Muscle Weakness in Older Americans:

Examining the Measurement, Health Outcomes and Life Course Determinants

by

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Dedication

This dissertation is dedicated to my endlessly supportive and loving husband, partner and best friend, Zlato, and to my beautiful, funny and sweet son, Arlo.

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Preface

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Abstract

Muscle weakness, as measured by hand grip strength, has been shown to be an important indicator of future disability, chronic disease status and early mortality. While muscle weakness is considered an important prognostic indicator, how best to measure weakness, the long term health outcomes associated with muscle weakness across different sub-populations and the life course determinants remain poorly understood. Indeed, there is little agreement on how best to measure muscle weakness across different groups and how to screen for muscle weakness in order to prevent disability and premature mortality.

We begin by first deriving cutpoints for muscle weakness in a nationally representative sample of older adults from the Health and Retirement Study. After using Classification and Regression Tree (CART) models to identify cutpoints, we found that fifty-five percent of men (max grip strength <39kg) and 47% of women (<22kg) were classified as weak. Higher cutpoints were identified for Black males (<40kg) and females (<31kg), and the prevalence of weakness (57% and 88%, respectively), was higher compared to Whites.

As an extension to these results, we examine the validity of these cutpoints in a longitudinal setting to determine whether muscle weakness is associated with disability dynamics and premature mortality. We found that clinical muscle weakness, as identified by sex/race specific population-derived cutpoints from Aim 1, is strongly associated with the onset,

progression and persistence of physical disability status. The odds of experiencing an onset of ADL disability were 54% higher among weak individuals compared those who were not weak at baseline. We also found that weak individuals had a steeper decline in their survival trajectory, compared to non-weak individuals. Specifically, weak individuals were over 50% more likely to die earlier than non-weak individuals.

Lastly, the third aim of this dissertation seeks to quantify and understand whether experiencing stressful and traumatic events across the life course influences trajectories of grip strength in later life. We found that life course trauma and stress experienced during emerging/early adulthood was associated with both mean grip strength at age 50 and trajectories of grip strength over time. Among Black men, stress and trauma experienced during emerging/early adulthood was not only related to higher mean grip strength at age 50, but also associated with steeper declines as individuals aged over time compare to White men. Among Black women, traumatic events during emerging/early adulthood were associated with lower mean grip strength at age 50.

Taken together, the results of this dissertation chart new territory in its overall goal to improve the measurement of muscle health across the diverse, older adult population and in identifying those most at risk for future disability and premature mortality. This dissertation also demonstrates the importance of investigating how life course social exposures drive differential vulnerability to muscle weakness among older adults. The results of this dissertation can be used to inform clinical practice in screening adults for muscle weakness while also seeking to shift the distribution of muscle weakness at the population level in order to intervene among those who are most vulnerable.

CHAPTER 1. Background

1.1 National Trends in Aging

The growth of the population of those aged 65 years and older is unprecedented and represents one of the most significant demographic shifts of recent time. Today, it is estimated that 46 million Americans are 65 years and older and this number is expected to more than double to 98 million by 2060.[1] Additionally, the number of individuals aged 85 years and older is estimated to triple from 6 million to nearly 20 million by 2060.[1] There has also been a rapid rise in the number of centenarians, or those aged 100 years and older. In 2010, roughly 53,000 individuals were 100 years or older and this number is expected to rise to 600,000 by 2060.[2]

In addition to the rapid growth of Americans aged 65 years and older, the U.S. population is also becoming more racially and ethnically diverse. Today, while 75 percent of those aged 65 years and older are predominately non-Hispanic White, current trends indicate that between 2030 and 2060, the number of non-Hispanic White individuals will drop by 17 percentage points. It is estimated that that the number of Hispanics aged 65 years and older will almost double from 11 to 22 percent by 2060.[1] During this same time period, Black population is also expected to increase from 41.2 to 61.8 million.[1] The aggregate minority population in the United States today is projected to become the majority by 2043.[3]

At the same time, life expectancy in the U.S. has increased. As of 2013, the average life expectancy was 79 years, compared to 68 years in 1950. This is largely attributed to reductions in mortality in older age.[3] Healthy life expectancy, defined as the number of disability-free years a person is expected to live, has also been increasing. Indeed, recent research indicates that between 1992 and 2008, overall healthy life expectancy among those aged 70 years and older increased by 1.8 years.[4] However, despite these gains, the current health status of Baby Boomers, those born between 1946 and 1964, indicate they are not fairing nearly as well. While Baby Boomers are less likely to smoke, have heart attacks or be diagnosed with emphysema, they are more likely to be obese or overweight, have higher rates of diabetes and high blood pressure, and be less active compared to previous birth cohorts at the same ages.[5] Thus, as Baby Boomers move into the ranks of the older adult population by 2030, it is possible that recent gains made in healthy life expectancy may soon be eroded.

1.2 Living Longer, Aging Well? The Importance of Studying Muscle Strength

The increase in life expectancy coupled with rising obesity rates have given rise to major concerns regarding the forecasted prevalence of disability in later life. Indeed, despite previous trends documenting a decrease in the overall rate of disability among older persons, recent research indicates that obese individuals are more likely to be disabled compared to obese individuals over a decade ago.[6] This has important implications since there is growing evidence that the excess risk of disability exceed obesity's excess risk of mortality.[7] Recent data from the National Health and Nutrition Examination Survey (NHANES) revealed a significant increase in obesity among the "young old", those aged 65 to 74.[8] Similarly, the number of people aging with chronic disease has also increased. Today, older adults are more likely to age with cardiovascular disease, cancer, diabetes mellitus, and dementia, all of which have been shown to be related to

physical functioning, disability and premature mortality.[9,10] These data are worrisome because they indicate that, while individuals may be living longer, it does not necessarily mean they are living well. Given recent demographic trends forecasting major increases in the prevalence of disability among older adults, understanding the key indicators that reduce disability while maximizing independence in older age is of critical public health importance.[11,12]

Advanced age is accompanied by a host of physiologic changes and an increase in co-morbidities that have been directly linked to health status and quality of life.[11] Chief among these changes is a decline in muscle mass and strength, also known as "sarcopenia". While age-related losses in muscle strength and mass are part of the normative aging process, individuals who undergo steeper declines in muscle strength may be more vulnerable to adverse outcomes in later life [13,14]. Indeed, sarcopenia has been linked to increased risk of physical disability, mobility limitations and premature mortality.[15–17] Annual direct costs attributable to compromised muscle functioning are estimated at around $20 billion in the United States.[18] Therefore, understanding how to measure, define and prevent muscle weakness in later age is a major public health concern.

1.3 Epidemiology of Muscle Weakness

It is estimated that skeletal muscle mass decreases by 50% on average between 20 and 90 years of age [19]. Similarly, muscle strength declines about 15% every decade beginning at age 50 and accelerates at age 70 with about 30% of strength being lost per decade thereafter [20]. Muscle weakness, also known as "dynapenia", was first described as an "age-related loss in strength that is not cause by neurologic or muscular diseases" [21] and has been found to be a primary

determinant of age-related loss of function, [22,23] mobility disability, [14,24,25] cardiovascular disease[26] and mortality [26,27].

Using the most recent criteria for muscle weakness from the Foundation for the National Institutes of Health (FNIH), the CDC recently estimated that among those 60 years and older, 5% are considered weak while 19% of individuals aged 80 years and older are considered weak [28]. While the consequences of muscle weakness for both men and women between the ages of 60-79 years are comparable (2% prevalence), sex disparities in muscle weakness have been observed in those aged 80 years and older: 15% of men and 22% of women are estimated to be weak[28]. Differences in muscle strength have also been reported by race/ethnicity: 5% of Non-Hispanic Whites, 6% of Non-Hispanic Blacks, 15% of Non-Hispanic Asians and 9% of Hispanics are estimated to have muscle weakness. However, it's worth nothing that this FNIH definition has yet to be fully accepted by some members of the scientific community and to date, no clear consensus exists regarding how best to measure muscle weakness at the population level.

Historically, muscle mass has been treated as the most important marker of overall muscle health. When the term "sarcopenia", formally defined as an age-related loss in muscle mass, was first coined in 1989, muscle strength was not acknowledged as an independent indicator of muscle health. However, beginning in the early 2000s, the muscle health literature began focusing on muscle strength as a separate risk factor that warranted individual examination. Despite recent efforts to delve deeper into the study of muscle weakness, a substantial body of research has exclusively focused only on the declines in muscle mass without considering the role of muscle strength[29].

The difficulty in studying muscle health has largely centered around what aspect of muscle health is most clinically relevant and how best to measure those components—should we focus on muscle mass? Strength? Quality? Since the 1980s, this debate has actively played out in the literature and continues to do so today. As evidenced by the most recent literature in this area, there is no single standardized, agreed upon definition as to how best to measure muscle health with respect to both strength and mass in older populations.

The examination of muscle weakness as an important contributing factor to aging related morbidity and mortality has not been linear. In 1988, a conference convened in Albuquerque, New Mexico focused on measurement issues in the field of health and nutrition among elderly adults. It was as this meeting that Irwin Rosenberg first coined the term "sarcopenia" and declared it to be a serious public health condition[30]. In a commentary by Rosenberg, he reflected:

> "I noted then that no decline with age is as dramatic as or potentially more significant than the decline in lean body mass. In fact, there may be no single feature of age-related decline more striking than the decline in lean body mass in affecting ambulation, mobility, energy intake, overall nutrient intake and status, independence and breathing. I speculated as to why we had not given this more attention a suggested that if this phenomenon were to be taken seriously, we had to give a name. This would provide recognition by the scientific community by the NIH. I proposed that the name for this phenomenon be derived from the Greek. I remind you that 'sarx' in Greek is flesh and 'penia' is loss." (pg. 990S) [30].

As demonstrated in the above quote, Rosenberg's definition of sarcopenia solely focused on muscle mass without any mention of the role muscle strength may play. Shortly after, the first epidemiological studies examining sarcopenia measured muscle mass using body impedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA) to assess sarcopenia in aging individuals. In one of first pioneering studies in this area, Baumgartner et al. were the first to use DXA, corrected for height, to formally define sarcopenia as two standard deviations below sex specific means of healthy young persons (18-40 years) of a reference population [31]. Based on this

definition, the prevalence of sarcopenia was estimated to be 50% in adults aged 80 years and older and that sarcopenia was also found to be associated with higher rates of self-reported disability [31]. This was the first study to demonstrate that muscle health had important implications for the field of public health and aging.

Since this seminal study, over one-thousand publications have used this definition[19]. Nonetheless, as the field continued to evolve, this original definition received major criticism on account of two methodological concerns. First, while DXA scans are considered the gold standard in measuring body composition, the results are highly dependent on water accumulation within the muscles, which can lead to an overestimate in one's lean muscle mass. Second, this definition assumed that as muscle mass decreased, there is a concomitant decline in muscle strength, [29] which had not been proven. On the contrary, as the research on muscle strength began to accumulate, several studies showed that declines in muscle strength outpaced that of muscle mass [12,32–34], implying that muscle strength may not only be an important predictor of muscle health but a better measurement with respect to clinical intervention compared to muscle mass.

1.4 Limitations of Only Relying on Muscle Mass

In an effort to highlight the differences in the operational definitions of sarcopenia influence the prevalence estimates of the condition, Batsis et al. quantified the prevalence of sarcopenia using NHANES data based on 8 different study definitions of sarcopenia [35]. Seven of the studies used DXA scans while 1 used BIA to formally assess body composition. Three studies diagnosed sarcopenia at 2 standard deviations below the mean appendicular skeletal muscle mass of the subject-specific cohort or a healthy reference population. Three studies diagnosed sarcopenia at the lowest two quintiles for relative muscle mass within the study

sample. In the other two studies, individuals who fell 2 standard deviations below the sex-specific normal means for a young reference population were considered sarcopenic.

Based on these definitions, across all eight studies, in men, the prevalence of sarcopenia ranged from 10 to 80% in 60-69 year olds, 20 to 82% in 70-79 year olds and 20 to 93% in those aged 80+ years [35]. Similarly, in women, the prevalence of sarcopenia among those aged 60-69 years ranged from 10 to 96%, 9 to 96% for those 70-79 years of age and 8 to 97% in those aged 80+ years [35]. This study was the first to highlight how the range in sarcopenia definitions, which only accounted for muscle mass, contributed to major heterogeneity in the prevalence estimates of sarcopenia using nationally representative data.

As a result, Clark and Manini called on the research community to reconsider the definition of sarcopenia as a term that applies only to declines in muscle mass. In their groundbreaking article entitled "Sarcopenia ≠ Dynapenia", the authors noted that applying the term sarcopenia to the study of muscle strength implied a causal relationship between muscle mass and muscle strength, which was incorrect and resulted in a literature that overemphasized the role of muscle mass. Thus, the authors proposed a new operational term, known as "dynapenia", be used in the study of muscle strength:

> "It is imperative that a greater understanding of the mechanisms of age-associated losses in strength be developed. Therefore, to encourage research endeavors focusing on understanding the mechanisms of strength, we propose changes in the nomenclature that distinctly separates the age-associated changes in muscle mass and strength. We suggest that sarcopenia be limited to its original definition of an age-related loss in skeletal muscle mass, and that the term **"**dynapenia**"** be applied to describe the age-related loss of strength." (pg. 829)[29].

As a result of this distinction, several expert groups such as the International Working Group on Sarcopenia, The European Working Group on Sarcopenia in Older People, and other researchers, sought to incorporate strength based measures into their definition of sarcopenia [22,23]. While this

represented an important step forward, these definitions were also criticized since they did not rely on evidenced-based research and suffered similar methodological flaws to that of the original Baumgartner definition[36]. These methodological shortcomings included: relying on standard referent populations [22,23], using non-representative data[24], and a lack of uniform body composition measurement techniques to assess muscle mass (i.e., DXA, BIA, etc.) or strength (i.e., grip strength, leg extensor strength)[22–24,37], which ultimately translated into vast differences in how both sarcopenia and dynapenia were defined and quantified. These definitions were also derived in cross-sectional study samples where the long-term health outcomes had not been evaluated [22,23]. Additionally, when the muscle mass and strength based definitions were first applied within longitudinal settings to examine long-term outcomes, the preponderance of evidence was mixed [12,32,38] and pointed to the fact that muscle mass may be a poor predictor of health and functioning while muscle strength as a single indicator may be more important to examine and intervene upon over time.

1.5 Measuring Muscle Weakness: Making the Case for Hand Grip Strength

The case for examining muscle strength in older populations extends beyond recent studies showing muscle weakness is a better indicator than muscle mass. Indeed, there are several important methodological advantages to measuring total body muscle weakness instead of muscle mass. First, previous research has demonstrated that handgrip strength, an easily obtainable indicator, is highly correlated with other reliable and valid measurements of total body muscle strength, including elbow flexion strength (r=. 67), knee extension strength (r=. 51) and trunk extension strength (r=. 54) [39]. Second, grip strength has been found to be independently associated with functional limitations [14,24,40] , disability [14,41], incident CVD[26], diabetes[42] and mortality[26,39]. Mid-life grip strength has even been found to be associated with

incident negative health outcomes 25 years later [14]. Third, grip strength measurements can easily be measured by a dynamometer, a small, simple and inexpensive device that an individual squeezes to obtain an overall value of strength (usually in kilograms) that is both easy to administer and non-invasive [43]. Based on these findings, hand grip strength is now accepted as a strong, robust proxy for total body muscle strength[14,40,44]. Given the strong association between grip strength and several important negative health outcomes combined with its ease in administration, it has been suggested that grip strength measurements be incorporated into clinical examinations in order to identify individuals who may be most at risk to adverse health events [39,40,42,44]. Yet, despite the clear advantages of this approach and acceptance of grip strength as a reliable proxy of total body muscle strength, there is still no consensus as to what is considered low muscle strength or "true weakness" across different populations.

In 2012, the Foundation for the National Institutes of Health became the latest group of experts to weigh in on how best to measure both low muscle strength and mass. The FNIH "Sarcopenia Project" was founded as a private-public partnership that included representatives from government, academia, and the pharmaceutical industry and was created amidst growing frustrations by the lack of consensus on how best to define low muscle mass and weakness. The primary goal of the project was to "gather together previously collected data from multiple, diverse cohorts of older adults, including both observation studies and randomized trials, with longitudinal measures of muscle mass and function, to conduct analyses to develop definitions of muscle weakness and low lean mass that were clinically oriented, evidence-based and empirically derived" (pg. 589)[45]. Based on this approach, the FNIH pooled together eight observational cohort studies and six clinical trials, which included 26,000 men and women aged 65 years and older[36].

In a series of 5 papers [36,37,46–48], the FNIH proposed diagnostic cutpoints for both low muscle appendicular muscle mass and muscle strength for both men and women based on having mobility impairment, which they defined as having a slow walking speed of less than 0.8 meters per second [36]. They also longitudinally examined the association between these cutpoints and mobility impairment and mortality across a 3-year period [47]. They stated that these proposed cutpoints should be used in the clinical setting to identify individuals who may have "low muscle lean muscle mass or weakness" (pg. 549) [36]. As such, the FNIH refrained from using the term "sarcopenia" or "dynapenia" due to "prior confusion" [36] around the many previous definitions that had been proposed. Nonetheless, the FNIH cutpoints for lean mass and muscle weakness have become the clinical gold standard and are already being used in clinical practice [49–51].

The FNIH proposed guidelines to classify older adults as clinically weak based on having a low grip strength cutpoints (25.99 kg for men and 15.92 kg for women)[36,37]. However, these cutpoints were derived from non-nationally representative, pooled data across 8 observational and 6 clinical trial studies that do not reflect the growing racial and ethnic diversity in the U.S. population[37]. Therefore, part of this dissertation will examine sex and race/ethnic specific cutpoints for clinical weakness in a nationally representative sample of Black and White older adults.

1.6 Hand Grip Strength: A Biomarker of Healthy Aging

The perception of grip strength as a "biomarker of aging" may be apropos because it of its strong predictive relationship with a wide range of negative health outcomes. [17] Grip strength has been shown to be useful in identifying those who may be at greatest risk for adverse events[14,26,41–43]. While the mechanisms underlying the strength-health pathway are poorly understood, there are likely several potential mechanisms at play. First, the strength-health

association may be fully or partially mediated through physical activity. [39] That is, once an individual becomes weak they may be less likely to maintain physical activity, leading to a greater risk of disability, chronic disease risk and early mortality. However, it is also well established that individuals with low levels of physical activity are more likely to become weak due to an increase in muscle atrophy over time, and as a result, more vulnerable to the consequences of disability and at greater fall risk. [52] Second, repeated exposure to stressful life events and social adversity might also influence muscle strength over time. While the mechanism by which social stress and trauma could affect muscle strength is not well studied, the distinct physiologic cascade the takes place following exposure to stressful events is well documented.[53] Furthermore, exposure to chronic stress, such as those negative events that persist over time (i.e., taking care of a sick family member) or experiencing an acute, traumatic event (i.e., being the victim of a crime) are believed to be the most potent forms of stress.[54]

When a stress response is activated, cortisol is released by the hypothalamic-pituitary-adrenocortical (HPA) axis. While the initial release of cortisol and other hormones is viewed as adaptive by slowly digestion and breaking down metabolic compounds in order to quickly produce energy, cortisol remains elevated the longest amount of time in the body.[54] This has been replicated over decades of research demonstrating that repeated activation of the HPA pathway is harmful to health. The proposed mechanism, increased inflammation, has grave implications for multiple bodily systems, including, but not limited to, the skeletal muscle system.[53,54] Indeed, higher levels of interleukin-6 (IL-6), interleukin-1 receptor (IL-1R) and tumor necrosis (TNF) and C-reactive protein (CRP), all primary markers of an elevated inflammatory state, have been found to be associated with reduced muscle strength.[55,56]

Lastly, another potential pathway that could mediate the strength-health association is through nutritional intake. Studies have shown that older adults with comprised nutritional status may be at greater risk for becoming weak. Specifically, individuals with low levels of vitamin E,[57] carotenoids, [58] and selenium [59] have been found to have lower muscle strength, however the mechanisms underlying this relationship are not fully understood. Indeed, teasing apart the muscle-health relationship is difficult to establish due to problems of reverse causality and the need to further elucidate the underlying, complex physiologic mechanisms.

1.7 Muscle Weakness and Frailty

In the last 20 years, growing interest into the study of muscle weakness and physical frailty has led to the development of two parallel literatures. In general, sarcopenia and muscle weakness has largely been examined within the basic science research realm while the study of frailty has occurred in the applied, clinical setting.[60] While sarcopenia is typified by losses in muscle mass and strength, frailty is a clinical syndrome that is characterized by multi-system impairments "associated with increased vulnerability to stressors" that results in an increased risk to negative health outcomes.[61]

The complex interplay between muscle weakness and frailty has been noted extensively in the literature.[62–65] One primary example of this is the widely used Fried Frailty Index (FFI), which includes muscle weakness as a primary indicator of frailty in addition to unintentional weight loss, poor endurance and energy, low physical activity and slow walking speed.[63] In order for an individual to meet criteria for the weakness indicator, they have must fall below stratified sex and BMI cutpoints. For example, a man who has a BMI of 27 would be considered weak if he had a grip strength measurement of ≤30 kg and a woman who has a BMI ≤23 would be considered weak if she had grip strength ≤17 kg.[63]

1.8 Muscle Weakness and Physical Disability

Previous studies have found a strong association between muscle weakness and functional limitations [14,24,40] and disability. [14,41] One possible explanation for this is that individuals with higher levels of muscles strength are believed to have a built-in "reserve" that protects them from future disability compared to those who are weaker. Thats is, having adequate muscle strength is needed in order to perform basic activities of daily living.

There is a well-established body of work demonstrating that muscle weakness is consequential in maintaining physical functioning in later life. For example, Rantanen et al. found that individuals in the lowest tertile of grip strength were at greater odds of experiencing difficulty when doing heavy household work, walking a ½ mile, walking up 10 stairs, lifting 4.5kg, dressing, bathing, toileting and eating 25 years later compared to those in the middle and highest grip strength tertiles, even after adjusting for other chronic conditions, age, education, height, physical activity, and smoking status. [14] In a 3-year longitudinal study by Onder et al., higher handgrip strength was found to be protective against incident ADL disability.[66] Giampaoli et al. found that after adjusting for age, the incidence of disability in older men, defined by difficulty with any ADL or IADL, increased with decreasing muscle strength from 26% in the highest quartile to 48% in the lowest quartile of hand grip strength across the 4-year period.[67]

Using data from the Health and Retirement Study, Germain et al. found that tertile-specific low muscle strength was associated with higher odds of physical and functional outcomes, although those analyses were cross-sectional.[68] Additionally, a 4-year longitudinal study found that higher handgrip strength was associated with a reduced risk in the development of new functional difficulties.[69] Taken together, these results, along with other studies, [12,40,41,47] imply that a minimum level of muscle strength is needed to do everyday tasks as one ages and

that those who are at weak may be more vulnerable to the consequences of disability in later age [70].

1.9 Muscle Weakness and Premature Mortality

Muscle strength has also been found to be highly predictive of early mortality. Indeed, there a growing body of research has documented that muscle weakness, as measured by hand grip strength, is associated with mortality.[12,13,17,26,71–73] Several epidemiological studies have found grip strength to be inversely related to all-cause and cause-specific mortality in mid-life[74–77], older[12,17,47,78] and the oldest old[79] populations, although in a few studies, this relationship held for men but not women.[17,71] In a meta-analysis by Cooper et al. comprised of 14 studies and close to 54,000 participants, those in the lowest quartile of grip strength measurement were 67% more likely to die earlier compared to those in the highest quartile, even after adjusting for sex, body mass and age.[27] In the PURE study among nearly 140,000 adults 35-70 years of age with 4 years of follow-up, Leong and colleagues demonstrated that poor grip strength was the strongest predictor of early cardiovascular and all-cause mortality, even compared to other traditional clinical indicators such as systolic blood pressure.[26] Thus, muscle strength remains an important and robust predictor of mortality risk as individuals' age over time.

While the mechanisms underlying the muscle weakness-mortality association have not been fully elucidated, several studies have shown muscle weakness to be associated with higher fasting insulin levels[80] and a precursor to insulin resistance.[81] Muscle weakness has also been found to be independently associated with an increased odds of experiencing diabetes[42,82] and metabolic syndrome in adults. [83] Maintaining muscle strength may play a critical role in preventing metabolic and cardiovascular disease risk with aging, and thus protecting against premature mortality.

Weak individuals are also more likely to report greater difficulty in completing basic self-care activities [13,14] and experience greater odds of disability onset, progression and persistence over time.[15] Therefore, the association between muscle weakness and mortality may be mediated by changes in physical functioning. Individuals with low levels of physical activity are more likely to experience declines in muscle strength, thereby entering a negative feedback loop where weak individuals are unable to participate in physical activity and are more vulnerable to declines in their physical health status, leading to subsequent declines and risk for early mortality. Taken together, handgrip strength may function as a "a crude but effective will to live meter"[84] even if the underlying mechanisms of the strength-mortality association may not be fully understood.[85]

1.10 Life Course and Social Determinants of Muscle Weakness

Life course epidemiology has been used to elucidate how seemingly unrelated physical and social exposures experienced during gestation, childhood, adolescence, young adulthood and middle age drive disease outcomes in later life.[86] Life course epidemiology's theoretical underpinnings are driven by a developmental perspective in which distinct time periods are marked by specific life events and transitions where certain stressors/protective factors may be more or less likely to occur.[86,87] For example, childhood is often defined by gains in education while adolescence is an important window of development when young people begin to assert their independence, make life style choices and establishes health behaviors that will often persist into adulthood.[88] The emerging/early period of adulthood is best characterized by the establishment of one's career, marriage, parenthood and asset acquisition that has a lasting effects on health and SES in later life.[89–91] Lastly, the midlife period (mid 40s to early 60s) is

often typified by gains (or losses) in health status as a result of early health behaviors and exposures.

Two conceptual models within life course theory have been proposed to understand how antecedent events drive health outcomes in older age: the critical period and the accumulation of risk models.[86] The critical period model suggests that a specific life stage in which an individual experiences adverse exposures may have crucial consequences on their health in later life. This conceptual model is largely rooted in the fetal origins hypothesis, which linked poor maternal nutrition in utero to increased risk of coronary heart disease and diabetes in later life.[92] One well documented example is literature showing that childhood SES is directly associated with cardiovascular disease,[93] stroke,[94,95] physical functioning[96,97] and lower levels of grip strength[98] in older adults. Similarly, experiencing physical, sexual and emotional abuse during childhood is associated with increased risk of adverse physical and mental health outcomes in later life. [99,100]

The accumulation of risk model posits that negative exposures gradually accumulate across the life course, ultimately influencing health status in later life.[101] This model has been used to explain why socioeconomic differentials in health exist across a wide range of diseases.[86] For example, early childhood conditions may set individuals on risk trajectories of cumulative advantage/disadvantage with those from lower SES backgrounds experiencing a faster decline in health compared to those from higher SES backgrounds, ultimately leading to widening health disparities in later life.[102,103] The accumulation of risk model has been applied to examine physical health outcomes. For example, physical inactivity, smoking, heavy drinking, social isolation, fair/poor perceived health and prevalence of chronic symptoms and conditions across a 30-year period of emerging and midlife adulthood was associated with increased risk of frailty in a community dwelling sample of older adults.[104]

There is also growing interest in the role early and midlife factors play in the preservation of muscle strength in later life. However, the majority of research has almost exclusively focused on anthropometric indicators showing higher birth weight to be associated with greater muscle strength adulthood.[105] In the Hertfordshire Ageing Study, lower birth weight and weight at year one was significantly associated with lower grip strength 60-70 years later. This relationship, while somewhat attenuated, remained significant after adjusting for body size, indicating that one's early environment may be of critical underlying importance.[106] Pre-pubertal growth has also been found to be associated with midlife grip strength.[107]

More recently, several studies have demonstrated that socioeconomic conditions experienced across the life course may also be linked to muscle health in later life. A recent systematic review found modest, positive associations between childhood SES and later life grip strength, even after adjusting for adult SES and current body size.[97] Wealth in later life was found to be inversely associated with grip strength in a sample of older Europeans, while education, income and occupation were not, suggesting that earnings accrued across the life course may be important in maintaining grip strength in later life.[108] Results from a British birth cohort study indicated that higher levels of material deprivation (i.e., not having a car, not owning one's home) were inversely related to grip strength in later life.[98] Low income and low education were found to be significantly associated with decreased grip strength among an elderly sample of Korean men.[109] More recently, childhood misfortune was found to be related to lower handgrip strength in men, but not in women. [110]

A substantial body of literature has demonstrated that one's social context is consequential for health. Previous studies have found social and economic hardships

experienced both in childhood[111] and throughout the life course are associated with mental and physical health outcomes in later life.[112,113] There is evidence to suggest that exposure to stress and trauma throughout one's life may be linked to poorer health outcomes in later life. Indeed, social stress has been found to be associated with mental health status and depression among older adults.[114,115] Traumatic events have been shown to have a strong relationship on both immediate and long-term health outcomes. Trauma in particular may be especially consequential for health. Pearlin (2005) noted that trauma may be the most potent forms of stressors, characterized by their "magnitude of their onerousness…and by their sudden and violent character" (pg. 210) that have negative consequences for health in later life.[116] Despite the known links between stress and trauma with later life physical health, no studies have directly examined whether stress and trauma experienced throughout the life course is associated with muscle health in later life.

1.11 Emerging Racial/Ethnic Disparities in Muscle Weakness

Racial/ethnic disparities in health are pervasive and persistent in the United States.[117] Non-Hispanic Blacks are have a higher prevalence of several chronic conditions, [118] live more years with chronic health problems[119] and have higher rates of disability[120,121] compared to Non-Hispanic Whites. Similarly, among sub-groups of Hispanics, Hispanics have been found to have higher rates of chronic disease and have worse functional health.[122,123] However, mortality rates, particularly among Mexican Americans, appear to be comparable and in some cases exceed all-cause mortality for Non-Hispanic Whites.[124] Racial/ethnic disparities in physical functioning, mobility and disability are also well documented.[119,121,125,126]

In seeking to understand why these disparities persist, many studies have examined socioeconomic status (SES) as a key explanatory contributor. Indeed, several studies have shown

that after accounting for SES, disparities in functional health between Blacks and Whites become partially attenuated, and in some cases, disappear[121,127]. However, the evidence regarding the association between SES and functional health remains equivocal. Other studies investigating this relationship have found that even after accounting for SES differences, disparities in disability and physical functioning persist, [128] suggesting that other explanatory factors may be at play.

While little research exists examining the relationship between race/ethnicity and muscle weakness specifically, several studies have demonstrated that disparities in physical health outcomes persist across racial/ethnic groups. Blacks have been shown to have higher rates of disability and physical functioning impairments compared to Whites. [120,121,129] Haas et al. found that US-born Blacks and Hispanics had slower gait speeds. US-born Blacks had worse lung function and US-born Hispanics had worse grip strength compared to US-born Whites. Moreover, even after adjusting for childhood and adult health and SES, US-born Blacks had worse health across all physical performance measures compared to Whites. [130] Seeman et al. found that Blacks had lower scores on a physical performance index, which included grip strength, compared to Whites and were more likely to show steeper declines over time. [131] Using data from the Hispanic EPESE study, Snih et al. found that hand grip was found to be an independent predictor of disability status among an older cohort of Mexican Americans [41]. Although Hispanics, specifically Mexican Americans, have mortality rates comparable to that of Whites, they are more likely to live more disabled years.[132] Therefore, based on this accumulation of literature, there is reason to believe that, similar to other physical health indicators, disparities in muscle weakness may be exist across racial/ethnic groups, even though

the measurement of muscle weakness has not been specifically examined in non-white populations [45].

1.12 Summary

Given the background presented above, this dissertation will chart new territory in addressing many of the gaps that currently exist in the muscle health literature with respect to the measurement, health outcomes and life course determinants of muscle weakness in older adults. First, while major progress has been made in identifying muscle weakness as a key determinant of the aging process, there is an ongoing debate as to how to define muscle weakness at the population in identifying those most at risk for declines in muscle strength in older age. Additionally, much of the work that has been previously conducted has been done in all-white samples and used non-nationally representative data population level data that does not reflect the growing diversity of older adults in the United States. Therefore, the first aim of this dissertation seeks to establish cutpoints for clinical muscle weakness at the population level using a racially/ethnically diverse and nationally representative dataset of older American adults.

Second, once we have established race/sex specific cutpoints for clinical weakness, the second aim of this dissertation will examine the health consequences of muscle weakness in a nationally representative and diverse sample of older adults. While few studies have examined the longitudinal outcomes of muscle weakness in large scale, epidemiologic setting, we will use cutpoints derived in a nationally representative, diverse sample to examine long term risk to disability and mortality. Specifically, we are interested in understanding whether weak individuals at baseline are at an increased risk of changes in their disability status (Aim 2A) and early mortality (Aim 2B) based on the cutpoints established in aim 1.

Lastly, given the compelling literature that exists demonstrating the important role early and midlife social experiences, specifically that of stressful and traumatic life events, play in predisposing individuals to physical health deficits in later life, the third aim of this dissertation seeks to understand stress and trauma experienced across the life course may influence trajectories of muscle weakness in older adults.

1.13 Specific Aims and Hypotheses

The specific aims and hypotheses for this dissertation are as follows:

Aim 1: To establish race- and sex-specific cutpoints of grip strength from a nationally-representative, racially-diverse sample of Americans aged 65 years and older, and to estimate the race-sex specific prevalence of muscle weakness.

> *Hypothesis 1: We hypothesize that grip strength cutpoints in nationally representative data may be lower because of the greater likelihood of chronic health problems and disability in a heterogeneous national sample.*

Aim 2: To examine the predictive ability of our cutpoints in quantifying the association between baseline muscle weakness and physical disability and mortality in a nationally representative sample, diverse sample of older Americans.

> *Hypothesis 2a: We hypothesize that individuals who are weak at baseline, as identified by our previously defined subgroup specific cutpoints (see Aim 1), will be at greater odds of experiencing physical disability onset and progression across the 2-year time period compared to non-weak individuals.*

Hypothesis 2b: We hypothesize that individuals who are weak at baseline, as identified by our previously defined subgroup specific cutpoints, will be more likely to die earlier compared to non-weak individuals, even after accounting for time-varying confounders.

Aim 3: To identify the whether life course stress and trauma is associated with grip strength trajectories in a nationally representative sample older Americans and to examine whether the timing of stressful and traumatic events experienced at distinct life stages is associated with changes in grip strength over time.

Hypothesis 3a: Individuals who experience greater stress and trauma will undergo steeper declines in muscle strength in older age compared to those who experience none or fewer stressful and traumatic events.

Hypothesis 3b: Greater accumulation of stressful and traumatic events across the life course will be associated with steeper declines in grip strength trajectories in older age, compared to experiencing these events at a critical life stage.

CHAPTER 2. Cutpoints for Clinical Muscle Weakness Among Older Americans

2.1 Abstract

Background: Muscle weakness is an important indicator of disability, chronic disease and early mortality. Grip strength is a simple, cost-effective measure of overall muscle strength. The Foundation of the National Institutes of Health (FNIH) recently proposed sex-specific grip strength cutpoints for clinical muscle weakness. However, these criteria were established using non-nationally representative data. The objective of this study was to use nationally representative data on Americans age 65+ to identify race and sex-specific cutpoints for clinical muscle weakness and quantify the prevalence among older Blacks and Whites by sex.

Methods: Classification and Regression Tree (CART) models were used to identify cutpoints based on individual-level grip strength associated with slow gait speed (<0.8 m/s) among 7,688 individuals (57% female, 8% Black, mean age= 74.6±6.79 years) from the 2010/2012 Health and Retirement Study during January-April 2016. Identified cutpoints were then used to quantify the prevalence of weakness by race/sex sub-group.

Results: Fifty-five percent of men (max grip strength <39kg) and 47% of women (<22kg) were classified as weak. Higher cutpoints were identified for Black males (<40kg) and females

(<31kg), and the prevalence of weakness (57% and 88%, respectively), was higher compared to Whites. Fifty-five percent of individuals had slow gait speed (<0.8 m/s).

Conclusions: Prevalence of weakness was substantially higher than previous reports, underscoring the importance of using population level data to identify individuals at greatest risk for adverse health outcomes. This is the first study to establish cutpoints for muscle weakness in a nationally representative sample by race and sex.

2.2 Introduction

Muscle weakness is a primary determinant of age-related loss of function, [22,23] and is associated with mobility disability, [14,24,25]cardiovascular disease[26] and mortality [26,27]. Hand grip strength has been shown to be a reliable and cost-effective surrogate of overall muscle strength[133,134] and is a robust prognostic indicator of dynapenia, subsequent functional limitations[14,24] and future disease status[26]. Leong et al. found grip strength to be a stronger predictor of all-cause and cardiovascular mortality than systolic blood pressure[26].

The current guidelines used to classify older adults as clinically weak were derived from grip strength cutpoints developed by the Foundation of the National Institutes of Health (FNIH) (25.99 kg for men and 15.92 kg for women)[36,37]. However, these cutpoints were derived from non-nationally representative, pooled data across 8 observational and 6 clinical trial studies that do not reflect the growing racial and ethnic diversity in the U.S. population[37]. The primary objectives of the current study were to establish race- and sex-specific cutpoints of grip strength from a nationally-representative, racially-diverse sample of Americans aged 65 years and older, and to estimate the race-sex specific prevalence of muscle weakness. We hypothesize that grip

strength cutpoints in nationally representative data may be lower because of the greater likelihood of chronic health problems and disability in a heterogeneous national sample [24,135].

2.3 Methods

Data come from the Health and Retirement Study (HRS), a nationally-representative, multistage area probability survey of non-institutionalized, community dwelling Americans aged 51 years and older. Study details have been previously described [136]. HRS is the longest running longitudinal study of older Americans in the United States, with consistent response rates of ~85% [136]. Sampled persons have been re-interviewed biannually since 1992. New cohorts have been added to the original sample to maintain the nationally-representative nature of the survey over time [136].

Starting in 2006, a random one-half sample of HRS participants was selected for an enhanced face-to-face interview that included physical measurements (gait speed for those 65+ and hand grip strength), and the other random one-half completed the same interview in 2008 [137]. Proxy interviews and nursing home residents were ineligible to participate.

We used the latest cross-sectional waves of HRS data (2010/2012) to identify cutpoints for clinical muscle weakness, herein referred to as clinical weakness, in the most recent cohorts of older Americans. Our analytic sample is composed of adults aged 65+ in 2010 (n= 4,898) and 2012 (n= 4,652), creating one cross-sectional dataset (N=9,550). Excluding proxy interviews and nursing home residents (n=1,475) as well as those self-reporting as “other” race (n=387), resulted in a final analytic sample of 7,688 individuals.

The HRS was approved by the Behavioral Sciences Committee institutional review board at the University of Michigan. The data used in this analysis are publically available and contain no unique identifiers thereby ensuring respondent anonymity.

Measures

Hand grip strength

Hand grip strength was assessed using a Smedley spring-type hand dynamometer (Scandidact, Denmark). Participants were instructed to squeeze the device with the dominant hand as hard as they could and then let go. Grip strength assessments were administered while participants were standing with their arm at their side, with the elbow flexed at a 90 degree angle.[137] After one practice trial, two measurements were taken with each hand, alternating hands. The maximum measurement from the four trials was used for the analysis.

Timed Walking Test

Following existing work[22,36,37], slow gait speed was used as the primary outcome for calibrating grip strength cutpoints for clinical weakness. Gait speed was assessed using a timed walking test administered by trained raters in participants' homes [137]. A space of approximately 12 feet in length was needed to set up the walking course. Study participants were timed while walking at their "normal pace" along an 8-foot course. Participants were permitted to use a walking aid if they normally used one to walk. The interviewer stopped the time as soon as the participant's foot was completely past the tape marking the finish line and flat on the floor. Two trials were administered and the average of the two times was used to create a measure of usual gait speed (meters per second (m/sec)). A binary indicator of slow gait speed was created based on a

walking speed of less than 0.8 m/sec, which is highly predictive of incident disability[138] and mortality in both blacks and whites [139].

Missing data for gait speed (n=832) (for those with recent surgeries, injuries, or other health conditions (n=125), feeling unsafe (n=222), or not having suitable space for the test (n= 283)) were imputed using the multiple imputation methods in SAS 9.3 (PROC MI) with standard error corrections performed using PROC MIANALYZE [140].

Covariates

We included all relevant covariates that the FNIH included in their models in order to replicate their study as closely as possible,[37] including age, sex, self-reported race/ethnicity, number of chronic conditions (a three-level summary score based on having less than, at least one, or more than one self-reported medically diagnosed chronic health condition, e.g. arthritis, diabetes, heart condition), and body mass index (BMI) (weight in kilograms/(height in meters)^2).

Activities of Daily Living

Diagnostic properties of the grip strength cutpoints were assessed by quantifying the sensitivity and specificity of weakness corresponding to two clinically important outcomes: slow gait speed and difficulty with activities of daily living (ADLs) [141,142]. ADL disability was assessed using self-reported difficulty with six self-care activities of daily living (eating, bathing, dressing, transferring, toileting and walking across a room) [143]. For each activity, difficulty was recorded as present (i.e., difficulty with activity or cannot do at all) or absent (no difficulty). A dichotomous variable was created to identify participants that reported difficulty with one or more activities versus none.

Statistical Analysis

Analyses were conducted from January-April 2016. Classification and Regression Tree (CART) models were used to identify grip strength cutpoints for clinical weakness that were associated with slow gait speed (<0.8m/sec). CART models recursively partition data to identify those predictors with the strongest relationship with the outcome based on the criterion of minimum prediction error.[144,145] Candidate predictors entered into the model included: (1) maximum grip strength, (2) number of chronic conditions, (3) age, and (4) BMI. Individual models were run for each sex-race group. In order to avoid over fitting, cross-validation was employed for each of the sex and race specific trees by randomly partitioning the data into 10 mutually exclusive datasets. Each fully-grown tree was then applied to each of the subsamples where the error variance was obtained. All trees were then pruned based on established recommendations [144] to yield a final set of sex and race specific grip strength cutpoints.
All statistical analyses were conducted using SAS 9.3[140] and R version 3.1.2 using the *rpart* package[144]. Differences between individuals who were weak versus non-weak were assessed using t-tests for continuous variables and chi-squared tests for categorical variables. Descriptive analyses were weighted using HRS sampling weights and statistical significance was assessed with a two-tailed alpha of 0.05

2.4 Results

The age, sex and race breakdown of the sample is consistent with that of Americans aged 65 years and older based on 2012 U.S. census data.[143] Table 2.1 presents the weighted socio-demographic characteristics for all study participants. Fifty-seven percent were women, 91% were White, and the mean age was 75.2 years (range 65-100 years).

---- Table 2.1 ----

Men had a higher overall mean grip strength (39 kg) compared to women (22 kg) ($p<0.001$). Black women had significantly higher mean grip strength (24.5 kg) compared to White women (22.1 kg) ($p<0.001$); however, no differences were found between Black and White men. Slow gait speed was highly prevalent in this national sample, with over 55% walking slower than 0.8 m/sec. Among Whites, 44% of men and 58% of women had slow gait speed, compared to 75% percent of Black men and 87% of Black women.

After running sex-specific CART models, a primary split was on race was identified, indicating that grip strength cutpoints may differ across subgroups. As a result, subgroup specific models for black men, black women, white men, and white women were run. Results from the CART models indicate that grip strength had the greatest predictive power of slow gait speed, appearing as the primary split in all models. The cutpoints and prevalence estimates by sex are presented in Table 2.2, along with the published cutpoints by FNIH [37] for comparison. Based on the HRS cutpoints, over half of this nationally representative sample of men and women (55% of all men (<39kg) and 47% of all women (<22kg)) were classified as weak, compared to 10% and 12% for men (<25.99 kg) and women (<15.92 kg), respectively, using the FNIH cutpoints. Cutpoints for clinical muscle weakness based on a walking speed of 0.6 m/sec are provided as a supplementary table (Supplementary Table 2.4).

---- Table 2.2 ----

Results from the CART models and associated prevalence estimates for the sex/race specific subgroups are presented in Table 2.3. Among Whites, 37% of men (<35kg) and 48% of women (<22kg) were considered weak; whereas among Blacks, 57% of men (<40kg) and 88% of

women (<31kg) were categorized as weak. A visual representation of each CART tree is presented in Figure 2.1.

---- Figure 2.1 ----

---- Table 2.3 ----

The HRS grip strength cutpoints were found to have moderately high sensitivity and specificity with respect to slow gait speed and ADL disability (Supplementary Table 2.5). For slow gait speed, sensitivity of the weakness cutpoints was 75% and 60% for white men and women, respectively. Specificity was also moderately high for white women (68%) and moderate for white men (54%). Sensitivity for Black men (69%) and Black women (90%) was notably higher, while specificity was somewhat lower for Black men (65%) and women (29%). When comparing individuals on both weakness and ADLs, moderately high sensitivity and moderate specificity values for all subgroups were identified, providing further support that grip strength cutpoints were consistently identifying individuals with impaired function

2.5 Discussion

This is the first study to identify grip strength cutpoints for clinical weakness using nationally-representative data for older Americans. Findings indicate that muscle weakness is highly prevalent in the population, affecting over half of men and women age 65+, and cutpoints varied widely by sex and race.

While there has been an ongoing debate in the literature on the validity of different cutpoints for clinical weakness,[21] the FNIH cutpoints were intended for clinical practice[36] and are already being utilized in research [49,50]. The identified FNIH thresholds for grip strength are markedly lower than those we obtained using population-based data, despite replicating their analysis using the same outcome (gait speed <0.8 m/sec) with CART models. When quantifying

the prevalence of clinical weakness using the FNIH cutpoints for men (<25.99kg) and women (<15.92kg) in the HRS data, only 10% of men and 12% of women were classified as weak. Using the FNIH cutpoints may, therefore, only identify the weakest and frail individuals in the population.

There is always a trade-off between sensitivity and specificity when cut-points are assigned to a continuous screening variable. However, from a public health and prevention perspective, the choice to utilize a more conservative cut-point may misclassify a large percentage of people who are actually at risk for future adverse health outcomes. We argue that it is far better to screen aggressively and provide early opportunities for identifying individuals that might actually benefit from a targeted intervention to delay and/or prevent steeper declines in function and health.

The grip strength cutpoints we obtained for White men and women are consistent with a recent population-based survey in Finland, in which the association between grip strength cutpoints (<37kg in men and <22kg in women) and future incident mobility limitations was examined.[24] Similarly, research conducted by Cruz-Jentoft et al. found that among community dwelling older adults in Italy, having a grip strength <30kg in men and <20kg in women was associated with slow gait speed and an inability to walk 1 kilometer without difficulty.[22]

We found that grip strength cutpoints varied markedly by race, resulting in substantial differences in the prevalence of weakness by race and sex. Compared to White men (<35kg) and women (<22kg), grip strength cutpoints for clinical weakness were higher for Black men (<40kg) and women (<31kg), indicating slow gait speed at higher levels of muscle strength. The accumulation of risks across the life course [146,147] may offset the strength advantage in Blacks. In addition, other competing risks may partly explain the high prevalence of slow walking speed in

Blacks. Notably, 44% of Black women and 33% of Black men were obese in our study, and weight status has been found to be an important predictor of slow walking speed.[148] Thus, muscle strength may not confer the same level of protection for functional health outcomes in obese individuals. However, we found similar results when using relative grip strength (grip strength/BMI) in our CART models.

The results presented in this study are the first to address a critically important and stark health disparity among older Black Americans, a minority group that has been largely overlooked in the muscle weakness literature, despite being at greater risk for physical functioning deficits and disability in later life.[130] This work moves the field forward in identifying race-specific cutpoints while simultaneously shedding light on emerging health disparities that, if left untreated, may lead to a disproportionate burden of disability among Blacks.

Strengths/Limitations

This study has several notable strengths. First, we used a novel statistical method in a nationally-representative sample to obtain sex-specific cutpoints of clinical weakness by race. Although CART has been used in clinical research, tree-based approaches have been largely underutilized within observational epidemiology[149,150]. While variations in body composition across racial and ethnic groups are well established [37], this is the first study to examine racial differences in muscle weakness in diverse sample of older American adults. In addition, using nationally representative data is an important strength of our study because the results can be generalized to American adults aged 65 years and older, rather than a select few. Given the emerging burden of weakness at the population level, the use of nationally representative data provides a critical first step in screening efforts used to identify individuals who may be a

greatest risk, and ultimately for determining where best to direct preventive interventions. Previous work has derived cutpoints from sample-specific distributions,[22] and relied on non-representative reference populations,[24,31] or non-nationally representative, pooled data sources to establish definitions for weakness[37], all of which may not be generalizable at the population level for identifying and treating clinical weakness.

Despite these strengths, this study is not without limitations. We did not have enough power to explore muscle weakness cutpoints by other racial/ethnic groups. Future work is needed to examine grip strength cutpoints for older Hispanics since this is a rapidly growing subgroup projected to increase by nearly 115% between 2014 and 2060 in the U.S.[152] Given the cross-sectional nature of this analysis, the temporal relationship between grip strength and gait speed could not be established. Longitudinal data are needed in order to directly assess the directional link between strength loss and mobility impairment, and to test whether clinical weakness at baseline predicts negative health outcomes in later life. The timed walk was assessed by trained interviewers using home-based measurements that may be subject to measurement error. However, when using a more conservative criterion of 0.6 m/sec for slow gait speed,[153] we found that 29% of men and 22% of women were classified as weak, which is still greater than twice the prevalence identified using the FNIH cutpoints[37]. Despite substantial evidence documenting the utility of walking speed as a robust determinant of future health risk,[139,154,155] the slow walking speed cutpoint may penalize individuals who are overweight or obese. That is, because overweight individuals have more mass to move, they are more likely to be deemed "slow" walkers. While having extra fat mass is an independent risk factor for many negative health outcomes, in using the slow walking variable as the key calibrating variable in defining weakness, there is an implicit assumption that slow walkers are inevitably weak, which may not

be the case. Thus, using the slow walking speed cutpoint in defining weakness may be especially problematic since, in our sample, 72% and 78% of Black men and women, respectively, were overweight/obese. Future research should explore other calibrating variables in defining muscle weakness in a diverse setting. Lastly, one major driver of sarcopenia is the subsequent loss in muscle mass[12]. We were unable to assess appendicular muscle mass because body composition measurements were not available in HRS.

2.6 Conclusions

The cutpoints established in this study can serve as an easy and accessible clinical tool for identifying individuals who may be at risk for experiencing adverse health outcomes, including future falls,[156] incident disability,[14,24] morbidity [26] and all-cause mortality.[26,27] Early identification of those at risk provides the greatest opportunities for effective interventions (e.g., resistance training) aimed at increasing muscle strength. We observed a high prevalence of both weakness and slow gait speed in older Americans, which considered concurrently, have important implications for future disability risk in the US population. Our results underscore the importance of using population level data to identify individuals at greatest risk for adverse health outcomes.

2.7 Tables & Figures

Table 2. 1 Demographic Characteristics of Study Sample by Race and Sex: Health and retirement Study age 65+ (n=7,688).

	Whites (n= 6,628)		**Blacks (n= 1,058)**	
	Men (n= 2,799)	**Women (n= 3,829)**	**Men (n=383)**	**Women (n=675)**
Variables	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*	*Mean (SD)*
Age (y)	75.5 (6.7)	75.4 (7.0)	73.6 (5.8)	73.9 (6.2)
Maximum Grip Strength (kg)	37.8 (8.7)	22.1 (5.7)	37.2 (8.7)	24.5 (5.8)
Gait Speed (meters/second)	0.83 (.25)	.75 (.25)	.67 (.21)	.59 (.21)
	N[a] (%)[b]	*N (%)*	*N (%)*	*N (%)*
Slow Walking Speed				
Slow Walkers (<.8 m/s)	1297 (44.0)	2249 (58.7)	287 (74.9)	582 (87.3)
Normal Walkers (≥.8 m/s)	1502 (56.0)	1580 (41.4)	96 (25.1)	93 (12.7)
Body Mass Index				
Underweight (<18.5)	19 (.7)	89 (2.1)	7 (1.4)	10 (2.4)
Normal Weight (18.5-24.9)	688 (23.5)	1319 (35.7)	100 (27)	129 (19.8)
Overweight (25-29.9)	1253 (45.1)	1289 (34.3)	151 (38.7)	228 (33.3)
Obese (≥30)	830 (30.7)	1067 (28.3)	123 (32.9)	303 (44.6)
Activities of Daily Living (ADLs)				
0	2289 (85.8)	3175 (81.7)	317 (79.7)	490 (67.2)
1+	410 (14.2)	654 (18.3)	66 (20.3)	185 (32.8)
Chronic Conditions				

	No chronic conditions	178 (7.2)	212 (5.7)	21 (6.1)	17 (2.5)
condition	At least one chronic	479 (18.0)	678 (18.0)	68 (18.2)	85 (13.3)
	2+ more chronic conditions	2141 (74.7)	2939 (76.2)	294 (75.7)	573 (84.1)

[a] Number of participants, unweighted
[b] Percentage, weighted

Table 2. 2 Comparing Grip Strength Cutpoints for Muscle Weakness and Prevalence Estimates by Sex between the HRS AND FNIH.

	HRS			
	All Men (n=3,182)		All Women (n=4,506)	
Classification	Cutpoint (kg)	N (%)*	Cutpoint (kg)	N (%)[a]
Weak	<39	1845 (55)	<22	1998 (47)
Normal	≥39	1274 (45)	≥22	2317 (53)

	FNIH			
	All Men		All Women	
Classification	Cutpoint (kg)	N (%)*	Cutpoint (kg)	N (%)*
Weak	<25.99	317 (10)	<15.92	523 (12)
Intermediate	≥25.99	554 (17)	≥15.92	863 (20)
Normal	≥31.83	2248 (73)	≥19.99	2929 (68)

[a] Weighted percentages

Table 2. 3 Cutpoints and Prevalence Estimates for Clinical Muscle Weakness by Race/Sex in the Health and Retirement Study.

HRS Total Sample (N= 7,688)								
	White Males		Black Males		White Women		Black Women	
	(n=2,799)		(n=383)		(n=3,829)		(n=675)	
Classification	Cutpoint (kg)	N (%)	Cutpoint (kg)	N (%)	Cutpoint (kg)	N (%)	Cutpoint (kg)	N (%)
Weak	<35	1111 (37)	<40	223 (57)	<22	1794 (48)	<31	557 (88)
Normal	≥35	1639 (63)	≥40	145 (43)	≥22	1885 (52)	≥31	78 (12)

Figure 2. 1 Classification and regression trees for clinical muscle weakness by race/sex in the Health and Retirement Study.

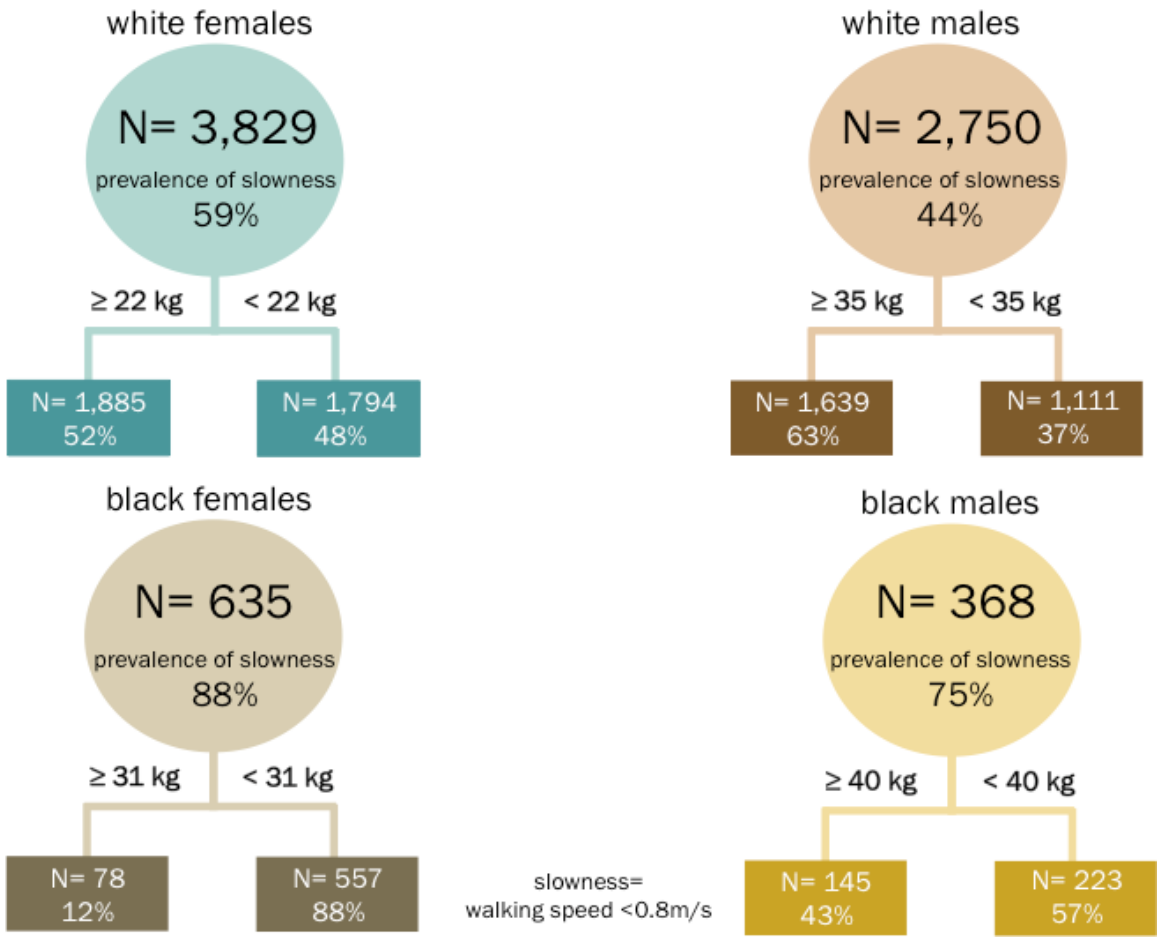

Table 2. 4 Cutpoints and Prevalence Estimates for Clinical Muscle Weakness by race/sex in the Health and Retirement Study (walking speed <.6 meters/second).

HRS Total Sample (N= 7,688)

	White Males		Black Males		White Women		Black Women	
	(n=2,799)		(n=383)		(n=3,829)		(n=675)	
Classification	Cutpoint (kg)	N (%)	Cutpoint (kg)	N (%)	Cutpoint (kg)	N (%)	Cutpoint (kg)	N (%)
Weak	<31	675 (25)	<39	213 (58)	<18	792 (22)	<25	318 (50)
Normal	≥31	2075 (75)	≥39	155 (42)	≥18	2887 (78)	≥25	317 (50)

Table 2. 5 Diagnostic properties for Grip Strength Cutpoints in the Prediction of Slow Walking Speed and Activities of Daily Living (ADL) in the Health and Retirement Study.

Slow Walking Speed (<.8 m/s)

White Males (n=2,750)

		Slow Walking Speed		
		Yes	No	
Weak	Yes	953	678	1631
	No	315	804	1119
		1268	1482	2750
	Sensitivity	75.16		
	Specificity	54.25		

Black Males (n=368)

		Slow Walking Speed		
		Yes	No	
Weak	Yes	190	33	223
	No	84	61	145
		274	94	368
	Sensitivity	69.34		
	Specificity	64.89		

White Females (n=3,679)

		Slow Walking Speed		
		Yes	No	
Weak	Yes	1296	498	1794
	No	847	1038	1885
		2143	1536	3679
	Sensitivity	60.48		
	Specificity	67.58		

Black Females (n=635)

		Slow Walking Speed		
		Yes	No	
Weak	Yes	494	63	557
	No	52	26	78
		546	89	635
	Sensitivity	90.48		
	Specificity	29.21		

Activities of Daily Living (0 vs. 1+)

White Males

		ADLs (1+ vs. 0)		
		Yes	No	
Weak	Yes	288	1343	1631
	No	104	1015	1119
		392	2358	2750
	Sensitivity	73.47		
	Specificity	43.04		

Black Males

		ADLs (1+ vs. 0)		
		Yes	No	
Weak	Yes	45	178	223
	No	16	129	145
		61	307	368
	Sensitivity	73.77		
	Specificity	42.02		

White Females

		ADLs (1+ vs. 0)		
		1	0	
Weak	Yes	400	1394	1794
	No	186	1699	1885
		586	3093	3679
	Sensitivity	68.26		
	Specificity	54.93		

Black Females

		ADLs (1+ vs. 0)		
		1	0	
Weak	Yes	159	398	557
	No	9	69	78
		168	467	635
	Sensitivity	94.64		
	Specificity	14.78		

CHAPTER 3. Chapter 3. Muscle Weakness And Physical Disability In Older Americans: Longitudinal Findings From The U.S. Health And Retirement Study

3.1 Abstract

Importance: Muscle weakness is an important indicator of disability, chronic disease and mortality. While we recently proposed sex/race specific grip strength cutpoints for clinical muscle weakness in a diverse, nationally representative sample of older Americans, the extent to which these cutpoints predict physical disability remains unknown.

Objective: To examine whether sex/race specific muscle weakness cutpoints predict physical disability status in a nationally representative sample of Americans age 65+.

Design: We used data from the 2006-2010 Health and Retirement Study. Fully-adjusted, weighted multinomial logistic regression models were used to quantify the odds of experiencing the onset, progression or persistence of disability in activities of daily living (ADL) among weak versus non-weak individuals over a 2-year period.

Setting: General community, nationally representative sample of older Americans

Participants: Population-based, community dwelling sample of older American adults aged 65-years+; 57 percent were women, 91% were White and the mean age was 75 years.

Main Outcome(s) and Measure(s): The primary outcome of interest was disability dynamics, defined by changes in ADL status across at 2- year period. The primary exposure was clinical

muscle weakness as defined by previously identified cutpoints. Hypotheses were formulated before analyses were conducted.

Results: In this nationally representative sample (n= 8,725), 44% of individuals were classified as weak at baseline. At follow-up, 55% remained independent with no change in their ADL status, 11% had an onset of disability and 4% progressed in their disability status. The odds of experiencing an onset of ADL disability was 54% higher among weak individuals compared those who were not weak at baseline (OR= 1.54, 95% CI= 1.54, 1.5, p<.0001); the odds of experiencing a progression in physical disability status was 2.16 times higher among those who were weak at baseline compared to non-weak individuals (OR= 2.16, 95% CI= 2.15, 2.16, p<.0001).

Conclusions: This is the first study to use grip strength weakness cut-points to identify those who may be at greatest risk for experiencing physical disability in later life. Results underscore the importance of using population-specific cutpoints for clinical weakness in order to identify individuals at greatest risk for adverse health outcomes.

3.2 Introduction

Muscle weakness is a primary determinant of age-related loss of function, [22,23] and is associated with mobility disability, [14,24,25] cardiovascular disease[26] and early mortality.[26,27] Hand grip strength has been shown to be a reliable and cost-effective surrogate of overall muscle strength[16,157] and is a robust prognostic indicator of subsequent functional limitations[14,24] and future disease status[26]. While age-related losses in muscle strength and mass are a natural part of

the aging process, individuals who undergo steeper declines in muscle strength may be more vulnerable to changes in physical disability status in later life. [14,41,67]

Despite a well-documented literature linking muscle weakness to disability[14,41,70,158] and a host of other negative health outcomes,[26,42,159] an ongoing debate remains regarding how best to define muscle weakness in a clinical setting. Recent efforts to define clinical muscle weakness proposed by the Foundation for the National Institutes of Health were derived using non-nationally representative, pooled data that do not reflect the growing racial and ethnic diversity in the U.S. population.[37] As a result, we recently established cutpoints for clinical muscle weakness (Table 3.1) in a nationally-representative, racially-diverse cross-sectional sample of Americans aged 65 years and older.[160] and found a higher prevalence, where 55% of men (max grip strength <39kg) and 47% of women (max grip strength <22kg) were clinically weak. In addition, we identified stark race/ethnicity disparities, with 57% of Black men (<40kg) and 88% of Black women (<31kg) were considered to have clinical muscle weakness compared to 37% and 48% of White men and women, respectively. While these data represent an important step forward in defining muscle weakness at the population level, it is still not known whether these cutpoints can be used to predict subsequent changes in disability status over time. Understanding disability dynamics is an important health outcome that has significant implications for the rapidly aging US older adult population.

---- Table 3.1 ----

Therefore, in order to address these gaps, the primary objectives of this study were to examine the predictive ability of the population-based cutpoints for clinical muscle weakness, and to quantify the association between baseline muscle weakness and the onset, progression and

persistence of physical disability in a nationally-representative sample of older Americans during a 2-year time period. We hypothesize that older adults that are strong at baseline, as identified by previously defined sex/race specific cutpoints, will be at reduced odds of experiencing onset, progression and persistence of disability and more likely to improve across a 2-year time period, compared to weak individuals.

3.3 Methods

Design and Sample Population

Data come from the Health and Retirement Study (HRS), a nationally-representative, multistage area probability survey of non-institutionalized, community dwelling Americans aged 51 years and older. Study details have been previously described [136]. HRS is the longest running longitudinal study of older Americans in the United States, with consistent response rates of ~85%.[136] Sampled persons have been re-interviewed biannually since 1992, and new cohorts have been added to the original sample to maintain the nationally-representative nature of the survey over time.[136] Ongoing surveillance via the National Death Index provide continuous mortality status, including date of death, for all participants.

In 2006, half the sample of HRS participants was randomly selected for an enhanced face-to-face interview that included physical measurements (gait speed for those 65+ and hand grip strength), and the other random one-half completed the same interview in 2008.[137] The 2006 and 2008 random sub-samples were then combined to yield the full, eligible baseline sample. Proxy interviews and nursing home residents were ineligible to participate.

Individuals who made up the 2006 (n= 5,809) and 2008 (n= 5,542) HRS waves were combined to yield a full baseline sample of 11,351 eligible individuals. We subsequently

excluded individuals who were less 65 years of age (n=7,832), identified as "other" race (n=393), and those who required a proxy interview or were in a nursing home at the time of the interview (n=2,167). After applying these exclusion criteria, our final analytic sample was composed of 8,725 individuals. Two-year follow-up data were included for all individuals from 2008 and 2010.

Measures

Hand grip strength

Hand grip strength was assessed using a Smedley spring-type hand dynamometer (Scandidact, Denmark). Participants were instructed to squeeze the device with the dominant hand as hard as they could, and then let go. Grip strength assessments were administered while participants were standing with their arm at their side, and with the elbow flexed at a 90 degree angle.[137] After one practice trial, two measurements were taken with each hand, alternating hands. The maximum measurement from the four trials was used for the analysis. HRS sub-group specific cutpoints for clinical weakness were then applied to identify those who were weak versus not weak at baseline[160]. The cutpoints are summarized in Table 3.1.

Physical Disability

Physical disability was assessed using self-reported difficulty with six self-care activities of daily living (ADLs): eating, bathing, dressing, transferring, toileting and walking across a room.[143] For each activity, difficulty was recorded as present (i.e., difficulty with activity or cannot/does not do) or absent (no difficulty). An ADL summary score was computed for each individual based on the sum of all reported difficulties across all 6 activities. For example, if an individual reported 3 ADL difficulties, then they received an ADL summary score of 3. Two

ADL summary scores were calculated for each individual—one at baseline (2006/2008) and then at follow-up 2 years later (2008/2010).

In order to assess changes in physical disability status across the 2-year period, an ADL change score was calculated as the difference between the ADL summary score at follow-up and baseline. After creating the ADL change score for each person, a 6-level outcome variable was created based on the six types of change observed across the entire sample: (1) “No Disability, No Change”, no ADL difficulties reported at both baseline and follow-up; (2) “Persistent disability”, individuals reporting the same number of ADL difficulties at baseline and at follow-up; (3) “Onset”, individuals who reported no ADL difficulties at baseline and at least one or more ADL difficulties at follow-up; (4) “Progression”, one ADL difficulty at baseline and more than one ADL difficulty at follow-up, (5) “Improvement”, individuals who reported at least one ADL difficulty at baseline and at least one fewer ADL difficulty at follow-up; and (6) “Lost to follow-up”, individuals who received an ADL score at baseline but were lost to follow-up (including mortality) 2 years later. This last group (n=938) was included in order to account for missingness and to avoid biasing the analysis, which could occur if these individuals were excluded. The “No Disability, No Change” group served as the reference group in the analysis since this group had the best outcome and the highest level of functioning.

Covariates

The following relevant baseline covariates were included in our model: age (continuous), sex, self-reported race/ethnicity, education (3-level categorical variable, less than a high school degree, high school degree, some college/college degree), number of chronic conditions (continuous summary measure, based on 8 self-reported medically diagnosed chronic health

condition: high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems and arthritis), body mass index (BMI) ((measured weight in kilograms/ (measured height in meters)^2), and gait speed (continuous measure, assessed using a 8-foot long timed walking test administered by trained raters in participants' homes over).[137]

Statistical Analysis

All statistical analyses were conducted using SAS software 9.3 (Cary, NC).[140] Bivariate differences between individuals who were weak versus non-weak were assessed using t-tests for continuous variables and chi-squared tests for categorical variables. Descriptive analyses were weighted using HRS sampling weights and statistical significance was assessed with a two-tailed alpha of 0.05. Fully-adjusted models (including age, sex, self-reported race/ethnicity, education, number of chronic conditions, BMI, and gait speed), weighted multinomial logistic regression models were used to quantify the odds of experiencing an onset or progression in ADL disability status among weak versus non-weak individuals, over a 2-year period. Interactions by sex were also examined with a 2-level interaction term in the fully-adjusted model.

3.4 Results

The age, sex and race breakdown of our sample is consistent with that of Americans aged 65 years and older based on U.S. census data.[143] Table 3.2 presents the weighted socio-demographic characteristics for all study participants. Fifty-seven percent were women, 91% were White, and the mean age was 75 years. Forty-four percent of individuals were identified as weak based on the previously identified sub-group specific cutpoints. There was a high prevalence of slow walking speed (<0.8 meters/second) with 60 percent of individuals classified as slow. At baseline, 80% of individuals had no difficulty with any ADLs. Over the 2-year

follow up period the majority of the sample (55%) remained independent with no change in their ADL status, 11% had an onset of disability and 4% progressed in their disability status. Six percent of the sample improved and 21% of individuals were lost to follow up (678 individuals died and 265 were lost due to sample attrition (i.e., unable to locate, refusals) across the 2-year follow-up window). Table 3.3 presents the results from the adjusted multinomial logistic regression, which assessed the odds of experiencing a change in physical disability status across the 2-year follow-up period (2008/2010) compared to the "No Disability, No Change" reference group.

--- Table 3.2 ---

--- Table 3.3---

Disability Onset Versus No Disability, No Change

Compared to the "No Disability, No Change" reference group, the odds of experiencing an onset of physical disability was higher among weak individuals compared to non-weak individuals (OR= 1.54, 95% CI= 1.54, 1.55) (Model A, Table 3.3). Females were at greater odds of experiencing disability onset (OR= 1.04, 95% CI= 1.04, 1.05) compared to males. Individuals with less than a high school degree (OR= 1.17, 95% CI= 1.16, 1.17) or had only a high school degree (OR= 1.50, 95% CI= 1.50, 1.51) were at greater odds of disability onset compared to individuals with some college or a college degree. Blacks were at greater odds of disability onset compared to Whites across the two-year period (OR=1.12, 95% CI= 1.11, 1.12), net of covariates.

Disability Progression versus No Disability, No Change

Compared to the "No Disability, No Change" reference group, the odds of experiencing a progression in physical disability were substantially higher among those who were weak at baseline compared to non-weak individuals (OR= 2.14, 95% CI= 2.13, 2.15) (Model B, Table 3.3). Individuals with less than a high school degree were at greater odds (OR= 1.45, 95% CI= 1.44, 1.45) of disability progression compared to those with some college or a college degree. For each additional chronic condition, individuals had over a 50% higher odds of experiencing a progression in their disability status (OR= 1.58, 95% CI= 1.58, 1.58). Blacks were also at greater odds of experiencing a progression in their disability status compared to Whites across the two-year period (OR=1.06, 95% CI= 1.05, 1.06).

Persistent Disability versus No Disability, No Change

Weak individuals had almost a two-fold higher odds (OR= 1.90, 95% CI= 1.89, 1.91) of experiencing persistent disability across the 2-year period compared to non-weak individuals (Model C, Table 3.3). Blacks were at greater odds (OR= 1.18, 95% CI= 1.18, 1.19) of persistent disability compared to Whites. Individuals who had less than a high school degree had 18% increased odds of persistent disability compared to their college-educated counterparts. For each additional chronic condition, the odds of persistent disability increased by almost 50% (OR= 1.49, 95% CI= 1.49, 1.49). Older age, slower walking speed and higher body mass index were also associated with remaining persistently disabled over the observation period (all $p<0.01$).

Improved versus No Disability, No Change

Compared to the "No Disability, No Change" group, the odds of experiencing an improvement in physical disability was 63% more likely for weak versus non-weak individuals (OR=1.63, 95% CI= 1.63, 1.64) (Model D, Table 3.3).

Sex by Weakness Interaction

In examining whether the association of muscle weakness and disability status differed by sex, we found that muscle weakness was strongly associated with disability status for both groups; however, the magnitude of this association was stronger for men compared to women. Specifically, among men, compared to the "No Disability, No Change" group, the odds of experiencing disability onset was 71% more likely for weak men compared to non-weak men (OR= 1.71, 95% CI= 1.71, 1.72); the odds of experiencing disability progression was 3.16 times more likely for weak men compared to non-weak men (OR= 3.16, 95% CI= 3.15, 3.18); and, the odds of experiencing disability recovery was 2.19 times more likely for weak men compared to non-weak men (OR= 2.19, 95% CI= 2.19, 2.20) across the 2-year period.

Among women, compared to the "No Disability, No Change" group, the odds of experiencing disability onset was 38% more likely for weak versus non-weak women (OR= 1.38, 95% CI= 1.37, 1.38); the odds of experiencing disability progression was 70% more likely for weak versus non-weak women (OR= 1.70, 95% CI= 1.69, 1.70); and, the odds of experiencing disability recovery was 38% more likely for weak versus non-weak women (OR= 1.38, 95% CI= 1.37, 1.38) across the 2-year period. There was no effect modification by race/ethnicity.

3.5 Discussion

To the best of our knowledge, this is the first nationally-representative study to examine the pace of disability onset, progression and persistence in relation to muscle weakness in older Americans. Consistent with existing work,[14,41,70,161] the results of this study indicate that older adults with clinical muscle weakness, as identified by sex/race specific population-derived cutpoints,[160] are at significantly increased risk of experiencing a deterioration in their ability to

engage in basic self-care activities of daily living across a two year time period. Specifically, we found that clinical muscle weakness is strongly associated with the onset, progression and persistence of physical disability status, highlighting the importance of screening efforts to identify those who are most vulnerable to the consequences of clinical muscle weakness as they age.

The results of this study bolster the existing literature by using population-derived cutpoints for clinical weakness to demonstrate the consequences of muscle weakness for multiple patterns of change in physical functioning among older adults over time. Previous work that has sought to measure and define clinical muscle weakness has derived cutpoints from sample-specific distributions,[22] and relied on non-representative reference populations,[24,31] or non-nationally representative, pooled data sources to establish definitions for weakness,[37] all of which may not be generalizable at the population level for identifying and treating clinical weakness. Additionally, by examining the development of disability onset, progression and persistence of disability, the results of this study indicate that muscle weakness may in fact influence the *pace* of disability. This has important health implications for older adults since previous research has shown that disability onset and progression are associated with increased risk of hospitalization,[162] institutionalization,[163] and mortality.[164] Prior work examining the association between muscle weakness and disability have typically relied on binary definitions of disability status (presence/absence),[14,165] which may underestimate the weakness-disability association at the population level since disability has been shown to fluctuate over time.[96,165–167]

Nonetheless, our results are consistent with others that have examined the link between muscle weakness and ADL disability and physical functioning. Rantanen et al. found that low hand grip strength among 45-68 year olds was strongly associated with disability status 25 years

later.[14] Using HRS data, Germain et al. found that tertile-specific low muscle strength was associated with higher odds of physical and functional outcomes, although those analyses were cross-sectional.[68] In a 3-year longitudinal study by Onder et al., higher handgrip strength was found to be protective against incident ADL disability.[66] Additionally, a 4-year longitudinal study found that higher handgrip strength was associated with a reduced risk in the development of new functional difficulties, although this analysis was restricted to the oldest old.[69]

We also found that the association between muscle weakness and disability was stronger for males than females across all levels of the disability outcome. While previous work investigating sex differences and disability status has found that females are more likely to be disabled in older age [168,169], our findings suggest that other contextual factors may play an important role in driving disability status among women. In our sample, we found that women had greater chronic disease impairment, less education, as well as lower maximum grip strength at baseline. Thus, the attenuated estimates observed for women may reflect a complex array of risk factors acquired across the life course that differentially impact the relationship between muscle weakness and disability status.

An unexpected finding was that weak individuals were more likely to improve across the 2-year time period compared to those who were not weak at baseline. While these results were unexpected, previous research has found that the probability of experiencing an improvement in physical functioning is inversely related to the severity of the disability.[170,171] In our study, 75% (n=324) of individuals who experienced an improvement in disability had only 1 ADL limitation at baseline, implying that the interventions needed to improve one's disability status may have been more attainable and/or accessible compared to individuals with greater disability severity (i.e., 3+ ADL limitations). Additionally, several studies have noted that disability trajectories are

fluid and may change over time, especially when studied within a longitudinal design setting with closely measured, repeated time points.[170]

The term "intermittent disability" has been used in the literature to characterize individuals who report disability at one time point but not at subsequent follow up points, implying that gains made over short intervals may not be permanent. In a 5-year prospective cohort study of community-living older adults, Gill et al. (2006) found that the majority of participants experienced at least one episode of intermittent disability and that these episodes lasted, on average, about 6 months.[167] In our study, we found that 75% (n=324) of the individuals who reported 1 ADL disability at baseline went on to report no ADL disability at follow-up. However, 42% (n=159) of these same individuals went on to report 1 or more ADL disability in the subsequent 2 years period (2010/2012). These results imply that while these individuals may have improved in the short-term that may have "relapsed" and become disabled two years later. Thus, intermittent disability episodes may partially explain the counterintuitive findings with respect to weakness in this study.

Strengths and Limitations

Our study is not without limitations. First, this analysis examined the association between weakness and disability across a two-year interval. It is possible that other competing events, such as acute hospitalization, could partially explain the observed weakness-disability association. Second, we were unable to control for underlying conditions (i.e., paresis, neuropathy, etc.) that may have led to changes in ones' disability status. Despite this limitation, we were able to account for baseline chronic disease status, which is an important indicator since multi-morbidity has been found to be associated with both disability and physical functioning.[172]

Third, while research suggests that muscle strength may be an important risk factor in middle age [14], the cutpoints utilized in this study were derived in adults aged 65+ years. There is growing interest in the role grip strength may play as a mid-life biomarker of future physical functioning and disability since previous research has found that disability rates are increasing among middle-aged Americans.[173] Therefore, future research should focus on middle age as a potentially critical window for screening and intervention. Fourth, the primary outcome was assessed as self-reported difficulty in activities of daily living, which may have led to an underestimate of the true association if sicker individuals were less likely to report changes in their ADL status. Lastly, as in any longitudinal design setting, we had 10% attrition due to losses to follow-up. However, we accounted for those lost to follow-up in our multinomial ADL outcome variable, which reduced potential bias that would have occurred if we had excluded these individuals from our analysis.

Despite these limitations, this study has several notable strengths. First, we used handgrip strength as our primary exposure, which is a cost-effective, reliable proxy for total body muscle strength that can be easily administered in the clinical setting [43,174]. The results of this study imply that the grip strength cutpoints utilized in this study can be used for identifying those individuals most at risk for changes in disability status without involving invasive diagnostic tools or time-intensive screening questionnaires. Additionally, our findings provide support for the prognostic utility of the population-derived muscle weakness cutpoints used in this study, which has important implications since screening and intervention efforts cannot be fully realized until clinical and epidemiologic communities coalesce around standardized cutpoints to identify individuals who may be a greatest risk. Finally, our results provide support for tailoring

interventions to each individual's unique dynamic disability status in an effort to prevent steeper declines as individuals age.

3.6 Conclusions

This is the first study to use muscle weakness cut-points derived in a nationally-representative sample of older Americans to identify those who may be at greatest risk of experiencing onset, progression and persistence in their disability status in later life. Results underscore the importance of using population-specific cutpoints to identify individuals at greatest disability risk.

3.7 Tables and Figures

Table 3. 1 Cutpoints for clinical muscle weakness by race/sex in the Health and Retirement Study.

2006/2008 HRS Total Sample (N= 8,725)

	White Males	Black Males	White Women	Black Women
	(n=3,279)	(n=422)	(n=4,286)	(n=738)
	Cutpoint (kg)	Cutpoint (kg)	Cutpoint (kg)	Cutpoint (kg)
Weak	<35	<40	<22	<31
Normal	≥35	≥40	≥22	≥31

Table 3. 2 Demographic characteristics in weak and non-weak older adults, Health and Retirement Study, 2006/2008 (N= 8,725).

	Mean	*SD*
Age (y)	74.9	7.1
Maximum Grip Strength (kg)	29.2	10.4
Gait Speed (meters/second)	3.9	2.1
	*N**	*%***
Sex		
Female	5024	*56.8*
Race/Ethnicity		
White	7565	91.9
Black	1160	8.1
Muscle weakness		
Weak	3813	44.3
Non-weak	4654	55.7
Activities of Daily Living (ADLs)		
Independent, no change	5673	55.0
Persistent	299	2.8
Onset	233	11.2
Progression	337	4.2
Improved	645	5.6
Lost to follow up	938	21.2
Slow Walking Speed		
Slow Walkers (<.8 m/s)	5245	60
Normal Walkers (≥.8 m/s)	3480	40
Body Mass Index		
Underweight (<18.5)	142	1.9
Normal Weight (18.5-24.9)	2734	32.9
Overweight (25-29.9)	3319	38.0
Obese (≥30)	2436	21.2
Chronic Conditions		
No chronic conditions	673	7.9
At least one chronic condition	1819	20.8
2+ more chronic conditions	6232	71.3

*Number of participants, unweighted

** Percentage, weighted

Table 3. 3 Disability and Muscle Weakness: Multinomial Logistic Regression Models for Disability Status*, Health and Retirement Study, 2006/08-2008/10.

	A. Disability Onset vs. Independent, No Change		B. Disability Progression vs. Independent, No Change		C. Disability Persistence vs. Independent, No Change		D. Disability Improvement vs. Independent, No Change	
	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI	Odds Ratio	95% CI
Variable								
Weak								
Non-Weak	Ref		Ref		Ref		Ref	
Weak	1.54	1.54, 1.55	2.16	2.15, 2.16	1.90	1.89, 1.91	1.64	1.63, 1.64
Sex								
Males	Ref		Ref		Ref		Ref	
Females	1.04	1.04, 1.05	0.99	0.99, 0.99	0.98	0.98, 0.98	1.30	1.30, 1.31
Race/Ethnicity								
Whites	Ref		Ref		Ref		Ref	
Blacks	1.12	1.11, 1.12	1.06	1.05, 1.06	1.18	1.18, 1.19	0.99	0.99, 1.00
Education								
Some college/College	Ref		Ref		Ref		Ref	
High school	1.50	1.5, 151	0.89	0.88, 0.89	1.02	1.01, 1.02	1.00	1.00, 1.01
Less than high school	1.17	1.16, 1.17	1.45	1.44, 1.45	1.18	1.18, 1.19	1.47	1.47, 1.48
Chronic conditions	1.42	1.41, 1.42	1.58	1.58, 1.58	1.49	1.49, 1.49	1.54	1.53, 1.54
Age	1.06	1.05, 1.06	1.05	1.04, 1.05	1.05	1.05, 1.06	1.03	1.03, 1.03
Walking speed	1.21	1.2, 1.21	1.39	1.39, 1.39	1.31	1.3, 1.31	1.39	1.39, 1.39
Body Mass Index	1.02	1.02, 1.02	1.07	1.06, 1.07	1.06	1.06, 1.06	1.05	1.05, 1.05

*Reference Group: Independent, No Change

CHAPTER 4. Do Nationally Representative Cutpoints For Clinical Muscle Weakness Predict Mortality? Results From Nine Years Of Follow-Up In The Health And Retirement Study

4.1 Abstract

Background: Muscle weakness, as measured by handgrip strength, is associated with cardiovascular and all cause-mortality; however, there are wide inconsistences in the magnitude of these effects due to divergent definitions used to define muscle weakness across studies. Therefore, the objective of this study was to examine the relationship between previously defined sex/race-specific cutpoints of clinical muscle weakness and early mortality.

Methods: Data comes from the 2006-2014 Health and Retirement Study. Time-varying clinical muscle weakness, as defined by handgrip strength cutpoints, was the primary exposure. Time to death, ascertained from the National Death Index, was the outcome of interest. The association between time-varying clinical muscle weakness and early mortality across a 9-year observation period was determined using Kaplan-Meier methods and extended Cox regression.

Results: Out of the 8,326 individuals in the study, 1,799 deaths (21%) occurred during the observation period. Median follow-up time was 8.3 years (SD ±1.9 years). Weak individuals had a steeper decline in their survival trajectory, compared to non-weak individuals (Log-Rank test, p<.001). After adjusting for sociodemographic factors and time-varying smoking history, weak individuals were over 50% more likely to die earlier than non-weak individuals (HR=1.52, 95% CI= 1.15, 1.47).

Conclusions: This is the first study to use muscle weakness cut-points derived in a nationally-representative sample to identify those individuals who may be at greatest risk for premature mortality. Results underscore the importance of muscle weakness, as defined by handgrip strength, as a key risk factor for premature mortality in older Americans.

4.2 Introduction

Muscle weakness, as measured by handgrip strength, is associated with a host of negative health outcomes, including physical functioning limitations,[1,2] disability,[3–5] and multimorbidity.[6,7] There is also a growing body of evidence linking muscle weakness with both cardiovascular[8] and all cause-mortality.[1,8–12] However, there are inconsistences in the magnitude of these effects. For example, the Foundations of National Institutes of Health (FNIH) Sarcopenia Project found a 74% and 48% greater mortality risk over 10 years for weak men and women, respectively, in a study comprised of 6 cohort studies.[1] Similarly, the estimated risk of death was 36% among men and women with low grip strength in the Health ABC study over 4-years of follow-up.[11] In contrast, no relation between weak hand grip strength and mortality was

found in a sample of older adults with chronic kidney disease[13] while low grip strength was associated with a 49% increased risk of death in men, but not in women.[14]

Part of the reason for these inconsistent findings may stem from the multiple ways in which muscle weakness has been measured and operationally defined. The Prospective Urban Rural Epidemiology (PURE) used study-specific grip strength tertiles[8] whereas the Adult Health Study (AHS) compared men and women in the highest and lowest quintiles of hand grip strength among 5,000 individuals in Japan,[15] and the FNIH Sarcopenia Project used grip strength thresholds calculated from a specific set of cohort studies and clinical trials.[1] In the absence of consistent, population-derived cutpoints of clinical muscle weakness based on hand grip strength, the true consequences of muscle weakness for premature mortality remain unclear.

In earlier work, sex/race-specific cutpoints for clinical muscle weakness were identified using data from a nationally-representative sample of older Americans in the U.S. Health and Retirement Study (Table 1).[16] In subsequent analyses, these weakness cutpoints were shown to be predictive of incident physical disability over a 4-year period.[4] What remains to be determined is the extent to which these cutpoints predict early mortality.

---- Table 4.1 ----

The primary aim of this study was to examine the relationship between clinical muscle weakness, as defined by our previously published sex/race-specific grip strength cutpoints, and early mortality across a 9-year period from a nationally-representative sample of American adults aged 65 years and older. It was hypothesized that weak individuals would have a shorter survival compared to non-weak individuals, even after accounting for time-varying health and sociodemographic covariates.

4.3 Methods

Design and Sample Population

Data came from the Health and Retirement Study (HRS), a nationally representative, multistage area probability survey of non-institutionalized, community dwelling Americans aged 51 years and older. Study details have been previously described.[17] Briefly, HRS is the longest running longitudinal study of older Americans in the United States, with consistent response rates of ~85%.[17] Sampled persons have been re-interviewed biannually since 1992, and new cohorts have been added to the original sample to maintain the nationally-representative nature of the survey over time.[17]

In 2006, half the sample of HRS participants was randomly selected for an enhanced face-to-face interview that included physical measurements, and the other random one-half completed the same interview in 2008.[18] Baseline collection of variables began in 2006 and was repeated every two years going forward. Proxy interviews and nursing home residents were ineligible to participate in the enhanced physical measurement protocol.

We used 5 waves of longitudinal data from the 2006-2014 Health and Retirement Study. Analyses were restricted to Black and White community-dwelling adults aged 65 years and older. Individuals who reported to be "other" race were excluded from the analysis (n=487). Individuals who were missing on grip strength across all waves were excluded from the analysis (n=169), yielding a final sample of 8,326 individuals.

Measures

Hand grip strength

Hand grip strength, our primary exposure variable, was assessed using a Smedley spring-type hand dynamometer (Scandidact, Denmark). Participants were instructed to squeeze the device as hard as they could and then let go. Grip strength assessments were administered while participants were standing with their arm at their side, and with the elbow flexed at a 90 degree angle.[18] After one practice trial, measurements were taken with each hand, first with the dominant hand and then with the non-dominant hand. Two additional measurements were taken for both hands and the maximum measurement in kilograms (kg) from the four trials was used for the analysis. Among those missing on handgrip strength (n=169), the majority had a health problem (63%) or the interviewer did not feel it was safe for the respondent to participate (37%).

Race/sex-specific cutpoints for clinical weakness were used to classify those who were weak versus not weak at each follow-up.[16] The HRS hand grip strength cutpoints were previously found to have moderate to moderately high sensitivity in relation to slow walking speed for black and white men (range, SE: 69-75%, SP: 54.3-64.9%) and black and white women (range, SE: 60.5-90.5%, SP: 29.2-67.6%).[16] Time-varying grip strength was used in the analyses.

Mortality

Mortality was ascertained through HRS linkages with the National Death Index or from contact with household members at each data collection wave through December 2014. Previous HRS tracking studies have indicated a 98.8% validation of deaths.[17] Survival time was calculated based on an individual's age in months from the start of their first interview until the end of observation period (December 31, 2014) or until death, which ever occurred first. Individuals who were alive at the end of the follow-up period or lost to follow-up were censored.

Covariates

The following covariates were included: age (continuous), sex, self-reported race/ethnicity and education (5-level categorical variable, less than a high school degree, GED, high school degree, some college, and college and above). Smoking status, which was measured every 2-years, was included as a time-varying covariate and was categorized as current, former and never smoker based on self-report. Physical activity was assessed based on whether an individual reported taking part in sports or activities that were "moderately energetic" (i.e., gardening, cleaning the car, walking at a moderate pace). Individuals who reported hardly ever or never were classified as "inactive" while those who engaged in moderate activity more than once a week, once a week, one to three times a month were considered "active". Body mass index (BMI) defined as weight in kilograms/(height in meters)^2. Number of chronic health conditions was assessed based on the sum of eight self-reported medically diagnosed chronic health conditions (high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems and arthritis).

Analytic Approach

All statistical analyses were conducted using SAS software 9.4 (Cary, NC).[19] Bivariate differences between individuals who were weak versus non-weak were assessed using t-tests for continuous variables and chi-squared tests for categorical variables. Descriptive analyses were weighted using HRS sampling weights and statistical significance was assessed with a two-tailed alpha of 0.05. The Kaplan-Meier method was used to generate time-to-event unadjusted baseline survival curves in which the median survival time was calculated. Log-rank tests were used to

test whether the survival curves differed between weak versus non-weak individuals across the study period.

Weighted, fully-adjusted, extended Cox models for time-dependent variables were used to estimate hazard ratios for mortality among weak versus non-weak individuals.[20] Survival was defined as time from baseline interview to date of death, proxy-reported death, or last interview. Hazard ratios and 95% confidence intervals were obtained.

4.4 Results

Baseline demographic characteristics of the study sample are reported in Table 2. In this nationally-representative sample of 8,326 older adults (mean age= 79.9 years, SD=± 6.59 years), 46% were considered weak at baseline based on the sex/race specific grip strength cutpoints. Weak individuals were more likely to be older compared to non-weak individuals (82 years of age vs. 78 years, respectively; $p<.001$), and women were more likely to be weak than men (65% vs. 35%, respectively; $p<.001$). Whites were more likely to be weak compared to Blacks (87% vs. 13%, respectively; $p<.001$).

---- Table 4.2 ----

Across the 9-year study period, the median follow-up time was 8.3 (±1.9 SD) years. 1,743 (21%) individuals died and 6,593 (79%) individuals were censored. Among those who censored, 6,570 were alive at the end of the study period and 23 were lost to follow up. Out of the 1,743 individuals who died, and 1,267 (72%) were weak at baseline and 532 (28%) were non-weak. When comparing the baseline survival curves of weak versus non-weak individuals across the 9-year observation period, the results of the Log-Rank test indicated they were significantly different from one another ($p< .001$) (Figure 4.1).

---- Figure 4.1 ----

---- Table 4.3 ----

Table 3 presents the results from the extended Cox models. In the unadjusted model (Model 1, Table 3), muscle weakness was associated with a nearly 60% greater risk of death over the follow-up period (Hazard Ratio (HR) =1.59, 95% confidence interval (CI)= 1.42, 1.77). After adjusting for sociodemographic factors and smoking history (Model 2, Table 3) weak individuals were over 50% more likely to die earlier compared to non-weak individuals (HR=1.52, 95% CI= 1.15, 1.47) (Model 2, Table 3). Further adjusting for time-varying body mass, number of chronic health conditions, and physical activity resulted in an attenuation of hazard ratio, however the association remained significant (Model 3, Table 3).

4.5 Discussion

Using data from a nationally-representative sample of older Americans, this study demonstrated that muscle weakness, as indexed by validated thresholds of hand grip strength, was strongly associated with early mortality, even after accounting for other known risk factors. Across a 9-year follow-up period with time-varying measures of weakness, older adults classified as weak were 50% more likely to die earlier compared to those who were not weak, even after adjusting for other time-varying risk factors. These findings provide support that grip strength is an important clinical marker for identifying those who may be most at risk for negative health outcomes, including early mortality.

The majority of studies focusing on the relationship between muscle weakness and mortality have relied on sample-specific definitions [3,7,10,21] and/or utilized data that are not representative of the diverse and rapidly growing population of older adults in the United

States.[2,22] For example, the FNIH Sarcopenia Project recently proposed cutpoints for clinical muscle weakness and mass but were unable to explore differences in defining muscle weakness by various subgroups due to small sample size.[23] Similarly, the European Working Group on Sarcopenia in Older People (EWGSOP) proposed muscle weakness cutpoints that relied on a sample-specific definition derived in cross-sectional setting.[24] As a result, there is a paucity of research that has adequately quantified the true burden of muscle weakness on survival in older Americans within a longitudinal, racially/ethnically diverse context.

The results of this study are consistent with a growing body of research that has demonstrated that muscle weakness, as measured by hand grip strength, is associated with mortality.[8,12,25] Indeed, several epidemiological studies have found grip strength to be inversely related to all-cause and cause-specific mortality in mid-life[9,26], older[1,6,10] and the oldest old[27] populations, although in a few studies, this relationship held for men but not women.[6,28] In a meta-analysis comprised of 14 studies and close to 54,000 participants, those in the lowest quartile of grip strength measurement were 67% more likely to die earlier compared to those in the highest quartile, even after adjusting for sex, body mass and age.[29] In the PURE study among nearly 140,000 adults 35-70 years of age with 4 years of follow-up, poor grip strength was the strongest predictor of early cardiovascular and all-cause mortality, even compared to other traditional clinical indicators such as systolic blood pressure.[8] Thus, muscle strength remains an important and robust predictor of mortality risk as individuals age over time.

Despite previous cross-sectional work that has almost exclusively focused on muscle mass, a growing body of longitudinal research has demonstrated that declines in muscle strength outpaces that of muscle mass,[11,30,31] implying that muscle strength may not only be an important predictor of muscle health but a more sensitive measurement with respect to clinical intervention.

Moreover, hand grip strength, which is the most common assessment of muscle strength in research and clinical practice,[32] has been found to be independently associated with mobility limitations, physical functioning and disability.[4,33] Therefore, there is a growing call among researchers and clinicians to consider muscle strength as a composite biomarker of muscle mass and function.[34]

While the mechanisms underlying the muscle weakness-mortality association have not been fully elucidated, there are likely several underlying pathways driving the association between muscle weakness and premature mortality**.** Several studies have shown muscle weakness is associated with higher fasting insulin levels[35] and a precursor to insulin resistance.[36] Muscle weakness has also been found to be independently associated with an increased odds of experiencing diabetes[37] and metabolic syndrome[38] in adults. Maintaining muscle strength may play a critical role in preventing metabolic and cardiovascular disease risk with aging, and thus protecting against premature mortality.

Weak individuals are also more likely to report greater difficulty in completing basic self-care activities[25] and experience greater odds of disability onset, progression and persistence over time.[4] Therefore, the association between muscle weakness and mortality may be mediated by changes in physical functioning. Individuals with low levels of physical activity are more likely to experience declines in muscle strength, thereby entering a negative feedback loop where weak individuals are unable to participate in physical activity and are more vulnerable to declines in their physical health status, leading to subsequent declines and risk for early mortality. Taken together, handgrip strength may function as a "a crude but effective will to live meter"[39] even if the underlying mechanisms of the strength-mortality association may not be fully understood.

Of note, we found that the estimated survival functions for weak and non-weak individuals at baseline did not begin to diverge until month 50, a little more than 4-years into the follow-up period. We interpret this observation to mean that muscle weakness is associated with a slow decline in health and functioning that may be indirectly associated with the onset of premature mortality. In other words, muscle weakness does not lead to an immediate, precipitous decline in health, but rather may initiate a cascade of negative health events associated with compromised survival in later life. Indeed, understanding the complex, underlying pathways driving the results observed in this study warrants further investigation.

The results of this study support the use of nationally representative grip strength cutpoints for clinical muscle weakness derived in a diverse sample of older adults[16] as a brief screening tool to easily identify those who may be most vulnerable to negative health outcomes. Given the ease and cost-effectiveness of measuring hand grip strength, combined with the robust literature demonstrating that grip strength may serve as a biomarker of healthy aging, the cutpoints utilized in this study can be applied in other data that seek to define muscle weakness. These cutpoints can also be used in the clinical setting as a quick and inexpensive way of identifying those older adults who may be most vulnerable to future declines in health status.

This study had several notable strengths. First, to the best of our knowledge, this is the first study using sex/race-specific muscle weakness cutpoints derived in a nationally-representative, diverse sample of older Americans to examine the relationship between clinical, time-varying muscle weakness and mortality. Therefore, the results presented in this manuscript can be generalized to community-dwelling, older Black and White American adults aged 65 years and older in the United States. Second, the statistical analysis used both time-varying weakness variables and time-varying covariates, an important analytic consideration when

examining a longitudinal association when exposure status is known to change over time. Previous research examining the muscle weakness-mortality association included fixed, baseline covariates only. This approach makes the assumption that muscle weakness remains stable over time, which is unlikely to be the case.[12] Third, the cutpoints utilized in this study to define muscle weakness were derived using handgrip strength measurements. Grip strength dynamometers have been shown to be a cost effective, quick and a simple instrument that can be readily utilized within the clinical setting.[40] Therefore, the grip strength cutpoints presented in this paper offer clinicians the opportunity to incorporate handgrip assessments into medical practice for screening and identifying at risk older individuals.

Despite these strengths, this study has several limitations. First, participants were interviewed every 2 years and there may be other competing events (i.e., acute hospitalization following a medical event) in the intervening period that could not be accounted for. Future studies should examine the muscle weakness-mortality association in surveys that have more frequent follow-up over time. Second, the results of this study can only be generalized to individuals aged 65 years and older. Since the cutpoints utilized in this study were derived in an older population, we are unable to assess the muscle weakness-mortality association in middle age, which may serve as an important age for intervention.

This is the first study to use muscle weakness cut-points derived in a nationally-representative sample of Black and White older Americans to identify those who may be at greatest risk for premature mortality. Results underscore the importance of muscle weakness as a key risk factor for premature mortality in older Americans.

4.6 Tables and Figures

Table 4. 1 Cutpoints for clinical muscle weakness by race/sex in the Health and Retirement Study.

	2006/2008 HRS Total Sample (N= 8,725)			
	White Males	Black Males	White Women	Black Women
	(n=3,279)	(n=422)	(n=4,286)	(n=738)
	Cutpoint (kg)	Cutpoint (kg)	Cutpoint (kg)	Cutpoint (kg)
Weak	<35	<40	<22	<31
Normal	≥35	≥40	≥22	≥31

Table 4. 2 Baseline demographic characteristics of adults age 65+ in the Health and Retirement Study (n=8,326), 2006-2014.

	Weak	**Non-Weak**	p-value
	Mean (SD)	*Mean (SD)*	
Age (y)	78.4 (6.9)	82.6 (5.6)	<.0001
BMI	25.9 (5.2)	27.3 (5.8)	<.0001
Chronic Conditions	3.1	2.7	0.2
	N[a] (%)[b]	*N[a] (%)[b]*	
Sex			<.0001
Males	1339 (35)	2235 (49.6)	
Females	2482 (65)	2270 (50.4)	
Race/Ethnicity			<.0001
Whites	3011 (86.9)	4254 (56.9)	
Blacks	810 (78.1)	251 (21.9)	
Education			
Less than a HS degree	1102 (56.5)	834 (43.5)	<.0001
GED	146 (39.6)	221 (60.4)	
High School	1270 (46)	1543 (54)	
Some College	692 (41.9)	955 (58.1)	
College and above	611 (38.8)	951 (61.2)	
Smoking Status			<.0001
Never	1757 (48.5)	1873 (51.5)	
Former	1816 (44.2)	2284 (55.8)	
Current	248 (40.6)	348 (59.4)	
Physical Activity			<.0001
Active	1951 (37)	3176 (63)	
Inactive	1870 (59.4)	1329 (40.6)	

[a]Number of participants, unweighted

[b] Percentage, weighted

Figure 4. 1 Kaplan Meir Baseline Survival Curves: Comparing Weak vs. Non-Weak Individuals (N=8,326), 2006-2014.

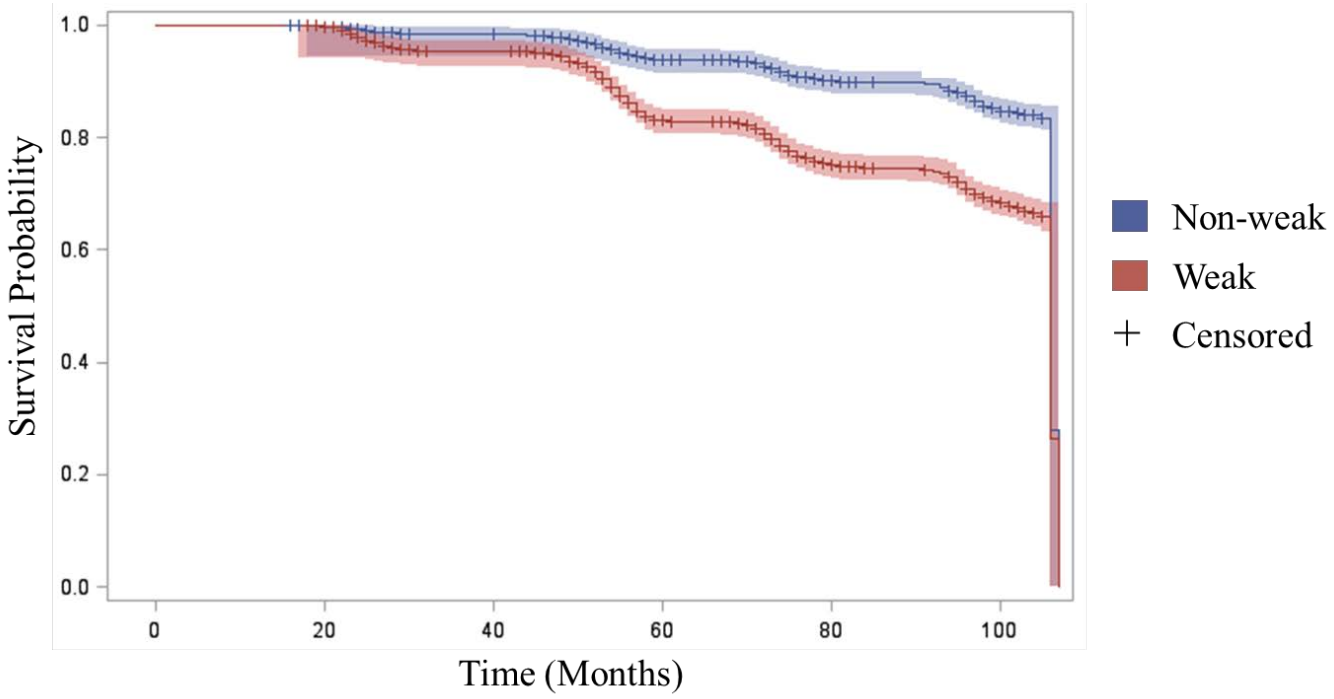

Table 4. 3 Extended Cox Proportional Hazard Models: Association between Muscle Weakness and Mortality in the Health and Retirement Study (N=8,326), 2006-2014.

	Model 1		Model 2		Model 3[†]	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Weak[a]	1.59***	1.42, 1.77	1.52***	1.15, 1.47	1.77***	1.43, 2.21
Demographic Factors						
Age (years)			1.02**	1.01, 1.03	1.04***	1.02, 1.05
Female[b]			0.73***	.66, .81	0.69	.57, .87
Black[c]			0.86	.74, 1.01	0.76	.58,.99
Education[d]						
GED			0.78*	.60, 1.00	1.18	.77, 1.78
High School			0.71***	.63, .82	0.76	.60, .96
Some college			0.71***	.63, .83	0.89	.68, 1.16
College and above			0.54***	.46, .64	0.85	.63, 1.14
Smoking Status[e]						
Former			1.42***	1.27, 1.59		
Current			2.06***	1.70, 2.49		

* p<.05
**p<.01
***p<.0001
[a] Reference group is Non-weak
[b] Reference group is Male
[c] Reference group is White
[d] Reference group is Less than High School education
[e] Reference group is Never Smoker
[†] Further adjusted for body mass index, chronic conditions and physical activity

CHAPTER 5. Life Course Determinants Of Muscle Weakness: The Role Of Stress And Trauma

5.1 Abstract

Background: Muscle weakness, as measured by handgrip strength, is associated with disability, physical functioning and mortality; however, the extent to which grip strength trajectories among older adults are shaped by social adversity experienced earlier in the life course is unknown.

Methods: Using data from the Health and Retirement Study (N= 20,472, Mean Age= 63.8 years), we employed gender-stratified growth curve models to investigate whether traumatic and stressful events experienced both across the life course and at distinct life stages were associated with trajectories of grip strength in a nationally representative sample of older adults.

Results: We found that life course trauma and stress experienced during emerging/early adulthood (18-42 years) was associated with both mean grip strength at age 50 and trajectories of grip strength over time. Among Black men, stress and trauma experienced during emerging/early adulthood was not only related to higher mean grip strength at age 50, but also associated with steeper declines as individuals aged over time compare to White men. Among Black women, traumatic events during emerging/early adulthood were associated with lower mean grip strength at age 50.

Discussion: Results shed light on the importance of considering how one's social environment shapes grip strength trajectories among older adults and may also contribute to racial/ethnic disparities in muscle weakness in later life, particularly among Black Men and Women.

5.2 Introduction

Muscle weakness, as measured by handgrip strength, is associated with a host of negative health outcomes, including physical functioning limitations, [24,47] disability,[14,15,41,70] multimorbidity,[17,76,175] and both cardiovascular[17,26] and all cause-mortality.[12,26,47,73,74,78,176] In the United States, it is estimated that 55% of older men and 45% of older women have muscle weakness.[179] Racial disparities in muscle weakness have also been uncovered by recent research showing that 55% of Black Males and 88% of Black women meet criteria for clinical muscle weakness compare to 37 % of White men and 48% of White women.[179] The implications of compromised muscle strength in later age may be especially consequential since older Black adults also have a higher prevalence of mobility limitations compared to Whites.[183] Thus, a "dual burden" of muscle weakness combined with greater mobility limitations may exacerbate physical health disparities in later age and lead to greater challenges associated with the recovery process.

While physical activity[184], gender [13], chronic disease status[185] and nutrition[75] in older age have been identified as important determinants of muscle weakness, significant unexplained variability remains in identifying which individuals become weak in older age. One of the primary reasons for this may be that research has largely focused on proximal determinants of muscle weakness among older adults and less on early and midlife risk factors. It is possible that a better grasp of the risk factors earlier in the life course would not only help identify those who

are both most at risk for muscle weakness in older age but also who would benefit most from early intervention.

An enhanced understanding of the upstream social factors that drive differential vulnerability to muscle weakness in later life is of critical public health importance. There is a well-established body of evidence documenting how social stress and trauma "gets under the skin" to impact physical health in older age. [114,116,186] However, to date, few studies have investigated the role social stress and trauma plays in the development of muscle weakness in later age, and whether previously observed disparities in muscle weakness may be exacerbated due to differential exposure to social stress and trauma. Therefore, this study addresses a major gap in the literature by explicitly testing in a longitudinal setting whether exposure to stress and traumatic events experienced across the life course influence trajectories of muscle weakness in older age within a nationally-representative, diverse group of Americans. This chapter will begin by first reviewing several related bodies of literature integral to our understanding of the relationship between life course risk factors and muscle weakness in a middle and older aged adults. I first review life course epidemiology, followed by stress and trauma as independent risk factors for physical and mental health, and conclude with a brief review of how these factors may shape racial/ethnic disparities in health.

Life Course Epidemiology: Theoretical underpinnings and conceptual models

Life course epidemiology has been used to elucidate how seemingly unrelated physical and social exposures experienced during gestation, childhood, adolescence, young adulthood and middle age drive disease outcomes in later life.[86] From a life course perspective, aging is seen from a developmental lens in which distinct phases of adulthood are marked by specific life

events and role transitions where certain stressors/protective factors may be more or less likely to occur.[86,87] For example, childhood is often defined by gains in education while adolescence is an important window of development when young people begin to assert their independence, make life style choices and establishes health behaviors that will often persist into adulthood.[88] The emerging/early period of adulthood (typically occurring in the 20's to late 30's and early 40's) is typically characterized by the establishment of one's career, marriage, parenthood and asset acquisition that has a lasting effects on health and SES in later life.[89–91] Lastly, the midlife period (mid 40s to early 60s) is often typified by changes in health status as a result of early life health behaviors and life chances.

While the life course framework is useful in helping to identify the timing and potential impact of when and how events unfold, it is important to note that historically, life course theory has made assumptions about an "institutional pattern" regarding how individuals transition through different life stages. Thus, as Kohli suggests, thinking of the life course as a unified, institutional model has become increasingly inappropriate as the life course has become more differentiated and heterogeneous over time, particularly with respect to gender and race/ethnicity.[187] Since a life course framework often examines how individuals move in and out of various social systems (i.e., educational system, criminal justice system, labor markets, etc.), disparities arise when the amount of time spent is shorter for some groups than for others. [188] For example, Oppenheimer et al. found that among those with a high school degree, ~20% of Black men married within 4 years of graduation, compared with 40% of White men.[189]

Despite the variation in the life course with respect to race, gender and economic resources, two general conceptual models within life course theory have been proposed to understand how early life antecedent events drive health outcomes in older age: the critical

period model and the accumulation of risk model.[86] The critical period model suggests that there are important life stages in which an individual experiences adverse events and exposures that may have crucial consequences on their health in later life. This conceptual model is largely rooted in the fetal origins hypothesis, which linked poor maternal nutrition in utero to increased risk of coronary heart disease and diabetes in later life.[92] One well documented example is literature showing that childhood SES is directly associated with cardiovascular disease,[93] stroke,[94,95] physical functioning[96,97] and lower levels of grip strength[98] in older adults. Similarly, experiencing physical, sexual and emotional abuse during childhood is associated with increased risk of adverse physical and mental health outcomes in later life. [99,100]

The accumulation of risk model posits that negative exposures gradually accumulate across the life course, ultimately influencing health status in later life.[101] This model has been used to explain why socioeconomic differentials in health exist across a wide range of diseases.[86] For example, early childhood conditions may set individuals on risk trajectories of cumulative advantage/disadvantage with those from lower SES backgrounds experiencing a faster decline in health compared to those from higher SES backgrounds, ultimately leading to widening health disparities in later life.[102,103] The accumulation of risk model has been applied to examine physical health outcomes. For example, physical inactivity, smoking, heavy drinking, social isolation, fair/poor perceived health and prevalence of chronic symptoms and conditions across a 30-year period of emerging and midlife adulthood was associated with increased risk of frailty in a community dwelling sample of older adults.[104]

Life Course Epidemiology & Muscle Weakness

There is growing interest in the role early and midlife factors play in the preservation of muscle strength in later life. However, the majority of research has almost exclusively focused on early life anthropometric indicators showing higher birth weight to be associated with greater muscle strength adulthood.[105] In the Hertfordshire Ageing Study, lower birth weight and weight in the first year of life were significantly associated with lower grip strength 60-70 years later. This relationship, while somewhat attenuated, remained significant after adjusting for body size, indicating that one's early environment may be of critical underlying importance.[106] Pre-pubertal growth has also been found to be associated with midlife grip strength.[107]

More recently, several studies have demonstrated that socioeconomic conditions experienced across the life course may also be linked to muscle health in later life. A recent systematic review found modest, positive associations between childhood SES and later life grip strength, even after adjusting for adult SES and current body size.[97] Wealth in later life was found to be inversely associated with grip strength in a sample of older Europeans, while education, income and occupation were not, suggesting that earnings accrued across the life course may be important in maintaining grip strength in later life.[108] Results from a British birth cohort study indicated that higher levels of material deprivation (i.e., not having a car, not owning one's home) were inversely related to grip strength in later life.[98] Low income and low education were found to be significantly associated with decreased grip strength among an elderly sample of Korean men.[109] More recently, childhood misfortune was found to be related to lower handgrip strength in men, but not in women. [110]

Stress, Trauma and the Life Course

A substantial body of literature has demonstrated that one's social context is consequential for health. Previous studies have found social and economic hardships experienced both in childhood[111] and throughout the life course are associated with mental and physical health outcomes in later life.[112,113] There is evidence to suggest that exposure to stress and trauma throughout one's life may be linked to poorer health outcomes in later life.

Previous research investigating the downstream cascade that emerges after experiencing stress and trauma early in the life course suggests there are several important mediators on the causal pathway between stress, trauma and muscle weakness in later life. Indeed, experiencing stressful and traumatic events earlier in life may lead to maladaptive coping[190], which in turn may lead to higher levels of BMI since previous research has shown that victims of trauma may use food to "anaesthetize" themselves from unpleasant feelings and memories.[191] Research also shows that individuals who experience greater levels of stress and trauma are more likely to smoke.[192] As a result, individuals who experience higher levels of stress and trauma may be less likely to engage in physical activity which may lead to a higher prevalence of chronic conditions.[193]

Social stress has been found to be associated with mental health status and depression among older adults.[114,115] Traumatic events have been shown to have a strong relationship on both immediate and long-term health outcomes. Trauma in particular may be especially consequential for health. Pearlin (2005) noted that trauma may be the most potent form of stress, characterized by the "magnitude of their onerousness…and by their sudden and violent character" (pg. 210) that have negative consequences for health in later life.[116] Despite the known links between stress and trauma with later life physical health, no studies have directly

examined whether stress and trauma experienced throughout the life course, and specifically among distinct critical life periods, is associated with muscle health in later life.

Racial/ethnic health disparities

Racial/ethnic disparities in health are pervasive and persistent in the United States.[117,147] Non-Hispanic Black Americans have a higher prevalence of several chronic conditions[118], live more years with chronic health problems[119] and have higher rates of disability[120,121] compared to Non-Hispanic White Americans. Similarly, among sub-groups of Hispanics, Hispanic Americans have been found to have higher rates of chronic disease and have worse functional health.[122,123] However, mortality rates, particularly among Mexican Americans, appear to be comparable and in some cases exceed all-cause mortality for Non-Hispanic Whites.[124] Racial/ethnic disparities in physical functioning, mobility and disability are also well documented.[119,121,125,126]

In seeking to understand why these disparities persist, many studies have examined socioeconomic status (SES) as a key explanatory contributor. Indeed, several studies have shown that after accounting for SES, disparities in functional health between Blacks and Whites become partially attenuated, and in some cases, disappear[121,127]. However, the evidence regarding the association between SES and functional health remains equivocal. Other studies investigating this relationship have found that even after accounting for SES differences, disparities in disability and physical functioning persist, [128] suggesting that other explanatory factors may be at play.

Social adversity and racial/ethnic disparities in health

While several studies have shown racial/ethnic minorities to have a higher prevalence of lifetime stress and trauma[194], this evidence is largely mixed. Nonetheless, individuals in more advantaged social positions have better access to resources and opportunities in early life, which can offset or reduce exposure to negative life events, while those in more disadvantaged social positions are at greater risk of negative life events on account of reduced access and opportunity[195]. Moreover, since the root of disadvantage is structural and often experienced in all aspects of one's life, persistent advantage or disadvantage can become compounded over time, ultimately leading to a widening in racial/ethnic health disparities across populations.[196] As a result, it can be hypothesized that disparities in muscle strength between Whites, Blacks and Hispanics may be indirectly related to differential exposure to stress and trauma across the life course, a view that is consistent with the accumulation of risk theory.

Based on the above, the primary objectives of this study are twofold: (1) To identify whether life course stress and trauma are associated with grip strength trajectories in a nationally representative sample older Americans followed across an 8-year period, and; (2) To examine whether the timing of when these stressful and traumatic events across the life course and at distinct life stages is associated with changes in grip strength in racially and ethnically diverse, longitudinal study of Americans aged 50 years and older.

5.3 Methods

Study Design and Sample Population

Data came from the Health and Retirement Study (HRS), a nationally representative, multistage area probability survey of non-institutionalized, community dwelling Americans aged 51 years and older. Study details have been previously described.[136] Briefly, HRS is the longest

running longitudinal study of older Americans in the United States, with consistent response rates of ~85%.[136] Sampled persons have been re-interviewed biannually since 1992, and new cohorts have been added to the original sample to maintain the nationally-representative nature of the survey over time.[136]

In 2006, half the sample of HRS participants was randomly selected for an enhanced face-to-face interview that included physical measurements, and the other random one-half completed the same interview in 2008.[137] Additionally, in the same 2006 survey wave, HRS began collecting data on psychological and social well-being that was left behind after the enhanced face-to-face interview.[197] Participants completed these questions and then mailed in their responses. For this analysis we used 5 waves of longitudinal data from the 2006-2014 Health and Retirement Study.

Our initial population included 26,163 individuals who were 50+ years old and community-dwelling. Individuals who had died (n=1,429), reported "other" for their race/ethnicity (n=745), or were missing on grip strength across all waves (n=3,517) were excluded, yielding a final analytic sample of 20,472 Black, White, Hispanic men and women who were 50 years and older at the time they received their first grip strength measurement (baseline).

Measures

Hand grip strength

Hand grip strength, our primary outcome of interest, was assessed using a Smedley spring-type hand dynamometer (Scandidact, Denmark). Participants were instructed to squeeze the device with the dominant hand as hard as they could and then let go. Grip strength

assessments were administered while participants were standing with their arm at their side, and with the elbow flexed at a 90 degree angle.[137] After one practice trial, two measurements were taken with each hand, alternating hands. The maximum measurement in kilograms (kg) from the four trials was used for the analysis.

Life Course Cumulative Trauma and Stress

As part of the leave behind self-administered questionnaire, participants were asked to answer a series of questions pertaining to traumatic and stressful life events experienced across the life course (yes/no). Example of trauma indicators included: “Has a child of yours ever died?”, “Did you ever have a life-threatening illness or accident?”, and; “Have you ever been in a major fire, flood, earthquake, or other natural disaster?” Life course cumulative trauma was defined as the sum of all traumatic events at any wave based on whether a respondent answered “yes” to a series of 11 questions (Range: 0-11). The full list of questions pertaining to traumatic life events are presented in supplementary table 5.3.

Participants were also asked about stressful life events. These indicators inquired about stressful life events (yes/no) experienced across the life course. Examples of stressful life events questions included: “At any time in your life, have you ever been unfairly denied a bank loan”, “Before you were 18 years old, did you ever have to do a year of school over again?”, and, “Have you involuntarily lost a job for reasons other than retirement at any point in the past five years?”. Life course cumulative stress was defined as the sum of all stressful life events reported in the series of 11 questions (Range: 0-11). The full list of questions pertaining to stressful life events are presented in supplementary table 5.4.

Life Stage Trauma and Stress

If a respondent answered "yes" to any of the traumatic and/or stressful life event indictors, they were then asked to record the year it occurred. In order to calculate the age at which the respondent experienced the stressful or traumatic event we subtracted the respondent's birth year from the year they experienced the event. Summary stress and trauma variables were then created for three critical life stages: Early Childhood (age 0-17 years), Emerging/early adulthood (age 18-42 years) and Midlife (age 43-67 years). Since the stressful life event questions largely focused on events pertaining to job and financial security, there were no stressful life events recorded in the childhood period. This resulted in five key exposure variables (2 stressful life event summaries in emerging/early adulthood and midlife, and 3 trauma event summaries in childhood, emerging/early adulthood and midlife) that capture the total number of stressful and traumatic events experienced during these distinct life stages.

Stress and trauma variables were missing for 3,182 individuals in the leave behind survey and were excluded from analyses with any of the exposure variables. These individuals were not significantly different from those who did complete the questions with respect to age, number of chronic conditions or BMI. However, individuals who were missing on the stress/trauma questions were more likely to report more difficulty with activities of daily living (ADL) than those who answered the stress/trauma questions (mean number of ADL limitations = .42 vs. .29, respectively).

Sociodemographic variables

The following time invariant covariates were included in the analysis: (1) Age was defined continuously in number of years; (2) Race/Ethnicity was self-reported and 3 dummy indicators were created for Non-Hispanic Black, Non-Hispanic White (referent) and Hispanic

individuals; (3) Gender was treated as dummy variable coded 1 for females and 0 for males; (4) Education was modeled as a binary dummy variable contrasting those with greater than or equal to 12 years of education compared to those with less than 12 years of education. Since educational attainment is a known risk factor for stress and trauma[198] and is also related to muscle weakness,[199] it was included as a confounder variable and was adjusted for in the statistical models.

The following time-varying covariates were included as hypothesized mediators in the causal pathway between earlier life stress/trauma and muscle strength in later age: (1) Smoking, categorized as current, former and never (referent) smoker based on self-report; (2) Physical activity was assessed based on whether an individual reported taking part in sports or activities that were "moderately energetic" (i.e., gardening, cleaning the car, walking at a moderate pace). Individuals who reported hardly ever or never were classified as "inactive" while those who engaged in moderate activity more than once a week, once a week, one to three times a month were considered "active"; (3) Body mass index (BMI) defined as weight in kilograms/(height in meters)^2; (4) Number of chronic health conditions was assessed based on the sum of eight self-reported medically diagnosed chronic health conditions (high blood pressure, diabetes, cancer, lung disease, heart disease, stroke, psychiatric problems and arthritis).

Analytic Approach

Growth curve models were used to examine trajectories of grip strength over mid to late-adulthood. Due to the established gender differences in grip strength, separate models were estimated for men and women. Growth curve models are a type of mixed model that account for correlations and clustering between and within individuals over time.[200] A two-level model was

specified using 5 waves of HRS data across an 8 year time period (2006-2014). Age in years was used as the primary time indicator from age 50 to 99, which was centered at age 50 to aid in parameter interpretation (setting age 50 to 0). The functional form of age was tested as linear, quadratic and cubic terms in order to capture potential non-linearity in trajectories of grip strength with aging. However, only the linear and quadratic terms were significant, and were retained in all models.

The structure of this model can be expressed by equations at each level. At level 1 (within-person model), maximum grip strength scores are nested with individuals (*i*) as defined by the following statement:

$$GS_{ti} = \pi_{0i} + \pi_{1i}(age - 50)_{ti} + \pi_{2i}(age - 50)^2 + r_{ti} \quad (1)$$

where π_{0i} is the expected maximum grip strength score for person *i* at age 50 (centered age), π_{1i} captures the linear rate of change in grip strength with age, π_{2i} captures the quadratic rate of change in grip strength, and r_{ti} captures the within-person residual (the part of an individual's grip strength at time *t* that cannot be explained by time/age) and is assumed to have a normally distributed mean of 0 and variance of σ^2.

The level-1 parameters are then modeled as a function of the individual characteristics at level-two. The level-2 between person sub-model assumes that grip strength intercepts and slopes vary across individuals, and we explicitly model these difference based on the following equations using race/ethnicity as a working example:

$$\pi_{0i} = \beta_{00} + \beta_{01}(black) + \beta_{02}(hispanic) + e_{0i} \quad (2.1)$$

$$\pi_{1i} = \beta_{10} + \beta_{11}(black) + \beta_{12}(hispanic) \quad (2.2)$$

$$\pi_{2i} = \beta_{20} + \beta_{21}(black) + \beta_{22}(hispanic) \quad (2.3)$$

In the equations above, the intercept and age slopes from equation 1 are modeled as a function of race/ethnicity, where β_{01} represents the difference in grip strength (intercept) for Blacks compared to Whites at age 50, β_{11} represents the difference in the rate of change (linear slope) of grip strength for Blacks compared to Whites and β_{21} represents the difference in the rate of change (quadratic slope) of grip strength for Blacks compared to Whites. Similarly, β_{20} represents the difference in grip strength (intercept) for Hispanics compared to Whites at age 50, β_{12} represents the difference in the rate of change (linear slope) of grip strength for Hispanics compared to Whites and β_{22} represents the difference in the rate of change (quadratic slope) of grip strength for Hispanics compared to Whites. The residual error (e_{0i}) captures the random error in the intercept across individuals. Random variance around the slope coefficients were not estimated due to problems with model convergence. Substituting equations 2.1 - 2.3 into equation (1) yields the full composite model:

$$\begin{aligned} Grip\ Strength_{ti=}\ & \beta_{00} + \beta_{01}(black) + \beta_{02}(hispanic) + \beta_{11}(black)(age-50) \\ & + \beta_{12}(hispanic)(age-50) + \beta_{21}(black)(age-50)^2 \\ & + \beta_{22}(hispanic)(age-50)^2 + e_{0i} + r_{ti} \end{aligned}$$

We used the MIXED procedure in SAS 9.4 to estimate the linear mixed models using full information maximum likelihood. The distribution of the residuals showed a good approximation to normality with little deviation from the diagonal in the normal probability plots, justifying the linear model. Nested models were compared using the following goodness-of-fit indices: (1) Change in the -2log likelihood, which follows a χ^2distribution where the degrees of freedom as the same between nested models, (2) Bayesian Information Criterion (BIC), where models with a

lower BIC indicate better model fit, and; (3) Proportion of variance in grip strength that is explained by a model (pseudo R^2), which is calculated by squaring the correlation between the observed and predicted grip strength values. We also tested for mediation by adding each hypothesized mediator individually to assess change in the estimate of our primary exposure.

5.4 Results

We first present descriptive statistics by gender and race/ethnicity in separate tables for men (Table 5.1A) and women (Table 5.1B) and proceed in discussing the model results for men (Table 5.2A) and women (Table 5.2B) separately below.

Results for Men

Descriptive Statistics

Among the 8,847 men included in this analysis, 17% were Black, 70% were White and 13% were Hispanic (Table 5.1A). White men were slightly older (63.5 years) compared to Black (61.1 years) and Hispanic (61.1 years) men. White men had the highest mean grip strength at 43.6 kg while Hispanic men had the lowest at 39.8 kg. Black men had a mean grip strength of 42.1 kg. The average number of chronic conditions was relatively similar across all three race/ethnic groups (range= 1.7-1.9 conditions). The average body mass index was also comparable across Black, White and Hispanic men (mean BMI range= 28.5-29.2 kg/m^2). While physical activity and smoking levels were similar across all groups, there were notable differences in educational attainment. Fifty-nine percent of White men had 12 or more years of education compared to 42% of Black men and only 28% of Hispanic men.

When examining the distribution of trauma across the life course, roughly one in 4 men reported no traumatic event from birth through age 67 (Table 5.1A). On average, Black men

experienced slightly higher levels of trauma (mean= 1.9 events) compared to Whites (1.7 events) and Hispanics (1.8 events). The distribution of the number of traumatic events by race/ethnicity was relatively similar, although Black and Hispanic men were somewhat more likely to report 3 or more traumatic events over the life course compared to White men. However, there were notable race/ethnic differences as to when these events occurred in the life course. In early childhood (0-17 years old), half of Black men and 46% of White men reported experiencing 1 or more traumatic events compared to 37% percent of Hispanic men. The number of traumatic events experienced during emerging/early adulthood (18-42 years) and midlife (43-67 years) were relatively comparable across race/ethnic groups.

There were also noticeable race/ethnic differences in the number of stressful life events experienced over the life course. Black men experienced more stressful life events (mean= 1.7 events) across the life course compared to Whites (1.2) and Hispanics (1.3). Thirty-two percent of Black men reported 3 or more stressful life events compared to 19% of White men and 22% of Hispanic men. The life stage breakdown as to when these events occurred also varied by race/ethnicity. Black men were more likely to report one or more stressful life event in emerging/early adulthood (30%) compared to White (20%) and Hispanic (17%) men. This was also the case for stressful life events experienced during midlife with 40% of Black men reporting one or more event compared to 32% of White men and 36% of Hispanic men.

---- Table 5.1A ----

Growth Curve Models

Unconditional Growth Model

Results for the growth curve model for men are presented in Table 5.2A. In the unconditional growth model (Model A), the mean grip strength for men at age 50 is 48.6 kg and there is a significant negative linear and quadratic time effect indicating that grip strength declines with age. For each additional year of age, men lose, on average, .31 kg per year ($p< .0001$) and this decline accelerates with age (significant quadratic term of -.007 kg per year^2).

---- Table 5.2A about here ----

Race/Ethnicity

When adding race/ethnicity to the model (Model B Table 5.2A), White men at age 50 have a mean grip strength of 50.3 kg (the intercept, $p< .0001$) while both Black and Hispanic men have statistically significant lower average grip strengths of 46.7 kg ($\beta= -3.6$, $p< .0001$) and 45.4 kg ($\beta= -4.9$, $p<.0001$), respectively, at age 50. However, there were no significant differences in the rate of decline in grip strength with age by race/ethnicity (coefficients for rate of change by race/ethnicity, Model B). Predicted grip strength trajectories based on this model are plotted in Figure 5.1.

---- Figure 5.1 about here ----

Life Course and Life Stage Trauma

Model C (Table 5.2A) adds the traumatic life event variables to the race adjusted models. The total number of traumatic events experienced cumulatively across the life course was not associated with either mean grip strength at age 50 or rates of change in grip strength for Black, White or Hispanic men (results not shown). However, we did find that traumatic life events experienced at the critical life stage of emerging/early adulthood were associated with

differences in trajectories of grip strength by race. (Experiencing trauma during childhood or midlife was not associated with grip strength trajectories for any race/ethnic group (results not shown).) After adjusting for education (Model D, Table 5.2A) Black men who experienced one additional trauma in emerging/early adulthood had higher mean grip strength at age 50 (β= 1.66, $p<.001$) and faster rates of decline in grip strength with age (β= -.08, $p< .001$) than Black men who did not experience a traumatic event during this life stage. In contrast, the experience of traumatic events was not associated with differences in grip strength trajectories for either White or Hispanic men.

Despite starting out with a higher mean grip strength at age 50, Black men with one additional trauma underwent a steeper decline in grip strength with age. Specifically, Black men who experienced one additional traumatic event in emerging/early adulthood lose, on average, an additional .08 kg in their grip strength each year (β= -.08, $p< .001$; Model D Table 5.2A). This means that, at age 80, for example, Black men who did not experience any traumatic event have a predicted grip strength of 33.7 kg while Black men who experienced two traumatic events have a predicted grip strength of 27.4 kg—over a 6 kg difference, as shown in Figure 5.2.

---- Figure 5.2 ----

Racial differences in the effects of trauma on trajectories of grip strength have notable consequences for the observed disparities in later life grip strength by race. For example, at age 80, the predicted grip strength for a White man who experienced two traumatic events during emerging/early adulthood is comparable to a Black men who experienced no traumatic events (34.7 kg vs. 33.7 kg, respectively), indicating that even Black men who are free from the

experience of trauma during emerging/early adulthood have similar hand grip strength to White men who have experienced two traumatic events during this life stage.

Life course and Life Stage Stress

Results for models including the measures of stressful life events are presented in Models E and F (Table 5.2A). We found no association between the total number of stressful life events and either mean hand grip strength or rates of change in grip strength over time (results not shown). However, we did find that experiencing stressful life events during emerging/early adulthood was significantly associated with trajectories of grip strength, and these effects varied by race. (Stressful life events experienced during midlife were not associated with grip strength trajectories.) After adjusting for education (Model F, Table 5.2A) White men who experienced one stressful life event during emerging/early adulthood had lower mean grip strength at age 50 than White men who experienced no stressful life events ($\beta = -.78$, $p < .01$). However, similar to the findings for traumatic life events (above), Black men who reported one additional stressful life event during emerging/early adulthood had a higher mean grip strength at age 50 ($\beta = 2.4$, $p < .0001$) but faster rates of decline in grip strength with age ($\beta = -.06$, $p < .05$) than Black men reporting no stressful life events during this life stage. Extrapolating these results to age 80, Black men who experience 2 stressful life events in emerging/early adulthood have a predicted grip strength at age 80 that is 3 kg lower than Black men who do not report experiencing any stressful life events (30.3 kg vs. 33.5, respectively) and fully 4 kg lower than White men who do not report any stressful life events (34.5 kg). Predicted trajectories by race and stressful life events are plotted in Figure 5.3.

---- Figure 5.3 ----

Testing Potential Mediating Pathways

As a final step in the modeling process, we included the hypothesized mediators in the pathway between traumatic/stressful life events and grip strength, including time-varying chronic conditions, BMI, smoking status, and physical activity. Since these variables are both potential mediators and potential confounders in this longitudinal model, we report these results with caution. After entering each hypothesized mediator into both the emerging/early adulthood trauma (Model D) and stress (Model F) models (Table 5.2), we found no meaningful change in the relationship between stress and trauma on the grip strength intercept and trajectories by race/ethnicity. Specifically, the intercept and slope differences found for Black men did not change even after including these mediating/confounding variables, indicating that trauma and stress in emerging/early adulthood has a net direct effect on grip strength for Black men in later life. This also indicates that the observed association between emerging/early adulthood stress, trauma and muscle strength is not operating through the time-varying, health behaviors that were hypothesized to be on the causal pathway.

Results for Women

Descriptive Statistics

The sample characteristics for Black, White and Hispanic women are presented in Table 5.1B. Out of the 11,624 women included in the sample, 20% were Black, 67% were White and 13% were Hispanic. The average age at baseline for White women was slightly older (65.2 years) compared to Black (62.4 years) and Hispanic (62.2 years) women. Black women had higher mean grip strength (27.1 kg) compared to White women (25.7 kg) and Hispanic women (24.1 kg). Black women and Hispanic women had a higher mean BMI (31.5 and 29.6 kg/m^2,

respectively) compared to White women (27.8 kg/m$^{2)}$ and Black women had a greater prevalence of chronic health conditions at baseline (mean 2.2 conditions) compared to White and Hispanic women (mean=1.8 conditions for both groups). There were notable racial inequalities in attained education with 51% of White women having a high-school education or higher, compared to only 43% of Black women and 23% of Hispanic women. White women were also more likely to report engaging in moderate physical activity 3 times per week (80.2%) compared to 73.1% of Black women and 77% of Hispanic women. Current smoking status was roughly comparable across all three groups.

---- Table 5.1B ----

When examining the distribution of lifetime trauma, Black women reported a slightly higher mean number of traumas (mean= 1.7 events) compared to White (1.6 events) and Hispanic (1.6 events) women. Black women were more likely to report 3 or more traumatic life events (30.8%) compared to White women (25.8%) and Hispanic women (28.4% 3). Black (33.6%), White (36.4%) and Hispanic women (39.8%) were more likely to report experiencing one or more traumatic event during childhood than in emerging/early adulthood or in the midlife period. Black women also reported a higher mean number of stressful life events (mean= 1.3 events) compared to White (.85 events) and Hispanic (.96 events) women. Black women were more likely to report experiencing 3 or more stressful life events across the life course (23.4%) compared to White (12%) and Hispanic (14.3%) women ($p<.05$). When examining the timing of when these events occurred, Black (34.6%), White (25.2%) and Hispanic (25.2%) women were more likely to report experiencing stressful life events during midlife than in emerging/early adulthood.

Growth Curve Models

Results for the growth curve models for women are presented in Table 5.2B.

---- Table 5.2B ----

Unconditional Growth Model

In the unconditional growth model (Model A), the mean grip strength for women at age 50 is 29.8 kg (the intercept, $p< .0001$) and there is a significant, negative linear and quadratic time effect indicating that grip strength declines over time. Specifically, for each additional year of age, women lose, on average .2 kg of grip strength per year ($\beta=-.196$, $p<.0001$) and this decline accelerates over time (significant quadratic effect for age).

Race/Ethnicity

Model B (Table 5.2B) presents the results after adjusting for race/ethnicity. Hispanic women have significantly lower average grip strength at age 50 than White women (27.1 kg vs. 30.5 kg, respectively ($\beta= -3.4$, $p< .0001$) but experience a slower rate of decline in grip strength with age ($\beta = .094$, $p<.001$). Black women have a slightly lower mean grip strength at age 50 than White women (vs. 30.0kg vs. 30.5kg), respectively, although this difference was not statistically significant ($\beta= -.443$, $p= .27$) However, as seen from the predicted trajectories in Figure 5.4, Black women experience a slower rate of decline in grip strength with age compared to White women ($\beta =.110$, $p<.001$, Model B, Table 5.2B).

---- Figure 5.4 ----

Life Course and Life Stage Trauma

We found no association between the total accumulation of traumatic events over the life course and women's grip strength in later life (results not shown). However, we did find that traumatic events experienced in emerging/early adulthood proved to be a critical window of exposure and varied by race. While traumatic events had no effect on grip strength grip strength for either White or Hispanic women, Black women who experienced a traumatic life event over emerging/early adulthood had significantly lower levels of grip strength in later adulthood. After adjusting for education (Model D, Table 5.2B), Black women who experienced one additional traumatic event had significantly lower mean grip strength than Black women who did not experience a traumatic event ($\beta = -.69$, $p < .05$). We also tested whether lifetime and life stage stressors were associated with grip strength in women but found no significant associations.

---- Figure 5.5 ----

Testing Potential Mediating Pathways

While the association between trauma in emerging/early adulthood and mean grip strength at age 50 remained significant after adding time-varying chronic health conditions, smoking status and physical activity to the model, time-varying BMI significantly attenuated the coefficient representing the effect of trauma for Black women (Model D, Table 5.2B). After adjusting for time varying BMI, the intercept for Black women who had experienced traumatic life events in emerging/early adulthood was reduced (-.69 to -.63) and was no longer significant. This suggest that BMI is a partial explanatory factor in the relationship between early adult traumatic events and later life grip strength for Black compared to White women. However, we present these results with caution, because these variables are both mediators and confounders in the longitudinal relationship between life events and grip strength. Further work should test these

complex relationships with other analytic methods (i.e., marginal structural models) that are better equipped to deal with simultaneous mediating and confounding in longitudinal models.

5.5 Discussion

There is growing interest in the life course determinants of muscle strength in older age. While a few studies have investigated the role of early life anthropometry and socioeconomic status in differential vulnerability to muscle weakness,[107,201,202] less is known about how one's lived social experience unfolds over the life course to influence trajectories of grip strength in later life. This study is an important contribution to the literature because it not only examined longitudinal changes in grip strength over time by race/ethnicity but also considered to what extent earlier negative life events impacted grip strength trajectories in later life.

There are several key findings from this study. First, we found that life course trauma and stress experienced during emerging/early adulthood were associated with differences in levels of grip strength and rates of change in grip strength over mid to late adulthood.

Specifically, among Black men, stress and trauma experienced during emerging/early adulthood were not only related to higher mean grip strength at age 50, but also associated with steeper declines as individuals aged over time compare to White men. Second, for Black women, traumatic events during emerging/early adulthood were associated with lower mean grip strength at age 50. Third, the accumulation of traumatic and stressful events across the life course was not associated with grip strength in later life for any group. This finding supports the critical period hypothesis, whereby experiencing stressful events experienced during emerging/early adulthood may have disproportionate negative consequences for maintaining and preserving muscle strength in later age, particularly for Black men and women. Lastly, contrary to our hypothesis,

no differences in grip strength were observed for White and Hispanic men and women even after accounting for stress and trauma.

To the best of our knowledge, no studies have directly examined the relationship between life course social stress and trauma and muscle strength in later age. After considering the type and timing of the exposure, our study suggests that one's lived experience, particularly during emerging/early adulthood, is consequential for muscle health in older age. Findings from this study are consistent with previous work documenting a strong association between stress, trauma and other physical and mental health. Indeed, there is a well-established literature that has found stress and trauma experienced earlier in the life course to be associated with a host of negative health outcomes, including depression,[203] cardiovascular disease [204] and impaired immune function.[53]

The mechanism by which social stress and trauma could affect muscle strength is not well studied. However, the distinct physiologic cascade the takes place following exposure to stressful events is well documented.[53] Furthermore, exposure to chronic stress, such as those negative events that persist over time (i.e., taking care of a sick family member) or experiencing an acute, traumatic event (i.e., being the victim of a crime) are believed to be the most potent forms of stress.[54] When a stress response is activated, cortisol is released by the hypothalamic-pituitary-adrenocortical (HPA) axis. While the initial release of cortisol and other hormones is viewed as adaptive by slowly digestion and breaking down metabolic compounds in order to quickly produce energy, cortisol remains elevated the longest amount of time in the body.[54] This has been replicated over decades of research demonstrating that repeated activation of the HPA pathway is harmful to health. The proposed mechanism, increased inflammation, has grave implications for multiple bodily systems, including, but not limited to, the skeletal muscle

system.[53,54] Indeed, higher levels of interleukin-6 (IL-6), interleukin-1 receptor (IL-1R) and tumor necrosis (TNF) and C-reactive protein (CRP), all primary markers of an elevated inflammatory state, have been found to be associated with reduced muscle strength.[55,56] Based on the disproportionate burden of stressful life events experienced by Black men and women relative to Whites and Hispanics in our study, we would anticipate that the physiologic wear and tear or "weathering"[205] could be a salient mechanism leading to impaired muscle strength in later life.

While considering the individual-level, physiologic mechanisms by which stressful events "get under the skin" and lead to steeper declines in muscle strength, it is important to remember that this is only a partial explanation of the findings observed in this study. Indeed, previous scholars have noted that while accounting for non-social factors is valuable, doing so "should not preclude consideration of the integral, often antecedent ways racialization may condition disease and distributions".[206,207] Previous research on the social determinants of health, coupled with recent calls to incorporate Critical Race Theory into the realm of health disparity research,[208,209] provide a clear rationale for looking at macro, upstream factors in order to understand the structural contributors to the racial/ethnic disparities in muscle strength observed in this study.

One of the primary structural drivers of the racial and ethnic disparities observed in health operates through structural racism. Structural racism, defined as "the macro-level systems, social forces, institutions, ideologies, and processes that interact with another to generate and reinforce inequities among racial and ethnic group"[210] has insidious consequences for health.[207] A growing body of research has documented how the consequences of structural racism shape social and economic inequities that are largely produced along racial and ethnic lines.[147,211,212]

The insidious effects of structural racism on health are multidimensional and far reaching by simultaneously restricting access to a myriad of domains that include, but are not limited to, health-promoting resources such was wealth, income, safe neighborhoods, quality education and healthcare, as well as maintaining a system where socially marginalized groups lack the basic and essential resources needed to prevent and treat diseases.[213–215]

In this study, Black men and women were more likely to positively endorse items pertaining to experiences of major lifetime discrimination, a pervasive symptom of structural racism. For example, Black men were more likely to experience being denied a bank loan (20% compared to 6% of White and 10% of Hispanic men), prevented from moving into a neighborhood because the landlord or realtor refused to sell or rent you a house or apartment (12% compared to 1% of White and 2% Hispanic men) and unfairly stopped, searched, questioned physically threatened or abused by the police (34% compared to 10% of Whites and 19% of Hispanic men). These differences were also observed in Black women as well with 14% reporting being denied a loan (5% of White and 6% of Hispanic women), 9% reporting not being able to move into a certain neighborhood (1% of Whites and 2% of Hispanic women) and 11 percent endorsing unfair treatment by the police (3% of Whites and 4% of Hispanic women). We did not find differences in the grip strength trajectories by stress for White men or women. This may be due to the fact that when Whites experience unfair treatment, they are more likely to interpret the unfair treatment as an individual and not due to their particular group membership.[216]

In connecting the distal and proximal pathways stated above, we believe that the disparities observed in this study are the result of a larger structural-physiologic pathway whereby entrenched macro-level forces of structural racism that operate through stressful

experiences of discrimination, stress and trauma, lead to chronic activation of the HPA axis, which in turn lead to a wear and tear on the body, that produce declines in muscle strength for Black men and women in later life.

Consistent with a life course approach, we sought to examine whether the timing of when stressful and traumatic events occurred matters in preserving muscle strength in older age. We found that when trauma and stress were experienced during the emerging/early adulthood period, a life stage rooted in distinct transitions and the establishment of key social roles,[90,112] muscle strength was compromised in later life. In other words, trauma and stress experienced during emerging/early adulthood was associated with a faster decline in muscle strength compared to those who did not experience any traumatic or stressful events during this same period. Therefore, our results suggest that emerging/early adulthood may prove to be "critical period" in which excess exposure to stress and trauma may have far reaching and adverse consequences for muscle strength compared to other time periods, particularly for Black men and women. Our findings are consistent with past work that has found emerging/early adulthood to be a critical period for health outcomes in later life. For example, Clarke & Wheaton found that consequences of neighborhood poverty and unemployment experienced during the developmental period of adulthood (23-38 years of age), compared to other life stages, was linked to higher levels of depression in later life.[217]

A major finding in this study is that the consequences of trauma and stress were experienced differentially with regard to muscle strength in later life. Specifically, Black men and women were disproportionately impacted as steeper declines in grip strength were observed for both men and women on account of earlier negative events compared to those did not experience stressful and traumatic life events during emerging/early adulthood. Although men

who experienced one traumatic or stressful event during emerging/early adulthood had higher grip strength by the time they reached age 50, this reserve quickly eroded over time such these same Black men and women who had experienced stress and trauma earlier in the life course had markedly lower grip strength in later life compared to their non-exposed peers. Moreover, the grip strength declines observed in this study among Black men were also notable relative to the longitudinal changes in White men. In extrapolating our findings, we found that by age 80, the grip strength profile of a Black men who had experienced no stressful/traumatic events during emerging/early adulthood looked similar to White men who had experienced 2 or more stressful/traumatic events, opposite of what we could expect.

The question as to why experiencing stress and trauma would be especially consequential for Black men during emerging/early adulthood with respect to their later life grip strength is not fully understood. However, research suggests that racial disparities in health are rarely the result of sudden changes in health in later life but rather the byproduct of a long-standing, cumulative process subject to larger structural systems of racialization.[102,195] In other words, the differential vulnerability observed in this study is not due to biological differences, but rather a consequence of one's social context. Through this lens, being exposed to major life stress and trauma during emerging/early adulthood, the time in which the establishment of one's career, marriage, and parenting becomes of critical importance to future income, earnings and health status may lead to a particularly devastating consequences for Black men. That is, Black men who lack the resources and opportunities to rebound and recover due to structural factors may experience far reaching effects due to stress and trauma.[195] It would follow that the stress Black men experience associated with trauma has the potential to derail and limit future opportunities, above and beyond experiencing the same events at a different point later in the life course and it is this

heightened vulnerability that may compromise health in later life, and in this case, muscle strength.

This study has several strengths. First, to the best of our knowledge, this is the first study to investigate the association between stress and trauma and its consequences of muscle strength in older age in a racially/ethnically diverse sample of older adults. Second, the results of were obtained in a nationally representative sample of adults and can therefore be generalized to community-dwelling Black, White and Hispanic adults aged 50 years and older living in the United States. Third, we used data that considered not only what type of stressor was experienced but at what point in the life course it occurred. This enabled us to apply a life course approach in our inquiry of how stress and trauma impacts later life muscle strength. Previous studies documenting how early life exposures impact later life health have been largely been relegated to examining childhood exposures (i.e., maternal education) due to limits in the assessment of life course social experiences. Lastly, a major strength of this study was our ability to examine whether muscle strength trajectories differ by race/ethnicity and gender. Past work examining longitudinal changes in grip strength have largely focused on White populations.[17,47] Given the rapidly changing demographic makeup of older adults in the United States,[3] understanding how muscle strength changes over time across a variety of groups is essential in delaying or preventing the onset of disability, physical functioning limitations in order to maximize independence in older age.

Despite these strengths, this study is not without limitations. First, participants were asked to retrospectively recall their exposure to stressful and traumatic events throughout the life course. Thus, participants had to rely on their memory of when certain events took place, which may be subject to recall bias especially if events that occurred earlier in one's life history may be

more difficult to recall. Despite this potential limitation, previous research has found that when individuals are asked to recall the timing of past traumatic events, they do so with reasonable accuracy.[218] For example, in one study, participants were prospectively assessed via self-report as to when they experienced childhood communicable diseases, accident, hospitalizations, surgeries and other illnesses, and by age 50, 85% of the these events were correctly recalled.[219]

Second, as with any longitudinal study of older adults, we cannot overlook the potential for selective survival bias in our sample, particularly among older Black and Hispanic men. Previous research estimates that in the HRS, only 40 percent of Black men born between 1931 and 1941 live to age 60.[132] Additionally, because this study did not include those whom are homeless or incarcerated, the results presented in this study a likely an underestimate of the true association since those who were not enrolled/died before age 50 are likely to be the most disadvantaged. Lastly, we were unable to adequately adjust for both mediators and confounders as many of the hypothesized mediators in this study could also be considered time-varying confounders. Future work in this area should consider other analytic techniques that can accommodate both mediator-confounders in order to obtain controlled estimates that are able to tease apart the independent effects of mediator and confounding in a longitudinal setting.

The results of this study underscore the importance of considering how structural systems of inequality, as experienced through life course exposure to stress and trauma, lead to steeper declines in muscle strength, particularly among older Black men and women. Moreover, we believe these findings are a call to action for future research in this area by focusing less on individual-level risk factors of muscle strength in older life and begin placing greater emphasis in the inquiry of how one's social context shapes trajectories of muscle strength as adults age over time.

5.6 Tables and Figures

Table 5.1A Baseline descriptive statistics for Men in the Health and Retirement Study, N=8,847 (2006-2014).

	Black Men (n=1506)	**White Men (n=6200)**	**Hispanic Men (n=1127)**
Variable	**Mean* (SD)**	**Mean* (SD)**	**Mean* (SD)**
Age (in years) (range 46-99)	61.1 (9.0)	63.5 (10.3)	61.1 (8.9)
Grip Strength (kg)	42.1 (10.1)	43.6 (9.8)	39.8 (9.2)
Chronic Conditions (Range: 0-8)	1.9 (1.5)	1.8 (1.5)	1.7 (1.4)
Body Mass Index (kg/m^2)	28.6 (5.5)	28.5 (5.1)	29.2 (5.1)
	%*	**%***	**%***
Education			
<HS	57.7	41	71.8
≥ HS	42.3	59	28.2
Physical Activity			
Inactive/Sedentary	16.9	14.7	15
Active	83.1	85.3	85
Smoking			
Current	19.1	13.5	14.6
Former	46	48.7	49.1
Never	34.8	37.8	36.4
Traumatic Events Across Life Course (range 0-11)			
0	24.5	22.3	24
1	21.3	26.8	25.2
2	21.2	21.4	18
3	13.2	14.8	13.4
4	11.2	7.9	8
5+	8.6	6.8	10.8
Stressful Events Across the Life Course (range 0-11)			
0	30	44	40.5
1	22	23.2	23.5
2	15.7	13.6	14.1
3	10.5	9.2	8.6
4+	21.8	10	13.4
Traumatic Events Across Life Stages			
Early childhood trauma (0-17 years)			
0	50.3	53.2	49.6
1	30.3	29.9	29.8
2	14	12.2	13,8

3+	5.5	4.8	6.8
Emerging adulthood trauma (18-42 years)			
0	69.3	69.3	69.4
1	21.4	21.8	22.8
2	6.9	6.9	6.5
3+	2.5	2.1	1.3
Midlife trauma (43-67 years)			
0	68	65.8	68.1
1	21.2	24.4	19.5
2	7.2	7.4	9.1
3+	3.6	2.4	3.3
Stressful Events Across Life Stages			
Emerging adulthood stress (18-42 years)			
0	70.4	80.4	82.8
1	17.7	14.2	9.6
2	7.7	4.4	6.2
3+	4.2	1	1.4
Midlife stress (43-67 years)			
0	60.7	68	63.5
1	20.6	17.2	19.2
2	9.6	7.3	8.5
3+	9	7.4	8.7

*Weighted mean and percentages

Table 5.2A Growth curve models for hand grip strength in Men in the Health and Retirement Study (N=8,847), 2006-2014.

	Unconditional Growth Model	**+Race/ Ethnicity**	**+ Trauma in Emerging/Early Adulthood**	**+Trauma and Education**	**Stress in Emerging/Early Adulthood**	**+ Stress and Education**
	Model A	Model B	Model C	Model D	Model E	Model F
Intercept	48.58***	50.27***	50.39***	50.63***	50.64***	50.89***
Race/Ethnicity						
Blacks		-3.56***	-3.39***	-3.26***	-3.89***	-3.38***
Hispanics		-4.89***	-4.67***	-4.43***	-5.13***	-4.88***
Education						
≤HS[a]				-0.71***		-0.701***
Traumatic Events			-0.013	-0.024		
Trauma*Black			1.7**	1.66**		
Trauma*Hispanic			-4.67***	-0.412		
Stressful Events					-.764**	-0.779***
Stress*Black					2.42***	2.40***
Stress*Hispanic					1.09	1.04
Rate of Change						
Age	-0.308***	-0.339***	-.34***	-.336***	-.347***	-.342***
Age2	-.007***	-.007***	-0.007***	-.007***	-.007***	-.007***
Race/Ethnicity						
Blacks*Age		0.024	-0.004	-0.004	0.009	0.009
Blacks*Age^2		0.002	0.002	0.003	0.002	0.002
Hispanics*Age		-0.09	-0.082	-0.086	-0.061	-0.066
Hispanics*Age^2		0.003	0.032	0.002	0.002	0.002
Traumatic Events						
Trauma*Age			0.007	0.007		
Stressful Events						
Stress*Age					0.016	-0.014

Trauma & Race/Ethnicity						
Trauma*Black*Age			-.08**	-.081**		
Trauma*Hispanic*Age			0.032	0.031		
Stress & Race/Ethnicity						
Stress*Black*Age					-.063*	-.062*
Stress*Hispanic*Age					-0.023	-0.021
Goodness-of-Fit Statistics						
BIC	167264.4	166857.7	145419.7	14515.1	14.5549.7	145545.2
Within Person Variance	13.04	13.01	13.25	13.25	13.25	13.26
Pseudo R2		0.23	0.02	0.02	0.02	0.02

* p<.05

** p<.01

*** p<.001

[a] Reference is High School degree or higher

Figure 5.1 Grip strength growth curve trajectories for Men by Race/ethnicity in the Health and Retirement Study (N=8,847), 2006-2014.

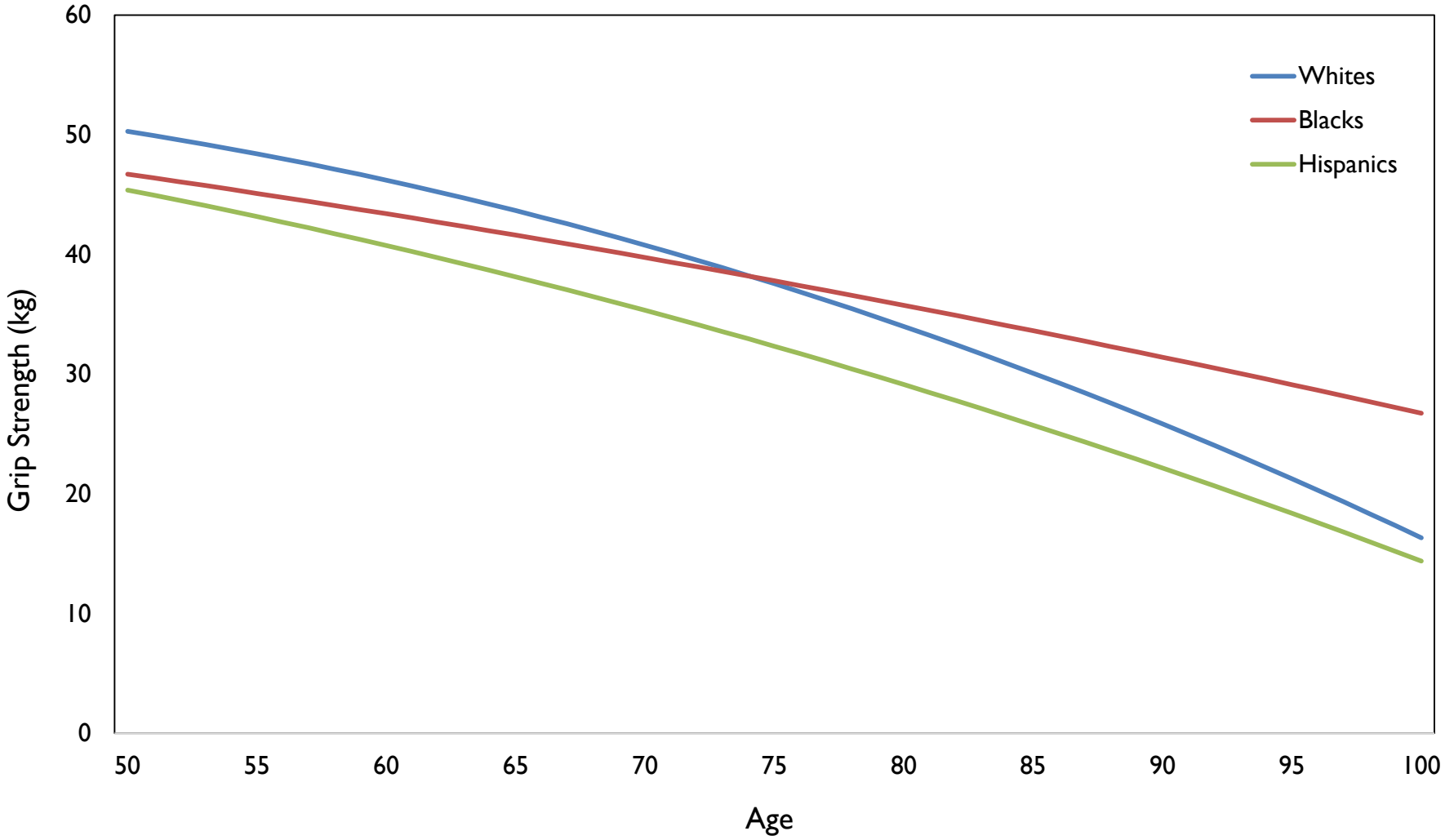

Figure 5. 2 Grip strength growth curve trajectories for Men by Race/ethnicity and Levels of Traumatic Events in the Health and Retirement Study (N=8,847), 2006-2014.

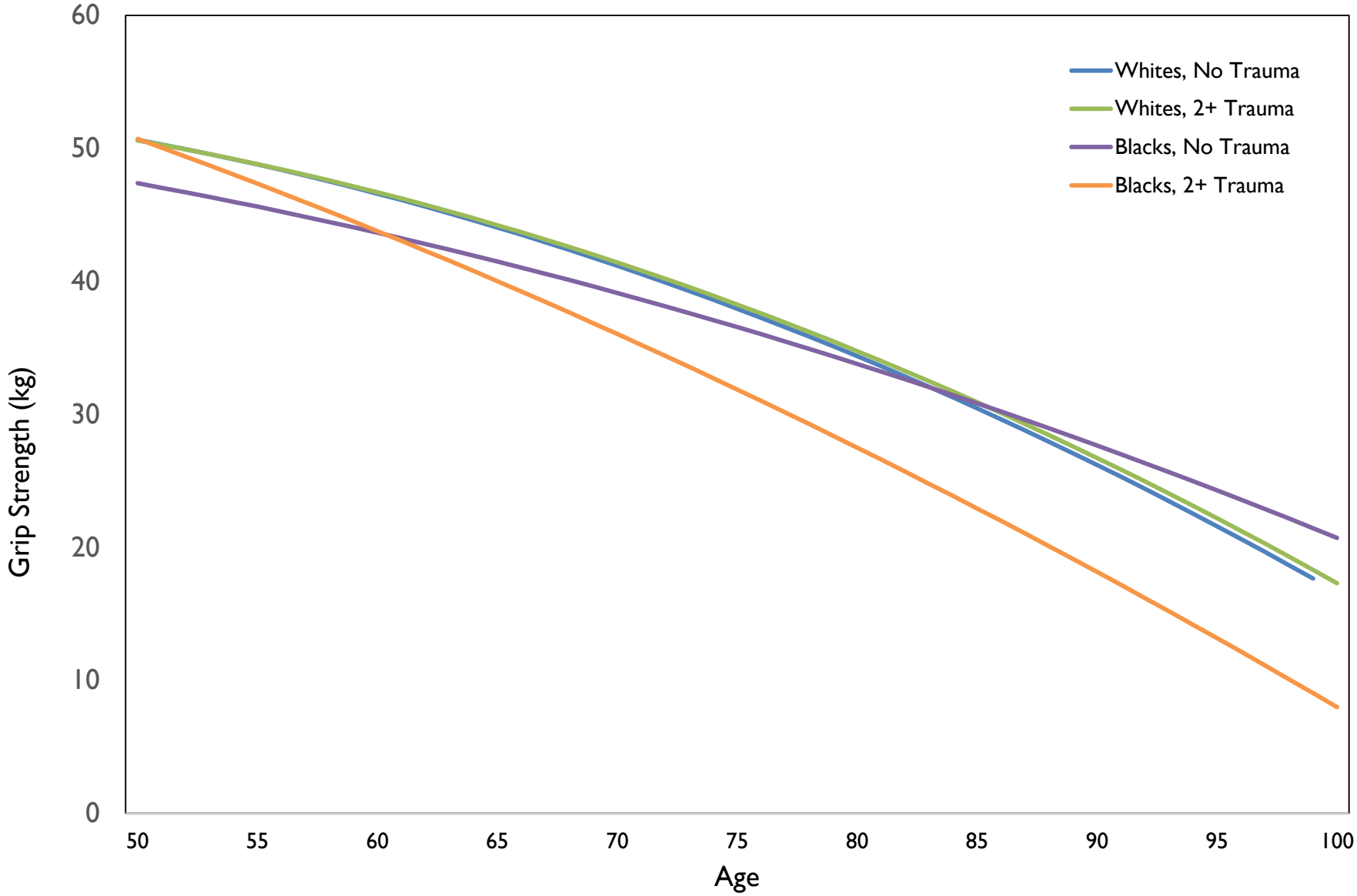

Figure 5. 3 Grip strength growth curve trajectories for Men by Race/ethnicity and Levels of Stressful Events in the Health and Retirement Study (N=8,847), 2006-2014.

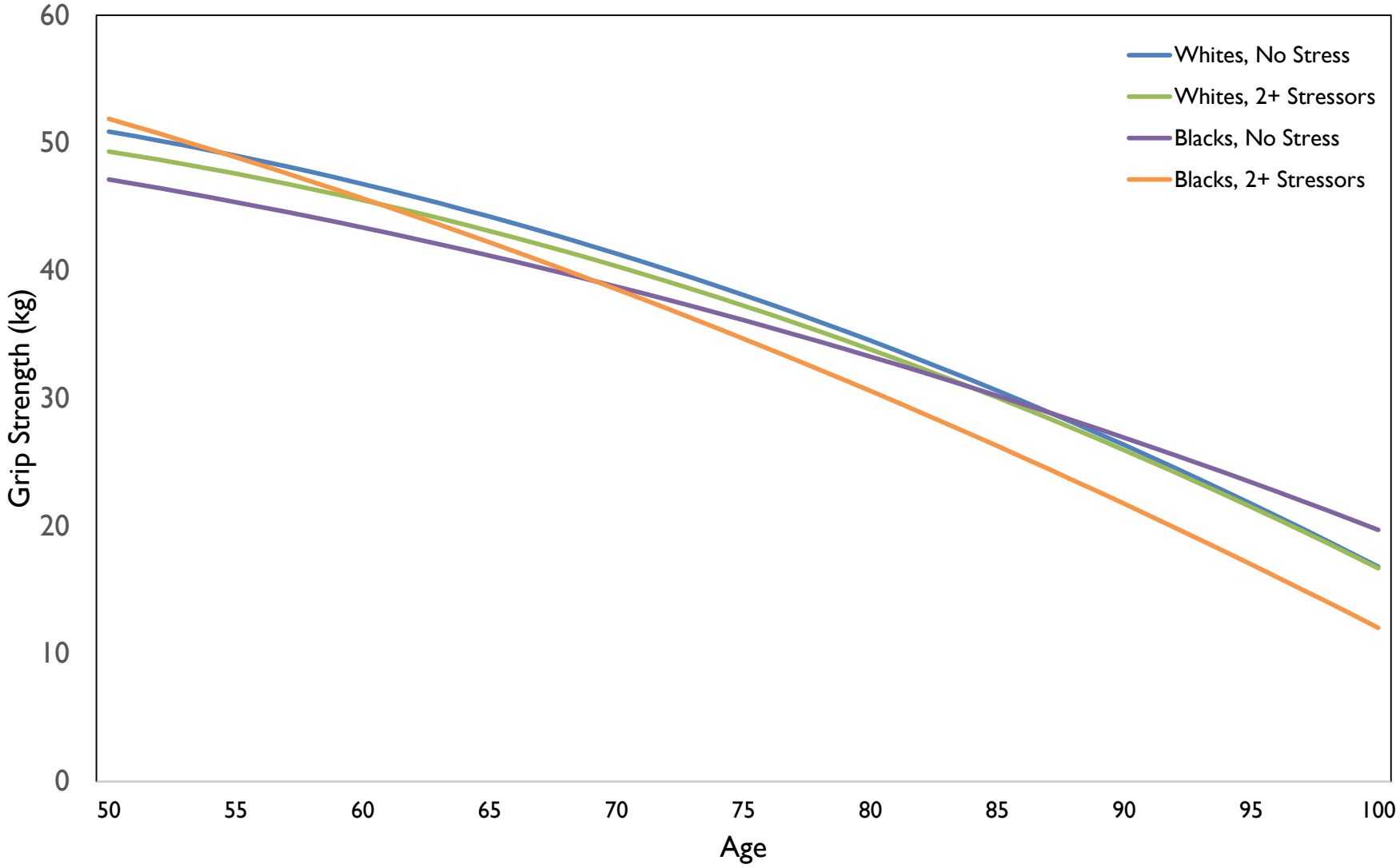

Table 5.1B Baseline descriptive statistics for Women in the Health and Retirement Study (N=11,624), 2006-2014.

Variable	Black Women (n=2,354) Mean* (SD)	White Women (n=7,797) Mean* (SD)	Hispanic Women (n=1,458) Mean* (SD)
Age (in years) (range 46-99)	62.4 (9.6)	65.2 (10.7)	62.2 (9.4)
Grip Strength (kg)	27.1 (6.9)	25.7 (6.5)	24.1 (5.9)
Chronic Conditions (Range: 0-8)	2.2 (1.4)	1.8 (1.4)	1.8 (1.4)
Body Mass Index (kg/m^2)	31.5 (7.3)	27.8 (6.2)	29.6 (6.4)
	%*	%*	%*
Education			
<HS	57.3	48.6	77
≥ HS	42.8	51.4	23
Physical Activity			
Inactive/Sedentary	26.9	19.8	23.4
Active	73.1	80.2	76.6
Smoking			
Current	14.2	12.5	9.1
Former	36.8	37.6	35.2
Never	49	49.9	55.7
Traumatic Events Across Life Course (range 0-11)			
0	28.2	26	29.5
1	22.6	28	21.7
2	18.4	20.2	20.5
3	15.8	13.1	15
4	7.3	7.4	6.6
5+	7.7	5.3	6.8
Stressful Events Across the Life Course (range 0-11)			
0	40.3	55	51.5
1	22.2	21.5	22.1
2	14.2	11.5	12.2
3	10.2	6.4	7.3
4+	13.2	5.6	7
Traumatic Events Across Life Stages			
Early childhood trauma (0-17 years)			
0	66.4	63.6	60.2
1	23.5	25.6	27.9
2	8.1	7.9	9.3
3+	2	2.9	2.6
Emerging adulthood trauma (18-42 years)			
0	73.2	74.5	64.4

1	19	18.4	24.2
2	6.5	5.2	8.7
3+	1.3	1.8	2.8
Midlife trauma (43-67 years)			
0	66	64.4	70.3
1	24.7	24.1	20.2
2	7.2	8.7	6.1
3+	2	2.8	3.3
Stressful Events Across Life Stages			
Emerging adulthood stress (18-42 years)			
0	82.2	87.8	90.8
1	12.7	9.3	7.6
2	3.3	2.1	1.1
3+	1.8	0.8	0.5
Midlife stress (43-67 years)			
0	65.4	74.8	74.8
1	18.7	13.7	11.5
2	8.4	5.9	8
3+	7.5	5.6	5.7

*Weighted percentages

Table 5.2B Growth curve models for handgrip strength in Women in the Health and Retirement Study (N=11,624), 2006-2014.

	Unconditional Growth Model	**+Race/Ethnicity**	**+ Trauma in Emerging/Early Adulthood**	**+Trauma and Education**
	Model A	Model B	Model C	Model D
Intercept	29.84***	30.47***	30.68***	31.91***
Race/Ethnicity				
Blacks		-0.443	-0.131	-0.072
Hispanics		-3.38***	-3.59***	-3.42***
Education				
≤HS[a]				-.566***
Trauma During Emerging Adulthood			-0.077	0.108
Trauma*Black			-0.661*	-0.689*
Trauma*Hispanic			0.009	0.001
Rate of Change				
Age	-0.196***	-0.238***	-.246	-.247***
Age2	-.004***	-.003***	-.003	-.003***
Race/Ethnicity				
Blacks*Age		.110***	.117***	.113***
Blacks*Age^2		.002**	-.002**	-0.002*
Hispanics*Age		0.094**	.139***	.129**
Hispanics*Age^2		-0.001	-0.003**	-.003*
Trauma Events				
Trauma*Age			-0.077	0.001
Trauma & Race/Ethnicity				
Trauma*Black*Age			0.026	-.027
Trauma*Hispanic*Age			-0.013	-0.013

Goodness-of-Fit Statistics				
BIC	199489.7	199196.4	179686.7	179688.6
Residual	6.354	6.352	6.47	6.48
Pseudo R2		0.00	0.02	0.02

* p<.05
** p<.01
*** p<.001
[a] Reference is High School degree or higher

Figure 5. 4 Grip strength growth curve trajectories for Women by Race/ethnicity in the Health and Retirement Study (N=11,624), 2006-2014.

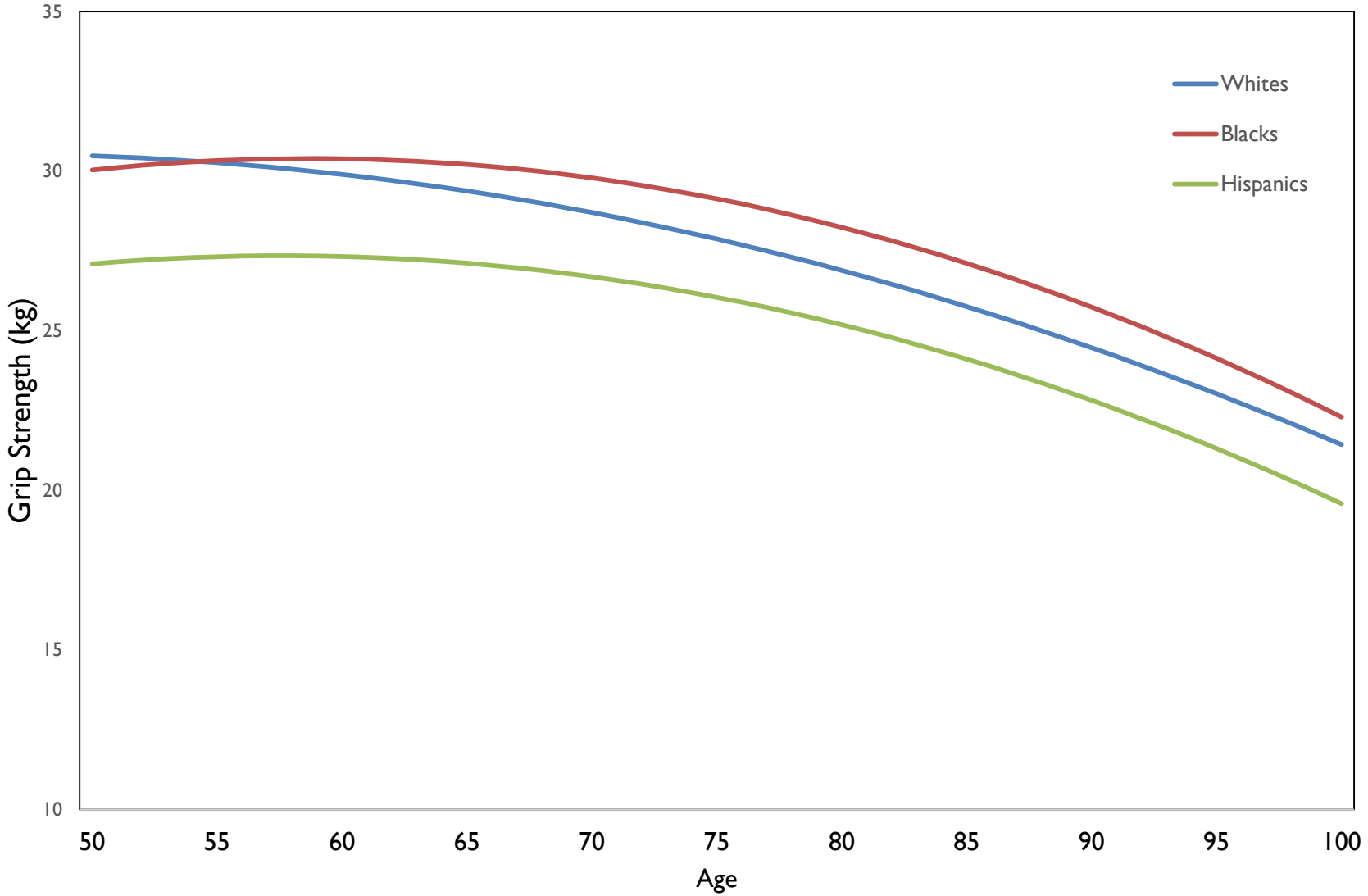

Figure 5. 5 Grip strength growth curve trajectories for Women by Race/ethnicity and Levels of Stressful Events in the Health and Retirement Study (N=11,624), 2006-2014.

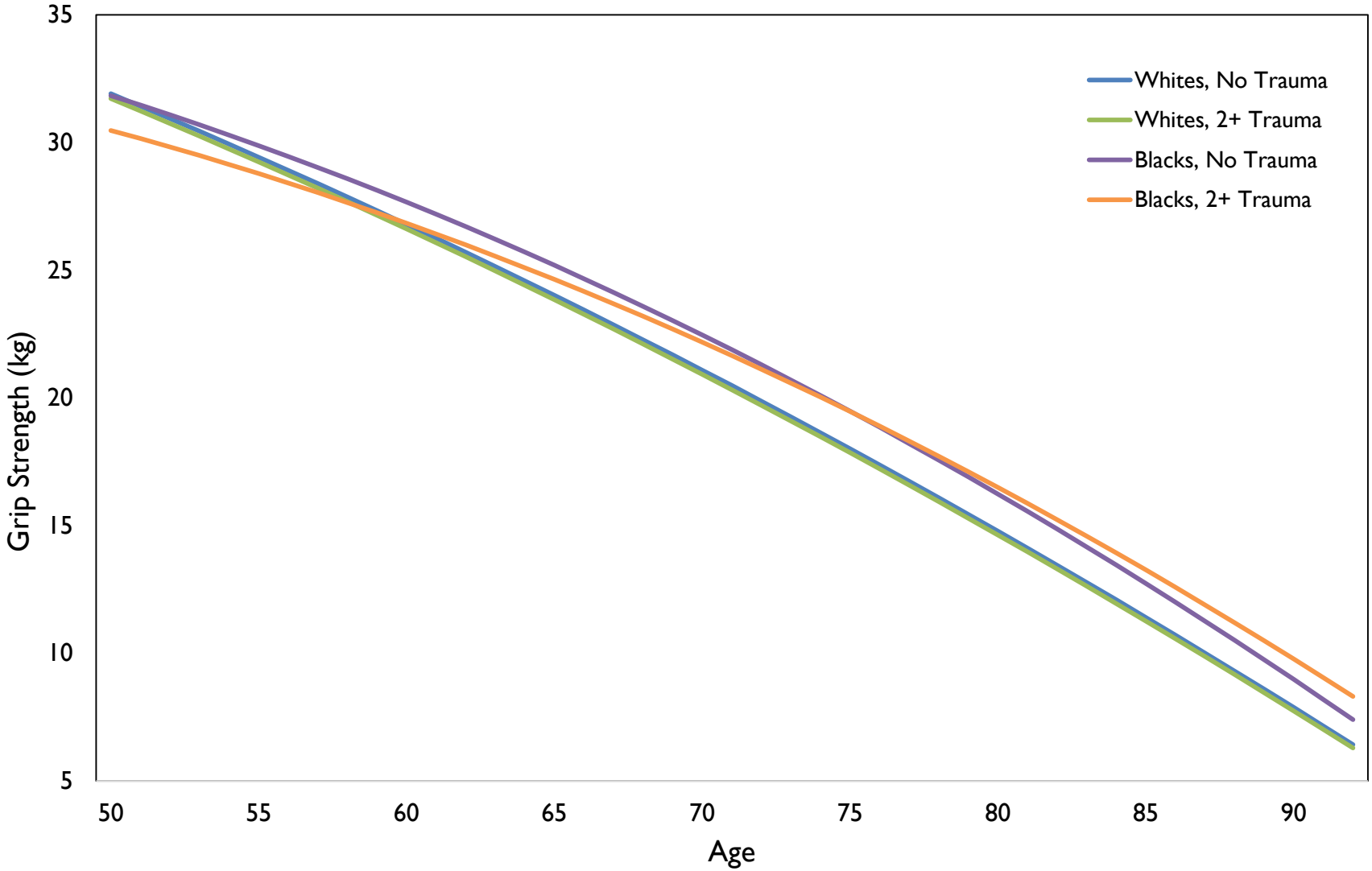

Table 5.3 A Traumatic Life Event Questions from the HRS Participant Leave-Behind Questionnaire

For each of the following events, please indicate whether the event occurred AT ANY POINT IN YOUR LIFE. If the event did happen, please indicate the year in which it happened MOST RECENTLY. (Mark (X) one box for each line. If "Yes", indicate which year.)

1. Has a child of yours ever died?
2. Have you ever fired a weapon in combat or been fired upon in combat?
3. Has your spouse, partner, or child ever been addicted to drugs or alcohol?
4. Have you ever been in a major fire, flood, earthquake, or other natural disaster?
5. Did you ever have a life-threatening illness or accident?
6. Were you the victim of a serious physical attack or assault?
7. Did your spouse or a child of yours ever have a life-threatening illness or accident?

For this next set of events, please think about your childhood growing up, BEFORE YOU WERE 18 YEARS OLD. (Mark (X) one box for each line.)

8. Before you were 18 years old, did you have to do a year of school over again?
9. Before you were 18 years old, did either of your parents drink or use drugs so often that it caused problems in the family?
10. Before you were 18 years old, were you ever physically abused by either of your parents?
11. Before you were 18 years old, were you ever in trouble with the police?

Table 5.3 B Stressful Life Event Questions from the HRS Participant Leave-Behind Questionnaire.

For each of the following events, please indicate whether the event occurred AT ANY POINT IN

YOUR LIFE. If the event did happen, please indicate the year in which it happened MOST

RECENTLY. (Mark (X) one box for each line. If "Yes", indicate which year.)

CHAPTER 1. At any time in your life, have you ever been unfairly dismissed from a job?

CHAPTER 2. Have you ever been unfairly denied a promotion?

CHAPTER 3. Have you ever been unfairly prevented from moving into a neighborhood because the landlord or a realtor refused to sell or rent you a house or apartment?

CHAPTER 4. For unfair reasons, have you ever not been hired for a job?

CHAPTER 5. Have you ever been unfairly stopped, searched, questioned, physically threatened, or abused by the police?

CHAPTER 6. Have you ever been unfairly denied a bank loan?

Now please think about the LAST 5 YEARS and indicate whether each of the events below occurred. If the event did happen, please indicate the year in which it happened MOST RECENTLY. (Mark (X) one box for each line. If "Yes", indicate year.)

CHAPTER 7. Have you involuntarily lost a job for reasons other than retirement at any point in the past five years?

CHAPTER 8. Was anyone else in your household unemployed and looking for work for longer than 3 months in the past five years?

CHAPTER 9. Have you moved to a worse residence or neighborhood in the past five years?

CHAPTER 10. Have you been unemployed and looking for work for longer than 3 months at some point in the past five years?

CHAPTER 11. Were you robbed or did you have your home burglarized in the past five years?

CHAPTER 6. Conclusions

6.1 Summary and Implications of Main findings

There is increasing recognition that muscle strength, as measured by hand grip strength, is an important and independent indicator of future negative health outcomes. The muscle health field is currently undergoing a shift as it begins to embrace the utility of handgrip strength, as opposed to muscle mass, as a primary indicator of muscle weakness and even sarcopenia. This is due to the fact that not only is grip strength a reliable proxy of total body muscle strength, but it is also an easy and cost-effective tool to assess muscle health in both clinical and epidemiologic settings to identify those most at risk for adverse health consequences. However, despite this recent evolution in promoting the use of handgrip strength in the assessment of muscle weakness, there is currently no agreed upon standard as to how best to measure muscle weakness at the population level. As a result, the long-term health outcomes and life course social determinants of muscle strength using representative, longitudinal data remain poorly understood.

The primary goals of this dissertation were to: (1) chart new territory for muscle health screening at the population level; (2) ascertain the clinical parameters of muscle weakness across the diversity of the US older adult population; (3) determine the impact of weakness on disability and premature mortality; (4) identify the life course determinants of muscle weakness and how

they impact trajectories of grip strength in later life; and, lastly (5) to provide critical information that can be used to influence policy decision-making to address much needed interventions for those most at risk. To that end, the findings presented in this dissertation advance our knowledge in each of these goals in order to improve muscle health in both the clinical setting and at the population level.

In Chapter 2, we addressed an ongoing debate regarding how best to measure muscle weakness and whether differences exist in a diverse sample of older adults. Up until this study was conducted, the examination of muscle weakness had been largely unexplored across various sub-populations since previous research had failed to include non-White populations in the quest for consensus surrounding the definition of muscle weakness. Additionally, the majority of studies previously conducted had not utilized nationally representative data, which is imperative when seeking to make clinical and policy recommendations for older Americans.

Our study findings indicated that a one-size-fits-all approach in measuring weakness may not be appropriate as CART models identified different cutpoints for clinical muscle weakness by race/ethnicity in addition to gender. When estimating the prevalence of muscle based on these cutpoints, we found that burden of muscle weakness was high across all sub-groups, although Black men and women were disproportionately affected. Fifty-five percent of men and 47% of women were classified as weak. The proportion of weakness was even higher among Blacks with 57% of men and 88% of women being classified as weak.

The results of this study have important implications for both clinical and epidemiologic practice. Given the emerging burden of weakness at the population level, the use of nationally representative data provides a critical first step in informing screening efforts to identify

individuals who may be a greatest risk, and ultimately, for determining where best to direct preventive interventions. Additionally, the results generated from this study are the first to address an important and stark health disparity of weakness among Black Americans, a group that has been largely overlooked in the muscle weakness literature, despite being at greater risk for physical functioning deficits and disability in later life.[130] Therefore, the findings presented in Chapter 2 significantly moves the field forward in identifying cutpoints for Blacks while simultaneously shedding light on emerging health disparities that, if left untreated, could potentially lead to a disproportionate burden of disability among older Black Americans. These findings also emphasize the importance of working with data that reflects the diverse, older adult population.

In Chapters 3 and 4, we applied the muscle weakness cutpoints generated from Aim 1 to examine the long-term health consequences of muscle weakness. We undertook two separate analyses to investigate whether muscle weakness was associated with disability dynamics and premature mortality. Additionally, since we defined baseline weakness based on the cutpoints established in the first aim, we were seeking to test the validity of the cutpoints in predicting long-term health outcomes in an ethnically diverse and nationally representative dataset.

When examining the association between muscle weakness and disability dynamics in Chapter 3, we found that, compared to non-weak individuals, the odds of experiencing an onset of ADL disability was 54% higher among weak individuals. We also found that the odds of experiencing a progression in physical disability status was more than two times higher for weak individuals compared to non-weak individuals at baseline across a 2-year period. The results generated from this aim are a major contribution to the literature since the majority of existing studies examining the longitudinal consequences of muscle weakness have used a dichotomous

definition of disability (i.e., presence/absence). This aim extends past work by employing a deeper examination of muscle weakness by exploring the onset, persistence and progression of disability outcomes, which has not been done before in a nationally representative, diverse sample of older Americans.

The results from this study are important for several reasons. First, these findings provide support for the prognostic utility of the population-derived muscle weakness cutpoints identified as identified Aim 1 (Chapter 2). These data have implications for public health screening and intervention efforts cannot be fully realized until clinical and epidemiologic communities coalesce around standardized cutpoints to identify individuals who may be a greatest risk. Second, by examining the development of disability onset, progression and persistence of disability we found that muscle weakness may in fact influence the pace of disability. This also has important implications for older adults since previous research has shown that disability onset and progression are associated with increased risk of hospitalization,[162] institutionalization,[163] and mortality.[164] Finally, our results provide public health support for tailoring interventions to each individual's unique dynamic disability status in an effort to prevent steeper declines as individuals' age.

We also examined whether the muscle weakness cutpoints from Aim 1 were associated with premature mortality in Chapter 4. Specifically, we used the cutpoints to determine weakness status at baseline and examined whether weak individuals were more likely to die earlier, compared to non-weak individuals across a 9-year period. In this study, we showed that muscle weakness, as indexed by the validated thresholds of handgrip strength in Aim 1, was strongly associated with early mortality, even after accounting for other known risk factors. Across a 9-year follow-up period with time-varying measures of weakness, older adults classified as weak

were 50% more likely to die earlier compared to those who were not weak, even after adjusting for other time-varying risk factors.

The results from this study provided several important insights. First, muscle weakness, as defined by our cutpoints, is associated with long-term mortality. In other words, weak individuals are more likely to die earlier compared to those who are non-weak. Therefore, our data make a strong case for clinicians to incorporate handgrip assessments into medical practice for screening and identifying at risk older individuals. Second, since mortality is an important public health outcome that indicates how well the population is fairing, these results should not be taken lightly given the rapidly growing older adult population. The high prevalence of obesity combined with lower physical activity levels among Baby Boomers indicates that the proportion of weak individuals could increase exponentially in the coming years, which could potentially translate into an increase in premature mortality due to muscle weakness. As a result, reducing the burden of muscle weakness across individuals to improve population health is of critical importance.

In Chapter 5, we examined whether stress and trauma experienced across the life course were associated with grip strength trajectories in later life. In addition, we also tested whether the timing of when these stressful and traumatic events occurred were associated with changes in grip strength over time. Several important findings emerged from this study: First, life course trauma and stress experienced during emerging/early adulthood was associated with both mean grip strength at age 50 and trajectories of grip strength over time. Specifically, among Black men, stress and trauma experienced during emerging/early adulthood was not only related to higher mean grip strength at age 50, but also associated with steeper declines as individuals aged over time compare to White men. Second, for Black women, traumatic events during

emerging/early adulthood were associated with lower mean grip strength at age 50. Third, the accumulation of traumatic and stressful events across the life course was not associated with grip strength in later life for any group. This finding supports the critical period hypothesis, whereby experiencing stressful events experienced during emerging/early adulthood may have disproportionate negative consequences for maintaining and preserving muscle strength in later age, particularly for Black men and women.

The results of this study have several important implications. First, since we examined handgrip strength as a continuous variable instead of relying cutpoints validated in a 65+ sample, we were able to include younger individuals into this analysis whom had previously been excluded. This enabled us to expand our line of inquiry to examine mean grip strength at age 50 and how grip changes over time during the critical transition from midlife to older age. Our results provide support for studying muscle weakness earlier in the life course in order to reduce and even avoid rapid declines in muscle strength in later life. Since it is estimated the declines in muscle start at around age 30 and accelerate after age 50,[19,220] implementing interventions to preserve muscle during this time period are critically important. Second, our findings underscore the importance of considering how structural systems of inequality, as experienced through exposure to stress and trauma, lead to steeper declines in muscle strength, particularly among older Black men and women. While there is well established literature linking structural racism to cardiovascular disease, blood pressure, premature birth, and a host of other negative health outcomes,[207,211,215] to the best of our knowledge no studies have examined how structural racism and inequality, through exposure to stress and trauma, get the under the skin *and into the muscle* to impact trajectories of muscle strength over time. Thus, the findings presented in this aim have

important implications for the muscle weakness field and represent an important new avenue for research.

6.2 Strengths and Limitations

While this dissertation is at the forefront in our understanding of muscle weakness among older adults, it has several important limitations that warrant discussion. First, we derived cutpoints for clinical muscle weakness based on having a slow gait speed (less than 0.8 meters per second). While this outcome was used by the FNIH and has been shown to be independently associated with early mortality,[139] it is limited on several fronts. In Aim 1 (Chapter 2), Black men and women were more likely to be overweight/obese which would translate into a slower walking speed since these individuals have more mass to move. This may account for the unexpected paradox that, despite Black men and women having a higher mean grip strength, there were more likely to be clinically weak based on the cutpoints, which is opposite to what we would expect. Given the high prevalence of obesity and slow walking speed, it is unclear if slow walking speed is the right calibrating variable across various sub-populations, particularly among those who have a higher prevalence of obesity. Since the FNIH proposed cutpoints that based on non-representative, pooled data, more research is needed regarding the application of different calibrating variables using diverse, representative samples and how this affects cutpoints for muscle weakness across various sub-groups.

Second, as an extension to the previous point, another limitation of this dissertation is that we derived cutpoints for muscle weakness among older adults aged 65+ years. As a result, we were only able to include samples that were aged 65 years and older when examining the consequences of muscle weakness in Chapter 3 and 4. While these cutpoints are an important contribution to the literature since they were derived in a nationally representative sample and

examined differences by gender and race/ethnicity, we were limited in our ability to derive cutpoints among younger adults because walking speed was only collected among individuals aged 65+ years. Indeed, the results from Chapter 5 coupled with a growing literature indicating that midlife is a critical time for intervention,[14,221] underscores the importance of considering younger populations in the study of muscle weakness.

Third, handgrip strength is a reliable proxy for total body muscle strength[44] and is simple, cost-effective measure to use, however, it is note routinely assessed in the clinical setting. The Centers for Medicare and Medicaid Services (CMS) Clinical Quality Measures, which specifies the recommended core measures for adult recipients of both Medicare and Medicaid, has not recommended the assessment of muscle strength as part of their priority health care improvement goals. And, when grip strength is assessed, there is wide variability in the protocol used to assess weakness with respect to numerous variables, including, but not limited to, body position (wrist, forearm, elbow, shoulder), posture, effort, encouragement, and the type of dynamometer used, for example.[222] Despite this limitation, the results presented in this dissertation, which utilized hand grip strength from the HRS, has a detailed protocol that is consistent with other large-scale epidemiologic studies that have also collected grip strength data.[62]

Lastly, an inherent limitation of conducting research in older adult populations is the potential for selective survival. Selective survival poses a threat to internal validity if attrition is systematic or related to the outcome of interest. Since we excluded those who are homeless, incarcerated or in a nursing home in Chapters 2-5, and only included those age 65 years and older (Chapters 2, 3, &4), selective survival may be at play. This may be especially problematic in the estimates obtained for Blacks because of the reduced life expectancy compared to Whites.[223] Therefore, we would expect that the results presented in each of these aims are likely

an underestimate of the true association since individuals who are excluded or die before the inclusion age are more likely to be sicker, have higher rates of disability and represent the most disadvantaged.

This dissertation has several strengths. First, the results presented in this dissertation utilized data from the Health and Retirement Study (HRS). The HRS is the longest running nationally representative, longitudinal study of Americans aged 50 years and older. Therefore, the research findings generated from this dissertation can be generalized to older Americans aged 65 years and older (and 50 years and older in Chapter 5) since the study sample is nationally representative. This is a particularly important strength since previous research examining muscle strength has tended to rely on small-scale, clinical datasets.

Second, we uniquely conceptualized both exposure and outcome variables as demonstrated in several chapters. For example, in Chapter 3, we employed a dynamic definition of disability status that sought to capture the fluidity of physical limitations in activates of daily living. Previous research investigating disability and muscle weakness have relied on a static definition of disability that does not reflect the changing nature of physical functioning over time. Similarly in Chapter 5, we examined stress and trauma as a primary exposure in investigating its association with muscle strength in later life. While accounting for this social exposure was novel in and of itself, we also applied a life course approach to our understanding of one's lived experience by incorporating at what point in the life course these exposures were experienced. To the best of our knowledge, no studies have investigated life course exposure to stress and trauma and its impact on muscle strength in later life.

Third, while the incorporation of grip strength in routine practice remains a formidable challenge, the application of handgrip strength in both the clinical and epidemiologic setting is a major strength to study of muscle weakness. Hand grip strength has been shown to be cost-effective, reliable proxy for total body muscle strength that can be easily administered in the clinical setting [43,174]. Compared to other measures of muscle weakness such as, body impedance analysis, DXA and muscle biopsy, a dynamometer is a small, simple and inexpensive device that is both easy to administer and non-invasive [43].

6.3 Public Health Significance and a New Path Forward

This dissertation builds upon previous work that has shown muscle weakness to be an important determinant of physical health in later age. However, the collective results generated from this dissertation extend well beyond this conclusion and lay the groundwork for a new path forward in the study of muscle strength. This has been accomplished on several fronts. First, we incorporated the measurement of dynamic processes in relation to muscle weakness. In Chapter 3, we examined dynamics of disability and how muscle weakness influenced the onset, progression and persistence ADL limitations in a longitudinal setting. In Chapter 4, we examined the association between time-varying muscle weakness and mortality rather than relying on baseline muscle weakness. And, in Chapter 5, we focused on the dynamic timing by which stressful and traumatic life experiences occur to influence muscle strength trajectories in later life by accounting for different stages across the life course.

Second, this dissertation charts a new path forward by bringing grip strength research into the real world. Instead of relying on highly selective clinical samples, we utilized data from a nationally, representative sample of Black and White older adult adults aged 65 years and older in Chapter 2. Thus, the cutpoints generated from this aim have major public health significance

because they can be applied to older American adults as opposed to a select few. Additionally, the cutpoints require no special calculations or norming and could therefore be readily implemented within the clinical setting.

Third, and perhaps of most importance, this dissertation brings a social epidemiologic lens to the study of muscle strength. This is an essential step forward because, to date, most work conducted within the study of muscle weakness has predominately relied on risk-factor epidemiology and focused on individual level interventions without acknowledging the larger structural forces that shape risk to muscle weakness at the population level. This approach is problematic because individuals are embedded within populations and therefore the "risk of illness cannot be considered in isolation from the disease risk of the population in to which she belongs".[224] Therefore, the integration of a social epidemiology combined with a traditional epidemiologic approach enabled us to identify the distribution of muscle weakness at the population level (Chapter 2), identify its health outcomes (Chapters 3 and 4) and consider the social conditions that drive declines in muscle strength in later life (Chapter 5).

6.4 Future Directions

The penultimate chapter in this dissertation serves as a fertile jumping off point for future research. While we present a compelling case for considering why the social context is important for the preservation of muscle strength in later life, the underlying mechanism by which this occurs remains unknown. A closer examination of the causal pathway that explores the complex relationship between one's social context and muscle weakness in older age is warranted.

Neighborhood residence has been shown to be a salient explanatory mechanism in understanding the pathway between socioeconomic conditions experienced in childhood and

later life health outcomes because of the social and physical attributes that effect individual health.[225,226] The neighborhood built environment is associated with obesity,[227] hypertension,[228] coronary heart disease[229] and mobility disability.[230] Therefore, one possible pathway of future exploration is examining the "long arm" [218,231] of childhood SES and how it shapes where one lives, the neighborhood level conditions and resources individuals are exposed to and the subsequent health behaviors that emerge on account of ones surroundings, and, ultimately how it influences who may be at greatest risk for muscle weakness as one ages.

This has never been examined as research on muscle weakness has almost exclusively focused on later adulthood, at a time when it becomes a clinical condition and interventions may be less effective. Future work should focus on examining how early life childhood SES, as mediated through cumulative exposure to neighborhood factors and health behaviors, influence the onset of muscle weakness in early and midlife adulthood in order to delay or prevent the onset of muscle weakness in older age.

6.5 Conclusion

I hope the results from my dissertation research can be utilized to advance clinical research while helping to identify the underlying mechanisms and structural processes of muscle weakness in order to improve muscle health at the population level. It is also my hope that by understanding the early determinants of weakness and their impact on health related outcomes, we can create effective early interventions leading to improved health, mobility and enhanced overall well-being, especially among the most vulnerable Americans.

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