Published in final edited form as:

Biodemography Soc Biol. 2016 ; 62(1): 105–125. doi:10.1080/19485565.2016.1138395.

DIFFERENTIAL VULNERABILITY TO EARLY-LIFE PARENTAL DEATH: THE MODERATING EFFECTS OF FAMILY SUICIDE HISTORY ON RISKS FOR MAJOR DEPRESSION AND SUBSTANCE ABUSE IN LATER LIFE*

Michael S. Hollingshaus, Ph.D.* , Hilary Coon, PhD, Sheila E. Crowell, PhD, Douglas D. Gray, MD, Heidi A. Hanson, PhD, Richard Pimentel, MSCS, and Ken R. Smith, PhD

Abstract

Only a portion of those exposed to parental death in early life (PDE) develop behavioral health disorders. We utilized demographic pedigree data from the Utah Population Database to test for differential vulnerability to PDE by creating a risk score of familial susceptibility to suicide (FS) at the population level. Using logistic panel regression models, we tested for multiplicative interactions between PDE and FS on the risks of major depressive disorder (MDD) and substance abuse (SA), measured with Medicare claims, after age 65. The final sample included 155,983 individuals (born 1886 through 1944), yielding 1,431,060 person-years at risk (1992 through 2009). Net of several potential confounders, including probability of survival to age 65, for females we found an FS $\times$ PDE interaction, where PDE and FS as main effects had no impact but jointly they increased MDD risk. No statistically significant main or interactive effects were found for SA among females, or for either phenotype among males. Our findings are consistent with a differential vulnerability model for MDD in females, where early-life stress increases the risk for poor behavioral health only among the vulnerable. Furthermore we demonstrate how demographic and pedigree data might serve as tools for investigating differential vulnerability hypotheses.

Keywords

Mental health; Biobehavioral health; Early origins of health; Genetics; Life course

Introduction

Adult behavioral health disorders are complex phenotypes with multifactorial causes. Exposure to early-life traumas might alter the developmental trajectory of a child, increasing risk for later-life behavioral health disorders. One such potential trauma is experiencing the death of a parent in early-life (PDE). Not everyone exposed to PDE develops a behavioral health disorder, and it is hypothesized that such an outcome may only occur among those with inherited vulnerabilities to stress (Agid et al. 1999). However, obtaining a sufficient

* Michael S. Hollingshaus, Department of Sociology, University of Utah, 380 S 1530 E Rm 301, Salt Lake City, UT 84112, msh9@utah.edu.

sample size to measure interactions between inherited and environmental exposures can be a daunting task (Manolio, Bailey-Wilson, and Collins 2006).

Accordingly, this paper has two key objectives. First, we demonstrate how the sample size problem might be addressed by linking ubiquitous vital records with demographic pedigree data. Since most psychiatric conditions elevate suicide risk (American Psychiatric Association 2013), we utilize the Utah Population Database to reconstruct family histories of suicide to approximate a familial risk score for psychopathology. Second, we test for differential vulnerability to PDE by estimating how associations with later-life major depressive disorder (MDD) and substance abuse (SA) are moderated by familial suicide susceptibility (FS). Since this study relies upon pedigree data, to maintain clarity we frequently identify the individual at risk of the PDE exposure and associated health outcomes as the “ego”. For convenience, a table of acronyms is included as Table 1.

Background

Parental Death in Early Life

Empirical research has linked early parental death to later-life behavioral health risk (Nickerson et al. 2013). PDE may affect later-life health through physiological change or “scarring” (Preston, Hill, and Drenth 1998, 1232). The causal argument primarily invokes attachment theory, where separation from a parent during early sensitive stages distresses the offspring (Bowlby 1980). Hypothesized biological mechanisms leading to compromised behavioral health include conditioning of the hypothalamic-pituitary-adrenal (HPA) axis, inflammatory response patterns, and the sympathetic nervous, immune and neuroendocrine systems (Beauchaine et al. 2011, Rostila, Saarela, and Kawachi 2013). These changes may further pose risks for behavioral health through disorganized attachment, impulsivity, aggression and asociality (Bakermans-Kranenburg and Van IJzendoorn 2007, Beauchaine et al. 2011, Brent et al. 2004). Physiological scarring may be intensified as the initial stressor of parental death proliferates into a series of secondary social stressors (Pearlin, Aneshensel, and Leblanc 1997), including decreased social integration (Hollingshaus and Smith 2015) that might accumulate throughout the life-course (Dannefer 2003). These persistent social deprivations may “get under the skin” to affect health (Hertzman and Boyce 2010, 329).

Inherited Vulnerabilities

There is considerable heterogeneity of responses to the adverse effects of early-life stress (Hertzman and Boyce 2010). Differential vulnerability to early-life stress—including PDE (Agid et al. 1999)—is one model proposed as a possible explanation for inter-person variation in resultant phenotypes (Belsky and Pluess 2009). This hypothesis suggests that a vulnerability and a pertinent type of stressor synergistically compound to increase the likelihood of phenotypic expression. Research has shown heritable risks for MDD and SA (Brent et al. 2004), which might affect behavioral health by increasing vulnerability to stress (Caspi et al. 2003, Pishva et al. 2014).

Genetic transmission has been proposed as a possible mechanism by which such vulnerability might be intergenerationally propagated (Agid et al. 1999). Waddington's Epigenetic Landscape (McClearn, Vogler, and Hofer 2001, Waddington 1957) visualizes the genome as a topography of possibilities for phenotypic expression. PDE might therefore alter patterns of gene expression, as directed by the genotype, to forge a poor behavioral health phenotype. The counterfactual argument is that in the absence of a risky genotype, PDE would have little to no effect upon one's behavioral health. Several genes have been implicated for behavioral health disorders (Flint and Kendler 2014, Rietschel and Treutlein 2013), and recent research suggests these may interact with early-life stress to increase behavioral health risk (Pishva et al. 2014, van Winkel et al. 2014).

However, genetic inheritance is but one mechanism whereby familial susceptibility may be intergenerationally propagated. Heritability in general has been linked to major depression and substance abuse, and might reflect socialized patterns or traditions of coping (Brodsky et al. 2008). For example, poor coping behaviors such as alcohol consumption might be learned from parents (Mares, Lichtwarck-Aschoff, and Engels 2013). Conversely, protective behaviors, such as marriage (Denney et al. 2009), may also be partially heritable (Horn et al. 2013).

Despite recent work on differential vulnerability, we have been unable to identify studies that examine whether behavioral health phenotypes following PDE vary by inherited susceptibility, though such an interaction has been proposed (Agid et al. 1999). Neither have we identified any study examining early-life interactions on outcomes measured in later adulthood, despite indications that heritable factors are still impactful at advanced ages (Kim et al. 2014, Levine et al. 2014). We suspect the dearth of inquiry may partially be due to difficulties in procuring sufficient data.

Measuring Vulnerability

Methods for studying vulnerability-environment interactions often suffer from certain limitations. Frequently, risky genotype is measured as a dichotomous construct; but for complex quantitative traits, interval-level measures allow for finer granularity of measurement, and these combinations of individual variants are more likely contribute to environmental vulnerability than a single variant alone (Boardman et al. 2014). Genetic risk scores have had some success in addressing this issue (Belsky and Israel 2014). However, obtaining adequate statistical power for detecting interactions may also require large sample sizes (Manolio, Bailey-Wilson, and Collins 2006) and whole-genome sequencing can be expensive. Genetic studies can also only adequately measure genetic vulnerability, and might miss other important socially-determined vulnerabilities.

Whether one has a family history of susceptibility is an alternative approach that also suffers from potential measurement issues. How to determine the family history of a given phenotype is not straightforward and may rely upon heuristic devices—such as whether or not a parent expressed the given phenotype—thereby compromising inter-study reliability. Such an approach also fails to account for potential genetic influences (Avenevoli and Merikangas 2006).

Here we utilize a measure of susceptibility called the Familial Standardized Incidence Ratio (FSIR). This construct is based in the methods of population genetics and has been previously proposed for examination of familial $\times$ environment interactions (Kerber 1995). The level of measurement is interval, constituting a risk score that could be more appropriate for complex phenotypes (Belsky and Israel 2014) and increase statistical power (Ragland 1992). It can be constructed at the population level in the absence of biospecimens, thereby boosting the sample size to further increase statistical power (Manolio, Bailey-Wilson, and Collins 2006). This risk score also encapsulates both genetic and non-genetic modes of familial transmission.

The details of construction are outlined in the Methods section below. However, we here note a couple of challenges this risk score presents. First, to calculate the family history of a phenotype using all available information, one should use the information available from the ego. If the ego expresses MDD, this should be used in the calculation of the familial rate. Predicting the risk of MDD from that measure then introduces a possible tautology. This can be addressed by using a proxy measure, such as suicide. Another argument for approximating familial psychopathology with suicide is that extended pedigrees may be necessary to obtain reliable FSIR estimates (Kerber 1995), and suicide measures can be reliably obtained from death certificates (Pescosolido and Mendelsohn 1986) at the population level.

Method

Data

The Utah Population Database (UPDB) served as the basis for the data. The UPDB is a premiere and unique genealogical database containing information on nearly eight million individuals. It includes genealogies and vital records of the founders of Utah from the 19th century to present time, as well as their descendants. It is annually updated with records of Utah birth and death certificates, driver licenses, and extensive medical and vital records. The database now includes over two million Utah birth certificates and around 800,000 death certificates spanning almost a century. The Utah Resource for Genetic and Epidemiologic Research (RGE) administers access to these data through a review process of the project proposal, and all research requires human subjects and RGE approval (Wylie and Mineau 2003). The confidentiality of individuals represented in these records is maintained based on agreements between RGE and the data contributors. While UPDB has shown associations of early parental death with morbidity and mortality (Smith et al. 2014, Smith et al. 2009, Norton et al. 2011, Hollingshaus and Smith 2015), the potential impacts of differential vulnerability have not been systematically tested.

Sample

From the full UPDB, we identified a *Selection Sample* of 434,995 ego-mother-father triads that relied on several eligibility and exclusion criteria. All members of the trio had known birth years and none were polygamous. The ego was born between 1886 and 1944, which is the latest year an ego could be born and still be at least age 65 in our CMS records. The ego was not adopted, the father had not died prior to ego's birth, and the father and mother were

deceased prior to the ego's 18th birthday or had follow-up data up to ego's 18th birth-year. These restrictions are consistent with prior UPDB studies (Hollingshaus and Smith 2015). Of the egos in these triads, 332,176 survived and had follow-up information to at least age 65. Eligible egos were required to link with FS measures (detailed below) and Centers for Medicare and Medicaid Services (CMS) Medicare records, yielding a *Final Sample* of N=155,983 egos. Data were then placed into panel person-year format with an observation for each complete year each ego was enrolled in Medicare parts A and B during the years 1992 through 2009 yielding 1,431,060 person-years of data. It was during this later-life time period the individual was at-risk for a claim of major depressive disorder or substance abuse. Follow-up for any given individual could begin in one of three ways. First, an individual could be age 65 or older in 1992, and have the first wave of follow-up begin in that year. Alternatively, an individual could turn age 65 during 1992-2009, with follow-up beginning at the year age 65 was achieved. Third, for an individual that met one of the previous criteria, but were not yet enrolled in Medicare, follow-up began in the first year of complete enrollment as described above.

Key Variables

Major Depression and Substance Abuse—Diagnoses on Medicare claims were the basis for our measures of MDD and SA. ICD9 codes obtained from CMS files were used to identify episodes of MDD (ICD9 296.2X, 296.3X) and SA (303.XX, 305.0X, 291.XX, 304.XX, 305.2X-305.9X). The presence of at least one claim for each diagnosis in a given year indicated the presence of the condition for that person-year. We note that CMS records require a claim be submitted, so there will be some measurement error in that some conditions may go untreated or be covered through a mechanism outside Medicare. Nevertheless, such records have been used to great effect in previous studies because of the rich information they provide, and we suspect any findings are biased towards the null.

Familial Susceptibility for Suicide (FS)—FS was derived from Familial Standardized Incidence Ratios (Kerber 1995), which measures the relative risk of a phenotype for each pedigree relative to that expected for the population, standardizing by age and sex and weighting by the probability the founder shared a gene with a pedigree member at a given locus. We identified all individuals who did not have a parent in the dataset and treated them as founders of the Utah population. From these founders, we identified pedigrees with at least 1,000 members and at least two suicides; the latter condition was imposed as a marker indicating that the pedigree members link to death certificates and are not unusually protected against suicide. Consistent with prior research, suicides used for calculating FSIR's were identified from death certificates spanning 1904-2010 in UPDB with ICD codes E963, E970-E979 (ICD6-7), E950-E959 (ICD8-9), and X60-X84, Y87.0, U03 (ICD10) or a manner-of-death of suicide recorded directly on the certificate (Hollingshaus and Smith 2015).

We calculated FSIR's for each founder. For this analysis, we simplified Kerber's (1995) fourth equation (p. 294) from

$$FSIR_i = \frac{\sum_{j=1}^J c_j f(i, j)}{\sum_{k=1}^K \sum_{j=1}^J t_{jk} \lambda^k f(i, j)} \quad (1)$$

to

$$FSIR = \frac{\sum_{j=1}^J c_j f(j)}{\sum_{k=1}^K \sum_{j=1}^J t_{jk} \lambda^k f(j)} \quad (2)$$

where in both Equations 1 and 2, k was one of 14 age-sex-specific strata (age categories 0-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-120 for each sex); c_j was 1 if the j^{th} member of the pedigree died by suicide, 0 otherwise; t_j was the age at which the j^{th} member of the pedigree was last known alive in Utah (i.e., number of person-years person j was at risk for suicide); and λ^k was the incidence of suicide per person-years in stratum k of the reference population. In Equation 1, i was an indicator for each individual in the pedigree (as was j), and $f(i, j)$ was the kinship coefficient (Malecot 1948) between each person in the pedigree. To calculate familial, or pedigree-specific, susceptibility, we only calculated the FSIR for the founder, thus simplifying to Equation 2 where $f(j)$ was the kinship coefficient between the founder and each descendent in the pedigree.

We then considered only those founder FSIR's greater than 1.0. This avoided possible data issues surrounding family-specific underreporting of suicide in vital records (Timmermans 2005). The *Final Sample* of 155,983 egos linked to 5,262 unique founders. The founder's FSIR then determined the *familiality* of suicide risk for that *pedigree*. The distribution of FSIR's for pedigrees is shown in Figure 1. This approach often yielded more than one FSIR for each ego. Therefore, we used the mean of all FSIR's for each ego as that ego's familial suicide susceptibility. The distribution of FS for the *Final Sample* is displayed in Figure 2.

Parental Death in Early Life (PDE)—Parental death is treated as a continuous variable, where the ego could experience the death of zero, one, or two biological parents previous to reaching age 18. This operationalization theoretically measures a gradient of exposure, and empirically improves statistical power.

Control Variables

Time-invariant—Age at first observation in the Medicare claims data was controlled for, because some individuals aged into Medicare before 1992, our first year of measurement. Early-life socioeconomic status (SES) was measured as the greater of the biological mother's or father's *Nam Powers score* (Nam and Powers 1983) obtained from the occupation recorded on the parent's death certificate, consistent with previous research linking PDE to behavioral health disorders (Niederkrötenhaler et al. 2012). This score ranges from 1-99, with higher values representing higher SES. We recoded SES into six categories: four quartiles; a special category for farmers (Nam Powers score 40), as they represented a large

and unique proportion of the sample; and a category for missing data. Since our latest cohort of egos was born in 1944, the parents are a nearly extinct cohort, and the missing data therefore mostly represent those for whom Utah death certificates were unavailable. *Number of siblings* was a four-category variable with one category for egos with no siblings, and the remainder divided into tertiles. *Parity* was a four-category variable with one category for egos that were nulliparous (or had missing child data), and the remainder divided into tertiles. We controlled for *the number of FSIRs (i.e., UPDB founders)* we obtained for each individual during FSIR construction (see above); and for *the number of complete years enrolled* in Medicare parts A and B (which included a 12 month period, or a partial period if they aged in or died during the year), as this affected the at-risk period for having a claim. While Medicare Part A generally covers hospital, nursing, and hospice care; Part B covers such claims as ambulance, medical equipment, and mental health. Therefore, we required these enrollments to ensure the necessary data were available. If an individual was enrolled in a Health Maintenance Organization (HMO), we unfortunately did not have the necessary data. Finally, time-invariant controls included a statistic called the *Inverse Mills ratio* to account for sample selection (see below) before age 65 via a Heckman two-step selection equation (Fu, Winship, and Mare 2004).

Time-varying—*Marital status* was a categorical variable measured as never married, currently married, and currently widowed. We also included later-life “own” socioeconomic status (SES) by using a measure of *dual-eligibility* for both Medicare and Medicaid, the latter being a means-tested program indicating low income. CMS policy changes occurred in 1998 and 2006 so accordingly we controlled for time periods 1992-1997, 1998-2005, and 2006-2009 with dummy variables.

Non-Random Sample Selection—The inverse Mills ratio (IMR) was used to measure possible selection and is a covariate in the final models reported here. Selection was a particular concern because we required that egos survive to age 65, and therefore the most frail would be culled from the sample. Note that individuals from very early cohorts were possibly required to live even longer than 65 to be seen at our earliest claims data in 1992, but controlling for year of ego's birth addressed this issue.

To calculate the IMR, we estimated a probit model where the dependent variable was a dichotomy, assigned a value of 1 when the ego survived to at least age 65, and 0 otherwise (Fu, Winship, and Mare 2004). Variables included in the probit were *year of ego's birth*, *maternal and paternal age* at ego's birth, whether the ego was *born in Utah*, and greater of father's and mother's *Nam Powers score* (coded as described above). Also included was an indicator of ego's *baptism* into the Church of Jesus Christ of Latter-day Saints by age nine, which is considered normative for children born into that faith (Lyon, Gardner, and Gress 1994).

Analytic Plan

First, we examined descriptive statistics, with an emphasis on FS-related variables. Next, we estimated sex-specific Heckman selection equations for the *Selection Sample* of 434,995 egos that survived to at least age 65 and generated IMR's for all egos. Then, utilizing the

Final Sample of 155,983 egos, we estimated sex-specific logistic panel regression models with mixed (fixed and random) effects for each behavioral health disorder (MDD and SA), yielding four models. Logistic regression enables unbiased testing of gene-environment ($G \times E$) interactions (Mukherjee et al. 2012). We extended this $G \times E$ methodology to familial-environment ($F \times E$) interactions, as they are conceptually similar phenomena. Models were estimated via the *xtlogit* command in Stata/SE 10.0, using with the *re* (or “random effects”) option. This allowed a random effect for each individual to account for within-individual dependencies over time. Since we are not interested in interpreting the intercepts or random effects, we do not consider them in detail. Interested readers are directed to Allison (2009). We now turn our attention to those portions of the model that directly address the research question. Each model included PDE, FS, $FS \times PDE$, and all controls. Continuous variables were centered about their respective grand means to address multicollinearity concerns in the presence of interaction effects and facilitate the interpretation of main effects (Dearing and Hamilton 2006).

While the logistic model is technically non-linear, an underlying linear model is implied (Allison 2009), and may be simply written as (subscripts to represent individuals are not shown for simplicity):

$$Y = \beta_0 + \beta_{PDE} PDE + \beta_{FS} FS + \beta_{FS \times PDE} FS \times PDE + \beta_C CONTROLS + U \quad (3)$$

where Y is the logit of the respective behavioral health disorder, β_{PDE} and β_{FS} are “main” effects of PD and FS, $\beta_{FS \times PDE}$ represents the multiplicative $F \times E$ interaction of interest, β_0 is the intercept, and the individual-specific random intercept is $U \sim N(0, v^2)$ — v being the variance of the unexplained heterogeneity.

To graphically illustrate the nature of the $F \times E$ interaction, and to assist with interpretation, we then graphed the linear marginal effect of PDE upon the logit of the respective behavioral health disorder over the range of FS in the sample, along with 95% confidence intervals (Brambor, Clark, and Golder 2006). This approach can help identify regions of significance that are useful for disentangling $G \times E$ patterns (Roisman et al. 2012). The marginal effect (ME) of parental death in early life, conditional upon familial suicide susceptibility, may be derived from Equation 3, and written as a vector of marginal β estimates

$$ME(PDE|FS) = \frac{\partial Y}{\partial PDE} = \beta_{PDE} + \beta_{FS \times PDE} FS \quad (4)$$

with a vector of marginal standard errors

$$\hat{\sigma}_{\frac{\partial Y}{\partial PDE}} = \sqrt{var(\hat{\beta}_{PDE}) + FS^2 var(\hat{\beta}_{FS \times PDE}) + 2FS cov(\hat{\beta}_{PDE}, \hat{\beta}_{FS \times PDE})} \quad (5)$$

calculated over the range of FS values, where $var(.)$ and $cov(.)$ are the variances and covariances of the estimated model parameters (Brambor, Clark, and Golder 2006), which

we obtained using Stata's *estat vce* post-estimation command. These estimates were then used to create charts using R's *ggplot2* package.

Findings

Table 2 shows descriptive statistics for the *Selection Sample*. Estimates from the Heckman selection equation are displayed in Table 3. Later birth year, later maternal age, and being baptized increased the probability of surviving to age 65. Later paternal age, being born in Utah, and lower SES decreased this probability.

Table 4 displays descriptive statistics for time-invariant predictors in the *Final Sample* (those who survived to 65 and were successfully linked with the FS and CMS data). A few statistics not included in the Table 4 are also of interest. The mean FS for the entire *Final Sample* (i.e., both sexes together) was 1.528, with a standard deviation, minimum and maximum, of 0.319, 1.002, and 6.527 (see Figure 2). The mean number of FSIR's per person used to obtain the final FS value (calculated as mean FSIR) was 4.768 for the *Final Sample*, with a standard deviation, minimum, and maximum of 3.028, 1, and 36.

Table 5 shows descriptive statistics for time-varying variables, with person-years (i.e., “waves”) being the denominator. As expected, there were higher rates of MDD for females and SA for males (Kessler 2003); and higher rates of dual-enrollment in Medicare and Medicaid (a proxy for low income) among females (Minkler and Stone 1985).

Table 6 displays the odds ratios and significance values from regressions, and Table 7 shows the variance-covariance matrices (from the same regressions) for the two key independent variables and interaction. In conjunction with Equations 4 and 5, these latter estimates were necessary for calculating confidence intervals for marginal effects that are displayed in Figures 3 and 4. We discuss the results separately for females and males.

Females

Early parental death and familial suicide susceptibility have no statistically significant main effects upon the odds ratio for major depressive disorder. However, the $FS \times PDE$ interaction term is statistically significant ($p=0.015$) and greater than 1.0. While the effect size is similar for SA, it is not statistically significant. Figure 3 depicts these trends using the logit. Note how the marginal effect of the parental death exposure upon major depressive disorder increases as familial susceptibility to suicide increases. The pattern is similar for both MDD and SA, although the 95% confidence bands for SA are much larger, yielding insignificant results. The graphs suggest the statistically significant risk of early parental death on major depression occurs when familial susceptibility is greater than about 2.5 (or the person has at least 2.5 times the average population familial suicide susceptibility).

For the control variables, risks for both MDD and SA decrease with age. Having more children is protective, and having more siblings is suggestive of a protective effect. Being widowed is a significant risk factor. The association between early-life SES and later-life behavioral health is neither straightforward nor compelling. Own adult SES, measured by dual-enrollment in both Medicare and Medicaid, is a prominent risk factor for both

phenotypes. The inverse Mills ratio shows that those less likely to be selected into the sample are also at increased risk for both phenotypes.

Males

For males, we find no statistically significant effects of the main variables or the interaction in later life. Figure 4 shows that for males, the confidence intervals never exclude zero. In terms of control variables, many of the trends are similar to those for females. Risk of SA decreases with age, but no such trend is seen for MDD. Having more children is protective, and more siblings appear to be protective, though again insignificant. Being widowed is a significant risk for poor behavioral health, and being never married, as opposed to married, is also a risk for substance abuse. The effects of early-life SES are similar to those for females. And concurrent low SES is a large risk factor. Being more likely to have died before reaching age 65 (high inverse mills ratio), is also a risk factor for both phenotypes.

Robustness Checks

We performed a variety of robustness tests. First, some of the control variables were time-invariant, while others were later-life conditions that could change over time. The later-life control variables, such as marital status or poverty, could be mechanisms through which the earlier time-invariant predictors increase poor behavioral health risk (Kuh and Ben-Shlomo 2004). To consider the possibility we were over-controlling by including these later-life factors in the models, we estimated the regression models without them. The results did not significantly change in any meaningful way. Also, since suicides were used to create the measure of FS, it is possible the ego may have gone on to die by suicide after the major depression or substance abuse record, particularly in cases of PDE. While not technically a tautology, we felt a sensitivity test removing egos known to die by suicide was worthwhile. Further, it is possible that for a given PDE the parent's cause of death was also a suicide. To control for these potential confounding factors, we again estimated the regression models excluding all egos who died by suicide or had a parent die by suicide. Again, the results did not appreciably change. Finally, we estimated models where the sexes were pooled, and included variables for sex along with interaction terms with the three key variables. The findings for each sex did not substantially change—i.e., there were no differential effects of parental death by level of familial suicide risk for males, but there was a synergistic interaction for females for major depression. However, this test also did not provide sufficient evidence ($p=0.131$) that this effect for females was different than for males.

Discussion

Not all who experience early parental death will go on to develop a behavioral health disorder (Agid et al. 1999). Why does one individual who experienced such a traumatic and life-altering event during their formative years suffer from a devastating mental illness, while another is relatively unscathed? This is the crux of the differential vulnerability framework—that health outcomes following a traumatic experience may vary because some people are more vulnerable to the stressor. Amongst the disparate variables that could account for such divergence, inherited genetic predisposition is a likely candidate. Indeed, previous research has suggested that genes and environment work in collaboration to increase the risk of

psychopathology (Caspi et al. 2003, Kim et al. 2014). Our foremost objective was to revisit this question with a large population-based sample, by considering whether a family history of suicide (measured with linked death certificates), interacts with early parental death to affect the risk of behavioral health disorders in later life (measured with administrative records).

For females, we found a significant interaction between familial suicide susceptibility and early-parental death that elevates the risk of major depressive disorder. This specific finding lends support for a differential vulnerability hypothesis, suggesting the inherited risk and stressful environment interact to increase risk for major depressive disorder in later life. We found similar effect sizes for substance abuse, though the results were not statistically significant—likely a function of fewer females expressing SA. We found no significant effects for males.

These findings add to other literature that suggests a potential synergistic gene $\times$ environment interaction for the risk of psychopathology (Caspi et al. 2003, Kim et al. 2014). Certain individuals may have a genetic vulnerability to early-life stressors, such as PDE, that translates into poor behavioral health in later life. However, as we measured familial predispositions to disease, and not specific genetic variants, our measure of susceptibility may also reflect family traditions of coping—a dynamic rarely addressed in previous literature.

Our null findings for males may reflect some selection bias though this seems unlikely given our controls for differential survival. Another possible explanation is that there is a ceiling effect, where it is difficult to increase a relative risk that is already high. However, as males generally have lower risks of major depression, we should not expect this to be an issue. Our study also relied upon the assumption that MDD and SA strongly correlate with suicide risk, and while previous studies have shown strong positive correlations between psychiatric disorders and suicide, the association may be stronger for females than males (Qin, Agerbo, and Mortensen 2003). The implication is that familiarity of suicide may be a coarser approximation for familiarity of MDD and SA for males, which could bias our results towards the null. Yet, this approximation was necessary to harvest the strength of information provided by the population coverage of vital records and avoid the tautology associated with predicting an outcome using the same metric as the predictor. It is also possible that early-parental death is simply not as severe a stressor for males (Hollingshaus and Smith 2015), because PDE operates upon health through not only biological, but also social mechanisms that may be especially salient for females (House, Umberson, and Landis 1988).

In addition to our key findings, we found evidence that kin networks can be protective against poor behavioral health in later adulthood, a result consistent with prior research (McAvay, Seeman, and Rodin 1996). We found mixed effects of early-life SES upon later-life behavioral health. But we found current SES was an extremely powerful risk factor, reinforcing the gravity of SES for health (Link and Phelan 1995).

A secondary goal of this study was to show how a large pedigree and population database could be utilized to test familial $\times$ environmental interactions. This was accomplished by constructing a genetically-weighted familial risk score (i.e., the FSIR). Our approach benefitted from a large sample size, which is generally necessary to provide sufficient statistical power for testing such interactions (Manolio, Bailey-Wilson, and Collins 2006). Another feature of the study was the use of the FSIR as a quantitative trait of possible genetic risk. This differs from genetic studies where the inputs are frequently discrete and may be less powerful for detecting interactions for complex phenotypes, though recent advances in computing genetic risk scores as continuous measures may improve the utility of genetic studies for obtaining adequate power (Belsky and Israel 2014, Ragland 1992). Additionally, the measure can account for non-genetic modes of heritability, while still incorporating information on expected genetic relationships via kinship weights. These strengths make the FSIR an attractive construct.

The FSIR also presents some challenges for characterizing familial susceptibility. As previously discussed, predicting an individual's risk for any given phenotype using a measure that is informed by that same phenotype introduces a potential tautology. Therefore, it may be more appropriate to use a proxy phenotype to create the FSIR, as we have done using suicide as a general proxy for psychopathology. This approximation is not perfect, and we suspect that since many who express major depressive disorder or substance abuse will not die by suicide, any misclassification introduces a conservative statistical bias when approximating psychopathology. Furthermore, since it is unreasonable to assume underreporting of suicide is randomly distributed across families, studies of a protective suicide phenotype might be unfeasible.

A few additional considerations involve fertility patterns and modes of inheritance. The fertility of the pedigree members is likely affected by the very phenotype used for its construction, which could affect pedigree structure. We found it conceptually and methodologically appealing to approach this issue by defining a pedigree by its founder and then rely on all known biological descendants. Reliance upon the founder also greatly simplified computation, which proves intractable when applied to each individual in large samples. This often resulted in several FSIR's for each ego, an issue we addressed by utilizing the mean value. The approximation likely biased our findings towards the null. Calculating familial susceptibilities also draws attention to the fact that individuals do not fall into mutually exclusive pedigrees within a population—no one is truly independent. Additionally, the kinship coefficient used in the FSIR's construction relies upon the assumption that the traits for suicide are transmitted by simple Mendelian mechanisms. While this assumption ideally allows for a close approximation of genome-specific phenomena (Kerber 1995), the kinship weights may be tailored to specific phenotypes when a different inheritance pattern is known or suspected. Indeed, alternative models can be used to create the kinship weights and then tested against the data. Despite these potential challenges, we believe the FSIR provides unique strengths that can overcome some of the limitations inherent in other familial measures, and suggest researchers place this risk score in their toolbox of measures.

In addition to the implications this paper has for researchers considering hypotheses of differential vulnerability, there are also potential policy implications. We found evidence of differential vulnerability to early-life parental death, as assessed by the moderating effects of familial suicide susceptibility upon major depressive disorder for females in later-life. The observed interaction pattern also indirectly implies that inherited vulnerabilities may be just that—vulnerabilities. If certain population-level social policies can decrease the frequency or intensity of a potential stressor, or “trigger” (Shanahan and Hofer 2005, 65), then the influence of inherited vulnerabilities upon the future public behavioral health burden may attenuate. Finally, when patients have experienced early parental death, this information might inform behavioral health professionals as new practices are pursued in an era of Big Data and personalized medicine (Murdoch and Detsky 2013).

Acknowledgments

This work was supported by National Institutes of Health grant AG022095 (Early Life Conditions, Survival and Health; Smith PI). We wish to thank the Huntsman Cancer Foundation for database support provided to the Pedigree and Population Resource of the HCI, University of Utah. We also thank Alison Fraser and Diana Lane Reed for assistance in managing the data; and Rebecca L. Utz and Ming Wen for suggestions. Partial support for all datasets within the UPDB was provided by the HCI Cancer Center Support Grant, P30 CA42014 from National Cancer Institute. A similar version of this work appeared previously as part of the primary author's doctoral dissertation.

References

- Agid O, Shapira B, Zislin J, Ritsner M, Hanin B, Murad H, Troudart T, Bloch M, Heresco-Levy U, Lerer B. Environment and Vulnerability to Major Psychiatric Illness: a Case Control Study of Early Parental Loss in Major Depression, Bipolar Disorder and Schizophrenia. *Molecular Psychiatry*. 1999; 4(2):163–172. doi: 10.1038/sj.mp.4000473. [PubMed: 10208448]
- Allison, Paul D. Fixed Effects Regression Models. SAGE Publications; Los Angeles: 2009.
- American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM 5. Fifth ed.. American Psychiatric Association; Washington, DC: 2013.
- Avenevoli, Shelli; Ries Merikangas, Kathleen. Implications of High-risk Family Studies for Prevention of Depression. *American Journal of Preventive Medicine*. 2006; 31(6 Suppl 1):S126–35. doi: 10.1016/j.amepre.2006.07.003. [PubMed: 17175407]
- Bakermans-Kranenburg, Marian J.; Van Ijzendoorn, Marinus H. Research Review: Genetic Vulnerability or Differential Susceptibility in Child Development: the Case of Attachment. *Journal of Child Psychology and Psychiatry*. 2007; 48(12):1160–1173. doi: 10.1111/j.1469-7610.2007.01801.x. [PubMed: 18093021]
- Beauchaine, Theodore P.; Neuhaus, Emily; Zalewski, Maureen; Crowell, Sheila E.; Potapova, Natalia. The Effects of Allostatic Load on Neural Systems Subserving Motivation, Mood Regulation, and Social Affiliation. *Development and Psychopathology*. 2011; 23(4):975–999. doi: 10.1017/S0954579411000459. [PubMed: 22018077]
- Belsky, Daniel W.; Israel, Salomon. Integrating Genetics and Social Science: Genetic Risk Scores. *Biodemography and Social Biology*. 2014; 60(2):137–155. doi: 10.1080/19485565.2014.946591. [PubMed: 25343363]
- Belsky, Jay; Pluess, Michael. Beyond Diathesis Stress: Differential Susceptibility to Environmental Influences. *Psychological Bulletin*. 2009; 135(6):885–908. doi: 10.1037/a0017376. [PubMed: 19883141]
- Boardman, Jason D.; Domingue, Benjamin W.; Blalock, Casey L.; Haberstick, Brett C.; Mullan Harris, Kathleen; McQueen, Matthew B. Is the Gene-Environment Interaction Paradigm Relevant to Genome-Wide Studies? The Case of Education and Body Mass Index. *Demography*. 2014; 51(1): 119–139. doi: 10.1007/s13524-013-0259-4. [PubMed: 24281739]
- Bowlby, John. Loss: Sadness and Depression. Basic Books; New York: 1980.

- Brambor, Thomas; Roberts Clark, William; Golder, Matt. Understanding Interaction Models: Improving Empirical Analyses. *Political Analysis*. 2006; 14(1):63–82. doi: 10.1093/pan/mpi014.
- Brent, David A.; Oquendo, Maria; Birmaher, Boris; Greenhill, Laurence; Kolko, David; Stanley, Barbara; Zelazny, Jamie; Brodsky, Beth; Melhem, Nadine; Ellis, Steven P.; John Mann, J. Familial Transmission of Mood Disorders: Convergence and Divergence With Transmission of Suicidal Behavior. *Journal of the American Academy of Child and Adolescent Psychiatry*. 2004; 43(10): 1259–1266. doi: 10.1097/01.chi.0000135619.38392.78. [PubMed: 15381893]
- Brodsky, Beth S.; John Mann, J.; Stanley, Barbara; Tin, Adrienne; Oquendo, Maria; Birmaher, Boris; Greenhill, Laurence; Kolko, David; Zelazny, Jamie; Keller Burke, Ainsley; Melhem, Nadine; Brent, David A. Familial Transmission of Suicidal Behavior: Factors Mediating the Relationship Between Childhood Abuse and Offspring Suicide Attempts. *Journal of Clinical Psychiatry*. 2008; 69(4):584–96. doi: 10.4088/JCP.v69n0410. [PubMed: 18373384]
- Caspi, Avshalom; Sugden, Karen; Moffitt, Terrie E.; Taylor, Alan; Craig, Ian W.; Harrington, HonaLee; McClay, Joseph; Mill, Jonathan; Martin, Judy; Braithwaite, Antony; Poulton, Richie. Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene. *Science*. 2003; 301(5631):386–389. doi: 10.1126/science.1083968. [PubMed: 12869766]
- Dannefer, Dale. Cumulative Advantage/Disadvantage and the Life Course: Cross-Fertilizing Age and Social Science Theory. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2003; 58(6):S327–S337. doi: 10.1093/geronb/58.6.S327.
- Dearing, Eric; Hamilton, Lawrence C. V. Contemporary Advances and Classic Advice for Analyzing Mediating and Moderating Variables. *Monographs of the Society for Research in Child Development*. 2006; 71(3):88–104. doi: 10.1111/j.1540-5834.2006.00406.x.
- Denney, Justin T.; Rogers, Richard G.; Krueger, Patrick M.; Wadsworth, Tim. Adult Suicide Mortality in the United States: Marital Status, Family Size, Socioeconomic Status, and Differences by Sex. *Social Science Quarterly*. 2009; 90(5):1167–1185. doi: 10.1111/j.1540-6237.2009.00652.x. [PubMed: 20161640]
- Flint, Jonathan; Kendler, Kenneth S. The Genetics of Major Depression. *Neuron*. 2014; 81(3):484–503. doi: 10.1016/j.neuron.2014.01.027. [PubMed: 24507187]
- Fu, Vincent Kang; Winship, Christopher; Mare, Robert D. Sample Selection Bias Models.. In: Hardy, Melissa A.; Bryman, Alan, editors. *Handbook of Data Analysis*. SAGE Publications, Inc.; Thousand Oaks, CA: 2004. p. 409-430.
- Hertzman, Clyde; Boyce, Tom. How Experience Gets Under the Skin to Create Gradients in Developmental Health. *Annual Review of Public Health*. 2010; 31:329–347. doi: 10.1146/annurev.publhealth.012809.103538.
- Hollingshaus, Michael S.; Smith, Ken R. Life and Death in the Family: Early Parental Death, Parental Remarriage, and Offspring Suicide Risk in Adulthood. *Social Science & Medicine*. 2015 doi: 10.1016/j.socscimed.2015.02.008.
- Horn, Erin E.; Xu, Yishan; Beam, Christopher R.; Turkheimer, Eric; Emery, Robert E. Accounting for the Physical and Mental Health Benefits of Entry into Marriage: a Genetically Informed Study of Selection and Causation. *Journal of Family Psychology*. 2013; 27(1):30–41. doi: 10.1037/a0029803. [PubMed: 23088795]
- House JS, Umberson D, Landis KR. Structures and Processes of Social Support. *Annual Review of Sociology*. 1988; 14:293–318. doi: 10.2307/2083320.
- Kerber, Richard A. Method for Calculating Risk Associated with Family History of a Disease. *Genetic Epidemiology*. 1995; 12(3):291–301. doi: 10.1002/gepi.1370120306. [PubMed: 7557350]
- Kessler, Ronald C. Epidemiology of Women and Depression. *Journal of Affective Disorders*. 2003; 74(1):5–13. doi: 10.1016/S0165-0327(02)00426-3. [PubMed: 12646294]
- Kim, Jae-Min; Stewart, Robert; Kim, Sung-Wan; Kang, Hee-Ju; Kim, Seon-Young; Lee, Ju-Yeon; Bae, Kyung-Yeol; Shin, Il-Seon; Yoon, Jin-Sangs. Interactions Between a Serotonin Transporter Gene, Life Events and Social Support on Suicidal Ideation in Korean Elders. *Journal of Affective Disorders*. 2014; 160:14–20. doi: 10.1016/j.jad.2014.02.030. [PubMed: 24709017]
- Kuh, Diana; Ben-Shlomo, Yoav. *A Life Course Approach to Chronic Disease Epidemiology*, edited by Diana Kuh and Yoav Ben-Shlomo. Oxford University Press; New York: 2004. Introduction.; p. 3-14.

- Levine, Morgan E.; Crimmins, Eileen M.; Prescott, Carol A.; Phillips, Drystan; Arpawong, Thalida E.; Lee, Jinkook. A Polygenic Risk Score Associated with Measures of Depressive Symptoms Among Older Adults. *Biodemography and Social Biology*. 2014; 60(2):199–211. doi: 10.1080/19485565.2014.952705. [PubMed: 25343367]
- Link, Bruce G.; Phelan, Jo. Social Conditions As Fundamental Causes of Disease. *Journal of Health and Social Behavior*. 1995; 35(Extra Issue):80–94. doi: 10.2307/2626958. [PubMed: 7560851]
- Lyon, Joseph L.; Gardner, Kent; Gress, Richard E. Cancer incidence among Mormons and non-Mormons in Utah (United States) 1971–85. *Cancer Causes and Control*. 1994; 5(2):149–156. doi: 10.1007/BF01830261. [PubMed: 8167262]
- Malecot, Gustave. *Les Mathematiques de l'Heredité*. Masson; Paris: 1948.
- Manolio, Teri A.; Bailey-Wilson, Joan E.; Collins, Francis S. Genes, Environment and the Value of Prospective Cohort Studies. *Nature Reviews Genetics*. 2006; 7(10):812–820. doi: 10.1038/nrg1919.
- Mares, Suzanne H.W.; Lichtwarck-Aschoff, Anna; Engels, Rutger C.M.E. Intergenerational Transmission of Drinking Motives and How They Relate to Young Adults' Alcohol Use. *Alcohol and Alcoholism*. 2013; 48(4):445–451. doi: 10.1093/alcalc/agt025. [PubMed: 23531719]
- McAvey, Gail J.; Seeman, Teresa E.; Rodin, Judith. A Longitudinal Study of Change in Domain-Specific Self-Efficacy among Older Adults. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 1996; 51B(5):P243–P253. doi: 10.1093/geronb/51B.5.P243.
- McCleary, Gerald E.; Vogler, George P.; Hofer, Scott M. Environment-Gene and Gene-Gene Interactions.. In: Masaro, Edward J.; Austad, Steven N., editors. *Handbook of the Biology of Aging*. Academic Press; 423-444: San Diego: 2001.
- Minkler, Meredith; Stone, Robyn. The Feminization of Poverty and Older Women. *The Gerontologist*. 1985; 25(4):351–357. doi: 10.1093/geront/25.4.351. [PubMed: 4029671]
- Mukherjee, Bhramar; Ahn, Jaeil; Gruber, Stephen B.; Chatterjee, Nilanjan. Testing Gene-Environment Interaction in Large-Scale Case-Control Association Studies: Possible Choices and Comparisons. *American Journal of Epidemiology*. 2012; 175(3):177–190. doi: 10.1093/aje/kwr367. [PubMed: 22199027]
- Murdoch, Travis B.; Detsky, Allan S. The Inevitable Application of Big Data to Health Care. *JAMA*. 2013; 309(13):1351–1352. doi: 10.1001/jama.2013.393. [PubMed: 23549579]
- Nam, Charles B.; Powers, Mary G. *The Socioeconomic Approach to Status Measurement*. Houston. Cap and Gown Press; TX: 1983.
- Nickerson, Angela; Bryant, Richard A.; Aderka, Idan M.; Hinton, Devon E.; Hofmann, Stefan G. The Impacts of Parental Loss and Adverse Parenting on Mental Health: Findings from the National Comorbidity Survey-Replication. *Psychological Trauma: Theory, Research, Practice, and Policy*. 2013; 5(2):119–127. doi: 10.1037/a0025695.
- Niederkröthaler, Thomas; Floderus, Birgitta; Alexanderson, Kristina; Rasmussen, Finn; Mittendorfer-Rutz, Ellenor. Exposure to Parental Mortality and Markers of Morbidity, and the Risks of Attempted and Completed Suicide in Offspring: an Analysis of Sensitive Life Periods. *Journal of Epidemiology and Community Health*. 2012; 66(3):233–239. doi: 10.1136/jech.2010.109595. [PubMed: 20924054]
- Norton, Maria. C.; Smith, Ken R.; Østbye, Truls; Tschanz, JoAnn T.; Schwartz, Sarah; Corcoran, Chris; Breitner, John C. S.; Steffens, David C.; Skoog, Ingmar; Rabins, Peter V.; Welsh-Bohmer, Kathleen A. Early Parental Death and Remarriage of Widowed Parents as Risk Factors for Alzheimer Disease: the Cache County Study. *American Journal of Geriatric Psychiatry*. 2011; 19(9):814–24. doi: 10.1097/JGP.0b013e3182011b38. [PubMed: 21873837]
- Pearlin, Leonard I.; Aneshensel, Carol S.; Leblanc, Allen J. The Forms and Mechanisms of Stress Proliferation: The Case of AIDS Caregivers. *Journal of Health and Social Behavior*. 1997; 38(3): 223–236. doi: 10.2307/2955368. [PubMed: 9343962]
- Pescosolido, Bernice A.; Mendelsohn, Robert. Social Causation or Social Construction of Suicide? An Investigation into the Social Organization of Official Rates. *American Sociological Review*. 1986; 51(1):80–100. doi: 10.2307/2095479.
- Pishva, Ehsan; Drukker, Marjan; Viechtbauer, Wolfgang; Decoster, Jeroen; Collip, Dina; Van Winkel, Ruud; Wichers, Marieke; Jacobs, Nele; Thiery, Evert; Derom, Catherine. Epigenetic Genes and

- Emotional Reactivity to Daily Life Events: A Multi-Step Gene-Environment Interaction Study. *PloS one*. 2014; 9(6):e100935. doi: 10.1371/journal.pone.0100935. [PubMed: 24967710]
- Preston, Samuel H.; Hill, Mark E.; Drevenstedt, Greg L. Childhood Conditions that Predict Survival to Advanced Ages among African-Americans. *Social Science and Medicine*. 1998; 47(9):1231–1246. doi: 10.1016/s0277-9536(98)00180-4. [PubMed: 9783866]
- Qin, Ping; Agerbo, Esben; Bo Mortensen, Preben. Suicide Risk in Relation to Socioeconomic, Demographic, Psychiatric, and Familial Factors: A National Register– Based Study of All Suicides in Denmark, 1981–1997. *American Journal of Psychiatry*. 2003; 160(4):765–72. doi:10.1176/appi.ajp.160.4.765. [PubMed: 12668367]
- Ragland, David R. Dichotomizing Continuous Outcome Variables: Dependence of the Magnitude of Association and Statistical Power on the Cutpoint. *Epidemiology*. 1992; 3(5):434–40. [PubMed: 1391136]
- Rietschel, Marcella; Treutlein, Jens. The genetics of alcohol dependence. *Annals of the New York Academy of Sciences*. 2013; 1282(1):39–70. doi: 10.1111/j.1749-6632.2012.06794.x. [PubMed: 23170934]
- Roisman, Glenn I.; Newman, Daniel A.; Chris Fraley, R.; Haltigan, John D.; Groh, Ashley M.; Haydon, Katherine C. Distinguishing Differential Susceptibility from Diathesis– stress: Recommendations for Evaluating Interaction Effects. *Development and Psychopathology*. 2012; 24(02):389–409. doi: 10.1017/S0954579412000065. [PubMed: 22559121]
- Rostila, Mikael; Saarela, Jan; Kawachi, Ichiro. Mortality From Myocardial Infarction After the Death of a Sibling: A Nationwide Follow-up Study From Sweden. *Journal of the American Heart Association*. 2013; 2(2):1–10. doi: 10.1161/JAHA.112.000046.
- Shanahan, Michael J.; Hofer, Scott M. Social Context in Gene–Environment Interactions: Retrospect and Prospect. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences*. 2005; 60(Special Issue 1):65–76. doi: 10.1093/geronb/60.Special_Issue_1.65.
- Smith, Ken R.; Hanson, Heidi A.; Norton, Maria C.; Hollingshaus, Michael S.; Mineau, Geraldine P. Survival of Offspring who Experience Early Parental Death: Early Life Conditions and Later-life Mortality. *Social Science & Medicine*. 2014; 119(0):180–190. doi: 10.1016/j.socscimed.2013.11.054. [PubMed: 24530028]
- Smith, Ken R.; Mineau, Geraldine P.; Garibotti, Gilda; Kerber, Richard. Effects of Childhood and Middle-adulthood Family Conditions on Later-life Mortality: Evidence from the Utah Population Database, 1850–2002. *Social Science & Medicine*. 2009; 68(9):1649–1658. doi: 10.1016/j.socscimed.2009.02.010. [PubMed: 19278766]
- Timmermans, Stefan. Suicide Determination and the Professional Authority of Medical Examiners. *American Sociological Review*. 2005; 70(2):311–333. doi: 10.2307/4145372.
- van Winkel, Mark; Peeters, Frenk; van Winkel, Ruud; Kenis, Gunter; Collip, Dina; Geschwind, Nicole; Jacobs, Nele; Derom, Catherine; Thiery, Evert; van Os, Jim; Myin-Germeys, Inez; Wichers, Marieke. Impact of Variation in the BDNF Gene on Social Stress Sensitivity and the Buffering Impact of Positive Emotions: Replication and Extension of a Gene–environment Interaction. *European Neuropsychopharmacology*. 2014; 24(6):930–938. doi: 10.1016/j.euroneuro.2014.02.005. [PubMed: 24613654]
- Waddington, Conrad Hal. *The Strategy of the Genes*. Macmillan; New York: 1957.
- Wylie, Jean E.; Mineau, Geraldine P. Biomedical databases: protecting privacy and promoting research. *Trends in Biotechnology*. 2003; 21(3):113–116. doi: 10.1016/S0167-7799(02)00039-2. [PubMed: 12628367]

Figure 1. Histogram of suicide familial standardized incidence ratios (FSIR's) for founders ($N=5,262$).

Figure 2. Histogram of familial suicide susceptibility (i.e., mean suicide familial standardized incidence ratio) for egos in the final sample ($N=155,983$).

Figure 3.

Females: marginal effect of early-life parental death upon the logit of major depression and substance abuse, given familial suicide susceptibility.

Note. Solid line: point estimate. Gray ribbon: 95% confidence band. Horizontal dashed line: zero = no effect. Vertical dashed line: 1.53 = mean relative suicide susceptibility.

Figure 4.

Males: marginal effect of early-life parental death upon the logit of major depression and substance abuse, given familial suicide susceptibility.

Note. Solid line: point estimate. Gray ribbon: 95% confidence band. Horizontal dashed line: zero = no effect. Vertical dashed line: 1.53 = mean relative suicide susceptibility.

Table 1

Acronyms

Acronym	Term
CMS	Centers for Medicare and Medicaid Services
$F \times E$	Familial-Environment Interaction
FS	Familial Susceptibility to Suicide
$FS \times PDE$	Familial-Early life parental death interaction
FSIR	Familial Standardized Incidence Ratio
$G \times E$	Gene-Environment Interaction
HMO	Health Maintenance Organization
HPA	Hypothalamic-Pituitary-Adrenal (axis)
ICD	International Classification of Diseases
IMR	Inverse Mills Ratio
MDD	Major Depressive Disorder
ME	Marginal Effect(s)
PDE	Parental Death in Early Life
RGE	Utah Resource for Genetic and Epidemiologic Research
SA	Substance Abuse
SES	Socioeconomic Status
UPDB	Utah Population Database

Table 2Descriptive Statistics for the *Selection Sample*.

<i>N</i>	Female		Male	
	216,729	100.0%	218,266	100.0%
Categorical Variables	Frequency	Percentage	Frequency	Percentage
<i>Survived to at Least Age 65</i>	171,989	79.4%	160,187	73.4%
<i>Baptized</i>	139,752	64.5%	133,718	61.3%
<i>Born in Utah</i>	183,075	84.5%	186,380	85.4%
<i>Nam Powers SES Score</i> ^a				
76-99	24,702	11.4%	24,948	11.4%
51-75	41,913	19.3%	42,441	19.4%
26-50 (excluding 40)	27,235	12.6%	27,532	12.6%
1-25	16,534	7.6%	16,310	7.5%
40 (Farming)	61,432	28.3%	63,506	29.1%
Missing	44,913	20.7%	43,529	19.9%

Continuous Variables	Mean	Std. Dev.	Mean	Std. Dev.
<i>Birth year</i>	1918.25	16.32	1918.60	16.36
<i>Maternal Age at time of Ego's Birth</i>	28.68	6.55	28.65	6.54
<i>Paternal Age at time of Ego's Birth</i>	32.76	7.89	32.72	7.89

Notes:

^a The greater of the subject's mother's or father's Nam Powers Score obtained from parent's death certificate (higher values represent higher SES).

Table 3Probit Estimates from Heckman Selection Equation using *Selection Sample*.

	Females (N=216,729)			Males (N=218,266)		
	Beta	Std. Er.	p-val	Beta	Std. Er.	p-val
<i>Birth year</i>	0.005	0.000	<0.000	0.006	0.000	<0.000
<i>Maternal Age</i>	0.002	0.001	0.002	0.002	0.001	0.001
<i>Paternal Age</i>	-0.003	0.001	<0.000	-0.002	0.001	0.004
<i>Baptized</i>	0.135	0.006	<0.000	0.180	0.006	<0.000
<i>Born in Utah</i>	-0.036	0.009	<0.000	-0.026	0.008	0.002
<i>Nam Powers SES Score</i> ^a						
51-75	-0.012	0.012	0.283	-0.058	0.011	<0.000
26-50 (excluding 40)	-0.023	0.013	0.067	-0.051	0.012	<0.000
1-25	-0.063	0.014	<0.000	-0.115	0.014	<0.000
40 (Farming)	0.021	0.011	0.063	0.009	0.011	0.418
Missing	-0.074	0.012	0.000	-0.056	0.011	<0.000
<i>Constant</i>	-7.884	0.373	<0.000	-10.832	0.355	<0.000

^a ref. is 76-99 (highest SES)

Table 4Descriptive Statistics (*Final Sample*) at Person Level for Time-invariant Variables.

<i>N</i>	Female		Male	
	83,547	100.0%	72,436	100.0%
Categorical Variables	Frequency	Percentage	Frequency	Percentage
<i>Parity</i>				
Nulliparous / Missing	10,180	12.2%	7,760	10.7%
1-3	33,481	40.1%	28,534	39.4%
4-5	25,613	30.7%	22,897	31.6%
6+	14,273	17.1%	13,245	18.3%
<i>Siblings</i>				
Only Child	2,622	3.1%	2,394	3.3%
1-4	38,124	45.6%	34,894	48.2%
5-6	18,254	21.8%	15,795	21.8%
7+	24,547	29.4%	19,353	26.7%
<i>Nam Powers SES Score^a</i>				
76-99	11,275	13.5%	10,399	14.4%
51-75	16,642	19.9%	14,722	20.3%
26-50, excluding 40	10,782	12.9%	9,590	13.2%
1-25	5,693	6.8%	4,743	6.5%
40 (Farming)	23,691	28.4%	20,210	27.9%
Missing	15,464	18.5%	12,772	17.6%

Continuous Variables	Mean	Std. Dev.	Mean	Std. Dev.
<i>Number of Early Parental Deaths</i>	0.15	0.37	0.14	0.36
<i>Familial Susceptibility</i>	1.53	0.32	1.53	0.32
<i>Number of FSIR's</i>	4.69	3.00	4.85	3.06
<i>Number of Complete Years Enrolled (Waves)</i>	9.56	5.32	8.73	5.28
<i>Age at First Wave</i>	71.69	7.54	70.33	6.54
<i>Inverse Mills Ratio</i>	0.34	0.04	0.42	0.05

Notes:

^aThe greater of the subject's mother's or father's Nam Powers Score obtained from parent's death certificate (higher values represent higher SES).

Table 5Descriptive Statistics (*Final Sample*) at Person-year Level^a for Time-varying Variables (Including Outcomes).

	Female		Male	
	Frequency	Percentage	Frequency	Percentage
<i>N</i>	798,537	100.0%	632,523	100.0%
Outcomes				
<i>Major Depression</i>	17,808	2.2%	6,878	1.1%
<i>Substance Abuse</i>	2,448	0.3%	3,356	0.5%
Time-Varying Predictors				
<i>Period</i>				
1992-1997	278,302	34.9%	213,166	33.7%
1998-2005	382,721	47.9%	302,771	47.9%
2006-2009	137,514	17.2%	116,586	18.4%
<i>Marital Status</i>				
Never Married	31,045	3.9%	21,437	3.4%
Married	427,179	53.5%	531,533	84.0%
Widowed	340,313	42.6%	79,553	12.6%
<i>Dual Enrolled in Medicaid</i>	44,117	5.5%	15,174	2.4%

Notes:

^aOne observation for each year the individual was considered at-risk for major depressive disorder or substance abuse. Years of follow-up were restricted to 1992-2009, and only after the individual was at least age 65 and completely enrolled in Medicare parts A and B.

Table 6

Odds Ratios from Logistic Regressions Predicting Major Depression or Substance Abuse Diagnosis from Parental Death in Early Life (PDE), Familial Susceptibility (FS) and FS $\times$ PDE, with Controls.

	Females (N=83,547 persons, 798,537 person-years)		Males (N=72,436 persons, 632,523 person-years)	
	Major Depression	Substance Abuse	Major Depression	Substance Abuse
Key Variables				
<i>PDE</i>	0.94	0.95	1.07	1.15
<i>FS</i>	1.02	1.18	1.13	1.16
<i>FS $\times$ PDE</i>	1.41 *	1.31	1.00	0.82
Controls (Time-invariant)				
<i>Age at first wave</i>	0.97 ***	0.94 ***	1.01	0.90 ***
<i>Childhood Nam Powers SES Score^a</i>				
51-75	0.87 *	1.04	0.78 **	0.78 *
26-50 (excluding 40)	0.90	0.88	0.87	0.91
1-25	0.73 ***	0.59 **	0.75 *	0.59 ***
40 (Farming)	0.78 ***	0.86	0.68 ***	1.06
Missing	0.69 ***	0.67 **	0.81 *	0.60 ***
<i>Number of Siblings^b</i>				
1-4	1.02	0.77	0.87	0.98
5-6	0.96	0.73	0.76	0.89
7+	0.90	0.72	0.77	0.99
<i>Parity^c</i>				
Nulliparous/Missing	1.05	1.01	1.11	1.04
4-5	0.91 *	0.77 ***	1.02	0.67 ***
6+	0.64 ***	0.54 ***	0.80 **	0.44 ***
<i>Number of FSIR's</i>	0.99	1.01	0.98 *	0.97 **
<i>Number of Complete Years Enrolled (Waves)</i>	0.96 ***	0.91 ***	0.96 ***	0.89 ***
<i>Inverse Mills Ratio^d</i>	1.71 ***	2.84 ***	1.23 **	2.97 ***
(Time-varying)				
<i>Period^e</i>				
1998-2005	1.21 ***	1.51 ***	1.46 ***	1.31 ***
2006-2009	1.13 ***	1.72 ***	1.39 ***	1.32 ***
<i>Marital Status^f</i>				
Never	1.19	1.24	1.30	1.59 **

	Females (N=83,547 persons, 798,537 person-years)		Males (N=72,436 persons, 632,523 person-years)	
	Major Depression	Substance Abuse	Major Depression	Substance Abuse
Widowed	1.49 ***	1.62 ***	2.10 ***	2.11 ***
<i>Dual Eligible</i>	2.06 ***	2.44 ***	3.51 ***	5.68 ***

Notes:

^a ref. is 76-99 (highest SES)

^b ref. is no siblings/only child

^c ref. is 1-3 children

^d scaled by a factor of 10

^e ref. is 1992-1997

^f ref. is married

*
p < 0.05

**
p < 0.01

p < 0.001

Table 7

Variance Covariance Matrix for Parental Death in Early Life (PDE), Familial Susceptibility (FS), and FS $\times$ PDE estimates from Logistic Regression Models.

		Females			Males		
		<i>PDE</i>	<i>FS</i>	<i>FS</i> $\times$ <i>PDE</i>	<i>PDE</i>	<i>FS</i>	<i>FS</i> $\times$ <i>PDE</i>
Major Depression	<i>PDE</i>	0.00249			0.00534		
	<i>FS</i>	0.00004	0.00372		0.00006	0.00798	
	<i>FS</i> $\times$ <i>PDE</i>	-0.00059	-0.00339	0.01988	-0.00059	-0.00729	0.04577
Substance Abuse	<i>PDE</i>	0.00735			0.00668		
	<i>FS</i>	0.00025	0.01025		0.00019	0.00991	
	<i>FS</i> $\times$ <i>PDE</i>	-0.00245	-0.00940	0.05461	-0.00103	-0.00907	0.06013