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Impact of Offspring Death on Cognitive Health in Late Life. The Cache County Study

Daylee Bradford, M.S.¹, JoAnn T. Tschanz, Ph.D.², Ken R. Smith, Ph.D.³, Truls Østbye, M.D., Ph.D.⁴, Chris Corcoran, Sc.D.⁵, Kathleen A. Welsh-Bohmer, Ph.D.⁶, Maria C. Norton, Ph.D.^{1,2}, and For the Cache County Investigators

¹Department of Family Consumer and Human Development, Utah State University

²Department of Psychology, Center for Epidemiologic Studies, Utah State University

³Department of Family and Consumer Studies; Population Sciences, Huntsman Cancer Institute, University of Utah

⁴Duke Global Health Institute, Duke University, and Duke – NUS Graduate Medical School, Singapore

⁵Department of Mathematics and Statistics, Center for Epidemiologic Studies, Utah State University

⁶The Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Duke University

Abstract

Objectives—Experiencing the death of a child is associated with negative short-term mental health consequences, but less is known about cognitive outcomes and whether such associations extend to late-life. We tested the hypothesis that experiencing an offspring death (OD) is associated with an increased rate of cognitive decline in late life.

Design—A population-based longitudinal study with up to four cognitive status observations spaced 3–4 years apart, linked to an extensive database containing objective genealogical and vital statistics data.

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

Participants—3,174 subjects, initially without dementia, aged 65–105.

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Address correspondence to: Dr. Maria Norton, Department of Family Consumer and Human Development, Utah State, University, 2905 Old Main Hill, Logan, UT 84322-2905; Phone: 435-797-1599; maria.norton@usu.edu; Fax: 435-797-2771.

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Portions of this paper were presented at the Gerontological Society of America annual conference in November, 2010 in New Orleans, LA.

Measurements—Cognitive status was measured with the Modified Mini-Mental State exam (3MS) at baseline, 3, 7 and 10 year follow-ups. OD was obtained from the Utah Population Database, which contains statewide birth and death records.

Results—In linear mixed models, controlling for age, gender, education, and APOE status, subjects who experienced OD while younger than 31 years of age experienced a significantly faster rate of cognitive decline in late life, but only if they had an $\epsilon 4$ allele. Re-classifying all OD (regardless of age) according to subsequent birth of another child, OD was only related to faster cognitive decline when there were no subsequent births.

Conclusions—Experiencing OD in early adulthood has a long-term association with cognitive functioning in late life, with a gene-environment interaction at the APOE locus. Subsequent birth of another child attenuates this association.

“There's no tragedy in life like the death of a child. Things never get back to the way they were. “

-- Dwight D. Eisenhower

OBJECTIVE

Death of any family member is difficult, but losing a child may be the most traumatic, as it is an “off-timing” event that violates the natural order of life. Further, it is often not the number of stressful events, but rather the timing of these events that determines the amount of stress individuals experience⁽¹⁾. Experiencing the death of a child may lead parents to have lasting psychological distress⁽²⁾, especially since it is associated with longer and more intense periods of grief than the loss of a spouse or parent⁽³⁾. Some parents experience sadness not only for the loss of their child, but also feel as though a part of themselves has died with their child⁽⁴⁾.

Bereavement-related stress after offspring death may be compounded by concomitant experiences. Nearly half of parents who experience the death of a child report strained marital relationships, lack of communication between spouses, or distancing in the relationship, often resulting in divorce⁽⁵⁾. This added stress may result in negative lifestyle behaviors, also raising the risk of adverse health outcomes and mortality^(6,7). Loss of a child may increase the risk of several negative health outcomes, such as myocardial infarction⁽⁸⁾, diabetes⁽⁹⁾, and multiple sclerosis⁽¹⁰⁾. Thus, experiencing the death of a child disrupts parental health and well-being, with effects that may be manifested short- and long-term over the course of parents' lives⁽¹¹⁾.

Less well-studied is the potential impact of death of a child or other close family members on late-life dementia risk. Death of spouse has been associated with more rapid cognitive decline in later life⁽¹²⁾, and death of father during childhood with higher dementia risk⁽¹³⁾, net of adjustment for socioeconomic status. Because most bereaved parents feel as though their grief is a continual process that does not have a definitive end⁽⁷⁾, they will experience stress from the loss of their child for a number of years after their child's death.

A possible explanation for the association between chronic psychological stress and dementia risk derives from observations showing that chronic exposure to psychological

stress leads to a sustained increase in stress hormone production, which in turn can produce excess free radicals that may damage tissues and organs, including the brain⁽¹⁴⁾. The *RCAN1* gene is thought to play a role in the development of tau-pathies such as Alzheimer's Disease, and *RCAN1* proteins can be induced by psychosocial and emotional stress⁽¹⁵⁾. In addition, aged individuals have an impaired ability to discontinue the production of stress hormones (glucocorticoids); paradoxically, which may lead to the so-called "glucocorticoid cascade" cycle that can have serious neurological consequences⁽¹⁶⁾.

The objective of the current study was to assess the impact of a child death on cognitive decline in late life, hypothesizing that such adversity would be associated with chronic psychological stress and result in faster cognitive decline. The study used a large population-based sample of older adults, using objective records to define exposure to OD, thereby eliminating recall bias. Cognitive functioning generally declines over time as a natural function of age, and there is also evidence from animal studies suggesting that neuronal resilience to stress may be lost with age, given that the brains of older rats self-repaired less readily after stress than younger rats⁽¹⁷⁾. These observations suggest that older the individual when experiencing the death of a child, the greater the impact on cognitive health. However, young adults are much more likely than older adults to use coping strategies that suggest lower levels of impulse control and self-awareness, which are indicative of their lower levels of maturity⁽¹⁸⁾. Younger individuals may therefore be less successful at coping with the traumatic event of losing a child. While there is some evidence to suggest that age of a child at death can influence the grieving process for parents⁽¹⁹⁾, the findings are mixed regarding the link between OD and parental outcomes when using child's age at death as an independent variable⁽²⁰⁾. The current study therefore examined whether associations between OD and cognitive decline varied by timing of OD and age of the offspring at death. Furthermore, because women are 1.5–2 times as likely to experience depression (potential marker of psychological stress) than men⁽²¹⁾, we hypothesized that this association would be stronger among females. Additionally, because APOE genotype has been shown to moderate associations between other psychosocial stressors and dementia risk, for example, higher dementia risk among APOE ϵ 4 carriers who also experienced low childhood socioeconomic status⁽²²⁾ or a large family size⁽²³⁾, we hypothesized that individuals who were ϵ 4 positive would have a stronger association.

METHODS

Study Design

The Cache County Memory Study (CCMS) is a prospective, population-based epidemiological study of dementia. Four waves of ascertainment were conducted between 1995 and 2008 (baseline and follow-up interviews at 3, 7, and 10 years). The present study utilized data on cognitive status (across all four study waves), and linkage to an objective data source to define OD exposure.

Subjects

The original CCMS cohort included 5,092 participants (90% of county residents aged 65 or older in January 1995). We excluded 359 participants with prevalent dementia²⁴ (see

Breitner et al, 1999 for detailed description of dementia ascertainment protocol), leaving 4733. Thirty confirmed nulliparous subjects were excluded, leaving 1529 with missing (1049 with no offspring records and 480 with offspring noted on genealogy records but lacking all dates) and 3174 with non-missing offspring data.

Cognitive Decline Measurement

The Modified Mini-mental State exam (3MS;25,26) was used to assess cognitive status at baseline and each of three follow-up assessments. The 3MS is a 100-point adaptation of the Mini-Mental State Exam⁽²⁷⁾ and assesses attention, concentration, orientation to time and place, memory, constructional praxis, and expressive and receptive language. It was administered by interviewers trained by a study neuropsychologist as to standardized administration and scoring.

Offspring Death Assessment

OD was operationalized objectively through linkage between the Utah Population Database (UPDB) and CCMS records. The UPDB, compiles demographic, genetic, and epidemiological information on Utah residents⁽²⁸⁾ and contains information on 7 million individuals, representing over 14 million records. UPDB records are already linked with CCMS; 5,091 out of 5,092 CCMS subjects appear in the UPDB.

The UPDB provided information about the number of children born to each participant as well as the date of each child's birth and death. Offspring deaths were coded along two dimensions: age of subject (i.e. the parent) at OD and age of offspring at OD. OD dates were ignored if occurring after subject's death date or dementia onset (if diagnosed with dementia). Separate variables were derived, with age ranges chosen to approximate young/emerging adulthood, younger middle age and later middle age: age 17–30 years, age 31–44 years, and late middle age age 45–64 years. These were each coded trichotomously, as: OD during age 17–30 years vs. OD during some other stage of life vs. no OD experience (similarly for the other two life stages). We further considered examination of the manner of death (accidental/homicide/ suicide vs. natural), but 82% of the cohort missed data on this variable, precluding its analysis.

We defined childbearing years according to the maximum gender-specific parental age at child birth (49 years for females and 60 years for males), then coded: OD without replacement (*during* childbearing years), OD without replacement (*after* childbearing years), OD with replacement birth, and no OD. In exploratory analyses, we hypothesized that OD without the subsequent birth of another child (during childbearing years) would be associated with faster cognitive decline than OD with a "replacement child" birth.

Covariates

APOE genotype was determined from buccal DNA using polymerase chain reaction (PCR) amplification and a restriction isotyping method described by Saunders and colleagues⁽²⁹⁾. Subjects were coded as carriers or non-carriers of at least one ϵ 4 allele. Age as of baseline interview and educational attainment were measured in years. Total number of children born to subject was derived through birth records in the UPDB.

Statistical Analyses

Descriptive analyses—One way analyses of variance were computed on continuous variables and χ^2 tests were computed on categorical variables to determine bivariate associations between key covariates and the experience of OD to explore possible confounding. To assess potential non-response bias, participants in the final sample were compared to those who were removed due to missing offspring data, using t-tests for continuous variables and χ^2 tests for categorical variables.

Rate of cognitive decline—General linear models were used that accommodate repeated measures, incorporating a quadratic (non-linear) term for time. This approach models the association between fixed factors (OD) and trajectory of an outcome (cognition), while accounting for within-subject correlation in cognitive scores across time. Models were parameterized to allow examination of differences in baseline cognitive score and differences in rate of decline, as a function of OD exposure. When a significant interaction between OD and time was observed, additional models examined moderation of this association by APOE and gender. If the interaction between OD*APOE*time was significant at $p<.10$, we conducted stratified models by APOE genotype (similarly for gender interaction). In a separate model, the “OD with/without replacement” exposure variable was tested for association with cognitive decline.

We first studied OD exposure before baseline interview, with separate variables to focus on each life stage. Then we studied OD exposure after baseline (among unexposed before baseline), coded 0 as of baseline, then set to 1 at the first cognitive measurement following the incident OD (and thereafter).

Statistical analyses were conducted using SPSS Version 21 software. In all models, the difference in the log likelihood between nested models was tested; only if this test was significant was the more complex model retained. All models included age, gender, education and APOE status as covariates.

RESULTS

Bivariate associations between Offspring Death and Demographic Variables

In the final analysis sample of 3,174 subjects, 68.0% were female, 99% were Caucasian, 30.4% had at least one ϵ 4 allele at *APOE*. *Mean (SD)* age and education were $M=74.8$; $SD=7.0$ and $M=13.1$; $SD=2.7$, respectively. In the sample, 420 (13.2%) persons developed incident dementia. The number of children born ranged from 1 to 14 ($M=3.42$, $SD=2.10$). There were 209 with OD during 17–30, 175 with OD during age 31–44 years, 122 with OD during age 45–64 years (overlap consisted of: 19 during first two intervals, 7 during second and third intervals, 7 during first and third intervals, and none with OD in all three intervals). Another 127 with OD only after baseline, and 2481 unexposed to OD.

Participants with missing offspring data were more likely to be male (65.3%) compared to the final sample (32%; $\chi^2=474$, $df=1$, $p<0.001$), and were also more highly educated ($M=13.43$, $SD=3.3$) than the final sample ($M=13.1$, $SD=2.7$; $t=4.09$, $df=4719$, $p<0.001$). Subjects missing offspring data were, on average, older ($M=76.3$, $SD=7.1$ years) than

subjects with non-missing data ($M=74.8$, $SD=7.0$ years; $t=6.99$, $df=4731$, $p<0.001$). The two groups were not significantly different on APOE status (Fisher's Exact test $\chi^2=0.10$, $df=1$, $p=0.756$; see Table 1).

In bivariate tests of association between sociodemographic variables and whether or not subject had ever experienced OD (removing the missing OD group), APOE was not significant ($\chi^2=0.158$, $df=1$, $p=.691$; Table 1). There was a significant association between gender and OD; 24.0% of women and 17.1% of men experienced OD ($\chi^2=20.2$, $df=1$, $p<.001$). Education was significantly associated with OD ($t=-4.783$, $df=1141$, $p<.001$), with participants who had experienced an OD having lower average education ($M=12.7$, $SD=2.6$ years) than those without OD exposure ($M=13.2$, $SD=2.7$). Age was significantly associated with OD ($t=7.22$, $df=989$, $p<.001$), with the average age of OD exposed participants ($M=76.6$, $SD=7.8$ years) lower than average age of unexposed participants ($M=74.3$, $SD=6.7$ years).

Subject (Parent) Age at Offspring Death

Experiencing OD while subject was under 31 years of age was significantly related to faster cognitive decline, and presence of the $\epsilon 4$ allele at APOE moderated this association. Results are displayed in Table 2 showing statistical significance for the omnibus test and single-df interaction terms between OD and time and time² demonstrating association between OD and rate and acceleration of cognitive decline, respectively. Additionally, (not shown) there were non-significant differences in baseline cognitive scores between exposure groups (p -values ranged from .543 to .586 across all models for omnibus F test of OD main effect in the various models). In separate models, subjects with no $\epsilon 4$ allele had no significant association with OD while subjects with one or more copies of the $\epsilon 4$ allele had significant linear and quadratic association with OD, with 1.24 points/year faster decline than those with no OD exposure. Figure 1 depicts the different cognitive trajectories as a function of OD exposure and APOE status, where effect sizes can be discerned at various points along the time axis by visual comparison of "OD" and "no OD" curves, separately for " $\epsilon 4$ positive" and " $\epsilon 4$ negative" subgroups. Gender did not moderate this association. When total number of children born to subject was included as a covariate (not shown), the model results were virtually unchanged. To explore the impact of having excluded subjects with missing offspring data, we conducted additional models (not shown) adding these subjects back into the sample as another exposure group. This ambiguous group did not differ on rate of cognitive decline compared to subjects with no OD experience ($B=0.0006$, $t=0.063$, $df=1947$, $p=.950$), but results for the group with OD exposure during 17–30 years ($B=-0.51$, $t=-2.47$, $df=2007$, $p=.014$) were nearly identical to analyses without inclusion of the missing group.

OD when subject was age 31–44 years or when subject was age 45–64 years, were not significantly related to rate of cognitive decline. (Additional analyses were conducted examining association between OD and cognitive decline, according to offspring age at death; these variables were highly correlated with OD according to subject's age at time of OD and are therefore not included in this report, e.g. $\chi^2=1574$, $df=4$, $p<.001$).

In the model examining OD occurrence with vs. without subsequent birth of a “replacement child,” subjects experiencing OD (*during* childbearing years) without replacement, (n=99) had an average 0.77 points/year faster cognitive decline than those without OD exposure (n=2572), consistent with our hypothesis. OD with replacement (n=77) and OD (*after* childbearing years) without replacement (n=427) was not significantly related to rate of cognitive decline. Figure 2 depicts the different cognitive trajectories as a function of OD exposure when categorized into these four groups, clearly showing that subjects with “OD (during childbearing years) without replacement” experience more rapid cognitive decline.

Time-varying Exposure to Offspring Death

A separate model tested the association between OD exposure after baseline as a time-varying covariate, and rate of cognitive decline, including only those subjects who had not been exposed to OD before baseline. Individuals exposed to OD after baseline exhibited a trend for faster decline with an average 1.38 points/year faster rate of decline than those without OD exposure after baseline.

CONCLUSIONS

The key finding of this investigation is that OD during young parental age (< 31 years) predicts a faster rate of cognitive decline in late-life, net of several known predictors. This is consistent with other studies that describe shorter-term effects of parental bereavement^(2,7,9,11), with the present study extending this to include cognition in late life. The results are also in line with previous studies that have demonstrated longer-term associations between other “loss event” stressors such as paternal death during age 0–4 years⁽³⁰⁾, maternal death during adolescence⁽¹⁴⁾, and the death of a spouse⁽¹³⁾ and with late-life cognitive health.

Finding that OD was only associated with faster cognitive decline if experienced during the teens and twenties suggests that individuals in earlier developmental stages of life may have fewer resources (financial, social, emotional) to help them deal with the stress of an OD. Because the brain continues to develop throughout adolescence and early adulthood, individuals in this stage may have an increased vulnerability to stress-related physiological processes that lead to negative consequences in the brain⁽³¹⁾. Also, young adults display a tendency to choose less helpful coping mechanisms compared to older adults⁽¹⁹⁾. This increased vulnerability may therefore exacerbate the negative physiological effect of stress and raise the risk for negative cognitive outcomes in late life. Experiencing adversities in the earlier stages of life may also prevent the brain from reaching full maturity, placing these individuals at higher risk of AD in late life⁽³²⁾. It has also been shown that early life adversity can alter Hypothalamic Pituitary Axis (HPA) stress responses, leading to negative outcomes on brain functioning later in life⁽³³⁾. The HPA also plays a role in cognition in late life; malfunctions in the HPA are observed in the early stages of AD and result in increased glucocorticoid levels⁽³⁴⁾, which can lead to hippocampal damage as well as learning and memory deficits⁽³⁵⁾.

Importantly, the association between early life OD and cognitive decline was significant only among persons with at least one ϵ 4 allele at APOE. Some studies⁽²⁴⁾ but not all⁽³³⁾,

have similarly found that APOE is a strong moderator of early-life adversity on AD risk, suggesting that heightened genetic vulnerability for AD may define a subpopulation that is more vulnerable to the effects of early-life psychological stress. Neurodegenerative processes may begin decades before the onset of dementia, and the combination of OD as a stressor in the presence of genetic risk may accelerate this process. Support for this assertion can be found in research which concludes that prolonged exposure to stress results in memory decline in older, non-demented individuals who have an $\epsilon 4$ allele⁽³⁶⁾.

We also found that it was only those individuals experiencing OD, without the subsequent birth of another child, who had significantly faster cognitive decline. The birth of a “replacement child” may have provided the grieving parent with a new target for their parental affection, thus buffering the effects of their earlier loss⁽³⁷⁾.

A limitation to the current study is the high percentage of missing offspring data, particularly for men, suggesting that our findings may be somewhat more generalizable to women. Even so, our principal finding of faster late-life cognitive decline among individuals experiencing OD in young adult life was robust when analyses included those with missing offspring data in a separate category. To the extent that this “missing data” subgroup contained individuals who had experienced OD, our results would be a conservative estimate of effects. Another limitation is ethnic homogeneity, as the sample for the study is comprised almost exclusively of Caucasian individuals. A strength is that the study utilizes a population-based sample, with results that are more representative of the community than a clinical sample alone, such as one comprised of persons who seek medical evaluation or intervention in a memory disorders clinic. Another strength is the long period of follow-up, spanning up to 12 years. Finally, we used objective data to measure exposure to OD, rather than reliance on retrospective self-reports, known to have problems with recall bias.

Summary

This study provides evidence extending the adverse physical and mental health outcomes associated with parental bereavement to include faster cognitive decline in late life, a strong risk factor for eventual dementia. Additional research is warranted to examine the mechanism(s) is via chronic exposure to stress-related hormones, heightened risk for depression, less healthy lifestyle choices in bereaved parents, or other factors. Moreover, situational, intrapersonal, and interpersonal factors, as well as coping styles, interact to determine the ultimate outcome of a bereavement experience⁽³⁸⁾. Additionally, each of these children died for a reason, whether after a long illness, a sudden traumatic event, or other circumstance. The OD experience may also have coincided with other chronic stressors at the time of OD, possibly with weak social support system or other adverse contextual factors. Thus, a wide range of circumstances surrounding the death may explain the cognitive decline of the participant in later life. These factors likely interact in complex ways to impact bereavement outcomes. Further research should focus on manner of death, social support network of parent, and other circumstances surrounding the death of the child. Ultimately, such studies may inform interventions targeted at bereaved parents and parents of terminally ill children, to provide appropriate support to help buffer the stress associated with the death of a child.

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Figure 1.

Cognitive trajectory of the Modified Mini-mental State Exam for persons experiencing offspring death under the age of 31 years old vs. at some later age vs. not at all, stratified by presence vs. absence of $\epsilon 4$ allele at APOE.

Offspring Death with/without Replacement Birth

Figure 2.

Cognitive trajectory of the Modified Mini-mental State Exam as a function of offspring death experience (with or without subsequent birth of a “replacement child”)

Table 1

Demographic Summary of Participants by Prevalent Offspring Death

	Final Sample		Excluded from final sample	
	No OD n=2564 (58%)	1+ OD n=610 (14%)	p-value*	Missing Offspring Information n=1196 (27%)
Education (M, SD)	13.2, 2.7	12.7, 2.6	<.001	13.7, 3.4
Baseline Age, years (M, SD)	74.3, 6.7	76.6, 7.8	<.001	75.1, 6.5
Total # of offspring (M, SD)	3.2, 2.0	4.5, 2.2	<.001	-
Gender: Male (N, %)	879 (45.9%)	136 (7.1%)	<.001	875 (73.2%)
<i>APOE</i> ε4 carrier (N, %)	777 (57.6%)	187 (13.9%)	.866	372 (27.6%)
				.641

* p-values are from independent groups t-tests for comparisons of age, education and number of offspring; p-values are from χ^2 tests for comparisons of gender and *APOE* status; Groups being compared in first column of p-values is for participants with no OD vs. those with one or more OD (all had at least one offspring born), to address potential confounding; Groups being compared in second column of p-values is for participants in the final sample (combining no OD and 1+ OD groups) vs. those excluded from final sample due to missing offspring information, to address potential non-response bias

Table 2

Linear mixed models of Modified Mini-mental State Exam over 10 years of observation, as a function of various measures of Offspring Death experience (n=3,157)

Model #	Effect	Parameter estimate* (p-value) OD × Time	Parameter estimate (p-value) OD × Time ²
<u>OD during subject 17–30 yrs: F(2,1456)=3.41, p=.033 (linear); F(2,1137)=3.84, p=.022 (quadratic)</u>			
1	OD at subject age other than 17–30 yrs	0.13 (p=.433)	–0.03 (p=.056)
	OD at subject age 17–30 yrs	–0.50 (p=.016)	0.04 (p=.067)
<u>OD during subject 31–44 yrs: F(2,1438)=0.41, p=.663 (linear); F(2,1118)=0.09, p=.912 (quadratic)</u>			
2	OD at subject age other than 31–44 yrs	–0.002 (p=.938)	–0.004 (p=.881)
	OD at subject age 31–44 yrs	–0.14 (p=.365)	–0.007 (p=.679)
<u>OD during subject 45–64 yrs: F(2,1466)=0.49, p=.614 (linear); F(2,1147)=0.09, p=.919 (quadratic)</u>			
3	OD at subject age other than 45–64 yrs	–0.23 (p=.368)	–0.001 (p=.956)
	OD at subject age 45–64 yrs	–0.07 (p=.634)	–0.01 (p=.681)
4	<u>OD during subject 17–30 yrs: OD *APOE F(2,1540)=2.93, p=.054 (linear); F(2,1219)=3.40, p=.034 (quadratic)</u>		
5	<u>(e4 negative) subject 17–30 yrs: F(2,1073)=0.61, p=.546 (linear); F(2,829)=1.08, p=.342 (quadratic)</u>		
6	<u>(e4 positive) subject 17–30 yrs: F(2,420)=5.15, p=.006 (linear); F(2,331)=4.05, p=.018 (quadratic)</u>		
	OD at subject age other than 17–30 yrs	0.24 (p=.393)	–0.04 (p=.252)
	OD at subject age 17–30 yrs	–1.24 (p=.003)	0.12 (p=.012)
7	<u>OD during subject 17–30 yrs: OD *Gender F(2,1422)=0.04, p=.961 (linear); F(2,1094)=0.24, p=.784 (quadratic)</u>		
8	<u>OD with/without “replacement child” F(3,1561)=3.11, p=.025 (linear); F(3,1242)=1.59, p=.191 (quadratic)</u>		
	OD without replacement (after childbearing yrs)	0.15 (p=.289)	–0.014 (p=.315)
	OD with replacement	0.36 (p=.309)	–0.04 (p=.289)
	OD without replacement (during childbearing yrs)	–0.77 (p=.009)	0.05 (p=.118)
9	<u>OD with/without “replacement child”: OD *APOE F(3,1582)=0.28, p=.838 (linear); F(3,1248)=0.68, p=.566 (quadratic)</u>		
10	<u>OD with/without “replacement child”: OD *Gender F(3,1570)=0.92, p=.431 (linear); F(3,1228)=0.25, p=.860 (quadratic)</u>		
11	<u>Post-baseline OD **: F(1,1073)=2.31, p=.129 (linear); F(1,896)=3.15, p=.076 (quadratic); n=2594</u>		
	Incident OD	–1.38 (p=.129)	.117 (p=.076)

* Type III F tests are for omnibus test of overall effect of the given OD variable on rate and acceleration of cognitive decline. Single degree of freedom parameter estimates in the first/second column indicate how much slower (positive values) or faster (negative values) the rate/acceleration of cognitive decline is, on average, for subjects experiencing the given OD stressor.

** Among subjects without OD before baseline, the number of subjects experiencing OD after baseline was: 73 subjects, 73 subjects, and 70 subjects, occurring in first, second, and third post-baseline interval, respectively.