Published in final edited form as:

Am J Geriatr Psychiatry. 2011 September ; 19(9): 814–824. doi:10.1097/JGP.0b013e3182011b38.

Early Parental Death and Remarriage of Widowed Parents as Risk Factors for Alzheimer's Disease. The Cache County Study

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Abstract

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Author Disclosures:

Drs. Norton, Breitner, Corcoran, Smith, Tschanz, Østbye, and Ms. Schwartz have no disclosures.

Dr. Welsh-Bohmer: Speaker for Elan and Wyeth Pharmaceuticals. Consultant to Medivation and Zynfandel Pharmaceuticals.

Dr. Rabins: Legal testimony for Janssen Pharmaceutica

Dr. Skoog: Research funding from the Swedish Research Council, Swedish Council for Working Life and Social Research, The Alzheimer's Association; Speaker for Shire, JansenCilag, General Electric

Dr. Steffens: Consultant to Transform Pharmaceuticals, Inc (Johnson & Johnson); Speaker for Forest Pharmaceuticals and Wyeth Pharmaceuticals; Travel support to present at a scientific meeting from Bristol-Myers Squibb; Grant support from the National Institute of Mental Health.

Neuropsychological testing and clinical assessment procedures were developed by Dr. Welsh-Bohmer and Dr. Breitner. Dr. Tschanz provided training and oversight of all field staff and reviewed all individual neuropsychological test results to render professional diagnoses. The board-certified or board-eligible geriatric psychiatrists or neurologists who examined the study members included Drs Steinberg, Breitner, Steffens, Lyketsos, Gagliardi, Raj, Christopher, and Green. Dr. Williams also examined several subjects and provided expert neurologic consultation. Autopsy examinations were conducted by Dr. Townsend. Ms. Leslie coordinated the autopsy enrollment program. Diagnosticians at the expert consensus conferences included Drs Breitner, Burke, Lyketsos, Plassman, Steffens, Steinberg, Toohill, Tschanz, and Welsh-Bohmer.

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Objectives—Early parental death is associated with lifelong tendencies toward depression and chronic stress. We tested the hypothesis that, early parental death is associated with higher risk for Alzheimer’s disease (AD) in offspring.

Design—A population-based epidemiological study of dementia with detailed clinical evaluations, linked to one of the world’s richest sources of objective genealogical and vital statistics data.

Setting—Home visits with residents of a rural county in northern Utah.

Participants—4,108 subjects, aged 65-105.

Measurements—Multi-stage dementia ascertainment protocol implemented in four triennial waves, yielding expert consensus diagnoses of 570 participants with AD and 3,538 without dementia. Parental death dates, socioeconomic status and parental remarriage after widowhood were obtained from the Utah Population Database, a large genealogical database linked to statewide birth and death records.

Results—Mother’s death during subject’s adolescence was significantly associated with higher rate of AD in regression models that included age, gender, education, APOE genotype, and socioeconomic status. Father’s death before subject age 5 showed a weaker association. In stratified analyses, associations were significant only when the widowed parent did not remarry. Parental death associations were not moderated by gender or APOE genotype. Findings were specific to AD and not found for non-AD dementia.

Conclusions—Parental death during childhood is associated with higher prevalence of AD, with different critical periods for father’s vs. mother’s death, with strength of these associations attenuated by remarriage of the widowed parent.

OBJECTIVE

Parental death during childhood is often a significant stressor affecting long-term emotional, cognitive, social, spiritual and physical well-being. Bereaved children and adolescents are at increased risk for psychiatric disorders (1) including major depression and posttraumatic stress disorder (2) and alcohol or substance abuse (3) after parental death. Childhood stressors such as early parental death and divorce have been shown to extend into adulthood with increased risk for poorer cardiovascular health (4), pulmonary disease (5) and premature mortality (6). Another, less studied association is between early life adversity and late-life cognitive health and risk for Alzheimer’s disease (AD).

Emerging biological evidence suggests that psychological stressors are associated with detrimental effects to brain structures also affected in AD. In animal studies, physical and psychological stressors in rats have been shown to cause death of hippocampal and cortical cells (7). In other animal studies, excess glucocorticoids (and stress) reduced neurogenesis of cells in the dentate gyrus of the hippocampus whereas adrenalectomy increased the proliferation of these cells (8). Human studies have demonstrated that HPA axis dysregulation may be a risk factor for poorer cognitive performance in older persons. Prolonged exposure of older, nondemented individuals to stress is associated with poorer memory performance (9), and increased levels of glucocorticoids are linked with poorer cognitive function (10) and hippocampal atrophy (11).

Such physiological changes from chronic stress undergird psychological experiences that may influence late-life health outcomes via lifelong patterns of emotion regulation and stress responsiveness (12). In a recent review of early-life risk factors for AD, Borenstein and colleagues (13) suggest that neurodegenerative changes may begin decades before clinical

disorder and that emergence of AD results from complex interactions between genetics and environmental exposures experienced throughout life.

Childhood parental loss is an early-life stressor that may exert effects throughout the lifespan, as evidenced by its association with increased risk for adulthood depression (14). Such non-normative and traumatic events typically pose the greatest adaptive challenges, especially for individuals with inadequate social and emotional resources to adapt (15). Even with living parents, socioeconomic adversity early in life has been associated with a 2-fold higher rate of AD (16) in offspring. With parental death, socioeconomic adversity may compound with emotional challenges, increasing risk for adulthood depression (14), which has in turn been associated with increased risk for AD (17).

In a sample of elderly Swedes, a 6-fold increase in dementia risk was observed among participants experiencing a parental death before age 16 (18). Similarly, we recently reported a 3-fold increase in dementia risk among participants in Cache County (Utah) who reported paternal death prior to age 5, with a non-significant effect for early maternal death (19). These results are limited by possible survival bias among those who survived and participated in the third study wave, the cross-sectional design, and an unknown degree of recall bias in reported dates of parental death.

With the recent linkage of clinical data from the Cache County Memory Study (CCMS) to the objective Utah Population Database (UPDB), we now report a re-examination of this effect. As was done in a smaller study of 239 AD patient registry cases and matched controls (16), we removed the potential problem of recall bias common in retrospective self-reports of early-life stressors. Sample size more than doubled to over 4,000, extending study of all-cause dementia to an examination of effects on Alzheimer's disease (AD) and non-AD dementia, in order to determine the specificity of early parental death effects. We hypothesized that effects would be stronger for AD dementia than for non-AD dementia, because of evidence linking elevated glucocorticoid levels to hippocampal damage, implicated in the neurodegeneration of AD.

Linkage with the UPDB also permitted the opportunity to test our hypothesis that the effects of early parental death would be robust after adjustment for childhood socioeconomic status. We further hypothesized that the deleterious effects of early parental death would be reduced if the widowed parent remarried when the offspring was still a minor. We also investigated the moderating effect of the $\epsilon 4$ allele of APOE, as it has been shown to have a role in other studies of psychosocial stress and AD (11,16).

METHODS

Subjects

In 1995 we asked all elderly (age 65 or older) permanent residents of Cache County to participate in the first wave of the CCMS 5,092 participants (90%) consented. In primary analyses of AD, we excluded 294 cases of non-AD dementia and 189 subjects where cognitive status could not be determined. Additionally, there were 501 subjects with missing data, for a final sample of 4,108 participants, 570 with a diagnosis of AD and 3,538 without dementia. Another 294 subjects were diagnosed with non-AD dementia, 266 of whom had no missing data and were included in secondary analyses to examine specificity of effects. 202 of the 570 AD cases were prevalent and 368 were incident, while 94 of the 266 non-AD dementia cases were prevalent and 172 were incident.

Subjects were 57.4% female; 29.8% had one and 2.7% had two $\epsilon 4$ alleles at APOE. Average (SD) age was 75.7 (7.1) years, and average education was 13.3 (2.9) years.

Diagnostic Procedures

The CCMS utilized a multi-stage dementia ascertainment protocol described elsewhere (20), repeated in four triennial waves, beginning in 1995. Screening began with an in-person interview that included the Modified Mini-Mental State examination (3MS; 21) and, for those whose 3MS score was below 60 out of 100, also the Informant Questionnaire for Cognitive Decline in the Elderly (22). Participants who screened positive for possible dementia completed an in-depth clinical assessment (CA), as did a 19% sub-sample of “designated controls.” Specially trained nurses and psychometric technicians administered the CA, which included a brief physical evaluation, a detailed history of medical and cognitive symptoms, a structured neurological examination, and a one-hour battery of neuropsychological tests.

A geriatric psychiatrist and neuropsychologist reviewed these data; subjects with a working diagnosis of dementia (per DSM-III-R(23)) were selected for psychiatrist examinations and laboratory studies including neuroimaging, and an 18-month follow-up CA. A consensus panel of experts in neurology, geriatric psychiatry, neuropsychology, and cognitive neuroscience reviewed all available data and assigned final consensus diagnoses. Alzheimer’s Disease (AD) was diagnosed according to NINCDS-ADRDA criteria (24). Of the 570 diagnosed cases of AD, there were 64 AD cases that were comorbid with vascular dementia (VaD; per NINDS-AIREN criteria (25)), and 25 AD cases that were comorbid with other dementia.

To determine specificity of effects for AD, we also tested associations with non-AD dementia in an additional 266 subjects (not included in the above sample of 4,108) diagnosed with non-AD dementia, 107 with VaD only, 155 with other dementia, and a small group (number suppressed per CMS privacy policy) with a combination of VaD and other dementia.

Time of dementia onset was defined as the year in which a participant unambiguously met DSM-III-R criteria for dementia. The reference category was no dementia ($n=3,538$), either after CA or negative screening. Because the exposure of interest was immutable and occurred in childhood decades prior to AD risk period, we include here both prevalent and incident AD cases.

Informed consent was obtained for each interview. All procedures were approved by the Institutional Review Boards (IRB) of Utah State University (USU), Duke University, and Johns Hopkins University. UPDB usage was approved by the IRB of USU and the University of Utah, and the Utah Resource for Genetic and Epidemiologic Research.

The Utah Population Database (UPDB)

The UPDB is one of the world’s richest sources of linked population-based information for demographic, genetic, epidemiological, and public health studies. It provides access to over 14 million records or documents representing over 7 million individuals (for more details see <http://www.hci.utah.edu/groups/ppr>). The central component of the UPDB is a vast set of multigenerational Utah family histories. Genealogy records have been linked to cancer records, birth and death certificates, driver license records, and census records.

Parental Death Exposure Variables

Parental death dates from the UPDB were extracted from genealogical records and death certificates and compared to subject’s birth date, with subject age at paternal/maternal death grouped as: age 0-4 years (birth to preschool), 5-10 years (early childhood), 11-17 years (adolescence), and age 18 or older or subject’s father/mother still living (reference

category). Using remarriage dates from the UPDB, the 4-level exposure variables were redefined with separate levels depending on whether widowed parent remarried prior to subject age 18 years.

Covariates

Subject's age, gender, and education were included as covariates. *APOE* genotypes were determined from buccal DNA using polymerase chain reaction (PCR) amplification and a restriction isotyping method described by Saunders and colleagues (26).

Childhood socioeconomic status was based on "usual occupation" on the father's death certificate, using a methodology developed by Nam & Powers (NP-SES) (27). This method uses Census-wide information about the association between education and income, as they relate to individual occupations. Higher NP-SES has been found to be negatively associated with mortality risks for both men and women (28). Because a large number of subjects had missing NP-SES scores, we coded SES into four discrete categories, including farmer (the most common), NP-SES score: lower SES than farmer, greater SES than farmer, or missing. An alternative SES measure used mean imputation for missing values.

Because later motherhood has been associated with mitochondrial DNA dysfunction and higher risk of Alzheimer's disease in offspring (29) and later fatherhood associated with decreased learning capacity in offspring (30), reduced fetal viability in offspring of older parents is a potential confound. Therefore, we separately examined maternal and paternal ages at subject's birth.

Data Analysis

Logistic regression analyses examined associations between early paternal death and early maternal death and AD, considered singly then together, after adjustment for covariates. Differential effects by participant gender and presence of the e4 allele at APOE were tested with two-way interaction between exposure, and gender and presence of e4 allele, respectively. A second set of models investigated effects of remarriage of widowed parents. A final model included both expanded parental death variables and all covariates. In secondary analyses, similar models were run to examine effect of early maternal and paternal death on risk for non-AD dementia. Secondary analyses were also conducted including only prevalent, then including only incident cases.

RESULTS

The final sample of 4,108 participants included those experiencing early maternal death at age 0-4 years (n=87), 5-10 years (n=99), 11-17 years (n=108), while early paternal death included participants who experienced paternal death at age 0-4 years (n=69), 5-10 years (n=122), 11-17 years (n=174; Table 1). Subject's education, mother's and father's age at subject's birth, and AD diagnosis in late life were associated with early maternal death and early paternal death, with subject's age at baseline interview associated with early maternal death (Table 1).

In an initial model, older age, female gender, and one or two copies of the APOE e4 allele were associated with greater risk for AD, while education was non-significant (Table 2). After covariate adjustments, the overall association between early paternal death and AD diagnosis in late life was marginal, with paternal death before subject age 5 linked to a doubling in prevalence of AD. Mother's death during adolescence was likewise associated with more than double the prevalence of AD. The final model adjusted for (categorical) Nam-Powers SES, which was not significantly associated with AD. Further, after SES adjustment, associations for both mother's death and father's death were virtually identical

(similar results for SES adjustment using mean imputation, not shown). Additional models (not shown) adjusted for number of siblings, where associations for both mother death and father death were likewise virtually unchanged.

In separate models (not shown), participant gender was tested as potential moderator of mother's death and father's death associations with late-life diagnosis of AD. Gender did not moderate either association (Wald=4.22, df=3, p=.239; Wald=2.651, df=3, p=.449, gender interactions, respectively). Similarly, presence of the e4 allele did not moderate these associations (Wald=1.98, df=5, p=.851; Wald=8.06, df=6, p=.234, respectively). In models including only incident cases, and then only prevalent cases (not shown), results were essentially unchanged. Mother's death and father's death were not associated with non-AD dementia risk (models not shown; Wald=3.01, df=3, p=.391; Wald=3.97, df=3, p=.264, respectively, full model). Thus, associations between early parental loss and dementia were specific to AD.

We explored lifetime history of major depression as partial evidence that childhood bereavement may generate stress with lasting emotional, developmental and physiologic impacts. Subjects with maternal death during adolescence had lifetime prevalence of major depression of 30%, while those exposed at ages younger than 11 years and those with maternal death in adulthood each had major depression prevalence of 23%. This association did not reach statistical significance ($\chi^2=2.645$, df=2, p=.266).

Separate models (not shown) were computed to examine older parental age at subject's birth, potentially resulting in heightened risk for chronic diseases such as AD later in life. In simple bivariate models, both maternal age (OR=1.02, Wald=5.71, df=1, p=.017) and paternal age (OR=1.01, Wald=5.46, df=1, p=.019) at subject's birth were associated with higher rates of AD. However, when tested for their association with AD net of maternal and paternal death, both maternal age (OR=1.01, Wald=.699, df=1, p=.403) and paternal age (OR=1.00, Wald=.00, df=1, p=.966) at subject's birth were no longer associated with AD. However, the associations between mother death during subject's adolescence (OR=2.27, Wald=10.218, df=1, p=.001) and father's death before subject age 5 (OR=2.10, Wald=5.32, df=1, p=.021) with AD remained robust after adjustment for parental ages at subject's birth.

In additional models, we tested the seven-category exposure variable (paternal death and maternal death with/without remarriage of widowed parent during remaining years of subject's childhood). In the final model with this expanded exposure variable, paternal death was no longer associated with AD (Table 3). However, maternal death during subject's adolescence was associated with a higher rate of AD when the widowed father did not remarry.

Our sample included a small number (n=27) of subjects whose mother and father both died during subject's childhood. In exploratory analyses, orphanhood was not associated with higher rate of AD (OR=1.59, Wald=0.78, df=1, p=.378).

DISCUSSION

In this population-based study of Alzheimer's disease, we capitalized on a rich genealogical and vital statistics database to re-examine associations between parental death during childhood and risk of AD during late life. The use of the vital statistics data base removed recall bias as a potential confound. Mother's death during offspring adolescence was uniquely associated with more than double the risk of AD, with attenuated effects if the widowed father remarried, with equivalent correlations for sons and daughters. Controlling for socioeconomic status at the time of the parent's death did not attenuate the association. A

similar result was found for father's death during the first five years of life, but this was marginal with overall effect not reaching statistical significance after covariate adjustments.

Our findings were specific to AD, with no association between parental death and non-AD dementia. Clément et al (31) reported significant associations between childhood, marital and work-related life events and all-cause dementia status, but found no differences in reported histories of these life events between dementia subtypes of AD, frontotemporal dementia and vascular dementia, however, this study had few cases (n=25, n=17, and n=12, respectively). Other studies focused entirely on AD (12,13) or on all-cause dementia (16,17), so AD vs. non-AD effects were not presented. While others have reported that associations between early life socioeconomic adversity (i.e. unskilled laborer occupation and large family size) and AD were significantly greater for $\epsilon 4$ positive individuals (12,13), we found no interaction with APOE genotype.

While childhood maternal death can be traumatic and potentially have long-term consequences regardless of its timing, our key finding is the correlation between mother's death during adolescence and AD. Adolescence is a period of physical and psychological turbulence and adolescents with ready emotional support and coping strategies generally experience healthier bereavement outcomes (32). Adolescent self-esteem has been shown to be a significant mediator between parental bereavement stress and internalizing and externalizing mental health problems (33). Bereaved adolescents may also experience feelings of being alone and alienated, even if support from others is not actively sought (34). Born in an era and living in a community that may have held to more traditional gender roles, maternal death would have deprived the adolescent of the parent with primary role in childrearing and emotional support. However, the mechanisms by which this association operates are likely complex, given the multiplicity of effects of maternal (and paternal) death on contextual factors such as the immediate and broader environment (e.g. nuclear family, extended family, school, church and neighborhood supports) as potential moderators.

The association we observed between paternal death in the first five years of life and AD is consistent with the observation that this is a period of extraordinary development that may be sensitive to such dramatic loss events. Another potential mechanism for higher levels of perceived stress and ultimately greater physiological burden is through fear of abandonment, shown to mediate the relation between child stressors and subsequent mental health problems in parentally bereaved children (35).

Limitations and Strengths

Early parental death may impact socioeconomic status (SES) due to income loss (and possibly higher medical expenses incident to the deceased parent's condition). These in turn can affect offspring nutrition, quality of housing, access to medical care, all of which may have implications for later adulthood health outcomes. We therefore adjusted for childhood SES and found that associations between early parental death and AD were robust. This suggests that these associations were not entirely mediated by early life economic losses. However, our SES adjustment was limited by a large proportion of subjects with missing SES. Rather than remove these cases, we analyzed them as a separate group, in addition to using mean imputation (the latter performed better than more sophisticated imputation methods in a recent study by Paul et al (36; page 20). The majority of respondents were farmers, so results might differ in populations with more SES heterogeneity.

Another limitation of the study is the lack of information on subjects who were lost to follow-up or developed dementia before age 65 and therefore were not part of the study. Because early parental death is associated with increased mortality risk (6), our results may

be a conservative estimate of effects. Similarly, the lack of data on parental causes of death does not allow an examination of a potential contribution of familial/constitutional factors other than stress such as cardiovascular health.

We examined lifetime depression history and found a slightly higher (though non-significant) depression rate in subjects exposed to maternal death during adolescence, compared to maternal death at younger or older ages. Given that anxiety and personality factors may also provide evidence of stress, similar comparisons would have been desirable, however, such data were not available.

Strengths of this study include the use of a large, population-based sample, which has been shown to have less selection bias than clinic-based samples where participants are seeking treatment (37). Clinical evaluation for dementia, and many years of follow-up, are additional strengths. The high participation rate also helps reduce non-responder bias (38). One of this study's greatest strengths is elimination of exposure recall bias through use of objective records.

Conclusion

The present study provides further evidence that the traumatic event of parental death during childhood is associated with higher rates of AD in late life. Of particular note is the finding that the strength of association between mother's or father's death and AD depends on timing within childhood of the parent's death, and that effects are stronger when the widowed parent does not remarry. This finding extends our prior work by demonstrating that this association is specific to AD, and argues for additional studies of mechanisms.

Depression--one indicator of maladaptation to stressors--has been associated with a doubling in risk for dementia (39). Thus, depression and other distress proneness indicators, may have independent modifying effects on the stressor/dementia association. Future studies should investigate interactions between early life stressors and depression (before and after stressor exposure) on subsequent dementia risk. In this sample, the modestly higher rate of major depression is insufficient to infer that this early life event precipitated chronic stress universally across all persons so exposed. Indeed, acute and chronic stressors are not experienced uniformly by all persons. Since there is wide variation in the subjective interpretation of stressors and on coping resources across individuals, future studies of the associations reported here should investigate subjective stress, a potentially modifiable variable, as a moderator.

The present study does not provide evidence about possible physiologic mechanisms, nor does it clarify whether these associations derive from post-developmental injury or early-life dispositional styles. Future research should examine stress-related biomarkers to determine which biological pathways most strongly mediate stressor/AD associations observed here.

Although early-life parental death, is not easily modifiable, establishing a clear link between psychosocial adversity and increased vulnerability to AD in critical stages of development (40) will aid in the identification of at-risk individuals for more targeted interventions. Effective interventions may reduce the perception of stress and the intensity of the body's physiological stress response and vulnerability to neurodegenerative diseases such as AD.

Acknowledgments

This work was supported by National Institute of Health grants: AG-031272, AG-011380, and AG-021136. We acknowledge the contributions of the following individuals whose activities have helped to ensure the success of the project: Cara Brewer, BA, Tony Calvert, BSC, Carol Leslie, M.S., Georgiann Sanborn, M.S., Michelle McCart,

Heidi Wengreen, Ph.D., RD, James Wyatt, and Peter P. Zandi, Ph.D., M.P.H., Roxane Pfister, M.S., Nancy Sassano, Ph.D.

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Table 1
Descriptive Summary of Subjects Who Were Exposed and Unexposed to Early Maternal and Early Paternal Death

Independent Variable	Subject's Age at Maternal Death				p value *	Subject's Age at Paternal Death				p value *
	0-4 years	5-10 years	11-17 years	18+ years		0-4 years	5-10 years	11-17 years	18+ years	
N=4108	N=87	N=99	N=108	N=3814		N=69	N=122	N=174	N=3742	
Age (mean, sd)	77.10 (6.7)	77.57 (7.8)	75.78 (6.9)	75.62 (7.1)	0.013	77.02 (6.8)	76.32 (7.3)	75.99 (6.9)	75.65 (7.1)	0.284
Education (mean, sd)	12.64 (2.9)	12.09 (2.5)	12.19 (3.1)	12.31 (2.85)	<.001	12.70 (2.53)	12.93 (2.97)	12.70 (2.9)	13.28 (2.9)	0.012
NP-SES w/imp (mean, sd)	43.19 (6.1)	44.74 (9.9)	44.46 (7.2)	45.15 (9.7)	0.245	44.44 (9.5)	43.43 (8.9)	44.38 (8.6)	45.18 (9.7)	0.156
Father age @ birth of subject (mean, sd)	33.82 (7.8)	35.02 (9.5)	34.81 (7.4)	33.0 (7.8)	0.002	39.31 (11.5)	37.09 (9.9)	36.90 (9.6)	32.70 (7.4)	<.001
Mother age @ birth of subject (mean, sd)	29.53 (6.6)	29.75 (6.7)	31.47 (6.9)	29.14 (6.5)	0.006	31.88 (6.6)	31.31 (6.8)	31.02 (7.0)	29.02 (6.4)	<.001
APOE e4+ 1 copy	30 (34.5%)	27 (27.3%)	30 (27.8%)	1139 (29.9%)	0.606	17 (24.6%)	32 (26.2%)	57 (32.6%)	1120 (29.9%)	0.471
2 copies (N, %)	†	†	†	103 (2.7%)		†	†	†	99 (2.6%)	
Female gender (N, %)	54 (62.1%)	60 (60.6%)	62 (57.4%)	2183 (57.2%)	0.745	43 (62.3%)	66 (54.1%)	104 (59.4%)	2146 (57.3%)	0.677
Any AD (N, %)	17 (19.5%)	13 (13.1%)	25 (23.1%)	515 (13.5%)	0.014	18 (21.6%)	18 (14.8%)	27 (15.4%)	507 (13.5%)	0.025

* p value is one-way ANOVA F test for continuous variables (df₁=3, df₂=4104), and chi-square test of independence for categorical variables (df=6 for APOE, df=3 for Female gender and Any AD)

† Number and frequency suppressed to comply with privacy policy of Center for Medicare and Medicaid Services

Logistic regression analysis of early paternal and early maternal death on offspring risk for Alzheimer's disease (Odds ratios and p-values; N=4108)

Table 2

MODEL	1 Covariates only n	2 Mother death + covariates	3 Father death + covariates	4 Father & Mother death + covariates	5 Father & Mother death + covariates +NP-SES
- 2Log Likelihood	2831.427	2819.742	2825.066	2814.951	2810.980
Chi-square test, comparing -2LL between models *		vs. Model #1: $\chi^2 = 11.685$ d.f.=3 p= .009	vs. Model #1: $\chi^2 = 6.361$ d.f.=3 p= .095	vs. Model #2 $\chi^2 = 4.791$ d.f.=3 p= .188	vs. Model #4: $\chi^2 = 3.971$ d.f.=3 p= .265
				vs. Model #3 $\chi^2 = 10.115$ d.f.=3 p= .018	
Maternal Death (ref=18+)		(.005)		(.005)	(.006)
0-4 yrs	87	1.452 (<.001)		1.413 (.243)	1.417 (.240)
5-10 yrs	99	0.735 (.346)		0.736 (.348)	0.726 (.328)
11-17 yrs	108	2.266 (.001)		2.315 (.001)	2.271 (.001)
Paternal Death (ref=18+)			(.073)	(.065)	(.064)
0-4 yrs	69		2.228 (.009)	2.265 (.008)	2.263 (.008)
5-10 yrs	122		1.145 (.628)	1.166 (.581)	1.180 (.554)
11-17 yrs	175		1.059 (.803)	1.059 (.805)	1.071 (.767)
Subject age (yrs)		1.123 (<.001)	1.124 (<.001)	1.124 (<.001)	1.124 (<.001)
Subject education (yrs)		1.009 (.614)	1.012 (.485)	1.010 (.576)	1.010 (.596)
Subject gender=F (ref=M)	2359	1.333 (.005)	1.338 (.004)	1.331 (.005)	1.330 (.005)
APOE (ref=0)		(<.001)	(<.001)	(<.001)	(<.001)
1 copy	1226	3.077 (<.001)	3.083 (<.001)	3.093 (<.001)	3.098 (<.001)
2 copies	109	10.528 (<.001)	10.852 (<.001)	10.558 (<.001)	10.922 (<.001)

MODEL	1 Covariates only	2 Mother death + covariates	3 Father death + covariates	4 Father & Mother death + covariates	5 Father & Mother death + covariates +NP-SES
	n				
NP-SES (ref=40/farmer)					(.543)
Less than 40	139				0.851 (.588)
More than 40	441				1.241 (.490)
Unknown	2412				1.082 (.490)

* All other p values given in this table are associated with Wald tests of significance of individual effects within models. Paternal Death and Maternal Death omnibus tests both have $df=3$, with tests for individual levels each having $df=1$ when contrasted to reference category of "parental death at subject age 18+ years or parent still living". Covariates of age, education and gender are tests with $df=1$, and APOE omnibus test has $df=2$ with individual tests for having 1 vs. 0 e4 alleles and 2 vs. 0 e4 alleles each having $df=1$.

Logistic regression analysis of early paternal and early maternal death on offspring risk for Alzheimer's disease, when widowed parent does or does not remarry during offspring's childhood (Odds ratios and p-values; N=4108)

Table 3

MODEL	1 Covariates only n	2 Mother death + covariates	3 Father death + covariates	4 Father & Mother death + covariates	5 Father & Mother death + covariates +NP-SES
- 2 Log Likelihood	2831.427	2818.874	2824.663	2811.896	2809.700
Chi-square test, comparing - 2LL between models *		vs. Model #1: $\chi^2 = 12.553$ df=6 p= .051	vs. Model #1: $\chi^2 = 6.764$ df=6 p= .343	vs. Model #2 $\chi^2 = 6.978$ df=6 p= .323 vs. Model #3 $\chi^2 = 12.767$ df=6 p= .047	vs. Model # 4: $\chi^2 = 2.996$ df=3 p= .533
Maternal Death (ref=18+)		(.035)		(.032)	(.038)
0-4 yrs NO remarriage	41	1.664 (.201)		1.542 (.282)	1.531 (.292)
0-4 yrs W/ remarriage	46	1.246 (.615)		1.271 (.582)	1.292 (.557)
5-10 yrs NO remarriage	51	0.588 (.259)		0.576 (.241)	0.567 (.228)
5-10 yrs W/ remarriage	48	0.926 (.865)		0.951 (.911)	0.942 (.895)
11-17 yrs NO remarriage	79	2.390 (.003)		2.439 (.003)	2.410 (.003)
11-17 yrs W/ remarriage	29	1.959 (.171)		2.016 (.153)	1.943 (.178)
Paternal Death (ref=18+)			(.284)	(.266)	(.261)
0-4 yrs NO remarriage	49		2.402 (.017)	2.423 (.018)	2.399 (.019)
0-4 yrs W/ remarriage	20		1.896 (.245)	1.956 (.223)	1.999 (.207)
5-10 yrs NO remarriage	106		1.135 (.669)	1.160 (.616)	1.167 (.604)
5-10 yrs W/ remarriage	16		1.219 (.803)	1.263 (.769)	1.334 (.718)
11-17 yrs NO remarriage	171		1.038 (.873)	1.039 (.871)	1.050 (.835)
11-17 yrs W/ remarriage	7		2.005 (.563)	2.070 (.545)	2.189 (.515)
Subject age (years)		1.123 (<.001)	1.124 (<.001)	1.124 (<.001)	1.124 (<.001)
Subject education (yrs)		1.009 (.614)	1.012 (.505)	1.013 (.460)	1.009 (.613)
Female gender (ref=M)	2359	1.333 (.005)	0.336 (.005)	1.336 (.005)	1.329 (.006)
APOE (ref=0)		(<.001)	(<.001)	(<.001)	(<.001)

MODEL		1 Covariates only	2 Mother death + covariates	3 Father death + covariates	4 Father & Mother death + covariates	5 Father & Mother death + covariates +NP-SES
	n					
	1 copy	1226	3.077 (<.001)	3.085 (<.001)	3.090 (<.001)	3.094 (<.001)
	2 copies	109	10.528 (<.001)	10.527 (<.001)	10.889 (<.001)	10.921 (<.001)
NP-SES (ref=40/farmer)						(.534)
	Less than 40	139				0.851 (.588)
	More than 40	441				1.245 (.219)
	Unknown	2412				1.084 (.482)

* All other p values given in this table are associated with Wald tests of significance of individual effects within models. Paternal Death and Maternal Death omnibus tests both have $df=6$, with tests for individual levels each having $df=1$ when contrasted to reference category of parental death at subject age 18+ years or parent still living. Covariates of age, education and gender are tests with $df=1$, and APOE omnibus test has $df=2$ with individual tests for having 1 vs. 0 e4 alleles and 2 vs. 0 e4 alleles each having $df=1$.

† Number and frequency suppressed to comply with privacy policy of Center for Medicare and Medicaid Services