masliah E. Age at onset is associated with disease severity in Lewy body variant and Alzheimer's disease. *Neuroreport*. 2002; 13:1825–1828. [PubMed: 12395133]
- Honea RA, Swerdlow RH, Vidoni ED, Burns JM. Progressive regional atrophy in normal adults with a maternal history of Alzheimer disease. *Neurology*. 2011; 76:822–829. [PubMed: 21357834]
- Honea RA, Swerdlow RH, Vidoni ED, Goodwin J, Burns JM. Reduced gray matter volume in normal adults with a maternal family history of Alzheimer disease. *Neurology*. 2010; 74:113–120. [PubMed: 20065246]
- Honea RA, Vidoni ED, Swerdlow RH, Burns JM. Maternal family history is associated with Alzheimer's disease biomarkers. *Journal of Alzheimer's Disease*. 2012; 31:659–668.
- Jarvik L, LaRue A, Blacker D, Gatz M, Kawas C, McArdle JJ, Morris JC, Mortimer JA, Ringman JM, Ercoli L, Freimer N, Gokhman I, Manly JJ, Plassman BL, Rasgon N, Roberts JS, Sunderland T, Swan GE, Wolf PA, Zonderman AB. Children of persons with Alzheimer disease: what does the future hold? Alzheimer disease and associated disorders. 2008; 22:6–20. [PubMed: 18317242]
- Jarvik LF, Blazer D. Children of Alzheimer patients: an overview. *Journal of Geriatric Psychiatry and Neurology*. 2005; 18:181–186. [PubMed: 16306236]
- Jayadev S, Steinbart EJ, Chi YY, Kukull WA, Schellenberg GD, Bird TD. Conjugal Alzheimer disease: risk in children when both parents have Alzheimer disease. *Arch Neurol*. 2008; 65:373–378. [PubMed: 18332250]
- Kantarci K, Lowe V, Przybelski SA, Weigand SD, Senjem ML, Ivnik RJ, Preboske GM, Roberts R, Geda YE, Boeve BF, Knopman DS, Petersen RC, Jack CR Jr. APOE modifies the association between A β load and cognition in cognitively normal older adults. *Neurology*. 2012; 78:232–240. [PubMed: 22189452]
- Katzman R. Alzheimer's disease. *New England Journal of Medicine*. 1986; 314:964–973. [PubMed: 2870433]
- Lautenschlager NT, Cupples LA, Rao VS, Auerbach SA, Becker R, Burke J, Chui H, Duara R, Foley EJ, Glatt SL, Green RC, Jones R, Karlinsky H, Kukull WA, Kurz A, Larson EB, Martelli K, Sadovnick AD, Volicer L, Waring SC, Growdon JH, Farrer LA. Risk of dementia among relatives of Alzheimer's disease patients in the MIRAGE study: what is in store for the oldest old? *Neurology*. 1996; 46:641–650. [PubMed: 8618660]

- Logan J, Fowler JS, Volkow ND, Wolf AP, Dewey SL, Schlyer DJ, MacGregor RR, Hitzemann R, Bendriem B, Gatley SJ. Graphical analysis of reversible radioligand binding from time-activity measurements applied to [N-11C-methyl]-(-)-cocaine PET studies in human subjects. *J Cereb Blood Flow Metab.* 1990; 10:740–747. [PubMed: 2384545]
- Marshall GA, Fairbanks LA, Tekin S, Vinters HV, Cummings JL. Early-onset Alzheimer's disease is associated with greater pathologic burden. *Journal of Geriatric Psychiatry and Neurology.* 2007; 20:29–33. [PubMed: 17341768]
- Mayeux R. Epidemiology of neurodegeneration. *Annu Rev Neurosci.* 2003; 26:81–104. [PubMed: 12574495]
- Mayeux R. Clinical practice. Early Alzheimer's disease. *N Engl J Med.* 2010; 362:2194–2201. [PubMed: 20558370]
- Miech RA, Breitner JCS, Zandi PP, Khachaturian AS, Anthony JC, Mayer L. Incidence of AD may decline in the early 90s for men, later for women: The Cache County study. *Neurology.* 2002; 58:209–218. [PubMed: 11805246]
- Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology.* 1993; 43:2412–2414. [PubMed: 8232972]
- Mosconi L, Brys M, Switalski R, Mistur R, Glodzik L, Pirraglia E, Tsui W, De Santi S, de Leon MJ. Maternal family history of Alzheimer's disease predisposes to reduced brain glucose metabolism. *Proc Natl Acad Sci USA.* 2007; 104:19067–19072. [PubMed: 18003925]
- Mosconi L, Murray J, Tsui WH, Li Y, Spector N, Goldowsky A, Williams S, Osorio R, McHugh P, Glodzik L, Vallabhajosula S, de Leon MJ. Brain imaging of cognitively normal individuals with 2 parents affected by late-onset AD. *Neurology.* 2014; 82:752–760. [PubMed: 24523481]
- Mosconi L, Rinne JO, Tsui WH, Berti V, Li Y, Wang H, Murray J, Scheinin N, Någren K, Williams S, Glodzik L, De Santi S, Vallabhajosula S, de Leon MJ. Increased fibrillar amyloid- β burden in normal individuals with a family history of late-onset Alzheimer's. *Proc Natl Acad Sci USA.* 2010; 107:5949–5954. [PubMed: 20231448]
- Mosconi L, Rinne JO, Tsui WH, Murray J, Li Y, Glodzik L, Mchugh P, Williams S, Cummings M, Pirraglia E, Goldsmith SJ, Vallabhajosula S, Scheinin N, Viljanen T, Någren K, de Leon MJ. Amyloid and metabolic positron emission tomography imaging of cognitively normal adults with Alzheimer's parents. *Neurobiol Aging.* 2013; 34:22–34. [PubMed: 22503001]
- Navarro A, Boveris A. The mitochondrial energy transduction system and the aging process. *Am J Physiol Cell Physiol.* 2007; 292:C670–C686. [PubMed: 17020935]
- Perneczky R, Drzezga A, Diehl-Schmid J, Li Y, Kurz A. Gender differences in brain reserve : an (18)F-FDG PET study in Alzheimer's disease. *J Neurol.* 2007; 254:1395–1400. [PubMed: 17934882]
- Rabinovici GD, Furst AJ, Alkalay A, Racine CA, O'Neil JP, Janabi M, Baker SL, Agarwal N, Bonasera SJ, Mormino EC, Weiner MW, Gorno-Tempini ML, Rosen HJ, Miller BL, Jagust WJ. Increased metabolic vulnerability in early-onset Alzheimer's disease is not related to amyloid burden. *Brain.* 2010; 133(Pt 2):512–528. [PubMed: 20080878]
- Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JBS, Alexander GE, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, Dekosky ST, Caselli RJ. Fibrillar amyloid β burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA.* 2009; 106:6820–6825. [PubMed: 19346482]
- Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA. Cognition, reserve and amyloid deposition in normal aging. *Ann Neurol.* 2010; 67:353–364. [PubMed: 20373347]
- Ryan JJ, Paolo AM. A screening procedure for estimating premorbid intelligence in the elderly. *Clinical Neuropsychologist.* 1992; 6:53–62.
- Silverman JM, Ciresi G, Smith CJ, Marin DB, Schnaider-Beeri M. Variability of familial risk of Alzheimer disease across the late life span. *Arch Gen Psychiatry.* 2005; 62:565–573. [PubMed: 15867110]
- Silverman JM, Smith CJ, Marin DB, Mohs RC, Propper CB. Familial patterns of risk in very late-onset Alzheimer disease. *Arch Gen Psychiatry.* 2003; 60:190–197. [PubMed: 12578437]

- Smith CD, Chebrolu H, Andersen AH, Powell DA, Lovell MA, Xiong S, Gold BT. White matter diffusion alterations in normal women at risk of Alzheimer's disease. *Neurobiol Aging*. 2010; 31:1122–1131. [PubMed: 18801597]
- Swerdlow RH, Burns JM, Khan SM. The Alzheimer's disease mitochondrial cascade hypothesis. *J Alzheimers Dis*. 2010; 20(Suppl 2):S265–S279. [PubMed: 20442494]
- Trifunovic A, Wredenberg A, Falkenberg M, Spelbrink JN, Rovio AT, Bruder CE, Bohlooly YM, Gidlof S, Oldfors A, Wibom R, Tornell J, Jacobs HT, Larsson NG. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature*. 2004; 429:417–423. [PubMed: 15164064]
- Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*. 2002; 15:273–289. [PubMed: 11771995]
- Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. *Journal of psychiatric research*. 1982; 17:37–49. [PubMed: 7183759]

Highlights Maye Family History Paper

- A β was measured via PiB-PET in aging adults with parental history (FH) of dementia.
- PiB retention was higher in maternal but not paternal FH, relative to no FH.
- Additionally, greater PiB retention was associated with younger maternal onset.
- Findings support a FH A β relationship and also implicate maternal onset age role.

Table 1

Analysis characteristics

Analysis #	1	2	3	4
Model type	Linear Regression	Linear Regression	Linear Regression	Hazard Regression
Purpose	PiB comparison of those with: Maternal FH vs. those without FH; Paternal FH vs. those without FH	PiB comparison of those with: Maternal FH vs. no maternal FH; Paternal FH vs. no paternal FH	Association of parent AO (continuous) with offspring PiB retention	Alternative analysis for association of parent AO and offspring PiB retention
N	65 PET subjects (offspring) (subset with dementia status known for both parents)	147 PET subjects (offspring) (dementia status known for at least one parent)	25 PET subjects (offspring)	147 PET subjects (offspring)
Comparison group abbreviations and details	7 FHmat+(subset), 7 FHpat+ (subset), and 51 FHneg	13 FHmat+ vs. 93 FHmat– 12 FHpat+ vs. 79 FHpat–	13 FHmat+ and 12 FHpat+	AO or age at death without dementia data for one or both parents of 147 PET subjects.
Corresponding Demographics Table #	3	2	2	2

Key:

FHmat+= Positive maternal dementia history at parent age 75, regardless of whether paternal status was known

FHmat– =Negative maternal dementia history at parent age 75, regardless of whether paternal status was known

FHmat+(subset)= Subset of FHmat+: positive maternal history of dementia, negative paternal history of dementia at parent age 75

FHpat+= Positive paternal dementia history at parent age 75, regardless of whether maternal status was known

FHpat– = Negative paternal dementia history at parent age 75, regardless of whether maternal status was known

FHpat+(subset)= Subset of FHpat+: positive paternal history of dementia, negative maternal history of dementia at parent age 75

FHneg= Negative history of dementia in both parents at parent age 75.

AO= Parental dementia age of onset

Table 2

Demographic information for offspring with at least one parent definitively classified (positive/negative) with respect to dementia at parent age 75.

Parental History Group	Entire sample	Entire sample with APOEε4 non-missing	Maternal information known	Maternal FH positive (FHmat+)	Maternal FH negative (FHmat-)	Paternal information known	Paternal FH positive (FHpat+)	Paternal FH negative (FHpat-)
N	147	105	106	13	93	91	12	79
Age, y	75 (7.6)	76 (7.1)	74 (7.5)	74 (6.9)	74 (7.6)	74 (7.7)	72 (7.8)	75 (7.7)
N, % Female	79 (54%)	57 (54%)	55 (52%)	6 (46%)	49 (53%)	48 (53%)	6 (50%)	42 (53%)
N, % CDR 0.5	43 (29%)	28 (27%)	28 (26%)	4 (31%)	24 (26%)	31 (34%)	6 (50%)	25 (32%)
CDR-SB	0.46 (0.79)	0.40 (0.71)	0.39 (0.70)	0.5 (0.89)	0.37 (0.68)	0.55 (0.84)	0.73 (0.90)	0.52 (0.84)
PIB FLR	1.22 (0.22)	1.24 (0.23)	1.22 (0.22)	1.43 (0.35)	1.19 (0.18)	1.24 (0.24)	1.31 (0.26)	1.24 (0.24)
APOEε4*	77/28/42	77/28/0	53/21/32	8/5/0	45/16/32	49/20/36	4/4/4	42/13/24
Education	16.1 (2.7)	16.1 (2.7)	16.2 (2.7)	16.2 (2.8)	16.2 (2.7)	16.2 (2.6)	15.8 (2.6)	16.3 (2.6)

Note: In this table, those with known parent onset of dementia after age 75 are considered negative, and those with last follow-up prior to age 75 are considered inconclusive and are excluded. No subject had both a maternal and paternal FH.

Key:

Values: Mean (SD)

* APOEε4: non-carrier/carrier/missing

FHmat+= Positive maternal dementia history at parent age 75, regardless of whether paternal status was known

FHmat-= Negative maternal dementia history at parent age 75, regardless of whether paternal status was known

FHpat+= Positive paternal dementia history at parent age 75, regardless of whether maternal status was known

FHpat-= Negative paternal dementia history at parent age 75, regardless of whether maternal status was known

Table 3

Demographic information for offspring with both a mother and father who could both be definitively classified (positive/negative) with respect to dementia at parent age 75.

Parental History Subset	Entire subset	Entire subset with APOE4 non-missing	FHmat+(subset)	FHpat+(subset)	(FHneg)
N	65	43	7	7	51
Age, y	73.4 (8.0)	73.5 (7.0)	74 (6.3)	69 (7.8)	74 (8.2)
N, % Female	35 (54%)	26 (60%)	3 (43%)	4 (57%)	28 (55%)
N, % CDR 0.5	19 (29%)	13 (30%)	3 (43%)	2 (29%)	14 (27%)
CDR-SB	0.48 (0.80)	0.44 (0.77)	0.71 (1.07)	0.58 (1.20)	0.43 (0.71)
PIB FLR	1.25 (0.25)	1.27 (0.25)	1.59 (0.36)	1.27 (0.22)	1.20 (0.20)
APOE4*	30/13/22	30/13/0	3/4/0	1/3/3	26/6/19
Education	16.4 (2.6)	16.0 (2.7)	16.3 (2.1)	16.4 (2.7)	16.4 (2.7)

Note: In this table, those with known parent onset of dementia after age 75 are considered negative, and those with last follow-up prior to age 75 are considered inconclusive and are excluded. The 51 FHneg subjects are also represented in both the FHmat– and FHpat– columns of Table 2.

Key:

Values are mean (SD)

* APOE4: non-carrier/carrier/missing

FHmat+(subset)= Subset of FHmat+: positive maternal history of dementia, negative paternal history of dementia at parent age 75

FHpat+(subset)= Subset of FHpat+: positive paternal history of dementia, negative maternal history of dementia at parent age 75

FHneg= Negative history of dementia in both parents at parent age 75.