

Structural, Biological, and Psychosocial Determinants of Frailty in Community-Dwelling  
Older Adults in the US

by

Shamatree Shakya

Department of Nursing  
Duke University

Date: \_\_\_\_\_

Approved:

\_\_\_\_\_  
Michael Paul Cary Jr., Chair

\_\_\_\_\_  
Susan Gray Silva, Co-chair

\_\_\_\_\_  
Eleanor Schildwachter McConnell

\_\_\_\_\_  
Sara Jane McLaughlin

Dissertation submitted in partial fulfillment of  
the requirements for the degree of Doctor  
of Philosophy in Nursing in  
the Graduate School  
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2023

ABSTRACT

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## **Abstract**

Frailty is a common geriatric syndrome associated with a host of adverse outcomes. Frailty disproportionately affects women, older adults who identify as Hispanic, non-Hispanic Black, and those with less income relative to men, non-Hispanic White, and those with high income in the United States (U.S.). Although an increasing body of evidence shows that frailty is modifiable and reversible in its early stage, the underlying mechanism through which co-occurring modifiable factors contribute to frailty and related disparities is poorly understood. This dissertation aimed to elucidate whether structural social determinants (gender, race/ethnicity, and education) operate through intermediary biological (cardiometabolic) factors and psychosocial stressors and influence frailty in community-dwelling older adults in the U.S.

The World Health Organization's conceptual framework of action on social determinants of health (CSDH) underpinned this dissertation. The CSDH framework posits that location in a social hierarchy is contingent on individuals' gender, race, ethnicity, and education; these social hierarchies and rankings offer structural advantages and disadvantages. Based on the ranking in the social hierarchy, people may be differentially exposed to intermediary health-promoting or damaging factors, which in turn are associated with disparate health outcomes. This dissertation hypothesized that structural social determinants (gender, race, ethnicity, and education) are associated with disproportionate exposure to intermediary biological cardiometabolic factors and psychosocial stressors, which can be related to the differential frailty risk.

As part of Chapter 2, a systematic review was conducted to examine the relationship between modifiable cardiometabolic risk factors and frailty and to highlight some critical gaps in the literature. The systematic review findings showed that co-occurring cardiometabolic risk factors increase the frailty risk in older adults; however, combinations of cardiometabolic factors associated with frailty are unclear from the current literature. It is because the existing study examined the influence of a cumulative number of cardiometabolic factors on frailty rather than exploring the combinations of cardiometabolic factors related to frailty. Most of the studies adjusted for the effect of structural determinants and other demographic characteristics; their role was unclear in association with cardiometabolic factors and frailty.

This dissertation aimed to address these gaps in literature through two quantitative studies (Chapters 3 and 4). Chapters 3 and 4 are cross-sectional, descriptive, correlational studies that involved secondary analysis of the existing data from the Health and Retirement Study (HRS). These quantitative studies involved approximately 8000 older adults (65 years and above) who provided physical assessments, cardiometabolic biomarker measurements, and psychosocial information in 2006 and 2008. Frailty was operationalized using the Fried phenotype criteria, which classifies frailty based on at least three features: poor handgrip strength, slow gait speed, fatigue, weight loss, and low physical activity. Chapter 3 examined whether structural determinants operate through distinct cardiometabolic typologies and influence frailty. Chapter 4 examined whether

structural determinants operate through cumulative psychosocial stress and influence frailty.

Chapter 3 used latent class analysis to identify subgroups of older adults with distinct combinations of cardiometabolic indicators (elevated blood pressure, sugar, C-reactive protein, total cholesterol; obesity, abdominal obesity, and low high-density lipoprotein). Path analysis involving a series of logistic regression models was used to examine the relationships between structural determinants, cardiometabolic typologies, and frailty and explore whether cardiometabolic typologies mediate the relationship between structural determinants and frailty. The results confirmed that frailty disparities persist. Females, those identifying as Hispanic, non-Hispanic Black, and those with less education had a higher frailty risk relative to males, those identifying as non-Hispanic White, and those with high education. The latent class analysis identified three subgroups of older adults with distinct cardiometabolic typologies, which were labeled as 1) insulin resistance, 2) hypertensive dyslipidemia, and 3) hypertensive subgroups. Structural determinants were significantly related to these latent cardiometabolic subgroups. The members of the insulin resistance subgroup were more likely to be female, were more likely to identify as non-Hispanic Black, and were more likely to be college non-graduates. The members of the hypertensive dyslipidemia subgroup were more likely to identify as a non-Hispanic other minority and were more likely to be high school graduates. The members in the hypertensive subgroup were more likely to be male and college graduates. The frailty risk differed among these latent subgroups of older adults

such that the insulin resistance subgroup had a higher frailty risk than hypertensive dyslipidemia and hypertensive subgroups. In contrast, the frailty risk did not differ in the latter two subgroups. The mediation for cardiometabolic typologies could not be established.

Chapter 4 assessed cumulative psychosocial stress based on additive counts of six dichotomized psychosocial factors (loneliness, financial strain, perceived everyday discrimination, low subjective social status, poor neighborhood, and experience of traumatic life events) originating from multiple life domains. Path analysis involving a series of multivariable regression models was used to examine the relationship between structural determinants, cumulative psychosocial stress, and frailty and the mediating role of cumulative psychosocial stress. Consistent with Chapter 3, females, Hispanic, non-Hispanic Black, and those with less education had higher frailty risk. Cumulative psychosocial stress ranged from zero to six (average=1.35). Structural determinants were significantly related to cumulative psychosocial stress such that older adults who identified as Hispanic, non-Hispanic Black, and as a non-Hispanic other minority and those with less education experienced greater cumulative psychosocial stress. Greater cumulative psychosocial stress was associated with higher frailty risk; however, the mediation effect for cumulative psychosocial stress could not be established.

These findings highlight that structural determinants, cardiometabolic typologies, and cumulative psychosocial stress independently contribute to frailty. These findings reinforce the multifactorial nature of frailty. The knowledge from this dissertation study

can inform the development of a tailored intervention to delay and prevent frailty by targeting specific cardiometabolic typologies and psychosocial stressors. Furthermore, this dissertation sets the foundation for exploring other biological and psychosocial stressors contributing to frailty and examining their potential mediating roles.

## **Dedication**

I dedicate this work to my family. Especially to my maa and baa for paving the path for my brothers and me and giving us opportunities and education. Thank you for teaching us the values of integrity, selfless love, and service. To my grandmas for showering the family with their kindness, blessings, and compassion and being symbols of resilience. To my brothers (Sandeep and Sudeep) and sister-in-law (Tripty) for being pillars of support and taking care of the family while I was away. To my cousin sister (Somin) — my best friend — for being empathetic and my biggest cheerleader in this journey. To my nephew (Satvik), thank you for bringing so much joy into our lives.

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# 1. Introduction

The global population is aging, and the number of older adults (aged 65 years and above) is estimated to rise from 727 million in 2020 to 1.5 billion by 2050 (United Nations [UN], 2020). In the United States (US), the number of older adults is projected to increase from 52 million people in 2020 to an estimated 98 million by 2060 (Administration for Community Living [ACL], 2021). Although older adults are living longer, they bear a disproportionate burden of chronic diseases. One in six US older adults has at least one chronic disease, such as hypertension, ischemic heart disease, heart failure, stroke, diabetes mellitus, chronic lung disease, and cancer (ACL, 2021). Even more, a substantial proportion of older adults worldwide (42.4%) and in the US (81%) live with multiple, co-occurring chronic diseases (Ho et al., 2022; Ofori-Asenso, Chin, Curtis, et al., 2019). Older adults with multiple chronic conditions are more likely to develop altered homeostatic reserve resulting in a clinical syndrome — also known as frailty (Zazzara et al., 2019). Frailty afflicts approximately 16% and 15% of older adults globally (O’Caoimh et al., 2021) and within the US (Bandein-Roche et al., 2015). The incidence of frailty is estimated to rise sharply due to rapid growth in the aging population, with at least forty per thousand older adults per year likely to develop frailty (Hoogendijk et al., 2019; Ofori-Asenso, Chin, Mazidi, et al., 2019). Thus, frailty is a pressing public health challenge globally and in the US.

## **1.1 Frailty and Adverse Outcomes**

Frailty is a clinical syndrome attributable to the depleted homeostatic reserve of multiple physiological systems (Clegg et al., 2013; Morley et al., 2013). The underlying deterioration of skeletal muscle, immune, endocrine, and inflammatory systems in frailty reduces the ability to endure stressors such as temperature dysregulation, injuries, and infection (Clegg et al., 2013), thereby increasing the risk of adverse health outcomes (Vermeiren et al., 2016). Frailty is a major contributor to adverse events, for instance falls (Kojima, 2015), fractures (Kojima, 2016), cognitive decline (Kojima et al., 2016), premature disability (Kojima, 2017), long-term care institutionalization (Kojima, 2018), and deaths, (Kojima et al., 2018) in older adults. Older adults with frailty are more likely to experience complications, such as cardiac arrest, septic shock, hemorrhage, pulmonary embolism, and myocardial infarction (Chen, 2015; Chen et al., 2019; Panayi et al., 2019). Recent evidence showed that frailty is a leading contributor to developing complications and mortality among patients diagnosed with severe acute respiratory syndrome coronavirus 2 (more commonly referred to as SARS-CoV-2 or Covid-19) (Yang et al., 2021; Zhang et al., 2021). Frailty has substantial financial implications, as acute and skilled nursing care (Chang et al., 2018) utilization in older adults with frailty is three times more than for those without frailty (Ensrud et al., 2018; Ensrud et al., 2020; Kojima, 2018). Healthcare expenses incurred due to frailty are far costlier and exceed \$1616 to 32,550 more than care provided to those without frailty (Chi et al., 2021). A growing body of evidence has documented that frailty is reversible and modifiable

(Takatori & Matsumoto, 2021; Travers et al., 2019); thus, understanding factors influencing frailty can inform interventions to promote independent, healthy living in older adults and prevent adverse health outcomes.

## ***1.2 Frailty and Health Disparities in the US***

Substantial disparities exist in the prevalence of frailty in the US across structural social determinants of health (hereafter, structural determinants). Structural determinants, including gender, education, race, and ethnicity, shape location in a social hierarchy and generate and maintain disparities through disparate exposure to health-promoting and damaging risk factors and differential access to protective resources and opportunities. In the US, the frailty prevalence is disproportionately higher in women (17%) than men (13%) and in those identifying as Hispanic (25%) and non-Hispanic Black (23%) relative to non-Hispanic White (14%) (Bandeem-Roche et al., 2015); it is also higher among those of lower socioeconomic status (Pandit et al., 2019; Usher et al., 2021). Women, Hispanic, and Non-Hispanics Black older adults are more likely to bear a greater burden of frailty-related adverse events such as surgical complications, extended hospital stays, functional impairment, and repeated hospitalization following discharge relative to men and non-Hispanic White older adults (Bandeem-Roche et al., 2015; Dharmasukrit et al., 2021; Pandit et al., 2019). As the older adult population in the US becomes more gender, race, and ethnically diverse, the increasing burden of frailty will further widen the health gap across these subgroups (Abeliansky et al., 2020).

The mechanism and factors contributing to frailty disparities are poorly understood, but may stem from differential exposure to biological and psychosocial risks (Feng et al., 2017; Freitag & Schmidt, 2016). Hence, examining frailty from a social determinants of health framework can better elucidate mechanisms contributing to frailty and related disparities. Understanding the mechanistic pathway can lay the groundwork for developing interventions to delay and prevent frailty and eradicate frailty disparities.

### ***1.3 Multimorbidity and Frailty***

More than 80% of older adults in the US live with two or more chronic conditions (Buttorff et al., 2017). Among chronic morbidities, cardiometabolic diseases, including coronary heart disease, heart failure, atrial fibrillation, ischemic heart disease, stroke, myocardial infarction, and diabetes mellitus, are among the leading causes of morbidity and mortality in the US (Gerds & Regitz-Zagrosek, 2019; Miranda et al., 2019). Cardiometabolic diseases are commonly reported biological predictors of frailty (Gao et al., 2021). Notably, frailty risk is two to three times higher in those with cardiometabolic conditions such as coronary heart disease (Marinus et al., 2021), atrial fibrillation (Polidoro et al., 2013), heart failure (Denfeld et al., 2017), stroke (Palmer et al., 2019), and diabetes (Aguayo et al., 2019; Garcia-Esquinas et al., 2015). These chronic diseases are linked with loss of muscle mass, strength, and anabolism, which are key features of frailty (Inglés et al., 2014; Nakayama et al., 2016; Saum et al., 2015). Identifying modifiable determinants of cardiometabolic diseases and their relationship with frailty can be informative in developing interventions for the early management of frailty.

## **1.4 Co-occurring Cardiometabolic Factors and Frailty**

Cardiometabolic diseases share modifiable risk factors such as elevated blood sugar, elevated blood pressure, abdominal obesity, obesity, dyslipidemia, and elevated proinflammatory markers (Cannon, 2007; Leiter et al., 2011), which are prevalent in more than half (55 %) of older adults in the US (Kuk & Ardern, 2010). Although the co-occurrence of cardiometabolic risk factors is associated with a greater frailty risk (Lee et al., 2020; Pérez-Tasigchana et al., 2017), the combinations of co-occurring cardiometabolic factors typologies— related to frailty is unknown (Shakya et al., 2022). The distribution of cardiometabolic factors varies by gender, race, ethnicity, and education. For example, older women have a higher prevalence of hyperglycemia and dyslipidemia than older men (Kuk & Ardern, 2010). Hispanic and Non-Hispanic Black adults experience a higher prevalence of hyperglycemia, hypertension, dyslipidemia, and co-occurring cardiometabolic factors than non-Hispanic White adults (He et al., 2021; Hirode & Wong, 2020). The burden of cardiometabolic risk factors is higher among those with less education (McCurley et al., 2017). Thus, understanding how structural social determinants influence frailty via co-occurring cardiometabolic typologies can be informative in developing interventions to delay and prevent frailty in older adults.

## **1.5 Co-occurring Psychosocial Stressors and Frailty**

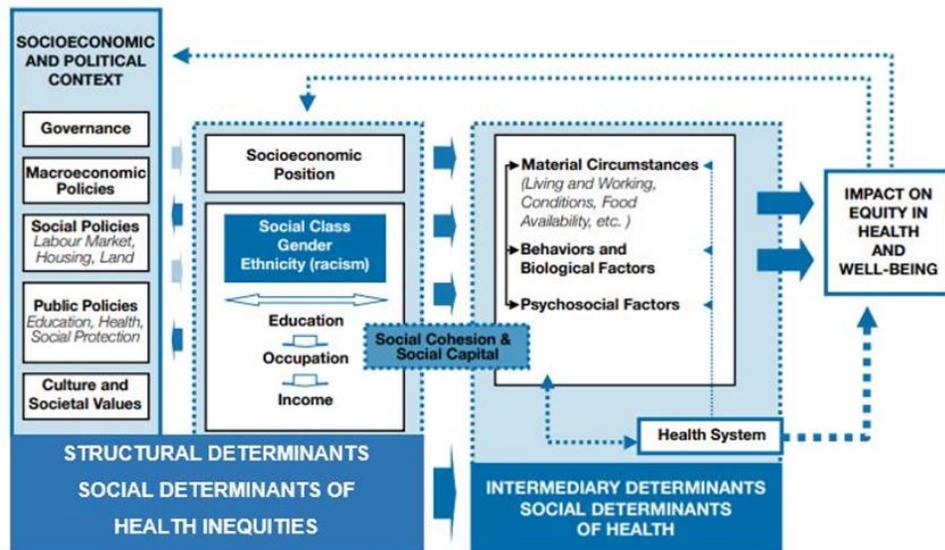
Older adults experience various psychosocial stressors originating from multiple life domains (Crosswell et al., 2020; Scott et al., 2011). Loneliness, financial problems, poor subjective social status, perceived discrimination, poor neighborhood cohesion, and

traumatic life events are commonly reported psychosocial stressors in older adults (Scott et al., 2011; Switsers et al., 2021). Psychosocial stressors are related to many adverse physical and mental health outcomes (O'Connor et al., 2021). The exposure to these psychosocial stressors may vary by structural determinants, and women, those who identify as Hispanic, non-Hispanic Black, and those with less education are more likely to report co-occurring psychosocial stressors (Alhasan et al., 2020; Brown et al., 2020; Ferreira et al., 2018). Few studies have examined the influence of individual psychosocial stressors on frailty. For example, a lack of social support is associated with a greater risk of frailty, whereas social support can protect against frailty (Freitag & Schmidt, 2016; Haapanen et al., 2018). Similarly, stress resulting from financial problems and living in a poor neighborhood was related to the development of frailty in Mexican American older adults (Peek et al., 2012). While examining the role of individual psychosocial stressors on frailty is informative, it might undermine the magnitude of the influence of co-occurring psychosocial stressors on frailty. Thus, examining if structural determinants influence frailty through co-occurring psychosocial stressors can inform interventions seeking to eliminate related disparities.

## ***1.6 Theoretical Framework***

The World Health Organization's (WHO) Conceptual Framework for Action on the Social Determinants of Health (CSDH) informs this dissertation study. As shown in Figure 1, the CSDH posits a complex pathway through which structural and intermediate social determinants interplay to shape the health and well-being of individuals (Solar &

Irwin, 2010). The CSDH conceptual framework encompasses three fundamental constructs: a) structural social determinants of health, b) intermediary social determinants of health, and c) equity in health and well-being, as shown in Figure 1. As described below, different structural and intermediary social determinants can influence health and well-being.



**Figure 1: Conceptual Framework for Action on the Social Determinants of Health**

### **1.6.1 Structural Social Determinants of Health**

In the CSDH conceptual framework, structural social determinants of health (structural determinants) are social, cultural, economic, and political contexts and socioeconomic positions that function at the macro-level shaping day-to-day life “where people are born, grow, live, work, and age.” Structural determinants influence the distribution of resources, power, and prestige according to individuals’ social position engendering and maintaining social hierarchy or social stratification. Social hierarchy is a societal structure where individuals might enjoy greater structural advantages/disadvantages based on their gender, race, ethnicity, social class, education, and wealth. Social ranking in the social hierarchy influences disparate exposure to health-promoting and damaging factors as well as the ability to access protective resources/opportunities (Solar & Irwin, 2010). Structural determinants precede intermediary determinants in the mechanistic pathway and shape health and well-being through differential exposure to intermediary factors.

### **1.6.2 Intermediary Social Determinants of Health**

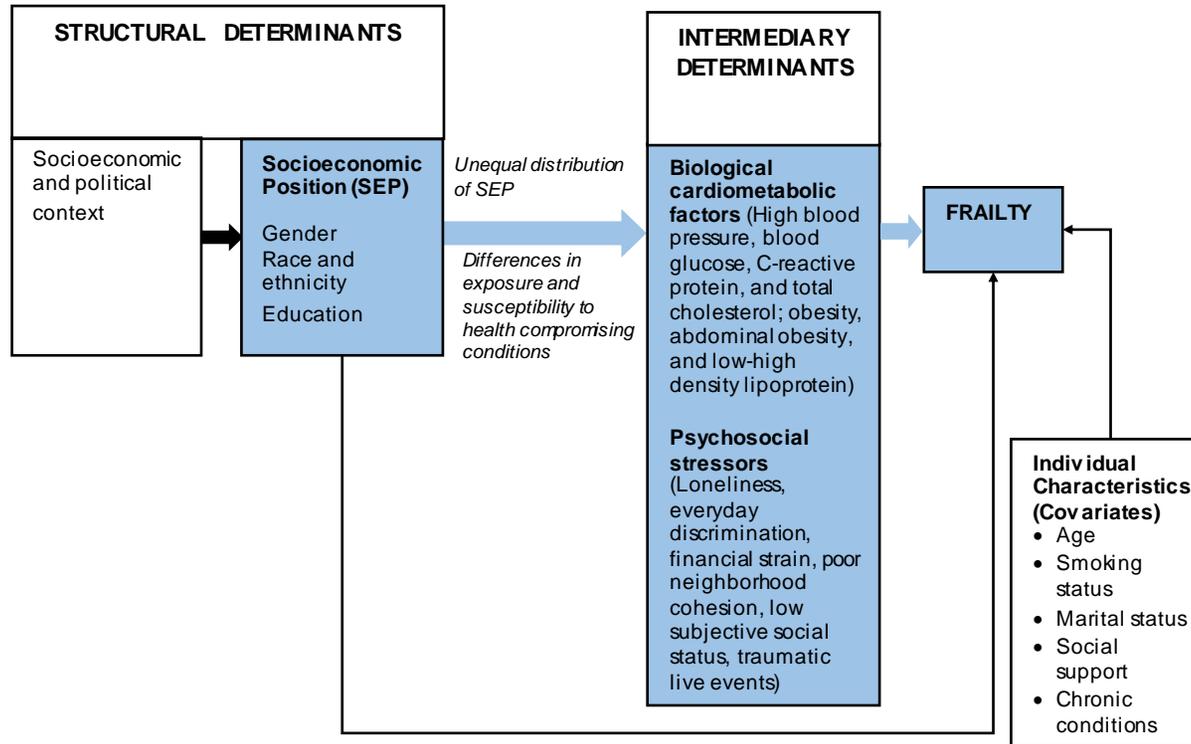
In the CSDH conceptual framework, intermediary social determinants (hereafter intermediary determinants) lie more proximal to health outcomes, as shown in Figure 1. Intermediary determinants include various material circumstances, psychosocial, biological, and behavioral factors. Structural determinants act through a range of these intermediary determinants to shape health and well-being. Material circumstances encompass housing, neighborhood, occupational work environment, and purchasing

capacity to buy healthy food and warm clothing. Depending on the clinical conditions, biological factors can include a range of clinical factors, such as lipid, glucose level, blood pressure, and insulin resistance (Matthews et al., 1989). Psychosocial risk factors include stressful living circumstances, intrapersonal, interpersonal, and social relationships, resulting in psychosocial stress and coping behavior. Behavioral factors encompass risky or protective health behaviors, such as lifestyle, dietary habits, tobacco intake, and drinking behavior (Solar & Irwin, 2010).

### **1.6.3 Health, Well-being, and Inequities**

The CSDH conceptual framework asserts that health is a product of an intricate interplay between structural determinants and intermediary factors. Structural determinants drive health, well-being, and inequities by generating and reinforcing social hierarchies that create advantages and disadvantages. People from disadvantaged groups are more likely to be exposed to a greater magnitude and frequency of biological, psychosocial, material, and environmental risk factors with fewer protective resources and opportunities leading to disparate health outcomes (Solar & Irwin, 2010).

## 1.6.4 The Conceptual Model of the Dissertation



**Figure 2: Modified social determinants of health conceptual model**

The conceptual model for this dissertation was adapted from the WHO's CSDH conceptual framework (see Figure 2). The examination of the sociopolitical component of the CSDH conceptual framework is beyond the scope of this dissertation; thus, the conceptual model for this dissertation encompasses three main concepts: a) structural determinants, b) intermediary determinants, and c) frailty. Although the sociopolitical context was not examined in this dissertation study, the sociopolitical context is assumed to shape socioeconomic position and social hierarchies, where individuals may attain structural advantages and disadvantages contingent on their gender, race, ethnicity, and education. People who are structurally disadvantaged can be disproportionately exposed to health-damaging factors, which results in disparate health outcomes. In the current study, this multilevel conceptual model proposed that structural determinants (gender, race, ethnicity, and education) result in differential exposure to intermediary determinants— co-occurring cardiometabolic factors and psychosocial stressors. This differential exposure to intermediary cardiometabolic factors and psychosocial stressors may influence the risk of frailty.

## **1.7 Overall Purpose of Dissertation Chapters**

The overall purpose of this dissertation was to examine whether structural determinants operate through co-occurring biological factors (cardiometabolic) and psychosocial stressors and contribute to frailty in community-dwelling older adults.

Chapter 1: Discuss the significance of frailty in the context of population aging, health disparities, potential cardiometabolic and psychosocial factors influencing frailty, and the conceptual framework informing the dissertation.

Chapter 2: Synthesize prior literature investigating the association between cardiometabolic factors and frailty.

Chapter 3: Identify distinct subgroups of older adults with different typologies of cardiometabolic factors and examine whether structural determinants operate through these cardiometabolic typologies and influence frailty.

Chapter 4: Examine co-occurring psychosocial stressors in the form of cumulative psychosocial stress among older adults and examine whether structural determinants operate through cumulative psychosocial stress and influence frailty.

Chapter 5: Synthesize the findings from each chapter, discuss limitations and practice implications, and propose recommendations for future research.

## **2. The Association Between Cardiometabolic Risk Factors and Frailty in Older adults: A Systematic Review**

### **2.1 Introduction**

Frailty is a state of compromised homeostasis in multiple body systems, increasing the susceptibility to adverse health outcomes even in exposure to minor stressors (Clegg et al., 2013). The Fried phenotype model defines frailty as having at least three of these features: poor grip strength, gait speed, and physical activity; weight loss, and fatigue. The manifestation of any one of these features is termed pre-frailty— a precursor of frailty, and the absence of any features is a non-frail state (Fried, Tangen, Walston, Newman, Hirsch, Gottdiener, Seeman, Tracy, Kop, & Burke, 2001). Other commonly used frailty instruments, such as Edmonton, Cumulative frailty index (Rockwood & Mitnitski, 2011), and FRAIL scale (Thompson et al., 2020), also utilize the history of comorbidities, drug intake, and general health status to operationalize frailty. The prevalence of frailty is disproportionately higher among older people (75 years and above), women, and certain race/ethnic subgroups (Bandeem-Roche et al., 2015; O'Caoimh et al., 2021). Specifically, the likelihood of frailty is greater among those living with chronic cardiometabolic diseases such as diabetes (Garcia-Esquinas et al., 2015), cardiovascular diseases (Aguayo et al., 2019; Marinus et al., 2021), atrial fibrillation (Polidoro et al., 2013), heart failure (Denfeld et al., 2017), stroke (Palmer et al., 2019), and chronic kidney diseases (Chowdhury et al., 2017). Older adults with co-

existing cardiometabolic diseases and frailty are less likely to tolerate advanced medical/surgical interventions such as anesthesia (Lin et al., 2018), cardioverter-defibrillator placement (Chen et al., 2019), surgery (Panayi et al., 2019), and chemotherapy (Runzer-Colmenares et al., 2020).

Although the exact mechanism underpinning the association between cardiometabolic diseases and frailty is unknown, several potential inflammatory mechanisms are underscored. Chronic inflammatory changes involved in cardiometabolic diseases are likely to increase the risk of frailty (Ferrucci & Fabbri, 2018). Chronic inflammatory changes and oxidative stress in cardiometabolic diseases (Amdur et al., 2016) are marked by an increased level of inflammatory markers such as interleukin-6, C-reactive protein (CRP), and tumor necrosis factor-alpha (TNF-  $\alpha$ ) (Cesari et al., 2003; Marcos-Pérez et al., 2020). These inflammatory markers and sustained chronic inflammation are linked with frailty (Gale et al., 2013) and associated features such as declining muscle mass and strength (Bano et al., 2017). Some studies have also indicated that frailty is associated with an increased risk for cardiometabolic diseases, alluding to the likely bidirectional association between cardiometabolic diseases and frailty (Veronese, Cereda et al., 2017; Veronese, Siggeirsdottir et al., 2017). Thus, a greater understanding of the underlying association between potentially modifiable cardiometabolic risk factors and frailty can inform the strategies to delay and prevent frailty and adverse health outcomes.

Cardiometabolic risk factors include abdominal obesity (high waist circumference), insulin-resistant elevated blood glucose, dyslipidemia (low high-density lipoprotein [HDL], elevated triglycerides, and high total cholesterol [TC]), and elevated blood pressure (Alberti et al., 2009). Cardiometabolic risk factors instigate a state of pro-inflammation and sub-acute systemic inflammation, altering homeostasis in multiple body systems (Noren Hooten et al., 2012), likely associated with frailty. Several observational studies have investigated the associations between cardiometabolic risk factors and frailty; however, no prior review has systematically evaluated and summarized the associations between a range of cardiometabolic risk factors and frailty. The intention of this review is not to delineate the mechanistic pathways between cardiometabolic risk factors and frailty. Instead, this review aimed to conduct a systematic review of the existing body of evidence to summarize the association between a range of potentially modifiable cardiometabolic risk factors and frailty in older adults. This review examined the patterns-similarities and differences in the unidirectional associations between potentially modifiable cardiometabolic risk factors and frailty. The findings of this systematic review can inform clinical interventions, clinical and public health practices to prevent and manage frailty.

## **2.2 Methods**

Our initial search showed no prior studies or ongoing studies published or registered in PROSPERO and systematic reviews and meta-analyses indexed in PubMed

on this topic. This systematic review protocol was registered at PROSPERO (registration no. CRD42021252565). This systematic review was carried out using the "Finding What Works in Health Care: Standards for Systematic Reviews" (Institute of Medicine [IOM], 2011). This systematic review was reported following the PRISMA 2020 statement: an updated guideline for reporting systematic reviews (Page et al., 2021).

### **2.2.1 Data Sources and Search Strategy**

The databases searched included MEDLINE (via PubMed), Embase (via Elsevier), and Web of Science (via Clarivate). The primary reviewer (S. Shakya) and a professional medical librarian (L. Ledbetter) outlined possible search terms defining study participants, concepts, and designs. Appendix Tables B1 and B2 show the combinations of terms used to identify the potential studies. As shown in Appendix Table A1, the professional librarian used a mix of keywords and subject headings representing cardiometabolic risk factors, cardiovascular risk factors, frailty, and the older adult population, respectively. A search hedge to select for study types such as randomized control trials, prospective studies, and retrospective studies, as well as a database filter to remove publication types, such as editorials, letters, comments, and animal-only studies, was applied as was appropriate for each database. We did not limit the initial search by the date of publication or language of publication. Appendix Table A3 shows the results of search term in the Web of Science (via Clarivate). The initial search was conducted by the librarian to find the articles from the date of inception to February 3, 2021. The

librarian updated the search on November 19, 2021, to find any new articles. Thus, the search included articles from the date of inception to November 19, 2021. The search found a total of 10,550 citations. Complete reproducible search strategies, including date ranges and search filters, for all databases, are detailed in the Appendix. We identified additional manuscripts by reviewing the reference list of a prior systematic review (Amiri et al., 2020) and Google Scholar.

### **2.2.2 Selection of Evidence Sources**

After the search, all identified studies were uploaded into Covidence (Veritas Health Innovation, Melbourne, Australia), a software system for managing systematic reviews, and 4,474 duplicates were removed by the software. A final set of 6,026 citations were left to be screened in the title/abstract phase, and 50 articles were selected for the full-text review. From Google Scholar, six articles were selected for the full-text review. Of 56 articles deemed eligible for the full-text review, 12 studies met the inclusion criteria for data extraction, as shown in Figure 3 (Page et al., 2021). Two authors (S. Shakya, R. Bajracharya) independently carried out the selection process as presented in the flowchart as per PRISMA guidelines (Figure 3). The studies that met the eligibility criteria guided by PEOS (Population Exposure Outcome and Study types) guidelines were included in the final review.

### **2.2.2.1 Population**

The cutoff points to classify the older adult population vary widely depending on countries' eligibility criteria for social security and healthcare programs (Börsch-Supan & Coile, 2018); our review included those studies involving community-dwelling older adults (60 years and above) as the study participants, irrespective of country of origin.

### **2.2.2.2 Exposure**

Cardiometabolic risk factors were the primary exposures of interest.

Cardiometabolic risk factors include a group of potentially modifiable factors, including elevated waist circumference, blood glucose, blood pressure, triglycerides, total cholesterol [TC], low-density lipoprotein [LDL]; and reduced high-density lipoprotein [HDL] (Alberti et al., 2009). Since there is some overlap between cardiometabolic risk factors and cardiovascular risk factors, cardiovascular risk factors were also used in the search strategy to capture cardiometabolic risk factors. Thus, this review includes studies involving a range of cardiometabolic risk factors.

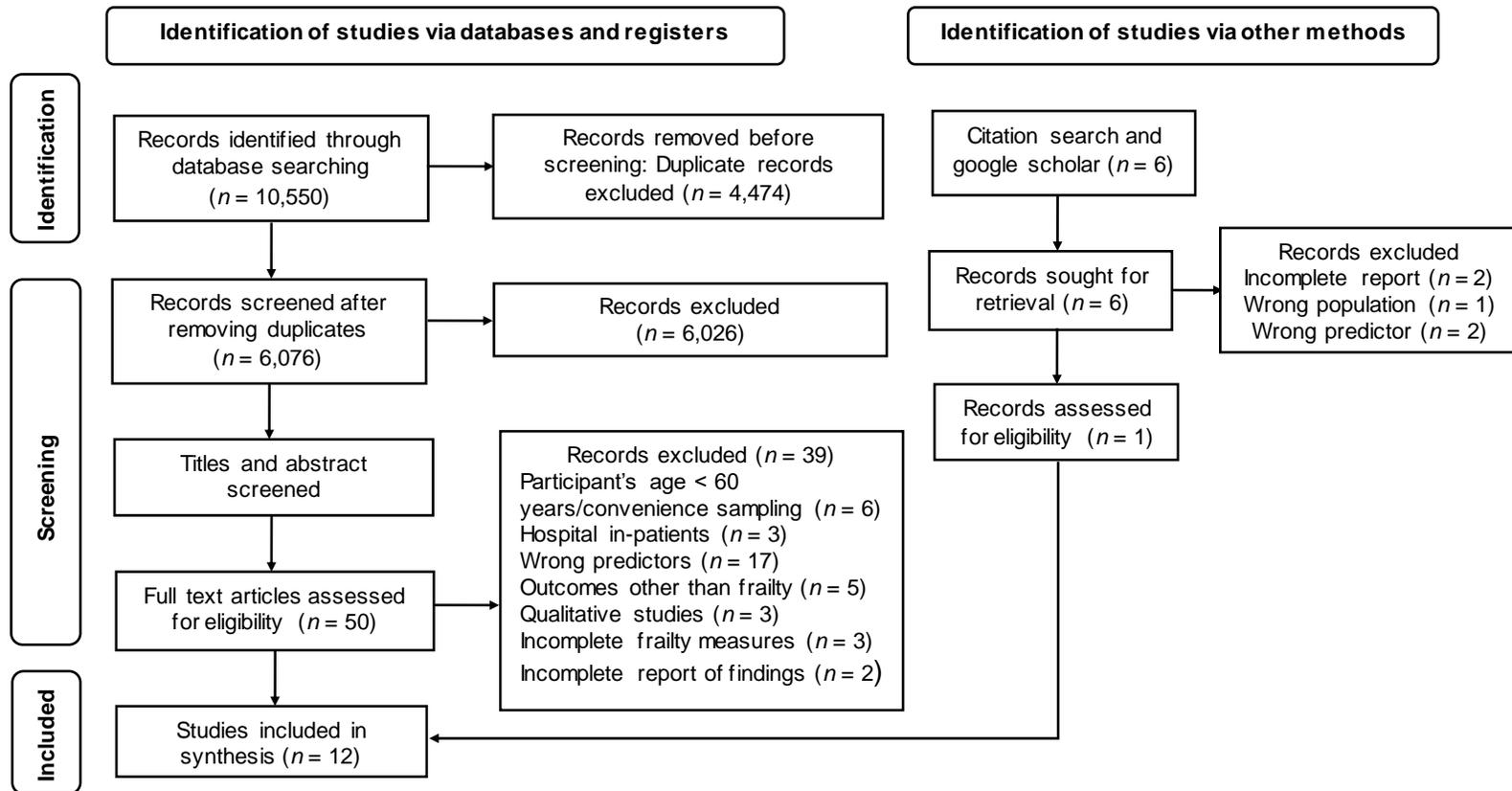
### **2.2.2.3 Outcome**

Only those studies that investigated frailty as the main study outcome were included in the review. Several valid tools exist, such as the FRAIL scale, Edmonton frail scale, Tilburg, cumulative frailty index, and Fried phenotype model, that use a combination of physical assessments and self-reported measures to operationalize frailty (Faller et al., 2019). Studies using a well-tested and valid instrument (Faller et al., 2019)

for operationalizing frailty were included in this review, whereas those studies reporting partial or incomplete features (e.g., grip strength or gait speed only) to define frailty were excluded from the review.

#### **2.2.2.4 Study Types**

All observational studies (including cross-sectional, prospective cohort, longitudinal, and case-control studies), experimental study designs (quasi-experimental and randomized clinical trials), and abstracts that provided quantitative statistical reports for describing the association between cardiometabolic risk factors and frailty were included in the review. Articles without empirical reporting were excluded (e.g., review articles, editorials, commentaries, conference proceedings, columns, or book chapters). In addition, articles were excluded if a) cardiometabolic risk factors were examined as mediators or confounders and b) there was a lack of explicit cardiometabolic risk factors. Every effort was made to obtain the full text of the articles, but where it could not be accessed, the article was excluded. For papers not published in English, due to restrictions in funding, we chose not to have these papers translated, and these papers were excluded at the full text-screening phase.



**Figure 3: PRISMA diagram for search strategy and study selection process**

### **2.2.3 Study Appraisal**

The Joanna Briggs Institute (JBI) critical appraisal tools for cross-sectional and prospective cohort studies were used to appraise the methodological quality of retrieved studies. The two reviewers independently assessed the evaluation criteria in the JBI appraisal tool for cross-sectional/prospective cohort studies (Moola et al., 2020). The quality scores of individual articles were reflective of the sum of “yes” responses. The table showing study appraisal is available in the Appendix section (Appendix A: Table A4).

### **2.2.4 Data Extraction and Synthesis**

The primary reviewer (S. Shakya) extracted data from each study using a standardized data-extraction form and recorded data in a standardized data-extraction file. The following data were extracted from each study: citation, publication year, country of origin, sample size, sampling techniques, study design, participants’ age, cardiometabolic risk factors, frailty assessment tools, covariates, and statistical associations indicating strength and direction of the association.

The included studies showed the variation in participants’ ages, origin, follow-ups, frailty measurements, cardiometabolic risk factors and covariates, indicative of clinical heterogeneity. Similarly, the differences in sampling techniques and study designs across the included studies reflect methodological heterogeneity (see Tables 2 and 3). Clinical and methodological heterogeneity can result in statistical heterogeneity,

and aggregating statistical estimates in the presence of such heterogeneity can lead to inaccurate pooled estimate effects and misleading conclusions (Gagnier et al., 2012). Thus, for the present systematic review, we synthesized findings without meta-analysis. This approach included identifying patterns across the studies by critically analyzing similarities and differences across the study findings (Campbell et al., 2020).

## **2.3 Results**

### **2.3.1 Study Characteristics**

Twelve studies met the inclusion criteria and were included in the systematic review. As shown in Tables 1 and 2, the summary of study characteristics and findings is shown in the alphabetical order of the first author's last name and the year of publication. Table 1 provides an overall summary of reviewed studies, including the origin of the study, study design, and sampling techniques. The publication year ranged from 2007 to 2021 for reviewed studies (Anker et al., 2021; Barzilay et al., 2007). These studies were conducted in six different countries, including the USA ( $n = 5$ ), China ( $n = 2$ ), England ( $n = 1$ ), Spain ( $n = 2$ ), Switzerland ( $n = 1$ ), and Taiwan ( $n = 1$ ). Five studies used cross-sectional designs (Blaum et al., 2009; Crow et al., 2019; Lee et al., 2020; Liao et al., 2018; Song et al., 2020), and seven studies used longitudinal designs (Anker et al., 2021; Barzilay et al., 2007; Gale et al., 2014; Graciani et al., 2016; Kalyani et al., 2012; Pérez-Tasigchana et al., 2017; Zaslavsky et al., 2016). For the studies with a longitudinal design, the follow-up period ranged from 3.5 to 12 years (Anker et al., 2021; Pérez-

Tasigchana et al., 2017). The number of study participants within a given study ranged from 346 to 6,320 (Kalyani et al., 2012; Liao et al., 2018). Most studies included a nationally representative population or population representing a state, county, or province. Stratified random sampling or random sampling was a frequently used sampling technique to recruit study participants, as shown in Table 1.

**Table 1: Summary of study characteristics**

Study	Country	Predictors of interest	Sample Size	Sampling techniques	Study design	Years of follow up	Cohort name	Participant's age
Anker et al., 2021	Switzerland	Systolic and diastolic blood pressure	4,200	Random sampling	Longitudinal study	12 years	Lausanne cohort Lc65+	65-70 years
Barzilay et al. 2007	US	Metabolic syndrome	2826	Age and sex-stratified random sampling	Prospective cohort study	9 years	Cardiovascular Health Study	≥ 65 years
Blaum et al. 2009	US	Hyperglycemia	543	Age stratified random sampling	Cross-sectional	-	Women's Health and Aging Studies I and II	≥ 60 years
Crow et al. 2019	US	Abdominal obesity	4,984	Multistage, probability sampling design	Cross-sectional	-	National Health and Nutrition Examination Survey (NHANES)	≥60 years
Gale et al. 2014	England	Framingham cardiovascular risk	1,726	Stratified sampling	Longitudinal study	4 years	English Longitudinal Study of Aging (ELSA)	≥ 60 years
Graciani et al. 2016	Spain	Ideal cardiovascular risk	2,617	Stratified cluster	Prospective cohort study	3.5 years	Not available	≥ 60 years
Kalyani et al. 2012	US	Hyperglycemia	346	Age stratified random sampling	Longitudinal study	8.6 ± 3.6 years	Women's Health and Aging Study II	≥ 70 years
Lee et al. 2020	Taiwan	Metabolic syndrome	1,006	Multiple proportional to size	Cross-sectional study	-	The Social Environment and Biomarkers of Aging Study (SEBAS)	≥ 65 years
Liao et al. 2018	China	Abdominal obesity	6,320	Multistage sampling	Cross-sectional	-	Beijing Longitudinal Study on Aging	≥ 65 years
Pérez-Tashighana et al. 2017	Spain	Metabolic syndrome	1,499	Not available	Longitudinal prospective cohort study	3.5 years	Senior ENRICA	≥ 60 years and above
Song et al. 2020	China	Abdominal obesity	995	Random multi-stage clustering	Cross-sectional	-	Not available	≥ 65 years

				sample				
Zaslavsky et al. 2016	US	Hyperglycemia	1,848	Random sampling	Prospective cohort study	4.8 years	Adult Changes in Thought (ACT)	≥ 65 years

**Table 2: Associations between cardiometabolic factors and frailty**

Study	Cardiometabolic risk factors	Frailty assessment tool	Adjusted variables	Statistical analysis	Results
Barzilay et al. 2007	Metabolic syndrome and individual risk factor <ul style="list-style-type: none"> <li>• blood pressure</li> </ul>	Fried frailty phenotype	Age, sex, smoking status, education, income, marital status, BMI, depression, cognitive status, clinical morbidities (diabetes mellitus, heart disease, stroke, cancer)	Multivariate discrete time proportional hazard models	In unadjusted and adjusted models after controlling for age, sex, smoking status, education, income, marital status, BMI, depression, cognitive status, clinical morbidities, such as diabetes mellitus, heart disease, stroke, and cancer: <ul style="list-style-type: none"> <li>• Cardiometabolic syndrome was associated with a new onset of frailty;</li> <li>• Elevated systolic blood pressure was not associated with the new onset of frailty.</li> <li>• Insulin resistance-Homeostasis model assessment (IR-HOMA) was associated with a new onset of frailty.</li> </ul>
Blaum et al. 2009	Hyperglycemia	Fried frailty phenotype	Age, race, education, BMI, IL-6, chronic diseases (osteoarthritis, coronary heart disease, stroke, diabetes mellitus, COPD)	Multiple variable multinomial logistic regression	Hyperglycemia was significantly associated with a greater risk of frailty in the adjusted model controlling for BMI, IL-6, and chronic morbidities such as diabetes mellitus, osteoarthritis, coronary heart disease, stroke, and COPD.
Crow et al. 2019	Abdominal obesity	Modified Fried frailty phenotype	Age, gender, race, ethnicity, marital status, education, BMI, chronic diseases (diabetes, heart failure, CAD, arthritis)	Multiple linear regression models and multiple logistic regression	Abdominal obesity was significantly associated with a greater risk of frailty in unadjusted and adjusted models controlling for age, gender, smoking, and education. It was not significantly associated with frailty after adjusting for age, gender, smoking,

					education, diabetes, heart failure, CAD, and arthritis.
Gale et al. 2014	Framingham cardiovascular risk and individual risk factors <ul style="list-style-type: none"> <li>total cholesterol</li> <li>high density lipoprotein</li> <li>blood pressure</li> </ul>	Modified Fried frailty phenotype	Cognitive function, household wealth, BMI, age, hypertension treatment, smoking, diabetes	Multinomial logistic regression	In participants without CVDs, increased Framingham cardiovascular risk was significantly associated with greater risk of frailty and pre-frailty in the adjusted model after controlling for age, anti-hypertensive treatment, smoking, and diabetes. In the adjusted model controlling for cognitive function, household wealth, BMI, age, hypertension treatment, smoking, and diabetes: <ul style="list-style-type: none"> <li>Elevated total cholesterol and reduced high-density lipoprotein (HDL) were significantly associated with a greater risk of frailty;</li> <li>Elevated systolic blood pressure was associated with a greater risk of frailty.</li> </ul>
Kalyani et al. 2012	Hyperglycemia	Modified Fried frailty phenotype	BMI, IL-6, chronic morbidities (diabetes mellitus, osteoarthritis, COPD, CAD, peripheral renal disease)	Cox regression model	Hyperglycemia was significantly associated with a new onset of frailty in the adjusted model controlling for BMI, IL-6, and chronic morbidities such as diabetes mellitus, osteoarthritis, COPD, CAD, and peripheral renal disease.
Lee et al. 2020	Metabolic syndrome and individual risk factors <ul style="list-style-type: none"> <li>abdominal obesity</li> <li>hyperglycemia</li> <li>triglycerides</li> <li>high-density lipoprotein</li> <li>blood pressure</li> </ul>	Frailty index of 35 items	Age, sex, education, smoking, alcohol consumption status	Multiple logistic regression	In the adjusted model controlling for age, sex, education, smoking, and alcohol consumption status: <ul style="list-style-type: none"> <li>Metabolic syndrome, abdominal obesity, hyperglycemia, elevated triglycerides, and elevated blood pressure were significantly associated with a greater risk of frailty.</li> <li>Lowered HDL was not significantly associated with a greater risk of frailty.</li> </ul>

Liao et al. 2018	Abdominal obesity	Rockwood's 33-items frailty index	Sex, age, education, lifestyle factors- smoking, alcohol consumption, sleeping, physical activities, living alone, number of chronic diseases (hypertension, diabetes mellitus, CVD, COPD, stroke, arthritis, tumor, dementia, heart failure, renal failure)	Multiple logistic regression	<p>Abdominal obesity and general obesity (excess BMI) were significantly associated with a greater risk of frailty in unadjusted models.</p> <p>In the adjusted model controlling for sex, age, education, lifestyle factors- smoking, alcohol consumption, sleeping, physical activities, living alone, chronic diseases - hypertension, diabetes mellitus, CVD, COPD, stroke, arthritis, tumor, dementia, heart failure, and renal failure:</p> <ul style="list-style-type: none"> <li>• Abdominal obesity was significantly associated with a greater risk of frailty;</li> <li>• General obesity (excess BMI) was not significantly associated with a greater risk of frailty.</li> </ul>
Pérez-Tashighana et al. 2017	<p>Metabolic syndrome and individual risk factors</p> <ul style="list-style-type: none"> <li>• abdominal obesity</li> <li>• hyperglycemia</li> <li>• triglycerides</li> <li>• high-density lipoprotein</li> <li>• blood pressure</li> </ul>	Fried frailty phenotype	Sex, age, education, diet, tobacco, alcohol consumption, physical activities, sedentary activities, total energy intake, asthma, chronic bronchitis, cancer, depression, musculoskeletal disease	Logistics regression	<p>In unadjusted and adjusted models controlling for sex, age, education, diet, tobacco, alcohol consumption, physical activities, sedentary activities, total energy intake, asthma, chronic bronchitis, cancer, depression, and musculoskeletal disease:</p> <ul style="list-style-type: none"> <li>• In participants without diabetes mellitus and CVD, cardiometabolic syndrome was significantly associated with the new onset frailty;</li> <li>• Abdominal obesity was significantly associated with the new onset of frailty;</li> <li>• Lowered HDL cholesterol did not significantly increase the risk of frailty;</li> <li>• Hyperglycemia and elevated blood pressure were not significantly associated with frailty.</li> </ul>

					<ul style="list-style-type: none"> <li>Elevated triglyceride level was significantly associated with the new onset of frailty in an unadjusted model. However, the association was not statistically significant in the adjusted model controlling for sex, age, education, diet, tobacco, alcohol consumption, physical activities, sedentary activities, total energy intake, asthma, chronic bronchitis, cancer, depression, and musculoskeletal disease.</li> </ul>
Song et al. 2020	Abdominal obesity	Tilburg Frailty Indicator	Age, gender, marital status, educational level, lifestyle factors: smoking, alcohol consumption, physical activity, diet, chronic diseases (cancer, CVD, COPD, diabetes, and others)	Multiple linear regression	Abdominal obesity was significantly associated with a greater risk of frailty in unadjusted and adjusted models controlling for age, gender, income, marital status, education, lifestyle, and chronic conditions.
Zaslavsky et al. 2016	Hyperglycemia	Modified Fried frailty phenotype	Age, sex, race, education, depression level, smoking status, self-rated health, BMI, depression, cognitive functioning, chronic diseases (congestive heart failure, CAD, or COPD)	Cox-regression model	<p>Hyperglycemia was significantly associated with a new onset of frailty in two subgroups of participants with and without diabetes.</p> <ul style="list-style-type: none"> <li>In participants without diabetes, persistent higher glucose level (&gt; 100 mg/dl) was significantly associated with a new onset of frailty across five years.</li> <li>In participants with diabetes, a U-shaped association was observed, such that glucose lower than 160 mg/dl and higher than 180 mg/dl were significantly associated with the new onset of frailty across five years.</li> </ul>

### **2.3.2 Operationalization of Cardiometabolic Risk Factors and Frailty**

Table 2 provides the summary of patterns- similarities and discrepancies in the associations between potentially modifiable cardiometabolic risk factors and frailty. Various instruments were used to operationalize frailty. Nine studies used the Fried or modified Fried frailty model (Anker et al., 2021; Barzilay et al., 2007; Blaum et al., 2009; Crow et al., 2019; Gale et al., 2014; Graciani et al., 2016; Pérez-Tasigchana et al., 2017; Zaslavsky et al., 2016) , two studies used the Cumulative frailty index (Lee et al., 2020; Liao et al., 2018), and one study used the Tilburg frailty indicator (Song et al., 2020) to operationalize frailty. The included studies examined the association between cardiometabolic risk factors, such as abdominal obesity (marked by elevated waist circumference), hyperglycemia (marked by elevated fasting glucose or glycated hemoglobin [HbA1C]), dyslipidemia (marked by elevated triglycerides, total cholesterol [TC], or lowered high-density lipoprotein [HDL]), and high blood pressure (marked by elevated systolic blood pressure), and frailty or development of frailty (new onset) in baseline non-frail older adults. These studies examined the association of frailty with individual cardiometabolic risk factors or co-occurring cardiometabolic risk factors using measures such as cardiometabolic syndrome, ideal cardiovascular risk score, and Framingham cardiovascular risk score.

### **2.3.3 Association Between Individual Cardiometabolic Risk Factors and Frailty**

#### **2.3.3.1 Hyperglycemia and Frailty**

Hyperglycemia, indicated by elevated fasting blood glucose or glycated hemoglobin, was investigated as a risk factor of frailty in two cross-sectional studies (Blaum et al., 2009; Lee et al., 2020) and four prospective longitudinal studies (Graciani et al., 2016; Kalyani et al., 2012; Pérez-Tasigchana et al., 2017; Zaslavsky et al., 2016). Hyperglycemia was associated with an increased risk of frailty in two cross-sectional studies (Blaum et al., 2009; Lee et al., 2020) and three longitudinal studies (Graciani et al., 2016; Kalyani et al., 2012; Zaslavsky et al., 2016) after adjusting for sex, education, BMI, IL-6, and chronic comorbidities such as diabetes mellitus, osteoarthritis, coronary heart disease, stroke, chronic pulmonary disease, and renal diseases, irrespective of participant's diabetic status. Mainly, glycated hemoglobin above 6.5% was associated with an increased risk of frailty (Blaum et al., 2009; Kalyani et al., 2012). Only one study compared the association between hyperglycemia and frailty in subgroups of participants with and without diabetes mellitus, and hyperglycemia was associated with frailty in both subgroups (Zaslavsky et al., 2016). Persistent high fasting blood glucose (> 110 mg/ dl) was associated with the new onset of frailty in non-diabetic participants. In diabetic participants, fasting blood glucose lower than 160 mg/dl and higher than 180 mg/dl were associated with the new onset of frailty (Zaslavsky et al., 2016). In two studies involving non-diabetic participants (Graciani et al., 2016; Pérez-Tasigchana et al., 2017), only one

study showed that optimum blood glucose was associated with a reduced likelihood of developing frailty after adjusting for age, sex, and education (Graciani et al., 2016). Hyperglycemia was significantly associated with frailty features such as lower grip strength (Pérez-Tasigchana et al., 2017).

### **2.3.3.2 Abdominal Obesity and Frailty**

Abdominal obesity, marked by elevated sex-specific waist circumference, was examined as a risk factor of frailty in four cross-sectional studies (Crow et al., 2019; Lee et al., 2020; Liao et al., 2018; Song et al., 2020) and a longitudinal study (Pérez-Tasigchana et al., 2017). Abdominal obesity was consistently associated with an increased risk of frailty in all four cross-sectional (Crow et al., 2019; Lee et al., 2020; Liao et al., 2018; Song et al., 2020) and longitudinal (Pérez-Tasigchana et al., 2017) studies after adjusting for sociodemographic factors— age, sex, education, lifestyle factors—smoking, alcohol intake, physical activities, and chronic diseases such as diabetes mellitus, heart failure, coronary artery disease, chronic obstructive pulmonary disease, cardiovascular diseases. In particular, abdominal obesity was associated with frailty features such as lowered grip strength and fatigue (Pérez-Tasigchana et al., 2017). Liao et al. (2018) compared the associations of abdominal obesity and general obesity (marked by greater BMI) with frailty. This study found that abdominal obesity was only associated with the risk of frailty when adjusted for sociodemographic and chronic conditions (Liao et al., 2018).

### **2.3.3.3 Dyslipidemia and Frailty**

Dyslipidemia was indicated using elevated triglycerides (Lee et al., 2020; Pérez-Tasigchana et al., 2017), total cholesterol (Gale et al., 2014; Graciani et al., 2016), and lowered high-density lipoprotein (Gale et al., 2014; Lee et al., 2020; Pérez-Tasigchana et al., 2017). The associations between dyslipidemia and frailty were examined in one cross-sectional (Lee et al., 2020) and three longitudinal studies (Gale et al., 2014; Graciani et al., 2016; Pérez-Tasigchana et al., 2017). There was inconsistency across the studies regarding the associations of dyslipidemia and frailty. Among one cross-sectional (Lee et al., 2020) and two longitudinal studies (Gale et al., 2014; Pérez-Tasigchana et al., 2017), only one longitudinal study indicated that lowered HDL was associated with the new onset of frailty after adjusting for age, BMI, smoking, diabetes, and cognitive status (Gale et al., 2014). Elevated triglycerides were shown to be associated with frailty in cross-sectional (Lee et al., 2020) and longitudinal studies (Pérez-Tasigchana et al., 2017) after adjusting for sociodemographic, lifestyles factors, and chronic morbidities. Elevated triglycerides were related to unintentional weight loss—a key feature of frailty (Pérez-Tasigchana et al., 2017). Among two longitudinal studies (Gale et al., 2014; Graciani et al., 2016), only one study showed an association between elevated total cholesterol level and new onset of frailty after adjusting for age, BMI, smoking, diabetes, and cognitive status (Gale et al., 2014).

#### **2.3.3.4 Elevated Blood Pressure and Frailty**

Elevated blood pressure, marked by high systolic or diastolic blood pressure, was examined as a risk factor of frailty in one cross-sectional (Lee et al., 2020) and five longitudinal studies (Anker et al., 2021; Barzilay et al., 2007; Gale et al., 2014; Graciani et al., 2016; Pérez-Tasigchana et al., 2017). There were inconsistencies across the studies regarding the associations between elevated blood pressure and frailty after adjusting for sociodemographic and chronic diseases. Elevated systolic blood pressure was associated with an increased risk of frailty in one cross-sectional (Lee et al., 2020) and new onset of frailty in non-frail older adults in one prospective study after adjusting for age, BMI, smoking, diabetes, hypertension treatment (Gale et al., 2014). However, optimum blood pressure was not associated with a new onset of frailty (Graciani et al., 2016). Similarly, elevated blood pressure did not influence transitions in non-frailty, pre-frailty, and frailty states over a 12 year study period adjusting for age, sex, hypertension, hypertension treatment, hypercholesterolemia, diabetes, cardiovascular disease, and polypharmacy (Anker et al., 2021).

#### **2.3.4 Association Between Co-occurring Risk Factors and Frailty**

One cross-sectional (Lee et al., 2020) and four longitudinal studies (Barzilay et al., 2007; Gale et al., 2014; Graciani et al., 2016; Pérez-Tasigchana et al., 2017) examined the associations between multiple co-occurring cardiometabolic risk factors and frailty. The co-occurrence of multiple cardiometabolic risk factors indicated by

cardiometabolic syndrome (Barzilay et al., 2007; Lee et al., 2020; Pérez-Tasigchana et al., 2017) and Framingham cardiovascular risk score (Gale et al., 2014) were associated with a greater likelihood of frailty and pre-frailty adjusting for sociodemographic characteristics, smoking, alcohol consumption, and chronic diseases in one cross-sectional and four longitudinal studies. Even in participants without diabetes, cardiometabolic syndrome was associated with the new onset of frailty after adjusting for sociodemographic characteristics, lifestyles, depression, and chronic conditions (Pérez-Tasigchana et al., 2017). Similarly, in participants without diabetes and cardiovascular diseases, optimum cardiovascular health marked by ideal blood pressure, total cholesterol, blood glucose, and other protective factors such as non-smoking status, normal body weight, and physically active lifestyle were associated with the reduced risk of frailty in older adults after adjusting for sociodemographic characteristics, lifestyles, BMI, and chronic conditions (Graciani et al., 2016).

## **2.4 Discussion**

Abdominal obesity, hyperglycemia, and the co-occurrence of multiple cardiometabolic risk factors were consistently associated with an increased risk of frailty across cross-sectional and longitudinal studies after adjusting for potential covariates: sociodemographic-age, sex, education; lifestyle factors- physical activity, smoking, tobacco use, alcohol intake; and chronic conditions- diabetes mellitus, osteoarthritis, coronary heart disease, stroke, chronic pulmonary disease, and renal diseases. However,

the associations between dyslipidemia, elevated blood pressure, and frailty were inconsistent across the included studies.

Our analysis suggests that abdominal obesity, hyperglycemia, and co-occurrence of multiple cardiometabolic risk factors are associated with an increased likelihood of frailty or the development of frailty. Our findings align with a past systematic review that demonstrated a considerably greater risk of frailty in older adults with abdominal obesity (Yuan et al., 2021). Similarly, the association between hyperglycemia and frailty further confirms that chronic uncontrolled diabetes contributes to frailty. In addition, an alternative indicator of hyperglycemia and insulin resistance, such as insulin resistance-homeostasis model assessment (IR-HOMA), could be used to examine the risk of frailty (Barzilay et al., 2007). The inconsistent association between elevated blood pressure and frailty in our study also concurs with a past systematic review showing a similar conflicting association between elevated blood pressure and frailty (Vetrano et al., 2018). The inconsistencies across the studies might stem from heterogeneity in the operationalization of cardiometabolic risk factors and frailty, study design, and population. More studies are needed to examine the association between dyslipidemia and, elevated blood pressure and frailty using uniform assessment criteria to quantify frailty.

Although this study did not aim to examine the causal mechanisms between cardiometabolic risk factors and frailty, existing literature describes the potential

associations between cardiometabolic risk factors and frailty. Cardiometabolic risk factors induce inflammation even in the absence of a pathological agent. Abdominal obesity, a marker of visceral fat, instigates a state of chronic low-grade inflammation (Vandanmagsar et al., 2011) and increases the release of pro-inflammatory markers and chemokines such as interleukin (IFs) and tumor necrosis factors (TNFs) (Dahlén et al., 2014; Hermsdorff et al., 2011). Similarly, hyperglycemia induces inflammatory processes characterized by increased levels of cortisol, pro-inflammatory cytokines, and reactive oxygen species (Kir et al., 2019; Stentz et al., 2004). High-density lipoprotein is demonstrated to have anti-inflammatory properties, and lower HDL along with higher total cholesterol, triglycerides, and low-density lipoprotein (LDL) appear in several chronic diseases, suggesting that dyslipidemia has an inflammatory role (Batuca et al., 2009; Can et al., 2015; Pietrzak et al., 2019). Moreover, hypertension can result from inflammatory changes, and it can further aggravate inflammatory changes (Idris-Khodja et al., 2014; Nosalski et al., 2017). A substantial body of evidence shows that chronic low-grade inflammation is linked to a loss of muscle mass, muscle anabolism, reduced muscle strength, and poor handgrip strength (Bano et al., 2017; Gale et al., 2013; Tuttle et al., 2020) —hallmarks of frailty. Thus, a strong body of evidence suggests that chronic inflammatory changes instigated by cardiometabolic risk factors can perpetuate frailty (Soysal et al., 2016).

Our findings suggest several research implications. Firstly, there is wide variation in existing studies regarding the operationalization of frailty and cardiometabolic risk factors. The use of uniform measures of frailty and cardiometabolic risk factors, as well as consistent study design, follow-up, and covariates, will aid quantitative comparison and the combination of findings. Although existing studies show that the co-occurrence of multiple cardiometabolic risk factors is associated with a greater likelihood of frailty, a greater understanding of the composition of co-occurring cardiometabolic factors would allow for better tailoring of interventions to manage and prevent frailty. Thus, identifying subgroups of older adults with unique combinations of cardiometabolic risk factors and their association with frailty/frailty features could enhance precision-based care. In addition, future studies should examine the associations between cardiometabolic risk factors and frailty and the role of underlying inflammatory mechanisms. A better understanding of mechanisms underlying the association between cardiometabolic risk factors and frailty can inform treatment strategies. Future studies should examine how associations between cardiometabolic risk factors and frailty vary by sociodemographic attributes such as gender, race, and ethnicity. More studies are needed to explore whether antecedent life determinants, including exposure to biopsychosocial stressors, influence the associations between cardiometabolic risk factors and frailty. Examining gender, race/ethnic stratification, and biopsychosocial stressors influencing the associations between cardiometabolic risk factors and frailty would help allocate resources for

tailored/targeted health programs to prevent and manage frailty. In clinical settings, healthcare professionals need to prioritize the assessment of frailty among patients with greater cardiometabolic risk factors. Care providers should be cautious of frailty in those with cardiometabolic risk before devising a care and treatment strategy.

#### **2.4.1 Strengths and Limitations**

The main strength of this systematic review was the rigorous methodologies involved in identifying and selecting the existing studies from multiple databases. This study is the first to synthesize the association between a range of potentially modifiable cardiometabolic risk factors and frailty. Future studies can use comprehensive search strategies to replicate data collection. The risk of bias in each study was evaluated using widely accepted tools. However, our findings should be interpreted in light of several limitations. The included studies had cross-sectional and longitudinal designs, restricting causal associations between cardiometabolic risk factors and frailty. The effect estimates demonstrating the associations between cardiometabolic risk factors and frailty were heterogeneous, which could stem from variation across the studies in terms of a) clinical characteristics (participants' age, race/ethnicity, gender, cardiometabolic risk severity, clinical comorbidities) and b) methodological characteristics (settings, designs, sample size, operationalization of cardiometabolic risk factors, frailty, and covariates). A pooled estimate could not be computed due to clinical and methodological heterogeneity across

the studies, limiting the generalizability of findings and comparison of results with other reviews (Lee, 2019).

## **2.5 Conclusion**

Our review demonstrates that hyperglycemia, abdominal obesity, and co-occurrence of multiple cardiometabolic risk factors are associated with a greater likelihood of frailty among older adults. More studies are needed to examine the association between other cardiometabolic risk factors, including dyslipidemia and elevated blood pressure, and frailty. Our review revealed considerable heterogeneity in the study population, designs, operationalization of frailty, cardiometabolic risk factors, and covariates, limiting the quantitative synthesis of findings. Therefore, more studies are needed to examine the association between cardiometabolic risk factors and frailty using a uniform definition of frailty and cardiometabolic risk factors adjusting for potential covariates. Future studies need to identify specific combinations of cardiometabolic risk factors in older adults and their associations with frailty to inform precision-based clinical intervention and practice. Including multi-racial and ethnic groups in future studies increase understanding of the differential impact of cardiometabolic risk burden on frailty, and helps identify high-risk groups.

## **3. Structural Determinants and Cardiometabolic Typologies Related to Frailty**

### ***3.1 Introduction***

Frailty is a clinical syndrome attributed to compromised physiological reserve, afflicting over 6 million older adults (15%) in the United States (US) (Bandeen-Roche et al., 2015). Striking disparities exist in the distribution of frailty across structural social determinants of health (hereafter, structural determinants) in the US (Bandeen-Roche et al., 2015). Structural determinants, including gender, race and ethnicity, and education, shape disparate health outcomes attributed to social stratification leading to unequal distribution of intermediary risk or protective factors (Solar & Irwin, 2010). In the US, frailty is disproportionately higher in women (17%) than men (13%). Similarly, frailty prevalence is higher in Hispanic (24%) and non-Hispanic Black older adults (22%) than non-Hispanic White older adults (14%) and among lower socioeconomic groups (Bandeen-Roche et al., 2015). Frailty-associated adverse health outcomes such as falls (Kojima, 2015), fractures (Kojima, 2016), premature disabilities (Kojima, 2017), and death (Kojima et al., 2018) are higher among older women, Hispanic and non-Hispanic Black adults (Dharmasukrit et al., 2021). Identifying factors contributing to frailty and related disparities is pivotal to informing interventions designed to better manage complex geriatric syndromes, eliminate disparities, and prevent adverse health outcomes.

The number of older adults with chronic diseases is increasing. Research has shown that frailty is associated with lung disease (Marengoni et al., 2018), cancer (Ness & Wogksch, 2020), diabetes mellitus (Aguayo et al., 2019), coronary artery disease (Marinus et al., 2021), heart failure (Denfeld et al., 2017), and stroke (Palmer et al., 2019). Multimorbidity, having two or more chronic diseases simultaneously, is present in more than 80% of older adults (Buttorff et al., 2017). Chronic cardiometabolic diseases such as diabetes mellitus and cardiovascular disease often co-occur and increase the frailty risk (Gao et al., 2021). Potentially modifiable risk factors for these chronic cardiometabolic diseases (e.g., elevated blood sugar, obesity, abdominal obesity, increased C-reactive protein (CRP), dyslipidemia, and elevated blood pressure) may inform novel interventions to better manage and delay frailty (Shakya et al., 2022). While the co-occurrence of multiple cardiometabolic factors is linked with frailty (Lee et al., 2020; Pérez-Tasigchana et al., 2017; Shakya et al., 2022), the relationship between specific combinations (typologies) and frailty is unclear. Identifying distinct cardiometabolic typologies may assist clinicians in identifying older adults who need focused interventions to delay frailty and facilitate independent aging in the community.

Structural determinants of health, such as gender, race and ethnicity, and education, can influence cardiometabolic typologies and subsequent frailty. Prior studies have documented a disproportionate distribution of cardiometabolic factors by structural determinants. For example, non-Hispanic Black adults are more likely to experience

elevated blood pressure, high blood sugar, and a lower burden of dyslipidemia than non-Hispanic White adults (He et al., 2021; Kuk & Ardern, 2010). Women are more likely to manifest abdominal obesity, lipid disorders, and elevated blood pressure in later life than men (Kuk & Ardern, 2010). Individuals with lower education experience more cardiometabolic factors (McCurley et al., 2017). To our knowledge, no studies have examined the role of both structural determinants and cardiometabolic typologies on frailty.

Building upon prior work, the goal of this study was to identify distinct cardiometabolic typologies in community-dwelling older adults and then characterize their relationship with structural determinants and frailty, covarying for individual characteristics related to frailty (age, social/behavioral factors, and chronic conditions) (Feng et al., 2017). We aimed to 1) identify distinct latent subgroups of older adults with different combinations of cardiometabolic factors (cardiometabolic typologies), 2) determine the relationship between structural determinants (gender, race/ethnicity, education) and identified cardiometabolic typologies, and 3) examine the relationship between cardiometabolic typologies and frailty among older adults.

## **3.2 Method**

### **3.2.1 Design**

This cross-sectional, correlational, descriptive study was an exploratory secondary analysis of data from the Health and Retirement Study (HRS) designed to identify

subgroups of community-dwelling older adults with distinct cardiometabolic typologies and characterize their relationship with structural determinants and frailty.

### **3.2.2 Conceptual Framework**

The World Health Organization's [WHO] Conceptual Framework of Action on Social Determinants of Health (CSDH) framework guided this study. This framework posits that structural determinants, including socioeconomic, political context and indicators of socioeconomic position (gender, race and ethnicity, and education), shape the social hierarchy. Social hierarchies engender and maintain the disproportional distribution of intermediary biological, psychosocial, material, and physical risk factors, resulting in health disparities (Solar & Irwin, 2010). Structural determinants shape individuals' position in a social hierarchy, with a more favorable position having better access to resources that protect health (Solar & Irwin, 2010). The multilevel conceptual model applied in this study details the hypothesized relationships between the structural determinants, cardiometabolic typologies, and frailty among community-dwelling older adults (See Appendix A1).

### **3.2.3 Data Source**

Data were from the Health and Retirement Study (HRS), a biennial, longitudinal, nationally representative survey of US adults aged 51 years and above (Sonnegg et al., 2014). The HRS started collecting biomarkers, physical assessments, and psychosocial information from a random half of the participants in 2006. Data were collected from the

remaining half in 2008, with the process repeated in subsequent waves. Participants were excluded from physical and biomarker assessments if they 1) were living in a nursing home at the time of the interview, 2) required the help of a proxy respondent, and 3) completed the interview via telephone. Data for structural determinants, social factors, behavioral factors, chronic conditions, and physical assessments were retrieved from the RAND HRS (Bugliari et al., 2019). The biomarker data were retrieved from sensitive HRS files (Servais, 2010). This study pooled the random halves of participants interviewed in 2006 and 2008 to form a cross-sectional cohort with physical and biomarker assessments required for assessing frailty and cardiometabolic indicators. We obtained an exemption from the Institutional Review Board for this secondary analysis of deidentified data and special permission from the University of Michigan to use the sensitive cardiometabolic biomarker data.

### **3.2.4 Analysis Sample**

The subpopulation of interest was community-dwelling older adults aged 65 years and above, with physical and biomarker assessments in 2006 or 2008. Out of 11,352 participants ( $\geq 65$  years), 1464 were excluded because they were ineligible for physical and biomarker assessments, as described earlier. Of the 9888 eligible participants, only 8355 consented to participate in physical and biomarker assessments. Finally, 371 participants were excluded because their sample weight was assigned to zero ( $n = 168$ ) or

was missing (n = 203). Our final analytic sample included 7984 adults aged 65 and older (Appendix Figure B2).

### **3.2.5 Measures**

#### **3.2.5.1 Frailty**

Frailty was operationalized using the Fried phenotype measure (Fried, Tangen, Walston, Newman, Hirsch, Gottdiener, Seeman, Tracy, Kop, Burke, et al., 2001), as shown in Appendix B1. It included five features: 1) poor handgrip strength (strength below gender and BMI cutoffs), 2) slow gait speed (speed below gender and height cutoffs), 3) perceived exhaustion or fatigue (affirmative response to either “could not get going” or “felt everything was an effort”), 4) weight loss (10 pounds or more in the past two years), and 5) reduced physical activities (low participation in moderate or vigorous physical activities equivalent to expending less than 300 kcal/week). Each feature was dichotomized (0 = no/absent or 1 = yes/present). The presence of at least three features met the criteria for frailty, coded as 0 (no) or 1 (yes).

#### **3.2.5.2 Cardiometabolic Factors**

Seven cardiometabolic factors were assessed and included as indicators in the LCA: 1) elevated blood pressure (BP, systolic BP  $\geq$  130 mm Hg or diastolic BP  $\geq$  85 mm Hg or self-reported hypertension or use of antihypertensive medication), 2) abdominal obesity (> 102 cm for men, and > 88 cm for women), 3) general obesity (BMI  $\geq$  30 kg/m<sup>2</sup>), 4) elevated total cholesterol (> 240 mg/dl), 5) elevated blood sugar (glycated

hemoglobin  $\geq$  5.7% or self-reported use of medication for controlling blood glucose) (Sherwani et al., 2016), 6) lower HDL ( $<$  40mg/dl for men and  $<$  50 mg/dl for women) (Alberti et al., 2009), and 7) elevated CRP ( $>$  3 mg/dl) (Pearson et al., 2003). Each factor was coded as a binary indicator (0 = no/absent or 1 = yes/present) for the LCA.

### **3.2.5.3 Structural Determinants**

Structural determinants included self-reported gender: male or female; race and ethnicity: Hispanic or Latino, irrespective of race (hereafter, Hispanic); non-Hispanic African American/ Black (hereafter, Black), non-Hispanic Caucasian/White (hereafter, White); and non-Hispanic other racial and ethnic minority groups [included those who identify as American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander]); and education: less than high school, high school or GED, some years of college or associate degree, and a four-year college degree or higher, collected as part of HRS survey.

### **3.2.5.4 Individual Characteristics**

Individual characteristics were age in years (65-69, 70-74, 75-79, and 80 and above), marital status (married/partnered or not), smoking history (current/former smoker or non-smoker), and chronic conditions. Self-reported chronic conditions included cardiovascular disease (heart attack, coronary heart disease, angina, congestive heart failure, or heart problem), stroke, chronic lung disease, diabetes, and cancer, each coded

as (yes/ present or no/absent). These individual characteristics were included as covariates in the analytic models based on prior research (Feng et al., 2017).

### **3.2.6 Statistical Analysis**

Descriptive statistics were used to characterize the sample and key analytic variables (Appendix Table B1). Unweighted descriptive statistics were calculated for key variables before applying multiple imputation methods and sampling weights. Weighted descriptive and inferential results reflect data for which both imputation methods and sampling weights had been applied. Non-directional statistical tests were conducted with a significance set at 0.05 for each test. Effect sizes and 95% confidence intervals (CI) addressed clinical significance. HRS-provided sampling weights were applied in all analyses to adjust for under- and over-representation of demographic subpopulations, and standard errors were adjusted for clustering and stratification. Analyses were conducted using SAS 9.4.2® (Cary, NC) and IVEware (University of Michigan, MI).

#### **3.2.6.1 Multiple Imputations**

Missing data rates ranged from 0 to 0.7% for sample characteristics (structural determinants and individual characteristics), 0.05 to 6.3% for frailty features, and 0% to 19.2% for cardiometabolic factors. To avoid biasing the results by excluding individuals with missing data, IVEware was used to multiply impute missing data (Jakobsen et al., 2017). Multiple imputations were performed 40 times with 20 iterations and a random seed (White et al., 2011).

### 3.2.6.2 Aim 1 Latent Class Analysis (LCA)

LCA is a person-centered modeling technique based on the premise that individuals can be divided into latent subgroups (classes) based on an unobserved construct (Lanza & Rhoades, 2013). A sequence of LCA models with seven cardiometabolic indicators was examined for the multiply imputed datasets (Basagaña et al., 2013). Each model differed in the specified number of latent classes (subgroups) to determine the best-fitting model for cardiometabolic indicator data and the optimal number of subgroups of older adults. The following goodness of fit indices were used to evaluate each model: Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), sample-adjusted Bayesian Information criterion (aBIC), and Bootstrap Likelihood Ratio Test (BLRT). Lower AIC, BIC, and aBIC values reflect a better fitting model, and BLRT ( $p \leq .05$ ) was also used to select between two sequential models. We also considered entropy to determine the final optimal model. Entropy values can range from 0-1, with higher scores indicating a greater degree of subgroup (class) separation. Although entropy  $> 0.80$  is recommended (Lanza & Rhoades, 2013), values between 0.60 to 0.70 were considered acceptable in a recent LCA study evaluating cardiometabolic indicators (Ahanchi et al., 2019).

Rao-Scott chi-square ( $\chi^2$ ) tests followed by pairwise contrasts were used to examine LCA subgroup differences in the proportion of each cardiometabolic indicator and determine the cardiometabolic typologies of the older adults comprising each

identified subgroup. *A posteriori* pairwise comparisons were performed when there was a statistically significant overall subgroup effect ( $p \leq .05$ ).

### 3.2.6.3 Aim 2 LCA Subgroups and Structural Determinants

The association between structural determinants (gender, race/ethnicity, and education) and each LCA subgroup (cardiometabolic typologies) was examined. Rao-Scott  $\chi^2$  tests were performed to examine the bivariate association between the LCA subgroups and each structural determinant. We then conducted a covariate-adjusted multivariable logistic regression analysis that included all three structural determinants and individual characteristics (covariates) as explanatory variables in the model to determine their relationship with each LCA subgroup. Rather than conducting a multinomial logistic regression with all cardiometabolic subgroups as levels of the LCA outcome, we conducted a separate analysis for each cardiometabolic typology subgroup (0 = no, 1 = yes, member of the subgroup of interest) because a distinct healthy reference subgroup with a low proportion of seven cardiometabolic indicators did not emerge from the LCA analysis. *A priori* pairwise contrasts were performed to examine the relationship of structural determinants and covariates with each cardiometabolic subgroup. *A priori* contrasts were deemed suitable because of a lack of prior studies guiding the relationship between cardiometabolic typologies and structural determinants of health and the exploratory nature of the analyses. Adjusted odds ratios (aORs) and their 95% CIs were reported.

#### **3.2.6.4 Aim 3: LCA Subgroups and Frailty**

Bivariate and covariate-adjusted logistic regression analyses with *a priori* contrasts were conducted to examine the relationship between LCA subgroups and frailty to identify older adults at greater risk for frailty based on their cardiometabolic typologies.

#### **3.2.6.5 Supplemental Mediation Analysis**

A mediation analysis with *a priori contrasts* was conducted to explore whether the LCA subgroup variable (representing the different cardiometabolic typologies) was a mediator of the relationship between the structural determinants and frailty.

Recommendations and guidelines proposed by Baron and Kenny (1986) and Kraemer et al. (2002) were applied. The criterion for each of the four paths (A, B, C, and C') must be met to establish the LCA subgroup as a mediator (Appendix B, Figure B1). For the mediation analysis, all paths were tested with covariate-adjusted models. For Path A, a significant relationship must exist between one or more structural determinants and one or more LCA subgroups. For Path B, a significant relationship must exist between the LCA subgroup and frailty. For Path C, a significant relationship must exist between one or more structural determinants and frailty. For Path C', a previously established significant relationship between the structural determinant and frailty must diminish when controlling for the mediator (LCA subgroup as a covariate in the model).

### **3.2.6.6 Statistical Power**

A sample size of 500 or more is recommended for the LCA analysis (Sinha et al., 2021). Our sample size of 7984 was adequate to identify LCA subgroups of older adults. The sample size provided at least 80% statistical power to conduct the multivariable logistic regression analyses with *a priori* pairwise contrasts, assuming medium effects (aOR = 1.44 to 2.46) and two-tailed significance set at 0.05 (Schoenfeld & Borenstein, 2005).

## **3.3 Results**

### **3.3.1 Sample Characteristics**

Table 3 details the unweighted and weighted sample characteristics (N = 7984). The following describes weighted results. Age ranged from 65 to 101 years, with 30% in the 65-69 age group. Most participants were female (57%), White (85%), not married or partnered (58%), and current/former smokers (57%). The common chronic diseases were cardiovascular disease (32%), diabetes mellitus (22%), and cancer (19%).

### **3.3.2 Cardiometabolic and Frailty Characteristics**

As shown in Table 4, the most common cardiometabolic characteristics were elevated blood pressure (81%), followed by abdominal obesity (64%), and elevated blood sugar level (52%). Elevated total cholesterol (TC) was present in only 16% of older adults, and less than 3% of older adults had no cardiometabolic indicators.

The frailty prevalence was 22.0%. The prevalence for pre-frailty (1-2 features) and non-frailty (no features) was 51% and 28%, respectively. The most commonly occurring features were reduced physical activity (43%), followed by slow gait speed (40%), fatigue (32%), and poor grip strength (28%). Only 2.6% experienced weight loss.

**Table 3: Sociodemographic and clinical characteristics of participants (N = 7984)**

Characteristic	N	Unweighted		Weighted	
		f	%	%	95% CI
Female gender	7984	4596	57.6%	56.8%	55.7-57.9%
Race/ethnicity	7983				
Hispanic/Latinx		607	7.6%	5.5%	3.8-6.9%
NH White		6286	78.8%	85.4%	83.3-87.4%
NH Black/AA		965	12.1%	7.7%	6.6-8.7%
NH Others		125	1.6%	1.7%	1.1-2.2%
Education	7984				
Less than High School		1904	23.1%	22.3%	20.6-23.9%
High School Graduate		3021	37.8%	37.6%	36.2-39.1%
Some college		1568	19.6%	19.9%	18.9-21.1%
College or higher		1491	18.7%	20.1%	18.1-22.1%
Age category	7984				
65-69 years old		2368	29.7%	29.6%	27.9-31.2%
70-74 years old		2129	26.7%	23.5%	22.7-24.7%
75-79 years old		1836	23.0%	23.2%	21.9-24.4%
80 years and above		1651	20.7%	23.6%	22.3-25.0%
Married/partnered	7984	3029	37.9%	41.5%	40.1-42.9%
Current/former smoker	7927	4512	56.9%	57.4%	55.8-59.0%
Chronic conditions					
Heart diseases	7983	2507	31.4%	31.6%	30.4-32.7%
Diabetes mellitus	7979	1863	23.2%	21.5%	20.4-22.6%
Stroke	7982	639	8.0%	8.4%	7.8-8.9%
Chronic lung disease	7978	988	12.3%	12.7%	11.7-13.8%
Cancer	7981	1501	18.8%	19.3%	18.1-20.4%

*Note.* N = Non-missing data available prior to imputations, f = Unweighted frequencies, 95% CI = 95% Confidence Interval, NH = Non-Hispanic/Non-Latinx, AA = African American, Education: Some college/Associate = Associate's degree

**Table 4: Cardiometabolic and frailty characteristics of participants (N = 7984)**

Characteristic	Unweighted			Weighted	
	<i>N</i>	<i>f</i>	%	%	95% <i>CI</i>
CM indicators					
Elevated blood pressure	7984	6497	80.7%	81.1%	80.3-81.9%
Elevated blood sugar	7025	3696	50.9%	52.3%	50.7-50.7%
Lower high-density lipoprotein	6454	2127	32.7%	33.1%	31.6-34.6%
Elevated total cholesterol	7498	1166	15.6%	15.6%	14.4-16.7%
Abdominal obesity	7532	5010	63.8%	64.1%	62.6-65.6%
Obesity	7532	2748	35.4%	36.5%	35.2-37.9%
Elevated C-reactive protein	7616	2905	37.4%	39.5%	38.1-40.9%
Frailty features					
Poor grip strength	7482	1879	26.4	27.5%	26.1-28.9%
Slow gait speed	7491	2578	34.1	40.3%	38.3-42.3%
Fatigue	7968	2546	31.9	31.9%	30.4-33.4%
Low physical activities	7980	3464	42.9	42.9%	41.6-44.4%
Weight loss	7701	193	2.6	2.6%	2.3-3.0%
Total # cardiometabolic indicators	5178				
0 indicator		148	2.9%	2.6%	2.2-3.0%
1 indicator		557	10.8%	10.9%	9.9-11.7%
2 indicators		1056	20.4%	20.3%	19.1-21.5%
3 indicators		1112	21.5%	22.5%	21.4-23.6%
4 indicators		1139	22.0%	22.1%	21.0-23.2%
5 indicators		801	15.5%	15.2%	14.3-16.2%
6 indicators		345	6.7%	6.0%	5.4-6.6%
7 indicators		20	0.4%	0.3%	0.2-0.5%
Frailty categories	7019				
Non-frailty		2104	26.4%	27.5%	25.8-29.2%
Pre-frailty		3664	45.9%	50.5%	49.2-51.9%
Frailty		1251	15.7%	22.0%	20.8-23.2%

*Note.* *N* = Non-missing data available prior to imputations, *f* = Unweighted frequencies, 95% *CI* = 95% Confidence Interval

### 3.3.3 Aim 1. LCA Subgroups

We reviewed results from the LCA models with two to five classes (subgroups) specified after applying imputation methods and sampling weights. We compared the model results from LCA analyses performed for 40 multiply imputed datasets, each with the specified number of classes. Table 5 provides the fit indices and entropy for the imputed datasets with the best-fitting model results. We determined that the three-class (subgroup) model provided the optimal solution based on fit indices and entropy values when applied to the 40 imputed datasets (Basagaña et al., 2013). Entropy ranged from 0.57 to 0.73 for the three-class models for the imputed datasets, which is consistent with findings from prior studies using LCA on cardiometabolic indicators (Ahanchi et al., 2019). Older adults were then assigned to a subgroup based on their most frequent optimal class assignment and highest posterior probability values generated by LCA for each of the 40 imputed datasets (Basagaña et al., 2013).

We determined a brief descriptor for each subgroup based on their typologies of cardiometabolic indicators. The first subgroup was insulin resistance (N = 3547), which was characterized by multiple cardiometabolic indicators, specifically elevated blood pressure, elevated blood sugar, abdominal obesity, obesity, and elevated CRP. The second subgroup, hypertensive dyslipidemia (N = 1246), was the smallest, with low HDL and elevated blood pressure as salient characteristics. The third subgroup, hypertensive (N = 3191), comprised older adults with primarily elevated blood pressure. Using

weighted data, bivariate Rao-Scott  $\chi^2$  tests demonstrated a statistically significant relationship between the subgroup and each cardiometabolic characteristic (all  $p < .0001$ , Appendix Table B2), with *a posteriori* pairwise contrasts, further supporting the above cardiometabolic typologies for each subgroup.

**Table 5: Latent Class Analysis: Model fit indices for the specified number of classes**

Number of LCA classes (subgroups)	LL	AIC	BIC	aBIC	Entropy	BLRT <i>p</i>
2 subgroups	-32112.7	462.1	566.8	519.2	0.69	0.01
3 subgroups	-32028.5	309.8	470.4	397.3	0.73	0.01
4 subgroups	-31974.0	216.8	433.3	334.8	0.51	0.01
5 subgroups	-31956.2	197.1	469.5	345.6	0.51	0.01

*Note.* The 3-class (3 subgroups) model selected as the optimal model based on model fit indices and entropy. LCA = Latent Class Analysis; LL = Log-likelihood, AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion, aBIC = adjusted BIC, BLRT = Bootstrap Likelihood Ratio test

### 3.3.4 Aim 2. Association Between LCA Subgroups and Structural Determinants

Bivariate results demonstrated a significant association between the LCA subgroups and each structural determinant (all  $p \leq .0007$ , Appendix Table B). Table 6 presents the covariate-adjusted multivariable logistic regression model results for each LCA subgroup (0 = no, 1 = yes, member of the subgroup).

The insulin resistance subgroup members were significantly more likely to be female, identify as Black, and be a college non-graduate. Members in this subgroup were less likely to identify as Other race and ethnic minority groups. In contrast, members of the hypertensive dyslipidemia subgroup were significantly more likely to be high school graduates and of Other race and ethnicity; and gender was not related to this subgroup. Members of the hypertensive subgroup were more likely to be male and college graduate. Race and ethnicity were not related to the hypertensive subgroup.

Results for the relationship between LCA subgroups and individual characteristics (covariates) indicated that members in the insulin resistance subgroup were more likely to be 65-69 years, not married/partnered, and have diabetes and chronic lung disease. Participants in the hypertensive dyslipidemia subgroup were more likely to be 75 years and older and have cancer but less likely to have diabetes. Participants in the hypertensive subgroup were more likely to be 80 years or older and married/partnered but were less likely to have CVD, diabetes, and cancer.

**Table 6: Association between structural determinants and LCA subgroups**

Mediation Analysis	Outcome: Each LCA Subgroup Membership						
	Path A with Covariates	Insulin Resistance (IR)		Hypertensive Dyslipidemia (HD)		Hypertensive (HTN)	
		<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>
<b>Gender</b>	---	---	---	---	---	---	
Female vs male	1.2***	1.1-1.4	0.9	0.8-1.2	0.8**	0.7-0.9	
<b>Race/ethnicity</b>	---	---	---	---	---	---	
Hispanic vs NH White	1.1	0.8-1.4	1.2	0.9-1.5	0.9	0.7-1.1	
NH Black vs NH White	1.3***	1.2-1.6	0.7**	0.6-0.9	0.9	0.7-1.0	
NH Other vs NH White	0.6*	0.4-0.9	2.3***	1.4-3.7	0.9	0.6-1.3	
NH Black vs Hispanic	1.3	0.9-1.7	0.6***	0.4-0.9	1.0	0.8-1.3	
NH Black vs NH Other	2.1**	1.3-3.6	0.3***	0.2-0.5	0.9	0.6-1.6	
Hispanic vs NH Other	1.7*	1.1-2.8	0.5**	0.3-0.8	0.9	0.6-1.5	
<b>Education</b>	---	---	---	---	---	---	
LHS vs HS	1.2*	1.0-1.4	1.0	0.8-1.2	0.8**	0.7-0.9	
LHS vs some college	1.3**	1.1-1.5	1.2	0.9-1.5	0.7***	0.6-0.8	
LHS vs ≥ college	1.6***	1.3-1.9	1.1	0.9-1.3	0.6***	0.5-0.7	
HS vs some college	1.0	0.9-1.2	1.2*	1.0-1.5	0.9	0.8-1.0	
HS vs ≥ college	1.3**	1.1-1.5	1.1	0.9-1.3	0.8**	0.6-0.9	
Some college vs ≥ college	1.2*	1.0-1.5	0.9	0.7-1.1	0.8	0.7-1.0	
<b>Age group</b>	---	---	---	---	---	---	
Age 80+ vs 65-69	0.5***	0.4-0.6	1.7***	1.4-2.0	1.4***	1.3-1.7	
Age 75-79 vs 65-69	0.8**	0.9-1.0	1.4**	1.1-1.7	1.1	1.0-1.3	
Age 70-74 vs 65-69	0.8*	0.5-1.0	1.1	0.9-1.4	1.1	0.9-1.3	
<b>Marital status</b>	---	---	---	---	---	---	
Married/partner vs not	0.8***	0.7-0.9	1.0	0.9-1.2	1.2*	1.0-1.4	
<b>Smoking behavior</b>	---	---	---	---	---	---	
Former/current smoker vs not	1.1	0.9-1.2	0.9	0.8-1.0	1.0	0.9-1.1	
<b>Chronic conditions</b>	---	---	---	---	---	---	
Heart disease vs not	1.1	0.9-1.3	1.2	1.0-1.4	0.8*	0.7-0.9	
Diabetes mellitus vs not	2.6***	2.2-2.9	0.8*	0.6-0.9	0.4***	0.3-0.5	
Stroke vs not	1.1	0.9-1.3	1.2	0.9-1.5	0.8	0.7-1.0	
Chronic lung disease vs not	1.3***	1.2-1.6	0.9	0.7-1.1	0.8*	0.8-0.9	
Cancer vs not	1.0	0.9-1.2	1.3*	1.1-1.6	0.8	0.7-1.0	

*Note.* *aOR* = adjusted Odds Ratio, *95% CI* = 95% Confidence Interval, NH = Non-Hispanic, LHS = Less than High school (high school non-graduate), HS = High school graduate,  $\geq$  college = College graduate or higher, Covariate-adjusted multivariable logistic regression model results: \* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

### 3.3.5 Aim 3. Association Between LCA Subgroups and Frailty

Table 7 presents the results from the bivariate (Model 1) and covariate-adjusted logistic regression analyses (Model 2) examining the relationship between LCA subgroups and frailty. LCA subgroup was significantly related to frailty after adjusting for covariates. The covariate-adjusted pairwise comparisons indicated that the frailty risk was significantly higher in the insulin resistance subgroup compared to hypertensive dyslipidemia (aOR = 2.1,  $p < .001$ ) and hypertensive subgroups (aOR = 2.2,  $p < .001$ ), which is clinically significant. However, the latter subgroups did not differ (aOR = 1.1,  $p > 0.05$ ). Frailty risk was significantly greater for those 70 years or older and non-married/non-partnered, as well as those with a history of heart disease, diabetes, stroke, and chronic lung disease, but not cancer (Model 2).

**Table 7: Association between structural determinants, LCA subgroup, and frailty**

	Model 1 Path B		Model 2 Path B with Covariates		Model 3 Path C with Covariates		Model 4 Path C' with Mediator	
	<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>
LCA subgroup	---	---	---	---			---	---
IR vs HD	1.7***	1.4-2.0	2.1***	1.7-2.5			2.0***	1.6-2.5
IR vs HTN	2.2***	1.9-2.5	2.2***	1.9-2.6			2.0***	1.8-2.3
HD vs HTN	1.3*	1.0-1.6	1.1	0.9-1.3			0.9	0.8-1.2
Gender								
Female vs male					1.7***	1.4-2.1	1.7***	1.4-2.0
Race/ethnicity					---	---	---	---
Hispanic vs NH White					1.7***	1.3-2.1	1.7***	1.3-2.0
NH Black vs NH White					1.9***	1.5-2.4	1.9***	1.5-2.3
NH Other vs NH White					1.0	0.6-1.8	1.1	0.6-1.9
NH Black vs Hispanic					1.1	0.8-1.5	1.1	0.8-1.5
NH Black vs NH Other					1.9	1.0-3.5	1.7	0.9-3.4
Hispanic vs NH Other					1.7	0.9-3.2	1.6	0.8-3.1
Education					---	---	---	---
LHS vs HS					1.7***	1.4-2.1	1.6***	1.4-2.0
LHS vs some college					2.6***	1.9-3.4	2.5***	1.9-3.4
LHS vs ≥ college					3.9***	2.8-5.2	3.7***	2.7-4.9
HS vs some college					1.5***	1.2-1.9	1.5***	1.2-1.9
HS vs ≥ college					2.2***	1.8-2.8	2.2***	1.7-2.7
Some college vs ≥ college					1.5**	1.2-1.9	1.5**	1.1-1.9
Age group			---	---	---	---	---	---
Age 80+ vs 65-69			4.3*	3.5-5.3	3.9***	3.2-4.9	4.6***	3.6-5.9
Age 75-79 vs 65-69			2.1***	1.7-2.5	1.9***	1.6-2.3	2.0***	1.7-2.5
Age 70-74 vs 65-69			1.3***	1.0-1.6	1.3*	1.0-1.6	1.3*	1.1-1.6
Marital status			---	---	---	---	---	---
Married/partner vs not			0.6***	0.5-0.7	0.8**	0.7-0.9	0.9	0.7-1.0
Smoking behavior			---	---	---	---	---	---
Former/current smoker vs not			1.0	0.9-1.2	1.2*	1.0-1.3	1.2	0.9-1.3
Chronic conditions			---	---	---	---	---	---
Heart disease vs not			1.5***	1.2-1.8	1.6***	1.4-1.9	1.6***	1.3-1.9

Diabetes mellitus vs not	1.7***	1.4-1.9	1.8***	1.5-2.1	1.6***	1.3-1.9
Stroke vs not	2.0***	1.6-2.4	1.9***	1.6-2.4	1.9***	1.6-2.4
Chronic lung disease	2.0***	1.7-2.5	2.0***	1.7-2.5	2.0***	1.6-2.4
Cancer vs not	0.9	0.8-1.1	1.1	0.9-1.3	1.1	0.9-1.3

*Note:* *aOR* = adjusted Odds Ratio, *95% CI* = 95% Confidence Interval, NH = Non-Hispanic, LHS = Less than high school (high school non-graduate); HS = High school graduate,  $\geq$  college = College graduate or higher, \* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$ , Model 1: Path B examining association between LCA subgroups and frailty, Model 2: Path B examining association between LCA subgroup and frailty after adjusting for covariates, Model 3: Path C examining association between structural determinants of health and frailty after adjusting for individual characteristics, Model 4: Path C' examining association between structural determinants of health and frailty after adjusting for LCA subgroup and individual characteristics.

### 3.3.6. Mediation Analysis

The following describes results from the covariate-adjusted regression models controlling for individual characteristics. Path A was tested as part of the Aim 2 examining the relationship between structural determinants and LCA subgroups. As detailed earlier, Path A results indicated that structural determinants (gender, race, ethnicity, and education) were significantly associated with LCA subgroups (Table 6). Path B was tested as part of Aim 3, examining the association between LCA subgroups and frailty. Path B covariate-adjusted results described earlier also indicated that LCA was significantly related to frailty, with the highest risk among those in the insulin resistance subgroup (Table 7, Model 2,  $p \leq 0.001$ ).

Next, we conducted the Path C analysis to determine if there was a significant relationship between one or more structural determinants and frailty. Gender, race, ethnicity, and education were significantly related to frailty (Table 7, Model 3). The frailty risk was significantly higher in females ( $aOR = 1.7, p \leq 0.001$ ). In terms of race, ethnicity, the frailty risk was significantly higher in Black older adults relative to White older adults ( $aOR = 1.9, p \leq 0.001$ ) as well as Hispanic older adults compared to White older adults ( $aOR = 1.7, \leq 0.001$ ). For education, the frailty risk increased with decreasing education. Regarding individual characteristics, the frailty risk was significantly associated with increasing age, being non-married/non-partnered, smoking history, and chronic conditions except for cancer (Table 7, Model 3, all  $\leq 0.001$ ). All

statistically significant determinants of frailty had clinically significant aORs (*aORs* > 1.44).

Finally, we conducted the Path C' analysis to examine the relationship between the structural determinants and frailty with the LCA subgroup (proposed mediator) in the model (Table 7, Model 4). Results indicated that including the mediator in the model did not diminish the influence of any of the structural determinants of frailty. Thus, cardiometabolic typologies did not mediate the relationships between structural determinants of frailty in community-dwelling older adults.

### **3.4 Discussion**

To our knowledge, this study is the first to identify distinct latent subgroups of older adults with unique cardiometabolic typologies and describe their relationships with structural determinants of health and frailty using a nationally representative cohort of community-dwelling older adults in the US. We identified three distinct latent subgroups of community-dwelling older adults (65 years and older) with cardiometabolic typologies, namely, insulin resistance, hypertensive dyslipidemia, and hypertensive. Frailty risk among the insulin resistance subgroup was higher than the other subgroups. Older adults in the insulin resistance subgroup were more likely to be female, Black, and reported less education.

Compared to hypertensive dyslipidemia and hypertensive subgroups, the frailty was risk higher in the insulin resistance subgroup, showing salient features such as

abdominal obesity, obesity, elevated blood sugar, elevated blood pressure, and elevated CRP. Our findings align with past studies reporting the relationship between frailty and multiple co-occurring cardiometabolic indicators (Gao et al., 2021; Lee et al., 2020; Pérez-Tasigchana et al., 2017) and individual factors, such as abdominal obesity (Pérez-Tasigchana et al., 2017), obesity (Yuan et al., 2021), and elevated blood sugar (Kalyani et al., 2012). Our results make a novel contribution to the existing literature by elucidating the characteristics of co-occurring cardiometabolic indicators related to frailty. Our results suggest that cardiometabolic indicators in the insulin resistance subgroup co-occur and have a magnifying influence on frailty. The frailty risk did not vary significantly between hypertensive dyslipidemia and hypertensive subgroups; thus, comparing frailty risk between older adults with these cardiometabolic typologies and optimal cardiometabolic health can further clarify the role of cardiometabolic typologies on frailty.

Prior studies provide potential explanations for the role of insulin resistance on frailty. Insulin resistance is reported to instigate non-pathogenic inflammatory responses, including activation of oxidative stress and accumulation of pro-inflammatory markers and reactive oxygen species in the body (Esser et al., 2014; Vona et al., 2019). Sustained exposure to chronic low-grade inflammation is believed to be linked to frailty in older adults (Wang et al., 2019). Future studies should examine the inflammatory links between cardiometabolic typologies and frailty.

Congruent with the WHO's CSDH framework, structural determinants were important predictors of frailty (Solar & Irwin, 2010). In our study, frailty risk was higher among females relative to males and in Hispanic and Black older adults relative to White older adults, which concurs with results from prior studies (Feng et al., 2017; Gordon et al., 2017; Usher et al., 2021). Similar to this study, higher frailty risk in those with lower education status has been reported in the Women's Health and Aging studies and other longitudinal studies (Hoogendijk et al., 2014; Szanton et al., 2010). Our results further support that disparities in frailty exist across gender, race/ethnicity, and educational status using a national dataset.

Contrary to our expectations and the WHO's CSDH framework, cardiometabolic typologies did not mediate the relationship between structural determinants and frailty. Several reasons may explain these unexpected results. Frailty is multifactorial, and several biological and psychosocial factors may mediate the relationship between structural determinants and frailty (Feng et al., 2017). For example, women experience a marked decline in the reproductive hormones with menopause relative to men who do not experience such a drop in testosterone, which might be protective against frailty (Hägg & Jylhävä, 2021). Exposure to psychosocial factors such as discrimination, financial strain, social isolation, and poor social support may act as mediators between structural determinants and frailty (Wang et al., 2019). Females, racial and ethnic minority groups, and those with less education are more likely to be exposed to psychosocial factors

(Brown et al., 2020) and subsequent frailty (Wang et al., 2019). Future studies need to examine additional biological and psychosocial mediators between structural determinants and frailty.

The results of this study should be interpreted in the context of its strengths and limitations. Particularly, our study extends the existing evidence by describing the combination of cardiometabolic indicators related to frailty; it suggests that certain combinations of cardiometabolic indicators magnify the frailty risk. These results lay the groundwork to inform interventions to manage and delay frailty. Our results support current evidence by demonstrating disparities of frailty across gender, race, ethnicity, and education, which can be important for developing culturally adapted interventions to mitigate frailty disparities. Our study involves a nationally representative sample of community-dwelling older adults; thus, results are generalizable to community-dwelling US older adults. Future studies should examine the relationship between structural determinants, cardiometabolic typologies, and frailty in different populations and settings.

Despite the strengths of our study, we acknowledge several limitations. First, this is a cross-sectional study; therefore, a causal relationship between structural determinants, cardiometabolic typologies, and frailty cannot be established. Second, response bias is widely discussed in clinical and behavioral research where self-reported data are used. Our study involved several self-reported clinical and behavioral measures,

which can be prone to biases. Less than 3% of participants were free of cardiometabolic factors; the ‘ideal healthy’ subgroup could have served as a reference point for evaluating frailty differences across different cardiometabolic typologies. Finally, our analytic sample included participants who completed the physical and biomarker assessments in the HRS survey. These participants might be relatively healthier than non-participants, which could have underestimated cardiometabolic factors and frailty among participants. We applied *a priori* contrasts at the 0.05 level due to the exploratory nature of the relationships of structural determinants, cardiometabolic typologies, and frailty in older adults to avoid missing important associations that may exist. Although our main concern was false negatives, we recognize that the false positive (Type I) error rate may exceed 5% due to the number of multiple comparisons.

### **3.5 Conclusion**

Our national study provides a better understanding of the relationship among cardiometabolic typologies, structural determinants, and frailty in community-dwelling older adults. Relative to hypertensive dyslipidemia and hypertensive subgroups, the frailty risk was greater in the insulin resistance subgroup, whose participants were more likely to be females, Black older adults, and reported less education. Cardiometabolic typologies did not mediate the relationship between structural determinants of health and frailty. Further research is encouraged to 1) evaluate the potential biological and psychosocial factors that may mediate the relationship between structural determinants of

health and frailty and 2) investigate the barriers experienced by older adults at the greatest risk for frailty if such disparities are to be eliminated.

## **4. Structural and Psychosocial Determinants of Frailty in Community-dwelling Older Adults**

### ***4.1 Introduction***

Frailty is a geriatric syndrome attributed to physiologic dysfunction (Proietti & Cesari, 2020) and contributes to falls (Kojima, 2015), fractures (Kojima, 2016), premature disability (Kojima, 2017), and deaths (Kojima et al., 2018) in older adults. Frailty affects more than 16 million or 15% of older adults 65 years and above in the United States (US) (Bandeen-Roche et al., 2015). Frailty prevalence is starkly higher in women (16%), those with low income (25%), and older adults who identify as Hispanic (24.6%) and non-Hispanic Black (22.9%) than in men (13%), those with high income (6%), and White older adults (14%) (Bandeen-Roche et al., 2015). Women, Hispanic, and non-Hispanic Black older adults are more likely to experience worse outcomes, such as functional decline, rehospitalization, and poor surgical outcomes attributed to frailty relative to their respective counterparts, reflecting multiple adverse burdens among historically socioeconomically disadvantaged subpopulations (Dharmasukrit et al., 2021). Frailty is reversible, and its development can be delayed (Coelho-Júnior et al., 2021); thus, identifying modifiable factors contributing to frailty can inform interventions to prevent and delay frailty and eliminate frailty disparities. However, the underlying mechanism contributing to the disparate distribution of frailty is unclear.

Social determinants of health are key drivers of health and health disparities that work through a complex interplay between structural social determinants and intermediary factors. Structural social determinants of health (hereafter, structural determinants) encompass socioeconomic, political, and cultural contexts that shape socioeconomic position and social hierarchies contingent on individuals' gender, race, ethnicity, and education, leading to differential exposure to intermediate health-protective/ damaging factors (Solar & Irwin, 2010). Social hierarchies confer structural advantages and disadvantages such that disadvantaged groups are disproportionately exposed to a host of health-damaging factors with poor access to protective resources/opportunities (Singh et al., 2017). Investigating frailty through the lens of social determinants of health can elucidate mechanisms through which structural determinants operate and contribute to frailty disparities. Frailty disparities exist even after controlling for established biological (cardiovascular disease, stroke, diabetes mellitus, lung disease, obesity) and behavioral (smoking) factors (Usher et al., 2021); thus, there is a need to explore other contributors to frailty beyond these biological/behavioral factors. Currently, scant evidence exists on the potential mediating role of psychosocial stressors.

Older adults experience co-occurring psychosocial stressors stemming from multiple life domains (Scott et al., 2011). Exposure to psychosocial stressors varies by structural determinants as women, Hispanic individuals, non-Hispanic Black older adults,

and those with less education report experiencing a multitude of psychosocial stressors, including loneliness, discrimination, financial strain, low subjective social status, traumatic life events, and poor neighborhood cohesion, than their respective counterparts (Brown et al., 2020; Marshall et al., 2022; Mayor, 2015). Although psychosocial stressors are linked with adverse physical and mental health outcomes (O'Connor et al., 2021; Turner et al., 2020), only a few studies have examined the negative role of individual psychosocial stressors on frailty. Studies have documented that social isolation and poor neighborhood cohesion increase the risk of frailty (Fritz et al., 2020; Gale et al., 2018). However, no prior studies have examined the cumulative influence of multiple, co-occurring psychosocial stressors on frailty and frailty disparities.

#### **4.1.1 Conceptual Framework**

We used the World Health Organization's conceptual framework for action on the social determinants of health (CSDH) to inform this study (Solar & Irwin, 2010). According to this framework, health is a product of an intricate interplay between structural determinants and intermediary factors. Structural determinants include socioeconomic, political, and cultural contexts, which shape socioeconomic position generating social hierarchies based on gender, race, ethnicity, and education. Structural determinants precede intermediary factors in the mechanistic pathways such that individuals' ranking in social hierarchies can influence differential exposure to health-protective or damaging factors. Social hierarchies engender and perpetuate health

disparities through disproportional exposure to intermediary material, biological, physical, and psychosocial risk factors, and differential access to protective resources. The multilevel conceptual model used in this study hypothesizes that structural determinants (gender, race, ethnicity, and education) are related to the differential exposure to cumulative psychosocial stress, which may contribute to frailty disparities among community-dwelling older adults (See Appendix Figure C1).

#### **4.1.2 Research Aims**

Building on existing evidence, the objective of this study was to extend our understanding of the role of structural determinants (gender, race, ethnicity, and education) and cumulative psychosocial stress on frailty among community-dwelling older adults. Specifically, the aims were to 1) develop a measure to assess cumulative psychosocial stress, 2) determine the relationship between structural determinants of health and cumulative psychosocial stress, covarying for individual characteristics, 3) determine the relationship between structural determinants of health and frailty, covarying for individual characteristics, and 4) determine whether cumulative psychosocial stress mediates an existing relationship between structural determinants and frailty, covarying for individual characteristics. A deeper understanding of how structural determinants operate through psychosocial stress and influence frailty can inform the development of interventions for preventing/ delaying frailty.

## **4.2 Methods**

### **4.2.1 Design**

This cross-sectional, descriptive, correlational study was a secondary analysis of data from the Health and Retirement Study.

### **4.2.2 Data Source**

HRS is an ongoing biennial, nationally representative survey of US adults aged 51 years and older (Fisher & Ryan, 2018). In 2006, HRS initiated enhanced face-to-face interviews among a random half of the participants. Physical and biomarker data were collected via examination, and psychosocial information was collected via self-administered questionnaires among the random half of the participants. The remaining half was assessed in 2008, with the same process replicated in successive waves. Participants were eliminated from the enhanced HRS interview if they 1) were institutionalized at the time of the HRS survey, 2) completed the HRS survey with the assistance of a proxy, and 3) participated in the HRS survey by telephone. We combined random halves of participants from 2006 and 2008 to form a single cross-sectional cohort with data to assess psychosocial factors and frailty. This study involving the secondary analysis of the deidentified data was reviewed and exempted by the Institutional Review Board (IRB) at Duke University.

### **4.2.3 Analytic Sample**

Our subpopulation of interest was community-dwelling older adults ( $\geq 65$  years) assessed for physical and psychosocial factors in 2006 and 2008. Among 11,352 participants ( $\geq 65$  years), 1,464 were ineligible for enhanced interviews for the reasons stated earlier. Among 9,888 eligible participants, 8,355 consented to participate in the enhanced interview. We removed 676 participants with sampling weights assigned to zero because they were not cohort eligible, deceased, or did not meet the eligibility criteria described earlier; the analytic sample included 7,679 participants (see Appendix Figure C2).

### **4.2.4 Measures**

#### **4.2.4.1 Frailty**

We operationalized frailty using the Fried phenotype (Fried et al., 2001) by assessing 1) poor handgrip strength (strength below gender and body mass index [BMI] specific cutoffs), 2) slow walking speed (speed below gender and height cutoffs), 3) weight loss ( $\geq 10$  pounds in the previous two years), 4) fatigue or exhaustion (endorsed either “could not get going” or “felt everything was an effort”), and 5) low physical activity (non-participation in heavy/moderate activities or expending less than 300 kcal/week), each coded yes or no. We examined the prevalence rates of frailty, pre-frailty, and non-frailty. The absence of these features was coded as non-frailty, and the presence of one or two features was coded as pre-frailty. The manifestation of three or

more of these features was considered frailty. For the regression analyses, frailty was coded as 1 (yes) or 0 (no).

#### **4.2.4.2 Psychosocial Factors**

We examined six psychosocial stressors: (1) loneliness, (2) everyday discrimination, (3) financial strain, (4) poor neighborhood cohesion, (5) low subjective social status, and (6) traumatic life events. Based on prior empirical studies, each psychosocial variable was dichotomized into high (1) and low psychosocial (0) stressor (Cobb et al., 2022; Ferreira et al., 2018; Mendes de Leon et al., 2009; Steptoe et al., 2013; Tutz, 2021).

**Loneliness.** HRS assessed loneliness using the abbreviated UCLA Loneliness Scale (Russell, 1996) and asked participants to rate the perception of a) a lack of companionship, b) feeling left out, and c) being isolated from others. For each item, responses were rated on a Likert scale (1, *often*; 2, *sometimes*; and 3, *hardly ever/never*). The scores across these items were added to obtain an overall score ranging from 3 to 9; a lower score reflects greater perceived loneliness. The midpoint split technique was used to dichotomize the overall score into high loneliness (overall score = 3-5) and low loneliness (overall score = 6-9) based on the scale midpoint (Steptoe et al., 2013).

**Everyday Discrimination.** HRS assessed everyday discrimination using the abbreviated Everyday Discrimination Scale (Williams & Mohammed, 2009). This scale assesses the daily encounter of a) being treated with less courtesy or respect than other

people, b) receiving poorer service than others at restaurants or stores, c) being treated as not smart, d) people acting afraid, and e) being threatened or harassed. Responses for each item were rated on a 5-point Likert scale (1, *almost every day*; 2, *at least once a week*; 3, *a few times a week*; 4, *a few times a month*; 5, *less than once a year*; and 6, *never*). We averaged the scores across the items to obtain an overall score of perceived discrimination (Cobb et al., 2022). Encountering discrimination on a “daily,” “weekly,” or “monthly” basis was categorized as high perceived everyday discrimination (overall score = 1 to 4.9), and the rest was categorized as low perceived everyday discrimination (overall score = 5 to 6) (Jackson et al., 2019).

**Financial Strain.** We assessed financial strain by assessing difficulty in meeting monthly bills. Responses were rated on a 5-point Likert scale (1, *not at all difficult*; 2, *not very difficult*; 3, *somewhat difficult*; 4, *very difficult*; 5, *completely difficult*) (Wilkinson, 2016). Those affirming it to be “very difficult” or “completely difficult” were categorized into high financial strain, and the rest were categorized into low financial strain.

**Neighborhood Cohesion.** In HRS, participants’ perception of neighborhood cohesion was assessed by asking if they perceived a) being part of the local area, b) trust among people in the neighborhood, c) friendliness among people, and d) safety while walking alone. For each item, responses were rated on a 7-point Likert scale (ranging from 1, *strongly agree* to 7, *strongly disagree*). The scores from the four items were averaged to get an overall score ranging from 1 to 7, with a lower score indicating greater

neighborhood cohesion (Mendes de Leon et al., 2009). We used the mid-point split technique to dichotomize categories into high (overall score = 1 to 3.9) and low neighborhood cohesion (overall score = 4 to 7) based on the scale midpoint.

**Subjective Social Status.** HRS assessed subjective social status using the MacArthur Scale, which encompasses ranking oneself on the social ladder (ranging from 1 to 10). A lower score represents a worse position with little money, little education, and poor or no job (Adler et al., 2000). The score was dichotomized into low (score = 1 to 3) and middle/high subjective social status (score = 4 to 10) (Ferreira et al., 2018).

**Traumatic Life Events.** Traumatic life events were assessed using the Life Events Checklist for the Diagnostic and Statistical Manual of Mental Disorders-5 [DSM-5] collected in HRS (Crosswell et al., 2020; Weathers et al., 2013). The presence of any traumatic life events was coded as a) death of a child, b) experience of a major fire, flood, earthquake, or natural disaster, c) having a spouse, partner, or child ever addicted to drugs or alcohol, d) experience of a life-threatening illness or accident, or e) having a spouse or child with a life-threatening illness or accident.

#### **4.2.4.3 Structural Determinants.**

Structural determinants were based on self-reported gender: male and female; race and ethnicity: Hispanic/Latino, irrespective of race (hereafter, Hispanic), non-Hispanic Black/African American (hereafter, Black), non-Hispanic Caucasian/White (hereafter, White), and non-Hispanic other race and ethnic minorities (those who identify

as American Indian, Alaska Native, Asian, Native Hawaiian, Pacific Islander); and education: less than high school, high school or General Educational Development [GED], some years of college or associate degree, and a four-year college degree or higher, as documented in the HRS survey.

#### **4.2.4.4 Individual Characteristics**

Individual characteristics included age in years (65-69, 70-74, 75-79, and 80 and above), self-reported marital status (being married/partnered versus not), smoking history (current/former smoker versus non-smoker), and chronic conditions (cardiovascular disease, stroke, chronic lung disease, diabetes, and cancer, each coded as yes or no). These individual characteristics were included as covariates in the analytic models. Appendix Table C1 details the operationalization of key variables.

#### **4.2.5 Data Analysis**

We used descriptive statistics to summarize sample characteristics and key variables. We reported unweighted descriptive statistics before applying imputation methods and weighted descriptive and inferential statistics after applying imputation. We conducted non-directional statistical tests with a significance set at 0.05 for each test. We reported effect sizes and 95% confidence intervals (*CIs*) to address clinical significance. Standard errors were adjusted for the complex survey design. Data analyses were conducted using SAS 9.4.2® (Cary, NC) and IVEware (University of Michigan, MI).

#### **4.2.5.1 Multiple Imputation**

We ran descriptive statistics to examine missing rates; missing rates ranged from 0.0% to 0.7% for sample characteristics (structural determinants and individual characteristics), 3.1% to 12.4% for psychosocial factors, and 3.8% to 9.7% for frailty features. Excluding those with missing data may introduce biases; thus, we imputed missing data using multiple imputation (40 imputations, 20 iterations, and a random seed) (White et al., 2011).

#### **4.2.5.2 Aim 1. Cumulative Psychosocial Stress**

Consistent with prior work, we created a cumulative psychosocial stress index from co-occurring psychosocial factors by adding the six dichotomized psychosocial stressors originating from multiple life domains (Sauerteig et al., 2022). The score ranges from 0 to 6, with a higher score indicating greater cumulative psychosocial stress.

#### **4.2.5.3 Aim 2. Relationship Between Structural Determinants and Cumulative Psychosocial Stress**

We used multiple linear regression analysis to examine the influence of structural determinants on cumulative psychosocial stress adjusting for individual characteristics. Multicollinearity among structural determinants and individual characteristics was tested by examining tolerance (*TOL*).

#### **4.2.5.4 Aim 3. Relationship Between Structural Determinants and Frailty**

We used multivariable logistic regression analysis to examine the relationship between structural determinants and frailty, adjusting for individual characteristics.

#### **4.2.5.5 Aim 4. Mediation Analysis**

We conducted a mediation analysis following the guidelines and recommendations proposed by Baron and Kenny (1986) and Kraemer et al. (2002) to examine whether cumulative psychosocial stress mediates the relationship between structural determinants and frailty. All criteria (Path A, B, C, and C') must be met to establish cumulative psychosocial stress as a mediator between structural determinants and frailty. Path A requires a significant relationship between one or more structural determinants and cumulative psychosocial stress (Aim 2). Path B requires a significant relationship between cumulative psychosocial stress and frailty. Path C requires a significant relationship between one or more structural determinants and frailty (Aim 3). Path C' tests the relationship between structural determinants and frailty after adjusting for individual characteristics and cumulative psychosocial stress, where a previously established significant relationship between the structural determinants and frailty must dissipate, controlling for the mediator (cumulative psychosocial stress).

#### **4.2.5.6 Statistical Power**

A sample size of 7679 was adequate to provide at least 80% statistical power to conduct multiple regression analyses and multivariable logistic regression with the assumptions of two-tailed statistical significance set at 0.05 and clinically significant effect sizes (medium effects or larger,  $R^2 \geq .06$  or small effects or larger,  $aORs \geq 1.44$ ).

These effect sizes were selected because they represent the smallest clinically meaningful effect sizes for the relationships under consideration (Cohen, 1988).

## **4.3 Results**

### **4.3.1 Sample Characteristics**

Table 8 presents unweighted and weighted sample characteristics ( $N = 7679$ ). The weighted results show that participants' age ranged from 65 to 101 years. More than half of the weighted sample was female (57.9%), not married/partnered (59.3%), and reported current/ past smoking behavior (56.6%). While 84% of the weighted sample identified as White, 6.6% and 7.9% identified as Hispanic and Black, respectively. Most participants reported having heart disease (32%), diabetes (22%), and cancer (19%).

**Table 8: Unweighted and weighted sample characteristics (N = 7679)**

Characteristic	Unweighted			Weighted	
	<i>N</i>	<i>f</i>	%	%	95% <i>CI</i>
Female gender	7679	4446	57.9%	57.9%	56.8-58.8%
Race/Ethnicity					
Hispanic/Latino	7678	533	6.9%	6.6%	4.3-8.7%
Non-Hispanic Black/AA		859	11.2%	7.9%	6.9-8.9%
Non-Hispanic White		6175	80.4%	83.9%	81.5-86.4%
Non-Hispanic Other		111	1.4%	1.6%	1.0-2.1%
Education					
Less than High School	7678	1736	22.6%	23.1%	21.2-25.0%
High School or GED		2967	38.6%	37.5%	36.3-38.9%
Some college		1538	20.0%	19.9%	18.8-21.1%
College graduate		1437	18.7%	19.3%	17.4-21.1%
Age category	7678				
65-69 years		2273	29.6%	29.2%	27.7-30.7%
70-74 years		2076	27.0%	23.6%	22.4-24.9%
75-79 years		1778	23.2%	23.1%	21.9-24.3%
80 years and above		1551	20.2%	22.6%	22.6-25.5%
Married/partnered	7678	4761	62.0%	40.7%	57.9-60.6%
Current/ former smoker	7624	4329	56.9%	56.6%	54.9-58.3%
Chronic conditions					
Heart disease	7677	2417	31.5%	32.3%	30.9-33.7%
Diabetes	7674	1732	22.6%	21.9%	20.7-23.2%
Stroke	7676	603	7.9%	8.1%	7.4-8.8%
Chronic lung disease	7673	950	12.4%	12.4%	11.4-13.4%
Cancer	7675	1456	18.9%	19.1%	18.0-20.2%

*Note.* *N* = Non-missing data available prior to imputations, *f* = Unweighted frequencies, 95% *CI* = 95% Confidence Interval, AA = African American, GED = General Educational Development

**Table 9: Unweighted and weighted psychosocial and frailty characteristics (*n* = 7679)**

Characteristics	Unweighted raw score			Weighted with imputation	
	<i>N</i>	<i>f</i>	%	%	95% <i>CI</i>
Psychosocial factors					
Loneliness	7423	1851	24.9%	25.5%	24.1-26.9%
Everyday discrimination	7414	1183	15.9%	15.8%	14.7-16.8%
Financial strain	7442	412	5.5%	5.5%	4.7-6.2%
Poor neighborhood cohesion	7267	1222	16.4%	16.7%	15.6-17.8%
Low subjective social status	6996	362	4.5%	5.6%	4.9-6.4%
Traumatic life events	7243	4815	66.5%	66.7%	65.3-68.1%
Frailty markers					
Poor grip strength	7212	1784	26.5%	27.7%	26.4-28.9%
Slow gait speed	7455	2852	38.7%	40.3%	38.4-42.2%
Fatigue	7667	2393	31.9%	31.9%	30.4-33.4%
Low physical activity	7679	3294	43.2%	43.2%	41.8-44.6%
Weight loss	7444	187	2.6%	2.6%	2.2-3.0%
Frailty category	7016				
None		2018	28.6%	27.1%	25.5-28.8%
Pre-frailty		3686	51.8%	50.9%	49.5-52.4%
Frailty		1312	19.6%	21.9%	20.7-23.2%
	<i>N</i>	<i>Mean</i>	<i>SE</i>	<i>Mean</i>	95% <i>CI</i>
Cumulative psychosocial stress	6171	1.3	0.02	1.35	1.3-1.4

*Note.* *N* = Non-missing data available prior to imputations, *f* = Unweighted frequencies, 95% *CI* = 95% Confidence Interval. Cumulative psychosocial stressors ranged from 0 to 6, unweighted median = 1, 25<sup>th</sup> - 75<sup>th</sup> percentile = 1-2.

### **4.3.2 Cumulative Psychosocial Stress**

As shown in Table 9, the most common psychosocial stressors reported were traumatic life events (66.7%), loneliness (25.5%), poor neighborhood cohesion (16.7%), and everyday discrimination (15.8%). The cumulative psychosocial stress index ranged from 0 to 6. Most participants reported experiencing one (46.2%) or two psychosocial stressors (22.4%). The average cumulative psychosocial stress score was 1.35 (95% CI = 1.3 to 1.4).

### **4.3.3 Frailty Characteristics**

The prevalence of frailty was 22%, and pre-frailty and non-frailty were 51% and 27%, respectively. Low physical activity (43.2%), slow gait speed (40.3%), and fatigue (31.9%) were the most frequently occurring frailty features (Table 9).

**Table 10: Relationship between structural determinants and cumulative psychosocial stress**

Mediation Analysis	Outcome: Cumulative psychosocial stress	
Path A with Covariates	$\beta$	<i>SE</i>
Gender (ref = male)	---	---
Female	-0.02	0.03
Race and ethnicity (ref = Non-Hispanic White)	---	---
Hispanic	0.21***	0.05
Non-Hispanic Black	0.29***	0.05
Non-Hispanic Other	0.29*	0.14
Education (ref = College graduate)	---	---
Less than high school	0.32***	0.05
High school or GED	0.08*	0.03
Some college	0.07	0.04
Age group (ref = 65 -69 years)	---	---
Age 80+	-0.04	0.03
Age 75-79	-0.05	0.03
Age 70-74	-0.21***	0.04
Marital status (ref = not)	---	---
Married/partner	-0.33***	0.03
Smoking behavior (ref = not)	---	---
Former/current smoker	0.07*	0.03
Chronic conditions (ref= not)	---	---
Heart disease	0.22***	0.03
Diabetes Mellitus	0.14***	0.03
Stroke	0.19***	0.06
Chronic Lung Disease	0.2***	0.03
Cancer	0.07***	0.03

*Note.*  $R^2 = 0.08$ ,  $\beta =$  standardized beta coefficient from multiple linear regression model examining the relationship between structural determinants and cumulative psychosocial stress adjusting for individual

characteristics, *SE* = Standard error, GED = General Educational Development, \* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

#### **4.3.4 Structural Determinants and Cumulative Psychosocial Stress**

As shown in Table 10, multiple linear regression showed significant relationships between structural determinants and cumulative psychosocial stress (Path A, Appendix C Figure C1). Overall, the model explained 8% of the variation in cumulative psychosocial stress ( $R^2 = 0.08$ , indicating a medium effect size). Although gender was not related to cumulative psychosocial stress ( $p > 0.05$ ), race and ethnicity were significantly related to cumulative psychosocial stress after adjusting for individual characteristics. Relative to White older adults, those who identified as Hispanic ( $p < 0.001$ ), Black ( $p < 0.001$ ), and other race and ethnic minorities ( $p < 0.05$ ) experienced greater cumulative psychosocial stress. Compared to college graduates, high school graduates ( $p < 0.05$ ) and those with less than a high school diploma ( $p < 0.001$ ) were more likely to experience greater cumulative psychosocial stress.

Among the covariates, those not married/partnered, reporting smoking behavior, cardiovascular disease, diabetes, stroke, chronic lung disease, and cancer, were more likely to experience greater cumulative psychosocial stress. Tolerance statistics provided no evidence of severe multicollinearity among the examined structural determinants and individual characteristics ( $TOL > 0.1$ ).

### 4.3.5 Structural Determinants and Frailty

As shown in Table 11, there were significant associations between gender, race and ethnicity, education, and frailty (Model 2, Path C). The frailty risk was significantly greater among females than males ( $aOR = 1.5, p < 0.001$ ), and relative to White older adults, the frailty risk was greater in Black ( $aOR = 1.9, p \leq 0.001$ ) and Hispanic older adults ( $aOR = 1.7, p \leq 0.001$ ). In terms of education, the odds of frailty increased with decreasing education. Among individual characteristics, increasing age, being non-married/non-partnered, and chronic conditions except for cancer were associated with increased frailty risk (Table 11, Model 2, Path C, all  $p \leq 0.01$ ). All the statistically significant correlates of frailty had clinically significant  $aORs$  of 1.44 or greater (indicating small-to-large effects), except for being non-married/non-partnered (married/partner versus not:  $aOR = 0.8$  or inversely non-married/non-partnered versus married/partnered:  $aOR = 1.25$ ).

### 4.3.6 Mediation Analysis

There were significant relationships between structural determinants and cumulative psychosocial stress after adjusting for covariates (see Table 11 and Appendix C Figure C1, Path A). Cumulative psychosocial stress was significantly related to frailty after adjusting for covariates (Table 11, Model 1, Path B,  $aOR = 1.4, p \leq 0.001$ ), indicating a small but clinically meaningful relationship. Path C demonstrated that structural determinants (gender, race and ethnicity, and education) were significantly

related to frailty (Table 11, Model 2). Path C' examined the relationship between structural determinants and frailty after adjusting for cumulative psychosocial stress (proposed mediator) and individual characteristics (Table 11, Model 3). Including cumulative psychosocial stress (mediator) in the model did not diminish the influence of structural determinants on frailty. Thus, cumulative psychosocial stress did not mediate the relationships between structural determinants and frailty. For Path C', structural determinants that were statistically associated with frailty had clinically significant *aORs* of 1.44 or higher, and the *aORs* for the cumulative psychosocial stress and frailty relationship was  $< 1.44$  after controlling for structural determinants and individual factors (Table 11, Model 3, indicating very small clinical effect).

**Table 11: Relationship of structural determinants and cumulative psychosocial stress with frailty**

	Model 1		Model 2		Model 3	
	Path B with Covariates		Path C with Covariates		Path C' with Mediator	
	<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>	<i>aOR</i>	<i>95% CI</i>
Cumulative psychosocial stress	1.4***	1.3-1.5			1.3***	1.3-1.4
Gender (ref = male)						
Female			1.5***	1.3-1.8	1.5**	1.3-1.9
Race/ethnicity (ref = Non-Hispanic White)						
Hispanic			1.7***	1.4-2.2	1.6***	1.3-2.1
Non-Hispanic Black			1.9***	1.5-2.4	1.8***	1.4-2.3
Non-Hispanic Other			1.0	0.6-1.9	0.9	0.5-1.8
Education (ref = College graduate)						
Less than high school			3.9***	2.8-5.3	3.6***	2.6-4.9
High school or GED			2.5***	1.9-3.1	2.4***	1.9-3.1
Some college			1.4**	1.1-1.8	1.4*	1.1-1.7
Age group (ref = 65-69years)						
Age 70-74	1.4***	1.3-1.5	1.4***	1.2-1.7	1.5***	1.2-1.8
Age 75-79	2.2***	1.2-1.8	2.1***	1.7-2.5	2.1***	1.8-2.6
Age 80 years and older	4.4***	3.6-5.4	4.2***	3.3-5.3	4.6***	3.7-5.8
Marital status (ref = not)						
Married/partner vs not	0.7***	0.6-0.9	0.8**	0.7-0.9	0.9	0.7-1.0
Smoking behavior (ref = not)						
Former/current smoker	1.0	0.9-1.2	1.2	0.9-1.4	1.1	0.9-1.3
Chronic conditions (ref = not)						
Heart Disease	1.3**	1.1-1.6	1.6***	1.3-1.9	1.5***	1.2-1.8
Diabetes Mellitus	1.7***	1.5-1.9	1.6***	1.4-1.9	1.5***	1.3-1.8
Stroke	1.8***	1.4-2.3	1.9***	1.5-2.4	1.8***	1.4-2.2
Chronic Lung Disease	1.9***	1.5-2.3	1.9***	1.6-2.4	1.8***	1.5-2.2
Cancer	1.0	0.9-1.2	1.2	0.9-1.4	1.1	0.9-1.3

*Note.* *aOR* = adjusted odds ratio from logistic regression models, *95% CI* = 95% Confidence Interval, GED = General Educational Development, \* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$ , Model 1: Path B examining the association between cumulative psychosocial stress and frailty adjusting for individual characteristics,

Model 2: Path C examining association between structural determinants of health and frailty after adjusting for individual characteristics, Model 3: Path C' examining association between structural determinants of health and frailty after adjusting for cumulative psychosocial stress and individual characteristics.

#### **4.4 Discussion**

Our national study is the first to examine whether structural determinants operate through cumulative psychosocial stress and contribute to frailty disparities in community-dwelling older adults in the US. Females, Hispanic, and Black older adults and those with less education had greater frailty risk than their male, White, and college-educated counterparts, with clinically meaningful significance. Structural determinants were significantly related to cumulative psychosocial stress such that Hispanic, Black, and other race/ethnic minorities and those with less education experienced greater cumulative psychosocial stress. While the frailty risk heightened with increasing cumulative psychosocial stress, cumulative psychosocial stress did not mediate the relationship between structural determinants and frailty.

Consistent with the WHO's CSDH framework and prior work, there were significant relationships between structural determinants and cumulative psychosocial stress, which were clinically significant. Compared to White older adults, those who identified as Hispanic, Black, and Other race and ethnic minorities experienced greater cumulative psychosocial stress originating from multiple life domains (Alhasan et al., 2020; Brown et al., 2020; Ferreira et al., 2018; Marshall et al., 2022; Mouzon et al., 2020). Our results further strengthen the evidence showing race and ethnic disparities in exposure to psychosocial stress, which may be attributed to socioeconomic stratification, structural disadvantages, and social inequities (Mouzon et al., 2020). Older adults with

less education were more likely to experience greater cumulative psychosocial stress than college graduates. This finding aligns with prior studies and suggests that education may buffer against psychosocial stress by improving access to social resources and ties (Mouzon et al., 2020; Taylor et al., 2022; Yang, 2021). Cumulative psychosocial stress did not vary by gender, contrasting with prior results reporting greater psychosocial stress among females (Matud & García, 2019; Seematter-Bagnoud et al., 2010). Our finding indicates that irrespective of gender, older adults may experience greater psychosocial stress. Our finding indicates that gender does not impact on cumulative psychosocial stress. Future studies can identify specific or combinations of specific psychosocial stressors and their variation by gender.

Older adults with greater cumulative psychosocial stress had a higher frailty risk. Potential explanations describing the influence of psychosocial stress on frailty include 1) behavioral and 2) neurobiological pathways (O'Connor et al., 2021). The behavioral pathway explains that poor coping behaviors, including smoking and poor dietary choices, in response to psychosocial stress are related to chronic cardiometabolic disorders (Rodgers et al., 2021). These risky behaviors and chronic conditions may contribute to frailty. The neurobiological pathway suggests that psychosocial stress activates the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenal-medulla (SAM) axes, which trigger systemic inflammatory pathways and the subsequent release of inflammatory markers (O'Connor et al., 2021). Chronic inflammation is believed to be

linked to frailty (Ferrucci & Fabbri, 2018). Psychosocial stress accelerates biological aging processes and epigenetic changes, which may lead to frailty (Polsky et al., 2022). Future longitudinal studies should examine the neurobiological and behavioral pathways linking psychosocial stress and frailty by examining inflammatory and behavioral mediators.

In contrast to our expectations and the CSDH framework, cumulative psychosocial stress did not mediate the relationships between structural determinants and frailty. Several reasons may explain the absence of a mediating effect. Firstly, our study examined only six psychosocial stressors; however, older adults may experience a host of psychosocial stressors not measured in this study, such as psychosocial stress attributed to caregiving strain, relationship strain, food insecurity, and loss of independence. Similarly, we could not control for the role of social connections, social resources, self-efficacy, stress appraisal, and coping skills that may alter the influence of psychosocial stress on frailty (Fuller-Iglesias, 2015). Future research should examine a comprehensive set of psychosocial stressors and their cumulative influence on frailty to more fully investigate the mediating role of psychosocial stress.

Our study has several limitations. The cross-sectional nature of this study limits us from drawing a causal link between structural determinants, cumulative psychosocial stress, and frailty. Psychosocial factors were self-reported and can be prone to reporting bias. In this study, we dichotomized six psychosocial measures in the HRS study; future

studies might explore different measures or cut points for operationalization. Our study did not account for the disproportionate exposure to psychosocial stressors incurred due to regional differences in the allocation of resources or pertaining to structural racism. Our analytic sample only included those community-dwelling older adults who consented to participate in the enhanced HRS survey, and it might underestimate frailty and psychosocial stressors.

Despite these limitations, our study has many strengths. Building on smaller regional studies, this study reinforces the multifactorial nature of frailty by demonstrating the significant role of structural determinants and cumulative psychosocial stress on frailty using a large national dataset. Our results highlight a critical need to expand our understanding beyond individual-level biological and behavioral risk factors of frailty and further examine psychosocial stressors influencing frailty. Notably, our study highlights the need to address structural and psychosocial stress disparities contributing to frailty. Future examination of specific psychosocial mediators of frailty might inform strategies to mitigate the influence of psychosocial stressors to prevent/delay frailty. Our study suggests a need to develop multilevel interventions to alleviate the influence of psychosocial stressors on frailty among older adults and eliminate disparities. These might include individual-level interventions enhancing coping skills and well-being in the face of psychosocial stressors (Gaffey et al., 2016) and community-level interventions promoting a safe neighborhood environment to foster social support among older adults

(Friedman et al., 2019). These strategies are of the utmost importance to expanding and supporting healthy aging. Further, structural changes are needed to eradicate discrimination and remove barriers, promote equitable access to resources, and eliminate differential exposure to psychosocial stress (Zhang et al., 2019).

#### **4.5 Conclusion**

Structural determinants and cumulative psychosocial stress significantly increased the frailty risk among community-dwelling older adults. Surprisingly, cumulative psychosocial stress did not mediate the relationships between structural determinants and frailty. Thus, future studies should examine other psychosocial mediators. Our results suggest a need for multilevel intervention efforts to alleviate the influence of psychosocial stress to delay/prevent frailty and eradicate disparities.

## 5. Summary and Conclusion

Frailty is a common geriatric syndrome and a major predictor of adverse outcomes (for example, falls, injuries, premature disability, and mortality). Stark disparities exist in the prevalence of frailty. Women, older adults who identify as Hispanic and Black, and those with lower socioeconomic status bear a greater burden of frailty and related outcomes relative to male, White older adults, and those with high income. Modifiable co-occurring factors contributing to frailty and frailty disparities have not been rigorously examined. As frailty is reversible, examining the role of co-occurring biological and psychosocial risk factors contributing to frailty can be beneficial in informing interventions to delay/ prevent frailty. Informed by the WHO's multilevel conceptual model, this study examined whether structural determinants (gender, race, ethnicity, and education) influence frailty via co-occurring intermediary cardiometabolic and psychosocial factors.

This dissertation accomplished this purpose through a systemic review (Chapter 2), which synthesized the current literature examining the relationship between modifiable cardiometabolic factors and frailty and identified the existing gaps in the literature. Informed by the systematic review, two quantitative databased chapters (Chapters 3 and 4) examined whether structural determinants influence frailty via co-occurring cardiometabolic and psychosocial factors among community-dwelling older adults in the U.S.

Chapter 2 synthesizes the results from twelve observation studies conducted in six countries. The findings from this systematic review underscore that co-occurring cardiometabolic factors increased the risk of frailty in older adults; however, the relationship between individual cardiometabolic factors and frailty was inconsistent across the studies. These findings suggest that specific combinations of cardiometabolic factors heighten the frailty risk in older adults. The combinations of cardiometabolic factors related to frailty are unclear, as existing studies have only examined the influence of a cumulative number of cardiometabolic factors on frailty. Furthermore, the findings demonstrated a need to examine the relationship between cardiometabolic factors and frailty in the frame of the social determinants of health.

Informed by the systematic review, Chapter 3 aimed to identify the distinct subgroups of older adults with unique combinations of cardiometabolic factors—typologies—using latent class analysis. The relationships between structural determinants and cardiometabolic typologies with frailty were examined with the exploration of the mediating role of cardiometabolic typologies. A path analysis model involving a series of logistic regressions was used to determine the relationship between structural determinants, cardiometabolic typologies, and frailty.

Results from Chapter 3 further confirmed that female, older adults who identify as Hispanic, non-Hispanic Black, and those with less education had a higher frailty risk than male, non-Hispanic White older adults, and those with high education. Structural

determinants were significantly related to latent subgroups with distinct cardiometabolic typologies. The members of the insulin resistance subgroup were more likely to be female and identify as non-Hispanic Black, and were college non-graduates. The members of the hypertensive dyslipidemia were more likely to identify as non-Hispanic other minorities and were high school graduates. The members in the hypertensive subgroup were more likely to be male and college graduates. In terms of the frailty risk, the frailty risk was higher in the insulin resistance subgroup relative to both hypertensive dyslipidemia and hypertensive subgroups, covarying for individual characteristics. In contrast, the frailty risk did not differ between hypertensive dyslipidemia and hypertensive subgroups. Contrary to expectations, cardiometabolic typologies did not mediate the relationship between structural determinants and frailty. These results underscore the need to identify other non-biological/ behavioral contributors to frailty and examine their mediating role.

Based on results from earlier chapters, Chapter 4 examined whether structural determinants influence frailty via co-occurring psychosocial stressors. A range of psychosocial stressors stemming from multiple life domains was counted to form a cumulative psychosocial stress index. A path analysis model involving a series of multivariable regression models was used to examine the relationship between structural determinants, cumulative psychosocial stress, and frailty and determine the mediating role of cumulative psychosocial stress. Consistent with Chapter 3, the frailty risk was

higher in female, Hispanic, non-Hispanic Black older adults, and those with less education. As expected, older adults who identified as Hispanic, non-Hispanic Black, non-Hispanic other ethnic minorities, and those with less education experienced greater cumulative psychosocial stress. Greater cumulative psychosocial stress was associated with higher frailty risk; however, mediation for cumulative psychosocial stress could not be established.

Altogether, these results show that structural determinants, co-occurring biological cardiometabolic factors, and psychosocial stressors independently contribute to frailty and reinforce the multifactorial nature of frailty. These results set the foundation for exploring other biological and psychosocial stressors contributing to frailty and examining their mediating roles.

## ***5.1 Limitations***

The results from this dissertation should be interpreted by considering its limitations. This study used cross-sectional data, which limits drawing causal links between structural determinants, cardiometabolic factors, psychosocial stressors, and frailty. This study included only those participants who consented to participate in an enhanced HRS interview involving physical, blood biomarker assessments and self-administered psychosocial information. As such, this study might underestimate the actual frailty prevalence, cardiometabolic factors, and psychosocial stressors. Due to the exploratory nature of our study, we used data from 2006 and 2008; thus, future studies

need to be reproduced using the most recent data. Due to a secondary analysis of existing data, only six psychosocial stressors were examined without considering their severity and chronicity. These psychosocial stressors may not be an exhaustive list as older adults may experience an array of psychosocial stressors, such as caregiving strain, food insecurity, loss of independence, and relationship strain, not measured in this study. In addition, coping skills and stress appraisal that may confound the effect of psychosocial stressors on frailty could not be adjusted. In both Chapters 3 and 4, a conventional mediation analysis approach was used to examine the mediating roles of cardiometabolic typologies and cumulative psychosocial stress in the relationships between structural determinants and frailty. This traditional approach may underestimate the mediating effect; thus, future research needs to use novel mediation analysis to examine the mediating roles of cardiometabolic typologies and cumulative psychosocial stress.

## ***5.2 Future Research Implications***

This dissertation reinforces the multifactorial nature of frailty, as results clearly show that structural, cardiometabolic, and psychosocial determinants significantly contribute to frailty in older adults. The results from this dissertation further confirm that frailty disproportionately affects female, Hispanic, and non-Hispanic Black older adults, and those with less education than their respective counterparts. Cardiometabolic typologies and cumulative psychosocial stress independently increased frailty risk even if the mediation effect could not be established for these intermediary health determinants.

However, these results lay the groundwork for extending current evidence and indicate a need to identify a comprehensive range of biological risks and psychosocial stressors that may contribute to frailty. Future studies should examine the complex interplay among structural determinants, biological risk factors, and psychosocial stressors to elucidate the mechanisms driving frailty and related disparities in older adults.

This dissertation underscores some critical research gaps. Chapter 3 examined only cardiometabolic factors as biological predictors of frailty. However, older adults may experience a host of biological changes, including metabolic decline, hormonal dysregulation, epigenetic, and inflammatory changes, that may influence frailty (Bisset & Howlett, 2019). The members of historically socioeconomically disadvantaged groups may not only experience a greater burden of biological risk factors, but structural disadvantages may further exacerbate the biological influences on frailty. Future studies should examine the extensive array of biological mediators, such as metabolic decline, hormonal dysfunction, epigenetic changes, and immunological changes, which might mediate the relationship between structural determinants and frailty.

Results from Chapter 3 show that frailty risk varies among subgroups of older adults with distinct cardiometabolic typologies. Although the healthy subgroup with optimal cardiometabolic health would have been the ideal reference group for comparison, the healthy subgroup of older adults with ideal cardiometabolic factors was not identified from latent class models. Future studies should compare frailty risk in older

adults with varying cardiometabolic typologies and those with optimal cardiometabolic health. Chapter 3 is cross-sectional; thus, longitudinal studies are needed to understand the influence of cardiometabolic factors on the trajectories of frailty development. Future studies should be replicated in different populations and settings to validate the relationship between cardiometabolic typologies and frailty. Even though Chapter 3 documented a significant association between cardiometabolic typologies and frailty, the underlying pathways contributing to frailty are unclear. Based on existing evidence, it is postulated that inflammatory changes attributed to cardiometabolic factors may be related to frailty; thus, future research is needed to validate this proposition.

Chapter 4 showed that greater cumulative psychosocial stress contributed to the higher frailty risk in older adults; however, mediation could not be established for cumulative psychosocial stress. It might be because Chapter 4 examined six psychosocial stressors available in the HRS dataset. Older adults can experience a multitude of psychosocial stressors, such as caregiving strain, food insecurity, interpersonal conflict, limited social network, perceived stress due to health problems, poor access to transportation, or loss of independence, not measured in this study. Future studies should examine a comprehensive range of psychosocial stressors to thoroughly understand the mediating role of cumulative psychosocial stress. Future studies are needed to explore the independent effect of individual psychosocial factors and the collective effect of combinations of psychosocial factors on frailty to inform interventions to mitigate the

influence of psychosocial stress on frailty. Future studies should examine the neurobiological, epigenetic, and behavioral pathways through which psychosocial stressors may influence frailty.

Moreover, the influence of cardiometabolic factors and psychosocial stressors on frailty were examined separately in this dissertation; however, older adults might experience biological factors and psychosocial stressors concurrently. Thus, future research should examine the influence of co-occurring cardiometabolic factors and psychosocial stressors on frailty. Chapter 4 is cross-sectional; thus, future longitudinal studies are needed to examine the influence of psychosocial factors on the development of frailty in older adults without frailty at the baseline.

Future research is encouraged to examine community-level determinants contributing to inequities in the distribution of resources exacerbating biological risk and psychosocial stress burden. Community-level determinants, such as residential segregation and food desert, can be related to disproportionate access to resources, such as safe-neighborhood spaces, social environment, transportation, healthy food options, social support resources, and primary care services. In addition, future research should examine the “cause of the causes” acting at the macro-level and engendering/ maintaining structural barriers and inequities and contributing to unequal distribution of intermediary biological risk and psychosocial stress burden and frailty. These structural barriers and inequities may include spatial inequality in the distribution of community resources.

Social negativity, such as structural racism, ageism, and sexism, may create structural barriers to accessing protective resources and disproportionate exposure to unequal biological risk and psychosocial stress burden related to frailty disparities.

### ***5.3 Practice Implications***

This dissertation highlights several important practice implications. Our study further validates that frailty disproportionately affects females, Hispanic, Black older adults, and those with less education than males, non-Hispanic White, and those with higher education. This result is critical from a clinical standpoint as clinicians and nurses can screen for frailty risk in the aging population and pay particular attention to highly susceptible subgroups in the community and clinical settings. Early screening provides opportunities to take necessary health actions to prevent and delay frailty and related adverse outcomes. Addressing cardiometabolic risk and psychosocial stress burden on frailty require the development of multilevel interventions.

Results from Chapter 3 can be vital from the clinical perspective. Results clearly signify the need to develop and implement tailored interventions targeting specific cardiometabolic typologies to prevent and delay frailty. The knowledge of structural and individual characteristics related to each cardiometabolic subgroup highlights the need to develop culturally adapted, person-centered interventions catering to lifestyles, ethic/cultural beliefs, values, practices, and traditions to alleviate the influence of cardiometabolic typologies on frailty. The insulin resistance subgroup members with

greater cardiometabolic risk burden were female, non-Hispanic Black, and with less education. These findings may suggest that structural inequities drive greater cardiometabolic risk burden in the specific subpopulation.

Chapter 4 advances the current understanding of the influence of structural determinants on frailty via cumulative psychosocial stress. Hispanic, Black, and non-Hispanic ethnic minorities and those with less education were more likely to experience greater cumulative psychosocial stress, which may indicate structural inequities and unequal access to social resources. Greater cumulative psychosocial stress was significantly related to the increased frailty risk, although mediation for cumulative psychosocial stress could not be established. Our findings accentuate the need to examine and intervene psychosocial stressors in addition to biological and behavioral contributors to frailty. These findings highlight the importance of addressing structural determinants and psychosocial stressors to alleviate their influence on frailty through multilevel interventions. For example, individual-level interventions may be beneficial in enhancing individual coping skills in the presence of psychosocial stress. Similarly, community-based programs can promote social and emotional support to alleviate psychosocial stressors among older adults.

In addition to individual-level interventions, community and structural-level changes are needed to address structural inequities/ barriers contributing to the differential cardiometabolic risk and psychosocial stress burden. Expanding social and

healthcare services might help mitigate social and health inequities and promote equal distribution of resources to alleviate psychosocial stress. Wider policy-level changes might help eradicate structural barriers perpetuating discrimination and inequities to reduce psychosocial stress. Cultural and linguistically tailored programs might promote delivering culturally adapted health and social care services to diverse older adults and mitigate structural inequities.

## Appendix A. Chapter 2. Systematic Review Search Database Search Trails and Quality Appraisal

**Table A1: Search terms in PubMed, Elsevier, and Web of Science**

Concepts	Search terms
Population	<p>Terms used:            "Frail Elderly"[Mesh] OR "Aged"[Mesh] OR "Aged, 60 and over"[Mesh] OR "Geriatrics"[mesh] OR elderly[tiab] OR aged[tiab] OR geriatric[tiab] OR geriatrics[tiab] OR elderly[tiab] OR elder[tiab] OR elders[tiab] OR "older people"[tiab] OR "older person"[tiab] OR senior[tiab] OR seniors[tiab]</p>
Exposure	<p>"Cardiovascular Diseases"[Mesh] OR "Heart Disease Risk Factors"[Mesh] OR "Cardiometabolic Risk Factors"[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Blood Pressure"[Mesh] OR "Blood Glucose"[Mesh] OR "Insulin"[Mesh] OR "Lipoproteins"[Mesh] OR "Metabolic Syndrome"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Hypertension"[Mesh] OR "Obesity"[Mesh] OR cardiovascular[tiab] OR metabolic[tiab] OR cardiometabolic[tiab] OR "blood pressure"[tiab] OR "blood sugar" OR "blood glucose"[tiab] OR cholesterol[tiab] OR triglycerides[tiab] OR triglyceride[tiab] OR lipoprotein[tiab] OR lipoproteins[tiab] OR obesity[tiab] OR "heart disease"[tiab] OR diabetes[tiab] OR insulin[tiab]</p>
Outcomes Studies	<p>"Frailty"[Mesh] OR Frail[tiab] OR frailty[tiab] OR Frailties[tiab] OR Frailness[tiab] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Cohort Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Interrupted Time Series Analysis"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Meta-analysis as topic"[Mesh] OR "Evaluation studies as topic"[Mesh] OR "Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR "Clinical Trial"[pt] OR "Observational Study"[pt] OR "Evaluation Studies"[pt] OR "Comparative Study"[pt] OR "Meta-Analysis"[pt] OR "Systematic Review"[pt] OR systematic[subset] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR trials[tiab] OR groups[tiab] OR "single blind"[tiab] OR "single blinded"[tiab] OR "double blind"[tiab] OR "double blinded"[tiab] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR cohort[tiab] OR cohorts[tiab] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR retrospective[tiab] OR retrospectively[tiab] OR follow-up[tiab] OR "follow up"[tiab] OR followup[tiab] OR case-control[tiab] OR "case control"[tiab] OR "case controlled"[tiab] OR case-controlled[tiab] OR cross-sectional[tiab] OR "cross sectional"[tiab] OR crossover[tiab] OR "cross over"[tiab] OR "comparative study"[tiab] OR "comparative studies"[tiab] OR meta-analysis[tiab] OR meta-analyses[tiab] OR "meta-analysis"[tiab] OR "meta analyses"[tiab] OR metaanalysis[tiab] OR metaanalyses[tiab] OR meta-analytic[tiab] OR "meta analytic"[tiab] OR metaanalytic[tiab]</p>

*Note:* The results of search are shown in Appendix.

**Table A2: Search results in databases— CINAHL (via EBSCO), Embase (via Elsevier), and MEDLINE (via new PubMed).**

Search	Query	Results
1	"Frailty"[Mesh] OR Frail[tiab] OR frailty[tiab] OR Frailties[tiab] OR Frailness[tiab]	24,817
2	"Cardiovascular Diseases"[Mesh] OR "Heart Disease Risk Factors"[Mesh] OR "Cardiometabolic Risk Factors"[Mesh] OR "Obesity, Abdominal"[Mesh] OR "Blood Pressure"[Mesh] OR "Blood Glucose"[Mesh] OR "Insulin"[Mesh] OR "Lipoproteins"[Mesh] OR "Metabolic Syndrome"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Hypertension"[Mesh] OR "Obesity"[Mesh] OR cardiovascular[tiab] OR metabolic[tiab] OR cardiometabolic[tiab] OR "blood pressure"[tiab] OR "blood sugar" OR "blood glucose"[tiab] OR cholesterol[tiab] OR triglycerides[tiab] OR triglyceride[tiab] OR lipoprotein[tiab] OR lipoproteins[tiab] OR obesity[tiab] OR "heart disease"[tiab] OR diabetes[tiab] OR insulin[tiab]	4,320,907
3	"Frail Elderly"[Mesh] OR "Aged"[Mesh] OR "Aged, 80 and over"[Mesh] OR "Geriatrics"[mesh] OR elderly[tiab] OR aged[tiab] OR geriatric[tiab] OR geriatrics[tiab] OR elderly[tiab] OR elder[tiab] OR elders[tiab] OR "older people"[tiab] OR "older person"[tiab] OR senior[tiab] OR seniors[tiab]	3,720,480
4	1 and 2 and 3	4282
5	4 NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp]) NOT (animals[mesh] NOT humans[mesh])	4091
6	"Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Cohort Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR "Longitudinal Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Retrospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Cross-Sectional Studies"[Mesh] OR "Controlled Before-After Studies"[Mesh] OR "Interrupted Time Series Analysis"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Meta-analysis as topic"[Mesh] OR "Evaluation studies as topic"[Mesh] OR "Randomized Controlled Trial"[pt] OR "Controlled Clinical Trial"[pt] OR "Clinical Trial"[pt] OR "Observational Study"[pt] OR "Evaluation Studies"[pt] OR "Comparative Study"[pt] OR "Meta-Analysis"[pt] OR "Systematic Review"[pt] OR systematic[subset] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR randomly[tiab] OR trial[tiab] OR trials[tiab] OR groups[tiab] OR "single blind"[tiab] OR "single blinded"[tiab] OR "double blind"[tiab] OR "double blinded"[tiab] OR "evaluation study"[tiab] OR "evaluation studies"[tiab] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR cohort[tiab] OR cohorts[tiab] OR longitudinal[tiab] OR longitudinally[tiab] OR prospective[tiab] OR prospectively[tiab] OR retrospective[tiab] OR retrospectively[tiab] OR follow-up[tiab] OR "follow up"[tiab] OR followup[tiab] OR case-control[tiab] OR "case control"[tiab] OR "case controlled"[tiab] OR case-controlled[tiab] OR cross-sectional[tiab] OR "cross sectional"[tiab] OR crossover[tiab] OR "cross over"[tiab] OR "comparative study"[tiab] OR "comparative studies"[tiab] OR meta-analysis[tiab] OR meta-analyses[tiab] OR "meta analysis"[tiab] OR "meta analyses"[tiab] OR metaanalysis[tiab] OR metaanalyses[tiab] OR meta-analytic[tiab] OR "meta analytic"[tiab] OR metaanalytic[tiab]	8,465,068
7	5 AND 6	2901

**Table A3: Results of search in database (including vendor/ platform): Web of Science (via Clarivate)**

Search	Query	Results
1	TS = (frail OR frailty OR frailties OR frailness)	37,798
2	TS = (cardiovascular OR metabolic OR cardiometabolic OR "blood pressure" OR "blood sugar" OR "blood glucose" OR cholesterol OR triglycerides OR triglyceride OR lipoprotein OR lipoproteins OR obesity OR "heart disease" OR diabetes OR insulin)	2,777,740
3	TS = (aged OR geriatric OR geriatrics OR elderly OR elder OR elders OR "older people" OR "older person" OR senior OR seniors)	4,925,183
4	#1 and #2 and #3	5,237
5	#4 AND ALL = (randomized OR randomised OR randomization OR randomisation OR placebo OR randomly OR trial OR trials OR groups OR "single blind" OR "single blinded" OR "double blind" OR "double blinded" OR "evaluation study" OR "evaluation studies" OR "intervention study" OR "intervention studies" OR cohort OR cohorts OR longitudinal OR longitudinally OR prospective OR prospectively OR retrospective OR retrospectively OR follow-up OR "follow up" OR followup OR case-control OR "case control" OR "case controlled" OR case-controlled OR cross-sectional OR "cross sectional" OR crossover OR "cross over" OR "comparative study" OR "comparative studies" OR meta-analysis OR meta-analyses OR "meta analysis" OR "meta analyses" OR metaanalysis OR metaanalyses OR meta-analytic OR "meta analytic" OR metaanalytic)	3,701
6	#5 AND Articles or Review Articles (Document Types)	3,638

**Table A4: Quality appraisal of studies using the Joana Briggs Instrument**

Name of article	Sample inclusion criteria	Study subjects and settings	Valid and reliable measurement of exposure	Identification of confounding factors	Adjustment for confounding factors	Valid and reliable measurement of outcomes	Appropriate statistical analysis techniques
Crow	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liao	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Song	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Blaun	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kalyani	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Zaslavsky	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Anker	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lee	Yes	Yes	Yes	No	Yes	Yes	Yes
Perez-Tasigchana	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Barzilay	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Graciani	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gale	Yes	Yes	Yes	Yes	Yes	Yes	Yes

## Appendix B. Chapter 3. Structural Determinants and Cardiometabolic Typologies Related to Frailty

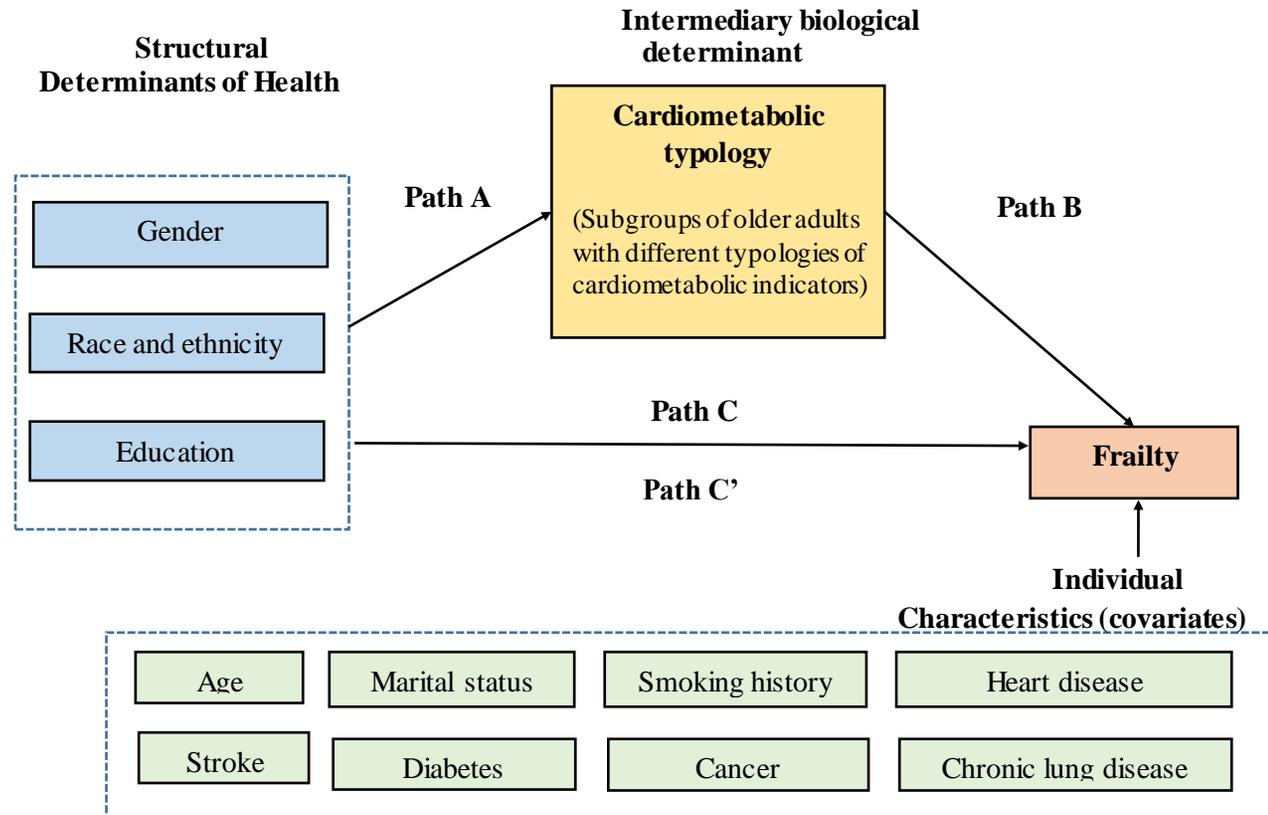
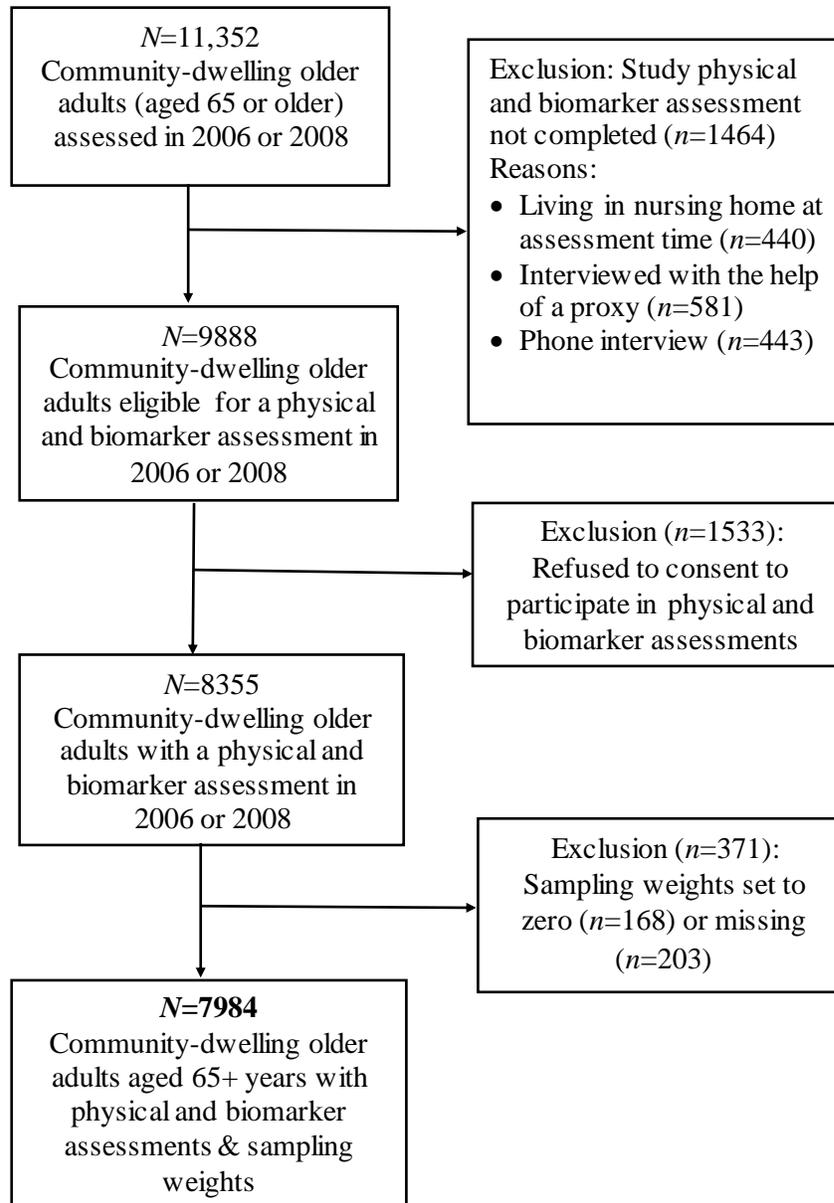


Figure B1: Structural and cardiometabolic determinants of frailty model



**Figure 4**

**Table B1: Operationalization of key variables**

	Measures	Operational Definition and Coding
Structural determinants	Gender	Participant's self-reported gender: 1=Male, 2=Female
	Race and ethnicity	Participant's self-reported race and ethnicity: 1=Hispanic/Latino, 2=Non-Hispanic White, 3=Non-Hispanic Black, 4=Non-Hispanic Other minority groups (Asian, Native Hawaiian, Pacific Islander, Alaska Native, Other)
	Education	Participant's self-reported education, defined as: 1=Less than high school, 2=High school or GED, 3=Some years of college, 4=College or higher degrees
Latent Class Cardiometabolic indicators	Elevated blood pressure	Elevated blood pressure: 0=No, 1=Yes, defined as Systolic Blood Pressure (SBP) $\geq$ 130 mm Hg or Diastolic Blood Pressure (DBP) $\geq$ 85 mm Hg or self-reported hypertension or taking medications for hypertension
	Abdominal obesity	Abdominal Obesity: 0=No, 1=Yes, defined as Waist circumference for men $>$ 102 cm and Waist Circumference for women $>$ 88 cm
	General obesity	General obesity: 0=No, 1=Yes, defined as BMI $>$ 30 kg/m <sup>2</sup>
	Total Cholesterol	Elevated total cholesterol, 0=No, 1=Yes, defined as TC $>$ 240 mg/dL
	High Density Lipoprotein	Lowered HDL: 0=No, 1=Yes, defined as HDL for men: $<$ 40 mg/dL and HDL for women: $<$ 50 mg/dL
	Elevated blood sugar	Elevated blood sugar: 0=No, 1=Yes, defined as HbA1c $\geq$ 5.7% or taking medications for diabetes 0=No, 1=Yes
	Elevated C-reactive protein	Elevated CRP: 0=No, 1=Yes, defined as CRP $>$ 3mg/dl
Frailty features and outcome	Poor Grip Strength	Poor grip strength: 0=No, 1=Yes, defined as <b>Grip strength for men</b> Grip strength $\leq$ 29 kg for BMI $\leq$ 24 kg/m <sup>2</sup> Grip strength $\leq$ 30 kg for 24 $<$ BMI $\leq$ 26 kg/m <sup>2</sup> Grip strength $\leq$ 32 kg for BMI $>$ 26 kg/m <sup>2</sup> <b>Grip strength for women</b> Grip strength $\leq$ 17 kg for BMI $\leq$ 23 kg/m <sup>2</sup> Grip strength $<$ 18 kg for 23 $<$ BMI $\leq$ 29 kg/m <sup>2</sup> Grip strength $<$ 21 kg for BMI $>$ 29 kg/m <sup>2</sup>
	Slow Gait Speed	Slow gait speed: 0=No, 1=Yes, defined as <b>Gait speed for men</b> Gait speed $\leq$ 0.653 m/s (time $\geq$ 7 seconds) for height $\leq$ 173 cm Gait speed $\leq$ 0.762 m/s (time $\geq$ 6 seconds) for height $>$ 173 cm <b>Gait speed for women</b> Gait speed $\leq$ 0.653 m/s (time $\geq$ 7 seconds) for height $\leq$ 159 cm Gait speed $\leq$ 0.762 m/s (time $\geq$ 6 seconds) for height $>$ 159 cm
	Weight loss	Weight loss: 0=No, 1=Yes, defined as weight loss of $\geq$ 10 pounds in last 2 years
	Fatigue	Exhaustion: 0=No, 1=Yes, defined as self-report of yes to a) felt that everything I did was an effort or b) could not get going in the last week

	Low physical activity	Low physical activity: 0=No, 1=Yes, defined as lower participation in vigorous or moderate physical activities equivalent to expending less than 300 kcal/day.
	Frailty	Frailty outcome: 0=No, 1= Yes, defined as presence of 3 or more frailty features
Individual characteristics	Age	Participant's age: 1=65-69 years, 2=70-79 years, 3=75-79 years, 4=80 and above
	Marital status	Marital status: 0=Separated, divorced/widowed, 1=Married/partnered
	Smoking history	Smoking history: 0=Never smoker, 1=Current/former smoker
	Chronic conditions	Self-report of cardiovascular disease, stroke, diabetes mellitus, chronic lung disease, cancer as per physician's diagnosis at the time of the survey assessment, each condition coded as 0=No, 1=Yes.

**Table B2: Cardiometabolic typology of each LCA subgroup**

Cardiometabolic indicators	Subgroup 1 Insulin Resistance (IR) (N=3547)		Subgroup 2 Hypertensive Dyslipidemia (HD) (N=1246)		Subgroup 3 Hypertensive (HTN) (N=3191)		<i>p-value</i>	<i>Pairwise comparisons</i>
	%	95 % CI	%	95% CI	%	95 % CI		
Elevated BP	88.9%	87.7-90.2%	74.8%	72.4-77.3%	75.2%	73.6-76.7%	<.0001	IR>(HTN=HD)
Elevated blood sugar	63.5%	61.2-65.7%	50.4%	47.5-53.3%	41.2%	38.8-43.6%	<.0001	IR>HD>HTN
Low HDL	43.5%	41.3-45.7%	80.1%	76.5-83.6%	4.2%	3.1-5.3%	<.0001	HD>IR>HTN
Elevated TC	14.5%	12.6-16.3%	1.9%	0.7-3.1%	21.9%	20.4-23.5%	<.0001	HTN>IR>HD
Abdominal obesity	99.0%	98.4-99.7%	31.4%	27.9-34.9%	39.6%	37.6-41.7%	<.0001	IR>HTN>HDL
Obesity	79.7%	78.0-81.3%	3.4%	1.9-4.8%	3.7%	2.7-4.6%	<.0001	IR>(HTN=HD)
Elevated CRP	55.6%	53.7-57.6%	28.9%	25.9-31.9%	26.5%	24.7-28.3%	<.0001	IR>(HD=HTN)

*Note.* Weighted percentages and 95% Confidence Intervals (CI), IR=Insulin resistance, HD=Hypertensive dyslipidemia, HTN=hypertensive, BP=Blood pressure, HDL=High-density lipoprotein, TC=Total cholesterol, CRP=C-reactive protein. Rao Scott chi-s square test *p-value* is for overall subgroup effect; pairwise comparisons: “>” indicates significantly higher proportion at the 0.05 level in the one subgroup compared to other subgroup(s), while “=” indicates no significant differences at the 0.05 level in proportions between the subgroups comparison

**Table B3: Bivariate association between structural determinants and LCA subgroups**

Structural Determinant	Subgroup 1 Insulin Resistance (IR) (N=3547)		Subgroup 2 Hypertensive Dyslipidemia (HD) (N=1246)		Subgroup 3 Hypertensive (HTN) (N=3191)		<i>p-value</i>
	%	95% CI	%	95% CI	%	95% CI	
	Gender						
Female	59.5%	57.8-61.3%	56.5%	52.9-59.9%	54.1%	52.2-55.9%	
Male	40.5%	38.8-42.2%	43.5%	40.0-47.0%	45.9%	44.1-47.8%	
Race/ethnicity							<.0001
Hispanics	6.2%	4.2-8.1%	5.9%	4.1-7.6%	4.2%	2.8-5.6%	
NH White	82.8%	80.2-85.3%	85.7%	83.1-88.3%	87.9%	86.0-89.8%	
NH Black	9.8%	8.4-11.2%	5.5%	4.5-6.5%	6.2%	5.1-7.4%	
NH Others	1.8%	0.7-1.9%	2.9%	1.5-4.3%	1.6%	1.0-2.3%	
Education							<.0001
Less than High school	25.5%	23.4-27.6%	24.4%	21.5-27.2%	18.1%	16.2-19.9%	
High school graduate	37.9%	35.7-40.2%	39.5%	36.1-42.8%	36.6%	34.7-38.5%	
Some college	19.6%	17.8-21.5%	17.2%	14.9-19.6%	21.5%	20.2-22.7%	
College or higher	16.9%	14.9-18.9%	18.9%	16.7-21.3%	23.9%	21.0-26.7%	

*Note:* Weighted percentages and 95% Confidence Intervals (CI), NH=Non-Hispanic, College=4-year college graduate; 95% CI= 95% Confidence Interval, *p-value* for Rao-Scott chi-square test

## Appendix C. Chapter 4. Structural and Psychosocial Determinants of Frailty

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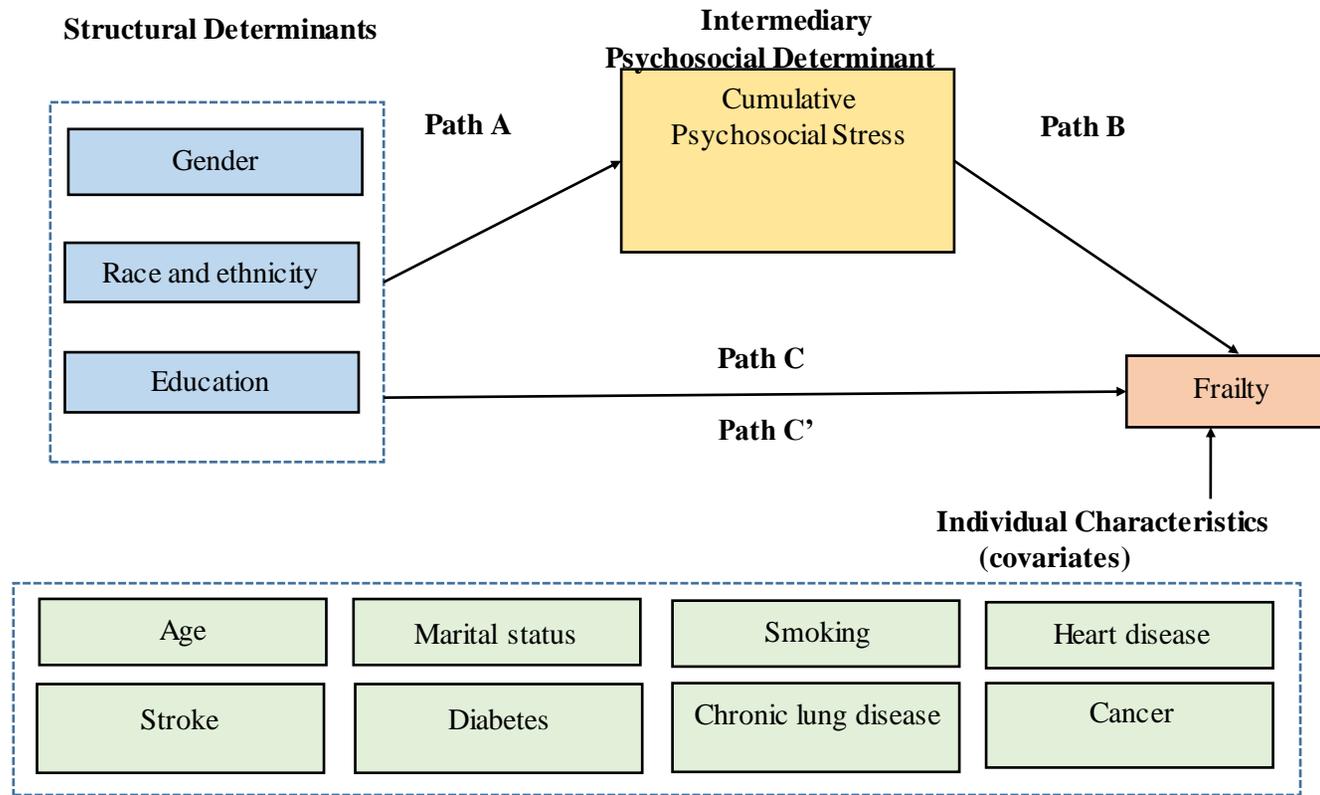
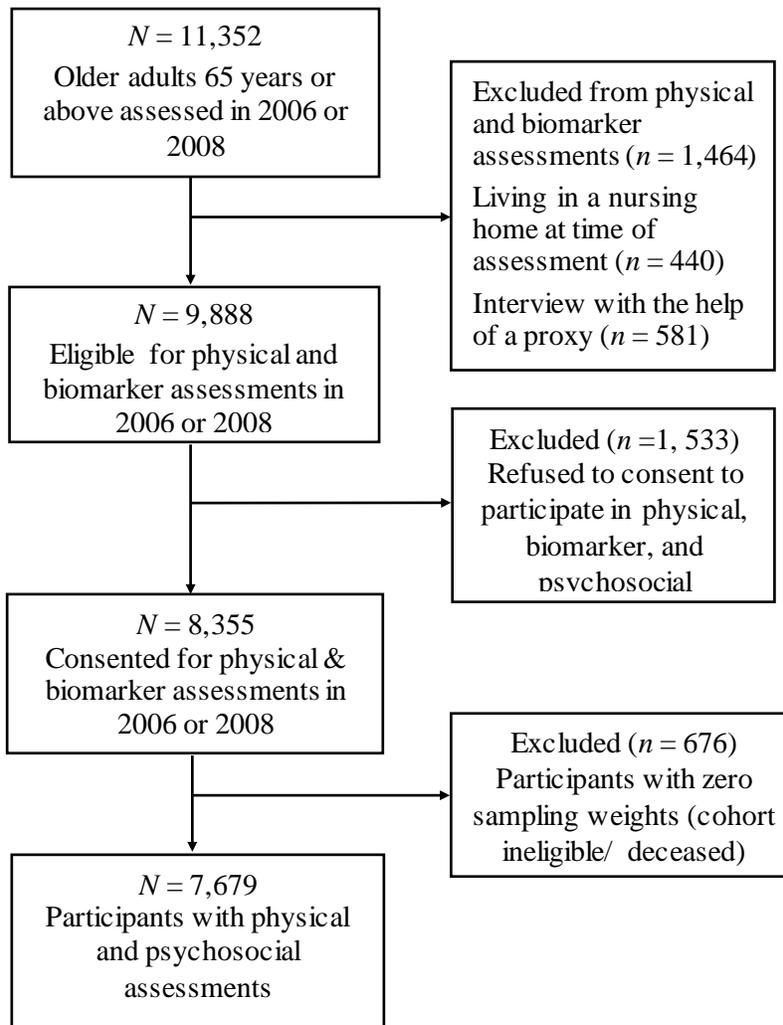


Figure C1: Structural and psychosocial determinants of frailty model



**Figure C2: Analytic sample size**

**Table C1: Operationalization of key variables**

Key Variables		Operational Definition and Coding
Structural Social Determinants of Health	Gender	Participant's self-reported gender: 1 = Male, 2 = Female
	Race and ethnicity	Participant's self-reported race and ethnicity, coded as :1 = Hispanic/Latino, 2 = Non-Hispanic Caucasian/ White, 3 = Non-Hispanic Black or African American, 4 = Non-Hispanic Other race and ethnic minority groups (Asian, Native Hawaiian, Pacific Islander, Alaska Native, Other)
	Education	Participant's self-reported education, coded as:1 = Less than high school, 2 = High school or General Educational Development (GED), 3 = Some years of college, 4 = College or higher degrees
Psychosocial indicators	Loneliness	Loneliness was assessed using the abbreviated <b>UCLA loneliness scale</b> , which asked participants, "How much of the time do you feel a) you lack companionship, b) left out, c) that you are isolated?" Responses were captured using a Likert scale ranging from 1(often), 2(sometimes), 3(hardly ever/ never). <b>Coding:</b> Scores across three items were added to get an overall score ranging from 3 to 9. The mid-point split technique was used to determine <b>high loneliness (1) = overall score 3 to 6 and low loneliness (0) = overall score 7 to 9.</b>
	Perceived everyday discrimination	Perceived discrimination was assessed using the abbreviated <b>William's discrimination scale</b> , which asked participants, "In day-to-day life how often have any of the following things happened to you?" a) "You are treated with less courtesy or respect than other people"; b) "You receive poorer service than other people at restaurants or stores"; c) "People act as if they think you are not smart", d) "People act as if they are afraid of you"; and e) "You are threatened or harassed." Responses ranged from 1 (almost every day), 2 (at least once a week), 3 (a few times a week), 4 (a few times a month), 5 (less than once a year), and 6 (never). <b>Coding:</b> Scores across these items were added and averaged to get an overall score ranging from 1 to 6. Experience of everyday discrimination on a "daily" and "weekly" basis was used to categorize as <b>high everyday discrimination (1) = overall score 1 to 4.9</b> , and experience of discrimination less than once a year or never was coded as <b>low everyday discrimination (0) = overall score 5 to 6.</b>
	Financial strain	Financial strain was assessed by asking, "How difficult is it for (you/your family) to meet monthly payments on (your/your family's) bills?" Responses included 1. not at all difficult, 2. not very difficult, 3. somewhat difficult, 4. very difficult, 5. completely difficult <b>Coding:</b> The mid-point split technique was used to determine <b>high financial strain (1) = "very difficult" or "completely difficult"</b> and <b>low financial strain (0) = "not at all difficult" or not very difficult" or "somewhat difficult."</b>
	Neighborhood cohesion	Neighborhood cohesion was based on questions asking participants, "how do you feel about your local area that is everywhere within a 20 minutes walk or about a mile of your home: a) I feel part of this local area, b) most people in the neighborhood can be trusted, c) most people in this area are friendly, d) people feel safe walking alone". Responses were captured using a 7-point Likert scale, ranging from 1, "strongly agree" to 7, "strongly disagree"

	disagree”. <b>Coding:</b> Scores across the items were added and averaged to get an overall score ranging from 1 to 7. The mid-point split technique was used to determine <b>low neighborhood cohesion (1)</b> = overall score 4 to 7 and <b>high neighborhood cohesion (0)</b> = overall score 1 to 3.9.
Subjective social status	Subjective social status was measured using the <b>MacArthur scale of subjective social status</b> , which asked participants to place themselves on the social ladder ranging from 1 to 10, a lower score representing a worse position with the least money, least education, and poor jobs or no jobs. <b>Coding:</b> Based on prior literature, the score was categorized into <b>low subjective social status (1)</b> = 1 to 3 and <b>moderate/higher subjective social status (0)</b> = 4 to 10.
Traumatic life events	Participants were asked a set of questions based on the <b>Diagnostic and Statistical Manual of Mental Disorders</b> to assess their experience of traumatic life events, a) Did you ever have a life-threatening illness or accident? 1. Yes 0. No, b) Did your spouse or child have a life-threatening illness or accident? 1. Yes 0. No, c) Have you been in a major fire, flood, earthquake, or other natural disasters? 1. Yes 0. No, d) Has a child of yours ever died? 1. Yes 0. No, e) Has your spouse, partner, or child ever been addicted to drugs or alcohol? 1. Yes 0. No” <b>Coding:</b> The experience of any of these traumatic life events were coded as <b>traumatic life events (1)</b> versus <b>not (0)</b> .
Cumulative psychosocial stress	A cumulative psychosocial stress score was determined by adding scores across these dichotomized psychosocial factors ranging from 0 to 6. Higher score indicates greater psychosocial stress.
Frailty features and outcome	Poor grip strength Poor grip strength: 0 = No, 1 = Yes, defined as <b>For men</b> Grip strength $\leq 29$ kg/m <sup>2</sup> for BMI $\leq 24$ Grip strength $\leq 30$ kg/m <sup>2</sup> for $24 < \text{BMI} \leq 26$ Grip strength $\leq 32$ kg/m <sup>2</sup> for BMI $> 26$ <b>For women</b> Grip strength $\leq 17$ kg/m <sup>2</sup> for BMI $\leq 23$ Grip strength $< 18$ kg/m <sup>2</sup> for $23 < \text{BMI} \leq 29$ Grip strength $< 21$ kg/m <sup>2</sup> for BMI $> 29$
	Slow gait speed Slow gait speed: 0 = No, 1 = Yes, defined as <b>For men</b> Gait speed $\leq 0.653$ m/s (time $\geq 7$ seconds) for height $\leq 173$ cm Gait speed $\leq 0.762$ m/s (time $\geq 6$ seconds) for height $> 173$ cm <b>For women</b> Gait speed $\leq 0.653$ m/s (time $\geq 7$ seconds) for height $\leq 159$ cm Gait speed $\leq 0.762$ m/s (time $\geq 6$ seconds) for height $> 159$ cm
	Weight loss Weight loss: 0 = No, 1 = Yes, defined as weight loss of $\geq 10$ pounds in last 2 years
	Fatigue Exhaustion: 0 = No, 1 = Yes, defined as self-report of yes to: a) felt that everything I did was an effort or b) could not get going in the last week
	Low physical activity Low physical activity: 0 = No, 1 = Yes, defined as lower participation in vigorous or moderate physical activities equivalent to expending less than 300 kcal/day.

	Frailty	Frailty outcome: 0 = No, 1 = Yes, defined as presence of 3 or more frailty features
Individual characteristics	Age	Participant's age: 1 = 65-69 years, 2 = 70-79 years, 3 = 75-79 years, 4 = 80 and above
	Marital status	Marital status: 0 = Separated, divorced, widowed, 1 = Married/partnered
	Smoking history	Smoking history: 0 = Never smoker, 1 = Current/former smoker
	Chronic conditions	Self-report of cardiovascular disease, stroke, diabetes, chronic lung disease, cancer as per physician's diagnosis at the time of the survey assessment, each condition coded as 0 = No, 1 = Yes.

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## **Biography**

Shamatree is originally from Nepal. She earned her Bachelor of Science in Nursing (2014) from Tribhuvan University, Nepal. While working as a neurocritical nurse, she deepened her interest in understanding and managing multimorbidity, geriatric syndrome, and cognitive aging. She pursued a Master's in Gerontological Studies at Miami University (2019), Ohio, and worked as a graduate research assistant at Scripps Gerontology Center, Ohio. She was introduced to a range of theoretical frameworks underpinning health and health disparities at her master's and Doctoral levels. In her dissertation, she solidifies her understanding on social determinants of health, as she investigates biological, psychosocial contributors to frailty and frailty disparities through the lens of social determinants of health.