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Family Member Deaths in Childhood Predict Systemic Inflammation in Late Life

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Abstract

Biological and epidemiological evidence has linked early-life psychosocial stress with late-life health, with inflammation as a potential mechanism. We report here the association between familial death in childhood and adulthood and increased levels of high-sensitivity C-reactive protein (CRP), a marker of systemic inflammation. The Cache County Memory Study is a prospective study of persons initially aged 65 and older in 1995. In 2002, there were 1,955 persons in the study with data on CRP (42.3 percent male, mean [*SD*] age = 81.2 [5.8] years), linked with objective data on family member deaths. Using logistic regression, high (> 10 mg/L) versus low (< 10 mg/L) CRP was regressed on cumulative parental, sibling, spouse, and offspring deaths during childhood and during early adulthood, adjusted for family size in each period (percentage family depletion; PFD). Findings revealed PFD during childhood to be significantly associated with CRP (OR = 1.02, 95% CI [1.01, 1.04]). Individuals with two or more family deaths were 79 percent more likely to have elevated CRP than those with zero family deaths (OR = 1.79, 95% CI [1.07, 2.99]). Early adulthood PFD was not related to CRP. This study demonstrates a link between significant psychosocial stress in early life and immune-inflammatory functioning in late life, and suggests a mechanism explaining the link between early-life adversity and late-life health.

Introduction

The aging of the U.S. population underscores the public health importance of late-life health. In recent decades, biological and epidemiological evidence has implicated chronic stress in the etiology of late-life conditions. Although acute stress activates physiological

responses that enable survival, persistent stress can lead to adverse effects, including psychological disturbances such as depression (Caspi et al. 2010; Karg et al. 2011) and cardiovascular problems such as stroke (Maselko et al. 2009), atherosclerosis, and oxidative stress (Nation et al. 2011). In addition, chronic stress has been associated with mild cognitive impairment (Wilson et al. 2007) and Alzheimer's disease pathology (Dong et al. 2004; Sotiropoulos et al. 2011) and increased prevalence of Alzheimer's disease (AD; Wilson et al. 2005). Taken together, this evidence indicates the impact of chronic stress on a wide range of diseases of public health relevance.

To understand the link between chronic stress and late-life health, studies have turned to systemic and neuroinflammation as a potential mechanism. In reaction to chronic stress, the body can exhibit an immune response in which receptors on immune cells transcribe proinflammatory C-reactive proteins (CRPs; Iwata, Ota, and Duman 2013). There is evidence that the release of CRPs in response to stress can lead to an array of late-life morbidities. For instance, evidence indicates increased inflammation to be associated with excess risks for depression symptoms including anhedonia, reduced locomotor activity, lethargy, anxiety, sleepiness, weight loss, and diminished concentration (Kubera et al. 2011), and that blocking inflammation in response to stress by using anti-inflammatory medications can alleviate depression (Iwata, Ota, and Duman 2013). Such inflammation-mediated stress has also been linked to vascular conditions such as atherosclerosis, arterial stiffness, stroke, decreased cerebral blood flow (Nation et al. 2011), and coronary heart disease (Steptoe and Kivimaki 2012), which in turn are related to impaired neurogenesis and amyloid- β accumulation and aggregation, cognitive decline, and AD (Kubera et al. 2011; Nation et al. 2011; Wium-Andersen et al. 2013; Wyss-Coray 2006). This evidence implicates chronic inflammation as a mediator linking stress and late-life health and suggests the importance of examining inflammation as a marker of psychological adversity.

To examine the link between chronic stress and late-life health, epidemiological studies have investigated familial stressors, such as death of a loved one. According to stress process theory (Pearlin et al. 1981), the development of stress depends on background characteristics, such as age, subjective or objective stressors, and manifestations of stress. Deaths of first-degree relatives (i.e., children, parents, siblings) represent substantial objective stressors, including significant and lasting social disruption resulting from changes in financial security, living arrangements, and social status, as well as subjective stressors, such as increased fear and guilt. Indeed, familial death has been linked to markers of chronic stress, including increased cortisol levels and sympathetic nervous system activity; with increased psychological morbidity, including greater anxiety and depression (Hollingshaus et al. 2016); with cardiovascular problems, including increased heart rate, hypertension, coronary heart disease (CHD), and disruption of arterial plaques among persons with CHD (Buckley et al. 2010); and with late-life cognitive health, including risk of AD (Hatch, Schwartz, and Norton 2015), with evidence suggesting these bereavement-related changes to be mediated by systemic inflammation (Schultze-Florey et al. 2012).

Psychosocial stress experienced in childhood may be particularly detrimental for later life outcomes. Childhood may signal a period of vulnerability to social disruption relative to other developmental periods, such as emerging adulthood. In addition, it has been theorized

that childhood adversity may program one to greater stress reactivity throughout life (Marsland 2013), particularly among children with diminished coping resources. Consistent with this theory, early-life adversity has been linked with greater CRP levels and depression in adulthood (Caspi et al. 2010; Hollingshaus et al. 2016; Karg et al. 2011; Schrepf, Markon, and Lutgendorf 2014), with excess adult mortality (Smith et al. 2014), and with AD in later life (Moceri et al. 2000). Early parental death (EPD) has received particular attention as an early-life stressor. EPD has been linked with AD, with maternal death during adolescence and paternal death before age 5 associated with a doubling of AD risk (Norton et al. 2011), and death of either parent before age 11 associated with a four-fold increased risk for dementia (Whalley et al. 2013).

Though some studies have examined the association between EPD and morbidity, very few have examined the extent to which this risk factor predicts systemic inflammation in late life. Such an association would be consistent with the hypothesis of early-life adversity's effect on late-life health from mediation through systemic inflammation. This study reports secondary analysis of a 12-year population-based study of dementia and AD with 5,000+ participants age 65 and older linked with objective data on familial deaths in childhood. We hypothesized that greater exposure to familial deaths in childhood would be associated with higher levels of C-reactive protein, a marker of systemic inflammation.

Methods

Subjects

In 1995, we asked all permanent residents of Cache County, Utah who were aged 65 years or older to participate in the first wave of the Cache County Memory Study (CCMS; NIH R01-AG11380). A total of 5,092 individuals (90 percent) participated in the baseline interview, and in three follow-up triennial waves of data collection, there were 3,411 (wave 2), 2,324 (wave 3), and 1,481 (wave 4) individuals who participated, with attrition primarily due to mortality. Of the wave 3 participants, 2,186 donated a venous blood sample.

These subjects were linked to the Utah Population Database (UPDB), described below, in order to obtain objective data on family member deaths, including offspring. For 25 subjects, the UPDB data confirmed (from original genealogical records) that these individuals were nulliparous. For another 231 subjects nulliparity could not be confirmed due to missing offspring records. We retained the 25 nulliparous subjects and excluded from the sample the 231 with missing offspring data, for a final sample size in the current report of 1,955 subjects (89.4 percent of the 2,186 persons with blood samples).

Procedures

At the wave 3 screening interview, participants' current cognitive and health status was assessed and they were made aware that a blood sample was being requested. A separate visit for blood collection was conducted soon after the interview by a certified phlebotomist. All procedures were approved by the Institutional Review Boards of all collaborating institutions. UPDB usage was also approved by the Utah Resource for Genetic and Epidemiologic Research.

The Utah Population Database

The UPDB is a rich source of linked population-based information for demographic, genetic, epidemiological, and public health studies. It provides access to records or documents representing over eight million individuals (Smith et al. 2009; for more details see <http://healthcare.utah.edu/huntsmancancerinstitute/research/updb/>). The central component of the UPDB is a vast set of multigenerational Utah family histories. Genealogy records in UPDB have been linked to cancer records, birth and death certificates, driver's license records, and individual-level historic census records.

Measuring Family Deaths

The key predictor for this investigation is based on measures of deaths of first-degree relatives during two life-span periods: birth to age 17.9 (childhood) and age 18 to 30 (emerging adulthood). This was derived by examining every individual record in the UPDB linked to the index CCMS subject as having the relationship of biological father, mother, or child; spouse; or full sibling of the index subject. Because of the historic and on-going surveillance of deaths within the UPDB, we are able to identify the death date of the individual or the date at which he or she could be affirmed to be alive.

We acknowledge that a single death in a large family may be experienced differently than the death of a parent or sibling in a very small family. To that end, in order to measure deaths in the family that would adjust for the number of relatives at risk of death in a given period (childhood and emerging adulthood), the number of deaths of such relatives was computed, then divided by the number of family members alive during at least a portion of this period (i.e., including siblings and children born during the interval) and the quotient then multiplied by 100, to derive the percentage of a participant's family that was depleted due to death (percentage family depleted; PFD). Subjects confirmed to be nulliparous (1.3 percent), subjects lacking any sibling records (3.1 percent), and subjects lacking any marriage records (5.5 percent) were retained, thereby contributing zero to both numerator and denominator from offspring, siblings, and spouses, respectively. To investigate a possible dose-response relationship with CRP, the absolute number of deaths of family members was also coded trichotomously into zero, one, or two or more deaths. This coding was used because the number of subjects experiencing multiple deaths of family members diminished markedly after two family member deaths, resulting in insufficient statistical power to examine effect at numbers higher than this.

Measuring Systemic Inflammation

At the wave 3 interview, participants' current cognitive and health status was assessed, and a blood sample was requested. At a separate visit, generally within 6 months of that interview, a certified phlebotomist collected a nonfasting blood sample. Included in the lab values evaluated from these samples was high-sensitivity C-reactive protein (hereafter, "CRP"), a measure of systemic inflammation. In consideration of two potential mechanisms whereby early-life adversity may affect late-life health, we dichotomized CRP with two different cutoff values. Raw scores were dichotomized as low (≤ 10 mg/L) or high (> 10 mg/L) to define high systemic inflammation linked to greater distress and depression risk (Wium-Andersen et al. 2013). Additionally, raw scores were dichotomized as low (≤ 3 mg/L) or

moderate (> 3 mg/L) to define moderate systemic inflammation linked to greater cardiovascular and metabolic syndrome risk (Ridker 2003).

Covariates

Several covariates were included in the present analyses. Gender (coded 1 = female, 0 = male), age at wave 3 screening interview (in years), and education as self-reported in wave 1 (in years) were included. Also, because apolipoprotein E (APOE) modulates inflammatory responses in the etiology of neurodegenerative diseases such as Alzheimer's disease (Zhang, Wu, and Wu 2011), and has been found to independently predict CRP (Hubacek et al. 2010), the gene *APOE* was included, so as to examine the role of family deaths net of this genetic factor. *APOE* genotypes were determined from buccal DNA using polymerase chain reaction (PCR) amplification and a restriction isotyping method described by Saunders and colleagues (1993). *APOE* was dichotomized into zero versus at least one $\epsilon 4$ allele. Socioeconomic status (SES) was measured using the methodology of Nam and Powers (NP-SES; 1983). This method uses 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 (Smith et al. 2009). For the present study, we utilized subjects' offspring records, if available, to ascertain NP-SES for the adulthood period. Appearing on Utah birth certificates of the subject's offspring, the father's occupation and its corresponding NP-SES code were available; however, the mother's occupation was almost exclusively either blank or coded as "homemaker." Thus, when a male subject had offspring records, we utilized the maximum such value across all of his offspring, and when a female subject had offspring records, we utilized this same value (derived from her husband's occupations, since his occupation was almost exclusively what determined her adulthood socioeconomic status). When NP-SES was not available from offspring birth certificates, the subject's "usual occupation" (and corresponding NP-SES) appearing on the subject's death certificate was used. To assess acute illness that could affect inflammation on the day of the blood draw, we also included the white blood cell count (WBC) from the same blood draw that was available for a subsample of participants ($n = 1,314$), for an objective measure of acute infection.

Data Analysis

Using logistic regression, the dichotomous dependent variable, elevated CRP, was regressed on PFD from each life stage (childhood and emerging adulthood) with adjustment for covariates. Age and education were significantly associated with both PFD and CRP and were therefore included as covariates. Gender, *APOE* $\epsilon 4$ allele, and NP-SES were also included to assess the effect of these on CRP, as was white blood cell count for a subsample of persons for whom this was available. For each life stage in which PFD significantly predicted elevated CRP, CRP was regressed on the absolute number of family member deaths, coded trichotomously (zero, one, or two or more deaths), in order to investigate a possible dose-response relationship. In addition, PFD from each life stage was modeled simultaneously, so as to test for the independent effects of familial death at each stage. SPSS version 20 was used in all analyses.

Results

Among the 1,955 subjects, 57.7 percent were female, 99.7 percent white, mean (*SD*) age was 81.2 (5.8) years, and mean (*SD*) education was 13.5 (2.8) years (see Table 1). Having no familial deaths or one familial death during childhood was common ($n = 1,268$ [64.9 percent] and $n = 507$ [25.9 percent]), whereas having two or more familial deaths during childhood was less common ($n = 180$ [9.2 percent]). A similar pattern was found for familial death during emerging adulthood: zero family deaths: $n = 1,364$ (69.8 percent); one family death: $n = 470$ (24.0 percent); two or more family deaths: $n = 121$ (6.2 percent). Exposure to familial death was unrelated across periods, in that percentage familial loss during childhood was not correlated with percentage loss in adulthood ($r = .002$, $p = .92$). There were 178 (9.1 percent) participants with high CRP (above 10 mg/L), and 881 (41.5 percent) with moderate CRP (above 3 mg/L). These percentages are similar to national estimates of 13 percent for high CRP and 47 percent for moderate CRP, based on the National Health and Nutrition Examination Survey (NHANES 1999–2002; Woloshin and Schwartz 2005). Bivariate exploratory analyses revealed *APOE* $\epsilon 4$ allele and high education to be associated with high CRP ($\chi^2 = 4.14$, $p = .04$ and $t = 2.02$, $p = .04$), and high white blood cell count and high percentage family depletion during childhood to also be associated with high CRP ($t = -5.12$, $p < .001$ and $t = -3.25$, $p = .001$). Results were similar for moderate CRP, with the exception that female gender was associated with moderate CRP ($\chi^2 = 9.78$, $p = .002$), while percentage family depletion during childhood was not associated with moderate CRP (see Table 1).

As shown in Table 2, after controlling for covariates, PFD during childhood was significantly related to high CRP, with every 1 percent increase in PFD being associated with a 2 percent increase in odds of having elevated systemic inflammation in late life (OR = 1.02, 95% CI [1.01, 1.04]). In contrast, PFD during adulthood was not significantly related to CRP (OR = 0.99, 95% CI [0.97, 1.02]). In order to adjust the effect of PFD during childhood for any acute infection on the day of the blood draw, and for familial deaths occurring later during adulthood, we re-ran an additional model with white cell count (WBC) as another covariate (in the subsample of $n = 1,314$ with WBC data) and a model with PFD during adulthood as a covariate, and found the effect of deaths during childhood to be robust to these additional adjustments (OR = 1.02, 95% CI [1.004, 1.04] and OR = 1.02, 95% CI [1.009, 1.04], not shown in Table 2).

In a separate model using absolute number of childhood family member deaths trichotomized into three groups, a greater number of deaths was associated with greater risk for high CRP (omnibus $p = .06$). Specifically, while participants experiencing a single death were no more likely to have high late-life CRP than those with zero deaths (OR = 1.30, 95% CI [.89, 1.89]; see Table 3), those experiencing two or more deaths had 79 percent greater probability of high CRP (OR = 1.79, 95% CI [1.07, 2.99]).

When the above models were re-run for moderate CRP, which included a much higher proportion of the sample in this outcome category, PFD was not significantly related to CRP (OR = 1.004, 95% CI [0.995, 1.01] for childhood PFD and OR = 1.00, 95% CI [0.99, 1.02] for adulthood PFD; see Table 2). Findings for moderate CRP were also not significant for

absolute number of childhood family deaths (single death: OR = .87, 95% CI [.69, 1.09]; two or more deaths: OR = 1.22, 95% CI [.86, 1.72]; see Table 3).

Discussion

Our study has shown that deaths of first-degree relatives during childhood—a highly salient form of psychological adversity—were associated with elevated systemic inflammation in late life. Psychological stress is a common occurrence in everyday life, but repeated stressful experiences may be a causal factor in illnesses of the central nervous system. The immune response can detect diverse danger signals and produce the accompanying immune-inflammatory reactions, with the potential for influence on brain and peripheral systems (Iwata, Ota, and Duman 2013). The stress/inflammation association may arise from psychological stress promoting vascular inflammation (Lu et al. 2013), and can lead to diminished late-life health, such as increases in depression (Iwata, Ota, and Duman 2013) and AD risk (Nation et al. 2011).

While we found elevated inflammation associated with deaths during childhood, the same adversity in young adulthood was not related to late-life inflammation. Deaths of parents and siblings during childhood may be more devastating than deaths at a later age and are sources of high levels of chronic distress. Thus, our findings are consistent with those of Appleton et al. (2011), who found that childhood emotional functioning, as measured by distress proneness and inappropriate self-regulation at age 7, predicted significantly higher young adulthood CRP levels. Our findings extend this association to inflammation in late life. Schrepf, Markon, and Lutgendorf (2014) similarly observed that childhood trauma was associated with elevated adulthood CRP levels, with compensatory emotional eating as a coping mechanism. Childhood adversity may have a “programming” effect on an inflammatory phenotype of higher levels of systemic inflammation and increased health risk in later life (Marsland 2013). Elevated CRP has been observed in children living in neighborhoods with high levels of poverty or crime, suggesting a psychosocial pathway indicative of early development of cardiovascular risk due to chronic stress from a socially disordered environment during childhood (Broyles et al. 2012). Early parental death deprives children of the emotional support of the deceased parent and the concomitant experience of a distressed surviving parent, often with compromised ability to tend to the children’s psychological needs. In some children, there is the added fear or sense of guilt that they were in some manner responsible for the parent’s death. The death of a sibling often presents a different kind of adversity in the loss of a lifelong companion and confidante. Our findings that a single death during childhood did not increase risk of elevated CRP in late life, but multiple deaths did, suggests that exposure to extreme psychological hardship due to the deaths of multiple members of the nuclear family may have exacerbated vulnerabilities derived from the initial death (assuming that the deaths were not simultaneous), increasing the likelihood of lifelong programming for higher inflammatory response to stress and higher risk for late-life morbidities. While childhood familial deaths predicted elevated CRP as defined by the higher cut-point associated with depression risk, it did not predict elevated CRP as defined by the lower cut-point associated with risk for cardiovascular and metabolic syndrome, the latter likely including an etiologically more diverse group. These results are consistent with the hypothesis that

childhood adversity (in this case through family deaths) exerts its effects on late-life inflammation more clearly through psychological vulnerabilities and less so through a much broader range of life experiences that result in late-life cardiovascular disease risk. Additional research examining and contrasting full mediation models will be needed to more fully explicate these associations. For instance, models testing inflammation as a mediator in the link between psychological adversity and depression could be compared to those testing inflammation as a mediator of psychological adversity and cardiovascular disease. Such investigations would further explicate the links between adversity-derived inflammation and subsequent cardiovascular disease or depression.

The association we found between childhood family deaths and late-life systemic inflammation was robust to adjustments for covariates, including gender, education, *APOE* status, age, adulthood socioeconomic status, and family size (siblings in nuclear family and offspring in adult family). Thus, while the effect we observed was not confounded with any of these factors, the phenomenon is likely quite complex, and there are likely other unmeasured variables that mediate this relationship.

Limitations of the present study include the absence of data on the subjective stress experience of our cohort members during childhood at the time of the loss of family member(s), available psychosocial coping resources at the time, and individual personality traits or late-life medical comorbidities that could also have affected elevated CRP levels. Additionally, the sample is almost exclusively Caucasian, which may limit generalizability of our findings. Additionally, we did not have a sample sufficiently large to compare the effects of parental death with those of sibling death. Given that these exposures can entail different effects on the stress process, future studies would benefit from such an analysis.

The strengths of the study include the objective measurement of the exposure to family member deaths through the use of linked vital records available in the UPDB. Because 99.9 percent of CCMS cohort members were linked to the UPDB, we were able to eliminate recall bias, of particular concern among older respondents or those with impaired memory. Another strength is that the study utilizes a population-based sample, which is likely to be more representative of the community than a clinical sample. Whereas most studies published to date linking childhood adversity to adulthood systemic inflammation measure the latter in early adulthood, our study extends this association to late life, providing a rare examination of lifelong effects of early adversity.

The present study provides a foundation for further study of mechanisms linking early-life adversity to late-life health, in particular, systemic inflammation. Future investigations should include the examination of lifetime depression history as a marker of maladaptive stress coping, a possible mediator. Additionally, lifestyle behaviors (smoking, alcohol consumption, physical activity level, diet quality) and self-reported social support, both assessed in the CCMS cohort 7 years prior to CRP measurement, could be examined for moderation through possible stress-buffering effects of healthier lifestyles. Finally, capitalizing on the richness of the UPDB, it is possible to derive measures of additional psychosocial stressors across the adult life span (e.g., offspring death; see Greene et al.

2014) to facilitate the examination of differential, additive, and possibly interactive effects of exposure to chronic stressors in childhood versus adulthood.

In summary, the present study has demonstrated that childhood adversity in the form of family member deaths (especially multiple deaths) is predictive of systemic inflammation decades later in late life, and it has done so with objective measures of familial death. While additional studies are needed to further explicate the mechanisms responsible for this observed effect, the present study with its unique data resources provides evidence consistent with lifelong residual health effects of early-life adversity.

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Table 1.

Demographics and percentage family depletion by elevated high-sensitivity C-reactive protein.

	Overall	Elevated hsCRP: 10 mg/L*			Elevated hsCRP: 3 mg/L**		
		< 10 n = 1,777	10 n = 178		< 3 n = 1,144	3 n = 811	
Age	81.2 (5.8)	81.1 (5.7)	82.0 (6.1)	$t = -1.86$	81.2 (5.8)	81.2 (5.7)	$t = -0.20$
Female gender	1129 (57.7%)	1018 (57.3%)	111 (62.4%)	$\chi^2 = 1.71$	627 (54.8%)	502 (61.9%)	$\chi^2 = 9.78^{**}$
APOE e4	628 (32.1%)	583 (32.9%)	45 (25.4%)	$\chi^2 = 4.14^*$	405 (35.5%)	223 (27.6%)	$\chi^2 = 13.6^{**}$
Education	13.5 (2.8)	13.6 (2.8)	13.1 (2.6)	$t = 2.02^*$	13.7 (2.9)	13.2 (2.6)	$t = 3.97^{**}$
NP-SES	61.8 (22.3)	62.1 (22.3)	59.0 (22.4)	$t = 1.65$	62.6 (22.5)	60.8 (22.0)	$t = 1.59$
White blood cell count	6.7 (2.8)	6.6 (2.8)	8.0 (2.8)	$t = -5.12^{**}$	6.4 (2.9)	7.1 (2.6)	$t = -4.11^{**}$
Percentage family depleted, birth-18	6.9 (11.3)	6.7 (10.9)	9.5 (13.9)	$t = -3.25^{**}$	6.7 (10.8)	7.2 (11.9)	$t = -0.89$
Percentage family depleted, 18-30	4.2 (7.5)	4.2 (7.5)	3.9 (6.7)	$t = 0.41$	4.0 (7.0)	4.4 (8.0)	$t = -1.13$

Note. Means and standard deviations reported for continuous variables, frequency number and percentage reported for discrete variables.

Percentage family depleted = $100 \times (\text{no. of family member deaths} / \text{no. of family members})$.

* Indicative of higher risk for depression (Wium-Andersen et al. 2013).

** Indicative of higher risk for cardiovascular disease (Ridker 2003).

* $p < .05$, ** $p < .01$.

Table 2.

Logistic regression models of clinically elevated high-sensitivity C-reactive protein regressed on “percentage family depleted” (due to death of family members) during childhood, using thresholds indicative of two possible mechanisms; $n = 1,955$.

	Elevated hsCRP defined as: 10 mg/L**		Elevated hsCRP defined as: 3 mg/L***	
	OR	95% CI	OR	95% CI
Percentage family depleted*	1.02	1.01, 1.04	1.004	.995, 1.01
Covariates				
Age	1.01	.99, 1.04	1.00	.98, 1.02
Gender	1.22	.87, 1.72	1.34	1.09, 1.63
<i>APOE</i> ε4	.64	.44, .94	0.68	.55, .84
Education	.97	.90, 1.04	0.94	.90, .98
NP-SES	.998	.99, 1.01	1.00	0.996, 1.01

Note.

* Percentage family depleted = $100 \times (\text{no. of family member deaths/no. of family members})$.

** Indicative of higher risk for depression (Wium-Andersen et al. 2013).

*** Indicative of higher risk for cardiovascular disease (Ridker 2003).

Table 3.

Logistic regression models of clinically elevated high-sensitivity C-reactive protein regressed on absolute number of childhood family member deaths, using thresholds indicative of two possible mechanisms; $n = 1,955$.

	<u>Elevated hsCRP defined as: 10 mg/L *</u>		<u>Elevated hsCRP defined as: 3 mg/L **</u>	
	OR	95% CI	OR	95% CI
Family Member Deaths ***				
1	1.30	.89, 1.89	.87	.69, 1.09
2 or more	1.79	1.07, 2.99	1.22	.86, 1.72
Covariates				
Age	1.01	.98, 1.04	1.0	.98, 1.02
Gender	1.21	.86, 1.71	1.33	1.09, 1.63
<i>APOE</i> ϵ 4	.64	.44, .94	.68	.55, .84
Education	.97	.91, 1.04	.94	.90, .98
NP-SES	1.0	.99, 1.01	1.0	.996, 1.01

Note.

* Indicative of higher risk for depression (Wium-Andersen et al. 2013).

** Indicative of higher risk for cardiovascular disease (Ridker 2003).

*** Reference category: 0 family member deaths.