A Comprehensive Evaluation of Life Purpose, Psychosocial Wellbeing, and Mortality

by

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Dedication

This dissertation is dedicated to my family,

who always encourage me to chase my dreams.

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Preface

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Abstract

Life purpose encompasses the meaning and direction a person has in life. A significant body literature has suggested that "purposeful living" is associated with better mental and physical health, but there are gaps in our understanding of these relationships. Life purpose, alongside many psychosocial constructs, has been studied for its effects on mortality, but comprehensive, well-designed studies are needed. Also, no previous analyses have explored the association between life purpose and cause-specific mortality. Moreover, psychosocial constructs are generally studied in isolation and their interconnectedness and shared biological pathways are ignored. Additionally, prior research has indicated that genetics are linked with life purpose, but no genome-wide association study (GWAS) on life purpose has previously been conducted. This dissertation aimed 1) to evaluate the association between life purpose and all-cause and cause-specific mortality; 2) to explore direct and indirect effects between psychosocial constructs and mortality; and 3) to identify genetic variants associated with life purpose.

Aim one examined the association between life purpose and four-year all-cause and cause-specific mortality through the Cox-proportional hazard model among the Health and Retirement Study (HRS) participants. We found life purpose was statistically significantly associated with all-cause mortality (hazard ratio (HR)=2.43; 95%CI:1.57,3.75, comparing the lowest life purpose category with the highest category). Some significant cause-specific mortality associations with life purpose were also observed (heart conditions: HR=2.66; 95%CI:1.62,4.38). This work was published in JAMA Network Open in 2019.

Aim two quantified the effect of a large set of psychosocial constructs on all-cause mortality and further evaluated whether behavioral or physical health status mediated the relationship. HRS collected data on 48 psychosocial constructs including life purpose. Latent class analysis was used to divide participants into mutually exclusive psychosocial wellbeing groups based on their pattern of psychosocial constructs. Psychosocial wellbeing group (good, average, and poor) was considered as the "exposure", and physical health (functional status and comorbid conditions) and behavioral characteristics (physical activity, smoking, and alcohol) were mediators. We observed strong and statistically significant total effects for the association between survival time and psychosocial wellbeing (e.g., good versus poor survival rate (SR)=1.73; 95%CI:1.50,2.01). Through the mediation analysis, the direct effect via psychosocial wellbeing accounted for more than half of the total effect of this relationship (SR=1.46; 95%CI:1.27,1.67). However, indirect effects with individual mediators were also observed.

In aim three, we conducted the first GWAS to identify genetic variants associated with life purpose in individuals of European ancestry (n=8,959) and African ancestry (n=1,641) using data from HRS. No SNPs achieved genome-wide significance ($p>5\times10^{-8}$) in either ancestry group. We also performed a GWAS meta-analysis among European ancestry samples in HRS and Michigan Genomics Initiative Epidemiological Questionnaire Study using a single question on life purpose that overlapped between the two studies. The meta-analysis found no statistically significant SNP.

Overall, the results of this dissertation add findings to our understanding of life purpose and psychosocial wellbeing. Aim one indicates that stronger life purpose was associated with decreased all-cause mortality. Aim two highlights the interconnectedness of psychosocial constructs, and shared indirect effects through physical and behavioral health factors between the association of psychosocial wellbeing and survival. Aim three serves as a stepping-stone to better

understanding the genetic pathways that underpin life purpose. Future research should focus on evaluating the association of life purpose interventions with health outcomes, which could have major public health impacts.

Chapter 1 Introduction

1.1 Overview of the dissertation

This dissertation explored various facets of life purpose and psychosocial wellbeing through a comprehensive set of research projects, utilizing a variety of data types and advanced analytic methods. Findings from this dissertation provide guidance for clinical interventions related to life purpose and more broadly psychosocial wellbeing. The first aim examined the association between life purpose and all-cause and cause-specific mortality using data from the Health and Retirement Study (HRS). Considering the interconnectedness of life purpose and other psychosocial constructs, the second aim quantified the effect of a large set of psychosocial wellbeing constructs (including life purpose) on survival and further evaluated whether physical and behavioral health factors mediate the relationship between psychosocial wellbeing and survival. Data from the HRS was also used for this aim. The third aim focused on identifying the genetic determinants of life purpose through a Genome-Wide Association Study (GWAS) using data from HRS and the Michigan Genomics Initiative Epidemiological Questionnaire Study (MGI EPI-Q).

The dissertation includes six chapters. Chapter 1 serves as the introduction to the dissertation and the three aims. Chapter 2 provides the background on life purpose and psychosocial wellbeing to demonstrate the motivation for the dissertation projects. Chapters 3-5 present manuscripts for each of the three aims. Chapter 6 is the conclusion, which synthesizes the significance of the findings for each aim, highlights the impact of this dissertation on public health, and provides directions for future research.

1. **Specific Aim 1:** To perform a comprehensive evaluation of the association between life purpose and all-cause and cause-specific mortality using data from the Health and Retirement Study (HRS).

   Hypothesis: We hypothesized that the stronger life purpose is associated with lower all-cause and cause-specific mortality among HRS participants over four years of follow-up.

2. **Specific Aim 2:** To determine the direct and indirect effects between the association of psychosocial wellbeing constructs and all-cause mortality in the HRS.

   Sub Aim 2.1: To quantify the effect of a large set of psychosocial wellbeing constructs on survival using data from the HRS.

   Sub Aim 2.2: To evaluated the extent to which the association between psychosocial wellbeing constructs and overall survival is mediated by behavioral (smoking, alcohol consumption, and physical activity) and physical (chronic disease conditions and functional status) health factors in HRS.

   Sub Aim 2.3: To provide a workflow to overcome the methodological challenges of mediation analysis in the survival context using imputed data from a study that employed a complex survey design.

   Hypotheses: We hypothesized that psychosocial wellbeing is associated with all-cause mortality in the HRS within eight years of follow-up. We further hypothesized that behavioral (smoking, alcohol consumption, and physical activity) and physical (chronic disease conditions and functional status) health factors mediate the association between psychosocial

wellbeing and survival. Lastly, we hypothesized that among HRS participants, there is still a direct effect between psychosocial wellbeing and survival after accounting for mediators.

3. **Specific Aim 3:** To identify the genetic determinants of life purpose using data from HRS and Michigan Genomics Initiative Epidemiological Questionnaire Study (MGI EPI-Q).

   Sub Aim 3.1: To conduct a common variant genome-wide association study (GWAS) with a seven-item life purpose scale among individuals of European or African ancestry using data from the HRS.

   Sub Aim 3.1: To conduct single-question life purpose GWASs among individuals of European ancestry using data from the HRS and MGI EPI-Q, and then meta-analyze the results from the two GWASs.

   Hypothesis: We hypothesized that we will identify common single nucleotide polymorphisms (SNPs) reaching at least the 'suggestive' statistical significance p-value level ($p<10^{-5}$) through the life purpose GWAS or GWAS-meta-analysis.

Chapter 2 Background

2.1 Life Purpose Definitions and Measurements

This section covers the definition of life purpose and my view of the four essential components of life purpose. It also covers the ways in which life purpose is measured and a critical evaluation of these instruments.

2.1.1 Definition of Life Purpose

Life purpose has been defined by several researchers (Table 2-1). Life purpose is an essential element of positive psychosocial well-being[1,2], and it is reflected in the goals[2-5], values[2,4,5], actions[3-5], and activities[5,6] around which individuals organize their lives. Individuals derive life purpose in different ways; for some, it may be childrearing or religiosity[7,8] whereas, for others, it could be their professional endeavors[8] or volunteering[8,9]. Essentially, life purpose is individualized[4] and it can be developed overtime[10]. After an extensive literature review, my synthesis is that there are three essential components of life purpose: 1) Values; 2) Goals; and 3) Control

Table 2-1. Definition and dimensions of life purpose/meaning in life from previous literature.

Reference	Definition and dimensions
Viktor Frankl, 1945[7]	"The degree to which people perceive life to have purpose and meaning."
Crumbaugh, and Maholick, 1964 [11]	"A person's experience in life, motivations for living and goals are reflected in purpose in life "
Reker GT et al, 1978[3]	"Meaning refers to making sense, order, or coherence out of one's existence. Purpose refers to intention, some function to be fulfilled, or goals to be achieved. Having a sense of personal meaning means having a purpose and striving toward a goal or goals." Reler believed that life purpose contains "Zest for life, fulfillment, contentment, satisfaction"

Ryff CD et al, 1995[1,2,12]	"Purpose in life means, one has goals in life and a sense of directedness, feels there is meaning to present and past life, holds beliefs that give life purpose, has aims and objectives for living."
Patrick E. McKnight, 2009[4]	'Purpose is a central, self-organizing life aim that organizes and stimulates goals, manages behaviors, and provides a sense of meaning." Patrick indicated that there are three-dimensional continuums—scope, strength, and awareness
Victor J. Strecher, 2016[5]	"A life purpose, like a goal, also helps you focus on what's important and question what's not, and it is also a product of deeply held values. Purpose in life comes from the most valuable things in your life: Achievement, community, creativity, enjoyment, expertise, independence, kindness, relationships, reputation, responsibility, security, self-control, spirituality, tradition, vitality."

2.1.2 Four Essential Components of Life Purpose

1) Values: Individuals with a life purpose have established values[3]. Values could be interpreted as an individual's judgment of what is crucial in life or one's behavior principles[13]. Values could be personal values for life or religious beliefs[10].

2) Goals: Individuals with a life purpose can define their goals in the present and future[3,4]. They have a direction in their life, and they are able to refine their goals as time goes by[3,4]. Goals can be defined as steps and actions for self-improvement and a pathway to motivation and further achievement[14]. In addition, these goals can be personal or beneficial to others (family, friends, communities, or the entire world).

3) Control: Individuals with a life purpose feel in control and capable of managing their behaviors to achieve their goals[4]. The stronger their life purpose is, the more likely they are going to execute goals effectively[4]. The ability to manage behaviors and achieve goals gives them a sense of personal growth[15]. This sense of achievement positively impacts and leads to another meaningful goal and a stronger life purpose.

Overall, the three components of life purpose interact in a complex, integrated, and synergistic fashion.

2.1.3 Measurements of Life Purpose

One-item Instruments

Over the past decade, various measurement tools have been developed for life purpose. Overall, there are instruments with one single question to measure life purpose, such as "Do you have a life purpose in your life?" (3-point Likert scale: Yes, uncertain, no)[21] or "How do you evaluate your present usefulness to others and society? "(4-point scale: Quite a bit, some, a little, not at all)[22]. This type of one-item instrument has been widely used in Japan[21-25]. A one-item question instrument has a few advantages (Table 2-2). First, it is easy for participants to understand the question. Second, because it does not explicitly focus on a particular domain of life purpose, it allows diverse interpretations for people with different perspectives. For example, one person may refer to her/his work purpose, whereas others may interpret it as purpose from religiosity. Last, the response is measured by a Likert scale with a neutral response option. This enables people who are indifferent to a subject to select the neutral instead of being forced to choose a response that does not reflect their true beliefs. However, there are some limitations to the one-item instrument. It only consists of one general question; thus, it may not fully reflect all dimensions of life purpose. Also, some people may require guidance through multiple questions to fully reveal their overall life purpose which isn't possible with one question.

Multi-items Instruments

Overview: Some instruments evaluate multiple dimensions of life purpose, such as values, purpose, goals, and behaviors[2,26-28]. A comparison of select multi-item instruments is shown in Table 2-2. Overall, multi-item instruments capture multiple dimensions of meaning in life or life purpose. The response is also measured by a Likert scale, which allows a neutral response and

enables people who are indifferent to a subject to select the neutral instead of being forced to choose a response that does not reflect their true beliefs. The common shortcoming of all the instruments is that none was developed or validated among cancer patients. Next, I will provide a critical evaluation on the multi-item instrument I will utilize in my dissertation research as it was used in the Health and Retirement Study (HRS).

Ryff and Keyes's scales: The most commonly used instrument to assess life purpose is the Ryff and Keyes's scales of Psychological Well-Being[2]. There are several strengths to this instrument. First, this scale covers the present and future life purpose, spirituality, and activities. They are important elements for life purpose. Second, this scale has been validated[29,30] and utilized[27,28,31-35] by many researchers as a reliable instrument. However, this instrument also has a critical limitation. This scale may not accurately capture the life purpose among patients with severe illness, such as cancer patients. For instance, one of the questions in this scale is, "I live life one day at a time and don't really think about the future." To a healthy person, living life one day at a time may not be purposeful. However, to a cancer patient, being able to live life one day at a time might be his/her life purpose at this specific stage of their life. Thus, utilizing this questionnaire directly in cancer research may introduce measurement errors and bias the results.

Instruments in My Dissertation

The Ryff and Keyes's scale of Psychological Well-Being for purpose in life is used by the HRS. In my dissertation, all three aims utilized the HRS data. Thus, this scale was the main instrument in my dissertation research. Aim three also used the data from the Michigan Genomics Initiative Epidemiological Questionnaire Study (MGI EPI-Q). Life purpose was measured by using the 21-items Comprehensive Measure of Meaning (CMM) in the MGI EPI-Q. To make these two life purpose instruments comparable, we used a single question within the CMM scale: "I have

a sense of direction and purpose in my life" and the same single item from Ryff and Keyes's scale to define life purpose in the GWAS meta-analysis. The utilization of different tools in my dissertation provided me the opportunity to better understand these instruments.

Table 2-2.Advantages and disadvantages of various life purpose measurements.

		Advantages	**Disadvantages**
One-item measurement			
1	**Do you have ikigai in your life? "Ikigai means life worth living."**	Short and easy to answer Not specific, allows different interpretations	Response Categories: Yes/No-(no neutral response) Too general, people need guidance
2	**How often do you feel useful to family and/or friends?**	Short and easy to answer Not specific, allows different interpretations Likert scale, allows a neutral response	One dimension Too general, people need guidance
3	**How do you evaluate your own present usefulness to others and society?**	Short and easy to answer Not specific, allows different interpretations Likert scale, allows a neutral response	One dimension Too general, people need guidance
Multi-items measurement			
1	**7 questions from Ryff and Keyes's scales of Psychological Well-Being for purpose in life**	Multiple dimensions of life purpose Captures the significance and direction of life purpose Likert scale, allows a neutral response Developed and validated in the US population Commonly used in the US Used by HRS	It does not reconcile the past life purpose Some items overlap each other. It is not validated among cancer patients It is not an appropriate tool to reflect life purpose among cancer patients.
2	**8 questions from Krause's Meaning in Life Questionnaire**	Multiple dimensions of life purpose Reconciles the past, and captures significance and direction of life purpose Likert scale, allows a neutral response Validated in adults and shown a good reliability	It is not as widely used as the Ryff's and Keyes's scales and only a small number of studies have utilized this measure. It is not validated among cancer patients
3	**20 questions from Crumbaugh and Maholick's Purpose-in-Life Test (PIL)**	Multiple dimensions of life purpose Likert scale, allows a neutral response Developed and validated in the US population	It focuses on life satisfaction or enthusiasm more than life purpose. Item such as suicide is included in the measure, it might be extremely sensitivity for some individual. It is not validated among cancer patients. It is consisted of 20 items, which is longer than any of the questionnaire. It may be time consuming for participants to answer.
4	**21 questions from the Comprehensive Measure of Meaning by Hanson, J.A. and VanderWeele, T.J**	Multiple dimensions of meaning in life Captures global and individual level of life purpose Reconciles the past, and captures significance and direction of life purpose Likert scale, allows a neutral response	It is newly developed and it has not been validated by other researchers yet It is consisted of 21 items, which is longer than any of the questionnaire. It may be time consuming for participants to answer. It is not validated among cancer patients

2.2 Life Purpose Determinants

This section provides an overview of the existing literature on the determinants of life purpose including personal characteristics, lifestyle factors, and genetics.

2.2.1 Personal Characteristics and Lifestyle Factors

Overview of Findings

Gender: A few studies have examined the relationship between gender and life purpose, but findings from those studies are inconsistent. One study found that women have a stronger desire to form life purpose[3]. On the other hand, two studies have found no gender[10,36] differences for life purpose.

Age: Life purpose appears to increase with age through adulthood (18-65 years old)[3,10,36] and then decreases among seniors (>65 years old)[10,37]. Interpreting this association using my four life purpose elements standpoint, it is reasonable that individuals at a very young age may not have clear and defined values or goals; with the increase of age and experience in their life, personal values and goals are developed over time. At a very old age, some life events such as retirement, change of marital status, and physical health may affect life purpose, and it is physically challenging for them to control and achieve some goals.

Socioeconomic Status (SES): Three studies suggest that SES may play a crucial role in developing a strong life purpose. A research team used 29 years of longitudinal data and they observed that higher SES was associated with higher life purpose[38]. A recent study using the HRS data found that greater physical assets and retirement account assets predicted stronger life purpose[39]. Another study among black adolescents living in and around public housing found that

lower life purpose was associated with lower SES and more exposures to violence[40]. Again, interpreting these associations using my four life purpose elements, the negative environments such as violence, lower SES, or lack of education are obstacles to develop values and goals. The negative environment may also be a key barrier to achieve goals. However, we cannot exclude some exceptional individuals who may develop a strong resilience and life purpose in an adverse environment.

Physical Activity: Previous studies have demonstrated a positive association with physical activity and stronger life purpose[41,42]. Recently, Steptoe and colleagues found the association between physical activity and life purpose is a bidirectional relationship[43]. They observed that greater physical activity at baseline predicted strong meaning in life in 2 years, and they also found an increase in meaning in life was also associated with increased likelihood of engaging in vigorous physical activities in 2 years, independent of baseline physical activity[43].

Smoking: Generally, smoking history is associated with lower level of life purpose. A four-year prospective study from Hungary observed higher meaning in life after 4 years among nonsmokers compared to daily smokers[44]. A cross-sectional study also from Hungary reported nonsmokers had a higher meaning in life compared to daily smokers[45].

Critical Evaluation

Overall, most of the studies failed to adjust for important confounders such as baseline behavioral, health and psychosocial factors. Furthermore, half of the prior studies are cross-sectional studies with very small sample sizes. Thus, we cannot establish a temporal relationship between physical activity, smoking, violence, and SES, and life purpose. In addition, results for the age differences in life purpose were reported from cross-sectional studies. Personal life purpose trajectory requires a longitudinal study to establish. Lastly, the meta-analysis from Pinquart and

colleagues have some noticeable limitations: First, many studies included in the meta-analysis did not analyze life purpose as an outcome in a longitudinal study design. Thus, it is hard to establish temporality between these risk factors and life purpose. Second, all the studies that were included in this meta-review did not utilize an advanced statistical analysis technique such as regression analysis to examine the association between life purpose and risk factors. Instead basic correlation analysis was conducted to explore the linear relationship between life purpose and risk factors. A drawback of the correlation analysis is that a low correlation might result from a very strong but nonlinear relationship, and in this case, this non-linear relationship will not be captured through a correlation analysis. Moreover, a number of the studies did not control for potential confounders, thus results from those studies are potentially biased. Overall, there is a need to use a well-designed longitudinal epidemiologic study to establish potential factors that determine life purpose in the future.

2.2.2 Genetic Determinants of Life Purpose

Genetics may also determine an individual's life purpose in addition to personal characteristics and environmental factors. However, there has been little investigation into the genetics of life purpose; only two research studies have been conducted to our knowledge. Briefly, a twin study design compares the phenotypic similarities of identical (monozygotic: MZ) and fraternal (dizygotic: DZ) twins[46]. Variance in traits can be decomposed into the additive genetic, shared environment, and unique environmental components[46]. One twin study used 837 pairs of adult twins from U.S.[46], and the second study used 742 pairs of twins from Italy[47]. Both studies used the Ryff and Keyes's scales of Psychological Well-Being for purpose in life scale[46,47], and observed substantial genetic influences on life purpose[46,47]. Findings from twin studies provided

crucial evidence to further understand the role of genetics on life purpose through a genome-wide association study (GWAS). Yet, to date, there has been no GWAS of life purpose conducted.

Life purpose has been found to associate with a variety of other facets of the psychosocial wellbeing domain, including resilience[48-50], positive affect[51], depression[49,51,52], anxiety[51], and loneliness[49,51]. Furthermore, GWAS has proven to be a successful method for the identification of genetic variants that increase susceptibility to complex psychiatric traits such as depression[53], major depression disorder[54], neuroticism[53], anxiety[55], schizophrenia[56], post-traumatic stress disorder[57]. In addition, two studies reported associations between common genetic variants and subjective wellbeing[53,58]. Three SNPs ware linked to subjective well-being in a large GWAS study published in Nature [53], where subject well-being was measured by life satisfaction, positive affect, or (in some cohorts) a measure combining life satisfaction and positive affect[53]. Furthermore, another study found that stronger wellbeing was associated with decreased expression of proinflammatory genes[58]. Given the success of GWAS in other psychosocial constructs and the twin studies of life purpose, the genetic contribution to life purpose is an area that needs investigation. My dissertation aim three carried out a common variants GWAS with life purpose.

2.3 Life Purpose and Non-cancer Health Outcomes

This section covers the existing literature on the association between life purpose and a variety of non-cancer health outcomes, excluding mortality.

Overview of Findings

Many observational studies have established that life purpose has a positive influence on a diverse set of health outcomes, including mental and physical health.

Mental Health Benefits of Purpose: Studies found having a strong life purpose has important implications for mental health. Most recently, Kim and his colleague using the data from

the HRS found that comparing individuals in the highest quartile of life purpose score to those in the lowest quartile, they had lower hopelessness score (beta =-0.35, 95% CI:0.41, -0.29), lower loneliness score (beta =-0.45, 95% CI:-0.56,-0.35), higher optimism score (beta = 0.41, 95% CI:0.35,0.47), and higher positive affect score (beta = 0.59, 95% CI: 0.53,0.65), as well as 43% reduced risk of depression (OR=0.43,95% CI:0.46,0.69)[51]. Another research study conducted in the US found that individuals with a low life purpose were 1.85 times more likely to have depression compared to individuals with a higher life purpose (OR=1.85, 95%CI:1.33,2.57).[59]. Lastly, a study on coping behavior of PTSD symptoms in earthquake survivors found that one unit increase in life purpose score resulted in a 0.195 unit decrease in PTSD symptoms score when other covariates hold constant(beta=-0.195, $p<0.01$)[60].

Physical Health Benefits of Purpose: Generally, researchers found having a life purpose is associated with a wide range of chronic disease outcomes. For example, in the HRS, Kim and colleagues found that a one unit increase in life purpose score (on a six-point scale) was associated with a statistically significant 10% decrease in the incidence of sleep disturbances (Odds ratio (OR)=0.90, 95%CI: 0.81, 0.99)[33], a 14% decrease in stroke incidence (OR=0.86, 95%CI: 0.74,1.00)[31], and a 24% reduced risk of myocardial infarction (OR=0.76, 95%CI: 0.58,1.00)[32], after adjusting for demographic, psychological distress, health behaviors and health status at baseline. In addition, a prospective cohort study across two very different cultures, one in Berlin, Germany, and the other in Ibadan, Nigeria, on quality of life after stroke, showed that higher life purpose score was associated with increased post-stroke quality of life in both cities[61]. Moreover, a cross-sectional study from the upper Midwestern United States found that each unit increase in life purpose resulted in an approximate 10% decrease in diabetes prevalence (OR=0.90, 95%CI:0.83,0.98) after controlling for age, race, and difficulties with emotion regulation[62].

Another study found that greater life purpose was associated with a substantially reduced risk of Alzheimer's disease (Hazard Ratio (HR)=0.48, 95%CI:0.33,0.69) among community-dwelling older persons after adjusting for age, sex, and education[34]. Lastly, it has been shown that greater life purpose was associated with a reduced risk of disability in basic activities of daily living (HR= 0.60, 95%CI: 0.45,0.81), instrumental activities of daily living (HR = 0.56, 95%CI: 0.40,0.78), and mobility disability (HR = 0.61, 95%CI: 0.44,0.84) among community-dwelling older persons[35].

Critical Evaluation

Overall, most of the studies I described above are longitudinal prospective cohort studies with relatively large sample sizes. Those studies provide strong evidence supporting the fact that having a strong life purpose has various health benefits. However, a few limitations across these studies should be addressed. First, the majority of the studies were conducted among an older population. The HRS[31-33,63] is a cohort study among adults aged 50 or older; the mean age in the Rush Memory and Aging Project[34,35] is 80.4 years. Hence, there might be limited generalizability due to the older age inclusion criterion. Results from these studies may not be generalizable to a younger population. Second, all the studies by definition excluded participants with missing life purpose from the analysis, such exclusion may lead to non-response bias, which may underestimate the true association between life purpose and health outcomes. It is possible that non-response may be affected by exposure and outcome (or an unmeasured risk factor for the outcome). This may result in a selection bias (non-response bias). For instance, it's possible that people who did not fill out the life purpose questionnaire were in a lower social economic status (SES), and lower SES was associated with lower life purpose[38]. Furthermore, lower SES is associated with higher mortality[64]. Thus, the non-response is associated with exposure (life

purpose) and outcome (mortality), and people in the study could be a group of people who with a higher life purpose in general compared to those with a missing life purpose. However, not a single study evaluated this non-response bias. As a whole, those methodological limitations should be considered in future research.

2.4 Life Purpose and Mortality

This section covers the existing literature on the association between life purpose and mortality. In the section below, the findings of each study by region (domestic/international) are summarized and a critical evaluation of this literature is provided. Overall, the critical assessment suggests that despite several limitations with the existing literature, there are convincing data demonstrating that a stronger life purpose is associated with lower all-cause mortality both in domestic and international studies[21-28,65-67]. Lastly, this section also covers existing literature on the association between other psychosocial wellbeing constructs and mortality.

2.4.1 Domestic Studies

Overview of Domestic Studies

To date, there are five studies that have evaluated the relationship between life purpose and all-cause mortality in the US population[23,26-28,67]. Table 2-3 provides detailed information regarding the recruitment, sample size, study design, measures of exposure, outcome, and covariates included in each domestic study. Briefly, all studies used a prospective cohort design and included more than 1,000 participants[23,26-28,67]. Three studies utilized a population-based recruitment strategy [26,27,67] whereas the others used community-based cohorts[23] or retirement communities[28]. Furthermore, two of the five studies included adults over 25 years of age[27,68], however, two studies were restricted to adults older than 65 years of age[26] and 70 years of age[23].

One study did not clearly state the recruitment age, but the mean age of participants in this study was 78 years of age[28]. The primary exposure is life purpose and it was measured using various tools. Boyle et al. and Hill et al. both used the Ryff and Keyes' scales of psychological well-being to measure life purpose[27,28]. Gruenewald et al. used a single question scale[23] and Krause used a scale for life purpose which he developed[26]. Keyes and colleagues assessed life purpose through the measurement of flourishing[67]. All five studies followed-up participants for at least 5 years. Vital status was proxy reported in two studies[26,28] and verified through the National Death Index in the other three[23,27,67]. Lastly, all five studies controlled for a number of important covariates, including age, gender, education, physical activity, and smoking status, but none of the studies included a comprehensive set of confounders.

Overview of Findings in Domestic Studies.

An inverse association between life purpose and all-cause mortality was found in all studies[23,26-28,67]. Specifically, in a sample of 1,030 aged 70 years or older adults, Gruenewald and his colleague found that the odds of participants rated themselves useful is 3.13 times higher among people who survived than people who were dead (OR= 3.13, 95%CI: 1.43,6.84)[23]. In addition, Krause and his colleagues demonstrated a similar inverse but not statistically significant relationship between stronger life purpose and higher all-cause mortality (OR= 0.97, 95%CI: 0.93,1.01)[26] among adults older than 65 years of age. Furthermore, using a similar older population from Memory and Aging Project and Minority Aging Research Study, Boyle and his team demonstrated people who have a sense of life purpose were 0.6 times less likely to die compared to those who do not (HR= 0.60, 95% CI: 0.42,0.87)[28]. Recently, Hill et al. examined this relationship in a population with a wider age range (≥25 years old), they found people 0.85 times less likely to die compared to those who have a sense of life purpose and those do not (HR=0.85,

95%CI: 0.78,0.93)[27]. Moreover, another study estimated the relationship between flourishing and 10 years of all-cause mortality in a population aged from 25 to 75 years of age, that life purpose is one component of the flourishing measurement in this study. Although the specific life purpose result was not provided in the study, they found the odds of non-flourishing were 1.62 times higher among people who died compared to people who reported flourishing (OR=1.62, 95%CI: 1.00,2.62)[67].

Critical Evaluation of Domestic Studies.

A few limitations across all domestic studies on life purpose and all-cause mortality should be addressed (Table 2-5).

1). Limited generalizability due to area-specific recruitment strategies. Some of the studies were population-based, and participants were randomly selected from a nationwide system, such as Medicare and Medicaid Service[26] or non-institutionalized adults phone roster across the US[27,67]. However, the rest of the studies recruited participants from retirement communities[28], senior housing facilities[28], and community-based cohorts[23] from certain cities, such as Chicago[28], Duham[23], East Boston[23], and New Haven[23]. Results generated from a senior population may not be generalized to a young adult population. Moreover, results from a non-national wide sample may not be generalized to the entire nation.

2). Measurement error due to life purpose measuring tool. As previously discussed, all the instruments for life purpose have limitations to some degree. For example, The Crumbaugh and Maholick's Purpose-in-Life Test (PIL) was criticized by a number of researchers that it focuses on life satisfaction rather than life purpose[69]. Moreover, one single question may not fully capture one's life purpose. There is measurement error due to imperfect instruments, however, measurement error does not differentiate by exposure status itself since within a study the same

life purpose instrument was used to measure life purpose among all study participants. Overall, the bias should be toward the null.

3). Non-response bias due to the exclusion of participants with missing life purpose, which may underestimate the true association between life purpose and all-cause mortality. It has been shown in our study that was published in JAMA, people who did not fill out the life purpose questionnaire were in a lower social economic status (SES)[70], and lower SES was associated with lower life purpose[38]. Thus, people in the study could be a group of people who have a higher life purpose in general compared to those with a missing life purpose. Furthermore, there is evidence that low SES is related to higher mortality[64,71]. When the non-response is affected by both exposure and outcome or an unmeasured risk factor for the outcome, the selection bias occurs. However, not a single study evaluated this non-response bias[23,26-28,67].

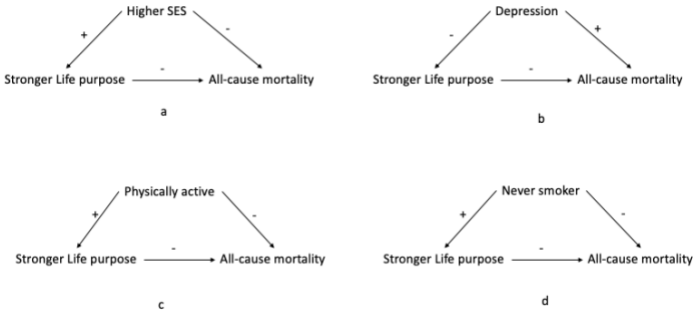
4). Measurement error due to the proxy reported outcome is unlikely to be an issue given that the date of death is not difficult to remember. Thus, even though two studies relied on the proxy responses this is unlikely to be an issue.

5). None of the studies examined the cause-specific mortality in addition to all-cause mortality. It may be informative to determine whether associations between life purpose and mortality are different by specific causes of death.

6). Unmeasured confounders. At least four potential unmeasured confounders exist among these studies: SES, depression, physical activities, smoking status. Figure 2 illustrates the direction of the association between unmeasured confounder, life purpose, and all-cause mortality through the directed acyclic graphs (DAGs). First, SES is an important confounder between life purpose and all-cause mortality, lower SES is associated with lower life purpose[38] and lower mortality[71]. SES is a complex term to reflect economic, social, and work status, measured by income or wealth,

education, and occupation, respectively[72]. One study only used retirement status as a proxy for SES[27], and four studies used education level as a proxy for SES[23,26,28,67]. Without appropriately adjusting for SES in the analysis may introduce negative bias and overestimate the true association. Second, psychosocial constructs, such as depression, have been shown related to a lower life purpose[10] and a higher risk of all-cause mortality[73,74]. Only one out of five studies adjusted for depression[28], three studies adjusted for other psychosocial constructs[23,27,67], and one did not adjust for any psychosocial constructs[26]. Without adjusting depression in the analysis may introduce negative bias and overestimate the true association. Third, health behavioral factors such as never smoking, and being physically active are associated with higher life purpose[75] and lower all-cause mortality[76,77]. Only two of the five studies adjusted for physical activities and smoking status[23,67]. Without adjusting smoking status and physical activity in the analysis may introduce negative bias and overestimate the true association.

Figure 2. Directed acyclic graphs (DAGs) for unmeasured confounders.



a. Higher SES is associated with a stronger life purpose and a lower risk of all-cause mortality. Not adjusting for SES will introduce a negative bias, which will overestimate the true association.
b. More depression symptoms are associated with a lower life purpose and a higher risk of all-cause mortality. Not adjusting for depression will introduce a negative bias, which will overestimate the true association.
c. Psychically active is associated with a stronger life purpose and a lower risk of all-cause mortality. Not adjusting for psychical activities will introduce a negative bias, which will overestimate the true association.
d. Never smoker is associated with a stronger life purpose and a lower risk of all-cause mortality. Not adjusting for smoking status will introduce a negative bias, which will overestimate the true association.

8). Reverse causation. It is possible that people with a worse comorbid condition may cause them to have a lower life purpose, and more likely to die. Such reverse causation may result in an overestimation of the true association. None of the studies excluded such a population nor conducted a sensitivity analysis to address this bias.

9). Lastly, no study considered mediation effects through behavioral and physical health factors. To fully understand the direct effect through life purpose and all-cause mortality, it is important to evaluate the indirect effect through other potential causal pathways.

2.4.2 International Studies

Overview of Findings in International Studies.

The inverse association between life purpose and all-cause mortality was also observed in studies from Canada[66] and Japan[21,22,24,25](Table 2-4). A small prospective cohort study of 128 people aged 65 years and older from a Nursing Home in Montreal found an inverse but not statistically significant association between meaning in life and four years all-cause mortality (HR=0.91, 95%CI:0.77,1.09)[66]. In Japan, the relationship between usefulness and all-cause mortality has been examined by various studies[21,22,24,25]. A prospective cohort study of 1,419 individuals who were aged 65 years and older in Japan, the authors found that people were 2.22 times more likely to die compared to people who had a strong life purpose at both baseline and end of follow-up, compared to people who had a strong life purpose at baseline and did not have a purpose at the end of follow-up (HR=2.22, 95%CI:1.44,3.42)[25]. Moreover, another cohort study in Japan found that among a similar older population in Japan (HR=2.24 95%CI:1.17,4.26)[22]. In addition, a larger cohort study in Japan with a national representative sample of 43,391 participants aged from 40 to 79 years old, found that people were 1.4 times more likely to die compared those who had no meaning in life to those had meaning in life (HR=1.4, 95%CI: 1.2,1.6)[24]. Another

similar population-based study examined the relationship between usefulness and mortality by sex and reported similar findings regardless of sex[21].

Critical Evaluation of International Studies.

Similar to studies were conducted in the US, these studies in Canada and Japan also have similar limitations as the domestic studies, such as, limited generalizability due to area-specific recruitment[22] or older sample population[22,25,66], non-response bias due to exclusion of missing life purpose[21,22,24,25,66], unmeasured confounders such as SES[22,25], depression[21,22,24,25,66], physical activates[22,25], and smoking status, failed to examine the cause-specific outcome[21,22,24,25,66], and mediation effects[21,22,24,25,66], lastly potential reverse causation[21,22,24,25,66]. Besides those limitations, there are a few additional disadvantages. First, the study in Canada has only 128 participants in the study. Such a small sample size might be the reason that an inverse but a non-statistically significant result was observed. Second, all these five studies in Japan used one single question to measure life purpose/usefulness "ikigai" in Japanese, and one study only included response options Yes/No[25]. This one-single question may not capture all aspects and levels of life purpose. However, since the same scale was used for all participants within each study, this measurement error does not differentiate by exposure group. Thus, the direction of the true association may not be affected, but the validity of the association is affected.

Table 2-5 summarizes the potential biases across all the domestic and international studies on life purpose and all-cause mortality. As shown in Table 2-5 and discussed earlier, some bias underestimated the true association, but some overestimated it, and the magnitude of the bias is hard to determine. Generally speaking, the direction of the overall bias is difficult to conclude, but I believe there are convincing data to support an inverse association between life purpose and all-cause mortality, and a comprehensive analysis should be conducted. In my dissertation aim one,

we performed a comprehensive evaluation of the associations between life purpose and all-cause or cause-specific mortality among older adults using data from the HRS. Furthermore, to improve the validity of the observed results, we implemented a number of method considerations with our analysis.

2.4.3 Other Psychosocial Wellbeing Constructs and Mortality

To date, most previous studies only examined one or a few psychosocial wellbeing constructs at a time and thus far have been in favor of a positive association with longer survival and good psychosocial wellbeing [65,67,78-81]. Notably, Puterman et al. investigated 57 economic, behavioral, social, and psychosocial factors using the HRS data and found associations between many psychosocial factors and mortality [82]. For example, they found an increased risk of all-cause mortality (ranked by the effect size) was associated with lower life satisfaction (Hazard Ratio (HR) = 1.31, 95% CI = 1.19,1.45), higher negative affect (HR = 1.23, 95% CI = 1.14,1.33), higher anxiety (HR=1.21, 95% CI = 1.12,1.31), higher cynical hostility (HR = 1.16, 95% CI = 1.07,1.26), higher pessimism (HR =1.16, 95% CI = 1.07,1.25), higher hopelessness(HR = 1.14, 95% CI = 1.06,1.23), lower positive affect (reverse-coded, HR = 1.14, 95% CI = 1.05,1.23) lower optimism (reverse-coded, HR = 1.13, 95% CI = 1.05,1.22), higher loneliness (HR = 1.12, 95% CI = 1.04,1.21), and lower purpose in life (reverse-coded, HR = 1.12, 95% CI = 1.03,1.21)[82].

The major limitation of the existing literature surrounding associations between psychosocial wellbeing and health behaviors and outcomes is the lack of a comprehensive analytic effort to account for a full range of wellness constructs simultaneously. My dissertation aim two examined the associations between a wide range of psychosocial wellbeing constructs

and mortality, and we demonstrated the indirect effects of psychosocial wellbeing through behavioral and physical health factors.

Table 2-3.Literature summary of life purpose and all-cause mortality among domestic studies.

Author Year	Recruitment	Recruitment age	Mean age (y)	Sample size	Study design	Life purpose Measure	Verification of the endpoint	Outcome	Follow-up years	Covariates	Finding
Gruenewald et al, 2007[23]	Recruited on the basis of age and cognitive and physical functioning levels from three community-based cohorts (Durham, East Boston, and New Haven)	Age>=70	74	1,030	Prospective cohort study	Single question "Feelings of usefulness"	National Death Index	All-cause mortality	7	· Demographics: Age, education, · Health behavioral: physical activity, alcohol, smoking, · Psychological: volunteer, social ties, depressed mood, self-efficacy	OR= 3.13, 95%CI: 1.43-6.84 Compared those Never/rarely feel useful with those who felt useful to others used
Krause et al, 2009[26]	Random selection the Medicare and Medicaid Services (Population-based)	Age>=65	78	1,361	Prospective cohort study	8 questions from Krause's Meaning in Life Questionnaire	Proxy report	All-cause mortality	7	· Demographics: Age, sex, education, marital status, · Health behavioral: self-rated health, serious illness, non-serious illness, functional disability	OR= 0.967, 95%CI: 0.926-1.007; Compared those have a sense of purpose in life and those do not.
Boyle et al, 2009[28]	Recruited on the basis of age from the continuous care retirement communities and senior subsidized housing facilities	NA	78	1,238	Prospective cohort study	10 questions from the Ryff Scales of Psychological Well-Being	Proxy report and social security death index	All-cause mortality	5	· Demographics: Age, sex, education, race, · Psychological: depressive	HR= 0.60, 95% CI: 0.42-0.87; Each unit increase of life purpose score
Keyes et al, 2012[67]	Random-digit-dialing sample of non-institutionalized adults between the ages 20–75 (Population-based)	Age>=25	48	6,163	Prospective cohort study	Flourishing That life purpose is one component.	National Death Index	All-cause mortality	14	· Demographics: Age, retirement status · Psychological: social interactions, positive affect, negative affect,	OR=1.62 95%CI: 1.00-2.62 for adults not flourishing relative to those who were flourishing.
Hill et al, 2014[27]	Random-digit-dialing sample of non-institutionalized adults between the ages 20–75 (Population-based)	Age>=25	47	3,030	Prospective cohort study	3 questions from the Ryff Scales of Psychological Well-Being	National Death Index	All-cause mortality	10	· Demographics: race, age, education, gender, · Health behavioral: smoking status, physical inactivity, comorbidities, BMI. · Psychological: any mental illness	HR=0.85, 95%CI: 0.78-0.93 Compared purposefulness to purposelessness

Table 2-4.Literature summary of life purpose and all-cause mortality among international studies.

Author Year (Reference)	Recruitment	Recruitment age	Mean age (y)	Sample size	Study design	Life purpose Measure	Verification of the end point	Outcome	Follow-up years	Covariates	Finding
O'Connor et al, 1998[66]	Recruited from Nursing Home in Montreal	Age>=65	80.5	128	Prospective cohort study	4 Questions for meaning in life	Nursing home records	All-cause mortality	4	· Demographics: Age, sex · Health behavioral: self-rated health, nurse rated health, doctor visits, No. of daily pills, strength of pills · Psychological: depression, self-esteem, satisfaction with life	Hazard Ratio (HR)= 0.91, 95%CI=0.77-1.09 Compared people with higher meaning in life score to those with lower meaning in life score.
Nakanishi et al,2003[25]	Random selection Computerized sex-age register	Age>=65	65~92	1,419	Prospective cohort study	Single Question "Feelings of usefulness	Death Certificates	All-cause mortality	6	· Demographics: Age, sex, · Health behavioral: disability, daily health promotional practices, medical treatments, · Psychological: social activities, relationships	HR=2.22, 95%CI:1.44-3.42 Compared people had a strong life purpose at baseline and end of follow-up to who had a strong life purpose at baseline and did not have a purpose at the end of follow-up.
Okamoto et al, 2004[22]	Random selection Living in a rural town in Japan	Age>=65	73	748	Prospective cohort study	Single question "Feelings of usefulness	Death Certificates	All-cause mortality	6	· Demographics: Age, sex, marital status, · Health behavioral: self-rated health, comorbidities, depression, · Psychological: social contact and social roles	HR=2.24 95%CI:1.166–4.26 Compared those who rated their usefulness as ''a little or not at all'' compared with those with a ''quite a bit'' rating,
Sone et al, 2008[24]	A self-administered questionnaire was distributed to all living in the catchment areas, Japan	Age>=40	60	43,391	Prospective cohort study	Single question "Feelings of usefulness	Death Certificates	All-cause mortality	7	· Demographics: Age, sex, marital status, education, employment status, · Health behavioral: self-rated health, bodily pain, physical function, body mass index, smoking, alcohol, time spent	HR=1.4, 95%CI: 1.2-1.6; Compared those who found a sense of ikigai, to those who did not find a sense of ikigai.

	(Population-based)									walking, sleep duration, comorbidities · Psychological: perceived mental stress	
Tanno et al, 2009[21]	A self-administered questionnaire was distributed to who attended to the National screening program (Population-based)	Age>=40	57	30,155 male; 43,117 female	Prospective cohort study	Single question "Feelings of usefulness	Death Certificates	All-cause mortality	5	· Demographics: Age, sex, marital status, education, job status · Health behavioral: BMI, smoking, alcohol, physical activity, sleep duration, hypertension, diabetes · Psychological: perceived mental stress	Men: HR=0.85, 95%CI: 0.80–0.90 Women: HR=0.93 95%CI: 0.86–1.00 Compared those who did not find a sense of ikigai, to those who found a sense of ikigai.

Table 2-5. Bias summary of life purpose and all-cause mortality studies.

Author Year (Reference)	Limited Generalizability	Measurement error due to life purpose measurement tool	Non-response bias	Measurement error due to the proxy reported outcome	Unmeasured confounder SES	Unmeasured confounder depression	Unmeasured confounder physical activates and smoking status	Reverse Causation
Bias direction	Affected external validation	Same across the exposure, do not change the direction of the association	Underestimated the true association	Less likely exit due to death is a memorable event	Overestimated the true association	Overestimated the true association	Overestimated the true association	Overestimated the true association
O'Connor et al, 1998[66]	X	X	X		X		X	X
Nakanishi et al,2003[25]	X	X	X		X	X	X	X
Okamoto et al, 2004[22]	X	X	X		X	X	X	X
Sone et al, 2008[24]		X	X			X		X
Tanno et al, 2009[21]		X	X			X		X
Gruenewald et al, 2007[23]	X	X	X			X		X
Krause et al, 2009[26]	X	X	X	X		X	X	X
Boyle et al, 2009[28]	X	X	X	X			X	X
Keyes et al, 2012[67]		X	X			X	X	X
Hill et al, 2014[27]		X	X		X	X		X

2.5 Biological and Behavioral Mechanisms

This section covers hypothesized causal pathways between psychosocial wellbeing and survival, as well as existing literature on the associations between psychosocial wellbeing and health behaviors and medical health.

A fundamental question intrigues me: how do psychosocial factors such as life purpose affect survival? To date, limited studies have investigated the relative contributions of causal pathways connecting stronger life purpose to better survival. Life purpose is one component of the overall psychosocial wellbeing, hence, a better understanding of the total effect and indirect effect of psychosocial wellbeing on survival will shed light on the potential pathways between life purpose and survival.

Psychosocial wellbeing is a broad construct that has been defined in various ways[83]. It could be measured by both objective and subjective measures that demonstrate one's mental state or the cognitive and affective evaluations of one's life[83,84]. Psychosocial wellbeing constructs include positive and adverse factors, such as life purpose, life satisfaction, happiness, depression, or loneliness. Many observational studies have established that psychosocial wellbeing influences disease risk[84-87] and mortality[70,88-90]. However, psychosocial wellbeing constructs are often studied in isolation from each other. In real life, it is challenging to disentangle the differences between all psychosocial wellbeing constructs and if the mechanisms through which survival is affected are different. We hypothesize that they go through a similar pathway.

2.5.1 Hypothesized Causal Pathways Between Psychosocial Wellbeing and Survival

The potential causal pathways between psychosocial wellbeing and survival include 1) neuroendocrine regulation of stress responses and 2) health-related behavioral pathways. First,

through the neuroendocrine system[91,92], where we hypothesize that positive psychosocial wellbeing, such as life purpose or positive affect[93,94], provides buffers and protects against the increase of hypothalamic–pituitary–adrenocortical (HPA) axis and sympathoadrenal system responses when stress occurs. Then it balances the allostatic load over the long term, further regulates inflammatory responses[93-97], and ultimately affects the cells aging[84], functional disability, and disease progression[84-89]. In contrast, poor psychosocial wellbeing, such as depression or negative affect[93], amplifies the stress signals and increases the HPA and sympathoadrenal system response to promote inflammation[93,95,98,99].

The second potential pathway psychosocial wellbeing may influence survival is through the behavioral pathways, where having a good psychosocial wellbeing may enhance the probability that individuals participate in restorative healthy behaviors[100] such as healthy eating[101,102], physical activity[103-106], volunteering[107,108], social engagement[109,110], use of preventive services[63], and adherence to medical regiments[103]. Meanwhile, positive psychosocial wellbeing may reduce the probability that individuals participate in unhealthy behaviors such as alcohol consumption[111-113], smoking[114-117], substance use[118], and unhealthy diet[100]. Such behaviors are important risk factors influencing disease risk.

2.5.2 Existing Evidence: Psychosocial Wellbeing and Health Behaviors and Medical Health

To date, mounting research reveals associations between facets of psychosocial wellbeing and various behavioral and physical health outcomes. To provide an overview of current evidence rather than list all the studies, we focused on several of the most studied psychosocial wellbeing constructs, modifiable health behaviors (physical activity, alcohol consumption, and smoking), and easy measurable medical health factors (chronic disease conditions and functional status).

Behavioral Factors. The association between many psychosocial wellbeing constructs and physical activity has been well-studied through cross-sectional[105,106], longitudinal cohort[116,119-123], and intervention[124] studies in many populations. Increased physical activity has been associated with stronger life purpose[103,104], higher life satisfaction[105], higher positive affect[122], stronger social support[121,124], higher self-efficacy[121,124], and better psychosocial wellbeing[119]. Inverse relationships between physical activity and social isolation[106], loneliness[121,125], pessimism[116], and depression symptoms[123] were also observed. A small number of null findings have also been noted[106,116,117]. Next, investigators have generally noted low life satisfaction[105], low life purpose[114,115,120], low self-esteem, low optimism[117,126], and high pessimism[116] are important psychosocial predictors of onset or escalation of smoking. Furthermore, research on psychosocial wellbeing constructs and alcohol consumption has tended to focus on teens and young adults[112,113,127,128], rather than older adults[120,129,130]. Moreover, the direction of the effect varies by the level of alcohol consumption. Generally, a positive relationship has been found between light to moderate alcohol consumption and less emotional loneliness[127]. Heavy alcohol consumption is associated with depression[129], pessimism[126], high social self-efficacy[113], low emotional self-efficacy[113], low life satisfaction[112], high hopelessness[128], and more social loneliness[127]. A few studies also reported null findings[105,120,130].

Medical Health Factors. A growing body of literature supports our hypothesis that psychosocial wellbeing influences functional disability and disease progression, especially among the elderly. Several national wide cross-sectional[131,132] and longitudinal cohort[133,134] studies have shown that higher life satisfaction[134], stronger positive affect[134], stronger social support[131,134], social participation[134], and more social connections[134] are associated with better health outcomes. These include slower rate of functional disability and reduced risk of chronic disease (e.g., heart

disease[85], diabetes[86,87]). Adverse psychosocial wellbeing constructs such as depression[131-133] and negative affect[134] increase the rate of functional disability and higher risk of chronic disease[85].

2.5.3 Limitations of Existing Evidence

Overall, these pioneering studies have contributed substantially to the literature. We can conclude that good psychosocial wellbeing is associated with being more physically active, less smoking, less heavy drinking, better functional status, and lower risk of chronic disease. Poor or adverse psychosocial wellbeing was related to less physical activities, smoking, heavy drinking, poor functional status, and higher risk of chronic disease. Current literature examined psychosocial wellbeing constructs separately might be based on individual conceptual models. However, the interconnectedness amongst a full set of psychosocial wellbeing constructs was not been fully investigated due to the complexity of the relationships. Only, a few studies were simultaneously accounting for one or two other psychosocial wellbeing constructs during the evaluation. Furthermore, none of the studies demonstrated the observed effects on the behavioral and medical health factors were independent of all other psychosocial wellbeing constructs.

Furthermore, being physically inactive, smoking, and heavy alcohol consumption are well-established behavior factors that increase the risk of mortality. Better medical health conditions among the elderly such as better functional status, and fewer chronic conditions, are essential to prolonging survival. To date, none of the research has attempted to investigate these potential behavioral and medical health pathways linking a comprehensive set of psychosocial wellbeing constructs and mortality within the same dataset. To answer this research question, the desirable research method is to conduct a mediation analysis. Nonetheless, there are several methodological challenges to implement multiple exposures and mediators mediation analysis. We believe those

challenges are the key reason current studies have not investigated behavioral pathways linking a comprehensive set of psychosocial wellbeing constructs and mortality within the same dataset.

Investigations into these potential biobehavioral pathways linking psychosocial wellbeing and survival are needed. My dissertation aim two sheds light on the potential pathways linking psychosocial wellbeing and all-cause mortality in HRS. With the goal of developing effective interventions, my dissertation aim two focused on the easy measurable medical health factors (chronic disease conditions and functional status) and modifiable behavioral (smoking, alcohol consumption, and physical activity) pathways.

Overall, the entire body of research in my dissertation is helping to define and refine the relevant research questions in life purpose and psychosocial wellbeing research.

Chapter 3 Association Between Life Purpose and Mortality Among US Adults Older Than 50 Years

3.1 Abstract

A growing body of literature suggests that having a strong sense of purpose in life leads to improvements in both physical and mental health and enhances overall quality of life. There are interventions available to influence life purpose; thus, understanding the association of life purpose with mortality is critical. To evaluate whether an association exists between life purpose and all-cause or cause-specific mortality among older adults in the United States. The Health and Retirement Study (HRS) is a national cohort study of US adults older than 50 years. Purpose in life was assessed for the 2006 interview period with a 7-item questionnaire from the modified Ryff and Keyes's Scales of Psychological Well-being scale. Five categories of life purpose scores were used (1.00-2.99, 3.00-3.99, 4.00-4.99, 5.00-5.99, and 6.00). All-cause and cause-specific mortality were assessed between 2006 and 2010.Weighted Cox proportional hazards models were used to evaluate life purpose and mortality. Of 6985 individuals included in the analysis, 4016 (57.5%) were women, the mean (SD) age of all participants was 68.6 (9.8) years, and the mean (SD) survival time for decedents was 31.21 (15.42) months (range, 1.00-71.00 months). Life purpose was significantly associated with all-cause mortality in the HRS (hazard ratio, 2.43; 95%CI, 1.57-3.75, comparing those in the lowest life purpose category with those in the highest life purpose category). Some significant cause-specific mortality associations with life purpose were also observed (heart, circulatory, and blood conditions: hazard ratio, 2.66; 95%CI, 1.62-4.38). This study's results indicated that stronger purpose in life was associated with decreased mortality.

Purposeful living may have health benefits. Future research should focus on evaluating the association of life purpose interventions with health outcomes, including mortality. In addition, understanding potential biological mechanisms through which life purpose may influence health outcomes would be valuable.

3.2 Introduction

A growing body of literature suggests that having a sense of purpose in life is associated with both physical and mental health and overall quality of life[65,135]. Purposeful living has been defined in various ways. In generally, purpose in life can be defined as "a self-organizing life aim that stimulates goals"[65], promotes healthy behaviors, and gives meaning to life[2,4].

Individuals lacking purpose in life may feel hopeless and not have motivations to live an active and healthful life. Some studies report that those with a strong purpose in life engage in healthy behaviors[136] and have better health outcomes for sleep disturbances[137], stroke incidence[138], post-stroke quality of life[139], depression[135], and diabetes[62]. The association between life purpose and overall mortality has also been explored previously, with Cohen and colleagues carrying out a meta-analysis of nine prospective studies that examined this association[65]. The studies utilized a variety of different measures of life purpose with six[21,24,25,140,141] of the nine studies[21,24-26,28,140-142] relying on a single question[65]. For example, in the studies conducted in Japan, participants are asked if they have "Ikigai", which is defined as "something to live for, the joy and goal of living"[21,24]. The aforementioned meta-analysis showed that compared with individuals with lower life purpose, higher scores on study-specific life purpose scales were associated with survival (relative risk=1.17, 95% CI 0.75-0.91)[65].

The modified Ryff and Keyes's Scales of Psychological Well-Being assessment is the most comprehensive, validated scale for purpose in life[1,2,12,29,30,65,136]. Only two of the studies included in the aforementioned meta-analysis[65] used this instrument and both found associations indicating that individuals with stronger purpose in life had lower all-cause mortality[28,142]. Furthermore, each of the studies included in the meta-analysis adjusted for some potentially confounding factors, but none comprehensively accounted for other psychological well-being constructs such as depression, anxiety, cynical hostility, negative affect, optimism, positive affect, and social participation.

The Health and Retirement Study (HRS) is a U.S. nationally representative, prospective cohort study that began in 1992 and has collected comprehensive data, including information on life purpose and other psychological well-being constructs. Life purpose was originally assessed in the HRS using an unvalidated measurement instrument designed by an HRS investigator; an initial study[26] using this measurement found no association with all-cause mortality. However, in 2006 the HRS implemented the modified Ryff and Keyes's Scales of Psychological Well-Being[2] assessment to measure life purpose. To our knowledge, there have been no previous analyses in HRS exploring the association between life purpose and cause-specific mortality using the modified Ryff and's Scales of Psychological Well-Being assessment. Therefore, we used the HRS data from 2006 through 2010 to examine whether purpose in life is associated with all-cause or cause-specific mortality among older adults. We were able to adjust for a large number of potential confounders, including other psychological well-being constructs that may affect the association between life purpose and mortality.

3.3 Methods

3.3.1 Study design and participants

Adults between the ages of 51 and 61 were enrolled in the HRS and their spouses or partners were enrolled, regardless of their age. Initially, individuals born between 1931 and 1941 were enrolled starting in 1992, but subsequent cohort enrichment was carried out. Details on HRS recruitment and data collection have been previously published[143] and are presented in Supplementary Section. The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies with the exception of reporting 2 levels of confounder-adjusted estimates rather than including fully unadjusted estimates for the sake of brevity. This study used deidentified, publicly available data from the HRS; therefore, the Institutional Review Board at the University of Michigan exempted the present study from the need for review. Written informed consent was obtained from all HRS participants.

In 2006, half of the HRS participants were randomly selected to complete an additional psychological questionnaire; this was a leave-behind questionnaire that participants returned by mail and included the modified Ryff and Keyes's Scales of Psychological Well-Being assessment. Although the remaining half of the HRS participants were asked to fill out the additional psychological questionnaire in the next interview wave in 2008[144], the present study focuses on only on the first half of participants who completed the psychological questionnaire in 2006. For the present study, this group was followed up through their 2010 visit.

The present sample was drawn from the 8,419 participants who were more than 50 years of age and who had filled out the psychological questionnaire during the HRS 2006 wave. Of these 8,419 participants, we excluded 1,142 (non-responders) with incomplete life purpose data, 163

with missing sample weights, 81 with loss to follow-up, 1 with incorrect survival time, or 47 with missing information on marital status, educational level, smoking status, alcohol use, or physical activity. Our final sample for analysis was 6,985 individuals (Figure 3-2).

3.3.2 Determination of Vital Status

The HRS assessed all-cause and cause-specific mortality between 2006 and 2010. Month and year and cause of death were recorded from a combination of two data sources those reported by household members and those obtained through matching with the National Death Index. A 98.8% validation of deaths with essentially zero false positives has previously been reported by HRS tracking studies[145]. Survival time was calculated as the number of months from the date of 2006 interview to date of death. In total, 776 deaths occurred among our analytic cohort from 2006 to 2010. In addition to all-cause mortality, we further focused on the four most common causes of death in HRS: 1) heart, circulatory and blood conditions (n=297); 2) cancer and tumors (n=208); 3) respiratory tract system conditions (n=108); and 4) digestive tract system conditions (n=86).

3.3.3 Censoring

Participants who were still alive at the end of their last follow-up were censored. Censoring dates were determined as follows (1) participants who were still alive and were followed up during the 2010 wave were censored at the date of the last interview from the 2010 interview wave (n=5,966) or (2) participants who were followed up during the 2008 wave, but not the 2010 wave were censored at the date of the last interview from the 2008 interview wave (n=138) or (3) participants who were not followed up during the 2008 or 2010 wave, but were

interviewed during the 2012 wave were censored at the date of the last 2010 interview for any participant (n=105).

3.3.4 Assessment of Purpose in Life

Purpose in life was assessed in the 2006 interview wave by using a seven-item questionnaire from the modified Ryff and Keyes's Scales of Psychological Well-Being [2]. The questionnaire used a Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree). Ratings for items that were negatively worded were flipped such that higher scores indicated greater purpose in life on all questions. The mean of the individual scores was then calculated for each participant to create a final, composite life purpose score. For the all-cause mortality analysis, further categorization was conducted to create five categories of life purpose score for ease of interpretation: (1.00- 2.99, 3.00 – 3.99, 4.00 – 4.99, 5.00 – 5.99, and 6.00). For the cause-specific mortality analysis, some categories were combined owing small numbers. Life purpose was also fit as a continuous variable and in quartiles and the results were consistent with those observed with the aforementioned categories.

On the basis of the HRS recommendations for coding[144], participants who answered fewer than three questions among the seven life purpose questions were considered to have incomplete life purpose data and were excluded (n=1,142 non-responders; Table 3-6). Because these non-responders are part of the ongoing HRS cohort, we were able to examine the sociodemographic and other characteristics of this group to provide insight into potential generalizability and selection bias issues (Table 3-6). A total of 944 individuals would have been eligible for this analysis if they had completed the questionnaire (Figure 3-2); Table 3-6 provides a description of the demographic and relevant clinical characteristics of this group of individuals.

3.3.5 Other Covariates

All covariates were assessed by self-report in 2006 and included sociodemographic characteristics, baseline health and behavioral characteristics, and psychological factors. Sociodemographic characteristics included age (50-54, 55-59, 60-64, 65-69, 70-74, 75-79, or 80 years old), sex (male or female), marital status (married, separated or divorced, widowed, or never married), race/ethnicity (non-Hispanic white, non-Hispanic and Hispanic black, Hispanic white, or other), and educational level (less than high school, high school degree, some college, college degree, or master's or professional graduate degree). Baseline health behaviors/status included smoking status, functional status, frequency of physical activity, alcohol consumption, presence of 1 or more chronic health conditions, and body mass index (calculated as weight in kilograms divided by height in meters squared). Details on how these variables were modeled are available in the Supplementary Section. Psychological status included four negative psychological constructs (depression, anxiety, cynical hostility, and negative affect) and three positive psychological constructs (optimism, positive affect, and social participation). These constructs have been considered in previous analyses of life purpose data from the HRS and were thus considered here; they could be confounders or mediators. Each psychological construct consisted of multiple questions and was combined into a summary score based on the instructions from HRS for each of the seven constructs[144]. A description and Cronbach alphas values for these seven psychological constructs are given in Supplementary Table 3-3. Each psychological construct was fit as a categorical variable based on quartiles.

3.3.6 Data Analysis

Descriptive statistics for those who died and for those were censored were calculated. Trend tests for continuous variables and heterogeneity for categorical variables were tested across groups using linear regression models and Chi- square tests, respectively. Sub-sample specific

weights provided by HRS were used in the present analysis to account for the HRS stratified, multistage area probability design[146]. Weighted Cox proportional hazards models were fit to examine the association between life purpose score (categorical; see above) and all-cause and cause-specific mortality using person-months as the underlying time metric. Two models were fit: Model 1 was adjusted for sociodemographic factors as well as health characteristics at the 2006 interview which included smoking status, physical activity, alcohol consumption, BMI, presence of chronic health conditions, and functional status; and Model 2 was adjusted for sociodemographic and health characteristics as well as psychological constructs. We estimated multivariate hazard ratios (HRs) and 95%CIs for all-cause and cause-specific mortality. In those analyses, we also took into account clustering within households given that individuals from the same household were invited to participate. In addition, we produced survival curves using the R package survminer (ggadjustedcurves) software to illustrate the association between life purpose and mortality. That curve was fully adjusted for sociodemographic and health characteristics and the psychological constructs.

3.3.7 Sensitivity Analysis

In addition to our main analysis, we also conducted sensitivity analyses restricted to 1774 individuals who had no reported chronic health conditions (ie, cancer, heart disease, stroke, diabetes, lung disease, or high blood pressure) in 2006, and we treated 53 participants who died in the first year of follow-up as censored rather than as having the event. These analyses were undertaken to consider the potential for reverse causation as an explanation of our findings. We were concerned that being near to death leads to low life purpose or having a chronic illness leads to low life purpose. The goal of the sensitivity analysis was to determine whether there continued to be an association between life purpose and mortality in these population subsets. The power for

these analyses was reduced because the sample size was smaller; thus, we evaluated only the trends in these data. All analyses were conducted from June 5, 2018, to April 22, 2019, using SAS, version 9.4 (SAS Institute Inc). A 2-sided $P < .05$ was considered statistically significant.

3.4 Results

3.4.1 Descriptive analysis

In total, 6985 individuals were included in the analysis; 4016 participants (57.5%) were women, and the mean (SD) age of all participants was 68.6 (9.8) years. The mean survival time for decedents was 31.21 months (SD, 15.42 months; range, 1.00-71.00 months). Overall, individuals who were older, male, or not currently married were more likely to have died (Table 3-1). In addition, there was a greater percentage of individuals with less than a high school degree who died (283 of 776 [36.5%]) compared with that in the censored group (1378 of 6209 [22.2%]). Individuals who died were more likely to be a current or former smoker, be nonalcohol drinkers, be physically inactive, and have a lower functional status at the time of completing the life purpose questionnaire in 2006 (Table 3-1). The life purpose distribution is also provided in Table 3-1.

There were 1142 HRS participants who were eligible to complete the life purpose questionnaire in 2006 but either did not complete it at all (940 [82.3%]) or completed fewer than 3 questions (202 [17.7%]) (Table 3-6). The HRS participants who did not complete the life purpose questionnaire were no more likely to die than the individuals included in the analysis (121 of 944 [12.8%] compared with 776 of 6985 [11.1%]; $P = .12$). They were, however, more likely to be older, female, widowed, or African American; have less than a high school degree; and have weaker functional status at baseline compared with the participants who did complete the questionnaire. In addition, 191 of 1141 participants (16.7%) who did not complete the life purpose

questionnaire were lost to follow-up between 2006 and 2010 compared with 81 of 7277 participants (11.1%) who did complete the questionnaire.

3.4.2 Life purpose and all-cause mortality

There was a significant association between life purpose and all-cause mortality (Table 3-2 and Figure 3-1). This was true for both the model adjusted for sociodemographic and health characteristics (model 1 comparing individuals in the lowest life purpose group with individuals in the highest group: HR, 3.15; 95%CI, 2.07-4.77; P < .001 for trend) (Table 3-2) as well as model 2, which was additionally adjusted for psychological well-being constructs. In model 2, the HR was 2.43 for comparing individuals in the lowest life purpose group to individuals in the highest group (95%CI, 1.57-3.75; P < 0.001 for trend). Further adjustment for the psychological well-being constructs (model 2) attenuated the estimated HR in each category of life purpose score, but there remained a significant association between life purpose and mortality (Table 3-2; Figure).

We carried out sensitivity analyses to explore the potential of reverse causation as an explanation for the findings. After censoring participants who died during the first year of follow-up, the association between life purpose and risk of death was similar although modestly attenuated (highest vs lowest life purpose score: HR, 2.24; 95%CI, 1.44-3.50; model 4) (Table 3-3). Similarly, after excluding participants with a chronic health condition at baseline, there was still an association between life purpose and mortality (models 5 and 6) (Table 3-3).

3.4.3 Life purpose and cause-specific mortality

There was a significant association between life purpose and mortality attributed to heart, circulatory, and blood conditions when the lowest and highest life purpose categories were compared (HR, 2.66; 95%CI, 1.62-4.38; P = 0.02 for trend) and between life purpose and digestive

tract system conditions when the lower life purpose categories and the highest category were compared (for life purpose scores 3.00-3.99: HR, 4.54; 95%CI, 1.77-11.66; for life purpose scores 4.00-4.99: HR, 3.04; 95%CI, 1.34-6.89; P = 0.01 for trend) (Table 4-4). For cancer and tumors (HR, 1.16; 95%CI, 0.60-2.25; P = 0.95 for trend) and respiratory tract system conditions (HR, 1.83; 95%CI, 0.80-4.20; P = 0.40 for trend), however, no association with mortality was observed.

3.5 Discussion

Low purpose in life was significantly associated with death among 6,985 older adults participating in the HRS. This finding was robust to adjustment for psychological well-being constructs and also showed a trend of with decreasing life purpose. This finding is in agreement with previous literature that used a different life purpose measurement tool, often only a single question, and adjustment for only a subset of the potential confounders for which we were able to control[21,24-26,28,140-142].

There are several possible mechanisms through which life purpose might potentially be associated with mortality. Fredrickson and colleagues showed that stronger well-being, of which purposeful living is a component, was associated with decreased expression of pro-inflammatory genes[58]. In another small study, stronger purpose in life was associated with lower cortisol levels and lower levels of pro-inflammatory cytokines[12]. There is evidence to suggest that elevated levels of inflammatory markers such as C-reactive protein[147-149] and cytokines such as interleukin 6[148,149] are associated with increased mortality and this represents one possible mechanism through which purpose in life influences mortality. However, to our knowledge there have been no life purpose intervention studies that have then measured the association with health outcomes (including mortality), cytokines or other biomarkers.

The present results from the cause-specific mortality analysis were less clear. The association between mortality and life purpose was only evident only for heart and blood diseases and digestive tract system diseases (Table 3-4). There is little published literature on cause-specific mortality and life purpose. Tanno and colleagues reported that the risk of cardiovascular mortality, but not coronary heart disease or cerebrovascular disease mortality was significantly associated with life purpose among Japanese men[21]. In addition, that study found a null association between life purpose and cancer as the cause of mortality, regardless of sex, which is in line with our null finding. Additional research on cause-specific mortality and life purpose is needed.

There are a number of method considerations with our analysis. Our study included a comprehensive analysis of psychological well-being constructs, including 4 negative psychological measures (depression, anxiety, cynical hostility, and negative affect) and 3 positive psychological measures (optimism, positive affect, and social participation). It is possible that some or all of these psychological well-being constructs are mediators; if this is the case, adjusting for these variables took the potential mediation into account. To address this issue, we presented results with or without adjustment for these measures (Table 3-2; model 1 vs model 2). Currently, more sophisticated methods for mediation analysis are not available because of the correlated nature of the psychological constructs and because this is a survival analysis. When such methods become available, it would be interesting to carry out a formal mediation analysis.

A potential concern with the present analysis is that life purpose at baseline may have been influenced by the presence of a chronic or life-threatening illness (reverse causation); however, this did not appear to be the case. We conducted sensitivity analyses in which all individuals who died during the first 2 years of follow-up were censored and included in a separate analysis, and we excluded all individuals who reported a chronic illness at baseline (Table 3-3). The results of

these sensitivity analyses continued to suggest an association between life purpose and mortality (although not statistically significant given the major decrease in the number of events in the chronic conditions analysis), providing supporting evidence that reverse causation does not account for the association we observed.

Selective loss to follow-up does not appear to be a concern in the present study given that only 1% of the 7727 participants who completed the life purpose questionnaire were lost to follow-up. However, selection bias is a potential issue because among 1142 HRS participants in 2006 who were eligible to complete the life purpose questionnaire, 940 did not complete it at all, and 202 completed fewer than 3 questions. Those HRS participants were no more likely to die than the individuals included in the analysis (12.8%compared with 11.1%, P = 0.12), and we adjusted for the characteristics of those who were more likely to not complete the life purpose questionnaire; however, we cannot rule out selection bias.

3.6 Conclusion

In summary, in the HRS, a stronger purpose in life was associated with lower mortality. There are a number of interventions that have been developed with the goal of improving life purpose. Intervention studies of volunteering[150-152], well-being therapy[153], and mediations[154] among adults have shown improvements in purpose in life, quality of life and various health outcomes. Mindfulness is one component of life purpose and studies of this construct have been carried out among breast cancer survivors[155,156]. Those studies have shown promise in improving psychological well-being measures[155,156] and quality of life[156], but associations with mortality have not been evaluated. There are also eHealth applications designed to influence life purpose (e.g., Purposeful). Future research should focus on the mechanism of how life purpose may influence all-cause mortality and cause-specific mortality; and on the appropriate timing of life purpose

interventions in a diseased population. Ultimately, a randomized trial exploring life purpose interventions and disease outcomes, quality of life and mortality are warranted.

Table 3-1. Descriptive characteristics of the 6,985 HRS participants included in this analysis.

	No Event (N=6209)		**Death** (N=776)		**P-value** [b]
Measure	**N**	**Mean(SD)/%**	**N**	**Mean(SD)/%**	
Age					<.001
50-54	475	7.65%	13	1.68%	
55-59	977	15.74%	34	4.38%	
60-64	976	15.72%	56	7.22%	
65-69	1266	20.39%	121	15.59%	
70-74	1052	16.94%	116	14.95%	
75-79	732	11.79%	129	16.62%	
80+	731	11.77%	307	39.56%	
Gender					<.001
Male	2588	41.68%	381	49.10%	
Female	3621	58.32%	395	50.90%	
Marital status					<.001
Married	4118	66.32%	411	52.96%	
Separated/Divorced	813	13.09%	76	9.79%	
Widowed	1110	17.88%	266	34.28%	
Never Married	168	2.71%	23	2.96%	
Race/ethnicity					0.12
Non-Hispanic White	4827	77.74%	621	80.03%	
Non-Hispanic and Hispanic Black	780	12.56%	96	12.37%	
Hispanic White	327	5.27%	40	5.15%	
Other	275	4.43%	19	2.45%	
Education					<.001
<High school	1378	22.19%	283	36.47%	
High school	3145	50.65%	368	47.42%	
Some College	277	4.46%	19	2.45%	
College	838	13.5%	59	7.6%	
Master or Professional degree	571	9.2%	47	6.06%	
Smoking status					<.001
Never	2758	44.42%	256	32.99%	
Current smoker	774	12.47%	125	16.11%	
Former smoker	2669	42.99%	393	50.64%	
Smoker but don't know whether current	8	0.13%	2	0.26%	
Drink alcohol					<.001
No	4079	65.69%	588	75.77%	
1-2 days per week	994	16.01%	100	12.89%	
3-4 days per week	411	6.62%	22	2.84%	
5-6 days per week	208	3.35%	13	1.68%	
Everyday	517	8.33%	53	6.83%	
Vigorous physical activity					<.001
Every day	174	2.80%	20	2.58%	
More than once a week	1338	21.55%	76	9.79%	
Once a week	502	8.09%	30	3.87%	
One to three times a month	423	6.81%	28	3.61%	
Hardly ever or never	3772	60.75%	622	80.15%	
Functional status score	6209	0.21(0.66)	776	0.75(1.26)	<.001
Presence of Chronic Illness					
No	1695	27.3%	79	10.18%	<.001
Yes	4514	72.7%	697	89.82%	
BMI (kg/cm^2)[a]					<.001
≤18.5	191	3.08%	62	7.99%	
18.51-24.99	1840	29.63%	292	37.63%	
25–29.99	2355	37.93%	230	29.64%	
≥30	1823	29.36%	192	24.74%	
Life purpose score	6209	4.57(0.92)	776	4.05(0.96)	<.001
Life purpose score group					<.001
1-2.99	217	3.49%	83	10.7%	

3-3.99	1403	22.6%	281	36.21%
4-4.99	2186	35.21%	266	34.28%
5-5.99	1998	32.18%	129	16.62%
6	405	6.52%	17	2.19%

[a]. BMI as weight in kilograms divided by the square of the height in meters, then categorized according to the recommendations of the World Health Organization: below-normal weight (<18.5 kg/m^2), normal range (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2)

[b]. P-values obtained through chi-square test.

Table 3-2. Adjusted hazard ratio and 95% confidence intervals for life purpose and all-Cause mortality, 2006–2010 HRS (N=6,985). [a]

	Model 1[d]		**Model 2[e]**	
Life purpose score	**HR[b]**	**95CI%[c]**	**HR**	**95CI%**
1-2.99	3.15**	2.07,4.77	2.43**	1.57,3.75
3-3.99	2.13**	1.41,3.21	1.72*	1.13,2.62
4-4.99	1.90*	1.27,2.84	1.67*	1.12,2.49
5-5.99	1.30	0.85,1.99	1.26	0.82,1.93
6	1	Reference	1	Reference
P for Trend	*<.001*		*<.001*	

* Indicates p-value<0.05.

** Indicates p-value<0.001.

a All Cox proportional hazard models were weighted, and Life purpose score = 6 is reference group.

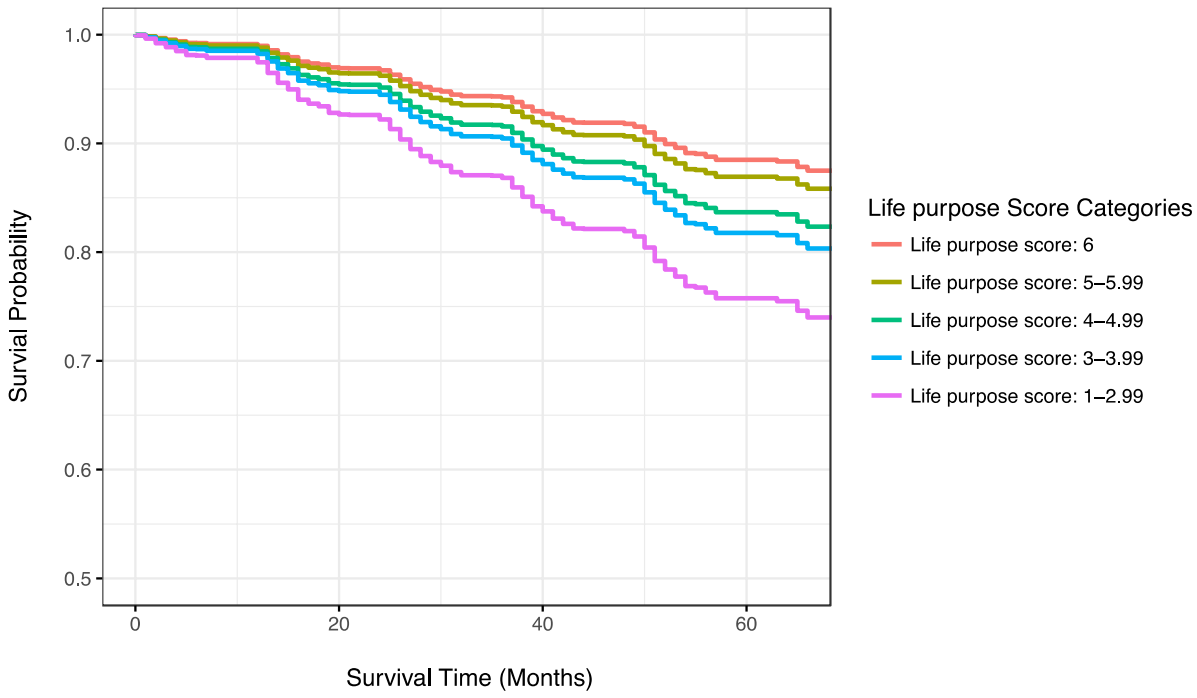
[b] Hazard Ratio

[c] Confident Interval

d Model 1 Cox proportional hazards model analysis after adjusting for age, gender, education, race, marital status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2), functional status, and presence of one or more chronic conditions.

e Model 2 Cox proportional hazards model analysis after adjusting for age, gender, education, race, marital status, functional status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2), presence of one or more chronic conditions, depression, anxiety, cynical hostility, negative affect optimism, positive affect, and social participation.

Figure 3-1. Survival curves illustrating the association between life purpose and mortality. [a]



[a] Survival curves are adjusted for age, gender, education, race, marital status, functional status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2), depression, anxiety, cynical hostility, negative affect, positive affect, optimism, and social participation. Adjusted survival curves are constructed by first generating a pseudo-population based on study population characteristics. For each life purpose score category, a survival curve is estimated for this pseudo-population based on the fitted Cox proportional hazards model presented in Table 3-2 assuming that all subjects fall into that specific life purpose score category. This figure illustrates the relationship between life purpose and mortality on a covariate balanced pseudo-population, with those in the lowest category (1-2.99 – red line) having significantly worse survival compared to those in the highest life purpose category (6 – purple line).

Table 3-3.Sensitivity analysis: adjusted hazard ratio and 95% confidence intervals for all-cause mortality, 2006–2010 HRS. a

	First year death exclusion N=6,985 (Event n=723)				Chronic disease free at the baseline N=1,774 (Event n=79)			
	Model 3[b]		Model 4[c]		Model 5[b]		Model 6[c]	
Life purpose score	**HR[d]**	**95CI%[e]**	**HR**	**95CI%**	**HR**	**95CI%**	**HR**	**95CI%**
1-2.99	2.85*	1.85,4.33	2.24**	1.44,3.50	1.42	0.22,9.30	0.78	0.09,6.59
3-3.99	1.96*	1.30,2.96	1.61*	1.06,2.45	2.69	0.56,12.98	1.57	0.27,9.19
4-4.99	1.78*	1.20,2.64	1.58*	1.06,2.34	2.31	0.47,11.22	1.71	0.33,8.87
5-5.99	1.29	0.85,1.96	1.24	0.81,1.90	1.07	0.21,5.48	0.96	0.18,5.08
6	1	Reference	1	Reference	1	Reference	1	Reference
P for Trend	*<.001*		*0.002*		*0.80*		*0.97*	

* Indicates p-value<0.05.

[a] Sensitivity analysis was conducted by censoring those who died in the first year of follow-up and excluding those with a chronic disease at baseline (2006). All Cox proportional hazard models were weighted, and Life purpose score = 6 is reference group.

[b] Model 3 and 5 Cox proportional hazards model analysis after adjusting for age, gender, education, race, marital status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2),functional status, and one or more chronic conditions.

[c] Model 4 and 6 Cox proportional hazards model analysis after adjusting for age, gender, education, race, marital status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2), presence of one or chronic conditions, functional status, depression, anxiety, cynical hostility, and negative affect optimism, positive affect, and social participation.

[d] Hazard Ratio

[e] Confident Interval

Table 3-4. Adjusted hazard ratio and 95% confidence intervals for cause specific mortality, 2006–2010 HRS (N=6,985). [a]

	Model 1 [b]		Model 2 [c]	
Life purpose score	**HR[d]**	**95CI%[e]**	**HR**	**95CI%**
Heart and blood diseases				
1-2.99	2.53*	1.69,3.78	2.66*	1.62,4.38
3-3.99	1.51	1.92,2.49	1.56	0.93,2.62
4-4.99	1.39	0.87,2.22	1.40	0.87,2.27
5-6	1	Reference	1	Reference
P for Trend	*<0.001*		*0.02*	
Cancer				
1-2.99	1.49	0.79,2.80	1.16	0.60,2.25
3-3.99	1.11	0.66,1.86	0.95	0.53,1.69
4-4.99	1.16	0.77,1.74	1.02	0.66,1.56
5-6	1	Reference	1	Reference
P for Trend	*0.43*		*0.95*	
Respiratory system diseases				
1-2.99	3.43*	1.57,7.50	1.83	0.80,4.20
3-3.99	1.68	0.99,2.86	1.04	0.56,1.93
4-4.99	1.62*	1.03,2.54	1.24	0.73,2.11
5-6	1	Reference	1	Reference
P for Trend	*0.02*		*0.40*	
Digestive system diseases				
1-2.99	2.68	0.83,9.13	2.05	0.52,8.13
3-3.99	5.95**	2.71,13.08	4.54*	1.77,11.66
4-4.99	3.52*	1.57,7.89	3.04*	1.34,6.89
5-6	1	Reference	1	Reference
P for Trend	*<.001*		*0.01*	

* Indicates p-value<0.05.

[a] All Cox proportional hazard models were weighted, and Life purpose score range from 5 to 6 is reference group.

[b] Model 1 Cox proportional hazards model analysis after adjusting for age, gender, education, race, marital status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2), functional status, and one or more chronic conditions.

[c] Model 2 Cox proportional hazards model analysis after adjusting for age, gender, education, race, marital status, functional status, smoking status, frequency of physical activity, alcohol consumption, BMI (kg/cm2), one or more chronic conditions. depression, anxiety, cynical hostility, negative affect, optimism, positive affect, and social participation.

[d] Hazard Ratio

[e] Confident Interval

3.7 Supplementary Section

HRS Study Design. HRS cohort enrichment was carried out in 1993 (the Asset and Health Dynamics of the Oldest Old Cohort (AHEAD)), 1998 (Children of the Depression Cohort (CODA) and War Baby), 2004 (The Early Baby Boomers Cohort (EBB)) and 2010 (The Mid Baby Boomers Cohort (MBB) and Minority oversample) to enroll more birth cohorts [143]. Face-to-face interviews are conducted every two years to collect information on participants' health, economics, demographics, and the retirement process; the data are publicly available [143,146]. HRS used a stratified, multistage area probability design, in which Blacks, Hispanics, and Floridians were oversampled [143,157] and we accounted for the sampling weights in our analyses.

Covariate Coding. Smoking status was determined as never, current smoker, or former smoker. Individuals who reported being a smoker on previous questionnaires, but did not answer the question on the 2006 questionnaire, were placed into a separate "smoker, but current status unknown" category to prevent them from being excluded from the analysis. The functional status score was calculated by summation of five activities of daily living (bathing, eating, dressing, walking across a room, and getting in or out of bed). A higher score indicated weaker functioning (continuous). Physical activity was assessed based on the reported frequency of vigorous activity (such as running or jogging, swimming, cycling, aerobics or gym workout, tennis, or digging with a spade or shovel) and categorized as 1) every day; 2) more than once a week; 3) once a week; 4) one to three times a month; 5) hardly ever or never. Alcohol consumption was measured based on two questions "Do you ever drink any alcoholic beverages such as beer, wine, or liquor? and "If yes, in the last three months, on average, how many days per week have you had any alcohol to drink?" We further divided alcohol consumption into 1) non-drinkers 2) drink 1-2 days per week,

3) drink 3-4 days per week, 4) drink 5-6 days per week, and 5) drink everyday. BMI was calculated using self-reported weight and height, and categorized according to the recommendations of the World Health Organization [158]: below-normal weight (<18.5 kg/m2), normal range (18.5–24.9 kg/m2), overweight (25.0–29.9 kg/m2), and obese (≥30.0 kg/m2).

Time-varying association between life purpose and mortality. We investigated temporal variation in hazard ratio (HR) estimates across time intervals since 2006 using the continuous life purpose score. First, the Cox proportional hazards assumptions were tested using Schoenfeld residuals and the corresponding p-values. We found that those assumptions were not violated in our model. Thus, the Cox proportional hazards model can be used in the time-varying analysis. Next, an additional model was fit using six-time intervals since 2006 (0 to 1 year, >1 to 2 years, >2 to 3 years, >3 to 4 years, >4 to 5 years, and greater than 5 years). This time-varying analysis allowed us to observe a more refined estimation of the protective association between life purpose and mortality during particular time windows. It further allowed us to assess if being proximal to death leads to lower life purpose. All models were adjusted for the complete sets of covariates. As shown in Figure 3-3. We observed the protective effect of life purpose on mortality was strongest between years 1 and 2 (HR=0.71, 95%CI:0.70, 0.72), and the HR estimation subtly decreased over time. However, the estimated protective effects were statistically significant at all time points. Our time-varying analysis demonstrated the association between life purpose and mortality is not time-dependent. However, the effect of disease burden on the association between life purpose and mortality should be investigated in future research.

Supplementary Tables and Figures

Figure 3-2. 2006–2010 HRS data cleaning flowchart.

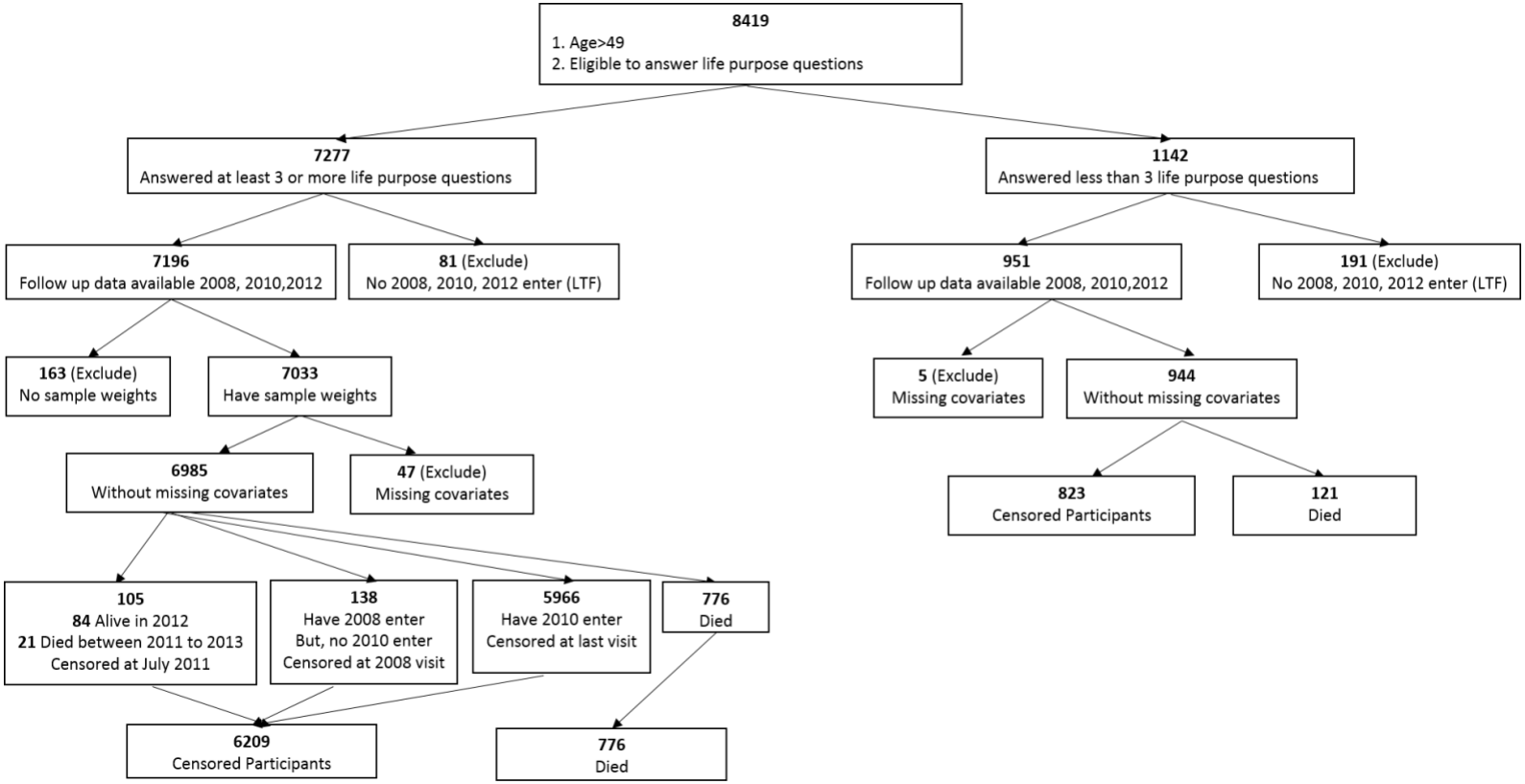


Table 3-5. Descriptive statistics for psychological factors for the 2006–2010 HRS (N=6,985).

Psychological covariates	**No Event N=6,029**			**Death N=776**			**Cronbach alphas**[a]
	Range	Mean	SD	Range	Mean	SD	
Negative							
Anxiety	1-4	1.54	0.56	1-4	1.72	0.64	0.81
Cynical hostility	1-6	2.94	1.13	1-6	3.1	1.18	0.79
Depression	0-8	1.45	1.9	0-8	2.25	2.12	0.54
Negative affect	1-5	1.6	0.63	1-5	1.87	0.77	
Positive							
Optimism	1-6	4.09	0.87	1-6	4.00	1.00	0.52
Positive affect	1-5	3.6	0.68	1-5	3.45	0.72	0.92
Social participation	0-8	4.19	1.66	0-8	3.07	1.69	0.87

[a] Standardized alpha coefficient provides information about how each variable reflects the reliability of the scale with standardized variables.

Table 3-6. Descriptive characteristics of the 944 HRS participants with incomplete life purpose questionnaire.

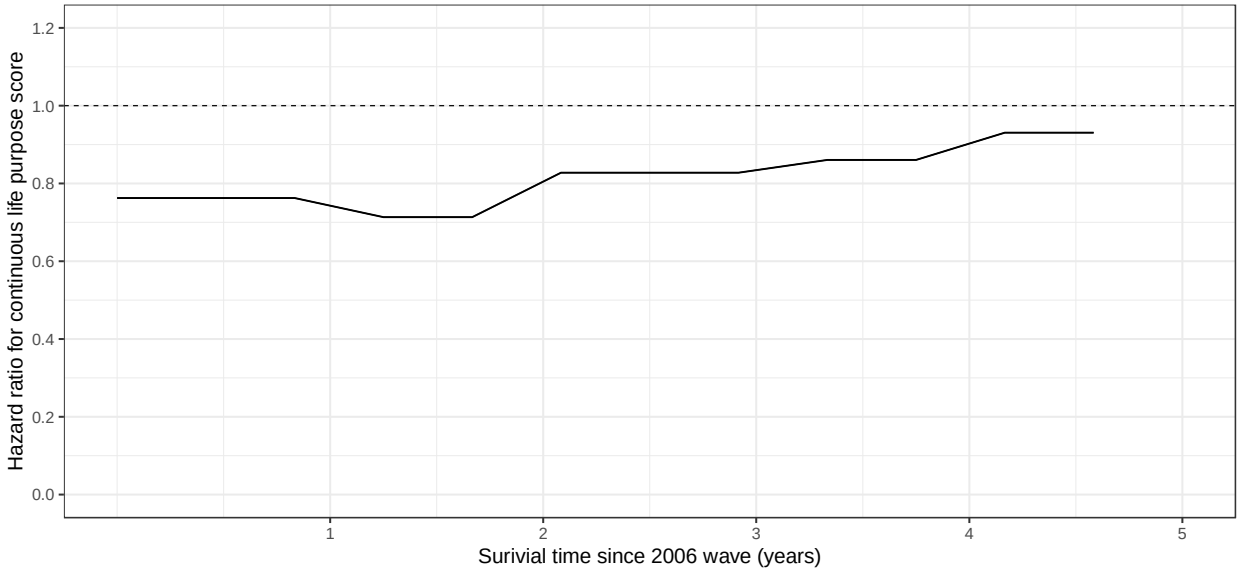
	Total (N=944)		**No Event** (N=823)		**Death** (N=121)	
Measure	**N**	**Mean(SD)/%**	**N**	**Mean(SD)/%**	**N**	**Mean(SD)/%**
Age						
50-54	126	13.35%	125	15.19%	1	0.83%
55-59	148	15.68%	145	17.62%	3	2.48%
60-64	110	11.65%	106	12.88%	4	3.31%
65-69	143	15.15%	129	15.67%	14	11.57%
70-74	120	12.71%	103	12.52%	17	14.05%
75-79	84	8.90%	71	8.63%	13	10.74%
80+	213	22.56%	144	17.50%	69	57.02%
Gender						
Male	397	42.06%	342	41.56%	55	45.45%
Female	547	57.94%	481	58.44%	66	54.55%
Marital status						
Married	503	53.28%	458	55.65%	45	37.19%
Separated/Divorced	143	15.15%	132	16.04%	11	9.09%
Widowed	266	28.18%	205	24.91%	61	50.41%
Never Married	32	3.39%	28	3.40%	4	3.31%
Race/ethnicity						
Non-Hispanic White	546	57.84%	469	56.99%	77	63.64%
Non-Hispanic and Hispanic Black	252	26.69%	222	26.97%	30	24.79%
Hispanic White	73	7.73%	66	8.02%	7	5.79%
Other	73	7.73%	66	8.02%	7	5.79%
Education						
<High school	361	38.24%	309	37.55%	52	42.98%
High school	385	40.78%	330	40.10%	55	45.45%
Some College	34	3.60%	31	3.77%	3	2.48%
College	93	9.85%	86	10.45%	7	5.79%
Master or Professional degree	71	7.52%	67	8.14%	4	3.31%
Smoking status						
Never	401	42.48%	357	43.38%	44	36.36%
Current smoker	162	17.16%	146	17.74%	16	13.22%
Former smoker	377	39.94%	317	38.52%	60	49.59%
Smoker but don't know whether current	4	0.42%	3	0.36%	1	0.83%
Drink alcohol						
No	660	69.92%	570	69.26%	90	74.38%
1-2 days per week	133	14.09%	124	15.07%	9	7.44%
3-4 days per week	56	5.93%	49	5.95%	7	5.79%
5-6 days per week	32	3.39%	30	3.65%	2	1.65%
Everyday	63	6.67%	50	6.08%	13	10.74%
Vigorous physical activity						
Every day	21	2.22%	20	2.43%	1	0.83%
More than once a week	153	16.21%	147	17.86%	6	4.96%
Once a week	57	6.04%	54	6.56%	3	2.48%
One to three times a month	36	3.81%	32	3.89%	4	3.31%
Hardly ever or never	677	71.72%	570	69.26%	107	88.43%
Functional status score	944	0.54(1.21)	823	0.41(1.03)	121	1.39(1.82)
Presence of Chronic Illness						
No	243	25.74%	226	27.46%	17	14.05%
Yes	701	74.26%	597	72.54%	104	85.95%
BMI (kg/cm^2)[a]						
≤18.5	58	6.14%	50	6.08%	8	6.61%
18.51-24.99	304	32.2%	249	30.26%	55	45.45%
25–29.99	330	34.96%	296	35.97%	34	28.10%
≥30	252	26.69%	228	27.70%	24	19.83%
Life purpose score	944	3.95(0.33)	823	3.95(0.33)	121	3.94(0.37)

Life purpose score group						
1-2.99	12	25.00%	10	23.81%	2	33.33%
3-3.99	9	18.75%	8	19.05%	1	16.67%
4-4.99	15	31.25%	14	33.33%	1	16.67%
5-5.99	8	16.67%	7	16.67%	1	16.67%
6	4	8.33%	3	7.14%	1	16.67%
Missing	896		781		115	

[a]. BMI as weight in kilograms divided by the square of the height in meters, then categorized according to the recommendations of the World Health Organization: below-normal weight (<18.5 kg/m^2), normal range (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obesity (≥30.0 kg/m^2)

[b]. P-values obtained through chi-square test.

Figure 3-3. Estimated time-varying hazard ratio for continuous life purpose score.



This figure illustrated the HR and 95% confidence intervals for one unit increase in life purpose score. We observed the estimated protective effects were statistically significant at all time points.

Chapter 4 Decomposing the Association of Psychosocial Wellbeing with All-Cause Mortality: The Mediating Role of Physical Health and Behaviors

4.1 Abstract

Previous studies of the association between psychosocial constructs and mortality have generally focused on single factors, ignoring the interconnectedness and shared biologic pathways between these exposures. This study quantified the effect of a comprehensive set of 48 psychosocial constructs on survival and further evaluated the indirect effects of this association through behavioral and physical health factors. 7,698 individuals from the nationally-representative Health and Retirement Study were included in the analysis. Latent class analysis was used to divide participants into mutually exclusive psychosocial wellbeing groups based on their pattern of psychosocial constructs. Psychosocial wellbeing group (good, average, and poor) was considered as the "exposure", and physical health (functional status and comorbid conditions) and behavioral characteristics (physical activity, smoking, and alcohol consumption) were considered as potential mediators. We also created a composite health index measure representing the summative effect of the mediators. We observed strong and statistically significant total effects from the accelerated failure time model for the association between survival time and psychosocial wellbeing (e.g. good versus poor psychosocial class had a survival rate (SR)=1.73 with 95% confidence interval (CI):1.50,2.01). Through the mediation analysis, the direct effect via psychosocial wellbeing accounted for more than half of the total effect of this relationship (SR=1.46, 95%CI:1.27,1.67). However, indirect effects with the health index and individual

mediators were also observed. Our findings highlight the interconnectedness of psychosocial wellbeing constructs and physical and behavioral health factors on survival.

4.2 Introduction

The importance of psychological wellbeing on health outcomes has become clear over the past decade[84,159-162]. Psychosocial wellbeing constructs include positive and adverse factors, such as life satisfaction, happiness, life purpose, depression, and loneliness. Although many observational studies have established that psychological wellbeing influences disease risk[84-87] and mortality[70,89,90], these constructs are often studied in isolation which does not reflect the interconnectedness of these exposures and outcomes or shared biologic pathways.

The potential causal pathways between psychological wellbeing and health outcomes, including survival, include neuroendocrine regulation of stress responses and health-related behavioral pathways. Specifically, through the neuroendocrine system[91,92], positive psychological wellbeing may balance allostatic load over the long term, regulate inflammatory responses[93-97], and ultimately affect cellular aging[84] and functional disability to lower the risk of chronic disease[84-87,89]. Strong psychological wellbeing may also act through behavioral pathways to influence disease risk by reducing the likelihood that individuals engage in unhealthy behaviors such as excessive alcohol consumption[112,113], smoking[114-116], or physical inactivity[103,104,106].

Current literature examined psychosocial wellbeing constructs separately based on individual conceptual models. However, the interconnectedness amongst a full range of psychosocial wellbeing constructs was not been fully investigated due to the complexity of the relationships. To further our understanding of the total effect of psychosocial wellbeing on mortality and the pathways underlying this association, in particular, to understand whether the

total effect of psychosocial wellbeing on mortality is mediated through physical and behavioral health factors one needs large, representative data and modern tools for mediation analyses. However, the implementation of such an analysis in the survival context is methodologically challenging, particularly with data from cohorts that employed a complex survey design and have missing data. Thus, nuanced application of advanced mediation analysis methods with complex, imperfect data has been limited.

The U.S. Health and Retirement Study (HRS) is a nationally representative cohort that has collected comprehensive data on psychosocial wellbeing and health behaviors using a complex survey design[143]. In the present paper, we have used data from the HRS to quantify the effect of a large set of psychosocial wellbeing constructs on mortality. We have further evaluated the extent to which the association between psychosocial wellbeing constructs and overall survival is mediated by behavioral (smoking, alcohol consumption, and physical activity) and physical (chronic disease conditions and functional status) health factors in this cohort. Lastly, we provide an analytic workflow to overcome the methodological challenges of conducting mediation analysis with time to event outcomes and multiple imputed missing covariate data from a study that employed a complex survey design.

4.3 Methods

4.3.1 Study Population

This analysis used de-identified, publicly available data from the HRS. HRS is nationally representative, longitudinal cohort study of older adults in the U.S. aged between 51 to 61 at enrollment and their spouses or partners, regardless of age[143]. HRS used a stratified, multistage area probability design, in which Blacks, Hispanics, and Floridians were oversampled[143]. HRS began collecting data in 1992 and every two years thereafter. In addition, in 2006 and every four

years thereafter, half of the HRS participants were randomly selected to complete an additional psychological and lifestyle questionnaire[144]. The remaining half of the HRS participants were asked to fill out the psychological and lifestyle questionnaire at the next interview wave (2008) and every four years thereafter[144]. This questionnaire covers six substantive areas: 1) subjective well-being; 2) social relationships; 3) lifestyle and experience of stress and trauma; 4) self-related beliefs; 5) personality; and 6) work-related beliefs and experience. HRS also assesses all-cause and cause-specific mortality every two years[143].

The analytic sample for the present study was drawn from the 18,469 participants who were under observation in 2006. From these participants, 8,681 participants were randomly selected by HRS to fill out the psychological and lifestyle questionnaire in 2006. This was the first group of HRS participants to complete this questionnaire. From the 8,681 eligible participants, we excluded individuals missing sample weights in 2006 (n=564), those who were younger than 50 years old (n=2) and those with no follow-up data beyond baseline in 2006 (n=417). This left us with an analytic sample of 7,698 individuals (Figure 4-3).

4.3.2 Measures

Psychosocial Constructs. The exposures of interest were the psychosocial constructs that were covered in the five predefined substantive areas from the psychological questionnaire: 1) subjective well-being, 2) social relationships, 3) lifestyle and experience of stress and trauma, 4) self-related beliefs, and 5) personality. Psychosocial constructs that were covered in the work-related beliefs and experience were excluded from the current study because of the large degree of missingness (~70%). In total, 48 psychosocial constructs across these five domains were evaluated in 2006 (Table 4-6). Each psychosocial construct was assessed from a multi-item questionnaire. Details about specific psychosocial construct questionnaires can be found in HRS

documentation[144]. A summary score for each psychosocial construct was created by either averaging the individual items or summing the multi-item questionnaire based on the guidance from HRS[144]. All psychosocial constructs were centered prior the analyses.

All-cause Mortality. HRS assesses all-cause mortality every two years through "exit interviews" taken on behalf of deceased respondents. Month and year and cause of death are recorded from a combination of two data sources: (1) report by household members and (2) National Death Index[143]. Participants who were still alive at the end of their last follow-up were censored. Survival time was calculated as the number of months from the date of 2006 interview to the date of death or the date of their last follow-up interview through 2014 (for those who are censored). In total, 1902 deaths (24.7 % of participants) occurred among our analytic cohort from 2006 to 2014.

Behavioral and Physical Health Characteristics. Behavioral and physical health characteristics that were self-reported in 2006 were considered as potential mediators of the relationship between psychosocial wellbeing and overall survival. Behavioral health characteristics included smoking status (0=current smoker, and 1=former smoker or never smoked), frequency of vigorous physical activity (0= hardly ever or never, and 1= sometimes or every day), and alcohol consumption (0=non-drinkers and 1=some weekly consumption). Physical health characteristics were functional status and comorbid conditions. The functional status score was calculated by summing the values of five activities of daily living (bathing, eating, dressing, walking across a room, and getting in or out of bed), with a higher score indicated better functioning. Comorbid conditions of diabetes, lung disease, heart disease, hypertension, cancer, stroke, and arthritis were categorized as present or absent and then summed. The range for

comorbid conditions was 0-7, but for analytic purposes, 5, 6, and 7 conditions were collapsed into a 5+ category.

Other Covariates. Sociodemographic characteristics and body mass index (BMI) were considered important *a priori* confounders. Sociodemographic characteristics were self-reported in 2006 and included age (five-year age groups from 50-79 and 80+ years old), gender (male/female), marital status (married, separated/divorced, widowed, and never married), race/ethnicity (non-Hispanic White, non-Hispanic and Hispanic Black, Hispanic White, and other), education (less than high school, high school degree, some college, college degree, and master or professional degree graduate degree), total household income (quartiles), and total wealth (quartiles). BMI was calculated using the 2006 weight and height measures collected by trained HRS staff and categorized according to the recommendations of the World Health Organization: below-normal weight (<18.5 kg/m^2), normal range (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (>=30.0 kg/m^2).

Timing of Exposures, Mediators, and Covariates. It should be noted that only the 2006 measures of exposures, mediators, and other covariates were used, although mediators were re-measured in 2010. The major concern of using the 2010 mediator measures was potential selection bias due to the exclusion of participants who died before 2010, and those who did not fill out behavioral and physical health questionnaires in 2010. We were concerned that individuals with lower psychosocial wellbeing were more likely to drop out of the study and not fill out the questionnaires in 2010. Under such a scenario, the probability of being included in our analysis is related to both exposure (psychosocial wellbeing) and the outcome (survival). Thus, such exclusion may introduce selection bias, leading to overestimating the true association between psychosocial wellbeing and survival. Using the 2006 exposure and mediator measures is a

conservative approach that helps reduce concerns about potential selection bias. All five behavioral and physical health characteristics from 2006 were assessed as mediators, all 48 psychological constructs in 2006 were evaluated as exposures, and age, gender, race, marital status, education, total household income, total wealth, and BMI were controlled as *a priori* confounders.

4.3.3 Statistical Analysis

Treatment of Missing Data. As shown in Table 4-5, our analytic sample (n=7,698 HRS participants) had similar demographic characteristics compared to the full sample (n=18,469) in 2006. From the analytic dataset (n=7,698), the complete case sample size was 2,300. HRS participants who had no missing measures (n=2,300) were more likely to be in the ages between 55-70 years, male, Non-Hispanic white; married; had a master or professional degree, compared to all HRS participants in 2006 wave (n=18,469). Overall, the complete cases were not representative of the HRS population (Table 4-5). Thus, multiple imputation via chained equations (*mice* package in R)[163] was used for imputing the missing exposures, mediators, and covariates in 2006. In total, 50 imputed datasets were generated from the original data, and each imputed dataset consisted of a sample size of 7,698.

Latent Class Analysis among Exposures. To evaluate 48 psychosocial constructs (exposures) simultaneously in the mediation analysis, a two-step approach was implemented (Figure 4-1). Step one: The effect of individual psychosocial constructs on all-cause mortality was examined separately for each psychosocial wellbeing construct. Those associations were examined using Cox Proportional-Hazards regression models adjusted for *a priori* confounders; those with *p*-values ≤ 0.20 were kept for step two (Table 4-6). Step two: A latent class analysis was conducted using the selected psychosocial constructs from step one. Through the Gaussian mixture model (GMM), the latent class analysis used the psychosocial constructs we provided to define a latent

class (cluster) for each participant. In total, 83 model variations were computed; the optimal number of latent classes was determined to be three based on the smallest Bayesian Information Criteria (BIC) value and the interpretability (Figure 4-5 and Table 4-7). As a result, 7,698 participants were divided into three mutually exclusive psychosocial wellbeing groups (good, average, and poor), based on their pattern of psychosocial constructs (Table 4-8 and Figure 4-6)[164]. The latent class analysis was implemented using the *mclust* package in R[165]. A detailed description of the latent class analysis is provided in supplementary section. Overall, the three-level psychosocial wellbeing derived from the latent class analysis was used as the final exposure in the mediation analysis.

Confirmatory Factor Analysis among Mediators. With a goal of creating a composite score for the physical health (functional status and the number of comorbid conditions) and behavioral characteristics (vigorous physical activity, smoking status, and weekly alcohol consumption), a confirmatory factor analysis with maximum likelihood estimation was used to estimate a latent summary variable (named health index, see Figure 4-1). Confirmatory factor analysis dealt with the internal correlation among variables and was used as a dimension reduction tool[166]. All five factors contributed to the summary score (Table 4-9). The confirmatory factor analysis was implemented through the *lavaan* package in R[167].

Descriptive Analysis. Descriptive statistics for covariates and potential mediators in 2006 for those who died and those who were censored (including HRS participants were alive at 2014 and those who were lost to follow-up between 2006 and 2014) were calculated. Linear trends for continuous variables and heterogeneity for categorical variables were tested across mortality outcome (alive or dead) between 2006 and 2014 using linear regression and Chi-square tests, respectively.

Exposure-Mediator-Outcome Associations. Exposure-outcome associations were evaluated by Cox Proportional-Hazards regression models. The three-level psychosocial wellbeing (good, average, and poor) derived from the latent class analysis was the independent variable and all-cause mortality (time-to-death) was the outcome. We first fit a model adjusted for the *a priori* confounders and then a second model further adjusted for the five behavioral and physical health mediators. Exposure-mediator and mediator-outcome associations were also evaluated, details are available in the supplementary section. Overall, mediators (composite health index and five individual behavioral and physical health factors) that demonstrated associations with both exposure (psychosocial wellbeing) and outcome (mortality) were considered for mediation analysis in the next step.

Mediation Analysis. The primary analytic objective was to estimate the total effect of psychosocial wellbeing (good, average, and poor) on survival. We further evaluated the direct effects through psychosocial wellbeing and indirect effects through each physical and behavioral health characteristic, as well as the health index, a composite measure of these five variables. Two types of models were constructed to obtain the direct effects and indirect effects in the pairwise mediation analysis. The mediator model used a linear regression model for each of the potential mediators regressed on the psychosocial wellbeing group, adjusted for *a priori* confounders. The individual physical and behavioral health factors were adjusted for each other. The outcome model was a parametric survival analysis through an Accelerated Failure Time model (AFT) with a Weibull distribution including the three-level psychosocial wellbeing and adjusted for *a priori* confounders. For individual physical and behavioral health factors we fit all five variables in the same outcome model. The health index was fit alone in the outcome model and adjusted for *a priori* confounders. In those analyses, we also took sample weights and strata from the HRS

complex survey design into account. Analysis was performed 50 times separately in each imputed dataset. Next, Rubin´s Rules[168] were used to obtain the pooled total effects, pooled indirect effects, and pooled direct effects (Figure 4-2). Sensitivity analyses were conducted to evaluate the robustness of our findings, including evaluation of variable selection prior to the latent class analysis, reverse causation, the mediator model, as well as measured and unmeasured confounders. A detailed description of each sensitivity analysis is provided in the supplementary section.

4.4 Results

4.4.1 Descriptive Analysis

Descriptive characteristics of the 7,698 HRS participants stratified on whether they had died or were censored by 2014 are presented in Tables 1 and 2. Between 2006 and 2014, about 25% of HRS participants died (n=1,902), and the mean survival time over this period of time for decedents was 87 months (standard deviation (SD), 24 months). Around 57% of participants were women; the mean (SD) age of participants was 68.6 (10.0) years. About 75% of participants were non-Hispanic white, 63% were married, and 49% had a high school degree. Individuals who were older, male, non-Hispanic and Hispanic black, and had a lower education level were more likely to have died. Participants who were physically inactive, had poor functional status, or had more than three comorbid conditions were also more likely to have died.

4.4.2 Exposure-Mediator-Outcome Associations

Exposure-Outcome Association: The exposure of interest was psychosocial wellbeing which was categorized as poor, average, or good based on the latent class analysis. About 38% of the HRS participants who died had a poor psychosocial wellbeing, while 24% of the HRS participants who were still alive in 2014 had a poor psychosocial wellbeing (Table 4-2). We

observed a statistically significant inverse relationship between all-cause mortality and psychosocial wellbeing (Table 4-3); those who had a good psychosocial wellbeing were 55% less likely to die during the follow-up period compared to those who had a poor psychosocial wellbeing status (hazard ratio (HR)=0.45, 95% confidence interval (CI)=0.35,0.54), after controlling for covariates. Similarly, those with average psychosocial wellbeing had a lower risk of dying than those with poor psychosocial wellbeing (HR=0.75, 95%CI=0.66,0.84).

Mediator-Outcome and Exposure-Mediator associations: The potential mediators of interest were the physical health and behavioral factors (i.e., functional status and the number of comorbid conditions and vigorous physical activity, smoking status, and weekly alcohol consumption, respectively), as well as the summary health index measure comprised of these five variables. The exposure-mediator relationships (Table 4-10) and mediator-outcome (Table 4-11) relationships were examined for both magnitude and statistical significance of the associations. Most of the individual physical health and behavioral factors as well as the combined health index were strongly and statistically significantly associated with both exposure (psychosocial wellbeing; Table 4-10) and the outcome (all-cause mortality; Table 4-11). Therefore, all potential mediators were included in the mediation analysis.

4.4.3 Mediation Analysis

The mediation analysis results of decomposing total effects into direct effects and indirect effects in the survival time ratio scale are shown in Table 4-4. Similar to the results from the Cox Proportional Hazard model shown in Table 4-3, we observed strong and statistically significant total effects from the accelerated failure time model for the associations between survival time and psychosocial wellbeing (Table 4-4).

The individual physical health and behavioral factors mediated the association between survival time and good versus poor psychosocial wellbeing; functional score had the largest indirect effect (% mediated 12.4%) and alcohol had the smallest (% mediated 1.6%). Overall, we found that 36.2% of the total effect between survival time and good compared to poor psychosocial wellbeing was mediated through the summary health index measure. We observed a similar pattern but higher percentage of mediation effects through all the mediators between survival time and average versus poor psychosocial wellbeing. Functional score still had the largest indirect effect (% mediated 26.7%) and alcohol had the smallest (% mediated 2.4%). Overall, the health index mediated 50.9% of the total effect between survival time and average compared to poor psychosocial wellbeing. Lastly, results from the sensitivity analyses presented in the supplementary section revealed the robustness of our findings.

4.5 Discussion

The current study investigated the relationship between psychosocial wellbeing and survival in a nationally representative sample of U.S. adults aged 50 or over. Based on our findings, psychosocial wellbeing is a strong contributor to survival directly and indirectly through physical health and behavioral exposures. Overall, those with the highest psychological wellbeing score were 73% more likely to survive compared to those with the lowest wellbeing (survival rate, 95% CI 1.50,2.01). There was a trend in this association with individuals with average psychological wellbeing 23% more likely to survive compared to those with a poor wellbeing score (95% CI 1.14,1.34).

The health index, a composite measure of the five behavioral and physical health mediators, accounted for 36% of the total effects between psychosocial wellbeing good versus poor and survival; it accounted for 51% of the total effects of average versus poor psychosocial

wellbeing. The sum of the percentage mediated through the five individual physical and behavioral health factors (good versus poor: 41.6%; average versus poor: 72.13%) was larger than the effects through the composite health index measure. Most likely, this was because the computation of the health index through the confirmatory factor analysis dealt with the internal correlation among those variables. For this reason, the composite score (health index) was a better measure to demonstrate the overall indirect effect between psychosocial wellbeing and survival. However, given that the summary measure does not illustrate the magnitude of indirect effects of each behavioral and physical health factors, both analytic approaches offer insight.

Furthermore, we observed a higher percent of mediation through all the mediators when comparing average versus poor psychosocial wellbeing to good versus poor psychosocial wellbeing. This could be explained by the difference of overall survival rate (SR) by psychosocial wellbeing group. Briefly, as shown in Table 4-4, the total effect (TE) of having a good psychosocial wellbeing on survival (health index, $SR_{TE(good\ versus\ poor)}$=1.73, 95%CI:1.27,1.69) was a lot larger than the TE of having an average psychosocial wellbeing on survival (health index, $SR_{TE(average\ versus\ poor)}$=1.23, 95%CI:1.03,1.21). When the indirect effects (IE) ($SR_{IE(good\ versus\ poor)}$=1.18 and $SR_{IE(average\ versus\ poor)}$=1.11) on survival through the mediator (health index) are not so different, the percent mediated is larger relative to a smaller TE.

Our results are in accordance with and expand upon previous studies investigating psychosocial wellbeing and survival. To date, most previous studies only examined one or a few psychosocial wellbeing constructs at a time and thus far have been in favor of a positive association with longer survival and good psychosocial wellbeing[65,67,78-81], including our own work on life purpose and all-cause mortality in the HRS[70]. Notably, Puterman et al. investigated 57 economic, behavioral, social, and psychological factors using the HRS data and found associations between

many psychological factors and mortality[82]. Our study concluded that good overall psychosocial wellbeing had a strong protective effect on mortality. Puterman and colleague's study reported the top psychosocial predictors of mortality including: life satisfaction, negative affect, and social interaction[82]. Future wellbeing interventions should incorporate findings from both studies. In addition to examine the total effect between psychosocial wellbeing and mortality, we demonstrated the indirect effects of psychosocial wellbeing through behavioral and physical health factors.

The results from our mediation analysis support and expand current evidence of relationships between psychosocial wellbeing and behavioral and physical health factors. The positive association between many psychological wellbeing constructs and being physically active has been well-studied through cross-sectional[105,106], longitudinal[119-121,123], and intervention[124] studies. With regard to smoking, investigators have generally noted that low life satisfaction[105], low life purpose[115,120], and high pessimism[116] are important psychosocial predictors of initiation or escalation of smoking. Furthermore, past findings on psychological wellbeing constructs and alcohol consumption vary by the level of alcohol consumption. Generally, a positive relationship has been found between light to moderate alcohol consumption and less emotional loneliness[127]; heavy alcohol consumption is associated with high social self-efficacy[113], low emotional self-efficacy[113], low life satisfaction[112], high hopelessness[128], and more social loneliness[127], but this has not been observed in all studies[105,120,130]. In our study, the binary categorization of alcohol consumption (never/ever) could be a potential reason we did not observe any mediation effect. Several nation-wide studies support our hypothesis that psychological wellbeing influences functional disability[131,134] and disease progression (e.g., heart disease[85], diabetes[86,87]).

This present study has several strengths. First, many past studies investigating psychosocial wellbeing and mortality relied on a single domain of psychosocial wellbeing. We overcame this limitation and utilized the comprehensive HRS data to explore the relationship between a large set of psychosocial wellbeing constructs and all-cause mortality. Our analytic approach addressed the issue of correlation between psychosocial factors and allowed us to demonstrate a strong association between good, average and poor psychosocial wellbeing and survival overall. But, we are also able to represent the contributions of the individual psychosocial factors which is critical for the development of interventions (Figure 4-6 and Table 4-8). Furthermore, HRS has missing data, and our evaluation of the missing pattern showed that the missingness is more likely based on other observed participants' characteristics. Ignoring the missingness and simply conducting a complete cases analysis may lead to biased and unreliable parameter estimates. To overcome this limitation, we used multiple imputation that allowed individuals with incomplete data to be included in analyses. Lastly, this study overcame several methodological challenges of conducting a mediation analysis with 1) multiple exposures and mediators, 2) a time-to-death survival outcome, 3) complex survey design and 4) imputed data. To date, none of the existing mediation programs in SAS or R can directly handle such a complex scenario. This present study provided a workflow for future research on how to execute such a mediation analysis.

A few limitations should be noted in our study. First, although the current analysis is a longitudinal study design in nature, we cannot establish temporality between exposures and mediators. This is because we intended to avoid potential selection bias as we illustrated in length in the methods section, therefore the measures of exposures and mediators in 2006 were used, although mediators were re-measured in 2010. Next, there is potential reverse causation between psychosocial wellbeing and chronic conditions. We were concerned that some severely ill people

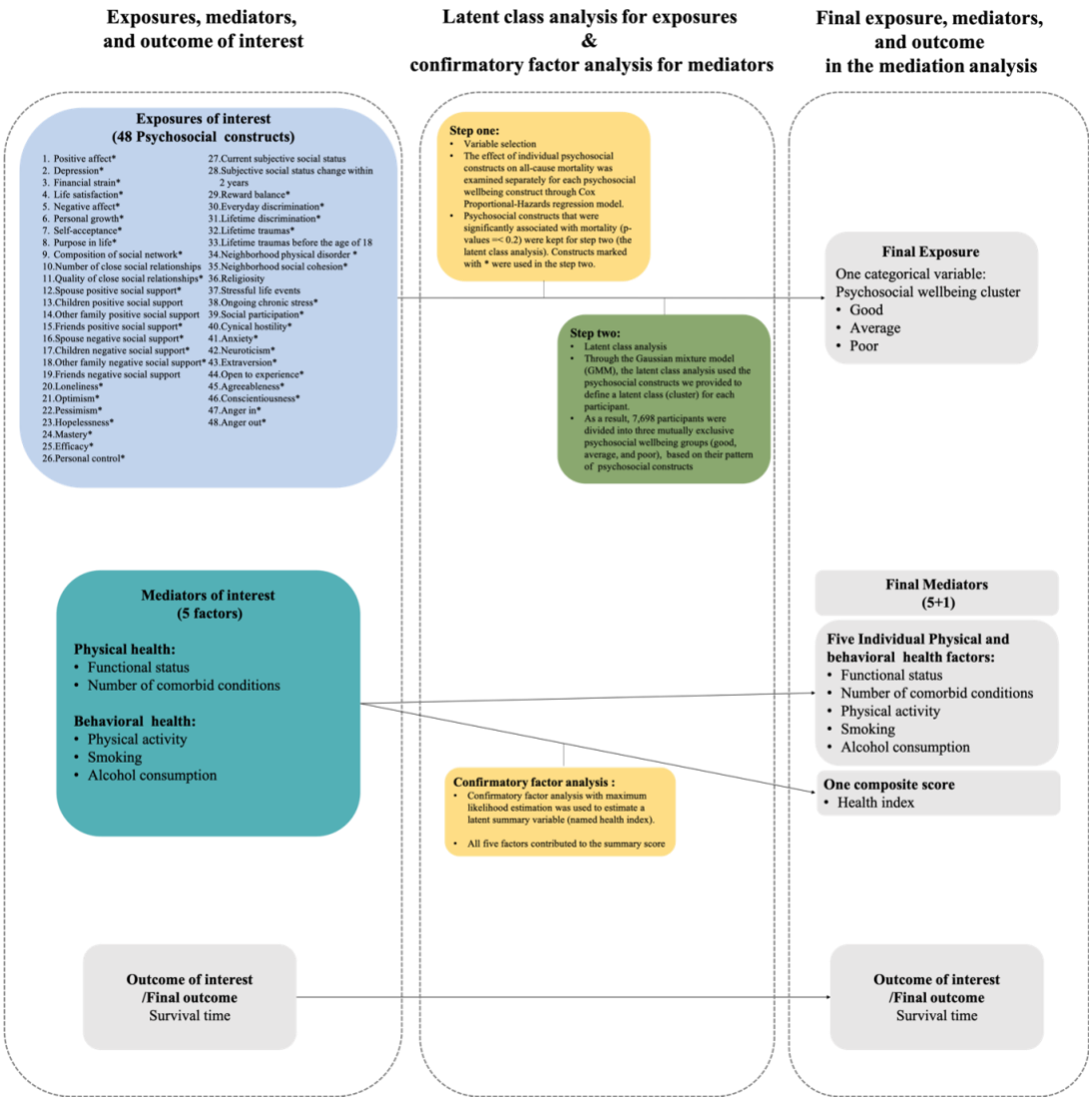
have poor psychosocial wellbeing as a result of their illness. We conducted sensitivity analysis by stratifying individuals with no reported chronic conditions and individuals with at least one chronic condition. Our stratified analysis demonstrated a similar estimate between psychosocial wellbeing and mortality across the strata. Therefore, reverse causation due to chronic conditions is not a major concern in our study (Table 4-14).

Furthermore, one may argue there is potential reverse causation between psychosocial wellbeing and survival. However, we hypothesize it's a confounding issue due to severe illness rather than reverse causation. First, reverse causation refers to the situation in which the outcome precedes and causes the exposure. When mortality is the outcome, no exposure will be preceded after death. Second, the concern of being near to death causes low psychosocial wellbeing is actually because severe illness affects both psychosocial wellbeing (exposure) and survival (outcome). We controlled for chronic conditions in our analyses. Additionally, our study was still subject to unmeasured confounding, but our E-values suggested that the mediation effects through health index, functional score, comorbid conditions, and physical activity that we observed were at least somewhat robust to unmeasured confounding (Table 4-17). Lastly, there is potential measurement error due to the uncertainty of the factor analysis and latent class analysis, and bias can be toward or away from the null. Due to the complexity of our data and mediation analysis nature, we did not account for the uncertainties. However, we presented results on individual mediators in addition to health index. Additionally, a recent study shows when latent classes are well distinguished, such as our study, the ignorance of uncertainties is preferred than joint modeling [169].

4.6 Conclusion

In summary, in the HRS, psychosocial wellbeing was associated with longer survival largely via a direct effect, but also mediated through other physical health and behavioral factors. Our findings highlight the interconnectedness of these psychosocial wellbeing constructs and shared physical and behavioral health pathways for survival. Interventions that consider a broader set of psychosocial wellbeing constructs need to be developed and validated. Next, interventions to increase overall survival among adults over age 50 should focus on improving both mental and physical wellbeing. Lastly, the present study only evaluated physical and behavioral health pathways between psychosocial wellbeing and survival due to data availability in HRS. Future research should focus on the mechanism of neuroendocrine regulation of stress responses while simultaneously accounting for a full range of wellness constructs.

Figure 4-1. Schematic diagram of the steps to deal with multiple mediators and exposures in the present study.

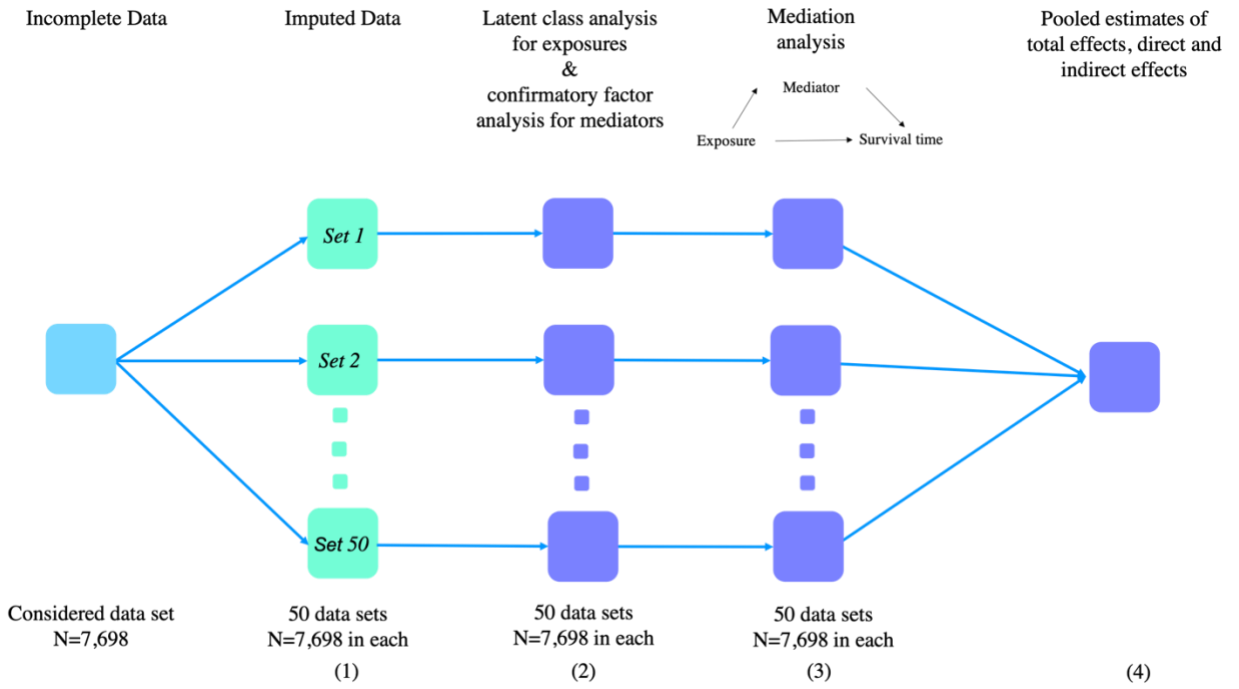


Exposures: To evaluate psychosocial constructs (# of exposures=48) simultaneously in the mediation analysis, a two-step approach was implemented by grouping HRS participants based on their overall psychosocial wellbeing attributable to each construct. Step one: The effect of individual psychosocial constructs on all-cause mortality was examined separately for each psychosocial wellbeing construct. Those associations were examined using Cox Proportional-Hazards regression models separately for each psychosocial construct as an independent variable and adjusted for covariates (age, gender, race, marital status, education, total household income, total wealth, and BMI); those with p-values= < 0.20 were kept for step two. Step two: A latent class analysis was conducted using the selected psychosocial constructs from step one. Through the Gaussian mixture model (GMM), the latent class analysis used the psychosocial constructs we provided to define a latent class (cluster) for each participant. As a result, 7,698 participants were divided into three mutually exclusive psychosocial wellbeing groups (good, average, and poor), based on their pattern of psychosocial constructs. The final exposure in the mediation analysis was this three-level categorical variable named psychosocial wellbeing.

Mediators: With a goal of creating a composite score for all five physical health (functional status and the number of comorbid conditions) and behavioral characteristics (vigorous physical activity, smoking status, and weekly alcohol consumption), a confirmatory factor analysis with maximum likelihood estimation was used to estimate a latent summary variable (named health index) and all five factors contributed to the summary score. In the mediation analysis, five physical health and behavioral characteristics and the composite score health index were evaluated as mediators.

Outcome: Survival time was calculated as the number of months from the date of the 2006 interview to the date of death or the date of their last follow-up interview through 2014 (for those who are censored).

Figure 4-2. Overview of data analysis in the Health and Retirement Study.



(1) Performed multiple imputation by chained equations to impute missing exposures, mediators, and covariates in 2006.
(2) Performed latent class analysis for exposures, and confirmatory factor analysis for mediators. See detailed description in Figure 4-1. The categorical variable psychosocial wellbeing was used as the exposure in the mediation analysis. Five individual health and behavioral variables, as well as health index, were mediators in the mediation analysis.
(3) Performed mediation analysis within each imputed dataset and estimated total effects, natural direct effects and natural indirect effects within each imputed data. The mediator model was the multivariable linear regression model, and the outcome model was the multivariable accelerated failure time model (AFT) with a Weibull distribution, and survival time was the outcome. In this step, we also took sample weights and strata from the HRS complex survey design into account in the mediation analysis.
(4) Used Rubin's rule to obtain the pooled total effect, natural direct effects and natural indirect effects.

Table 4-1. Descriptive characteristics for *a priori* knowledge confounders among the 7,698 HRS participants included in this analysis by outcome.

	Total n = 7698 Mean(SD)/Count(%)	**Alive** n = 5796 Mean(SD)/Count(%)	**Dead** n = 1902 Mean(SD)/Count(%)	P-Value [a]
Age (years)				<0.001
50-54	573 (7.4%)	533 (9.2%)	40 (2.1%)	
55-59	1142 (14.8%)	1061 (18.3%)	81 (4.3%)	
60-64	1108 (14.4%)	979 (16.9%)	129 (6.8%)	
65-69	1484 (19.3%)	1209 (20.9%)	275 (14.5%)	
70-74	1241 (16.1%)	947 (16.3%)	294 (15.5%)	
75-79	929 (12.1%)	597 (10.3%)	332 (17.5%)	
80-84	680 (8.8%)	325 (5.6%)	355 (18.7%)	
85-89	378 (4.9%)	122 (2.1%)	256 (13.5%)	
90+	163 (2.1%)	23 (0.4%)	140 (7.4%)	
Gender				<0.001
Male	3292 (42.8%)	2362 (40.8%)	930 (48.9%)	
Female	4406 (57.2%)	3434 (59.2%)	972 (51.1%)	
Race/ethnicity				0.009
Non-Hispanic white	5796 (75.3%)	4361 (75.2%)	1435 (75.4%)	
Non-Hispanic and Hispanic black	1116 (14.5%)	812 (14%)	304 (16%)	
Hispanic white	435 (5.7%)	329 (5.7%)	106 (5.6%)	
Others	351 (4.6%)	294 (5.1%)	57 (3%)	
Marital status				<0.001
Married	4876 (63.3%)	3859 (66.6%)	1017 (53.5%)	
Separated/Divorced	1009 (13.1%)	811 (14%)	198 (10.4%)	
Widowed	1600 (20.8%)	961 (16.6%)	639 (33.6%)	
Never married	213 (2.8%)	165 (2.8%)	48 (2.5%)	
Education				<0.001
<High school	1989 (25.8%)	1295 (22.3%)	694 (36.5%)	
High school	3775 (49%)	2892 (49.9%)	883 (46.4%)	
Some college	314 (4.1%)	256 (4.4%)	58 (3%)	
College	949 (12.3%)	782 (13.5%)	167 (8.8%)	
Master or professional degree	671 (8.7%)	571 (9.9%)	100 (5.3%)	
Total household income ($)				<0.001
1st Quartiles (Mean(SD))	$12,000 ($4,000)	$11,000 ($5,000)	$12,000 ($4,000)	
2nd Quartiles (Mean(SD))	$28,000 ($5,000)	$28,000 ($5,000)	$27,000 ($5,000)	
3rd Quartiles (Mean(SD))	$52,000 ($10,000)	$53,000 ($10,000)	$51,000 ($10,000)	
4th Quartiles (Mean(SD))	$163,000 ($369,000)	$168,000 ($393,000)	$128,000 ($75,000)	
Total wealth($)				<0.001
1st Quartiles (Mean(SD))	$9,000 ($66,000)	$9,000 ($51,000)	$7,000 ($91,000)	
2nd Quartiles (Mean(SD))	$127,000 ($45,000)	$128,000 ($45,000)	$123,000 ($45,000)	
3rd Quartiles (Mean(SD))	$356,000 ($94,000)	$356,000 ($94,000)	$353,000 ($91,000)	
4th Quartiles (Mean(SD))	$1,575,000 ($2,007,000)	$1,576,000 ($1,947,000)	$1,571,000 ($2,250,000)	
BMI (kg/cm^2)[b]				<0.001
Less than 18.5	123 (1.6%)	61 (1.1%)	62 (3.3%)	
18.5 to <25	2420 (31.4%)	1692 (29.2%)	728 (38.3%)	
25.0 to <30	2884 (37.5%)	2247 (38.8%)	637 (33.5%)	
30.0 or higher	2271 (29.5%)	1796 (31%)	475 (25%)	

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

[a] Obtained through $\chi 2$ tests.

[b] Categorized according to the recommendations of the World Health Organization: below-normal weight (<18.5 kg/m^2), normal range (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (>=30.0 kg/m^2).

Table 4-2. Descriptive characteristics for potential mediators and psychosocial wellbeing status among the 7,698 HRS participants included in this analysis by outcome.

	Total n = 7698 Mean(SD)/Count(%)	**Alive** n = 5796 Mean(SD)/Count(%)	**Dead** n = 1902 Mean(SD)/Count(%)	P-Value [a]
Vigorous physical activity				<0.001
Hardly ever or never	4936 (64.1%)	3431 (59.2%)	1505 (79.1%)	
Sometimes or everyday	2762 (35.9%)	2365 (40.8%)	397 (20.9%)	
Smoking status				0.002
Current smoker	1020 (13.3%)	728 (12.6%)	292 (15.4%)	
Never or former smoker	6678 (86.7%)	5068 (87.4%)	1610 (84.6%)	
Frequency of alcohol consumption				<0.001
Never	4608 (59.9%)	3301 (57%)	1307 (68.7%)	
Sometimes	3090 (40.1%)	2495 (43%)	595 (31.3%)	
Functional score (Mean (SD))	5.70 (0.84)	5.82 (0.62)	5.34 (1.22)	<0.001
Number of comorbid conditions				<0.001
0	1029 (13.4%)	919 (15.9%)	110 (5.8%)	
1	1952 (25.4%)	1639 (28.3%)	313 (16.5%)	
2	2157 (28%)	1677 (28.9%)	480 (25.2%)	
3	1567 (20.4%)	1034 (17.8%)	533 (28%)	
4	694 (9%)	394 (6.8%)	300 (15.8%)	
5+	229 (3.9%)	133 (2.3%)	166 (8.7%)	
Diabetes				<0.001
Absent	6092 (79.1%)	4737 (81.7%)	1355 (71.2%)	
Present	1606 (20.9%)	1059 (18.3%)	547 (28.8%)	
Hypertension				<0.001
Absent	3219 (41.8%)	2564 (44.2%)	655 (34.4%)	
Present	4479 (58.2%)	3232 (55.8%)	1247 (65.6%)	
Stroke				<0.001
Absent	7159 (93%)	5511 (95.1%)	1648 (86.6%)	
Present	539 (7%)	285 (4.9%)	254 (13.4%)	
Heart disease				<0.001
Absent	5727 (74.4%)	4627 (79.8%)	1100 (57.8%)	
Present	1971 (25.6%)	1169 (20.2%)	802 (42.2%)	
Cancer				<0.001
Absent	6529 (84.8%)	5073 (87.5%)	1456 (76.6%)	
Present	1169 (15.2%)	723 (12.5%)	446 (23.4%)	
Lung disease				<0.001
Absent	6891 (89.5%)	5335 (92%)	1556 (81.8%)	
Present	807 (10.5%)	461 (8%)	346 (18.2%)	
Arthritis				<0.001
Absent	2969 (38.6%)	2362 (40.8%)	607 (31.9%)	
Present	4729 (61.4%)	3434 (59.2%)	1295 (68.1%)	
Psychosocial wellbeing status				<0.001
Poor	2114 (27.5%)	1397 (24.1%)	717 (37.7%)	
Average	3939 (51.2%)	2987 (51.5%)	952 (50.1%)	
Good	1645 (21.4%)	1412 (24.4%)	233 (12.3%)	

[a] Obtained through $\chi 2$ tests.

Table 4-3. Exposure-outcome association among the 7,698 HRS participants included in this analysis.[a]

		Model 1		Model 2	
	Count(%)	**Hazard Ratio (95% CI) [b]**	**P-value**	**Hazard Ratio (95% CI) [b]**	**P-value**
Psychosocial wellbeing					
Poor	2114 (27.5%)	Ref		Ref	
Average	3939 (51.2%)	0.75 (0.66,0.84)	<0.001	0.87 (0.78,0.98)	0.02
Good	1645 (21.4%)	0.45 (0.35,0.54)	<0.001	0.59 (0.49,0.70)	<0.001

a. Exposure is psychosocial wellbeing and the outcome is all-cause mortality (time-to-death). Estimates were calculated from two separate Cox proportional hazard models adjusting for covariates. Model 1: adjusted for age, gender, race, marital status, education, total household income, total wealth, and BMI. Model 2: Additionally adjusted for all potential mediators (better functional score, fewer number of comorbid conditions, vigorous physical activity, smoking status, and frequency of alcohol consumption).
b. CI :confidence interval.

Table 4-4. Role of health index or individual physical and behavioral health factors in explaining the association between psychosocial wellbeing and all-cause mortality among the 7,698 HRS participants included in this analysis. [a]

Psychosocial wellbeing	**Total Effect** Survival Rate [a] (95%CI [c])	**Natural Direct Effect** Survival Rate [a] (95%CI [c])	**Natural Indirect Effect** Survival Rate [a] (95%CI [c])	**Proportion Mediated** [b] %
Good vs Poor				
Individual physical and behavioral measures				
Better functional score [d]	1.52 (1.31,1.76)	1.43 (1.24,1.65)	1.04 (1.02,1.06)	12.43%
Fewer number of comorbid conditions [e]	1.49 (1.29,1.71)	1.43 (1.24,1.65)	1.04 (1.02,1.06)	11.73%
More vigorous physical activity	1.47 (1.27,1.69)	1.43 (1.24,1.65)	1.03 (1.01,1.05)	8.70%
Never or former smoker	1.46 (1.27,1.68)	1.43 (1.24,1.65)	1.02 (1.01,1.04)	7.12%
More weekly alcohol consumption	1.44 (1.25,1.65)	1.43 (1.24,1.65)	1.00 (1.00,1.01)	1.62%
The composite measure				
Health index [f]	1.73 (1.50,2.01)	1.46 (1.27,1.67)	1.18 (1.13,1.22)	36.21%
Average vs Poor				
Individual physical and behavioral measures				
Better functional score [d]	1.16 (1.07,1.26)	1.11 (1.02,1.20)	1.03 (1.02,1.05)	26.66%
Fewer number of comorbid conditions [e]	1.12 (1.03,1.21)	1.11 (1.02,1.20)	1.02 (1.01,1.04)	20.08%
More vigorous physical activity	1.12 (1.03,1.21)	1.11 (1.02,1.20)	1.01 (1.01,1.02)	13.53%
Never or former smoker	1.11 (1.03,1.21)	1.11 (1.02,1.20)	1.00 (0.97,1.03)	9.49%
More weekly alcohol consumption	1.11 (1.02,1.20)	1.11 (1.02,1.20)	1.00 (0.95,1.05)	2.37%
The composite measure				
Health index [f]	1.23 (1.14,1.34)	1.12 (1.03,1.21)	1.11 (1.08,1.14)	50.86%

a. Survival rate is interpreted as a ratio of time to death compared good psychosocial wellbeing status to poor (or average compared to poor).If survival rate equals to 1, then there is null association between exposure and survival; if survival < 1, exposure is associated with earlier time to death; and if survival rate > 1, exposure is associated with later time to death.
b. Proportion mediated calculated from the equation NDE*(NIE-1)/(NDE*NIE-1)*100% for each mediator separately.
c. CI : confidence interval.
d. Better functional score (ordinal, a higher score means a better functional status).
e. Fewer number of comorbid conditions (ordinal, reverse coded, a higher score means a fewer number of comorbid conditions).
f. Health index (continuous, a higher score means a better overall health).

4.7 Supplementary Section

Supplementary Tables and Figures

Figure 4-3. HRS data flow chart for aim two.

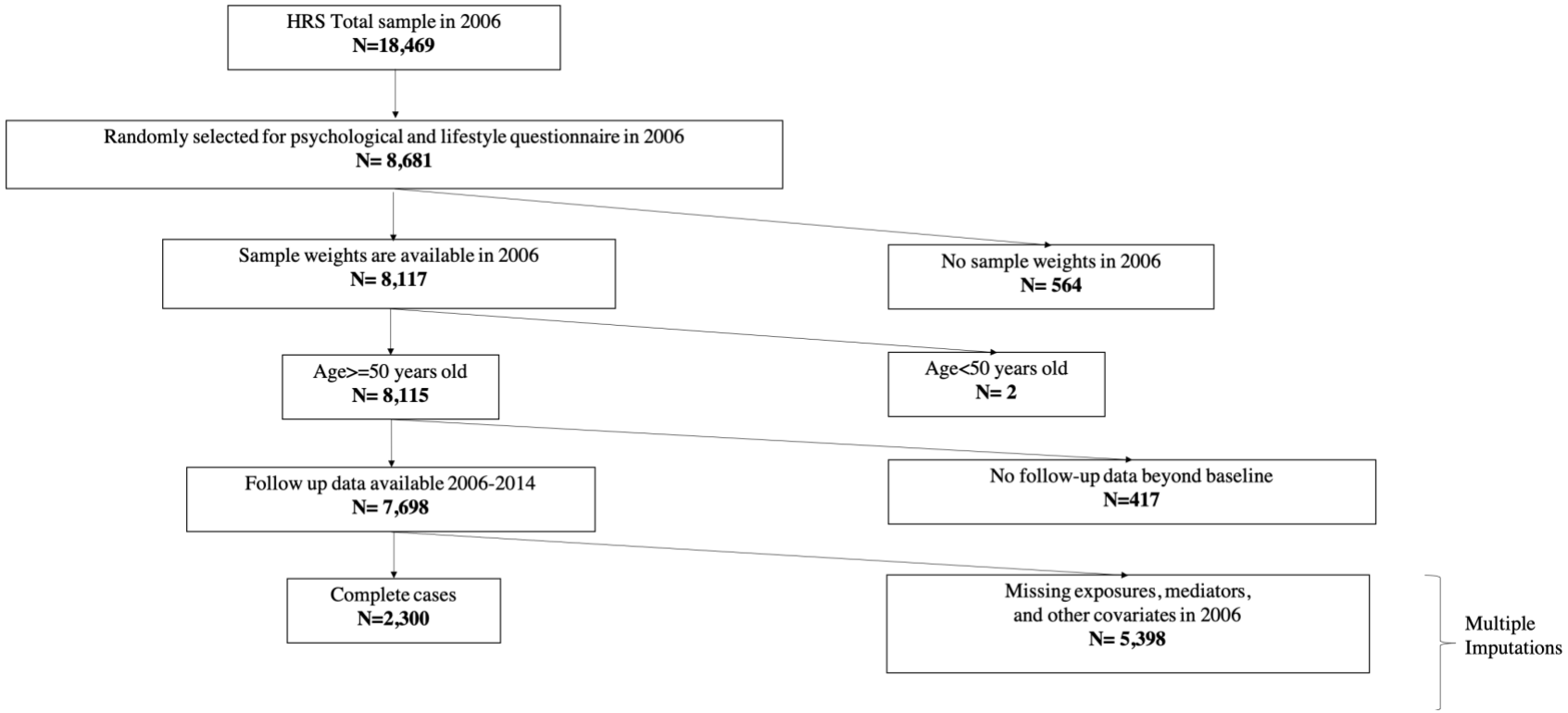


Table 4-5. Demographic distributions by various subsets in the HRS.

	All participants in 2006 Wave	Randomly selected for psychological and lifestyle questionnaire in 2006		Mediation sample	Complete cases
	Total	No	Yes		
	n = 18,469	n = 9,788	n = 8,681	n = 7,698	n=2,300
Age					
<50	539 (2.9%)	277 (2.8%)	262 (3%)	0 (0%)	0 (0%)
50-54	1653 (9%)	850 (8.7%)	803 (9.3%)	573 (7.4%)	181 (7.9%)
55-59	2523 (13.7%)	1323 (13.5%)	1200 (13.8%)	1142 (14.8%)	394 (17.1%)
60-64	2399 (13%)	1227 (12.5%)	1172 (13.5%)	1108 (14.4%)	432 (18.8%)
65-69	3416 (18.5%)	1848 (18.9%)	1568 (18.1%)	1484 (19.3%)	523 (22.7%)
70-74	2827 (15.3%)	1493 (15.3%)	1334 (15.4%)	1241 (16.1%)	359 (15.6%)
75-79	2034 (11%)	1056 (10.8%)	978 (11.3%)	929 (12.1%)	249 (10.8%)
80-84	1564 (8.5%)	827 (8.4%)	737 (8.5%)	680 (8.8%)	119 (5.2%)
85-89	993 (5.4%)	564 (5.8%)	429 (4.9%)	378 (4.9%)	35 (1.5%)
90+	521 (2.8%)	323 (3.3%)	198 (2.3%)	163 (2.1%)	8 (0.3%)
Gender					
Male	7586 (41.1%)	3986 (40.7%)	3600 (41.5%)	3292 (42.8%)	1148 (49.9%)
Female	10883 (58.9%)	5802 (59.3%)	5081 (58.5%)	4406 (57.2%)	1152 (50.1%)
Race/ethnicity					
Non-Hispanic white	13701 (74.2%)	7190 (73.5%)	6511 (75%)	5796 (75.3%)	1962 (85.3%)
Non-Hispanic or Hispanic black	2582 (14%)	1343 (13.7%)	1239 (14.3%)	1116 (14.5%)	173 (7.5%)
Hispanic white	1198 (6.5%)	699 (7.1%)	499 (5.7%)	435 (5.7%)	86 (3.7%)
Others	988 (5.3%)	556 (5.7%)	432 (5%)	351 (4.6%)	79 (3.4%)
Marital status					
Married	11419 (61.8%)	5884 (60.1%)	5535 (63.8%)	4876 (63.3%)	2190 (95.2%)
Separated/Divorced	2462 (13.3%)	1332 (13.6%)	1130 (13%)	1009 (13.1%)	71 (3.1%)
Widowed	4024 (21.8%)	2264 (23.1%)	1760 (20.3%)	1600 (20.8%)	32 (1.4%)
Never Married	561 (3%)	306 (3.1%)	255 (2.9%)	213 (2.8%)	7 (0.3%)
NA	3 (0%)	2 (0%)	1 (0%)	0 (0%)	0 (0%)
Education					
<High school	4995 (27%)	2788 (28.5%)	2207 (25.4%)	1989 (25.8%)	396 (17.2%)
High school	8882 (48.1%)	4628 (47.3%)	4254 (49%)	3775 (49%)	1184 (51.5%)
Some College	758 (4.1%)	397 (4.1%)	361 (4.2%)	314 (4.1%)	118 (5.1%)
College	2205 (11.9%)	1119 (11.4%)	1086 (12.5%)	949 (12.3%)	359 (15.6%)
Master or Professional degree	1575 (8.5%)	827 (8.4%)	748 (8.6%)	671 (8.7%)	243 (10.6%)
NA	54 (0.3%)	29 (0.3%)	25 (0.3%)	0 (0%)	0 (0%)

NA: Not available.

Figure 4-4. Missingness in psychological constructs among HRS participants in 2006.

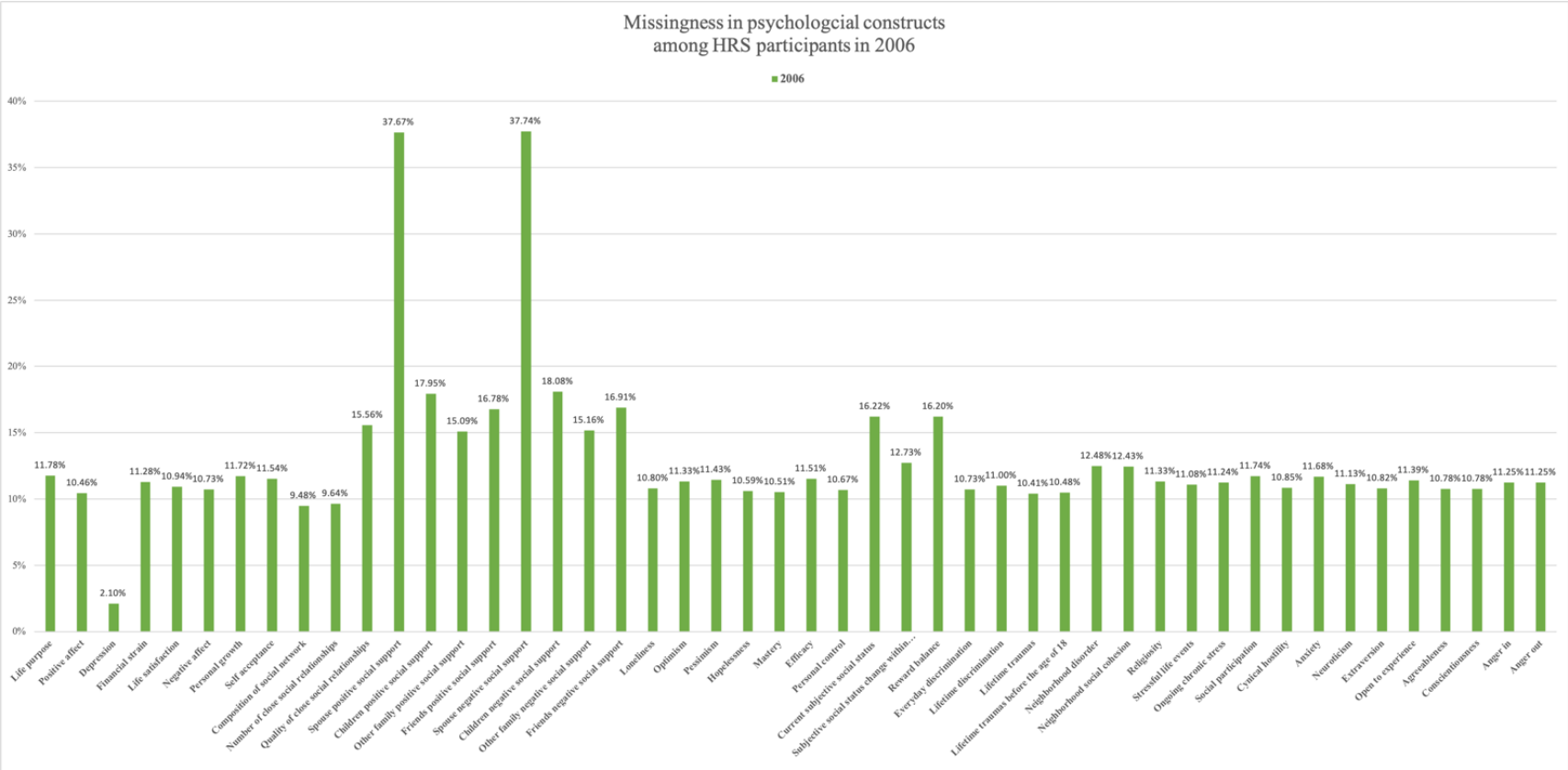


Table 4-6. Descriptive of psychosocial constructs and their associations with all-cause mortality among the 7,698 HRS participants included in this analysis.

Five substantive areas predefined by HRS	Individual Psychosocial constructs	Descriptive			Association with mortality [a]	
		Variable Type	Range (Min-max)	Mean (SD)	HR [b]	P-value
Subjective wellbeing	Positive affect*	Continuous	1-5	3.57 (0.69)	0.82	<0.001
	Depression*	Ordinal	0-8	1.51 (1.99)	1.09	<0.001
	Financial strain*	Ordinal	1-5	2.01 (1.00)	1.05	0.134
	Life satisfaction*	Continuous	1-6	4.36 (1.21)	0.89	<0.001
	Negative affect*	Continuous	1-5	1.65 (0.66)	1.35	<0.001
	Personal growth*	Continuous	1-6	4.51 (0.91)	0.88	<0.001
	Self-acceptance*	Continuous	1-6	4.62 (0.93)	0.84	<0.001
	Purpose in life*	Continuous	1-6	4.51 (0.92)	0.79	<0.001
Social relationships	Composition of social network*	Continuous	0/1	0.86 (0.18)	0.58	0.001
	Number of close social relationships	Continuous	0-59	3.33 (3.33)	0.99	0.246
	Quality of close social relationships*	Continuous	1-6	3.65 (0.82)	0.92	0.003
	Spouse positive social support*	Continuous	1-4	3.37 (0.73)	0.90	0.008
	Children positive social support	Continuous	1-4	3.26 (0.72)	0.96	0.264
	Other family positive social support	Continuous	1-4	2.87 (0.86)	0.98	0.366
	Friends positive social support*	Continuous	1-4	3.03 (0.75)	0.94	0.094
	Spouse negative social support*	Continuous	1-4	2.01 (0.68)	1.11	0.010
	Children negative social support*	Continuous	1-4	1.73 (0.63)	1.14	0.013
	Other family negative social support*	Continuous	1-4	1.59 (0.61)	1.08	0.162
	Friends negative social support	Continuous	1-4	1.44 (0.50)	1.07	0.270
	Loneliness*	Continuous	1-3	1.50 (0.54)	1.20	<0.001
Self-related beliefs	Optimism*	Continuous	1-6	4.51 (1.15)	0.90	<0.001
	Pessimism*	Continuous	1-6	2.65 (1.30)	1.10	<0.001
	Hopelessness*	Continuous	1-6	2.48 (1.35)	1.14	<0.001
	Mastery*	Continuous	1-6	4.73 (1.12)	0.89	<0.001
	Efficacy*	Continuous	1-10	7.10 (2.25)	0.91	<0.001
	Personal control*	Continuous	1-6	2.27 (1.19)	1.15	<0.001
	Current subjective social status	Ordinal	1-10	6.54 (1.77)	0.99	0.792
	Subjective social status change within 2 years	Ordinal	1-3	2.63 (0.72)	1.02	0.705
	Reward balance*	Continuous	1-5	3.96 (0.88)	0.90	<0.001
Lifestyle and experiences of stress and traumas	Everyday discrimination*	Continuous	1-6	1.67 (0.74)	1.10	0.007
	Lifetime discrimination* (reverse coded)	Continuous	1-30	27.99 (3.81)	0.99	0.128
	Lifetime traumas*	Continuous	0-7	1.23 (1.19)	1.09	0.001
	Lifetime traumas before the age of 18	Ordinal	1-20	17.41 (3.19)	0.99	0.208
	Neighborhood physical disorder *(reverse coded)	Continuous	1-7	4.66 (1.06)	0.94	0.052
	Neighborhood social cohesion*	Continuous	1-7	5.47 (1.37)	0.97	0.090
	Religiosity	Continuous	1-6	5.00 (1.38)	0.98	0.398

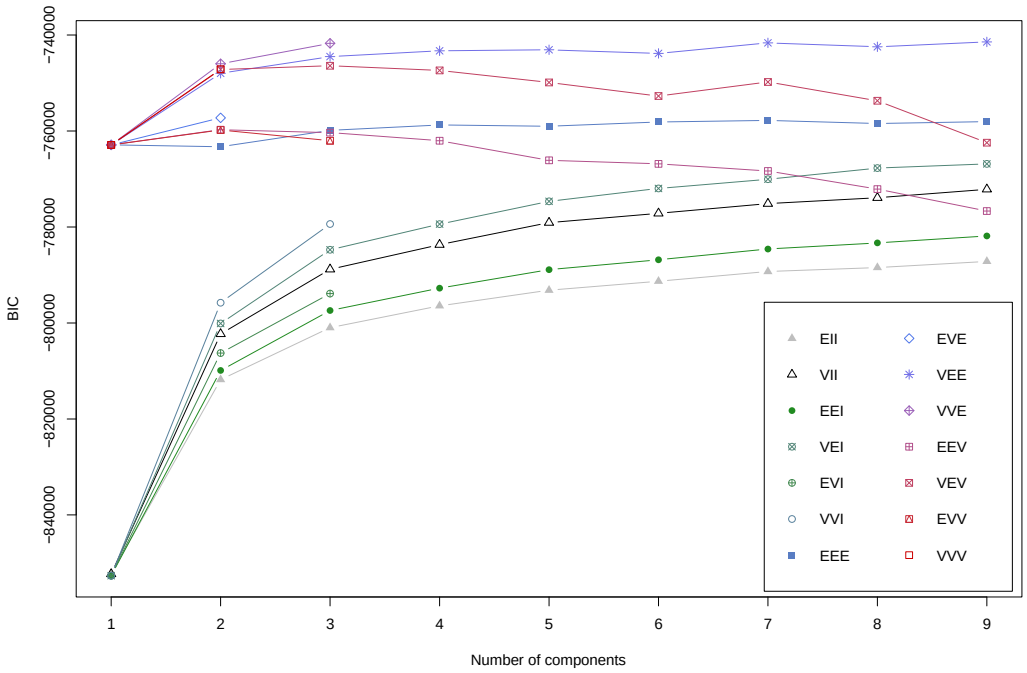
	Stressful life events	Ordinal	0-5	0.24 (0.56)	1.04	0.528
	Ongoing chronic stress*	Continuous	1-32	11.77 (3.62)	1.03	0.002
	Social participation*	Ordinal	0-7	3.96 (1.74)	0.85	<0.001
Personality	Cynical hostility*	Continuous	1-6	2.99 (1.14)	1.05	0.138
	Anxiety*	Continuous	1-4	1.58 (0.58)	1.23	<0.001
	Neuroticism*	Continuous	1-4	2.07 (0.60)	1.14	0.001
	Extraversion*	Continuous	1-4	3.19 (0.54)	0.71	<0.001
	Open to experience*	Continuous	1-4	2.93 (0.55)	0.82	0.001
	Agreeableness*	Continuous	1-4	3.52 (0.47)	0.81	<0.001
	Conscientiousness*	Continuous	1-4	3.29 (0.44)	0.66	<0.001
	Anger in*	Continuous	1-4	2.14 (0.67)	1.12	0.004
	Anger out*	Continuous	1-4	1.49 (0.52)	1.16	0.003

a. Those associations were examined by Cox regression models separately for each psychosocial construct and adjust for age, gender, race, marital status, education, total household income, total wealth, and BMI).

b. HR indicates Hazard Ratio.

* Psychosocial constructs that were significantly associated with mortality (p-values =< 0.2) were kept for the latent class analysis.

Figure 4-5. Bayesian information criteria (BIC) values by number of components for different covariance models through latent class analysis.

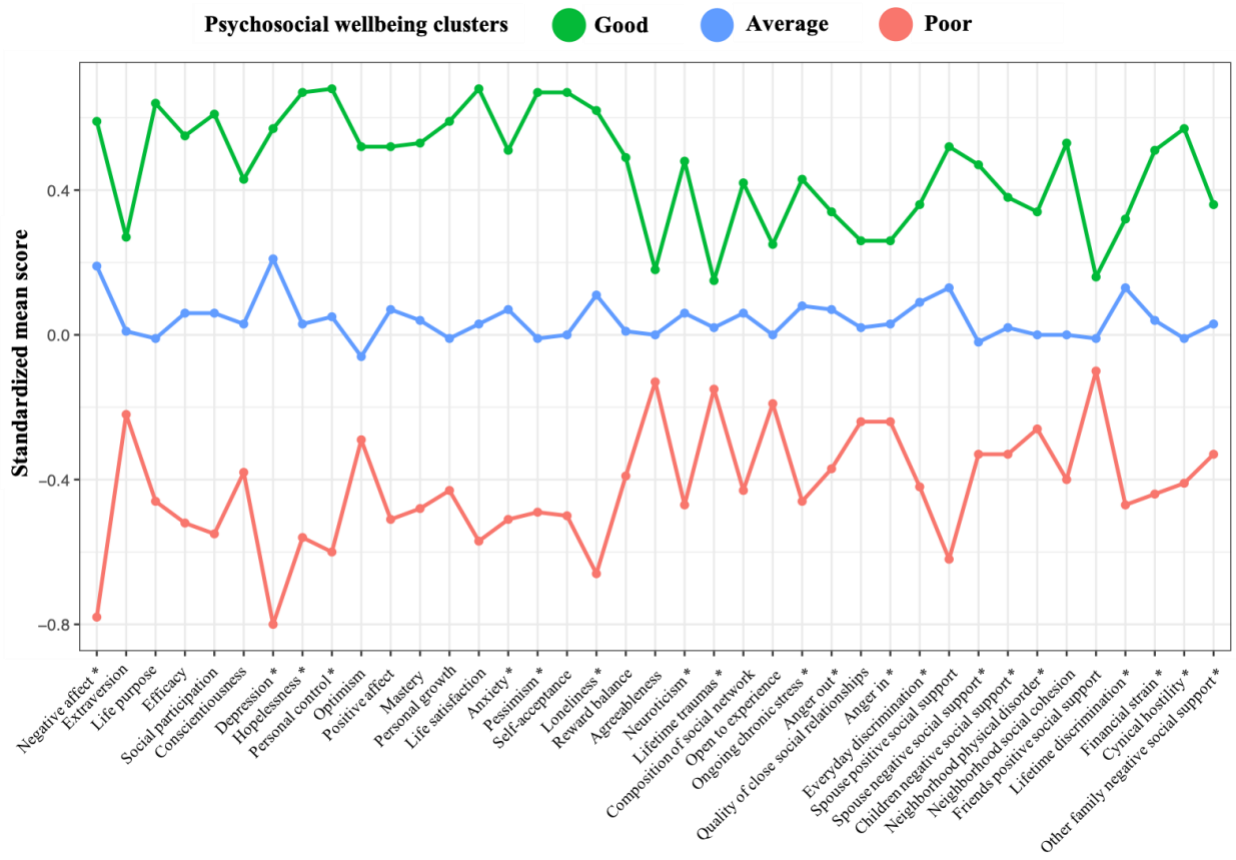


As shown in the figure, we plotted Bayesian Information Criteria (BIC) for all model variations where parameters optimized for up to nine components and all ten covariance structures currently available in the *mclust* software[165]. The BIC can be defined as the value of the maximized log-likelihood with a penalty on the number of model parameters. In the latent class analysis, the BIC allows the comparison of models with differing parameterizations and/or differing numbers of clusters[164]. The top three best BIC values out of the 83 model variations were -741449, -741642, and -741740 for model VEE,9, VEE,7, and VVE,3, respectively. The explanation of acronyms for model variations was illtreated in Table 4-7 down below.

Table 4-7. Parameterizations of the covariance matrix for various models through the latent class analysis.

Model	Family	Volume	Shape	Orientation	Identifier
1	Spherical	Equal	Equal	NA	EII
2	Spherical	Variable	Equal	NA	VII
3	Diagonal	Equal	Equal	Axes	EII
4	Diagonal	Variable	Equal	Axes	VEI
5	Diagonal	Equal	Variable	Axes	EVI
6	Diagonal	Variable	Variable	Axes	VVI
7	General	Equal	Equal	Equal	EEE
8	General	Equal	Variable	Equal	EVE
9	General	Variable	Equal	Equal	VEE
10	General	Variable	Variable	Equal	VVE
11	General	Equal	Equal	Variable	EEV
12	General	Variable	Equal	Variable	VEV
13	General	Equal	Variable	Variable	EVV
14	General	Variable	Variable	Variable	VVV

Figure 4-6. Distributions of the individual psychosocial constructs standardized mean score by three clusters of the psychosocial wellbeing.



Through the Gaussian mixture model (GMM), the latent class analysis used the psychosocial constructs we provided to define a latent class (cluster) for each participant. As a result, 7,698 participants were divided into mutually exclusive latent classes, based on their pattern of psychosocial constructs. Overall, the latent class analysis divided HRS participants into three mutually exclusive psychosocial wellbeing groups: good (in green), average (in blue), and poor (in red). * Indicates reverse coded in this figure.

Table 4-8. Descriptive characteristics of psychosocial constructs by psychosocial wellbeing status among the 7,698 HRS participants included in this analysis.

Five substantive areas predefined by HRS	**Individual Psychosocial constructs**	**Psychosocial wellbeing**			
		Poor n = 2114 Mean(SD)	**Average** n = 3939 Mean(SD)	**Good** n = 1645 Mean(SD)	P-Value
Subjective wellbeing	Positive affect	3.20 (0.86)	3.62 (0.57)	3.94 (0.42)	<0.001
	Depression	3.19 (2.54)	1.09 (1.36)	0.36 (0.69)	<0.001
	Financial strain	2.47 (1.15)	1.97 (0.92)	1.49 (0.63)	<0.001
	Life satisfaction	3.65 (1.38)	4.39 (1.06)	5.20 (0.59)	<0.001
	Negative affect	2.19 (0.84)	1.52 (0.46)	1.25 (0.27)	<0.001
	Personal growth	4.10 (0.94)	4.50 (0.86)	5.06 (0.68)	<0.001
	Self-acceptance	4.14 (1.01)	4.61 (0.82)	5.26 (0.62)	<0.001
	Purpose in life	4.07 (0.97)	4.49 (0.84)	5.11 (0.67)	<0.001
Social relationships	Composition of social network	0.78 (0.21)	0.87 (0.16)	0.94 (0.12)	<0.001
	Quality of close social relationships	3.44 (0.89)	3.66 (0.79)	3.86 (0.70)	<0.001
	Spouse positive social support	2.89 (0.95)	3.47 (0.55)	3.76 (0.34)	<0.001
	Friends positive social support	2.95 (0.81)	3.02 (0.74)	3.15 (0.66)	<0.001
	Spouse negative social support	2.25 (0.79)	2.02 (0.63)	1.69 (0.47)	<0.001
	Children negative social support	1.94 (0.76)	1.71 (0.59)	1.48 (0.43)	<0.001
	Other family negative social support	1.80 (0.74)	1.57 (0.57)	1.36 (0.41)	<0.001
	Loneliness	1.87 (0.62)	1.44 (0.46)	1.16 (0.27)	<0.001
Self-related beliefs	Optimism	4.16 (1.33)	4.44 (1.10)	5.13 (0.72)	<0.001
	Pessimism	3.32 (1.40)	2.66 (1.20)	1.76 (0.81)	<0.001
	Hopelessness	3.27 (1.49)	2.45 (1.21)	1.57 (0.74)	<0.001
	Mastery	4.19 (1.35)	4.77 (1.00)	5.32 (0.60)	<0.001
	Efficacy	5.87 (2.71)	7.24 (1.95)	8.36 (1.23)	<0.001
	Personal control	3.01 (1.33)	2.21 (1.04)	1.44 (0.55)	<0.001
	Reward balance	3.60 (1.02)	3.97 (0.82)	4.40 (0.59)	<0.001
Lifestyle and experiences of stress and traumas	Everyday discrimination	2.00 (0.99)	1.61 (0.60)	1.40 (0.44)	<0.001
	Lifetime discrimination (reverse coded)	26.07 (5.58)	28.50 (2.74)	29.24 (1.80)	<0.001
	Lifetime traumas	1.42 (1.29)	1.21 (1.17)	1.04 (1.06)	<0.001
	Neighborhood physical disorder (reverse coded)	4.37 (1.26)	4.67 (1.02)	5.03 (0.67)	<0.001
	Neighborhood social cohesion	4.89 (1.59)	5.48 (1.30)	6.22 (0.72)	<0.001
	Ongoing chronic stress	13.52 (4.60)	11.49 (3.09)	10.18 (2.15)	<0.001
	Social participation	2.95 (1.75)	4.06 (1.59)	5.02 (1.30)	<0.001
Personality	Cynical hostility	3.48 (1.22)	3.00 (1.06)	2.32 (0.85)	<0.001
	Anxiety	1.88 (0.70)	1.54 (0.50)	1.28 (0.33)	<0.001
	Neuroticism	2.36 (0.66)	2.03 (0.54)	1.78 (0.47)	<0.001
	Extraversion	3.07 (0.60)	3.19 (0.53)	3.35 (0.46)	<0.001
	Open to experience	2.82 (0.61)	2.93 (0.53)	3.07 (0.47)	<0.001
	Agreeableness	3.45 (0.53)	3.52 (0.46)	3.61 (0.39)	<0.001
	Conscientiousness	3.12 (0.50)	3.31 (0.41)	3.49 (0.35)	<0.001
	Anger in	2.32 (0.77)	2.12 (0.64)	1.95 (0.57)	<0.001
	Anger out	1.70 (0.70)	1.46 (0.43)	1.31 (0.31)	<0.001

Table 4-9. Factor loadings for physical and behavioral health variables through confirmatory factor analysis among the 7,698 HRS participants included in this analysis.

Individual physical and behavioral measures	Factor loading
Better functional score	1.422
Fewer number of comorbid conditions	0.935
More vigorous physical activity	1.000
Less smoking	-0.001
More weekly alcohol consumption	0.755

Table 4-10. Exposure-mediator association among the 7,698 HRS participants included in this analysis. [a]

Potential Mediators	Psychosocial wellbeing			
	Average vs Poor		Good vs Poor	
	Beta (95% CI [b])	P-value	Beta (95% CI [b])	P-value
Individual physical and behavioral measures				
Better functional score [c]	0.26 (0.19,0.32)	<0.001	0.32 (0.25,0.38)	<0.001
Fewer number of comorbid conditions [d]	0.17 (0.08,0.26)	0.002	0.28 (0.18,0.38)	<0.001
Vigorous physical activity [e]				
Hardly ever or never	Ref		Ref	
Sometimes or everyday	0.38 (0.21,0.55)	<0.001	0.65 (0.42,0.89)	<0.001
Smoking status [e]				
Current smoker	Ref		Ref	
Never or former smoker	0.15 (-0.07,0.37)	0.19	0.56 (0.24,0.89)	0.002
Frequency of alcohol consumption [e]				
Never	Ref		Ref	
Sometimes	0.13 (-0.01,0.28)	0.091	0.25 (0.08,0.43)	0.010
The composite measure				
Health index [f]	0.14 (0.11,0.16)	<0.001	0.21 (0.18,0.25)	<0.001

a. Beta coefficients were calculated from separate linear or logistic regression models.
b. CI :confidence interval.
c. Better functional score (ordinal, a higher score means a better functional status). Better functional score was fit in a linear regression model as the dependent variables and adjusted for age, gender, race, marital status, education, total household income, total wealth, BMI, and rest of the individual mediators.
d. A fewer number of comorbid conditions (ordinal, reverse coded, a higher score means a fewer number of comorbid conditions). A fewer number of comorbid conditions was fit in a linear regression model as the dependent variables and adjusted for age, gender, race, marital status, education, total household income, total wealth, BMI, and rest of the individual mediators.
e. Three behavioral health mediators were fit in logistic regression models separately as the dependent variables and adjusted for age, gender, race, marital status, education, total household income, total wealth, BMI, and rest of the individual mediators.
f. Health index (continuous, a higher score means a better overall health). Health index was fit in a linear regression model as the dependent variable and adjusted for age, gender, race, marital status, education, total household income, total wealth, and BMI.

Table 4-11. Mediator-outcome association among the 7,698 HRS participants included in this analysis. [a]

Potential Mediators	Hazard Ratio [b] (95% CI) [b]	P-value
Individual physical and behavioral measures	**Model 1**	
Better functional score [c]	0.81 (0.76,0.86)	<0.001
Fewer number of comorbid conditions [d]	0.81 (0.77,0.85)	<0.001
Vigorous physical activity		
Hardly ever or never	Ref	
Sometimes or everyday	0.73 (0.63,0.84)	<0.001
Smoking status		
Current smoker	Ref	
Never or former smoker	0.54 (0.45,0.65)	<0.001
Frequency of alcohol consumption		
Never	Ref	
Sometimes	0.83 (0.74,0.94)	0.002
The composite measure	**Model 2**	
Health index [e]	0.34 (0.29,0.40)	<0.001

a. Estimates were calculated from two separate Cox proportional hazard models adjusting for covariates. Model 1: all individual mediators were fit in the model at the same time and adjusted for age, gender, race, marital status, education, total household income, total wealth, and BMI. Model 2: health index was fit in the model and adjusted for age, gender, race, marital status, education, total household income, total wealth, and BMI.

b. CI :confidence interval.

c. Better functional score (ordinal, a higher score means a better functional status).

d. A fewer number of comorbid conditions (ordinal, reverse coded, a higher score means a fewer number of comorbid conditions).

e. Health index (continuous, a higher score means a better overall health).

Table 4-12. Sensitivity analysis results with respect to the choice of defining psychosocial wellbeing cluster : Role of health index or individual physical and behavioral health factors in explaining the association between two cluster of psychosocial wellbeing ((Good vs Poor)and all-cause mortality among the 7,698 HRS participants included in this analysis. [a]

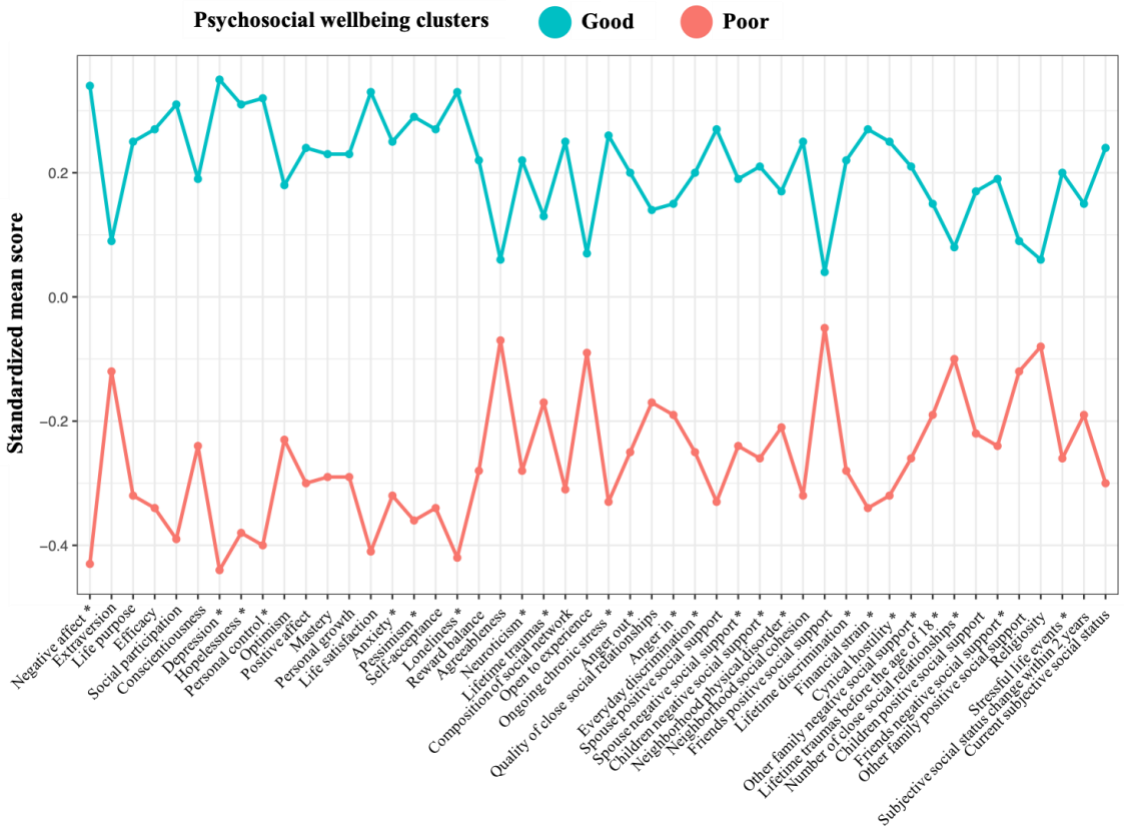
Psychosocial wellbeing (Good vs Poor)	**Total Effect** Survival Rate [a] (95%CI [c])	**Natural Direct Effect** Survival Rate [a] (95%CI [c])	**Natural Indirect Effect** Survival Rate [a] (95%CI [c])	**Proportion Mediated** [b] %
Individual physical and behavioral measures				
Better functional score [d]	1.22 (1.09,1.35)	1.17 (1.05,1.30)	1.03 (1.02,1.04)	16.25%
A fewer number of comorbid conditions [e]	1.20 (1.08,1.34)	1.17 (1.05,1.30)	1.02 (1.01,1.04)	14.29%
More vigorous physical activity	1.18 (1.06,1.31)	1.17 (1.05,1.30)	1.01 (1.01,1.02)	9.44%
Less smoking	1.18 (1.06,1.32)	1.17 (1.05,1.30)	1.01 (1.00,1.02)	5.91%
More weekly alcohol consumption	1.17 (1.05,1.30)	1.17 (1.05,1.30)	1.00 (1.00,1.00)	1.07%
The composite measure				
Health index [f]	1.33 (1.19,1.48)	1.19 (1.07,1.33)	1.10 (1.07,1.13)	38.21%

a. Survival rate is interpreted as a ratio of time to death compared good psychosocial wellbeing status to poor (or average compared to poor).If survival rate equals to 1, then there is null association between exposure and survival; if survival < 1, exposure is associated with earlier time to death; and if survival rate > 1, exposure is associated with later time to death.
b. Proportion mediated calculated from the equation NDE*(NIE-1)/(NDE*NIE-1)*100% for each mediator separately.
c. CI : confidence interval.
d. Better functional score (ordinal, a higher score means a better functional status).
e. A fewer number of comorbid conditions (ordinal, reverse coded, a higher score means a fewer number of comorbid conditions).
f. Health index (continuous, a higher score means a better overall health).

Table 4-13. Comparison of the three clusters and two clusters of psychosocial wellbeing among the 7,698 HRS participants included in this analysis. [a]

		Psychosocial wellbeing status 3 clusters		
	Total	**Poor**	**Average**	**Good**
	7698	2114	3939	1645
Psychosocial wellbeing status two clusters				
Poor	3414	2052 (97.1%)	1340 (34%)	22 (1.3%)
Good	4284	62 (2.9%)	2599 (66%)	1623 (98.7%)

Figure 4-7. Distributions of the individual psychosocial constructs standardized mean score distributions by two clusters of the psychosocial wellbeing.



Through the Gaussian mixture model (GMM), the latent class analysis used the psychosocial constructs we provided to define a latent class (cluster) for each participant. As a result, 7,698 participants were divided into mutually exclusive latent classes, based on their pattern of psychosocial constructs. Overall, the latent class analysis divided HRS participants into two mutually exclusive psychosocial wellbeing groups: good (in blue) and poor (in red).* Indicates reverse coded in this figure.

Table 4-14. Sensitivity analysis results with respect to reverse causation due to chronic conditions.

	Without chronic condition [a]		With one or more chronic conditions [a]	
	Hazard Ratio (95% CI) [b]	**P-value**	**Hazard Ratio (95% CI) [b]**	**P-value**
Psychosocial wellbeing				
Poor	Ref		Ref	
Average	0.62 (0.39,0.98)	0.04	0.75 (0.69,0.84)	<0.001
Good	0.52 (0.28,0.96)	0.04	0.47 (0.39,0.55)	<0.001

a. Cox proportional hazard models were used and adjusted for age, gender, race, marital status, education, total household income, total wealth, and BMI.
b. CI : confidence interval.

Table 4-15. Sensitivity analysis for all-cause mortality with respect to reverse causation due to near to death. [a]

		Model 1		Model 2	
	Count(%)	**Hazard Ratio (95% CI) [b]**	**P-value**	**Hazard Ratio (95% CI) [b]**	**P-value**
Exclusion of those died within 1 year					
Psychosocial wellbeing					
Poor	2078 (27.3%)	Ref		Ref	
Average	3899 (51.2%)	0.75 (0.67,0.85)	<0.001	0.87 (0.77,0.99)	0.03
Good	1643 (21.6%)	0.47 (0.39,0.56)	<0.001	0.61 (0.51,0.73)	<0.001
Exclusion of those died within 2 years					
Psychosocial wellbeing					
Poor	1971 (26.6%)	Ref		Ref	
Average	3799 (51.4%)	0.78 (0.69,0.88)	<0.001	0.89 (0.79,1.02)	0.09
Good	1628 (22.0%)	0.50 (0.41,0.61)	<0.001	0.64 (0.52,0.79)	<0.001
Exclusion of those died within 3 years					
Psychosocial wellbeing					
Poor	1870 (26.1%)	Ref		Ref	
Average	3685 (51.5%)	0.79 (0.68,0.93)	0.004	0.90 (0.77,1.06)	0.21
Good	1607 (22.4%)	0.55 (0.44,0.69)	<0.001	0.68 (0.55,0.86)	0.001
Exclusion of those died within 4 years					
Psychosocial wellbeing					
Poor	1787 (25.8%)	Ref		Ref	
Average	3570 (51.5%)	0.77 (0.66,0.91)	0.001	0.87 (0.75,1.03)	0.12
Good	1576 (22.7%)	0.53 (0.42,0.68)	<0.001	0.66 (0.53,0.84)	<0.001
Exclusion of those died within 5 years					
Psychosocial wellbeing					
Poor	1699 (25.4%)	Ref		Ref	
Average	3445 (51.5%)	0.76 (0.63,0.91)	0.003	0.86 (0.71,1.03)	0.11
Good	1551 (23.2%)	0.56 (0.42,0.74)	<0.001	0.70 (0.53,0.92)	0.01

a. Exposure is psychosocial wellbeing and the outcome is all-cause mortality (time-to-death). Estimates were calculated from two separate Cox proportional hazard models adjusting for covariates. Model 1: adjusted for age, gender, race, marital status, education, total household income, total wealth, and BMI. Model 2: Additionally adjusted for all potential mediators(better functional score, fewer number of comorbid conditions, vigorous physical activity, smoking status, and frequency of alcohol consumption).

b. CI : confidence interval

Table 4-16. Sensitivity analysis results with respect to the choice of mediator model: Logistic regression model was implemented as the mediator model for three binary behavioral health factors in explaining the association between psychosocial wellbeing and all-cause mortality among the 7,698 HRS participants included in this analysis. [a]

Psychosocial wellbeing	**Total Effect** Survival Rate [a] (95%CI [c])	**Natural Direct Effect** Survival Rate [a] (95%CI [c])	**Natural Indirect Effect** Survival Rate [a] (95%CI [c])	**Proportion Mediated** [b] %
Good vs Poor				
Vigorous physical activity				
Every day or some	1.47 (1.27,1.69)	1.43 (1.24,1.65)	1.03 (1.01,1.05)	9.90%
Hardly ever or never	Ref	Ref	Ref	
Smoking status				
Never or former	1.46 (1.27,1.68)	1.43 (1.24,1.65)	1.04 (1.01,1.07)	11.58%
Current	Ref	Ref	Ref	
Weekly alcohol consumption				
Some	1.44 (1.25,1.65)	1.43 (1.24,1.65)	1.00 (1.00,1.01)	1.45%
Never	Ref	Ref	Ref	
Average vs Poor				
Vigorous physical activity				
Every day or some	1.11 (1.03,1.21)	1.11 (1.02,1.20)	1.02 (1.01,1.03)	16.79%
Hardly ever or never	Ref	Ref	Ref	
Smoking status				
Never or former	1.11 (1.03,1.21)	1.11 (1.02,1.20)	1.01 (0.99,1.03)	10.95%
Current	Ref	Ref	Ref	
Weekly alcohol consumption				
Some	1.11 (1.02,1.20)	1.11 (1.02,1.20)	1.00 (1.00,1.01)	2.21%
Never	Ref	Ref	Ref	

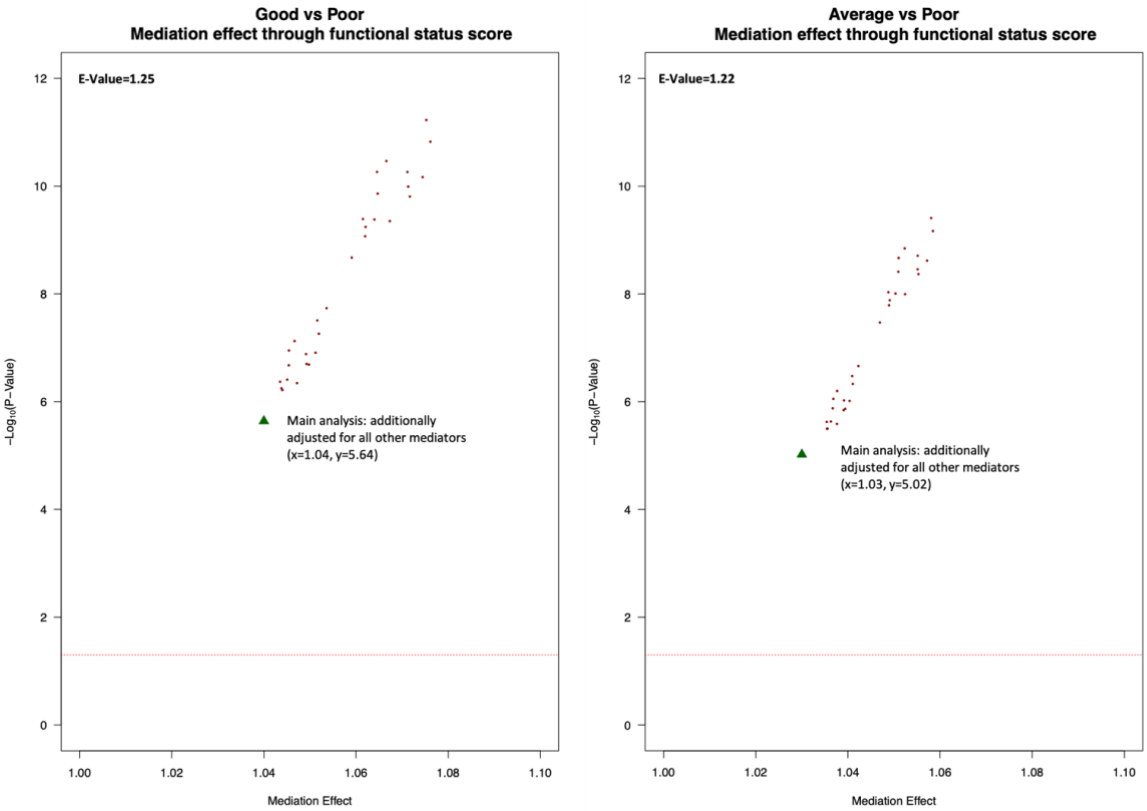
a. Survival rate is interpreted as a ratio of time to death compared good psychosocial wellbeing status to poor (or average compared to poor).If survival rate equals to 1, then there is a null association between exposure and survival; if survival < 1, exposure is associated with earlier time to death; and if survival rate > 1, exposure is associated with later time to death.
b. Proportion mediated calculated from the equation NDE*(NIE-1)/(NDE*NIE-1)*100% for each mediator separately.
c. CI: confidence interval.

Table 4-17. Sensitivity analysis with respect to the effect of unmeasured confounders on indirect effects. [a]

Potential Mediators	**Psychosocial wellbeing**	
	Good vs Poor	Average vs Poor
	E-value	E-value
Individual physical and behavioral measures		
Better functional score [b]	1.25	1.22
Fewer number of comorbid conditions [c]	1.24	1.18
More vigorous physical activity	1.20	1.14
Less smoking	1.18	1.11
More weekly alcohol consumption	1.08	1.05
The composite measure		
Health index [d]	1.64	1.46

a. E-value estimation was calculated for each mediator from pairwise mediation analysis, using the survival rate(SR) of mediation effect estimate. If the SR for mediation effect is smaller than 1, thus this formulate was used: E-Value= 1/SR + sqrt(1/SR*(1/SR-1)), respectively for all mediation effects, whereas if the SR for mediation effects is smaller than 1, thus this formulate was used: E-Value= SR + sqrt(SR*(SR-1)).
b. Better functional score (ordinal, higher score means better functional status).
c. A Fewer number of comorbid conditions (ordinal, reverse coded, higher score means a fewer number of comorbid conditions).
d. Health index (Continuous, higher score better overall health).

Figure 4-8. Sensitivity analysis results with respect to covariates adjustment in the models: Scatter plot of mediation effects for functional status score (x-axis) and -Log10(P-value) (y-axis) for all possible combinations of five covariates (ncombo=31).



Horizontal dashed red line indicates p-value <0.05. Combinations with p-value <0.05 are highlighted in red, while combinations with p-value> 0.05 are highlighted in grey. In addition to the a priori knowledge confounders (age, gender, race, marital status, education, total household income, total wealth, and BMI), we evaluated five additional covariates include smoking status, vigorous physical activity, frequency of alcohol consumption, BMI (kg/cm2), number of comorbid conditions that were measured at 2006. Mediation effects and -Log10 (P-value) of 31 possible covariates adjustments combinations analyses were compared and visualized.

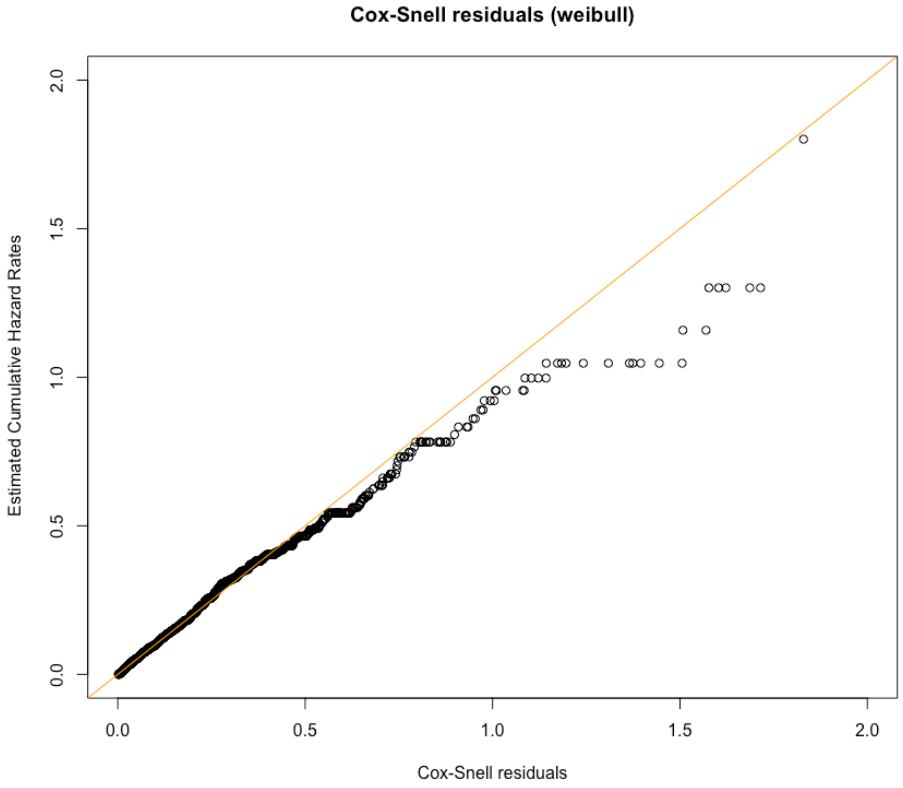
E-value estimation was calculated for the mediator (functional status score) in the main pairwise mediation analysis, using the approximation of survival rate of the mediation effect estimate.

Table 4-18. Comparison of model fit statistics for different accelerated failure time(AFT) distributions. [a]

AFT distribution	Log likelihood	AIC [b]
Weibull	-5061.947	10179.89
Exponential	-5692.037	11438.07
Log normal	-5056.215	10168.43
Log logistic	-5101.201	10258.4
Gaussian	-5092.631	10241.26

a. All models adjusted for age, gender, race, marital status, education, total household income, and total wealth.
b. Akaike's Information Criterion (AIC)

Figure 4-9. Cox-Snell residuals for testing goodness of fit of the Weibull distribution.



Supplementary Methods

Data Source: The Health and Retirement Study

The HRS sample was built up over time. Initially, individuals born between 1931 and 1941 were enrolled starting in 1992, but subsequent cohort enrichments were carried out in 1993 (the Asset and Health Dynamics of the Oldest Old Cohort (AHEAD)), 1998 (Children of the Depression Cohort (CODA), and War Baby), 2004 (The Early Baby Boomers Cohort (EBB)), and 2010 (The Mid Baby Boomers Cohort (MBB) and Minority oversample) to enroll more birth cohorts[143]. These subsequent cohort enrichments have maintained a steady sample size over time.

HRS used a stratified, multistage area probability design, in which Blacks, Hispanics, and Floridians were oversampled[143,157]. The multistage area probability design sample includes four selection stages. Stage one is probability proportionate to size (PPS) selection of U.S. Metropolitan Statistical Areas (MSAs) and non-MSA counties[170]. The following stage is sampling of area segments (SSUs) within sampled primary stage units (PSUs)[170]. The third sampling stage is a systematic selection of housing units from all housing units listings for the sample SSUs[170]. The last stage is the selection of the household financial unit within a sample housing units[170]. Oversampling was implemented in addition to the multistage area probability sample. It was designed to increase the numbers of Black and Hispanic HRS respondents and the number of HRS respondents who are residents of the state of Florida[170].

Analytic Strategy

1. Treatment of Missing Data

Treatment of Missing Data. The percentage of missing data for the psychosocial constructs, mediators, and covariates ranged from 0.02% to 37.74% (Figure 4-4). From the analytic dataset (n=7,698 HRS participants), the complete case sample size was 2,300. HRS participants who had no missing measures (n=2,300) were more likely to be in the ages between 55-70 years, male, Non-Hispanic white; married; had a master or professional degree, compared to all HRS participants in 2006 wave (n=18,469). Overall, the complete cases were not representative of the HRS population (Table 4-5). Thus, multiple imputation via chained equations (*mice* package in R) [163] was used for imputing the missing exposures, mediators, and covariates in 2006. In total, 50 imputed datasets were generated from the original data, and each imputed dataset consisted of a sample size of 7,698.

2. Definition of Variables

Sociodemographic characteristics and BMI were considered important *a priori* confounders and were included in all models. Race/ethnicity was assessed by the combination of two questions "What race do you consider yourself to be: White, Black or African American, American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander, or something else?", and "Do you consider yourself Hispanic or Latino?". Total household income was calculated as the sum of respondent and spouse earnings, pensions, annuities, supplemental security income, social security disability, social security retirement, unemployment and workers compensation, other government transfers, household capital income, and other income[171]. Total wealth was

calculated as the sum of all wealth components minus all debt[171]. All wealth components included the primary residence, the secondary residence if present, the net value of other real estates, the net value of vehicles, the net value of businesses, the net value of all individual retirement accounts and Keogh accounts, the net value of stocks and mutual funds, the value of checking, savings, money market accounts, the value of certificates of deposit, government savings bonds, treasury bills, the net value of bonds or bond funds, and the net value of all other savings. Total debt was the sum of the value of all mortgages, values of other home loans, values of other debt[171]. BMI was calculated using the weight and height measures collected by trained HRS staff.

Physical health and behavioral factors were the mediators. Smoking status was assessed based on two questions "Have you ever smoked cigarettes?" and "If yes, do you smoke cigarettes now?". Physical activity was assessed based on the reported frequency of vigorous activity (such as running or jogging, swimming, cycling, aerobics or gym workout, tennis, or digging with a spade or shovel). Alcohol consumption was measured based on two questions "Do you ever drink any alcoholic beverages such as beer, wine, or liquor?" and "If yes, in the last three months, on average, how many days per week have you had any alcohol to drink?". The functional status score was calculated by summing the values of five activities of daily living (bathing, eating, dressing, walking across a room, and getting in or out of bed). A higher score indicates stronger functioning. Data on diabetes, chronic lung disease, heart disease, hypertension, cancer, stroke, and arthritis were collected through one question for each comorbid condition, "Have you ever had, or has a doctor told you, that you have/had X?"

3. Latent Class Analysis among Exposures.

The latent class analysis was conducted through the *mclust* package in *R*[167]. As shown in Figure 4-5, we first plotted Bayesian Information Criteria (BIC) for all model variations where parameters optimized for up to nine components and all ten covariance structures currently available in the *mclust* software [167]. The BIC can be defined as the value of the maximized log-likelihood with a penalty on the number of model parameters [165] In the latent class analysis, the BIC allows the comparison of models with differing parameterizations and/or differing numbers of clusters [165].

The top three best BIC values out of the 83 model variations were -741449, -741642, and -741740 for model VEE,9, VEE,7, and VVE,3, respectively (Figure 4-5). The explanation of acronyms for model variations was illtreated in and Supplementary Table Supplementary 4-3. Briefly, the covariance matrix for each model describes the geometry of the clusters, namely, the volume, shape, and orientation of the clusters [165]. For instance, "VVE, 3" stands for there are 3 clusters with variable volume, variable shape, equal orientation, and ellipsoidal distribution (also referred to as general family). We chose to fit the data in the VVE model with three clusters for the following reasons. First, the BIC values were not too different between VEE,9 and VVE,3, both of them outperformed the rest of the 80 model variations. Second, when the model preformation is not too different, a smaller number of clusters is more interpretable in the real-life data, especially for mediation analysis. Third, fitting a three-level variable reduces the degree of freedom and is less likely to overfit the model compared to fit a nine-level variable in a model. As

a result, the latent class analysis divided HRS participants into three mutually exclusive groups by their psychosocial wellbeing status (good , average, and poor).

4. Examination of Exposure-Mediator Associations.

The potential mediators of interest were the physical health (functional status and the number of comorbid conditions) and behavioral factors (vigorous physical activity, smoking status, and weekly alcohol consumption) as well as the summary health index measure of these five variables. The exposure-mediator associations were evaluated through six separate models. Models 1-5: each individual physical and behavioral health factor was fit as the dependent variable separately using linear regression or logistic regression with the three-level psychosocial wellbeing as the independent variable, adjusted for *a priori* confounders (age, gender, race, marital status, education, total household income, total wealth, and BMI). Also, the individual physical and behavioral health factors were included as covariates. Model 6: health index was fit as a dependent variable using linear regression with the three-level psychosocial wellbeing as the independent variable and adjusted for *a priori* confounders only.

5. Examination of Mediator-Outcome Associations.

The mediator-outcome associations were evaluated through two separate models using Cox Proportional-Hazards regression models with all-cause mortality (time-to-death) as the outcome. Model 1: all five individual physical and behavioral health factors were fit in the same model as the independent variables and adjusted for *a priori* confounders. Model 2: health index was fit in the model as the independent variable and adjusted for *a priori* confounders. Finally, mediators (composite health index and five individual behavioral and physical health factors) that

demonstrated associations with both exposure (psychosocial wellbeing) and outcome (mortality) were considered for mediation analysis in the next step.

6. Mediation Analysis

Explanations for Choosing the AFT Model as the Outcome

Accelerated failure time (AFT) model with a Weibull distribution was chosen as the outcome model because it has been shown to outperform Cox Proportional Hazards regression models in mediation analysis settings with non-rare outcomes (>10%) [172-174]. In particular, in settings with non-rare outcomes (like the present study with mortality = 24.7%), using proportional hazards models with either the product method or difference method will yield invalid estimates of direct and indirect effects, whereas utilizing AFT models with the product method will yield valid estimates [172-174]. The Weibull distribution was selected from a set of five possible distributions available for the AFT model by comparing Akaike's Information Criterion (AIC), conducting likelihood ratio tests, and assessing the fit of Cox-Snell residuals. The log-normal and Weibull distribution models had the best and the second-best fit for HRS data (Table 4-18). Considering the current mediation analysis methods with survival outcome have only been developed for Cox Proportional Hazards regression model and AFT with the Weibull distribution model [172-174], we decided to proceed with the AFT model with the Weibull distribution. However, the fit of the Weibull distribution model for time to death through the Cox-Snell residuals was assessed, and it was shown to be a reasonable fit to the data as the residuals were relatively linear through the origin (Figure 4-9).

Mediation Analysis Assumptions

We assumed the measured covariates included in the models were sufficient to control for confounding and 1) no unmeasured exposure-outcome confounding, 2) no unmeasured exposure-mediator confounding, 3) no unmeasured mediator-outcome confounding, and 4) no unmeasured and measured exposure-caused confounding [175].

Mediation Analysis Model Equations

Six separate linear regression model was used as mediator models for each mediator:

$$M^{(i)} = \beta_0^{(i)} + \beta_1^{(i)} a + \beta_2^{(i)} c + \varepsilon^{(i)}, for\ i = 1 - 6, \quad (1)$$

where $M^{(i)}$ represents one of the six potential mediators, a corresponds to the exposure, psychosocial wellbeing status, and c represents confounders.

Next, six outcome models initially took the following general form:

$$\log(T^{(i)}) = \theta_0^{(i)} + \theta_1^{(i)} a + \theta_2^{(i)} m^{(i)} + \theta_3^{(i)} a m^{(i)} + \theta_4^{(i)} c + \sigma^{(i)} \varepsilon^{(i)}, for\ i = 1 - 6, (2)$$

where $m^{(i)}$ represents one of the six potential mediators, a and c again represent the exposure and confounders, respectively, σ describes the Weibull distribution scale and shape parameters, and ε symbolizes the errors. After the evaluation of the interaction term, θ_3, no exposure-mediator interaction was observed. Thus, the outcome model was reduced to

$$\log\left(T^{(i)}\right) = \theta_0^{(i)} + \theta_1^{(i)} a + \theta_2^{(i)} m^{(i)} + \theta_3^{(i)} c + \sigma^{(i)} \varepsilon^{(i)}, for\ i = 1 - 6, (3)$$

After modeling the mediator models and the outcome models the Natural Direct Effect (NDE) and the Natural Indirect Effect (NIE) on survival time ratio scale were calculated as follow:

$$NDE^{(i)} = \exp\{E\left[logT\left(a, M^{(i)}(a^*)\right) - logT\left(a^*, M^{(i)}(a^*)\right)\right] | c\}, \quad for\ i = 1 - 6, (4)$$

$$NIE^{(i)} = \exp\{E\left[logT\left(a, M^{(i)}(a)\right) - logT\left(a, M^{(i)}(a^*)\right)\right]|c\}, \ \ for\ i = 1-6, (5)$$

After modeling the mediator models and the outcome models no exposure-mediator interaction was observed in our sample. Thus, when no exposure-mediator interaction was observed the NDE and NIE were reduced to

$$\widehat{NDE^{(i)}} = \exp\left(\hat{\theta}_1^{(i)}(a - a^*)\right), \ for\ i = 1-6, (6)$$

$$\widehat{NIE^{(i)}} = \exp\left(\hat{\beta}_1^{(i)}\hat{\theta}_2^{(i)}\ (a - a^*)\right), \ for\ i = 1-6, (7)$$

where a is the good or average psychosocial wellbeing status, and a^* is poor psychosocial wellbeing status (reference). The NDE and NIE were on a survival time ratio scale. Survival rate is interpreted as ratio of time to death compared good psychosocial wellbeing status to poor (or average compared to poor). If survival rate equals to 1, then there is a null association between exposure and survival; if survival < 1, exposure is associated with earlier time to death; and if survival rate > 1, exposure is associated with later time to death. Proportion mediated calculated from the equation NDE*(NIE-1)/(NDE*NIE-1)*100% for each mediator separately.

The calculation of the standard errors for the NIEs, we utilized the formulate that was developed by VanderWeele and Vansteelandt for a dichotomous outcome with a continuous mediator[176]. When no exposure-mediator interaction was observed:

$$\widehat{SE}_{NIE^{(i)}} = \sqrt{\hat{\theta}_2^{(i)2}\hat{\sigma}_{\hat{\beta}_1^{(i)}} + \hat{\beta}_1^{(i)2}\hat{\sigma}_{\hat{\theta}_2^{(i)}}}\ , \ for\ i = 1-6, (8)$$

$\hat{\sigma}_{\hat{\beta}_1^{(i)}}$ is the covariance in model (1), and $\hat{\sigma}_{\hat{\theta}_2^{(i)}}$ is the covariance in the model (3); these covariances are given in the regression output of standard statistical software.

7. Sensitivity Analysis

7.1. Sensitivity Analysis- Latent factor analysis with all psychosocial constructs

To provide an additional understanding of the initial set of 48 psychosocial constructs HRS measured in 2006, we re-conducted the latent class analysis without variable selection and used all 48 constructs. The latent class analysis grouped HRS participants into two clusters (Table 4-13 and Figure 4-7). The new two-level psychosocial wellbeing clusters were used as the new exposure variable, and we reevaluated the indirect effects through each mediator.

7.2. Sensitivity Analysis- Reverse causation due to chronic conditions

We conducted a stratified analysis to evaluate the potential reverse causation between psychosocial wellbeing and chronic conditions. We were concerned that some severely ill people have poor psychosocial wellbeing as a result of their illness. So we conducted a sensitivity analysis stratified by individuals who had no reported chronic conditions and individuals who had at least one chronic condition. The goal of the sensitivity analysis was to determine whether there continued to be an association between psychosocial wellbeing and mortality in these population subsets.

7.4. Sensitivity Analysis- Evaluation of binary mediators as binary variables

In the main analysis, linear regression models were used to construct the mediator models for all mediators. As shown in the equation #7, when linear regression model was used, the NIE estimation does not involve the estimates of covariates. However, when a logistic regression model is used as the mediator model for a binary mediator, the estimation of the NIE is conditioning on the covariates (as shown below in equation #15). In sensitivity analysis, we additionally performed

mediation analyses by fitting three binary behavioral mediators (vigorous physical activity, smoking status, and weekly alcohol consumption) in logistic regression models to validate the observed NIEs in the main analysis.

Binary Mediator Mediation Analysis Model Equations

Three separate mediator models through logistic regression model were used for each mediator (vigorous physical activity, smoking status, and weekly alcohol consumption):

$$logit\{P(M^{(i)} = 1|a, c)\} = \beta_0^{(i)} + \beta_1^{(i)}a + \beta_2^{(i)}c, for\ i = 1 - 3, (9)$$

where $M^{(i)}$ represents one of the six potential mediators, a corresponds to the exposure, psychosocial wellbeing status, and c represents confounders. Next, three outcome models initially took the following general form:

$$\log(T^{(i)}) = \theta_0^{(i)} + \theta_1^{(i)}a + \theta_2^{(i)}m^{(i)} + \theta_3^{(i)}am^{(i)} + \theta_4^{(i)}c + \sigma^{(i)}\varepsilon^{(i)}, for\ i = 1 - 3, (10)$$

where $m^{(i)}$ represents one of the three potential mediators, a and c again represent the exposure and confounders, respectively, σ describes the Weibull distribution scale and shape parameters, and ε symbolizes the errors. After the evaluation of the interaction term, θ_3, no exposure-mediator interaction was observed. Thus, the outcome model was reduced to

$$\log(T^{(i)}) = \theta_0^{(i)} + \theta_1^{(i)}a + \theta_2^{(i)}m^{(i)} + \theta_3^{(i)}c + \sigma^{(i)}\varepsilon^{(i)}, for\ i = 1 - 3, (11)$$

After modeling the mediator models and the outcome models the Natural Direct Effect (NDE) and the Natural Indirect Effect (NIE) on survival time ratio scale were calculated as follow:

$$NDE^{(i)} = E[T(a, M^{(i)}(a))]|c\ /\ E[T(a, M^{(i)}(a^*))]|c, \quad for\ i = 1 - 3, (12)$$

$$NIE^{(i)} = E[T(a, M^{(i)}(a^*))]|c\ /\ E[T(a^*, M^{(i)}(a^*))]|c, \quad for\ i = 1 - 3, (13)$$

After modeling the mediator models and the outcome models no exposure-mediator interaction was observed in our sample. Thus, when no exposure-mediator interaction was observed the NDE and NIE were reduced to

$$\widehat{NDE^{(i)}} = \frac{\exp(\hat{\theta}_1^{(i)}a)\{1+\exp(\hat{\theta}_2^{(i)}+\hat{\theta}_3^{(i)}a+\hat{\beta}_0^{(i)}+\hat{\beta}_1^{(i)}a^*+\hat{\beta}_2^{(i)}c)\}}{\exp(\hat{\theta}_1^{(i)}a^*)\{1+\exp(\hat{\theta}_2^{(i)}+\hat{\theta}_3^{(i)}a^*+\hat{\beta}_0^{(i)}+\hat{\beta}_1^{(i)}a^*+\hat{\beta}_2^{(i)}c)\}} \quad for\ i = 1-3, (14)$$

$$\widehat{NIE^{(i)}} = \frac{\{1+\exp(\hat{\beta}_0^{(i)}+\hat{\beta}_1^{(i)}a^*+\hat{\beta}_2^{(i)}c)\}\{1+\exp(\hat{\theta}_2^{(i)}+\hat{\theta}_3^{(i)}a+\hat{\beta}_0^{(i)}+\hat{\beta}_1^{(i)}a+\hat{\beta}_2^{(i)}c)\}}{\{1+\exp(\hat{\beta}_0^{(i)}+\hat{\beta}_1^{(i)}a+\hat{\beta}_2^{(i)}c)\}\{1+\exp(\hat{\theta}_2^{(i)}+\hat{\theta}_3^{(i)}a+\hat{\beta}_0^{(i)}+\hat{\beta}_1^{(i)}a^*+\hat{\beta}_2^{(i)}c)\}} \quad for\ i = 1-3, (15)$$

where a is the good or average psychosocial wellbeing status, and a^* is poor psychosocial wellbeing status (reference).

We followed the delta method to calculated the SE for NIE. Delta method utilizes a first-order Taylor approximation to estimate errors of functions of random variables. A detailed the description and formula was provided by Dr. VanderWeele.

$$\widehat{SE}_{NIE^{(i)}} = \sqrt{\Gamma^{(i)}\Sigma^{(i)}\Gamma^{(i)\prime}}, \quad for\ i = 1-3, (16)$$

where, Σ is the covariance matrices for the estimated betas and thetas. Γ are the partial derivatives of the logarithm of the NIE, where $\Gamma^{(i)} = (d_1^{(i)}, d_2^{(i)}, d_3^{(i)}, d_4^{(i)}, d_5^{(i)}, d_6^{(i)}, d_7^{(i)}, d_8^{(i)})$, and letting

$$d_1^{(i)} = (D+Q)-(K+B)\ for\ i = 1-3, (17)$$

$$d_2^{(i)} = a^*[D-B]+a[Q-K]\ for\ i = 1-3, (18)$$

$$d_3^{(i)} = c'[(D+Q)-(K+B)] for\ i = 1-3, (19)$$

$$d_4^{(i)} = 0 \quad for\ i = 1-3, (20)$$

$$d_5^{(i)} = 0 \quad for\ i = 1-3, (21)$$

$$d_{6}^{(i)} = Q - B \;\; for\; i = 1 - 3, (22)$$

$$d_{7}^{(i)} = a[Q - B] \;\; for\; i = 1 - 3, (23)$$

$$d_{8}^{(i)} = 0' \;\; for\; i = 1 - 3, (24)$$

then

$$Q^{(i)} = \frac{\exp\left(\hat{\theta}_2^{(i)} + \hat{\theta}_3^{(i)}a + \hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a + \hat{\beta}_2^{(i)}c\right)}{\{1+\exp\left(\hat{\theta}_2^{(i)} + \hat{\theta}_3^{(i)}a + \hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a + \hat{\beta}_2^{(i)}c\right)\}} \;\; for\; i = 1 - 3, (25)$$

$$B^{(i)} = \frac{\exp\left(\hat{\theta}_2^{(i)} + \hat{\theta}_3^{(i)}a + \hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a^* + \hat{\beta}_2^{(i)}c\right)}{\{1+\exp\left(\hat{\theta}_2^{(i)} + \hat{\theta}_3^{(i)}a + \hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a^* + \hat{\beta}_2^{(i)}c\right)\}} \;\; for\; i = 1 - 3, (26)$$

$$K^{(i)} = \frac{\exp\left(\hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a + \hat{\beta}_2^{(i)}c\right)}{\{1+\exp\left(\hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a + \hat{\beta}_2^{(i)}c\right)\}} \;\; for\; i = 1 - 3, (27)$$

$$D^{(i)} = \frac{\exp\left(\hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a^* + \hat{\beta}_2^{(i)}c\right)}{\{1+\exp\left(\hat{\beta}_0^{(i)} + \hat{\beta}_1^{(i)}a^* + \hat{\beta}_2^{(i)}c\right)\}} \;\; for\; i = 1 - 3, (28)$$

7.5. Sensitivity Analysis- Evaluation of Measured Confounders

To provide more insight about the mediation effects under various observed covariates adjustments, pairwise mediation sensitivity analysis with a different set of covariates was conducted. We took functional status as the demonstration of the sensitivity analysis. In the main analysis, the indirect effect through functional status was adjusted for *a priori* confounders and all other mediators in 2006 (smoking status, frequency of vigorous physical activity, alcohol consumption, and the number of comorbid conditions). In this sensitivity analysis, we kept age, gender, race, marital status, education, total household income, and total wealth in the model as the base model and evaluated 31 possible combinations of the rest of the covariates adjustments

(smoking status, vigorous physical activity, frequency of alcohol consumption, number of comorbid conditions, and BMI).

7.6. Sensitivity Analysis- Evaluation of Unmeasured Confounders

To assess how robust the study results are to violations of the unmeasured confounding assumptions for the mediation analysis, sensitivity analyses using E-values were conducted [177]. E-value estimations were calculated for all six mediators. It used the survival rate (SR) of the mediation effect estimates. The E-value can be defined as the minimum strength of the association that an unmeasured confounder would need to have with both the exposure and outcome (survival), conditional on the measured covariates, to fully explain away the association [177]. If the survival rate for mediation effect is smaller than 1, thus this formulate was used: E-Value= 1/SR + sqrt(1/SR*(1/SR-1)), respectively for all mediation effects, whereas if the survival rate for mediation effect is smaller than 1, thus this formulate was used: E-Value= SR + sqrt(SR*(SR-1)).

Supplementary Results

Sensitivity Analysis

Table 4-12 demonstrates mediation analysis results when we used the new two-level psychosocial wellbeing cluster as the exposure. We observed a similar pattern as the main analysis results. Our stratified analysis demonstrated a similar estimate between psychosocial wellbeing and mortality across the group. Therefore, reverse causation due to chronic conditions is not a major concern in our study (Table 4-14). The sensitivity analysis of fitting three binary mediators (vigorous physical activity, smoking status, and weekly alcohol consumption) in logistic regression models validated the results in the main analysis (Table 4-16). The total effects, and direct effects were unchanged regardless of the choice of the mediator model. E-values suggested that the mediation effects through the health index, functional score, comorbid conditions, and physical activity were moderately robust to unmeasured confounding (Table 4-17). Moreover, regardless of the adjustment of various combinations of covariates, the indirect effect through better functional status remained strong and significant (Figure 4-8).

Chapter 5 First Genome-Wide Association Study on Life Purpose

5.1 Abstract

A significant body of literature has suggested that "purposeful living" improves physical and mental health. However, little investigation has been conducted into the genetics of life purpose and only twin studies demonstrated substantial genetic influences on life purpose. Findings from twin studies provided crucial evidence to further understand the role of genetics on life purpose through a genome-wide association study (GWAS). We conducted the first GWAS to identify genetic variants associated with life purpose in individuals of European ancestry (n=8,959) and African ancestry (n=1,641) in a large, population-based study, the Health and Retirement Study (HRS). No SNPs achieved genome-wide significance in either ancestry group ($p>5\times10^{-8}$). To improve the statistical power, we performed a GWAS meta-analysis among individuals of European ancestry in HRS and Michigan Genomics Initiative Epidemiological Questionnaire Study (MGI EPI-Q). The meta-analysis found no statistically significant SNP ($p>5\times10^{-8}$). This study serves as a stepping-stone to better understand the genetic pathways that underpin life purpose. Future research should consider exploring common, uncommon and rare variants through whole-genome approaches with much larger samples.

5.2 Introduction

Life purpose encompasses the meaning and direction a person has in life. A significant body of literature has suggested that "purposeful living" is associated with better physical[31-34] and mental health[51,59]. Previous research showed that having a strong life purpose was associated with decreased incidence of sleep disturbances[33], stroke[31], myocardial infarction[32], and Alzheimer's disease[34]. Additionally, there is a substantial body of literature showing that stronger life purpose is inversely associated with mortality[65,70]. For example, data from the U.S. Health and Retirement Study (HRS) suggested that individuals with the highest life purpose were 2.43 times less likely to die compared to those with the lowest life purpose (hazard ratio,95%CI:1.57,3.75)[70].

Life purpose has also been associated with a variety of other facets of psychosocial wellbeing, including depression[51,59], hopelessness[51], loneliness[51], optimism[51], anxiety[178,179], and resilience[48-50]. Previous study has indicated that individuals with a low life purpose were 1.85 times more likely to have depression compared to individuals with a higher life purpose (Odds Ratio (OR)=1.85, 95%CI:1.33,2.57)[59]. Most recently, Kim et al. used the data from the HRS and found that individuals in the highest quartile of life purpose score had 43% reduced risk of depression (OR=0.43,95% CI:0.46,0.69) compared to those in the lowest quartile of life purpose score[51]. They also observed HRS participants in the highest quartile of life purpose score had a lower hopelessness score (beta (β) =-0.35, 95% CI:-0.41,-0.29), lower loneliness score (β =-0.45, 95% CI:-0.56,-0.35), higher optimism score (β = 0.41, 95% CI:0.35,0.47), and higher positive affect score (β = 0.59, 95% CI: 0.53,0.65) compared to those in the lowest quartile[51].

Genome-wide association studies (GWAS) have identified variants associated with complex psychiatric traits such as depression[53], major depression disorder[54], neuroticism[53], anxiety[55], schizophrenia[56], and post-traumatic stress disorder[57]. In addition, Okbay and colleagues

reported associations between common genetic variants and subjective well-being[53]. There is also some evidence suggesting a genetic component to life purpose. Twin studies, using the Ryff and Keyes's life purpose measurement instrument, have estimated heritability of 21-30% [46,47].

Given the suggested association between genetics and life purpose, and the success of identifying genetic variants associated with other psychosocial wellbeing constructs, we carried out a life purpose GWAS. Data from the HRS and the Michigan Genomics Initiative Epidemiological Questionnaire Study (MGI EPI-Q)[180-182] were used for this analysis. A greater understanding of life purpose from a genetic perspective may offer new insights into the underlying biology of this psychosocial construct. Further, identifying individuals who are predisposed to lower life purpose could be useful in offering targeted interventions to improve life purpose.

5.3 Methods

5.3.1 Study Design and Source Population

HRS is a national, longitudinal cohort study of Americans over the age of 50 and their spouses or partners[143]. HRS began collecting data in 1992 and every two years thereafter. The HRS study covers several different facets, including a core survey, a psychosocial and lifestyle leave-behind participant questionnaire, and genetic data[183,184]. Half of the HRS participants were randomly selected in 2006 and every subsequent four years to complete a psychological and lifestyle questionnaire in which life purpose was evaluated. In 2008 and every subsequent four years, the remaining half of the HRS participants were asked to complete the psychological and lifestyle questionnaire[144]. Additionally, between 2006 and 2010, HRS participants' saliva samples were collected during enhanced face-to-face interviews[185]. HRS was approved by the Institutional

Review Board of the University of Michigan, and all participants provided informed consent. Data used in this study are de-identified and available for researchers through an application process.

5.3.2 Phenotype Definition

Genetic data were downloaded from dbGap (phs000428.v2.p2). In HRS, saliva DNA was genotyped on the Illumina HumanOmni2.5 BeadChip and performed by the Center for Inherited Disease Research (CIDR)[185]. Overall, HRS followed standard quality control recommendations to exclude samples and markers, including CIDR technical filters, removing single nucleotide polymorphisms (SNPs) that were duplicates, had missing call rates >2%, >4 discordant calls, >1 Mendelian error, deviations from Hardy-Weinberg equilibrium (at P-value$<1\times10^{-4}$), and sex differences in allele frequency >0.2). Genotype imputation from the 1000 Genomes Project cosmopolitan reference panel phase 1, version 3 was performed using SHAPEIT2[186,187] and IMPUTE2[188]. All HRS participants were imputed together[185,189]. Overall, about 23 million SNPs were imputed from the original 1,905,968 SNPs that were genotyped and passed quality control (QC)[185,189]. Further detail is provided in the HRS documentation[185].

5.3.3 Post-imputation Quality Control of SNPs and Samples

SNPs Quality Control (QC). In addition to the QC standards set by HRS and described above, we additionally excluded sex chromosome, insertion-deletion and structural variants as well as SNPs with a minor allele frequency of <5%, imputation quality score (info) <0.9, or missing call rates >1% for both European and African ancestry groups. Within ancestry groups, Hardy-Weinberg equilibrium was evaluated and variants with a p-value $<10^{-6}$ were excluded. Overall, 4,386,589 SNPs (European ancestry) and 4,386,577 SNPs (African ancestry) passed QC and were used in the GWAS analysis (Figure 5-1). QC procedures were performed using PLINK[190].

Sample Quality Control. The study sample included the 15,567 participants who completed the life purpose questionnaire between 2006 and 2010 and for whom genotype data were available. Of these, HRS participants were excluded from the analysis if they had >1% of SNPs missing (n=29), gender mismatch between self-report and genotype-derived sex (n=1), incomplete data on life purpose (n=2,262), or no genetic ancestry specific components available (n=2,675). Overall, 8,959 participants with European ancestry and 1,641 participants with African ancestry were used in the GWAS analysis (Figure 5-1). QC procedures were performed using PLINK[190] and R[191].

5.3.4 Covariates

Age and sex were assessed for each participant in the same interview where life purpose was measured. Genetic ancestry and ancestry-specific principal components (PCs) were obtained from the HRS. Age (continuous variable in years), sex (1=male and 2=female), and the first 10 ancestry-specific PCs were included as covariates in all models to account for population stratification and avoid potential confounding effects from demographic factors.

5.3.5 Statistical Analyses

Genome-wide Association Study (GWAS)

The GWAS was performed using the Genome-wide Efficient Mixed Model Association (GEMMA) toolkit to identify genetic loci associated with the full 7-item life purpose phenotype separately for European and African ancestry samples. Multivariate linear mixed models were used for each SNP independently in relation to life purpose. The multivariate linear mixed model in GEMMA was utilized to further correct for residual population structure due to ancestry or cryptic relatedness[192]. In this genome-wide search, the rank norm-transformed life purpose score was the dependent variable, and the SNPs were independent variables. Analyses were adjusted for age,

sex, and the first 10 PCs within ancestry. P-value thresholds of 1×10^{-5} and 5×10^{-8} were used to indicate suggestive and significant findings, respectively. Once GWAS results were obtained, SNPs were clumped in PLINK 1.9[190] to remove highly correlated SNPs. This clumping procedure applied the following thresholds to identify independent SNPs: (1) SNPs that had linkage disequilibrium (LD) $r2 \geq 0.1$ and (2) SNPs that were within 250 kb. Quantile-quantile (QQ) plots to visualize and quantify potential overdispersion and Manhattan plots to visualize associations across all autosomes were generated using R[191].

Sensitivity Analysis Through Region Analysis

To increase the statistical power of detecting genetic variations on life purpose, we performed region analysis using Sequence Kernel Association Testing (SKAT)[193]. The region-based analysis allowed for the investigation of associations between SNP sets and life purpose within each ancestry group. The most highly associated SNPs (i.e., those with a $p \times 10^{-5}$) identified from the GWAS analysis were used to select regions for SKAT. If a SNP overlapped with a gene, then a region was defined including all SNPs within a 20 kilobase (kb) region up and downstream of the gene locus. If there were no overlapping genes, then a region was defined including all SNPs within a 20 kb region up and downstream of the index SNP. Overall, 24 independent regions were identified, and SKAT was performed for all regions for European and African ancestries separately. All SKAT adjusted for age, sex, and the first 10 PCs.

Sensitivity Analysis Through Polygenic Risk Score

The correlation between the full 7-item life purpose phenotype and polygenic risk score (PRS) of life purpose was examined. Independent SNPs that had p-value$<1\times10^{-5}$ from the GWAS presented above were used to construct a weighted PRS of life purpose within each ancestry. The PRS of life purpose was determined by summing up the alleles that either confer risk, or protect

against life purpose, and weighting alleles by beta-coefficients for their association with life purpose. Person correlation was used to evaluate the association between the PRS and 7-item life purpose among each ancestry separately.

Sensitivity Analysis Through Meta-Analysis of Single-Question GWASs

To increase the statistical power to detect the top genetic variants associated with life purpose, we performed an additional GWAS using the only overlapping question on this topic between the HRS and the Michigan Genomics Initiative Epidemiological Questionnaire study (MGI EPI-Q), and then meta-analyzed the results. The overlapping life purpose question was "I have a sense of direction and purpose in my life"[69] This single question has been used to measure life purpose in several studies[21,24,194]. This GWAS was only performed among individuals of European ancestry, as the African ancestry sample in MGI EPI-Q was too small for a meaningful analysis.

MGI EPI-Q. The Michigan Genomics Initiative (MGI) is a biobank linking genotypes and medical profiles of participants via the electronic medical records at the University of Michigan[180]. Epidemiological Questionnaire (EPI-Q) is a survey study amongst individuals enrolled in MGI, aiming to collect additional behavioral, physical, and mental health data[181]. The single question for life purpose (mentioned above) was measured through the EPI-Q in the Comprehensive Measure of Meaning (CMM) questionnaire. DNA from blood samples of MGI EPI-Q participants at the University of Michigan Health System was genotyped on the Illumina Infinium CoreExome array[180]. Genotypes of the Haplotype Reference Consortium were imputed into the phased MGI genotypes[180]. MGI Freeze 4 genotype data were used[195]. Further details on the cohort description, genotyping, imputation, and quality control can be found elsewhere[180,195]. Overall, 2,194 participants with European ancestry and ~10 million SNPs were used in the MGI EPI-Q GWAS.

Study Specific GWAS. The HRS and MGI EPI-Q datasets were first analyzed in a study-specific fashion, allowing for adjustment for appropriate covariates. The HRS GWAS was performed using GEMMA to examine the association between each variant and the one-item life purpose phenotype. In this genome-wide search, the one-item life purpose score was reverse coded and standardized, and analyses were adjusted for age, sex, and the first 10 PCs. The MGI EPI-Q GWAS was performed using the Scalable and Accurate Implementation of GEneralized mixed model (SAIGE)[196]. In this GWAS, the one-item life purpose score was inverse normalized, and analyses were adjusted for age, sex, batch, study, and the first 10 PCs.

Meta-Analysis. LiftOver was used to convert coordinates of the HRS GWAS summary statistics to human genome assembly GRCh38 (UCSC Genome Browser Store, https://genome-store.ucsc.edu)[197]. Next, markers with matching chromosome, base pair, and alleles across the two studies were considered for the meta-analysis. To ensure the quality of the SNPs across the two GWAS, we plotted effect allele frequencies (EAF) in HRS data against the MGI EPI-Q data. SNPs that indicated some potential allele flips were removed before the meta-analysis. A subsequent meta-analysis of point estimates and standard errors was conducted using an inverse-variance weighted fixed-effects model with METAL software (https://genome.sph.umich.edu/wiki/METAL)[198]. Sample size was used to weight the meta-analysis.

5.4 Results

5.4.1 GWAS

As shown in the Q-Q plot, there was no evidence of inflation in either the European ancestry (genomic control inflation factor λ =0.998) or the African ancestry GWAS (λ=0.995;

Figure 3). This suggests that the selected covariates (i.e., age, sex, and PCs) and the use of GEMMA provided reasonable control for population stratification.

Overall, as presented in the Manhattan plot, no SNP achieved genome-wide statistical significance ($p>5\times10^{-8}$) in either ancestry group (Figure 5-2). In the European ancestry sample, nine SNPs had $p<1\times10^{-5}$ (Figure 5-2) which was our pre-specified significance level for considering an association suggestive. Clumping was used to remove highly correlated SNPs and keep the most important SNP per genomic region. As a result of the clumping, three SNPs in the European ancestry sample were independent (Table 5-1). These variants were intragenic and located within the genes *CTB-57H20.1 (uncharacterized LOC105378210)*, Long Intergenic Non-Protein Coding RNA 426 (*LINC00426)*, and Purkinje Cell Protein 4 (*PCP4)*. In the African ancestry sample, 83 SNPs had $p<1\times10^{-5}$, and after clumping, 21 SNPs were independent (Table 5-1). The peak signal in the African ancestry sample ($p=8.25\times10^{-7}$) was for SNP rs6541360 located in Down-Regulator of Transcription 1 gene (*DR1)*. The second strongest association signal was observed at rs12047247 ($p=1.49\times10^{-7}$), located in Calmodulin Binding Transcription Activator 1 gene (*CAMTA1)*.

5.4.2 Sensitivity Analysis Through Region Analysis

Using SKAT, 24 regions (three in the European ancestry group and 21 in the African ancestry group) harboring variants that showed suggestive evidence ($p<1\times10^{-5}$) of an association with the 7-item life purpose phenotype were investigated. None of regions evaluated among the European ancestry group showed an association (Table 5-2). However, among individuals of African ancestry, two regions (*CAMTA1* and rs75656895 region) were found to have statistically significant associations (Bonferroni corrected p-value <0.001) and three regions showed marginally significant associations (p-value<0.05; Table 5-2).

5.4.3 Sensitivity Analysis Through the Polygenic Risk Score (PRS)

Among individuals of European ancestry, no correlation was observed between 7-item life purpose phenotype and the PRS, which was constructed from three SNPs (person correlation coefficient r=0.08; Figure 5-4). Conversely, among the African ancestry sample, a weak correlation was observed between 7-item life purpose phenotype and the PRS, which was constructed from 21 SNPs (r=0.45; Figure 5-4). Life purpose likely has a polygenic architecture and is influenced by many, many SNPs. A critical next step will be to develop a genome-wide PRS using continuous shrinkage to obtain an accurate picture of the role of common genetic variation on life purpose.

5.4.4 Sensitivity Analysis Through Meta-Analysis of the HRS and MGI Data

For the single-question GWAS, 4,241,715 variants overlapped and passed QC between the HRS and MGI data and were thus used for meta-analysis. The meta-analysis results of the GWAS using data in HRS and MGI EPI-Q are presented in Table 5-3 and Figure 5-5. No genome-wide statistically significant associations ($p<5\times10^{-8}$) were found in the meta-analysis. The smallest p-value in the meta-analysis was on chromosome 8 (rs13272748, $P=1.81\times10^{-6}$); the nearest gene for rs13272748 is *AC104417.2*. The Q-Q plot shows p-values below the diagonal line in the upper-right quadrant of the plot, demonstrating that there are some SNPs with associations less statistically significant than expected. This indicates that we were underpowered (Figure 5-6). The λ value of 0.955 implies that the selected covariates and PCs within study-specific analyses provided reasonable control for population stratification.

5.5 Discussion

In this present study, we conducted a GWAS using data from HRS to identify common variants related to life purpose among individuals of European and African ancestries. Our study found that no SNPs reached the conventional level of genome-wide significance ($p<5\times10^{-8}$) in either ancestry sample. We detected three independent SNPs in the European ancestry sample, and 21 independent SNPs in the African ancestry sample that had $p<1\times10^{-5}$ with the 7-item life purpose phenotype. However, there was no indication of association between the African ancestry-identified variants within the European group and vice versa.

Our results suggest common SNPs do not strongly influence life purpose among individuals of European and African ancestries, though our power was limited given our small sample size. We had 80% power to detect associations in European ancestry (n=8,959) and 0.3% in African ancestry (n=1,641) with a type I error rate of 5×10^{-8}, an effect size of 0.1, and a minor allele frequency of 0.33. The lack of genome-wide statistically significant findings is likely due to the insufficient sample size to detect small effect sizes for a complex phenotype. We observed more independent SNPs among individuals of African ancestry (N SNPs=21) than European ancestry (N SNPs=3); this may be due to the smaller sample size in the African ancestry group and the variation in linkage disequilibrium between two ancestries. Additionally, in our data, mean life purpose score is not differentiated by ancestry (European: mean(SD)=4.5(0.9); African: mean(SD)=4.6(0.9)). Furthermore, the lack of association with common variants in our study does not rule out a role for uncommon or rare variants with life purpose. There are rare variant associations with other psychosocial phenotypes, such as depression[199,200]. Therefore, more whole-genome approaches in much larger samples are required to reveal the impact of uncommon and rare variants on life purpose.

Although no genome-wide statistically significant loci were detected in our GWAS, several interesting findings deserve further attention. In the European ancestry sample, a top SNPs (rs2037916) from the 7-item HRS GWAS was located within the Purkinje Cell Protein 4 gene (*PCP4* alias *PEP-19*). *PCP4* is a protein-coding gene, and it is highly expressed in the Purkinje cells[201]. Purkinje cells are the output neuron from the cerebellum[202]. Previous studies have shown that *PCP4* is involved in the calmodulin-dependent kinase signaling pathway[203] and positive regulation of neuron differentiation[204]. A recent study found a 12-week-long exercise improved cardiac function in aged rats, where the improved cardiac function was related to increased expression of *PCP4* gene[205]. In observational epidemiologic studies, stronger life purpose has been shown associations with reduced risk of developing cardiovascular disease[32] and lower mortality[70]. It is possible that individuals who have a strong life purpose have higher *PCP4* expression. The *PCP4* protein can decrease the release of *Ca2+* from cardiac cells[206], which may reduce the risk of adverse cardiovascular events.

Additionally, the top SNPs, rs140176641 and rs12279260, in the HRS/MGI EPI-Q single-question GWAS meta-analysis fall within the Dihydrolipoamide Dehydrogenase gene (*DLD*) and the Teneurin Transmembrane Protein 4 (*TENM4*), respectively, which are associated with neurodegenerative[207,208] and neuropsychiatric[209] disorders. *DLD* was linked to Alzheimer's disease in vitro[207,208], and *TENM4* was related to unipolar depression through a case–case genome-wide association study (CC-GWAS)[209]. Prior research has shown that stronger life purpose was associated with a lower risk of developing Alzheimer's disease[34,210] and depression[51]. Our findings may indicate that life purpose has some protective effect on neurodegenerative and neuropsychiatric disorders. Nonetheless, it is also likely that the observed signals in these genes are due to the correlations between life purpose and those disorders.

Furthermore, in the African ancestry sample, the top variant from the 7-item HRS GWAS, rs12047247, falls in the Calmodulin Binding Transcription Activator 1 locus (*CAMTA1*). The SKAT analysis also detected a statistically significant signal in the *CAMTA1* region with life purpose among individuals of African ancestry. *CAMTA1* is a protein-coding gene previously linked to cerebellar dysfunction with variable cognitive and behavioral abnormalities (CECBA)[211]. CECBA is an autosomal dominant neurologic disorder, and autism and obsessive-compulsive disorder are part of the symptoms[212]. Overall, the detected signals in these genes provide biologic plausibility to these genetic associations with life purpose, and further follow-up is warranted even though our GWAS was underpowered.

Our study has multiple strengths. To our knowledge, this is the first GWAS to identify potential genetic variants associated with life purpose. We also conducted two sensitivity analyses to increase the statistical power of detecting associations between variants and life purpose. First, we performed region-based analysis using SKAT, which allowed us to explore the impact of multiple variants in a region even if the region did not contain any SNP reaching genome-wide significance. Second, we conducted GWAS meta-analysis using a single-question measure of life purpose using HRS and MGI EPI-Q data; this single question is used in many life purpose studies[21,24,194].

Nevertheless, several limitations exist. First, our analysis was underpowered to detect genome-wide statistically significant associations. Future studies with larger sample sizes of both European and African ancestry individuals are needed to further explore the underlying genetic architecture of life purpose. Second, like other psychosocial phenotypes, life purpose is a complex trait, and its variability can be due to a combination of genetic and environmental factors. Gene-environment interactions were not investigated in our study. Previous research has suggested such

interactions with other psychosocial phenotypes[38,40]. Future research should investigate whether gene-environment interaction analyses enhance the discovery genetic variants associated with life purpose.

5.6 Conclusion

In summary, we reported the first GWAS on life purpose, and our results suggest at best modest associations between common SNPs and life purpose in either dataset we analyzed (HRS or MGI EPI-Q). This research serves as a stepping-stone toward a better understanding of the genetic pathways underpinning life purpose. It is imperative that future research should consider exploring common, uncommon, and rare variants using whole-genome approaches with much larger sample sizes. Also, gene-environment interactions with life purpose should be explored.

Figure 5-1. Post-imputation quality control of samples and single nucleotide polymorphisms (SNPs) in the HRS.

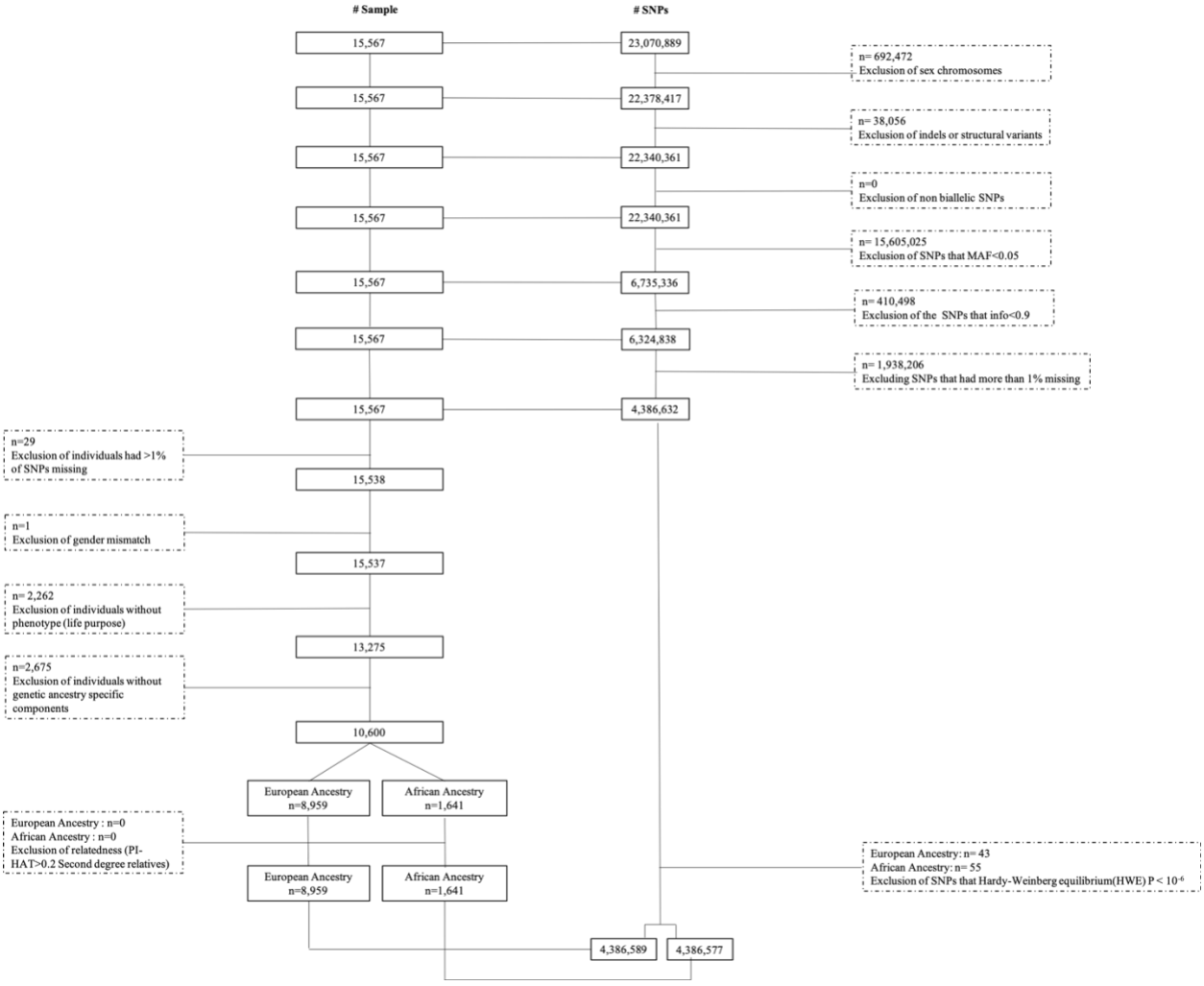
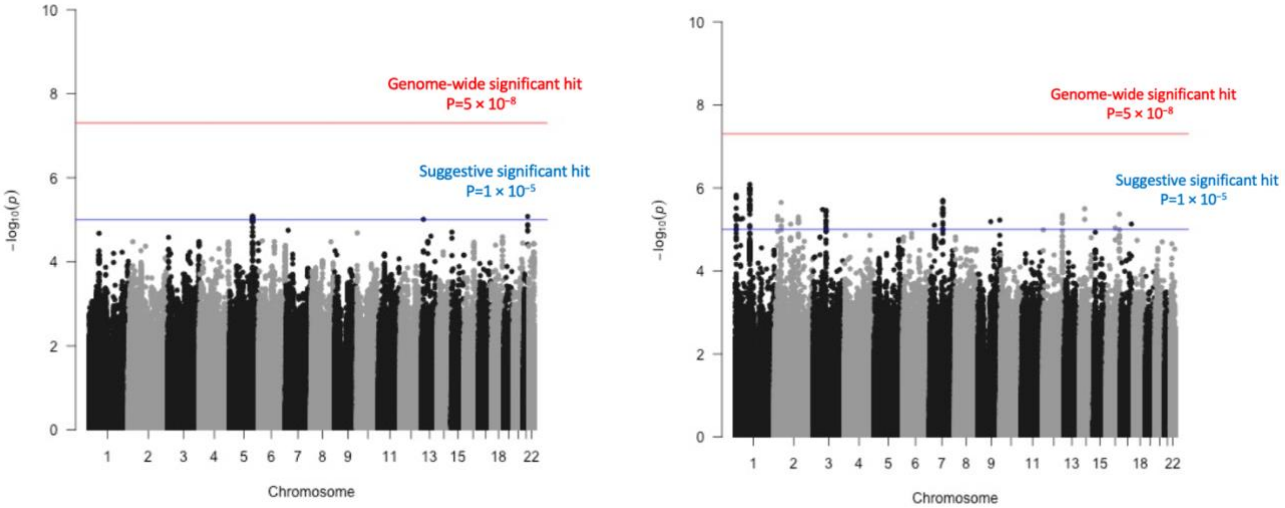


Table 5-1. Characteristics of the independent single nucleotide polymorphisms (SNPs) reaching suggestive significant hit ($p<10^{-5}$) in the European ancestry sample and the African ancestry sample from the 7-item life purpose GWAS in the HRS.

Chr	Position	SNP	Overlapping Gene	Effect Allele	Other Allele	Effect Allele Frequency	Beta	SE	P-value
European Ancestry									
5	143127912	rs325234	*CTB-57H20.1*	C	T	0.37	-0.07	0.02	8.22×10^{-06}
13	30942955	rs7983230	*LINC00426*	A	G	0.30	0.07	0.02	9.76×10^{-06}
21	41254456	rs2037916	*PCP4*	T	C	0.41	-0.06	0.01	8.34×10^{-06}
African Ancestry									
1	6847563	rs12047247	*CAMTA1*	G	C	0.02	-0.72	0.15	1.49×10^{-06}
1	35157716	rs10915020	*None*	A	T	0.12	-0.26	0.06	5.65×10^{-06}
1	48212615	rs10789515	*None*	T	C	0.19	-0.22	0.05	5.45×10^{-06}
1	93570439	rs6688513	*MTF2*	T	C	0.3	0.18	0.04	3.37×10^{-06}
1	93823327	rs6541360	*DR1*	T	C	0.29	0.20	0.04	8.25×10^{-06}
2	20226403	rs7558777	*None*	T	C	0.19	-0.21	0.05	4.84×10^{-06}
2	42475879	rs17029385	*EML4*	C	T	0.25	-0.20	0.04	2.24×10^{-06}
2	43153115	rs895504	*None*	T	C	0.15	0.23	0.05	8.63×10^{-06}
2	46463334	rs9789585	*None*	C	T	0.32	-0.18	0.04	6.02×10^{-06}
2	102636864	rs2072476	*IL1R2*	T	C	0.23	-0.20	0.04	7.47×10^{-06}
2	151491400	rs4664694	*AC104777.4*	A	G	0.35	0.17	0.04	5.03×10^{-06}
3	61615565	rs1320234	*PTPRG*	C	T	0.33	-0.18	0.04	3.32×10^{-06}
3	83280111	rs75656895	*None*	A	G	0.03	-0.53	0.11	3.50×10^{-06}
7	29208720	rs11979687	*CPVL CHN2*	C	T	0.26	-0.18	0.04	7.87×10^{-06}
7	82263062	rs10232895	*None*	T	C	0.19	-0.21	0.04	2.02×10^{-06}
9	137566937	rs4841922	*COL5A1*	T	C	0.29	-0.18	0.04	5.93×10^{-06}
12	122336827	rs1168661	*PSMD9 RP11-87C12.2*	T	C	0.2	0.21	0.05	4.57×10^{-06}
14	53168000	rs12892461	*None*	T	C	0.36	-0.18	0.04	3.19×10^{-06}
16	56985156	rs193695	*None*	A	G	0.37	0.16	0.04	9.21×10^{-06}
16	83293075	rs62040391	*CDH13*	G	A	0.05	-0.40	0.09	4.29×10^{-06}
17	68337964	rs10512574	*CTD-2378E21.1*	C	T	0.11	-0.25	0.06	7.42×10^{-06}

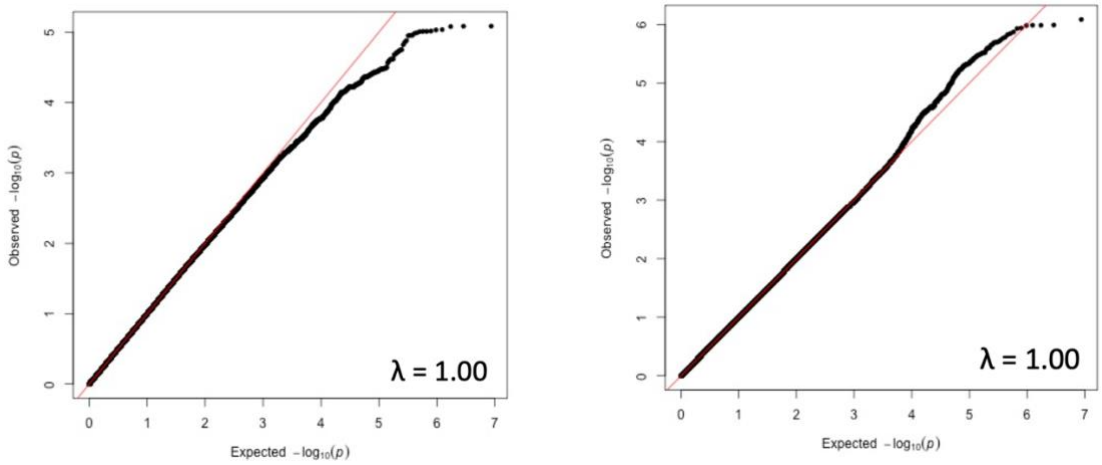
Chr: Chromosome
SNP: single nucleotide polymorphism
Beta is the effect estimate for the association between the SNP and rank-norm transformed life purpose score from the GWAS results using GEMMA.
SE is the standard error of beta.

Figure 5-2. Manhattan plots of genome wide association studies of 7-item life purpose for ~4 million genotype and imputed SNPs in the samples of European ancestry (a) and African ancestry (b) from the HRS. The red line indicates the threshold for genome-wide significance ($P<5\times10^{-8}$) and the blue line for suggestive associations ($P<1\times10^{-5}$).



(a) EA (b) AA

Figure 5-3. Quantile-Quantile (QQ) plots of genome wide association studies of 7-item life purpose for ~4 million genotype and imputed SNPs in the samples of European ancestry (a) and African ancestry (b) from the HRS.



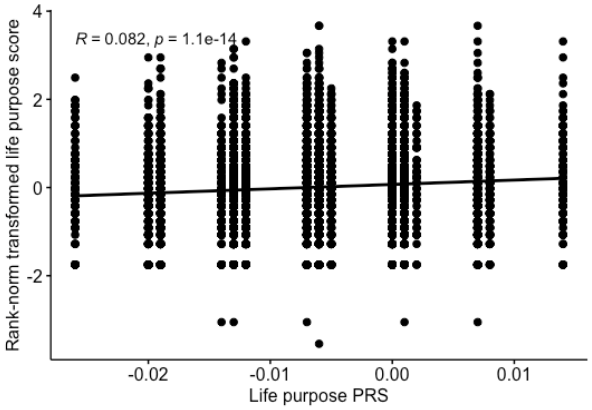
(a) EA (b) AA

Table 5-2. Region analysis results through Sequence Kernel Association Testing (SKAT) in the HRS.

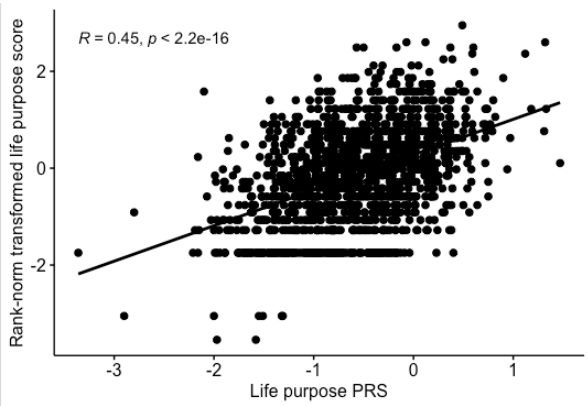
Region	Index SNP Source	Variation ID	Chr	Overlapped Gene	Number of Markers	P-value in EA	P-value in AA
1	EA GWAS	rs325234	5	*CTB-57H20.1*	459	0.79	0.24
2	EA GWAS	rs7983230	13	*LINC00426*	117	0.30	0.51
3	EA GWAS	rs2037916	21	*PCP4*	223	0.24	0.79
4	AA GWAS	rs12047247	1	*CAMTA1*	1506	0.23	1×10^{-05}
5	AA GWAS	rs10915020	1	*None*	56	0.40	0.03
6	AA GWAS	rs10789515	1	*None*	21	0.46	0.96
7	AA GWAS	rs6688513	1	*MTF2*	123	0.24	0.24
8	AA GWAS	rs6541360	1	*DR1*	123	0.13	0.01
9	AA GWAS	rs7558777	2	*None*	45	0.79	0.18
10	AA GWAS	rs17029385	2	*EML4*	364	0.33	0.02
11	AA GWAS	rs895504	2	*None*	58	0.06	0.14
12	AA GWAS	rs9789585	2	*None*	45	0.80	0.22
13	AA GWAS	rs2072476	2	*IL1R2*	177	0.62	0.20
14	AA GWAS	rs4664694	2	*AC104777.4*	143	0.15	0.94
15	AA GWAS	rs1320234	3	*PTPRG*	1299	0.16	0.06
16	AA GWAS	rs75656895	3	*None*	10	0.61	1×10^{-05}
17	AA GWAS	rs11979687	7	*CPVL/CHN2*	589	0.13	0.59
18	AA GWAS	rs10232895	7	*None*	24	0.99	0.09
19	AA GWAS	rs4841922	9	*COL5A1*	401	0.81	0.38
20	AA GWAS	rs1168661	12	*PSMD9/RP11-87C12.2*	98	0.69	0.30
21	AA GWAS	rs12892461	14	*None*	13	0.14	0.44
22	AA GWAS	rs193695	16	*None*	46	0.99	0.08
23	AA GWAS	rs62040391	16	*CDH13*	3882	0.47	0.02
24	AA GWAS	rs10512574	17	*CTD-2378E21.1*	199	0.93	0.07

Chr: Chromosome
EA: European Ancestry
AA: African Ancestry

Figure 5-4. Scatter plots between 7-item life purpose phenotype and the polygenic risk scores (PRS) in the HRS by ancestry.



European Ancestry



African Ancestry

Table 5-3. GWAS meta-analysis results across the HRS and MGI EPI-Q (p-values < 1×10^{-5}) for one-item life purpose phenotype in the European ancestry sample.

Chr	Position	SNP	Overlapping or Nearest Gene	Effect Allele	Other Allele	Weighted Average Effect Allele Frequency	Z-score	P-value	Direction
7	107922343	rs140176641	*DLD*	A	C	0.05	4.49	7.11×10^{-06}	++
8	142039663	rs13272748	*AC104417.2*	T	C	0.42	4.77	1.81×10^{-06}	++
11	79460974	rs12279260	*TENM4*	T	C	0.77	-4.60	4.29×10^{-06}	--
11	79459511	rs7952698	*TENM4*	A	G	0.23	4.60	4.31×10^{-06}	++
11	79462986	rs4644671	*TENM4*	T	C	0.23	4.59	4.42×10^{-06}	++
11	79463378	rs17138383	*TENM4*	A	G	0.23	4.58	4.61×10^{-06}	++
11	79462973	rs4447199	*TENM4*	T	C	0.23	4.58	4.72×10^{-06}	++
11	79463095	rs11237845	*TENM4*	A	G	0.77	-4.57	4.86×10^{-06}	--
11	79463487	rs4604915	*TENM4*	A	G	0.23	4.55	5.30×10^{-06}	++
11	79463733	rs4644672	*TENM4*	T	C	0.23	4.55	5.30×10^{-06}	++
11	79463847	rs4554918	*TENM4*	T	C	0.23	4.55	5.31×10^{-06}	++
11	79463336	rs17138382	*TENM4*	T	G	0.23	4.55	5.32×10^{-06}	++
11	79463840	rs4517555	*TENM4*	T	G	0.23	4.55	5.32×10^{-06}	++
11	79463503	rs4604916	*TENM4*	A	G	0.23	4.55	5.42×10^{-06}	++
11	79463452	rs5015504	*TENM4*	T	C	0.23	4.54	5.52×10^{-06}	++
11	79463472	rs4582999	*TENM4*	T	C	0.23	4.54	5.52×10^{-06}	++
11	79464128	rs7129961	*TENM4*	A	G	0.23	4.52	6.14×10^{-06}	++
11	79470010	rs17138398	*TENM4*	C	G	0.23	4.52	6.21×10^{-06}	++
15	99499450	rs7173311	*AC015660.4*	T	C	0.24	-4.42	9.88×10^{-06}	--

Chr: Chromosome
SNP: single nucleotide polymorphism

Figure 5-5. Manhattan plot of the one-item life purpose GWAS meta-analysis in European ancestry samples. The red line indicates the threshold for genome-wide significance ($P<5\times10^{-8}$) and the blue line for suggestive associations ($P<1\times10^{-5}$).

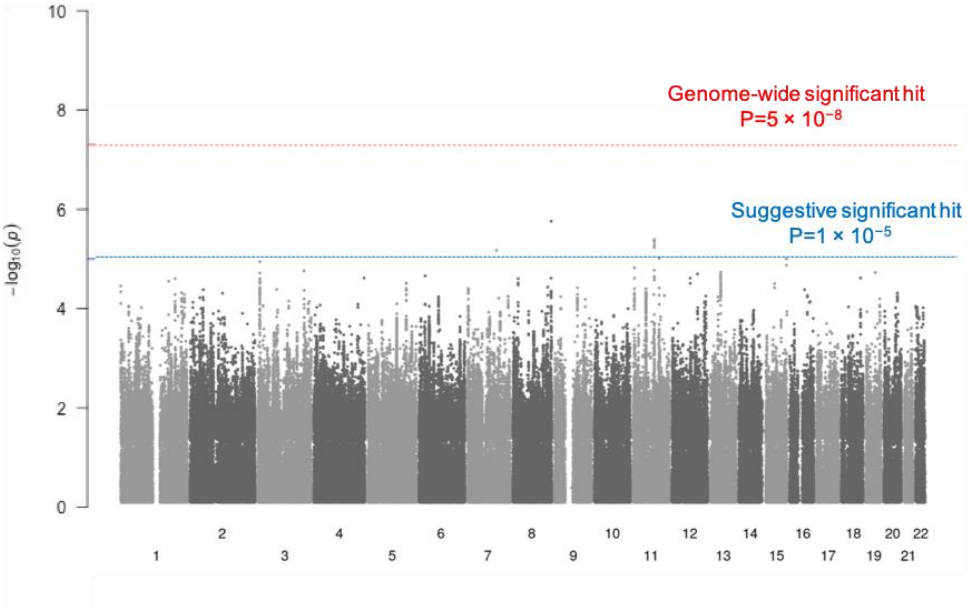
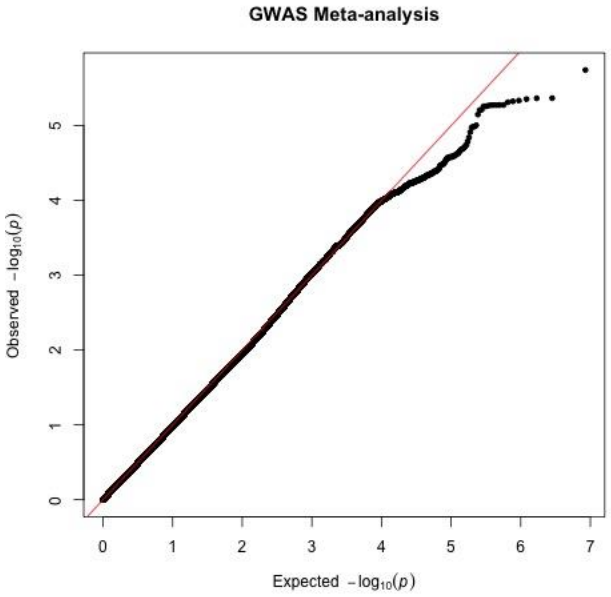


Figure 5-6. Quantile-Quantile (QQ) plot of the one-item life purpose GWAS meta-analysis in European ancestry samples.



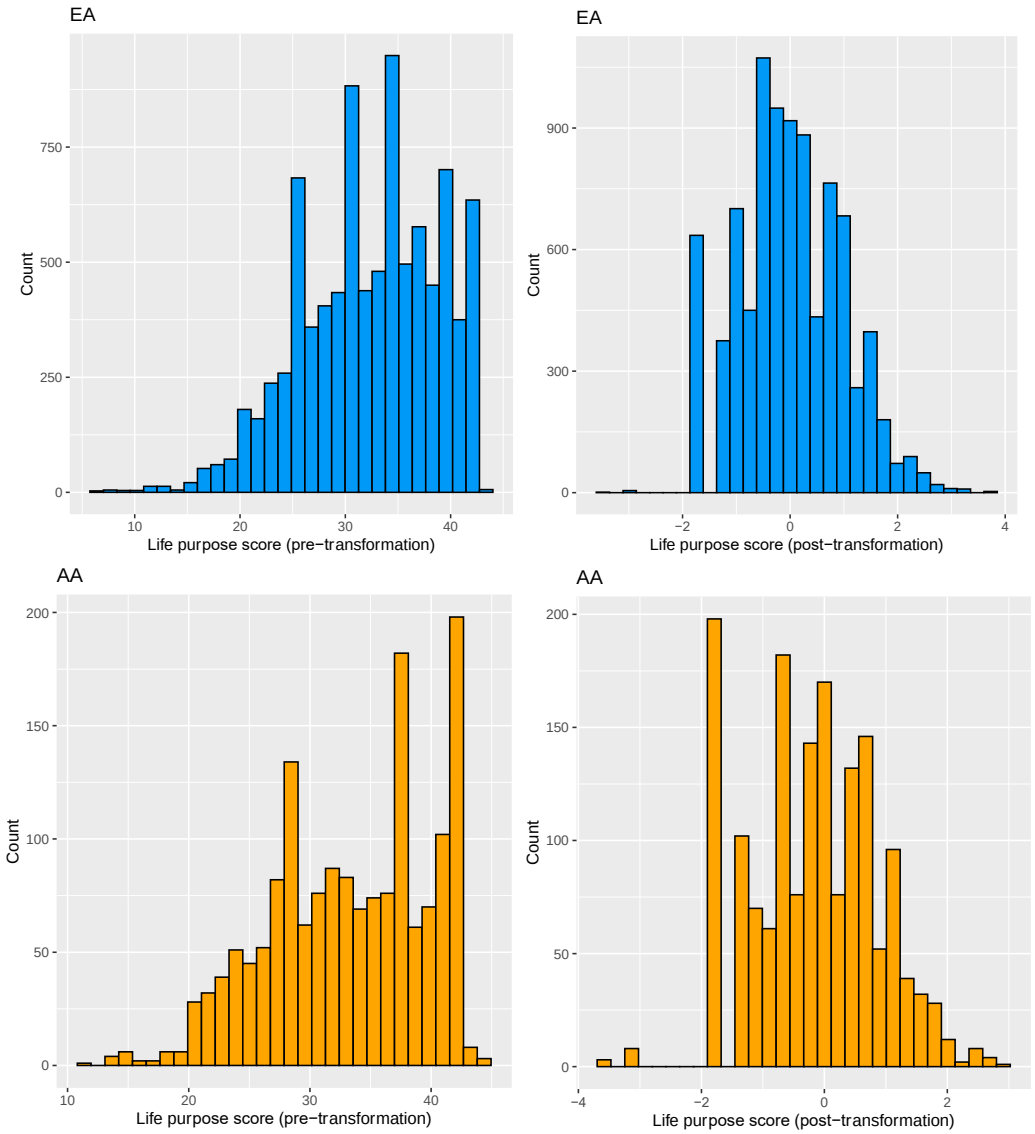
5.7 Supplementary Section

Supplementary Tables and Figures

Table 5-4. Demographic distribution of the participants in the HRS included in the main analysis.

	European Ancestry Mean/Count (SD/%) n = 8959	**African Ancestry** Mean/Count (SD/%) n = 1641
Sex		
Male	3761 (42%)	583 (35.5%)
Female	5198 (58%)	1058 (64.5%)
Age (years)		
<40	13 (0.1%)	10 (0.6%)
[40,45)	66 (0.7%)	14 (0.9%)
[45,50)	183 (2%)	38 (2.3%)
[50,55)	914 (10.2%)	249 (15.2%)
[55,60)	1230 (13.7%)	333 (20.3%)
[60,65)	1163 (13%)	262 (16%)
[65,70)	1545 (17.2%)	275 (16.8%)
[70,75)	1448 (16.2%)	221 (13.5%)
[75,80)	1137 (12.7%)	118 (7.2%)
>=80	1260 (14.1%)	121 (7.4%)
Life purpose score (Pre-transformation)		
	32.4 (6.4)	33.3 (6.5)

Figure 5-7. Histogram of 7-item life purpose by ancestry in the HRS.



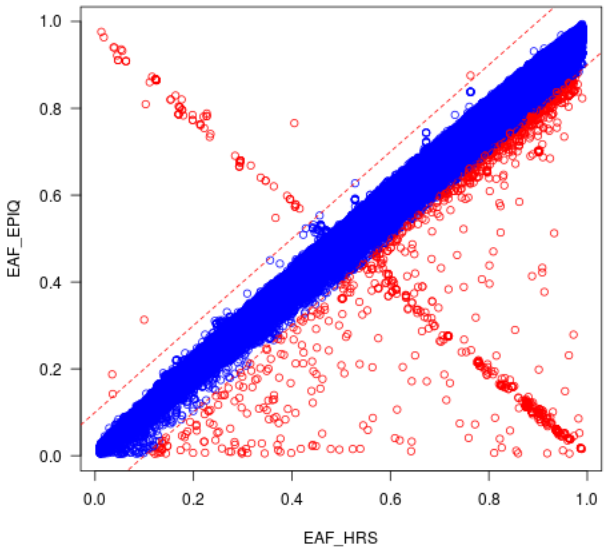
EA: European Ancestry
AA: African Ancestry

Table 5-5. Comparison of independent single nucleotide polymorphisms (SNPs) reach suggestive significant hit across ancestries in the 7-item life purpose HRS GWAS.

				European Ancestry						African Ancestry					
SNP Source	**Chr**	**SNP**	**Position**	**Effect Allele**	**Other allele**	**MAF**	**Beta**	**SE**	**P**	**Effect Allele**	**Other allele**	**MAF**	**Beta**	**SE**	**P**
EA	5	rs325234	143127912	C	T	0.37	-0.07	0.01	8.22×10^{-06}	C	T	0.06	0.01	0.08	0.92
EA	13	rs7983230	30942955	A	G	0.30	0.07	0.02	9.76×10^{-06}	A	G	0.27	-0.09	0.04	0.02
EA	21	rs2037916	41254456	T	C	0.41	-0.06	0.01	8.34×10^{-06}	T	C	0.08	-0.05	0.07	0.50
AA	1	rs12047247	6847563	G	C	0.09	-0.01	0.02	0.63	G	C	0.02	-0.72	0.15	1.49×10^{-06}
AA	1	rs10915020	35157716	A	T	0.09	-0.02	0.03	0.35	A	T	0.12	-0.26	0.06	5.65×10^{-06}
AA	1	rs10789515	48212615	C	T	0.44	-0.01	0.01	0.34	T	C	0.19	-0.22	0.05	5.45×10^{-06}
AA	1	rs6688513	93570439	T	C	NA	NA	NA	NA	T	C	0.30	0.18	0.04	3.37×10^{-06}
AA	1	rs6541360	93823327	T	C	NA	NA	NA	NA	T	C	0.29	0.20	0.04	8.25×10^{-06}
AA	2	rs7558777	20226403	T	C	0.20	-0.01	0.02	0.70	T	C	0.19	-0.21	0.05	4.84×10^{-06}
AA	2	rs17029385	42475879	C	T	0.13	-0.01	0.02	0.52	C	T	0.25	-0.20	0.04	2.24×10^{-06}
AA	2	rs895504	43153115	T	C	0.26	-0.02	0.02	0.28	T	C	0.15	0.23	0.05	8.63×10^{-06}
AA	2	rs9789585	46463334	C	T	0.18	0.02	0.02	0.19	C	T	0.32	-0.18	0.04	6.02×10^{-06}
AA	2	rs2072476	102636864	T	C	0.10	0.01	0.02	0.61	T	C	0.23	-0.20	0.04	7.47×10^{-06}
AA	2	rs4664694	151491400	A	G	0.35	-0.02	0.02	0.26	A	G	0.35	0.17	0.04	5.03×10^{-06}
AA	3	rs1320234	61615565	C	T	0.47	-0.02	0.01	0.10	C	T	0.33	-0.18	0.04	3.32×10^{-06}
AA	3	rs75656895	83280111	A	G	0.07	0.01	0.03	0.68	A	G	0.03	-0.53	0.11	3.50×10^{-06}
AA	7	rs11979687	29208720	C	T	0.12	0.00	0.02	0.97	C	T	0.26	-0.18	0.04	7.87×10^{-06}
AA	7	rs10232895	82263062	T	C	0.09	0.00	0.03	0.96	T	C	0.19	-0.21	0.04	2.02×10^{-06}
AA	9	rs4841922	137566937	T	C	0.11	-0.04	0.02	0.12	T	C	0.29	-0.18	0.04	5.93×10^{-06}
AA	12	rs1168661	122336827	T	C	0.30	-0.02	0.02	0.16	T	C	0.20	0.21	0.05	4.57×10^{-06}
AA	14	rs12892461	53168000	T	C	0.46	-0.04	0.01	0.01	T	C	0.36	-0.18	0.04	3.19×10^{-06}
AA	16	rs193695	56985156	A	G	0.35	0.03	0.02	0.02	A	G	0.37	0.16	0.04	9.21×10^{-06}
AA	16	rs62040391	83293075	G	A	0.08	-0.04	0.03	0.16	G	A	0.05	-0.40	0.09	4.29×10^{-06}
AA	17	rs10512574	68337964	C	T	0.19	0.00	0.02	0.85	C	T	0.11	-0.25	0.06	7.42×10^{-06}

AA: African Ancestry, EA: European Ancestry
NA: Not available.

Figure 5-8. The effect allele frequencies (EAF) plot.



In the graph the MIG EPI-Q allele frequencies reported on the y-axis are plotted against the HRS allele frequencies, reported on the x-axis. The red dots in the diagonal indicated some potential allele flips that need to be removed before the meta-analysis. We applied an arbitrary threshold of max 10% EAF difference. The other red dots outside the diagonal might be genotyping or imputation issues.

Table 5-6. Information for the three SNPs of subjective well-being in our study.

SNP ID	Chr.	Position (bp)	OA	EA	EAF	Beta	SE	P value
Cobay et al 2016 paper Subjective well-being								
rs3756290	5	130951750	G	A	0.24	-0.02	0.00	$9.6 \times 10{-}9$
rs4958581	5	152187729	C	T	0.66	0.02	0.00	$2.3 \times 10{-}8$
rs2075677	20	47701024	G	A	0.76	0.02	0.00	$1.5 \times 10{-}8$
HRS GWAS of Ryff and Keyes's life purpose								
rs3756290	5	130951750	G	A	0.24	0.02	0.02	0.186
rs4958581	5	152187729	T	C	0.35	-0.01	0.02	0.493
rs2075677	20	47701024	A	G	0.24	-0.01	0.02	0.705
HRS GWAS of 1-item life purpose								
rs3756290	5	130951750	G	A	0.24	0.02	0.02	0.223
rs4958581	5	152187729	T	C	0.35	-0.01	0.02	0.540
rs2075677	20	47701024	A	G	0.24	-0.03	0.02	0.133
EPI-Q GWAS of 1-item life purpose								
rs3756290	5	130951750	G	A	0.25	0.02	0.04	0.612
rs4958581	5	152187729	T	C	0.35	0.01	0.03	0.827
rs2075677	20	47701024	A	G	0.25	0.00	0.04	0.977
GWAS Meta-analysis of 1-item life purpose								
SNP ID	**Chr.**	**Position (bp)**	**OA**	**EA**	**EAF**		**Z-score**	***P* value**
rs3756290	5	130951750	G	A	0.24		0.87	0.39
rs4958581	5	152187729	T	C	0.35		0.45	0.65
rs2075677	20	47701024	A	G	0.24		1.33	0.18

Chapter 6 Conclusions

6.1 Summary of the dissertation

Specific Aim 1 Significance *Association Between Life Purpose and Mortality Among US Adults Older Than 50 Years*

As presented in Chapter 3, we performed a comprehensive evaluation of the association between life purpose and all-cause and cause-specific mortality among older adults using data from the Health and Retirement Study (HRS). We observed a statistically significant association between low life purpose and all-cause mortality among 6,985 HRS participants (highest vs. lowest life purpose score: hazard ratio (HR)=3.15, 95% CI:2.07,4.77). Further adjustment for psychosocial wellbeing constructs attenuated the estimated association between life purpose and mortality, but the association remained strong and statistically significant (highest vs. lowest life purpose score: HR=2.43, 95% CI:1.57,3.75). Moreover, the association between cause-specific mortality and life purpose was only evident only for heart and blood diseases (HR=2.66, 95% CI:1.62,4.38) and digestive tract system diseases (HR=2.05, 95% CI: 0.52,8.13).

The present study has several substantial contributions to the existing literature. Previous studies of the association between life purpose and all-cause mortality were not comprehensive because of the lack of adjustment for confounders and failure to account for non-response bias due to the exclusion of individuals with missing life purpose. Also, reverse causation as a possible explanation for an association between life purpose and mortality must be considered. Lastly,

analyses of the association between life purpose and cause-specific mortality have not been done before.

To fill these gaps from the previous literature, we implemented several methodological considerations within our analysis. First, we adjusted a comprehensive set of covariates to control for confounding. Next, demographic characteristics and survival outcome were compared between the HRS participants who did and did not complete the life purpose questionnaire (non-responders). We provide a discussion around this issue based on our analyses and the differences observed between these two groups. Third, two sensitivity analyses were conducted to evaluate the potential for reverse causation, and our results suggested that reverse causation due to chronic illness and near to death status did not account for the association we observed. Lastly, this study is the first study that examined the association between life purpose and cause-specific mortality. The cause-specific results imply that there may be variation in the biological processes by which the purpose of life influences the course of disease. Overall, our findings significantly add to the body of research supporting a strong association between life purpose and mortality.

Specific Aim 2 Significance: *Decomposing the Association of Psychosocial Wellbeing with All-cause Mortality: The Mediating Role of Physical Health and Behaviors*

In Chapter 4, we investigated the relationship between psychosocial wellbeing and overall survival in the HRS. Based on our findings, psychosocial wellbeing is a strong contributor to survival directly as well as indirectly through physical health and behavioral exposures. Overall, those with the good psychosocial wellbeing were 73% more likely to survive compared to those with the poor wellbeing (survival rate (SR)=1.73, 95% CI:1.50,2.01) during the follow-up period. Through the mediation analysis, the direct effect via psychosocial wellbeing accounted for more

than half of the total effect of this relationship (SR=1.46, 95%CI:1.27,1.67), and the composite health index measure (physical health and behaviors) accounted for 36% of the total effect.

This is the first study to simultaneously account for a full range of wellbeing constructs when examining the direct and indirect effects between psychosocial wellbeing and survival. Our findings highlight the interconnectedness of these psychosocial wellbeing constructs and shared physical and behavioral health pathways for survival. Results from the present study fill in the gaps in the literature and further elucidate the focus of future interventions for improving survival. Interventions that consider a broader set of psychosocial wellbeing constructs need to be developed and validated. Next, interventions to increase overall survival among adults over age 50 should focus on improving both mental and physical wellbeing.

Specific Aim 3 Significance *First Genome-Wide Association Study on Life Purpose*

In Chapter 5, we conducted two genome-wide association study (GWAS) in the HRS and one in the Michigan Genomics Initiative Epidemiological Questionnaire Study (MGI EPI-Q) to identify common variants related to life purpose. Our first GWAS in the HRS based on the full seven item life purpose measurement tool found that no common single nucleotide polymorphisms (SNPs) reached the genome-wide statistical significance of $p<5\times10^{-8}$ in either ancestry sample. We detected three independent SNPs in the European ancestry sample, and 21 independent SNPs in the African ancestry sample that reached the suggestive threshold of $p<1\times10^{-5}$. Our GWAS meta-analysis using data from the HRS and MGI EPI-Q focused on a single overlapping life purpose question from the two studies. This analysis also yielded no statistically significant associations at the $p>5\times10^{-8}$ level, but 4 independent SNPs reached the suggestive threshold of $p<1\times10^{-5}$.

To our knowledge, our study was the first life purpose GWAS. Although we did not identify genome-wide significant associations, we observed several interesting suggestive findings ($p<1\times10^{-5}$). The detected signals in the *PCP4, DLD, TENM4, and CAMTA1* genes are linked to neurological or psychiatric diseases, which provide biologic plausibility to these genetic associations with life purpose. This research serves as a stepping-stone toward a better understanding of the potential genetic pathways underpinning life purpose.

6.2 Public Health Implications

"The purpose of life is not to be happy. It is to be useful, to be honorable, to be compassionate, to have it make some difference that you have lived and lived well."

— Ralph Waldo Emerson

The main purpose of this dissertation is to add to the collective knowledge in the research of life purpose with the hope that it will lead to interventions to improve wellbeing and health in society. Findings from this dissertation provided compelling evidence for the importance of having a strong life purpose. Aim one was published in May 2019 in JAMA Network Open; the manuscript has garnered significant lay and scientific interest. It has more than 149,000 views, 110 citations, and an Altmetric score of 1,931 that places it in the top 5% of all research outputs scored by Altmetric. This suggests that this body of work has reached both scientific and lay audiences. We likely raised life purpose literacy among the general population and sparked researchers' interest in conducting life purpose-related research.

Access to wellbeing resources and public perceptions of positive psychosocial wellbeing are undoubtedly on the rise. Life purpose is a modifiable psychosocial construct, and all three aims from this dissertation highlight the need to develop interventions that aim to improve life purpose.

Life purpose interventions should be evaluated among various populations, including, healthy individuals and patients with chronic medical conditions. Designing and assessing a life purpose intervention is the clear next step for this line of research. Based on the early work in this dissertation (Aim 1), we initiated an intervention study that seeks to assess the feasibility, acceptability, and effectiveness of using an eHealth application (app) to improve life purpose and quality of life among ovarian cancer patients. In the section 6.3.4, we will go over this work in further detail.

6.3 Future Research Directions

Several directions could be taken in future research to build upon our findings.

6.3.1 Psychosocial constructs and mortality: Evaluating of the pathway through neuroendocrine regulation of stress responses.

Aim two evaluated physical and behavioral health pathways between psychosocial wellbeing and survival in the HRS. A potential unstudied causal pathway between psychosocial wellbeing and survival is neuroendocrine regulation of stress responses. Specifically, through the neuroendocrine system[91,92], positive psychosocial wellbeing may balance allostatic load over the long term, regulate inflammatory responses[93-97], and ultimately affect cellular aging[84] and functional disability to lower the risk of chronic disease[84-87,89]. Previous research suggests that elevated levels of inflammatory markers such as C-reactive protein[147-149] and cytokines such as interleukin 6[148,149] are associated with increased mortality. Future research on psychosocial wellbeing and survival should focus on neuroendocrine regulation of stress responses while simultaneously accounting for a full range of wellness constructs.

6.3.2 GWAS meta-analysis on life purpose with a large sample size.

Findings from aim three advanced our knowledge about the associations between common genetic variants and life purpose. No common SNPs in our life purpose GWAS achieved genome-wide significance in either ancestry sample ($p>5\times10^{-8}$). Replication efforts are needed to characterize whether our suggestive findings are observed in other studies. Future GWAS with larger samples of both European and African ancestry individuals are needed to further explore the underlying genetic architecture of life purpose. Additionally, the lack of genetic association with common variants in our study does not rule out a role for uncommon or rare variants with life purpose. Lastly life purpose is a complex trait, and its variability could be due to a combination of genetic and environmental factors. Gene-environment interactions should be investigated in future studies to enhance the discovery of genetic variants associated with life purpose.

6.3.3 Validation of life purpose instruments among cancer patients.

As I addressed in length in Chapter 2, the Ryff and Keyes's scales of Psychological Well-Being for purpose in life scale has a major limitation. This scale may not accurately capture the life purpose among patients with severe illnesses, such as cancer patients. For instance, one of the questions in this scale is, "I live life one day at a time and don't really think about the future." To a healthy person, living life one day at a time may not be purposeful. However, to a cancer patient, being able to live life one day at a time might be his/her life purpose at this specific stage of their life. Thus, utilizing this questionnaire directly in cancer research may introduce measurement error and bias the results. Future research through a focus group study or an instrument validation study among cancer patients should be conducted to evaluate the Ryff and Keyes's scales of

Psychological Well-Being for purpose in life and other instruments designed to measure life purpose. This will allow us to better understand all the instruments and develop an updated rating scale and calculation method for the overall life purpose score among individuals with cancer.

6.3.4 Life purpose interventions.

Although the benefits of purposeful living are becoming increasingly clear, there are two more gaps in the research to date. First, the role of purposeful living among cancer survivors has not been fully assessed, and second, interventions to improve life purpose have not been evaluated among cancer patients. Future research should focus on clinical trials exploring life purpose interventions and cancer outcomes. We have taken such a step and initiated a clinical trial to test the feasibility, acceptability, and effectiveness of ovarian cancer patients using an eHealth application (Purposeful) to improve life purpose. In the section below, we provide a description of the Purposeful app ovarian cancer trial.

Factors Related to Quality of Life in Ovarian Cancer Patients

Clinical and physical health factors. Previous studies suggest that clinical factors are not the predictors of quality of life[213-215], conversely, pre-existing health conditions are associated with quality of life among ovarian cancer patients[215,216]. In general, it appears that ovarian cancer patients with early and advanced stage disease experiences similar challenges, and that quality of life concerns are not different for individuals on or off treatment[213,214]. In addition, a research team from British Columbia also found that the global quality of life score did not vary by clinical factors such as age, stage, or histology among ovarian cancer patients[215]. However, they found that women with comorbidities such as cardiovascular ((p = 0.031) and respiratory (p=0.040) conditions had a lower global quality of life[215]. Furthermore, a prospective study of Australian

women with epithelial ovarian cancer observed that women with clinical insomnia symptoms had statistically significantly lower quality of life at baseline (8.4 points lower, 95% CI: 7.2–9.5), and lower quality of life three months after study enrollment (5.5 points lower, 95% CI: 3.4–7.6) compared to women with no insomnia[216].

Several psychosocial factors such as resilience[217], depression[218], anxiety[218], locus of control[219], optimism[220], and hopefulness[220] have been shown to be associated with quality of life among ovarian cancer patients[217-221]. A cross-sectional study among 200 ovarian cancer patients found that women with strong resilience often reported good physical health and excellent psychological health[217]. A prospective study of 123 ovarian cancer patients in China found that anxiety and depression were statistically significantly associated with poorer quality of life[218]. A cross-sectional study indicated higher levels of external locus of control predicted decreased quality of life among patients with newly diagnosed stages II–IV ovarian, primary peritoneal, or fallopian tube cancer[219]. Another cohort study found higher optimism and hopefulness at baseline were statistically significant predictors of a subsequent higher quality of life among ovarian cancer patients from the Australian Ovarian Cancer Study[220]. All of the research mentioned above indicates that enhancing psychosocial factors is critical for improving ovarian cancer patients' quality of life; more intervention studies should be undertaken in the future.

Overall, given the fact that quality of life and several psychosocial constructs have been shown to play a role in ovarian cancer survival, and because life purpose is a construct linked to both quality of life and wellbeing, the association between life purpose and quality of life among ovarian cancer survivors should be investigated. However, to date, no quantitative studies have examined this association.

Current life purpose interventions

In-person Interventions: There are some interventions related to life purpose that have been developed to influence a wide range of health outcomes. Intervention studies of yoga[222-224], volunteering[9,150-152,225], wellbeing therapy[153], and meditation[154,223,226-229] Tai Chi Chuan[230], mindfulness-based stress reduction[156,231] demonstrated that these activities were associated with improved physical[9,150,151,154,222,223,225-230] and psychosocial symptoms[9,153,154,222,223,225-229], life purpose[154], mindfulness[154], anxiety[153,222,223,228], depression[9,222,228], wellbeing[154,222], quality of life[151,156,222-224,226-229,231], level of physical activity[150], increased telomerase activity[154], insulin[230], cytokine levels[230], and survival[9,152,222] among adults[9,150-154,227], acquired immunodeficiency syndrome (AIDS) patients[229], and cancer patients[156,222,224,226,228,230-233]. A major limitation these studies shared is that most of the interventions required in-person interaction. In-person therapies necessitate the presence of professional practitioners as well as participants. These approaches are not scalable at the population level. Innovative approaches such as electronic health application (eHealth app) based interventions are more convenient and affordable, making them accessible to a broad range of patients.

E-Health Interventions: Nowadays, a number of eHealth app have also been developed to serve as a screening tool or an intervention device to improve individuals' health; such applications are more accessible to individuals. For instance, a free depression screening smartphone app has shown the potential to play an important role in depression screening, which was used for further evaluation of clinical depression in a cross-sectional study[234]. In addition, a qualitative assessment of a supportive health app during breast cancer treatment showed positive experiences among patients and their medical teams[235]. Several meditation apps has been developed to reduce stress and increase wellbeing and happiness[236,237]. Recently, eHealth apps have been developed with the

goal of helping individuals live a more purposeful life. One such application, which is available on smartphone platforms and as a web application is Purposeful[238]. Purposeful has been built upon the extensive literature on how to measure and improve life purpose, and also draws from the evidence base on behavior change, including motivational interviewing, the Health Belief Model, and Self-Determination Theory[238]. A beta version of Purposeful, called JOOL Classic, has been shown to improve life purpose in a relatively short period among a healthy population (unpublished data, Vic Strecher et al. 2018). However, this app has not been assessed in cancer patients. Furthermore, to our knowledge, there have not been any studies directly evaluating any other purposeful living interventions and their effects on ovarian cancer patients. To fill this research gap, we conducted a single-arm pilot study to evaluate whether an eHealth app, Purposeful, influences life purpose and quality of life among ovarian cancer patients.

A clinical trial assessing the feasibility and evaluation of a self-care app to enhance purposeful living among ovarian cancer patients: a single-arm pilot study (NCT04458168).

Study Design and Participants. This study is a 6-month single-arm interventional study (NCT04458168) aiming to assess the feasibility, acceptability, and effectiveness of a smartphone app-delivered intervention for improving life purpose and quality of life among ovarian cancer patients. This study received Institutional Review Board (IRB) approval from the University of Michigan Medical School (HUM00140226). Eligible patients were English-speaking women aged 18 years or older, had ovarian cancer, and were under treatment through the University of Michigan Rogel Cancer Center Gynecologic Oncology clinic or Brighton Center for Specialty Care Gynecologic Oncology Clinic.

Participants were recruited between June 28th, 2021 and June 27th, 2022 through a regular in-person clinic visit or a Zoom appointment. In total, 60 women were enrolled in this trial. To

identify an optimal intervention period, patients were recruited partially based on disease status: Group 1: just completed treatment, Group 2: have not experienced a recurrence after one year since the initial diagnosis, Group 3: have experienced a recurrence after primary treatment. Patients who signed the informed consent were provided with the Purposeful app and asked to fill out a baseline questionnaire, including 1) Demographics; 2) Life Purpose; 3) QoL; 4) Well-Being; 5) Fatigue; 6) Meaning in Life; and 7) Self-Care Assessment and Integrative Medicine Use. Participants' disease status, treatment information, performance status, CA125 measures and medications were also collected from medical records. After the enrollment, participants were asked to use the app daily for six months. Participants are followed up at months 1, 3, and 6; at each visit, participants complete questionnaires 2-7 and the Acceptability questionnaire.

Intervention: Purposeful App. Purposeful is a smartphone app that is designed to help users achieve greater purpose in life. In the trial, participants were asked to use the app to complete a daily reflection in the Today section, which takes no more than 5 minutes. Participants had freedom on how often to utilize the app. Depending on whether users choose to allow push notifications, they were notified daily to complete morning, afternoon, or evening reflections. Other resources provided within the app were optional for participants to use. After we complete the study follow-up visits for all participants in the next six months, we will characterize overall app usage as the main exposure.

Outcomes. The primary outcome is life purpose, and it is being assessed with the Ryff and Keyes's Scales of Psychological Well-Being and the Comprehensive Measure of Meaning (CMM)[69]. The secondary outcome is quality of life, and it is being assessed using the Ovarian Cancer Functional Assessment of Cancer Therapy Trial Outcome Index (FACT-O TOI), and the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue assessment tools[239,240].

Expected Results. We expect that the study is feasible and the Purposeful app is acceptable among ovarian cancer patients. We also expect that the use of the Purposeful app is associated with an increase in life purpose and quality of life among ovarian cancer patients within six months of follow-up. If there is a null association, it may be because there is truly no association. It is also possible that this is because the Purposeful app was not specifically developed for cancer patients. This would suggest that further work is needed to tailor the Purposeful app for individuals with cancer or that a new app is needed for cancer patients.

6.4 Conclusion

In conclusion, this dissertation explored various facets of life purpose and psychosocial wellbeing through a comprehensive set of research projects, utilizing a variety of data types and advanced analytic methods. The results of this dissertation add findings to our understanding of life purpose and psychosocial wellbeing. Aim one indicates that stronger life purpose was associated with decreased all-cause mortality. Aim two highlights the interconnectedness of psychosocial constructs, and shared indirect effects through physical and behavioral health factors between the association of psychosocial wellbeing and survival. Aim three offers a better understanding of the genetic pathways that underpin life purpose; it also indicates that non-genetic factors may be more essential determinants of life purpose. Overall, findings from this dissertation provide recommendations for clinical interventions relating to life purpose and overall psychological wellbeing.

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