SEEDS OF SORROW: A LIFE-COURSE APPROACH TO EARLY-LIFE PARENTAL DEATH AND LATER-LIFE SUICIDE AND BEHAVIORAL HEALTH RISK

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

This dissertation explores the effects of early-life parental death upon an offspring's later-life risk of suicide, major depression and substance abuse. By situating the question within a biopsychosocial life-course framework, we find that this association may lead to secondary stressors, be moderated by familial vulnerabilities, and occur in tandem with other early-life stressors. The study offers innovative, creative, and substantial contributions to the current literature on early parental death and later behavioral health by (1) disentangling social from biological mechanisms by using remarriage of surviving parent as a proxy for social integration, (2) testing for differential vulnerability by investigating the moderating effects of familial suicide history, and (3) constructing and testing the influence of a new measure called the Utah demographic childhood adverse exposures (DECADE) scale. The findings suggest that early-life stress, especially parental death, may impact later-life behavioral health, and the association is moderated by other contextual factors. The dissertation further demonstrates the utility of demographic pedigree databases for transdisciplinary studies of behavioral health, and proposes innovative quantitative measurements that might be utilized for future life-course studies.

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CHAPTER 1

INTRODUCTION

Suicide is the 10th leading cause of death in the United States. It results in not only the deaths of those affected, but excess grief in surviving family, potentially increasing their risk for suicide (Mitchell, Kim, Prigerson, & Mortimer-Stephens, 2004). The estimated national annual economic loss due to suicide is $34.6 billion (National Center for Injury Control and Prevention, 2012). Behavioral health disorders are also very prevalent (Clark et al., 2009), and are highly predictive of suicide (American Psychiatric Association, 2013). Mental and behavioral health disorders are some of the largest contributors to years living with disability, and generally constitute a heavy burden of disease in the United States (Murray et al., 2013) and throughout the world (Michaud, Murray, & Bloom, 2001).

In regards to behavioral health, Utah presents an interesting case. With the other Rocky Mountain States, Utah consistently has high rates of suicide compared to the rest of the United States (Centers for Disease Control and Prevention, 2011, 2013; Utah Department of Health, 2014). Recent studies reported Utah as having the highest estimated rates of suicidal thoughts and mental illness in the United States (Centers for Disease Control and Prevention, 2011; Substance Abuse and Mental Health Services Administration, 2014). While large confidence intervals hamper reliable interstate

comparisons, they do suggest Utah's rates are higher than the national average. Parental death in early life (PDE), which is frequently measured as experiencing the death of at least one parent prior to achieving 18 years of age (Chae, 2013; Luecken & Roubinov, 2012; UNICEF, UNAIDS, & USAID, 2004), is associated with numerous poor health outcomes (Smith, Hanson, Norton, Hollingshaus, & Mineau, 2014) , including suicide (Agerbo, Nordentoft, & Mortensen, 2002). In the United States, it is estimated that about 4% of children in contemporary cohorts will experience PDE (Social Security Administration, 2000), and it may therefore represent a significant public health burden.

The focus of this dissertation is how PDE impacts behavioral health, especially suicide, in the Utah population. Given Utah's high rates for poor behavioral health, it stands to benefit greatly from the analysis. The Utah Population Database (UPDB), which is extensively utilized herein, provides quantitative data sufficient to the task. It is my belief that findings will generalize to other populations, though replication is always desirable. Three empirical papers related to early-life bereavement, stress and behavioral health form the core of this work, each designed for independent publication in scientific peer-reviewed journals. Parental death in early life, it will be shown, is theoretically and empirically a prime detrimental exposure to examine, and each paper will consider different aspects and contexts surrounding its influences upon one's mental health risk.

Below, I outline my life-course theoretical framework for this dissertation, spotlighting its ability to bridge disciplinary divides to disentangle behavioral phenotypes' complex etiologies. Being trained as a sociologist and population scientist, I tend to dedicate more time to social approaches; however, consistent with cutting-edge collaborate research paradigms (Berkman, Glass, Brissette, & Seeman, 2000; Cuthbert &

Insel, 2013), I attempt to enmesh social approaches with biological and psychological views as much as possible. In the process, I discuss the particular early-life exposure of PDE and briefly introduce each paper conjointly with its theoretical relevance for the current literature. The data to be utilized from UPDB are then briefly introduced before embarking on the three core studies. My hope is that this work will ultimately lead to reductions in morbidity and mortality by informing policy and directing future scientific endeavors.

A Biopsychosocial Paradigm for Early-Life Stress and Behavioral Health

Sociological theory has a rich history in quantitative approaches to behavioral health. Durkheim's (1951) seminal treatise *Suicide* is considered a canonical work not only for suicidology, but for sociology in general (Szakolczai, 1998). Durkheim noted that larger, macrolevel social structures have the power to affect suicide rates. This vast power for large-scale social forces to affect individual behaviors was alluded to by C. Wright Mills (1959), who claimed that such settings "carry meanings not only for individual ways of life, but for the very character—the limits and possibilities of the human being" (p.158). Indeed, social forces can powerfully influence health (Berkman et al., 2000).

If social forces affect the "limits and possibilities of the human being," (Mills, 1959, p.158), so also do biological forces set parameters for the expression of human behavior. Waddington's (1957) e*pigenetic landscape* (McClearn, Vogler, & Hofer, 2001) visualized the genotype as a topography for human potential, with social or other

environmental experiences being variables that influenced the realized manifestation (i.e., the phenotype). Indeed, humans are biological organisms, and the social forces that affect human behaviors, or even psychological states, must therefore also act through biological mechanisms (Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Berkman et al., 2000).

While there has historically been some "biophobia" among sociologists (Freese, Li, & Wade, 2003, p.233), there is increasing recognition that interdisciplinary epidemiological examinations of human health and behavior are more realistic (Berkman & Kawachi, 2000). It is my opinion that further integration of sociological and biological approaches and explanations will lead to finer understandings of the risk factors and mechanisms leading to poor behavioral health, and result in improved interventions. This biopsychosocial approach could combine the past and current research and special expertise of sociologists, biologists, psychologists and medical practitioners, to solve such problems in the least biased and most efficient manner possible.

Life-Course Approach

A life-course approach can link macrolevel social settings to individual biographies of health (George, 2003), and therefore provides a nice template for integrating these paradigms into a biopsychosocial framework. In particular, the recognition that aging and health are not static states, but lifelong processes (Elder & Johnson, 2003) has drawn attention to the vulnerable periods of early-life exposure (Berkman & Kawachi, 2000). These sensitive stages (Armstrong et al., 2006) are periods where (1) the human body is in a state of great biological plasticity (Gluckman, Hanson,

& Buklijas, 2010) and may therefore be easily "scarred" (Preston, Hill, & Drevenstedt, 1998, 1232), and (2) the trajectory of life chances is set, with the pool of available socioeconomic and social resources providing a baseline for cumulative advantage or disadvantage throughout the life-course (Ben-Shlomo & Kuh, 2002; Dannefer, 2003).

Given their enormous capability to set a life trajectory of behavioral health outcomes, early-life conditions provide great potential for intervention (Hertzman, 2007). If social policies can decrease exposure to a given early-life stressor on a wide scale, then we should expect health to improve throughout the life-course for many people. Further, if we can elucidate the psychobiological and social mechanisms linking an early-life stressor to later-life health, we might better direct interventions to address the harmful sequelae of such stressors when they do occur. If a mechanism due to early-life exposure is primarily physiological in nature, such as chronic inflammation (Finch & Crimmins, 2004), then perhaps certain medical treatments could alleviate symptoms (Köhler et al., 2014). However, if social mechanisms, such as decreased availability to resources, are primarily responsible, then addressing that resource deficit might be more effective (Link & Phelan, 1995).

Disentangling Social from Biological Mechanisms

PDE can be expected to operate through biological, psychological and social mechanisms. Physiological insults resulting from PDE may be sufficient to affect later-life health *sans* further mediating social processes. For example, the sympathetic nervous system, the hypothalamo-pituitary-adrenal (HPA) axis, the neuroendocrine system, the immune system, and inflammatory responses might be altered by bereavement and affect

later-life physical health (Rostila, Saarela, & Kawachi, 2013) or behavioral health through intermediate psychological states such as disorganized attachment, impulsivity, aggression and asociality (Beauchaine et al., 2011; Brent et al., 2004). However, a facile approach such as this underestimates the full exposure load, because stressors tend to "proliferate" (Pearlin, Aneshensel, & Leblanc, 1997, p.224). PDE may increase the likelihood of secondary stressors, require an underlying vulnerability (a type of chronic stressor) to exact its full potential influence, or occur in tandem with other stressors. In particular, considering only direct psychobiological mechanisms ignores the ubiquity of *linked lives*—that social relationships, in particular those in one's birth family, powerfully affect an individual's life chances and experiences (George, 2003). These powerful social groups form *convoys* (Moen & Hernandez, 2009) that shuttle a person from birth to death, potentially providing social integration that can affect health through social regulation, support, and conflict (Berkman & Syme, 1979; House, Umberson, & Landis, 1988). Parental death in early life, then, is a unique stressor in that it introduces potential physiological insults during sensitive periods of peak physiological plasticity (Gluckman et al., 2010), while simultaneously depriving the child of a key social tie that could facilitate effective coping or avoidance of future stressors (Thoits, 1995).

Yet, research into the social mechanisms linking PDE to later-life suicide risk is scant. The first core paper in this dissertation addresses this limitation in two key ways. First, it considers the potential effect of the widowed parent's remarriage following the death. This provides potential additional social economic and emotional supports and social regulation for the surviving child and spouse. If the remarriage of widowed parent decreases the harmful association of PDE with suicide, then social interventions will

probably prove helpful, since remarriage hints at social more than biological mechanisms. Second, it compares the risk of suicide to risk of cardiovascular disease (CVD). The proposed mechanisms linking PDE to suicide and CVD differ slightly, and can help to disentangle the social from biological mechanisms. Again, knowledge of which mechanisms to target might help decrease risk for suicide associated with PDE.

Differential Vulnerability and Lifelong Risk

One should also consider that not all individuals who experience PDE suffer serious health consequences. While healthy grieving should occur, only a minority of individuals suffer from prolonged behavioral health symptoms (Dowdney, 2000). Why do effects seem to persist more for some than others? Some people may have innate qualities that help them adapt to stressors more effectively than others (Werner, 1995), including genetic predispositions (Labonte & Turecki, 2010). Indeed, an underlying chronic sensitivity to stress may be necessary in order for PDE to exert its deleterious effects. In the sociological literature, this phenomenon has been termed *differential vulnerability*, and the area is ripe for research (Hertzman & Boyce, 2010).

The second paper delves into this territory of differential vulnerability by examining how the association of PDE with behavioral health is conditioned by familial susceptibility. Specifically, I investigate how the presence of a high family history of suicide moderates the association of the PDE exposure with the risk of later-life major depression and substance abuse. This paper necessarily delves into both social and genetic literature by potentially examining how the Waddington's (1957) epigenetic landscape can direct social experiences into realized health outcomes, and thereby links

the sociological with genetic literature on early-life stress and behavioral health. The paper also reemphasizes the life-course principle that *development and aging are lifelong processe*s (Elder & Johnson, 2003), by examining behavioral health outcomes after age 65. The idea that a person's familial vulnerability can interact with an early-life exposure to affect behavioral health at advanced ages truly demonstrates the power of these early-life starting-points. Finally, the paper demonstrates how large demographic pedigree databases can be utilized to approximate genetic risk by implementing a measure called the familial standardized incidence ratio (Kerber, 1995). It thereby provides a creative twist on the concept of *linked lives* by literally linking lives and deaths observed in demographic pedigrees to create a familial measure of heritable risk. The end result is a transdisciplinary measure of vulnerability that can be utilized in future studies.

Empirically Coalescing Early-Life Costressors

The third paper synthesizes past findings on how linked lives and disparate early-life stressors affect health not only theoretically, but empirically, as I create a new measure of early-life stress called the Utah demographic childhood adverse exposures (DECADE) scale. The scale empirically and theoretically incorporates nine early-life stressors that the biodemographic literature has previously linked to later-life health through such mechanisms as linked lives, genetic risk, social integration, and inflammatory exposure. PDE is but one of these detrimental early-life exposures—though by no means a small one. I further test the scale, and subscales, for associations with suicide and all-cause mortality risk, and make appropriate inferences regarding social and biological mechanisms. I hope this paper will not only provide a substantial contribution

to the life-course literature on suicide and behavioral health, but also be utilized by other researchers for studying additional phenotypes of interest.

Data

Before embarking on the three papers, a brief overview of the data is in order. The Utah Population Database (UPDB) served as the basis of the data for this dissertation. The UPDB is a premiere and unique genealogical database containing information on nearly 8 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 2 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 institutional review board (IRB) human subjects and Utah Resource for Genetic and Epidemiologic Research (RGE) approval (Wylie & Mineau, 2003). The confidentiality of individuals represented in these records is maintained based on agreements between RGE and the data contributors.

Large genealogical databases of this order are ideal for life-course biopsychosocial investigations of health for numerous reasons (Gavrilov, Gavrilova, Olshansky, & Carnes, 2002), including the ability to examine linked lives, improving statistical power for identifying gene-environment interactions (Collins, 2004; Manolio, Bailey-Wilson, & Collins, 2006), and the ability to implement family-based study designs

(Vogler, 2001). It is here noted that UPDB is not the only such database in existence. The interested reader should consider an excellent paper by Gavrilova and Gavrilov (1999), and investigate more recent and even future databases, such as the Digitizing Scotland project (Longitudinal Studies Centre Scotland, 2014)

I believe that the reader will gain an increasing awareness of the utility of such databases for examining suicide and other behavioral health outcomes throughout this dissertation, and therefore further elaboration risks over-encumbering this introduction. Indeed, it is hoped that this approach of situating early-life stress and later-life behavioral health within a biopsychosocial life-course framework, and testing appropriately formed hypotheses with demographic pedigree data will greatly improve the present state of scientific knowledge. It is also hoped that the findings will lead to improved interventions that can help individuals, families and communities live longer, happier lives.

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CHAPTER 2

LIFE AND DEATH IN THE FAMILY: EARLY PARENTAL DEATH, PARENTAL REMARRIAGE, AND OFFSPRING SUICIDE RISK IN ADULTHOOD

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Life and death in the family: Early parental death, parental remarriage, and offspring suicide risk in adulthood

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Life-course

ABSTRACT

Early-life parental death (PD) may increase suicide and other mortality risk in adulthood. The potential implications of subsequent remarriage of the widowed parent (RWP) for suicide have not been well examined. Data came from the Utah Population Database for birth cohorts between 1886 and 1960, yielding a sample of N = 663,729 individuals, including 4533 suicides. Cox models showed PD was associated with increased adult suicide risk before age 50, and with increased risk of cardiovascular disease deaths (CVD) for adults of all ages. For females, RWP attenuated the suicide relationship before age 50 (though not statistically significant), but significantly exacerbated it after age 50. RWP had no significant impact for males. Further, for females, PD's positive association with suicide was stronger than with CVD before age 50. These findings reinforce the importance of biological and social mechanisms in linking early-life stressors to adult mental and physical health.

Suicide was the 10th leading age-adjusted cause of death in the United States for 2011 (Hoyert and Xu, 2012). While proximal stressors are known to affect suicide risk (Denney et al., 2009), early-life stressor have also been implicated (Agerbo et al., 2002). A potential early-life stressor implicated in suicide risk (and overall mortality) is early-life parental death (PD) (Niederkrotenthaler et al., 2012; Smith et al., 2009). Given that approximately four percent of children in the United States experience PD before age 18 (Social Security Administration, 2000), PD may represent a significant suicide risk for the population, and research into possible mechanisms might direct attention to effective interventions.

A life-course framework draws our attention to "linked lives" (George, 2003), where losing the parent deprives the surviving child of a prominent social tie. Remarriage of the widowed parent (RWP) might replace that lost tie thereby attenuating the risk triggered by PD, or further compound the risk through increased conflict. Yet, this potential dynamic has not been well researched. Since such associations across the life-course likely involve chronic stress mechanisms of allostatic load (McEwen and Stellar, 1993), comparisons of long-term suicide risk to a competing cause of death might also help clarify the operations of these mechanisms (Thoits, 1995).

We utilized the Utah Population Database (UPDB) to test the importance of RWP in the PD-suicide relationship, and to compare associations with cardiovascular disease death (CVD), the leading cause of death. Such research should provide health professionals with information from which to base interventions. This study deals with two generations—parent and child. To avoid ambiguity, we refer to the adult child (who might have experienced early parental death, and who may die by suicide) as the "subject". All other relationships are addressed in relation to the subject (e.g., subject's mother, subject's stepfather).

1. Background

Large population-based studies examining the relationship of PD on risk of completed suicide are rare. Agerbo et al. (2002) compared all 496 suicides from the population of Denmark aged 10–21 years between 1981 and 1997 with 24,800 sex- and age-matched controls. They showed that experiencing maternal death in early life increases suicide risk. Gravseth et al. (2010) studied the population of Norway born from 1967 to 1976 and followed them until 2004. Of the 610,359 individuals that still lived in Norway at their 19th birthday, they identified 1406 suicides. They showed a slightly higher risk of adulthood suicide for those experiencing PD by age 19. Also, a history of mother's marital instability was

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correlated with increased suicide risk, though they did not examine the effects of RWP *per se*. Linking data from multiple Swedish registers between 1969 and 2004, Wilcox et al. (2010) studied over 4 million parent-offspring pairs. After matching by sex and birth-year of parent and offspring, they found the risk of suicide increased among offspring whose parents died by suicide, but not among offspring whose parents died by other causes. Niederkrotenthaler et al. (2012) studied the population of Sweden born between 1973 and 1983 in a matched case-control study. They found PD after age 10 increased suicide risk, but PD previous to age 10 only significantly increased suicide risk when the PD was itself a suicide.

This body of literature is limited both in size and complexity. We build upon it by discussing and testing potential biological and social mechanisms within a life-course framework, which directs our attention to ensuing secondary chronic stressors (George, 2003; Kuh and Ben-Shlomo, 2004; Pearlin et al., 1997), considers the "linked lives" of family members (George, 2003), and views development and health as lifelong processes (Elder and Johnson, 2003). PD can be separated into two key subcomponents, each of which may independently affect adulthood mortality risk. The first is the experience of death, which may directly "scar" (Preston et al., 1998, p. 1232) the subject for life. The other is lost social integration and associated secondary stressors.

The stress associated with the death itself may lead to physical and emotional scarring, initiating direct psychobiological changes. Childhood is a sensitive period of development, and attachment theory predicts that death of a parent (particularly the mother) will devastate the child who relies upon the parent to sustain life (Bowlby, 1980). The grief following parental death may be intense, and affect health through acute or chronic mechanisms. If the grief-related shock is intense enough, a survivor may suffer from "broken heart syndrome", which might increase acute health responses such as myocardial infarction (Cramer et al., 2007; Rostila et al., 2013). Familial death may also lead to sudden suicide (Ajdacic-Gross et al., 2008). However, the chronic nature of stress should also be considered. Grief may persist throughout life (Bowlby, 1980), particularly since children may not be as capable as adults in proceeding through healthy grieving processes (Sood et al., 2006). As childhood is a period of great physiological plasticity (Heim et al., 2008), regulatory responses may be conditioned far into adulthood (Luecken and Roubinov, 2012). This suggests an increased likelihood of allostatic load, affecting health through such physiological mechanisms as the sympathetic nervous system, the hypothalamo–pituitary–adrenal (HPA) axis, the neuroendocrine system, the immune system, and inflammatory responses (Luecken and Roubinov, 2012; McEwen and Stellar, 1993; Rostila et al., 2013). These physiological mechanisms might increase the risk for prevalent chronic physical illnesses such as cardiovascular disease (CVD), psychiatric disorders such as major depression, borderline personality disorder, post-traumatic stress disorder, and substance abuse; and suicide (Beauchaine et al., 2011; Heim et al., 2008; Rostila and Saarela, 2011).

Unhealthy behaviors, such as smoking and substance abuse, may further increase the likelihood of poor health outcomes as the subject tries to cope (Martikainen and Valkonen, 1996). These behaviors might be compounded by a diminution in parental supervision following PD, because parental expectations often serve as a deterrent against unhealthy behaviors (Nash et al., 2005). This phenomenon highlights the fact that PD not only acts as a substantial psychogenic stressor, but that it also decreases social integration, which is related to suicide (Durkheim, [1897] 1951).

At the individual level, *social integration* may constitute the existence of a relationship of given type (House et al., 1988). When PD occurs, subjects lose one or two people in their social (parental) network, altering health through mechanisms involving changes in *social support*, *social regulation*, and *conflict* (House et al., 1988). *Social support* consists of instrumental or emotional assistance, both of which affect health (House et al., 1988). Losing a parent decreases potential socioeconomic resources. Early familial disruption can result in downward social mobility for the surviving family members (Biblarz and Gottainer, 2000), which can increase suicide risk (Breed, 1963). Lost *social regulation* here refers to the aforementioned diminution of informal social control against unhealthy behaviors such as substance abuse (Nash et al., 2005). *Conflict* may decrease if the relationship with the parent was unhealthy or even abusive (Umberson and Chen, 1994), though some research suggests families with high levels of conflict may actually fare worse following PD (Dowdney, 2000). Bereavement will also require emotional and instrumental adaptation of the surviving spouse, thereby temporarily decreasing their efficiency in the parental role (Luecken and Roubinov, 2012). For example, the foregone income due to PD may also require the widowed parent to devote more time to paid employment (Biblarz and Gottainer, 2000), reducing time available to emotionally support the subject. Therefore, in some ways the surviving child "loses" social resources from both parents.

Examining the moderating role of widowed parent's remarriage can help clarify these chronic mechanisms since RWP can restore lost social integration. A stepparent might not simply "replace" a biological parent, as step-parental relationships are often of poorer quality (Daly and Wilson, 2005). But, since RWP is beneficial for other health outcomes (Andersson et al., 1996; Norton et al., 2011), it likely also attenuates any increased suicide risk.

Examining multiple outcomes in the same study has been enjoined as another approach for clarifying stress-related mechanisms (Thoits, 1995). The physiological mechanisms discussed thus far influence one's risk not only for suicide, but possibly for other causes of death. Does PD increase the risk for suicide *per se*, or is it simply increasing the risk for bad health overall, of which suicide is but one indicator? While many potential causes of death could be compared to suicide, CVD provides an excellent comparative cause because it is positively associated with familial death and is believed to operate through similar mechanisms of allostatic load (McEwen and Stellar, 1993; Rostila et al., 2013; Rostila and Saarela, 2011). Even psychiatric disorders such as major depression and borderline personality disorder are risk factors for both CVD and suicide (but not so much other common causes of death such as diabetes) (El-Gabalawy et al., 2010). Furthermore, CVD is the leading cause of death in the United States (Hoyert and Xu, 2012), and might therefore conceptually be viewed as a general indicator of compromised health.

If PD is more strongly associated with suicide than with CVD, we might infer that some mechanisms are more specific to suicide. We therefore suggest that comparing these competing causes of death may help clarify the most salient chronic mechanisms, and provide guidance on potential interventions. Furthermore, the fact that many mechanisms generate similar mortality patterns suggests some subjects who might have died by suicide will die of a competing cause first, so comparisons might help clarify age-specific mechanisms.

Beyond the key foci of remarriage and competing risks, the relevance of sensitive stages and dose–response relationships should also be considered. Physiological plasticity may peak during specific sensitive substages of development within the childhood period (Niederkrotenthaler et al., 2012), conditioning the magnitude of associations. Attachment theory applies more specifically during the first few years of life when the child is completely dependent upon the parental figure (Bowlby, 1980); therefore, traumas occurring during this period might especially heighten the

subject's adverse chronic stress responses. Sensitive stages also have implications for RWP's impact. Younger stepchildren are more likely to "accept" a stepparent (Adler-Baeder and Higginbotham, 2004). Earlier PD increases the likelihood of RWP at an earlier age, possibly improving the step-relationship's quality.

If PD of one parent is a risk factor for suicide, then PD of both parents might be a stronger risk factor, consistent with a dose–response relationship. The term "orphanhood" may be used to refer to a special type of dual-PD where an individual comes under the care of the state with potential supports such as foster care or legal adoption (Triseliotis, 2002). This is probably more likely when both parents die at the same time or in close succession (very rare), and would further complicate the dynamics of social integration. However, it is worth noting that even in such cases, the individual is without the support of either biological parent. Showing a dose–response relationship can increase confidence that an observed association is not artifactual (Gordis, 2008).

Research Hypotheses. We propose the following six testable hypotheses.

H_1: PD will increase suicide risk for all subjects.
$H_{2:}$ Dual-PD will increase suicide risk more than PD of one parent.
H_3: Maternal PD will increase suicide risk more than paternal PD.
H_4: Among subjects exposed to PD, those experiencing RWP will experience a smaller increased suicide risk than those without RWP.
H_5: The relationship between PD and suicide risk will vary by the age PD was experienced.
H_6: The excess mortality risk following PD will be greater for suicide than for CVD.

2. Methods

The UPDB served as the basis for the data. UPDB is a genealogical and medical database containing information on nearly eight million individuals, and includes genealogies of the founders of Utah and their descendants up to the present time. It is a dynamic database that receives annual updates of Utah births, deaths, driver licenses, and health records. The database includes over two million Utah birth certificates and around 800,000 death certificates spanning a century. The Utah Resource for Genetic and Epidemiologic Research (RGE) is a special regulatory body created to administer access to UPDB for research purposes. All research requires IRB 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.

First, we constructed mother, father and subject triads. We identified 1,491,140 subjects born between 1886 and 1960, inclusive. Since our cause-of-death records began in 1904, and 18 years of age was our baseline age for measuring suicide risk, no subjects born prior to 1886 were included. We excluded subjects born subsequent to 1960 to improve availability of SES and baptism data (necessary controls). Linking subjects to parents yielded 1,255,818 triads. In order to satisfactorily test the hypotheses, we refined potential triads to those with complete data for all members. We excluded triads where the subject's sex or last date of Utah residence was unknown, birth year of either parent was unknown, the parents' follow-up data were inadequate, or the father was known to have died prior to the subject's birth. The new refined subsample consisted of 901,579 triads. We also excluded 5808 triads where the subject was known to be adopted and 10,109 triads where any of their members were polygamous. Since we were examining suicide risk in adulthood, we then excluded 198,927 triads where the subject did not have follow-up data to at least age 18 (note that of these, 35,969 were known to have died, 73 from suicide, with the rest lost to follow-up due to emigration or limited data). Finally, we excluded 23,006 triads where the mother or father did not have a recorded death date and we did not have follow-up information past the subject's 18th year.

The final sample comprised N = 663,729 subjects, including 4533 subjects who died by suicide. This represents 52.85% of the potential triads originally identified. The retained were significantly more likely to be female (53.91% vs. 51.87%), and had a higher mean birth-year (1931.41 vs. 1925.54). And those dying by suicide were significantly more likely to be retained (64.85% vs. 52.79%).

2.1. Measures

Health Outcomes. Suicide was measured using ICD codes (versions 6–10) and "manner of death" indicators obtained from Utah death certificates, which were available for years 1904–2010. Suicide was indicated by ICD codes E963, E970–E979 (ICD6/7); E950–E959 (ICD8/9); X60–X84, Y87.0, U03 (ICD 10)—or a manner of death indicating suicide. The risk of suicide in our sample peaked for men after age 75, and for women around age 50, consistent with prior research (National Center for Injury Prevention and Control, 2012). *CVD* was included as a competing risk of death with ICD codes 400–469 (ICD6/7); 390–459 (ICD8/9), I00-99 (ICD10) from death certificates.

Key Exposures. Early Life Death of Parent (PD) was determined from parent's death year and subject's birth year. If the parent's death year occurred previous to the subject reaching age 18, then that subject experienced PD. This specification was utilized in the *Basic Sequence* (see "Analytic Strategy" below). In the *Age Sequence*, this variable was separated into exposure categories *Age 0–5*, *6–11*, and *12–17*.

Remarriage of widowed parent (RWP) was considered when the widowed parent remarried before the subject reached age 18 and within five years of PD. This five-year requirement measured ongoing social integration throughout post-PD childhood by ensuring the subject had substantial time with the stepparent, and to address the potential confounding of RWP and age at PD. Regardless of age at PD, imposing the five-year requirement allotted fairly equal time periods for RWP. When both parents died in childhood (i.e., dual-PD), RWP was technically possible if the deaths occurred in different years, but was not considered due to small sample sizes.

Control Variables. Father and mother suicides were coded 1 when that parent died by suicide previous to the subject's death or censoring, and 0 otherwise, to account for possible familial suicide risk. Note this variable does not require PD, as the suicide may have occurred during subject's adulthood. *Maternal and paternal age at subject's birth* were continuous variables. *Subject's year of birth* was utilized to stratify Cox models. *Subject's baptism* by age nine measured membership in the Church of Jesus Christ of Latter-day Saints (LDS or Mormon), and was coded as a binary variable. As members of this church played a large role in the founding of the state of Utah, a large proportion of the population has historically belonged to this faith. Normative baptism age is shortly after age eight (Lyon et al., 1994), and membership may indicate abstention from alcohol, tobacco and other substances, and a supportive community structure (Mineau et al., 2004).

Subject marriage was treated as a time-varying covariate, assuming a value of 1 following the subject's year of first marriage, and 0 otherwise. *Early-life SES* was measured with the Nam-Powers SES Score, which recodes one's usual occupation (a qualitative

measure) into a quantitative value on a scale (1–99), with higher values representing higher SES (Nam and Powers, 1983). Father's and mother's usual occupation as recorded on a Utah death certificate were the basis for the subject's Nam Powers score. Consistent with prior PD-suicide research (Niederkrotenthaler et al., 2012), the greater of the two parental scores represented the subject's SES. We coded this score to a six-category variable: including four ranked quartiles (1–25, 26–50, 51–75, 76–99), farming (a score of 40), and missing. Farming was considered separately, because empirical analyses showed a large number of subjects in this group. Basic descriptive statistics for the sample are displayed in Tables 1 and 2.

2.2. Analytic strategy

Analyses were conducted in two phases. In the first phase, we estimated two series of nested Cox hazard models, where the outcome of interest was time to suicide after age 18 and censoring occurred at age the subject was last known alive in Utah. This censoring age was chosen because individuals may have emigrated and died by suicide in other states. Each model was stratified by subject's birth-year to control for cohort and period effects (Kom et al., 1997). Models were estimated separately for males and females, because they differ in suicide risk (National Center for Injury Prevention, 2012) and responses to stress (Heim et al., 2008). Comparisons between female and male subjects are not formally part of this analysis.

Two nested model sequences were utilized. A likelihood ratio test (G^2) tested each hypothesis by comparing the nested (unconstrained) model to its parent (constrained) model via their log-likelihood fit statistics. This nesting strategy enabled us to test the complex configurations of PD and RWP in one integrated statistical sequence.

The nesting configuration is diagrammed in Fig. 1, which shows the names of each model and the number of variables (including controls) each contains. The *Basic Sequence* informed whether each new variable set provided information that significantly affected hypotheses H_1–H_4, and the *Age Sequence* specifically tested H_5 (i.e., that age of the child at PD affected suicide risk). As each new set of variables was added, an associated variable for the interaction of each variable with age 50+ was also included. This heaviside function addressed the Cox model's proportionality assumption (Kleinbaum and Klein, 2005). Age 50 is deemed an appropriate life-course threshold, because couples often end childbearing and shift priorities towards later life about age 50 (Karp, 1989).

The *Basic Sequence* began with the *Null* model, which included all control variables. The *Parental Death* model added the additional variable of PD of at least one biological parent. In the three remaining models, this PD category was further segmented into mutually exclusive groups of increasing complexity to test hypotheses 2 through 4. The *Dual-PD* model divided PD into the categories of (1) exactly one PD and (2) dual-PD. The *Sex of Parent* model separated PD into categories of (1) maternal PD, (2) paternal PD, and (3) dual-PD. The *Parental Remarriage* model used PD categories of (1) exactly one PD without RWP; (2) exactly one PD with RWP; and (3) dual-PD. Note some models could not be nested within others, and the reader is referred to Fig. 1 for nesting configurations.

The *Age Sequence* included the same models from the *Basic Sequence*, except each key variable was further segmented into the three age groups of 0–5, 6–11, and 12–17. For example, the Age Sequence Parental Remarriage model included 25 variables: the seven variables PD age 0–5 without RWP, PD age 6–11 without RWP, PD age 12–17 without RWP, PD age 0–5 with RWP, PD age 6–11 with RWP, PD age 12–17 with RWP, dual PD; seven associated later-life interaction terms; and eleven control variables. Each of these models was nested within its *Basic Sequence* counterpart, and the associated G^2 tested H_5.

In the second analysis phase, those models that best informed H_1–H_4 were selected for further examination and testing, including

Table 1
Descriptive statistics for health outcomes, and parental death (PD) and remarriage of widowed parent (RWP) exposure Categories.

	Female		Male	
	Frequency	Percentage	Frequency	Percentage
Total	327,159	100.0%	336,570	100.0%
Health outcomes				
Suicide	951	0.3%	3582	1.1%
Cardiovascular death	53,353	16.3%	57,849	17.2%
Censored	272,855	83.4%	275,139	81.7%
PD category				
No PD	287,164	87.8%	297,026	88.3%
At least one PD	39,995	12.2%	39,544	11.7%
0–5	10,141	3.1%	9672	2.9%
6–11	13,060	4.0%	13,000	3.9%
12–17	16,794	5.1%	16,872	5.0%
Exactly one PD	38,040	11.6%	37,733	11.2%
0–5	9300	2.8%	8930	2.7%
6–11	12,319	3.8%	12,311	3.7%
12–17	16,421	5.0%	16,492	4.9%
One PD, RWP	30,087	9.2%	29,981	8.9%
0–5	5987	1.8%	5854	1.7%
6–11	9260	2.8%	9302	2.8%
12–17	14,840	4.5%	14,825	4.4%
One PD, no RWP	7953	2.4%	7752	2.3%
0–5	3313	1.0%	3076	0.9%
6–11	3059	0.9%	3009	0.9%
12–17	1581	0.5%	1667	0.5%
Maternal PD only	14,515	4.4%	13,942	4.1%
0–5	3940	1.2%	3646	1.1%
6–11	4906	1.5%	4665	1.4%
12–17	5669	1.7%	5631	1.7%
Paternal PD only	23,525	7.2%	23,791	7.1%
0–5	5360	1.6%	5284	1.6%
6–11	7413	2.3%	7646	2.3%
12–17	10,752	3.3%	10,861	3.2%
Dual-PD	1955	0.6%	1811	0.5%

Table 2
Descriptive statistics for control variables.

	Female		Male	
Categorical Variables	Frequency	Percentage	Frequency	Percentage
Total count	327,159	100.0%	336,570	100.0%
Categorical variables				
Maternal suicide	467	0.1%	471	0.1%
Paternal suicide	2012	0.6%	2127	0.6%
Baptized	175,426	53.6%	171,010	50.8%
Married	234,288	71.6%	236,257	70.2%
Nam powers score (SES)[a]				
76–99	47,946	14.7%	49,867	14.8%
51–75	65,934	20.2%	67,943	20.2%
26–50, excluding 40	43,764	13.4%	45,567	13.5%
1–25	20,891	6.4%	20,910	6.2%
40 (Farming)	66,291	20.3%	68,510	20.4%
Missing	82,333	25.2%	83,773	24.9%
Continuous variables	**Mean**	**Std. Dev.**	**Mean**	**Std. Dev.**
Subject's birth year	1931.0	21.4	1931.8	21.3
Maternal age	28.3	6.4	28.2	6.4
Paternal age	32.0	7.6	31.9	7.6
Subject's years of follow-up (from birth year)	63.5	19.4	61.1	18.1

[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.

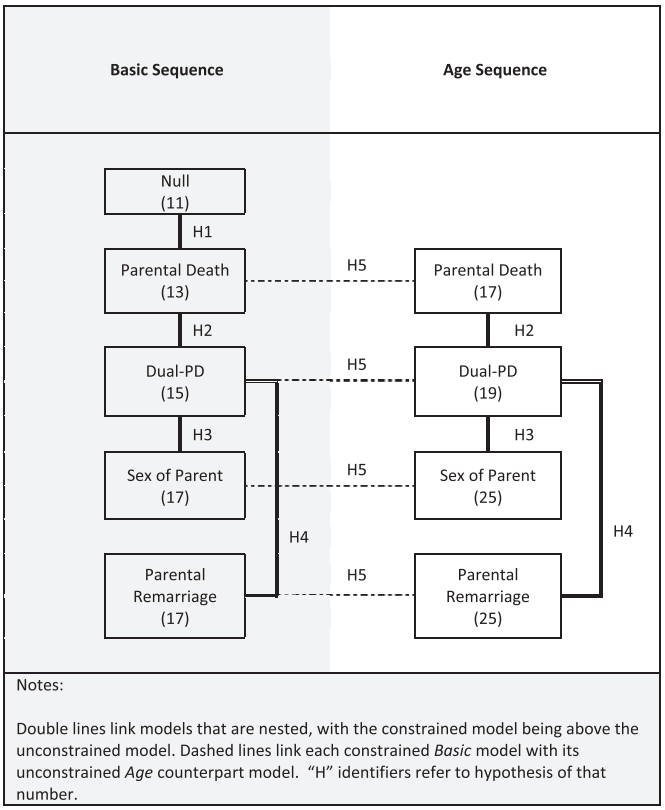

Fig. 1. Nested model sequence diagram.

comparisons to CVD mortality as a competing risk and additional Wald tests for equality of coefficients where appropriate. Here, suicide and CVD mortality were jointly modeled using the method of Lunn and McNeil (1995). This method modeled suicide considering all other outcomes as censored, while simultaneously modeling CVD mortality considering all other outcomes as censored. Modeling each separately would yield identical parameter and standard error estimates, but this simultaneous approach enabled direct statistical comparisons between suicide and CVD mortality hazards via Wald tests (Kleinbaum and Klein, 2005; Lunn and McNeil, 1995). Models were estimated in SAS 9.3 using PROC PHREG, and Wald tests for equality of coefficients were performed using SAS's "test" command within that procedure.

3. Findings

3.1. Model fit

Females. Subtable 3a displays the model fit statistics within the *Basic Sequence* for females. Cells directly testing hypotheses are shaded gray. Testing the *Null* model against the *Parental Death* model yielded a p-value <0.001, warranting further investigation of the *Parental Death* model. The other statistically significant comparison was *Dual-PD* vs. *Parental Remarriage*. Here, the crucial element was remarriage (RWP). In fact, the *Parental Remarriage* model significantly improved upon all more parsimonious models. Accordingly, remarriage may be an important moderator for females with respect to how parental death correlates with later suicide risk. Comparing the *Base* to *Age Sequences* (subtable 3b) did not significantly improve model fit. Thus, we found no evidence suggesting sensitive substages were important prior to age 18. Though not explicitly shown, we note that within the *Age Sequence*, comparing the *Dual-PD* to *Parental Remarriage* model significantly improved model fit. So, even when considering age at PD, remarriage proved important.

Males. In subtable 4a, the only statistically significant key comparison was between the *Null* and *Parental Death* models. Considering age at PD (subtable 4b) did not significantly improve model fit. Therefore, we found no evidence suggesting the sex of the parent, death of both parents, remarriage of widowed parent, or childhood substage were important moderating factors related to male suicide risk.

Table 3
Females: Likelihood ratio tests comparing model Fits.

Females
N=327,159

Subtable 3a: Comparisons between Models within Basic Sequence

Model Name	LL	df	Null	Parental Death	Dual-PD
			-7797.19	*-7789.08*	*-7787.65*
			11	*13*	*15*
Parental Death	*-7789.08*	*13*	16.22, 2 ***		
Dual-PD	*-7787.65*	*15*	19.08, 4 ***	2.86, 2	
Sex of Parent	*-7787.22*	*17*	19.95, 6 **	3.73, 4	0.87, 2
Parental Remarriage	*-7783.45*	*17*	27.48, 6 ***	11.26, 4 *	8.40, 2 *

Subtable 3b: Comparisons of Models between Basic and Age Sequences

Model Name	Base Models		Age Models		Chi-squared
	LL	df	LL	df	
Parental Death	*-7789.08*	*13*	*-7786.96*	*17*	4.25, 4
Dual-PD	*-7787.65*	*15*	*-7786.04*	*19*	3.21, 4
Sex of Parent	*-7787.22*	*17*	*-7784.43*	*25*	5.58, 8
Parental Remarriage	*-7783.45*	*17*	*-7778.70*	*25*	9.50, 8

Notes:

Each subtable consists of model fit log likelihood (LL) statistics and degrees of freedom (df) for nested model specifications.
In subtable a, constrained models are in the columns and unconstrained in rows. The cells are populated with the chi-square statistics from likelihood ratio tests in the format: chi-square value, df followed by statistical significance.

Subtable b compares the constrained *Basic* model to its counterpart unconstrained *Age* model in rows only.

*p<.05 **p<.01 ***p<.001

3.2. Cox model parameter estimates

We present and interpret results for the models that improved upon their simpler nested counterparts. For females, this includes the *Parental Death* and *Parental Remarriage* models in the *Basic Sequence*. For males, this includes only the *Parental Death* model in the *Basic Sequence*.

Females. Table 5 shows the hazard ratios (HR's) and significance levels predicting suicide, and cardiovascular death, for each variable in the two Cox models for females. It also displays statistical significance levels from Wald tests for equality between suicide and CVD HR's. Estimates for control variables barely varied across model specifications and were not our main focus. We do not interpret these estimates, but they are presented in Table 6 for the *Basic Parental Death Model*.

In the *Parental Death* model, for females under age 50, PD was associated with a 65% increased risk of suicide. The association with CVD was only 20%, and significantly smaller than the risk for suicide. This lends support for the hypothesis that PD will increase suicide risk more than CVD. This changed after age 50, where the association between PD and suicide disappeared, but the association with CVD remained and was statistically higher than the risk for suicide. In the *Parental Remarriage* model, PD of exactly one parent without remarriage of the widowed parent was associated with a significantly increased suicide risk, but there was no significant increase in suicide risk when remarriage occurred. An additional Wald test for equality between these two parameters yielded an insignificant p-value, so we cannot be certain the hazard ratio for those with RWP was smaller than for those without. Suicide risk for dual-PD females under 50 trebled the risk of those with no PD. An additional test showed the hazard for dual-PD was higher than for single-PD with remarriage, but not without remarriage. So once remarriage is considered, the death of both parents becomes significant, suggesting a possible dose–response to putative lost social integration. After age 50, we found a reverse association. Remarriage was associated with statistically higher suicide risk than no remarriage, suggesting possible late-onset harmful associations between parental remarriage and suicide.

Males. Table 5 also displays the *Parental Death* model for males. Before age 50, parental death was significantly associated with a 24% increased risk of suicide. The association was absent after age 50. There was no difference between suicide and CVD risk under age 50, but CVD risk was statistically greater than suicide risk after 50.

3.3. Additional tests

To deal with possible issues of independence of study subjects since sibships are present in the data, we performed two sensitivity analyses for the parameters specific to risk of suicide in the *Basic Sequence* models presented in Table 5. First, we re-estimated the models with the sandwich estimator (Kleinbaum and Klein, 2005) by computing robust standard errors clustered about the mother. The findings were substantively similar. Next, we re-estimated the

Table 4
Males: Likelihood ratio tests comparing model Fits.

Males
N=336,570

Subtable 4a: Comparisons between Models within Basic Sequence

Model Name	LL	df	Null	Parental Death	Dual-PD
			-29285.02	*-29280.58*	*-29280.04*
			11	*13*	*15*
Parental Death	*-29280.58*	*13*	8.87, 2 *		
Dual-Bereaved	*-29280.04*	*15*	9.95, 4 *	1.08, 2	
Sex of Parent	*-29278.09*	*17*	13.84, 6 *	4.98, 4	3.9, 2
Parental Remarriage	*-29278.43*	*17*	13.18, 6 *	4.32, 4	3.23, 2

Subtable 4b: Comparisons of Models between Basic and Age Sequences

Model Name	Base Models		Age Models		Chi-squared
	LL	df	LL	df	
Parental Death	*-29280.58*	*13*	*-29278.47*	17	4.23, 4
Dual-PD	*-29280.04*	*15*	*-29277.86*	19	4.37, 4
Sex of Parent	*-29278.09*	*17*	*-29274.12*	25	7.94, 8
Parental Remarriage	*-29278.43*	*17*	*-29274.82*	25	7.21, 8

Notes:

Each subtable consists of model fit log likelihood (LL) statistics and degrees of freedom (df) for nested model specifications.
In subtable a, constrained models are in the columns and unconstrained in rows. The cells are populated with the chi-square statistics from likelihood ratio tests in the format: chi-square value, df followed by statistical significance.

Subtable b compares the constrained *Basic* model to its counterpart unconstrained *Age* model in rows only.

*p<.05 **p<.01 ***p<.001

Table 5
Cox model hazard ratios and significance levels for suicide and cardiovascular death (CVD), and Lunn–McNeil Wald tests.

Females	Parental death Model			Parental remarriage Model		
N = 327,159	Suicide	=[b]	CVD	Suicide	=	CVD
Under 50						
At least one PD	1.65***	[*]	1.20***			
Exactly one PD						
One PD, no remarriage				1.70***	[**]	1.18**
One PD, remarriage				1.07		1.23*
Dual PD				3.06**	[*]	1.33
50-and-over[a]						
At least one PD	1.01	[***]	1.12***			
Exactly one PD						
One PD, no remarriage				0.83		1.13***
One PD, remarriage				1.77*	[*]	1.05
Dual PD				0.77		1.20***
Males	**Parental death model**			Omitted		
N = 336,570	**Suicide**	=	**CVD**			
Under 50						
At least one PD	1.24**		1.34***			
50-and-over[a]						
At least one PD	1.02	[*]	1.10***			

*p < 0.05 **p < 0.01 ***p < 0.001.
Reference group is no PD. Models include all control variables (not shown).
[a] For 50-and-over risk period, HR calculated as [HR for under 50* HR for over-50 interaction term (not presented)], significance level calculated with Wald test.
[b] P-values from Wald tests between suicide and CVD HR's.

models using a subsample formed by randomly selecting one sibling from each mother. Again, the findings were similar.

To test whether the cause of parental death was an important moderator, we further segmented the *Basic Sex of Parent* model into paternal and maternal PD by causes of CVD, respiratory, cancer, other, and unknown. G^2 comparing these models were not statistically significant, suggesting that the cause of the parental death

Table 6
Parameter estimates for control variables in basic sequence parental death model.

Controls variable	Females; N = 327,159			Males; N = 336,570		
	Suicide	=[b]	CVD	Suicide	=	CVD
Maternal suicide	2.22		1.20	2.62***	[***]	0.96
Paternal suicide	1.49		1.04	2.12***	[***]	1.01
Maternal age	0.99		0.99**	0.99*	[**]	1.01
Paternal age	1.01		1.01	1.01*	[**]	0.99*
Baptized	0.50***	[***]	0.88***	0.59***	[***]	0.86***
Married	0.86*		0.88***	0.73***	[*]	0.81***
Nam powers score (SES)[a]						
51–75	0.88	[**]	1.17***	1.03	[*]	1.17***
26–50, excluding 40	0.85	[**]	1.20***	1.14*		1.21***
1–25	0.81	[**]	1.30***	1.11		1.27***
40 (Farming)	0.62***	[***]	1.17***	1.02	[*]	1.16***
Missing	0.76**	[***]	1.07***	0.93	[*]	1.06**

*p < 0.05 **p < 0.01 ***p < 0.001.
[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. Reference group is 76–99 (highest SES).
[b] P-values from Wald tests between suicide and CVD HR's.

was not an important confounder in our sample. Sample sizes prohibited further segmenting cause of death. Finally, though not an explicit focus of this paper, additional analyses also suggested PD increased suicide risk more for females than males before age 50.

4. Discussion

Consistent with previous research, we found that early-life parental death was associated with an increased risk of suicide and CVD after age 18 for both sexes. We observed a dose–response relationship, where women with no living biological parents alive at age 18 had a higher risk for suicide than those with one biological parent and a stepparent before age 50. We suspect this association with remarriage may reflect the importance of lost social integration following PD, particularly since social relationships have been shown to be especially important for female health (House et al., 1988). However, this is not a foregone conclusion, since those who remarry are a non-randomly selected group, and RWP may indicate a latent propensity for healthy adaption that also protects against suicide.

For women over age 50, suicide risk was significantly greater in the presence of remarriage than in its absence. It is known women often provide support to aging parents (Fuller-Thomson et al., 1997). We suspect those women who experienced RWP may feel pressure to care for the stepparent, possibly providing additional stress since step-relationships are more prone to conflict (Daly and Wilson, 2005). We suggest future research attempt to replicate this finding and test possible explanations.

For males, we found no evidence for a moderating impact of widowed parent's remarriage, and no dose–response relationship with PD. It is possible the male suicide hazard is already so high that increasing it further is difficult. Additionally, since the ensuing suicide risk was not greater than CVD risk before age 50, males exposed to early parental death may be dying of CVD before dying by suicide.

Suicide risk generally attenuated after age 50, possibly due to developed resilience (Rattan, 2008; Wheaton, 1999) or mortality selection (Vaupel and Yashin, 1985) over the life-course. We also found that PD increased CVD risk for both males and females, which is consistent with many of the proposed chronic mechanisms linking PD to both health outcomes. For females, PD was a stronger risk for suicide than CVD mortality before age 50. Since this is the period when remarriage appears to be protective, social integration may be more specifically related to suicide. We also note that suicide requires an action by the victim, whereas CVD does not. It may be that certain women learn coping skills to avoid suicide, and that capacity increases over time (Wheaton, 1999); but the allostatic load (McEwen and Stellar, 1993) may accumulate for women and be reflected in higher later-life CVD risk.

We suggest our most important findings imply that the widowed parent's remarriage moderates the association of early parental death with later-life suicide risk for females. Future research should consider how stepsiblings, grandparents and other extended kin networks may further moderate these associations. Future research might also attempt to further disentangle how RWP's effects relate to the child's age at exposure to PD, since such stages have previously shown to be important for predicting suicide risk (Niederkrotenthaler et al., 2012). We note that in cases where the parent dies very early, the widowed parent has more time to remarry. This study tried to adjust for this possibility by requiring the parent to remarry within a five-year time period, and we further showed that considering subject's age at PD did not improve upon our basic predictive models. Further, the evidence suggested that even once age was considered, RWP was still an important moderator.

Subjects in our sample were required to live to age 18. Some research suggests mortality may be higher before age 18 following early parental death (Rostila and Saarela, 2011). Thus, deaths to adolescents may have culled the most susceptible from the population, and therefore we suggest our findings are more relevant to chronic than acute mechanisms. We also suspect some of our subjects that did not experience PD experienced early parental divorce, which is another prevalent form of early familial disruption known to increase suicide risk (Agerbo et al., 2002). Due to data limitations, we could not account for divorce in our study. Survival requirements and the omission of divorce data likely promote a conservative statistical bias. We were unable to measure the subjective quality of family relationships, and could not account for possible external institutions, such as foster home programs, that might become part of a child's life following single or dual-PD. Finally, we note that to obtain the large sample size needed for examining suicide, we coalesced a broad range of birth cohorts from 1886 through 1960. Early PD might be considered an off-time event that is more stressful because of its unexpectedness (Rostila and Saarela, 2011), and therefore parental death and remarriage might yield stronger associations in later cohorts when it is less common. While we stratified by birth-year in the analysis, this cohort heterogeneity may have nevertheless statistically biased estimates towards the null. Despite these potential limitations, this study offers a substantial contribution to the literature on early-life stress and suicide. Health professionals should keep these trends in mind when planning potential interventions.

In terms of policy, efforts aimed at preserving or restoring social resources may prove helpful. The most obvious primary policy implication involves preventing premature deaths of parents. Anything shown to protect the health of new parents, including resources such as education, healthcare, prenatal care, childcare and social welfare services (Marmot et al., 2012) could reduce exposure to the stressor of early parental death. Secondary preventions might involve economic support to the widow or child, including timely survivor benefits and therapies that help survivors cope. Tertiary preventions would include an individualized treatment approach as the clinician works to prevent suicide amongst at-risk individuals, and manage chronic illnesses associated with the early parental death.

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CHAPTER 3

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[1]

Abstract

A differential vulnerability framework suggests parental death in early life (PDE) should only deleteriously impact behavioral health among those at increased risk. We utilized demographic pedigree data from the Utah Population Database to create a risk score of familial susceptibility to suicide (FS) at the population level. Using random effects logistic panel regression models, we tested for a multiplicative interaction between PDE and FS on the risks of major depressive disorder (MDD) and substance abuse (SA), as measured with Medicare claims, after age 65. The final sample included 155,983 individuals, encompassing 1,431,060 person-years. Net of several potential confounders, including probability of survival to age 65, for females we found an FS × PDE interaction, where PDE and FS as main effects had no impact but jointly they

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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.

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

Background

Parental Death in Early Life

Empirical research has linked early parental death to later-life behavioral health risk (Nickerson, Bryant, Aderka, Hinton, & Hofmann, 2013). PDE may affect later-life health through physiological change or "scarring" (Preston, Hill, & Drevenstedt, 1998, p.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, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Rostila, Saarela, & Kawachi, 2013). These changes may further pose risks for behavioral health through disorganized attachment, impulsivity, aggression and asociality (Bakermans-Kranenburg & 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, & Leblanc, 1997), including decreased social integration (Hollingshaus & Smith, 2015) that might accumulate throughout the life-course (Dannefer, 2003). These persistent social deprivations may "get under the

skin" to affect health (Hertzman & Boyce, 2010, p.329).

Inherited Vulnerabilities

There is considerable heterogeneity of responses to the adverse effects of early-life stress (Hertzman & Boyce, 2010). Differential vulnerability to early-life stress—including PDE (Agid et al., 1999)—is one model proposed as a possible explanation for interperson variation in resultant phenotypes (Belsky & 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 (1957) epigenetic landscape (McClearn, Vogler, & Hofer, 2001) 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 & Kendler, 2014; Rietschel & 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, & Engels, 2013). Conversely, protective behaviors, such as marriage (Denney, Rogers, Krueger, & Wadsworth, 2009), may also be partially heritable (Horn, Xu, Beam, Turkheimer, & Emery, 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 & Israel, 2014). However, obtaining adequate statistical power for detecting interactions may also require large sample sizes (Manolio et al., 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 interstudy reliability. Such an approach also fails to account for potential genetic influences (Avenevoli & 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 × environment interactions (Kerber, 1995). The level of measurement is interval, constituting a risk score that could be more appropriate for complex phenotypes (Belsky & 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 et al., 2006). This risk score also encapsulates both genetic and nongenetic 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 & Mendelsohn, 1986) at the population level.

Methods

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 8 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 2 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 & 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 (Hollingshaus & Smith, 2015; Norton et al., 2011; Smith, Hanson, Norton, Hollingshaus, & Mineau, 2014; Smith, Mineau, Garibotti, & Kerber, 2009), 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 & 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 the ego was enrolled in Medicare parts A and B, yielding 1,431,060 person-years of data.

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.

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 FSIRs 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 & Smith, 2015).

We calculated FSIRs 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 FSIRs 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 FSIRs for pedigrees is shown in Figure 3.1. This approach often yielded more than one FSIR for each ego. Therefore, we used the mean of all FSIRs for each ego as that ego's familial suicide susceptibility. The distribution of FS for the Final Sample is displayed in Figure 3.2.

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 & Powers, 1983) obtained from the occupation recorded on the parent's death certificate, consistent with previous research linking PDE to behavioral health disorders (Niederkrotenthaler, Floderus, Alexanderson, Rasmussen, & Mittendorfer-Rutz, 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 an HMO, we unfortunately did not have the necessary data. Finally, time-invariant controls included a statistic called the i*nverse Mills ratio* to account for sample selection (see below) before age 65 via a Heckman two-step selection equation (Fu, Winship, & 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" 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.

Nonrandom 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 et al., 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 the 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 9, which is considered normative for children born into that faith (Lyon, Gardner, & 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 IMRs for all egos. Then, utilizing the Final Sample of 155,983 egos, we estimated sex-specific logistic panel regression models with random effects (Allison, 2009) for each behavioral health disorder (MDD and SA), yielding four models. Logistic regression enables unbiased testing of G × E interactions (Mukherjee, Ahn, Gruber, & Chatterjee, 2012). We extended this G × E methodology to F × E interactions, as they are conceptually similar phenomena. Models were estimated via the *xtreg* command in Stata/SE 10.0. Each model included PDE, FS, FS × 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 & Hamilton, 2006).

While the logistic model is technically nonlinear, an underlying linear model is implied (Allison, 2009) and may be written

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

where *Y* is the logit of the respective behavioral health disorder, and $\beta_{FS\times PDE}$ represents the multiplicative F × E interaction.

To graphically illustrate the nature of the F × 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, & Golder, 2006). This approach can help identify regions of significance that are useful for disentangling G × 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

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

calculated over the range of FS values, where *var(.)* and *cov(.)* are the variances and covariances of the estimated model parameters (Brambor et al., 2006), which we obtained using Stata's *estat vce* postestimation command. These estimates were then used to create charts using R's *ggplot2* package.

Findings

Table 3.1 shows descriptive statistics for the Selection Sample. Estimates from the Heckman selection equation are displayed in Table 3.2. 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 3.3 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 relevant statistics not included in the Table 3.3 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 3.2). The mean number of FSIRs 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 3.4 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 & Stone, 1985).

Table 3.5 displays the odds ratios and significance values from regressions, and Table 3.6 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 3.3 through 3.6. 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 × PDE interaction term is statistically significant and greater than 1.0. While the effect size is similar for SA, it is not statistically significant. Figures 3.3 and 3.4 depict these trends using the logit. In Figure 3.3, note how the marginal effect of the parental death exposure upon major depressive disorder increases as familial susceptibility to suicide increases. Comparing Figure 3.4 shows the pattern is similar for both MDD and SA, although the 95% confidence bands for SA are much larger, yielding insignificant results. Figure 3.3 further suggests 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. Figures 3.5 and 3.6 show 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. Also, 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 & 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.

Discussion

Our foremost question was to assess whether a family history of suicide interacts with early parental death to affect the risk of behavioral health disorders in later life. 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 × 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.

Our null findings for males may reflect some selection bias (Vaupel & Yashin, 1985), 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 already have lower risks of major depression than females, we should not expect this to be an issue for our MDD

findings for males. It is possible early parental death is simply not as severe a stressor for males as for females (Hollingshaus & Smith, 2015), because PDE operates upon health through not only biological, but also social mechanisms that may be more salient for females (House, Umberson, & 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, & Rodin, 1996). We found mixed effects of early-life SES upon later-life behavioral health. However, we found current SES was an extremely powerful risk factor, reinforcing the gravity of SES for health (Link & Phelan, 1995).

A secondary goal of this study was to show how a large pedigree and population database could be utilized to test familial × 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 et al., 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 & Israel, 2014; Ragland, 1992). Additionally, the measure can account for nongenetic 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. This often resulted in several FSIRs for each ego, an issue we addressed by utilizing the mean value. Indeed, calculating familial susceptibilities 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 be 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 & Hofer, 2005, p.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 & Detsky, 2013).

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Table 3.1. Descriptive Statistics, Selection Sample

	Female		Male	
N	216,729	100.0%	218,266	100.0%
Categorical Variables	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Survived to at Least Age 65	171,989	79.4%	160,187	73.4%
Baptized	139,752	64.5%	133,718	61.3%
Born in Utah	183,075	84.5%	186,380	85.4%
Nam Powers SES Score[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.**
Birth year	1918.25	16.32	1918.60	16.36
Maternal Age at time of Ego's Birth	28.68	6.55	28.65	6.54
Paternal Age at time of Ego's Birth	32.76	7.89	32.72	7.89

[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 3.2. Probit Estimates from Heckman Selection Equations, Selection Sample

	Females (N=216,729)			Males (N=218,266)		
	Beta	**Std. Er.**	**p-val**	**Beta**	**Std. Er.**	**p-val**
Birth year	0.005	0.000	<0.000	0.006	0.000	<0.000
Maternal Age	0.002	0.001	0.002	0.002	0.001	0.001
Paternal Age	-0.003	0.001	<0.000	-0.002	0.001	0.004
Baptized	0.135	0.006	<0.000	0.180	0.006	<0.000
Born in Utah	-0.036	0.009	<0.000	-0.026	0.008	0.002
Nam Powers SES Score[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
Constant	-7.884	0.373	<0.000	-10.832	0.355	<0.000

[a]reference is 76-99 (highest SES).

Table 3.3. Descriptive Statistics at Person Level for Time-Invariant Variables, Final Sample

	Female		Male	
N	83,547	100.0%	72,436	100.0%
Categorical Variables	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Parity				
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%
Siblings				
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%
Nam Powers SES Score[a]				
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.**
Number of Early Parental Deaths	0.15	0.37	0.14	0.36
Familial Susceptibility	1.53	0.32	1.53	0.32
Number of FSIRs	4.69	3.00	4.85	3.06
Number of Complete Years Enrolled (Waves)	9.56	5.32	8.73	5.28
Age at First Wave	71.69	7.54	70.33	6.54
Inverse Mills Ratio	0.34	0.04	0.42	0.05

[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 3.4. Descriptive Statistics at Person-Year Level for Time-Varying Variables (Including Outcomes), Final Sample

	Female		Male	
	Frequency	**Percentage**	**Frequency**	**Percentage**
N	798,537	100.0%	632,523	100.0%
Outcomes				
Major Depression	17,808	2.2%	6,878	1.1%
Substance Abuse	2,448	0.3%	3,356	0.5%
Time-Varying Predictors				
Period				
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%
Marital Status				
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%
Dual Enrolled in Medicaid	44,117	5.5%	15,174	2.4%

Table 3.5. Odds Ratios from Logistic Regressions Predicting Major Depression or Substance Abuse Diagnosis from Parental Death in Early Life (PDE), Familial Susceptibility (FS) and FS × PDE and Controls, Final Sample

	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				
PDE	0.94	0.95	1.07	1.15
FS	1.02	1.18	1.13	1.16
FS x PDE	1.41*	1.31	1.00	0.82
Controls				
(Time-invariant)				
Age at first wave	0.97***	0.94***	1.01	0.90***
Childhood Nam Powers SES Score[a]				
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***
Number of Siblings[b]				
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
Parity[c]				
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***
Number of FSIRs	0.99	1.01	0.98*	0.97**
Number of Complete Years Enrolled (Waves)	0.96***	0.91***	0.96***	0.89***
Inverse Mills Ratio[d]	1.71***	2.84***	1.23**	2.97***
(Time-varying)				
Period[e]				
1998-2005	1.21***	1.51***	1.46***	1.31***
2006-2009	1.13***	1.72***	1.39***	1.32***
Marital Status[f]				
Never	1.19	1.24	1.30	1.59**
Widowed	1.49***	1.62***	2.10***	2.11***
Dual Eligible	2.06***	2.44***	3.51***	5.68***

[a]reference is 76-99 (highest SES). [b]reference is no siblings/only child. [c]reference is 1-3 children.
[d]scaled by a factor of 10. [e]reference is 1992-1997. [f]reference is married.
*p<.05. **p<.01. ***p<.001.

Table 3.6. Variance-Covariance Matrix for Parental Death in Early Life (PDE), Familial Susceptibility (FS), and FS × PDE Estimates from Logistic Regression Models, Final Sample

		Females			Males		
		PDE	*FS*	*FS x PDE*	*PDE*	*FS*	*FS x PDE*
Major	*PDE*	0.00249			0.00534		
Depression	*FS*	0.00004	0.00372		0.00006	0.00798	
	FS x PDE	-0.00059	-0.00339	0.01988	-0.00059	-0.00729	0.04577
Substance	*PDE*	0.00735			0.00668		
Abuse	*FS*	0.00025	0.01025		0.00019	0.00991	
	FS x PDE	-0.00245	-0.00940	0.05461	-0.00103	-0.00907	0.06013

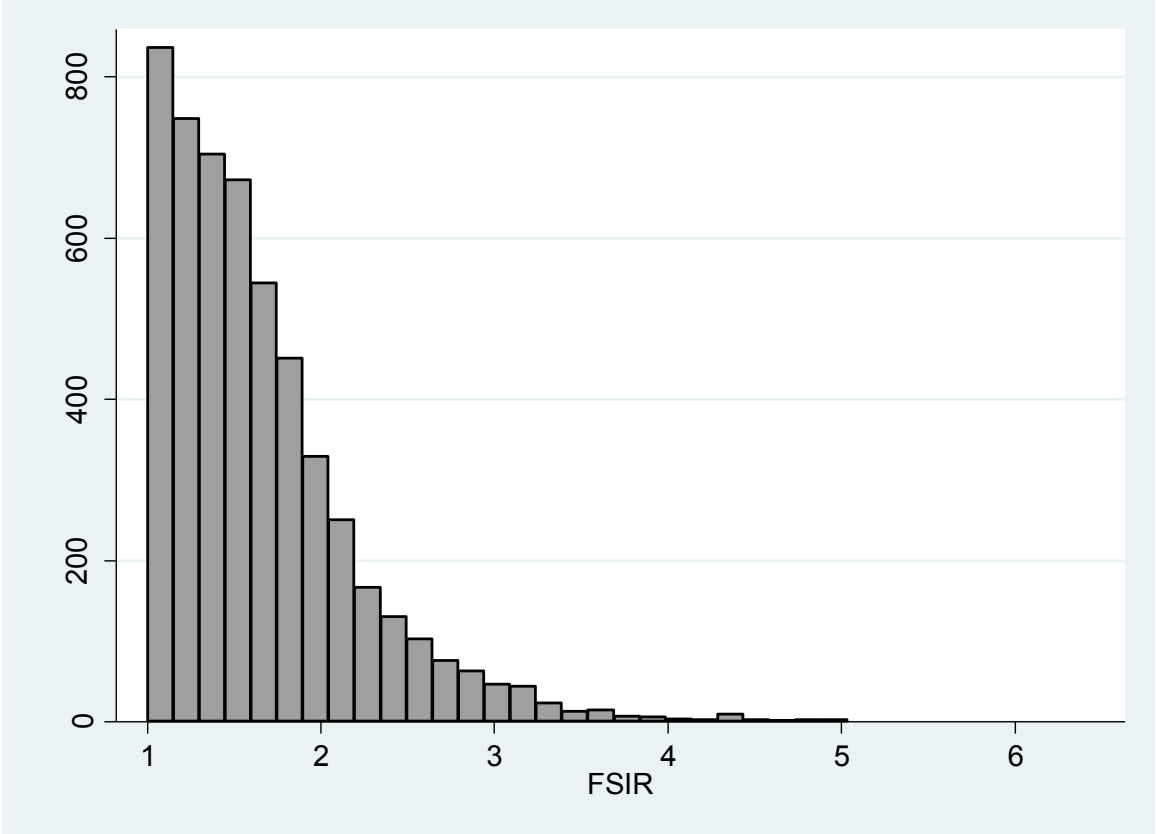

Figure 3.1. Histogram of Suicide Familial Standardized Incidence Ratios (FSIRs) for Founders (N=5,262)

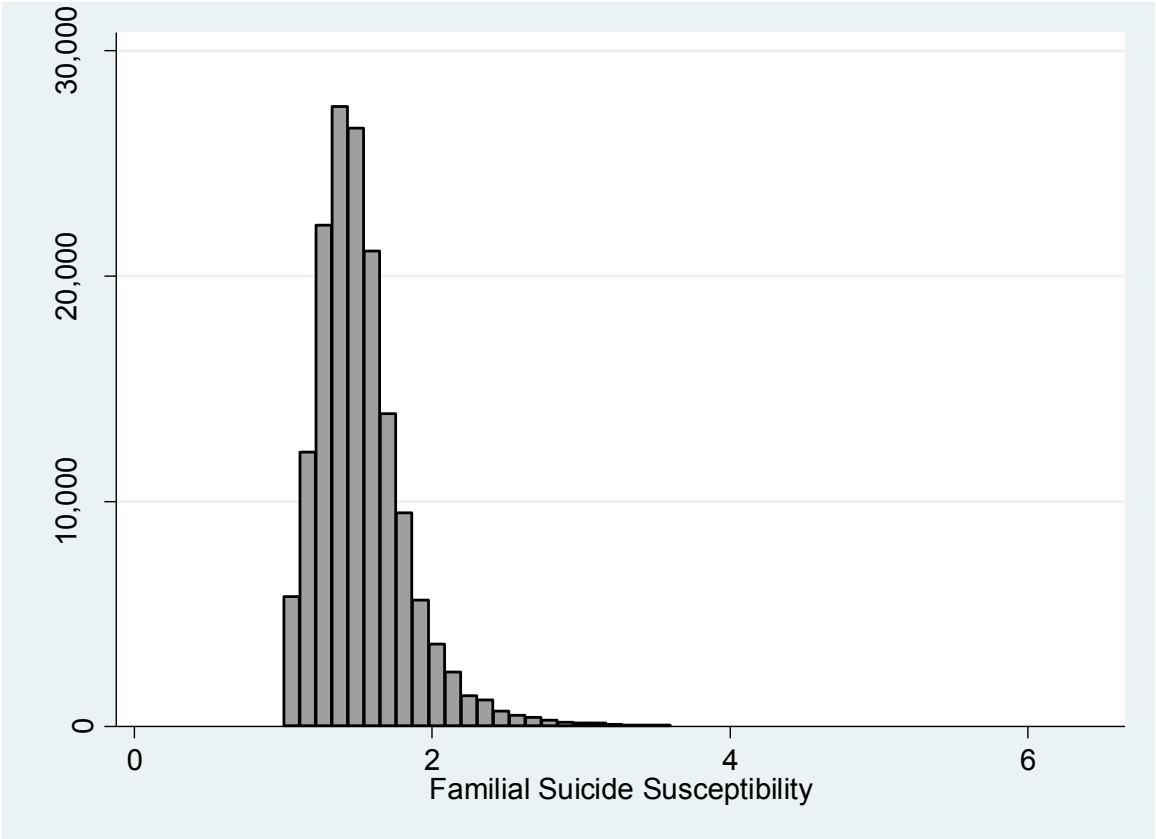

Figure 3.2. Histogram of Familial Suicide Susceptibility (i.e., Mean Suicide Familial Standardized Incidence Ratio) for Egos in the Final Sample (N=155,983)

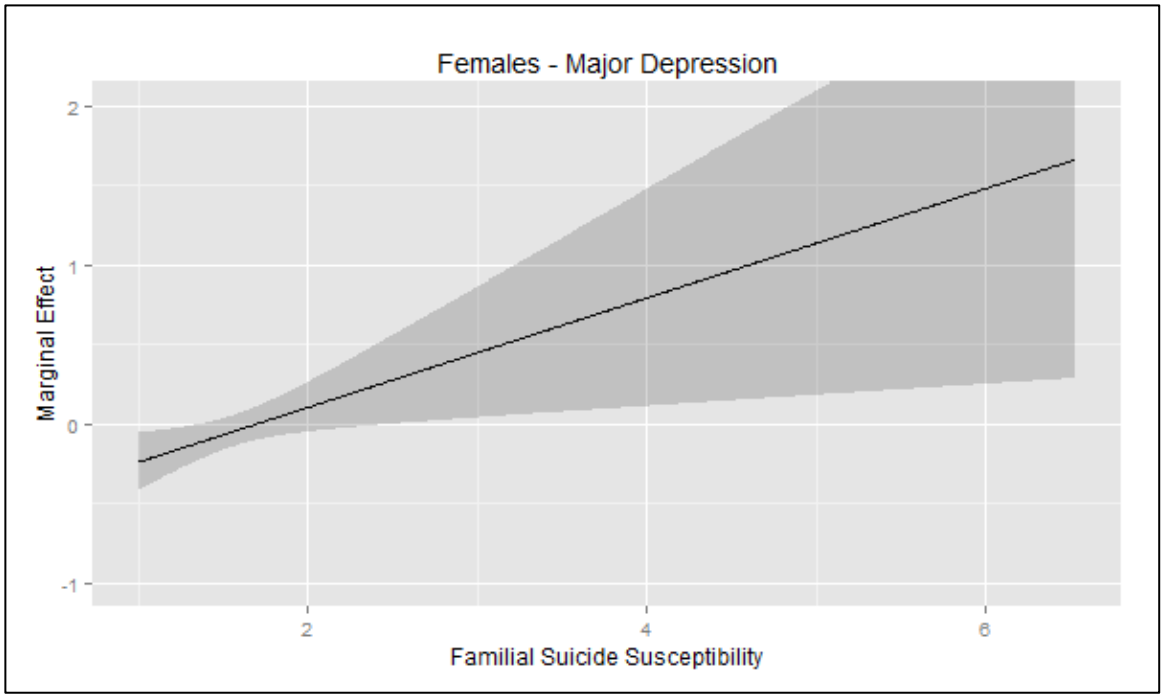

Figure 3.3. Females: Marginal Effect (with 95% Confidence Band) of Early-Life Parental Death Upon the Logit of Major Depression, Given Familial Suicide Susceptibility

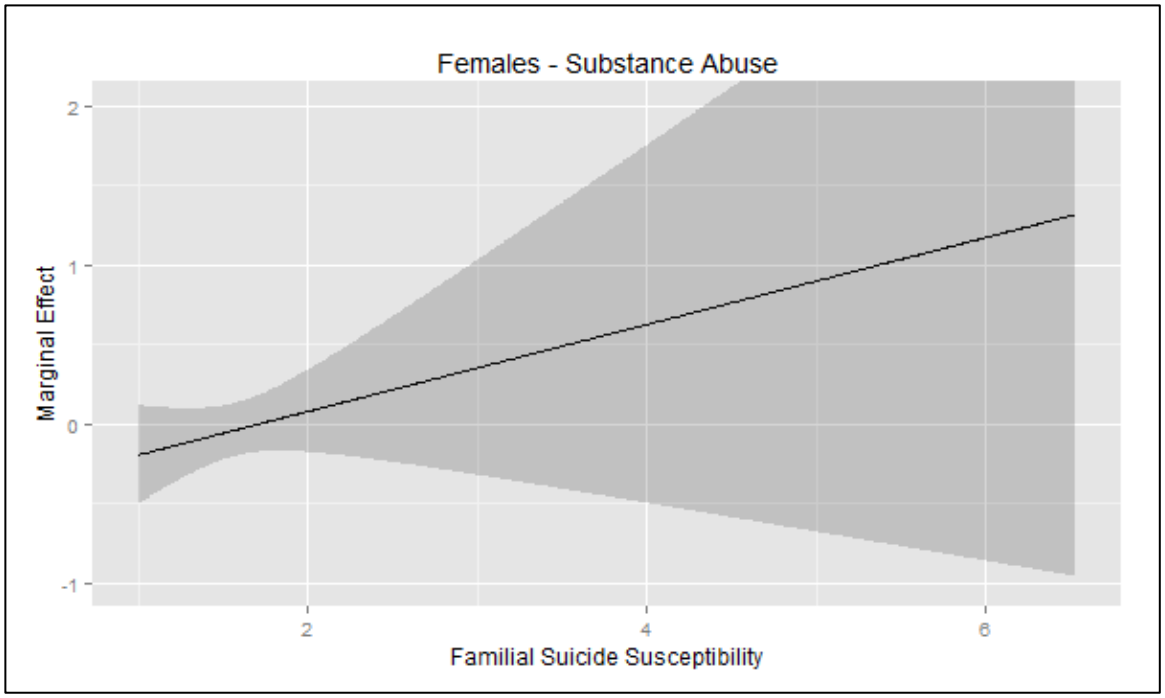

Figure 3.4. Females: Marginal Effect (with 95% Confidence Band) of Early-Life Parental Death Upon the Logit of Substance Abuse, Given Familial Suicide Susceptibility

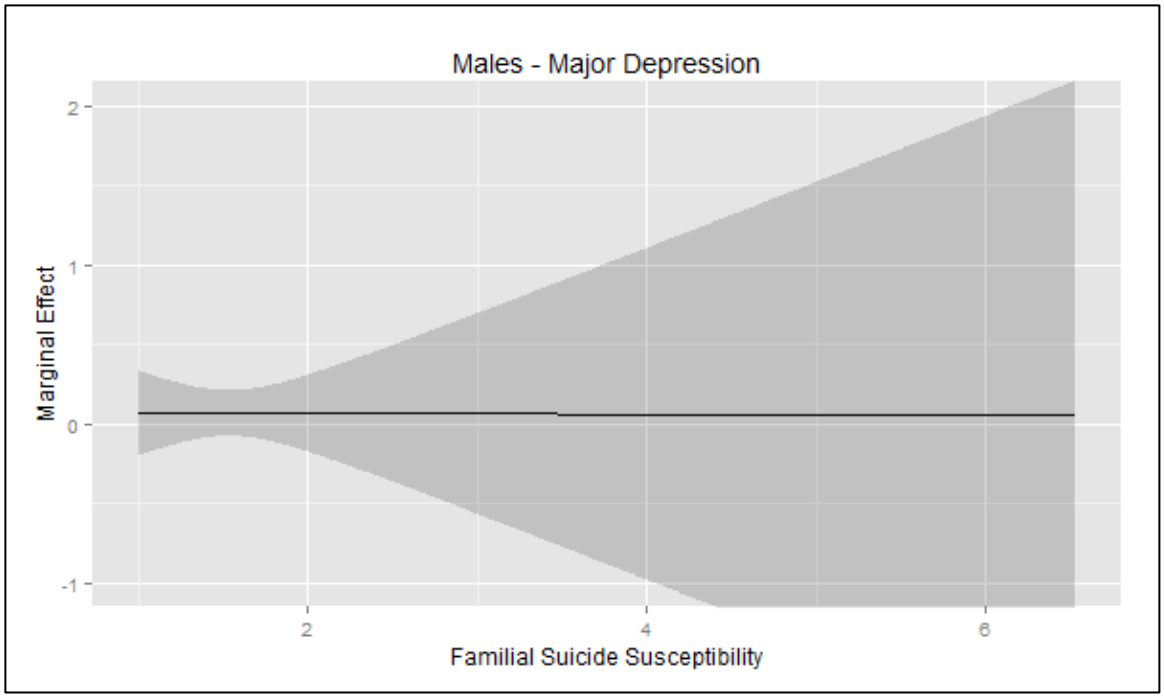

Figure 3.5. Males: Marginal Effect (with 95% Confidence Band) of Early-Life Parental Death Upon the Logit of Major Depression, Given Familial Suicide Susceptibility

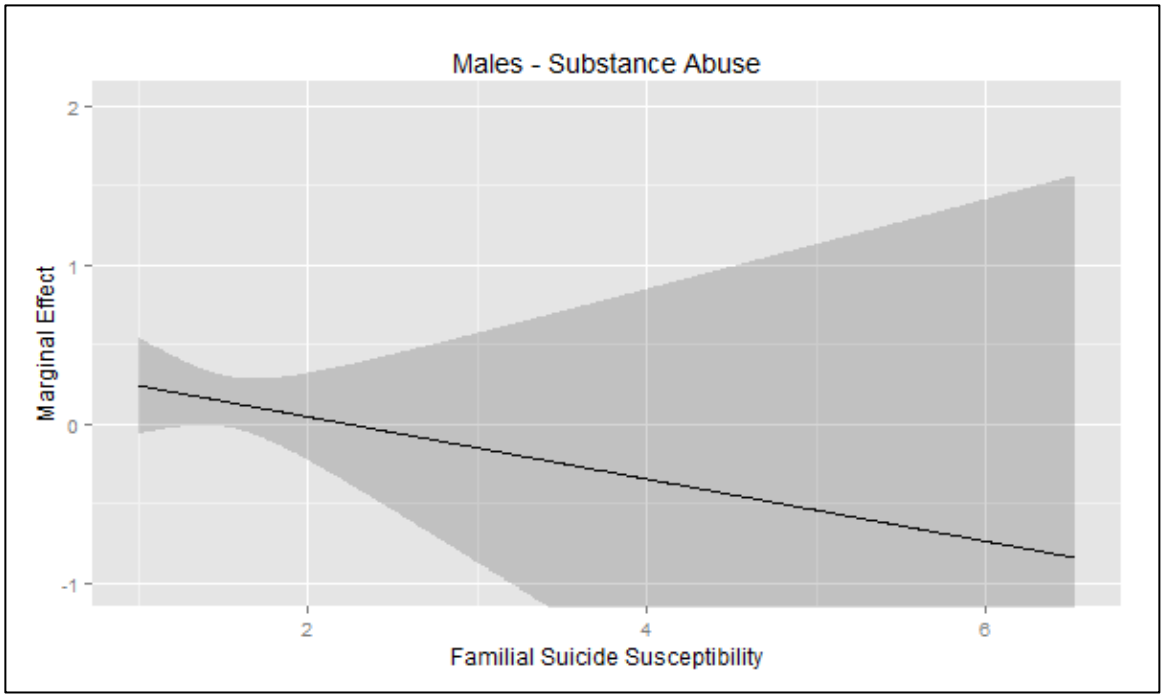

Figure 3.6. Males: Marginal Effect (with 95% Confidence Band) of Early-Life Parental Death Upon the Logit of Substance Abuse, Given Familial Suicide Susceptibility

CHAPTER 4

COLLECTIVE ADVERSE CHILDHOOD EXPOSURES AND THEIR EFFECTS ON ADULT SUICIDE AND MORTALITY RISK: DEVELOPMENT AND APPLICATION OF THE UTAH DEMOGRAPHIC CHILDHOOD ADVERSE EXPOSURES (DECADE) SCALE FOR ONE MILLION INDIVIDUALS[2]

Abstract

We utilized a sample of 964,167 individuals from birth cohorts 1849 through 1972 in the Utah Population Database to build a measurement model of adverse early-life stressors based on demographic measures. Utilizing exploratory and confirmatory factor analytic techniques on random distinct subsamples, we analyzed 13 putative early-life stressors. Nine of these—advanced maternal and paternal age, large sibship size, early maternal and paternal death, high infant mortality rate in county of birth, late birth order, whether a sibling died as an infant, whether a sibling died as a child—were utilized in the final model to construct a hierarchical reflective measurement model with excellent model fit. We identified three first-order latent factors, which we named "seasoned

[2] Coauthored by Heidi A. Hanson and Ken R. Smith. We wish to thank the Pedigree and Population Resource of the Huntsman Cancer Institute, University of Utah for providing the data and valuable computing support. This work was also supported by NIH grant AG022095 (Early-life Conditions, Survival and Health; Smith PI).

family," "compromised cohort," and "parental death." These loaded onto one second order factor which we call the Utah demographic childhood adverse exposures (DECADE) scale. A subsample of 791,937 individuals comprising birth cohorts 1886 through 1972 was identified for estimating sex-specific and birth-year-stratified Cox regression models. Results indicated that the Utah DECADE scale was associated with increased suicide and all-cause mortality risk for males and females before age 50, though these associations tended to dissipate after age 50. Relative to the weighted scale, a simple summative scale tended to overestimate all-cause mortality risk, and underestimate suicide risk. Cox estimates were also obtained and interpreted for the three subfactors. We suggest the DECADE scale might be implemented, adapted, and built upon by demographic researchers to obtain reliable and standardized interval-level measures of general early-life stress.

Introduction

Several stressful demographic early life conditions (ELCS) have been shown to increase mortality risk in later life (Elo & Preston, 1992; Smith & Hanson, 2015). In this paper, we analyze birth cohorts from 1849 through 1972 in the Utah Population Database (UPDB) to create a weighted scale of such conditions that might be utilized as a standardized measure in demographic databases. This scale, called the Utah demographic childhood adverse exposures (DECADE) scale, is multidimensional, with appropriately constructed subscales. We further assess the scale and subscales' respective merits by testing how general early-life stress is associated with increased individual suicide risk and all-cause mortality in later life.

Measurements models have a rich tradition in the social sciences, as attested by their continued use in surveys and research. For example, the social readjustment rating scale (Holmes & Rahe, 1967) and the Center for Epidemiological Studies depression scale (CES-D; Radloff, 1977) are measurement scales extensively utilized in research settings. This potential for measurement standardization across studies is not to be understated. Yet, while recent work has begun to address measurement of self-reported early-life stressors—see for the example, the adverse childhood experiences (ACE) scale (Middlebrooks & Audage, 2008)—we have not seen such a measure implemented for demographic ELCS though there is a clear need and opportunity for doing so.

In addition to standardization, a continuous scale of early-life stress would permit measurement of gradients of stressful exposure, which might be more theoretically appropriate for life-course hypotheses regarding how stress can "get under the skin" (Hertzman & Boyce, 2010, p.329) and even into the cell. It could also permit examination of potential dose-response relationships (Koskenvuo & Koskenvuo, 2014), and increase statistical power (Ragland, 1992). Summative scales of stressors might be easily implemented, but these do no account for redundancies of measurement, acknowledgement and quantification of differential contribution to the underlying latent construct, nor statistically account for error when creating the common construct.

Differential weighting of variables through factor analysis can adjust for redundant measurement and errors to create a scale that measures the construct of interest. Factor analytic methods including exploratory factor analysis (EFA) and confirmatory factor analysis (CFA) can help develop and refine measurements that solve these potential issues, and the ready availability of structural equation modeling (SEM) in

statistical packages, along with increased computational resources, have made such methodologies increasingly attractive (Worthington & Whittaker, 2006). CFA also enables development of hierarchical measurement models, where the scale is an overarching multidimensional variable constructed from subscales (Kline, 2011). These subscales can provide researchers with submeasures of narrower dimensions of early-life stress to address specific theoretical or data considerations.

In this paper, we identified 13 putative early-life stressors that might be reliably measured for a large group of cohorts in UPDB. From these we created the DECADE scale, with three empirically-derived subdimensions, and assessed their relative associations with later-life suicide and all-cause mortality risk. Because the methodology and analyses for this paper are space-intensive, we do not discuss these putative stressors in detail. Rather, the 13 stressors, hypothesized mechanisms, and example empirical literature for both all-cause mortality and suicide are summarized in Table 4.1. Note that since this paper utilizes pedigree data, to maintain clarity we often refer to the individual who experienced the putative early-life stress as the "ego."

Data and Samples

In this section we describe the datasets used, how variables were operationalized, and how the sample and subsamples were derived. These subsamples were necessary for conducting the disparate analyses while maximizing the number of observations available for study. The specific methodology for analyses conducted subsequent to data and sample identification are discussed in later sections.

Data used for this analysis are derived from the Utah Population Database, a

comprehensive population based resource containing nearly 8 million unique individuals from the genealogies of the founders of Utah and their descendants. This dynamic database is updated annually using Utah birth, death, driver license, and health records. This includes over 2 million Utah birth certificates and around 800,000 death certificates. Access to the data is administered through the Utah Resource for Genetic and Epidemiologic Research (RGE). All research requires prior institutional review board (IRB) and RGE approval (Wylie & Mineau, 2003), a requirement satisifed for this analysis. The confidentiality of individuals represented in these records is maintained based on agreements between RGE and the data contributors.

We wished to create a scale for birth cohorts spanning many decades utilizing the demographic and pedigree data available in the UPDB. Therefore, we included birth cohorts from 1849 through 1972, because settlement of Utah by founding pioneers earnestly began in 1849, and 1972 comprised the 95th percentile for UPDB birth-years when the necessary demographic and pedigree record linkages were made.

Given that availability of quality data for cohorts was dependent upon specific variable requirements, we first determined how to operationalize our variables. Table 4.2 shows the 13 variables, operationalizations, and threshold cutoffs. Cutoffs for dichotomous variables were empirically derived using the top or bottom 10th percentile, as appropriate, for all birth cohorts in UPDB with necessary data for that variable. Dichotomous variables are conceptually appealing, because they can be interpreted as indicating whether a stressor was present or not. This approach also permits us to compare the factor-analytically derived score to a simple summative scale, where the presence of each stressor has equal value. Note that while factor analysis typically relies

upon normally distributed variables, robustness tests are easily performed, and we implemented them as appropriate. Table 4.2 also shows descriptive statistics for the Measurement Sample (see below).

Given these operationalizations, we then created a nested hierarchy of logically coherent groups from which the data could be extracted. The nested group names, ego counts, and relative percentage retained are diagrammed in Figure 4.1. The entire data file consisted of 2,704,512 potential egos. This sample was eventually reduced to the Measurement Sample of 964,167 egos for the following reasons. Each lower data grouping required the same data constraints as all higher groupings, in addition to its own. The new restrictions imposed upon each group, and the variables that required those restrictions, are shown in Table 4.3. The benefit of this hierarchy was that if the data constraints seemed too severe, or variables seemed unnecessary, then the sample could be derived from a higher-order grouping to increase size.

We here note that in preliminary analysis, we took a measurement sample from the SES-S18 group, instead of the IMR-S18 group, in order to obtain appropriate SES data (Figure 4.1). We had further restricted birth cohorts to 1849 – 1939 for two key reasons: early-life SES was calculated from parents' death certificates and this cutoff ensured a nearly-extinct cohort of parents; and parents' marriage year was increasingly missing following 1940, affecting quality of our out-of-wedlock birth measure. However, the preliminary analyses showed miniscule factor loadings for these two variables (possibly due to data quality issues). Therefore, we excluded those two variables from further analysis, and derived the Measurement Sample from the IMR-S18 Group (Figure 4.1), which permitted the full cohort range of 1849 – 1972.

The Measurement Sample was divided into three subsamples: two distinct and mutually exclusive quarter samples for exploratory factor analysis (EFA), called Exploratory Samples 1 and 2, of 241,042 each; and a single half subsample, called the Confirmatory Sample, of 482,083 for confirmatory factor analysis (CFA). These subsamples were utilized for the different phases of scale construction.

Once the DECADE scale was built, we imposed additional data requirements to permit suicide and all-cause mortality prediction in cases of early parental death via Cox models. These constraints are also summarized in Table 4.3, and since they are the same as those exacted in a previous paper (Chapter 2)—the exception being that birth cohorts could be as late as 1972 (consistent with the Measurement Sample). The reasons for the restrictions are not here repeated. The final Prediction Sample consisted of 791,937 egos (387,932 female; 404,005 male), including 277,737 deaths, 4,902 of which were suicides.

Suicide was identified with linked Utah death certificates by ICD codes E963, E970-E979 (ICD 6 & 7); E950-E959 (ICD 8 & 9); X60-X84, Y87.0, U03 (ICD 10)—or a "manner of death," a separate field on the death certificate, indicating suicide. All-cause mortality could simply be identified with recorded year of death, which does not necessarily require a death certificate in UPDB. The only control variable included was ego's baptism as a member of the Church of Jesus Christ of Latter-day Saints (LDS or Mormon) by age 9, coded as a binary variable. In general, members raised in the faith are baptized shortly after age 8 (Lyon, Gardner, & Gress, 1994). This variable may be indicative of health behaviors, such as abstention from alcohol, tobacco and other substances, and a supportive community structure (Mineau, Smith, & Bean, 2004). Since fertility levels were often higher for members of this faith (Mineau, Bean, & Anderton,

1989), it was a potential confounding variable with the DECADE scale, which includes elements of fertility. In other words, since religious affiliation might provide resources that protect against morbidity and mortality but also increase fertility, we felt it appropriate to control for baptism. We did not include baptism (or its absence) in the DECADE scale, because it is not as theoretically well-integrated with the other measures.

Methodological Overview

The general method involved the application of EFA and CFA for different UPDB subsamples, an approach endorsed for new scale development (Worthington & Whittaker, 2006). We used EFA to identify the appropriate number of factors and loading patterns, from which we derived a theoretical model of first-order latent factors. We then used CFA to test the measurement model in another subsample. We then extended this same methodology to a second-order latent factor that could account for the variation in the three first-order factors. This second-order factor became the DECADE scale. We then compared predictions of suicide and all-cause mortality using the various scales. Since each step involved decisions that informed whether and how the next step was to be undertaken, we discuss the finer methodological details and findings of each in sequential order.

First-Order Scaling

First-Order Exploratory Factor Analyses

We first performed EFA independently for the 11 variables on both quarter subsamples (called Exploratory Samples 1 and 2). The main purpose of the EFA is to

identify the number of underlying factors and loading patterns. This step helps to develop a theoretically well-grounded scale based upon empirical data. While we might devise a theoretical model *a priori*, and then proceed straight to CFA, recent literature suggests EFA should be conducted first whenever possible, particularly in the absence of any previous research on the scale (Worthington & Whittaker, 2006).

First-order exploratory method

Several key decisions are involved in performing EFA (Schmitt, 2011). One of the most important decisions is the number of underlying factors to retain (Hayton, Allen, & Scarpello, 2004; Schmitt, 2011). This is important because misspecification of the number of factors tends to severely alter the factor loadings and structure, while other considerations are more robust across various procedures (Hayton et al., 2004). Parallel analysis (PA) has been shown to be the most accurate method for determining the correct number of factors in the population, primarily because it accounts for sampling error (Hayton et al., 2004) and relaxes the requirement for normally-distributed variables by invoking the central limit theorem (Dinno, 2009; Hayton et al., 2004). It is recommended by some journal editors as a preferred method (Henson & Roberts, 2006; Schmitt, 2011).

PA compares eigenvalues from the dataset to a null distribution of randomly-generated eigenvalues. If the factor's actual eigenvalue is greater than the simulated (i.e., the observed is greater than what is expected by chance alone), then that factor is retained. For example, if the actual eigenvalue for a given factor is greater than the 95th percentile for the simulated factor, it can be retained with a confidence level of 1-.05 (where .05 is the chosen alpha; Glorfeld, 1995). For more details beyond this

adumbration, they are described in more detail in other sources (Glorfeld, 1995; Hayton et al., 2004; Horn, 1965). We implemented PA in SAS 9.4 using the *%PARALLEL* macro provided by Kabacoff (2003). Adjustments were made including randomizing our variables to dichotomous values (0 or 1), and implementing minor aesthetic chart adjustments. We used 1,000 iterations and the 95th percentile of the simulated eigenvalues (i.e., alpha of 0.05).

In order to determine the general pattern of factor loadings, we next implemented PROC FACTOR with four different model specifications for each sample—two extraction methods using two rotation specifications each. For extraction methods, iterated principal-axis factor (PAF) extraction has no distributional assumptions, but does not provide confidence intervals, thereby impeding statistical tests. Maximum-likelihood (ML) extraction provides confidence intervals, but has strong assumptions of normality (Schmitt, 2011). Because we desired confidence limits for determining which factors to retain, we implemented each method separately. In light of recent published recommendations (Schmitt, 2011), we also implemented two rotation methods—oblique parsimax and oblique quartimax. The former generally allows for larger cross-loadings, and may be more appropriate for initial scale development, whereas the latter assumes smaller cross-loadings, but better generalizes to CFA (Schmitt, 2011). Since we were forming a new scale, but then wished to proceed immediately to CFA, we explored with both rotation types. We used oblique rotations as opposed to orthogonal, because we reasonably expected our factors to be positively correlated in light of the web of conditions that comprise most childhoods.

After each extraction, those variables that did not attain a statistically significant

loading of at least 0.1 were then excluded for poor performance, and the processes (including PA and extraction) were again repeated. While the 0.1 cutoff was lower than general rules of thumb (Kline, 2011), we note that our study is different from many psychometric studies because we are using historical demographic data, and do not therefore have leeway to write a new survey question to better capture the construct under consideration. Our exploratory method was repeated separately for Exploratory Samples 1 and 2.

First-order exploratory results

Upon initial inspection, PA recommended retaining three variables for each Exploratory Sample. Because multiple birth and small birth interval did not statistically exceed a rotated factor loading of 0.1 using the ML extraction method with either rotation, these items were removed from the scale. We were left with nine putative stressors, including advanced maternal and paternal age, large sibship size, early maternal and paternal death, high infant mortality rate in county of birth, late birth order, whether a sibling died as an infant, and whether a sibling died as a child. We present the actual PA findings for the final nine variables only.

Figures 4.2 and 4.3 display the results from PA in scree plots for the final nine variables, by comparing the "actual" estimated eigenvalues to the 95th percentiles of the simulated eigenvalues. Note that in both charts, the simulated eigenvalues are generally 1.0, with small negative slopes. The similarities between charts and the flat slopes are likely functions of large sample size, indicating there is little sampling error. Based on these PA scree plots, three factors fall above the simulated line. For exact comparisons,

the eigenvalues are displayed in Table 4.4. Note that three factors have empirically estimated eigenvalues higher than the simulated 95th percentiles; therefore, using an alpha=.05, we should retain three factors. Also note the scree plot ends its large drop-off after the third factor, offering additional visual confirmation for retaining three factors.

Correlations between the factors are listed in Table 4.5. Consistent with our expectations, note that the three factors are positively correlated. Table 4.6 shows the rotated factor patterns. In the interest of space, confidence intervals are omitted from Table 4.7, because the standard errors were so small. For illustrative purposes in guiding discussion, absolute loadings greater than .2 are shaded gray. Factor 1 (F1) fits with advanced maternal and paternal age, and being higher in the birth order. It makes empirical sense that these variables should load together, because spouses tend to be of similar age (Atkinson & Glass, 1985) and later siblings by definition have older parents, *ceterus paribus*. Factor 2 (F2) fits with having a large sibship size, losing a sibling as a child, losing a sibling as an infant, and being higher in the birth order. By definition, an ego is much more likely to be higher in the birth order if the sibship size is large. Also, having more siblings increases the risk of losing one to death, and parents may have more children to replace those lost. Factor 3 (F3) fits with early maternal and paternal death, though large sibship size loads negatively. We suspect this negative loading occurs because, in order to have a large sibship size, one's parents must almost by definition live longer on average. For Factor 3, we also note that the loadings seem generally smaller and more volatile than those for the first two factors. However, given the theoretical significance of early paternal mortality, we suggest the factor is meaningful, and CFA (see below) shows excellent model fit and thus justify its retention as well based on

statistical grounds.

Note that infant mortality rate has the lowest loadings of any variable. However, repeating parallel analysis without that variable yielded only two factors, and we judged that the extra variation afforded by the third factor was important for the development of our scale. In fact, constructing a properly-identified hierarchical model requires at least three first-order factors for each second-order factor (Kline, 2011). Theoretically, since high IMR in region of birth has been strongly linked to biologically-imprinted inflammation and longevity, consistent with what has been termed a "cohort morbidity phenotype" (Finch & Crimmins, 2004, p.1736), we again elected to retain it. High IMR might fit with Factor 2 or 3, but we suggest it fits best was with Factor 2, which indicates similar fertility and child mortality patterns theoretically consistent with classical demographic transition theory (Kirk, 1996).

Our theoretical model therefore involves three positively-correlated factors. The first loads with advanced maternal age, advanced paternal age, and being late in the birth order. We suggest this factor is best described as a "seasoned family." The second factor loads with large sibship size, losing a sibling as a child, losing a sibling as an infant, high IMR in county of birth for ego's birth cohort, and being higher in the birth order. As previously mentioned, these fertility and mortality patterns appear consistent with a pre-demographic transition environment, and what has been termed a "fast life history" (Nettle, 2010, p. 387)—earlier and faster fertility in anticipation of early mortality and a harsh environment. The imprint of such exposures might yield a "cohort morbidity phenotype," (Finch & Crimmins, 2004, p.1736), and therefore we name the factor "compromised cohort." The third factor loads with early paternal death, early maternal

death, and big sibship size (negatively). Since this factor primarily involves deaths of parents, with large sibship size almost appearing as a confounder, we simply name it "parental death."

First-Order Confirmatory Factor Analyses

First-order confirmatory method

Following EFA, confirmation of the empirically-derived theoretical model is relatively straightforward, and can simply be implemented with structural equation modelling (SEM) using SAS PROC CALIS. This analysis was performed using the Confirmatory Sample. Consistent with recent recommendations (Worthington & Whittaker, 2006), we present several model fit indices, including the Chi-square with degrees of freedom, adjusted goodness of fit index (AGFI), comparative fit index (CFI), standardized root mean square residual (SRMR), and root mean square error of approximation (RMSEA) with 90% confidence limits. Acceptable fit of the measurement model to the data can be generally indicated by a failure to reject the null hypothesis of acceptable model fit using the Chi-square test (i.e., low p-value suggests worse fit since this indicates differences between the predictions made by the model relative to the observed data), high CFI and AGFI, and low SRMR and RMSEA. While traditional rules of thumb vary, most fall somewhere around a CFI and AGFI > .9, and SRMR and RMSEA < .1 (Hatcher & O'Rourke, 2014; Kline, 2011). Since maximum-likelihood SEM assumes normally distributed population variables, we perform a robustness check utilizing the fully weighted least squares (WLS) method, which relaxes the assumption of multivariate normality in large samples (Kline, 2011).

First-order confirmatory results

Figure 4.4 shows the fit statistics and standardized factor loadings using the ML method, and Figure 4.5 shows the same information obtained from WLS. Note all model fit statistics, with the exception of Chi-square, are very good, beyond or close to traditional rules of thumb regarding good fit (Hatcher & O'Rourke, 2014), and all loadings are statistically significant. The only exception is the Chi-square statistic. We note here the likelihood of poor Chi-square fit increases with sample size, and Chi-square is therefore not as useful as the other statistics in our study (Hatcher & O'Rourke, 2014; Kline, 2011). Also, the ML and WSL methods produce similar estimates. We therefore suggest this measurement model may be reliably utilized to construct three subscales of early-life stress. Given that WLS does not have the assumptions of multivariate normality in large samples, we suggest those estimates should be utilized.

Second-Order Scaling

Second-Order Exploratory Factor Analyses

Since the three factors were positively correlated, it was reasonable to test for the presence of a higher-order factor. The second-order EFA was approached in stages. First, we created predicted values for the variables F1, F2, and F3 by applying PROC SCORES (using default specifications) to the confirmed first-order measurement model and the raw data for the Exploratory Samples. Then, PA was conducted on the three new variables. Figures 4.6 and 4.7 show the PA scree plots, and Table 4.7 compares the eigenvalues. This process demonstrated that the three factors might be reduced to one higher-order global factor. Actual loadings for the exploratory analyses are unimportant,

because the theoretical model is determined by all three first-order factors loading on the second-order DECADE scale, and exact loadings can be determined in CFA.

Second-Order Confirmatory Factor Analyses

CFA was formally conducted with both ML and WLS methods, and the path diagrams are displayed in Figures 4.8 and 4.9. Note that this step did not require predicting the factor scores first, because CFA is easily applied in a multilevel framework via SEM. Note the model fit is again excellent. Given the nonnormal distribution of the variables, we take the second-order factor from the WLS estimates as our DECADE scale.

Distribution of the DECADE Scale

At this point, we had four scales with which to measure varying elements of early-life stress—the DECADE scale, and three subfactors, which we named "seasoned family," "compromised cohort," and "parental death," respectively. Using SAS, we applied PROC SCORES (using default specifications) to the final second-order estimates and raw data from the entire Measurement Sample to predict values for the four scales. For comparative purposes, we also created an additional fifth variable for a simple summative scale by summing the nine raw stress indicators.

The distributions of these five variables are graphed in Figures 4.10 through 4.14. The variables are all positively skewed, and, except for the summative scale, centered about the mean. Most egos experienced no early-life stressors as measured here. Note the simple summative score is rigidly discrete, and visually appears almost like a Poisson

distribution with a relatively constant probability of experiencing one additional stressor. We would expect demographic early-life stress to decrease for later birth-cohorts due to such improvements as improved hygiene, nutrition, medical care, education, and public health and sanitation (Kirk, 1996); all forces that would alter the preavlence of our early life stressors. Since a large group of cohorts were retained for scale creation, it is likely the factors correlate negatively with birth year. Therefore, one potential issue of the DECADE scale is whether it measures ELCS, or simply one's birth cohort. The correlations between year of birth, the DECADE scale, the summative scale, and each subfactor are displayed in Table 4.8. As expected, all scales and subscales are highly positively correlated with each other, and negatively correlated with birth year. Birth year is more strongly correlated with the summative scale than the DECADE scale. Note also that Factor 2, "compromised cohort," is the most strongly correlated with birth year, consistent with what is known in terms of fertility and mortality change over time. Since Factor 2 is much more strongly correlated with the summative score than the DECADE scale, the summative scale is also strongly correlated with birth year. Thus, the DECADE scale is not as associated with birth cohort, likely because it lends less weight to the high fertility and mortality coincident with big sibship size, high infant mortality, and being late in the birth order. We suggest that greater independence from birth cohort is a strength of the DECADE scale.

Prediction of Suicide and All-Cause Mortality

Prediction Method

The Prediction Sample of 791,937 was utilized to predict suicide and all-cause mortality. Cox models were estimated, the two outcomes being time to suicide and all-cause mortality, with censoring occurring at the date last known alive in Utah. Egos were followed from birth-year through year of the event or censoring, with potential follow-up data to 2013. We tested the predictive power of six models, (1) The DECADE scale, (2) The summative scale, (3-5) Each subfactor (F1-F3) alone, and (6) The three subfactors in the same model. The models were also estimated separately for males and females, because they generally differ in their stress response patterns (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Since all-cause mortality and suicide were both examined as health outcomes, the strategy involved estimating 24 models. Each Cox model was stratified by birth year to control for distinct cohort and period effects (Kom, Graubard, & Midthune, 1997), and included the baptism variable to adjust for this potential confounder. A Heaviside interaction term measuring time before and after age 50 was included to account for nonproportional hazards of the various scales. We implemented the sandwich estimator to obtain robust standard errors clustered about each set of parents to account for dependent observations (Kleinbaum & Klein, 2005). Because the models are not all nested and the sixth model has more degrees of freedom, the AIC and BIC fit statistics were utilized to compare model fits, and individual Chi-squares and p-values were utilized to interpret statistical significance of hazard ratios (HR).

Prediction Results

Descriptive statistics are shown in Table 4.9. Model fit for the suicide Cox models are shown in Table 4.10. For all-cause mortality, the BIC and SBC suggest the three-factor model provides the best overall model fit. This might be expected, because hierarchical CFA permits error terms for the first-order factors; therefore using the individual factors will capture more variation. However, the DECADE scale measures the commonalities between the three subfactors, and therefore we suggest it is more appropriate if a single measure of early-life exposure to stress is desired. Among the single first-order factors, F3 provides the best fit for suicide. It may be that early-life parental death is more salient for suicide than a compromised cohort or seasoned family. F3 may also indicate a parental suicide in early-life, which could be particularly traumatic (Wilcox et al., 2010) or possibly indicate heritable mortality risk (Sørensen, Nielsen, Andersen, & Teasdale, 1988). F3 also yields better fit for mortality than either of the higher scales. It may be that parental death is simply an overpowering tragic event that yields many negative effects, but we also note the factor may capture heritable premature mortality risk (Sørensen et al., 1988). For the larger more inclusive scales, the DECADE scale produces a better model fit than the summative scale for suicide; but, for all-cause mortality, the opposite occurs. As previously shown, the summative scale weights the fertility and child mortality variables more heavily, and we therefore suspect F2 may be stronger for all-cause mortality than suicide.

Table 4.11 shows the Cox model parameter estimates for suicide. First, we examine the DECADE and summative scales. For males, both are associated with later-life suicide risk, but Chi-square comparisons indicate the DECADE scale is a better

predictor (as was also suggested by the model fit statistics). After age 50, this impact of early-life stress appears to wane, though the p-values are suggestive of significance. For females, the DECADE scale significantly predicts suicide, but the summative scale does not. This further suggests the summative scale underestimates the impact of early-life stress on suicide. In the models with each of the three subfactors alone, F1 and F3 significantly relate to increased suicide risk for males, but only F3 for females. Chi-square estimates indicate F3, parental death, is by far the strongest of the three factors for the larger scales. Again, associations appear to attenuate after age 50. For the model with all three factors, F3 is the only predictive early-life stress subfactor. Model diagnostics for the three-factor model showed the lowest condition index to be 3.11, and so multicollinearity should not be an issue (Belsley, Kuh, & Welsch, 1980).

Results for all-cause mortality are displayed in Table 4.12. The DECADE and summative scales are both associated with increased risk for all-cause mortality under age 50. Chi-square indicates the summative scale is a stronger predictor. This suggests that the summative scale might be overestimating the effects of early-life stress on all-cause mortality. Note that, under age 50, the three subfactors are all associated with increased risk when modeled separately (the exception being F1 for females). Similar to the results for suicide, F3 appears to be the strongest predictive scale. Note that in the three-factor model, the direction of F1 reverses both before and after age 50. We suspect that, once "parental death" is controlled for, having older parents may be protective because it potentially indicates robustness (Smith, Gagnon, et al., 2009), and increased social support from parents that have fewer role demands and more established careers at advanced ages (Mare & Tzeng, 1989).

In all models, the Chi-square and HR values indicate baptism to be strongly protective. This suggests to us that social supports and health behaviors associated with membership in the LDS church (Mineau et al., 2004) have protective effects independent of early-life stress. A caution, however, is that those who are not LDS may be members of other faiths that provide similar social support, but generally do not have the proscriptions related to alcohol and tobacco use.

Discussion

In this paper, we showed how nine early-life demographic stressors of advanced maternal and paternal age, large sibship size, early maternal and paternal death, high infant mortality rate in county of birth, late birth order, sibling died as an infant, and sibling died as a child, can be viewed as indicators for three common underlying factors, which can in turn be viewed as indicators for one general underlying factor of demographic childhood adverse exposures. This DECADE scale accounts for the intercorrelations between the variables, and thereby identifies the measurement that is common to them all. We further showed that this scale is associated with increased mortality and suicide risk prior to age 50 for males and females, though these associations dissipate after age 50, due in part to mortality selection (Vaupel & Yashin, 1985). We suggest this scale might be utilized to examine the effects of stressful early-life conditions upon any later-life phenotype for historical cohorts.

We further argue that the early-life subscales of "seasoned family," "compromised cohort," and "parental death" may be utilized independently to examine different subcategories of early-life stress. These additional subscales might also prove

useful when not all variables are available for measurement. We also note that F3, the early parental death factor, is the strongest predictive subfactor. In particular, F3 may be indicative of heritable longevity patterns, and other controls for familial longevity might help to disentangle this possibility.

Our research highlights the fact that many early-life biodemographic indicators of stress are intercorrelated. Examinations of a single variable, such as being late in the birth-order or exposure to high infant mortality rate, should at the least consider the potential confounding effects of other correlated variables to avoid bias.

We suggest this scale is but a first attempt to identify commonalities between early-life indicators of stress. It should be replicated in other samples, particularly where additional variables or more refined measurements are available. For example, we excluded early-life SES and out-of-wedlock birth for poor loadings, and suspect fuzzy measurement may be to blame. Also, we did not have measurements for some important early-life stressors such as low birth-weight or nutritional deprivation in utero. As such data become increasingly available for later cohorts, this scale should be revised to be cohort-specific, and similar methodology may be utilized. In particular, simple summative scales may overestimate the impact of certain variables, creating a potential Type I error. The factor analytic methods should be more accurate as they account for variable intercorrelations.

In regards to methodology, we note that factor analysis requires many decisions, and the interpretation will be affected accordingly. While we have detailed our methodological rationale and choices in detail, our methods examining underlying commonalities are more conducive to a reflective scale, which theoretically assumes the

underlying commonalties are causally prior to the indicators (Schmitt, 2011). A formative scale, which theoretically assumes the indicators are causally prior to the latent construct, might be better suited to interpretations of mechanisms (Schmitt, 2011). Therefore, we urge caution in how mechanisms are interpreted utilizing this version of the DECADE scale. Still, the parsimonious virtues of a single variable for early-life stress should not be underestimated.

Future researchers should attempt to replicate these findings, and refine or extrapolate upon them as appropriate. In particular, we suggest F2, which measures high child mortality and fertility, might prove useful for further examinations of trends in demographic transition theory. Historical cohorts with large population samples would be well-suited to this analysis. We also note that the inclusion of early parental and sibling death requires the ego survive to a threshold age, creating a period of risk. While age 18 is commonly used as a threshold for early-life parental death (Chae, 2013), other cutoffs are certainly available, and our sample construction followed a logical method that illustrates how this can be easily adapted as needs require.

Finally, our findings suggest that early-life stress is associated with increased later-life all-cause mortality and suicide risk. Our sample was large, and offers a substantial contribution to this body of literature. Our findings also have implications for policy, as protections against stress in the early-life stages may have cumulative preventive effects throughout the life-course. Furthermore, clinicians might develop secondary or tertiary intervention strategies as appropriate.

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Table 4.1. Thirteen Putative Early-Life Stressors, Plausible Mechanisms Linking to Later-Life Mortality, and Example Literature

Stressor	**Plausible Mechanisms**	**Example Mortality Literature**	
		All-Cause	**Suicide**
Advanced maternal age	Genetic mutation load	(Gavrilov & Gavrilova, 1997; Gavrilov & Gavrilova, 2004; Mirowsky, 2005)	(Chen et al., 2013; Miller et al., 2010)
Advanced paternal age	Same as above	Same as above	Same as above
Large sibship size	Maternal depletion, low SES, early "scarring"	(Hart & Davey Smith, 2003; Smith, Mineau, Garibotti, & Kerber, 2009)	(Chen et al., 2013; D. Riordan, C. Morris, J. Hattie, & C. Stark, 2012)
Early maternal death	Grief and allostatic load, loss of support, cumulative disadvantage	(Andersson, Hogberg, & Åkerman, 1996; Smith, Hanson, Norton, Hollingshaus, & Mineau; Ken R. Smith et al., 2009)	(Agerbo, Nordentoft, & Mortensen, 2002; Niederkrotenthaler, Floderus, Alexanderson, Rasmussen, & Mittendorfer-Rutz, 2012)
Early paternal death	Same as above	Same as above	Same as above
High infant mortality rate for county of birth	Early "scarring," inflammation, infections	(Finch & Crimmins, 2004, 2005)	(Barker, Osmond, Rodin, Fall, & Winter, 1996; Erhardt et al., 2013; Pace et al., 2006; Salk, Sturner, Lipsitt, Reilly, & Levat, 1985; Sublette et al., 2011)
Late birth order	Maternal depletion, loss of bequests	(Modin, 2002; Nault, Desjardins, & Légaré, 1990)	(Bjorngaard et al., 2013; Chen et al., 2013; Gravseth, Mehlum, Bjerkedal, & Kristensen, 2010; Rostila, Saarela, & Kawachi, 2014)
Sibling died as infant	Early "scarring," inflammation, infections	(Finch & Crimmins, 2004, 2005)	(Barker et al., 1995; Erhardt et al., 2013; Salk et al., 1985; Sublette et al., 2011)
Sibling died as child	Grief and allostatic load, loss of support, cumulative disadvantage	(Rostila, Saarela, & Kawachi, 2012)	(Rostila, Saarela, & Kawachi, 2013)
Low initial SES	Cumulative disadvantage	(Galobardes, Lynch, & Smith, 2008)	(Agerbo et al., 2002; Chen et al., 2013; Gravseth et al., 2010)
Twin/multiple birth	Biological programming	(Baird, Osmond, Bowes, & Phillips; Braun, Ahlbom, Floderus, Brinton, & Hoover, 1995)	(Barker et al., 1995; Gravseth et al., 2010; Tomassini, Juel, Holm, Skytthe, & Christensen, 2003; Voracek, 2003)
Out-of-wedlock birth	Cumulative disadvantage	(Fors, Lennartsson, & Lundberg, 2011)	(Gravseth et al., 2010)
Short birth interval	Maternal depletion / biological programming	(Davanzo, Hale, Razzaque, & Rahman, 2008)	(Riordan, C. Morris, J. Hattie, & C. Stark, 2012; Rostila et al., 2014)

Table 4.2. Thirteen Early-Life Variables, Operational Definitions and Descriptive Statistics, Measurement Sample

Stressor	Operational Definition	Cutoff Percentile Value Used	Mean[a]	Std. Dev
Advanced maternal age	Mother's age at birth at least 90th percentile	38 years	0.097	0.296
Advanced paternal age	Father's age at birth at least 90th percentile	43 years	0.096	0.294
Large sibship size	Number of full siblings (including self) at least 90th percentile	10 siblings	0.143	0.350
Early maternal death	Mother died before ego reached age 18	n/a	0.048	0.215
Early paternal death	Father died before ego reached age 18	n/a	0.074	0.261
High infant mortality rate (IMR) for county of birth	County IMR at least 90th percentile	131.39 per 1,000	0.030	0.171
Late birth order	Birth order at least 90th percentile	6th child	0.170	0.375
Sibling died as infant	At least one sibling died by age 1	n/a	0.222	0.416
Sibling died as child	At least one sibling died between age 1 and 18	n/a	0.142	0.349
Twin/multiple birth	Ego shared same birth year and month with at least one maternal sibling	n/a	0.025	0.155
Short birth interval	Not firstborn, and number of months since previous sibling's birth at most 10th percentile	16 months	0.086	0.280
Low initial SES	Father's Nam Powers (NP) score[b] from usual occupation on Utah death certificate at most 10th percentile	NP score of 29	Removed from Measurement Sample for low loadings	
Out-of-wedlock birth	Parents' marriage year after ego's birth year	n/a	Removed from Measurement Sample for low loadings	

[a]Variables are dichotomous, and thus the mean is also the frequency proportion. [b]Nam Powers score converts occupation, a qualitative measure, to a quantitative SES score ranging from 1-100 (Low to high).

Table 4.3. New Variables Added for Each Lower-Nested Subgroup or Sample, and Associated Data Constraints

Group / Sample	New Variables	New Data Constraints
Base Group[a]	- [Ensures basic data quality for the study]	- ego's birth-year from 1849 through 1972 - ego's birth-month known - ego's latest year alive in Utah known[b] - ego's sex known - ego not adopted
Parent Group[a]	- Advanced maternal age - Advanced paternal age - Out-of-wedlock birth - Multiple birth - Early maternal death (S18 Group only) - Early paternal death (S18 Group only)	- mother and father have known birth-year and latest year alive in Utah[b] - neither parent was polygamous
Sibling Group[a]	- Large sibship size - late in birth order - small birth interval - a sibling died as an infant - a sibling died as child	All individuals with same mother and father as ego have known birth-year and birth-month [c]
IMR Group[a]	- High infant mortality rate	- ego's county of birth known - ego's county of birth had at least 20 births in birth-year cohort (imposed to obtain stable estimates)
SES Group[a]	- Low Early-life Socioeconomic Status	- Father or mother had a Utah death certificate with known occupation
Measurement Sample	N/A	- Basic data cleaning (removal of cases where data are clearly poor, such as ego born before parent)
Exploratory Sample 1	N/A	- 25% Random sample (no replacement)
Exploratory Sample 2	N/A	- 25% Random sample (no replacement)
Confirmatory Sample	N/A	- 50% Random sample (no replacement)
Prediction Sample	- Year of death - Cause of death - Baptized by age 9	- Earliest cohort moved to 1886, enabling potential cause of death after age 18 - Ego not polygamous - Father alive at year of ego's birth - If father or mother's latest year in Utah was prior to ego's 18th year of age, there must be a corresponding year of death

[a]Group has a corresponding subgroup, called the "S18 Group," where all egos were also known to survive to at least age 18. [b]Latest year known alive in Utah is a variable internal to UPDB, and often utilized for quality control and survival censoring. [c]No cohort restrictions were placed upon sibling birth-years.

Table 4.4. Actual vs. 95th Percentiles of Simulated Eigenvalues from First-Order Parallel Analyses Using 1,000 Simulations, Nine Raw Variables

	Exploratory Sample 1		Exploratory Sample 2	
Factor Position	**Actual**	**Simulated**	**Actual**	**Simulated**
F1	2.376	1.012	2.367	1.012
F2	1.329	1.008	1.339	1.008
F3	1.015	1.006	1.013	1.006
F4	0.958	1.003	0.959	1.003
F5	0.919	1.001	0.919	1.001
F6	0.793	0.999	0.796	0.999
F7	0.660	0.998	0.658	0.997
F8	0.513	0.996	0.510	0.996
F9	0.437	0.993	0.439	0.993

Note. Factors to retain are shaded gray

Table 4.5. Interfactor Correlations for First-Order Exploratory Analyses

	Principal-Iterated						Maximum Likelihood					
	Oblique Parsimax			Oblique Quartimax			Oblique Parsimax			Oblique Quartimax		
Exploratory Sample 1	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
F1	1.00			1.00			1.00			1.00		
F2	0.14	1.00		0.20	1.00		0.20	1.00		0.27	1.00	
F3	0.28	0.32	1.00	0.26	0.34	1.00	0.35	0.27	1.00	0.32	0.31	1.00
Exploratory Sample 2	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
F1	1.00			1.00			1.00			1.00		
F2	0.13	1.00		0.22	1.00		0.15	1.00		0.23	1.00	
F3	0.26	0.32	1.00	0.24	0.31	1.00	0.28	0.30	1.00	0.25	0.31	1.00

Note. For maximum likelihood estimates, standard errors are omitted because they were all very small (<.02). Standard errors are not available for principal-iterated estimates

Table 4.6. Rotated Factor Patterns (Standardized Regression Coefficients) for First-Order Exploratory Factor Analyses

	Principal-Iterated						Maximum Likelihood					
	Oblique Parsimax			Oblique Quartimax			Oblique Parsimax			Oblique Quartimax		
Exploratory Sample 1	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
Advanced Maternal Age	0.79	0.02	-0.03	0.78	0.02	-0.01	0.86	-0.10	-0.02	0.86	-0.05	-0.02
Advanced Paternal Age	0.64	0.00	0.13	0.64	0.02	0.14	0.58	-0.05	0.20	0.57	0.02	0.20
Late in Birth Order	0.44	0.42	0.05	0.42	0.45	-0.01	0.44	0.38	0.07	0.39	0.45	0.00
Lost Infant Sibling	0.00	0.40	0.17	-0.02	0.44	0.10	0.04	0.42	0.08	-0.01	0.46	0.01
Lost Child Sibling	0.03	0.35	0.17	0.01	0.39	0.11	0.06	0.37	0.10	0.01	0.41	0.04
High IMR	-0.05	0.11	0.18	-0.06	0.14	0.15	-0.03	0.14	0.09	-0.04	0.16	0.07
Big Sibship	0.10	0.81	-0.09	0.07	0.84	-0.21	0.14	0.76	-0.06	0.06	0.80	-0.18
Mother Died while Child	0.02	-0.01	0.20	0.01	0.02	0.19	0.03	0.01	0.13	0.02	0.04	0.12
Father Died while Child	0.13	-0.07	0.21	0.12	-0.04	0.21	0.02	-0.09	0.40	0.03	-0.04	0.40
Exploratory Sample 2	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
Advanced Maternal Age	0.78	0.03	-0.03	0.79	0.01	-0.04	0.81	-0.03	-0.01	0.81	-0.03	0.01
Advanced Paternal Age	0.65	0.02	0.10	0.65	0.03	0.09	0.62	0.00	0.12	0.62	0.03	0.12
Late in Birth Order	0.43	0.43	0.05	0.42	0.45	-0.03	0.44	0.41	0.06	0.42	0.44	-0.01
Lost Infant Sibling	-0.01	0.38	0.20	-0.01	0.44	0.11	0.01	0.40	0.17	-0.02	0.45	0.09
Lost Child Sibling	0.02	0.35	0.17	0.01	0.40	0.10	0.03	0.36	0.14	0.02	0.40	0.07
High IMR	-0.05	0.11	0.17	-0.05	0.15	0.13	-0.04	0.13	0.14	-0.05	0.16	0.11
Big Sibship	0.08	0.83	-0.10	0.06	0.85	-0.24	0.12	0.83	-0.13	0.08	0.85	-0.26
Mother Died while Child	0.02	-0.02	0.22	0.02	0.03	0.21	0.01	-0.01	0.23	0.01	0.03	0.22
Father Died while Child	0.15	-0.06	0.18	0.15	-0.03	0.18	0.11	-0.06	0.22	0.11	-0.02	0.22

Note. High IMR = High infant mortality rate. For maximum likelihood estimates, standard errors are omitted because they were all very small (<.02). Standard errors are not available for principal-iterated estimates. Values with an absolute value greater than 0.2 are shaded gray.

Table 4.7. Actual vs. 95th Percentiles of Simulated Eigenvalues from Second-order Parallel Analyses Using 1,000 Simulations, Three Factor Scores

	Exploratory Sample 1		Exploratory Sample 2	
Factor Position	**Actual**	**Simulated**	**Actual**	**Simulated**
F1	2.019	1.006	2.016	1.006
F2	0.710	1.001	0.713	1.001
F3	0.271	0.999	0.270	0.999

Note. Factors to retain are shaded gray

Table 4.8. Correlations Between Scales and Birth Year, Measurement Sample

	DECADE Scale	Summative Scale	F1	F2	F3	Birth Year
DECADE Scale	1.00					
Summative Scale	0.87	1.00				
F1	0.94	0.71	1.00			
F2	0.62	0.88	0.42	1.00		
F3	0.86	0.73	0.73	0.39	1.00	
Birth Year	-0.30	-0.49	-0.16	-0.50	-0.25	1.00

Note. All intercorrelations statistically significant at $p < .0001$.

Table 4.9. Descriptive Statistics, Prediction Sample

Variable	Female		Male		Total	
Interval-Ratio	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**
Birth year	1939.59	23.54	1940.21	23.28	1939.90	23.41
Years Followed	60.17	19.08	58.43	17.71	59.28	18.41
DECADE Scale	-0.02	0.20	-0.02	0.19	-0.02	0.20
Summative Scale	0.85	1.30	0.83	1.28	0.84	1.29
F1	-0.02	0.38	-0.02	0.38	-0.02	0.38
F2	-0.05	0.38	-0.06	0.37	-0.06	0.37
F3	-0.01	0.16	-0.01	0.16	-0.01	0.16
Dichotomous	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**	**Mean**	**Std. Dev**
Suicide	0.00	0.05	0.01	0.10	0.01	0.08
Died	0.33	0.47	0.37	0.48	0.35	0.48
Baptized	0.43	0.50	0.41	0.49	0.42	0.49

Table 4.10. Cox Model Fit Statistics, Prediction Sample

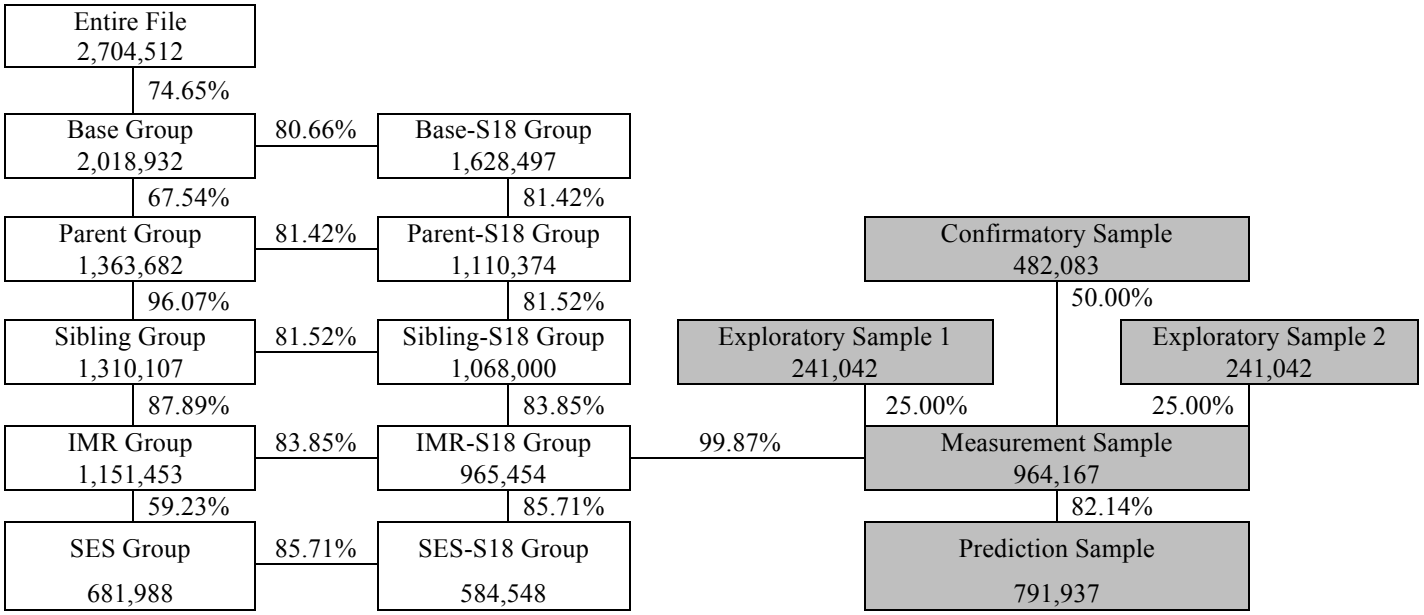
	Male		Female	
	AIC	**SBC**	**AIC**	**SBC**
Suicide				
DECADE Model	65,113.5	65,132.3	16,448.4	16,463.1
Summative Model	65,114.8	65,133.6	16,451.4	16,466.1
F1-Only Model	65,116.2	65,135.0	16,450.8	16,465.5
F2-Only Model	65,120.5	65,139.3	16,452.8	16,467.5
F3-Only Model	65,105.1	65,124.0	16,437.8	16,452.4
3-Factor Model	65,109.2	65,153.1	16,438.8	16,473.1
All-cause Mortality				
DECADE Model	2,207,796.6	2,207,826.4	1,877,382.6	1,877,411.8
Summative Model	2,207,763.2	2,207,793.0	1,877,348.7	1,877,378.0
F1-Only Model	2,207,870.5	2,207,900.2	1,877,438.0	1,877,467.3
F2-Only Model	2,207,866.5	2,207,896.2	1,877,424.0	1,877,453.3
F3-Only Model	2,207,665.2	2,207,694.9	1,877,265.3	1,877,294.5
3-Factor Model	2,207,610.1	2,207,679.5	1,877,195.1	1,877,263.5

Table 11. Cox Parameter Estimates for Suicide, Prediction Sample

Male					Female				
Variable	**HR**	**SE**	**Chi2**	**P-val**	**Variable**	**HR**	**SE**	**Chi2**	**P-val**
DECADE Model									
DECADE	1.35	0.11	7.38	0.007	DECADE	1.56	0.20	4.97	0.026
× 50+	0.73	0.17	3.54	0.060	× 50+	0.72	0.34	0.99	0.320
Baptized	0.56	0.04	214.66	<.001	Baptized	0.51	0.08	78.29	<.001
Summative Model									
Summative	1.05	0.02	5.86	0.016	Summative	1.05	0.04	1.66	0.197
× 50+	0.95	0.03	3.39	0.065	× 50+	0.96	0.06	0.57	0.449
Baptized	0.56	0.04	214.82	<.001	Baptized	0.51	0.08	77.65	<.001
F1-Only Model									
F1	1.12	0.05	4.41	0.036	F1	1.17	0.10	2.40	0.121
× 50+	0.86	0.08	3.08	0.079	× 50+	0.91	0.17	0.34	0.557
Baptized	0.56	0.04	213.56	<.001	Baptized	0.51	0.08	77.94	<.001
F2-Only Model									
F2	1.02	0.07	0.09	0.758	F2	0.93	0.14	0.25	0.617
× 50+	1.00	0.10	0.00	0.988	× 50+	1.02	0.21	0.01	0.920
Baptized	0.56	0.04	212.47	<.001	Baptized	0.51	0.08	75.86	<.001
F3-Only Model									
F3	1.68	0.13	16.12	<.001	F3	2.50	0.22	16.86	<.001
× 50+	0.63	0.20	5.33	0.021	× 50+	0.49	0.39	3.42	0.064
Baptized	0.56	0.04	213.80	<.001	Baptized	0.51	0.08	77.33	<.001
3-Factor Model									
F1	0.93	0.08	0.73	0.392	F1	0.83	0.15	1.72	0.189
× 50+	0.95	0.13	0.18	0.676	× 50+	1.24	0.24	0.82	0.365
F2	0.92	0.08	1.14	0.286	F2	0.76	0.16	2.86	0.091
× 50+	1.13	0.11	1.25	0.263	× 50+	1.18	0.24	0.51	0.477
F3	2.02	0.19	14.04	<.001	F3	4.17	0.32	19.48	<.001
× 50+	0.62	0.28	2.75	0.097	× 50+	0.30	0.53	4.97	0.026
Baptized	0.57	0.04	209.42	<.001	Baptized	0.52	0.08	74.32	<.001

Table 4.12. Cox Parameter Estimates for All-Cause Mortality, Prediction Sample

Male					Female				
Variable	**HR**	**SE**	**Chi2**	**P-val**	**Variable**	**HR**	**SE**	**Chi2**	**P-val**
DECADE Model									
DECADE	1.22	0.03	47.93	<.001	DECADE	1.17	0.04	19.05	<.001
× 50+	0.91	0.03	9.12	0.003	× 50+	0.94	0.04	2.44	0.118
Baptized	0.76	0.01	2495.13	<.001	Baptized	0.79	0.01	1557.92	<.001
Summative Model									
Summative	1.04	0.00	58.59	<.001	Summative	1.03	0.01	28.29	<.001
× 50+	0.98	0.01	11.63	<.001	× 50+	0.99	0.01	4.24	0.040
Baptized	0.76	0.01	2516.32	<.001	Baptized	0.79	0.01	1578.35	<.001
F1-Only Model									
F1	1.06	0.01	15.93	<.001	F1	1.04	0.02	3.59	0.058
× 50+	0.97	0.02	2.61	0.106	× 50+	0.99	0.02	0.21	0.650
Baptized	0.76	0.01	2477.66	<.001	Baptized	0.79	0.01	1544.53	<.001
F2-Only Model									
F2	1.06	0.02	11.64	<.001	F2	1.05	0.02	6.64	0.010
× 50+	0.98	0.02	0.98	0.322	× 50+	0.99	0.02	0.58	0.446
Baptized	0.76	0.01	2493.68	<.001	Baptized	0.79	0.01	1563.55	<.001
F3-Only Model									
F3	1.45	0.03	117.77	<.001	F3	1.38	0.04	56.53	<.001
× 50+	0.82	0.04	28.04	<.001	× 50+	0.87	0.05	9.48	0.002
Baptized	0.76	0.01	2465.97	<.001	Baptized	0.79	0.01	1539.12	<.001
3-Factor Model									
F1	0.89	0.02	28.64	<.001	F1	0.87	0.03	26.57	<.001
× 50+	1.07	0.02	7.97	0.005	× 50+	1.07	0.03	6.01	0.014
F2	1.02	0.02	1.77	0.184	F2	1.04	0.02	3.16	0.076
× 50+	1.00	0.02	0.02	0.883	× 50+	0.99	0.02	0.27	0.607
F3	1.74	0.05	127.90	<.001	F3	1.69	0.06	77.92	<.001
× 50+	0.73	0.05	34.65	<.001	× 50+	0.78	0.06	15.25	<.001
Baptized	0.76	0.01	2449.72	<.001	Baptized	0.79	0.01	1532.01	<.001



Note. Samples actually used for analysis are shaded gray, and are named "Sample." The others groupings were utilized in the variable construction process. "S18" stands for "Survived to 18," meaning the ego was known to survive to at least age 18 in the data. Each box contains the sample or grouping name with the ego count beneath. Percentages are the percent of the ego's retained when the new sample restriction was made.

Figure 4.1. Sample Diagram with Ego Counts

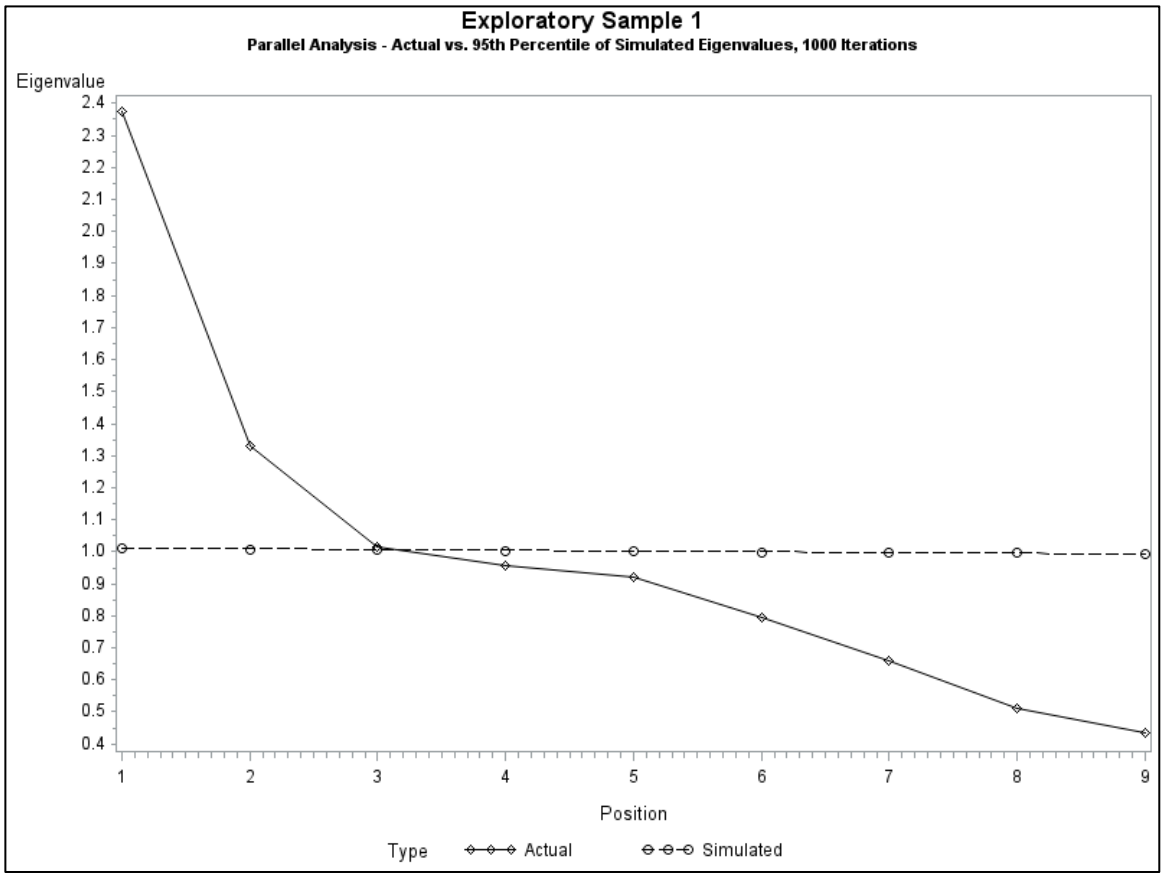


Figure 4.2. First-Order Parallel Analysis Scree Plot,
Exploratory Sample 1 (Nine Raw Variables)

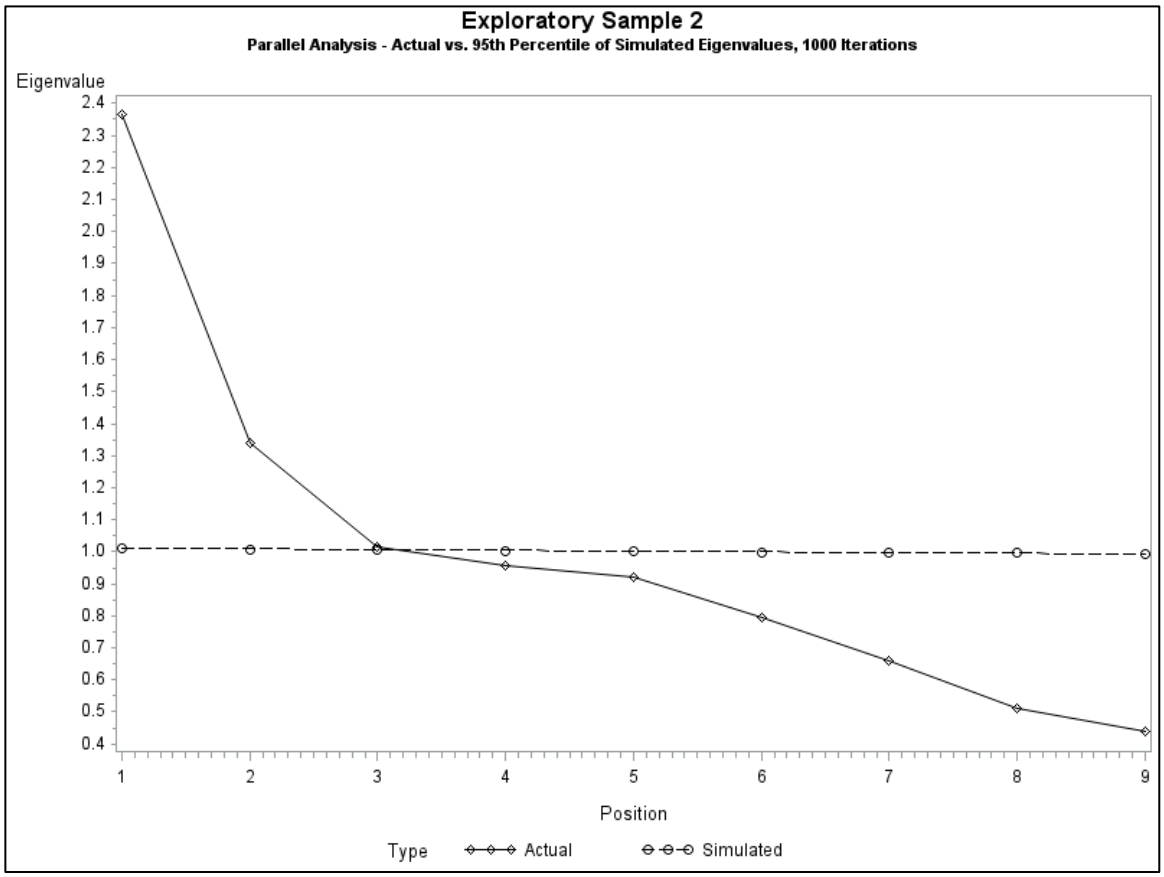
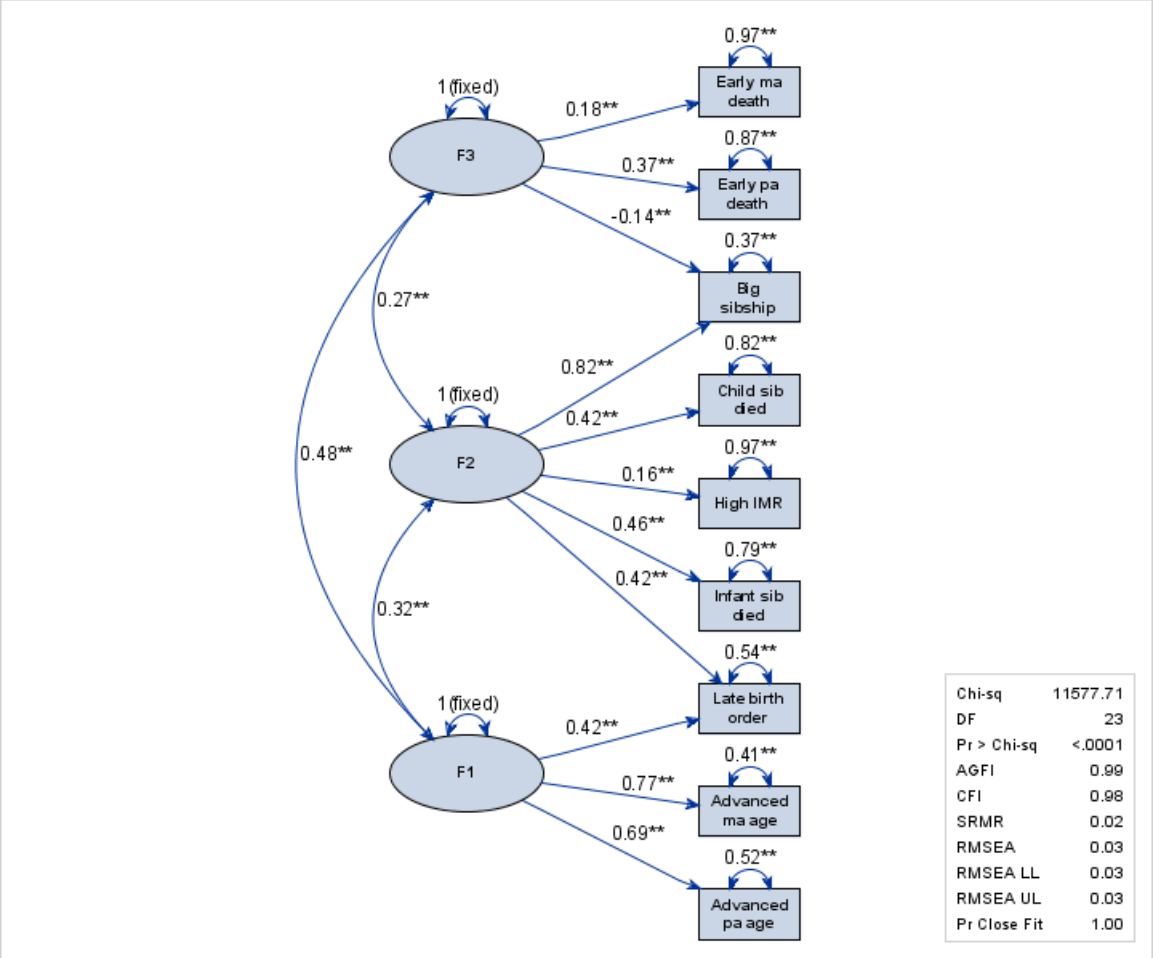
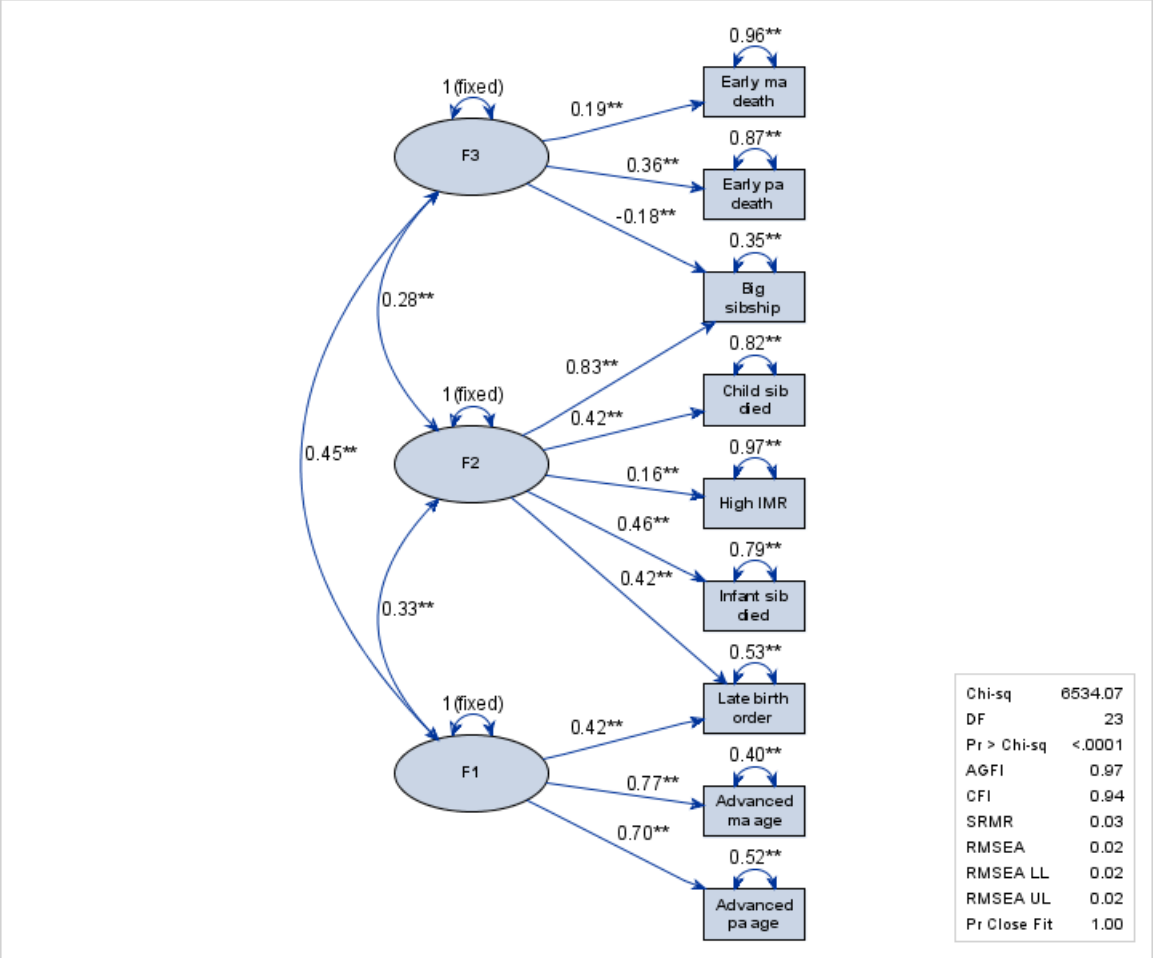


Figure 4.3. First-Order Parallel Analysis Scree Plot,
Exploratory Sample 2 (Nine Raw Variables)



*p<.05. **p<.01. ***p<.001.

Figure 4.4. Standardized Path Diagram and Fit Statistics for Maximum-Likelihood First-Order Confirmatory Factor Analysis, Confirmatory Sample



*p<.05. **p<.01. ***p<.001.

Figure 4.5. Standardized Path Diagram and Fit Statistics for Weighted Least Squares First-Order Confirmatory Factor Analysis, Confirmatory Sample

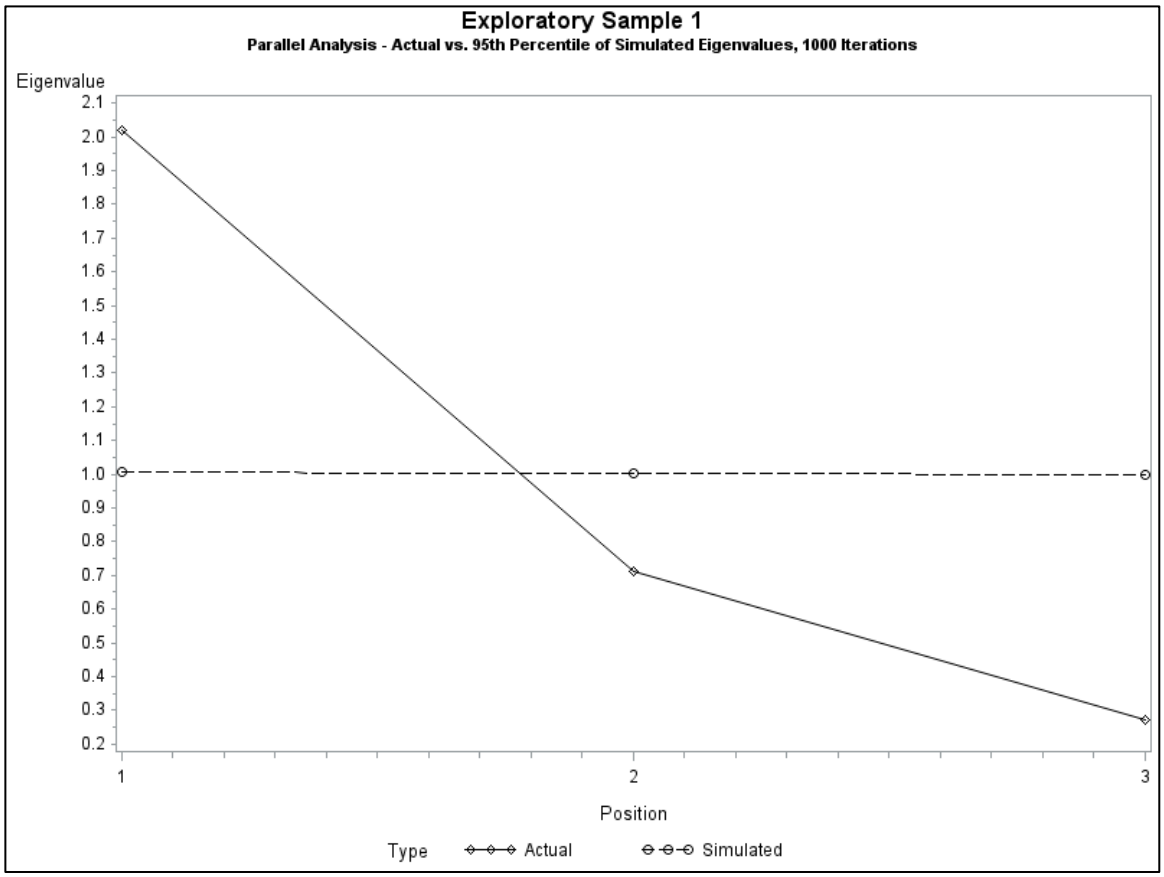


Figure 4.6. Second-Order Parallel Analysis Scree Plot,
Exploratory Sample 1 (Three Factor Scores)

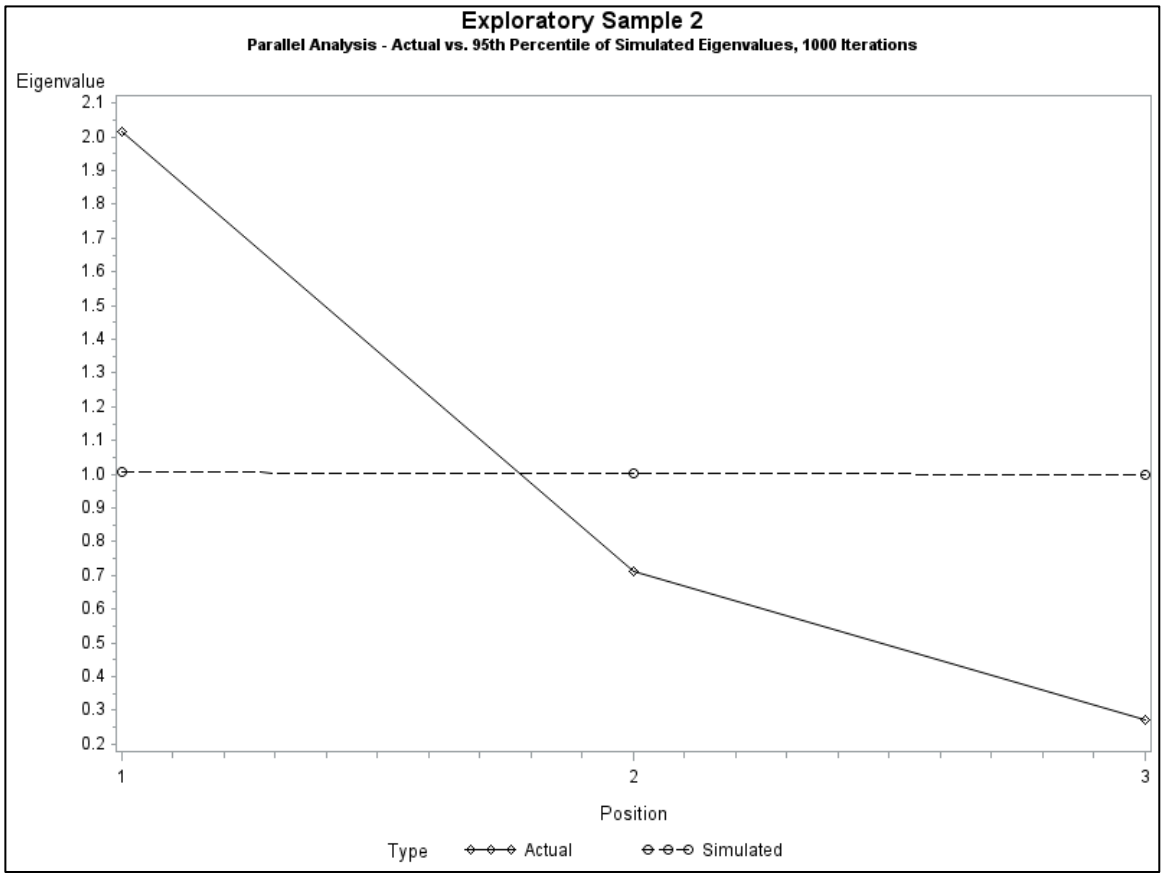
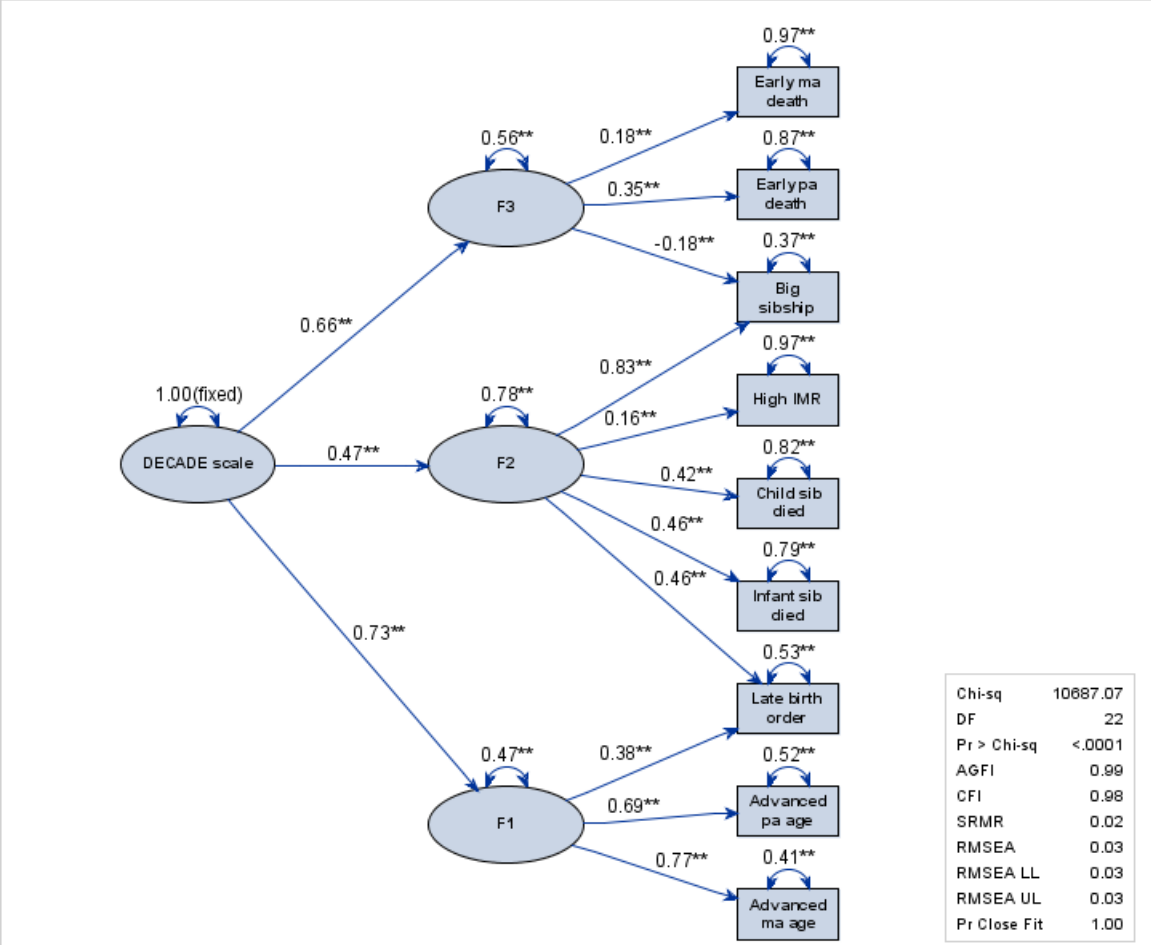
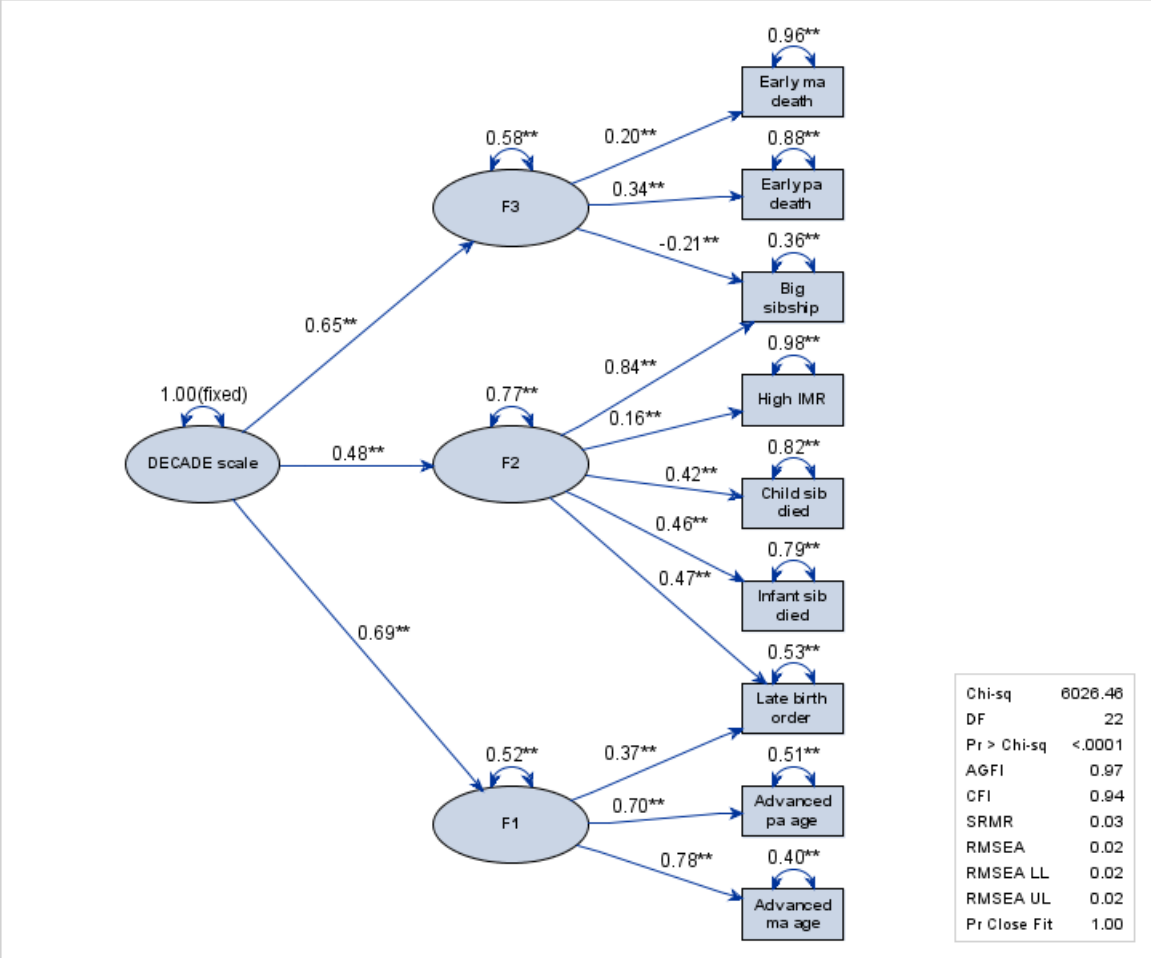


Figure 4.7. Second-Order Parallel Analysis Scree Plot,
Exploratory Sample 2 (Three Factor Scores)



*p<.05. **p<.01. ***p<.001.

Figure 4.8. Standardized Path Diagram and Fit Statistics for Maximum-Likelihood Second-Order Confirmatory Factor Analysis, Confirmatory Sample



*p<.05. **p<.01. ***p<.001.

Figure 4.9. Standardized Path Diagram and Fit Statistics for Weighted Least Squares Second-Order Confirmatory Factor Analysis, Confirmatory Sample

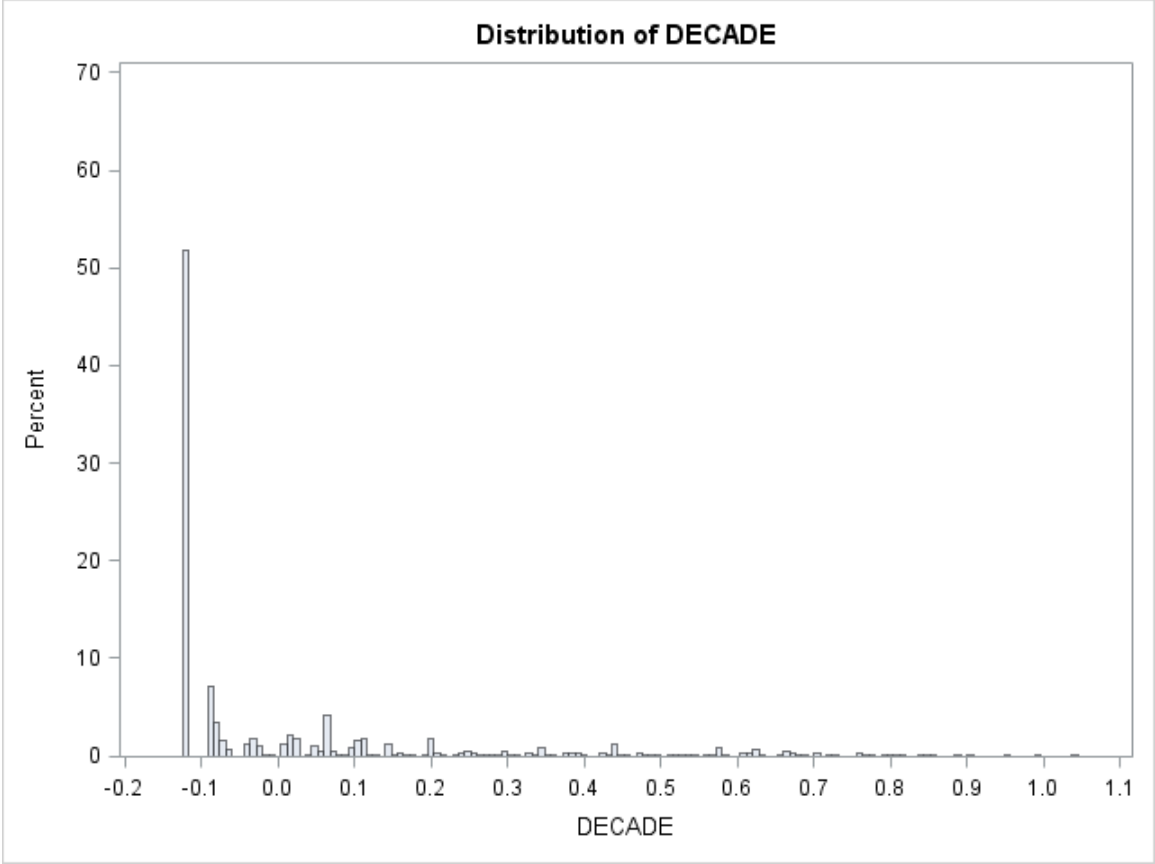


Figure 4.10. Histogram for the DECADE Scale, Measurement Sample

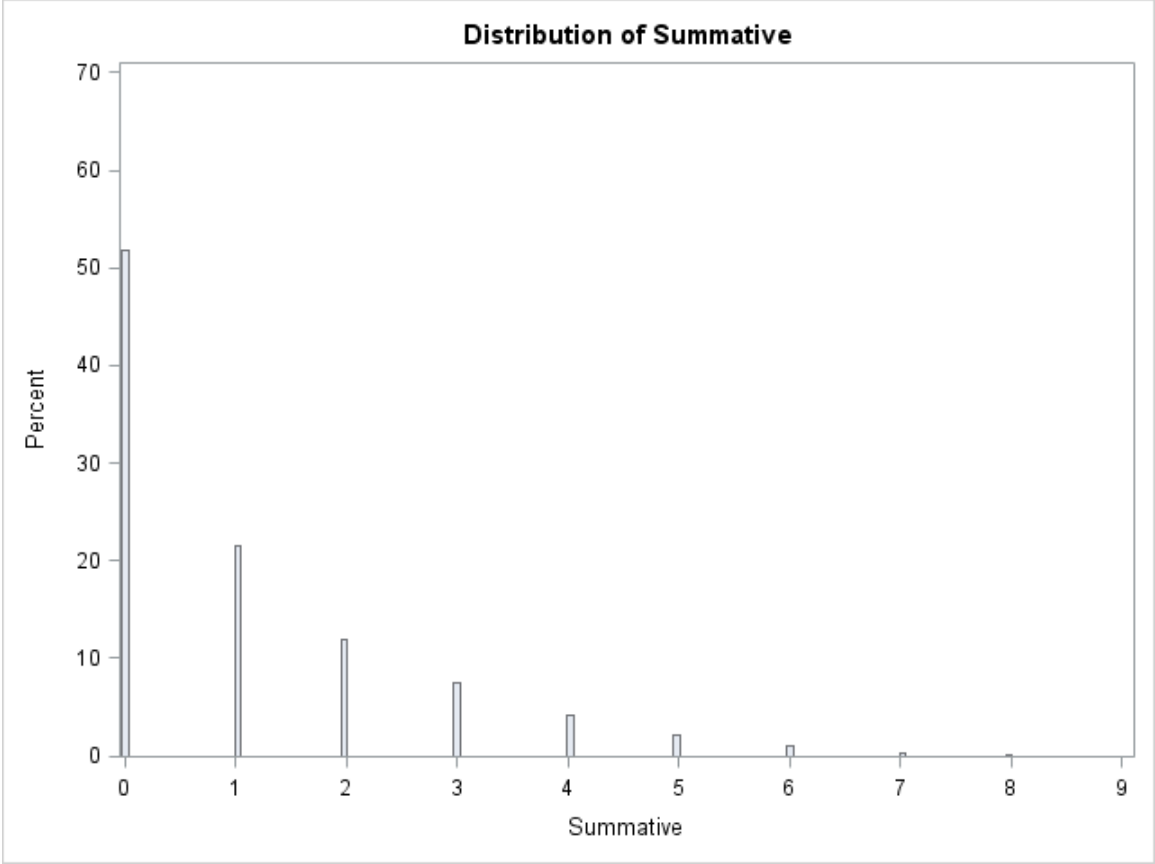


Figure 4.11. Histogram for the Summative Scale, Measurement Sample

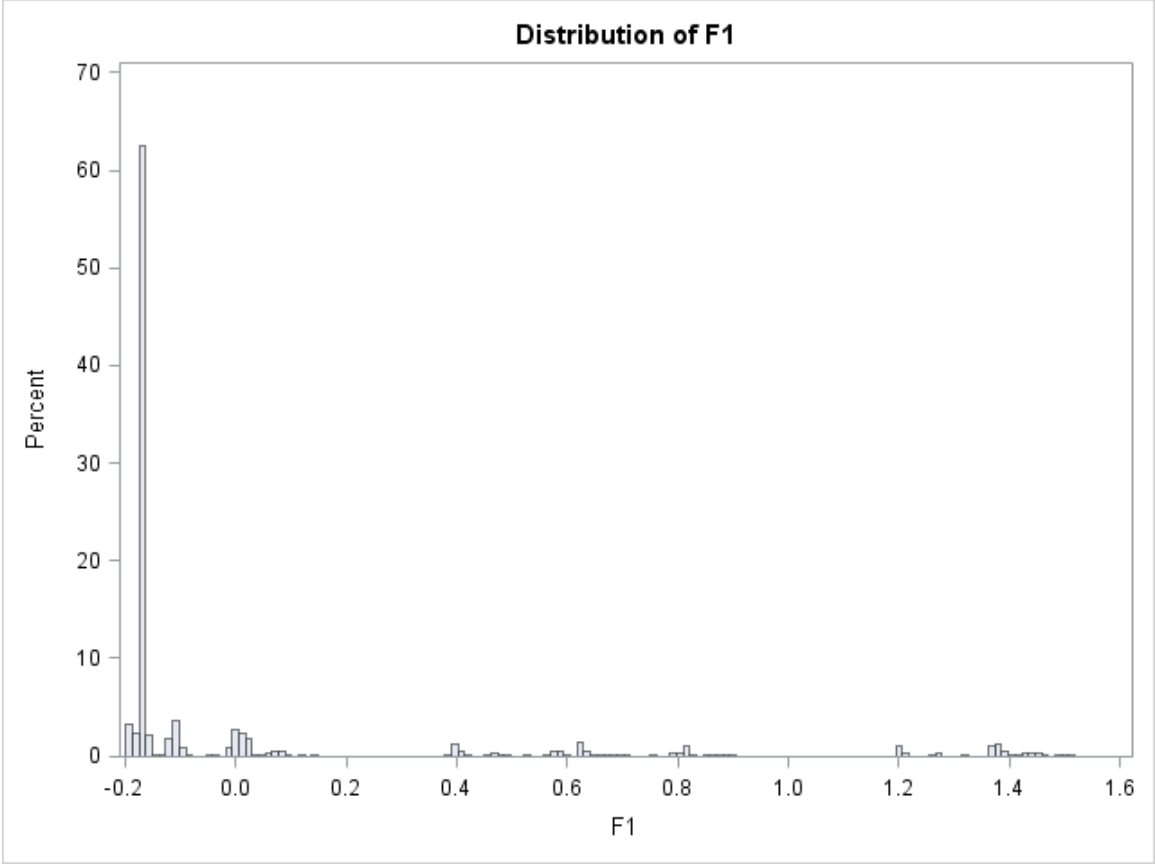


Figure 4.12. Histogram for the F1 Subscale, Measurement Sample

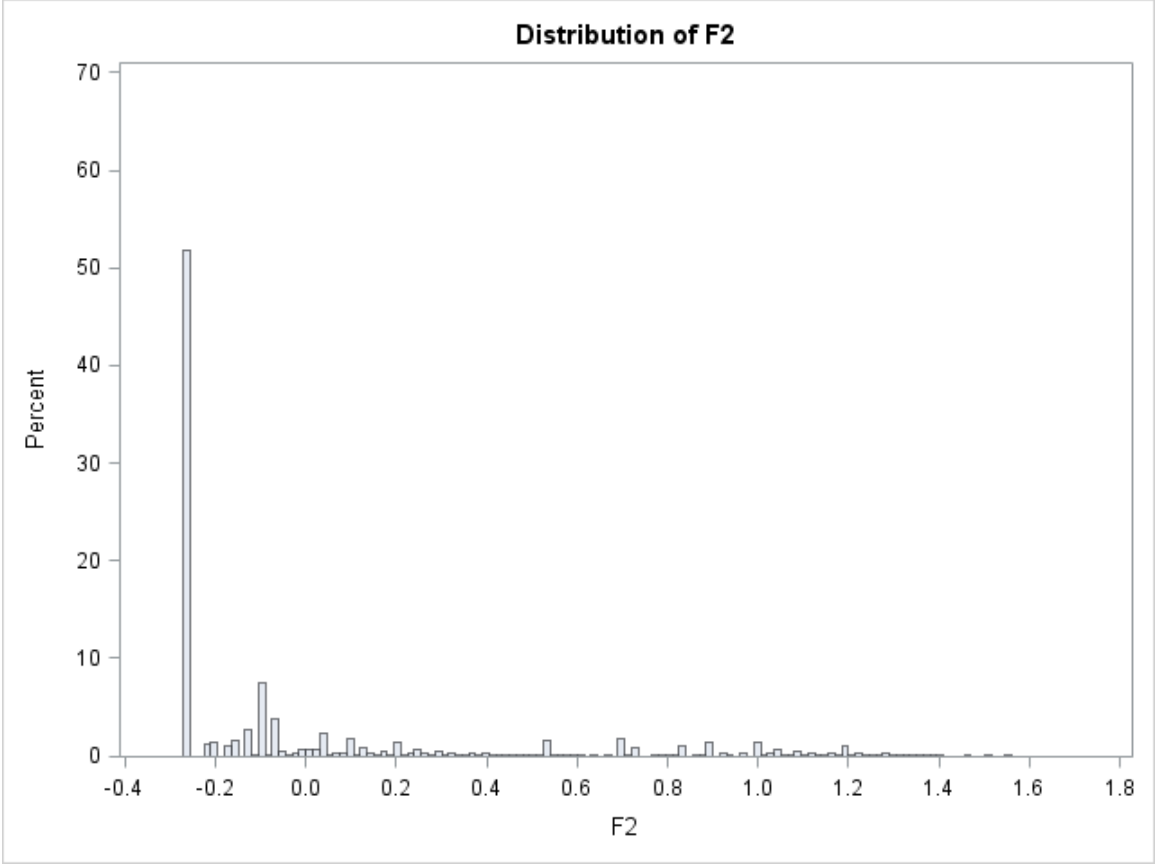


Figure 4.13. Histogram for the F2 Subscale, Measurement Sample

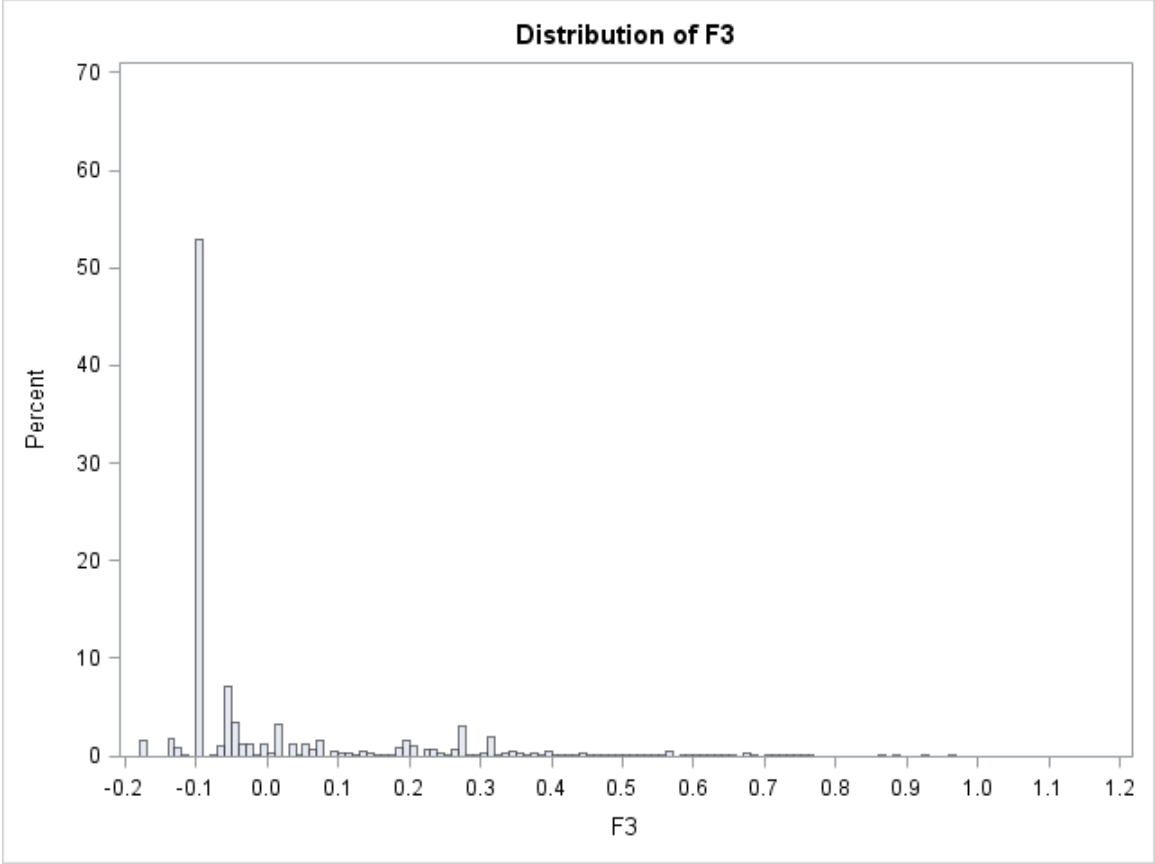


Figure 4.14. Histogram for the F3 Subscale, Measurement Sample

CHAPTER 5

CONCLUSION

Among the various social relationships we encounter throughout our lives, family relationships are among the most intimate and powerful (George, 2003). Disruptions in these life-long convoys (Moen & Hernandez, 2009) can have chronic repercussions for individual health (Berkman, Glass, Brissette, & Seeman, 2000), particularly if they occur during sensitive early-life stages of development (Gluckman, Hanson, & Buklijas, 2010; Hertzman & Boyce, 2010). Contemporary science is well-positioned to further build upon the foundations laid by previous scholars (Bowlby, 1980; Durkheim, 1951) to improve individual, family, and behavioral health outcomes. This will require transcending traditional disciplinary boundaries with a biopsychosocial approach to address the complex realities of individual, family and public health.

This dissertation situated the relationships between early-life parental death (PDE) and later-life behavioral health within a contemporary biopsychosocial life-course framework (Berkman et al., 2000). Throughout this work, I have referenced past research that shows biological mechanisms can link early parental death to later-life physical and mental health and mortality by scarring physiological systems, leading to unhealthy psychological states; and that the resultant loss of social resources from the parents can further amplify these compromised health states, leading to chronic exposures that may

seriously affect morbidity and mortality (Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Bowlby, 1980; House, Umberson, & Landis, 1988; Luecken & Roubinov, 2012; Preston, Hill, & Drevenstedt, 1998).

This dissertation also utilized contemporary statistical methods from a large demographic database—the Utah Population Database (UPDB). In an era of big populations and Big Data, such statistical approaches may be increasingly relevant for solving such problems with contemporary solutions and interventions (Mega, Sabatine, & Antman, 2014; Murdoch & Detsky, 2013). The large sample size, family linkages, and insurance claims data from this population sample have provided insights into long-standing problems. While there are limitations to the studies presented, each nonetheless offers a substantial contribution to the literature, and has implications for future research directions and public and medical policy.

Brief Review of Contributions

A brief review of the three papers, and how they contribute to the extant literature on the biopsychosocial dynamics of PDE and behavioral health, seems in order. The first paper, of which Chapter 2 consists, showed that early-life death of a parent was associated with increased risk of later adult suicide and cardiovascular disease death prior age 50 for both males and females. Social integration, as measured by remarriage of the surviving parent, appeared to ameliorate suicide risk for females before age 50, but not so much CVD risk. This suggests a possible protective effect of individual-level social integration (House et al., 1988), particularly for suicide (Durkheim, 1951). However, gaining a stepparent through remarriage appeared to further increase the risk of suicide

for females after age 50, which reinforces that development, health, and family dynamics are lifelong processes (Elder & Johnson, 2003; Umberson, Crosnoe, & Reczek, 2010), and suggests social integration might also be harmful if conflict is involved (Daly & Wilson, 2005; Umberson & Chen, 1994).

The second paper, found in Chapter 3, approached the theory of "differential vulnerability," which suggests individual poor health outcomes resulting from early-life parental death may vary by contexts of susceptibility, and some may react more negatively to stress than others (Hertzman & Boyce, 2010). A risk score of familial vulnerability for psychopathology, called the familial standardized incidence ratio (FSIR), was calculated using the incidence of suicide in extended pedigrees while adjusting for age, sex, and expected levels of genetic interrelatedness (Kerber, 1995). Even after accounting for differential survival to age 65, the multiplicative interaction of this risk score with early-life parental death was associated with increased depression risk for females over age 65. PDE became a significant predictor for female depression in later-life when the familial risk of suicide was over two-and-a-half times that for an average-risk family. This finding lends support for the operation of differential vulnerability to early-life stress, and reinforces the potential for early-life stress to affect health far across the life-span (Elder & Johnson, 2003). Furthermore, this paper shows the potential utility of demographic and pedigree data for examinations of differential vulnerability, and I hope other researchers will avail themselves of the FSIR's merits.

The third paper noted that early parental death as a stressor is not independent of other early-life biodemographic stressors. On the contrary, it is intercorrelated with other early-life indicators of stress. Failure to account for patterns of covariation between these

different early-life stressors may bias findings and interpretation. Using cutting-edge factor analytic methods I constructed a measurement model that showed nine previously-established biodemographic early-life stressors of advanced maternal and paternal age, large sibship size, early maternal and paternal death, high infant mortality rate in county of birth, late birth order, whether a sibling died as an infant, and whether a sibling died as a child could be viewed as indicators of three latent constructs; those could in turn be viewed as indicators of one larger scale of early-life exposure to stress, now labeled the Utah demographic childhood adverse exposures (DECADE) scale. I further found that early-life biodemographic stress, as measured by this single DECADE construct, was associated with increased risk of adult suicide and all-cause mortality prior to age 50. This reinforces the importance of accurate measurement in the stress literature. Furthermore, the DECADE scale itself should prove practically useful for future researchers examining any phenotype of interest, including behavioral health.

Limitations and Associated Possibilities

I believe this work offers a substantial creative contribution to sociology and studies of the life-course, early-life stress, suicide, and physical and mental health; and helps to bridge divides between disciplines, consistent with current recommended best practices (Berkman et al., 2000; Cuthbert & Insel, 2013). Nevertheless, given the complexity of the phenomena under question, there is only so much that could be reasonably achieved in this work. Therefore, it has certain potential limitations that should be addressed. These considerations may be methodological or theoretical in nature; but, future work could and should extend this work to address these issues.

Methodological Considerations

From a statistical standpoint, the issue of causality is problematic. While the data utilized were longitudinal, often covering entire lifespans or generations of families, advanced statistical methods are still not as well suited for determining causal associations as natural experimental studies (Pickles, Maughan, & Wadsworth, 2007). Work examining sequelae of early adverse exposures incident to natural disasters (Cas, Frankenberg, Suriastini, & Thomas, 2014), warfare (Olema, Catani, Ertl, Saile, & Neuner, 2014), and famine (Hoek, Brown, & Susser, 1998) holds great promise, but the absence of a robust data infrastructure has limited the questions that can be asked when such conditions present themselves.

One way to efficiently expand data infrastructure is to link existing archives (Elder, Jr. & Taylor, 2009). In particular, I echo the requests of other researchers to link family history data with current cohort studies to permit robust family-based study designs that increase statistical power and enable nationally-representative inferences (Collins, 2004). Since many cohorts have already been followed for several years, timely linkage could vastly expand data resources retrospectively without waiting for the cohort to age (Gordis, 2008). As an example, the Digitizing Scotland Project (Longitudinal Studies Centre Scotland, 2014) is taking this approach, and I suspect it will yield invaluable results. More detailed questions provided through additional surveys and qualitative work such as personal interviews or diary designs (Almeida & Wong, 2009) could also supplement demographic and medical data to further delineate stress-health associations and asses measurement reliability (Elder, Jr. & Taylor, 2009). Sample data could also help formulate a "gold standard" of measurement that, once linked with

administrative, register, and demographic data, leads to statistical adjustments to decrease measurement error in populations.

In the meantime, there is still much data already available that can be analyzed, and future studies should build upon the approaches taken in this dissertation. For example, recent approaches in causal modelling, particularly those utilizing instrumental variables, could more closely approach counterfactual arguments needed to provide strong evidence of causality (Costello & Angold, 2007; Pearl, 2009). Further, early-life health is not deterministic (Wise, 2003), and different epidemiological models might be implemented to better delineate chains of risk, where early disadvantage leads to additional risk of disadvantage in later life (Ben-Shlomo & Kuh, 2002), and formal tests could check for mediating stressors in lifelong human development (Dearing & Hamilton, 2006). For example, the mediating paths of substance abuse or personal marriage and divorce patterns could more clearly elucidate the pathways leading from early-life stress to later-life health.

Theoretical Considerations

Theoretically, this dissertation has taken a life-course approach as a guiding framework for integrating social, biological and psychological approaches to early-life stress and adult behavioral health. However, in the interest of space there are certain elements of the life-course I have not strongly addressed, but would prove quite fruitful for future research. In particular, lives are embedded in historical time and place (Elder, Jr. & Taylor, 2009; Mills, 1959). It is known that the historical period or cohort to which a person belongs may influence risk for suicide (Newman & Dyck, 1988). Knowing to

what level this is affected by or affects the relationship between early-life stress and later-life health could help develop effective policies. For example, war will likely increase the frequency of early-life parental death in a population, yielding greater early-life exposure for certain cohorts. A parent who has died might be viewed as a "war hero," an appellation that has changed in meaning over time (Lewis, 1995). If the parent is viewed as a hero, then the effect of PDE might be less severe. However, we suspect the social mechanisms incident to decreased social integration might still exact a toll if appropriate interventions are not implemented. Gun ownership increases risk for suicide at the individual and population levels (Hemenway, 2014), and so the modifying impacts of cohort, period and geographic patterns in preferences and laws regarding firearms might yield interesting results. Further, recent research suggests altitude has a positive statistical association with suicide—possibly due to direct internal physiological mechanisms (Huber, Coon, Kim, Renshaw, & Kondo, 2014), and therefore this three-dimensional geography has potential modifying implications for the effects of early-life stress upon later-life health.

I have also not thoroughly considered the life-course principle of agency (Elder & Johnson, 2003), which suggests that individuals do have choices that will affect their health, such as whether to engage in salubrious or deleterious health behaviors. Clearly, some people will choose to engage in self-harming behavior, and others will not. Suicide, as recorded on death certificates, requires an immediate behavior by the victim, whereas as most other causes of death do not. Agency is constrained by our social environments (Elder & Johnson, 2003; Mills, 1959), and it is an assumption of this paper that early-life stressors may increase an individual's likelihood of making that choice. However, the

immediate physiological mechanism whereby that motivation translates into the choice to engage in the behavior is beyond the scope of this dissertation.

There are two other important sociological dimensions that this dissertation has not addressed. First, racial-ethnic identification is associated with mental health outcomes (Hayward, Miles, Crimmins, & Yang, 2000). At present, the racial-ethnic data in UPDB are not sufficient to adequately address this dimension. However, these potential dynamics are important to understand for purposes of public health and social justice policy. Second, the relevance of sex and gender demands a few additional comments. While "sex" measures the biological chromosomal state, "gender" is social construct strongly dependent upon social traditions and conventions; and the theoretical implications of this separation is not currently well developed for biosocial research (Perry, 2013). Therefore, throughout this dissertation I have preferred the term "sex" over "gender," because it is more theoretically consistent and the data more adequately measure the former. Note also that in all three papers, I examined outcomes separately for each sex, and formal statistical comparisons are mostly absent. This is because the potential stress reactions and health outcomes differ so much by sex that, in order to enable unbiased comparisons of the other phenomena of interest, the stratification approach seemed appropriate. However, more formal comparisons of males to females should be undertaken.

Implications

The findings have implications for future research and policy. Many of these have already been discussed, but it seems apropos to make a few additional observations. First,

regarding research, I believe the biopsychosocial framework utilized yielded empirically and theoretically sound results regarding early-life parental death and adult behavioral health. A next step would be to further situate these questions within a statistical multilevel framework, including the social/environmental (including historical and geographic), behavioral/psychological, organ systems, cellular, and molecular (Anderson, 1998). However, despite the profusion of multilevel methodologies, it much easier to focus upon a few levels at first, as premature extensions to further levels may lead to erroneous findings (Anderson, 1998). Therefore, such collaborative work between those with historical, developmental, statistical and biological skills should proceed in an orderly fashion, but proceed nonetheless given the potential for effective interventions.

In terms of policy implications, I wish to reiterate that childhood is a sensitive period that "sets the stage" for future development, exposure, and coping resources; and small changes in these early-life parameters may drastically alter the trajectory of later-life health. This becomes clear if we extend our scope of potential intervention strategies beyond tertiary strategies, and consider the potential life-long or even intergenerational protective effects of primary and secondary prevention strategies (Hertzman, 2007).

For example, in the second paper I examined familial patterns of suicide across time to approximate what might be a possible genetic predisposition, and combined that with early parental death to examine poor behavioral health. The findings suggest that both elements, when combined, were associated with greatly increased risk of later-life depression for females. This suggests that even if genetic or other familial vulnerability might be necessary for poor behavioral health, social/environmental exposures or "triggers" might also be necessary (Shanahan & Hofer, 2005, p.65). The implication is

that if the likelihood of experiencing a stressful early-life trigger, such as early parental death, can be reduced by effective social policies such as education, healthcare, prenatal care, childcare and social welfare services (Marmot, Allen, Bell, Bloomer, & Goldblatt, 2012), then the impact of familial risk upon the child's future behavioral health should decrease. This might then increase that child's potential for positive parenting, thereby recursively improving health for generations. The possibility is further buttressed by recent work that suggests early-life stress might also effect epigenetic changes that transmit health across generations through direct biological pathways (Franklin et al., 2010). While all this work on transgenerational scarring is still in its infancy, it suggests that investments in primary interventions could potentially yield massive returns across generations through social and biological pathways.

I further suggest that personalized medicine, in tandem with Big Data can potentially decrease unhealthful outcomes of stressful early-life conditions that do occur, alleviating their impact throughout an individual's life and potentially into the next generation. This would require further investments in data resources and collaborations between scientists, including overcoming traditional disciplinary biases (Freese, Li, & Wade, 2003; Mega et al., 2014; Murdoch & Detsky, 2013). Such personalized professional approaches might not only help improve one individual's behavioral health, but be an investment for the future.

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