

UNDERSTANDING THE DETERMINANTS OF AGING AND
LONGEVITY: THE INFLUENCE OF THE SOCIAL
ENVIRONMENT, BIOLOGY, AND
HERITABILITY THROUGHOUT
THE LIFE COURSE

by

Heidi Anne Hanson

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STATEMENT OF DISSERTATION APPROVAL

The dissertation of _____ **Heidi Anne Hanson** _____
has been approved by the following supervisory committee members:

_____ **Ken R. Smith** _____ , Chair _____ **09/06/2013** _____
Date Approved

_____ **Rebecca Utz** _____ , Member _____ **09/06/2013** _____
Date Approved

_____ **Ming Wen** _____ , Member _____ **09/09/2013** _____
Date Approved

_____ **Sandra J. Hasstedt** _____ , Member _____ **09/09/2013** _____
Date Approved

_____ **Antoinette M. Stroup** _____ , Member _____ _____
Date Approved

and by _____ **Kim Korinek** _____ , Chair/Dean of
the Department/College/School of _____ **Sociology** _____

and by David B. Kieda, Dean of The Graduate School.

ABSTRACT

The purpose of this dissertation is to investigate the heterogeneity in patterns of aging and the factors throughout the life course that shape them. By focusing on variability within the population we are able to advance our knowledge of how circumstances throughout the life course affect the way individuals age. We find that the paths to disease and longevity are diverse and that the social environment plays an important role in shaping these patterns. Our results support a wide body of literature showing that morbidity is not an inevitable consequence of aging, even in the oldest old population. Health status and longevity are shaped by the historical circumstances and social environments that we live in. This study offers three innovative and significant contributions to the understanding of biological and environmental determinants of aging by (1) disentangling the biological and temporal sources of trends in cancer incidence among the elderly, (2) investigating the possible social and physiological effects of fertility history on comorbidity trajectories after age 65, and (3) studying heterogeneity in the heritable contributions to variation in longevity across early life family and social environments.

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CHAPTER 1

AGING AND LONGEVITY: THE PAST AND FUTURE TRENDS

Introduction

Demographers, biologists, social scientists, geneticists, historians, and other scientists have long embarked on the quest of uncovering the secrets of healthy aging and longevity. While the fascination with longevity is not unique to this time period, the rapid changes in life expectancy and population structure over the past century have elevated the importance of understanding determinants of healthy aging and longevity. The mortality profiles of the developed countries have especially undergone fundamental transformations over the past century. Life-expectancy in these populations has increased linearly by approximately 3 months per year for the past 160 years (Oeppen & Vaupel, 2002). Historically, these improvements have been largely due to improvements in survival in infancy and childhood. While less recognized, death rates at older ages have also greatly improved over the last half of the 20th century (Vaupel et al., 1998).

Significant declines in fertility during the demographic transition combined with gains in life expectancy past age 65 have led to population aging (rising proportions of the population age 65 and older) and increased levels of old-age dependency. These changes have had profound policy implications. It is estimated that the proportion of the

population age 65 years and older will increase from 12.3% in 2000 to 21.1% in 2050 in the United States (Uhlenberg, 2005). The oldest old population (ages 85+) is projected to more than triple from its current estimate of 5.7 million to 24 million by 2050 (Vincent, Velkoff, & Bureau, 2010), making it the fastest growing segment of the population. The rising proportions of the population above the age of 65, combined with increases in life expectancy and current trends in mortality decline in the oldest age categories, have made the determinants of longevity and healthy aging critical to understanding population health. Aging research is an extremely important domain of population health, and its significance will increase as the proportion of the population age 65 and older continues to rise.

The biological and social factors that determine healthy aging and longevity, and their interaction, are still not well understood. In the past, misconceptions about the limits of life-span have led demographers to underestimate the rate of decline in old-age mortality (Uhlenberg, 2005). Current projections suggest that if the present gains in life expectancy continue, more than half of individuals born after 2000 will live to see their 100th birthday (Christensen, Doblhammer, Rau, & Vaupel, 2009). Unfortunately, such projections ignore the complex interactions of social and biological factors that determine mortality.

This dissertation improves upon previous research by investigating the influence of the social environment, biology, and heritability throughout the life course on healthy aging and longevity. The studies presented in this manuscript seek to disentangle the biological and temporal sources of trends in cancer incidence, investigate the possible social and physiological effects of fertility history on comorbidity trajectories after age 65, and explore the heterogeneity in heritable components of total phenotypic variation in

longevity across early life family and social environments. A fuller understanding of heterogeneity in patterns of aging and the factors throughout the life course that shape them will lead to more accurate population prediction, identify at risk population that may benefit from more effective public health interventions, and characterize the process of aging in a diverse population.

A rigorous investigation into biological and social causes of healthy aging and longevity at advanced ages requires a theoretical framework capable of assimilating theories from multiple disciplines. Biodemography provides a multidisciplinary synthesis of biological, evolutionary, social science, ecological, life history and demographic theories and is primed to answer a range of questions including those about both how and why humans age (Vasunilashorn & Crimmins, 2008). Over the past few decades, demographers have broadened the focus of work in the demography of aging from a population aging perspective (i.e., measures of change in population age structure), to include a perspective that integrates health and biological explanations with traditional demographic and social theories of aging to explain variations in health and mortality within and between populations (Olshansky, Carnes, & Brody, 2002; Siegel, 2011; Vasunilashorn & Crimmins, 2008).

The Biodemographic Perspective of Aging

As developed countries began to recognize most of the longevity gains to be secured were achieved by improving infant and childhood mortality, questions began to surface about how much improvement can be made in mortality rates at the other end of the spectrum, what proportion of mortality at these ages is biologically determined, and whether we are approaching a maximum life expectancy or linear gains can continued to

be realized (Carnes & Olshansky, 2007; Vaupel et al., 1998). “Aging, Natural Death, and the Compression of Morbidity,” an article published by James Fries (1980), resulted in a lively debate about the limits of life-span within the field of demography, with some arguing that physiological decay was innately programmed (Fries, 1980), others suggesting that old age is not biologically determined but there are practical limits that will make steady improvements difficult (Carnes & Olshansky, 2007), and a third group projecting linear increases in life expectancy for the foreseeable future (Vaupel et al., 1998).

This debate is centered on a pivotal question; are we biologically programmed to die? Even under ideal conditions, there is a progressive increase in age-specific death rates and senescence (Carey & Judge, 2001). Theories aimed at answering why we senesce and inevitably die can be classified into two broad categories: thermodynamic and biological evolutionary theories of aging (Austad, 2001). Thermodynamic theories implicitly or explicitly claim that aging is the inescapable consequence of the physical nature of matter. These theories arrive at the conclusion that senescence is a genetically programmed rate of decay, the natural consequence of approaching one’s maximum possible life-span (Fries, 1980). Biological evolution theories explain senescence in terms of selection forces acting on life history traits (Kirkwood & Rose, 1991). Reliability theories of aging, optimization models, and nonadaptive mutation models (see Table 1.1 for a more detailed description of these theories) all describe senescence as a byproduct of evolution and not an innately programmed switch that is common to all organisms.

The compression of morbidity hypothesis (Fries, 1980) argues that morbidity and disability can be compressed to shorter periods toward the end of the life-span through

primary prevention such as maintaining a healthy lifestyle. Principally, he argued that the rectangularization of the survival curve would be accompanied by an increase in age at onset for chronic disease and disability which, in turn, compresses the time spent in a diseased or disabled state. Others argued the failure of success hypothesis, which suggests that improved survival of frail individuals will lead to increases in disease later in life (Gruenberg, 1977; Kramer, 1980). Not only did these hypotheses spark interest in determinants of life-span, but they also led to debate about heterogeneity in patterns of aging, whether increased life expectancy indicated increased healthy life expectancy, and whether centenarians escaped major age-related diseases.

The evidence consistent with morbidity compression is still uncertain. Most evidence for individuals younger than 85 suggests there has been a postponement in disease and disability over time, but little is known about trends in the population age 85+. This is largely because health data for this group of the population is not as readily available (Boscoe, 2008). Although there are some studies of disease in centenarians that suggest that a proportion of these exceptionally long-lived individuals delay or escape disease, there is still considerable variation in disease experience (Andersen, Sebastiani, Dworkis, Feldman, & Perls, 2012; Evert, Lawler, Bogan, & Perls, 2003). Uncertainty of the expected trends in morbidity with age coupled with the fiscal demands of the Medicare program have made the question of morbidity patterns above age 65 a central biodemographic question. While the association between morbidity and mortality is complex and varies across populations and environments (Siegel, 2011), most classifications of morbidity (for example, heart disease and dementia) lead to higher rates of death (Vaupel, 2010). Therefore, a more complete understanding of the determinates

of major morbid conditions and how these factors change over time can yield better predictions of morbidity and mortality trends at advanced ages.

In his 1980 paper, Fries made a prediction: life expectancy would not exceed 85 years. This prediction was quashed in 2007, when the average life-expectancy for Japanese women reached 86 years (Christensen et al., 2009). The continued steady rise in life expectancy suggests that if there is a fixed limit, we have not yet reached it. While limits in life expectancy suggested by those supporting a biological limit to life-span have been surpassed, Jean Calment's documented life-span of 122 years has yet to be broken. Therefore two questions still remain: are we biologically programmed to die, and what patterns of disease can we expect to see if life expectancy continues to rise? While these questions have important implications for future population projections, we cannot arrive at a suitable answer unless we consider another component that has been largely ignored up to this point in the discussion: the relationship between social context, healthy aging, and longevity.

Aging does not take place in isolation. It is heavily influenced by our environments. Understanding the interplay between social context and biological factors is imperative to understanding and predicting future trends in aging and mortality. Social and historical context must be considered when determining morbidity and mortality trends within a population. For example, studies have suggested that age, period, and cohort factors are all important factors that affect population trends in mortality (Preston & Wang, 2006; Yang, 2008). Mortality at ages 80 years and above has fallen at an unprecedented pace since the 1950s (Kannisto, 1996), but old-age mortality in the United States has stagnated since 1980 (Rau, Soroko, Jasilionis, & Vaupel, 2008). Other authors have also noted the potential flaws in predicting future trends in longevity without

considering the social and historical context which shapes it, and have suggested that the rapid increase in obesity may lead to declines in life expectancy in the near future (Jay Olshansky et al., 2005; Reither, Olshansky, & Yang, 2011). Accurate predictions of health and mortality of the aged population requires an approach that crosses disciplinary boundaries and integrates biological and sociological concepts.

Biodemographers embrace the view that sociological context affects healthy aging and longevity, for not only do social theories explain the demographic transition but the central idea that health and longevity is socially patterned is deeply rooted in the sociological tradition (Berkman & Syme, 1979; House, Landis, & Umberson, 1988; Link & Phelan, 1995; Wen, Browning, & Cagney, 2003; Wise, 2003). But by integrating biological theories and measures with sociological theories, the field of biodemography has great potential for making contributions that will improve public health by considering how social, economic, behavioral, and psychological conditions “get under the skin” to cause health problems (Crimmins & Seeman, 2004; Robine, 2006; Vasunilashorn & Crimmins, 2008). It has also become evident that proximate social circumstances alone cannot explain heterogeneity in aging and the experiences across the life course play an important role.

Biology, the Life Course, and Aging

Healthy aging and longevity cannot be understood by restricting analysis to a single life stage because aging is a lifelong process. The life course perspective places importance on both the historical and demographic parameters related to aging and longevity, as well as the biological, social and psychological factors that influence aging and longevity through direct (e.g., biological imprinting) and indirect (e.g., cumulative

and pathway) mechanisms throughout the life course (S. H. Preston, Hill, & Drevenstedt, 1998; Settersten, 2003). Simply put, it requires the researcher to consider how risk is shaped throughout the life course, beginning with biological development *in utero*.

Genetic influences have been cited as perhaps the earliest biological factor contributing to later life morbidity and mortality (Smith, Hanson, & Zimmer, 2012). The two types of longevity genes, gerontogenes and longevity-assurance genes, can be used to describe the effects of genes on longevity (Christensen, Johnson, & Vaupel, 2006; Sebastiani et al., 2012). Gerontogenes negatively affect longevity, thus life-span increases when their expression is blocked. Longevity assurance genes lead to a phenotypic expression of longer life-span and therefore longevity decreases when their expression is blocked. Thus, genetic endowments may either be protective, as in the case of familial excess longevity (Smith, Mineau, Garibotti, & Kerber, 2009), or detrimental, as in the case of certain apolipoprotein E (APOE) alleles (Ewbank, 2004).

Genes are fixed at birth, but is their expression? To answer this question, comparisons of monozygotic and dizygotic twins have been made to compare life spans while holding the childhood environment constant. These studies estimate heritability of life-expectancy to be 25% (Herskind et al., 1996; Skytthe et al., 2003). Twin studies have also revealed the variable nature of gene expression with age (Fraga et al., 2005; Petronis et al., 2003) and it has been suggested that epigenetic mechanisms cause individuals with the same genotype to have increasingly divergent phenotypes with age.

An individual's genotype is inherited at birth and can be considered immutable. However, gene expression is malleable because it is influenced by the environment through the epigenome. Epigenetic modifications can be defined as "the sum of heritable changes...that affect gene expression without changing DNA sequence" (Montesanto,

Dato, Bellizzi, Rose, & Passarino, 2012). Epigenetics is a bridge between genetics and environment and may explain a portion of the variation in the rate of aging and longevity. It is one of several possible biological mechanisms that allow social circumstances to get “under the skin,” and epigenetic modifications have the propensity to persist across subsequent generations (Feinberg, 2007). Differences in community and family environments may affect the epigenetic regulation of gene expression and lead to variation in the longevity phenotype. Recent studies suggest a relationship between strength of genetic correlations and the quality and variability of an environment (Charmantier & Garant, 2005). There may also be epigenetic changes in response to individual social experiences throughout the life course (Champagne, 2010). Does the social environment throughout the life course shape later life health and mortality?

Events throughout the life course can alter physiological functioning and affect later life health and longevity. Early life conditions have been shown to be significantly correlated with adult mortality for individuals and cohorts (Abel & Kruger, 2010; Barker, 1995; Doblhammer & Vaupel, 2001; Eriksson, Forsén, Tuomilehto, Osmond, & Barker, 2001). The fetal origins hypothesis and inflammation hypothesis are two theories that have been used to explain the biological programming of an individual early in life. According to the fetal origins hypothesis, individuals exposed to adverse conditions *in utero* may have altered morbidity and mortality trajectories due to altered development of key organ systems or epigenetic modifications during gestation. The inflammation hypothesis argues that exposures to infectious disease during infancy and childhood result in altered morbidity and mortality trajectories in adulthood (Crimmins & Finch, 2006; Finch & Crimmins, 2004). McDade, Rutherford, Adair, and Kuzawa (2010) have proposed a related but alternative hypothesis predicting a negative relationship between

exposure to infectious disease and inflammation in adulthood, arguing that exposure to infectious diseases are necessary for healthy development of the immune system.

Early life conditions may also be indirectly associated with morbidity and mortality outcomes through correlated environments, cumulative processes, health selection, and mortality selection. Indirect associations through correlated environments are based on the principle of continuity of the life course and that one's environment during childhood is the same or similar to one's adult environment. Selection mechanisms may also lead to an indirect association between early life circumstances and later life health outcomes. The health selection hypothesis argues that illness has social consequences that may lead to poor socioeconomic status (SES) later in life and that it may be the more proximate exposure to poor SES that is responsible for the observed association between early life conditions and later life health (Montez & Hayward, 2011). This continuity may lead to erroneously attributing the observed outcome to early life conditions, when it is the proximate environment that is leading to adverse health outcomes. Alternatively, genetic heterogeneity in the population may lead to differential mortality selection; with those at the highest risk, the frail, being culled from the population early leading to a population with a disproportionate representation of robust individuals at older ages (Elo & Preston, 1992; Hawkes, Smith, & Blevins, 2012).

Related to this argument is the cumulative advantage/disadvantage hypothesis, which argues that early life events can set into motion a trajectory where advantage/disadvantage is accumulated throughout the life course (O'Rand & Hamill-Luker, 2005). Sequential exposures to adverse environments may lead to excess stress or exposure to chronic stress that leads to increased risk for disease later in life.

Conceptualizing aging and longevity as a lifelong processes allows for the study of how

inequalities are created through the accumulation of advantage/disadvantage across the life course (Elder & Giele, 2009). Cumulative disadvantage can be set into motion by early life events or situations that lead to structural constraints throughout the life course (O'Rand & Hamil-Luker, 2005).

Physiological changes to the body in response to social conditions are not constrained to critical or sensitive periods of development. These changes can occur in response to prolonged exposure to stress throughout the life course. Allostasis, the ability to achieve stability through change, is maintained in the body through the autonomic nervous system, hypothalamic-pituitary-adrenal (HPA) axis, and the cardiovascular, metabolic, and immune systems (McEwen, 1998). Allostatic load describes a process through which exposure to chronic stress throughout the life course can lead to wear and tear in these systems and lead to poor health in adulthood (Geronimus, 1992; McEwen, 1998), and these effects can be attenuated or accentuated by an individual's access to economic, social, or personal resources (Elder & Giele, 2009). Under this hypothesis, individuals that are continually exposed to stress may experience physiological deterioration of key systems that lead to chronic disease later in life. Recent epigenetic research has also shown that epigenetic modifications occur across the life span (Champagne, 2010; Montesanto et al., 2012; Shanahan & Hofer, 2011). While more research needs to be done, it has been suggested that epigenetic changes during the aging process may directly contribute to malignant transformation of cells (Fraga, 2009).

Placing human lives in context is fundamental to life course research. The life course perspective promotes the view that social and physical environments vary by time and space and underscores the multiple layers of human experience. It also highlights the importance of historical change in determining health. These temporal changes in the

social or ecological environment are dependent upon the age of an individual and are unique to a group of people born during the same time period or birth cohort.

Biodemography adds to this concept by recognizing that we live in a very different environment from the one in which our life history evolved. Genetic, social, and economic history and environments play an important role in shaping health and disease patterns across populations and communities.

Birth cohorts are a measure of the social forces that shape health throughout the life course (Keyes, Utz, Robinson, & Li, 2010). They vary in size, demographics, social norms, prevalence of infectious disease, food availability, level of medical knowledge, education, occupation, urbanization, etc., making each cohort unique. For example, changes in smoking patterns or other environmental exposures over time may lead to cohort specific trends in cancer incidence. They have been regarded as fundamental units of social organization (Easterlin, 1998; Elder, 1999). Finch and Crimmins' cohort morbidity phenotype hypothesis suggests that differential exposure to infectious diseases during childhood will lead to cohort differences in old age morbidity and mortality (Crimmins & Finch, 2006; Finch & Crimmins, 2004). While cohort effects have proven important for a number of different outcomes related to aging and longevity (Chen, Yang, & Liu, 2010; Yang, 2008), some researchers are skeptical of the life course researcher's fascination with historical time (Fry, 2003), and others have argued that period factors play a more important role in determining mortality rates in old age (Gagnon & Mazan, 2009; Kannisto, 1996).

The life course perspective facilitates questions about possible pathways to later life health and potential confounding factors. The integration of biodemographic principles and the life course framework could lend important insight into how the

heritability of longevity may be altered by events throughout the life course. Biological, social, and psychological theories of development will be integrated in an attempt to create a more complete view of how later life health is shaped by a lifetime of past exposures.

Population aging is one of the greatest societal challenges of the next 50 years (Kalache, Barreto, & Keller, 2005; Schoeni & Ofstedal, 2010). There are both social and economic consequences of population aging. Accurate projections of how the elderly population ages has policy implications for forecasting Social Security and Medicare expenditures and predicting the costs of aging nationally and globally. The increase in the proportion of the population over the age of 65 will also change the types of illnesses and prevalent diseases in the population, affecting the types of medical services needed. The projected increase in the proportion of the population at advanced ages has grave implications for public pension programs, health care, and old age dependency. A greater understanding of the sociological, biological, and heritable determinants of aging and longevity is essential to maintaining a healthy population and economy.

The Determinants of Aging and Longevity

Perhaps the best way to elucidate mechanisms of aging and longevity is to study the heterogeneity in morbidity and longevity and determine what factors contributed to observed differences. This research contributes to the scientific understanding of aging and longevity patterns and the factors throughout the life course that influence them. Understanding the sources of variation in patterns of aging and longevity is important for creating accurate population predictions, identifying at-risk populations that may benefit

from public health interventions, and characterizing the process of aging in a diverse population.

Cancer was the second leading cause of death for individuals aged 65 and older in the United States in 2010 (Miniño & Murphy, 2011), making it an essential component to the study of aging and morbidity. Studies that do not account for changes in the environment, diet, health behaviors, and screening and diagnostic practices are ignoring the multifaceted determinants of cancer and may be inadvertently attributing temporal determinates of observed trends to biological mechanisms. Failing to account for cohort and period specific trends may confound the true age trajectory of cancer in this population. Chapter 2 disentangles these trends for individuals age 65 to 99 using Utah cancer incidence rates from 1963 to 2002, which lend better understanding to the true age-specific trends in cancer incidence, including the previously understudied oldest old age group (85+). It is important to account for cohort variations in aging and longevity in order to avoid misattributing patterns caused by historical circumstances to biological changes associated with age. Disentangling age, period, and cohort effects for major health conditions in the oldest old categories will allow for more definitive assertions about the possible causes of mortality deceleration and increased accuracy in forecasting of future trends used to predict the fiscal burdens of an aging population.

The pathology of chronic disease is multifaceted, determined by genetic profiles, biological and physiological development, and the social environment, with the strength and relative importance of each of these factors varying throughout the life course. Understanding longitudinal patterns of morbidity after age 65 is important to understanding the mechanisms of aging and longevity. Equally important is what

predicts the observed patterns. Are measures of fertility and reproductive health associated with morbidity profiles later in life?

Biological, evolutionary, and social theories all predict a relationship between fertility and later life morbidity trajectories. Chapter 3 examines the role of parity, young age at first birth, age at last birth, interbirth intervals, infant death, multiple births (twins), marital status at time of birth, birth weight of offspring, and preterm births for both men and women on disease progression after age 65. This study utilizes Centers for Medicare (CMS) data spanning from 1992 – 2009 linked to the Utah Population Database, which is a rich source of longitudinal data. Studying the effects of fertility history on men and women at several stages in the aging process will lend clues to biological, evolutionary, and social mechanisms that may lead to the observed outcomes.

For a more complete understanding of population heterogeneity in life-span and the forces behind it, one must not only understand the average contribution of genes and environment within a population toward explaining variation in adult mortality, but uncover the factors that influence patterns of variation within the population. While there is strong evidence supporting a genetic component to longevity, surprisingly, its size and relative importance is poorly understood. Longevity is a complex trait, determined by a multiplicity of genetic and environmental factors, with each factor contributing a potentially small amount to phenotypic variation. This phenotypic variation can be partitioned into genetic and environmental variation. Chapter 4 tests for heterogeneity in the heritability of longevity across several early and midlife environments and explores the possibility of gene-environment interactions (GxE). By examining sources of variation in heritability estimates, we can illuminate factors that modify the expression of genetic predisposition in a population. Understanding the role of biological and

environmental determinants of aging and mortality, and how they interact, can allow for the identification of sources of variation in morbidity and mortality and improve predictions of morbidity and mortality for future generations.

The final chapter provides a short summary of the findings from the studies presented in Chapters 2-3. These studies provide insight into patterns and processes of aging and highlight important factors to consider as the proportion of the population aged 65 years and older continues to grow. This chapter also gives direction for future research and policy implications.

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Table 1.1 Biological Evolution Theories
(Adapted from Kirkwood 1991)

<p>Reliability Theory of Aging</p>	<p>There are good engineering reasons to expect that complex systems designed to last for a specific amount of time outlast the expected survival time. If natural selection has designed systems to survive and reproduce as long as the environment allows, immediate death after that period is not expected (Austad Concepts Theories Aging)</p>
<p>Selection is not constant across the life course</p>	<p>Two types, optimization and nonadaptive age-specific mutation models</p> <p>Optimization models: forces of evolution are assumed to yield the best-possible design of a species life history</p> <p>-<i>Disposable soma theory:</i> Beneficial effect with a delayed cost- negative effect of increased reproductive rate on various somatic repair processes that reduce subsequent survival or fecundity (Partridge Ch5 - Zues, Kirkwood and Rose 1991, Abrams and Ludwig 1995). The soma is disposable relative to the germ line (Kirkwood 1977). This requires some form of exogenous mortality, separation of the germ and somatic cell lines, and trade-off between energy allocated to somatic repair and to germ line replication (Carey Judge 2001). “there may be a trade-off between reproductive success and longevity, because resources invested in longevity assurance may be at expense of reproduction” and this mechanism operates for both males and females (Westendorp and Kirkwood, 1998). It is selectively advantageous to limit the maintenance of somatic cells to accelerate development and reproduction, the downside- faster post reproductive deterioration and death. There is a cost to reproduction (Orzack 2003)</p> <p>-<i>Antagonistic Pleiotropy:</i> mutations that increase fitness in early life may be detrimental later on (Williams 1957). Antagonistic Pleiotropy is a special case of Disposable soma theory (Cary Judge 2001). This theory is appropriate to the study of variance and covariance of life-history characters within a population the effects of selection upon them (Kirkwood). Evidence in literature is mixed, however there is more support for this than mutation accumulation or disposable soma (Orzack 2003).</p> <p>Nonadaptive age-specific mutation models: Genes with deleterious effects in later life accumulate because they have escaped the force of natural selection.</p> <p>- Mutation accumulation: Later acting mutations escape the forces of natural selection. The fertility of mutation carriers is not compromised by the mutation. Selection is unable to exert tight control over the later portion of the lifespan (neutral process) (Kirkwood 1991).</p>

CHAPTER 2

AN AGE-PERIOD-COHORT ANALYSIS OF CANCER INCIDENCE

AMONG THE OLDEST OLD¹

Abstract

Disentangling age, period, and cohort effects for major health conditions in the oldest old categories will lead to better population projections of morbidity and mortality. Data from the Utah Cancer Registry (UCR), the U.S. Census, the National Center for Health Statistics (NCHS) and the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program are used to generate age-specific estimates of cancer incidence for ages 65–99 from 1973–2002 for Utah. Age-period-cohort (APC) analyses are used to describe the simultaneous effects of age, period and cohort on cancer incidence rates in an attempt to understand the population dynamics underlying their patterns. Our results show increasing cancer incidence rates up to the 85–89 age group

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followed by declines for ages 90–99 net of period and cohort effects. We find significant period and cohort effects, suggesting the role of environmental mechanisms in cancer incidence trends between the ages of 85 and 100.

Introduction

The demographic profile of the United States is changing, with proportionately more individuals surviving to very old ages. The oldest old population (ages 85+) is projected to more than triple from its current estimate of 5.7 million to 24 million by 2050 (Vincent, Velkoff, & Bureau, 2010), making it the fastest growing segment of the population. This substantial growth makes the study of morbidity and mortality for this age group increasingly important.

The deceleration of all-site mortality at advanced ages is a commonly observed phenomenon in both humans and animal species (Horiuchi & Wilmoth, 1998; Vaupel et al., 1998) and can be explained at the macrolevel due to changes in population composition (e.g., heterogeneity hypothesis) or at the microlevel attributable to physiological changes related to aging, (e.g., individual risk hypothesis). Alternatively, this observed trend may be the result of age misreporting in the oldest age categories, heterogeneous birth cohorts, and inaccurate measures of mortality in the oldest age categories (Gavrilov & Gavrilova, 2011). While the association between morbidity and mortality is complex (Siegel, 2011), studying patterns of human morbidity gives insight into the age related changes in morbidity and mortality (Svetlana V. Ukraintseva & Yashin, 2001), particularly for prevalent diseases such as cancer. A more complete understanding of the determinates of cancer and how these factors change over time can yield better predictions of morbidity and mortality trends at advanced ages.

Disentangling age, period, and cohort effects for major health conditions in the oldest old categories will allow for more definitive assertions about the possible causes of mortality deceleration and increased accuracy in forecasting of future trends used to predict the fiscal burdens of an aging population.

Little is known about age-specific disease incidence and prevalence among the oldest old, including cancer (Boscoe, 2008). In 2000, the oldest old age group accounted for 8% of all incident cancer cases, and this number is projected to rise to 17% by 2050 assuming current incidence rates continue (Hayat, Howlader, Reichman, & Edwards, 2007). Unfortunately, traditional surveillance methods limit our ability to examine age-specific cancer incidence in this subpopulation. The National Cancer Institute's Surveillance Epidemiology and End Results (SEER) program aggregates cancer incidence information for the 85+ age group, making it difficult to study cancer trends in the oldest old.

The few studies that examine cancer incidence trends after age 85 present evidence of a deceleration in cancer incidence, prevalence, and mortality at the oldest ages. (C. Harding, Pompei, Lee, & Wilson, 2008; Kaplan & Saltzstein, 2005; Saltzstein, Behling, & Baergen, 1998). While patterns for different time periods are presented for the oldest old population, the literature is limited with regard to analyzing change in the trends over time. Time is a dimension of context, or the structure of the physical and social environment related to a specific period or historical experiences unique to a birth cohort, that influences health (Suzuki, 2012). Recent studies have shown the importance of considering not only the effect of age, but also the role of period and cohort experiences when studying health outcomes (Reither, Hauser, & Yang, 2009; Yang, 2008). Sex-specific trends in both all-site and site-specific cancer also need to be

considered because there may be different biological and social determinants of cancer for men and women that vary by site (Yancik, 2005). This study aims to contribute to the current literature by examining age, period, and cohort trends in cancer incidence from 1973 to 2002 for ages 65 to 99 using data from the Utah Cancer Registry (UCR), the National Cancer Institute's Surveillance, Epidemiology and End-Results Program (SEER), the decennial Census, and the National Center for Health Statistics (NCHS).

Background

Disentangling Age, Period, and Cohort Effects

Age effects are generally understood to represent the biological characteristics of an individual. Cross-sectional studies of all-site cancer incidence and death rates show that rates generally increase with age, peaking between ages 75 and 85, and then plateauing before declining in advanced ages (Andersen et al., 2005; Arbeev, Ukraintseva, Arbeeveva, & Yashin, 2005a; C. Harding et al., 2008; Saltzstein et al., 1998; Stanta, 1997). However, many of these studies can only offer limited conclusions about cancer trends in the oldest old because they aggregated ages 85+, examined a single period, or failed to consider period and cohort influences.

Period effects can be described as the social and environmental context that modifies risk for all individuals in a population at a specific point in time. Changes in cancer screening technology may affect cancer incidence rates at all ages. Mammography screening became widespread during the 1980s, leading to an increase in incident female breast cancer diagnoses over the age of 65 (Edwards et al., 2002); colon cancer cases increased during the 1990s as a result of changes in colorectal screening (Edwards et al., 2002); and, there was a steep increase in incident prostate cancer cases

for males over the age of 65 between 1988 and 1992 due to the introduction of the Prostate-Specific Antigen (PSA) screening test for prostate cancer (Edwards et al., 2002). Changes in health care policy may also create period effects in cancer incidence. For example, Medicare began covering mammographies in 1991 (Kelaher & Stellman, 2000) and colon cancer screening in 2001 (Berkowitz, Hawkins, Peipins, White, & Nadel, 2008). Thus, the introduction of new diagnostic tools into the health care market, and changes in screening policies and medical practices have an impact on incidence rates over time.

Cohort effects describe the social or ecological environment unique to individuals born in the same group of years. Epidemiologists often describe cohort effects as the interaction between age and period, while sociologists conceptualize them as a measure of social forces that shape health throughout the life course (Keyes, Utz, Robinson, & Li, 2010). For example, changes in smoking patterns or other environmental exposures over time may lead to cohort specific trends in cancer incidence. Improvement in cancer screening technology may also have differential effects by birth cohort because the benefit is not equally shared amongst all ages. For example, the Agency for Healthcare Research and Quality does not recommend routine colonoscopies after the age of 75 (National Guideline), and questions about the efficacy of cancer screening for the oldest old have also been raised (Østbye, Greenberg, Taylor, & Lee, 2003). In addition to the age-based bias created by cancer screening recommendations, cancer incidence rates for these ages may be subject to detection bias because screening is difficult for frail individuals (Ukrainitseva & Yashin, 2003). A more comprehensive understanding of the age, period, and cohort factors contributing to cancer incidence rates in the oldest old is

essential for developing effective screening and treatment recommendations for this population.

Cross-sectional analyses show a decline in cancer incidence for the oldest old that is similar for men and women. However, results from previous studies indicate that the shape, height, and peak of age-specific incidence curves are sensitive to both historical period, cancer site, and study (C. Harding et al., 2008; Kaplan & Saltzstein, 2005; Saltzstein et al., 1998). If cancer incidence rates in this age group were based strictly on the biological factors contributing to aging, one would expect to see consistency in age-specific rates over multiple periods of study. However, the fluctuation in rates is evidence of the influence of external factors, related to period and birth cohort, contributing to cancer incidence. Treating the pattern of decline as an effect of aging neglects evidence of a social and ecological context that may alter age-specific trends and ignores the multifaceted determinates of cancer risk (Kaplan & Saltzstein, 2005; Stanta, 1997). Using a comprehensive approach that studies cancer trends over time and accounts for period and cohort effects will allow for a more accurate depiction of the age-specific trends in cancer incidence.

Aging and Cancer

Disagreement exists among theories explaining the relationship between cancer and aging and the observed decline in cancer incidence in the oldest old (Anisimov, 2003; Ukraintseva & Yashin, 2003). These controversies are similar to those surrounding mortality deceleration and may prove useful for understanding the mechanisms driving mortality deceleration.

There are three prevailing hypothesis explaining mortality deceleration (Gavrilov & Gavrilova, 2011; Horiuchi & Wilmoth, 1998). The first hypothesis asserts that the observed patterns of mortality deceleration are the result of age-misreporting and/or model misspecification (Gavrilov & Gavrilova, 2011), thereby suggesting that mortality does not decelerate with age, but is a statistical artifact. The other two hypotheses are the heterogeneity hypothesis and the individual risk hypothesis (Horiuchi & Wilmoth, 1998). These hypotheses lead to similar predictions about age related changes in cancer incidence.

Theories Predicting that an Individual's Cancer Risk Increases with Age (Deceleration is an Artifact)

The multistage theory predicts that cancer incidence rates should increase with age because the neoplastic transformation of cells occurs through several successive steps (Anisimov, 2003; Armitage & Doll, 1954). This framework describes cancer incidence as a power function of exposure time rather than age because cancer is caused by the dose and duration of carcinogenic exposure over a person's lifetime (Anisimov, 2003; Ukraintseva & Yashin, 2003). Under this scheme, the path to cancer is step-wise and irreversible, with each step leading to an increased probability of malignant transformation with exposure time and therefore age. However, exposure risks between cohorts may vary, giving rise to different patterns of age related incidence between birth cohorts.

Physiological mechanisms may also explain increases of cancer incidence with age. The cancer-longevity tradeoff hypothesis suggests that the cost of living a long life is cancer. Physiological changes in the tissue microenvironment, telomere dysfunction,

a decline in immune surveillance, loss in tumor suppressor function, and mutation accumulation are additional factors that have been cited as possible mechanisms leading to the increasing rates of cancer incidence with age (Anisimov, 2003; Campisi, 2003; Ukraintseva & Yashin, 2003). Many of these factors may be modified by environmental exposures and therefore the context of time. Factors such as diet, smoking, exposure to infectious disease (Ukraintseva & Yashin, 2003); and environmental interventions such as exercise, social support, and screening practices, may make age specific trends sensitive to temporal context.

Theories Predicting that an Individual's Cancer Risk Declines with Age (Individual Risk Hypothesis)

The individual risk hypothesis argues that the deceleration in morbidity and mortality rates at older ages can be explained in terms of physiology, evolution, and health behaviors (Horiuchi & Wilmoth, 1998; Vaupel et al., 1998). Although physiological mechanisms have been used to explain increasing cancer incidence with age, they may also predict the opposite—that cancer incidence in the oldest old age categories decelerate and decline. Physiological changes can contribute to the decline in cancer incidence in the oldest old through age-related declines in rates of cellular metabolism, suppression of tumor generation, and increased cellular doubling time (Ukraintseva & Yashin, 2003).

Natural selection may also affect age related declines in cancer incidence. Mutation accumulation theory argues that age-related declines in the force of natural selection may result in an accumulation of mutations that result in an increase in mortality beginning near the end of reproductive ages followed by mortality deceleration

in the oldest age categories (Horiuchi & Wilmoth, 1998). In addition, mechanisms which may protect against cancer may increase longevity, suggesting that individuals in the oldest old age groups may be less susceptible to cancer (Campisi, 2003).

Variation in age-related health behaviors could also explain a decrease in cancer incidence in the oldest old age groups. Cancer trends periodically shift due to changes in screening procedures and recommendations, but these period effects may not be equal across all ages. Routine cancer screening has increased in the general population (Edwards et al., 2002); however, studies have suggested that there is a decrease in surveillance for the oldest old and an increase in misdiagnosed or unreported tumors (Kaplan & Saltzstein, 2005; Stanta, 1997). These factors may lead to cohort specific trends in cancer incidence.

Population Heterogeneity Leads to Decreased Rates of Cancer

Incidence in the Oldest Old (Heterogeneity Hypothesis).

Population heterogeneity, differential risk patterns within a population, can be the result of both within and between cohort differences, making the context of cohort an important consideration. Within a single cohort heterogeneity can occur because the force of mortality may decrease at advanced ages (Horiuchi & Wilmoth, 1998), pointing researchers to a selection hypothesis to explain the decline. According to these hypotheses, there is differential selection in a heterogeneous population with the frail being selected out of the population at earlier ages (Hawkes, Smith, & Blevins, 2012). Individuals culled from the population may have a genetic or environmental predisposition to cancer, leaving their robust counterparts to survive to the oldest ages with a survival advantage that protects them from cancer. For example, individuals with

deleterious mutations, such as the BRCA1 mutation, have elevated cancer mortality rates as compared to the general population, making them less likely to survive to advanced ages (K. R. Smith, Hanson, Mineau, & Buys, 2011).

Population heterogeneity can also arise because different cohorts have experienced different mortality schedules, environmental exposures, public health initiatives (such as antismoking campaigns), and cancer screening recommendations. It has been suggested that the multistage theory is correct, and a plateau or decline in cancer incidence rates at old ages may reflect period and cohort trends (Yang, 2008). If exposure to different carcinogens such as tobacco smoke, changes in diet, or other environmental carcinogens, fluctuates over time the deceleration in incidence rates at the oldest ages may reflect these changes rather than somatic aging *per se*. A decline or deceleration in cancer trends in old ages may be a function of cohort experiences such as screening practices or health behaviors for this age group.

Understanding the relationship between cancer incidence and age will not only improve future predictions of cancer incidence, it will help U.S. understand the mechanisms leading to mortality deceleration in the oldest old population. Cancer trends for the oldest old population are understudied because cancer incidence rates are historically aggregated for all 85+ individuals (Boscoe, 2008). This study aims to improve upon current literature by examining temporal trends of cancer incidence from 1973 to 2002 for ages 65 to 99.

Methods

Data

This study uses data for the state of Utah from 1973 to 2002 collected from the Utah Cancer Registry (UCR), the National Cancer Institute's Surveillance, Epidemiology and End-Results Program (SEER), the decennial Census, and the National Center for Health Statistics (NCHS). Cancer incidence cases and the U.S. Census Bureau's Population Estimates for the state of Utah for ages 65 to 84 were obtained from SEER*Stat software (2010; 2012). Statewide cancer data are collected by the UCR as part of routine cancer surveillance for the Utah Department of Health and the National Cancer Institute's SEER Program. Cancer cases are reported to the UCR through health service providers and death certificates on which cancer is listed as a cause of death. Site and histology are coded according to the International Classification of Diseases for Oncology (ICD-O) at the time of diagnosis (Stroup, Dibble, & Harrell, 2008).

Age-specific incidence counts for ages 85 to 99 are not reported by the SEER program. At these ages, age misstatement is a widely recognized problem, making population estimates less reliable (Boscoe, 2008). Tabulated incidence data by year and age were provided by the UCR. Intercensal population estimates were calculated via the cohort-component and extinct-cohort methods using decennial data from the U.S. Census Bureau and mortality data from the National Center for Health Statistics (Shryock, Siegel, & Larmon, 1980). The cohort-component method starts with the cohort populations reported in the decennial census and then subtracts deaths to estimate population sizes. The use of census and death certificate data has been criticized because upward age-misstatement can lead to a downward bias of incidence rates for this population. However, age misstatement has been shown to be a relatively rare

occurrence with error rates improving over time (Boscoe, 2008; Hill, Preston, & Rosenwaike, 2000; SH Preston, Stewart, & Elo, 1999). Data collection issues have also caused errors in population estimates for the oldest old (Siegel & Passel, 1976). The extinct-cohort method is an alternative method of calculating population counts. It relies on death certificate data and is thought to be more reliable when cohorts are close to extinction because it is less subject to bias caused by age misreporting. Rates from both methods were compared and we found that when cohorts are farther from extinction estimates using the extinct-cohort method become less reliable. The cohort component method was selected as the basis for the final models. A detailed description of the methods and comparison between rates will be presented in an article by Rudy et al. and can be provided upon request. The final data set consisted of population level cancer incidence counts (numerators) and cohort-component population estimates (denominators) for the 65 to 99 year old Utah population from 1973 to 2002 by sex.

Statistical Methods

Sex- and site-specific cancer incidence trends from 1973-2002 for ages 65 to 99 for the state of Utah were selected for analysis. There were no incidence cases above age 100 from 1973 – 1982 and 1988 – 1997 for males and 1973 – 1977 for females; therefore we did not include this age category in the analysis. Cancer incidence rates were calculated as the ratio of incident cases to person years of exposure. Age-specific incidence rates were tabulated in age a by calendar year period p arrays with diagonal elements of the matrix corresponding to the birth cohorts c ($c = p + a - 1$), where the oldest cohort is observed for the oldest age interval during the earliest calendar period and the youngest cohort is observed for the youngest age interval during the latest

calendar period. Seven 5-year age groups, ranging from 65 – 69 to 95 – 99, and six 5-year time periods, from 1973 – 1977 to 1998 – 2002 were used in the analysis. There is some ambiguity in the measurement of cohorts because data are tabulated into 5-year age and period groupings. For example, an individual age 69 in 1973 would have a birth year of 1904 while an individual age 65 in 1978 would have a birth year of 1913. This yielded 12 successive ten year birth cohorts with midpoints ranging from 1878 – 1933, which were used for the age, period, and cohort (APC) analyses.

Traditional APC analyses suffer from an “identification problem” resulting from the linear dependency between age, period and cohort ($c=a+p$), precluding a unique solution. This problem can be solved by imposing constraints to the model to allow for an identifiable solution (Arbeev et al., 2005a; Arbeev, Ukraintseva, Arbeeva, & Yashin, 2005b; Carstensen, 2007; Yang, Fu, & Land, 2004). However, selection of the constraint requires some a priori knowledge of the disease under investigation and models are sensitive to the constraint selected. Other authors have suggested using a proxy characteristic for cohort (O'Brien, 1989, 2000; O'Brien, Stockard, & Isaacson, 1999). However, cohort characteristics may not entirely explain cohort effects and the residuals may still be confounded in the model estimates with age and period effects.

The Intrinsic Estimator (IE) proposed by Yang et al. (Yang et al., 2004; Yang, Schulhofer-Wohl, Fu, & Land, 2008) can also be viewed as a constrained approach; however, it does not require a priori assumptions about the constraints. Other studies have shown that the IE produces substantively meaningful and empirically valid results (Yang et al., 2008), and the effects can be interpreted like conventional regression coefficients (D. J. Harding, 2009). The limitations to this approach include the lack of a simple explanation of its assumptions and the lack of a full investigation of its properties

(D. J. Harding, 2009; H. L. Smith, 2004). After initial estimations of a series of Poisson log-linear models, we selected the IE to estimate the APC effects of cancer incidence based on evidence of distinct age, period, and cohort effects and model fit.

Descriptive plots were produced by age group and sex for all-site, breast, colon, and prostate cancers to assess the age, period, and cohort cancer incidence trends. Trends in lung cancer incidence rates were not assessed as part of this analysis because the incidence rates in Utah are very low (Jemal et al., 2008) and the case counts above age 85 were sparse. A similar approach to that used by Yang *et al.* (Yang et al., 2004; Yang et al., 2008) was used to identify an appropriate model to analyze the temporal trends in all-site and site-specific cancer incidence rates. A series of Poisson log-linear models were estimated for each site and sex:

$$\ln(m_{ijk}) = \ln(c_{ijk}/n_{ijk}) = \mu + \alpha_i + \beta_j + \gamma_k \quad (\text{eq. 2.1})$$

where m_{ijk} indexes the expected cancer incidence rate in cell (i, j, k) ; c_{ijk} indexes the observed number of cancer incidence cases; n_{ijk} indexes the number of person years; μ indexes the intercept of age adjusted mean rate; α_i indexes the i th row age effect for $i = 1, \dots, a$ age groups; β_j represents the j th column period effect for $j = 1, \dots, p$ periods; and γ_k represents the k th diagonal cohort effect for $k = 1, \dots, (a + p - 1)$ cohorts.

One-way models (a , p , or c), two factor models (ap , pc , ca) and IE models were compared. Both descriptive analyses and model fit, based on the Akaike Information Criterion (AIC), were used to select the final models. Full analyses are available upon request. The log-linear regression coefficients, standard errors, and model fit were computed using Stata 11. 2. Estimates of the full APC models using the IE approach and the `apc_ie.ado` downloaded from the Stata command line. To test whether our findings

were sensitive to method of denominator construction, the final models were replicated using denominators constructed using the extinct cohort method.

Results

To assess the variation in age-specific incidence by period a series of age-period plots were created. Figure 2.1 shows the sex-specific age and period all-site cancer incidence rate plots. Each panel displays the age-specific incidence trends by calendar period, ranging from 1973 - 1978 to 1998 - 2002. The solid lines present the full 85+ age-specific rates and the dashed lines display the trend when cancer rates are top-coded at age 85. These plots show that when rates are aggregated for the 85 plus age group, specious conclusions about the age at which incidence rates peak may be drawn. These plots indicate that for the vast majority of the periods, the age group with the highest incidence rates can be found in the 85 to 89 age groups. The peak is then followed by a leveling off or decline for the 90 to 94 and 95 to 99 age groups. These plots also show that the trends are not stable over time. If the only factor influencing cancer incidence trends were age, one would expect the age-specific curves for all periods to follow similar trajectories. However, the plots show variation in the intercept (depicted for age 65 - 69), slope, and shape of the curve. There has been a steady increase in the level of cancer incidence over time, with the most recent periods having the highest rates for a majority of the age groups.

Age-cohort plots were created to assess the variation in the age trends by birth cohort and sex. Figure 2.2 displays the variation in shape, slope, and peak in all-site cancer incidence age trends by cohort for both males and females. We are unable to observe a single cohort for the entire age range because we have data for a 30 year

window only, from 1973 - 2002. Age trends for the 1903 and 1908 cohorts have the longest follow-up, with incidence calculated for ages 70 to 99 and 65 to 94, respectively. There is less variation in the trend in age specific incidence rates between cohorts for females as compared to males. The plots suggest that for men the peak in incidence is moving to younger ages for more recent birth cohorts; however, these peaks coincide with the expected rise in incidence that resulted from the PSA testing for prostate cancer. There is a general increase in cancer incidence rates at younger ages for more recent cohorts for both males and females. For both sexes, the largest differences in cancer incidence occur at ages 90 – 99. The imprecision at advanced ages is partially a function of decreased sample sizes. The age-period and age-cohort plots indicate period and cohort factors may confound observed trends in age specific cancer incidence.

A series of Poisson log-linear and IE models were used to further investigate age, period, and cohort effects. The goodness-of-fit statistics for the log linear models are displayed in Table S1 in the online supplement. The IE model provided the best fit for both male and female all-site cancer, female breast cancer, and prostate cancer incidence. The fit statistics suggest weak cohort effects for women, with the IE model only providing a slightly better fit than the age-period models for both all-site and breast cancer incidence. The age-period model provided the best fit for both male and female colon cancer incidence models.

Figure 2.3 shows the IE results for all-site cancer incidence by sex. The figure shows an increase across ages in cancer incidence up to age 85. All-site cancer incidence rates are the highest for the 85 to 89 age group net period and cohort effects for both males and females. Female all-site incidence rates for ages 90 and above level off and the estimated coefficients are not statistically significant. There is a steeper decline in the

all-site incidence rate for males after age 85; however, it is noteworthy that the estimated coefficient for rates at age 90 ($p=0.06$) is still higher than the estimated rates for both the 60 to 64 and 65 to 69 age groups.

The period specific trends show that there has been a gradual increase in cancer incidence over time. While this gradual increase in cancer incidence with time may be indicative of changes in screening behaviors or environmental exposures, it may also be an artifact of changes in cancer surveillance methods, with more complete identification of cases recorded over time. The period effects for males are as expected based on the descriptive analyses and the known increase in cancer incidence between 1988 and 1992, which is attributable to shifts in prostate screening practices. The rates drop to pre-1988 levels in the next period and continue their decline into the 1998 – 2002 period.

Figure 2.3 also shows that there are moderate cohort effects for females. All-site cancer incidence was significantly higher for the 1888 and 1893 birth cohorts and lower for the 1928 birth cohort. The cohort effects for males resemble a trough, with slightly elevated risk (albeit insignificant) for early cohorts, followed by a decline and leveling off for the 1903 to 1917 birth cohorts, and ending with an increase that almost reaches the height of the 1883 birth cohort.

Figure 2.4 displays the IE estimates for breast and prostate cancer. The age effects for the site specific cancers are somewhat different than the all-sites trends. For females, the highest level of breast cancer incidence and the only estimate significantly different from zero, is found between the ages of 75 to 79 ($p=0.03$). The period effects are similar to those observed in the all-site rates as there is a gradual increase in female breast cancer incidence over time. Cohort effects play a small role in determining female breast cancer incidence over age 65. The decline in breast cancer incidence for the 1928

birth cohort is somewhat consistent with previous studies that show a decline in breast cancer incidence for the 1924 to 1938 birth cohorts (Lacey, Devesa, & Brinton, 2002). The age effect for males steadily increases up to age 75 where it reaches a plateau followed by a decline at age 90. Male prostate cancer incidence steadily increases up to 1988 and then sharply declines over time, again for reasons of PSA testing. Male cohorts between 1898 and 1918 have slightly lower rates of prostate cancer incidence. A steady rise in prostate cancer rates is seen in subsequent cohorts.

Figure 2.5 shows the estimated coefficients for the log-linear AP models of colon cancer incidence. Fit statistics showed that the two-factor model provided the best fit for colon cancer incidence, meaning that cohort effects can be constrained to zero. Fig. 2.5 indicates that there is a steady increase in colon cancer incidence with age up to age 85, followed by a slight decline (albeit still significantly higher than the referent category of 65 – 69) at the advanced ages. The period trends show a slight elevation in colon cancer incidence between 1983 and 1987 for females and between 1983 and 1992 for males as compared to the sex specific incidence rates in 1973 – 1977.

To test the sensitivity of our findings, the final models were estimated using denominators created using the extinct cohort method. The results did not substantively change the findings presented and are not shown here.

Discussion

This study found evidence supporting hypotheses of an increase in all-site cancer incidence up to ages 85-89 net period and cohort effects, followed by a modest decline up to age 99. Although incidence appears to drop after age 90, the rates up to age 99 are still higher than rates for individuals aged 65-74. This finding is supported by other studies

and highlights the importance of disaggregating cancer incidence rates for the oldest old (C. Harding et al., 2008; D. W. E. Smith, 1996). We found evidence of period and cohort effects influencing cancer trends, which highlights the importance of considering the social factors that influence biology when studying cancer trends in this population. The benefits of disaggregated estimates for the oldest old far outweigh the potential challenges related to age misreporting. As more people reach these advance ages, it will become increasingly important to understand the biological and social mechanisms affecting cancer trends in the oldest old. These results answer Boscoe's call for greater specificity in age-specific data for the oldest old (Boscoe, 2008).

We conclude that the age, period, and cohort effects of site specific cancer incidence varied by site and sex. Physiological mechanisms have been the primary mechanisms used to explain the decline in incidence by other authors. Harding *et al.* propose a simple senescence theory, claiming that increasing senescence reduces the ability of cells to divide and limits cancer incidence in the oldest old population (C. Harding et al., 2008; C. Harding, Pompei, & Wilson, 2012). Our results suggest that age is not the only factor contributing to the decline in cancer incidence in the oldest old age group. We are not arguing against a biological model of cancer decline, but we do advocate a more inclusive theory that considers socio-environmental factors and mortality selection, which may influence the age-specific trends.

For women, the gradual increase in all-site and breast cancer incidence over time may be partially due to increased detection by mammographic screening (Edwards et al., 2002) and improvements in data collection and classification. These trends in breast cancer incidence are also consistent with previously reported trends in breast cancer (C. Harding et al., 2008; Kaplan & Saltzstein, 2005; Saltzstein et al., 1998). For men, the

dramatic increase in cancer incidence up to the 1988 – 1992 period is consistent with other studies of period trends in prostate cancer incidence (Edwards et al., 2002) and the introduction of the PSA screening test. The clear period trends observed for both men and women bring attention to the importance of understanding how period factors influence cancer incidence.

In our study, cohort effects played a larger role for males than females and did not affect colon cancer incidence rates. Our results show variations in cohort trends of cancer incidence over time that coincide with changes in environmental exposure to tobacco products. Birth cohort did not explain variation in incidence trends for all sites in this study. The absence of a cohort trend in colon cancer incidence is inconsistent with other studies of colon cancer trends (Chu, Tarone, Chow, Hankey, & Ries, 1994); however, cancer mortality trends may reflect improvements in detection and treatment that prevent colon cancer mortality but do not necessarily modify the risk of colon cancer incidence (which was not reported in this study). Failing to account for heterogeneity between cohorts may lead to erroneous conclusions about deceleration in trends where none exists (Gavrilov & Gavrilova, 2011). We have shown that there is a difference in cancer susceptibility between cohorts, but controlling for these differences does not alter the conclusion that cancer incidence rates do not exponentially increase with age.

Heterogeneity within a birth cohort may also be an important mechanism driving the deceleration and decline in cancer incidence in the oldest old. Declines in the force of mortality at all ages may lead to increased population heterogeneity at old ages, thus possibly cohorts of individuals with more susceptibility to cancer (Hawkes et al., 2012). However, it is also possible that there is less within-cohort heterogeneity in more recent birth cohorts. Lynch and Brown (2001), have found evidence of less variation in

population frailty in birth cohorts in more contemporary cohorts, suggesting that the population is becoming more homogeneously robust (Lynch & Brown, 2001). If this is true, then it is possible that cancer incidence rates will decline in the future. The gradual increase in cancer incidence for males during more recent birth cohorts, reported here, suggests changing cohort susceptibility to cancer, a position inconsistent with the argument that populations shift to become more homogeneously robust. While it is difficult to separate the environmental factors from the changes in population heterogeneity, this finding emphasizes the importance of both improved surveillance in cancer trends for the oldest old and consideration of cohort effects when studying oldest old cancer trends.

Variation in health and cancer screening behaviors with age may also explain the decline in incidence and sex differences in period and cohort effects. Sex differences in cohort experiences may reflect sex differences in the timing, prevalence, and frequency of smoking; sex differences in environmental exposures to carcinogens in the work place; or sex differences in other risky behaviors that are patterned by generational experiences. For example, Preston and Wang (2006) have demonstrated the close relationship between a cohort's mortality trajectory and its history of cigarette smoking as well as sex differences in smoking prevalence within the cohort. It is unlikely that between-cohort variability or period specific shifts in health behaviors are strong determinants of the age-specific trend in cancer incidence because incidence rates decline above age 90 when controlling for cohort and period trends.

Screening bias is another individual level component that may reduce cancer incidence for the oldest old. For example, there were strong period effects associated with the introduction of PSA testing for males. The birth cohorts that would have been in

the oldest age categories at the time PSA testing was introduced have decreased cancer incidence rates relative to those cohorts that would have been under the age of 85. This finding emphasizes the importance of both improved surveillance in cancer trends for the oldest as well as further investigation into the causes of cohort differences in cancer incidence. Kaplan and Saltzstein note parallel downward sloping trends between breast cancer screening and prevalence in the aged population (Kaplan & Saltzstein, 2005). However, other studies not subject to screening bias show a similar trend (Stanta, 1997). This study also suggests that screening bias may not be the reason for decreases in cancer incidence with age. SEER data collection processes include checking death certificate information. Any cancer occurrence contributing to the cause of death of an individual is reported to the SEER registries. Only cancers that are not an underlying factor in the death would be missed by the system, suggesting that detection bias is not a likely cause in the observed decrease in cancer at advanced ages.

Our results differ slightly from previously reported trends in cancer incidence. The estimated peak in incidence in the 85 – 89 age category for males and females is higher than the Harding et al. (2008) estimates of 80. However, our results are consistent with the peak observed by Saltzstein et al. (1998). There are three possible explanations for the variation in the estimated peaks in age-specific incidence rates. First, previous studies of age-specific cancer incidence in the oldest old age group have not considered the role of period and cohort effects. Ignoring exogenous factors that may contribute to cancer incidence oversimplifies the problem and leads to the age-specific incidence rates that are confounded by period and cohort differences in cancer incidence. APC analyses of cancer incidence may provide less biased estimates of the true relationship between cancer and aging.

Second, the differences may be caused by error in the estimated denominators. Preston et al. (1999) found that the difference between the correct population distribution and one estimated with age overstatement increased with time (Preston et al., 1999). Any difference between the estimated peak cancer incidence and the true peak cancer incidence should be negative. If age-misstatement led U.S. to overestimate the size of the oldest old population, then our estimate of a peak in incidence between the ages of 85 and 89 is conservative. Furthermore, because other studies have also used decennial census data to construct their denominators (C. Harding et al., 2008; C. Harding et al., 2012), we argue that this is not the reason for the observed differences in peak age-specific incidence rates.

Third, while not directly assessed, our findings are suggestive of geographic variation in cancer incidence trends given the difference in the estimated peak of cancer incidence between our study and other U.S. studies of overlapping time periods (Harding et al., 2008; Harding et al., 2012; Saltzstein et al., 1998). Regional differences in cancer incidence trends may be attributable to differences in sociodemographic characteristics, health beliefs, access to resources, reproductive characteristics, and exposure to environmental carcinogens. Utah consistently has one of the lowest cancer incidence and mortality rates in the U.S. for both males and females and the lowest rates of lung cancer incidence and mortality (Jemal et al., 2008). However, Utah does not have low incidence rates for all cancer sites. Age-adjusted prostate cancer incidence rates are higher in Utah than the national averages (Stroup et al., 2008). More research should be done to quantify geographic differences as it will provide valuable information about the social forces shaping cancer incidence rates in these age groups.

There are several structural limitations to studying cancer trends in the oldest old age groups. Use of clinical and death certificate diagnoses may lead to an underreporting of trends in the oldest old (Kaplan & Saltzstein, 2005; Stanta, 1997). Trends calculated using cancer registry and census data are subject to error because the reliability of age estimates for individuals over the age of 85 may be questionable (Edwards et al., 2002; Vincent et al., 2010). However, we used several different methods to create measures of population size and found no substantive differences in the age, period, and cohort trends in all-site cancer incidence.

There is not widespread consensus in the cause of the decline in cancer rates at advanced ages because it has been largely understudied. This study contributes to the current literature by providing estimates of cancer incidence for the 85+ population within the broader context of period and cohort effects. This study supports the individual risk hypothesis and mortality selection arguments that predict a deceleration in incidence at advanced ages. Our findings do not support the position that deceleration is an artifact of variability in morbidity profiles between cohorts, nor do they support arguments that cancer incidence trends are strictly a function of biological mechanisms. Studies utilizing an APC approach to the analysis of cancer trends may provide less biased estimates of the relationship between cancer and aging and improve knowledge about the role of biological and social influences that modify trends. The existence of cohort and period effects also justifies the use of direct measures of the exogenous factors contributing to cancer incidence. Future studies should evaluate the proportion of variation in cancer incidence explained by direct measures of period influences and cohort characteristics. Future studies should also investigate morbidity trends in other major causes of death and explore the relationship between these trends and mortality

deceleration. We also show that there is variation in cancer incidence trends in the oldest old population and reiterate the importance of treating this population as heterogeneous. In order to gain a more comprehensive understanding of morbidity and mortality patterns for this rapidly growing segment of the population, cancer incidence and U.S. Census population estimates need to be disaggregated for the oldest old population.

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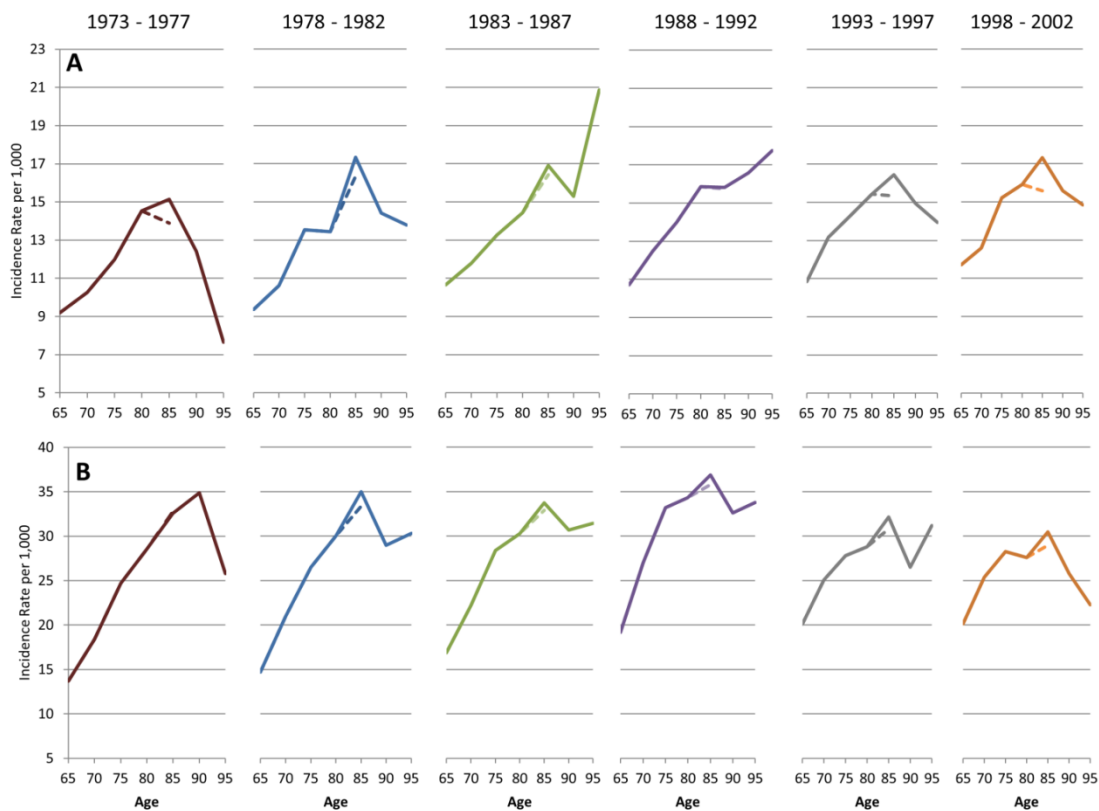


Figure 2.1. All-site cancer incidence rates by age and period. Panels A and B show Utah females and males, respectively. Solid lines show trends up to age 99 and dashed lines show the trend when cancer incidence is aggregated for individuals 85 years and above.

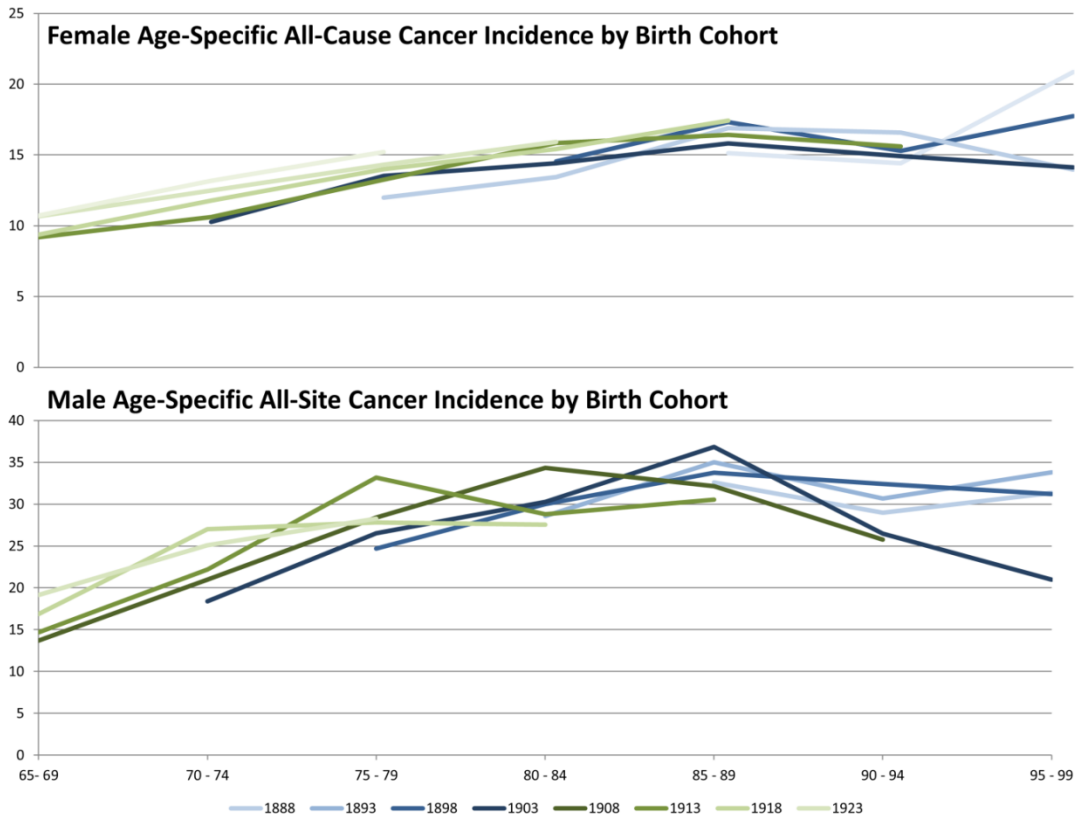


Figure 2.2. All-site cancer incidence by birth cohort. Panels A and B show Utah females and males, respectively. The scale of the y-axis is smaller than the scale for the male graphs to allow for the visibility of the variation. Female incidence rates are lower than male incidence rates and increase with age at a slower rate.

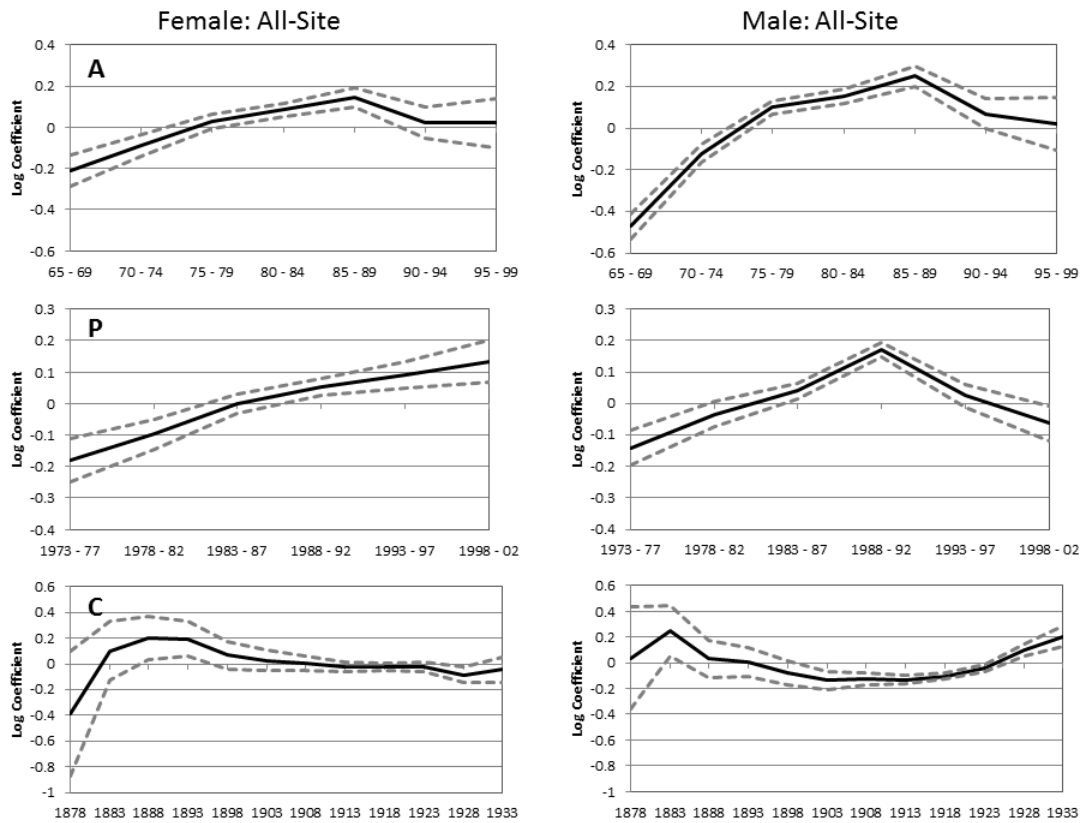


Figure 2.3. APC IE estimated trends of all-site cancer incidence rates for ages 65 to 99 in the state of Utah. Dotted lines represent 95% confidence intervals. Panel A: Age effects net period and cohort. Panel B: Period effects net age and cohort. Panel C: Cohort effects net age and period.

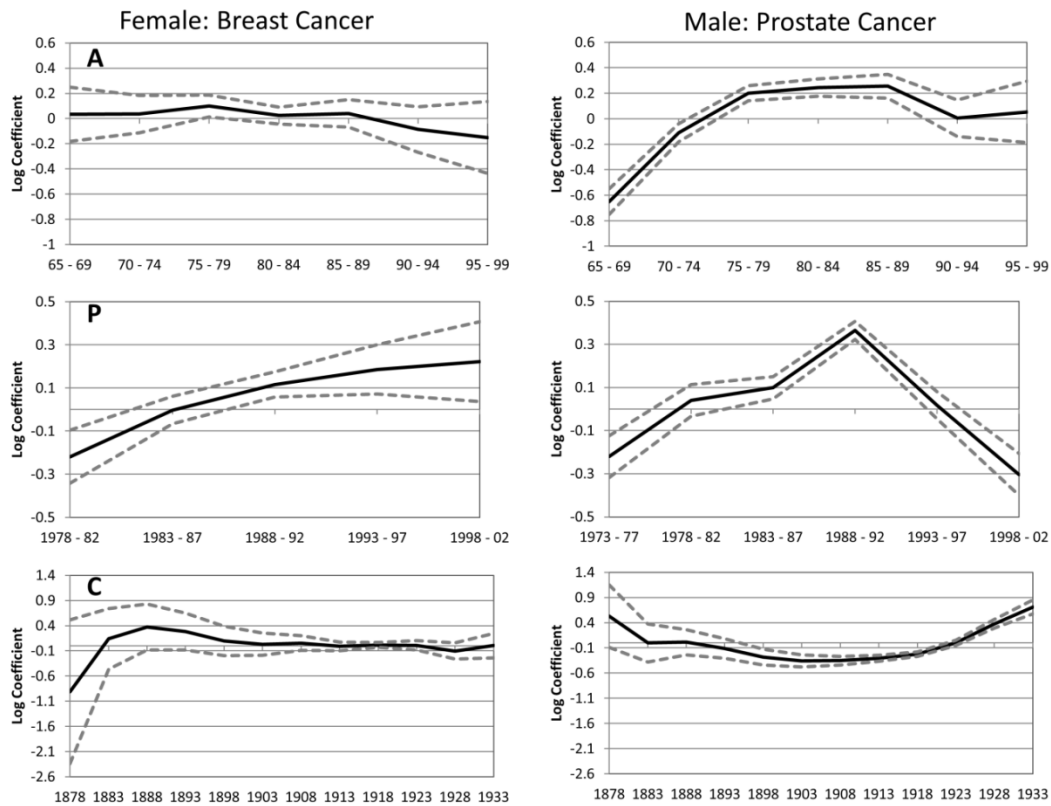


Figure 2.4. APC IE estimates of female breast and male prostate cancer incidence rates for ages 65 to 99 in the state of Utah. Dotted lines represent 95% confidence intervals. Panel A: Age effects net period and cohort. Panel B: Period effects net age and cohort. Panel C: Cohort effects net age and period.

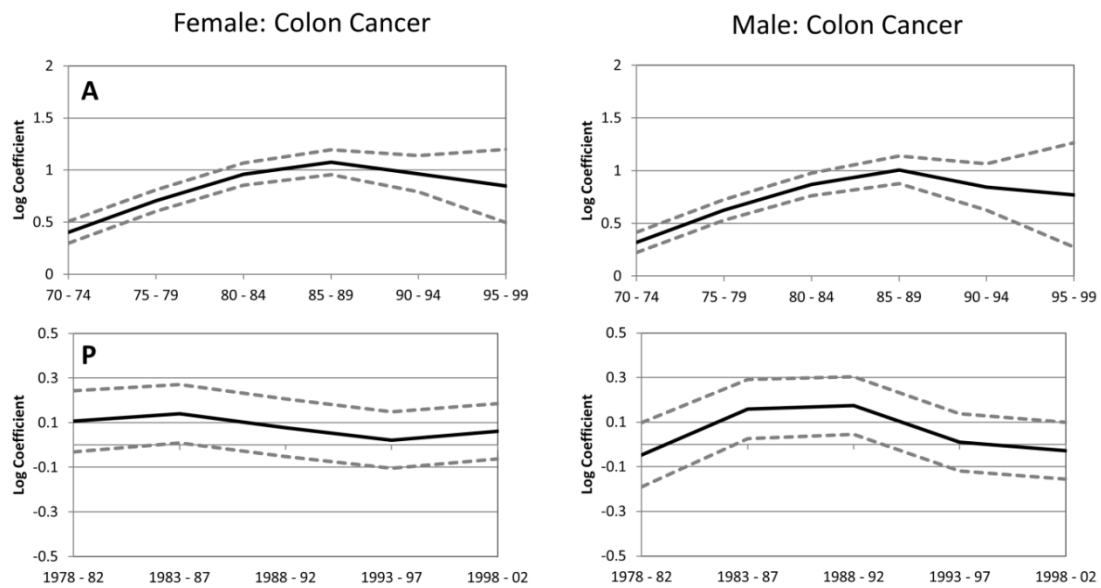


Figure 2.5. Poisson log-linear estimates of age and period effects on colon cancer incidence. Dotted lines represent 95% confidence intervals. Panel A: Age effects net period. Panel B: Period effects net age.

CHAPTER 3

REPRODUCTIVE HISTORY AND LATER-LIFE COMORBIDITY

TRAJECTORIES²

Abstract

The reproductive lives of men and women may provide significant insight into later-life health and mortality. Sociological, biological, and evolutionary theories predict a relationship between reproductive history and later-life health and mortality, however, current research is lacking consensus on the direction of the relationship. In this study, the relationship between reproductive history and later-life health is examined using data based on linkages between the Utah Population Database, a rich source of longitudinal data, and 18 years of Medicare Claims data. Later-life health is measured using the Charlson Comorbidity Index, a construct that summarizes nearly all serious illnesses afflicting older individuals. Single year comorbidity scores are constructed by year from 1992 to 2009. We used group based trajectory modeling that accounts for nonrandom attrition due to death to identify the number and types of morbidity trajectories by sex and age group for 52,924 individuals aged 65-84 in 1992. For both males and females,

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trajectory groups ranged from a robust group with little to no comorbid conditions during the period of observation to a frail group with a consistently high comorbidity. Parity, age at first birth, age at last birth, birth weight of offspring, having a child die as an infant, and having a preterm birth predicted trajectory group membership for women but had little association with trajectory group membership for men.

Introduction

Understanding how individuals experience disease after age 65 is important to understanding the mechanisms of aging and longevity. Equally important is what predicts the observed patterns. The etiological model of chronic disease has shifted its focus from adult risk factors to considering factors throughout the life course (Kuh & Ben-Shlomo, 2004). Central to the life course approach is the idea that there are certain periods of plasticity, where individuals may experience physiological or social change that alter their future health trajectories. The reproductive period is a sensitive period for both men and women, in which the timing of births, number of births, and birth outcomes might have adverse or protective effects on later-life health. It also presents a critical period for women as physiological changes related to pregnancy may have lifelong effects on the structure or function systems in the body (Kuh & Ben-Shlomo, 2004; Kuh & Hardy, 2002). Therefore, the reproductive lives of men and women may provide significant insight into later-life health and mortality, but current research is lacking consensus on the direction of the relationship.

This study will examine the role of parity, age at first birth, age at last birth, interbirth intervals, infant death, multiple births (twins), birth weight of offspring, and preterm births for both men and women on disease progression after age 65. This study

utilizes Centers for Medicare Services (CMS) data spanning from 1992 – 2009 linked to the Utah Population Database, which is a rich source of longitudinal data. The goals of this analysis are threefold: 1- identify distinct trajectories of comorbidity from 1992 - 2009 for individuals aged 66 – 84 in 1992 by sex and birth cohort; 2- estimate the association between measures of fertility and later-life comorbidity trajectories while controlling for early-life circumstances using information from a longitudinal, familial health database; 3- determine if the observed effects are part of a trajectory set in motion earlier during infancy and childhood (i.e., does fertility mediate known relationships between early-life circumstances and later-life comorbidity trajectories (K. R. Smith, Hanson, & Zimmer, 2012)).

Background

There is a substantial amount of variation in the morbidity profile of older adults, suggesting that morbidity is not an inevitable consequence of aging (Rowe & Kahn, 1987; Rowe & Kahn, 1997). Understanding the sources of variation in patterns of aging is important for creating accurate population predictions, identifying at risk populations that may benefit from public health interventions, and characterizing the process of aging in a diverse population. Sources of heterogeneity in patterns of aging cannot be understood by restricting analyses to a single life stage, nor can its intricacies be understood without simultaneously considering biological and social mechanisms. The pathology of chronic disease is multifaceted, determined by genetic profiles, biological and physiological development, and the social environment, with the strength and relative importance of each of these factors varying throughout the life course.

The majority of studies assessing the relationship between reproductive history and health have focused on mortality with mixed results. Numerous studies have also demonstrated the relationship between reproductive history and later-life health as measured by activities of daily living (ADL), depressive symptoms, type 2 diabetes, cardiovascular disease, self-rated health, self-reported limiting chronic illness, cancer, and mental health (D. Smith, Sterne, Tynelius, & Rasmussen, 2004; Grundy & Tomassini, 2005; Henretta, 2008; Kravdal, 1995; Lawlor et al., 2003; Myklestad et al., 2012; Spence, 2008; Yi & Vaupel, 2004). Yet none has looked at the relationship between reproductive history and comorbidity. These studies also often fail to account for early-life conditions that may influence reproductive history and later-life health.

Comorbidity is one of the major components of health aging, and its presence increases with age (L. P. Fried, Ferrucci, Darer, Williamson, & Anderson, 2004; Guralnik, 1996). However, there is variation in the rate at which a transition into a comorbid state occurs and the trajectory of disease once it has occurred. We assume that heterogeneity within a population follows a specific distribution, with robust individuals on one tail and frail individuals on the other. Therefore, unlike the geriatric definition of frailty which refers to a variable state of physiological decline, we intend to invoke the demographic meaning of the term. For example, individuals exhibiting a robust phenotype may delay or evade chronic disease completely, while individuals exhibiting the frail phenotype experience multiple morbid conditions (Andersen, Sebastiani, Dworkis, Feldman, & Perls, 2012; Evert, Lawler, Bogan, & Perls, 2003; Ken R. Smith et al., 2012). Identifying sources of this phenotypic variation is necessary for targeting periods of the life course that affect later-life health and to more fully understand the process of aging. Preston, Hill, and Drevenstedt (1998) have proposed a widely used

model explaining the direct and indirect effects of childhood circumstances on later-life health. A similar model can be used to classify the theories that predict a relationship between fertility history and later-life health. Evolutionary, biological, and social theories predict that parity, age at first birth, age at last birth, interbirth intervals, twinning, birth weight of offspring, and giving birth prematurely may all be associated with later-life morbidity and mortality.

Evolutionary and Genetic Theories Linking

Reproductive Health to Aging

Evolutionary theories predict a close relationship between fertility and mortality. Optimization hypotheses suppose that the forces of evolution select for traits that maximize the reproductive success of an organism. Two such hypotheses, disposable soma and antagonistic pleiotropy, predict a positive association between parity and comorbidity at advanced ages (Kirkwood & Rose, 1991). The disposable soma theory argues that the two physiological costly functions of reproduction and somatic maintenance are in direct competition for a limited amount of resources. This “trade-off” yields optimal reproductive success at the cost of longevity for females (Kirkwood & Rose, 1991). Similarly, antagonistic pleiotropy suggests that genetic mutations that increase postreproductive mortality may escape the force of natural selection because they increase fitness early on (Kirkwood & Rose, 1991; G. C. Williams, 1957). A recent study of fertility in carriers of the breast cancer genes BRCA1 and BRCA2 suggests that, although these mutations significantly increase the risk of mortality, they may increase reproductive fitness and therefore have not been selected out of the population (K. R.

Smith, Hanson, Mineau, & Buys, 2012). These theories predict that for females, young age at first birth and high parity are associated with increased comorbidity later in life.

High parity, late age at last birth, multiple births, and short birth intervals may also be associated with decreased comorbidity later in life. For example, it has been suggested that genetic variants influence both late female fertility and slowed rates of somatic aging (K. R. Smith et al., 2009). Fertility success may also be an indication of health status and robustness. Women with higher fertility, shorter birth intervals, twins, and later ages at last birth may have increased longevity because their fertility success is a marker of a robust phenotype (Hawkes, 2010; Robson & Smith, 2011, 2012). While evolutionary theories are an important factor in the relationship between fertility and later-life morbidity and mortality, it is necessary to consider the direct biological and indirect social effects of fertility history.

Direct Biological Effects of Reproductive Health and Biological Indicators of Later-Life Health

In the life course literature, physiological scarring has been used to define an event that permanently alters the physiological functioning of an organism. For women, pregnancy may trigger physiological changes that may favorably or adversely affect later-life health. Increased parity and early age at first birth have been shown to lower the risk of postmenopausal reproductive cancer and it has been posited that biological factors are responsible for this link. Pregnancy is one of several factors that determine life time exposure to endogenous hormones. Several hypotheses relate the level of endogenous hormones throughout the life course, such as androgen, insulin, progesterone, and estrogen, to cancer risk later in life (Kelsey, Gammon, & John, 1993;

Kobayashi et al., 2012; Lukanova & Kaaks, 2005). There is an inverse association between parity and cancer incidence in tissues sensitive to hormone levels, such as breast, endometrial and ovarian (Kelsey et al., 1993; Kobayashi et al., 2012; Kvale, Heuch, & Nilssen, 1994; Permuth-Wey & Sellers, 2009). Age at first birth has also a known risk factor for breast cancer, with younger age at first birth being a protective factor (MacMahon, Cole, & Brown, 1973).

Reproductive history may also lead to physiological changes that adversely affect a woman's health. Pregnancy related biological responses may lead to increased risk for coronary heart disease and obesity later in life (Bastian, West, Corcoran, & Munger, 2005; Lawlor et al., 2003). A study of men and women aged 60 to 79 in Britain found a positive association between number of children and adverse lipid profiles and diabetes for women but not men, suggesting possible biological mechanisms (Lawlor et al., 2003). However, life style factors were also found to play a role in the association. Birth spacing and having multiple births (twins) may also leave a physiological imprint on the mother. The maternal depletion hypothesis argues that the physiological demands of pregnancy diminish physical resources and short birth intervals do not give the mother ample time to recover from the stresses of the previous pregnancy (Jelliffe & Jelliffe, 1978; Kirkwood & Rose, 1991). These theories predict a positive relationship between parity, short birth intervals, and multiple births and later-life comorbidity.

Characteristics of a mother's offspring at time of birth can be used to gauge the woman's health during her reproductive period and may predict her health status as she ages. Birth weight of her child and giving birth prematurely are examples of markers of the health and vitality of the mother (G. D. Smith, Whitley, Gissler, & Hemminki, 2000). Giving birth to an infant that is considered large for its gestation age (LGA) may be an

indication of pregnancy complications that affect the mother's health, such as gestational diabetes (Casey, Lucas, McIntire, & Leveno, 1997), which is a known risk factor for diabetes and cardiovascular disease later in life (Bellamy, Casas, Hingorani, & Williams, 2009; Carr et al., 2006). Studies have shown that there is a positive association between birth weight of offspring and the mother's longevity (G. D. Smith et al., 1997; G. D. Smith et al., 2000). However, the studies do not test whether there is a threshold to this effect. There are several reasons for these associations. First, it may be an indicator of the social and physical environment of the mother, with conditions affecting the development and health of both mother and fetus. Second, it may be indicative of genetic variants carried by the mother or father that predispose them for cardiovascular disease later in life (Myklestad et al., 2012). These studies suggest that high birth weight, low birth weight, and preterm babies are positively associated with adverse health outcomes later in life.

Social Mechanisms Indirectly Linking Reproductive

History to Later-Life Health

Social theories predict both positive and negative relationships between parity and later-life morbidity. The social benefits of adult children may negate any adverse physiological effects of having children by providing social support, social engagement, and receipt of instrumental help. Strong social support may foster feelings of meaning, reduce feelings of stress, and minimize risky behavior. Individuals with more social support and intimate ties have better health and lower levels of mortality (Berkman & Syme, 1979; House, Landis, & Umberson, 1988). Children may provide a support network later in life, and having more children may increase the chance of having regular

contact with at least one child (Uhlenberg & Cooney, 1990) and receipt of help from children (Grundy & Read, 2012). Later ages at first birth may allow for accumulation of wealth and resources and prevent adverse health outcomes later in life.

Psychological, social, and economic impacts of children may also lead to a negative relationship between parity and later-life morbidity. Increasing parity is associated with obesity and coronary heart disease for both men and women, suggesting that lifestyle factors associated with high parity may lead to increased risk of morbidity later in life (Lawlor et al., 2003). Increased parity may not translate to increased social support. Smith (2002) suggests that high parity children may have fewer resources to devote to their parents and, due to the intergenerational transmission of fertility, high parity may lead to decreased social support from children later in life. These results suggest that the effect of fertility may be positive or negative for males and females.

Early parenthood may lead to decreased opportunities for education and employment (Ross & Huber, 1985; Waldron, Weiss, & Hughes, 1998), which has been shown to lead to adverse health consequences later in life (Mirowsky, 2005; Phelan, Link, & Tehranifar, 2010). Mirowsky (2005) suggests that the optimal period for childbirth in relation to health is the mid-thirties, but this finding may be unique to the historical and social environment. The current literature presents conflicting findings related to the benefits of age at last birth after age 39, with some studies suggesting that later ages at last birth are protective (K. Smith, G. Mineau, G. Garibotti, & R. Kerber, 2009; K. R. Smith et al., 2002) while others find adverse effects (Mirowsky, 2005).

Considering Events Throughout the Life Course that

Affect Fertility and Morbidity

Failure to look at the relationship between fertility and morbidity using a life course perspective and controlling for early-life circumstances can lead to an overstatement of their association. Early-life factors may affect the reproductive health and behaviors of men and women (Doblhammer & Oeppen, 2003; Rich-Edwards, 2002). Therefore, part of the observed association between fertility and later-life morbidity may be merely a reflection of genetic makeup or physiological changes during childhood. For example, adverse childhood and adolescent circumstances are also related to early motherhood (Geronimus & Korenman, 1992) and later-life health (Galobardes, Lynch, & Smith, 2008; Preston et al., 1998; K. R. Smith, G. P. Mineau, G. Garibotti, & R. Kerber, 2009). These are important confounders that must be controlled for when studying the effects of fertility on later-life morbidity. For this reason, we will include measures of early-life circumstances that may affect fertility and later-life health outcomes.

Hypotheses

The research question addressed in this paper is whether measures of fertility and reproductive health are associated with morbidity profiles later in life. We will examine the role of parity, young age at first birth, age at last birth, interbirth intervals, infant death, multiple births (twins), birth weight of offspring, and preterm births for both men and women. We are able to control for a range of early-life circumstances, including a familial predisposition to longevity, childhood socioeconomic status, and death of a parent during childhood. The specific hypothesis generated by suggested evolutionary, social, and biological mechanisms summarized in Table 3.1 are as follows:

- H1: *The optimization of life history traits leads to a “trade-off” between fertility and somatic maintenance.* According to this hypothesis, young age at first birth, increased parity and shorter birth intervals should be positively associated with comorbidity after age 65 for females, and age at last birth should be negatively associated with comorbidity after age 65.
- H2: *Childbirth leads to physiological changes that affect later-life health.* According to this hypothesis, increased parity, shorter birth intervals, later age at last birth, and unhealthy (high/low) birth weight of offspring should be adversely associated with later-life comorbidity after age 65 for females but not males. Early age at first birth and parity may also have protective effects for females but not males.
- H3: *Reproductive history is a marker of a robust phenotype.* According to this hypothesis, increased parity, shorter birth intervals, later age at last birth, and twinning should be negatively associated with comorbidity after age 65 for both sexes and is possibly stronger for females.
- H4: *Social mechanisms are responsible for the observed association between reproductive history and comorbidity after 65.* According to this theory, the observed effects of fertility history should be similar for males and females, but there are competing hypotheses about the direction of the effect.
 - H4a: Increased parity is negatively associated with comorbidity after age 65 because children provide material, instrumental, and social support for both men and women.

- H4b: Increased parity is positively associated with comorbidity after age 65 because the psychological, social, and economic effects of having children outweigh the social benefit. Children may also be unable to provide support because they are caring for their own large families.
- H4c: Early age at first birth is positively associated with comorbidity after age 65 because it leads to constrained economic and educational opportunities. Late age at first birth is negatively associated with comorbidity after age 65 because it leads to increased educational and economic opportunities.

Methods

Data

The majority of life-span epidemiological studies examine health influences of early and adult life conditions with relatively modest sample sizes. This study utilizes data drawn from the Utah Population Database (UPDB). The UPDB is one of the world's richest sources of linked population-based information for demographic, genetic, and epidemiological studies. UPDB has supported biodemographic studies as well numerous important epidemiological and genetic studies in large part because of its size, pedigree complexity, and linkages to numerous data sources. The full UPDB now contains data on nearly 7 million individuals due to longstanding and on-going efforts to add new sources of data and update records as they become available (e.g., including all statewide death certificate records (1904-present) and all Medicare claims (1992-2009)). We have identified thousands of members of birth cohorts from the first half of the 20th century,

individuals for whom early and midlife conditions are measured and who are linked to their adult medical records generated decades later. These complex data links provide unparalleled data quality and depth that focus on families (nuclear, multigenerational, full pedigrees) and health outcomes that span entire life spans of individuals and their relatives.

Given the large sample sizes and the quickly changing morbidity risks by age and sex, we will conduct all analysis by sex and 10 year age categories (66-74 and 75-84). The first age category begins at age 66 to eliminate the problems of prorating the partial year coverage of individuals who become age eligible part way into a year when they turn age 65. Ages are considered in 1992, the first year in which we have Medicare data. Separating samples by age effectively holds the cohort constant and allows us to analyze the trends by birth cohort for an 18 year period. Individuals aged 66 – 74 and 75 – 84 in 1992 are considered members of the young-old cohort (born between 1918 and 1926) and old-old cohort (born between 1908 and 1917), respectively.

We selected once married parous individuals. Once married individuals were selected to limit complications related to fertility spanning more than one marriage partner. We excluded individuals with a spouse deceased before the individual reached age 50 because they would not have completed childbearing (Gagnon et al., 2009). The CMS data requires an individual to survive to the age of 66, therefore, by definition, the remaining individuals would have completed their childbearing. Selecting parous individuals helps identify the multivariate effects of both the intensity and timing of fertility on comorbidity trajectories. It is also a necessary restriction because the UPDB is derived from descendent genealogies in which identification of nulliparous women is not reliable (Moorad, Promislow, Smith, & Wade, 2011). Accordingly, this analysis is

not intended to account for the impact of childlessness (Gagnon et al., 2009; K. R. Smith et al., 2002). Individuals were also required to have sufficient information about parents in the database, which allowed for the inclusion of early-life circumstances in the model.

Centers for Medicare Services (CMS) provides files that allow us to assess whether individuals are sufficiently represented in the Medicare claims data so that they can contribute to the construction of the morbidity trajectories. Our goal is to avoid characterizing someone as being disease-free when in fact their health events are simply not well represented in the Medicare data. CMS provides a monthly HMO indicator variable that describes when a beneficiary was enrolled in a managed care plan. As expected, few claims exist in the file for individuals during the time they are enrolled in a managed care plan. For the purposes of this analysis, we exclude persons who have at least 1 month of enrollment in a managed care plan. We also required all individuals to have at least 1 full year of data and, therefore, all individuals deceased in 1992 were excluded from the sample.

Subjects who met our data requirements (e.g., once married parous individuals for whom we have family data (parental death dates and full fertility history)) and had sufficient Medicare claims data are shown in Table 3.2. Individuals were then followed for a maximum of 18 years (to 2009), our last year of Medicare data, or until death. The total sample size is $N=41,158$; age specific sample sizes are shown in Table 3.2.

A secondary analysis of individuals aged 66 to 74 in 1992 was done using the information from birth certificates. Birth certificate information in the UPDB is available from 1915 to 1921 and 1943 to the present; however, birth weight was not recorded until 1947. Because we are interested in birth weight and prematurity, all individuals used in this analysis were required to have their first birth in 1947 or later and all births in Utah

(giving us complete fertility information). Approximately 40% (n=4,142) of women and 55% (n=6,192) of men in the young-old cohort have birth certificate records for all births. Individuals aged 66 and 74 in 1992 would have had to have their first birth at age 21 if they were the youngest members of the cohort and at age 29 if they were the oldest. For females, the average age at first birth in the birth certificate sample is 2.5 years greater than those excluded (25.8 vs. 23.3, $p<0.01$) and for males it is 1.4 years greater than those excluded (26.9 vs. 25.5, $p<0.01$). These requirements make this a select cohort, but the benefits of linking birth outcomes to later-life health trajectories makes this a valuable analysis.

Key Measures

Comorbidity

We are able to observe morbidity episodes from Medicare claims collected over time for each individual. Health experience over time is measured by the Charlson Comorbidity Index (CCI) (Charlson, Pompei, Ales, & MacKenzie, 1987). The CCI was adapted for use with ICD-9 codes by Deyo et al. (Deyo, Cherkin, & Ciol, 1992) and Romano et al. (Romano, Roos, & Jollis, 1993). Deyo et al. adapted the index for use with ICD-9 diagnosis and procedure codes. Romano et al. included some diagnoses that were not in the original Charlson index. Both modifications were intended for use with the Medicare Part A records (Klabunde, Potosky, Legler, & Warren, 2000). Klabunde and colleagues (Klabunde, Warren, & Legler, 2002) created two indices, one for Medicare Part A records and one for Medicare Part B records. Introducing information from physician claims data significantly enhanced the index's predictive value for the risk of mortality. In the present study, we have adopted this variant of the CCI based on the

SEER-Medicare Comorbidity macros

(<http://healthservices.cancer.gov/seermedicare/program/comorbidity.html>). We classified individuals into similar trajectory groups with respect to their morbidity patterns identified by their shared health experiences over time.

The SEER-Medicare macro calculates the CCI with respect to cancer based on the Deyo adaptation of the index. Given that cancer originally was the index disease, it was not included as a comorbid condition in this SEER-Medicare program. Accordingly, we have added cancer as a comorbid disease. We identified specific episodes of the following 17 major morbidities conditions occurring during the interval 1992-2009 on a per annum basis that form the basis of the CCI. Items are coded as “1” if they occur at any time during the year or “0” if they do not, and then weighted based upon their ability to predict mortality:

1. Myocardial Infarction
2. Congestive Heart Failure
3. Peripheral Vascular Disease
4. Cerebrovascular disease
5. Dementia
6. Chronic pulmonary disease
7. Rheumatologic disease
8. Peptic Ulcer Disease
9. Mild Liver Disease
10. Diabetes (mild to moderate)
11. Diabetes with chronic complications
12. Hemiplegia or paraplegia

13. Renal (kidney) disease
14. Any malignancy
15. Moderate or severe liver disease
16. Metastatic Solid Tumor
17. AIDS

The independent variables used in the analysis can be partitioned into three domains: demographic, early-life conditions (ELCs), and fertility.

Demographic Characteristics

All models controlled for age in 1992 centered on the mean for each sex and age group. Widowhood is a frequent occurrence among individuals in this age range and may be linked to changes in health status (K. Williams & Umberson, 2004). Time-varying covariates are used to allow for altered shape of the trajectories due to loss of a spouse. An indicator variable for each year was created for each year of observation and defined equal to “0” during all periods where the spouse is still alive and “1” during all periods where the spouse was deceased.

Measures of Early-life Conditions

Measures of age at parental death, childhood socioeconomic status, familial excess longevity (FEL), and religious participation are generated from the data within the UPDB. Death of a parent during childhood may have adverse effects on health later in life (Andersson, Hogberg, & Åkerman, 1996; Norton et al., 2011; Umberson & Chen, 1994), and disruption of the family may affect the transition into adulthood, including timing of childbirth. Birth, marriage and death dates are recorded comprehensively in the

UPDB and were used to construct eight categories of parental death. The gender of the deceased parent may have different social and economic implications. Therefore, two categories were created (one mother and one father) for each of the following circumstances related to parental death: mother/father died when child was under age 18, parent deceased after child was age 18 (reference category), and both parents deceased when child was under 18 (orphan).

Childhood socioeconomic status may directly and indirectly influence marriage and reproductive success, timing of childbirth, and later-life comorbidity (Doblhammer & Oeppen, 2003; Geronimus & Korenman, 1992; D. Kuh & Ben-Shlomo, 2004).

Childhood socioeconomic status is measured using usual occupation and industry information reported on a father's death certificate for fathers who died in Utah and for whom we have a death certificate (deaths occurring from 1904 forward). Occupational strings were converted to Nam-Powers socioeconomic (NP SES) scores, a measure of income and education based on occupational categories and range from 1 to 99, with higher scores being associated with higher socioeconomic status (Nam & Powers, 1983). NP SES scores were unavailable for approximately 20% of the sample. Values for these individuals were imputed by substituting the mean plus a random number multiplied by the distribution of nonmissing values and an additional variable indicating missing values. A large percentage of fathers from this era, a little over 30%, have the occupation "farmer," resulting in a large heaping at the NP SES score of 40. Farming may also confer a survival advantage related to life style factors (Gavrilov & Gavrilova, 2012), and a separate category was created for the occupation of farmer.

To control for unobservable genetic and shared environmental effects, we used a measure of family history of longevity, Familial Excess Longevity (FEL). FEL is a

statistic developed using deep genealogical data of multigenerational pedigrees drawn from the UPDB. We have published the development of this statistic (Kerber, O'Brien, Smith, & Cawthon, 2001) and have applied it to other life-span studies using UPDB (Garibotti, Smith, Kerber, & Boucher, 2006; Kerber, O'Brien, Boucher, Smith, & Cawthon, 2012; K. Smith et al., 2009). At its foundation, the FEL is based on the assumption that family history of longevity follows Mendelian patterns of inheritance. To construct familial excess longevity, we first measure individual level excess longevity, defined as the difference between an individual's attained age and the age to which that individual was expected to live according to a model that incorporates basic life-span predictors (sex, birth year). Expected longevity is estimated from an accelerated failure time (AFT) model, and excess longevity is simply the difference between expected and attained age. Expected longevity is based on the lognormal distribution and the AFT model was used because it provides a simple point estimate for duration that fits the observed data. Excess longevity is then extended to blood relatives who reached the age of 65 for each individual, a restriction that focuses on years less affected by external causes of death. The kinship coefficient, the probability that an individual shares a particular allele with another individual, is used as a weight in calculating familial excess longevity. Averaging the excess longevity of all blood kin over 65 for each ego, with the appropriate weighting scheme, generates a point estimate of familial excess longevity. We have found that individuals with high FEL live longer and experience more healthful disease trajectories as they age (K. R. Smith et al., 2012; K. R. Smith et al., 2009).

Active affiliation with The Church of Jesus Christ of Latter-day Saints (LDS or Mormon) church is associated with increased life expectancy (Enstrom & Breslow, 2008) and high fertility rates (Arland, 1979). Individuals actively affiliated with the LDS

church are more likely to abstain from alcohol and tobacco use, fast once a month, and participate in church related social activities (Mineau, Smith, & Bean, 2002). The UPDB contains information on baptism and endowment dates from family history records. These were used to classify individuals as active followers, inactive, or nonmembers. Individuals with an endowment date have agreed to live their lives following the doctrine of the Church and are considered active Church followers if endowed before age 40. Individuals with a baptism but no endowment date are considered inactive, and individuals with no baptism or endowment date are considered nonmembers (reference category).

Measures of Fertility

Fertility information in UPDB comes from a combination of information collected from Family Group Sheets obtained from the Utah Family History Library and linked vital records, including birth certificate data from 1915 – 1921 and 1943 to the present. All women in the sample have completed fertility by definition because they are required to survive to at least age 65 to be visible in the Medicare Claims data.

Parity was measured with a set of dummy variables to indicate whether a woman had 1-2, 3-5, 6-8, or 9+ children. On average, women in this sample had 4 children, and the category for 3-5 children was used as the reference category. To measure the effects of early and late childbirth, we created dummy variables for the following categories: age at first birth before the age of 18, between ages 18 and 24, and after age 25, with 18-24 used as the reference category. There were very few men under the age of 18, and therefore this category was combined with the 18-24 category for men. For age at last birth we constructed three categories: under age 35 (reference group), 35 – 39, and 40 or

older. A dummy variable is used to identify parents of multiples (twins). Short birth intervals are defined as interbirth intervals less than 18 months, and long birth intervals are defined as interbirth intervals > 60 months (Conde-Agudelo, Rosas-Bermudez, & Kafury-Goeta, 2007). Separate variables were created to identify individuals with one or more short or long interbirth interval.

Infant mortality may be a marker for maternal health and adverse environments (McCormick, Shapiro, & Starfield, 1984). Environments that lead to adverse health outcomes for the infant may also be risky for the parents. Individuals losing one or more children during the first year of life will also be identified with a dummy variable.

Birth certificate information in the UPDB is available from 1915 to 1921 and 1943 to the present. Birth certificates contain information on a mother's marital status, prematurity, and birth weight (starting in 1947). Using the information from the birth certificates, individuals are categorized as ever having a high birth weight baby ($> 4,000$ grams) or low birth weight baby ($< 2,500$ and carried 37+ weeks), which reflects the WIC Nutrition Risk Criteria (Medicine, 1996). Preterm birth was defined as the birth of an infant before 37 weeks of gestation. Table 3.3 presents the descriptive statistics of all the measures by sex and age group.

Constructing Morbidity Trajectories

We seek to determine how reproductive history and health affect the likelihood of having a particular later-life comorbidity trajectory. Assessment of comorbidity trajectories is accomplished through the application of a finite mixture modeling approach that is currently available as a SAS procedure called PROC TRAJ through the work of Dr. Daniel Nagin and his colleagues (Haviland, Nagin, Rosenbaum, & Tremblay,

2008; Jones & Nagin, 2007; Nagin & Tremblay, 2001). The group-based modeling approach allows for identification of distinct clusters of individual trajectories.

Given the quickly changing health landscape of an aging population, all models are estimated within age-sex categories. The excess mortality risks of men and the generally higher rates of morbidity of women necessitate that we use sex-specific models. As age profoundly affects the risks of morbidity as encompassed in the CCI, as noted above, we divide the sample into two birth cohorts determined by their age at baseline. Because the response variable in this analysis is a weighted count of the number of comorbid conditions, a zero-inflated Poisson (ZIP) based model was used. The ZIP model is an expansion of the Poisson model that corrects for overdispersion by accounting for more zeros than would be expected under a Poisson process. Both the Poisson and censored normal distributions were also considered, but the ZIP model provided the best fit for our data.

Trajectories were modeled for two to six groups as a quadratic function of time. Model fit was assessed using the Bayesian information criterion (BIC), the log likelihood plus a penalty for the number of parameters in the model. There are situations where BIC score continues to increase as more groups are added, but the additional groups are not necessary to summarize the distinct features of the data in a parsimonious way (Nagin, 2005). Therefore, average posterior probability of assignment, odds of correct classification, and estimated group probabilities versus the proportion of the sample assigned to the group (Nagin, 2005) were also used to assess the selected model's correspondence with the data.

Nonrandom attrition leads to altered characteristics of the population over time and can lead to biased estimates. Because we excluded individuals who were enrolled in

a managed care plan during any period of a given year, our only source of truncation is death. PROC TRAJ is used to simultaneously model the comorbidity trajectories and the probability of death, allowing the modeled probability of death to vary across trajectory groups. Individuals in the analysis were required to be alive at time “1,” and therefore the probability of dropout during this period is zero for all trajectory groups. All models accounted for nonrandom attrition due to death using the extension created by Haviland (Haviland, Jones, & Nagin, 2011; Zimmer, Martin, Nagin, & Jones, 2012). This extension jointly models the trajectories with a model of the logit of the dropout probability, in this case death, by group that includes dependence on the prior period response until dropout and age.

Trajectory group membership probabilities can vary as a function of time stable characteristics, or characteristics established before the observation periods (Jones & Nagin, 2007). This third component jointly estimates a multinomial logit model that captures the effects of time stable characteristics on the probability of group membership. This makes it possible to test the effect of early-life conditions and fertility on the probability of membership in each group (Daniel S. Nagin & Odgers, 2010). PROC TRAJ also allows for the inclusion of time-varying covariates measured during the observation time that may alter the shape of the observed trajectories, such as widowhood.

A series of mediation analysis were conducted to test the hypothesis that fertility history mediated the relationship between early-life conditions and later-life health. Mediation tests used the Clogg test of differences in coefficients produced when fertility variables were added to the model (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002).

For each group, the following analyses were conducted. First, we derived the basic trajectory groups in which comorbidity is a function of time only in order to select the best model. Second, we fit a model with covariates from the demographic and early life conditions (ELCs). Third, we fit a model with the covariates from the demographic, ELCs, and fertility domains. All models accounted for nonrandom attrition due to death. In addition, we examined how ELCs in the probability of trajectory membership are mediated by timing of childbirth (age at first and last birth), preterm birth, and parity.

Addressing Sample Selection

The data requirements for selection into the sample, once married parous individuals who survived to age 66, had a spouse survive until they were age 50, and never enrolled in a managed care plan during the observation period, could lead to biased estimates because the data are not representative of the population. To correct for the potential problem of selection, we use a Heckman two-stage modeling strategy (Heckman, 1979) performed using Stata 11.

In the first stage, a probit model assesses factors leading to selection into the sample among all individuals (see Table 3.2). The dependent variable is a dichotomous indicator of selection into the sample. This equation is used to generate the inverse Mills ratio (IMR), which is a nonlinear transformation of the probit index and a decreasing function of the probability of selection (Fu, Winship, & Mare, 2004). The IMR can be interpreted as the hazard of not being selected into the sample on which the comorbidity trajectories are based. The independent variables used in the selection equation are displayed in Table 3.4. For the model to be correctly specified, the selection equation

must include variables that are more closely related to sample selection than the dependent variable in the substantive equation.

Our sample selection is largely based on having complete information in UPDB and nonenrollment in a managed care organization (MCO). Therefore, we selected independent variables for the selection equation that are closely related to these factors. Age in 1992 is derived from the CMS records. The longitudinal information within the UPDB is more complete for individuals with a longer length of residence in the state of Utah. The UPDB holds information on the birth place of individuals, and this was used to create an indicator variable for place of birth, Utah versus outside of Utah.

Approximately 85% of the individuals selected into the sample were born in Utah, compared to 40% of those not selected into the sample. Area level characteristics of an individual's current place of residence may also predict selection into the sample.

Information about an individual's county of residence in 1992 was pulled from the 1990 US Decennial Census.

Table 3.4 shows that there are large differences in county level population and median family income between those selected and not selected into the final sample. Of those selected into the final sample, 61% resided in the Wasatch Front region of Utah, compared to 48% of the nonselected individuals. This contributes to the large difference in county level population between the groups because a larger proportion of individuals in the nonselected group resides in populous counties in California (such as LA county; population of 8.8 million in 1992). In the second stage, trajectory models are estimated with the IMR from the first stage added as a covariate in the model, the goal being to account for possible sample selection bias in the final models. The far right column in Table 3.4 shows all of the variables included in the probit models significantly predicted

selection into the sample, with the exception of age in the equation for males aged 75 – 84. Age and being born in Utah were positively associated with selection into the sample, while median family income and population were negatively associated with selection into the sample for all genders and cohorts (with the age exception mentioned above). A similar sample selection strategy was used by Gagnon et al. (2009) when examining the relationship between fertility and postreproductive survival.

Results

Trajectories of Comorbidity and Morbidity

The best fitting models for both males and females ages 66 – 74 (the young-old) in 1992 revealed six distinct groups of trajectory groups, while those for ages 75 – 84 (the old-old) showed five distinct groups. Figures 3.1- 3.4 show the predicted comorbidity trajectories by sex and age group. The figures show the diversity of comorbidity experience over the 18 year period of follow-up (the youngest individuals are 84 years old at the end of the follow-up period). To aid in the interpretation of results, trajectory groups have been labeled as follows: “robust”- characterized by the absence of comorbid conditions; “slow initiates”- individuals in this group begin the observation period with no comorbid conditions, but the number gradually increases over time; “accelerated initiates”- individuals in this group begin the observation period with no comorbid conditions but the number of conditions quickly increases over time and then decelerates during the last 2 years of the 18 year period; “chronic low”- characterized by the steady level of comorbidity over time; “ailing”- this group of individuals has moderate levels of comorbidity at baseline which steadily increase over time; “frail”- these individuals have the highest level of comorbidity at baseline which remains high over time.

In addition to using BIC as model selection criteria, several other measures were used to assess the correspondence of our models with the data (D. Nagin, 2005; Zimmer et al., 2012). First, we calculated the average posterior probability (APP) of membership in group j for all individuals who are most likely to belong to that group. The recommended criterion is that the APP for each group should exceed 0.70. All selected models met this criterion, with APP ranging from 0.79 to 0.92. Second, we compared estimated proportions of group membership generated by the maximum likelihood procedure to the actual proportion of the sample assigned to each group based on maximum posterior probability of group membership. For this criterion, our models were satisfactory, with no more than a 4 point difference in any of the selected models.

The shape of the trajectories is similar between males and females in their respective age groups, but the intercepts differ. Individuals surviving the full 18 year period range in age from 83 to 91 in 2009. For females in the young-old age category, trajectory membership is fairly evenly distributed among the robust (19.1%), slow initiate (18.8%), chronic (19.7%), and ailing (21.8%). Compared to females, males have lower percentages of individuals in the robust (15.7%) and slow initiate (16.4%) groups, and higher percentages of individuals in the ailing (26.1%), accelerated initiate (15.3%), and frail groups (8%). The frail category constitutes the lowest proportion of group membership for both males and females, 8% and 7.3%, respectively. These findings are somewhat unexpected given the health-survival paradox, where females have worse health and males have higher mortality. However, recently reported prevalence estimates support our findings. The 2011 summary statistics for US adults reports higher prevalence rates of heart disease, hypertension, and diabetes for men (Schiller, Lucas, & Peregoy, 2012). A separate report using National Health Interview Survey (NHIS) from

2009 estimated that a higher percentage of men (49%) than women (42.5%) had two or more chronic conditions (conditions considered included hypertension, heart disease, diabetes, cancer, stroke, chronic bronchitis, emphysema, current asthma, and kidney disease; V. Fried, Bernstein, & Bush, 2012).

Individuals in the old-old cohort surviving the full 18 year period range in age from 92 to 101 in 2009. For both sexes in this cohort, five distinct trajectory groups were identified. The ailing category, with a CCI of approximately “1” at baseline that gradually increases over time, has the highest trajectory membership for both sexes, with 29.7% of females and 35.3% of males falling into this category. Compared to the young-old, a smaller proportion of the old-old fall into the robust category (15.7% vs. 14.7% for males and 19.1% vs. 18.2% for females). As expected, the robust in the old-old cohort do not maintain a disease free trajectory over the period of 18 years, with a predicted CCI of 0.74 for females and 1.5 for males in 2009. While the pattern of this robust trajectory in the old-old cohort is similar to the pattern of the slow initiates in the young-old cohort, individuals in the old-old robust category have a slower rate of increase over time and end the period with a lower predicted CCI (the difference in CCI_{2009} is 0.82 for females and 0.44 for males). Compared to the young-old, there is a near doubling in the proportion of frail females and a 50% increase for the males. Another notable difference between the young-old and old-old frail trajectories is the maximum predicted CCI, which is higher in the young-old category for both sexes. While the two cohorts are not directly comparable, the results suggest that there may be a decrease in the heterogeneity of morbidity patterns with age, with fewer categories in the older age groups. The lower number of categories that fit the data may also be a function of the decreased sample size in the old-old cohort.

We found six distinct trajectory groups for the male and female birth certificate samples. The parameter estimates and estimated trajectory memberships were similar across samples (results not shown) with a slightly higher percentage in the robust group for both males and females compared to the full sample. This is not unexpected given the younger age distribution of these subsamples. The following trajectories were identified: robust (male=16.7%, female=20.3%); slow initiate (male=16.9%, female=19.2%); accelerated initiate (male=18.0%, female=14.3%); chronic low (male=16.1%, female=18.0%); ailing (male=25.2%, female=21.3%); and frail (male=6.9%, female=6.9%).

Figures 3.5 – 3.8 display the probability of death for each sex and age-group. The probability of dropout due to death is modeled as a function of age and the comorbidity measurement in the previous year and is allowed to vary by trajectory group. Mortality trajectories follow a similar hierarchy as the comorbidity trajectories, with the robust group generally having the lowest levels of mortality and the frail group having the highest. Mortality in all groups rises with time, with the accelerated initiates having the fastest rate of increase in mortality over the 18 year period for the young-old cohort, and the ailing and initiates having the fastest rates of increase for females and males respectively in the old-old cohort. Females have lower probabilities of death than males in their respective cohorts and comorbidity groups. The young-old have lower probabilities of death than the old-old. Both of these patterns are consistent with expected patterns of mortality in these age groups.

Widowhood altered the shape of the trajectory for some, but not all, trajectory groups. In general, experiencing the death of a spouse led to an increase in the level of comorbidity. Individuals in the frail categories and males in the old-old cohort were the

most impervious to the effects of widowhood, with few of the effects reaching significance. Because these results are central to the hypothesis, they are not shown here but are available upon request.

Fertility History and Later-Life Comorbidity

Once the best fitting trajectory models were selected, we jointly modeled multinomial logit models by sex and cohort, relating individual-level covariates to posterior probabilities to estimate the effects of ELCs and fertility on probability of group membership. The first set of nested models included only ELCs and the results are not displayed in this paper, but they are available upon request. Tables 3.5 – 3.8 display the odds ratios and 95% confident intervals for the full models that include demographic, ELCs, and fertility measures. Comorbidity is the existence of multiple diseases. Our results show that there are two groups in all models that escape transition into a comorbid state (two or more simultaneous conditions), the robust and chronic low. However, for ease of interpretation, the chronic low group will be referred to as a group with comorbid conditions. The contrast group in all tables is the robust category, meaning that we are comparing the probability of membership in trajectory groups with comorbid conditions with the probability of membership in the group with no comorbid conditions. All results discussed below are controlling for early-life events and demographic measures and, therefore, all results presented below are *ceteris paribus*. Also, unless otherwise noted, the results highlighted below are significant at the 0.05 level.

For females in the young-old cohort, we do not find a significant association between parity and trajectory membership. We do find a relationship between age at first birth and trajectory group. Table 3.5 shows that, compared to women having their first

birth between the ages of 19 and 24, young age at first birth (<18) nearly doubles the odds of being in the frail versus robust trajectory. The results also suggest that young age at first birth increases the odds of being in the other categories with increased comorbidity, but the differences are merely suggestive. Age at last birth confers a protective effect, with women having a last birth at age 35 or later having a decrease in the odds of being in a comorbid trajectory. Females who have their last birth between the ages of 35 and 39 and after age 40 have a 24% and 25% ($p=0.07$) respective decrease in the odds of being in the frail versus robust group compared to females ending childbearing earlier. There is a 33% decrease in the odds of being in the accelerated initiate group versus the robust trajectory for women having one or more infant deaths, but this pattern is not evident for other categories. There is no evidence of an association between twinning, short birth intervals, long birth intervals, and later-life comorbidity trajectories for females in the young-old cohort.

Table 3.6 shows the results for females in the old-old cohort. We find little association between parity and trajectory membership *ceteris paribus* for females in the old-old cohort with the exception of the frail group, where females having nine or more children are nearly twice as likely to be in the frail versus robust group. The relationship between age at first birth and trajectory membership are similar to the patterns observed in the young-old cohort. Females having their first birth during the teenage years are more likely to be in the chronic low, ailing, and frail versus robust groups. Females in this cohort having their first birth after age 25 are less likely to be in the chronic low and frail categories. Compared to females having their last birth before the age of 35, females having their last child after the age of 35 are more likely to be in the chronic low group versus the robust group. However, females having their last birth after the age of 40 have

a 24% decrease in the odds of being in the frail versus robust group. As with the female young-old cohort, we find no association between trajectory membership and twinning, infant death, and short birth intervals *ceteris paribus*. Having one or more long birth interval reduces the odds of being in any of the groups with more comorbid conditions versus the robust, with an 24%, 34%, 18%, and 27% respective decrease in the risk of being in the initiate, chronic low, ailing, and frail versus robust group (the difference in the magnitude of the effect across groups is not significant).

We find no association between parity and trajectory membership for males in the young-old and old-old cohorts *ceteris paribus*. Having a later age at first birth (over the age of 25 vs. less than 25) is protective for men in both cohorts. Table 3.7 shows that for males in the young-old cohort, having their first birth at the age of 25 or older reduces the odds of being in the accelerated initiates, chronic low, ailing, and frail groups by a little over 20% for each group compared to the robust. Table 3.8 shows that for males in the old-old cohort, having an older age at first birth is associated with an 18% and 29% reduction in the risk of being in the ailing and frail groups, respectively, compared to the robust group. Males in the old-old cohort having their last child after the age of 40 have a 26% decrease in the odds of being in the ailing versus robust group. We do not find an association between twinning, age at last birth, short birth intervals, long birth intervals, and infant deaths and group membership for males in these cohorts.

The results from of the birth certificate analysis are presented in Figures 3.9 and 3.10. Individuals included in these models were required to have birth certificate records for all births and, therefore, the results are based on a subsample of individuals in the young-old cohorts, with a higher percentage of the males from the full sample represented in the subsample than females ($N_{\text{Female}}=4,124$ and $N_{\text{Male}}= 6,192$). This is

because, on average, men have an older age at first birth and are therefore more likely to meet the selection criteria. All models controlled for early-life conditions and the fertility covariates presented used in the earlier models. As with the previous analyses, the multinomial logit model relates individual-level covariates to posterior probabilities of trajectory group membership. Models were run simultaneously with the trajectories, and the reference group is the robust, or group with the lowest number of comorbidities. All models control for early-life conditions and demographic variables and were jointly modeled with mortality trajectories.

We find that for females in the young-old cohort, having one or more high birth weight (defined as >4,000 g) children increases the odds of being in the chronic low, ailing, and frail versus the robust *ceteris paribus* by 39%, 60%, and 76%, respectively. Females having one or more preterm births (defined as <37 weeks gestation) have a 54% increase in the odds of being in the frail group versus the robust group. We do not find an association between ever having a low birth weight (carried to term) baby and later-life comorbidity trajectories for females. For males in the birth certificate analysis, we find no association between premature offspring and group membership. We do find that males having one or more high birth weight children have a 30% increase in the odds of being in the accelerated initiate versus the robust group. Fathers of low birth weight babies are also more likely to be in the chronic low and ailing groups compared to the robust group.

To account for sample selection bias, the inverse Mills' ratio (IMR) estimated from the probit model predicting selection into the sample was included in the analyses. Overall, the sample bias correction term (the IMR) has little effect on probability of group membership. We do find that an increased hazard of nonselection is associated

with an increase in likelihood of being in the frail group for females in the young-old cohort (OR=1.3, 95% CI= 1.02, 1.67) and the ailing group for males in the old-old cohort (OR=1.38, 95% CI=1.07, 1.78). Simply, individuals not predicted to be in the sample had a 30% and 38% increase in the odds of being in the frail and ailing groups for the young-old females and old-old males, respectively. The beauty of the IMR term is that it simultaneously tests for and corrects selection bias. Therefore, the selection bias present in models with significant terms has been corrected for by including the IMR in our models. However, this should be interpreted with some caution because selection models are sensitive to the choice of covariates in the selection equation (Fu et al., 2004).

The Mediating Effects of Fertility

Mediation analyses were performed to test the mediating effects of fertility on early-life conditions. Fertility variables were considered as possible intervening variables if they were significantly related to comorbidity group membership. While there were few significant differences in coefficients, the percent change in the effects of the ELCs was small (ranging from 0.5% to 8%) and inconsistent. Therefore, we concluded that fertility history did not significantly mediate the relationship between early-life conditions and later-life health (results not shown here but available upon request).

Discussion

The purpose of this study was threefold. First, we sought to identify distinct trajectories of comorbidity by sex for individuals in two age categories, the young-old and old-old. Second, we tested specific hypotheses relating fertility to trajectory group

membership. Third, we tested the mediating role of fertility on the relationship between early-life conditions and comorbidity. We found that there are distinct heterogeneous patterns of comorbidity that range from a robust group, escaping major morbid conditions for the majority of the observation period, to a frail group characterized by high comorbidity throughout the entire period of observation. Fertility history is associated with comorbidity trajectories after the age of 65 for both females and males when controlling for early-life circumstances, although it is clear that the fertility history has a greater impact on females. These results provide some evidence that evolutionary “trade-off” (H1), biological (H2), and social mechanisms (H4b, H4c) may all be associated with the observed relationship between fertility and later-life health. While we found independent effects of early-life conditions on later-life comorbidity trajectories, we did not find robust evidence that fertility history is on the causal pathway between early-life conditions and later-life comorbidity.

The observed relationships between parity, age at last birth and comorbidity group membership present evidence of a “trade-off” between fertility and aging for females in the young-old cohort. Our finding of adverse effects at 9+ births is higher than the 5+ births reported in other studies of contemporary populations (Doblhammer, 2000; Grundy & Tomassini, 2005). However, both studies top coded fertility at 5+ births. Our findings support other studies suggesting that high levels of fertility are needed for a trade-off mechanism to operate (Gagnon et al., 2009; Kitagawa & Hauser, 1973). We also find a consistent protective relationship between age at last birth and comorbidity group membership in the young-old cohort, with females having their last birth after age 35 more likely to be in the robust group. This is consistent with the prediction that older ages of reproduction are a marker for slowed rates of aging (Perls, Alpert, & Fretts,

1997). However, we do not see the same strong protective effect for females in the old-old cohort.

Related to the evolutionary theories discussed above are the biological mechanisms through which fertility is linked to later-life comorbidity for women. We did find some support for biological consequences to childbirth for women (H2), but we did not find evidence supporting the maternal depletion hypothesis or the link between low birth weight and comorbidity for women (Davey Smith et al., 2004; G. D. Smith et al., 1997). High parity (9+ births) had an adverse effect on later-life health for females but not males, suggesting the costs of increased parity are biological. Having at least one long birth interval had a protective effect on comorbidity later in life for females in the old-old cohort. Long birth intervals have been linked to complications during reproductive years (Conde-Agudelo et al., 2007). However, this study suggests that there are not long term consequences to widely spaced births for women in the old-old cohort.

We do not find strong evidence in favor of the robust phenotype hypothesis (H3), which argues that fertility success is a marker for female health and vitality. We find no association between short birth intervals and later-life comorbidity. While the negative relationship between late age at last birth and comorbidity may be a marker for robustness, the hypothesized negative relationship between increased parity, shorter birth intervals, and twinning were not significant across trajectory groups and cohorts. Other studies using this data from the UPDB have found evidence supporting the robust phenotype hypothesis (Robson & Smith, 2011, 2012). However, that study uses a historical cohort of women that survive to age 50. It is possible that twinning served as a selection filter, with only the most robust women giving birth to multiples during that historical time period surviving to age 50. The same effect is not observed in a

contemporary sample with women giving birth during a period where medical intervention could increase the rate of survival for mothers of multiples. Therefore, we are rejecting this hypothesis.

We do find evidence that social mechanisms explain some of the relationship between fertility and later-life health. We do not find strong evidence of decreased comorbidity for individuals with more children, and therefore reject the social support hypothesis (H4a). We find strong evidence supporting the association between age at first birth and comorbidity after age 65. Young motherhood is related to adverse health outcomes for both cohorts in this study, and postponing parenthood is protective for males and females when controlling for early-life circumstances including childhood socioeconomic status. This suggests that policy aimed at reducing teenage pregnancy may have significant effects on later-life health outcomes. The adverse effect of low birth weight for males but not females and high birth weight of offspring for males and females suggests that adverse birth outcomes may be a marker of risky environments (Kramer, Séguin, Lydon, & Goulet, 2000). We did not control for social environment at time of birth or current socioeconomic circumstance. There are large socioeconomic disparities in perinatal and infant mortality, low birth weight, and preterm birth and, in the United States, these disparities are often related to racial/ethnic disparities (Kramer, 1987; Kramer et al., 2000). Future research should not only consider the early-life social environment, but the social environment throughout the life course.

Fertility decisions and outcomes are heavily influenced by social and historical circumstances, making it important to consider the historical context of these individuals' lives. The oldest members of the old-old cohort would have been born in 1908 and entered childbearing age (assuming it is 15) in 1923, with the childbearing years

extending to 1965 for the youngest members of the cohort (assuming age at last birth is 50). The members of the young-old cohort would have initiated childbearing in 1933 and ended in 1974. Infertility drugs would have been available for some individuals in these cohorts. This means that parity and late age at last birth may not be completely biologically determined. Individuals in both cohorts may have served during WWII, which may affect the timing of fertility. Individuals in both cohorts would have been parous during the baby boom, when fertility rates peaked at 3.8 (Westoff, 1986). Members of the old-old cohort would also have been children during the 1918 influenza pandemic, an exposure that may have left them physiologically scarred, affecting both fertility and mortality. A study by Smith et al. suggests that individuals exposed to influenza or pneumonia as children during the pandemic have lower ages at last birth and increased mortality (Ken R. Smith, Reed, Hanson, Mineau, & Fraser, 2012).

This study has several limitations that should be addressed in future studies of the relationship between fertility and later-life health. First, these results are based on once married parous individuals. Future studies should consider the relationship between nulliparity and later-life comorbidity for both men and women. Second, we were unable to consider the role of all early-life and reproductive outcomes (including the number of sibling, number of sons and daughters, the proportion of offspring born prematurely, and the proportion of offspring born high/low birth weight) and later-life health. Third, while we controlled for childhood SES, we were unable to control for SES at the time of birth and baseline. We are currently in the process of creating files to begin these analyses. Fourth, sibling and spouse designs may improve understanding of the mechanisms linking reproductive history and health.

Conclusion

The paths to aging are heterogeneous and more research needs to be done to both characterize these different phenotypes and the factors that influence them. Approaching this problem using the life course lens allows us to explore events that can directly or indirectly affect later-life health. Understanding heterogeneity in the patterns of aging using a single period is an impossible endeavor because the biological functioning of an individual is dependent upon an array of circumstances from birth to death. While early-life conditions explain a portion of the heterogeneity in aging, midlife circumstances may also alter the trajectories of disease. Parity, timing of childbearing, and birth outcomes of offspring are significantly related to later-life health outcomes. The differences in risk factors between men and women suggest that evolutionary, biological, and social mechanisms must all be considered when studying these heterogeneous aging processes.

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Table 3.1. Hypothesized Relationship between Fertility and Later-Life Comorbidity

Hypothesis	Direction of prediction	Mechanisms	Gendered response		Fertility has a mediating role between ELCs and later life health
			Female	Male	
H1: The optimization of life history traits leads to a “trade-off” between fertility and somatic maintenance	<u>Increased comorbidity</u> : women with young age at first birth, high fertility, short birth intervals.	Disposable soma and antagonistic pleiotropy- Evolutionary forces select traits that optimize fertility and offspring survival.	X		No
	<u>Decreased comorbidity</u> : later age at last birth.				
H2: Childbirth leads to physiological changes that affect later life health.	<u>Increased comorbidity</u> : women with high fertility, short interbirth intervals, high birth weight offspring, and later age at last birth.	Biological scarring, maternal depletion, gestational diabetes, and exposure to endogenous hormones.	X		No
	<u>Decreased comorbidity</u> : women with early age at first birth and high fertility.				
H3: Reproductive history is a marker of a robust phenotype	<u>Increased comorbidity</u> : Preterm birth and low fertility are markers of frail individuals.	Healthier women have more reproductive success.	X		<u>Yes</u> : Early childhood exposures to adverse environments may lead to a frail phenotype with decreased fertility and increased later life comorbidity.
	<u>Decreased comorbidity</u> : women with high fertility, short interbirth intervals, twins/multiples, and later age at last birth.				
H4: Social mechanisms are responsible for the observed association between reproductive history and comorbidity after 65.	<u>Increased comorbidity</u> : Parity, early age at first birth, and preterm birth.	Social, psychological, and economic effects of childbearing. Social support. Cumulative disadvantage.	X	X	<u>No</u> : Early life conditions and fertility history have independent effects on later life health. <u>Yes</u> : Correlated environments and cumulative disadvantage.
	<u>Decreased comorbidity</u> : Parity and late age at first birth.				

Table 3.2. Description of Sample Selection by Sex and Age

Sex and Age at Baseline (1992)	Total Number of Records Linked to UPDB*	Ever Enrolled in an MCO	Deceased in 1992	Does not have family history information in UPDB**	No Spouse (Missing or Never Married) or Married More than Once	No Children (Missing or Nulliparous)	Missing Information on Births	Missing Information on One or Both Parents	Spouse Died Before Ego 50 (Completion of Fertility)	Sample
Female 66 -74	60709	20293	728	6664	9072	5478	3538	2300	446	12190
Female 75 -84	44324	9356	1352	5933	7945	4776	3566	886	411	10099
Male 66 -74	60215	20642	1057	6635	8475	6346	3342	2311	58	11349
Male 75 - 84	36731	8079	1571	5470	5459	4719	2851	1048	14	7520
Total	201979	58370	4708	24702	30951	21319	13297	6545	929	41158

Table 3.3. Descriptive Statistics by Gender and Age Group

	Female 66-74 in 1992 N=12,190	Female 75 - 84 in 1992 N=10,099	Male 66-74 in 1992 N=11,349	Male 75 - 84 in 1992 N=7,520
Early Life Conditions	N(% of total sample) or Mean (SD)			
Father's Nam-Powers SES Score	49.37 (19.54)	47.4 (18.19)	49.0 (19.14)	47.09 (17.96)
Father Farmer	3556 (29.2%)	3699 (36.6%)	3434 (30.3%)	2786 (37.1%)
Father Missing SES	2982 (24.5%)	2416 (23.9%)	2620 (23.1%)	1754 (23.3%)
Active LDS	6452 (52.9%)	5525 (54.7%)	5876 (51.8%)	4219 (56.1%)
InActive LDS	2886 (23.7%)	2883 (28.6%)	2643 (23.3%)	1843 (24.5%)
Non-LDS	2852 (23.4%)	1691 (16.7%)	2830 (24.9%)	1458 (19.4%)
FEL Bottom 25%	2841 (23.3%)	2335 (23.1%)	2693 (23.7%)	1640 (21.8%)
FEL Middle 50%	5321 (43.7%)	4525 (44.8%)	4869 (42.9%)	3648 (48.5%)
FEL Top 25%	2662 (21.8%)	2653 (26.3%)	2554 (22.5%)	1757 (23.4%)
FEL Missing	1366 (11.2%)	586 (5.8%)	1233 (10.9%)	475 (6.3%)
Mother Died when Ego <18	721 (5.9%)	746 (7.4%)	682 (6.0%)	555 (7.4%)
Mother Died when Ego 18+	11379 (93.4%)	9255 (91.6%)	10583 (93.3%)	6906 (91.8%)
Father Died when Ego <18	1060 (8.7%)	943 (9.3%)	951 (8.4%)	714 (9.5%)
Father Died when Ego 18+	11040 (90.6%)	9058 (89.7%)	10314 (90.9%)	6747 (89.7%)
Both Parents Died Before 18	90 (0.7%)	98 (1%)	84 (0.7%)	59 (0.8%)
Fertility History				
Children 1-2	3004 (24.6%)	3138 (31.1%)	2533 (22.3%)	2104 (28.0%)
Children 3-5	6798 (55.8%)	5287 (52.4%)	6605 (58.2%)	4087 (54.4%)
Children 6-8	2061 (16.9%)	1410 (14.0%)	1934 (17.0%)	1135 (15.1%)
Children 9+	327 (2.7%)	264 (2.6%)	277 (2.4%)	194 (2.6%)
Infant Death (Y/N)	730 (6.0%)	757 (7.5%)	637 (5.6%)	527 (7.0%)
Short Birth Interval (Y/N)	3380 (27.7%)	2238 (22.2)	3489 (30.7%)	1707 (22.7%)
Long Birth Interval (Y/N)	5201 (42.7%)	4684 (46.4%)	4568 (40.3%)	3513 (46.7%)
Mother/Father of Twin	580 (4.8%)	489 (4.8%)	486 (4.3%)	370 (4.9%)
Age at First Birth Less than 18	391 (3.2%)	316 (3.1%)	n/a	n/a
Age at First Birth 18 - 24	8590 (70.5%)	5871 (58.1%)	5815 (51.2%)	2687 (35.7%)
Age at First Birth 25+	3209 (26.3%)	3912 (38.7%)	5534 (48.8%)	4833 (64.3%)
Age at Last Birth 35 - 39	1848 (15.2%)	3105 (30.8%)	2864 (25.2%)	2188 (29.1%)
Age at Last Birth >=40	3827 (31.4%)	2369 (23.5%)	2864 (25.2%)	2995 (39.8%)
Age	70.09 (2.57)	79.00 (4.76)	70.0 (2.56)	78.6 (2.78)
Information from Utah Birth Certificates*				
At least 1 High Birth Weight Baby	668 (16.1%)		1126 (18.8%)	
At least 1 Low Birth Weight Baby	283 (6.8%)		434 (7.0%)	
At Least One Preterm Birth	572 (13.8%)		942 (15.2%)	
Adult Measures				
Spouse Alive at Baseline	9523 (78.1%)	5023 (49.7%)	10913 (96.2%)	6662 (88.6%)

*Female N=4142; Male N=6192

Note: Age 66-74 in 1992 with birth certificate data on all births, making this a select sample. Females are younger (avg age=69, range 66 - 74) and had to have their first birth after age 20 (1947 is the first year BC available). Males are younger and had to have their first birth after age 20.

Table 3.4. Sample Selection Means by Gender and Age

	Mean (StdDev) Excluded (N=48,519)	Mean (StdDev) Included (N=12,190)	Selection Model	
Female Age 66 - 74				
Age in 1992	69.81(2.55)	70.09(70.09)	0.024	<0.001
Born in Utah	0.39(0.49)	0.85(0.85)	1.186	<0.001
1990 County Med Family Income (Unit=10,000)	3.35(0.53)	3.28(3.28)	-0.085	<0.001
1990 County Population (Unit=100,000)	5.87(12.4)	3.63(3.63)	-0.018	<0.001
Missing 1990 Census Info	1%	0.30%	-0.444	<0.001
Constant			-2.911	<0.001
Female Age 75 - 84				
Age in 1992	78.95(2.79)	79(2.84)	0.01	0.01
Born in Utah	0.41(0.49)	0.83(0.38)	1.10	<0.001
1990 County Med Family Income (Unit=10,000)	3.33(0.55)	3.26(0.42)	-0.12	<0.001
1990 County Population (Unit=100,000)	6.07(13.26)	3.65(6.34)	-0.01	<0.001
Missing 1990 Census Info	1%	0.10%	-0.81	<0.001
Constant			-1.48	<0.001
Male Age 66 - 74				
Age in 1992	69.79(2.56)	69.97(2.56)	0.02	<0.001
Born in Utah	0.4(0.49)	0.86(0.34)	1.24	<0.001
1990 County Med Family Income (Unit=10,000)	3.34(0.57)	3.28(0.43)	-0.10	<0.001
1990 County Population (Unit=100,000)	6.09(13.52)	3.77(6.56)	0.00	<0.001
Missing 1990 Census Info	1%	0.30%	-0.55	<0.001
Constant			-2.61	<0.001
Male Age 75 - 84				
Age in 1992	78.67(2.75)	78.63(2.78)	0.00	0.61
Born in Utah	0.4(0.49)	0.84(0.37)	1.16	<0.001
1990 County Med Family Income (Unit=10,000)	3.28(0.57)	3.26(0.43)	-0.08	<0.001
1990 County Population (Unit=100,000)	5.63(13.1)	3.71(7.08)	-0.01	<0.001
Missing 1990 Census Info	1%	0.30%	-0.59	<0.001
Constant			-1.08	<0.001

Table 3.5. Effects of Early Life Conditions and Fertility on Comorbidity Trajectory Group Membership versus Robust Group (19.1%): Women Ages 66 – 74 in 1992

	Slow Initiates 18.8%	Accelerated Initiates 13.3%	Chronic Low 19.7%	Ailing 21.8%	Frail 7.3%
Early Life Conditions					
	Odd Ratio (95% CI)				
Age in 1992	2.47(1.88,3.26)	2.54(1.89,3.41)	3.52(2.71,4.58)	3.01(2.34,3.87)	3.16(2.24,4.45)
Active Member of LDS Church	0.76(0.61,0.94)	0.55(0.44,0.68)	0.72(0.58,0.88)	0.45(0.37,0.54)	0.47(0.37,0.61)
Inactive Member of LDS Church	0.84(0.66,1.06)	0.57(0.45,0.73)	0.78(0.62,0.98)	0.59(0.48,0.73)	0.56(0.42,0.73)
Non-Member (reference)	1	1	1	1	1
Father's NP SES (unit=10)	1.02(0.98,1.05)	0.98(0.94,1.02)	1.01(0.97,1.04)	0.99(0.96,1.03)	0.96(0.91,1)
Father Farmer	1.01(0.85,1.2)	0.8(0.67,0.96)	1.1(0.93,1.29)	0.79(0.68,0.92)	0.74(0.6,0.93)
Missing SES	0.91(0.76,1.09)	0.91(0.76,1.1)	1.08(0.91,1.28)	0.85(0.73,1.01)	1.08(0.87,1.34)
FEL in Bottom Quartile	1.19(0.99,1.44)	1.38(1.14,1.67)	1.24(1.04,1.48)	1.44(1.22,1.69)	1.27(1.02,1.59)
FEL in Mid 50% (reference)	1	1	1	1	1
FEL in Top Quartile	0.79(0.67,0.94)	0.75(0.62,0.91)	0.71(0.61,0.84)	0.58(0.49,0.68)	0.7(0.56,0.87)
FEL Missing	0.97(0.74,1.27)	0.75(0.57,1)	0.84(0.64,1.09)	0.56(0.44,0.72)	0.45(0.32,0.63)
Orphaned before Age 18	2.39(0.91,6.29)	1.78(0.62,5.14)	1.46(0.53,4.05)	2.62(1.08,6.36)	3.87(1.44,10.4)
Mother Died before Child 18	1.1(0.82,1.49)	1.28(0.94,1.73)	1.11(0.83,1.48)	1.24(0.95,1.63)	1.48(1.05,2.1)
Father Died before Child 18	1.12(0.87,1.45)	1.38(1.07,1.78)	1.12(0.88,1.43)	1.24(0.99,1.56)	1.32(0.98,1.78)
Both Parents Alive at 18 (reference)	1	1	1	1	1
Fertility					
1-2 Children	0.87(0.72,1.06)	1.07(0.88,1.31)	0.89(0.74,1.06)	0.95(0.8,1.13)	1.13(0.9,1.42)
3-5 Children (reference)	1	1	1	1	1
6-8 Children	1.09(0.87,1.35)	1.04(0.82,1.31)	1.1(0.9,1.36)	1.16(0.95,1.42)	1.1(0.83,1.45)
9+ Children	0.86(0.52,1.43)	1.06(0.65,1.74)	1.01(0.65,1.58)	1.2(0.79,1.84)	0.96(0.51,1.77)
Age at First Birth < 18	1.48(0.97,2.25)	1.48(0.96,2.3)	1.33(0.88,2.01)	1.44(0.98,2.12)	1.94(1.2,3.13)
Age at First Birth 18 - 24 (ref)	1	1	1	1	1
Age at first Birth >= 25	1.04(0.88,1.24)	0.86(0.71,1.03)	0.93(0.79,1.1)	0.86(0.74,1.02)	1.06(0.86,1.31)
Age at Last Birth 35 - 39	0.85(0.71,1.02)	0.83(0.68,1.01)	0.81(0.68,0.97)	0.82(0.69,0.97)	0.76(0.61,0.96)
Age at Last Birth >= 40	0.65(0.5,0.84)	0.8(0.61,1.05)	0.82(0.65,1.04)	0.66(0.52,0.83)	0.75(0.54,1.03)
Mother of Twins	1.17(0.84,1.62)	0.95(0.66,1.38)	0.96(0.69,1.32)	1.12(0.83,1.51)	1.01(0.67,1.54)
One or More Short Birth Intervals	1.01(0.85,1.19)	1.11(0.93,1.33)	0.92(0.78,1.08)	1.03(0.88,1.21)	1.06(0.85,1.31)
One or More Long Birth Intervals	1.01(0.87,1.19)	1.06(0.9,1.26)	0.93(0.8,1.09)	1.02(0.88,1.17)	0.97(0.79,1.19)
One or More Infant Deaths	0.93(0.69,1.24)	0.67(0.47,0.95)	0.83(0.62,1.1)	1.02(0.79,1.32)	1.13(0.8,1.6)
Sample Selection Bias					
IMR	1.13(0.92,1.39)	1.03(0.82,1.28)	1.06(0.86,1.29)	1.17(0.96,1.41)	1.3(1.02,1.67)

Note: Results shown in Table 3.5 are controlling for widowhood and jointly modeled with mortality trajectories.

Table 3.6. Effects of Early Life Conditions and Fertility on Comorbidity Trajectory Group Membership versus Robust Group (18.2%): Women Ages 75 – 84 in 1992

	Initiates 21.6%	Chronic Low 29.7%	Ailing 16.9%	Frail 13.6%
Early Life Conditions				
	Odd Ratio (95% CI)			
Age in 1992	1.84(1.38,2.44)	3.89(2.89,5.24)	2.77(2.16,3.55)	2.95(2.21,3.95)
Active Member of LDS Church	1.05(0.82,1.33)	0.83(0.65,1.07)	0.89(0.72,1.1)	0.93(0.72,1.19)
Inactive Member of LDS Church	1.12(0.87,1.45)	0.79(0.6,1.03)	0.97(0.78,1.22)	1.05(0.81,1.37)
Non-Member (reference)	1	1	1	1
Father's NP SES (unit=10)	1.02(0.98,1.07)	1.02(0.98,1.07)	1.02(0.98,1.06)	1(0.95,1.04)
Father Farmer	0.93(0.78,1.12)	1.07(0.87,1.31)	1.14(0.96,1.34)	0.93(0.77,1.13)
Missing SES	1.01(0.82,1.23)	1.07(0.86,1.34)	1.11(0.92,1.33)	1.08(0.87,1.34)
FEL in Bottom Quartile	1.44(1.17,1.77)	1.41(1.12,1.76)	1.59(1.33,1.91)	1.6(1.3,1.97)
FEL in Mid 50% (reference)	1	1	1	1
FEL in Top Quartile	0.77(0.64,0.91)	0.83(0.69,1.01)	0.65(0.56,0.77)	0.61(0.51,0.75)
FEL Missing	0.91(0.63,1.3)	1.11(0.77,1.6)	0.81(0.58,1.11)	0.78(0.53,1.14)
Orphaned before Age 18	0.88(0.42,1.85)	0.97(0.42,2.23)	1.29(0.68,2.43)	0.78(0.32,1.91)
Mother Died before Child 18	1.16(0.86,1.56)	1.31(0.96,1.78)	0.99(0.75,1.3)	1.35(1,1.81)
Father Died before Child 18	1.19(0.91,1.57)	1.15(0.86,1.54)	1.27(1,1.61)	1.24(0.94,1.63)
Both Parents Alive at 18 (reference)	1	1	1	1
Fertility				
1-2 Children	0.98(0.8,1.21)	0.96(0.77,1.2)	0.9(0.75,1.08)	0.89(0.72,1.11)
3-5 Children (reference)	1	1	1	1
6-8 Children	1.01(0.79,1.31)	0.93(0.7,1.23)	1.22(0.97,1.53)	1.15(0.88,1.52)
9+ Children	0.77(0.43,1.38)	0.68(0.36,1.29)	1.17(0.73,1.89)	1.98(1.18,3.32)
Age at First Birth < 18	1.45(0.84,2.49)	1.85(1.05,3.24)	1.97(1.24,3.13)	2.03(1.23,3.36)
Age at First Birth 18 - 24 (ref)	1	1	1	1
Age at first Birth >= 25	0.86(0.72,1.03)	0.77(0.63,0.94)	0.9(0.77,1.06)	0.78(0.64,0.95)
Age at Last Birth 35 - 39	1.07(0.87,1.31)	1.38(1.11,1.72)	1.01(0.84,1.21)	1.11(0.9,1.37)
Age at Last Birth >= 40	1.13(0.89,1.45)	1.34(1.03,1.75)	0.89(0.71,1.11)	0.76(0.58,0.99)
Mother of Twins	1.08(0.76,1.54)	0.96(0.64,1.44)	1.02(0.74,1.4)	1.19(0.83,1.71)
One or More Short Birth Intervals	1.04(0.85,1.26)	0.83(0.66,1.04)	1.03(0.87,1.23)	0.89(0.72,1.1)
One or More Long Birth Intervals	0.76(0.63,0.91)	0.66(0.54,0.8)	0.82(0.7,0.96)	0.73(0.61,0.88)
One or More Infant Deaths	0.78(0.57,1.06)	0.84(0.6,1.17)	1(0.78,1.29)	1.07(0.8,1.44)
Sample Selection Bias				
IMR	0.95(0.75,1.21)	1.13(0.87,1.45)	1.12(0.9,1.39)	1.12(0.87,1.44)

Note: Results shown in Table 3.6 are controlling for widowhood and jointly modeled with mortality trajectories.

Table 3.7. Effects of Early Life Conditions and Fertility on Comorbidity Trajectory Group Membership versus Robust Group (15.7%): Men Ages 66 – 74 in 1992

	Slow Initiates 16.4%	Accelerated Initiates 15.3%	Chronic Low 18.5%	Ailing 26.1%	Frail 8%
Early Life Conditions					
	Odd Ratio (95% CI)				
Age in 1992	1.4(1.01,1.94)	1.64(1.2,2.23)	2.33(1.73,3.15)	3.14(2.39,4.12)	3.41(2.36,4.91)
Active Member of LDS Church	0.76(0.59,0.98)	0.55(0.44,0.7)	0.82(0.65,1.03)	0.48(0.39,0.59)	0.4(0.31,0.52)
Inactive Member of LDS Church	0.66(0.5,0.86)	0.7(0.55,0.91)	0.75(0.58,0.97)	0.59(0.47,0.74)	0.45(0.34,0.6)
Non-Member (reference)	1	1	1	1	1
Father's NP SES (unit=10)	0.98(0.94,1.02)	1.01(0.97,1.05)	0.99(0.95,1.03)	1.02(0.98,1.05)	1.02(0.97,1.07)
Father Farmer	0.99(0.81,1.2)	1.05(0.87,1.27)	0.9(0.75,1.07)	1.13(0.96,1.33)	1.06(0.84,1.32)
Missing SES	1.05(0.85,1.3)	1.1(0.9,1.35)	0.96(0.79,1.18)	1.05(0.88,1.26)	1.14(0.9,1.44)
FEL in Bottom Quartile	1.2(0.96,1.49)	1.19(0.97,1.47)	1.28(1.05,1.57)	1.37(1.14,1.64)	1.3(1.03,1.65)
FEL in Mid 50% (reference)	1	1	1	1	1
FEL in Top Quartile	0.73(0.6,0.88)	0.71(0.59,0.86)	0.68(0.57,0.82)	0.66(0.56,0.78)	0.6(0.48,0.76)
FEL Missing	0.86(0.63,1.17)	0.88(0.65,1.18)	0.87(0.65,1.17)	0.55(0.42,0.72)	0.5(0.35,0.71)
Orphaned before Age 18	0.27(0.09,0.79)	0.57(0.24,1.34)	0.58(0.25,1.35)	0.72(0.37,1.41)	0.73(0.29,1.84)
Mother Died before Child 18	1.21(0.86,1.7)	1.18(0.85,1.64)	1.14(0.82,1.58)	1.21(0.9,1.62)	1.12(0.76,1.65)
Father Died before Child 18	1.14(0.85,1.54)	1.17(0.88,1.55)	1.08(0.82,1.43)	1.25(0.97,1.6)	1.07(0.77,1.5)
Both Parents Alive at 18 (reference)	1	1	1	1	1
Fertility					
1-2 Children	1.04(0.82,1.3)	1.17(0.94,1.46)	1.14(0.92,1.41)	1.01(0.83,1.23)	1.25(0.96,1.61)
3-5 Children (reference)	1	1	1	1	1
6-8 Children	0.84(0.65,1.08)	1.04(0.82,1.32)	0.91(0.72,1.15)	0.91(0.74,1.13)	1.19(0.9,1.58)
9+ Children	0.63(0.37,1.08)	0.87(0.53,1.42)	0.63(0.37,1.05)	0.71(0.45,1.1)	0.77(0.41,1.47)
Age at First Birth <25 (ref)	1	1	1	1	1
Age at first Birth >= 25	0.88(0.74,1.05)	0.79(0.66,0.93)	0.78(0.66,0.92)	0.74(0.63,0.86)	0.78(0.63,0.95)
Age at Last Birth 35 - 39	0.99(0.8,1.23)	1.15(0.93,1.42)	0.98(0.8,1.2)	1.02(0.85,1.22)	1.12(0.88,1.43)
Age at Last Birth >= 40	1.04(0.79,1.37)	1.21(0.93,1.57)	0.88(0.68,1.14)	1.09(0.87,1.38)	0.94(0.69,1.29)
Father of Twins	0.94(0.64,1.4)	0.95(0.65,1.39)	1.2(0.85,1.71)	1.01(0.72,1.4)	1.13(0.73,1.75)
One or More Short Birth Intervals	1.11(0.92,1.33)	0.94(0.78,1.13)	1.17(0.98,1.4)	1.01(0.86,1.18)	1.13(0.91,1.41)
One or More Long Birth Intervals	1.08(0.9,1.29)	0.98(0.82,1.17)	1.17(0.98,1.39)	0.97(0.83,1.13)	1.06(0.86,1.31)
One or More Infant Deaths	0.83(0.59,1.18)	1.07(0.78,1.47)	0.83(0.6,1.14)	0.85(0.64,1.14)	0.85(0.57,1.25)
Sample Selection Bias					
IMR	0.89(0.7,1.14)	0.9(0.71,1.13)	0.91(0.73,1.13)	1.06(0.87,1.29)	0.98(0.75,1.28)

Note: Results shown in Table 3.7 are controlling for widowhood and jointly modeled with mortality trajectories.

Table 3.8. Effects of Early Life Conditions and Fertility on Comorbidity Trajectory Group Membership versus Robust Group (14.7%): Men Ages 75 – 84 in 1992

	Initiates 17.4%	Ailing 35.3%	Chronic Low 20.2%	Frail 12.5%
Early Life Conditions				
	Odd Ratio (95% CI)			
Age in 1992	1.6(1.09,2.34)	2.24(1.65,3.05)	2.12(1.5,3)	2.82(1.94,4.1)
Active Member of LDS Church	0.81(0.6,1.07)	0.78(0.62,1)	0.8(0.61,1.05)	0.72(0.53,0.96)
Inactive Member of LDS Church	1.01(0.73,1.4)	0.98(0.75,1.28)	0.97(0.71,1.31)	0.97(0.7,1.34)
Non-Member (reference)	1	1	1	1
Father's NP SES (unit=10)	1(0.94,1.06)	1(0.95,1.04)	1.01(0.95,1.06)	0.96(0.9,1.02)
Father Farmer	0.95(0.75,1.21)	0.94(0.77,1.14)	0.95(0.76,1.19)	1.09(0.85,1.38)
Missing SES	1.06(0.81,1.38)	0.85(0.68,1.06)	0.9(0.7,1.16)	0.98(0.74,1.29)
FEL in Bottom Quartile	1.38(1.06,1.81)	1.7(1.36,2.13)	1.28(0.99,1.66)	1.89(1.46,2.46)
FEL in Mid 50% (reference)	1	1	1	1
FEL in Top Quartile	0.8(0.63,1.01)	0.77(0.64,0.94)	0.91(0.73,1.14)	0.67(0.52,0.87)
FEL Missing	0.71(0.45,1.11)	0.76(0.53,1.1)	0.99(0.66,1.49)	0.84(0.53,1.33)
Orphaned before Age 18	1.16(0.34,3.94)	1.28(0.5,3.24)	0.67(0.18,2.45)	0.43(0.1,1.84)
Mother Died before Child 18	1.14(0.78,1.68)	1.36(0.99,1.87)	1.11(0.77,1.61)	1(0.66,1.51)
Father Died before Child 18	1.01(0.73,1.39)	0.97(0.75,1.27)	0.79(0.57,1.09)	1(0.72,1.39)
Both Parents Alive at 18 (reference)	1	1	1	1
Fertility				
1-2 Children	1.01(0.76,1.34)	0.95(0.75,1.2)	1.07(0.82,1.39)	0.97(0.73,1.29)
3-5 Children (reference)	1	1	1	1
6-8 Children	0.81(0.59,1.12)	1.14(0.88,1.47)	0.89(0.66,1.19)	0.77(0.55,1.07)
9+ Children	0.82(0.43,1.57)	0.81(0.47,1.4)	0.76(0.41,1.4)	0.61(0.31,1.2)
Age at First Birth <25 (ref)	1	1	1	1
Age at first Birth >= 25	0.97(0.77,1.23)	0.82(0.68,1)	0.86(0.69,1.07)	0.71(0.56,0.9)
Age at Last Birth 35 - 39	0.96(0.72,1.28)	0.85(0.67,1.08)	0.79(0.6,1.04)	0.73(0.54,0.98)
Age at Last Birth >= 40	0.94(0.67,1.31)	0.74(0.56,0.97)	0.94(0.69,1.28)	0.81(0.58,1.12)
Father of Twins	0.86(0.54,1.37)	0.71(0.48,1.05)	1.25(0.84,1.86)	1.12(0.71,1.74)
One or More Short Birth Intervals	1.16(0.9,1.51)	0.92(0.74,1.14)	0.98(0.76,1.25)	1.15(0.88,1.49)
One or More Long Birth Intervals	1.11(0.88,1.39)	1.05(0.87,1.26)	1.12(0.9,1.38)	1.1(0.87,1.39)
One or More Infant Deaths	1.03(0.69,1.55)	1.27(0.92,1.76)	1.01(0.69,1.49)	0.96(0.64,1.46)
Sample Selection Bias				
IMR	1.21(0.89,1.64)	1.38(1.07,1.78)	1.15(0.86,1.54)	0.98(0.71,1.36)

Note: Results shown in Table 3.8 are controlling for widowhood and jointly modeled with mortality trajectories.

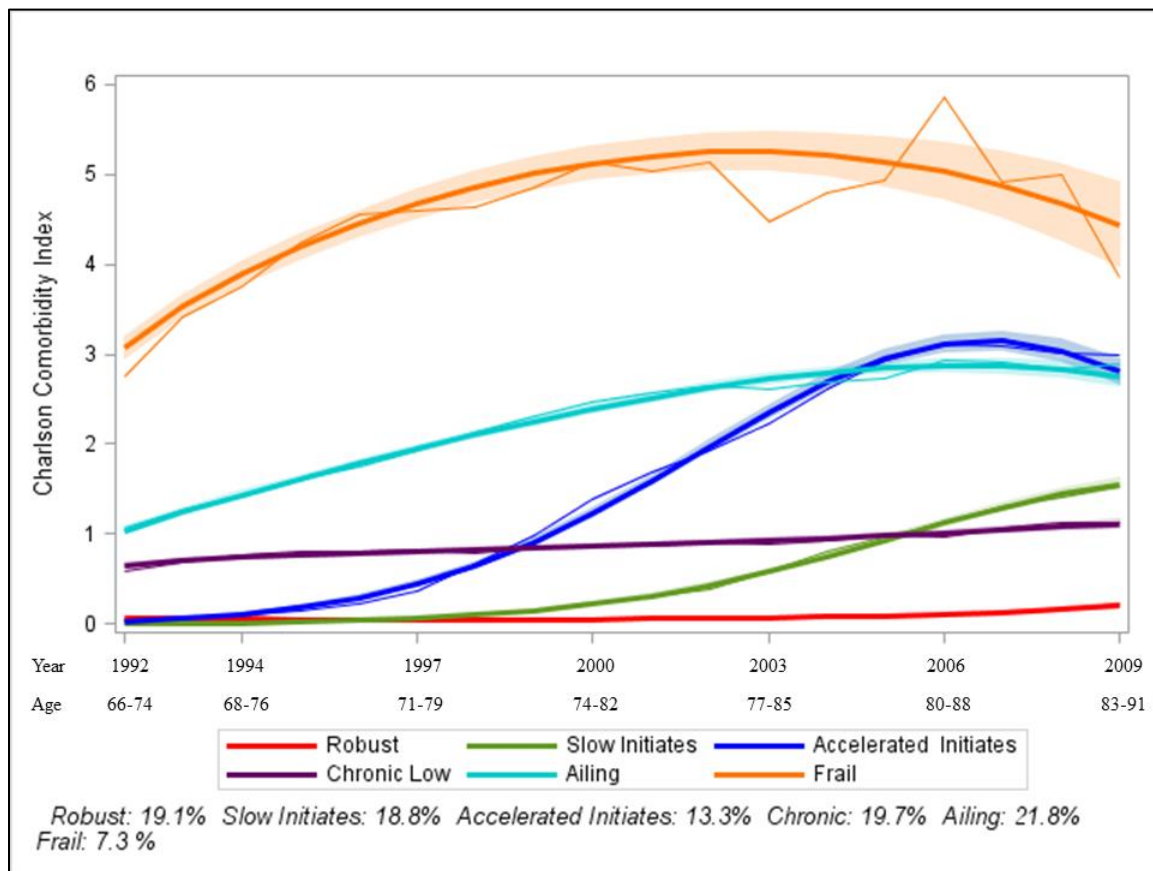


Figure 3.1. Comorbidity trajectories for females ages 66 – 74 in 1992.

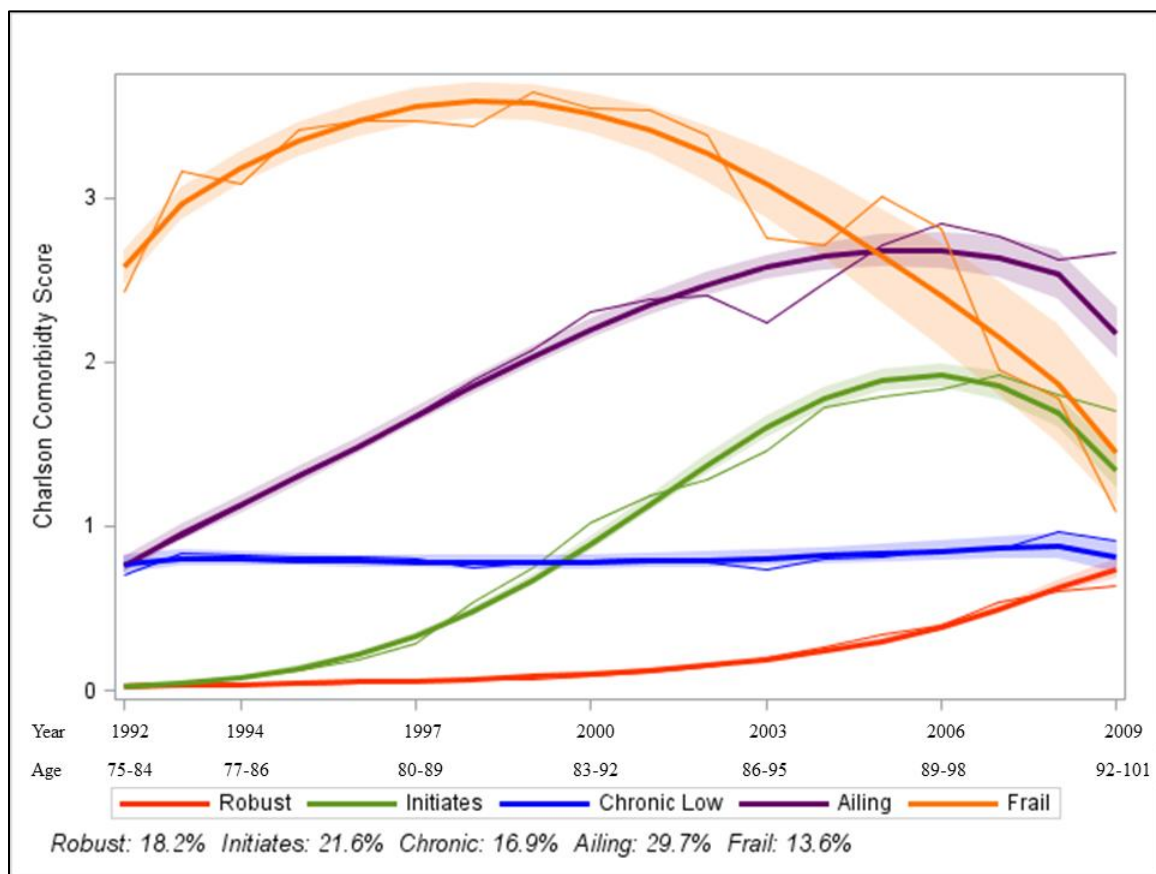


Figure 3.2. Comorbidity trajectories for females ages 75 – 84 in 1992.

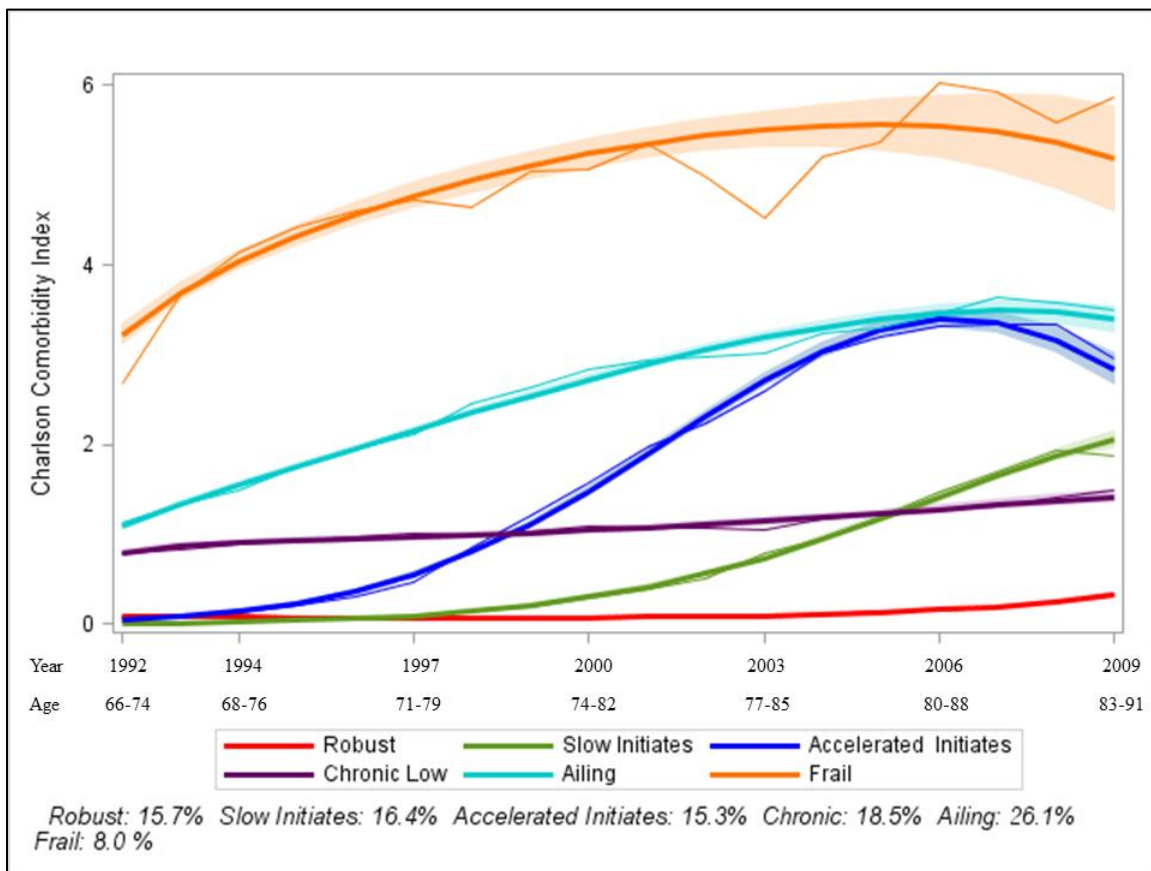


Figure 3.3. Comorbidity trajectories for males ages 66 – 74 in 1992.

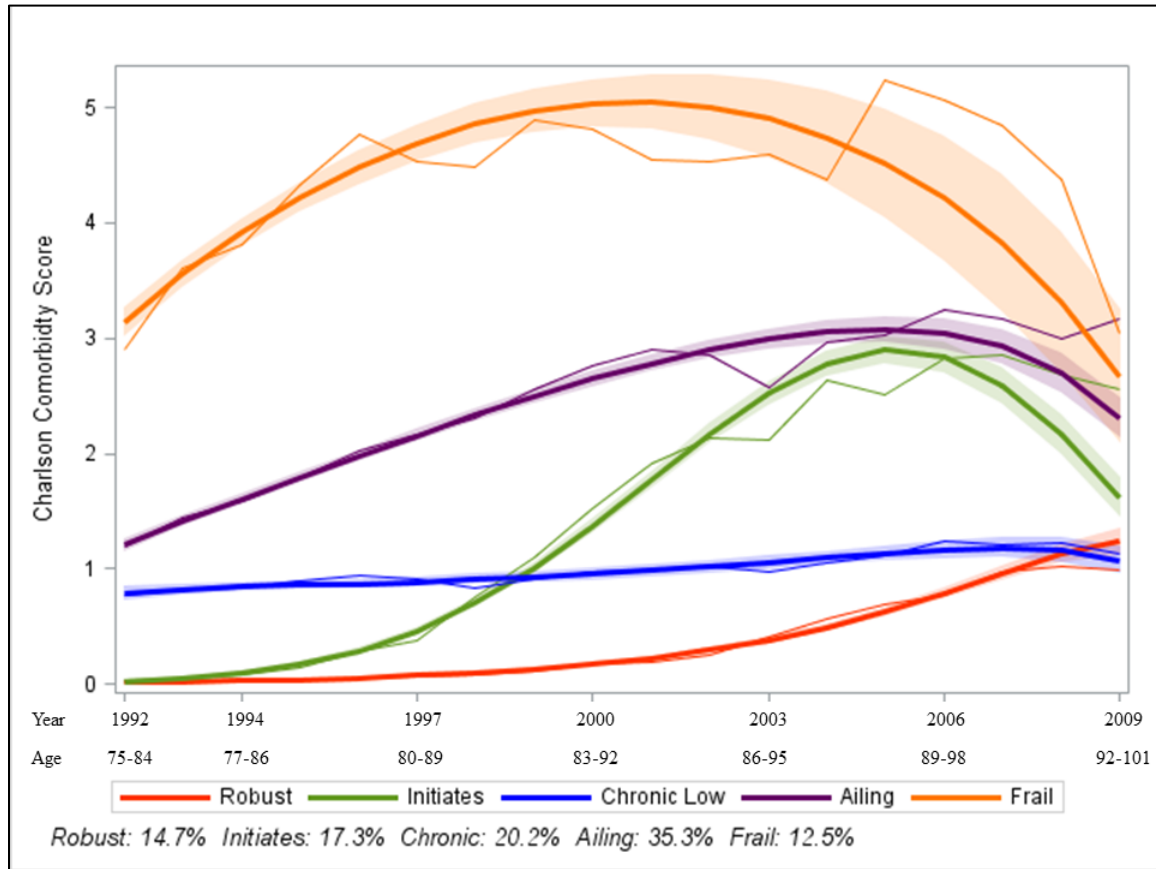


Figure 3.4. Comorbidity trajectories for males ages 75 – 84 in 1992.

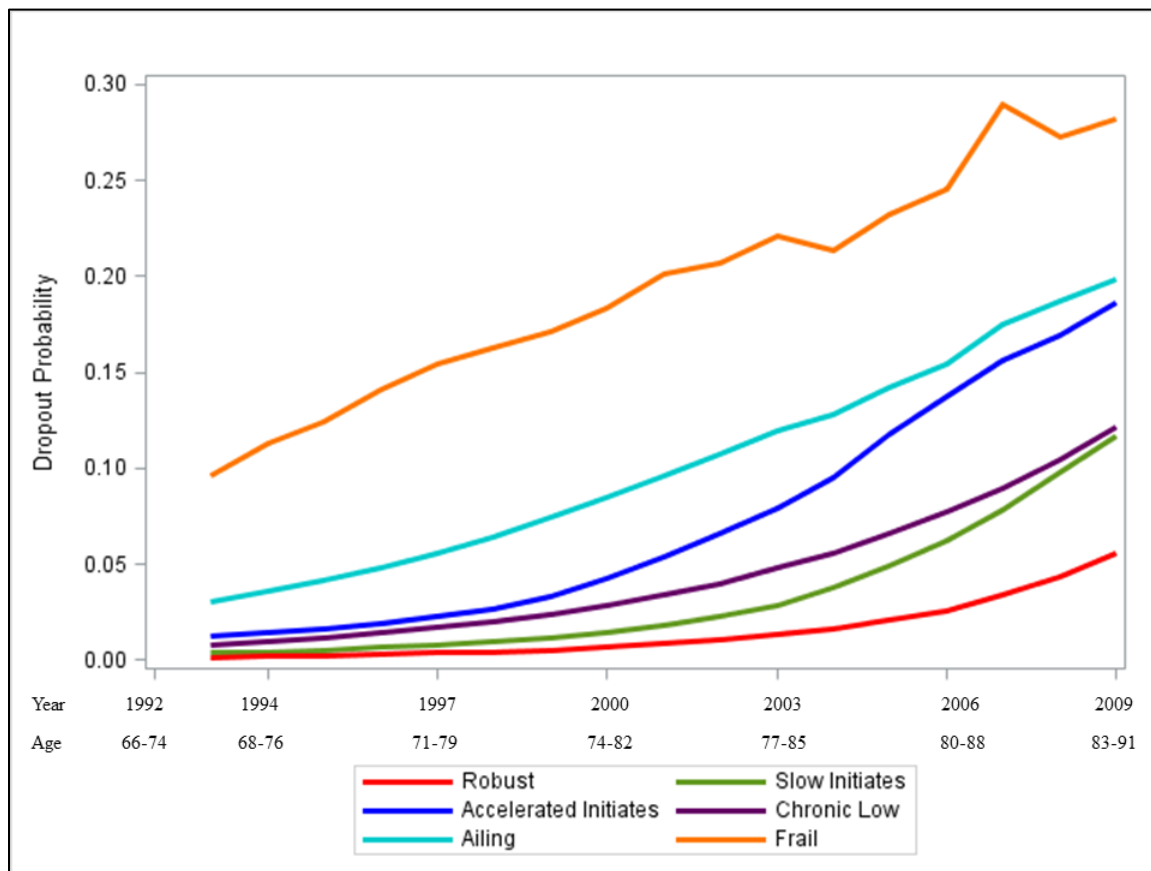


Figure 3.5. Morbidity trajectories for females ages 66 – 74 in 1992.

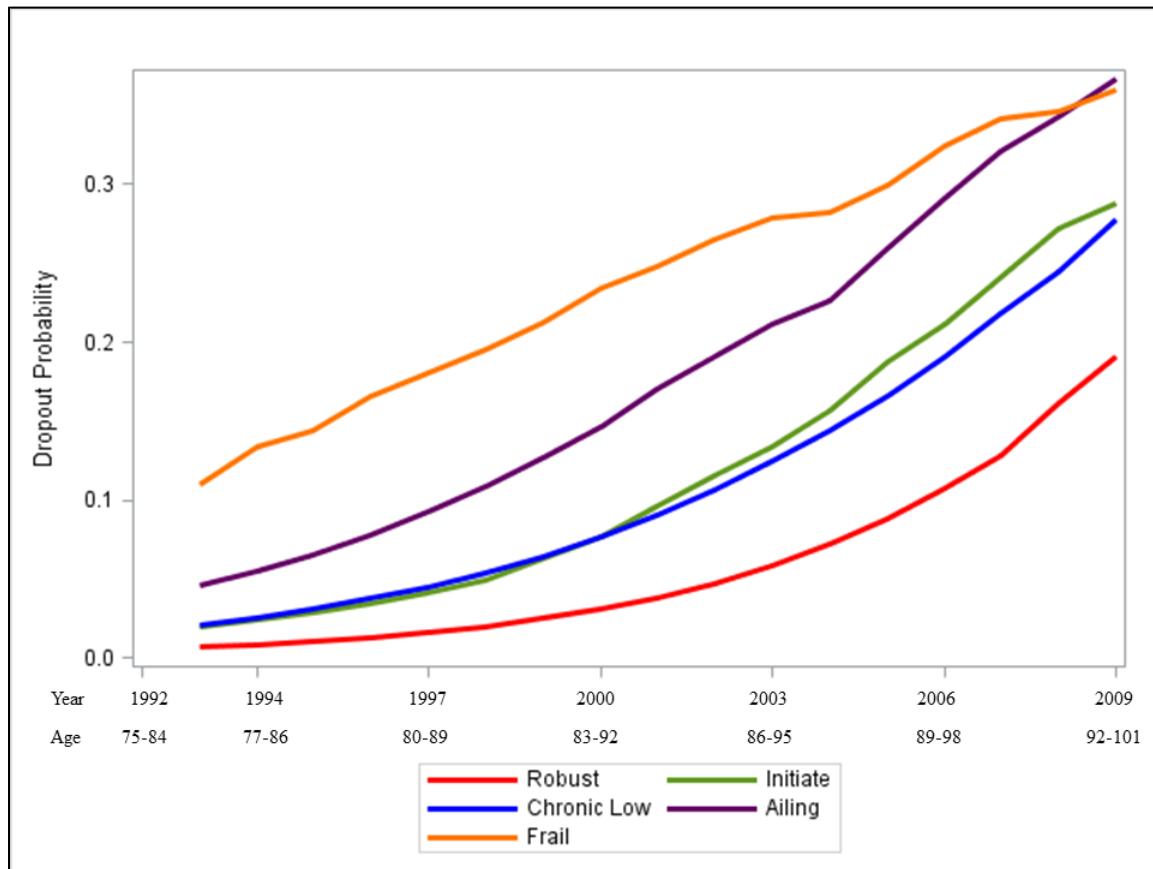


Figure 3.6. Morbidity trajectories for females ages 75 – 84 in 1992.

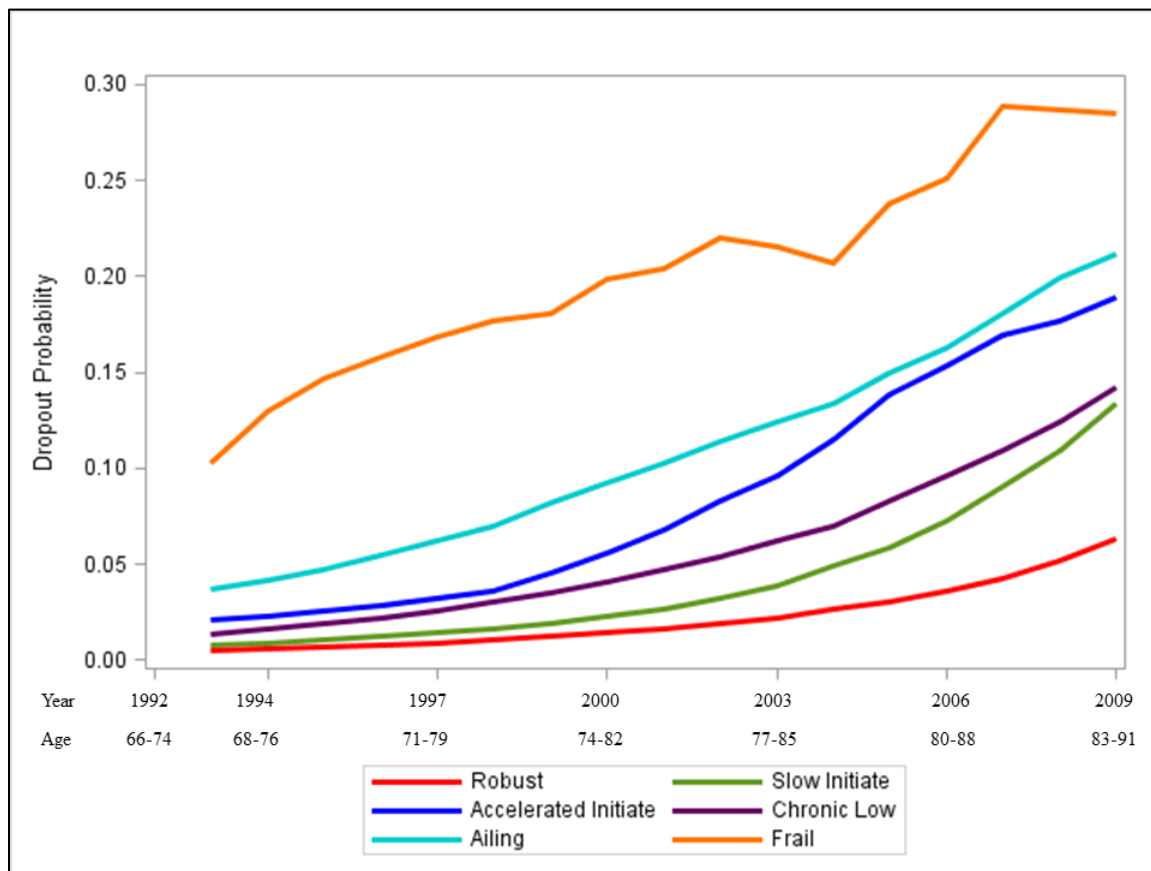


Figure 3.7. Morbidity trajectories for males ages 66 – 74 in 1992.

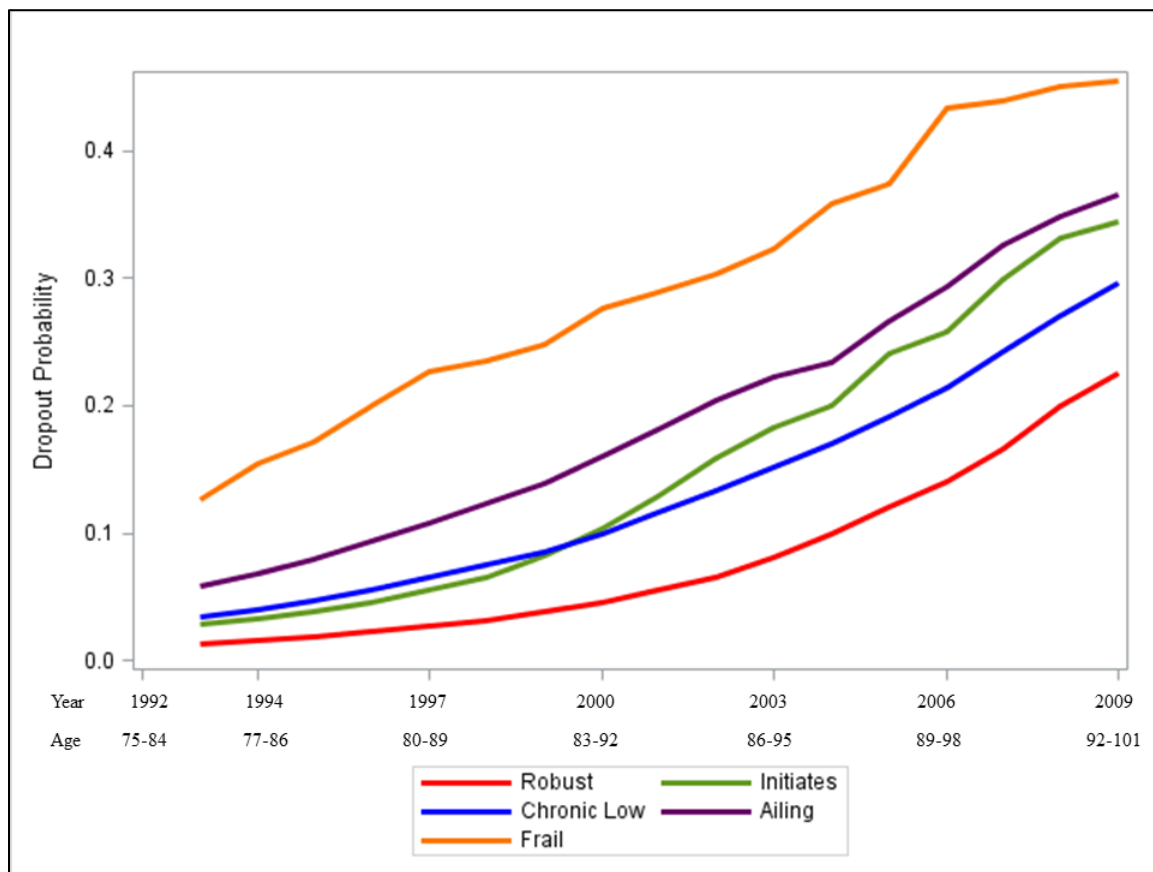


Figure 3.8. Morbidity trajectories for males ages 75 – 84 in 1992.

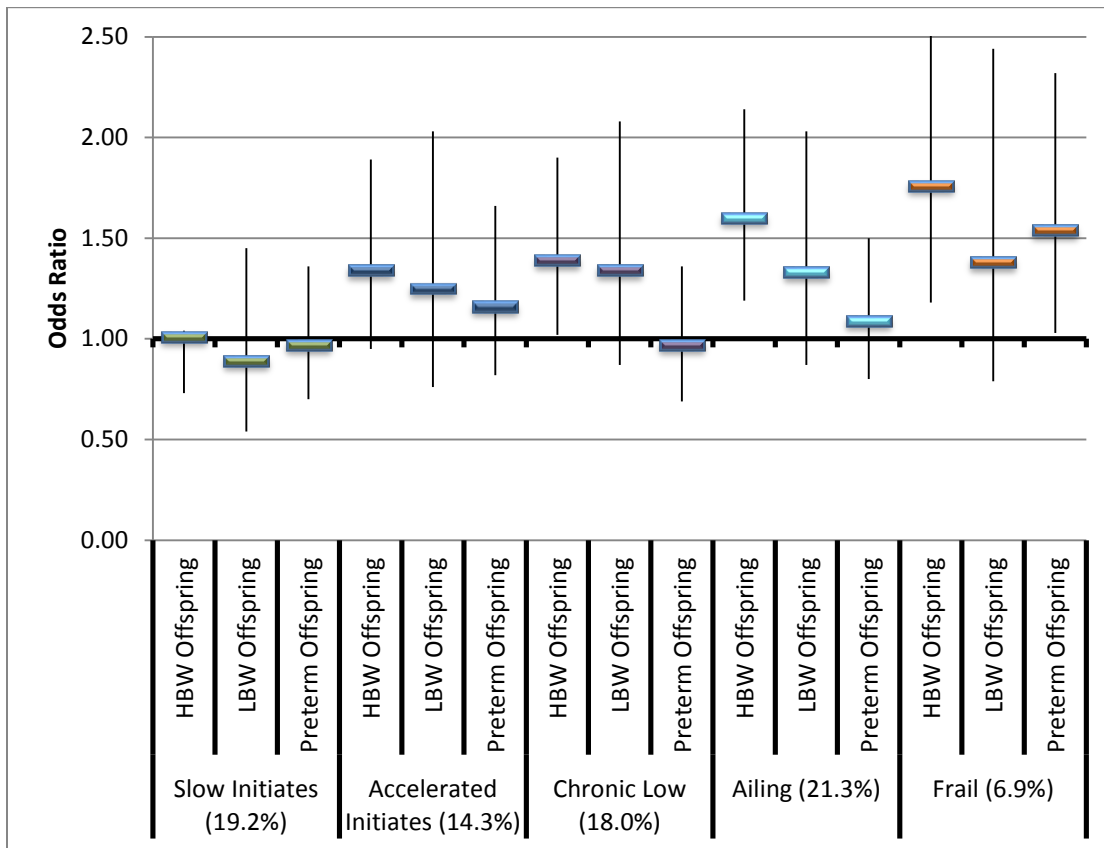


Figure 3.9. Female birth certificate results: Ages 66 – 74 in 1992. Controlling for early-life conditions, fertility variables, demographic characteristics, and jointly modeled with mortality trajectories. Birth certificate sample ($N=4,214$)

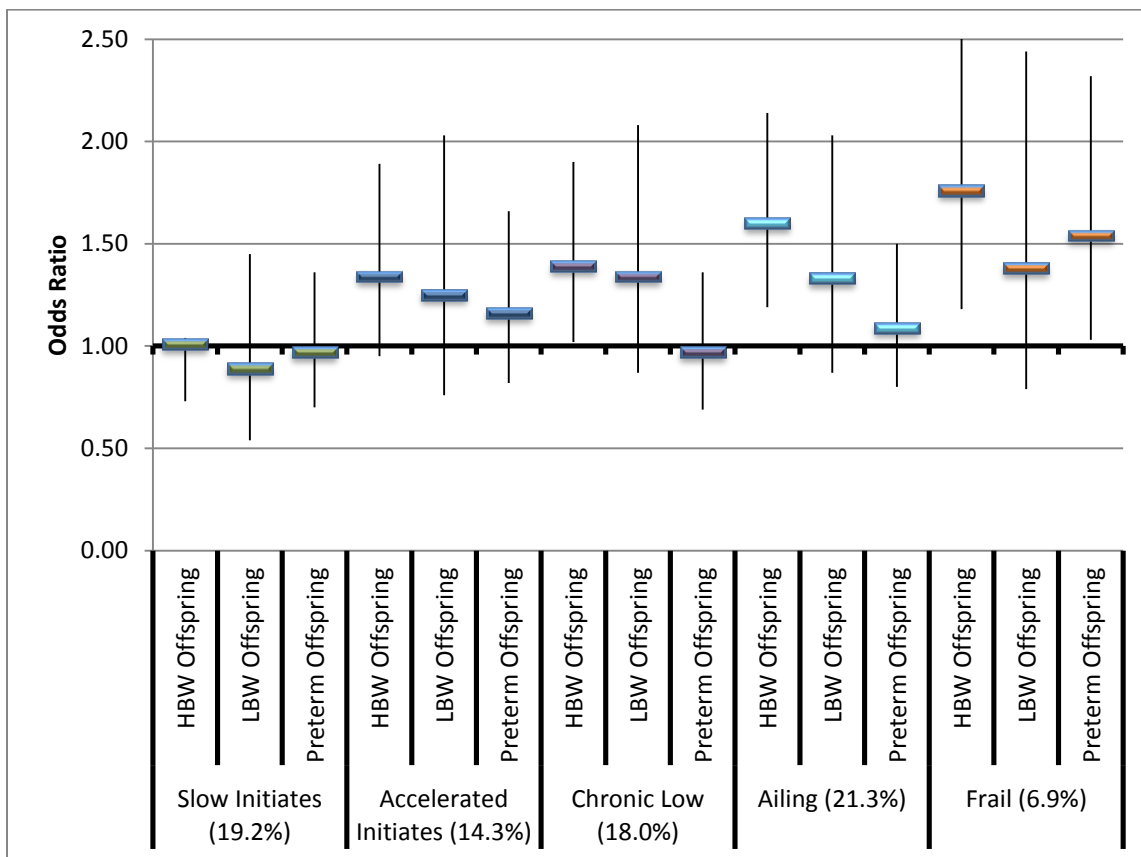


Figure 3.10. Male birth certificate results: Ages 66 – 74 in 1992. Controlling for early-life conditions, fertility variables, demographic characteristics, and jointly modeled with mortality trajectories. Birth certificate sample ($N=6,192$)

CHAPTER 4

HERITABILITY OF LONGEVITY AND THE ROLE OF EARLY AND MIDLIFE ENVIRONMENTS³

Introduction

Mortality is the quintessential measure of the health of a population, and large gains in human life expectancy over the past 150 years are evidence of the important relationship between social context and health. While there is certainly variability in longevity between populations, there is also wide variation in longevity within populations. Understanding the determinants of this heterogeneity is essential to understanding the processes of aging and health of a population. But how much of this variation is determined by genetic factors and how much is determined by the environment? While the question of heritability of longevity is not new, with heritability estimates of longevity ranging from 0 to 0.3 (Kerber, O'Brien, Smith, & Cawthon, 2001), we seek to determine if heritability estimates vary between subpopulations and explore the possibility of gene-environment interactions (GxE). By examining sources of

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variation in heritability estimates, we can illuminate factors that modify the expression of genetic predisposition in a population.

We will investigate heterogeneity in the genetic basis of longevity by assessing the phenotypic correlation between relatives. Variance components and heritability values will be generated using a large genealogical database with information on family structure as well as measures of the broader environment. This study will examine the relationship between social context and the amount of additive genetic variance in adult life-span and exceptional longevity using data from the Utah Population Database (UPDB), a rich source of linked population-based information for demographic, genetic, and epidemiological studies. The sample used in this study consists of 20,120 individuals from 802 three generation pedigrees. This analysis has two goals: 1) estimate the heritability of longevity after age 30 as well as exceptional longevity in a population using methods designed for use in multigenerational pedigree information; 2) test for differences in heritability estimates of life-span in populations stratified by environmental exposure.

Background

Heritability of Longevity

Over the past few decades, demographers have broadened the focus of work in the demography of aging from a population aging perspective (i.e., measures of change in population age structure) to include a perspective that integrates health and biological explanations with traditional demographic and social theories of aging to explain heterogeneity in health and mortality within and between populations (Olshansky, Carnes, & Brody, 2002; Siegel, 2011; Vasunilashorn & Crimmins, 2008). While it is

widely accepted that life-span is determined by a combination of genetic, social and physical environment, and stochastic factors, the interdependent and dynamic role of genes and environment is still not well understood. This may be partially due to fears of genetic determinism within the field of sociology (Shostak & Freese, 2010), the divergent paths of genetics and demography (Adams, 1990), and the difficulty of assessing the role of genes and environment biomarker data.

Longevity is a complex trait, determined by a multiplicity of genetic and environmental factors, each of which contributes to a potentially small amount of phenotypic variation. The genetic variation that is the natural background is a shortened life-span (relative to exceptional longevity) and exceptional longevity is the result of mutations. Genes affecting longevity have been parsed into two categories described as gerontogenes: genes that have a negative effect on longevity and longevity-assurance genes that promote longevity (Christensen, Johnson, & Vaupel, 2006). Findings from the New England Centenarian Study (NECS) have suggested that supercentenarians do not lack gerontogenes, but have longevity assurance genes that can counter the deleterious effects of genes and environment as well as slow the rate of aging and lead to delayed onset of age-related disease (Sebastiani et al., 2012). It is also believed that longevity mutations increase the ability to handle stress and robustness (Christensen et al., 2006). The proportion of variation in life-span due to genes is moderate, which can be illustrated by the fact that there is variation in life-span between monozygotic twins (Herskind et al., 1996).

In summary, longevity is determined by a complex relationship between both genes and environment. For a more complete understanding of population heterogeneity in life-span and the forces behind it, one must not only understand the average

contribution of genes and environment within a population toward explaining variation in adult mortality, but uncover the factors that influence patterns of variation within the population.

At the most basic level, phenotypic variation can be partitioned into additive genetic variance and general environmental variance. Additive genetic variance is the deviation from the average phenotype that is due to the inheritance of a particular allele and that allele's effect on the phenotype. General environmental variance can then be described as the remaining variance that cannot be attributed to genes. The proportion of variation due to inheritance of a particular allele is not fixed across all environments because the relationship between genotype and phenotype may vary by environment, a phenomenon known as phenotypic plasticity. Narrow sense heritability is a population level statistic that describes the amount of total phenotypic variation (V_T) that can be attributed to additive genetic variation (V_A) in the population ($h^2 = V_A/V_T$). The polygenic model can be used to partition variation into genetic and residual environmental effects. Because it is a population level statistic, it is important to keep in mind that it is not a property of individual traits. When h^2 equals zero, it indicates that all phenotypic variation within a population can be explained by individual differences, while an h^2 of 1 indicates that all the phenotypic variation is explained by genetic differences. This is not to say that high heritability suggests little environmental effect on the phenotype. When h^2 is elevated the environment may uniformly contribute to the expression of the trait and therefore contribute little to *differences* between people. It has been shown that heritability of traits can vary across subpopulations (Boardman, 2009; Boardman et al., 2012; Rowe, Almeida, & Jacobson, 1999). But how much of the population heterogeneity in life-span is determined by genetic factors?

There is evidence of the presence of familial clustering of longevity over many generations and across diverse populations, suggesting that there is a genetic or familial component to successful aging and longevity (Christensen et al., 2006; Finch & Tanzi, 1997; Herskind et al., 1996; Kerber et al., 2001; Perls, Kunkel, & Puca, 2002). The longevity literature has described the genetic and environmental contribution to mortality as being divided into one-third and two-third proportions, respectively (C. E. Finch & Tanzi, 1997; Siegel, 2011). It has also been suggested that 50% of the variation in life-span after age 30 can be ascribed to attributes (genetic and nongenetic) that are fixed prior to that age (Yashin & Iachine, 1997), and that genetics plays a stronger role with advancing age (Hjelmborg et al., 2006; Montesanto, Dato, Bellizzi, Rose, & Passarino, 2012; Vaupel et al., 1998; see J. W. Rowe and Kahn (1997) for a dissent from this view). If the proportion of variation in life-span that can be explained by genetic factors varies by age, is it also conditioned by social context? And if so, does this conditioning vary by age?

Conceptualizing the Relationship between Social Environment and Heritability of Longevity

Attempting to understand the genetic component of longevity without considering how it may be modified by specific environmental factors may not be a fruitful approach to gaining insights into the heritability of this complex trait (Petronis, 2010). The heritability of certain phenotypes may vary throughout the life course (Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003) and by gender (Visscher, Hill, & Wray, 2008). Given that humans are constantly interacting with the environment and the environment has the ability to alter gene expression, we must also understand how

environmental influences might modify the heritability of longevity. Accordingly, in this analysis, comparisons of heritability will be made between three subgroups of the population based on: 1) religious involvement; 2) early disease and nutritional environment; and 3) family environment during childhood.

This study assumes that the same genes affect longevity across environments within a population, but certain attributes of the environment serve to moderate the effect of genes on phenotypic variation. Shanahan and Hofer (2005) have presented a framework for gene and social context interactions that has been used to explain the relationship between the social environment and health behaviors (Boardman, 2009; Boardman et al., 2012). We present a slightly modified version that also utilizes concepts presented by Hoffmann and Merilä (1999) as well as new modifications to help formulate our hypotheses.

Under Shanahan and Hofer's framework for gene-environment (GxE) interactions, the environment is conceptualized as social context (Shanahan & Hofer, 2005). Four perspectives, described in detail below, can be used to depict how the social environment might affect heritable variation: triggering, compensation, social control, and enhancement. Figures 4.1 – 4.4 show a modified version of a schema presented by Sebastiani et al. (2012) describing the genetic components of aging. Sebastiani et al. have hypothesized that individuals living to exceptional ages have gerontogenes, but the longevity assurance genes counter the deleterious effects of genetic and environmental factors. Figure 4.1 shows the proportion of total phenotypic variance (V_T) that is attributable to additive genetic variance (V_A) and environmental variance (V_E), where the phenotype is longevity after age 30. We show that in a normal environment where there is no GxE interaction (panel A), individuals with shorter life-spans have higher

heritability of gerontogenes and individuals with exceptional life-spans have higher heritability of longevity assurance genes.

A triggering effect refers to an environment that interacts with personal predispositions to a diseased state and shortened life-span through, for example, environmental stressors or other factors that induce a biological change. Figure 4.2 shows the hypothesized triggering GxE interaction in which an adverse environment directly affects the phenotype. When triggering mechanisms are responsible for environmental differences in heritability, we expect to see a decrease in average longevity in adverse environments and an increase in additive genetic variance. This is because the environment leads to phenotypic expression that would otherwise be dormant. This relationship may change with exceptional longevity because selection mechanisms may change the heritability of a trait over time. If the genetically frail individuals are selected out of this population at an earlier age, the surviving population may be comprised of more robust individuals with a genetic predisposition for exceptional longevity (i.e., longevity assurance genes; Hawkes, Smith, & Blevins, 2012), leading to higher levels of heritability of exceptional longevity in environments detrimental to health. Therefore, under this formulation, we expect that individuals exposed to an unhealthy environment during childhood will have higher heritability of longevity, but a shorter life-span compared to those living in more advantageous circumstances. This may also translate into higher heritability of exceptional longevity in unhealthy environments because only the robust in an unhealthy environment survive to exceptional ages.

The second type of GxE interaction is compensation. According to this perspective, in normal and adverse environments the predisposition to a diseased state

and shortened life-span is realized but not in enriched settings. The expected change in additive genetic variance in an enriched environment is presented in Figure 4.3. The compensation GxE perspective assumes that the continuous exposure to a healthy environment prevents the expression of a genetic diathesis that predisposes an individual to premature death. Unlike the triggering mechanism, the relationship between environment and phenotype is not causal, but due to environmental variation. Therefore, we would expect to see an increase in average life expectancy in an enriched environment with lower additive genetic variance for the longevity phenotype.

Social control is the third GxE model. This interaction is not presented in Figures 4.1 – 4.4 because the expected outcomes are similar to those presented in Figure 4.3. Heritability of longevity may be attenuated in environments with high social control because social norms and structural constraints place limits on choices, and, therefore the environment suppresses phenotypic variance. This is similar to the evolutionary argument of canalization, which argues that selection favors suppression of quantitative traits in constant and structured environments, but the genotype maintains a potential for expressing certain phenotypes under particular environmental conditions (Hoffmann & Merilä, 1999). Thus, involvement with a religious institution that maintains strong social norms for health related behaviors such as alcohol consumption, smoking, social support, and dietary restrictions may lead to increased longevity and exceptional longevity for all members of the group and suppress genetic predispositions for disease. In this situation, we expect to see increased longevity and exceptional longevity for active religious participants with lower levels of heritability compared to nonparticipants.

The enhancement model of GxE is presented Figure 4.4. This is similar to the social control mechanism, but rather than suppressing a predisposition to a shortened life-

span, social context can serve to enhance genetic predispositions for longevity.

Individuals in advantaged and organized social settings may be more apt to realize their genetic potential for longevity, while disadvantaged environments lead to unrealized potential. For example, an environment of undernutrition or high levels of exposure to infectious agents may lead to physiological changes that alter an individual's ability to reach their genetic potential (Barker, 1995; Barker et al., 1993; Crimmins & Finch, 2006). Here, we would expect to see mean differences in survival between environments and higher heritability of life-span and exceptional longevity in environments more advantageous for health and longevity.

In this paper, we build on a body of literature that examines the heritability of longevity by comparing heritability of longevity and exceptional longevity between subpopulations exposed to different environments that are known to affect adult mortality risks. Using the GxE perspectives discussed above, we compare the heterogeneity of genetic effects by environment. We expect to see differences in the heritability of longevity between environments characterized as salubrious or unhealthy. The GxE categories of triggering, compensation, and social control predict higher levels of heritability of longevity in environments less beneficial to health, while the enhancement typology predicts increased heritability of longevity in healthy environments. We can make generalizations about what type of GxE interaction leads to the observed patterns, but the exact mechanism is not testable under this formulation. Comparing the components of variance between environments will add to the understanding of the relative importance of both genes and environment in determining longevity.

Methods

Data

The majority of life-span epidemiological studies examine health influences of early and adult life conditions with relatively modest sample sizes, particularly given the complexity of the phenomena and the manifold exposures and outcomes. This study utilizes data drawn from the Utah Population Database (UPDB). The UPDB is one of the world's richest sources of linked population-based information for demographic, genetic, and epidemiological studies. UPDB has supported biodemographic studies as well numerous important epidemiological and genetic studies in large part because of its size, pedigree complexity, and linkages to numerous data sources. In the mid-1970s, over 185,000 three-generation families were identified on Family Group Sheets from the archives at the Utah Family History Library. These families have been linked into multigenerational families and the full UPDB now contains data on nearly 7 million individuals due to longstanding and on-going efforts to add new sources of data and update records as they become available.

Mortality data are fundamental to the study of exceptional longevity. Information on deaths prior to 1904 comes from genealogical records obtained from the Utah Family History Library and linked to other records within the UPDB. All Utah death certificates are available from 1904 to the present. The UPDB also links to the U.S. Social Security Death Index (SSDI) for the years 1936 – 2011. The SSDI records provide information on deaths based on Social Security records regardless of place of death and are linked to the UPDB. The unique combination of genealogy, death certificates, and SSDI data provide wide spatial and temporal coverage for both the fact and date of death.

The sample used to construct measures of longevity comprises all individuals in the UPDB born between 1850 and 1927. We selected 1927 as the maximum birth year to allow us to observe mortality to at least age 85 for the youngest members of the cohort. To minimize variability in survival unrelated to aging and based on other evidence of the fixed attributes related to life-span after age 30 (Yashin & Iachine, 1997), we will model mortality beginning at age 30 (Hawkes et al., 2012). We identified 685,949 individuals who met the criteria listed above. Of those, approximately 9% (n=64,258) were right censored and 91% (N=621,961) had vital status follow-up information from family history group sheets, Utah death certificates, or linked Social Security Death Index (SSDI) information. The gender distribution of the sample was 52.5% male and 47.5% female.

Using individuals from the baseline survival analysis, we selected 111,324 three-generation families. Table 4.1 shows the restrictions imposed at the family level. We attempted to select families with the highest data quality and the most complete information. As a result, 31,322 families were excluded from the analysis because at least one grandparent had no information in the UPDB. All founding pedigree members were required to have a birth year greater than 1850 (Utah was settled in 1847) and all members of the family were required to be born before 1928, which allowed us to observe the youngest members of the cohort to age 84. On average, these families had 4 individuals in the first generation (by definition), 13 individuals in the second generation, and 19 individuals in the third generation (range = 1 to 83). Pedigree size ranged from 7 to 109 members. The final sample consisted of 802 three-generation families with 20,120 members with a calculated longevity measure and information on family of origin. To study exceptional longevity, a nearly deceased cohort is needed. Therefore, individuals

born between 1914 and 1927 were excluded from the exceptional longevity sample, yielding a sample of 14,618 individuals for these analyses.

Measuring Early and Midlife Environments

Both early and midlife conditions will be considered as possible social context that may modify phenotypic expression. To simplify both the measurement and conceptualization of the environment, each environment is treated as a simple dichotomy, comparing salubrious environments to those that are less advantageous to health. We will compare the heritability of longevity by religious participation, infant mortality rate (IMR) in the family of origin, childhood mortality rate (CMR) of the family of origin, and number of siblings. Justifications for each as the basis for deleterious and beneficial environments are described in turn below.

Religious involvement in general is associated with increased life expectancy (Hummer, Rogers, Nam, & Ellison, 1999). It is not surprising that active affiliation with the Church of Jesus Christ of Latter-day Saints (LDS or Mormon) church is also associated with increased life expectancy (Enstrom & Breslow, 2008). Individuals actively affiliated with the LDS church are more likely to abstain from alcohol and tobacco use, fast once a month, and participate in church related social activities (Mineau, Smith, & Bean, 2002). Therefore, affiliation with the LDS church will be treated as a social environment with defined healthy lifestyle norms for men and women. The UPDB contains information on baptism dates from family history records, which were used to classify individuals as followers of the LDS church. Individuals baptized as members of the LDS church before the age of 30 are considered followers of the LDS Church.

Individuals will be parsed into two environments: 1) LDS church involvement; and 2) no LDS church involvement.

Early life health can have long-term consequences on later life health and mortality (Elo & Preston, 1992; Smith, Mineau, Garibotti, & Kerber, 2009). While it is difficult to obtain a measure of early life exposure to disease and other adverse circumstances, we can use mortality outcomes of siblings as a sentinel for early life circumstances. Postneonatal mortality (the first year of life excluding the first 28 days) for our cohorts of study (1850 – 1927) is closely related to viral and bacterial disease, malnutrition, and income (B. K. Finch, 2003; McKeown, 1976; Preston & Haines, 1991). A similar argument has been made for childhood mortality by Crimmins and Finch (2006), who argue that birth cohorts with lower childhood mortality have increased longevity. As such, we use the death of a sibling during the first year of life (IMR in family of origin) or between ages 1 and 5 (CMR in family of origin) as indicators of an adverse childhood environment. Neonatal deaths, deaths within the first 28 days, and stillbirths are not included in our final measure of IMR because these deaths are likely due to endogenous causes and may not represent a family environment marked by disease, an assumption most likely to be true for the years considered here. We consider infant and childhood mortality as distinct environments because it has been suggested that the determinants of infant and childhood mortality decline over time differed during this period (Wolleswinkel-van den Bosch, van Poppel, Looman, & Mackenbach, 2000). Individuals with one or more infant or childhood death in their family of origin (i.e., death of a sibling) were considered to be in an environment of high infant or childhood mortality, respectively.

Sibship size (number of siblings) has been shown to be positively associated with lower educational achievement and unhealthy lifestyle choices (Downey, 1995; Hart & Davey Smith, 2003). Sibship size may also be related to exposure to infectious diseases, with children from large sibships having a greater risk of contracting an infectious disease (Hart & Davey Smith, 2003). However, a strong association between sibship size and adult mortality has not been demonstrated in all studies assessing this relationship (Smith et al., 2009). The definition of large sibship was derived empirically as having 7 or more siblings (75th percentile for the sample).

While sex is inherently a biological trait, sex differences in life expectancy are determined by both social and biological factors (Crimmins & Saito, 2001; Lindahl-Jacobsen et al., 2013; Rieker, Bird, & Lang, 2010). The effects of early life conditions on later life health may differ by sex. Male fetuses have higher mortality rates than female fetuses, a disadvantage that continues throughout the life course (Kraemer, 2000). Earlier studies have found slight differences in the heritability of longevity between males and females, with males having higher heritability than females (Herskind et al., 1996). Accordingly, we test for environmental differences in the heritability of longevity by sex.

Definition of Longevity

The mortality schedule for individuals born between 1850 and 1927 has changed considerably. Longevity, therefore, defined simply as years lived after age 30, is not appropriate because it is not directly comparable across birth cohorts. While much of the improvement in life expectancy seen during this period was due to improvements in infant and child mortality, there were also gains in adult mortality. Cohort life tables for Utah show that individuals born in 1850 and surviving to age 30 could expect to live an

additional 40.5 and 39.5 years for females and males, respectively, compared to 53.1 and 48.5 years of additional life after 30 for individuals born in 1920 (Lindahl-Jacobsen et al., 2013). Therefore, to de-trend the data, we define longevity as the difference between an individual's attained age (y) and the age to which that individual was expected to live (median predicted age of death conditioned on surviving to 30, \hat{y}) according to a model that incorporates two basic determinants of life-span: gender and birth year. Therefore, a longevity score (LS) is simply the difference between these two values, $y - \hat{y}$. The baseline survival models used to determine \hat{y} are described below. This approach is similar to one taken by Kerber et al. (2001) in calculating a measure of familial excess longevity using Utah genealogies.

Previous studies have suggested that the heritability of longevity increases with age (Hjelmborg et al., 2006; Yashin & Iachine, 1997), and may perhaps be the strongest for those surviving to the latest ages (Atzmon et al., 2004; Gudmundsson, Gudbjartsson, Frigge, Gulcher, & Stefánsson, 2000; T. T. Perls, Bubrick, Wager, Vijg, & Kruglyak, 1998). Exceptional longevity can be defined as an exceptionally long life-span compared to other individuals experiencing the same historical influences (birth cohort; Michael Anson et al., 2012). As done in previous studies, we will define the exceptional longevity (EL) phenotype as living to exceptional age, and explore differences in heritability of survival to the 90th and 95th percentile based on the baseline hazard models (Kerber, O'Brien, Boucher, Smith, & Cawthon, 2012).

Constructing Baseline Survival Models

We assume a parametric form for the survival distribution and a generalized class of accelerated failure time (AFT) models, the extended family of generalized gamma

models. Unlike proportional hazard models, AFT models assume that the effect of covariates is multiplicative with respect to survival time. We test the fit of the exponential, Weibull, log-normal, log-logistic, and gamma models. These models were selected because they provide a simple point estimate for duration that generally fits the observed data for adult mortality. While the Gompertz model is appropriate for modeling human mortality between 30 and 85 (Olshansky & Carnes, 1997), this study is concerned with exceptional longevity (past the age of 85) and therefore this model was not considered. The nested structure of the family of generalized gamma models (exponential, Weibull, log-logistic, and gamma) allows for use of the likelihood ratio test to assess model fit. The Akaike information criterion, or AIC, can be used to test the fit of nonnested models. Final models were selected for the construction of the longevity measures based on model fit.

The full sample of 685,949 individuals born between 1850 and 1927 meeting the sample criteria described in the data section above were used to estimate survival time for individuals surviving to age 30. Models were stratified by gender and included two covariates, birth year, and birth year squared. All models showed a significant positive relationship between birth year and survival. The generalized gamma model proved to be the best fit based on likelihood ratio test ($p < 0.001$) and AIC. The shape and scale parameters in the generalized gamma model are also significantly different than “0” and “1,” implying that the fitted distribution is different from the Weibull, log-normal, and exponential models. The change in the predicted 50th and 90th percentile by model and year is displayed in Figure 4.5. Panels A and B show the trend in predicted median and 90th percentile longevity respectively for men and panels C and D display the estimates for women. The exponential model does not fit the data well and therefore the results are

not shown. These figures show that the log-normal and log-logistic models, which provided the worst fit based on the AIC statistic, also predict out of range values for the 90th percentile. Both the Weibull and generalized gamma model provide sensible estimates. Therefore, the generalized gamma model was used to estimate \hat{y} and consequently LS.

LS was defined as the observed, minus the expected, life-span for all deceased individuals. The UPDB contains multiple sources of linked records that can be used to create a last observed date. Therefore, we know that individuals without a death record were alive until their last observed date in UPDB. The observed life-span for individuals born after 1905, not deceased, and with a known follow-up date that exceeded the median predicted survival time for their gender and birth cohort is calculated by subtracting the birth year from the last observed date in UPBD. Therefore, censored individuals that are likely still living were used in the LS analyses and have a positive LS score by definition. To test for biased results created by this specification, we ran sensitivity analysis using the nearly deceased cohort (N=14,618).

Heritability Estimates

Several forms of analysis of variance (ANOVA) are available to measure heritability of a phenotypic trait, such as parent-offspring regressions and sibling analyses. While these models have useful features, they are limited because they do not use information from multigenerational relationships and they require that sample sizes be well-balanced. Unlike other forms of analysis of variance (ANOVA), maximum likelihood (ML) estimators do not place special demands on the design or balance of the data, providing a powerful approach to estimating variance components using large

pedigrees (Lynch & Walsh, 1998) and minimizing the inflation of estimates of additive genetic variance due to shared environments between relatives. To allow for use of information on multigenerational relationships, heritability is estimated with a polygenic model using PAP v. 7.1 (Hasstedt, 2005).

Genotypic variance can be decomposed into additive (V_A), dominance (V_D), and epistatic (V_I). V_D and V_I are, however, extremely difficult to estimate in non-experimental settings (Kruuk, 2004). The polygenic model specifies the expected genetic relationship between relatives as a function of the coefficient of relationship, allowing for the estimation of variation due to genetic and residual environmental effects. The coefficient of relationship is $(1/2)^p$, where p is the degree of relationships (it is also commonly described as two times the probability that two individuals will share a common gene by descent (IBD)). For example, for a parent-child relationship the coefficient of relationship is 0.5, which equals 2×0.25 , where 0.25 is the probability that parent and child share a common allele. The polygenic model allows us to partition the total phenotypic variance (σ_T^2) into the following components:

$$\sigma_T^2 = \sigma_A^2 + \sigma_E^2 \quad (\text{eq. 4.1})$$

where σ_A^2 is the additive genetic variance and σ_E^2 is the residual variance, which includes environmental, dominance, and epistatic effects. These components are used to calculate heritability, with narrow sense heritability (h^2) being defined as the proportion of phenotypic variance, σ_T^2 , that can be attributed to the additive genetic effects, σ_A^2 :

$$h^2 = \sigma_A^2 / \sigma_T^2 \quad (\text{eq. 4.2})$$

The polygenic model is similar to a mixed model with fixed and random effects. The general model in matrix form is:

$$y = X\beta + Zu + e \quad (\text{eq.4.3})$$

where y is a column vector containing the phenotypic values for a trait measured in n individuals; β is a vector of fixed effects; u is a vector of random effects; \mathbf{X} and \mathbf{Z} are known incidence matrices; and e is a column vector of random residual effects. We assume that u follows a multivariate normal (MVN) distribution with mean zero and variance \mathbf{G} , and that e also follows a MVN distribution with mean zero and variance \mathbf{R} . Note that $\mathbf{G} = \sigma_A^2 \mathbf{A}$, where \mathbf{A} is an $n \times n$ matrix of kinship coefficients describing the genetic correlation between all individuals in the sample, and $\mathbf{R} = \sigma_E^2 \mathbf{I}$, where \mathbf{I} is the identity matrix. This general model can be used to estimate the variance components for a single trait (univariate model) and has been extended to allow for joint modeling of multiple traits (bivariate for two traits and multivariate for multiple traits). The univariate model was used to estimate the heritability of LS and exceptional longevity in the population. We then use the multivariate model to estimate h^2 by environment.

The multivariate model provides a means for estimating covariance and, therefore, correlation between traits. Falconer (1952) suggested that traits measured in two environments can be treated as two different traits. This allows comparisons between discrete environments of different types, where the bivariate model defines a trait as being expressed in environment one or two. For example, if individual i is in environment one, they have a value for trait one and are missing trait two. Conversely, if individual j is in environment two, they are missing trait one and have a value for trait two. This approach is more appropriate than stratification, because it allows for the joint estimation of heritability in two subpopulations. It is also slightly different than a normal bivariate trait model, which jointly models two phenotypes measured on the same individual because no individual expresses a trait in both environments. In this approach,

k traits (in our case $k=2$) are combined to form a vector $Z = \begin{bmatrix} y_1 \\ y_2 \end{bmatrix} = (y_{11}, \dots, y_{1n}, \dots, y_{2n})$

with mean μ_z and variance \mathbf{G} . The model in matrix notation is,

$$\mu_z = \begin{bmatrix} X_1 & 0 \\ 0 & X_2 \end{bmatrix} \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} + \begin{bmatrix} W_1 & 0 \\ 0 & W_2 \end{bmatrix} \begin{bmatrix} a_1 \\ a_2 \end{bmatrix} + \begin{bmatrix} e_1 \\ e_2 \end{bmatrix} \quad (\text{eq. 4.4})$$

where y_1 and y_2 are vectors of phenotypic values in environment one and two, respectively; β_1 and β_2 are the vectors of the fixed effects in environment one and two, respectively; a_1 and a_2 are the vectors of the random additive genetic effects in environment one and two, respectively; e_1 and e_2 are the vectors of random residual effects for environment one and two, respectively; \mathbf{X}_1 and \mathbf{X}_2 are the known incidence matrices relating the observations to the respective fixed effects in environments one and two; and \mathbf{W}_1 and \mathbf{W}_2 relate the observations to the random effects in environments one and two.

The variance-covariance matrix for \mathbf{Z} can be expressed as $\mathbf{V} = \mathbf{G} + \mathbf{R} = \mathbf{C} \otimes \mathbf{A} + \mathbf{E} \otimes \mathbf{I}_n$, where \mathbf{G} is the Kronecker product of \mathbf{C} and \mathbf{A} ($\mathbf{C} \otimes \mathbf{A}$). \mathbf{C} is the $k \times k$ matrix of additive genetic covariances, and \mathbf{E} is the $k \times k$ residual covariance matrix. \mathbf{A} and \mathbf{I} are respectively the $n \times n$ kinship coefficient and identity matrices, with $c_{ij} = \sigma_A(i, j)$ being the additive genetic covariance between characters i and j within an individual and cross-covariance $c_{ij} A_{lm}$ being the additive genetic value of character i in individual l and the additive genetic value of character j in individual m (Lynch & Walsh, 1998, p. 777). In a bivariate analysis, \mathbf{C} is a 2×2 matrix of the form:

$$\mathbf{C} = \begin{bmatrix} \sigma_A^2(1) & \sigma_A(1,2) \\ \sigma_A(1,2) & \sigma_A^2(2) \end{bmatrix} \quad (\text{eq. 4.5})$$

where $\sigma_A^2(1)$ and $\sigma_A^2(2)$ are the additive genetic variances for traits 1 and 2, respectively, and $\sigma_A(1,2)$ is the additive genetic cross covariance.

Defining the environment at the individual level and estimating heritability using the multivariate model without defining the genetic correlation between traits leads to biased estimates of heritability because heritability estimates from an environment only include information about family members in the same environment. To correct for this problem, we assume perfect genetic correlation between the trait values. A bivariate analysis that explicitly models genetic correlations exploits more information content of the data (Amos, de Andrade, & Zhu, 2001). The genetic correlation between traits can be defined as:

$$\rho_{x12} = \frac{\sigma_A(1,2)}{\sqrt{\sigma_{A1}^2 \sigma_{A2}^2}} \quad (\text{eq. 4.6})$$

where $\sigma_A(1,2)$, σ_{A1}^2 , and σ_{A2}^2 are all components of variance mentioned above and $\sigma_A(1,2) = \rho_{x12} \sigma_{A1} \sigma_{A2}$. By constraining ρ_{x12} to 1, we are requiring the covariance between traits to equal the square-root of the product of the variances and forcing the model to include information from both environments. Constraining the genetic correlation to unity allows for heritability and additive genetic variance to vary in both environments, but requires them to be dependent. In a bivariate trait analysis, where both phenotypes are measured for an individual, the genetic correlation is often estimated and used to describe the pleiotropic nature of the traits. However, estimating the genetic correlation across environments would be erroneous in our situation because when $\rho_x < 1$, we are only using partial information from the pedigree because the covariance is weighted by the correlation coefficient ($\rho_{x12} \sigma_{A1} \sigma_{A2}$). Algebraically, this solves the bias problem because it forces the measure of additive genetic variance for each environment to include information about family members from both environments. It is also

conceptually plausible because a genetic correlation of 1 indicates the effect of the same polygenes on the trait in both environments.

LS was Box-Cox transformed and standardized ($\mu=0$, $\sigma=1$) to improve computational performance and abide by distributional assumptions of the variance components models. The transformation was performed using Proc transreg in SAS, which uses a maximum likelihood approach to find the optimal transformation, which in this cases was $\lambda=1.75$. This transformation reduced the skewness coefficient from -0.85 to -0.26. The simple correlation between the transformed variable and the original measure of LS was 0.98.

To test the hypothesis of heterogeneity in heritability, the likelihood ratio statistic was used. Models were estimated, allowing heterogeneity in heritability estimates between environments, and compared to models where the heritability estimates were constrained to be equal across environments. Sex and birth year were not considered as covariates in the model because they were controlled for when creating the measures of longevity.

Results

Descriptive Statistics

Figure 4.6 shows the distribution of LS for the baseline survival cohort and the sample selected for the heritability estimates. Both distributions are slightly skewed with means of -1.2 and -1.7 for the full cohort and the heritability cohort, respectively. The skewed distribution reflects the change in the rate of mortality between ages 30 and the median predicted survival time for an individual's sex and cohort. Cohort life tables for Utah show that the q_x for females at age 30 in the 1900 birth cohort is 0.02, compared to

0.05 at age 60 and 0.29 at age 80 (Lindahl-Jacobsen et al., 2013). Therefore, it is not unexpected to see the long left tail in the LS distribution. The distributional skew is due to a combination of factors including model fit (the fit provides a good approximation of the survival curve, but does not fit the data exactly) and censoring of the youngest cohort.

Table 4.2 shows the descriptive statistics for individuals in the heritability samples. The longevity sample includes all 20,120 individuals with calculated longevity, LS, from the 802 selected pedigrees. Individuals in the exceptional longevity sample were required to be born before 1914 so that we could observe survival in the UPDB to age 99. Approximately 8% of males and females in this sample survive to the 90th percentile for their cohort and sex. This number is slightly smaller than 10% because the cut point for the 90th percentile is derived from the baseline survival models. Forty-eight percent of the sample is female and approximately three-fourths of the sample was affiliated with the LDS church. All members of a family with a sibling that died during infancy or childhood are counted as having an infant death in their family of origin and in historical cohorts. Children from large families experience excess infant and childhood mortality rates (Bean, Mineau, & Anderton, 1990; Knodel & Hermalin, 1984), so this percentage is slightly higher than the 17.4% and 18.5% percent of nuclear families with an infant or childhood death, respectively. There is not a substantial amount of overlap in these measures, with 6.4% of nuclear families having both an infant and childhood death.

Figure 4.7 shows the effect of environment on LS without considering family structure. Significant differences in LS exist in all environments. Panel A shows the distribution of LS by religious status, with individuals not affiliated with the LDS church on average having a 2 point reduction in longevity score ($p < 0.001$). The distribution of LS by infant and childhood mortality in family of origin is displayed in panels B and C,

respectively, with individuals having one or more sibling die during the postneonatal period having a 2 point reduction in LS ($p < 0.001$), and individuals with one or more sibling deaths during childhood having a 1.5 reduction in LS ($p < 0.001$). Panel D shows the distribution of LS by sibship size and illustrates the nearly 2-point reduction of LS for individuals having seven or more siblings.

Heritability Estimates

The overall heritability of LS in the sample is 0.18, which is within the range of previously reported estimates. We find that in the four environments considered when not conditioned on sex, the mean LS is lower in unhealthy environments but there are no significant differences in h^2 . The pattern of heritability of LS by environment is somewhat mixed, with higher heritability of LS in environments with low IMR and CMR, but lower heritability of LS in the other two healthy environments. It is important to note that heritability is a population statistic, thus we are comparing subpopulations defined by an environment and not average individual differences in phenotype. The addition of environment-specific means and variances significantly improve model fit for all environments, with lower means and environmental variances in environments that are considered beneficial to longevity.

To further investigate sex differences in heritability and GxE interactions, we considered models separately by sex. In a bivariate model, considering only sex differences, we find that heritability of LS is significantly lower for females compared to males, $h^2_{LSf} = 0.14$ and $h^2_{LSm} = 0.22$ (LR $\chi^2 = 9.03$, $p = 0.003$), and there is little difference between the mean and environmental variances by gender. The lack of difference in the mean LS is by design. LS was constructed as a gender specific measure (i.e., the baseline

survival models were stratified by sex), and therefore one would not expect to see gender differences in the average LS.

Multivariate models were used to calculate the heritability estimates for LS by environment and sex (results in Table 4.3). When considering the differences in heritability of LS by sex and environment, the mean differences in LS by environment are similar, with lower mean LS in environments considered unhealthy. We find no significant differences in the heritability of LS by environment with the exception of female environments classified by CMR, which show a 9 point difference in h^2_{LS} between the healthful and unhealthy environments. The heritability of LS is lower in female environments with high CMR when compared to female environments with low sibling CMR (LR $\chi^2=5.88$, $p=0.015$). This is in contrast to the higher heritability of LS clustered about a lower mean LS in the male environment with high CMR compared to an environment with low CMR, although these differences are not significant. For females, there is little difference in total phenotypic variance between the two CMR subpopulations (σ_T^2 is approximately 1.30 and 1.29 in high CMR and low CMR subpopulations, respectively). This is supportive of the enhancement hypothesis, which suggests that individuals are unable to realize their genetic potential in adverse environments.

Sensitivity analyses using the nearly deceased cohort ($n=14,618$) were run for the LS models. We found that heritability estimates were slightly smaller (0.17 vs. 0.18 in the larger sample), but the observed differences by gender and environment were all in the same direction. The differences in heritability by CMR environment remained significant.

We considered defining EL as survival to the 90th or 95th percentile conditioned on birth year and sex. The sample for these analyses is smaller than the sample used to obtain estimates of heritability of LS because observing EL requires a nearly extinct cohort ($N_{LS}=20,120$, $N_{EL}= 14,618$). Heritability estimates for the two phenotypes were very similar, with $h^2_{EL}=0.352$ when EL is defined as survival to the 90th percentile (shown in Table 3.4), and $h^2_{EL}=0.345$ (95% CI= 0.244, 0.447) when EL is defined as survival to the 95th percentile (results not shown). The small decline in heritability between the 90th and 95th percentiles suggests that heritability does not increase linearly with age, and that perhaps there is an upper limit to increases in heritability of longevity. However, the differences are negligible and not relevant to the main hypotheses of this paper. Therefore, we show results for survival to the 90th percentile conditioned on age and sex.

Table 4.4 shows the heritability estimates for EL by environment and gender. We find that heritability for EL is nearly twice the heritability of LS (0.18 vs. 0.35). Bivariate models were used to test for environmental differences in the heritability of EL. We find that allowing the prevalence to vary by environment significantly improves model fit, with higher prevalence of EL in healthful environments. We find no difference in heritability of EL by environment when not conditioned on gender. There are also no gender differences in the heritability of EL (LR $\chi^2= 0.552$, $p=0.46$), which differs from the LS findings.

When using the multivariate model to test for environmental differences in heritability of EL by gender and environment, we do not find evidence of significant differences with the exception of the male CMR environment. The heritability of EL is 31 points higher in male environments with high CMR compared to male environments

with low CMR (LR $\chi^2=4.25$, $p=0.04$), and there is no difference in the prevalence of exceptional longevity between environments. This suggests that a triggering GxE interaction may be operating through selection mechanisms, where the frail are selected out of the adverse populations at faster rates and only the genetically robust individuals with longevity assurance genes that are able to thwart the effects of gerontogenes survive to exceptional ages.

Discussion

Our analysis of longevity is based on information from 20,120 individuals from 802 three-generation families used to examine the heritability of longevity, defined as survival after age 30. We also estimated the heritability of exceptional longevity using information from a subset of that sample ($n=14,618$) that is nearly extinct. Our findings support previous studies suggesting a moderate heritable component to longevity that increases with age (Herskind et al., 1996; Hjelmborg et al., 2006; Kerber et al., 2001), although the adult ages at which this assessment is made varies across analyses. We find little difference between the heritability of survival to the 90th and 95th percentiles, suggesting that the increase in proportion of variance due to genetic factors may not be a constant linear increase as suggested by other studies (Hjelmborg et al., 2006). We find that sex differences in the heritability of longevity after age 30 support other studies showing higher heritability of longevity for males (Herskind et al., 1996), but no sex differences in the heritability of exceptional longevity. We investigated the heterogeneity of longevity and exceptional longevity by early and midlife social environments. We find some evidence that the heritability of longevity varies between environments, but

overall there is not strong support of a gene-environment interaction for the selected environments.

We find evidence that childhood environments marked by high child mortality, indicative of exposure to infectious disease and undernutrition for the surviving members, may affect the proportion of phenotypic variation attributable to genetic factors. The sex and age differences of the effects suggest an enhancement GxE interaction because adverse childhood circumstances limit the genetic potential of individuals to survive to older ages. Conceptually, CMR is used to identify environments with excess exposure to infectious disease and undernutrition. For females, genetic factors contribute little to the total variance in longevity in such environments, which suggests that genetic potential is not reached in such environments. While a similar pattern exists for EL, the difference in heritability between environments is not significant.

We see the opposite effect for male environments, although the observed patterns do not necessarily conflict with the female results. Males have a mortality disadvantage relative to females throughout the life course that is partially due to biological factors (Kraemer, 2000). Therefore, they may be more susceptible to environmental conditions that trigger genetic predispositions for disease and lead to higher mortality selection compared to females reared in the same environment. The difference in the direction of the effect for males suggests that the adverse environment may actually trigger genetic diatheses, with higher heritability clustered about a lower mean longevity in deleterious environments, but these differences are not significant. This results in higher heritability of exceptional longevity because individuals surviving to this age have some predisposition or genetic robustness that prevented them from being selected out of the population at earlier ages.

It is interesting that we find heterogeneity in CMR environments, but not in environments characterized by IMR. This may be partially due to differences in specific causes of death for the two groups, as suggested by Wolleswinkel-van den Bosch et al. (2000). We did consider variations of our definition of IMR, which included neonatal deaths, although this did not change the substantive conclusion that heritability of longevity does not vary between subpopulations with different rates of infant mortality.

While we find some evidence of heterogeneity in the heritability of longevity between environments, heritability estimates seem to be fairly impervious to early and midlife circumstances. Herskind et al. (1996) reported stability of heritability estimates over sex and cohort during periods of rapid change in living conditions. However, the birth cohorts selected for that study would still be children during periods with higher childhood mortality (1870 – 1900) than experienced during modern times. Our results suggest that improvements in social and health conditions that have caused declines in childhood mortality may lead to a higher proportion of variability in longevity attributable to genetic factors. More research needs to be done to test for other environmental differences in the heritability of longevity, including socioeconomic status and fertility history.

The nearly twofold increase in heritability of exceptional longevity compared to the heritability of longevity after age 30 suggests that selection mechanisms may affect the heritability of longevity throughout the life course. Individuals without longevity assurance genes may be selected out of the population at early ages, leaving a subset of the population that is made up of a higher proportion of robust individuals. While the heritability of longevity increases with age, exceptional longevity is still only moderately heritable, and the environment explains the largest amount of phenotypic variation. It is

also remarkable that there are gender differences in heritability of longevity after age 30, but not with respect to exceptional survival. This suggests that individuals surviving to exceptional ages have survived mortality selection because they have a genetic variant that increases the ability to handle stress and/or counteract deleterious effects of the environment or gerontogenes. This is further supported by other research suggesting the buffering role of longevity genes (Bergman, Atzmon, Ye, MacCarthy, & Barzilai, 2007; Sebastiani et al., 2012).

Epigenetics is one of several possible biological mechanisms that allow social circumstances to get “under the skin,” and it recently has been suggested that epigenetic changes have the propensity to persist across subsequent generations (Feinberg, 2007). This is a provocative idea that lends support to multigenerational transmission of social disparities. More research needs to be done to uncover the possible mechanisms leading to phenotypic variation across social environments and the possibility of transmitting the adverse effects to subsequent generations. We suggest further study into the possibility of GxE interactions and health and longevity outcomes. While we did not find an association between all environments, there is a suggestion that the social environment may play an important role in modifying the heritability of longevity.

In this paper, we assessed variation in heritability estimates of longevity after age 30. However, other cutoffs, such as postreproductive aging, should also be considered. Further modeling of heterogeneity of variance and the variance of longevity across other environments could be valuable in understanding how the social environment moderates the genetic component to aging. Care should be taken when interpreting polygenic heritability when the genetic correlation has been fixed to unity, because it is assumed that the same genes affect longevity across environments. While we feel this is a valid

assumption for subgroups of a single population, the reader should be aware of this constraint.

To our knowledge, this is the first study using multigenerational pedigree information to investigate heterogeneity in heritability of longevity across multiple early and midlife environments. Studies in other fields have examined heterogeneity in variance components by gender and age using a similar method (Giolo, Pereira, de Andrade, Krieger, & Soler, 2010; Pilia et al., 2006), lending validity to this approach.

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Table 4.1. Pedigree Selection

3 Generation Families from 1850 - 1927 Cohort*		111,324
Exclusions		
Families missing information on at least one grandparent (These people have placeholder genealogy records)	At least one of the grandparents is born before 1850	31,322
	A member of G3 born after 1927	52,780
		26,420
Total Number of 3-Generation Families for Analysis		802

*This is calculated by taking any member of the BC and ascending 3 generations. The result is 111,324 distinct treetops (defined by the unique combination of maternal and paternal grandparents). Families that did not meet our selection criteria were then excluded.

Table 4.2. Descriptive Statistics for Individuals from 802 Utah families

	Longevity (N=20,120)		Exceptional Longevity (N=14,618)	
	Male (N=10,393)	Female (N=9,727)	Male (N=7,532)	Female (N=7,086)
Birth Year	1897 (21.1)	1897 (20.3)	1889 (18.8)	1889 (18.0)
Longevity Score (LS)	-1.7 (15.2)	-1.9 (15.5)	-2.3 (15.4)	-2.7 (16.5)
Survived to the 90th Percentile (EL)			8.4%	8.0%
Survived to the 95th Percentile			4.2%	3.9%
Baptized Latter-Day Saint	72.5%	74.4%	75.6%	77.7%
One or more Postneonatal Infant Deaths in Family of Origin	19.5%	19.7%	23.9%	23.1%
One or more Childhood Deaths in Family of Origin	19.5%	19.9%	23.1%	24.2%
Large number of Siblings	29.6%	29.2%	35.6%	35.6%

Table 4.3. Summary of the Results Obtained for Polygenic Models of LS (N=20,120)

Environment		Male and Female			Male			Female		
		μ (95% CI)	h^2 (95% CI)	$\widehat{\sigma}_e^2$	μ (95% CI)	h^2 (95% CI)	$\widehat{\sigma}_e^2$	μ (95% CI)	h^2 (95% CI)	$\widehat{\sigma}_e^2$
	All	-0.10 (-0.12, -0.08)	0.18 (0.15,0.20)	1.10	-0.09 (-0.12,-0.07)	0.22 (0.18,0.26)	1.10	-0.09 (-0.11,-0.07)	0.14 (0.10,0.17)	1.11
LDS	Not Affiliated with LDS Church	-0.17 (-0.20, -0.14)	0.20 (0.14,0.25)	1.14	-0.21 (-0.25,-0.16)	0.27 (0.18,0.35)	1.15	-0.13 (-0.18,-0.09)	0.14 (0.07,0.21)	1.09
	Affiliated with LDS Church	-0.06 (-0.08, -0.03)	0.16 (0.13,0.19)	1.08	-0.04 (-0.07,-0.02)	0.19 (0.15,0.23)	1.07	-0.07 (-0.10,-0.04)	0.13 (0.09,0.17)	1.09
Infant Mortality Post Neonatal	High Infant Mortality	-0.16 (-0.20, -0.12)	0.16 (0.11,0.22)	1.13	-0.15 (-0.20,-0.10)	0.18 (0.10,0.26)	1.07	-0.17 (-0.23,-0.12)	0.15 (0.07,0.23)	1.19
	Low Infant Mortality	-0.07 (-0.10, -0.05)	0.18 (0.15,0.21)	1.10	-0.08 (-0.11,-0.05)	0.23 (0.19,0.27)	1.11	-0.07 (-0.10,-0.04)	0.13 (0.09,0.17)	1.08
Childhood Mortality	High Childhood Mortality	-0.19 (-0.23, -0.15)	0.15 (0.09,0.20)	1.17	-0.18 (-0.23,-0.13)	0.27 (0.17,0.37)	1.13	-0.20 (-0.25,-0.15)	0.07 (0.01,0.12)	1.21
	Low Childhood Mortality	-0.07 (-0.09, -0.05)	0.19 (0.16,0.22)	1.08	-0.07 (-0.10,-0.05)	0.21 (0.17,0.25)	1.09	-0.07 (-0.09,-0.04)	0.16 (0.12,0.20)	1.08
Sibship Size	Large Sibship	-0.21 (-0.25, -0.18)	0.19 (0.15,0.24)	1.17	-0.19 (-0.23,-0.15)	0.22 (0.16,0.29)	1.09	-0.24 (-0.29,-0.20)	0.16 (0.10,0.22)	1.25
	Small Sibship	-0.05 (-0.07, -0.03)	0.18 (0.15,0.21)	1.07	-0.06 (-0.09,-0.03)	0.22 (0.18,0.27)	1.10	-0.04 (-0.06,-0.01)	0.13 (0.09,0.17)	1.04

Table 4.4. Summary of the Results Obtained for Polygenic Models of EL

		Male and Female		Male		Female	
Environment		Prevalence (95% CI)	h ² (95% CI)	Prevalence (95% CI)	h ² (95% CI)	Prevalence (95% CI)	h ² (95% CI)
All		0.08 (0.08, 0.09)	0.35 (0.28,0.43)	0.08 (0.08,0.09)	0.32 (0.21,0.43)	0.08 (0.07,0.09)	0.39 (0.27,0.51)
LDS	Non LDS	0.07 (0.06, 0.08)	0.43 (0.21,0.65)	0.06 (0.05,0.07)	0.55 (0.21,0.90)	0.07 (0.06,0.09)	0.28 (-0.01,0.58)
	LDS	0.09 (0.08, 0.09)	0.33 (0.25,0.42)	0.09 (0.08,0.10)	0.28 (0.16,0.39)	0.08 (0.07,0.09)	0.40 (0.26,0.55)
Infant Mortality Post Neonatal	High Infant Mortality	0.07 (0.06, 0.08)	0.28 (0.13,0.43)	0.07 (0.06,0.08)	0.28 (0.04,0.51)	0.08 (0.06,0.09)	0.28 (0.05,0.51)
	Low Infant Mortality	0.09 (0.08, 0.09)	0.37 (0.28,0.46)	0.09 (0.08,0.10)	0.32 (0.19,0.45)	0.08 (0.07,0.09)	0.43 (0.28,0.58)
Childhood Mortality	High Childhood Mortality	0.07 (0.06, 0.08)	0.44 (0.27,0.62)	0.08 (0.08,0.09)	0.57 (0.29,0.84)	0.07 (0.06,0.08)	0.33 (0.09,0.57)
	Low Childhood Mortality	0.09 (0.08, 0.09)	0.33 (0.24,0.42)	0.08 (0.08,0.09)	0.26 (0.14,0.38)	0.08 (0.08,0.09)	0.41 (0.27,0.56)
Sibship Size	Large Sibship	0.07 (0.07, 0.08)	0.33 (0.20,0.46)	0.07 (0.06,0.08)	0.30 (0.12,0.47)	0.08 (0.06,0.09)	0.37 (0.18,0.56)
	Small Sibship	0.09 (0.08, 0.09)	0.37 (0.27,0.47)	0.09 (0.08,0.10)	0.35 (0.19,0.50)	0.08 (0.07,0.09)	0.40 (0.23,0.57)

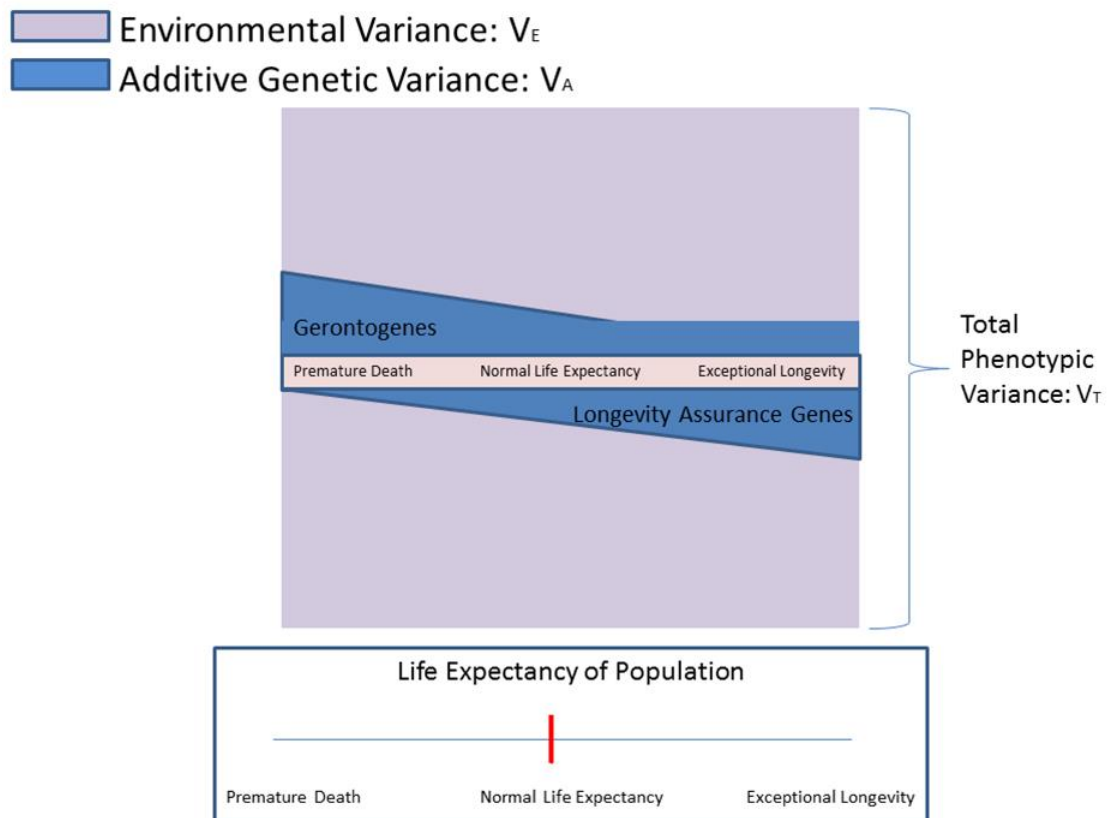


Figure 4.1. Hypotheses for GxE interactions: Expected. The expected phenotypic variation in a normal environment.

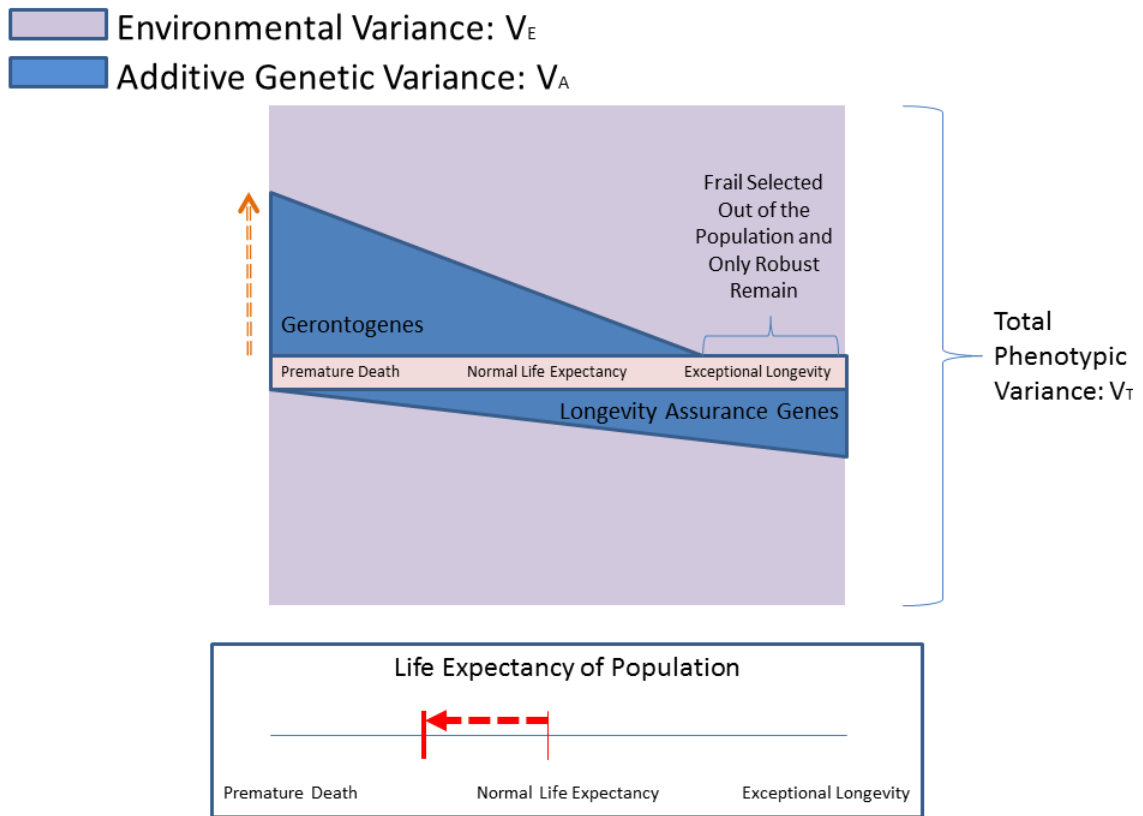


Figure 4.2. Hypotheses for GxE interactions: Triggering. A triggering GxE interaction in an adverse environment.

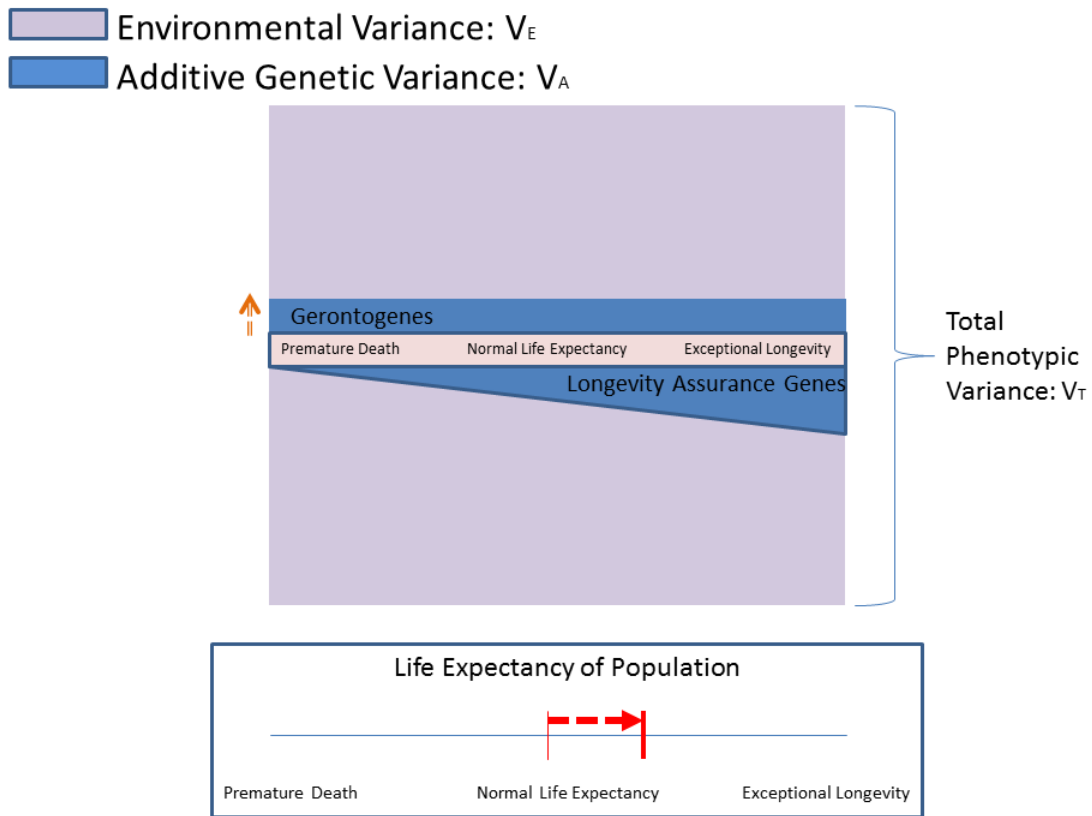


Figure 4.3. Hypotheses for GxE interactions: Compensation. A compensation GxE interaction in an enriched environment.

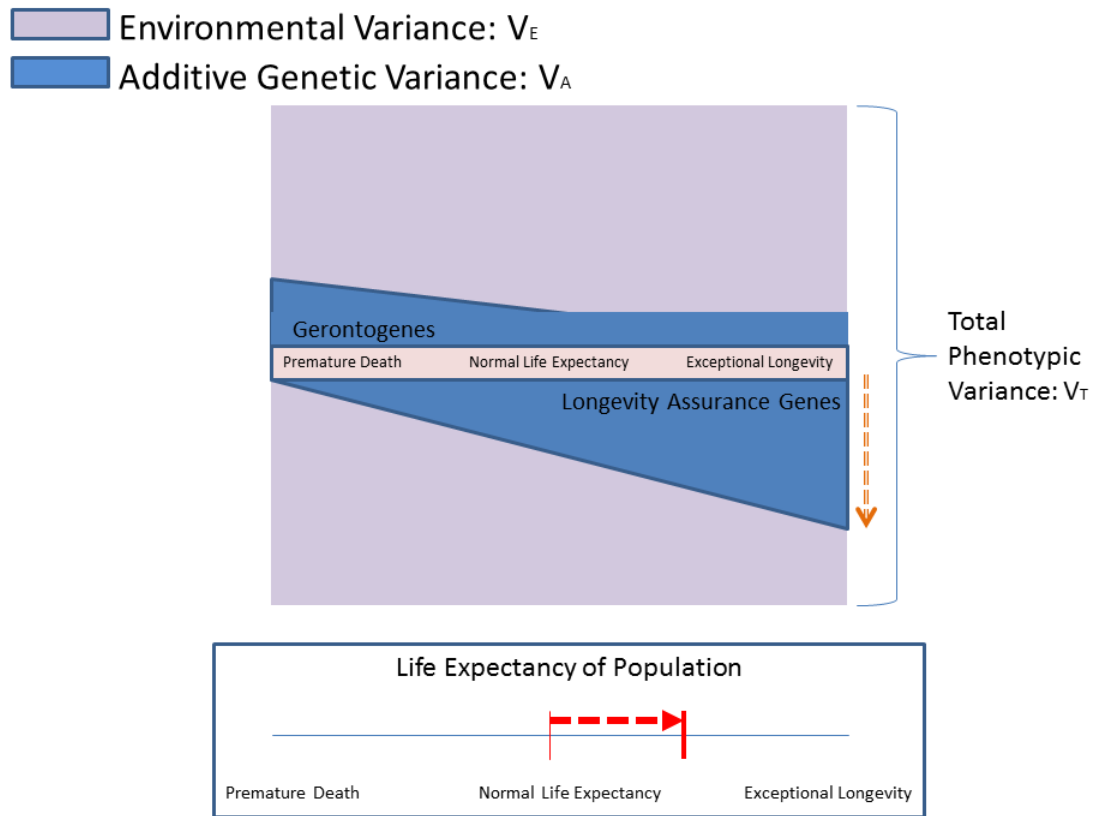


Figure 4.4. Hypotheses for G×E interactions: Enhancement. An enhancement interaction in an enriched environment.

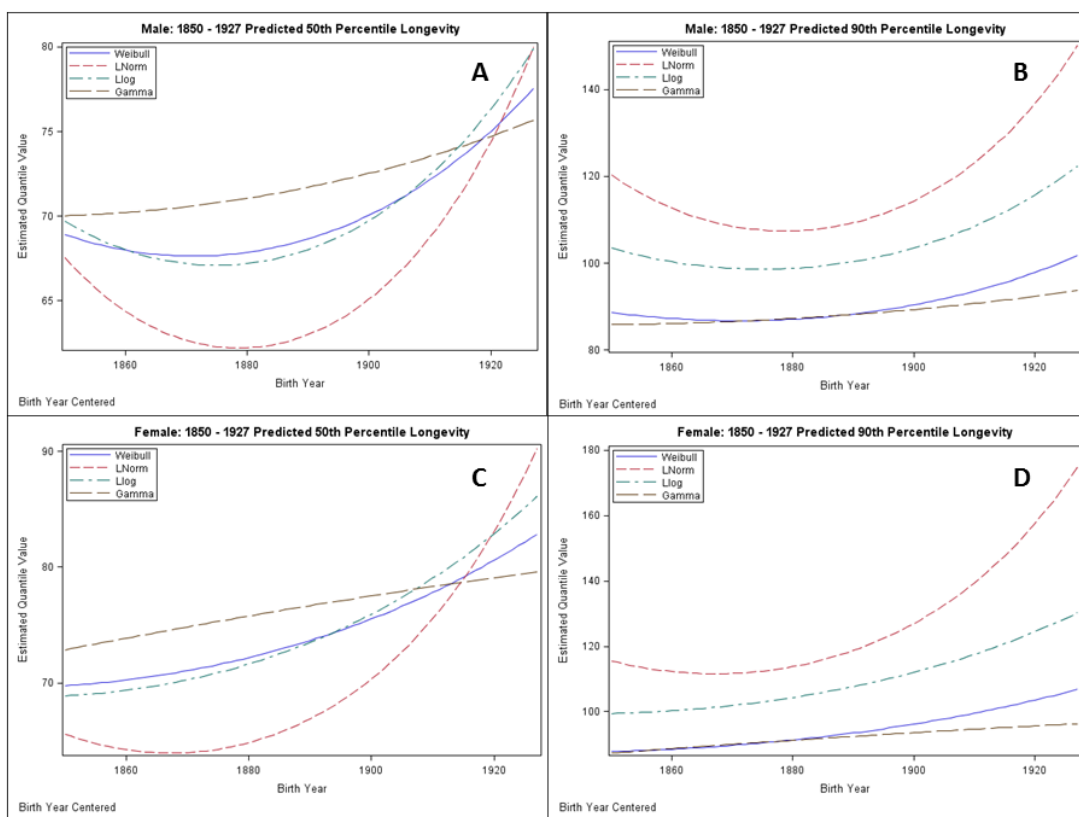


Figure 4.5. Predicted values of survival to the 50th and 90th percentiles by gender and birth year. Panels A and B show the estimates for male 50th and 90th percentile estimates, respectively. Panels C and D show estimates for female 50th and 90th percentiles, respectively.

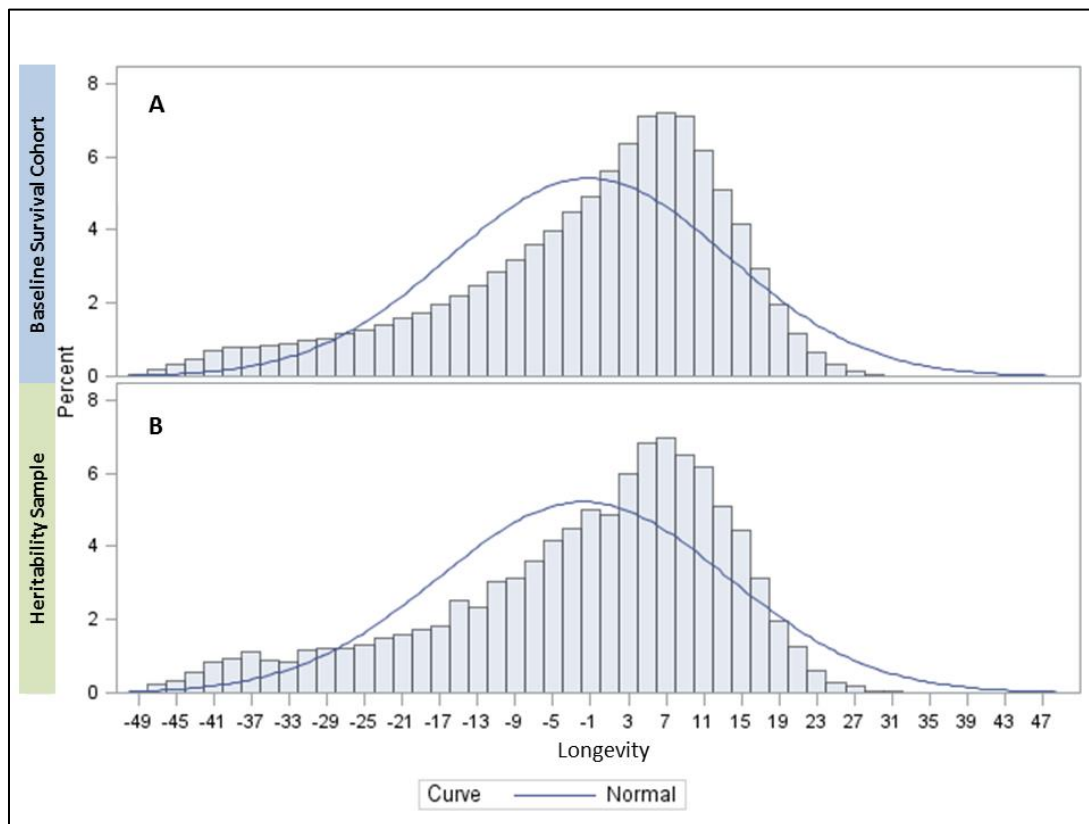


Figure 4.6. Distribution of calculated longevity for individuals born between 1850 and 1927 and surviving to age 30. Panel A shows the distribution for the cohort used in the baseline survival analysis (N=685,949). Panel B shows the distribution for the heritability sample (N=20,120).

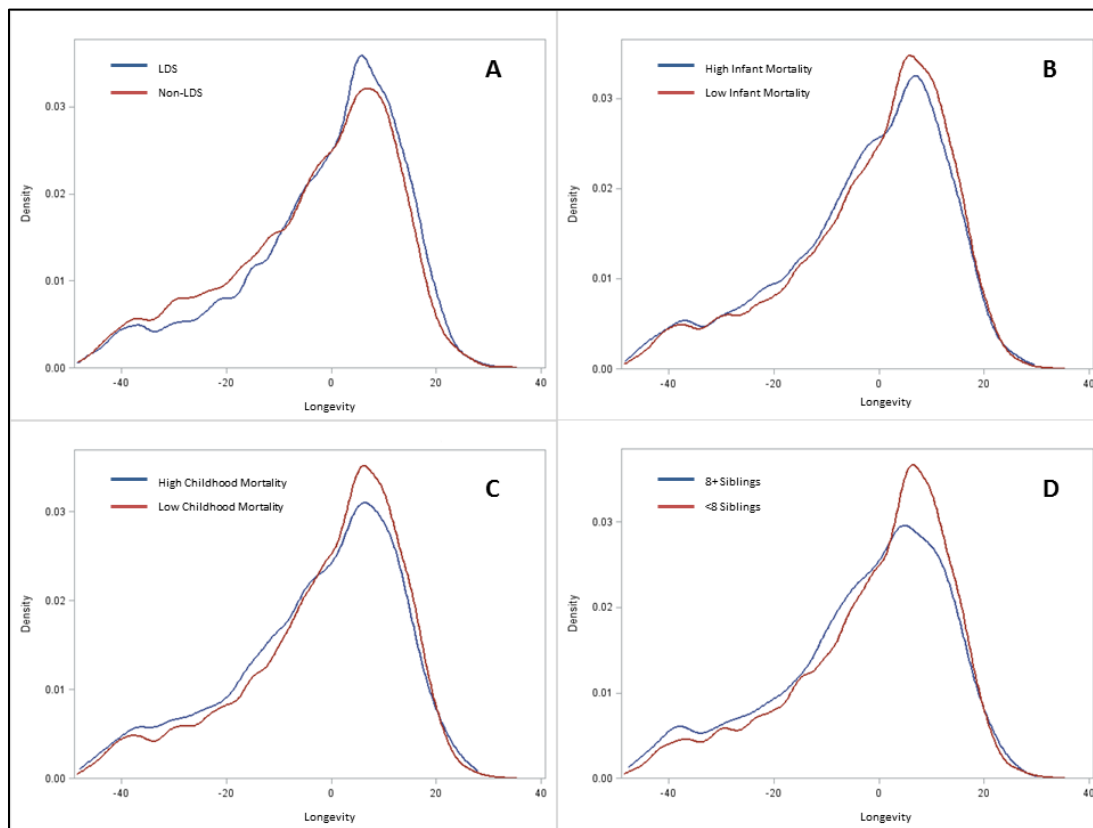


Figure 4.7. Distribution of longevity by environment. Empirical densities of longevity are plotted by environment. Panel A shows the distribution of longevity by LDS status. Panel B shows the distribution of longevity by infant mortality in family of origin. Panel C shows the distribution of longevity by childhood mortality in family of origin. Panel D shows the distribution of longevity by number of siblings.

CHAPTER 5

CONCLUSION

This dissertation investigated heterogeneity in patterns of aging and the factors throughout the life course that shape them. By focusing on variability within the population we are able to provide a clearer picture of how circumstances throughout the life course affect the way individuals age. We found that the paths to disease and longevity are diverse and that early and midlife factors play an important role in determining later life health and longevity. Our results support a wide body of literature showing that morbidity is not an inevitable consequence of aging, even in the oldest old population, but is shaped by the historical circumstances and social environments that we live in. This study offered innovative and significant contributions to the understanding of biological and socioenvironmental determinants of aging. Our research sought to disentangle the biological and temporal sources of trends in cancer incidence, investigating the possible social and physiological effects of fertility history on comorbidity trajectories after age 65, and studying the heterogeneity in the heritable components of the total phenotypic variation in longevity across early life family and social environments.

Fully understanding the sources of heterogeneity in the patterns of aging and longevity using only measures of the early life or proximate environment is an impossible endeavor because the biological functioning of an individual is dependent upon a vast array of circumstances from birth to death. Healthy aging and longevity phenotypes should be characterized as plastic and not one fixed at or near the time of birth. Trends in cancer incidence in the oldest old are sensitive to period and cohort influences. Fertility history affects disease progression later in life and these effects are independent of early life circumstances, including a family history of longevity. These findings suggest that childhood is not the only malleable period in the life course; midlife circumstances may also alter the trajectories of age related degeneration. The moderate heritability of exceptional longevity is evidence that genes are not the only factor contributing to this phenotype. There is also some evidence that heritability of longevity is sensitive to childhood environments. Therefore, it is essential to consider how events throughout the life course and their interrelationships influence aging and longevity.

Little is known about age-specific disease incidence and prevalence among the oldest old (Boscoe, 2008; Christensen, Johnson, & Vaupel, 2006). This study highlighted the heterogeneity of disease patterns in this population by analyzing age, period, and cohort (APC) effects on cancer incidence in the oldest old and individual trajectories of disease for two cohorts over an 18 year period. We found significant evidence of variance in disease patterns for this population and evidence that social context and events throughout the life course influence patterns of disease even for the exceptionally long lived. The APC analyses provided evidence that the decline in cancer incidence for this age group is not strictly related to biological phenomenon. Characterizing trajectories of disease up to age 91 in the young-old cohort and 101 in the old-old cohort

provides evidence that even into these advance ages the patterns of disease are diverse. We found that there are distinct heterogeneous patterns of comorbidity that range from a robust group, escaping major morbid conditions for the majority of the observation period, to a frail group characterized by high comorbidity throughout the entire period of observation. These findings underscore the importance of more rigorous and interdisciplinary research into the biological and social underpinnings of disease for this rapidly increasing segment of the population.

It is important to consider how mortality selection shapes age-related patterns of disease. While it is clear that longevity is only moderately heritable at extreme ages, heritability also increases with age. This suggests that there may be genetic variants that are protective against deleterious genetic and environmental effects. The buffering mechanisms in aging hypothesis suggests that longevity genes buffer against the harmful effects of deleterious genotypes (Huffman et al., 2012). The decline in cancer incidence above age 90 also suggests that individuals reaching the extreme ends of longevity may be less susceptible to disease. However, the diverse patterns of comorbidity experience provide evidence that longevity is not synonymous with disease free living.

Future Research

Sociological and demographic studies of aging and longevity should inform and be informed by the fields of genetics, epidemiology, and biology. More attention should be given to uncovering genetic and biological pathways to health and their interaction with the social environment. The integration of theories of aging from multiple disciplines is essential to unraveling the secrets of this multifactorial process. It is difficult to identify the mechanisms that separate the exceptionally longevous, salubrious

individuals from those with multiple morbidities and a shortened life-span; however, it is clear that these differences cannot be wholly explained by biological or social mechanisms. Therefore, future demographic work should continue to improve upon the specification of biological and social paths to health outcomes.

The studies presented in this dissertation utilized a range of tools to describe aging and longevity trends in the populations. Each of these tools has unique aspects that can be leveraged to further advance the field of aging and longevity. Age, period, and cohort (APC) analyses can be considered descriptive. It is not possible to make causal statement as to what factors led to the observed trends. However, this is not sufficient reason for demographers to abandon APC analyses. It is the ability to describe the multidimensionality of morbidity and mortality trends that give these analyses so much power and point to domains that may hold some of the answers to fundamental questions about the origins of longevity.

Making definitive statements about age-related trends using cross-sectional data or longitudinal data from a single cohort is a dangerous practice. The observed trends in cross-sectional data may be confounded by cohort differences in exposure, while longitudinal data from a small number of cohorts are not generalizable because the observed patterns may be specific to these cohorts. Therefore, we advocate a decomposition approach to understanding the underlying factors of disease by first defining age, period, and cohort effects of morbidity and cause-specific mortality. This first step does not provide a complete explanation for the trends, but it helps to elucidate what needs to be explained. The second step then involves further investigating the components and interrelationships in order to make more definitive causal statements about the disease process. Investigating population trends using this strategy can shed

considerable light on the ways that social environments intersect with biological factors determining disease.

The use of group-based trajectory modeling to construct heterogeneous patterns of aging is extremely informative to the studies of aging and longevity. It has become clear that there is not a linear pattern of decline in physiological function determined by chronological age at the population or individual level. Assessing unique patterns of disease and disability experience give us a more realistic picture of how people age. We also have much to learn about which experiences throughout the life course contribute to specific patterns of aging. Other sources of early life information, such as linked Decennial Censuses and military service records, will be available as part of the UPDB infrastructure in the near future. This will allow for further investigation into the association between early and midlife events and later life morbidity. We also suggest that study is warranted for investigating specific diseases or groups of disease (rather than composite measures only) with similar biological underpinnings to further understand the association between fertility and later life health.

Exploring gene-environment (GxE) interactions using a multigenerational database with information on early and midlife conditions is a fruitful approach to understanding how the social environment affects later life health. Not only can the study presented here be expanded to include other environments, but it can also be expanded to examine variation in heritability of other aging phenotypes. For example, we identified a group of robust individuals that experienced low levels of disease over an 18 year period in the trajectory analysis. It would be interesting to see if there is evidence of heritability of a “robust” phenotype. Other ways of investigating GxE interactions should also be explored. There is potential for using biomarker data, including *APO-E*

and telomere length, to investigate the possibility of environmentally altered phenotypic expression.

Population projections that assume future gains in healthy life expectancy and life expectancy in general will remain on a fixed path should be viewed with caution because life expectancy is sensitive to both historical and current sociological context. This is not to say that future improvements in healthy life expectancy and life expectancy in general are impossible, but they are dependent upon factors that are still not well understood. Also, much more research needs to be conducted in order to understand disease trajectories specific to the oldest old population. We cannot plan for proper care of this rapidly increasing population when we know so little about their healthcare needs.

Conclusions

This research contributes to a growing body of literature that draws attention to effects of early life circumstances on later life health. Health policies should be aimed at promoting the well-being of individuals throughout the life course. This research specifically highlights the importance of maternal well-being during childbearing years. The future health of women is not only affected while they are in their reproductive years, but it has been shown to affect the health of her offspring (Gluckman & Hanson, 2005). Therefore special attention should be given to this sensitive period that may alter the health of multiple generations. This research also highlights the importance of social context throughout the life course in determining later life health. Health risks are created and maintained by social structures and more work must be done to understand the social disparities that lead to disparities in health later in life and possibly across generations. As a more individuals advance into the oldest old ages, we will need to

review health and cancer screening recommendations of the past. The view that this age group is too frail or has too many comorbid conditions should be reconsidered (Østbye, Greenberg, Taylor, & Lee, 2003) based on trends in cancer incidence for this population.

Understanding the sources of variation in patterns of aging is important for creating accurate population predictions, identifying at risk populations that may benefit from public health interventions, and characterizing the process of aging in a diverse population. Rather than focusing on the average life expectancy or healthy life expectancy of the population and their trends over time, we should be focusing on the variability of these measures within a population and changes in the sources of variation over time. This is a subtle but important difference. By elucidating mechanisms that lead to heterogeneous patterns of aging, we can not only gain more insight into the determinants of aging, but focus on the factors that have the largest impact. Health policy should be focused on not only curing ailments once they present themselves, but more importantly, preventing them throughout the life course.

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