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Title: Exploring the Validity and Genetic Basis of Frailty

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Frailty is a clinical syndrome characterized by decreased resilience to stressors, resulting from dysregulation across multiple physiological systems. Frailty is prevalent in elders and is associated with a wide range of adverse outcomes including death, disability, hip fracture, and falls. In the absence of a gold standard, there is a lack of consensus on the operational definition of frailty. Fried and colleagues developed the physical frailty phenotype (PFP) scale using gait speed, grip strength, exhaustion, physical activity, and weight loss. Since its emergence, the PFP scale has been repeatedly validated and widely used in assessing frailty. The PFP scale, however, like all other frailty assessments, has limitations. First, precision is lost in the process of dichotomizing continuous indicators (e.g., gait speed). In addition, all five frailty indicators in the PFP scale are assumed to be of equal importance in measuring frailty. Moreover, the PFP scale is very effective in identifying the frailest elders but has limited ability to differentiate persons with low levels of frailty. This dissertation had two overarching goals. The first was to create a new continuous scale for assessing frailty and to comprehensively evaluate its construct and predictive validity as well as measurement properties. The second was to explore the genetic

basis of frailty. First, I demonstrated the feasibility to construct a continuous frailty scale that had high construct validity and desirable measurement properties. Second, I showed that the new continuous frailty scale had high predictive validity for adverse health outcomes including mortality, disability, hip fracture, and falls among older adults. Third, the new scale could provide additional risk stratification for adverse outcomes above and beyond the categorical PFP scale, especially at the lower to middle end of the frailty continuum. Fourth, the new frailty scale was strongly associated with recovery of and improvement in activities of daily living function among elders who were newly disabled. Fifth, older persons with higher scores on the new frailty scale were more likely to have prolonged length of hospital stay after undergoing myocardial infarction and coronary artery bypass grafting. Additionally, frailer elders had higher mortality after experiencing myocardial infarction, heart failure, pneumonia, and coronary artery bypass grafting. Lastly, several genetic variants that have biological plausibility were suggestively associated with frailty. From a methodological perspective, the new continuous frailty scale frailty is a valid continuous construct with a unidimensional factor structure robust to nuanced differences in measurements and invariant across cohorts and demographics including age and sex. In addition, the new frailty scale has high predictive validity for multiple health outcomes including death, disability, hip fracture, and falls among community-dwelling older adults. Moreover, the new frailty scale could capture elders' ability to recover from stressors (disability, medical events, and surgeries), which is considered one of the defining features of frailty. Findings from this dissertation could also have important public health and clinical implications. First, the new continuous frailty scale could further stratify risk of outcomes among robust and prefrail persons, suggesting these two subgroups were not homogeneous. Second, the new frailty scale was able to pinpoint frailty level in the early stage,

which may be valuable for identifying at-risk persons who are not frail yet and offers opportunities for interventions that prevent or slow down the progression of frailty and maintain health and function. Third, assessment of frailty may help clinicians, public health professionals, and researchers better identify at-risk elders after experiencing disability and acute diseases and provide useful information in making informed decisions about surgical procedures. Fourth, the new continuous frailty scale, due to its continuous and sensitive nature, may be suitable to evaluate the effectiveness of interventions for frailty and track trajectories of frailty over time.

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I understand that my dissertation will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my dissertation to any reader upon request.

Chenkai Wu, Author

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Exploring the Validity and Genetic Basis of Frailty

CHAPTER 1: GENERAL INTRODUCTION

1.1. Background

Frailty is defined by geriatricians as a clinical syndrome of decreased reserve and resilience to stressors, resulting from aging-related declines across multiple physiological systems and leading to increased vulnerability to adverse health outcomes.[1-8] Frailty is common among older adults and its prevalence increases with age and varies by sex, race/ethnicity, and regions.[9-25] A considerable amount of research has documented that frail older adults are at increased risk of a wide range of unfavorable outcomes, including mortality,[22,26-39] disability,[18,30,31,35,40-44], fractures,[26,31,44] falls,[26,30,31,35,40,42,45-48] hospitalization,[29,35,39,42,44,49] depression,[14,26,35,50-57] and poor cognitive outcomes,[14,18,35,38,47,58-64] in different cultural, social, and institutional contexts. In the absence of a gold standard, there is a lack of consensus on the operational definition or official diagnosis of frailty. Over the past several decades, researchers have proposed numerous instruments—derived from distinct theoretical perspectives—to operationalize frailty.[35,65-78] Among these measurements, the physical frailty phenotype (PFP) scale[35] has become the most widely used one. Using data from the Cardiovascular Health Study (CHS), Fried et al.[35] constructed the PFP scale using gait speed, grip strength, exhaustion, physical activity, and unintentional weight loss, all of which had been theoretically characterized as key elements in the development of frailty.[2,3,79-81] Sample-specific cutoff points (e.g., $\leq$ the lowest 20th percentile) were used to discretize continuously measured variables into dichotomous criteria (e.g., slow gait speed and weak grip strength). A frailty state is characterized if three or more of these criteria are met, a prefrail stage is identified if one or two criteria are met, and persons who meet none of the criteria are classified as robust or nonfrail.

Since its emergence, the PFP scale has been widely accepted as a valid tool for assessing frailty in both clinical and public health settings. It has been commonly used to understand the physiological or etiologic basis of frailty. The PFP scale, however, like all other frailty assessments, has limitations. First of all, precision is lost in the process of dichotomizing continuously measured variables; for example, older women with different gait speed were assigned the same score once their measures were slower than a height-specific cut-point. In addition, all frailty indicators in the PFP scale are assumed to be of equal importance in measuring frailty; however, it is questionable whether this untested assumption is tenable. In other words, it is possible that different indicators measure frailty with different strengths. Moreover, the PFP scale is very effective in identifying the frailest elders but has limited ability to differentiate persons at the lower end of frailty. In the CHS, approximately half of the participants did not meet any of five frailty criteria and were therefore classified into the same category—robust.[35] It is however questionable whether these participants had the same level of frailty.

One approach to overcome these limitations and challenges is to develop a finer-graded frailty scale that can utilize all useful information of five indicators and weight the indicators differently according to their relative contribution to assessing frailty. A finer graded scale may have the following advantages compared with the categorical PFP scale: (i) providing a greater differentiation of the frailty syndrome, (ii) further stratifying risk of health outcomes among robust, prefrail, and frail adults identified by the PFP scale, (iii) increasing statistical power for identifying genetic, physiological, behavioral, and environmental risk factors for development of frailty and transitions between frailty status over time, and (iv) enhancing power of frailty

instruments for predicting outcomes, and (v) better evaluating the effectiveness of interventions for frailty. Some of these advantages have been previously demonstrated in two rescaled PFP scales.[82,83]

Various adaptations of the PFP scale have arisen in the literature to assess frailty.[19,30,83-88] Relatively little is known about the validity of the PFP scale and its modified versions. There is, therefore, a critical need to determine whether and how five indicators comprising the PFP scale are correlated with the latent frailty construct (i.e., construct validity), and to identify whether these five indicators can capture one of the defining features of frailty—the ability to recover from stressors. In the absence of such knowledge, it is unlikely that the etiology and clinical utility of frailty will be completely understood.

In a recent meeting comprising experts in the field of frailty, researchers have claimed that a number of operational definitions of frailty were well validated for predictive/criterion validity (i.e., the extent to which frailty is associated with future outcomes).[89] However, in many of these investigations, the prognostic value and the classification power of frailty have been only gauged by statistical significance and magnitude of association. New literature has demonstrated that traditional methods based on magnitude of association are not suitable for evaluating a diagnostic or prognostic marker and may have serious pitfalls.[90] In addition, existing validations rarely report indices of model performance except for the C statistic, also known as area under the receiver operating characteristic curve (AUC), which may lead to overestimation of the overall prognostic value of frailty. Using a predictive modeling approach to evaluate the

predictive validity of frailty assessments may provide more convincing evidence about the utility of frailty in predicting health outcomes.

Over the past decade, research examining risk factors for frailty has proliferated. Identification of genetic, physiological, behavioral, and social determinants of frailty may serve as an essential component of well-designed and patient-tailored interventions of frailty. A wide range of socio-demographic,[9,10,15,17,24,35,44,53,91-94] behavioral,[10,11,44,85,92,95-98] nutritional,[51,99-113] physiological,[11,114-127] and psychosocial[128-134] characteristics have been identified as risk factors for frailty from both cross-sectional and longitudinal studies. However, little attention has been given to the genetic components of frailty. Using data from two large Danish studies, Dato et al.[135] reported a heritability estimate of 43% for frailty, measured by activities of daily living (ADLs), grip strength, body mass index (BMI), self-rated health, and cognition. Murabito et al.[136] showed that frailty, assessed by the PFP scale, was modestly heritable (19%) in the Framingham Heart Study. Recently, Sanders et al.[137] reported a heritability estimate of 23% for a rescaled PFP model (i.e., Scale of Aging Vigor in Epidemiology) using data from the Long Life Family Study. Taken together, these results suggest that frailty is moderately heritable and it is valid to identify genetic variants associated with frailty. To date, only a very limited number of genes for frailty have been examined in candidate gene association studies, with no genetic variants being consistently found to be associated with frailty.[138-143] Therefore, there is a pressing need to explore a wider range of genetic variants to better understand the genetic underpinnings of frailty. One approach to serve this purpose is genome-wide association study (GWAS), an efficient microarray technology that tests the associations of genetic variants (single nucleotide polymorphism [SNPs]) with phenotype (e.g., disease) across the entire human genome. GWAS

has been successful for identifying genetic variants involved in the development of complex diseases and traits (e.g., breast cancer and longevity).[144-146]

1.2. Goals, Specific Aims, & Hypotheses

This dissertation had two overarching goals: (i) creating a continuous frailty scale and comprehensively evaluating its construct and predictive validity; and (ii) exploring the genetic basis of frailty. Five specific aims were listed below:

Specific Aim 1: To investigate whether and to what extent five frailty indicators—gait speed, grip strength, exhaustion, physical activity, and weight loss—were correlated with the frailty construct.

- *Hypothesis 1a:* Each of the five indicators would be correlated with the frailty construct.
- *Hypothesis 1b:* Five indicators would be associated with one latent construct, frailty, with different strengths.

Specific Aim 2: To assess the performance of the continuous frailty scale in predicting mortality, disability, hip fracture, and falls among community-dwelling older adults.

- *Hypothesis 2a:* Frailty, as assessed by the continuous frailty scale, would be associated with mortality, disability, hip fracture, and falls, respectively, independent of socio-demographic, behavioral, and clinical covariates.
- *Hypothesis 2b:* Compared with the PFP scale, the continuous frailty scale would have better overall goodness-of-fit, higher discrimination ability, more precise calibration, and higher reclassification rates in predicting mortality, disability, hip fracture, and falls, respectively.

Specific Aim 3: To examine the association of frailty with the ability to recover from disability among community-dwelling older adults.

- *Hypothesis 3a:* frailty, as assessed by either the PFP scale or the continuous frailty scale, would be associated with lower ability to recover from disability among initially non-disabled older adults.

Specific Aim 4: To examine the association of frailty with the ability to recover from acute medical events and surgical procedures among community-dwelling older adults.

- *Hypothesis 4a:* frailty, as assessed by either the PFP scale or the continuous frailty scale, would be associated with longer length of hospital stay (LOS) after experiencing acute medical events and surgical procedures among older adults.
- *Hypothesis 4b:* frailty, as assessed by either the PFP scale or the continuous frailty scale, would be associated with shorter survival after experiencing acute medical events and surgical procedures among elders.

Specific Aim 5: To explore the genetic variants associated with frailty using a GWAS and to describe the functional roles of important SNPs and genetic loci.

- *Hypothesis 5:* novel genetic loci associated with frailty would be identified.

1.3. Dissertation Structure

The remainder of the dissertation was structured as follows. In Chapter 2, a broad survey of literature was discussed followed by a presentation of methodological limitations and inconsistencies in analytic strategy of prior research on frailty. Participants, operational

definitions of outcomes, predictors, covariates, analytic approaches, results, and discussion of Specific Aims 1, 2, 3, 4, and 5 were presented in Chapters 3, 4, 5, 6, and 7, respectively. In Chapter 8, a general discussion of findings and implications was presented followed by a general conclusion.

CHAPTER 2: LITERATURE REVIEW

2.1. Operational Definition and Measurement of Frailty

Geriatricians generally agree that frailty is a clinical syndrome characterized by decreased reserve and resilience to stressors, resulting from aging-related dysregulations across multiple physiological systems.[1-8] In the absence of a gold standard, however, there is a lack of consensus on the operational definition or official diagnosis of frailty. Over the past several decades, researchers have proposed numerous instruments, derived from distinct theoretical perspectives, to measure frailty. Assessments of frailty have been mainly developed based on three domains: biological syndrome, functional status, and accumulative deficits.[39,73,92,147-149] The physical frailty phenotype (PFP) scale[35] and the frailty index (FI)[75] have been the two most widely used ones.

2.1.1. Physical Frailty Phenotype Scale

Using data of 5,317 community-dwelling men and women aged ≥65 years from the Cardiovascular Health Study (CHS), Fried et al.[35] created the PFP scale using five variables: gait speed, grip strength, exhaustion, physical activity, and unintentional weight loss, all of which had been proposed as key markers involved in the development of frailty.[2,3,79-81] The lowest body size- (height for gait speed, body mass index [BMI] for grip strength) and sex-specific quantile values were used to discretize three continuously variables into dichotomous criteria: slow gait speed, weak grip strength, and low physical activity. Exhaustion was identified by two questions from the Center for Epidemiologic Studies Depression (CES-D) scale.[150] Unintentional weight loss was defined as self-reported loss of 10 or more pounds in prior year not due to exercise or diet, or loss of ≥5% body weight at follow-up (by direct measure of weight). Presence of each of

the five criteria (e.g., slow gait speed) was scored 1 and the total score ranged from 0 to 5. Frailty was defined if three or more of these criteria are met, a prefrail state (a hypothesized intermediate stage) was identified if one or two criteria are met, and persons who met none of the criteria were classified as robust or nonfrail. This landmark study is important because (i) it suggests that frailty can be operationally defined and assessed using standard measures that are theoretically relevant to frailty, (ii) it provided empirical evidence that frailty, disability, and comorbidity are overlapping but distinguished clinical concepts (26.6% of frail older adults were free of disability and comorbidity), and (iii) it demonstrated the utility of frailty in predicting adverse health outcomes, including falls, disability, hospitalization, and mortality.

Since its emergence, the PFP scale has been widely accepted as a valid tool for assessing frailty in both clinical and public health settings. It has been commonly used to understand the physiological or etiologic basis of frailty. However, the PFP scale is not without limitations. One methodological limitation is that precision is lost in the process of dichotomizing continuous variables; for example, older women with different gait speed are assigned the same score (i.e., 0) once their measures are slower than the lowest height-specific quintile. Dichotomization of continuous measures may lead to reduced statistical power in identifying risk factors for frailty. In addition, all five frailty indicators in the PFP scale are implicitly assumed to be of equal importance in measuring frailty; however, it is questionable whether this untested assumption is reasonable. Furthermore, although the PFP scale is very effective in identifying the most frail older adults, it has limited ability to differentiate persons who are minimally frail or robust. In the CHS, approximately 45% of the participants scored 0 in the PFP scale and were classified into the same category—robust. Without further investigation, it is difficult to rule out the

possibility that these persons had different frailty levels which might be associated with different risks of adverse health outcomes.

One possible approach to overcome these limitations and challenges is to develop a continuous frailty scale that utilizes all useful information of five indicators and weights indicators differently according to their relative contribution to assessing frailty. A finer graded continuous frailty scale may have the following advantages: (i) providing a greater differentiation of the frailty syndrome, (ii) further stratifying risk of outcomes among robust, prefrail, and frail adults identified by the PFP scale, (iii) increasing statistical power for identifying genetic, physiological, behavioral, and environmental risk factors for development of frailty and transitions between frailty status over time, and (iv) enhancing power of frailty instruments for predicting outcomes. Some of these advantages have been previously demonstrated in two rescaled PFP scales.[82,83]

Researchers have proposed numerous adaptations of the PFP scale, primarily motivated by unavailability of measures (e.g., no direct measure of weight in two waves to calculate weight loss) or desire for a quick patient evaluation in a busy clinical setting (e.g., replacement of performance-based grip strength and gait speed with self-report measures).[24,26,49,86] These studies have mostly focused on the effectiveness of modified PFP scales for risk prediction—predictive validity, whereas considerably less attention has been given to other types of validity, such as construct validity, divergent validity, and concurrent validity. Construct validity refers to whether and to what extent frailty indicators are correlated with the underlying frailty construct; divergent validity refers to the extent to which frailty is distinct from theoretically different

constructs such as disability and comorbidity; concurrent validity refers to the degree to which frailty assessment is concordant with the gold-standard measure of frailty. Achieving predictive validity is not sufficient for researchers to claim an assessment frailty to be valid. Future research that aims to develop new frailty assessments needs to evaluate validity in a more comprehensive fashion.

2.1.2. Frailty Index

In addition to the PFP scale, another well-known frailty assessment is the FI, which was initially proposed by Mitnitski et al.[151] in a secondary analysis of a representative sample of Canadians aged ≥65 years from the Canadian Study of Health and Aging. The FI was calculated as a ratio of number of observed deficits over the 20 selected binary deficits (the denominator is 20), including vision loss, hearing loss, impaired mobility, vascular problem, gait abnormality, impaired vibration sense, difficulty toileting, difficulty cooking, difficulty bathing, difficulty going out, difficulty grooming, difficulty dressing, skin problems, resting tremor, changes in sleep, urinary complaints, gastrointestinal problem, diabetes, hypertension, and limb tone abnormality. The FI ranges from 0 to 1, with higher score indicating a frailer status. Using data from the same cohort, Mitnitski et al.[75] later extended their analyses to all 92 binary deficits available in the data set and constructed the FI in the same way (the denominator is 92). Six major domains of health were covered, including symptoms (e.g., low mood), signs (e.g., decreased peripheral pulses), functional impairment (e.g., impaired mobility), diseases (e.g., hypertension), abnormal biomarker values (e.g., creatinine), and disability (e.g., activities of daily living [ADLs]). In a more recent study, Jones et al.[74] constructed a modified FI based on comprehensive geriatric assessment (CGA) to promote the utility of the FI in clinical practice

and to speed up decision making for geriatricians in busy clinical settings. CGA is a multidimensional and integral diagnostic tool used in geriatric care to determine an older adult's medical, functional, and psychosocial status.[152,153] Problems in each of the 10 domains (e.g., cognitive status, mobility, balance, ADL disability) were scored 0 (no problem), 1 (minor problem), or 2 (major problem). The total score ranged from 0 to 20 and three levels of frailty were defined: mild (score: 0-7), moderate (score: 8-12), and severe (score >13).

The FI was initially developed as an index of health status and biological aging to predict mortality. Therefore, any acquired aging-related markers that may contribute to the risk of mortality can be included in the FI. Compared with the PFP scale, the FI has been demonstrated as a more sensitive predictor of mortality, possibly due to its more inclusive (usually 30 or more measures) and finer-graded scale (continuous vs. categorical).[49,149] Another notable advantage of the FI is that the deficits can be randomly selected (e.g., 30 out of 40 available measures) without loss of predictive validity of mortality.[154] Moreover, the distribution of the FI is well characterized by the γ-distribution—a distribution that is often used for modeling systems with redundancy. This is considered an attractive mathematical feature of the FI because it represents the idea that frailty is featured by reduced physiological reserve and resilience to stressors.[155]

Despite its high predictability, great flexibility in measurement (number and choice of deficits), and attractive mathematical properties, the FI has several undesirable features that merit attention before it is to become a standard and valid assessment of frailty. First, there has been critique on the inclusion of comorbidity and disability measures in the FI. There is growing consensus among geriatricians that frailty, disability, and comorbidity are three empirically related but

conceptually distinct clinical entities.[156] Comorbidity has been shown as a predictor for frailty, while disability is considered one of the health consequences of frailty.[35] Inclusion of comorbidity and disability measures in a frailty assessment may hinder attempts to elucidate the specific etiology of frailty. In addition, frailty is theoretically considered a non-specific aging-related vulnerability under the accumulative deficit framework. However, absence of specificity in the FI limits its utility in identifying specific risk factors for frailty. Moreover, similar to the PFP scale, all deficits in the FI are assumed to be equally important in measuring frailty, whereas no investigations have tested this assumption.

2.1.3. Other Frailty Assessments

Study of Osteoporotic Fractures Index

Ensrud et al.[87] proposed a simple frailty index—Study of Osteoporotic Fractures (SOF) index—using only three components: excessive weight loss of 5% or more in previous year (irrespective of intent to lose weight), inability to rise from a chair five times without using arms, and low energy level (identified by answering "No" to the question "Do you feel full of energy?"). Frailty was identified if two or three components were present, persons having presence of one component were classified as having an intermediate status, and the rest was considered robust.

The concordance in classification of frailty status (robust, prefrail, and frail) between the SOF index and the PFP scale was high (74% for women and 71% for men).[31,87] This is not surprising because all three items used in the SOF index are similar to those used in the PFP scale. The SOF index was associated with recurrent falls, hip fracture, disability, and mortality, and had similar discrimination performance compared with the PFP scale among 6,701 women aged ≥69 years

from the SOF and 3,132 men aged ≥67 years from the Osteoporotic Fractures in Men Study (MrOS; a male version of the SOF).[31] In a more recent study, Kiely et al.[42] validated the predictive validity of the SOF index in the Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study, which comprised of 765 community-dwelling elders (≥70 years) from the greater Boston area. In addition, the SOF index was associated with overnight hospitalization and emergency department visits.[42]

The SOF index has three simple measures that are easy to administer in a clinical setting, has high concordance with the PFP scale—the most widely used frailty assessment, and is predictive of multiple adverse outcomes among older adults. However, very few investigators including those who developed it have used the SOF index. More research is needed to evaluate the construct and predictive validity of the SOF index, especially in populations other than whites who reside the U.S.

Fatigue, Resistance, Ambulation, Illness, and Loss Scale

One critique of the two most widely used frailty assessments—the PFP scale and the FI—is that neither measure is clinic-friendly (e.g., long administration time). The PFP scale requires measured performance (gait speed and grip strength) and sex- and body size-specific cutoffs derived from the underlying population. The FI includes numerous items (typically 30 or more) and may also include measured performance. A simple frailty assessment that only requires minimal administration time and effort may maximize the efficiency of identifying frailty in busy clinical settings.[157] Due to these considerations, the Geriatric Advisory Panel of the International Academy Nutrition and Aging (IANA) task force proposed a clinic-friendly frailty

assessment—Fatigue, Resistance, Ambulation, Illness, and Loss (FRAIL) scale—that can be accomplished exclusively through self-reports.[69,70]

The FRAIL scale includes five components: fatigue, resistance, ambulation, illness, and loss of weight.[69,70] Each item was scored 0 or 1; the sum score, which ranges from 0 to 5, was used to assess frailty. Similar to the PFP scale, frailty was defined with a score of 3-5, a prefrail state was identified with a score of 1-2, and persons with a score of 0 were classified as robust. Fatigue was assessed by asking participants how much time during the past four weeks they felt tired; an answer of "All of the time" or "Most of the time" was scored 1. Resistance was measured by asking participants if they had any difficulty walking up 10 steps alone without resting or aids; an answer of "Yes" was scored 1. Ambulation was scored 1 for participants who reported they had any difficulty walking several hundred yards alone without aids. Illness was measured by asking participants "Did a doctor ever tell you that you have [illness]?" A total of 11 illnesses were included: hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, heart failure (HF), angina, asthma, arthritis, stroke, and kidney disease. Participants who reported having five or more illnesses scored 1. Loss of weight was scored 1 for participants who reported loss of 5% or more body weight in the past year.

The FRAIL scale was first constructed by Hyde et al.[158] in a cohort of 3,616 community-dwelling men aged 70-88 years in Australia, and was later validated for predicting adverse outcomes by Morley et al.[157] in the African American Health project, which comprised of 998 African Americans aged 49-65 years from two socioeconomically diverse areas of St. Louis. Both frail and prefrail status were associated with higher risk of ADL disability and mortality. In

a later study, conducted by the same research group, Malmstrom et al.[159] showed that the FRAIL scale had similar discrimination of ADL disability and mortality compared with the PFP scale and the SOF index. Researchers have also evaluated the predictive validity of the FRAIL scale in independent cohorts. Using data from 2,929 men aged 40-79 years from the European Male Aging Study, Ravindrarajah et al.[160] found that the FRAIL scale was strongly associated with mortality and had similar discrimination of death compared with the PFP scale and the FI. In a study of 8,646 women aged 74-82 years from the Australian Longitudinal Study on Women's Health, Lopez et al.[161] found that a score of 3 or more on the FRAIL scale was associated with higher risk of mortality and ADL disability. Using data from 4,000 community-dwelling Chinese adults aged ≥65 years in Hong Kong, Woo et al.[162] showed that the FRAIL scale was associated with mortality and physical function limitations and had similar discrimination performance compared with the PFP scale and the FI.

The 5-item FRAIL scale has several strengths. First, it captures components of three domains that can potentially serve as criteria for assessing frailty: biological syndrome (fatigue and loss of weight), functional status (resistance and ambulation), and deficit accumulation (illness). In addition, the FRAIL scale can be assessed completely based on questionnaires without a long administration time, and may therefore serve as a good screening tool for identifying frail persons in clinical practice. Like other assessments of frailty, the FRAIL scale has limitations and undesirable features that deserve further investigation before it can become a standardized and valid screening tool for frailty. First, given that frailty is conceptually distinct from disability and comorbidity,[156] inclusion of illness may reduce the specificity of the FRAIL scale in measuring frailty. Rosas-Corrasco et al.[163] recently evaluated the internal validity of the Mexican

Spanish version of the FRAIL scale in the Frailty Dynapenia and Sarcopenia in Mexican Adults Study, which included 606 adults from two municipalities in Mexico City. They showed that illness was neither associated with the total score of the FRAIL scale (Spearman correlation = 0.07, $p = .10$), nor with indicators that are commonly used to assess frailty (e.g., gait speed and grip strength). These results raised questions about the appropriateness of including an illness measure in the FRAIL scale. In addition, in the FRAIL scale, persons who reported any five or more out of 11 chronic conditions scored 1; however, a person who had five cardiovascular diseases (e.g., hypertension, heart attack, HF, angina, and stroke) and a person with five non-cardiovascular diseases (e.g., diabetes, cancer, lung disease, asthma, and arthritis) may have hugely different health status and medical needs. Moreover, self-reported items are easier to implement and more cost effective than performance-based tests; however, self-reports are less objective, more easily affected by mood, cognitive status, and cultural differences, and more prone to recall and social desirability bias.

Tilburg Frailty Indicator

Gobbens et al.[164] proposed an integral conceptual model of frailty based on their own definition of frailty, "a dynamic state affecting an individual who experiences losses in one or more domains of human functioning (physical, psychological, social), which is caused by the influence of a range of variables and which increases the risk of adverse outcomes."[165] This integral conceptual model of frailty includes three domains of human functioning: physical, psychological, and social;[164] the Tilburg Frailty Indicator (TFI) was developed based on this conceptual framework. The TFI includes two parts: Part A has 10 questions on socio-demographics, life events, and chronic conditions (i.e., sex, age, marital status, country of birth,

highest education, monthly household income, lifestyle, number of comorbidity, stressful life event, and satisfaction of home living environment); Part B has 15 questions that capture physical, psychological, and social domains of frailty.[148] Physical domain includes eight items: low physical health, unexplained weight loss, difficulty in walking, difficulty in maintaining balance, poor hearing, poor vision, low strength in hands, and physical tiredness; psychological domain has four items: problems with memory, feeling down, feeling nervous or anxious, and inability to cope with problems; social domain includes three items: living alone, lack of social relations, and lack of social support. All items are self-reported. Each item is scored 0 or 1; the sum score (range: 0-15) assesses frailty, with higher score indicating a higher level of frailty.

The TFI was first constructed and validated by Gobbens et al.[148] using two samples of 479 community-dwelling adults aged ≥75 years from Roosendaal in the southern Netherlands. The TFI was cross-sectionally associated with disability and health care utilization. In a later prospective study, Gobbens et al.[166] showed that the TFI was associated with disability, health care utilization, and quality of life measured one or two years later.

The TFI is relatively easy to administer and its development is theory-guided; however, the integral nature of the TFI may hinder efforts to identify specific biomarkers and etiological pathways of frailty. In addition, Gobbens et al.[148] reported low Cronbach's α for psychological domain (0.63) and social domain (0.34), suggesting low internal consistency of the scale. Moreover, not all questions used in the TFI are routinely collected in aging studies, which limits its applicability and generalizability. Using a subset of 15 questions in the TFI is a workaround option, but the validity of these modifications remains largely unknown. Furthermore, the TFI

has been rarely tested for predictive validity using independent samples. In a recent study that comprised of 687 community-dwelling adults aged ≥70 years from the areas of Limburg and Utrecht in the Netherlands, Daniels et al.[167] showed that the TFI had limited value for predicting disability and mortality.

Groningen Frailty Indicator

The Groningen Frailty Indicator (GFI), developed by Steverink et al.[168] is another screening tool for assessing frailty that was developed based on an integral conceptual framework. A total of 22 items were initially selected in the GFI to cover nine measures of health: mobility, fitness, comorbidity, nutrition/weight loss, vision, hearing, cognition, loneliness, and psychological distress. A 15-item version was later proposed to capture domains of functioning: physical (mobility, physical fitness, comorbidity, weight loss, vision, and hearing), cognitive (perception), social (loneliness), and psychological (psychological distress).[169] All items are assessed by self-reports. Each item is scored 0 or 1; the sum score ranges from 0 to 15, with higher score indicating a frailer status.

The predictive validity of the GFI was first evaluated by Shuurmans et al.[169] among 1,338 elders aged ≥65 years from six municipalities in the northern regions of the Netherlands. Higher score on the GFI was cross-sectionally associated with lower self-management ability; however, only unadjusted estimates were reported. Studies using independent samples did not provide strong evidence that the GFI was able to identify at-risk older adults for unfavorable outcomes. In a study of 142 consecutive vascular surgery patients in the Netherlands, Pol et al.[170] found that the median GFI score was higher among patients who had postoperative delirium than those who did

not; however, the association did not persist after adjusting for confounders. In another cohort of 687 adults aged ≥70 years from the Netherlands, Daniels et al.[167] showed that the GFI had limited value in predicting disability and mortality.

One goal of this dissertation was to comprehensively evaluate the validity of the original PFP scale and a new continuous frailty scale using variables included in the PFP scale. Therefore, unless otherwise stated, the remainder of this chapter focused on discussion of studies using the PFP scale and its adaptations.

2.2. Prevalence of Frailty

2.2.1. Prevalence of Frailty in the U.S.

Frailty is common among older adults and its prevalence increases with age and varies substantially by socio-demographics and geographic regions.[9-25] Using a sample of 5,317 community-dwelling U.S. adults aged ≥65 years from the CHS, Fried et al.[35] reported that the overall prevalence of frailty and prefrailty was 6.9% and 46.7%, respectively. In a more recent study of 7,439 participants from the National Health and Aging Trends Study (NHATS), a nationally representative sample of Medicare enrollees aged ≥65 years in the U.S., Bandeen-Roche et al.[19] showed that 15.0% were frail and 45.0% were prefrail.

Substantial variations exist in the prevalence of frailty across racial/ethnic subgroups in the U.S. In the CHS, the prevalence of frailty was 2-fold higher among African Americans relative to Caucasians (12% vs. 6%).[35] In the NHATS, the prevalence of frailty was 13.8%, 22.9%, and 24.6% for Caucasians, African Americans, and Hispanics, respectively.[19] Compared with

Caucasians, African Americans and Hispanics had 66% and 78% higher prevalence of frailty, respectively. Researchers from the San Antonio Longitudinal Study of Aging have reported parallel findings for racial disparities in frailty prevalence.[171] In this cohort of 301 Mexican Americans and 305 European Americans, 12.2% of Mexican Americans were frail, whereas only 7.3% of European Americans were frail.

2.2.2. Prevalence of Frailty in Other Industrialized Countries

Many studies have reported the prevalence of frailty in the U.S. However, relatively scant data are available for other industrialized countries, most of which face the challenges of an aging population and a foreseeable rapid increase in the prevalence of frailty.

Using data from the Survey of Health, Aging and Retirement in Europe (SHARE), Santos-Eggimann et al.[24] estimated the prevalence of frailty among community-dwelling adults living in 10 European countries, including Austria, Denmark, France, Germany, Greece, Italy, the Netherlands, Spain, Sweden, and Switzerland. A total of 18,227 adults aged ≥50 years were included. Dramatic differences exist in frailty prevalence across geographic regions, especially between countries in southern and northern Europe. Among adults aged ≥65 years, the prevalence of frailty was only 5.8% in Switzerland and 8.6% in Sweden, whereas 23.0% of older adults in Italy and 27.3% of elders in Spain were frail. Hubbard et al.[172] was the first to report the prevalence of frailty in the United Kingdom. In a sample of 3,055 adults aged ≥65 years from the English Longitudinal Study of Ageing (ELSA), 8.1% were identified as frail and the prevalence was slightly higher in women than in men (9.0% vs. 7.0%). Duarte et al.[173] reported 34.9% of Portuguese older adults were frail. In countries outside Europe, the prevalence of

frailty ranged from 9.4% to 15.2% for community-dwelling men (≥70 years) in Australia (two studies),[158,174] 22.7% in Canadians elders aged ≥65 years (one study),[25] from 6.1% to 11.3% among Japanese adults aged ≥65 years (two studies),[175,176] and from 9.3% to 17.4% in South Korea (three studies).[177-179]

2.2.3. Prevalence of Frailty in Developing Countries

There has been little attention given to the prevalence of frailty in developing countries. In a recent systematic review, Nguyen et al.[180] summarized findings from four countries—Brazil, China, Mexico, and Russia—on the prevalence of frailty among community-dwelling older adults. The prevalence of frailty was estimated as 17.1% to 23.3% in Brazil (≥65 years),[9,181] 5% to 30% in China (≥55 years),[182-184] 15.0% in Mexico (≥70 years),[185] and 21.1% in Russia (≥65 years).[186] Researchers have reported relatively high prevalence of frailty in South and Central American countries. The prevalence was 32.3% among Costa Rican adults aged ≥60 years,[187] 21.6% among Cubans aged ≥65 years,[188] and ranged from 12.2% to 27.8% among Peruvians aged ≥60 years.[189,190]

2.2.4. Correlates of Prevalence of Frailty

Previous research has consistently shown that the prevalence of frailty increases steadily with age.[19,21,24,35,172] In the CHS, the prevalence of frailty was 3.2%, 5.3%, 9.5%, 16.3%, 25.7%, and 23.1% for 65-70, 71-74, 75-79, 80-84, 85-89, and 90+ age groups, respectively. In the NHATS, the prevalence of frailty increased from 8.0% among adults aged 65-69 years to 37.9% among the oldest group (≥90 years). Researchers have reported similar findings among European

populations. In the SHARE, a cohort study of over 18,000 adults across 10 European countries, 4.1% of the 50-64 group and 17.0% of the 65+ group were frail.

In addition to age, there is consistent evidence that women have greater prevalence of frailty than men.[19-21,24,35,87,172] In a systematic review, Collard et al.[21] showed that the weighted prevalence of frailty was 9.6% in women as opposed to 5.2% in men. Unfavorable socioeconomic status (low education, low income, poor household conditions and amenities),[18,19,35,51,92,171,188,191,192] living alone or having no spouse,[35,51] and poor social support[192] are related to high prevalence of frailty.

2.2.5. Difficulties in Estimating Prevalence of Frailty

One difficulty in estimating the prevalence of frailty is the absence of a gold standard for assessing frailty. Researchers have used various frailty assessments—e.g., the PFP scale and the FI—to estimate frailty prevalence. This diversity in frailty assessments largely explains the wide range in the estimates of frailty prevalence across similar study populations. In a systematic review of 21 community-based cohort studies, Collard et al.[21] showed that the considerable variation in frailty prevalence (4.0% to 59.1%) was substantially reduced by restricting the analyses to studies using the PFP scale (4.0% to 17.0%). Studies that used the PFP scale consistently reported substantially lower prevalence of frailty compared with those using other frailty assessments.

In addition to between-assessment variation—different assessments produce different estimates of frailty prevalence, within-assessment variation exists in studies utilizing the PFP scale because components of the PFP scale are often measured differently in different studies. In a recent

review article, Theou et al.[86] created 262 adaptations of the PFP scale based on modifications commonly seen in the literature (e.g., performance-based grip strength replaced by self-reported measure). The estimates of frailty prevalence ranged from 12.7% to 28.2%. Moreover, some criteria in the original PFP scale including grip strength, gait speed, and physical activity are defined based upon sample-specific cut-points, which may limit comparability between studies.

2.3. Consequences of Frailty

One of the defining features of frailty is increased vulnerability to adverse outcomes. Over the past 15 years, a considerable amount of effort has been devoted to identifying the health consequences of frailty. A preponderance of evidence has shown that frailty is associated with mortality[22,26-39], disability,[18,30,31,35,40-44] fractures,[26,31,44] falls,[26,30,31,35,40,42,45-48] hospitalization,[29,35,39,42,44,49] depression,[14,26,35,50-57] and poor cognitive outcomes[14,18,35,38,47,58-64] in different cultural, social, and institutional contexts. Numerous definitions and instruments of frailty exist, and how frailty is operationally defined and empirically assessed influences its associations with outcomes. I exclusively focused on studies that utilized the PFP scale or its adaptations to assess frailty.

2.3.1. Mortality

Using data from the CHS, Fried et al.[35] found that frail and prefrail persons aged ≥65 years had greater mortality risk than those who were robust. When compared with robust elders, frail and prefrail participants had a 32% and 63% higher risk for 7-year mortality, respectively. In a follow-up validation study, Bandeen-Roche et al[30] reported a stronger relationship between frailty and death among 784 women (aged 70-79 years) enrolled in the Women's Health and

Aging Study (WHAS) I and II. Compared with robust older women, the hazard ratio (HR) for 3-year mortality was 6.03 and 3.50 for frail and prefrail women, respectively. Ensrud et al.[26] extended these investigations by explicitly examining the association between frailty and death across age subgroups. In the SOF, a large U.S. cohort study of women aged ≥65 years, the association between frailty and mortality was slightly stronger among women aged ≥80 years than those <80 years (HR: 1.96 vs. 1.31). Interestingly, in a parallel study, Cawthon et al. showed that the relation was stronger among men aged <80 years than those aged ≥80 years (HR: 2.46 vs. 2.13).

Researchers have reported similar results regarding the relation between frailty and death among racial/ethnic minorities in the U.S. In the Hispanic Established Populations for the Epidemiologic Studies of the Elderly (H-EPESE), a population-based study of Mexican Americans aged ≥65 years, Graham et al.[22] reported that, compared with robust individuals, the HR for 10-year mortality was 1.81 and 1.25 among frail and prefrail adults, respectively. Masel and colleagues[36] have reported similar results in the same study using a different analytic approach. Over a 3-year study period, frailty was associated a substantially greater likelihood of death.

The detrimental effect of frailty on survival has also been demonstrated among non-U.S. populations. In the Frailty and Dependence in Albacete Study, a Spanish cohort study of adults aged ≥70 years, Abizanda et al.[37] found that frail elders had a significantly greater mortality risk than those who were not frail. Using the Geriatric Multidisciplinary Strategy for the Good Care of the Elderly Study, a Finnish cohort study comprised of adults aged 76-100 years, Kulmala et

al.[38] found that the risk of death was greater for frail men and women than their robust counterparts, respectively. Researchers from the French Three-City Study have showed similar but weaker association of frailty and death.[39] In this cohort of 6,078 adults aged ≥65 years, frailty was associated with slightly but not significantly higher risk of 4-year mortality.

2.3.2. Disability

Disability in old age is commonly defined as difficulty or dependency in performing basic daily activities that are essential to independent living.[156] Two most commonly used disability measures in old age are ADLs (e.g., bathing, eating) and instrumental ADLs (IADLs; e.g., shopping, using a map). Disability is associated with mortality,[193] increased health care utilization and expenditure,[194,195] declined quality of life,[196] and need for long-term care,[197] and remains to be one of the biggest threats to public health.

Researchers have consistently shown that frailty is a risk factor for disability.[18,30,31,35,40-44] Fried et al.[35] was among the first to examine the association of frailty with ADL disability. Frailty and prefrailty was associated with increased risk of worsening ADL disability—one new impairment in ADL since baseline—over both 3- and 7-year follow-ups. In a follow-up study that aimed to validate the PFP scale, Bandeen-Roche et al.[30] reported stronger association between frailty and disability among women over a longer study period. After multivariable adjustment, frail women aged ≥65 years had a more than 15-fold and 10-fold higher risk of severe ADL and IADL disability, defined as having any difficulty in ≥3 ADL or IADL tasks.

Qualitatively similar findings with regard to the relation between frailty and disability have been reported in other U.S. cohort studies. In the SOF study, the odds of incident IADL disability (≥1 new IADL impairment) was 179% and 89% higher among frail and prefrail women than the robust.[87] Similarly, Kiely et al.[42] found both frail and prefrail elders had significantly greater odds of having a lot of difficulty or inability to perform ≥1 IADL than the robust. Researchers have also reported parallel findings among racial/ethnic minority groups in the U.S. Among 1,645 community-dwelling Mexican Americans aged ≥67 years from the H-EPESE, the HR of ADL disability was 2.42 for frail persons and 1.32 for prefrail persons than the robust over a 10-year follow-up period.[43]

2.3.3. Fracture

In the Women's Health Initiative (WHI) Study, a prospective cohort study of 40,657 women aged 65-79 years, Woods et al.[44] examined the association of frailty with hip fracture and found that frailty was independently related to a 57% higher risk of incident hip fracture. In a subsequent investigation of 6,724 women aged ≥69 years, Ensrud and colleagues[26] examined non-spine fracture in addition to hip fracture. Both frail and prefrail persons had a significantly higher risk of incident hip and non-spine fracture than the robust over an average follow-up of nine years. Similar findings were reported for older men in the MrOS study by the same research group.[87]

The association of frailty with fracture is robust across geographic regions. Tom et al.[45] examined the association of frailty with fracture in the Global Longitudinal Study of Osteoporosis in Women, an international cohort study comprising over 60,000 women aged ≥55

years from 10 countries: Australia, Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, U.K., and U.S. Frail and prefrail women had 46% and 23% higher odds of fracture within one year of follow-up, respectively, than the robust. The associations were not modified by geographic region.

2.3.4. Falls

Falls are prevalent among older adults. According to the Centers for Disease Control and Prevention, one out of three older adults in the U.S. falls each year.[198] Falls are a risk factor for hip fractures,[199] hospitalization,[200] increased health care expenditure,[201] and impaired quality of life.[202] Given its severe consequences of falls and the rapidly growing elderly population worldwide, falls are among one of the major public health issues.

Kojima[46] recently conducted a meta-analysis of 11 studies, in which 68,723 community-dwelling participants aged ≥55 years were enrolled, to determine the association of frailty with falls. Compared with the robust, those who were frail and prefrail had 84% and 25% higher odds of falls, respectively. Frailty was associated with higher risk of falls (pooled HR = 1.24), whereas the association of prefrailty with falls did not reach statistical significance (pooled HR = 1.14).

2.3.5. Hospitalization

Fried et al.[35] assessed the association of frailty with incident overnight hospitalization. After multivariable adjustment, frailty and prefrailty were associated with increased risk of incident hospitalization over 3-year and 7-year follow-ups. Woods et al.[44] was among the first to replicate and extend findings from the CHS to other populations and racial/ethnic groups (Hispanic,

Asian/Pacific Islander, and Native American). Being frail and intermediate frail was associated with greater number of overnight hospitalizations per year among women aged 65-79 years at baseline. Kiely et al.[42] examined the association of frailty with overnight hospitalization as well as emergency department (ED) visit among 765 community-dwelling adults aged ≥70 years from the MOBILIZE Boston Study. Frail and prefrail adults were 4.45 and 1.97 times as likely as to be hospitalized as robust adults. In addition, the odds of experiencing an ED visit was more than three times higher among frail adults than those who were robust; the association between prefrail and ED visit did not reach statistical significance.

Qualitatively similar findings have been reported among 6,078 French non-institutionalized adults aged ≥65 years from the French Three-City Study.[39] The investigators showed that frail status was associated with significantly higher odds of incident hospitalization over a 4-year follow-up period. Prefrailty was associated with a slightly but not significantly higher odds of hospitalization.

2.3.6. Depression

A large number of cross-sectional studies have shown an association of frailty with depression.[14,26,35,50-54] Fried et al.[35] reported that the proportion of having a CES-D score of ≥10 was 31.0%, 14.0%, and 2.6% for frail, prefrail, and robust persons, respectively. In addition, the average Geriatric Depression Scale (GDS) score was 3.9, 2.2, and 0.6 for frail, prefrail, and robust older women enrolled in the SOF study, respectively.[26] Moreover, investigators from the WHAS I and II found that 46.3% of frail older women were mildly or severely depressed, defined by a GDS score of ≥9, as opposed to 13.3% for those who were robust.[50]

A few longitudinal studies have examined the association of frailty with onset and development of depression prospectively, all with positive findings.[55-57] Using data of 1,827 older Chinese adults aged ≥55 years from the Singapore Longitudinal Aging Study-I, Feng et al.[56] found that baseline frailty and prefrailty status was associated with significantly higher odds (odds ratios [ORs] = 3.09 and 1.86) of incident depression, defined by a GDS score of ≥5, in follow-ups (two and four years later). Results were similar for participants without depressive symptoms at baseline. In a 15-month prospective study of 3,025 community-dwelling Japanese elderly adults who were free of depressive symptoms, frailty was independently associated with higher odds of incident depression, defined by a score of ≥6 on a 15-item CES-D scale.[55]

2.3.7. Poor Cognitive Outcomes

There has been strong and consistent evidence from epidemiological and clinical studies showing that frailty is associated with a greater risk of poor cognitive outcomes, such as impaired memory,[58] cognitive impairment,[14,18,35,38,58-60] dementia,[38,61,64] and Alzheimer's disease.[62]

A number of cross-sectional studies have found lower cognitive function and higher risk of cognitive impairment in frail and prefrail elders compared with the robust.[14,18,35,58,59] Fried et al.[35] found that 15.1% of the frail, 8.3% of the prefrail, and 3.0% of the robust had the Modified Mini-Mental State Examination (3MS) score of 23 or lower (as opposed to 24-30). Data from the French Three-City Study showed that 21.9%, 12.0%, and 10.0% of frail, prefrail, and robust adults, respectively, were cognitively impaired, defined by being in the lowest 25th percentile of both the Mini-Mental State Examination (MMSE) and the Isaac's Set Test.[18] The relationships

between frailty and specific cognitive domains such as memory, verbal fluency, and orientation, have also been reported in cross-sectional studies.[58,59]

Numerous longitudinal studies have indicated that frailty was associated with an increased risk of greater cognitive decline,[47,62,63] incident mild cognitive impairment,[60] incident dementia,[64] and incident Alzheimer's disease.[62] Using data from 1,370 non-institutionalized Mexican Americans aged ≥65 years from the H-EPSES, Samper-Ternent et al.[47] found that frail elders had a higher rate of cognitive decline over 10 years compared with the robust (differed by 0.67 MMSE score per year). In a longitudinal study of more than 700 older adults with normal cognitive function at baseline, Boyle et al.[60] showed that frailty was associated with a higher risk of incident mild cognitive impairment, defined as diagnosis of cognitive impairment by the neuropsychologist but not meeting criteria for dementia. Each one-unit increase in frailty was associated with a 63% higher risk of incident mild cognitive impairment. Gray et al.[64] reported an association between frailty and higher risk of developing clinically diagnosed dementia among 521 adults aged ≥65 years from the Adult Changes in Thought study. Using data from the Rush Memory and Aging Project, Buchman et al.[62] found that both levels and rate of change of frailty were associated with an increased risk of incident Alzheimer's disease over a 3-year follow-up.

2.3.8. Limitations and Future Directions

Experts in frailty research recently claimed that many frailty definitions had been well validated for predictive validity.[89] However, in many of these investigations of frailty and adverse health outcomes, the predictive validity of frailty instruments has only been gauged by statistical significance and magnitude of association (e.g., OR). New literature has demonstrated that

traditional methods based on magnitude of association are not suitable for evaluating the predictability of a diagnostic or prognostic marker and may have serious pitfalls.[90] In addition, existing validations rarely report indices of model performance except for the C statistic, which may lead to overestimation of the overall prognostic values of a frailty assessment. Studies that evaluate different aspects of predictive validity such as discrimination, classification, prediction interment (i.e., additional value beyond existing markers), and clinical utility (e.g., cost benefit analysis) are needed.

Another limitation of existing studies on frailty and outcomes is that the vast majority of these investigations have only focused on the baseline level of frailty. A large body of research has shown that frailty is a dynamic process and transitions between frailty states are common over both short-term (e.g., 4.5 years) and long-term periods (e.g., 14 years).[95,203-208] Therefore, exclusively focusing on the baseline measure of frailty may lead to an oversimplification of the dynamic relationship between frailty and longitudinal changes in physiological, physical, and cognitive functions. Frailty researchers have raised the question whether a one-time measure of frailty—a dynamic process—is appropriate.[1] Future research needs to shed more light on the rate of change, trajectory, and variability of frailty to further our understanding of the health consequences of frailty.

2.4. Risk Factors of Frailty

Frailty is a complex syndrome that involves dysregulation across multiple organ systems and leads to loss of physiological reserve and resilience. The causes of frailty are likely to be multifactorial and multilevel, including genetic predisposition, physiological factors, behaviors,

and environmental exposures. Identification of genetic, physiological, behavioral, and social determinants of frailty may improve our understanding of the pathophysiology of frailty and identify targets for patient-tailored preventions and treatments for frailty. Researchers have identified a wide range of socio-demographic,[9,10,15,17,24,35,44,53,91-94] behavioral,[10,11,44,85,92,95-98] nutritional,[51,99-113] physiological,[11,114-127] and psychosocial[128-134] risk factors for frailty from both cross-sectional and prospective studies.

2.4.1. Socio-Demographic Risk Factors

Cross-sectional and longitudinal observational studies have consistently shown that old age,[10,15,35,53] female gender,[10,35,91] ethnic/racial minorities (e.g., African American),[35,44,94] and low socio-economic status (SES; e.g., low educational attainment, low income, poor living circumstance, low-wage occupation),[10,17,24,44,92,93] are strongly associated with frailty. There is also evidence linking life-course social conditions to frailty. Using data from over 10,000 men and women aged ≥60 years from seven Latin American and Caribbean cities, Alvarado et al.[17] found that poor childhood (poverty, hunger, poor health) and adulthood (low education, non-white-collar occupation) social conditions were associated with higher odds of frailty in later life.

2.4.2. Behavioral Risk Factors

Emerging evidence from epidemiological and clinical studies indicates that lifestyle behaviors are associated with frailty. In a large prospective cohort study, Woods et al.[44] analyzed the odds of frailty at 3-year follow-up in relation to the baseline behavioral risk factors among 40,657 women who were 65-79 years and were free of frailty at baseline. Older women who consumed <1 and 1-14 drinks per week had a 13% and 31% lower odds of incident frailty than never/past

drinkers, respectively. In addition, current and former smokers were 1.2 and 2.9 times as likely to become frail as never smokers, respectively. These results were consistent with studies of ethnic minority populations in the U.S. and non-U.S. populations. Using data from 14,082 middle-aged and older adults enrolled in the SHARE, Etman et al.[85] showed that drinking no alcohol was associated with a higher risk of worsening frailty status (from robust to prefrail/frail or from prefrail to frail) in two years. In a study of 777 Mexican Americans aged ≥65 years, Ottenbacher et al.[95] found that older adults who ever smoked (both past and current smokers) had a more severe frailty status at 10-year follow-up than those who never smoked.

In addition to above-mentioned traditional behavioral risk factors, Xue et al.[209] examined the association of a novel behavioral predictor—life space—with frailty. Life space refers as the size of the area a person moves through as well as the frequency of movement over a specific time period.[210,211] A total of 599 community-dwelling women who were ≥65 years and were not frail at baseline were classified into four life-space categories: not constricted (left the neighborhood ≥4 times per week), slightly constricted (left the neighborhood <4 times per week), moderately constricted (left home but remained in the neighborhood), and severely constricted (never left home). Compared with women who were not constricted, slightly and moderately constricted women were 1.7 times and 1.5 times more likely to become frail, respectively.

2.4.3. Nutritional Risk Factors

The importance of nutrition in the development of frailty is consistently confirmed across instruments of frailty, target populations, and study settings. Researchers have found that

different aspects of nutrition, such as micronutrients, nutritional status, energy and protein intake, and dietary quality and patterns to be associated with frailty.

Frail older adults are more likely to have micronutrient deficiencies. Using data from 802 Italian adults aged ≥65 years participating in the Invecchiare in Chianti, aging in the Chianti area (InCHIANTI) study, Bartali et al.[108] reported that elders with low intakes of Vitamins (A, C, D, E, and folate) were more likely to be frail. In a cross-sectional study of 754 women aged 70-80 years from the WHAS I and II, Michelon et al.[109] found that low β-carotene, lutein/zeaxanthin, and total carotenoids were associated with higher odds of frailty. In addition, utilizing a more integrative approach, Semba et al.[110] observed that the number of nutritional deficiencies was associated with an increased risk of becoming frail over a 3-year follow-up. Nine nutrients were included: retinol, α-tocopherol, 25-hydroxyvitamin D, vitamin B_6 vitamin B_{12}, folate, selenium, zinc, and total carotenoids.

There is a close relationship between dietary energy and protein intake and frailty. Bartali et al.[108] showed that low daily energy intake (≤21 kcal/kg) was associated with higher odds of being frail among older adults in Italy. In addition, a low intake of protein (men: <66g/day; women: <55g/day) was related to frailty, independent of total energy intake. Similar results were reported by Beasley et al.[111] in a prospective cohort study of over 20,000 women participants. They found that both energy intake and protein consumption measured at baseline were associated with a higher risk of frailty after three years of follow-up.

In addition to single nutrients, increasing evidence from epidemiological studies suggests an association of dietary quality and patterns with frailty. Dietary quality is commonly assessed by indices developed based upon adherence to a Mediterranean diet—a diet pattern that is considered one of the healthiest.[212] A typical Mediterranean diet involves high intake of vegetables, fruits, legumes, cereal, and fish, low intake of meat and dairy product, and moderate intake of alcohol. Using data from 690 Italian community-dwelling women aged ≥65 years, Talegawkar et al.[113] found that high adherence to a Mediterranean diet was associated with lower odds of developing frailty over a 6-year follow-up. Qualitatively similar results were reported by Bollwein et al.[100] in a cross-sectional study of 192 community-dwelling Germans aged ≥75 years. The odds of being frail was reduced by 74% among elders who were in the highest quartile of the Mediterranean diet score compared with those with scores in the lowest quartile.

2.4.4. Physiological Risk Factors

A large body of epidemiological and clinical evidence has established that inflammation and immune activity (e.g., C-reactive protein [CRP], Interleukin-6 [IL-6]), hormonal depletion (e.g., testosterone, growth hormone), anemia (i.e., decreased hemoglobin), neuromuscular skill (e.g., fine motor speed), and activation of blood clotting pathways (e.g., D dimer and factor XI α_1-antitrypsin) as important physiological correlates with frailty.[116-127]

2.4.4.1. Inflammation

Mounting evidence suggests that chronic inflammation is involved in the pathogenesis of frailty.[116-125] Using data from the CHS, Walston et al.[122] found that frail elders had a significantly higher level of CRP than the robust (5.5 vs. 2.7 mg/L). Leng et al.,[123] in a pilot study of 11 frail

and 19 robust participants, reported a positive association of frailty with chronic inflammation, marked by elevated levels of serum IL-6. Leng et al.[116] replicated their earlier findings and additionally showed that frail persons had a higher white blood cell count among 558 older women from the WHAS I. Other inflammatory markers, including tumor necrosis factor-α (TNF-α), fibrinogen, factor VIII, neutrophils, and monocytes, are also shown to be elevated among frail elders.[122,124-126] Moreover, markers of inflammation are inversely associated with hemoglobin,[123] hematocrit,[123] and insulin-like growth factor-1 (IGF-1),[119] all of which are associated with frailty.[119,123,127] These findings, taken together, suggest that chronic inflammation is involved in the pathogenesis of frailty both directly and indirectly through intermediary physiological processes.

2.4.4.2. Hormone

In an earlier clinical study conducted on 33 robust and 18 frail adults aged ≥74 years, Leng et al.[119] observed that serum levels of IGF-1 and dehydroepiandrosterone-sulfate (DHEA-S) were lower among frail vs. robust adults. IGF-1 is an endocrine hormone produced by liver and stimulated by growth hormone; it plays an important role in biological aging and maintenance of muscle mass.[213,214] DHEA-S is an adrenal androgen that is also critical to muscle strength and mass in old age.[215] In a more recent prospective cohort study of 1,586 Australian men aged 76-93 years, Hyde et al.[158] found that lower levels of total or free testosterone were associated with increased odds of being frail (identified by the FRAIL scale) over a follow-up period of 4-7 years. Testosterone is a steroid hormone that declines as men ages and is important for function of skeletal muscle and bone health.[216,217]

2.4.4.3. Anemia

Anemia, as indicated by decreased levels of hemoglobin and hematocrit in the whole blood, is a common clinical syndrome among older adults and is associated with inflammatory chronic diseases.[218-221] In a pilot study of 19 robust and 11 frail adults aged ≥74 years, Leng et al.[123] showed that frail older adults had a significantly lower serum hemoglobin and hematocrit than those who were robust. Chaves et al.[127] extended these findings by showing that low and slightly less than normal levels of hemoglobin were associated with higher risk of being frail vs. robust in a much larger study of 670 women aged 70-80 years. Similar results were reported by Fried et al.[118] in a more recent study; 10.1%, 13.3%, and 27.0% of robust, prefrail, and frail elderly women had abnormally low levels of hemoglobin (<12 g/dL), respectively.

2.4.5. Psychosocial Risk Factors

The relationship between psychosocial conditions and frailty has gained increasing research interest over the past decade.[128-134] The general consensus is that older adults with better psychosocial health are less likely to be frail.[128-133] Positive affect, defined as feelings of emotional happiness,[222] is beneficial for physical, cognitive, and mental health among elderly adults. In a prospective study of 1,558 initially robust older Mexican Americans living in five southwestern states in the U.S., Ostir et al.[133] found that higher positive affect (happiness) was associated with a lower risk of incident frailty over a 7-year period. Similar findings were reported among Caucasian women who were ≥65 years and were free of frailty at baseline.[132] Higher positive affect was associated with lower levels of inflammatory markers, such as CRP, IL-6, and white blood cell counts, which may lead to higher risk of frailty.[116,121,122,223]

In addition to positive affect, other dimensions of psychosocial well-being are associated with frailty. Gale et al.[129] examined the association of scores on a psychological well-being scale with frailty among 2,257 ELSA participants aged 60-90 years. Four domains were included: control (e.g., "I feel free to plan for the future"), autonomy (e.g., "I feel that I can please myself what I do"), self-realization (e.g., "I choose to do things that I have never done before"), and pleasure (e.g., "I enjoy the things that I do"). Older adults with a 1-SD higher score on the scale had a 38% and 21% lower risk of incident frailty and prefrailty, respectively, over the 4-year follow-up period.

2.4.6. Genomic Risk Factors

Besides environmental exposures (e.g., socio-economic, behaviors, nutrition), genetic predisposition may also play an important role in the development of frailty. Using data from a total of 3,719 adults aged ≥75 years from two Danish cohorts—the Danish 1905-Cohort and the Longitudinal Study of Aging Danish Twins Cohort, Dato et al.[135] showed that 43% of the observed variation in frailty—as measured by ADLs, grip strength, BMI, self-rated health, and cognition—could be explained by additive genetic effect (i.e., heritability). Males had higher estimate of heritability than females (53% vs. 29%). Murabito et al.[136] reported a heritability estimate of 19% for frailty among 2,207 elders (≥60 years) from the Framingham Offspring cohort. Recently, Sanders et al.[137] reported a heritability estimate of 23% for a rescaled PFP model (i.e., Scale of Aging Vigor in Epidemiology) using data from the Long Life Family Study. Taken together, these findings suggest a genetic basis of frailty and the potential roles of genetic variants in the pathogenesis of frailty. However, there is a paucity of research examining the genetic basis of frailty despite its moderate to high heritability. To date, only a very limited

number of genes have been examined using candidate gene association studies to identify potential risk generic variants for frailty.[138-143]

IL-6 gene is a protein-coding gene that encodes a cytokine that is involved in inflammation and infection responses; it is also associated with inflammatory conditions.[224-226] Walston et al.[140] examined whether single nucleotide polymorphisms (SNPs) in the *IL-6* gene were associated with serum IL-6 level and frailty. Fourteen SNPs in the *IL-6* gene were genotyped among 463 Caucasian and African American participants (aged 70-79 years) from the WHAS I and II. None of the SNPs showed a significant association with serum IL-6 or frailty. In addition, Almeida et al.[142] investigated the effect of another inflammation-related gene—*CRP* gene—on frailty in a cross-sectional study of 3,778 Australian men aged ≥65 years. Two SNPs (*rs1130864* and *rs1205*) were included and *rs1205* was significantly associated with higher odds of frailty. However, frailty was assessed by the FRAIL scale,[69,70] which limits the comparability of results from this study with those using the PFP scale.

Ciliary neurotrophic factor (*CNTF*) gene is a protein-coding gene that plays an important role in motor neuron survival and is related to muscle strength and mass.[227] Arking et al.[141] examined the associations of eight SNPs encompassing the *CNTF* gene with grip strength and frailty, respectively. Under a recessive model, older women homozygous (two identical copies) for the *rs1800169* null allele had a 3.80-kg lower grip strength. However, no relationship was identified between any of the SNPs and frailty.

Recently, Mekli et al.[228] selected genes that are involved in the steroid hormone and inflammatory pathways and examined their effects on frailty. A total of 620 SNPs encompassing these genes were genotyped among 3,160 adults aged ≥50 years from the ELSA. One SNP (*rs1800629*) in the promoter region of Tumor Necrosis Factor (*TNF*), three SNPs (*rs1566729*, *rs1566728*, and *rs2047812*) in the Protein Tyrosine Phosphatase, Receptor type, J (*PTPRJ*) gene, and one SNP (*rs611646*) in the Ataxia Telangiectasia Mutated (*ATM*) gene were significantly associated with frailty. However, none of these results reached statistical significance after Bonferroni correction (*p-value* < 8.5×10^{-5} for 590 independent tests).

In sum, no genetic variant has been consistently identified to be associated with frailty from candidate gene association studies. There is therefore a pressing need for exploring a wider range of genetic variants to better understand the genetic underpinnings of frailty. One approach to serve this purpose is genome-wide association study (GWAS), an effective technique that can test the associations between hundreds of thousands genetic variants and a phenotype (e.g., disease) across the entire human genome. Since its emergence about a decade ago, GWAS has been successful for identifying genetic variants involved in the development of complex diseases and traits, such as cancer,[229] coronary heart disease,[230] and longevity.[144]

CHAPTER 3: CONSTRUCTION, EVALUATION, AND MEASUREMENT PROPERTIES OF A CONTINUOUS FRAILTY SCALE

3.1. Introduction

In the absence of a gold standard, there is a lack of consensus on the operational definition of frailty. The physical frailty phenotype (PFP) scale,[35] in which gait speed, grip strength, exhaustion, physical activity, and weight loss are included, has been widely accepted as a valid tool for assessing frailty in clinical and public health settings. However, precision is lost in the process of dichotomizing continuously measured indicators; for example, older women with different gait speed are assigned the same score (i.e., 0) once their measures are slower than the lowest height-specific quintile. Dichotomization of continuous measures may also lead to reduced statistical power in identifying risk factors of frailty, and difficulties in capturing transition between frailty states over time. In addition, all five frailty indicators in the PFP scale are implicitly assumed to be of equal importance in measuring frailty—an assumption that has not been tested. Moreover, the PFP scale is very effective in identifying the frailest elders but has limited ability to differentiate persons at the low end of frailty. In the CHS, approximately half of the participants did not meet any of five frailty criteria and were therefore classified into the same category (i.e., robust). However, it is questionable whether these participants have the same level of frailty.

A finer graded frailty scale may have the following advantages compared with the categorical PFP scale: (i) providing a greater differentiation of the frailty syndrome, (ii) further stratifying risk of health outcomes among robust, prefrail, and frail adults identified by the PFP scale, (iii) increasing statistical power for identifying genetic, physiological, behavioral, and environmental

risk factors for development of frailty and transitions between frailty status over time, and (iv) enhancing power of frailty instruments for predicting outcomes, and (v) better evaluating the effectiveness of interventions for frailty.

In this chapter, I used confirmatory factor analysis (CFA) to examine the factor structure of frailty, as assessed by five variables—gait speed, grip strength, exhaustion, physical activity, and weight loss—among the Cardiovascular Health Study (CHS) cohort (Figure 3–1 displays the conceptual framework). Second, I investigated whether five indictors had equal importance in measuring frailty. I hypothesized that all five indicators would be associated with one latent construct (i.e., frailty) with different strengths. Third, I assessed the factor structure in demographic subpopulations (i.e., age and sex) and explored measurement invariance, that is, whether the same factor structure and similar factor loadings hold across subpopulations. Lastly, I created a continuous frailty scale by summing up frailty indicators weighted by factor loadings (i.e., correlations between the indicators and the latent frailty construct), assessed its distributional properties, and examined its relationship with the PFP scale. I validated the factor structure in the Health and Retirement Study (HRS) cohort.

3.2. Methods

3.2.1. Data Source

This dissertation included two nationwide prospective cohort studies: the CHS and the HRS. The CHS is an ongoing population-based, longitudinal cohort study of community-dwelling U.S. adults aged ≥65 years at enrollment. The primary objective of the CHS is to determine the risk factors for coronary heart disease and stroke.[231] Participants of the CHS were randomly sampled

from the Health Care Financing Administration's Medicare eligibility lists in four U.S. communities: Forsyth Country, North Carolina; Sacramento County, California; Washington County, Maryland; and Pittsburgh, Pennsylvania. Eligibility criteria were: (i) ≥65 years at enrollment, (ii) ability to provide informed consent without the assistance of a proxy respondent, (iii) not under treatment for cancer, and (iv) intention to remain in the current community for at least three years. A total of 5,201 participants (original cohort) were recruited at baseline (1989-90). In 1992-93 (3rd follow-up), an additional sample of 687 black participants (new cohort) from the field centers in North Carolina, California, and Pennsylvania were added, leading to a total of 5,888 participants. All participants were requested to complete an interview, health questionnaire, and comprehensive physical examination, and to provide blood specimens at enrollment and annually through 1999-2000. The study protocol was approved by institutional review boards (IRB) at each site and all participants signed informed consent. More details about the recruitment strategies, designs, and sampling approaches of the CHS have been published elsewhere.[231,232] The CHS is an ideal setting to achieve the goals of this dissertation because (i) it is the original cohort whether the PFP scale was developed, (ii) it has large sample size, frequent visits (annually), and sufficient length of follow-up (over 20 years), and (iii) it includes comprehensive measures of demographic and clinical characteristics of participants.

I used data from the HRS to cross-validate some of the findings from the CHS. The HRS is an ongoing longitudinal cohort study of a nationally representative sample of households in the contiguous U.S. of non-institutionalized residents. The HRS started in 1992 and had data available through 2014. The HRS is primarily funded by the U.S. National Institute on Aging and is designed, administered, and managed by the Institute for Social Research at the University

of Michigan.[233] The primary goal of the HRS is to describe changes in life patterns through the transition into retirement of middle-aged and older adults in the U.S. by collecting information about their health conditions, family network, social relations, financial situation, and employment status.[234] Baseline assessment was conducted in 1992-93 and a total of 12,654 respondents (from 7,704 households) aged ≥50 years were included. In Wave 2006-07, approximately half of the HRS participants were randomly selected to participate in an enhanced face-to-face interview, during which physical functioning measures (e.g., gait speed) and blood-based biomarkers were measured. The other half of the participants completed the functional measures and biomarkers in Wave 2008-09. Ethical approval was obtained from IRB at the University of Michigan and all participants signed informed consent. Further details about the recruitment strategies, designs, and sampling approaches of the HRS have been previously documented.[235] The HRS is an ideal validation data set because (i) frailty indicators in the HRS were measured in a similar fashion to CHS, (ii) it has an overlapping age range with the CHS, (iii) it includes a large nationally representative sample, and (iv) it has detailed demographic, economic, and health information of participants.

3.2.2. Analytic Sample

Cardiovascular Health Study

Instead of using the baseline data from the CHS, where only self-reported weight loss was available, I used data from the 1992-93 (3rd follow-up for the original cohort and baseline for the new cohort) and 1996-97 (7th follow-up for the original cohort, and 4th follow-up for the new cohort) examinations. In these two visits, Modified Minnesota Leisure Time Activities Questionnaire[236] was administered (it was only available at baseline and in the 3rd and 7th follow-

ups) and direct calculation of weight loss between two consecutive visits was possible. Visits 1992-93 and 1996-97 served as baseline for the original and new cohorts, respectively. The analytic sample was limited to 4,243 participants with complete data on five frailty indicators—gait speed, grip strength, exhaustion, physical activity, and weight loss.

Health and Retirement Study (HRS)

I used pooled data from the 2006-07 and 2008-09 survey waves of the HRS, when physical functioning measures were available. The analytic sample included 7,600 participants who were ≥65 years and had data on all five frailty indicators in the 2006 or 2008 wave (considered baseline for the HRS), depending when physical functions were assessed.

3.2.3. Measures

3.2.3.1. Frailty Indicators

Gait Speed. In the CHS, eligible participants were asked to walk a 15-foot (≈4.6-meter) course at their usual pace starting from a standstill. Gait speed was assessed by converting the amount of time (recorded using a stopwatch by a trained examiner; to 0.1 sec) required to complete the test into meter per second (m/s). In the HRS, gait speed was measured by converting the amount of time (recorded using a stopwatch by a trained interviewer; to 0.01 sec) required for participants to walk 98.5 inches (≈2.5 meters) at their usual pace (starting from a standstill) into meter per second (m/s). For both cohorts, an average gait speed was calculated based on two trials. To facilitate comparability of gait speed measure across participants with different sexes and body sizes, I fit sex-specific linear models regressing gait speed on standing height and calculated residuals to represent adjusted gait speed.

Grip Strength. In the CHS, grip strength (kg) was measured by a JAMAR handheld dynamometer. Participants were asked to squeeze the meter at their maximum capacity three times for each hand. Average reading of the dominant hand was used. Participants who had hand pain, wrist pain, or recent hand surgery were not requested to conduct the grip strength test. In the HRS, grip strength (kg) was measured using a Smedley spring-type hand dynamometer. Two attempts at maximal squeeze in a standing position were recorded for each hand. I used the average reading of dominant hand. Participants who had surgery, swelling, inflammation, severe pain or injury in both hands in the past six months were not asked to perform the test. For participants who had any of these symptoms in only one hand, grip strength of the other hand was used. To facilitate comparability of grip strength measure across participants with different sexes and body sizes, I fit sex-specific linear models regressing gait speed on BMI and calculated residuals that represent adjusted grip strength.

Exhaustion. Exhaustion was characterized by two items from the modified CES-D scale[150] including, "I could not get going" and "I felt that everything I did was an effort." In the CHS, participants were asked to indicate the frequency they felt that way during last week: "Rarely/none of the time; less than 1 day" (coded 0), "Some or a little of the time; 1 to 2 days" (coded 1.5), "A moderate amount of time; 3 to 4 days" (coded 3.5), or "Most of the time; 5 to 7 days" (coded 6). The sum score served as an index of exhaustion, ranging from 0 to 12. Participants who chose "Don't know" or refused to answer the question were coded as missing. Responses were coded according to the severity/duration of each symptom. In the HRS, participants answered "Yes" or "No" to whether they had experienced each of the two CES-D

questions for much of the time during previous week. “Yes” and “No” were scored 1 and 0, respectively; the sum score ranged from 0 to 2. Participants who responded “Don’t know or not ascertained” or refused to answer the question were coded as missing.

Physical Activity. In the CHS, physical activity was assessed using the Modified Minnesota Leisure Time Activities Questionnaire, a validated scale used for measuring energy expenditure in leisure-time activity.[236] Participants reported the frequency as well as duration of 18 activities in the prior two weeks (i.e., walking, mowing the lawn, raking the lawn, gardening, hiking, jogging, biking, exercise cycle, dancing, aerobics/aerobic dance, bowling, golf, singles tennis, doubles tennis, racquetball, calisthenics/general exercise, swimming, and other activity). Total kilocalories of energy expended on these activities were calculated. In the HRS, physical activity was measured by three questions asking frequency of vigorous (e.g., running or jogging, swimming, cycling, aerobics or gym workout, tennis), moderate (e.g., gardening, cleaning the car, walking at a moderate pace, dancing, floor or stretching exercises), and mild physical activities (e.g., vacuuming, laundry, home repairs). Vigorous, moderate, and mild physical activities were scored 8, 4, and 2, respectively, according to the Metabolic Equivalent of Task (MET).[237] A weighted sum score was calculated for each participant, representing the total energy cost physical activities (i.e., MET) accounting for intensity (vigorous, moderate, mild) and frequency. Weights were determined by the frequency of physical activity; “Everyday”, “More than once a week”, “Once a week”, “1-3 times a month”, and “Hardly ever” was scored 7, 4, 1, 0.5, and 0, respectively. I chose these Weights to represent the expected number of days performing specific physical activity per week. “Everyday” represents exercising 7 times per week, “More than once a week” represents exercising 2-6 times per week (4 is the expected

average), “Once a week” represents exercising 1 time per week, “1-3 times a month” represents exercising 0.25-0.75 times per week (0.5 is the expected average), and “Hardly ever” represents exercising 0 time per week. Physical activity has been operationally defined in a similar way in the HRS.[84]

Weight Loss. In the CHS, weight loss was calculated as the percentage and absolute change of weight (in pounds) in the prior year. Percentage weight loss was calculated as: (weight in previous year – current measured weight)/(weight in previous year)×100%. Absolute weight loss was computed as: (weight in previous year – current measured weight). A zero (i.e., no weight loss) was assigned to persons who lost weight (i.e., weight loss >0) but reported that diet or exercise was a major factor in weight change. In the HRS, weight loss was measured by the percentage and absolute change of weight (in pounds) between two consecutive waves (two years apart). Percentage weight loss was calculated as: (weight in previous wave – current measured weight)/(weight in previous wave)×100%. Absolute weight loss was computed as: (weight in previous wave – current measured weight).

3.2.3.2. Covariates in the Cardiovascular Health Study

Clinic site included Forsyth Country, North Carolina, Sacramento County, California, Washington County, Maryland, and Pittsburgh, Pennsylvania. Age (in years) was calculated by the difference between the visit date and a participant’s birth date. Sex, years of education, and race/ethnicity were identified based on self-report. Education was categorized as less than high school, high school or equivalent, and more than high school. Race/ethnicity was dichotomized

as white or others versus black as less than 1% of the CHS participants were neither white nor black.

Smoking status was assessed categorically as one of three possible responses: current smoker (reported smoking during the past 30 days), former smoker (not currently smoking but smoked more than 100 cigarettes or 5 packs of cigarettes in lifetime), and never-smoker. Body mass index (BMI) was calculated as body weight (kilograms) divided by height (meters) squared, and was categorized as underweight (BMI <18.5), normal (BMI = 18.5-24.9), overweight (BMI = 25.0-30.0), and obese (BMI >30). Because of small cell sizes, I collapsed underweight and normal categories.

History of coronary heart disease, heart failure (HF), stroke, hypertension (not hypertensive, borderline hypertension, or hypertension), diabetes (not diabetic, prediabetes, or diabetes), cancer or a malignant tumor (excluding minor skin cancer), and arthritis was assessed based on self-reported physician diagnosis. Self-rated health was measured by the question, "Would you say your health is excellent, very good, good, fair, or poor?", with higher score indicating more positive rating of health (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent). Cognitive function was measured by the Modified Mini-Mental State Examination (3MS); the 3MS has a total score ranging from 0 (lowest) to 100 (highest) and is a validated and widely used screening instrument for dementia.[238] Disability was assessed by activities of daily living (ADLs). Participants were asked "Do you have difficulty or are unable …" to preform each of six basic daily activities (i.e., dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room). Participants who responded "Yes" and "No" were considered having

and not having difficulty, respectively. Participants who answered "Can't do" were considered having difficulty; those who reported "Don't do", "Don't know or not ascertained", or "Refused" were coded missing. Difficulty in ADL disability was dichotomized as none versus any.

Systolic and diastolic blood pressure (BP) was measured in the right arm of participants in a seated position after a five-minute rest by trained personnel using a sphygmomanometer. Three blood pressure readings were obtained and the average of the last two was recorded and used. C-reactive protein (CRP; mg/L), a marker of inflammation, and cystatin C (mg/L), a sensitive indicator of kidney function among the elderly, were assessed by the BNII nephelometer (Dade Behring Inc., Deerfield, IL) utilizing particle-enhanced immunonephelometric assay. [239,240] Total cholesterol (mg/dL) and glucose (mg/dL) were measured based on fasting blood samples stored at -70℃, and analyzed by the Central Blood Analysis Laboratory at the University of Vermont.[231]

3.2.3.3. Covariates in the Health and Retirement Study

Age was calculated as the difference between the visit date (year and month) and a participant's birth date (year and month). Sex, years of education, race/ethnicity (non-Hispanic white, black, Hispanics, and other) were self-reported. Education was categorized as less than high school, high school or equivalent, and more than high school. Race/ethnicity was categorized as white, black, and others.

Smoking status was categorized as: current smoker (reported currently smoking), former smoker (not currently smoking but smoked more than 100 cigarettes or 5 packs of cigarettes in lifetime),

and never-smoker. BMI was calculated as body weight (kilograms) divided by height (meters) squared, and was categorized as underweight (BMI <18.5), normal (BMI = 18.5-24.9), overweight (BMI = 25.0-30.0), and obese (BMI >30). I collapsed underweight and normal categories due to small cell sizes.

History of cardiac disease (heart attack, coronary heart disease, angina, HF, or other heart problems), stroke, hypertension, diabetes, cancer or a malignant tumor (excluding minor skin cancer), and arthritis was measured based on self-reported physician diagnosis. Self-rated health was measured by the question, "Would you say your health is excellent, very good, good, fair, or poor?", with higher score indicating more positive rating of health (1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent). Cognitive function was assessed using a modified Telephone Interview for Cognitive Status (TICS),[241,242] a telephone-based version of the Mini-Mental State Examination (MMSE). The TICS score ranges from 0 to 10 with higher score indicating better cognitive function. Participants were asked "Because of a health or memory problem do you have any difficulty with each of six ADLs". Participants who responded "Yes" and "No" were considered having and not having difficulty, respectively. Participants who answered "Can't do" were considered having difficulty; those who reported "Don't do", "Don't know or not ascertained", or "Refused" were coded missing. Difficulty in ADL disability was dichotomized as none versus any.

Systolic and diastolic BP were measured by trained interviewers using automated sphygmomanometer. Three BP readings, 45-60 seconds apart, were taken in a sitting position with both feet on the floor and the left arm supported with the palm facing up.[243] The average of

the readings was used. CRP (mg/L) and cystatin C (mg/L) were measured by the BNII nephelometer (Siemens, Inc., Deerfield, IL) using a particle-enhanced immunonephelometric assay at the University of Vermont.[244] Total and high-density lipoprotein (HDL) cholesterol (mg/dL), glycosylated hemoglobin (HbA1c; %), an indicator of average blood glucose levels over the past 3 months, were assessed based on non-fasting blood samples by a number of different laboratories.[244]

3.2.4. Analytic Approaches

Descriptive Statistics

For the CHS participants, I compared baseline (1992-93 visit for the original cohort and 1996-97 visit for the new cohort) characteristics of the analytic sample (N = 4,243) and those who had at least one frailty indicator missing (N = 695). I used two-sample t-tests with unequal variance for continuous variables and χ^2 tests for categorical variables. I repeated these descriptive analyses for the HRS participants (7,600 had all five frailty indicators and 1,621 had at least one frailty indicator missing) using measures in Wave 2006 or 2008, depending on when frailty was assessed. I also compared characteristics between the two cohorts using the same statistical approaches documented above.

Factor Analysis

I fit a unidimensional CFA to examine the latent factor structure among the CHS participants (development set). CFA is a multivariate statistical tool widely used in social and psychological science to identify the association of a set of observed indicators with latent constructs; CFA has multiple advantages over exploratory factor analysis and principle component analysis.[245] Frailty

was hypothesized as a continuous latent factor with five indicators: gait speed residual, grip strength residual, exhaustion, physical activity, and percentage weight loss. The association of each indicator with the latent frailty construct was quantified by factor loading. Overall model fit was evaluated based on the χ^2 test, the root mean square error of approximation (RMSEA) and its 90% confidence interval based on the noncentral χ^2 dsitribution,[246] the Comparative Fit Index (CFI),[247] and the Tucker-Lewis Index (TLI).[248] The χ^2 test assesses whether the model sufficiently reproduces the variance-covariance matrix of five indicators; a non-significant *p*-value indicates a satisfactory fit. However, it is generally not reasonable to rely solely on this statistic to assess global model fit in the presence of sufficient statistical power (large sample size). Like the χ^2 test, the RMSEA evaluates the ability of a model to reproduce the data but is not overpowered in large samples; the RMSEA ranges from 0 to 1 with lower value indicating better model fit. The CFI assesses model fit relative to the null model where all indicators are restricted to be independent from each other; the CFI ranges from 0 to 1 with higher value reflecting better model fit. The TLI is similar to the CFI but has additional penalty for model complexity; the TLI can sometimes fall slightly outside the range of 0 to 1 with higher value indicating better model fit.[245] Ideal model fit was determined based on the following criteria: χ^2 test is not statistically significant ($p \geq .05$), RMSEA $\leq .05$, CFI $\geq .95$, and TLI $\geq .95$; acceptable model fit was identified if RMSEA $\leq .08$, CFI $\geq .90$, and TLI $\geq .90$.[249] Local goodness-of-fit was inspected using (i) standardized residuals, representing discrepancies between observed and estimated values, and (ii) modification indices,[250] reflecting the estimated reduction in the overall χ^2 statistic (i.e., improvement of model fit) if a constrained parameter is freely estimated. The initial CFA model assumed the residuals of five indicators were independent. I re-specified the

model by correlating residuals if the initial model did not reach satisfactory fit. Once an acceptable fit was achieved, I generated standardized loadings.

I then examined the factor structure in the HRS cohort (validation set) following the same procedure documented above. I generated standardized loadings for the HRS cohort compared results from the two cohorts.

Equal Importance

Once a satisfactory model was identified, I examined whether five frailty indicators had equal importance, as indicated by standardized factor loadings, in measuring the underlying frailty construct. First, I reverse coded exhaustion and weight loss variables so that a higher value indicates a higher level of robustness (i.e., less frail) for all five indicators. Otherwise, two indicators with the same strength but opposite direction (positive vs. negative) would be considered different. Then, I fit a CFA whereby all standardized factor loadings were constrained to have the same direction and magnitude, and compared it with the initial CFA in which all factor loadings were freely estimated. A statistically significant χ^2 difference test ($p < .05$) implied that not all five indicators were equally important. Subsequently, in order to evaluate the relative importance of five indicators in measuring frailty, I fit a series of CFAs with two factor loadings constrained to be equal, and then compared each of them separately with the initial CFA in which all factor loadings were freely estimated. Because there were 10 comparisons, I used a Bonferroni-corrected threshold ($\alpha = .05/10 = .005$) to determine whether the χ^2 statistic was significant. A statistically significant test statistic implied that two indicators that were constrained to have the same loading were not equally important in measuring frailty. If any two

of the three or four indicators were not significantly different in magnitude, I fit CFAs with three or four factor loadings constrained to be equal, and then compared them to the initial CFA in which all five factor loadings were freely estimated. A statistically non-significant test statistic suggested that these three or four indicators were of similar importance in measuring frailty.

Measurement Invariance and Subgroup Analyses

To evaluate whether the same latent structure (e.g., factor loadings) held across important demographic characteristics (i.e., age and sex), I fit a multiple-group CFA, in which a unidimensional CFA was fit to multiple subgroups simultaneously; invariance across age and sex was tested separately. I tested two types of measurement invariance: configural invariance and invariance of factor loadings. Configural invariance is achieved if the configuration of factor structure—e.g., number of factors, construct-indicator association—is qualitatively equivalent across subgroups; invariance of factor loadings is established when factor loadings are invariant across subgroups. Detailed description of these concepts have been documented elsewhere.[251]

I first fit a multiple-group CFA for "young old" (aged <75 years) and "old old" (aged ≥75 years). All factor loadings were freely estimated across the two subgroups. Cutoff was determined based on the sample distribution of age. Model fit was assessed using the aforementioned criteria (e.g., RMSEA ≤ .05, CFI ≥ .95, and TLI ≥ .95); adequate model fit was indicative of configural invariance of the relationship between five observed indicators and the latent frailty construct. If configural invariance was achieved, I proceeded to test invariance of factor loadings. I fit a nested model where each of five factor loadings were constrained to be equal between "young old" and "old old", and then compared it with the baseline multiple-group

CFA in which configural invariance was achieved. Invariance of factor loadings was tested using a χ^2 difference test and change in the CFI. A statistically non-significant χ^2 difference test and a change in the CFI of < .01 suggest establishment of weak invariance.[252] I then repeated the same analyses for testing measurement invariance across sex.

Sensitivity Analysis

Several sensitivity analyses were performed. First, I used absolute weight loss instead of percentage weight loss in the CFA. In addition, I assessed whether missingness in frailty indicators biased the results by fitting additional CFA using participants with at least one frailty indicator measured and comparing the results with those obtained from participants with complete data on five frailty indicators.

Construction of the Continuous Frailty Scale

I first computed standardized score for each frailty indicator by dividing the difference between observed value and sample mean by sample standard deviation (SD). I then added individual component scores to create the continuous frailty score, weighted by the standardized factor loadings estimated in CFA. Calculated continuous frailty score for an individual i is:

$$Frailty\ score_i = \sum_{j=1}^{5} z_{ji} \times w_j$$

where $z_{1i}, z_{2i}, \ldots z_{5i}$ represent standardized value of gait speed, grip strength, exhaustion, physical activity, and weight loss for individual *i*, respectively; $w_1, w_2, \ldots w_5$ indicate standardized factor loadings for five indicators. I also repeated the above process for each of the

four subpopulations (i.e., young-old, old-old, male, and female) to calculate age- and sex-specific frailty scores.

Relationship between the Continuous Frailty Scale and the Physical Frailty Phenotype Scale

I first examined the distribution of the continuous frailty score in two cohorts. I then investigated the distribution among participants who were classified as robust, prefrial, and frail based on the PFP scale. Five criteria of the PFP scale were:

1. *Slowness*: gait speed in the lowest 20%, adjusted for sex and height.
2. *Weakness*: grip strength in the lowest 20%, adjusted for sex and BMI.
3. *Exhaustion*: answering "A moderate amount of the time (3-4 days)" or "Most of the time (5-7 days)" to either of the two exhaustion questions (a score of 1 or 2 on the exhaustion for the HRS participants).
4. *Inactivity*: total caloric expenditure in the lowest 20%, adjusted for sex.
5. *Shrinking*: self-reported loss of ≥10 pounds or ≥5% of body weight in prior year.

Participants' frailty status was assigned based on the number of criteria met: those with 0 were "robust"; those with 1 or 2 were "prefrail"; and those with 3, 4, or 5 were "frail".

All tests were two-sided with a significance level of $p < .05$. Data management and statistical analyses other than CFA were conducted in Stata 13.1 (StataCorp, College Station, TX).[253] CFA was performed using maximum likelihood estimation with robust standard error in Mplus 7.2 (Mplus, Los Angeles, CA)[254] to account for non-normality of continuous indicators and non-independence of observations in the HRS (participants were nested in households). All indicators were treated continuously. Missing data in frailty indicators (for sensitivity analyses only) were

handled using the full information maximum likelihood estimation assuming data are missing at random—a type of missing data mechanism assuming missingness can only be explained by observed variables. Robust standard errors were used to account for the nested data structure of the HRS (participants nested within households).

3.3. Results

Cohort Characteristics

The analytic samples included 4,243 CHS participants and 7,600 HRS participants with complete data on all five frailty indicators. Average age was 72.1 years (SD = 5.0) in the CHS cohort; the HRS participants were slightly older, with an average age of 74.9 years (SD = 6.9; Table 3–1). Males comprised 42.1% of the CHS cohort and 43.6% of the HRS cohort. Whites consisted of 86.8% and 89.0% of the CHS and HRS cohorts, respectively. Compared with the HRS cohort, the CHS cohort was less likely to be obese, had lower prevalence of chronic conditions, including cardiac disease, stroke, hypertension, diabetes, cancer, and arthritis, and had higher prevalence of ADL disability. In addition, CHS participants had higher C reactive protein, and total cholesterol, but lower diastolic BP, and cystatin C in comparison to HRS participants. Moreover, participants with complete data on frailty indicators were younger, more likely to be male and white, and had a higher prevalence of chronic conditions, lower level of cognitive function, and unhealthier clinical measures compared with those who had at least one frailty indicator missing (Tables 3–2A & 3–2B).

Association of Indicators with Frailty in the Cardiovascular Health Study

Fitting a unidimensional model of frailty to the CHS cohort yielded a non-significant χ^2 test (χ^2 = 10.56, *df* = 5, *p* = .061; Table 3–3), indicating that the hypothesized factor structure satisfactorily reproduced the variance-covariance matrix of five indicators. In addition, each of the other global goodness-of-fit indices suggested that the unidimensional model fit the data satisfactorily: RMSEA = .016 (90% CI: .000, .030), CFI = .991, TLI = .982. Inspection of the standardized residuals and modification indices showed no localized points of ill fit. All freely estimated standardized loadings were statistically significant and all directions were as expected (Table 3–4).

I examined whether five indicators had equal importance in measuring frailty. A unidimensional model, in which five factor loadings were constrained to be equal, had a substantially worse fit compared with the model in which factor loadings were freely estimated ($\Delta\chi^2$ = 198.29, *df* = 4, *p* < .001; Table 3–5). These results implied that not all five indicators were equally important in measuring frailty. I then assessed the relative importance of five indicators. Grip strength, exhaustion, and physical activity did not have significantly different strengths in measuring frailty; the standardized factor loadings for these three indicators were -0.33, 0.37, and -0.33. Gait speed (factor loading = -0.55) was significantly more strongly associated with frailty than the other 4 indicators, while weight loss had the smallest contribution (factor loading = 0.09).

Association of Indicators with Frailty in the Health and Retirement Study

With the exception of a significant χ^2 test (χ^2 = 52.65, *df* = 5, *p* < .001; Table 3–3), each of the global goodness-of-fit indices indicated an adequate fit between the unidimensional model and the data among the HRS participants: RMSEA = .035 (90% CI: .027, .044), CFI = .976, TLI =

.951. I found no localized misfit by checking the standardized residuals and modification indices. All standardized loadings were statistically significant with the expected directions (Table 3–4).

Compared with the model with factor loadings being freely estimated, the model in which standardized factor loadings were constrained to have the same magnitude fit the data substantially worse ($\Delta\chi^2 = 530.72$, $df = 4$, $p < .001$; Table 3–5). This implied that not all indicators measured with equal strength. Magnitudes of factor loadings varied substantially, ranging from 0.15 for weight loss (weakest) to 0.61 for gait speed (strongest). Grip strength (-0.43), exhaustion (0.40), and physical activity (-0.47) did not have substantially distinct loading in magnitude. The CHS and HRS cohorts had a similar pattern with regard to the relative importance of five factor loadings, with gait speed being the strongest indicator of frailty, weight loss being the weakest, and grip strength, exhaustion, and physical activity having similar strength.

Measurement Invariance and Subgroup Analysis

Goodness-of-fit indices of multiple-group CFA, where all five factor loadings were freely estimated, indicated the configural invariance was achieved across age and sex (Tables 3–6 & 3–7). This implied that five indicators were unidimensional in all subgroups (i.e., one factor underlying five indicators). Difference in goodness-of-fit indices between the multiple-group CFA where configural invariance was achieved and the model imposing equality constraints on all factor loadings were supportive of invariance of factor loadings across age but not across sex in both cohorts. These results suggested the young-old and the old-old had the same factor loadings for five indicators, while loadings for females and males were slightly different.

However, the factor loadings obtained from the subgroups were similar to those derived from the entire analytic sample in both cohorts (Table 3–8). In both cohorts, the relative importance of five indicators with regard to measuring frailty changed minimally across age or sex. Gait speed was the strongest indicator of frailty, while weight loss was the weakest; grip strength, exhaustion, and physical activity were in the middle with similar strength (Figure 3–2).

Sensitivity Analyses

Results were robust against multiple sensitivity analyses. First, there were virtually no differences in factor loadings between models using different operational definitions of weight loss in both cohorts (Table 3–4). In addition, although participants with complete data on frailty indicators and those with at least one missing indicator had different characteristics (Tables 3–2A & 3–2B), missing data in frailty indicators had minimal impact on the estimates of factor loadings (Table 3–4).

Construction and Properties of the Continuous Frailty Scale

I calculated the continuous frailty score using the following two equations:

$$\text{CHS: frailty score}_i = -.33 \times \text{grip strength} + (-.55) \times \text{gait speed} + .37 \times \text{exhaustion} + (-.33) \times \text{physical activity} + .09 \times \text{weight loss}$$

$$\text{HRS: frailty score}_i = -.43 \times \text{grip strength} + (-.61) \times \text{gait speed} + .40 \times \text{exhaustion} + (-.47) \times \text{physical activity} + .15 \times \text{weight loss}$$

The calculated continuous frailty score in both cohorts was approximately normally distributed with a mean of 0 and a SD of 1 (Figure 3–3). I re-constructed the continuous frailty score using

age- and sex-specific factor loadings provided in Table 3–8. The correlations between each two of the three scores (i.e., derived from the entire cohort, derived using age-specific loadings, derived using sex-specific loadings) were exceptionally high in both cohorts (all correlation coefficients > .99). I therefore restricted further analyses to the continuous frailty score obtained from the entire cohort (separately for the CHS and HRS cohorts).

Association of the Continuous Frailty Scale with the Physical Frailty Phenotype Scale

In the CHS cohort, 1,905 (44.9%), 1,982 (46.7%), and 356 (8.4%) were classified as robust, prefrail, and frail, respectively, according to the PFP scale. Estimates were similar in the HRS cohort; 3,485 (45.9%) were frail, 3,413 (44.9%) were prefrail, and 702 (9.2%) were robust. The mean continuous frailty scores were considerably different between robust, prefrail, and frail adults in each of the two cohorts (Table 3–9). The overlap was not large between distributions of frailty score in robust, prefrail, and frail participants, especially for those who were robust and frail (Figures 3–4A & 3–4B). For robust older adults, only four (0.2%) CHS and 0 HRS participants had a continuous frailty score falling into the highest quintile (Table 3–10). For CHS and HRS participants who were classified as frail, 92.7% and 95.3% had a continuous frailty score falling in the highest quintile, respectively.

3.4. Discussion

I have described a satisfactory factor structure of five indicators (gait speed, grip strength, exhaustion, physical activity, and weight loss) and frailty among older adults aged ≥65 years using data from two nationwide cohort studies. All five frailty indicators were significantly associated with frailty with different strengths. Factor loadings, which represent the associations

of indicators and frailty, were similar across the CHS and HRS cohorts, implying that the factor structure was robust to nuanced differences in assessment of frailty indicators and not cohort-specific. In both cohorts, gait speed and weight loss were the strongest and weakest indicators of frailty, respectively, and grip strength, exhaustion, and physical activity had similar strength in measuring frailty. In addition, findings from the current study showed that a unidimensional factor structure fit the data satisfactorily in both cohorts, suggesting that frailty is a unidimensional construct and can be assessed by gait speed, grip strength, exhaustion, physical activity, and weight loss. These findings were echoed by an earlier study showing that a one-factor CFA model had a satisfactory fit with qualitatively similar factor structure across 12 European countries among 27,938 participants aged ≥50 years from the Survey of Health, Ageing and Retirement in Europe.[255] Moreover, I found that, in both cohorts, participants who were identified as robust and prefrail in the PFP scale had different scores on the new continuous frailty scale. These results suggest that there were huge variations among robust and prefrail persons, both of which were considered homogeneous subgroups in the PFP scale.

Gait speed, grip strength, exhaustion, physical activity, and weight loss have been widely used to characterize frailty and have demonstrated evidence of face validity.[156] However, with few exceptions,[30,67,255-257] little attention has been devoted to the construct validity of these five frailty measures. To my knowledge, this is the first application of CFA to empirically validate the frailty construct as measured by five indicators originally proposed by Fried et al.[35] My approach is different from previous work by Bandeen-Roche et al.,[30] in which a latent class analysis was applied to examine the construct validity of frailty, operationalized as a discrete syndrome. Both latent variable-based methods are useful to investigate the construct validity of frailty, a clinical

syndrome that is not directly measurable. CFA may be a more appropriate approach than latent class analysis in the present study because I conceptualize frailty as a continuum rather than a discrete phenomenon. These two statements do not necessarily contradict each other because frailty, which I conceptualize as a continuous variable, may be weakly associated with adverse outcomes in its low end and become clinically devastating above certain threshold.

Our results suggest that it may be valid and feasible to construct a continuous frailty scale based on five indicators originally used to construct the PFP scale. A finer graded continuous frailty scale may have the following advantages: (i) providing a greater differentiation of the frailty syndrome, (ii) further stratifying risk of outcomes among robust, prefrail, and frail adults identified by the PFP scale, (iii) increasing statistical power for identifying genetic, physiological, behavioral, and environmental risk factors for development of frailty and transitions between frailty status over time, (iv) enhancing power of frailty instruments for predicting outcomes, and (v) removing the ceiling effect of the categorical PFP scale. Some of these advantages have been previously demonstrated in two rescaled PFP scales.[82,83]

I found that not all five frailty indicators had the same strength in assessing frailty, with gait speed being the strongest indicator. Gait speed, a quick, easy, and inexpensive physical performance measure, is an integrative measure of health and a well-documented indicator for mortality, disability, and other adverse outcomes among older adults.[258-263] Gait speed, a key component in many frailty assessments, has been advocated by the Geriatric Advisory Panel of the IANA task force as the most suitable single-item measure of frailty in clinical practice.[70,264] Castell et al.[13] evaluated the performance of gait speed as being a single-item measure for

assessing frailty among 1,327 adults aged ≥65 years from two urban neighborhoods of northern Madrid in Spain. Over 99% of frail persons (identified by the PFP scale) had gait speed ≤0.8 m/s and none of the frail had gait speed >0.9 m/s. About one-third of persons aged ≥75 years with gait speed <0.8 m/s were classified as frail.

Strengths of this study include (i) a large, heterogeneous cohort of older adults, (ii) utilizing frailty indicators originally proposed by Fried et al., (iii) use of a validation cohort with similar assessment of frailty indicators, (iv) rigorous examination of measurement invariance across age and sex, and (v) establishment of a frailty assessment that has robust dimensional structure across cohorts and demographic subgroups.

I acknowledge several limitations. First, although five frailty indicators were measured similarly across the CHS and HRS cohorts, nuanced differences still exist. For example, gait speed was measured over a 15-foot course in the CHS, while a 96.5-inch (~8 feet) course was adopted in the HRS. However, factor loading estimates were similar across two cohorts, suggesting the factor structure of frailty was robust to nuanced differences in assessment of indicators. Second, I focused on the unidimensional model and did not evaluate whether a two-factor model fit could sufficiently explain the underlying factor structure of frailty. Sarkisian et al.[257] identified two sub-dimensions of frailty using principle component analysis among 1,118 high-functioning adults aged 70-79 years from the MacArthur Study of Successful Aging. One dimension was defined by gait speed, grip strength, and physical activity, and another dimension was characterized by exhaustion and weight loss. However, it does not seem necessary to test a multi-

factor model in the present study because, a unidimensional model, which may be preferred due to its simplicity and ease of application, fit the data satisfactorily in two large cohorts.

Our findings provided strong evidence that frailty is a valid continuous construct with a unidimensional factor structure robust to nuanced differences in measurement of indicators and invariant across cohorts and demographics including age and sex. Not all indicators had the same strength in measuring frailty, with gait speed being the strongest one. In Chapter 4, I will comprehensively evaluate the ability of this newly developed continuous frailty scale for predicting mortality, disability, hip fracture, and falls. In Chapter 5, I will examine the ability of the continuous frailty scale to capture older adults' ability to recover from stressors (e.g., disability, acute medical events), which is considered a defining feature of frailty.

Table 3–1. Characteristics of participants.

Characteristics	CHS N = 4,243	HRS N = 7,600	*p* [a]
Age, years, mean (SD)	72.1 (5.0)	74.9 (6.9)	<.001
Male, No. (%)	1,788 (42.1)	3,315 (43.6)	.067
Whites (vs. others), No. (%)	3,683 (86.8)	6,763 (89.0)	.123
Education			<.001
< High school, No. (%)	1,058 (25.0)	1,838 (24.2)	
= High school, No. (%)	1,212 (28.6)	2,729 (35.9)	
> High school, No. (%)	1,964(46.4)	3,032 (39.9)	
Smoking status			.036
Never, No. (%)	1,882 (45.2)	3,279 (43.4)	
Former, No. (%)	1,888 (45.4)	3,575 (47.3)	
Current, No. (%)	392 (9.4)	702 (9.3)	
Body mass index, kg/m^2			<.001
Underweight/Normal[b], No. (%)	1,589 (37.5)	2,009 (26.4)	
Overweight, No. (%)	1,793 (42.3)	2,856 (37.6)	
Obese, No. (%)	861 (20.3)	2,735 (36.0)	
Cardiac disease[c], No. (%)	1,237 (25.1)	2,341 (30.8)	<.001
Stroke, No. (%)	209 (4.9)	518 (6.9)	<.001
Hypertension[e], No. (%)	2,370 (55.9)	4,850 (63.9)	<.001
Diabetes[d], No. (%)	620 (15.1)	1,653 (21.8)	<.001
Cancer[f], No. (%)	600 (14.2)	1,453 (19.1)	<.001
Arthritis, No. (%)	1,929 (46.6)	5,196 (68.4)	<.001
ADL disability[g], No. (%)	430 (10.2)	1,146 (21.0)	<.001
Systolic BP, mmHg, mean (SD)	135.6 (21.2)	134.4 (20.8)	.213
Diastolic BP, mmHg, mean (SD)	70.7 (11.2)	78.4 (11.6)	<.001
C reactive protein, μg/L, mean (SD)	5.2 (9.7)	4.3 (8.6)	<.001
Cystatin C, mg/L, mean (SD)	1.1 (0.3)	1.2 (0.5)	<.001
Total cholesterol, mg/dL, mean (SD)	208.2 (38.5)	197.9 (41.7)	<.001

Abbreviations: CHS, Cardiovascular Health Study; HRS, Health and Retirement Study; SD, standard deviation; ADL, activities of daily living; BP, blood pressure.

[a] *p*-values were obtained from generalized linear regression with clustered sandwich estimator for comparison between the CHS and the HRS participants.

[b] Underweight and normal were collapsed due to small cell size in the underweight category.

[c] Coronary heart disease and heart failure were included in the CHS; myocardial infarction, coronary heart disease, angina, heart failure, or other heart problems were included in the HRS.

[d] Prediabetes was considered as diabetes in the CHS.

[e] Borderline hypertension was considered hypertension in the CHS.

[f] Non-melanoma skin cancer was excluded.

[g] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

Table 3–2A. Characteristics of participants from the Cardiovascular Health Study.

Characteristics	5 indicators measured (N = 4,243)	≥1 indicator measured (N = 695)	*p* [a]
Age, years, mean (SD)	72.1 (5.0)	74.4 (6.5)	<.001
Male, No. (%)	1,788 (42.1)	239 (34.4)	<.001
White (vs. Black), No. (%)	3,683 (86.8)	531 (76.4)	<.001
Education			<.001
< High school, No. (%)	1,058 (25.0)	289 (41.8)	
= High school, No. (%)	1,212 (28.6)	157 (22.7)	
> High school, No. (%)	1,964(46.4)	245 (35.5)	
Smoking status			.039
Never, No. (%)	1,882 (45.2)	327 (49.6)	
Former, No. (%)	1,888 (45.4)	264 (40.0)	
Current, No. (%)	392 (9.4)	68 (10.3)	
Body mass index, kg/m^2			.737
Underweight/normal[b], No. (%)	1,589 (37.5)	135 (37.7)	
Overweight, No. (%)	1,793 (42.3)	145 (40.5)	
Obese, No. (%)	861 (20.3)	78 (21.8)	
Coronary heart disease, No. (%)	926 (21.8)	194 (27.9)	<.001
Heart failure, No. (%)	241 (5.7)	99 (14.2)	<.001
Stroke, No. (%)	209 (4.9)	79 (11.4)	<.001
Hypertension			<.001
Borderline, No. (%)	632 (14.9)	79 (13.8)	
Hypertensive, No. (%)	1,738 (41.0)	306 (53.3)	
Diabetes			<.001
Prediabetes, No. (%)	407 (9.9)	33 (7.8)	
Diabetes, No. (%)	620 (15.1)	107 (25.4)	
Cancer[c], No. (%)	600 (14.2)	98 (14.1)	.963
Arthritis, No. (%)	1,929 (46.6)	372 (58.7)	<.001
3MS[d], mean (SD)	91.2 (8.4)	82.2 (17.6)	<.001
ADL disability[e], No. (%)	430 (10.2)	204 (30.8)	<.001
Systolic BP, mmHg, mean (SD)	135.6 (21.2)	138.6 (21.4)	.002
Diastolic BP, mmHg, mean (SD)	70.7 (11.2)	70.4 (12.9)	.583
C reactive protein, µg/L, mean (SD)	5.2 (9.7)	6.2 (11.7)	.101
Cystatin C, mg/L, mean (SD)	1.1 (0.3)	1.2 (0.5)	<.001
Total cholesterol, mg/dL, mean (SD)	208.2 (38.5)	210.0 (42.7)	.421
Fasting glucose, mg/dL, mean (SD)	108.1 (33.0)	108.9 (36.4)	.665

Abbreviations: SD, standard deviation; ADL, activities of daily living; BP, blood pressure.

[a] *p*-values were obtained from t test with unequal variance or χ^2 test for comparison between adults with complete frailty assessment and those with at least one indicator not measured.

[b] Underweight and normal were collapsed due to small cell size in the underweight category.

[c] Non-melanoma skin cancer was excluded.

[d] Ranging from 0 to 100 with higher score indicating a better global cognitive function.

[e] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

Table 3–2B. Characteristics of participants from the Health and Retirement Study.

Characteristics	5 indicators measured (N = 7,600)	≥1 indicator measured (N = 1,621)	*p* [a]
Age, years, mean (SD)	74.9 (6.9)	75.5 (7.8)	.005
Male, No. (%)	3,315 (43.6)	586 (36.2)	<.001
White (vs. others), No. (%)	6,763 (89.0)	1,260 (77.7)	<.001
Education			<.001
< High school, No. (%)	1,838 (24.2)	568 (35.1)	
= High school, No. (%)	2,729 (35.9)	545 (33.6)	
> High school, No. (%)	3,032 (39.9)	507 (31.3)	
Smoking status			.897
Never, No. (%)	3,279 (43.4)	660 (41.1)	
Former, No. (%)	3,575 (47.3)	737 (45.9)	
Current, No. (%)	702 (9.3)	210 (13.1)	
Body mass index, kg/m^2, mean (SD)			.289
Underweight/normal[b], No. (%)	2,009 (26.4)	417 (26.5)	
Overweight, No. (%)	2,856 (37.6)	544 (34.5)	
Obese, No. (%)	2,735 (36.0)	615 (39.0)	
Cardiac disease[c], No. (%)	2,341 (30.8)	585 (36.1)	<.001
Stroke, No. (%)	518 (6.9)	205 (12.7)	<.001
Hypertension, No. (%)	4,850 (63.9)	1,114 (68.9)	<.001
Lung disease, No (%)	867 (11.4)	1,369 (15.5)	<.001
Diabetes, No. (%)	1,653 (21.8)	458 (28.3)	<.001
Cancer[d], No. (%)	1,453 (19.1)	295 (18.2)	.389
Arthritis, No. (%)	5,196 (68.4)	1,210 (74.7)	<.001
TICS[e], mean (SD)	9.3 (1.2)	8.9 (1.7)	<.001
ADL disability[f], No. (%)	1,146 (21.0)	598 (44.3)	<.001
Systolic BP, mmHg, mean (SD)	134.4 (20.8)	133.7 (22.3)	.287
Diastolic BP, mmHg, mean (SD)	78.4 (11.6)	78.1 (12.6)	.431
C reactive protein, μg/L, mean (SD)	4.3 (8.6)	6.5 (12.6)	<.001
Cystatin C, mg/L, mean (SD)	1.2 (0.5)	1.3 (0.8)	<.001
HDL cholesterol, mg/dL, mean (SD)	54.2 (15.9)	52.0 (15.1)	<.001
Total cholesterol, mg/dL, mean (SD)	197.9 (41.7)	192.1 (40.9)	<.001
HbA1c, %, mean (SD)	5.9 (0.9)	6.0 (1.0)	<.001

Abbreviations: SD, standard deviation; ADL, activities of daily living; BP, blood pressure; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.

[a] *p*-values were obtained from generalized linear regression with clustered sandwich estimator for comparison between adults with complete data on frailty components and those with at least one frailty indicator not measured.

[b] Underweight and normal were collapsed due to small cell size in the underweight category.

[c] Myocardial infarction, coronary heart disease, angina, heart failure, or other heart problems.

[d] Non-melanoma skin cancer was excluded.

[e] Ranging from 0 to 10 with higher score indicating a better global cognitive function.

[f] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

Table 3–3. Goodness of fit indices of confirmatory factor analyses.

Goodness-of-fit Indices	Cardiovascular Health Study				Health and Retirement Study			
	5 indicators measured N = 4,243		≥1 indicator measured N = 4,938		5 indicators measured N = 7,600		≥1 indicator measured N = 9,221	
	Model A[a]	Model B[b]	Model A	Model B	Model A	Model B	Model A	Model B
χ^2_5 (p-value)	10.56 (.061)	11.74 (.038)	11.32 (.045)	12.43 (.029)	52.65 (<.001)	56.96 (<.001)	56.09 (<.001)	60.06 (<.001)
CFI	.991	.989	.992	.990	.976	.973	.978	.976
TLI	.982	.978	.984	.981	.951	.946	.957	.953
RMSEA (90% CI)	.016 (.000, .030)	.018 (.004, .031)	.016 (.002, .029)	.017 (.005, .030)	.035 (.027, .044)	.037 (.029, .046)	.033 (.026, .041)	.035 (.027, .043)
Ill localized fit	None	None	None	None	None	None	None	None

Abbreviations: CFI, Comparative Fit Index; TLI, Tucker-Lewis Index; RMSEA, root mean square error of approximation; CI, confidence interval.

Notes: CFI ≥ .90, TLI ≥ .90, and RMSEA ≤ .08 indicate reasonable model fit; CFI ≥ .95, TLI ≥ .95, and RMSEA ≤ .05 indicate ideal model fit; non-significant χ^2 statistic indicates perfect model fit.

[a] Gait speed adjusted for sex and height, grip strength adjusted for sex and body mass index, exhaustion, physical activity, and percentage weight loss were included.

[b] Gait speed adjusted for sex and height, grip strength adjusted for sex and body mass index, exhaustion, physical activity, and weight difference were included.

Table 3–4. Standardized factor loading estimates of five indicators.

Indicators	Cardiovascular Health Study				Health and Retirement Study			
	5 indicators measured N = 4,243		≥1 indicator measured N = 4,938		5 indicators measured N = 7,600		≥1 indicator measured N = 9,221	
	% weight loss	weight difference	% weight loss	weight difference	% weight loss	weight difference	% weight loss	weight difference
	Standardized factor loading (standard error)							
Gait speed[a]	-.55 (.03)	-.55 (.03)	-.58 (.03)	-.59 (.03)	-.61 (.02)	-.61 (.02)	-.60 (.02)	-.60 (.02)
Grip strength[b]	-.33 (.02)	-.33 (.02)	-.34 (.02)	-.34 (.02)	-.43 (.01)	-.44 (.01)	-.45 (.01)	-.46 (.01)
Exhaustion[c]	.37 (.02)	.37 (.02)	.44 (.02)	.44 (.02)	.40 (.02)	.40 (.02)	.43 (.01)	.43 (.01)
Physical activity[d]	-.33 (.02)	-.33 (.02)	-.33 (.02)	-.33 (.02)	-.47 (.02)	-.47 (.02)	-.50 (.01)	-.50 (.01)
Weight loss	.09 (.02)	.09 (.02)	.12 (.02)	.12 (.02)	.15 (.02)	.14 (.02)	.15 (.02)	.14 (.02)

[a] Gait speed (m/s) was measured over a 4.6-meter and a 2.5-meter course in the Cardiovascular Health Study and the Health and Retirement Study, respectively.
[b] Grip strength (kg) was measured by a hand dynamometer in both cohorts.
[c] Exhaustion was measured by two items from the Center for Epidemiologic Studies Depression Scale ("I could not get going" and "I felt that everything I did was an effort"); the total score ranged from 0-12 in the Cardiovascular Health Study and from 0-2 in the Health and Retirement Study.
[d] Physical activity was measured by self-reported total energy expenditure in the Cardiovascular Health Study and by self-reported frequency of light, moderate, and vigorous activities in the Health and Retirement Study.

Table 3–5. Tests of equal importance of five indicators in measuring the latent frailty construct.

Tests	CHS		HRS	
	All 5 indicators measured N = 4,243		All 5 indicators measured N = 7,600	
	$\Delta\chi^2$	*p* value	$\Delta\chi^{2a}$	*p* value
All indicators are equal	198.29	<.001	530.72	<.001
Gait speed[b] = Grip strength[c]	31.65	<.001	42.17	<.001
Gait speed = Exhaustion	22.92	<.001	51.23	<.001
Gait speed = Physical activity	34.01	<.001	18.61	<.001
Gait speed = Weight loss	189.37	<.001	345.33	<.001
Grip strength = Exhaustion[d]	0.56	.454	3.47	.063
Grip strength = Physical activity[e]	0.40	.527	1.50	.220
Grip strength = Weight loss	70.56	<.001	207.36	<.001
Exhaustion = Physical activity	2.04	.153	13.37	<.001
Exhaustion = Weight loss	84.52	<.001	214.77	<.001
Physical activity = Weight loss	57.10	<.001	292.60	<.001

Abbreviations: CHS, Cardiovascular Health Study; HRS, Health and Retirement Study.

[a] Robust χ^2 difference test was used for participants in the Health and Retirement Study because of the nested structure of the data.

[b] Gait speed (m/s) was measured over a 4.6-meter and a 2.5-meter course in the Cardiovascular Health Study and the Health and Retirement Study, respectively.

[c] Grip strength (kg) was measured by a hand dynamometer in both cohorts.

[d] Exhaustion was measured by two items from the Center for Epidemiologic Studies Depression Scale ("I could not get going" and "I felt that everything I did was an effort"); the total score ranged from 0-12 in the Cardiovascular Health Study and from 0-2 in the Health and Retirement Study.

[e] Physical activity was measured by self-reported total energy expenditure in the Cardiovascular Health Study and by self-reported frequency of light, moderate, and vigorous activities in the Health and Retirement Study.

Table 3–6. Testing measurement invariance across age (< and ≥75 years).

		χ^2	df	RMSEA (90% CI)	CFI	TLI	$\Delta\chi^{2a}$	Δdf	*P*	ΔCFI	Achieved
					Cardiovascular Health Study (N = 4,243)						
Model A[b]	Configural invariance[d]	11.14	10	.007 (.000, .025)	.998	.995					Yes
	Weak invariance[e]	16.20	14	.009 (.000, .024)	.996	.994	5.06	4	.281	.002	Yes
	Strong invariance	113.93	18	.050 (.042, .059)	.809	.788	97.73	4	<.001	.189	No
Model B[c]	Configural invariance	12.32	10	.010 (.000, .027)	.995	.991					Yes
	Weak invariance	16.20	14	.009 (.000, .024)	.996	.994	3.88	4	.422	-.001	Yes
	Strong invariance	113.53	18	.050 (.041, .059)	.810	.789	97.33	4	<.001	.186	No
					Health and Retirement Study (N = 7,600)						
Model A	Configural invariance	32.75	10	.024 (.015, .034)	.986	.972					Yes
	Weak invariance	46.32	14	.025 (.017, .033)	.980	.971	13.57	4	.002	.006	Yes
	Strong invariance	400.79	18	.075 (.069, .081)	.776	.751	340.58	4	<.001	.202	No
Model B	Configural invariance	34.10	10	.025 (.016, .035)	.985	.970					Yes
	Weak invariance	46.02	14	.021 (.014, .028)	.984	.979	11.92	4	.018	.001	Yes
	Strong invariance	459.95	18	.073 (.067, .079)	.782	.758	403.23	4	<.001	.197	No

Abbreviations: df, degrees of freedom; RMSEA, root mean square error of approximation; CI, confidence interval; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index.

[a] Robust χ^2 difference test was used for participants in the Health and Retirement Study because of the nested structure of the data.

[b] Gait speed adjusted for sex and height, grip strength adjusted for sex and body mass index, exhaustion, physical activity, and percentage weight loss were included.

[c] Gait speed adjusted for sex and height, grip strength adjusted for sex and body mass index, exhaustion, physical activity, and weight difference were included.

[d] The indicator-factor structure was similar across two subgroups (<75 and ≥75 years). Comparative Fit Index ≥ .90, Tucker-Lewis Index ≥ .90, and root mean square error of approximation ≤ .08 indicate that configural invariance was achieved.

[e] Magnitude and direction of each of the five frailty indicators was similar across two subgroups (<75 and ≥75 years). A non-significant $\Delta\chi^2$ and a change in Comparative Fit Index ≤ .01 indicate that weak invariance was achieved.

Table 3–7. Testing measurement invariance across sex.

		χ^2	*df*	RMSEA (90% CI)	CFI	TLI	$\Delta\chi^{2a}$	*Δdf*	*p* value	ΔCFI	Achieved
					Cardiovascular Health Study (N = 4,243)						
Model A[b]	Configural invariance[d]	19.62	10	.021 (.006, .035)	.985	.970					Yes
	Weak invariance[e]	50.67	14	.035 (.025, .046)	.942	.918	31.05	4	<.001	.043	No
Model B[c]	Configural invariance	20.33	10	.022 (.007, .036)	.984	.967					Yes
	Weak invariance	51.39	14	.035 (.025, .046)	.941	.916	31.06	4	<.001	.043	No
					Health and Retirement Study (N = 7,600)						
Model A	Configural invariance	58.32	10	.036 (.027, .045)	.976	.953					Yes
	Weak invariance	120.08	14	.045 (.037, .052)	.948	.926	61.76	4	<.001	.028	No
Model B	Configural invariance	63.91	10	.038 (.029, .047)	.974	.947					Yes
	Weak invariance	120.21	14	.045 (.038, .052)	.948	.926	56.30	4	<.001	.026	No

Abbreviations: *df*, degrees of freedom; RMSEA, root mean square error of approximation; CI, confidence interval; CFI, Comparative Fit Index; TLI, Tucker-Lewis Index.

[a] Robust χ^2 difference test was used for the HRS participants because of the nested structure of the data.

[b] Gait speed adjusted for sex and height, grip strength adjusted for sex and body mass index, exhaustion, physical activity, and percentage weight loss were included.

[c] Gait speed adjusted for sex and height, grip strength adjusted for sex and body mass index, exhaustion, physical activity, and weight difference were included.

[d] The indicator-factor structure was similar between females and males. Comparative Fit Index ≥0.90, Tucker-Lewis Index ≥0.90, and root mean square error of approximation ≤0.08 indicate that configural invariance was achieved.

[e] Magnitude and direction of each of the five indicators was similar between females and males. A non-significant $\Delta\chi^2$ and a change in Comparative Fit Index ≤0.01 indicate that weak invariance was achieved.

Table 3–8. Standardized factor loading estimates of five indicators within demographic subgroups.

Indicators	Cardiovascular Health Study				Health and Retirement Study			
	<75 years n = 2,511	≥75 years n = 1,732	Male n = 1,788	Female n = 2,455	<75 years n = 4,303	≥75 years n = 3,297	Male n = 3,315	Female n = 4,285
	Standardized factor loading (standard error)							
Gait speed[b]	-.46 (.04)	-.59 (.05)	-.58 (.04)	-.55 (.04)	-.52 (.02)	-.60 (.03)	-.58 (.03)	-.63 (.02)
Grip strength[a]	-.24 (.03)	-.33 (.03)	-.39 (.04)	-.30 (.03)	-.32 (.02)	-.43 (.02)	-.47 (.02)	-.43 (.02)
Exhaustion[c]	.44 (.04)	.38 (.03)	.35 (.03)	.43 (.03)	.46 (.02)	.38 (.02)	.38 (.02)	.41 (.02)
Physical activity[d]	-.30 (.03)	-.34 (.04)	-.31 (.03)	-.33 (.03)	-.47 (.02)	-.48 (.02)	-.46 (.02)	-.47 (.02)
Weight loss	.04 (.03)	.09 (.03)	.13 (.03)	.09 (.03)	.09 (.02)	.15 (.02)	.12 (.03)	.19 (.02)

[a] Gait speed (m/s) was measured over a 4.6-meter and a 2.5-meter course in the Cardiovascular Health Study and the Health and Retirement Study, respectively.
[b] Grip strength (kg) was measured by a hand dynamometer in both cohorts.
[c] Exhaustion was measured by two items from the Center for Epidemiologic Studies Depression Scale ("I could not get going" and "I felt that everything I did was an effort"); the total score ranged from 0-12 in the Cardiovascular Health Study and from 0-2 in the Health and Retirement Study.
[d] Physical activity was measured by self-reported total energy expenditure in the Cardiovascular Health Study and by self-reported frequency of light, moderate, and vigorous activities in the Health and Retirement Study.

Table 3–9. Continuous frailty score among robust, prefrail, and frail adults defined by the physical frailty phenotype scale.

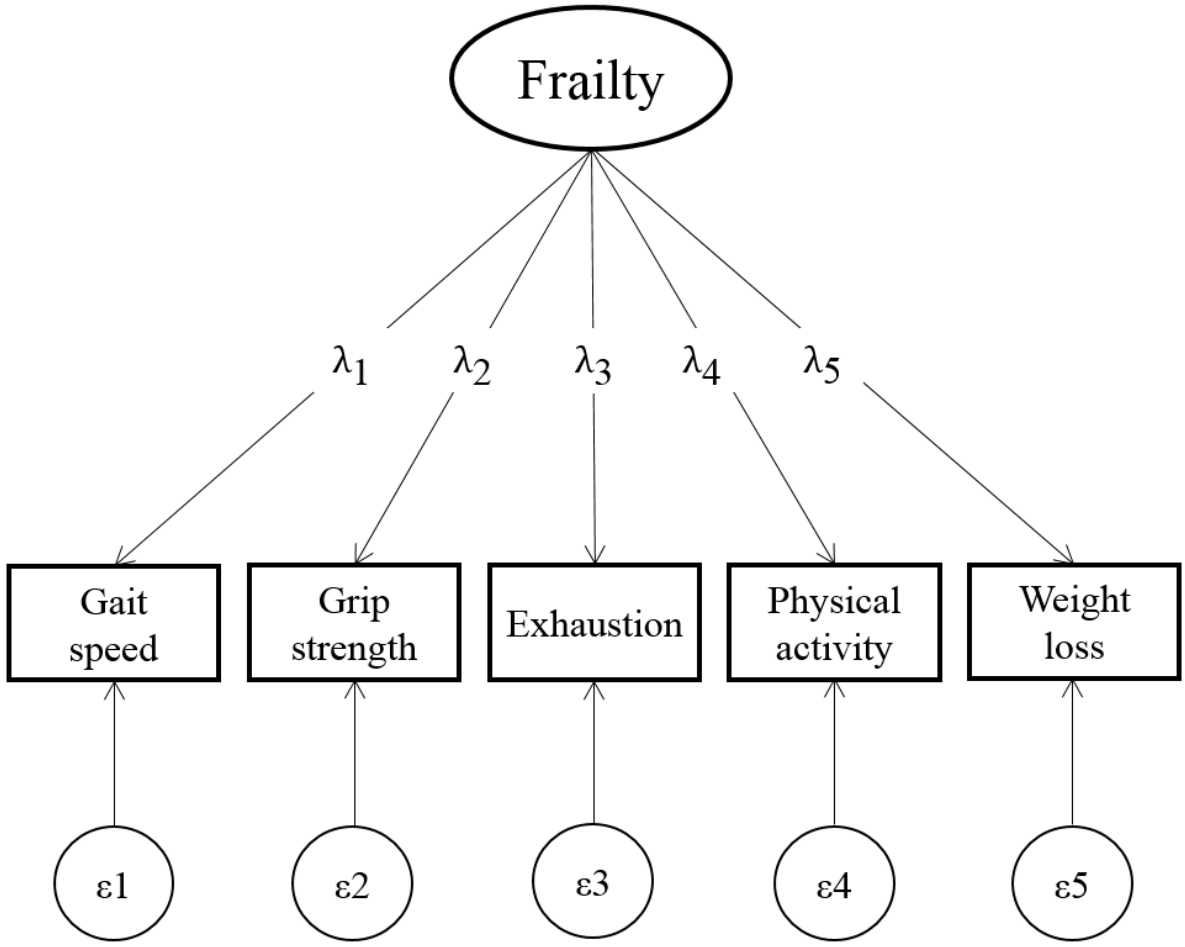
	Scores on the continuous frailty scale				
	Mean ± SD	Median	1st quartile	3rd quartile	*p*[a]
	Cardiovascular Health Study (N = 4,243)				
Robust	-0.69 ± 0.68	-0.63	-1.06	-0.22	Ref.
Prefrail	0.25 ± 0.74	0.32	-0.21	0.75	<.001
Frail	1.57 ± 0.67	1.52	1.14	1.99	<.001
	Health and Retirement Study (N = 7,600)				
Robust	-0.93 ± 0.85	-0.84	-1.48	-0.30	Ref.
Prefrail	0.45 ± 0.87	0.49	-0.10	1.02	<.001
Frail	2.10 ± 0.70	2.08	1.62	2.53	<.001

Abbreviations: SD, standard deviation.
[a] *p*-values from post hoc multiple comparisons in analysis of variance after Bonferroni correction.

Table 3–10. Cross-tabulation of quintiles of continuous frailty score and physical frailty phenotype scale.

	Cardiovascular Health Study (N = 4,243)		
	Physical frailty phenotype scale		
Continuous frailty score	Robust	Prefrail	Frail
1st quintile	698	145	0
2nd quintile	590	267	0
3rd quintile	439	407	7
4th quintile	174	648	19
5th quintile	4	515	330
Total	1,905	1,982	356
	Health and Retirement Study (N = 7,600)		
	Physical frailty phenotype scale		
Continuous frailty score	Robust	Prefrail	Frail
1st quintile	1,358	166	0
2nd quintile	1,088	418	0
3rd quintile	740	792	2
4th quintile	181	1,305	35
5th quintile	0	770	745
Total	3,367	3,451	782

Figure 3-1. Hypothesized relationship between indicators and the frailty construct.



Footnotes: Hypothesized causal relationship between the latent frailty construct and five indicators. The terms $\lambda 1 - \lambda 5$ represent factor loadings, quantifying the association of observed indicators (gait speed, grip strength, exhaustion, physical activity, and weight loss) with the latent factor (i.e. frailty). The terms $\varepsilon 1 - \varepsilon 5$ denote residual errors of indicators not accounted for by the latent factor (i.e. accounted for by other factors and/or random error). Oval represents the latent factor; squares represent manifest indicators; cycles represent variance of manifest indictors not accounted for by the latent factor.

Figure 3–2. Standardized estimates of factor loadings.

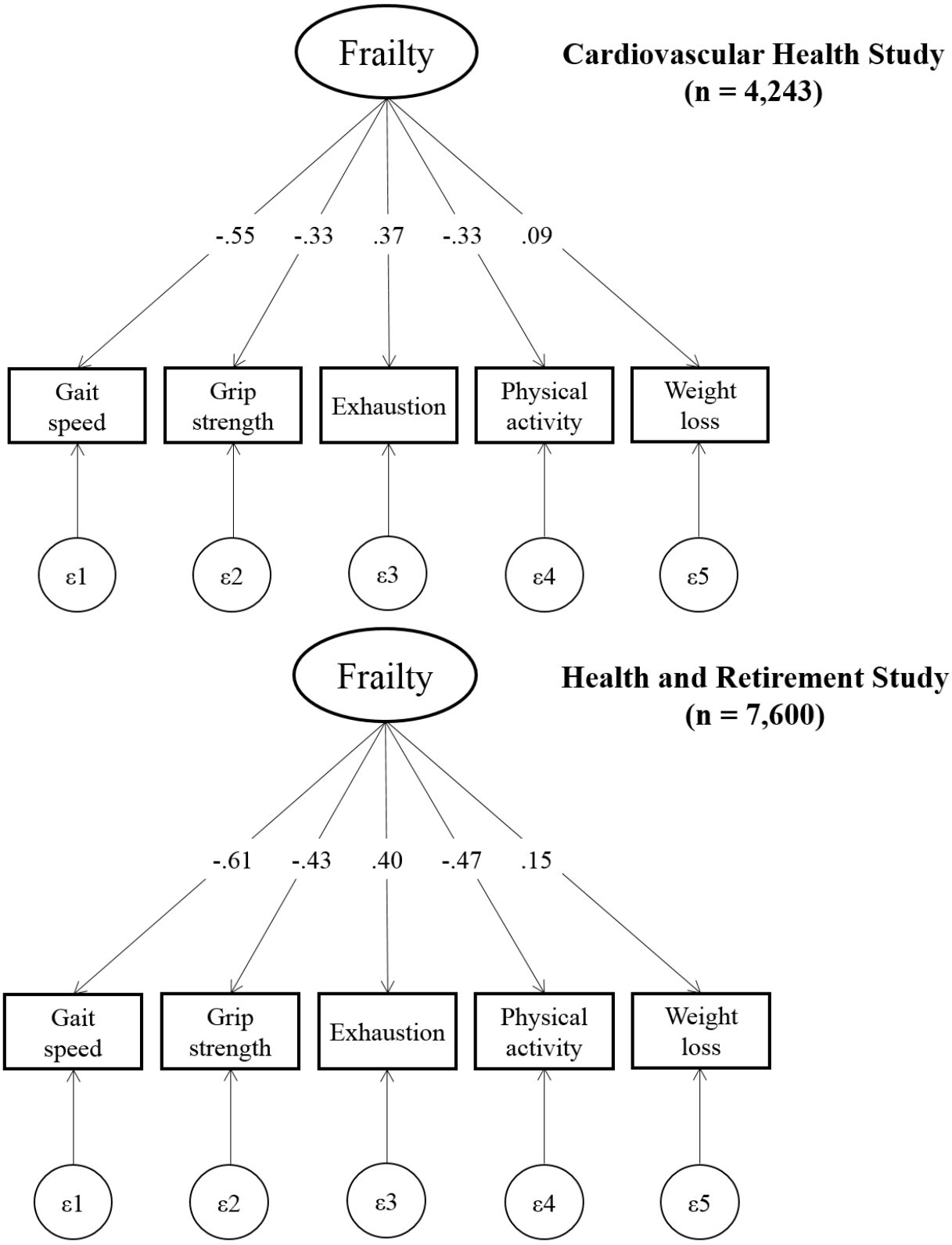


Figure 3–3. Distribution of the calculated continuous frailty score.

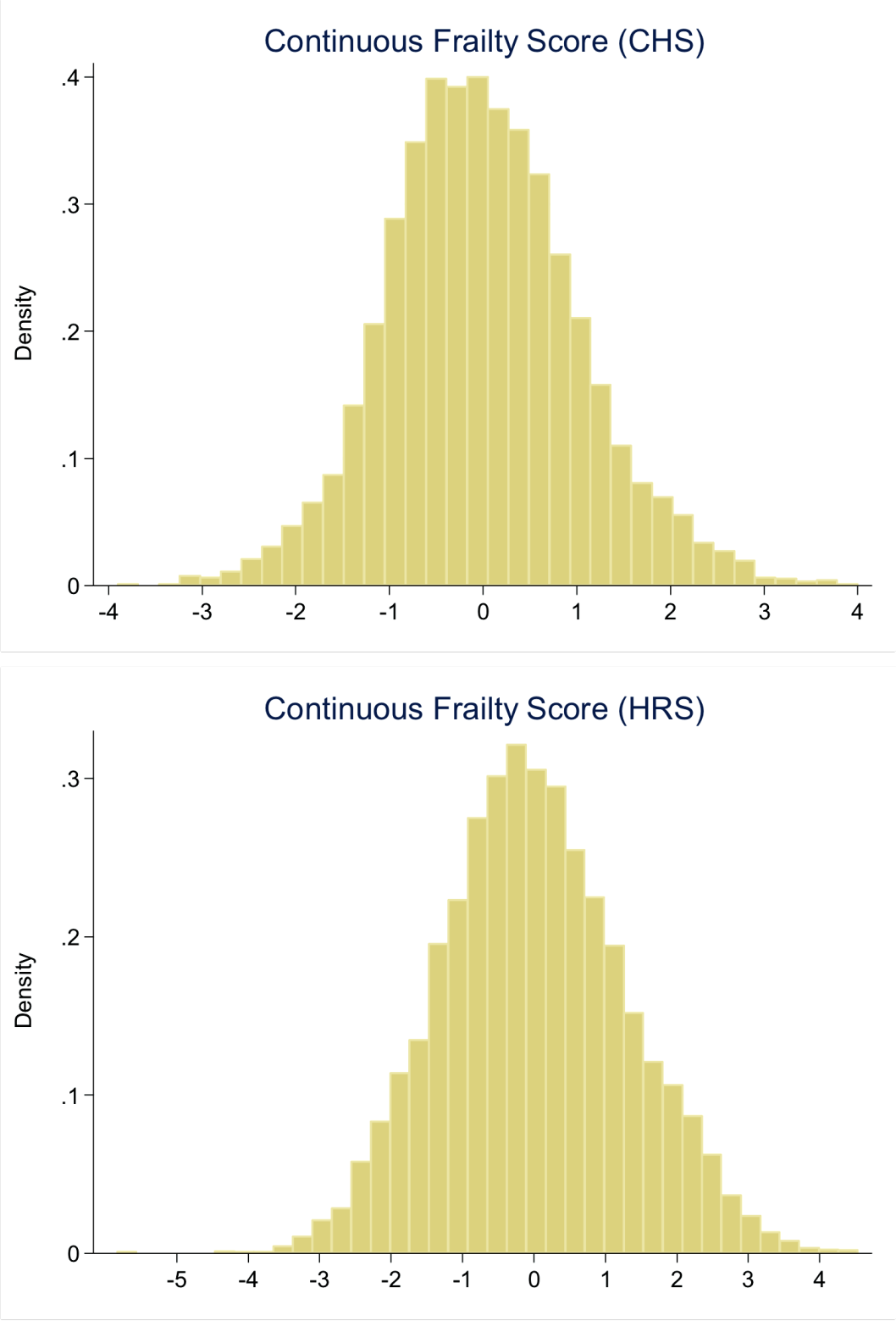


Figure 3–4A. Distribution of continuous frailty score by frailty status identified by the physical frailty phenotype scale, Cardiovascular and Health Study.

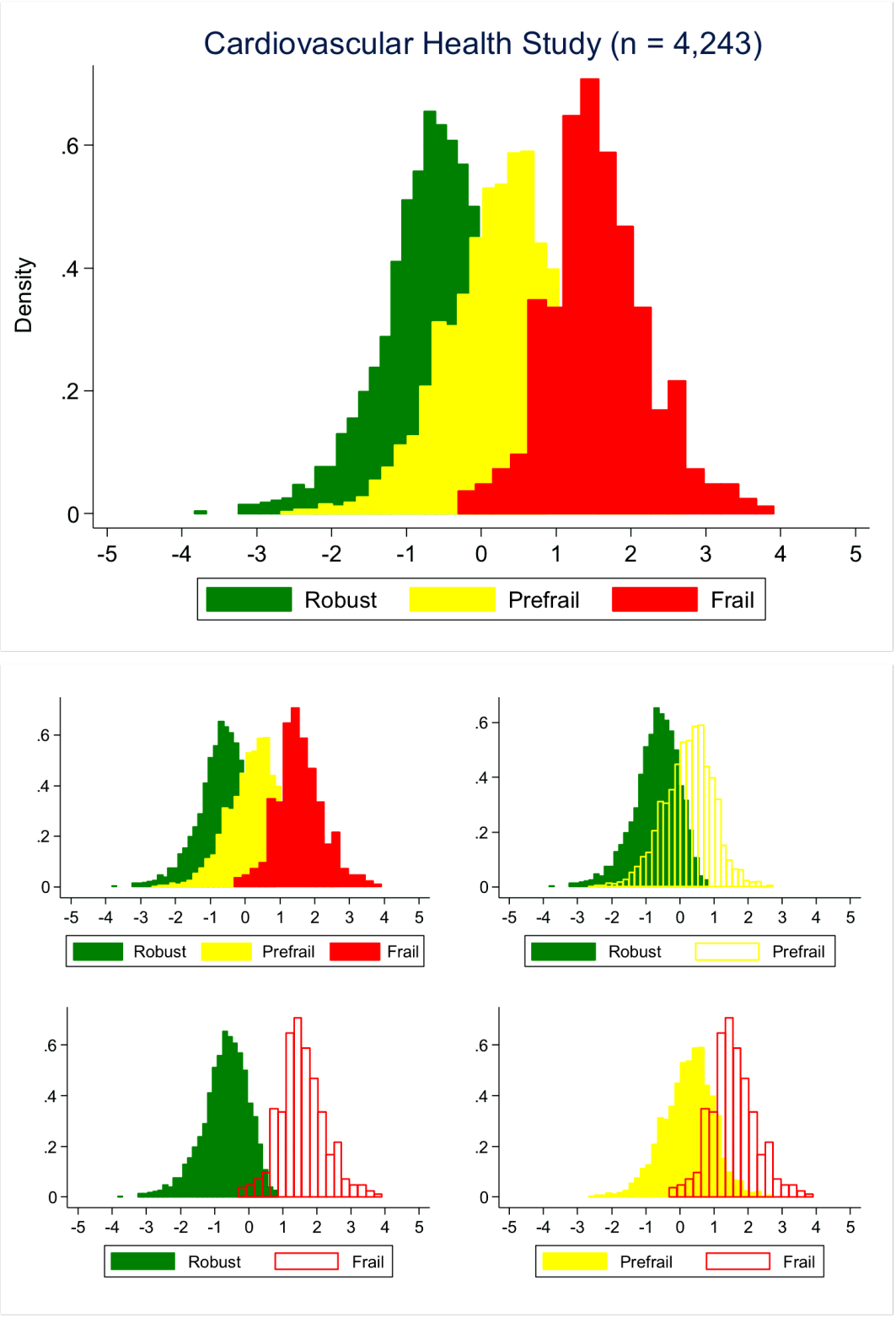
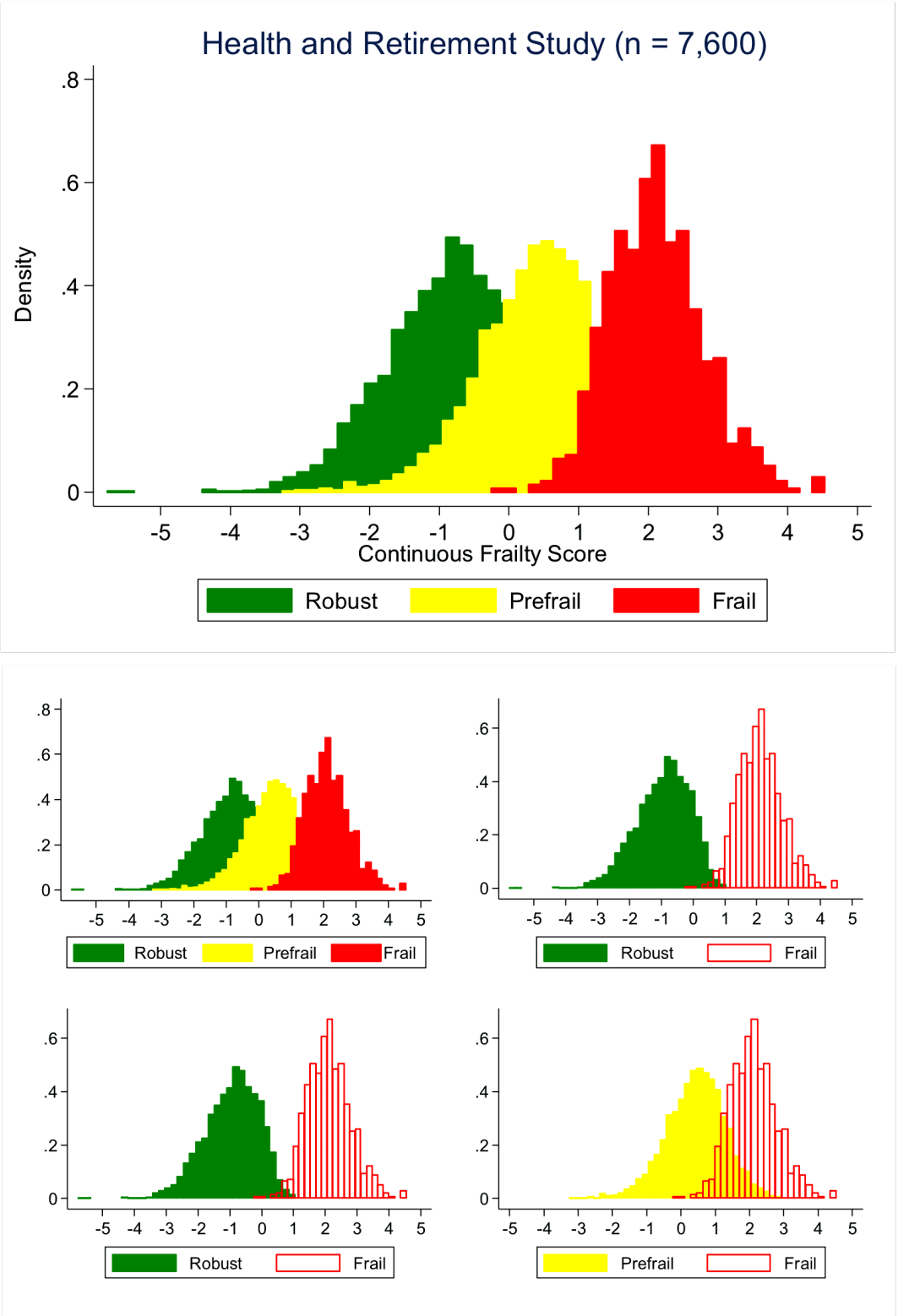


Figure 3–5B. Distribution of continuous frailty score by frailty status identified by the physical frailty phenotype scale, Health and Retirement Study.



CHAPTER 4: PREDICTIVE VALIDITY OF THE CONTINUOUS FRAILTY SCALE

4.1. Introduction

In a recent consensus meeting comprising experts in the field of frailty, researchers claimed that numerous assessments of frailty were well validated for predictive validity—the extent to which frailty is associated with future health outcomes.[89] In many of these investigations, however, the prognostic value of frailty has been gauged only by statistical significance and magnitude of association. New literature has demonstrated that traditional methods based on magnitude of association are not suitable for evaluating a diagnostic or prognostic marker and may have serious pitfalls.[90] In addition, existing validations of frailty rarely report indices of model performance except for the C statistic, which may lead to overestimation of the overall prognostic value of frailty. A comprehensive evaluation of the predictive validity of frailty assessments may provide more convincing evidence about the utility of frailty in research and clinical practice.

The purpose of this chapter was three-fold. First, I comprehensively evaluated the performance of the newly developed continuous frailty scale in predicting adverse outcomes, including mortality, disability, hip fracture, and falls. I hypothesized that frailty, as assessed by the continuous frailty scale, would be associated with mortality, disability, hip fracture, and falls, respectively, independent of socio-demographic, behavioral, health, and clinical covariates. Second, I examined the association of the continuous frailty score with outcomes among robust, prefrail, and frail persons identified by the physical frailty phenotype (PFP) scale. I hypothesized that the continuous frailty scale would provide additional value in risk stratification of outcomes beyond the PFP scale, and would therefore be associated with outcomes among robust, prefrail,

and frail persons, respectively. Third, I compared the predictive validity between the frailty assessments. The hypothesis was that the continuous frailty scale would have better performance in predicting outcomes than the PFP scale.

4.2. Methods

4.2.1. Analytic Sample

Cardiovascular Health Study

Detailed description of the Cardiovascular Health Study (CHS) was presented in Section 3.2.1. I used the 1992-93 and 1996-97 examinations, when all five variables used for constructing the continuous frailty scale were available. These two periods (1992-93 and 1996-97) served as the baseline for the original and new CHS cohorts, respectively, for subsequent analyses in this chapter. The analytic sample was limited to participants who had complete data on five frailty indicators (gait speed, grip strength, exhaustion, physical activity, and weight loss).

Health and Retirement Study

Detailed description of the Health and Retirement Study (HRS) was presented in Section 3.2.1. I used pooled data from the 2006-07 and 2008-09 survey waves of the HRS, when gait speed and grip strength—two key components of frailty—were measured. These two periods (2006-07 and 2008-09) served as the baseline for subsequent analyses of the HRS cohort in this chapter. The analytic sample of the HRS was restricted to participants who (i) were ≥65 years, (ii) reported sex and race/ethnicity, and (iii) had complete data on all five frailty indicators.

4.2.2. Frailty

Frailty was measured in two ways: the new continuous frailty scale and the PFP scale. Details of operational definitions of five measures used to construct the two frailty assessments were described in Section 3.2.3.1. For the continuous frailty scale, standardized score for each of the five frailty indicators was first calculated by dividing the difference between observed value and the sample mean by the standard deviation (separately for two cohorts). Then, five standardized scores were summed to create the continuous frailty score, weighted by the standardized factor loadings identified using confirmatory factor analysis (CFA; Table 3–4). In the PFP scale, participants were classified as robust, prefrail, and frail using all participants with complete data on five frailty indicators as reference population (analyzed separately; N = 4,243 in the CHS; N = 7,600 in the HRS). Five criteria of the PFP scale were provided in Chapter 3.

4.2.3. Outcomes

Mortality. Mortality data in the CHS were obtained according to review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care utilization database for hospitalizations and from household contacts; 100% complete follow-up for ascertainment of mortality status was achieved through intensive surveillance.[265] Vital status and date of death in the HRS were ascertained based on a variable recording participants' year of death taken from an exit interview or a partner's core interview. Mortality was ascertained on 7,519 (98.9%) HRS participants through April 2015. Participants were censored when lost to follow-up or the end of the analytic period (April 2014). Because the overall follow-up period differed substantially between the two cohorts (16.1 years for the CHS and 9.0 years for the HRS), I examined 5-year mortality to facilitate comparability. Participants were censored (i.e.,

considered alive) if they survived more than five years regardless of their actual survival status by the end of the study period.

Disability. Disability was assessed by difficulty in activities of daily living (ADLs) in both cohorts. Every year, the CHS participants were asked "Do you have difficulty or are unable …" to preform each of six basic daily activities: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room. Every two years, the HRS participants were asked "Because of a health or memory problem do you have any difficulty with each of six ADLs". Participants who responded "Yes" and "No" were considered having and not having difficulty, respectively. Participants who answered "Can't do" were considered having difficulty; those who reported "Don't do", "Don't know or not ascertained", or "Refused" were coded as missing. Participants who had difficulty in at least one ADL were considered having ADL disability (dichotomous). I examined 2-year incident ADL disability among persons who were not disabled at baseline (independent of all six ADLs). Of the 3,807 CHS participants who were non-disabled at baseline, 3,281 (86.2%) had ADL measures in the following two years (two annual assessments). Of the 6,454 HRS participants who were non-disabled at baseline, 5,949 (92.2%) had ADL measures in the following visit two years since baseline. Persons who were non-disabled at baseline but did not have ADL measures in the following visits due to any reason (e.g., loss to follow-up) were excluded from the primary analysis of disability.

Hip fracture. Occurrence and timing of hip fracture in the CHS was ascertained by self-report every 6 months (time-to-event outcome); 100% complete follow-up for ascertainment of hip fracture achieved in the CHS. In the HRS, participants were asked, "Have you broken your hip

since I talked in previous wave?" Participants who responded "Yes" and "No" were considered having and not having hip fracture, respectively. "Don't know or not ascertained" or "Refused" was coded as missing. Because the incidence rates of hip fracture were low in both cohorts, I examined incident hip fracture over a 6-year period—three biennial follow-up visits in the HRS—to allow adequate statistical power and to ensure comparability of the two cohorts. CHS participants were censored (i.e., considered not experiencing hip fracture) if they did not experience hip fracture within six years since baseline. Of the 4,243 CHS participants with frailty assessment, 29 experienced hip fracture prior to the assessment of frailty and were therefore excluded from the analysis of hip fracture. Of the 7,600 HRS participants with frailty assessment, 5,473 (72.0%) reported whether they had experienced hip fracture since previous wave in all three biennial follow-up visits. Participants who did not have measure of hip fracture in any of three follow-up visits were excluded from the analysis of hip fracture.

Falls. Occurrence and frequency of falls was evaluated based on self-report in both cohorts (evaluated every six months in the CHS and every two years in the HRS). "Don't know or not ascertained" or "Refused" were coded as missing. I examined incident falls over a 2-year period (corresponding to one biennial follow-up visit in the HRS). Of the 4,243 CHS participants with frailty assessment, 3,862 (91.0%) had measure of falls in the following two annual visits. Of the 7,600 HRS participants with complete data on five frailty components, 6,885 (90.6%) had falls in the following visit two years since baseline. Participants who did not have measure of falls in the following visits were excluded from the analysis of falls.

4.2.4. Analytic Approaches

I first compared persons who had and did not have data on outcomes—mortality, ADL disability, hip fracture, and falls—using a t-test with unequal variance for continuous variables and a χ^2 test for categorical variables. Each outcome was analyzed separately; each of the two cohorts were analyzed individually.

I calculated crude 5-year death rate and rate of incident hip fracture over six years per 1,000 person-years (PYs) across quintiles of the continuous frailty scale among the CHS participants. I calculated the numbers and proportions of CHS participants who had incident ADL disability over two years and incident falls over two years stratified by quintiles of the continuous frailty score. Cox proportional hazards models were used to determine the associations of frailty with all-cause mortality and hip fracture, respectively. I used Poisson models with robust variance estimator to assess the associations of frailty with ADL disability and falls, respectively. Compared with the logistic model, the Poisson model with robust variance estimator could provide approximate estimate of relative risk (RR)—an estimate that is more interpretable and more relevant to public health practice than an odds ratio. Log-binomial model is another alternative to provide unbiased estimate of RR;[266] however, the log-binomial model did not converge when estimating multivariable adjusted RR in the present study. This is a well-known drawback of using the log-binomial model to estimate RR for binary outcomes.[267,268] The continuous frailty scale was modeled both continuously and in quintiles with the 1st quintile being the reference. Clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh; categorical), age (years; continuous), sex (male or female), race/ethnicity (white or others), education (less than high school, high school or equivalent, or more than high school; categorical), smoking

status (current, previous, or never smokers; categorical), body mass index (BMI; <25.0, 25.0-30.0, or >30.0; categorical), history of coronary heart disease (yes or no), heart failure (yes or no), stroke (yes or no), hypertension (not hypertensive, borderline hypertensive, or hypertensive; categorical), diabetes (no diabetes, prediabetes, diabetes; categorical), cancer (yes or no), and arthritis (yes or no), self-rated health (continuous), cognitive function assessed by the Modified Mini-Mental State Examination (3MS; continuous), ADL disability (yes or no; not included in the analysis of ADL disability), systolic and diastolic blood pressure (BP, mmHg; continuous), C-reactive protein (CRP, μg/L; continuous), cystatin C (mg/L; continuous), total cholesterol (mg/dL; continuous), and fasting glucose (mg/dL; continuous) were included in the multivariable adjusted models. Operational definitions of covariates in the CHS were described in Section 3.2.3.2.

To evaluate whether the continuous frailty scale provided additional value in stratifying risk of adverse outcomes beyond the PFP scale, I assessed the association of the continuous frailty scale with four outcomes, respectively, among robust, prefrail, and frail persons identified by the PFP scale. I first computed rates for death and hip fracture and numbers and proportions for ADL disability and falls across quintiles of the continuous frailty scale among robust and prefrail persons. Results were not presented for frail persons because, in both cohorts, vast majority of them were in the 5th quintile of the continuous frailty scale (Table 3–10). Subsequently, I used Cox models to assess the association of frailty with mortality and hip fracture among robust, prefrail, and frail persons. The continuous frailty scale was modeled both continuously and in quintiles for the robust and prefrail, but only as a continuous predictor for the frail (vast majority

of frail persons had continuous frailty scores in the 5th quintile). Poisson models with robust variance estimator were used for ADL disability and falls.

I repeated all above analyses in the HRS cohort with a few modifications. First, because hip fracture was a binary instead of a time-to-event outcome in the HRS, I presented numbers and proportions of HRS participants who had hip fracture across quintiles of the continuous frailty score. Second, because hip fracture was a binary outcome in the HRS, instead of using Cox models (hip fracture was a time-to-event outcome in the CHS), Poisson models with robust variance estimates were utilized to identify the association of frailty with hip fracture. Third, age (years; continuous), sex (male or female), race/ethnicity (white or others), education (less than high school, high school or equivalent, or more than high school; categorical), smoking status (current, previous, or never smokers; categorical), BMI (<25.0, 25.0-30.0, or >30.0; categorical), history of cardiac disease (yes or no), stroke (yes or no), hypertension (yes or no), lung disease (yes or no), diabetes (yes or no), cancer (yes or no), and arthritis (yes or no), self-rated health (continuous), cognitive function assessed by the Telephone Interview for Cognitive Status (TICS; continuous), ADL disability (yes or no; not in the analysis of ADL disability), systolic and diastolic BP (mmHg; continuous), CRP (μg/L; continuous), cystatin C (mg/L; continuous), total and high-density lipoprotein (HDL) cholesterol (mg/dL; continuous), and glycosylated hemoglobin (HbA1c; %) were included in the multivariable adjusted models. Lastly, robust standard errors were used to account for the nested data structure in the HRS—participants were clustered within households. Details of how covariates were measured in the HRS were described in Section 3.2.3.3.

I used logistic models to assess the predictability of the continuous frailty scale and the PFP scale for four outcomes, respectively. All models assessing predictive performance were adjusted for age and sex only because the objective was to compare predictability between the two frailty assessments. Model performance within each cohort was evaluated using overall goodness of fit, discrimination, calibration, and reclassification.

Overall goodness of fit was assessed by the Nagelkerke's R^2, a commonly used index for assessing overall model performance for generalized linear models.[269,270] The Nagelkerke's R^2 (range: 0-1) is calculated based on the log-likelihood of the fitted model compared with the log-likelihood of an empty model (i.e., only intercept is included).

Discrimination performance was assessed by the C statistic, also known as the integrated area under the receiver operating characteristic (ROC) curve. The C statistic assesses how well a model distinguishes cases (i.e., persons who have the event) and non-cases (i.e., persons who do not have the event), and ranges from 0.5 (no better than chance alone) to 1.0 (perfect discrimination). A C statistic of 0.7, for instance, means that 70% of the time the predicted risk from the model for a case is greater than the predicted risk for a non-case. I also used the discrimination slope, which indicates the difference between the mean predicted risk of cases and non-cases, to evaluate discrimination.

I assessed calibration performance using the Hosmer-Lemeshow statistic, which measures how well the predicted event proportions match the observed event proportions over sub-categories

(usually deciles) of predicted risk.[271] I also summarized the mean predicted and observed risk across all deciles of the predicted risks.

Reclassification was measured by the category-free net reclassification index (NRI >0)[272] and the integrated discrimination index (IDI).[273] NRI (>0) and IDI have been increasingly used in the past decade as supplementary tools to evaluate the utility of adding a new marker in the existing prediction model. The NRI (>0) is a sum of two conceptually similar components: event NRI calculated based on cases and nonevent NRI calculated based on non-cases. The event NRI is calculated as the proportion of cases for whom the predicted risk from the new model is higher than the predicted risk from the baseline model (correctly reclassified) minus the proportion of cases for whom the predicted risk from the new model is lower than the predicted risk from the baseline model (incorrectly reclassified). Age in years and sex were adjusted in the baseline model. Similarly, the nonevent NRI is computed as the proportion of non-cases for whom the predicted risk from the new model is lower than the predicted risk from the baseline model (correctly reclassified) minus the proportion of cases for whom the predicted risk from the new model is higher than the predicted risk from the baseline model (incorrectly reclassified). The IDI indicates the absolute change in mean risk for cases compared with non-cases over the baseline model.

Bootstrap confidence intervals were computed for point estimates of model performance indices when asymptotic intervals were unavailable. All tests were two-sided with a significance level of $p < .05$. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX)[253] and the R Language for Statistical Computing 3.2.2.[274]

4.3. Results

Association of Frailty with All-cause Mortality

Over five years of follow-up, 713 (16.8%) deaths occurred and the rate of all-cause mortality was 36.1 per 1000 PYs for 4,243 CHS participants (Table 4–1A). Crude 5-year death rates were 18.5, 22.0, 26.0, 42.2, and 76.7 per 1000 PYs for persons with the continuous frailty scores in the 1st, 2nd, 3rd, 4th, and 5th quintile, respectively. In unadjusted models, hazard of death was 76% (95% confidence interval [CI]: 63%, 89%) higher per unit of the continuous frailty scale. The continuous frailty scale persisted to be associated with mortality after multivariable adjustment; hazard of death was 24% (95% CI: 12%, 36%) higher per unit of the continuous frailty scale. Compared with persons with the continuous frailty scores in the lowest quintile, hazard of death was 1.44 (95% CI: 1.06, 1.96) and 1.85 (95% CI: 1.35, 2.53) for those in the 4th and 5th quintile, respectively.

Of the 7,519 HRS participants who had mortality data (81 were missing), 1,248 (16.6%) died and the 5-year mortality rate was 35.8 per 1000 PYs (Table 4–1B). Crude death rates were 10.7, 16.4, 24.4, 49.5, and 87.4 per 1000 PYs for persons with the continuous frailty scores in the 1st, 2nd, 3rd, 4th, and 5th quintile, respectively. In multivariable adjusted model, hazard of death was 48% (95% CI: 40%, 57%) higher per unit of the continuous frailty scale. Compared with persons with the lowest frailty scores (1st quintile), the hazard of death was more than two (hazard ratio [HR] = 2.80, 95% CI: 2.17, 3.62) and almost four times (HR = 3.98, 95% CI: 3.06, 5.18) higher among those with the scores in the 4th and 5th quintile, respectively.

In the CHS, there was a clear increasing trend in death rates with higher continuous frailty scores among robust and prefrail persons identified by the PFP scale (Table 4–2A). Among 1,905 robust persons, the death rates ranged from 16.9 per 1000 PYs among those with the continuous frailty scores in the lowest quintile to 27.0 per 1000 PYs among those in the 4th or 5th quintile (only four robust persons were in the 5th quintile). Of the 1,982 prefrail persons, the death rate was approximately 2.5 times higher among those with the highest continuous frailty scores (5th quintile) than those in the lowest (65.0 vs. 26.1 per 1000 PYs). In multivariable adjusted models, the continuous frailty score was significantly associated with higher hazard of death among the prefrail (HR = 1.26, 95% CI: 1.07, 1.50) but not the robust or the frail.

In the HRS cohort, the continuous frailty score stratified the robust, prefrail, and frail persons by risk of death (Table 4–2B). After multivariable adjustment, each higher unit of the continuous frailty score was associated with 44%, 41%, and 31% greater hazard of death among robust, prefrail, and frail persons, respectively.

In the CHS, the Nagelkerke's R^2 increased from 0.13 for the PFP scale to 0.15 for the continuous frailty scale (Table 4–3A). The C statistic and the discrimination slope were similar for the two frailty assessments. Inclusion of either frailty assessment in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–1; *p's* <. 001). Both frailty assessments had an IDI of 0.03, indicating an absolute increase of 3% in average risk for persons with events (died) compared with those without events (alive) over the baseline model—model where age and sex were adjusted. The Hosmer-Lemeshow statistic was not significant for either frailty assessment, and the average predicted risk was within 5 percentage points of the average

observed risk in each decile of the predicted risks (Figure 4–2A). The category-free NRI (NRI>0) increased from 0.27 for the PFP scale to 0.41 for the continuous frailty scale (Δ NRI>0 = 0.14, 95% CI: 0.05, 0.23). The event NRI decreased from 0.22 for the PFP scale to 0.16 for the continuous frailty scale, although the difference was not statistically significant (Δ event NRI = -0.06, 95% CI: -0.21, 0.13). The non-event NRI increased from 0.05 for the PFP scale to 0.25 for the continuous frailty scale (Δ non-event NRI = 0.20, 95% CI: 0.11, 0.28).

In the HRS, the Nagelkerke's R^2 increased from 0.19 for the PFP scale to 0.21 for the continuous frailty scale (Table 4–3B). The C statistic increased from 0.75 for the PFP scale to 0.76 for the continuous frailty scale (Δ C statistic = 0.02, 95% CI: 0.01, 0.03). Inclusion of either frailty assessment in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–1; *p's* <. 001). The discrimination slope increased from 0.13 for the PFP scale to 0.14 (Δ discrimination slope = 0.01, 95% CI: 0.00, 0.04) for the continuous frailty scale. For both frailty assessments, the Hosmer-Lemeshow statistic was not significant, and the average predicted risk was within 3 percentage points of the average observed risk in each decile of the predicted risks (Figure 4–2B). When compared with the age- and sex-adjusted model, the PFP scale had an IDI of 0.04 as opposed to 0.06 for the continuous frailty scale (Δ IDI = 0.02, 95% CI: 0.01, 0.02). The NRI (>0) increased from 0.33 for the PFP scale to 0.53 for the continuous frailty scale (Δ NRI>0 = 0.20, 95% CI: 0.09, 0.29). The event NRI was the same for the two frailty assessments. The non-event NRI increased from 0.10 for the PFP scale to 0.30 for the continuous frailty scale (Δ non-event NRI = 0.20, 95% CI: 0.11, 0.27).

Association of Frailty with Incident Disability

Of the 3,807 CHS participants who had no difficulty in any ADLs at baseline, 3,281 (86.2%) were alive and had complete measure of ADL disability within two years. Among 6,454 HRS participants who were non-disabled at baseline, 5,949 (92.2%) were alive and had data on ADL disability within two years. In both cohorts, persons who died or did not have measure of ADL disability in two years since baseline were older, less educated, and more likely to be current smokers, had higher prevalence of chronic conditions, lower cognitive function, higher levels of CRP and cystatin C, and higher level of frailty compared with those who were alive and had complete measure of ADL disability (analytic sample; Tables 4–4A & 4–4B).

The continuous frailty scale stratified the CHS participants by risk of ADL disability (Table 4–5A). Of the 3,281 initially non-disabled persons, the crude proportion of ADL disability increased from 8.4% among those with the lowest continuous frailty scores (1st quintile) to 41.4% among those in the highest quintile. The unadjusted risk of ADL disability was 84% (95% CI: 72%, 97%) higher per unit of the continuous frailty scale. The continuous frailty scale persisted to be associated with ADL disability after multivariable adjustment; risk of ADL disability was 53% (95% CI: 39%, 68%) greater per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5th quintile) had 2.96-fold (95% CI: 2.17, 4.02) higher risk of ADL disability than those with the lowest frailty scores (1st quintile).

There was a steep risk gradient for ADL disability across the continuous frailty score in the HRS cohort (Table 4–5B). The crude proportion of ADL disability in persons with the highest continuous frailty scores (5th quintile) was more than 8-fold greater than those in the lowest quintile (32.5% vs. 3.9%). After multivariable adjustment, risk of ADL disability was 50% (95%

CI: 40%, 61%) higher per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5th quintile) had 3.85-fold (95% CI: 2.83, 5.25) higher risk of ADL disability than those with the lowest frailty scores (1st quintile).

There was a clear increasing trend in risk of ADL disability with higher continuous frailty scores among robust and prefrail CHS participants (Table 4–6A). Among 1,657 robust persons, the proportion of ADL disability ranged from 7.4% among those with the continuous frailty scores in the 1st quintile to 28.7% among those in the 4th or 5th quintile (only four robust persons were in the 5th quintile). Of the 1,459 prefrail persons, the proportion of ADL disability was 38.5% among those with the highest continuous frailty scores (5th quintile) as opposed to 13.5% among those with lowest frailty scores (1st quintile). In multivariable adjusted models, risk of ADL disability was 57% (95% CI: 19%, 107%) and 44% (95% CI: 23%, 69%) greater per unit of the continuous frailty scale among the robust and prefrail, respectively. The unadjusted risk of ADL disability was 38% (95% CI: 9%, 77%) higher per unit of the continuous frailty scale among the frail, although the association was not significant after multivariable adjustment.

In the HRS, the continuous frailty scale stratified robust, prefrail, and frail persons by risk of ADL disability (Table 4–6B). After multivariable adjustment, each higher unit of the continuous frailty score was associated with 34%, 43%, and 55% greater risk of ADL disability among robust, prefrail, and frail persons, respectively.

In the CHS, the Nagelkerke's R^2 increased from 0.10 for the PFP scale to 0.13 for the continuous frailty scale (Table 4–7A). The C statistic increased from 0.68 for the PFP scale to 0.70 for the

continuous frailty scale (Δ C statistic = 0.02, 95% CI: 0.01, 0.04). Inclusion of either frailty assessment in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–3; *p's* <. 001). The discrimination slope increased from 0.07 for the PFP scale to 0.09 for the continuous frailty scale (Δ discrimination slope = 0.03, 95% CI: 0.01, 0.05). The Hosmer-Lemeshow statistic was not significant for either of the two frailty assessments, and the average predicted risk was within 3 percentage points of the average observed risk in each decile of the predicted risks (Figure 4–4A). The IDI increased from 0.04 for the PFP scale to 0.07 for the continuous frailty scale (Δ IDI = 0.03, 95% CI: 0.02, 0.05). The NRI (>0) increased from 0.47 for the PFP scale to 0.55 for the continuous frailty scale (Δ NRI>0 = 0.09, 95% CI: 0.01, 0.19). The event NRI decreased from 0.35 for the PFP scale to 0.26 for the continuous frailty scale, although the difference was not statistically significant (Δ event NRI = -0.08, 95% CI: -0.17, 0.02). The non-event NRI increased from 0.12 for the PFP scale to 0.29 for the continuous frailty scale (Δ non-event NRI = 0.17, 95% CI: 0.12, 0.22).

In the HRS, the Nagelkerke's R^2 increased from 0.12 for the PFP scale to 0.15 for the continuous frailty scale (Table 4–7B). The C statistic increased from 0.71 for the PFP scale to 0.74 for the continuous frailty scale (Δ C statistic = 0.03, 95% CI: 0.02, 0.05). Inclusion of either frailty assessment in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–3; *p's* <. 001). The discrimination slope increased from 0.08 for the PFP scale to 0.10 for the continuous frailty scale (Δ discrimination slope = 0.02, 95% CI: 0.01, 0.04). For both frailty assessments, the Hosmer-Lemeshow statistic was not significant, and the average predicted risk was in 3 percentage points of the average observed risk within each decile of the predicted risks (Figure 4–4B). When compared with the age- and sex-adjusted baseline model,

the PFP scale had an IDI of 0.04 as opposed to 0.06 for the continuous frailty scale (Δ IDI = 0.02, 95% CI: 0.01, 0.03). The NRI (>0) increased from 0.49 for the PFP scale to 0.53 for the continuous frailty scale (Δ NRI>0 = 0.04, 95% CI: 0.01, 0.08). The event NRI decreased from 0.37 for the PFP scale to 0.23 for the continuous frailty scale (Δ event NRI = -0.14, 95% CI: -0.27, -0.01). The non-event NRI increased from 0.12 for the PFP scale to 0.31 for the continuous frailty scale (Δ non-event NRI = 0.19, 95% CI: 0.13, 0.23).

Association of Frailty with Incident Hip Fracture

Information about occurrence and timing of hip fracture was available to all CHS participants; participants were censored when they died or were lost to follow-up. Of the 7,600 HRS participants who had frailty assessment at baseline, 5,473 (72.2%) were alive and had data on hip fracture in six years, corresponding to three biennial follow-up visits. HRS participants who died or did not have measure of hip fracture in all three follow-up visits were older, more likely to be men, less educated, and more likely to be current smokers, had higher prevalence of chronic conditions (including cardiac disease, stroke, hypertension, lung disease, diabetes, and cancer) and ADL disability, lower cognitive function, and higher levels of CRP, cystatin C, and frailty than those who were alive and had complete measure of hip fracture in six years (analytic sample; Table 4–8).

Of the 4,219 CHS participants, 169 incident hip fractures occurred over six years and the rate was 6.8 per 1000 PYs (Table 4–9A). The continuous frailty scale stratified the rate of hip fracture among the CHS participants. Crude rates were 2.6, 3.7, 8.2, 9.0, and 10.6 per 1000 PYs for persons with the continuous frailty scores in the 1st, 2nd, 3rd, 4th, and 5th quintile, respectively.

The unadjusted hazard of hip fracture was 56% (95% CI: 34%, 81%) higher per unit of the continuous frailty scale. After multivariable adjustment, hazard was 34% (95% CI: 9%, 65%) greater per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5^{th} quintile) had 3.08-fold (95% CI: 1.45, 6.57) higher hazard of hip fracture than those with lowest frailty scores (1^{st} quintile).

I observed a steep risk gradient for hip fracture across the continuous frailty score in the HRS cohort (Table 4–9B). The crude proportion of having hip fracture in persons with the highest continuous frailty scores (5^{th} quintile) was more than 7-fold greater than those with lowest frailty scores (1^{st} quintile; 9.5% vs. 1.3%). After multivariable adjustment, risk of hip fracture was 37% (95% CI: 22%, 55%) greater per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5^{th} quintile) had 3.14-fold (95% CI: 1.77, 5.60) higher risk of hip fracture than those with lowest frailty scores (1^{st} quintile).

I found evidence that the risk of hip fracture increased with higher continuous frailty scores among the robust CHS participants (Table 4–10A). Of the 1,900 robust persons, the crude rate of incident hip fracture was 10.7 per 1000 PYs among those with continuous frailty scores in the 4^{th} or 5^{th} quintile as opposed to 2.9 per 1000 PYs for those with the frailty scores in the 1^{st} quintile. After multivariable adjustment, hazard of hip fracture was 92% higher per unit of the continuous frailty scale among the robust.

The continuous frailty score stratified the risk of hip fracture among the robust, prefrail, and frail persons from the HRS cohort (Table 4–10B). After multivariable adjustment, each higher unit of

the continuous frailty scale was associated with 70%, 36%, and 83% greater risk of hip fracture among robust, prefrail, and frail persons, respectively.

In the CHS, the Nagelkerke's R^2 increased from 0.05 for the PFP scale to 0.06 for the continuous frailty scale (Table 4–11A). The C statistic and the discrimination slope were virtually the same between the two frailty assessments. Inclusion of the continuous frailty scale but not the PFP scale in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–5; $p = 0.037$). The Hosmer-Lemeshow statistic was not significant for either of the two frailty assessments, and the average predicted risk was within 3 percentage points of the average observed risk in each decile of the predicted risks (Figure 4–6A). The NRI (>0) increased from 0.24 for the PFP scale to 0.30 for the continuous frailty scale (Δ NRI>0 = 0.06, 95% CI: -0.01, 0.15). The event NRI decreased from 0.24 for the PFP scale to 0.14 for the continuous frailty scale, although the difference was not statistically significant (Δ event NRI = -0.09, 95% CI: -0.30, 0.15). The non-event NRI increased from 0.00 for the PFP scale to 0.16 for the continuous frailty scale (Δ non-event NRI = 0.16, 95% CI: 0.02, 0.33).

In the HRS, the Nagelkerke's R^2 increased from 0.13 for the PFP scale to 0.15 for the continuous frailty scale (Table 4–11B). Inclusion of the continuous frailty scale but not the PFP scale in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–5; $p = .007$). The Hosmer-Lemeshow statistic was not significant for either of the two frailty assessments, and the average predicted risk was within 3 percentage points of the average observed risk in each decile of the predicted risks (Figure 4–6B). The event NRI decreased from 0.32 for the PFP scale to 0.12 for the continuous frailty scale, although the difference was not

statistically significant (Δ event NRI = -0.20, 95% CI: -0.45, 0.05). The non-event NRI increased from 0.04 for the PFP scale to 0.22 for the continuous frailty scale (Δ non-event NRI = 0.18, 95% CI: 0.08, 0.29).

Association of Frailty with Incident Falls

Among 4,243 CHS participants who had frailty assessment at baseline, 3,862 (91.0%) were alive and had complete measure of falls within two years (reported every six months). Of the 7,600 HRS participants who had frailty assessment at baseline, 6,885 (90.6%) were alive and had data on falls in the following visit. In both cohorts, participants who died or did not have measure of falls in two years since baseline were older and less educated, had higher prevalence of chronic conditions, lower cognitive function, and higher levels of CRP, cystatin C, and frailty than those who were alive and had measure of falls (analytic sample; Tables 4–12A & 4–12B).

The continuous frailty scale stratified the CHS participants by risk of falls (Table 4–13A). The crude proportion of falls was almost doubled (41.9% vs. 21.1%) among persons with the lowest continuous frailty scores (1st quintile) than those in the highest quintile. Unadjusted risk of falls was 33% (95% CI: 27%, 40%) higher per unit of the continuous frailty scale. After multivariable adjustment, risk of falls was 23% (95% CI: 15%, 31%) greater per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5th quintile) had 56% (95% CI: 28%, 89%) higher risk of falls than those with lowest frailty scores (1st quintile).

I observed a risk gradient for 2-year incident falls across the continuous frailty score in the HRS cohort (Table 4–13B). The crude proportion of falls increased from 28.4% among persons with

the lowest continuous frailty scores (1st quintile) to 50.0% among those with the highest frailty scores (5th quintile). After multivariable adjustment, risk of falls was 9% (95% CI: 6%, 13%) greater per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5th quintile) had 33% (95% CI: 18%, 49%) higher risk of falls than those with lowest frailty scores (1st quintile).

The continuous frailty scale stratified by risk of incident hip fracture among the robust, prefrail, and frail persons in the HRS cohort (Table 4–14A). Of the 1,793 robust persons, the crude proportion of incident falls increased from 20.8% among those with the continuous frailty scores in the 1st quintile to 34.7% among those in the 4th or 5th quintile (only four robust persons were in the 5th quintile). Among 1,783 prefrail persons, the proportion of incident falls was almost doubled (40.1% vs. 22.7%) among those with the highest continuous frailty scores (5th quintile) than those with lowest frailty scores (1st quintile). After multivariable adjustment, risk of falls was 12%, 25%, and 28% higher per unit of the continuous frailty scale among robust, prefrail, and frail persons, respectively.

In the HRS cohort, the continuous frailty scale stratified the risk of falls among the prefrail and the frail but not the robust (Table 4–14B). After multivariable adjustment, each higher unit of the continuous frailty score was associated with 5% and 14% greater risk of falls among the prefrail and the frail, respectively.

In the CHS, the Nagelkerke's R^2 increased from 0.05 for the PFP scale to 0.06 for the continuous frailty scale (Table 4–15A). The C statistic increased from 0.62 for the PFP scale to 0.63 for the

continuous frailty scale (Δ C statistic = 0.01, 95% CI: 0.00, 0.03). Inclusion of either of the two frailty assessments in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–7; *p's* <.01). The Hosmer-Lemeshow statistic was not significant for the continuous frailty scale only; the average predicted risk was within 5 percentage points of the average observed risk in each decile of the predicted risks for both frailty assessments (Figure 4–8A). The IDI increased from 0.01 for the PFP scale to 0.02 for the continuous frailty scale (Δ IDI = 0.01, 95% CI: 0.01, 0.02). The NRI (>0) increased from 0.16 for the PFP scale to 0.26 for the continuous frailty scale (Δ NRI>0 = 0.10, 95% CI: 0.01, 0.21). The event NRI increased from 0.08 for the PFP scale to 0.10 for the continuous frailty scale, although the difference was not statistically significant (Δ event NRI = 0.02, 95% CI: -0.14, 0.22). The non-event NRI increased from 0.07 for the PFP scale to 0.16 for the continuous frailty scale (Δ non-event NRI = 0.09, 95% CI: 0.01, 0.18).

In the HRS, the Nagelkerke's R^2 was the same for both frailty assessments (0.05; Table 4–15B). There was no difference in the C statistic or the discrimination slope between the two frailty assessments. Inclusion of either of the two frailty assessments in the age- and sex-adjusted baseline model significantly improved the C statistic (Figure 4–7; *p's* <.001). The Hosmer-Lemeshow statistic was not significant for only the PFP scale. For both frailty assessments, the average predicted risk was within 5 percentage points of the average observed risk in each decile of the predicted risks (Figure 4–8B). The IDI and NRI (>0) were similar between the two frailty assessments. The event NRI decreased from 0.19 for the PFP scale to 0.06 for the continuous frailty scale, although the difference was not statistically significant (Δ event NRI = -0.13, 95%

CI: -0.25, 0.01). The non-event NRI increased from 0.05 for the PFP scale to 0.14 for the continuous frailty scale (Δ non-event NRI = 0.09, 95% CI: 0.03, 0.14).

4.4. Discussion

In this chapter, I sought to (i) examine the association of the continuous frailty scale with adverse health outcomes, (ii) evaluate whether the continuous frailty scale could provide additional value in risk stratification of outcomes beyond the PFP scale, and (iii) compare the predictive validity between the continuous frailty scale and the PFP scale. I showed that the newly developed continuous frailty scale was strongly associated with all-cause mortality, ADL disability, hip fracture, and falls among older adults from two large, prospective cohort studies. In addition, I demonstrated that both frailty assessments had high predictive validity and the continuous frailty scale had slightly better performance for predicting outcomes than the PFP scale. Moreover, I found that the continuous frailty scale was strongly associated with adverse outcomes among elders who were classified as robust and prefrail by the PFP scale.

The newly developed continuous frailty scale was able to provide additional risk stratification for multiple geriatric outcomes above and beyond the categorical PFP scale, especially at the lower to middle end of the frailty continuum. These results suggest that the robust and the prefrail are two heterogeneous groups with different risks of developing unfavorable outcomes. Findings from the present study were echoed by an earlier study showing that the frailty index (FI) scores, constructed based on 46 deficits, were associated with poor self-rated health and high healthcare utilization among robust persons identified by a modified version of the PFP scale in the National Health Nutrition Examination Survey.[275] The authors concluded that the FI might be a

more sensitive assessment of frailty because the FI can stratify risk of outcomes into a broader spectrum than the PFP scale. In the present study, I demonstrated that the continuous frailty scale, developed based on the same five indicators used in the PFP scale, can achieve the same purpose—removing the ceiling effect of the original PFP scale (i.e., about half of the sample was scored 0 and classified as robust) and better differentiating the robust and those who were at an intermediate stage of frailty. The FI usually involves a long checklist of comorbidities, disability, and clinical conditions; the continuous frailty scale, in contrast, only includes five measures and differentiates frailty from disability and comorbidity. In this sense, the continuous frailty scale—a recalibration of the PFP scale—can improve risk stratification while not sacrificing specificity, which offers benefits to elucidate the physiological etiology of frailty and is essential for designing targeted interventions for frailty.[276]

In a recently published commentary, Cesari et al.[277] suggested that the PFP scale may be less sensitive to modifications than the FI because the PFP scale is a discrete scale with only three values while the FI is continuous. The continuous FI, therefore, could be more powerful to capture small but clinically meaningful changes in frailty status compared with the categorical PFP scale. However, the FI includes measures assessing numerous domains of health (e.g., disability, physical function, cognitive function, and diseases), all of which have specific pathogenesis and may require different interventions. A continuous version of the PFP scale may be more sensitive to detect change in frailty status than the categorical PFP scale and can be valuable in assessing the effectiveness of interventions and tracking trajectories of frailty over time.

The present study was among the first to evaluate the predictive validity of frailty assessments in a comprehensive fashion. Prior studies used only the C statistic to evaluate the prognostic value of frailty assessments and therefore may overestimate the overall predictive utility of frailty.[31,87,159,162,278] The C statistic, which indicates how well a model can distinguish cases and non-cases, is a commonly used measure of model discrimination. The C statistic, however, does not directly assess the clinical utility of a risk model because, in clinical practice, cases and non-cases do not usually present in pairs.[279] I comprehensively examined the predictive validity of the continuous frailty scale and the PFP scale using global goodness of fit, discrimination, calibration, and reclassification. Findings from this work provided strong evidence demonstrating the prognostic utility of the continuous frailty scale and the PFP scale in predicting multiple adverse outcomes among older adults. It is not surprising that the continuous frailty scale only had slightly better prediction performance than the PFP scale; both frailty assessments had the same five items, and the continuous frailty scale is essentially a weighted, continuous version of the PFP scale with weights determined by the strength of associations between five indicators and the underlying frailty construct.

The continuous frailty scale is a rescaled, continuous version of the PFP scale, these two similar frailty assessments, however, may serve very different purposes. The PFP scale classifies persons into three categories: robust, prefrail, and frail. This discrete nature is practitioner-friendly and may facilitate the implementation of frailty assessment into clinical practice.[277] Discrete classifications of frailty may also expedite risk stratification at a population level (i.e., prevalence), which helps evaluate the public health significance of frailty and provides information about socio-demographic and geographic disparities. On the other hand, the

continuous frailty scale provides a more sensitive measure of frailty than the categorical PFP scale, and therefore may be more suitable to evaluate the effectiveness of preventive or therapeutic interventions for frailty. In addition, the continuous frailty scale helps identify at-risk persons who are not frail yet and allows interventions to prevent them becoming frail. Moreover, the continuous frailty scale is potentially a more statistically powerful tool for identifying biomarkers for frailty to ultimately elucidate the underlying pathophysiology of frailty. By the same token, the continuous frailty scale may be used in genetic studies seeking to discover the biological basis of frailty. Frailty is an exceedingly complex phenotype that involves dysregulations of multiple physiological systems.[1-8] Any genetic effects of frailty are expected to be modest and are difficult to detect. Furthermore, the continuous frailty scale may offer benefits to describe the trajectories of frailty over time and allow interventions at an early stage. Gill et al.[207] reported that frailty is a dynamic process, but the likelihood of transitioning from being at an end stage of frailty (i.e., frail) to robust is extremely low, suggesting the importance of designing interventions for persons who are vulnerable but not yet frail.

This study has many strengths. First, I comprehensively examined the predictive validity of a newly developed continuous frailty scale in a large, heterogeneous sample with comprehensive set of measurements, and cross-validated all results externally using an independent sample with over seven thousand participants. Independent replication or validation of results, which has become a routine component of gene discovery studies, has been much less seen in epidemiological research. In a commentary for *Nature*, Collins and Tabak[280] discussed initiatives of the National Institute of Health (NIH) aimed at enhancing reproducibility of biomedical research. I believe that validation of results in an independent sample may play an important role

in self-correcting coincidental findings that happen to be statistically significant. In addition, this study is among the first to demonstrate that older adults who are identified as robust or prefrail by the PFP scale are two heterogeneous groups with different levels of frailty and vulnerability to adverse outcomes. Moreover, to my knowledge, this is the first study to evaluate and compare the predictive value of frailty assessments based on not only calibration but also other metrics including overall goodness of fit, discrimination, and reclassification. Lastly, most studies comparing multiple frailty assessments have focused on mortality; I evaluated the performance of the continuous frailty scale and the PFP scale for predicting mortality, disability, hip fracture, and falls.

In summary, I demonstrated that the newly developed continuous frailty scale was a useful frailty assessment for predicting mortality, ADL disability, hip fracture, and falls among community-dwelling older adults, using two large, population-based U.S. cohorts. The continuous frailty scale was able to provide risk stratification among older adults who were classified as robust and prefrail by the PFP scale, suggesting that persons who are at an early and intermediate stage frailty are two heterogeneous groups with different levels of frailty. The categorical PFP scale and the continuous frailty scale, both of which have been validated for construct and predictive validity, may serve different purposes. It is relatively easy to implement the PFP scale in clinical practice and use it to evaluate the public health significance of frailty (e.g., estimate prevalence). In contrast, the continuous frailty scale, due to its sensitive and continuous nature, may be more suitable for evaluating the effectiveness of interventions for frailty, depicting the trajectories of frailty over time, and discovering underlying genetic variants that are expected to have only modest effects.

Table 4–1A. Association of frailty with 5-year all-cause mortality among 4,243 adults, Cardiovascular Health Study.

Mortality	Rates per 1000 person-years	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Continuous frailty score		1.76 (1.63, 1.89)	1.24 (1.12, 1.36)
Quintiles			
1st quintile	18.5	Ref.	Ref.
2nd quintile	22.0	1.19 (0.88, 1.62)	1.04 (0.75, 1.44)
3rd quintile	26.0	1.41 (1.05, 1.90)	1.07 (0.78, 1.48)
4th quintile	42.2	2.32 (1.76, 3.04)	1.44 (1.06, 1.96)
5th quintile	76.7	4.30 (3.33, 5.54)	1.85 (1.35, 2.53)

Abbreviations: HR, hazard ratio; CI, confidence interval.
A total of 713 deaths occurred over five years and the rate was 36.1 per 1000 person-years.
[a] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

Table 4–1B. Association of frailty with 5-year all-cause mortality among 7,519 adults, Health and Retirement Study.

Mortality	Rates per 1000 person-years	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Continuous frailty score		1.83 (1.75, 1.92)	1.48 (1.40, 1.57)
Quintiles			
1st quintile	10.7	Ref.	Ref.
2nd quintile	16.4	1.54 (1.16, 2.05)	1.32 (0.99, 1.75)
3rd quintile	24.4	2.29 (1.76, 2.99)	1.72 (1.32, 2.26)
4th quintile	49.5	4.71 (3.69, 6.00)	2.80 (2.17, 3.62)
5th quintile	87.4	8.43 (6.67, 10.67)	3.98 (3.06, 5.18)

Abbreviations: HR, hazard ratio; CI, confidence interval.

Time-to-death information was not available for 81 participants in the Health and Retirement Study. A total of 1,248 deaths occurred over five years and the death rate was 35.8 per 1000 person-years.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–2A. Association of frailty with 5-year all-cause mortality among robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Cardiovascular Health Study.

Mortality	Rates per 1000 person-years	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Robust (n = 1,905)	20.4		
Continuous frailty score		1.36 (1.08, 1.71)	1.12 (0.87, 1.44)
Quintiles			
1st quintile	16.9	Ref.	Ref.
2nd quintile	17.9	1.06 (0.73, 1.54)	1.10 (0.73, 1.67)
3rd quintile	26.7	1.59 (1.10, 2.29)	1.05 (0.68, 1.61)
4th & 5th quintiles	27.0	1.61 (0.99, 2.61)	1.26 (0.74, 2.14)
Prefrail (n = 1,982)	42.2		
Continuous frailty score		1.64 (1.43, 1.89)	1.26 (1.07, 1.50)
Quintiles			
1st quintile	26.1	Ref.	Ref.
2nd quintile	31.3	1.21 (0.69, 2.12)	1.16 (0.62, 2.17)
3rd quintile	24.7	0.95 (0.55, 1.63)	0.87 (0.47, 1.61)
4th quintile	44.7	1.74 (1.06, 2.84)	1.17 (0.66, 2.08)
5th quintile	65.0	2.57 (1.57, 4.18)	1.51 (0.84, 2.71)
Frail (n = 356)[b]	97.4		
Continuous frailty score		1.08 (0.84, 1.39)	0.94 (0.69 ,1.27)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

[b] 93% of frail adults identified by the PFP scale were in the 5th quintile of the continuous frailty scale.

Table 4–2B. Association of frailty with 5-year all-cause mortality among robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Health and Retirement Study.

Mortality	Rates per 1000 person-years	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Robust (n = 3,335)	16.7		
Continuous frailty score		1.80 (1.50, 2.15)	1.44 (1.19, 1.73)
Quintiles			
1st quintile	10.0	Ref.	Ref.
2nd quintile	15.8	1.59 (1.15, 2.20)	1.30 (0.94, 1.81)
3rd quintile	23.1	2.34 (1.69, 3.24)	1.71 (1.21, 2.43)
4th quintile	48.6	4.99 (3.39, 7.36)	2.87 (1.86, 4.43)
5th quintile	n = 0	n = 0	n = 0
Prefrail (n = 3,410)	41.2		
Continuous frailty score		1.68 (1.53, 1.84)	1.41 (1.27, 1.57)
Quintiles			
1st quintile	16.4	Ref.	Ref.
2nd quintile	18.0	1.09 (0.58, 2.06)	0.96 (0.51, 1.80)
3rd quintile	25.6	1.56 (0.87, 2.79)	1.24 (0.70, 2.21)
4th quintile	49.5	3.05 (1.74, 5.33)	1.95 (1.11, 3.42)
5th quintile	64.3	3.99 (2.27, 7.01)	2.34 (1.32, 4.13)
Frail (n = 774)	110.5		
Continuous frailty score		1.56 (1.33, 1.82)	1.31 (1.11, 1.56)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–3A. Comparison in prediction of 5-year all-cause mortality between two frailty scales among 4,243 adults, Cardiovascular Health Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Death	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.13	.15
C statistic	.71 (.69, .73)	.72 (.70, .74)
Δ C statistic	Ref.	.01 (-.01, .04)
Discrimination slope	.09 (.08, .10)	.10 (.09, .11)
Δ Discrimination slope	Ref.	.01 (-.01, .03)
Hosmer-Lemeshow[c]	7.94 (p = .439)	3.33 (p = .912)
IDI[d]	.03 (.02, .04)	.03 (.02, .05)
Δ IDI	Ref.	.00 (-.01, .02)
NRI (>0)[e]	.27 (.14, .39)	.41 (.33, .49)
Δ NRI (>0)	Ref.	.14 (.05, .23)
Event NRI[e]	.22 (-.02, .38)	.16 (.11, .22)
Δ event NRI	Ref.	-.06 (-.21, .13)
Non-event NRI[e]	.05 (-.01, .18)	.25 (.21, .29)
Δ non-event NRI	Ref.	.20 (.11, .28)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[d] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[e] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–3B. Comparison in prediction of 5-year all-cause mortality between two frailty scales among 7,519 adults, Health and Retirement Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Death[c]	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.19	.21
C statistic	.75 (.73, .76)	.76 (.75, .78)
Δ C statistic	Ref.	.02 (.01, .03)
Discrimination slope	.13 (.12, .14)	.15 (.14, .15)
Δ Discrimination slope	Ref.	.02 (.01, .04)
Hosmer-Lemeshow[d]	3.66 (p = .886)	6.85 (p = .553)
IDI[e]	.04 (.03, .05)	.06 (.05, .07)
Δ IDI	Ref.	.02 (.01, .02)
NRI (>0)[f]	.33 (.24, .43)	.53 (.46, .58)
Δ NRI (>0)	Ref.	.20 (.09, .29)
Event NRI[f]	.23 (.09, .39)	.23 (.19, .27)
Δ event NRI	Ref.	.00 (-.16, .16)
Non-event NRI[f]	.10 (.03, .17)	.30 (.26, .33)
Δ non-event NRI	Ref.	.20 (.11, .27)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Death information was not available for 91 HRS participants.

[d] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[e] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[f] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–4A. Characteristics of initially non-disabled adults who had and did not have disability measures in two years, Cardiovascular Health Study.

Characteristics	ADL disability[a] Measured (n = 3,281)	ADL disability[a] Missing (n = 526)	*p* [b]
Age, years, mean (SD)	74.7 (4.8)	76.5 (5.4)	<.001
Male, No. (%)	1,411 (43.0)	244 (46.4)	.146
White (vs. Black), No. (%)	2,906 (88.6)	452 (85.9)	.081
Education			<.001
< High school, No. (%)	762 (23.3)	164 (31.3)	
= High school, No. (%)	944 (28.8)	158 (30.2)	
> High school, No. (%)	1,571 (47.9)	202 (38.6)	
Smoking status			.001
Never, No. (%)	1,472 (45.8)	199 (38.3)	
Former, No. (%)	1,450 (45.1)	254 (48.9)	
Current, No. (%)	293 (9.1)	66 (12.7)	
Body mass index, kg/m^2			.041
Underweight/normal[c], No. (%)	1,258 (38.3)	230 (43.7)	
Overweight, No. (%)	1,422 (43.3)	200 (38.0)	
Obese, No. (%)	601 (18.3)	96 (18.3)	
Coronary heart disease, No. (%)	662 (20.2)	138 (26.2)	.002
Heart failure, No. (%)	141 (4.3)	48 (9.1)	<.001
Stroke, No. (%)	123 (3.8)	33 (6.3)	.007
Hypertension			.014
Borderline, No. (%)	503 (15.4)	71 (13.5)	
Hypertensive, No. (%)	1,268 (38.7)	239 (45.4)	
Diabetes			.004
Prediabetes, No. (%)	313 (9.8)	46 (9.2)	
Diabetes, No. (%)	433 (13.6)	96 (19.1)	
Cancer[d], No. (%)	462 (14.1)	67 (12.8)	.043
Arthritis, No. (%)	1,401 (43.8)	216 (42.3)	.519
3MS[e], mean (SD)	91.9 (7.7)	88.8 (10.2)	<.001
Systolic BP, mmHg, mean (SD)	135.0 (20.8)	136.7 (22.4)	.116
Diastolic BP, mmHg, mean (SD)	70.9 (10.9)	70.1 (12.3)	.130
CRP, mg/L, mean (SD)	4.8 (9.1)	6.6 (12.0)	.002
Cystatin C, mg/L, mean (SD)	1.1 (0.3)	1.2 (0.4)	<.001
Total cholesterol, mg/dL, mean (SD)	208.9 (38.2)	202.9 (39.1)	.001
Fasting glucose, mg/dL, mean (SD)	106.9 (31.3)	110.6 (36.5)	.032
Continuous frailty score, mean (SD)	-0.2 (0.9)	0.1 (0.9)	<.001

Abbreviations: ADL, activities of daily living; SD, standard deviation; 3MS, Modified Mini-Mental State Examination; BP, blood pressure; CRP, C-reactive protein.

[a] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

[b] *p*-values were obtained from t test with unequal variance or χ^2 test for comparison between adults who had and who did not have measure of ADL disability in two years.

[c] Underweight and normal were collapsed due to small cell size in the underweight category.

[d] Non-melanoma skin cancer was excluded.

[e] Ranging from 0 to 100 with higher score indicating a better global cognitive function.

Table 4–4B. Characteristics of initially non-disabled adults who had and did not have disability measures in two years, Health and Retirement Study.

Characteristics	ADL disability[a] Measured (n = 5,949)	ADL disability[a] Missing (n = 505)	p [b]
Age, years, mean (SD)	74.2 (6.4)	77.1 (7.8)	<.001
Male, No. (%)	2,624 (44.1)	241 (47.7)	.117
White (vs. others), No. (%)	5,352 (90.0)	441 (87.3)	.060
Education			.002
< High school, No. (%)	1,302 (21.9)	137 (27.1)	
= High school, No. (%)	2,162 (36.4)	194 (38.4)	
> High school, No. (%)	2,484 (41.8)	174 (34.5)	
Smoking status			.001
Never, No. (%)	2,590 (43.8)	195 (38.8)	
Former, No. (%)	2,794 (47.3)	240 (47.7)	
Current, No. (%)	526 (8.9)	68 (13.5)	
Body mass index, kg/m^2, mean (SD)			<.001
Underweight/normal[c], No. (%)	1,566 (26.3)	193 (38.2)	
Overweight, No. (%)	2,320 (39.0)	174 (34.5)	
Obese, No. (%)	2.063 (34.7)	138 (27.3)	
Cardiac disease[d], No. (%)	1,655 (27.8)	197 (39.1)	<.001
Stroke, No. (%)	308 (5.2)	39 (7.8)	.015
Hypertension, No. (%)	3,689 (62.1)	329 (65.3)	.154
Lung disease, No (%)	573 (9.6)	75 (14.9)	<.001
Diabetes, No. (%)	1,165 (19.6)	125 (24.8)	.005
Cancer[e], No. (%)	1,073 (18.1)	126 (25.0)	<.001
Arthritis, No. (%)	3,878 (65.2)	321 (63.7)	.495
TICS[f], mean (SD)	9.4 (1.1)	9.0 (1.5)	<.001
Systolic BP, mmHg, mean (SD)	134.2 (20.5)	134.9 (22.2)	.496
Diastolic BP, mmHg, mean (SD)	78.6 (11.4)	77.5 (12.5)	.066
CRP, mg/L, mean (SD)	3.9 (7.8)	5.6 (12.5)	.008
Cystatin C, mg/L, mean (SD)	1.1 (0.4)	1.3 (0.6)	<.001
HDL cholesterol, mg/dL, mean (SD)	54.5 (15.8)	53.2 (16.3)	.115
Total cholesterol, mg/dL, mean (SD)	199.1 (41.6)	195.4 (43.6)	.093
HbA1c, %, mean (SD)	5.9 (0.9)	6.0 (1.1)	.004
Continuous frailty score, mean (SD)	-0.3 (1.2)	0.5 (1.2)	<.001

Abbreviations: ADL, activities of daily living; SD, standard deviation; TICS, the Telephone Interview for Cognitive Status; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.

[a] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

[b] p-values were obtained from t test with unequal variance or χ^2 test for comparison between adults who had and who did not have measure of ADL disability in two years.

[c] Underweight and normal were collapsed due to small cell size in the underweight category.

[d] Myocardial infarction, coronary heart disease, angina, heart failure, or other heart problems.

[e] Non-melanoma skin cancer was excluded.

[f] Ranging from 0 to 10 with higher score indicating a better global cognitive function.

Table 4–5A. Association of frailty with 2-year incidence of disability among 3,281 initially non-disabled adults, Cardiovascular Health Study.

ADL disability[b]	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Continuous frailty score		1.84 (1.72, 1.97)	1.53 (1.39, 1.68)
Quintiles			
1st quintile	64 (8.4%)	Ref.	Ref.
2nd quintile	91 (12.3%)	1.46 (1.08, 1.98)	1.36 (1.00, 1.87)
3rd quintile	113 (16.4%)	1.96 (1.47, 2.62)	1.45 (1.05, 1.98)
4th quintile	155 (25.0%)	2.98 (2.27, 3.91)	2.13 (1.57, 2.88)
5th quintile	193 (41.4%)	4.94 (3.82, 6.40)	2.96 (2.17, 4.02)

Abbreviations: RR, relative risk; CI, confidence interval; ADL, activities of daily living; FP, frailty phenotype.

[a] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

[b] Participants who reported having difficulty in any of six basic daily activities (dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room) were identified as having ADL disability.

Table 4–5B. Association of frailty with 2-year incidence of disability among 5,949 initially non-disabled adults, Health and Retirement Study.

ADL disability[b]	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Continuous frailty score		1.84 (1.74, 1.94)	1.50 (1.40, 1.61)
Quintiles			
1st quintile	55 (3.9%)	Ref.	Ref.
2nd quintile	88 (6.5%)	1.66 (1.20, 2.31)	1.33 (0.96, 1.84)
3rd quintile	137 (10.5%)	2.70 (1.99, 3.65)	1.85 (1.37, 2.52)
4th quintile	184 (16.4%)	4.21 (3.15, 5.62)	2.45 (1.82, 3.31)
5th quintile	241 (32.5%)	8.37 (6.33, 11.05)	3.85 (2.83, 5.25)

Abbreviations: RR, relative risk; CI, confidence interval; ADL, activities of daily living; FP, frailty phenotype.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

[b] Participants who reported having difficulty in any of six basic daily activities (dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room) were identified as having ADL disability.

Table 4–6A. Association of frailty with 2-year incidence of disability among 3,281 initially non-disabled robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Cardiovascular Health Study.

ADL disability[a]	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[b] RR (95% CI)
Robust (n = 1,657)	191 (11.5%)		
Continuous frailty score		2.01 (1.56, 2.58)	1.57 (1.19, 2.07)
Quintiles			
1st quintile	47 (7.4%)	Ref.	Ref.
2nd quintile	55 (10.6%)	1.44 (0.99, 2.09)	1.30 (0.88, 1.93)
3rd quintile	48 (13.4%)	1.82 (1.24, 2.66)	1.15 (0.74, 1.79)
4th & 5th quintiles	41 (28.7%)	3.89 (2.67, 5.68)	2.58 (1.65, 4.05)
Prefrail (n = 1,459)	350 (24.0%)		
Continuous frailty score		1.73 (1.51, 1.97)	1.44 (1.23, 1.69)
Quintiles			
1st quintile	17 (13.5%)	Ref.	Ref.
2nd quintile	36 (16.1%)	1.19 (0.70, 2.03)	1.16 (0.66, 2.05)
3rd quintile	63 (19.3%)	1.43 (0.87, 2.34)	1.16 (0.68, 1.99)
4th quintile	113 (24.2%)	1.79 (1.12, 2.86)	1.34 (0.80, 2.26)
5th quintile	121 (38.5%)	2.86 (1.80, 4.54)	1.92 (1.13, 3.25)
Frail (n = 165)	75 (45.5%)		
Continuous frailty score		1.38 (1.09, 1.77)	1.11 (0.77, 1.59)

Abbreviations: ADL, activities of daily living; RR, relative risk; CI, confidence interval.

[a] Participants who reported having difficulty in any of six basic daily activities (dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room) were identified as having ADL disability.

[b] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

Table 4–6B. Association of frailty with 2-year incidence of disability among 5,949 initially non-disabled robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Health and Retirement Study.

		Unadjusted	Adjusted[b]
ADL disability[a]	*N* (%) of events	RR (95% CI)	
Robust (n = 3,056)	195 (6.4%)		
Continuous frailty score		1.75 (1.44, 2.13)	1.34 (1.08, 1.66)
Quintiles			
1st quintile	51 (4.0%)	Ref.	Ref.
2nd quintile	62 (6.2%)	1.54 (1.07, 2.21)	1.13 (0.78, 1.64)
3rd quintile	58 (9.0%)	2.24 (1.55, 3.22)	1.40 (0.96, 2.05)
4th quintile	24 (18.1%)	4.50 (2.87, 7.06)	2.56 (1.58, 4.17)
5th quintile	n = 0	n = 0	n = 0
Prefrail (n = 2,586)	389 (15.0%)		
Continuous frailty score		1.76 (1.57, 1.96)	1.43 (1.26, 1.62)
Quintiles			
1st quintile	4 (2.8%)	Ref.	Ref.
2nd quintile	26 (7.3%)	2.60 (0.92, 7.31)	2.18 (0.79, 5.98)
3rd quintile	79 (12.0%)	4.29 (1.59, 11.52)	3.00 (1.14, 7.90)
4th quintile	159 (16.3%)	5.83 (2.19, 15.49)	3.44 (1.31, 9.00)
5th quintile	121 (26.8%)	9.59 (3.60, 25.52)	4.73 (1.78, 12.54)
Frail (n = 307)			
Continuous frailty score		1.64 (1.38, 1.95)	1.55 (1.26, 1.90)

Abbreviations: RR, relative risk; CI, confidence interval; ADL, activities of daily living.
[a] Participants who reported having difficulty in any of six basic daily activities (dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room) were identified as having ADL disability.
[b] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–7A. Comparison in prediction of 2-year incidence of disability between two frailty scales among 3,281 initially non-disabled adults, Cardiovascular Health Study.

	Age + Sex + PFP scale[a]	Age+ Sex + Continuous frailty scale[b]
Incident ADL disability[c]	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.10	.13
C statistic	.68 (.66, .70)	.70 (.68, .73)
Δ C statistic	Ref.	.02 (.01, .04)
Discrimination slope	.07 (.06, .08)	.09 (.08, .10)
Δ Discrimination slope	Ref.	.03 (.01, .05)
Hosmer-Lemeshow[d]	2.31 (p = .970)	6.78 (p = .561)
IDI[e]	.04 (.03, .06)	.07 (.05, .09)
Δ IDI	Ref.	.03 (.02, .05)
NRI (>0)[f]	.47 (.37, .55)	.55 (.47, .63)
Δ NRI (>0)	Ref.	.09 (.01, .19)
Event NRI[f]	.35 (.24, .43)	.26 (.21, .32)
Δ event NRI	Ref.	-.08 (-.17, .02)
Non-event NRI[f]	.12 (.08, .16)	.29 (.24, .33)
Δ non-event NRI	Ref.	.17 (.12, .22)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; ADL, activities of daily living; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Persons who reported difficulty in any of six basic daily activities (dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room) were considered disabled.

[d] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[e] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[f] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–7B. Comparison in prediction of 2-year incidence of disability between two frailty scales among 5,949 initially non-disabled adults, Health and Retirement Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Incident ADL disability[c]	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.12	.15
C statistic	.71 (.69, .73)	.74 (.72, .76)
Δ C statistic	Ref.	.03 (.02, .05)
Discrimination slope	.08 (.07, .08)	.10 (.09, .11)
Δ Discrimination slope	Ref.	.02 (.01, .04)
Hosmer-Lemeshow[d]	5.41 (p = .713)	12.56 (p = .128)
IDI[e]	.04 (.03, .06)	.06 (.05, .08)
Δ IDI	Ref.	.02 (.01, .03)
NRI (>0)[f]	.49 (.35, .57)	.53 (.46, .62)
Δ NRI (>0)	Ref.	.04 (.01, .08)
Event NRI[f]	.37 (.19, .46)	.23 (.18, .29)
Δ event NRI	Ref.	-.14 (-.27, -.01)
Non-event NRI[f]	.12 (.08, .17)	.31 (.27, .34)
Δ non-event NRI	Ref.	.19 (.13, .23)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; ADL, activities of daily living; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Persons who reported difficulty in any of six basic daily activities (dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room) were considered disabled.

[d] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[e] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[f] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–8. Characteristics of adults who had and who did not have measure of hip fracture in six years, Health and Retirement Study.

Characteristics	Hip fracture		
	Measured (n = 5,473)	Missing (n = 2,127)	*p* [a]
Age, years, mean (SD)	73.8 (6.2)	77.7 (7.2)	<.001
Male, No. (%)	2,281 (41.7)	1,034 (48.6)	<.001
White (vs. others), No. (%)	4,884 (89.2)	1,879 (88.3)	.262
Education			<.001
< High school, No. (%)	1,215 (22.2)	623 (29.3)	
= High school, No. (%)	1,968 (36.0)	761 (35.8)	
> High school, No. (%)	2,289 (41.8)	743 (34.9)	
Smoking status			<.001
Never, No. (%)	2,465 (45.3)	814 (38.5)	
Former, No. (%)	2,538 (46.6)	1,037 (49.1)	
Current, No. (%)	440 (8.1)	262 (12.4)	
Body mass index, kg/m^2, mean (SD)			<.001
Underweight/normal[b], No. (%)	1,329 (24.3)	680 (32.0)	
Overweight, No. (%)	2,104 (38.4)	752 (35.4)	
Obese, No. (%)	2,040 (37.3)	695 (32.7)	
Cardiac disease[c], No. (%)	1,485 (27.1)	856 (40.3)	<.001
Stroke, No. (%)	298 (5.5)	220 (10.4)	<.001
Hypertension, No. (%)	3,421 (65.6)	1,429 (67.3)	<.001
Lung disease, No (%)	528 (9.7)	339 (16.0)	<.001
Diabetes, No. (%)	1,121 (20.5)	532 (25.0)	<.001
Cancer[d], No. (%)	949 (17.4)	504 (23.7)	<.001
Arthritis, No. (%)	3,732 (68.2)	1,464 (68.9)	.586
TICS[e], mean (SD)	9.4 (1.0)	9.0 (1.5)	<.001
ADL disability[f], No. (%)	635 (11.6)	511 (24.0)	<.001
Systolic BP, mmHg, mean (SD)	133.8 (20.2)	135.9 (22.3)	<.001
Diastolic BP, mmHg, mean (SD)	78,5 (11.3)	77.9 (12.3)	.037
CRP, mg/L, mean (SD)	4.0 (8.2)	5.1 (9.7)	<.001
Cystatin C, mg/L, mean (SD)	1.1 (0.4)	1.4 (0.7)	<.001
HDL cholesterol, mg/dL, mean (SD)	54.7 (15.7)	52.9 (16.4)	<.001
Total cholesterol, mg/dL, mean (SD)	199.3 (41.6)	194.0 (41.5)	<.001
HbA1c, %, mean (SD)	5.9 (0.8)	6.0 (1.0)	<.001
Continuous frailty score, mean (SD)	-0.2 (1.2)	0.6 (1.3)	<.001

Abbreviations: SD, standard deviation; ADL, activities of daily living; TICS, the Telephone Interview for Cognitive Status; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.

[a] P-values were obtained from t test with unequal variance or χ^2 test for comparison between adults who had and who did not have measure of hip fracture in six years.

[b] Underweight and normal were collapsed due to small cell size in the underweight category.

[c] Myocardial infarction, coronary heart disease, angina, heart failure, or other heart problems.

[d] Non-melanoma skin cancer was excluded.

[e] Ranging from 0 to 10 with higher score indicating a better global cognitive function.

[f] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

Table 4–9A. Association of frailty with 6-year incidence of hip fracture among 4,214 adults, Cardiovascular Health Study.

Hip fracture[b]	Rates per 1000 person-years	Unadjusted HR (95% CI)	Adjusted[a] HR (95% CI)
Continuous frailty score		1.56 (1.34, 1.81)	1.34 (1.09, 1.65)
Quintiles			
1st quintile	2.6	Ref.	Ref.
2nd quintile	3.7	1.44 (0.71, 2.92)	1.53 (0.70, 3.35)
3rd quintile	8.2	3.17 (1.70, 5.91)	2.93 (1.44, 5.99)
4th quintile	9.0	3.47 (1.87, 6.44)	2.59 (1.25, 5.37)
5th quintile	10.6	4.11 (2.24, 7.54)	3.08 (1.45, 6.57)

Abbreviations: HR, hazard ratio; CI, confidence interval.
A total of 169 incident hip fracture occurred in 6 years and the rate was 6.8 per 1000 person-years.
[a] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.
[b] Twenty-four participants had hip fracture occurred before frailty was assessed, and were therefore excluded.

Table 4–9B. Association of frailty with 6-year incidence of hip fracture among 5,473 adults, Health and Retirement Study.

Hip fracture	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Continuous frailty score		1.70 (1.55, 1.86)	1.37 (1.22, 1.55)
Quintiles			
1st quintile	17 (1.3%)	Ref.	Ref.
2nd quintile	29 (2.4%)	1.83 (1.02, 3.33)	1.39 (0.77, 2.53)
3rd quintile	47 (4.0%)	3.05 (1.76, 5.28)	1.99 (1.13, 3.50)
4th quintile	71 (7.1%)	5.44 (3.23, 9.18)	2.80 (1.60, 4.90)
5th quintile	73 (9.5%)	7.34 (4.36, 12.34)	3.14 (1.77, 5.60)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–10A. Association of frailty with 6-year incidence of hip fracture among 4,219 robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Cardiovascular Health Study.

Hip fracture[a]	Rates per 1000 person-years	Unadjusted HR (95% CI)	Adjusted[b] HR (95% CI)
Robust (n = 1,900)	4.3		
Continuous frailty score		2.52 (1.52, 4.20)	1.92 (1.05, 3.52)
Quintiles			
1st quintile	2.9	Ref.	Ref.
2nd quintile	2.3	0.78 (0.32, 1.92)	0.72 (0.27, 1.96)
3rd quintile	6.6	2.26 (1.08, 4.74)	1.83 (0.77, 4.38)
4th & 5th quintiles	10.7	3.70 (1.63, 8.39)	2.54 (0.93, 6.96)
Prefrail (n = 1,967)	7.9		
Continuous frailty score		1.20 (0.91, 1.59)	1.03 (0.72, 1.48)
Quintiles			
1st quintile	1.2	Ref.	Ref.
2nd quintile	7.1	6.14 (0.79, 47.55)	No convergence
3rd quintile	10.2	8.86 (1.20, 65.47)	No convergence
4th quintile	8.2	7.12 (0.97, 52.14)	No convergence
5th quintile	8.0	6.95 (0.94, 51.37)	No convergence
Frail (n = 347)	14.9		
Continuous frailty score		0.97 (0.56, 1.65)	0.89 (0.47, 1.68)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a] A total of 24 participants had hip fracture before frailty was assessed, and were therefore excluded.

[b] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

Table 4–10B. Association of frailty with 6-year incidence of hip fracture among 5,473 robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Health and Retirement Study.

		Unadjusted	Adjusted[a]
Hip fracture	*N* (%) of events	RR (95% CI)	
Robust (n = 2,749)	74 (2.7%)		
Continuous frailty score		2.49 (1.68, 3.67)	1.70 (1.13, 2.56)
Quintiles			
1st quintile	15 (1.3%)	Ref.	Ref.
2nd quintile	20 (2.3%)	1.76 (0.90, 3.41)	1.24 (0.64, 2.40)
3rd quintile	26 (4.6%)	3.56 (1.90, 6.68)	1.96 (0.98, 3.91)
4th quintile	13 (11.1%)	8.69 (4.23, 17.80)	4.05 (1.92, 8.56)
5th quintile	n = 0	n = 0	n = 0
Prefrail (n = 2,370)	125 (5.3%)		
Continuous frailty score		1.68 (1.39, 2.04)	1.36 (1.11, 1.68)
Quintiles			
1st quintile	2 (1.5%)	Ref.	Ref.
2nd quintile	9 (2.8%)	1.88 (0.41, 8.59)	1.55 (0.34, 7.08)
3rd quintile	21 (3.4%)	2.31 (0.55, 9.75)	1.80 (0.43, 7.48)
4th quintile	58 (6.7%)	4.54 (1.12, 18.38)	2.62 (0.65, 10.66)
5th quintile	35 (8.0%)	5.41 (1.32, 22.19)	2.89 (0.70, 11.91)
Frail (n = 354)	38 (11.6%)		
Continuous frailty score		1.51 (0.96, 2.39)	1.83 (1.10 ,3.03)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–11A. Comparison in prediction of 6-year incidence of hip fracture between two frailty scales among 4,214 adults, Cardiovascular Health Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Hip fracture[c]	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.05	.06
C statistic	.68 (.64, .72)	.68 (.64, .72)
Δ C statistic	Ref.	.00 (-.01, .04)
Discrimination slope	.02 (.01, .02)	.02 (.01, .03)
Δ Discrimination slope	Ref.	.00 (-.01, .01)
Hosmer-Lemeshow[d]	8.68 (p = .370)	13.17 (p = .106)
IDI[e]	.00 (.00, .01)	.00 (.00, .01)
Δ IDI	Ref.	.00 (-.01, .01)
NRI (>0)[f]	.24 (-.03, .44)	.30 (.12, .40)
Δ NRI (>0)	Ref.	.06 (-.01, .15)
Event NRI[f]	.24 (-.44, .50)	.14 (.00, .20)
Δ event NRI	Ref.	-.09 (-.30, .15)
Non-event NRI[f]	.00 (-.09, .48)	.16 (.09, .22)
Δ non-event NRI	Ref.	.16 (.02, .33)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Twenty-four participants had hip fracture occurred before frailty was assessed, and were therefore excluded.

[d] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[e] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[f] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–11B. Comparison in prediction of 6-year incidence of hip fracture between two frailty scales among 5,473 adults, Health and Retirement Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Hip fracture	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.13	.15
C statistic	.77 (.73, .79)	.78 (.74, .80)
Δ C statistic	Ref.	.01 (-.01, .03)
Discrimination slope	.06 (.05, .06)	.06 (.06, .07)
Δ Discrimination slope	Ref.	.01 (.00, .02)
Hosmer-Lemeshow[c]	13.54 (p = .094)	4.07 (p = .851)
IDI[d]	.00 (.00, .01)	.01 (.01, .02)
Δ IDI	Ref.	.00 (-.01, .01)
NRI (>0)[e]	.35 (-.03, .49)	.34 (.23, .48)
Δ NRI (>0)	Ref.	.00 (-.15, .13)
Event NRI[e]	.32 (-.37, .46)	.12 (.04, .23)
Δ event NRI	Ref.	-.20 (-.45, .05)
Non-event NRI[e]	.04 (.00, .35)	.22 (.16, .28)
Δ non-event NRI	Ref.	.18 (.08, .29)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[d] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[e] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–12A. Characteristics of adults who had and did not have measure of falls in two years, Cardiovascular Health Study.

Characteristics	Falls		
	Measured (n = 3,862)	Missing (n = 381)	*p* [b]
Age, years, mean (SD)	74.9 (4.9)	77.0 (5.8)	<.001
Male, No. (%)	1,592 (41.2)	196 (51.4)	<.001
White (vs. Black), No. (%)	3,345 (86.6)	338 (88.7)	.248
Education			.002
< High school, No. (%)	936 (23.3)	122 (32.1)	
= High school, No. (%)	1,106 (28.7)	106 (27.9)	
> High school, No. (%)	1,812 (47.0)	152 (40.0)	
Smoking status			.048
Never, No. (%)	1,735 (45.8)	147 (39.2)	
Former, No. (%)	1,698 (44.8)	190 (50.7)	
Current, No. (%)	354 (9.4)	38 (10.1)	
Body mass index, kg/m^2			.229
Underweight/normal[c], No. (%)	1,431 (37.1)	158 (41.5)	
Overweight, No. (%)	1,644 (42.6)	149 (39.1)	
Obese, No. (%)	787 (20.4)	74 (19.4)	
Coronary heart disease, No. (%)	804 (20.8)	122 (32.0)	<.001
Heart failure, No. (%)	197 (5.1)	44 (11.6)	<.001
Stroke, No. (%)	176 (4.6)	33 (8.7)	<.001
Hypertension			.760
Borderline, No. (%)	573 (14.9)	59 (15.6)	
Hypertensive, No. (%)	1,577 (40.9)	161 (42.3)	
Diabetes			.004
Prediabetes, No. (%)	369 (9.8)	38 (10.6)	
Diabetes, No. (%)	545 (14.5)	75 (20.8)	
Cancer[d], No. (%)	549 (14.2)	51 (13.5)	.693
Arthritis, No. (%)	1,751 (46.5)	178 (47.7)	.661
3MS[e], mean (SD)	91.5 (8.0)	88.3 (10.7)	<.001
ADL disability[f], No. (%)	368 (9.5)	62 (16.3)	<.001
Systolic BP, mmHg, mean (SD)	135.5 (21.1)	136.8 (22.4)	.272
Diastolic BP, mmHg, mean (SD)	70.8 (11.1)	70.1 (12.4)	.272
CRP, mg/L, mean (SD)	5.0 (9.2)	7.2 (13.6)	.004
Cystatin C, mg/L, mean (SD)	1.1 (0.3)	1.3 (0.5)	<.001
Total cholesterol, mg/dL, mean (SD)	208.8 (38.2)	201.2 (40.7)	<.001
Fasting glucose, mg/dL, mean (SD)	107.6 (32.4)	113.0 (38.2)	.011
Continuous frailty score, mean (SD)	-0.1 (1.0)	0.3 (1.1)	<.001

Abbreviations: ADL, activities of daily living; SD, standard deviation; 3MS, Modified Mini-Mental State Examination; BP, blood pressure; ; CRP, C-reactive protein.

[a] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

[b] P-values were obtained from t test with unequal variance or χ^2 test for comparison between adults who had and who did not have measure of fall in two years.

[c] Underweight and normal were collapsed due to small cell size in the underweight category.

[d] Non-melanoma skin cancer was excluded.

[e] Ranging from 0 to 100 with higher score indicating a better global cognitive function.

[f] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

Table 4–12B. Characteristics of adults who had and did not have measure of falls in two years, Health and Retirement Study.

Characteristics	Falls		
	Measured (n = 6,885)	Missing (n = 715)	*p* [a]
Age, years, mean (SD)	74.5 (6.6)	78.1 (8.1)	<.001
Male, No. (%)	2,970 (43.1)	345 (48.3)	.009
White (vs. others), No. (%)	6,131 (89.1)	632 (88.4)	.593
Education			<.001
< High school, No. (%)	1,625 (23.6)	213 (29.8)	
= High school, No. (%)	2,468 (35.9)	261 (36.5)	
> High school, No. (%)	2,791 (40.5)	241 (33.7)	
Smoking status			.001
Never, No. (%)	3,006 (43.9)	273 (38.3)	
Former, No. (%)	3,225 (47.1)	350 (49.2)	
Current, No. (%)	612 (9.0)	89 (12.5)	
Body mass index, kg/m^2, mean (SD)			<.001
Underweight/normal[b], No. (%)	1,749 (25.4)	260 (36.4)	
Overweight, No. (%)	2,624 (38.1)	232 (32.5)	
Obese, No. (%)	2,512 (36.5)	223 (31.2)	
Cardiac disease[c], No. (%)	2,037 (29.6)	304 (42.6)	<.001
Stroke, No. (%)	442 (6.5)	76 (10.8)	<.001
Hypertension, No. (%)	4,277 (63.7)	473 (66.3)	.169
Lung disease, No (%)	737 (10.7)	130 (18.2)	<.001
Diabetes, No. (%)	1,445 (21.0)	208 (29.1)	<.001
Cancer[d], No. (%)	1,275 (18.5)	178 (24.9)	<.001
Arthritis, No. (%)	4,703 (68.3)	493 (69.1)	.694
TICS[e], mean (SD)	9.3 (1.1)	8.8 (1.7)	<.001
ADL disability[f], No. (%)	943 (13.7)	203 (28.4)	<.001
Systolic BP, mmHg, mean (SD)	134.3 (20.6)	134.8 (22.5)	.604
Diastolic BP, mmHg, mean (SD)	78.5 (11.4)	77.0 (12.6)	.003
CRP, mg/L, mean (SD)	4.1 (8.0)	6.2 (13.3)	<.001
Cystatin C, mg/L, mean (SD)	1.2 (0.5)	1.4 (0.8)	<.001
HDL cholesterol, mg/dL, mean (SD)	54.4 (15.9)	52.0 (16.2)	.001
Total cholesterol, mg/dL, mean (SD)	198.4 (41.4)	193.2 (43.8)	.007
HbA1c, %, mean (SD)	5.9 (0.9)	6.0 (1.0)	<.001
Continuous frailty score, mean (SD)	-0.1 (1.2)	0.8 (1.3)	<.001

Abbreviations: SD, standard deviation; ADL, activities of daily living; TICS, the Telephone Interview for Cognitive Status; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein; HbA1c, glycosylated hemoglobin.

[a] P-values were obtained from t test with unequal variance or χ^2 test for comparison between adults who had and who did not have measure of fall in two years.

[b] Underweight and normal were collapsed due to small cell size in the underweight category.

[c] Myocardial infarction, coronary heart disease, angina, heart failure, or other heart problems.

[d] Non-melanoma skin cancer was excluded.

[e] Ranging from 0 to 10 with higher score indicating a better global cognitive function.

[f] Having difficulty in any of the following six basic activities of daily living: dressing, eating, toileting, bathing, transferring or getting out of bed, and walking across a room.

Table 4–13A. Association of frailty with 2-year incidence of falls among 3,862 adults, Cardiovascular Health Study.

Falls	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Continuous frailty score		1.33 (1.27, 1.40)	1.23 (1.15, 1.31)
Quintiles			
1st quintile	167 (21.1%)	Ref.	Ref.
2nd quintile	181 (22.4%)	1.06 (0.88, 1.28)	1.03 (0.85, 1.25)
3rd quintile	180 (23.0%)	1.09 (0.90, 1.31)	0.97 (0.79, 1.18)
4th quintile	244 (31.9%)	1.51 (1.27, 1.79)	1.28 (1.06, 1.54)
5th quintile	300 (41.9%)	1.98 (1.69, 2.33)	1.56 (1.28, 1.89)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

Table 4–13B. Association of frailty with 2-year incidence of falls among 6,885 adults, Health and Retirement Study.

Falls	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Continuous frailty score		1.18 (1.15, 1.21)	1.09 (1.06, 1.13)
Quintiles			
1st quintile	414 (28.3%)	Ref.	Ref.
2nd quintile	422 (29.4%)	1.04 (0.93, 1.16)	0.99 (0.88, 1.11)
3rd quintile	484 (33.8%)	1.19 (1.07, 1.33)	1.06 (0.95, 1.19)
4th quintile	503 (37.4%)	1.32 (1.19, 1.47)	1.12 (1.00, 1.25)
5th quintile	603 (50.0%)	1.77 (1.60, 1.95)	1.33 (1.18, 1.49)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–14A. Association of frailty with 2-year incidence of falls among 3,862 robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Cardiovascular Health Study.

Falls	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Robust (n = 1,793)	413 (23.0%)		
Continuous frailty score		1.26 (1.10, 1.44)	1.12 (0.96, 1.31)
Quintiles			
1st quintile	137 (20.8%)	Ref.	Ref.
2nd quintile	124 (22.0%)	1.06 (0.85, 1.31)	0.97 (0.77, 1.21)
3rd quintile	94 (23.3%)	1.12 (0.89, 1.41)	0.91 (0.70, 1.18)
4th & 5th quintiles	58 (34.7%)	1.67 (1.29, 2.15)	1.40 (1.05, 1.86)
Prefrail (n = 1,783)	534 (30.0%)		
Continuous frailty score		1.39 (1.26, 1.54)	1.25 (1.11, 1.41)
Quintiles			
1st quintile	30 (22.7%)	Ref.	Ref.
2nd quintile	57 (23.4%)	1.03 (0.70, 1.52)	1.12 (0.75, 1.69)
3rd quintile	85 (22.8%)	1.00 (0.70, 1.45)	0.97 (0.65, 1.43)
4th quintile	183 (31.1%)	1.37 (0.98, 1.92)	1.21 (0.84, 1.75)
5th quintile	179 (40.1%)	1.77 (1.26, 2.47)	1.47 (1.01, 2.14)
Frail (n = 286)	125 (43.7%)		
Continuous frailty score		1.28 (1.07, 1.54)	1.28 (1.03, 1.60)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] Adjusted for clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, total cholesterol, and fasting glucose.

Table 4–14B. Association of frailty with 2-year incidence of falls among 6,885 robust, prefrail, and frail adults identified by the physical frailty phenotype scale, Health and Retirement Study.

Falls	*N* (%) of events	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Robust (n = 3,198)	907 (28.4%)		
Continuous frailty score		1.04 (0.97, 1.11)	0.97 (0.91, 1.04)
Quintiles			
1st quintile	365 (27.9%)	Ref.	Ref.
2nd quintile	290 (27.7%)	1.00 (0.87, 1.13)	1.01 (0.85, 1.15)
3rd quintile	202 (29.3%)	1.05 (0.91, 1.21)	1.03 (0.84, 1.26)
4th quintile	50 (32.5%)	1.16 (0.91, 1.48)	1.10 (0.92, 1.32)
5th quintile	n = 0	n = 0	n = 0
Prefrail (n = 3,106)	1,206 (38.8%)		
Continuous frailty score		1.14 (1.08, 1.20)	1.05 (1.00, 1.12)
Quintiles			
1st quintile	49 (31.4%)	Ref.	Ref.
2nd quintile	132 (33.9%)	1.08 (0.82, 1.42)	1.05 (0.80, 1.37)
3rd quintile	281 (37.8%)	1.20 (0.94, 1.55)	1.08 (0.85, 1.39)
4th quintile	441 (37.9%)	1.21 (0.95, 1.54)	1.05 (0.82, 1.33)
5th quintile	303 (46.3%)	1.48 (1.15, 1.89)	1.15 (0.90, 1.48)
Frail (n = 581)	313 (53.9%)		
Continuous frailty score		1.21 (1.08, 1.35)	1.14 (1.02, 1.27)

Abbreviations: RR, relative risk; CI, confidence interval.

[a] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, difficulty in activities of daily living (none vs. any), systolic and diastolic blood pressure, C-reactive protein, cystatin C, high-density lipoprotein cholesterol, total cholesterol, and glycosylated hemoglobin.

Table 4–15A. Comparison in prediction of 2-year incidence of falls between two frailty scales among 3,862 adults, Cardiovascular Health Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Incident falls	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.05	.06
C statistic	.62 (.61, .64)	.63 (.61, .65)
Δ C statistic	Ref.	.01 (.00, .03)
Discrimination slope	.04 (.03, .04)	.04 (.04, .05)
Δ Discrimination slope	Ref.	.01 (-.01, .02)
Hosmer-Lemeshow[c]	20.78 (p = .008)	8.59 (p = .378)
IDI[d]	.01 (.00, .02)	.02 (.01, .03)
Δ IDI	Ref.	.01 (.01, .02)
NRI (>0)[e]	.16 (.01, .27)	..26 (.19, .34)
Δ NRI (>0)	Ref.	.10 (.01, .21)
Event NRI[e]	.08 (-.31, .24)	.10 (.05, .14)
Δ event NRI	Ref.	.02 (-.14, .22)
Non-event NRI[e]	.07 (.00, .33)	.16 (.12, .20)
Δ non-event NRI	Ref.	.09 (.01, .18)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[d] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

[e] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Table 4–15B. Comparison in prediction of 2-year incidence of falls between two frailty scales among 6,885 adults, Health and Retirement Study.

	Age + Sex + PFP scale[a]	Age + Sex + Continuous frailty scale[b]
Incident falls	Estimate (95% CI)	
Nagelkerke's $\boldsymbol{R^2}$	.05	.05
C statistic	.61 (.60, .62)	.61 (.59, .62)
Δ C statistic	Ref.	.00 (-.02, .01)
Discrimination slope	.04 (.03, .04)	.04 (.03, .04)
Δ Discrimination slope	Ref.	.00 (-.01, .01)
Hosmer-Lemeshow[c]	6.35 (p = .608)	30.54 (p = .001)
IDI[d]	.02 (.01, .02)	.01 (.01, .02)
Δ IDI	Ref.	.00 (-.01, .02)
NRI (>0)[e]	.24 (.16, .31)	.20 (.15, .25)
Δ NRI (>0)	Ref.	-.04 (-.09, .02)
Event NRI[e]	.19 (.03, .27)	.06 (.03, .09)
Δ event NRI	Ref.	-.13 (-.25, .01)
Non-event NRI[e]	.05 (.02, .14)	.14 (.11, .17)
Δ non-event NRI	Ref.	.09 (.03, .14)

Abbreviations: PFP, physical frailty phenotype; CI, confidence interval; IDI, integrated discrimination index; NRI, net reclassification index.

[a] PFP scale was modeled as a 3-level categorical predictor (robust, prefrail, frail); age and sex were adjusted as covariates.

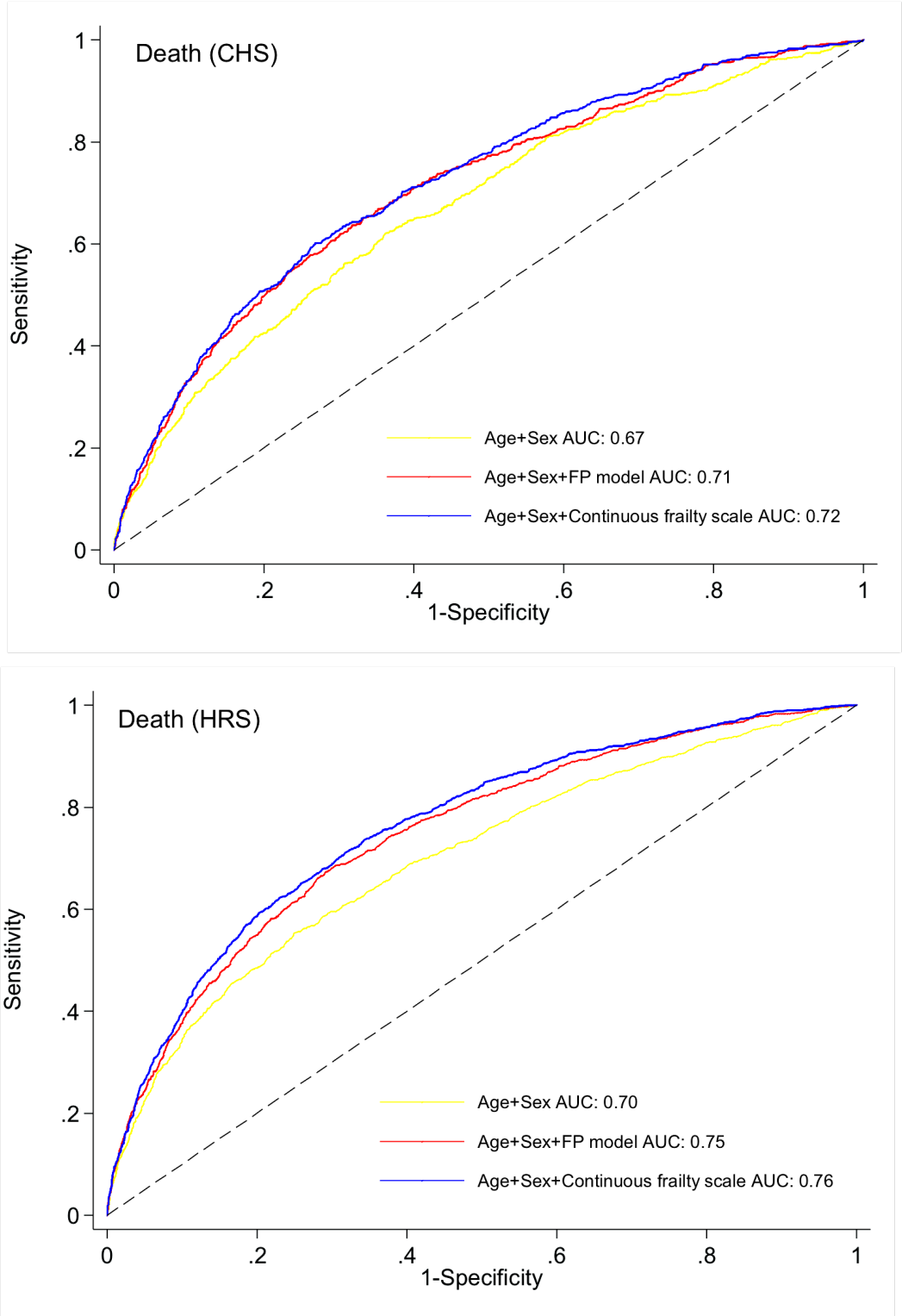
[b] Continuous frailty scale was modeled continuously; age and sex were adjusted as covariates.

[c] Hosmer-Lemeshow calibration statistic, for which the point estimate (mean square difference between predicted and observed risk across the deciles) and associated p value is shown.

[d] The integrated discrimination index was calculated using age- and sex-adjusted model as the reference model; bootstrapped 95% confidence interval was used.

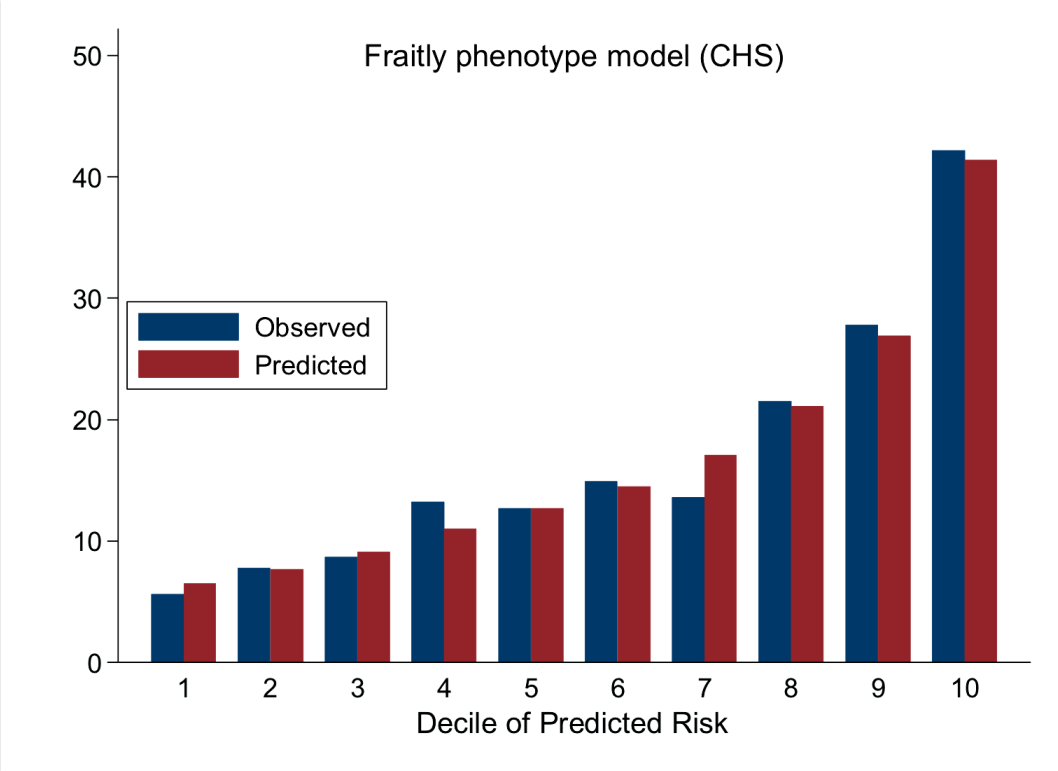
[e] Category-free NRI (>0) was calculated using age- and sex-adjusted model as the reference model and is the sum of event NRI and non-event NRI; bootstrapped 95% confidence interval was used.

Figure 4–1. Receiver operating characteristics curves for predicting death.



Notes: Age and sex were adjusted in all models. The black diagonal line represents a reference area under the curve (AUC) of 0.50 (no better than chance alone). CHS, Cardiovascular Health Study; HRS, Health and Retirement Study; AUC, area under the curve; FP; frailty phenotype.

Figure 4–2A. Agreement between predicted and observed death, Cardiovascular Health Study.



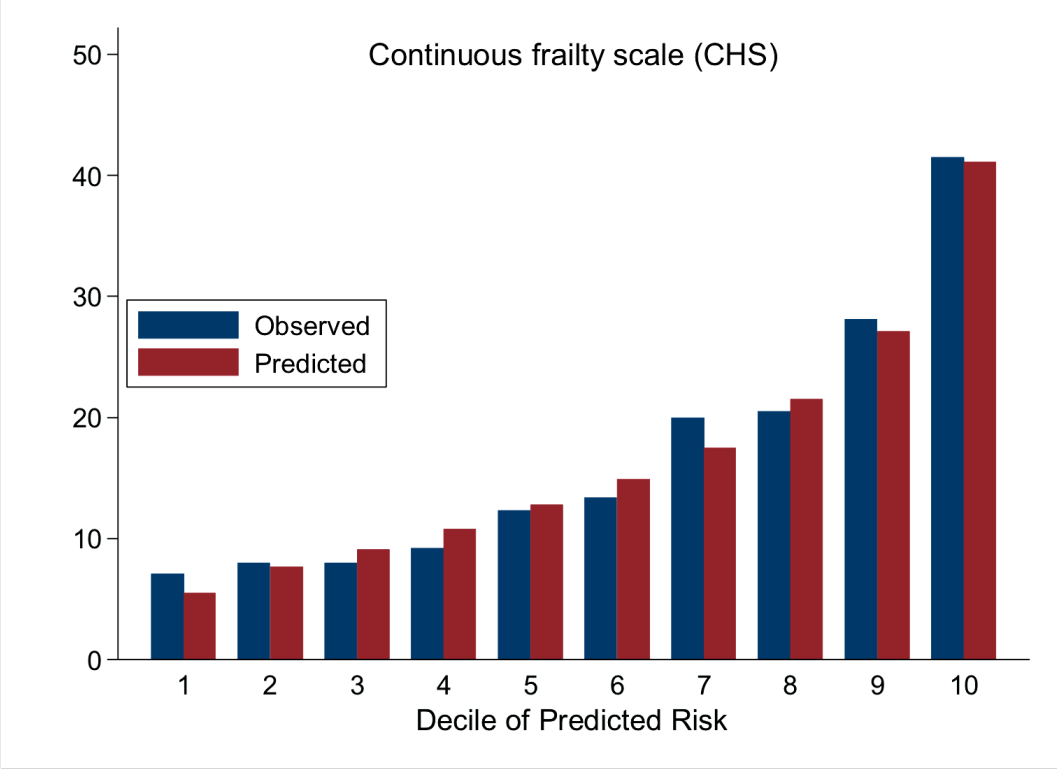
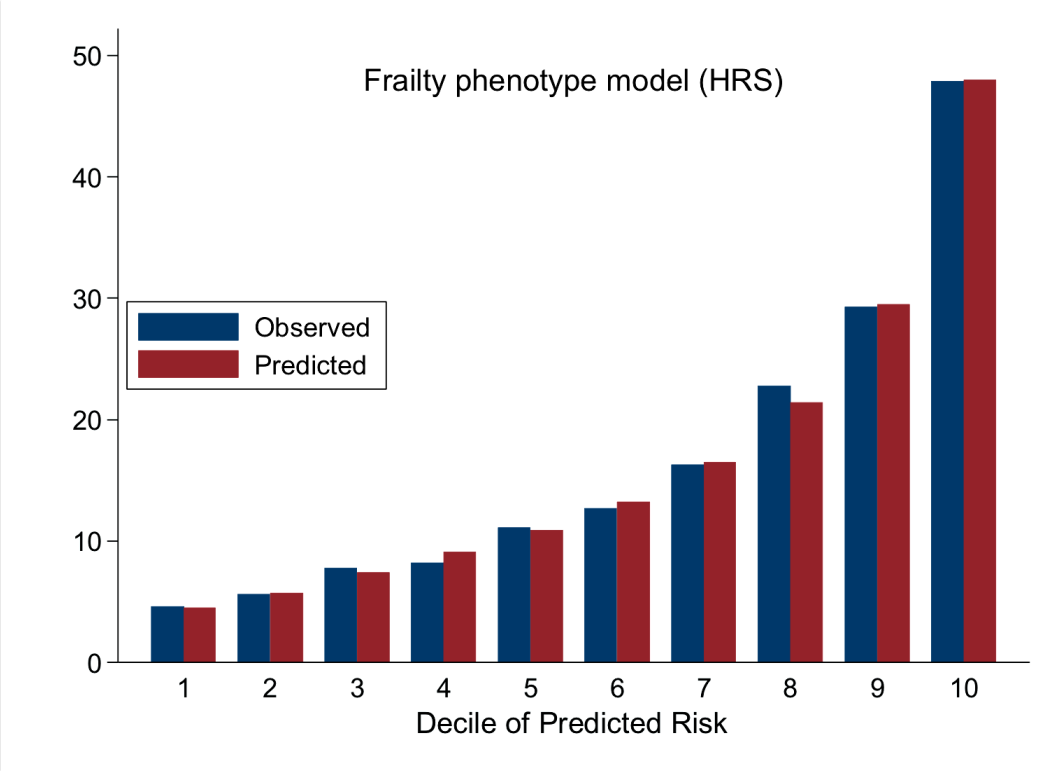


Figure 4–2B. Agreement between predicted and observed death, Health and Retirement Study.



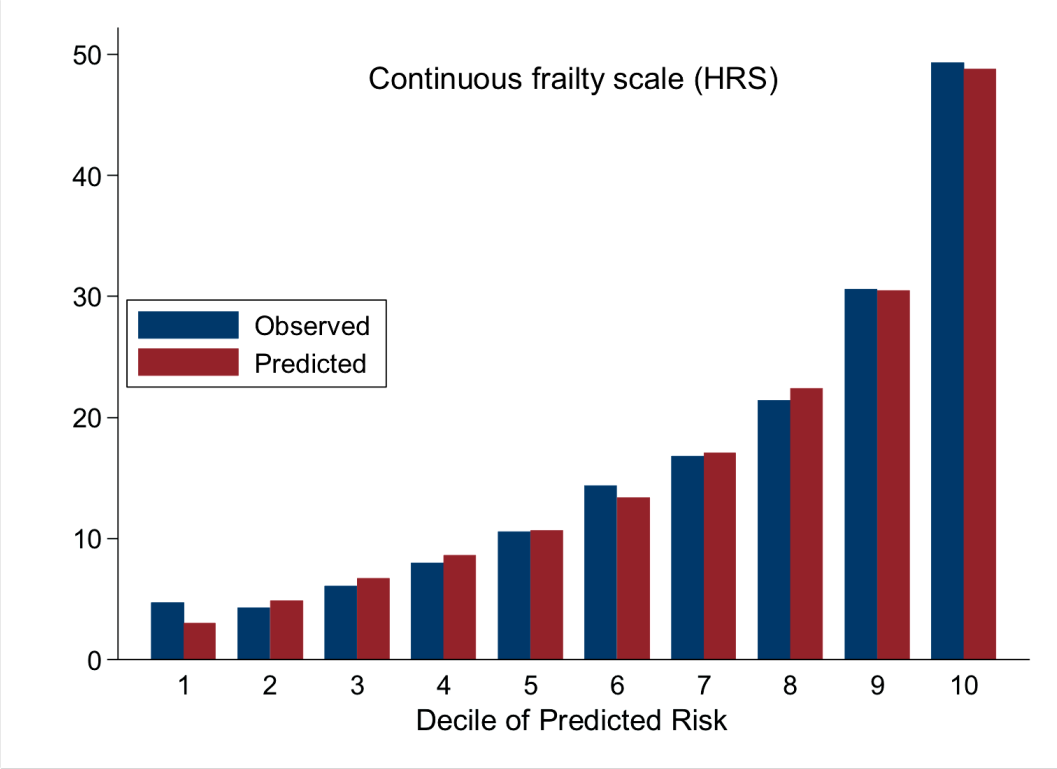
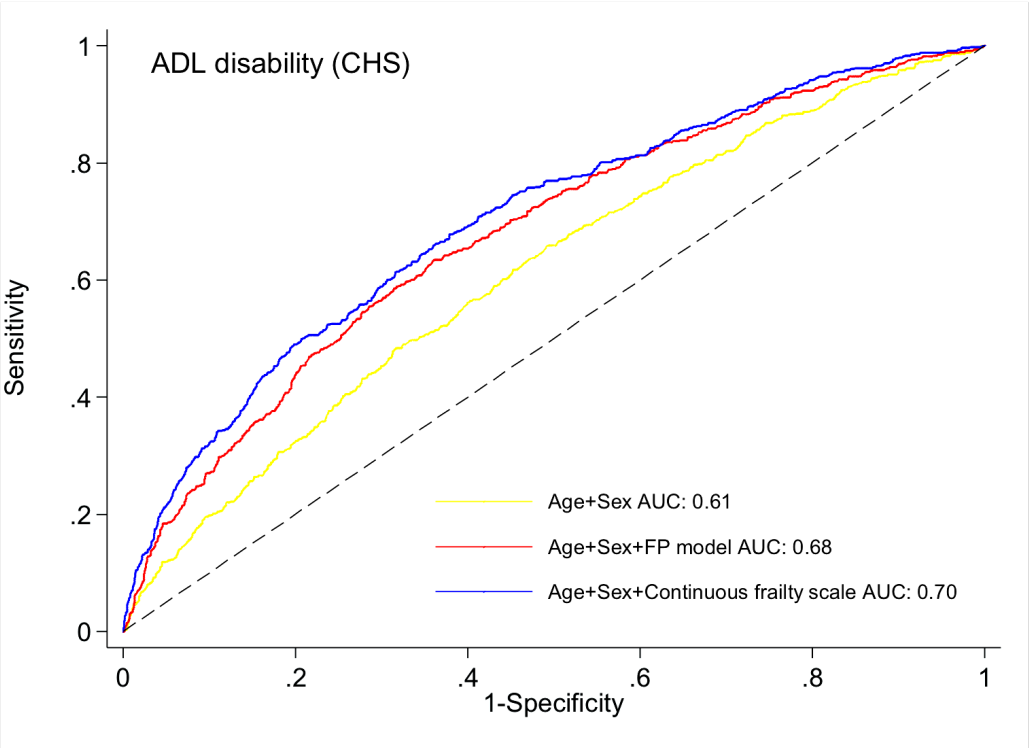
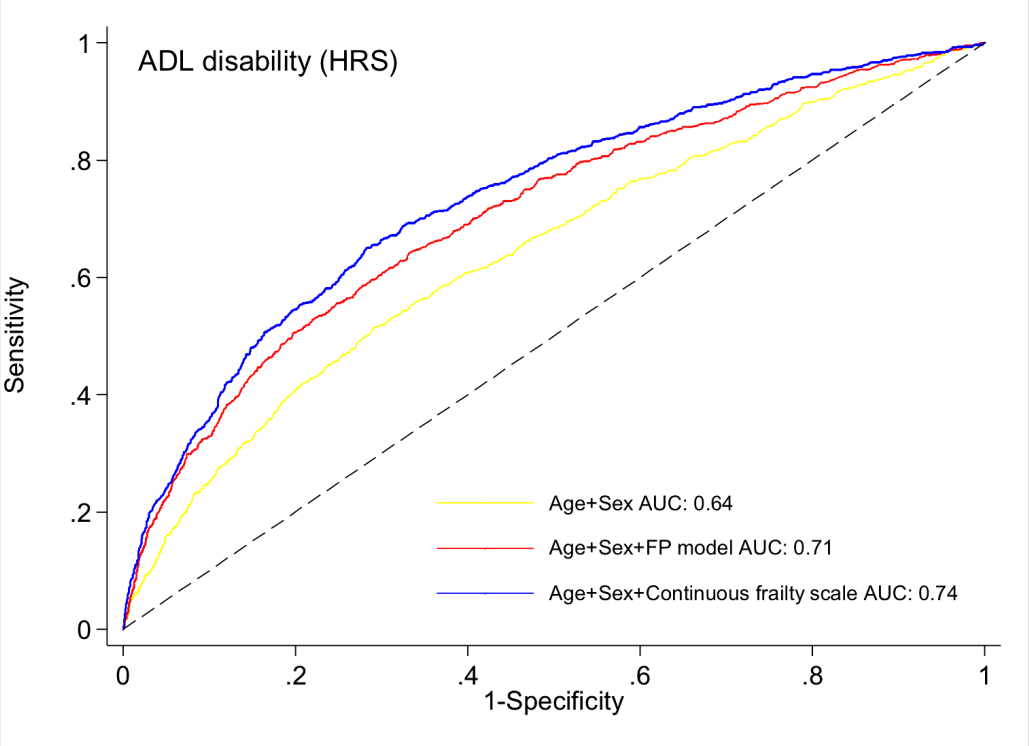


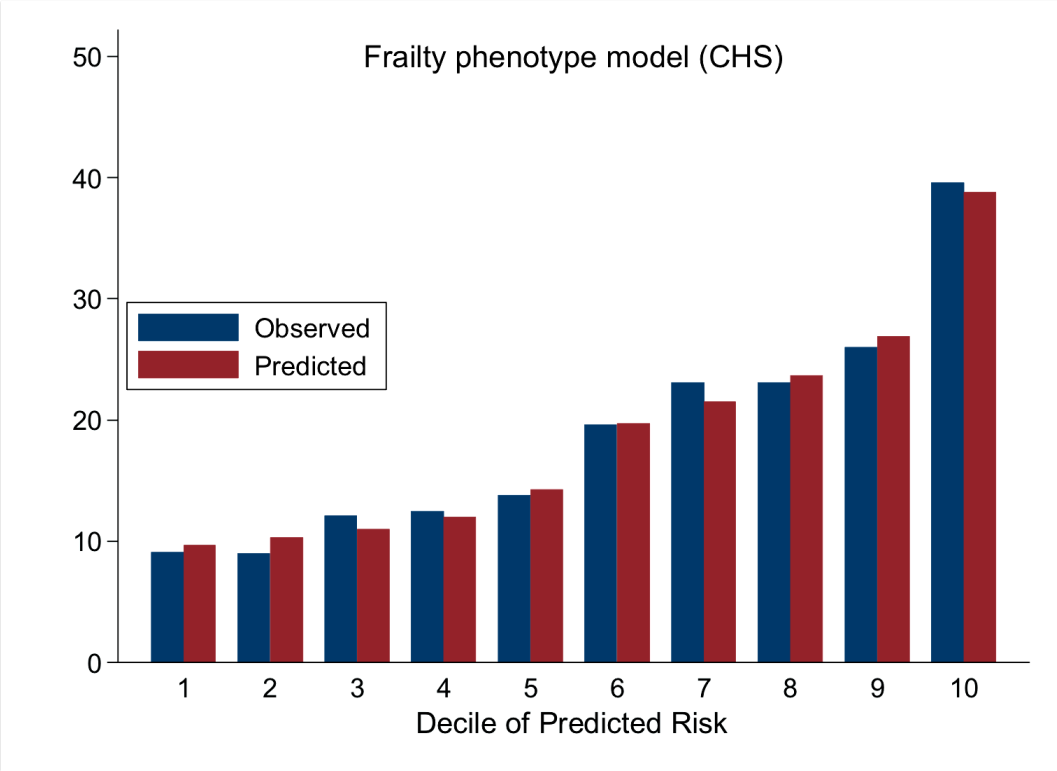
Figure 4–3. Receiver operating characteristics curves for prediction of disability.





Notes: Age and sex were adjusted in all models. The black diagonal line represents a reference area under the curve (AUC) of 0.50 (no better than chance alone). CHS, Cardiovascular Health Study; HRS, Health and Retirement Study; AUC, area under the curve; FP; frailty phenotype.

Figure 4–4A. Agreement between predicted and observed disability, Cardiovascular Health Study.



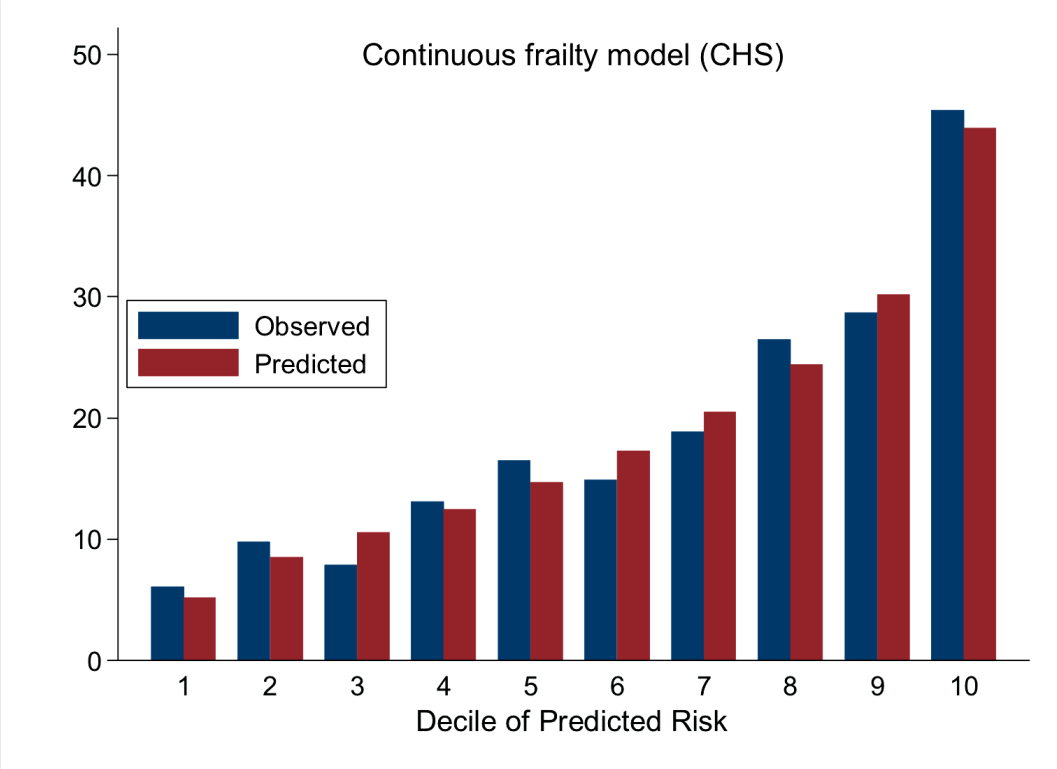
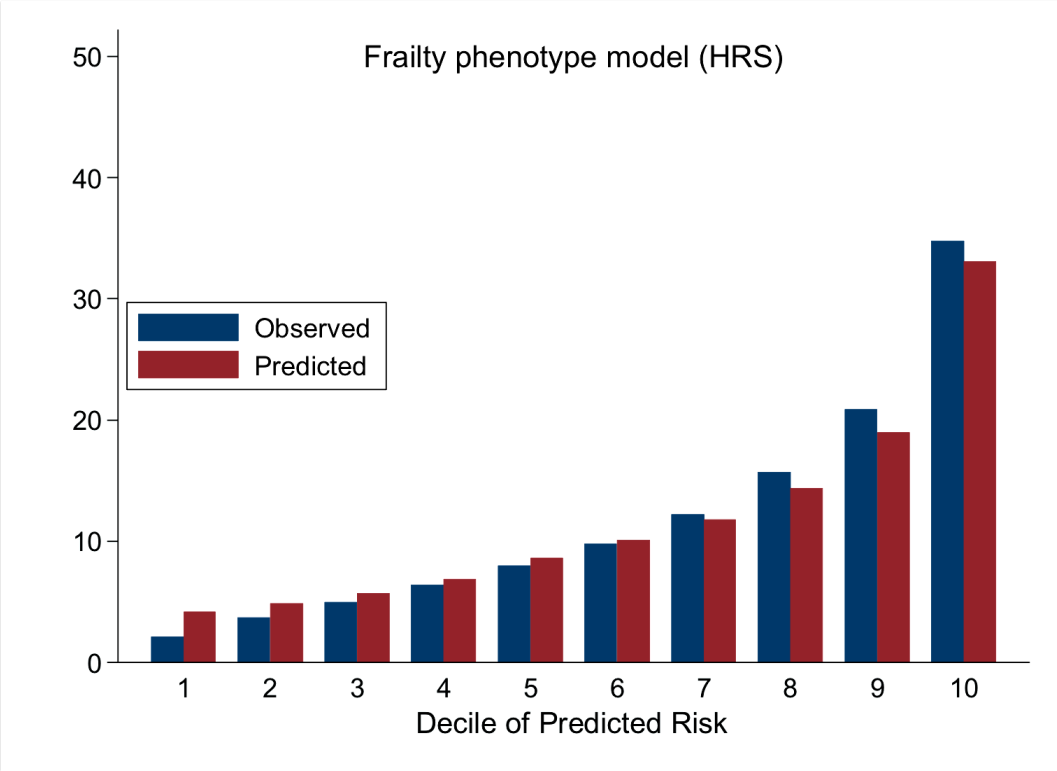


Figure 4–4B. Agreement between predicted and observed disability, Health and Retirement Study.



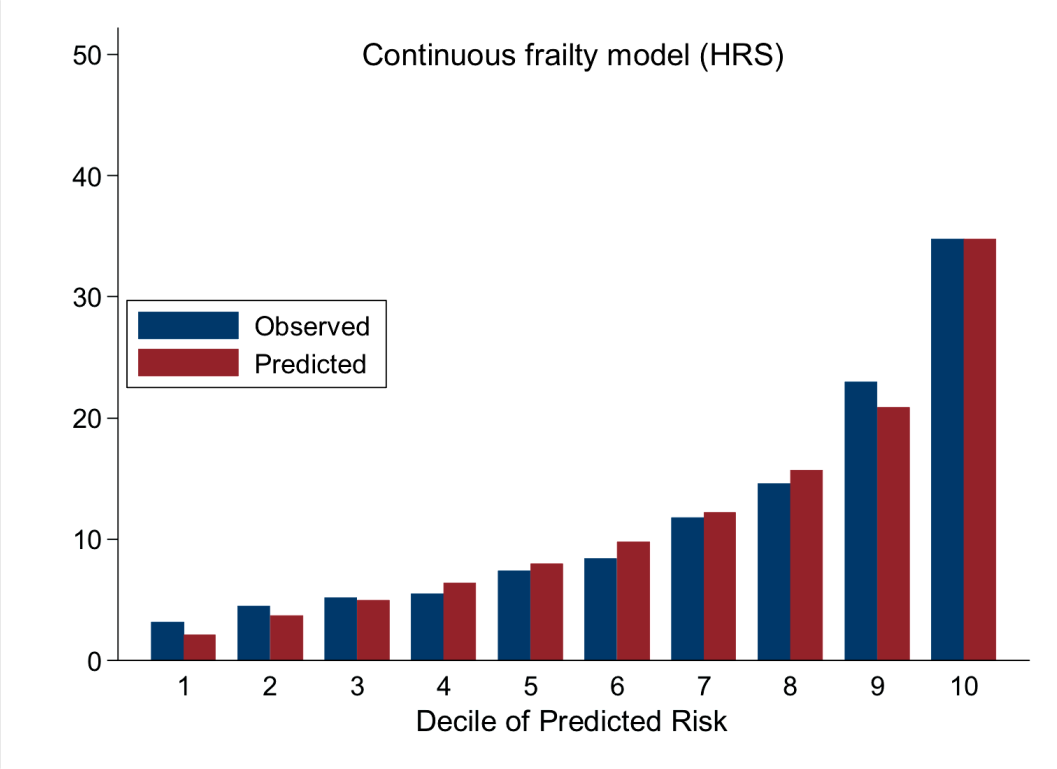
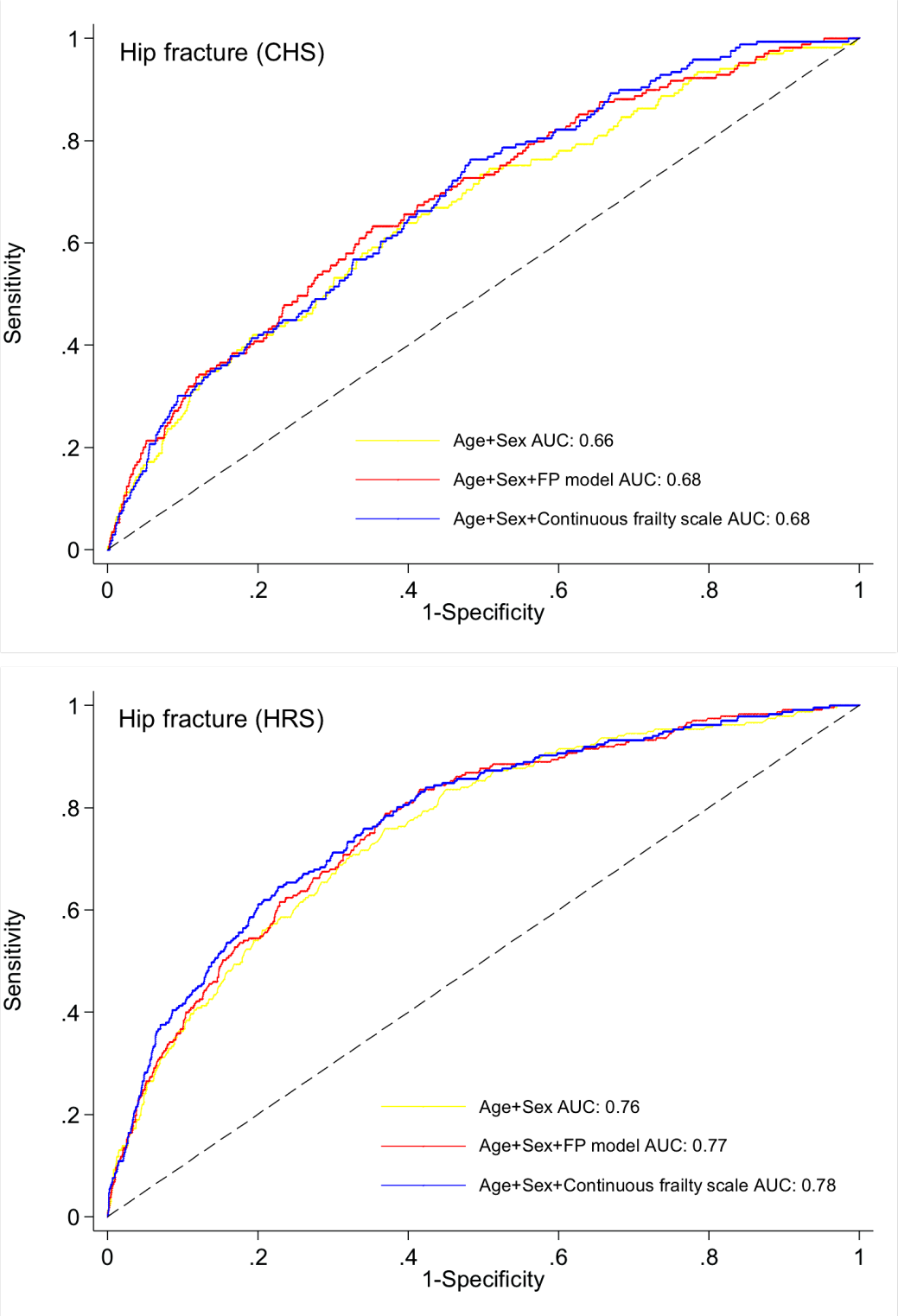
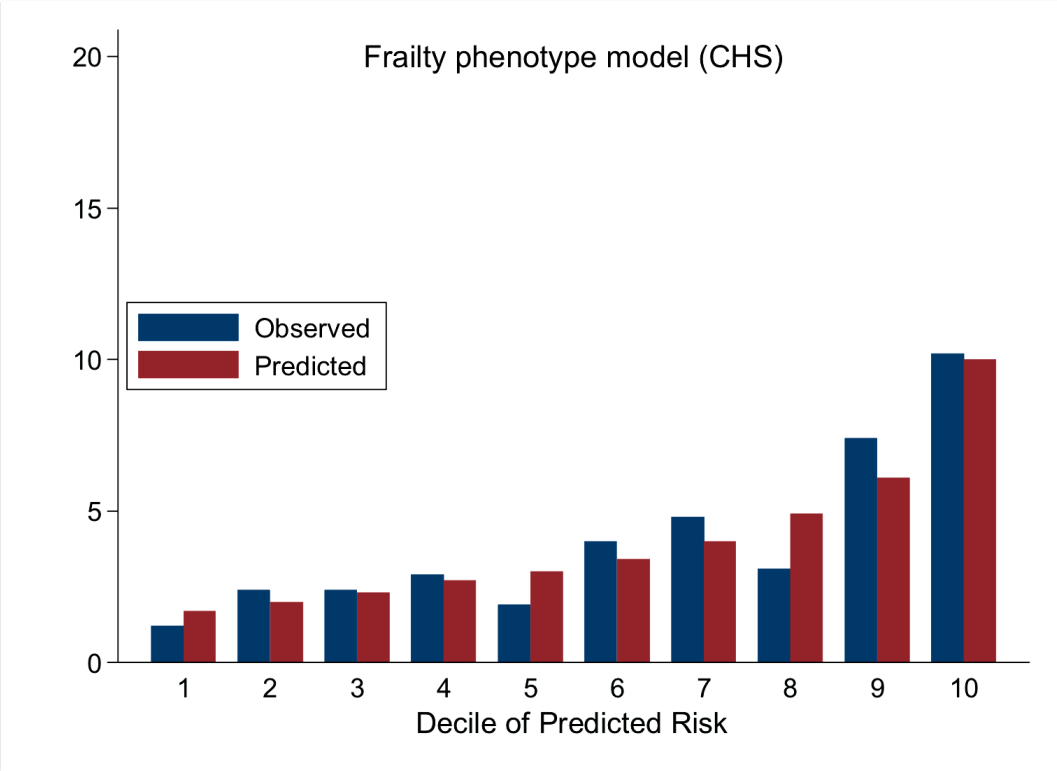


Figure 4–5. Receiver operating characteristics curves for prediction of hip fracture.



Notes: Age and sex were adjusted in all models. The black diagonal line represents a reference area under the curve (AUC) of 0.50 (no better than chance alone). CHS, Cardiovascular Health Study; HRS, Health and Retirement Study; AUC, area under the curve; FP; frailty phenotype.

Figure 4–6A. Agreement between predicted and observed hip fracture, Cardiovascular Health Study.



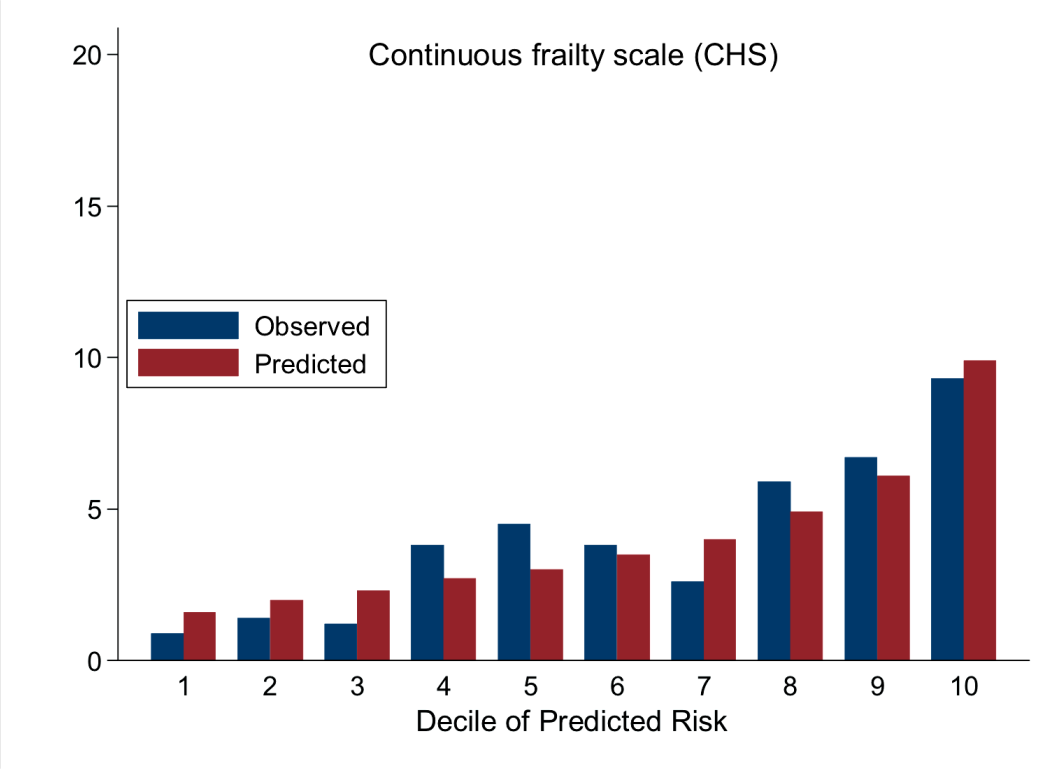
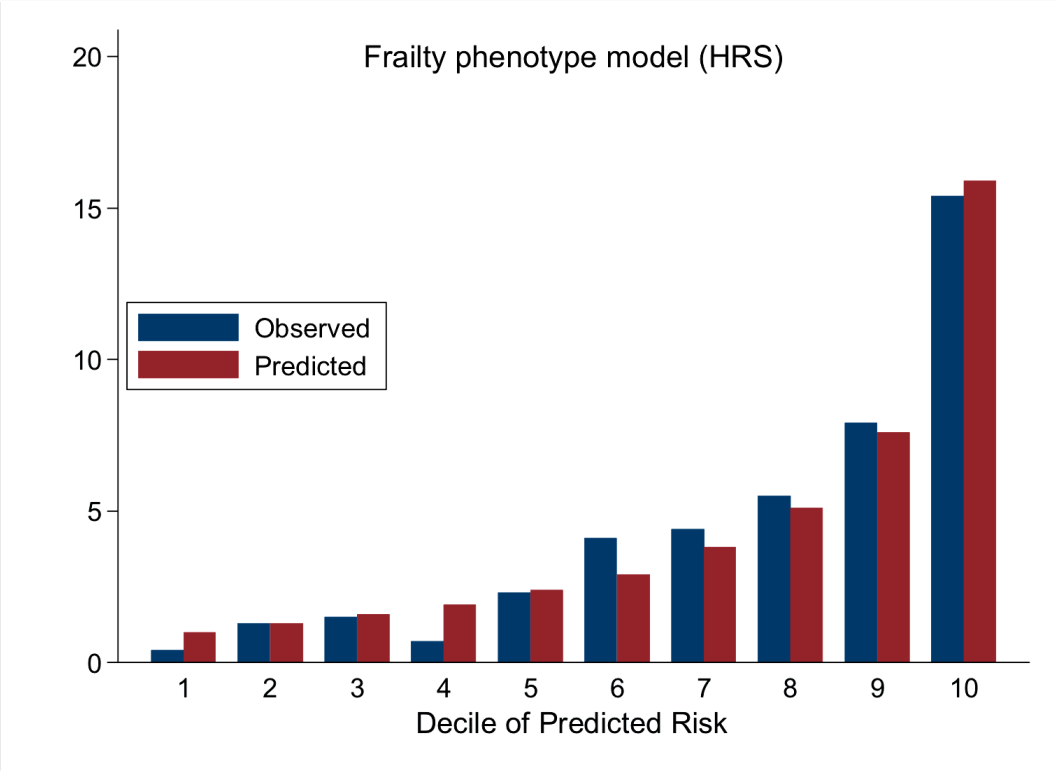


Figure 4–6B. Agreement between predicted and observed hip fracture, Health and Retirement Study.



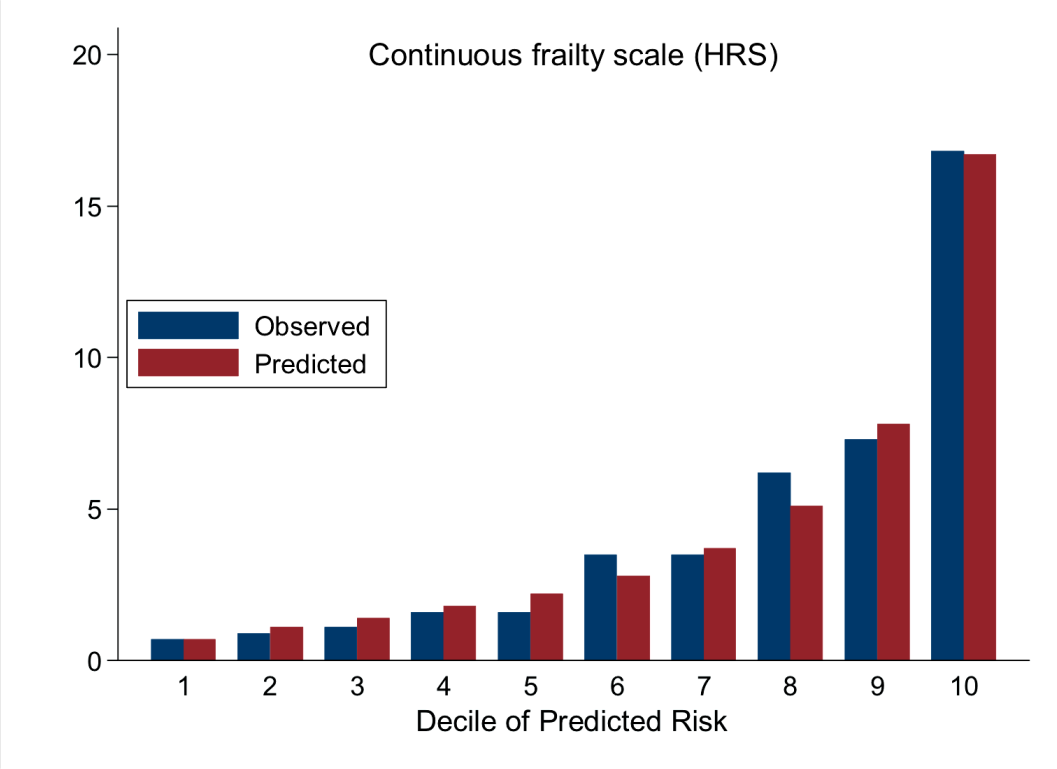
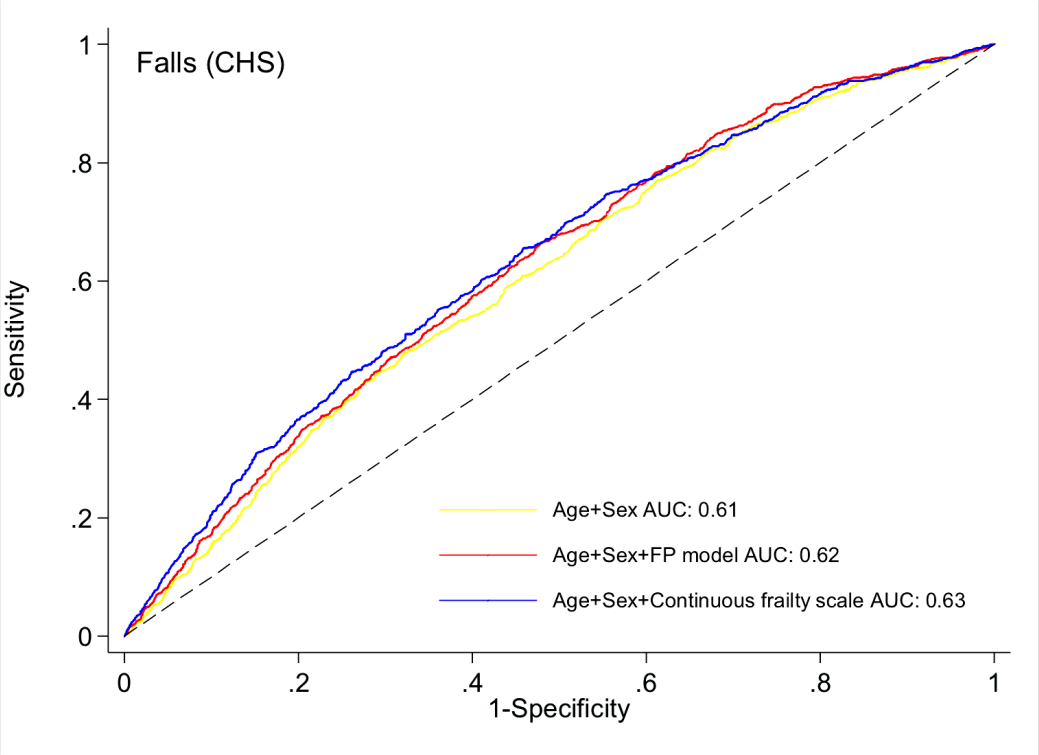
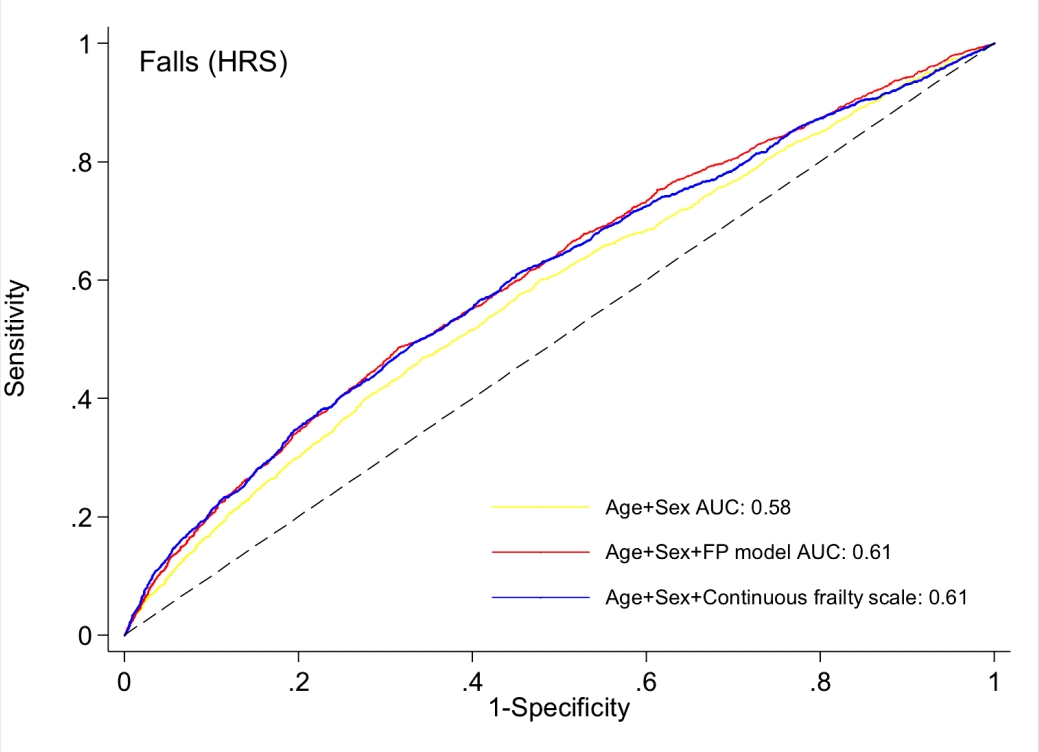


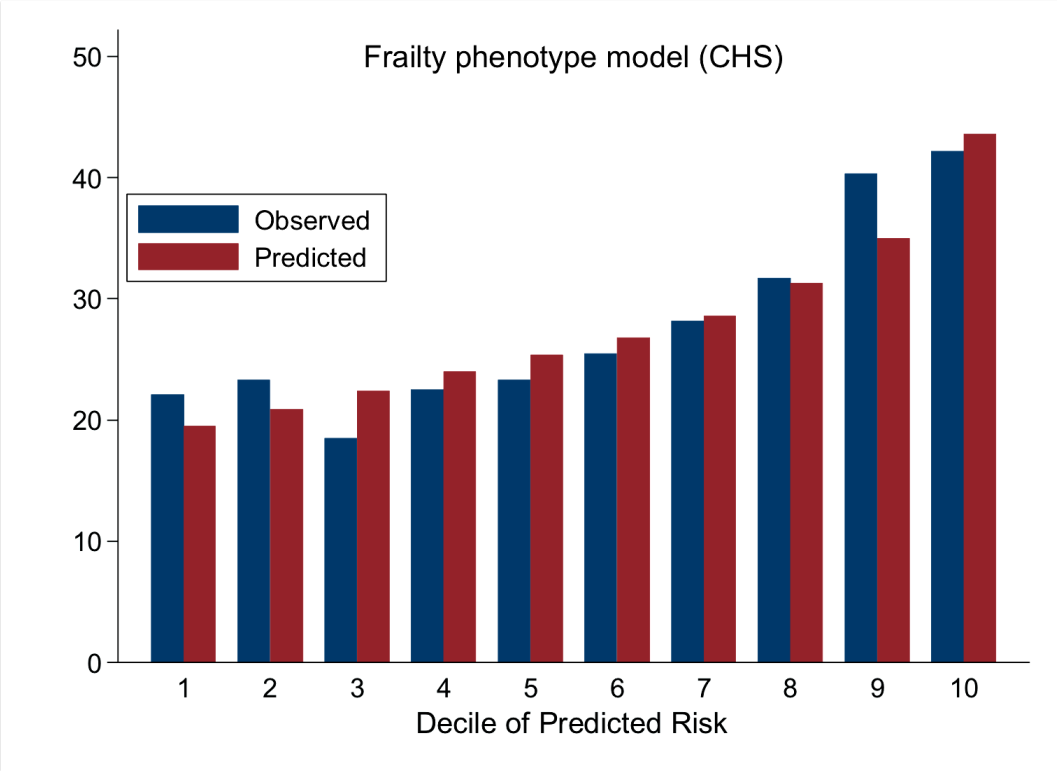
Figure 4–7. Receiver operating characteristics curves for prediction of falls.





Notes: Age and sex were adjusted in all models. The black diagonal line represents a reference area under the curve (AUC) of 0.50 (no better than chance alone). CHS, Cardiovascular Health Study; HRS, Health and Retirement Study; AUC, area under the curve; FP; frailty phenotype.

Figure 4–8A. Agreement between predicted and observed 2-year incidence of falls among 3,862 adults aged 65 years or older, Cardiovascular Health Study.



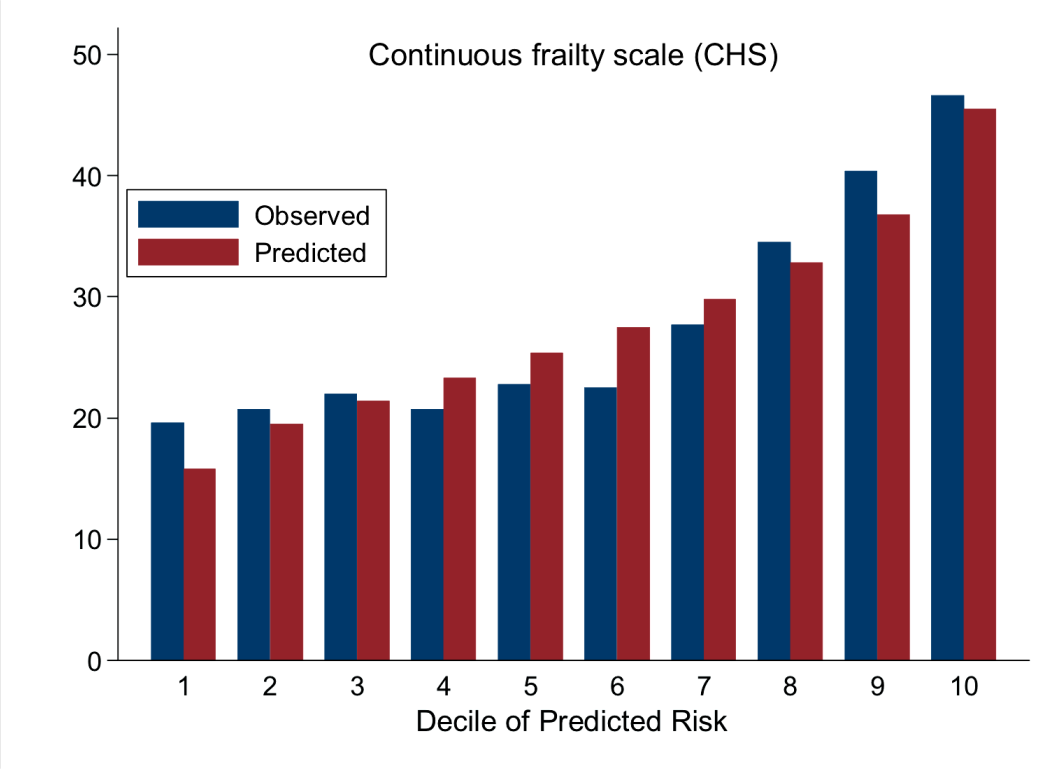
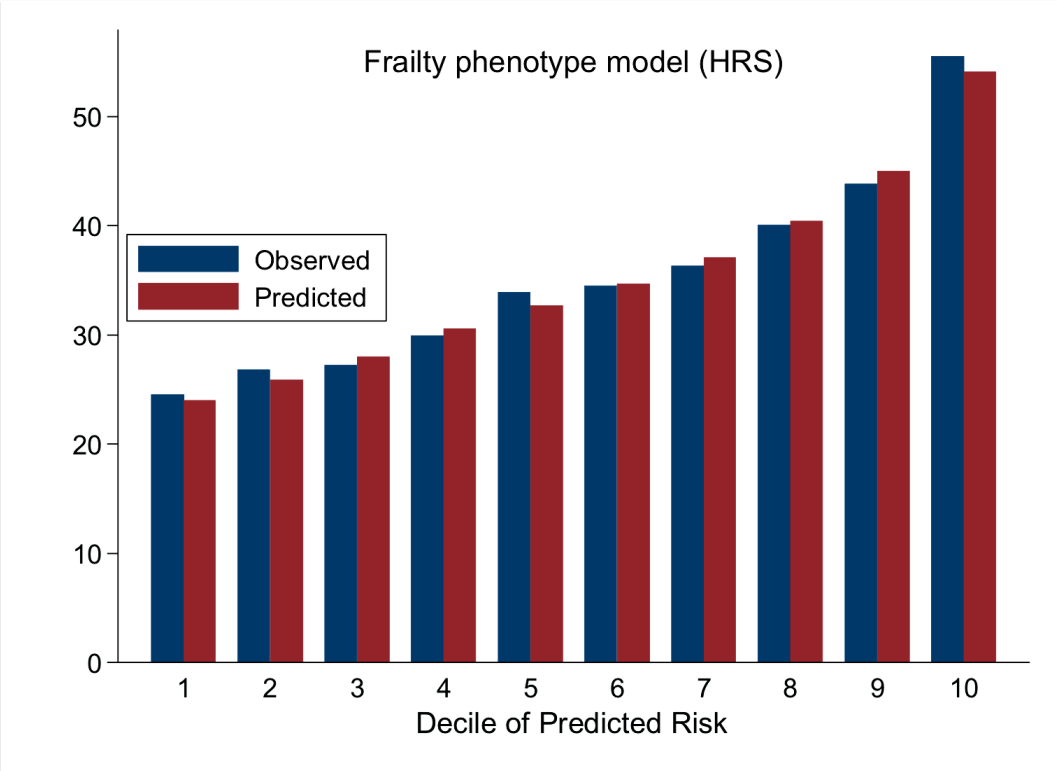
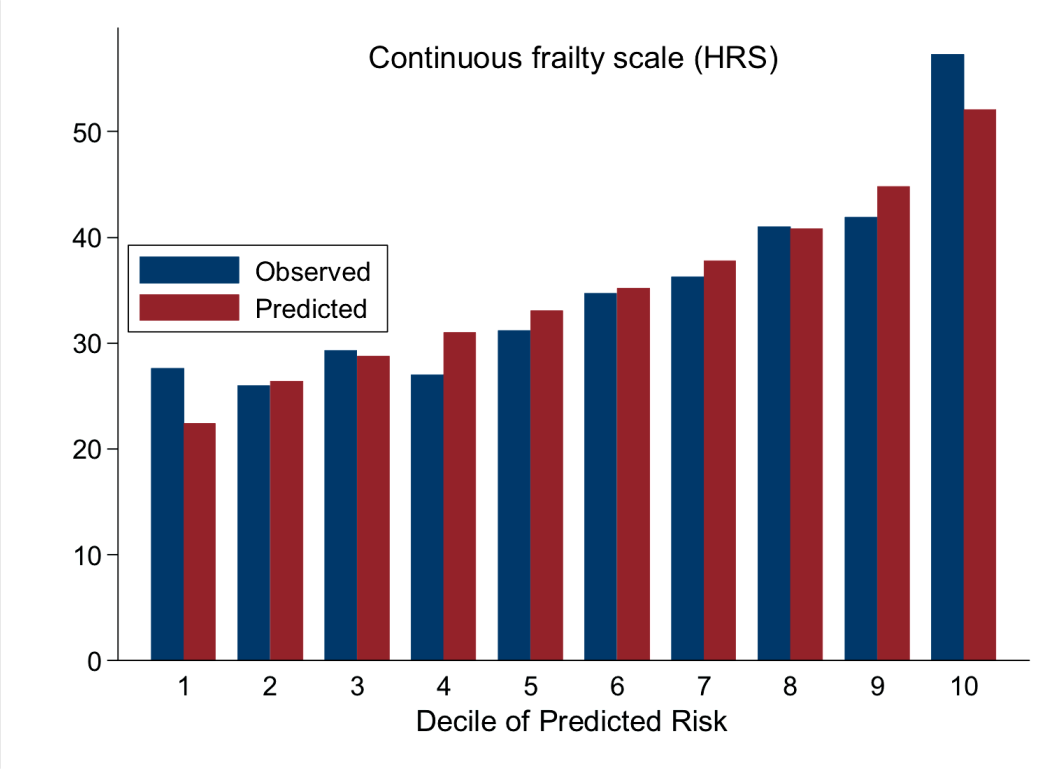


Figure 4–8B. Agreement between predicted and observed 2-year incidence of falls among 6,885 adults aged 65 years or older, Health and Retirement Study.





CHAPTER 5: ASSOCIATION BETWEEN FRAILTY AND RECOVERY FROM AND IMPROVEMENT IN DISABILITY AMONG OLDER ADULTS

5.1. Introduction

The prevalence of disability in activities of daily living (ADLs(has steadily declined among older Americans since early 1980s.[281,282] This promising trend, however, appears to have slowed, if not ceased, in the early 2000s.[283-285] Recent prevalence estimates range from 13.1% in those aged 65-69 years to 36.4% in those aged ≥85 years among community-dwelling older adults in the U.S.[286] ADL disability is associated with increased risk of mortality, hospitalization, and higher healthcare expenditures, placing a substantial burden on older persons, their informal caregivers, and health care resources.[193,195,287-290] Over the past two decades, a growing body of research has demonstrated that disability is a dynamic process rather than a progressive or irreversible event; transitions among different disability states are common, even among the oldest old or at the end of life.[291-299] Frailty has been well documented by epidemiologic research as a risk factor for disability among elders.[156] However, relatively little is known about the role of frailty in the process of disability recovery. Frailty, conceptualized as a physiologic state of decreased resilience to stressors, is an ideal candidate to capture reduced ability to recover from disability among elders.

In this chapter, I examined the association between frailty and both recovery of independence and improvement in ADL function among newly disabled older adults. Frailty was assessed by the newly developed continuous frailty scale and the physical frailty phenotype (PFP) scale.[35]

Given that the number of adults living with disability in the U.S. is expected to increase due to population aging, obtaining a better understanding of risk factors for recovery from disability is of significant interest to public health and has important implications for geriatric practice. In addition, knowledge of risk factors for resilience after disability may offer new opportunities for interventions and geriatric care targeted at promoting recovery from disability, maintaining the duration of recovery, and preventing recurrent disability.

5.2. Methods

5.2.1. Analytic Sample

Cardiovascular Health Study

Details of the Cardiovascular Health Study (CHS) were described in Section 3.2.1. I used the CHS Year 5 (1992-93) and Year 9 (1996-97), when all five measures used for constructing the continuous frailty scale were available (i.e., direct calculation of weight loss between two consecutive visits was possible). These two periods (1992-93 for the original cohort and 1996-97 for the new cohort) served as the baseline for the CHS cohort for subsequent analyses in this chapter. ADL disability was available at baseline and was measured every year thereafter. The analytic sample was limited to 780 persons who (i) had complete data on five frailty indicators (gait speed, grip strength, exhaustion, physical activity, and weight loss) at baseline, (ii) had independence in all ADLs at baseline, and (iii) had difficulty in at least one ADL function within three years (three annual follow-up visits).

Health and Retirement Study

The Health and Retirement Study (HRS) was described in detail in Section 3.2.1. I used pooled data from the 2006-07 and 2008-09 survey waves of the HRS, when gait speed and grip strength were measured. These two periods served as the baseline for the HRS cohort in subsequent analyses in this chapter; ADL disability was available at baseline and was measured every two years thereafter. I included 1,241 persons who (i) were ≥65 years, (ii) had complete data on all five frailty indicators at baseline (2006 or 2008 wave, depending when physical functions were assessed), (iii) were free of ADL disability at baseline, and (iv) had difficulty in at least one ADL function within four years (two biennial follow-up visits).

5.2.2. Frailty

Frailty was measured in two ways: the continuous frailty scale and the PFP scale. Details of operational definitions of five frailty indicators used to construct the two frailty assessments were described in Section 3.2.3.1. For the continuous frailty scale, standardized score for each of the five frailty indicators was first calculated by dividing the difference between observed value and the sample mean by the standard deviation (separately for two cohorts). Then, five standardized scores were summed to create the continuous frailty score, weighted by the standardized factor loadings identified using confirmatory factor analysis (CFA; Table 3–4). In the PFP scale, participants were classified as robust, prefrail, and frail using all participants with complete data on five frailty indicators as reference population (analyzed separately; N = 4,243 in the CHS; N = 7,600 in the HRS). Five criteria of the PFP scale were provided in Chapter 3.

5.2.3. Outcomes

I examined two indicators of resilience after onset of disability among non-disabled older adults: recovery from and improvement in disability. Recovery was defined as regaining independence

in all six ADLs in the following visit after disability (one year after in the CHS and two years after in the HRS). Improvement in disability was defined as a decrease in ≥1 unit of ADL score in the following visit after experiencing disability.

Persons who died before subsequent visit after the onset of new disability were presumed not to have recovered nor improved their ADL function. This is a commonly used strategy in dealing with missing data due to death,[300] justified by the fact that approximately 90% of community-dwelling older adults experience disability within one year of death.[301] Persons who were alive but not interviewed in the following visit after the onset of disability were considered missing and therefore were excluded from the primary analysis.

5.2.4. Analytic Approaches

I compared the baseline characteristics of persons who did and did not experience incident ADL disability using a t-test assuming unequal variance for continuous variables and a χ^2 test for categorical variables. The two study cohorts were analyzed separately.

I presented the numbers and proportions of persons who recovered from disability (regained independence in all six ADLs) and had improvement in ADL function stratified by quintiles of the continuous frailty score and by frailty status identified by the PFP scale (robust, prefrail, or frail), respectively. Subsequently, I determined the unadjusted and adjusted association of frailty with recovery from and improvement in ADL function, respectively. Clinic site (only for the CHS; Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age (years; continuous), sex (male or female), race/ethnicity (white or others), education (less than high school, high school or

equivalent, or more than high school; categorical), smoking status (current, previous, or never smokers; categorical), BMI (<25.0, 25.0-30.0, or >30.0; categorical), history of chronic conditions (yes or no for each condition), self-rated health (continuous), cognitive function (Modified Mini-Mental State Examination in the CHS and Telephone Interview for Cognitive Status in the HRS; continuous), severity of disability at onset assessed by number of difficulty in ADL functions, and years between frailty assessment and the onset of disability were included in the multivariable adjusted models. Operational definitions of covariates in two cohorts were presented in Sections 3.2.3.2 and 3.2.3.3. All covariates were measured at baseline. I did not use the most recent assessment of covariates prior to the onset of incident disability because adjusting for covariates measured after frailty may block the mediating pathway between frailty and indicators of resilience to disability and therefore underestimates the overall effect of frailty on the outcomes. I used a Poisson model with robust variance estimates to determine the associations between frailty and outcomes. The continuous frailty scale was modeled both as a continuous predictor and in quintiles with the first quintile serving as the reference; frailty status identified by the PFP scale was modeled as a 3-level categorical predictor with the robust being the reference. I used the locally weighted scatterplot smoothing approach to visually evaluate whether there was non-linear relationship between the continuous frailty score with recovery from and improvement in disability. All analyses were conducted separately for the two cohorts.

Several sensitivity analyses were performed. Frist, I included participants who were alive but did not participate in the following visit after the onset of ADL disability and considered them as “not recovered” and “not improved”. Additionally, I explored the association of frailty with recovery from and improvement in disability among participants who experienced severe

disability, defined as difficulty in ≥2 ADLs. I conducted several supplementary analyses. First, I determined the association of the continuous frailty score with indicators of recovery from disability among robust, prefrail, and frail adults to evaluate whether the continuous frailty scale provided additional value in stratifying risk of recovery from and improvement in ADL function beyond the PFP scale. In addition, I used the C statistic to compare the ability to predict recovery from disability between the two frailty assessments.

All tests were two-sided with a significance level of $p < .05$. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX)[253] and the R Language for Statistical Computing (version 3.2.2).[274]

5.3. Results

Sample Description

Of the 3,807 CHS participants who had no difficulty in any ADLs at baseline, 780 (20.5%) were newly disabled in ≥1 ADL function within three years. Among 6,450 HRS participants with no difficulty in any ADLs at baseline, 1,241 (19.2%) were disabled in ≥1 ADL function within four years. In both cohorts, participants who experienced ADL disability were older, were more likely to be female, and had higher BMI, more chronic conditions, lower cognitive function, and higher level of frailty (Tables 5–1A & 5–1B).

Of the 780 newly disabled CHS participants, 644 (82.6%) had ADL measures in the following visit and 40 (5.1%) died before the following visit; these 684 persons were included in the primary analysis for the CHS cohort. Ninety-six (12.3%) participants who were lost to follow-up

were excluded (Figure 5–1). Of the 1,241 newly disabled HRS participants, 954 (76.9%) had ADL measures in the following visit and 212 (17.1%) died before the subsequent visit; these 1,166 persons were included in the primary analysis for the HRS cohort. Seventy-five (6.0%) participants who were lost to follow-up and were excluded.

Association of Frailty with Resilience after Disability in the Cardiovascular Health Study

Of the 684 newly disabled CHS participants who had ADL measures in or died prior to the following visit, 349 (51.0%) and 392 (57.3%) had recovery of and improvement in ADL function, respectively (Table 5–2). The probabilities of recovering of and improving in ADL function both decreased steadily with higher score on the continuous frailty scale. Among persons with the continuous frailty scores in the lowest quintile, over two-thirds had recovery from disability and approximately three fourths had improvement in ADL function. In contrast, only two fifths and less than half of the persons with the highest frailty scores (5^{th} quintile) had full recovery of and improvement in ADL function, respectively. I observed similar results when frailty was assessed by the PFP scale. The proportion of recovery from disability decreased from 62.4% for robust persons to 35.4% for those who were frail; the proportion of improvement in ADL function declined from 68.4% for the robust to 47.7% for the frail.

I observed an approximate linear relationship between the continuous frailty score and two indicators of resilience to disability when one person with extreme frailty score was excluded (< -3.0; Figure 5–2). The unadjusted risk of recovering of and improving in ADL function was 18% (95% confidence interval [CI]: 11%, 24%) and 14% (95% CI: 8%, 20%) lower per unit of the continuous frailty score, respectively (Table 5–3). Compared with persons with the continuous

frailty scores in the lowest quintile, the probability of recovering from disability and improving in ADL function was 41% (95% CI: 25%, 53%) and 35% (95% CI: 20%, 47%) lower for those with the highest frailty scores (5th quintile), respectively. The association between frailty and resilience to disability persisted after multivariable adjustment. The adjusted probability of recovery of and improvement in ADL function was 12% (95% CI: 3%, 20%) and 10% (95% CI: 2%, 17%) lower per unit of the continuous frailty score, respectively. Persons with the highest frailty scores (5th quintile) were 27% (95% CI: 6%, 43%) and 26% (95% CI: 8%, 41%) less likely to recover from disability and improve in ADL function than those lowest frailty scores (1st quintile), respectively. When frailty was assessed by the PFP scale, prefrail persons had a 25% and 24% lower chance of recovery and improvement, respectively, than the robust; frail persons had a 43% and 40% lower chance of recovery and improvement, respectively, compared with those who were robust. After multivariable adjustment, only prefrail persons had a significantly lower chance of recovery and improvement than the robust.

Results were robust to several sensitivity analyses. I observed similar but slightly attenuated associations of frailty with recovery of and improvement in ADL function when I included 96 participants who were not interviewed in the following visit after experiencing disability (Figure 3). Results were also similar when only persons who had incident severe disability (difficulty in ≥2 ADL functions) were included (n = 163; Table 5–4).

Association of Frailty with Resilience after Disability in the Health and Retirement Study

Of the 1,166 newly disabled HRS participants who had ADL measures in or died prior to the following visit, 415 (35.6%) and 506 (43.4%) had recovery of and improvement in ADL

function, respectively (Table 5–5). The probabilities of recovering from disability and improving in ADL function both decreased steadily with higher scores on the continuous frailty scale. Among persons with the lowest continuous frailty scores (1st quintile), 51.5% had recovery from disability and 54.5% improved in ADL function. In contrast, approximately 20% and 30% of persons with the highest frailty scores (5th quintile) had recovery of and improvement in ADL function, respectively. Similar results were observed when frailty was assessed by the PFP scale. The proportion of recovery from disability decreased from 43.9% for robust persons to 16.8% for those who were frail; the proportion of improvement in ADL function declined from 50.7% for the robust to 23.6% for the frail.

I observed an approximate linear relationship between the continuous frailty scale and two indicators of resilience to disability when six persons with extreme frailty scores were excluded (< -3.0; Figure 5–4). The unadjusted risk of recovering from disability and improving in ADL function was 21% (95% CI: 16%, 26%) and 15% (95% CI: 10%, 19%) lower per unit of the continuous frailty score, respectively (Table 5–6). Compared with persons with the continuous frailty scores in the lowest quintile, the probability of recovery of and improvement in ADL function was 56% (95% CI: 42%, 66%) and 40% (95% CI: 24%, 52%) lower for those with the highest frailty scores (5th quintile), respectively. In adjusted models, the probability of recovering from ADL disability was 8% (95% CI: 2%, 15%) lower per unit of the continuous frailty scale. Persons with the highest continuous frailty scores (5th quintile) were 25% (95% CI: 1%, 43%) less likely to recover from ADL disability than those with the lowest continuous frailty scores (1st quintile). The association between the continuous frailty scale and improvement in ADL function was no longer statistically significant after multivariable adjustment; however, I

observed trends towards lower probabilities of improving in ADL function among persons with higher frailty scores. When frailty was measured by the PFP scale, prefrail persons had a 19% and 13% lower chance of recovery and improvement, respectively, than the robust; frail persons had a 62% and 54% lower chance of recovery and improvement, respectively, compared the robust. After multivariable adjustment, only frail persons had a significantly lower chance of recovery and improvement than the robust.

Results were robust to several sensitivity analyses. I observed similar but slightly attenuated associations I included 75 participants who were not interviewed in the following visit after experiencing disability (Figure 4–5). Results were also similar when only persons who had severe disability (difficulty in ≥2 ADL functions) were included (n = 442; Table 5–7).

Comparison between the Continuous Frailty Scale and the Physical Frailty Phenotype Scale

In both cohorts, I observed a moderate gradient of risk of recovery of and improvement in ADL function for the continuous frailty score among robust persons identified by the PFP scale (Figures 5–6A & 5–6B). There was variation in risk of recovery of and improvement in ADL function among the prefrail with different continuous frailty scores, although the trend was less clear.

In the CHS, two frailty assessments alone had similar discrimination performance (C statistic: 0.60 vs. 0.59, p = .564 for comparison; Figure 5–7). Both frailty assessments had higher C statistic than age alone (C statistic = 0.57), though neither of the differences were significant (p's = .409 and .238 for comparisons). In the HRS, the continuous frailty scale had significantly higher C statistic than the PFP scale (0.63 vs. 0.59, p <.001 for comparison).

5.4. Discussion

In this chapter, I aimed to examine the association between frailty and resilience after disability among initially non-disabled older adults. I showed that frailty, assessed by both the continuous frailty scale and the PFP scale, was strongly associated with recovery of and improvement in ADL function among newly disabled community-dwelling older adults from two large, population-based cohort studies. I also found suggestive evidence that the continuous frailty scale could capture the risk gradient in recovery of and improvement in ADL function among elders who were classified as robust and prefrail by the PFP scale. These results highlighted the potential prognostic importance of frailty to recovery of ADL function after being disabled and demonstrated that both the continuous frailty scale and the PFP scale—two frailty assessments that are guided by the PFP framework—can capture one of the defining features of frailty—reduced reserve and resilience to stressors.

Our findings were consistent with an earlier study conducted by Boyd et al.[302] showing that frailty, assessed by the PFP scale, was associated with decline in ADL function after hospitalization among 457 moderately to severely disabled community-dwelling older women. In addition to multi-component measures of frailty, prior studies have demonstrated associations between commonly used indicators of frailty—e.g., gait speed, physical activity, and weight loss—with recovery from disability.[291,303,304] Using data from 420 newly disabled persons from the Precipitating Events Project, a cohort study of 754 community-dwelling adults aged ≥70 years in greater New Haven, Connecticut, Hardy et al.[291] found that elders with slow gait speed, defined as spending >10 seconds walking back and forth over a 10-foot course as quickly as possible, were less likely to recovery from ADL disability. Using data from the same sample,

Hardy and Gill showed that habitual physical acidity was an independent risk factor for both time to and duration of recovery of ADL function.[303] More recently, Gill et al.[304] found that significant weight loss, denoted as self-report of a 10-pound weight loss in the previous year, was associated with lower likelihood of recovery of prehospital ADL function among 292 elders newly admitted to a nursing home with disability after an acute hospitalization. The present study extended previous research in several important ways. First, instead of using single-item measures of frailty, I measured frailty comprehensively using two multi-component frailty instruments grounded in the PFP framework. Second, because participants in this study were from two large, population-based cohorts with heterogeneous samples, findings are readily generalizable.

This study has many strengths, including its prospective design, comprehensive set of measurements of potential confounders, relatively large sample size, heterogeneity in demographic composition of study sample, and cross-validation of results in an independent data set. To my knowledge, this study is among the first to assess the association of frailty with recovery of and improvement in ADL function among community-dwelling older adults.

Despite these strengths, I acknowledge several limitations. First, numerous assessments of frailty have been proposed, but I only used two assessments—the continuous frailty scale and the PFP scale—grounded in the PFP framework. Compared with many other frailty assessments (e.g., frailty index [FI] and Fatigue, Resistance, Ambulation, Illness, and Loss [FRAIL] scale), the PFP framework-guided assessments consider frailty as a specific physiological state with its own definable phenotypic manifestation that is distinguishable from other clinical entities, such as

disability and cormorditiy.[276] Other frailty assessments are potentially of prognostic value in predicting recovery from disability; however, lacking a specific definition (e.g., inclusion of disability and/or comorbidity measures) may complicate interventions aimed at promoting disability recovery through mitigating frailty. In addition, I only focused on the relationship between frailty and recovery from incident disability. Recovery from recurrent disability might have different risk factor profiles, which deserves consideration for future research. Moreover, the associations of frailty assessed prior to disability and recovery indicators measured after disability only supported but did not imply causation.

In summary, I found that frailty was independently associated with resilience after ADL disability among community-dwelling older adults. The present study provides evidence that the continuous frailty scale and the PFP scale, both of which were developed under the PFP framework, are valid measures of frailty, characterized by reduced resilience to stressors and increased vulnerability to outcomes. Assessment of frailty may help clinicians, public health professionals, and researchers better identify at-risk elders after experiencing disability.

Table 5–1A. Characteristics of initially non-disabled older adults who were and were not disabled within three years, Cardiovascular and Health Study.

	Had ADL disability within 3 years[a]		
Characteristics	Yes n = 780	No n = 3,027	*p* [b]
Age, years, mean (SD)	72.7 (5.3)	71.7 (4.8)	<.001
Male, No. (%)	272 (34.9)	1,383 (45.7)	<.001
White (vs. Black), No. (%)	688 (89.2)	2,670 (88.2)	.999
Education			.576
< High school, No. (%)	194 (24.9)	732 (24.2)	
= High school, No. (%)	214 (27.5)	888 (29.4)	
> High school, No. (%)	371 (47.6)	1,402 (46.4)	
Smoking status			.831
Never, No. (%)	345 (45.3)	1,326 (45.3)	
Former, No. (%)	347 (45.6)	1,357 (45.6)	
Current, No. (%)	69 (9.1)	290 (9.1)	
Body mass index, kg/m^2			<.001
Underweight/normal[c], No. (%)	266 (34.1)	1,222 (40.4)	
Overweight, No. (%)	330 (42.3)	1,292 (42.7)	
Obese, No. (%)	184 (23.6)	513 (17.0)	
Coronary heart disease, No. (%)	180 (23.1)	620 (20.5)	.113
Heart failure, No. (%)	43 (5.5)	146 (4.8)	.429
Stroke, No. (%)	51 (6.5)	105 (3.5)	<.001
Hypertension, No. (%)	448 (57.6)	1,633 (54.0)	.208
Borderline, No. (%)	124 (15.9)	450 (14.9)	
Hypertensive, No. (%)	324 (41.7)	1,183 (39.2)	
Diabetes			<.001
Prediabetes, No. (%)	72 (9.6)	287 (9.7)	
Diabetes, No. (%)	142 (19.0)	387 (13.1)	
Cancer, No. (%)	130 (16.7)	399 (13.2)	.012
Arthritis, No. (%)	443 (58.4)	1,174 (39.8)	<.001
3MS[d], mean (SD)	90.4 (8.9)	91.8 (7.9)	<.001
Continuous frailty score, mean (SD)	0.2 (0.9)	-0.3 (0.9)	<.001
Physical frailty phenotype status			<.001
Robust, No. (%)	268 (34.4)	1,570 (51.9)	
Prefrail, No. (%)	435 (55.8)	1,313 (43.4)	
Frail, No. (%)	77 (9.9)	144 (4.8)	

Abbreviations: ADL, activity of daily living; SD, standard deviation; 3MS, Modified Mini-Mental State Examination.

[a] Having difficulty in ≥1 ADLs (ADL scored ≥1).

[b] *p*-values were taken from t test with unequal variance or χ^2 test for comparison between older adults who did and did not have difficulty in at least one ADL within three annual follow-up visits.

[c] Underweight and normal were collapsed due to small cell size in the underweight category.

[d] Ranging from 0 to 100 with higher score indicating a better global cognitive function.

Table 5–1B. Characteristics of initially non-disabled older adults who were and were not disabled within four years, Health and Retirement Study.

	Had ADL disability within 4 years[a]		
Characteristics	Yes n = 1,241	No n = 5,213	*p* [b]
Age, years, mean (SD)	76.9 (7.2)	73.8 (6.3)	<.001
Male, No. (%)	506 (40.8)	2,359 (42.3)	.004
White (vs. others), No. (%)	1,094 (88.2)	4,699 (90.1)	.037
Education			<.001
< High school, No. (%)	374 (30.1)	1,065 (20.4)	
= High school, No. (%)	430 (34.7)	1,926 (37.0)	
> High school, No. (%)	437 (35.2)	2,221 (42.6)	
Smoking status			.644
Never, No. (%)	537 (43.6)	2,248 (43.4)	
Former, No. (%)	573 (46.5)	2,461 (47.5)	
Current, No. (%)	122 (9.9)	472 (9.1)	
Body mass index, kg/m^2			.013
Underweight/normal[c], No. (%)	311 (25.1)	1,448 (27.8)	
Overweight, No. (%)	464 (37.4)	2,030 (38.4)	
Obese, No. (%)	466 (37.6)	1,735 (33.3)	
Cardiac disease[d], No. (%)	456 (36.7)	1,396 (26.8)	<.001
Stroke, No. (%)	115 (9.3)	232 (4.5)	<.001
Hypertension, No. (%)	819 (66.2)	3,199 (61.4)	.002
Lung disease, No (%)	184 (14.8)	464 (8.9)	<.001
Diabetes, No. (%)	308 (24.8)	982 (18.8)	<.001
Cancer[e], No. (%)	263 (21.2)	936 (18.0)	.009
Arthritis, No. (%)	957 (77.1)	3,242 (62.2)	<.001
TICS[f], mean (SD)	9.0 (1.4)	9.4 (1.0)	<.001
Continuous frailty score, mean (SD)	0.4 (1.2)	-0.4 (1.2)	<.001
Physical frailty phenotype status			<.001
Robust, No. (%)	382 (30.8)	2,854 (54.8)	
Prefrail, No. (%)	584 (55.1)	2,126 (40.8)	
Frail, No. (%)	175 (14.1)	233 (4.5)	

Abbreviations: ADL, activities of daily living; SD, standard deviation; TICS, the Telephone Interview for Cognitive Status.

[a] Having difficulty in at least one ADL (scored ≥1).

[b] *p*-values were from generalized linear regression with clustered sandwich estimator for comparison between older adults who did and did not have difficulty in at least one ADL within two biennial follow-up visits.

[c] Underweight and normal were collapsed due to small cell size in the underweight category.

[d] Heart attack, coronary heart disease, angina, heart failure, or other heart problems.

[e] Cancer or malignant tumor, excluding minor skin cancer.

[f] Ranging from 0 to 10 with higher score indicating a better global cognitive function.

Table 5–2. Cross-tabulation of frailty with recovery from and improvement in disability among newly disabled adults, Cardiovascular Health Study.

	ADL disability (n = 684)[a]	
	Recovery[b]	Improvement[c]
	Events (%)	
Total	349 (51.0)	392 (57.3)
Continuous frailty score[d]		
1st quintile	50 (67.6)	54 (73.0)
2nd quintile	63 (55.3)	72 (63.2)
3rd quintile	78 (55.3)	84 (59.6)
4th quintile	83 (49.4)	93 (55.4)
5th quintile	75 (40.1)	89 (47.6)
PFP scale[e]		
Robust	146 (62.4)	160 (68.4)
Prefrail	180 (46.8)	201 (52.2)
Frail	23 (35.4)	31 (47.7)

Abbreviations: ADL, activities of daily living; PFP, physical frailty phenotype.
Notes: Persons who recovered from disability and those who improved ADL function were not mutually exclusive. Persons who recovered also improved, but not all persons who improved recovered.
[a] Participants who died in the following visit after the onset of incident disability were included and considered not to recover nor to improve; Participants who were alive but not interviewed in the following visit after the onset of incident disability were not included.
[b] Having no difficulty on any ADLs (scored 0) in the following visit after the onset of incident ADL disability.
[c] A decrease in at least one unit of ADL score in the following visit after the onset of incident ADL disability.
[d] Quintiles were determined based on 4,243 adults who were at least 65 years and had frailty assessment at baseline.
[e] Robust, prefrail, and frail status were identified based on 4,243 adults who were at least 65 years and had frailty assessment at baseline.

Table 5–3. Association of frailty with recovery from and improvement in disability among newly disabled adults, Cardiovascular Health Study.

	Recovery from ADL[a]		Improving ADL[b]	
			n = 684	
	Unadjusted	Adjusted[c]	Unadjusted	Adjusted[c]
			RR (95% CI)	
Frailty score	0.82 (0.76, 0.89)	0.88 (0.80, 0.97)	0.86 (0.80, 0.92)	0.90 (0.83, 0.98)
Categories				
1st quintile	Ref.	Ref.	Ref.	Ref.
2nd quintile	0.82 (0.65, 1.03)	0.84 (0.67, 1.07)	0.87 (0.71, 1.05)	0.85 (0.70, 1.04)
3rd quintile	0.82 (0.66, 1.02)	0.78 (0.62, 0.99)	0.82 (0.67, 0.99)	0.79 (0.64, 0.97)
4th quintile	0.73 (0.59, 0.91)	0.77 (0.61, 0.97)	0.76 (0.62, 0.92)	0.79 (0.64, 0.96)
5th quintile	0.59 (0.47, 0.75)	0.73 (0.57, 0.94)	0.65 (0.53, 0.80)	0.74 (0.59, 0.92)
PFP scale				
Robust	Ref.	Ref.	Ref.	Ref.
Prefrail	0.75 (0.65, 0.87)	0.81 (0.69, 0.95)	0.76 (0.67, 0.87)	0.83 (0.72, 0.95)
Frail	0.57 (0.40, 0.80)	0.82 (0.59, 1.14)	0.70 (0.53, 0.91)	0.87 (0.66, 1.13)

Abbreviations: ADL, activities of daily living; RR, relative risk; CI, confidence interval; PFP, physical frailty phenotype.

Notes: Persons who recovered from disability and those who improved ADL function were not mutually exclusive. Persons who recovered also improved, but not all persons who improved recovered.

[a] No difficulty on any ADLs in the following visit after the onset of incident ADL disability.

[b] Any decrease in ADL score in the following visit after the onset of incident ADL disability.

[c] Adjusted for clinical site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the modified mini-mental status examination, severity of incident ADL disability at onset (i.e., number of difficulties in activities of daily living), and years between frailty assessment and the onset of incident ADL disability.

Table 5–4. Association of frailty with recovery from and improvement in disability among initially non-disabled adults who had incident severe disability, Cardiovascular Health Study.

	ADL disability (n = 163)[a]	
	Recovery[b]	Improvement[c]
	Events (%)	
Total	65 (39.9)	108 (66.3)
Continuous frailty score[d]		
1st quintile	9 (69.2)	13 (100.0)
2nd quintile	9 (32.1)	18 (64.3)
3rd quintile	14 (48.3)	20 (69.0)
4th quintile	12 (37.5)	22 (68.8)
5th quintile	21 (34.4)	35 (57.4)
PFP scale[e]		
Robust	29 (54.7)	43 (81.1)
Prefrail	27 (34.6)	48 (61.5)
Frail	9 (28.1)	17 (53.1)

Abbreviations: ADL, activities of daily living; PFP, physical frailty phenotype.
Notes: Persons who recovered from disability and those who improved ADL function were not mutually exclusive. Persons who recovered also improved, but not all persons who improved recovered.
[a] Participants who died in the following visit after the onset of incident disability were included and considered not to recover nor to improve; Participants who were alive but not interviewed in the following visit after the onset of incident disability were not included.
[b] Having no difficulty on any ADLs (scored 0) in the following visit after the onset of incident ADL disability.
[c] A decrease in at least one unit of ADL score in the following visit after the onset of incident ADL disability.
[d] Quintiles were determined based on 4,243 adults who were at least 65 years and had frailty assessment at baseline.
[e] Robust, prefrail, and frail status were identified based on 4,243 adults who were at least 65 years and had frailty assessment at baseline.

Table 5–5. Cross-tabulation of frailty with recovery from and improvement in disability among newly disabled adults, Health and Retirement Study.

	ADL disability (n = 1,166)[a]	
	Recovery[b]	Improvement[c]
	Events (%)	
Total	415 (35.6)	506 (43.4)
Continuous frailty score[d]		
1st quintile	52 (51.5)	55 (54.5)
2nd quintile	88 (47.6)	92 (54.8)
3rd quintile	109 (43.1)	126 (49.8)
4th quintile	88 (31.4)	124 (39.7)
5th quintile	76 (22.9)	109 (32.8)
PFP scale[e]		
Robust	156 (43.9)	180 (50.7)
Prefrail	232 (35.7)	288 (44.3)
Frail	27 (16.8)	38 (23.6)

Abbreviations: ADL, activities of daily living; PFP, physical frailty phenotype.
Notes: Persons who recovered from disability and those who improved ADL function were not mutually exclusive. Persons who recovered also improved, but not all persons who improved recovered.
[a] Participants who died in the following visit after the onset of incident disability were included and considered not to recover nor to improve. Participants who were alive but not interviewed in the following visit after the onset of incident disability were not included.
[b] Having no difficulty on any ADLs (scored 0) in the following visit after the onset of incident ADL disability.
[c] A decrease in at least one unit of ADL score in the following visit after the onset of incident ADL disability.
[d] Quintiles were determined based on 7,600 adults who were at least 65 years and had frailty assessment at baseline.
[e] Robust, prefrail, and frail status were identified based on 7,600 adults who were at least 65 years and had frailty assessment at baseline.

Table 5–6. Association of frailty with recovery from and improvement in disability among newly disabled adults, Health and Retirement Study.

	Recovery from ADL[a]		Improving ADL[b]	
		n = 1,166[c]		
	Unadjusted	Adjusted[d]	Unadjusted	Adjusted[d]
	RR (95% CI)			
Frailty score	0.79 (0.74, 0.84)	0.92 (0.85, 0.98)	0.85 (0.81, 0.90)	0.95 (0.89, 1.01)
Categories				
1st quintile	Ref.	Ref.	Ref.	Ref.
2nd quintile	0.92 (0.72, 1.18)	0.98 (0.77, 1.24)	1.00 (0.80, 1.26)	1.07 (0.86, 1.33)
3rd quintile	0.84 (0.66, 1.06)	1.01 (0.80, 1.28)	0.91 (0.74, 1.14)	1.07 (0.86, 1.34)
4th quintile	0.61 (0.47, 0.78)	0.85 (0.66, 1.09)	0.73 (0.58, 0.91)	0.95 (0.75, 1.20)
5th quintile	0.44 (0.34, 0.58)	0.75 (0.57, 0.99)	0.60 (0.48, 0.76)	0.87 (0.67, 1.12)
PFP scale				
Robust	Ref.	Ref.	Ref.	Ref.
Prefrail	0.81 (0.69, 0.95)	0.99 (0.84, 1.16)	0.87 (0.76, 0.99)	1.04 (0.91, 1.19)
Frail	0.38 (0.27, 0.55)	0.57 (0.39, 0.83)	0.47 (0.35, 0.63)	0.65 (0.48, 0.89)

Abbreviations: RR, relative risk; CI, confidence interval; ADL, activities of daily living; PFP, physical frailty phenotype.

Notes: Persons who recovered from disability and those who improved ADL function were not mutually exclusive. Persons who recovered also improved, but not all persons who improved recovered.

[a] No difficulty on any ADLs in the following visit after the onset of incident ADL disability.

[b] Any decrease ADL score in the following visit after the onset of incident ADL disability.

[c] People who died in the following visit after the onset of incident disability were included and considered not to recover nor to improve; People who were not interviewed in the following visit after the onset of incident disability were not included.

[d] Adjusted for age, sex, race (white, others), education (less than high school, high school or equivalent, more than high school), smoking status (current, former, never), body mass index (<25.0, 25.0-30.0, >30.0), history of cardiac disease (heart attack, coronary heart disease, angina, heart failure, or other heart problems), stroke, hypertension, lung disease, diabetes, cancer, and arthritis, self-rated health (excellent, very good, good, fair, poor), cognitive function measured by the Telephone Interview for Cognitive Status, severity of ADL disability at onset (i.e., number of difficulties in activities of daily living), years between frailty assessment and the onset of ADL disability.

Table 5–7. Cross-tabulation of frailty with recovery from and improvement in disability among initially non-disabled adults who had incident severe disability, Health and Retirement Study.

	ADL disability (n = 442)[a]	
	Recovery[b]	Improvement[c]
	Events (%)	
Total	78 (17.7)	169 (38.2)
Continuous frailty score[d]		
1st quintile	9 (33.3)	12 (44.4)
2nd quintile	15 (31.3)	27 (56.3)
3rd quintile	17 (22.7)	34 (45.3)
4th quintile	16 (13.3)	42 (35.0)
5th quintile	21 (12.2)	54 (31.4)
PFP scale[e]		
Robust	25 (23.6)	49 (46.2)
Prefrail	45 (17.9)	101 (40.1)
Frail	8 (9.5)	19 (22.6)

Abbreviations: ADL, activities of daily living; PFP, physical frailty phenotype.
Notes: Persons who recovered from disability and those who improved ADL function were not mutually exclusive. Persons who recovered also improved, but not all persons who improved recovered.
[a] Participants who died in the following visit after the onset of incident disability were included and considered not to recover nor to improve; Participants who were alive but not interviewed in the following visit after the onset of incident disability were not included.
[b] Having no difficulty on any ADLs (scored 0) in the following visit after the onset of incident ADL disability.
[c] A decrease in at least one unit of ADL score in the following visit after the onset of incident ADL disability.
[d] Quintiles were determined based on 7,600 adults who were at least 65 years and had frailty assessment at baseline.
[e] Robust, prefrail, and frail status were identified based on 7,600 adults who were at least 65 years and had frailty assessment at baseline.

Figure 5–1. Flow chart of analytic samples.

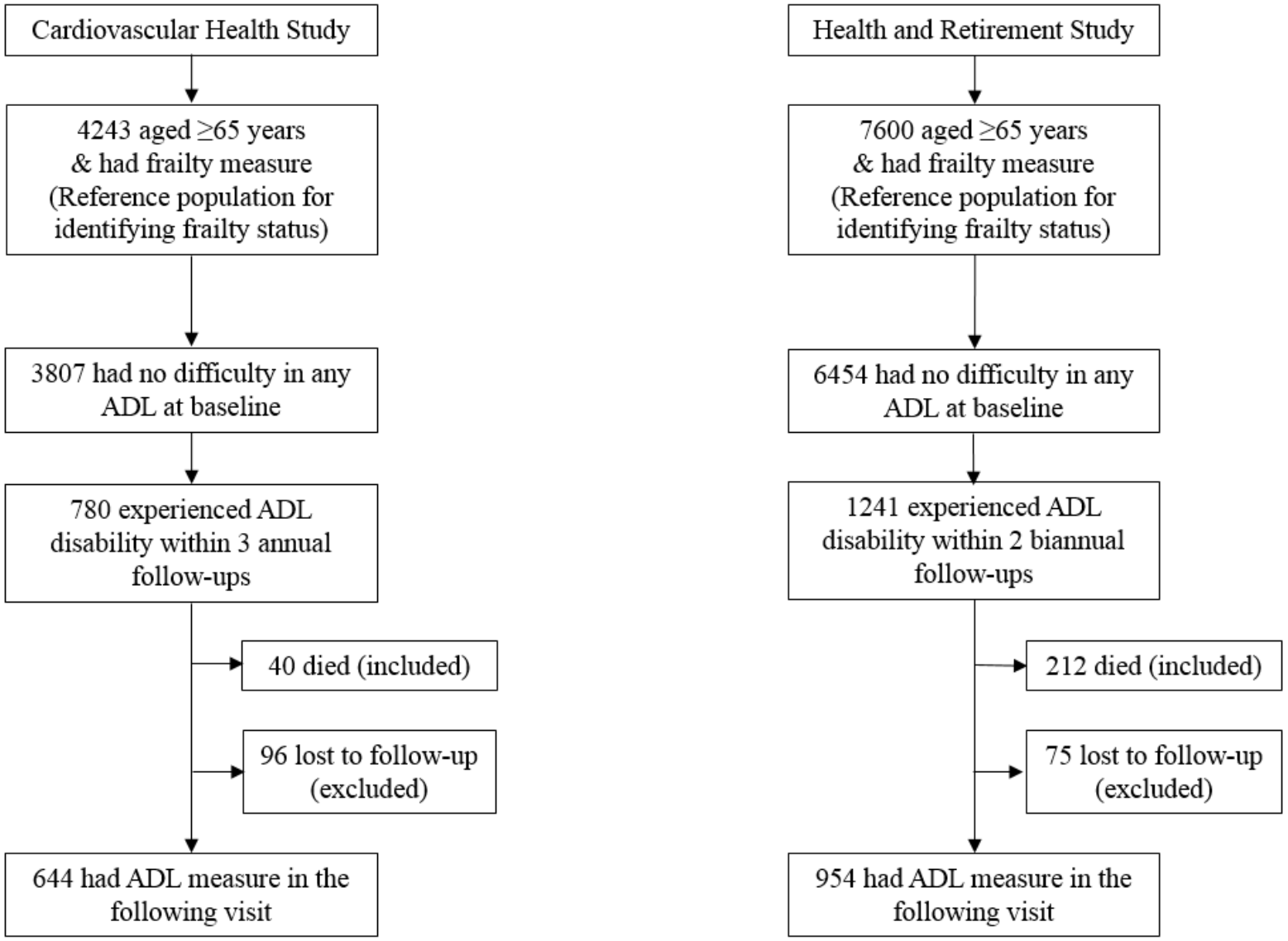
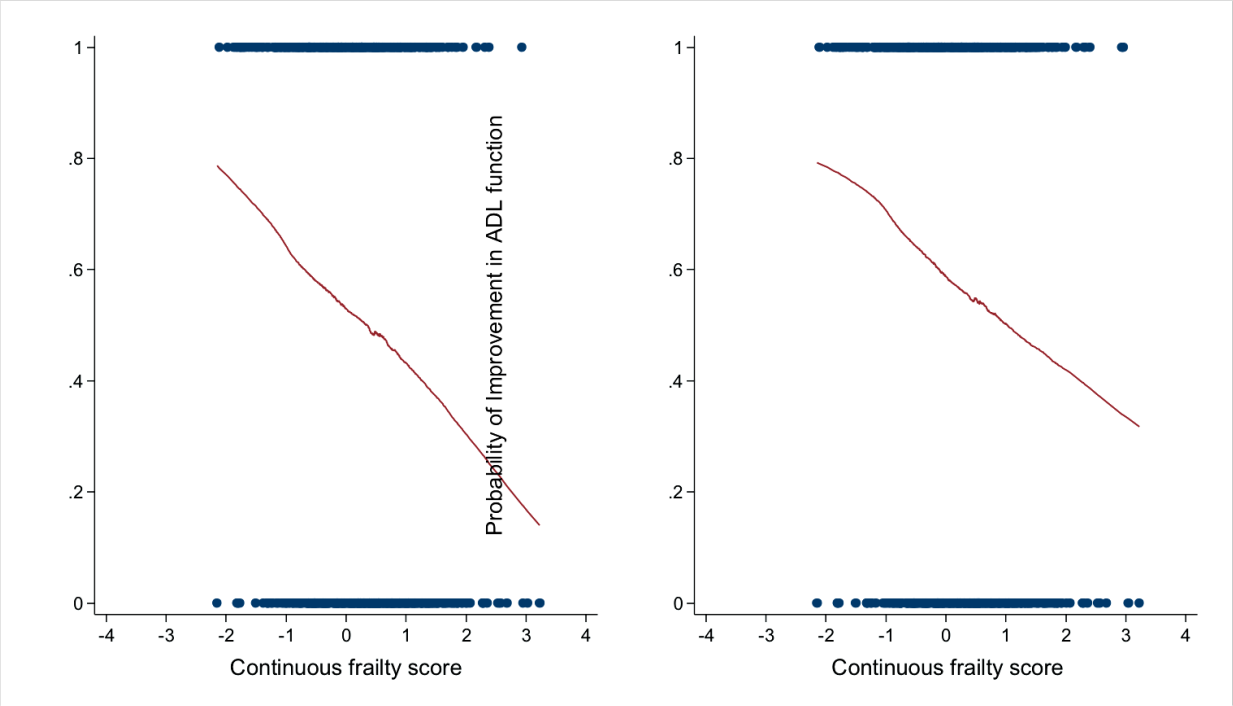
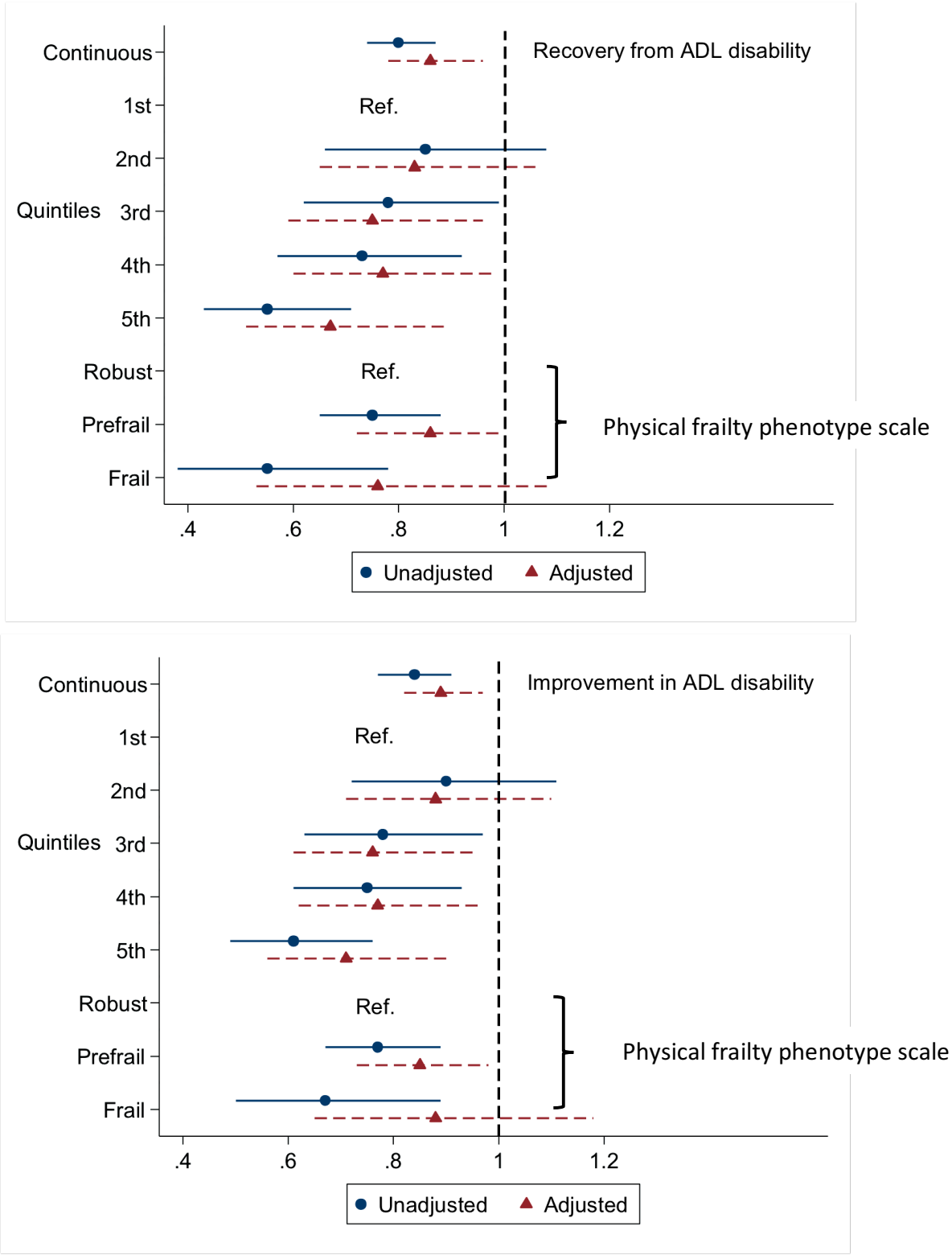


Figure 5–2. Association frailty with resilience after being disabled, Cardiovascular Health Study.



Notes: One person with a continuous frailty score < -3.0 was excluded. ADL, activities of daily living.

Figure 5–3. Sensitivity analysis of the association of frailty with resilience after being disabled, Cardiovascular Health Study.



Notes: Persons who were lost to follow-up were included and considered not recovered nor improved. ADL, activities of daily living.

Figure 5–4. Association frailty with resilience after being disabled, Health and Retirement Study.

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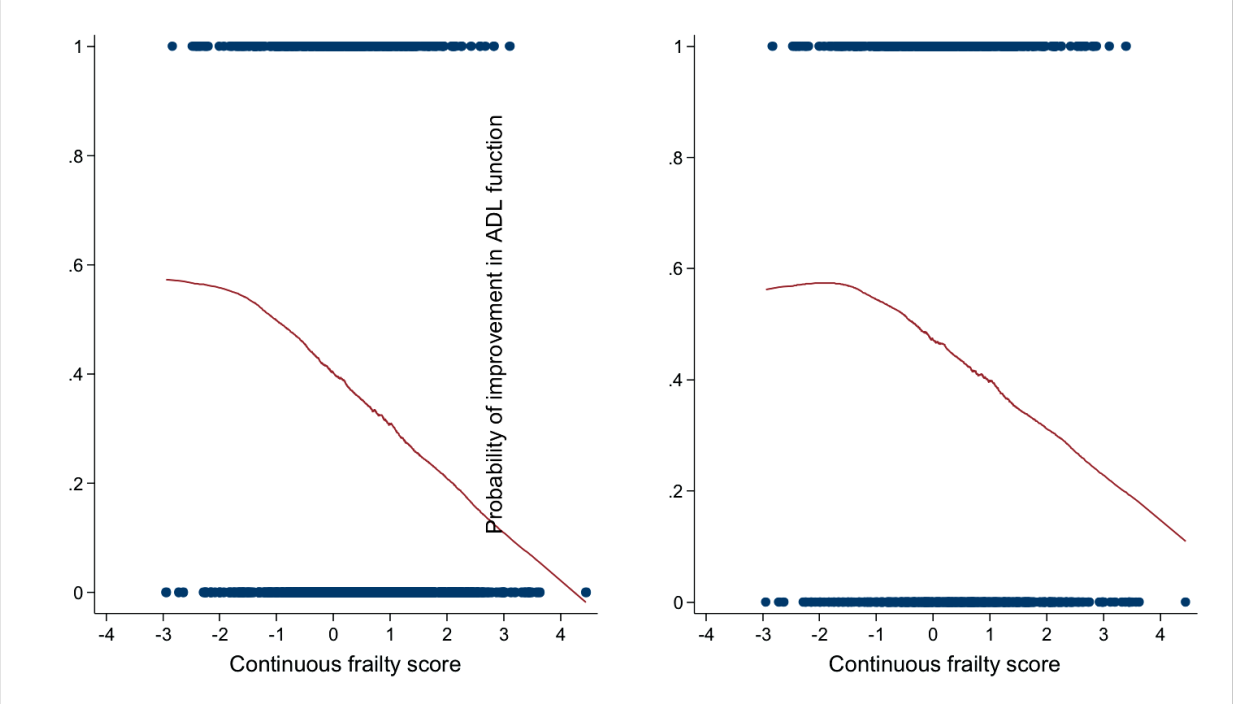
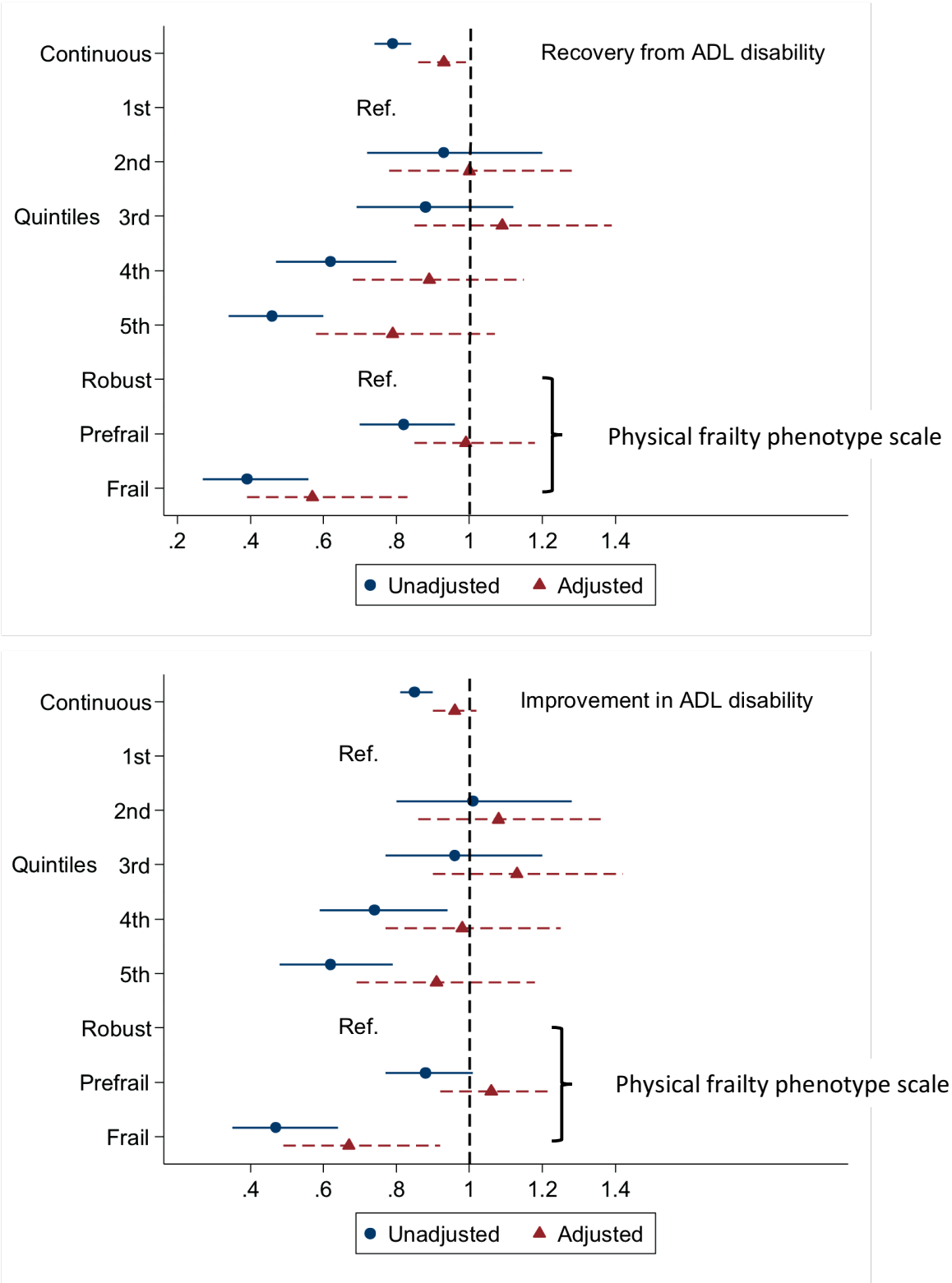


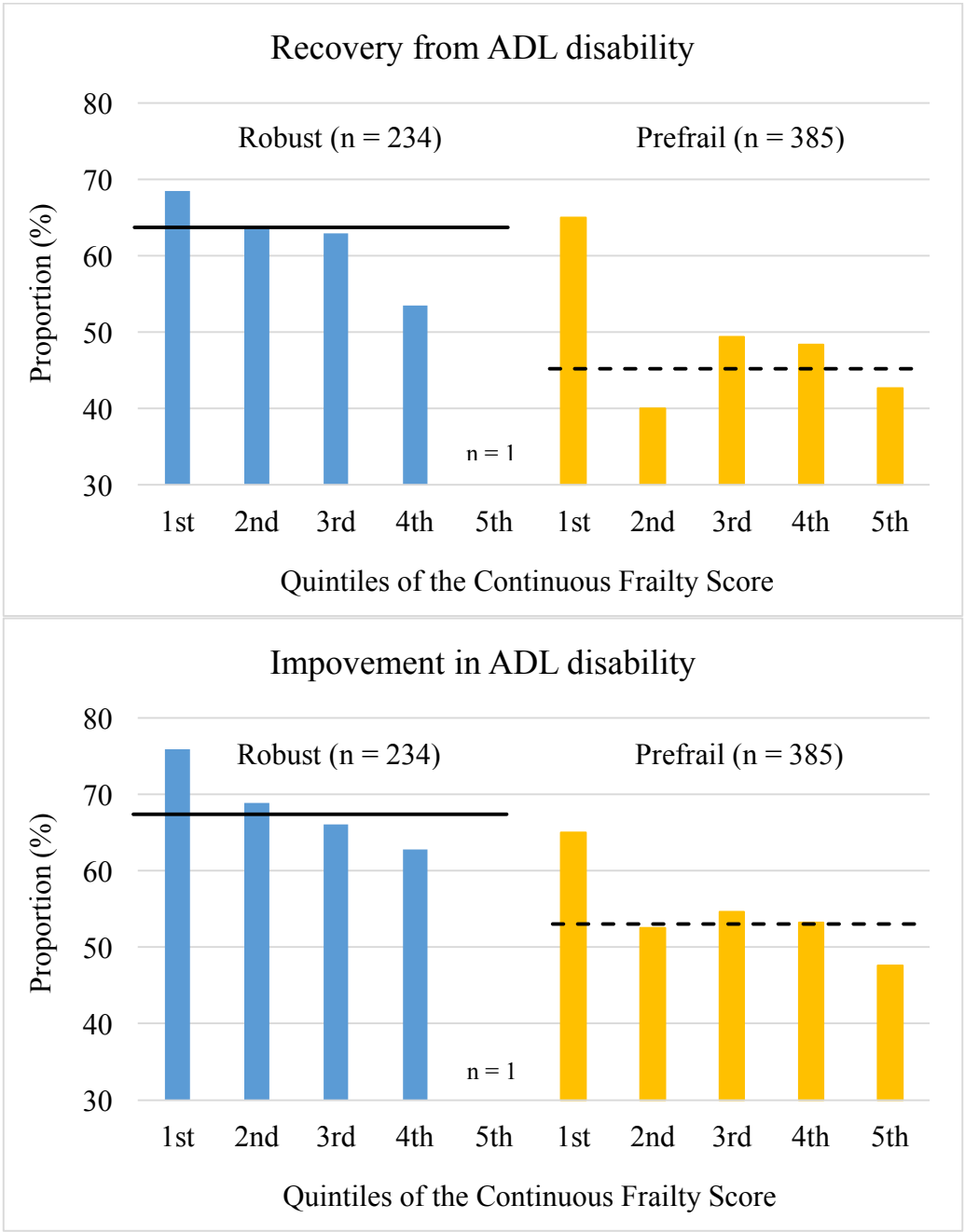
Notes: Six persons with a continuous frailty score < -3.0 were excluded. ADL, activities of daily living.

Figure 5–5. Sensitivity analysis of the association of frailty with resilience after being disabled, Health and Retirement Study.



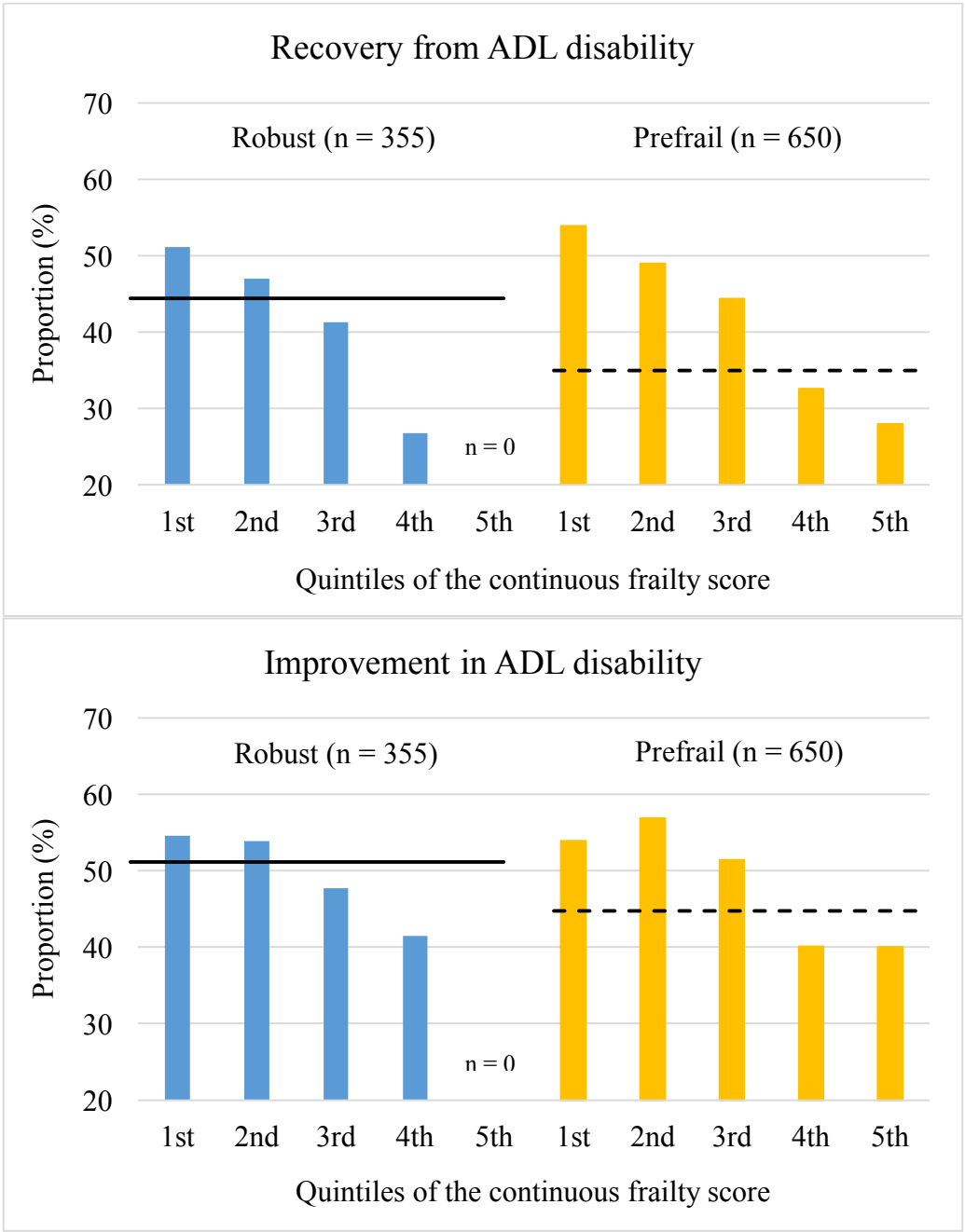
Notes: Persons who were lost to follow-up were included and considered not recovered nor improved. ADL, activities of daily living.

Figure 5–6A. Association of frailty with resilience after being disabled among robust and prefrail adults, Cardiovascular Health Study.



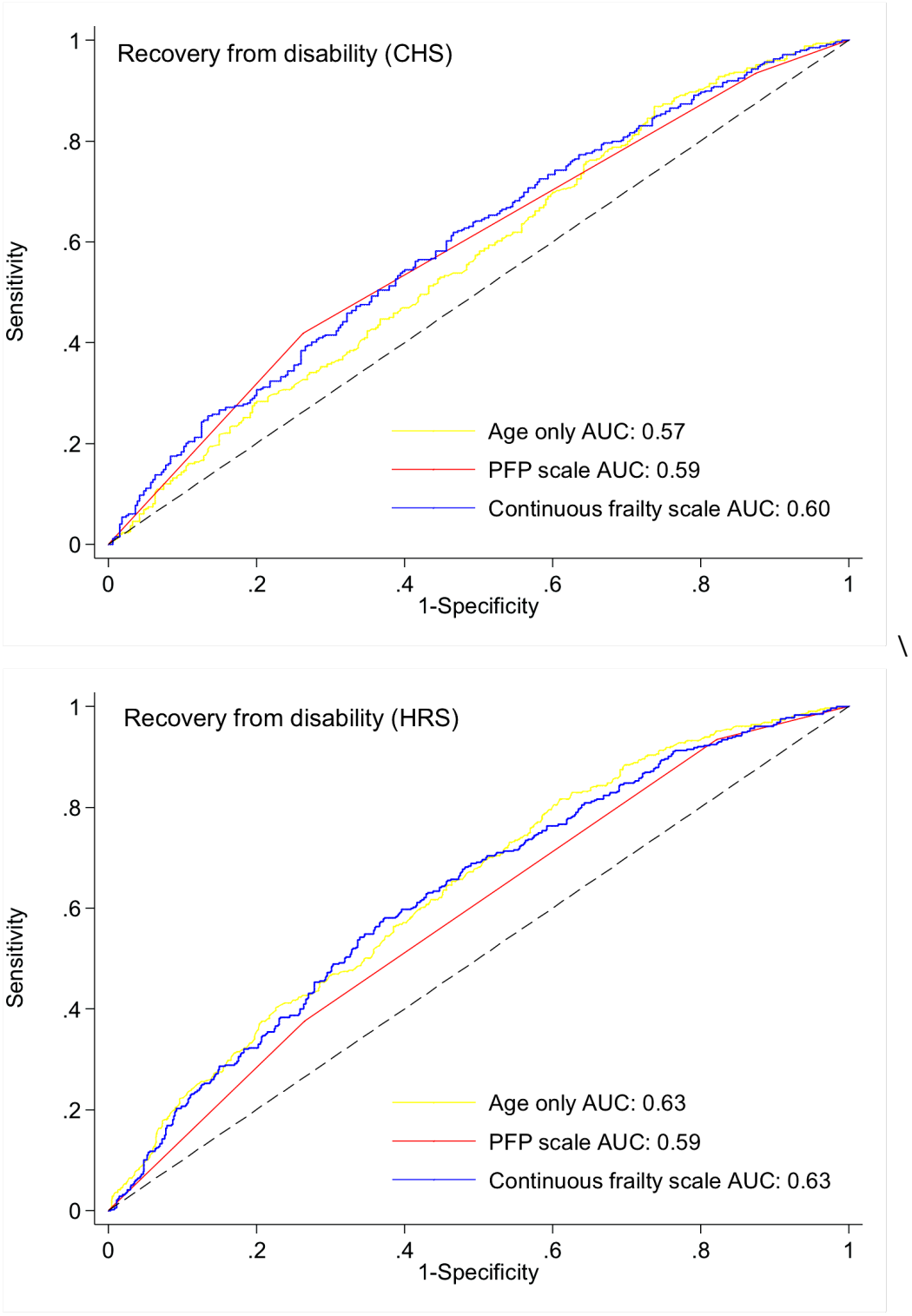
Notes: Solid lines represent the proportions of robust persons who had recovery from (62.4%) and improvement in (68.4%) disability. Dashed lines represent proportions of prefrail persons who had recovery from (46.8%) and improvement in (52.2%) disability. ADL, activities of daily living.

Figure 5–6B. Association of frailty with resilience after being disabled among robust and prefrail adults, Health and Retirement Study.



Notes: Solid lines represent the proportions of robust persons who had recovery from (43.9%) and improvement in (50.7%) disability. Dashed lines represent proportions of prefrail persons who had recovery from (35.7%) and improvement in (44.3%) disability. ADL, activities of daily living.

Figure 5–7. Receiver operating characteristic curves for prediction of recovery from disability.



Notes: Age was adjusted in all models. CHS, Cardiovascular Health Study; HRS, Health and Retirement Study; AUC, area under the curve; PFP, physical frailty phenotype.

CHAPTER 6: ASSOCIATION BETWEEN FRAILTY AND RESILIENCE TO ACUTE MEDICAL EVENTS AND SURGICAL PROCEDURES

6.1. Introduction

In Chapter 5, I demonstrated that frailty was independently associated with poor recovery from activity of daily living (ADL) disability among disabled older adults. These findings validated that frailty, as assessed by two assessments—the continuous frailty scale and the physical frailty phenotype (PFP) scale—developed under the PFP framework, is a marker of decreased reserve and resilience to stressors. In this chapter, I examined the association of frailty with resilience to acute medical events and surgical procedures among older adults; resilience was measured by two indicators, length of hospital stay (LOS) and survival. I hypothesized that frailty would be associated with longer LOS and shorter survival after experiencing each of the acute medical events and surgical procedures. Findings from this chapter would provide additional evidence regarding whether the continuous frailty scale and the PFP scale can capture decreased resilience to stressors—one of the defining features of frailty.

Four stressors I examined in this chapter include three acute medical events—myocardial infarction (MI), heart failure (HF), pneumonia, and one surgical procedure—coronary artery bypass grafting (CABG). Background information about these four stressors are provided below.

MI—commonly known as a heart attack—is defined as death of myocardial cell caused by prolonged ischemia.[305] MI occurs when blood flow that supplies oxygen to the heart muscle is severely reduced or completely blocked to the heart causing tissue damage. Common signs and symptoms of MI include chest, upper extremity, jaw, or epigastric discomfort that is not affected

by movement of the region and can be accompanied by nausea, shortness of breath, dizziness, or syncope.[305,306] According to data from the National Center for Health Statistics and National Heart, Lung, and Blood Institute, 11.3% men and 4.2% women aged 60-79 years reported having had a heart attack or MI in the U.S. The prevalence is much higher among persons aged 80 years or older, reaching to 17.3% for men and 8.9% for women.[307]

Numerous definitions exist for HF;[308-312] however, no consensus has been reached. According to the American Heart Association/American College of Cardiology guidelines, HF is defined as "a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or eject blood".[312] Loosely speaking, HF is a syndrome in which the heart muscle is not able to pump sufficiently to main blood flow to meet the body's requirements.[313] The etiology of HF is complex and many conditions including myocardial dysfunction, arrhythmias or conduction disorder, valve abnormalities, left-ventricular systolic dysfunction, pericardial disease can cause HF.[313,314] Typical signs and symptoms of HF include shortness of breath, fatigue, and peripheral oedema (e.g., ankle swelling).[313] Most heart failure occur among middle-aged and older adults. In the U.S., approximately 5.1 million persons have clinically manifest HF and over 650,000 new cases are diagnosed annually.[315,316]

Pneumonia is an infection of the lung, affecting the microscopic air sacs (alveoli) in the lung.[317] Pneumonia is typically caused by bacteria, viruses, mycoplasmas, and fungi.[318] Common signs and symptoms of pneumonia include cough, chest discomfort, fever, shortness of breath, and nausea, vomiting or diarrhea.[318] Pneumonia is the 8th leading cause of death in the U.S., accounting for over 55,000 deaths in 2014.[319] Pneumonia is also among the leading causes of

hospital admissions for older adults, accounting for over 5% of hospital admissions among persons aged ≥85 years.[320,321]

CABG, also known as coronary artery bypass surgery, is a surgical procedure aimed to improve blood supply to the heart and is commonly used to treat severe coronary heart disease. During a CABG, a blood vessel, taken from another part of the body, is attached to the narrowed or blocked section of the coronary artery to create a new blood vessel (i.e., graft). Although the annual rate of CABG decreased substantially from 1,742 per 1 million in 2001-02 to 1,081 per 1 million in 2007-08, CABG remains to be the most frequently performed open-heart surgery in the U.S.[322]

6.2. Methods

6.2.1. Analytic Sample

I used data from Cardiovascular Health Study (CHS); details of the CHS were presented in Section 3.2.1. I used the CHS Year 5 (1992-93, 3rd follow-up for the original cohort and baseline for the new cohort) and Year 9 (1996-97; 7th follow-up for the original cohort, 4th follow-up for the new cohort), when all five indicators for constructing the continuous frailty scale were available. These two periods (1992-93 and 1996-97) served as the baseline for subsequent analyses in this chapter. The analytic sample was limited to participants who (i) had complete data on five frailty indicators (i.e., gait speed, grip strength, exhaustion, physical activity, and weight loss) at baseline, and (ii) had at least one acute medical event (MI, HF, pneumonia, and sepsis) or surgical procedure (knee replacement, hip replacement, percutaneous coronary angioplasty [PTCA] with and without MI, CABG, heart valve procedures, peripheral vascular

bypass, procedures on spleen, and gastrectomy) that occurred within five years after frailty was measured. Two considerations guided these choices: i) the same procedure or event needs to produce similar amount of stress and ii) procedure or event needs to be common, at least not rare, among older adults.

6.2.2. Frailty

Frailty was measured in two ways: the continuous frailty scale and the PFP scale. Operational definitions of five measures—gait speed, grip strength, exhaustion, physical activity, and weight loss—used to construct the two frailty assessments were described in detail in Section 3.2.3.1. For the continuous frailty scale, standardized score for each of the five frailty indicators was first calculated by dividing the difference between observed value and the sample mean by the standard deviation (separately for two cohorts). Then, five standardized indicator scores were summed to create the continuous frailty score, weighted by the standardized factor loadings identified using CFA (Table 3–4). In the PFP scale, participants were classified as robust, prefrail, and frail using all participants with complete data on five frailty indicators as reference population (analyzed separately; N = 4,243 in the CHS; N = 7,600 in the HRS). Five criteria of the PFP scale were provided in Chapter 3.

6.2.3. Stressors

All medical events and surgical procedures were identified using the International Classification of Diseases (ICD) code in the Center for Medicare & Medicaid Services (CMS) data (Table 6–1). The ICD is the standard diagnostic tool of diseases and medical procedures for clinical, health management, epidemiology purposes.[323] I used the ICD, Ninth Edition (ICD-9) because all

events and procedures occurred from 1992-2002. I applied several inclusion and exclusion criteria for selecting eligible participants for the analysis of each event (Table 6–2). I included only incident events that occurred within five years after frailty was assessed; recurrent events and events occurring before frailty assessment were excluded. For acute medical events, I only counted those with ICD-9 diagnostic codes in the first position (i.e., first-listed). I assumed that first-listed codes represented the main cause or reason for the hospitalization. Events with a sample size <50 were excluded. As a result, three acute medical events (MI, HF, pneumonia) and one surgical procedure (CABG) were included.

6.2.4. Outcomes

Length of hospital stay (LOS). LOS was defined as the length of time in days from admission to the hospital until discharge from the hospital. Because the observation of LOS of participants who died in the hospital may be hindered by death (competing risk), I defined a new outcome, prolonged LOS (great than sample median LOS, separately for each stressor), and considered persons who died in the hospital having a prolonged LOS regardless of their actual LOS. For example, suppose that the median LOS for MI is six days, a person who died the second day after admission to the hospital was identified as having a prolonged LOS.

Survival. Mortality data were obtained according to review of obituaries, medical records, death certificates, and the Centers for Medicare and Medicaid Services health care utilization database for hospitalizations and from household contacts; 100% complete follow-up for ascertainment of mortality status was achieved through intensive surveillance.[265] Survival was defined as the length of time in days from the admission to the hospital until death due to any cause (censored

when lost to follow-up or the end of analytic period); fatal event or procedure (length of time = 0 day) was assigned a survival time of 0.1 days to allow their inclusion in the Cox proportional hazards model.

6.2.5. Analytic Approaches

I described the characteristics of the study population—CHS participants with incident MI, HF, pneumonia, or CABG. Means and SDs were presented for continuous variables; numbers and proportions were presented for categorical variables. All four stressors were analyzed separately.

I presented the numbers and proportions of persons who had prolonged LOS stratified by tertiles of the continuous frailty score and by frailty status identified by the PFP scale (robust, prefrail, frail). I used tertiles instead of quintiles, which were utilized in previous chapters due to small sample size for each event. Sample specific tertiles were used for each of four stressors. I used a χ^2 test to determine whether the risk of prolonged LOS differed by frailty. Subsequently, I assessed both unadjusted and adjusted associations of frailty measured within five years prior to stressor with prolonged LOS using Poisson regression with robust variance estimates. Clinic site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh; categorical), age (years; continuous), sex (male or female), race/ethnicity (white or others), education (less than high school, high school or equivalent, or more than high school; categorical), smoking status (current, previous, or never smokers; categorical), body mass index (BMI; <25.0, 25.0-30.0, or >30.0; categorical), history of chronic conditions (coronary heart disease, HF, stroke, hypertension, diabetes, and arthritis; yes or no for each condition), cognitive function measured by the Modified Mini-Mental State Examination (3MS; continuous), C-reactive protein (CRP, μg/L; continuous), cystatin C (mg/L;

continuous), systolic and diastolic blood pressure (BP, mmHg; continuous), and years between frailty assessment and the occurrence of stressor were included in the multivariable adjusted models. Measurements of covariates were described in detail in Section 3.2.3.2. All covariates were measured at baseline when frailty was assessed. I did not use the most recent assessment of covariates prior to the occurrence of acute medical event or surgical procedure because adjusting for covariates measured after frailty may block the mediating pathway between frailty and indicators of recovery from stressor and therefore underestimates the overall effect of frailty on the outcomes. The continuous frailty scale was modeled both continuously and in tertiles with the 1st tertile serving as the reference; frailty status identified by the PFP scale was modeled as a 3-level categorical predictor with the robust being the reference. All analyses were conducted separately for each stressor.

For survival outcome, I first presented the numbers and proportions of persons who died stratified by frailty. I used a χ^2 test to determine whether risk of death differed by frailty. I then used Cox models to examine the association of frailty measured within five years prior to stressor with mortality. All analyses were conducted separately for four stressors.

All tests were two-sided with a significance level of $p < .05$. All statistical analyses were performed using Stata 13.1 (StataCorp, College Station, TX).[253]

6.3. Results

Sample Description

Of the 4,243 CHS participants who had all five frailty components measured at baseline (1992-93 for the original cohort and 1996-97 for the new cohort), 190, 205, 105, and 91 had an incident MI, HF, pneumonia, and CABG within five years, respectively. The average age for persons who experienced MI, HF, pneumonia, and CABG was 75.9, 77.1, 78.6, and 73.6 years, respectively (Table 6–3). For all four stressors, the study population was comprised of more men and predominantly whites.

Association between Frailty and Prolonged Length of Hospital Stay

Myocardial Infarction

The median LOS was six days for 190 persons who had incident MI within five years after frailty was assessed (Figure 6–1). The probability of having a prolonged LOS after MI (≥7 days) increased steadily with higher scores on the continuous frailty scale. Among persons with the lowest continuous frailty scores (1st tertile), approximately 40% had prolonged LOS, whereas a prolonged LOS was observed among over 70% of persons with the highest frailty scores (3rd tertile). I observed similar results when frailty was assessed by the PFP scale. Approximately one-third of the robust participants had a prolonged LOS, as opposed to over 70% for the frail.

The unadjusted risk of prolonged LOS after MI was 21% (95% confidence interval [CI]: 8%, 37%) higher for each point higher on the continuous frailty scale (Table 6–4). Persons with the highest continuous frailty scores (3rd tertile) were 78% (95% CI: 28%, 148%) more likely to have a prolonged LOS compared with those with the scores in the 1st tertile. When frailty was assessed by the PFP scale, the risk of prolonged LOS was 2.08-fold (95% CI: 1.45, 2.99) higher among the prefrail and 2.23-fold (95% CI: 1.49, 3.35) higher among the frail than the robust.

After multivariable adjustment, frailty persisted to be a strong and independent risk factor for prolonged LOS after MI, and the point estimates changed minimally.

Heart Failure

The median LOS was four days for 205 persons having incident HF within five years after frailty was measured (Figure 6–1). The probability of having a prolonged LOS after HF (≥5 days) did not vary across tertiles of the continuous frailty scale (p = .362) nor frailty status identified by the PFP scale (p = .653). In either unadjusted or adjusted models, frailty was not associated with the risk of prolonged LOS after HF (Table 6–4).

Pneumonia

The median LOS was seven days for 105 persons who had incident pneumonia within five years after frailty was assessed (Figure 6–1). The probability of having a prolonged LOS after pneumonia (≥8 days) did not vary across tertiles of the continuous frailty scale (p = .891) nor frailty status identified by the PFP scale (p = .990). In either unadjusted or adjusted models, frailty was not associated with the risk of prolonged LOS after pneumonia (Table 6–4).

Coronary Artery Bypass Grafting

The median LOS was nine days for 91 persons who had CABG within five years after frailty was measured (Figure 6–1). The probability of having a prolonged LOS after CABG (≥6 days) increased steeply with higher score on the continuous frailty scale. Among participants with the lowest continuous frailty scores (1st tertile), less than one-fourth had a prolonged LOS, whereas approximately three-fourths of those with the highest frailty scores (3rd tertile) had a prolonged

LOS. I found similar results when frailty was assessed by the PFP scale. Less than one-third of the robust had a prolonged LOS, as opposed to over 80% for the frail.

In adjusted model, the risk of prolonged LOS after CABG was 79% higher for each point higher on the continuous frailty scale (Table 6–4). Compared with persons having continuous frailty scores in the lowest tertile, those in the highest tertile were more than three times (RR = 3.21, 95% CI: 1.56, 6.61) more likely to have a prolonged LOS. When frailty was assessed by the PFP scale, the risk of prolonged LOS was 2.16-fold (95% CI: 1.35, 3.45) higher among the prefrail and 2.66-fold (95% CI: 1.54, 4.58) higher among the frail than the robust. After multivariable adjustment, only prefrail persons had higher risk of prolonged LOS after CABG than the robust. Persons with frailty scores in the 3rd tertile had 3.21-fold (95% CI: 1.56, 6.61) higher risk of prolonged LOS compared with those with scores in the 1st tertile.

Association between Frailty and Survival

Myocardial Infarction

Over 16 years of follow-up, the rate of all-cause mortality was 147.6 per 1000 person-years (PYs) for 190 persons who had incident MI, and the median survival was 4.7 years (Table 6–5). Death rates for persons with the continuous frailty scores in the 1st, 2nd, and 3rd tertile were 110.6, 131.0, and 236.6 per 1000 PYs, respectively. Similarly, there was a steep gradient in death rates across frailty status identified by the PFP scale. Death rate was 100.1 for the robust, 180.2 for the prefrail, and 305.6 per 1000 PYs for the frail. The unadjusted hazard of death was 25% (95% CI: 8%, 44%) higher per unit of the continuous frailty scale (Table 6–6). Compared with persons with the lowest continuous frailty scores (1st tertile), those in the highest tertile had 90% (95%

CI: 29%, 179%) higher hazard of death. The association of frailty with mortality persisted after multivariable adjustment. The hazard of death was almost doubled (hazard ratio [HR] = 1.99, 95% CI: 1.21, 3.27) in persons with the highest continuous frailty scores (3rd tertile) than those in the lowest (Table 6–6). When frailty was assessed by the PFP scale, the adjusted hazard of death for the frail was approximately two times higher than the robust (HR = 2.01, 95% CI: 1.06, 3.81).

Heart Failure

The rate of all-cause mortality was 248.2 per 1000 PYs for 205 persons who had incident HF; the median survival was 2.5 years (Table 6–5). Death rates for persons with the continuous frailty scores in the 1st, 2nd, and 3rd tertile were 204.7, 231.9, and 337.4 per 1000 PYs, respectively. Similarly, there was a steep gradient in death rates across frailty status identified by the PFP scale. Death rate was 206.3 for the robust, 238.3 for the prefrail, and 484.3 per 1000 PYs for the frail. The unadjusted hazard of death was 20% (95% CI: 4%, 39%) higher per unit of the continuous frailty scale (Table 6–6). Compared with persons with the lowest continuous frailty scores (1st tertile), those in the highest tertile had 55% (95% CI: 10%, 110%) higher hazard of death. After multivariable adjustment, the hazard of death was 55% higher (HR = 1.55, 95% CI: 0.94, 2.41) in persons with the highest continuous frailty scores (3rd tertile) than those in the lowest tertile (Table 6–6). When frailty was assessed using the PFP scale, the adjusted hazard of death for the frail was more than two times higher than the robust (HR = 2.29, 95% CI: 1.38, 3.68).

Pneumonia

The rate of all-cause mortality was 243.2 per 1000 PYs for 105 persons who had incident pneumonia; median survival was 1.7 years (Table 6–5). Death rates for persons with the continuous frailty scores in the 1st, 2nd, and 3rd tertile were 168.0, 296.4 and 323.1 per 1000 PYs, respectively. Similarly, there was a steep gradient in death rates across frailty status identified by the PFP scale. Death rate was 145.1 for the robust, 276.0 for the prefrail, and 545.5 per 1000 PYs for the frail. Compared with persons with the lowest continuous frailty scores (1st tertile), those in the highest tertile had 81% (95% CI: 9%, 198%) higher hazard of death (Table 6–6). After multivariable adjustment, the hazard of death was 69% higher (HR = 1.69, 95% CI: 0.77, 3.68) in persons with the highest continuous frailty scores (3rd tertile) than those in the lowest (Table 6–6). When frailty was assessed using the PFP scale, the adjusted hazard of death for the frail was more than two times higher than the robust (HR = 2.33, 95% CI: 1.03, 5.29).

Coronary Artery Bypass Grafting

The rate of all-cause mortality was 80.0 per 1000 PYs for 91 persons who had incident CABG; median survival was 9.5 years (Table 6–5). Death rates for persons with the continuous frailty scores in the 1st, 2nd, and 3rd tertile were 54.5, 74.3 and 118.2 per 1000 PYs, respectively. Similarly, there was a steep gradient in death rates across frailty status identified by the PFP scale. Death rate was 67.3 for the robust, 98.4 for the prefrail, and 121.1 per 1000 PYs for the frail. Persons with the highest continuous frailty scores (3rd tertile) had 2.64-fold higher hazard of death than those with scores in the 1st tertile (Table 6–6). After multivariable adjustment, the hazard of death was more than 2.5 times higher (HR = 2.64, 95% CI: 1.10, 6.32) in persons with the continuous frailty scores in the highest tertile than those in the lowest (Table 6–6). When

frailty was assessed using the PFP scale, the hazard of death for the frail was more than three times higher than the robust, although the association was not statistically significant.

6.4. Discussion

In this chapter, I aimed to evaluate the association of frailty with recovery from MI, HF, pneumonia, and CABG, respectively, among older patients. Using CMS data from the CHS, I found that older persons with higher levels of frailty were more likely to have prolonged LOS after undergoing MI and CABG, respectively. I also found that frailer elders had higher risk of all-cause mortality after experiencing MI, HF, pneumonia, and CABG, respectively. Taken together, these findings provided evidence supporting that both the continuous frailty scale and the PFP scale, both developed under the PFP framework, could capture older patients' ability to tolerate stressful medical events.

I found that higher levels of frailty were associated with higher risk of prolonged LOS and all-cause mortality among elderly patients hospitalized for MI. These findings corroborate earlier reports that have examined the association of frailty with recovery outcomes for older patients with MI.[324,325] Ekerstad et al.[325] found that frailty, as identified by the Canadian Study of Health and Aging Clinical Frailty Scale, was independently associated with in-hospital mortality, 1-month mortality, and prolonged hospital care among 307 patients aged ≥75 years with non-ST-segment elevation MI treated at three hospitals in Sweden. Using the same sample, Ekerstad et al.[324] later showed that non-ST-segment elevation MI patients who were frail had higher risk of 1-year mortality than those who were robust. In addition, slow gait speed—often used as a single-item assessment of frailty—has been associated with post-MI outcomes in a sample of

472 Japanese middle-aged and older patients.[326] The present study has two distinctive features: one is I used CMS data from a prospective, multi-center cohort study, and another is I examined hospitalization as a recovery outcome in addition to mortality. Physicians have increasingly recognized frailty as an important risk factor for predicting prognosis in patients with MI.[327] These findings provide additional evidence supporting the role of frailty in clinical decision-making in patients presenting MI.

I found that frailty was associated with increased risk of death over 16 years among hospitalized patients with heart failure; these results are consistent with previous studies showing that frailty was associated with post-HF outcomes among older hospitalized patients.[328-330] In a single-center study, Vidán et al.[330] found that frailty, as defined by having three or more of the five PFP criteria, was associated with higher risk of 30-day functional decline, 1-year all-cause mortality, and 1-year hospital readmission among 450 patients aged ≥70 years hospitalized for HF in Spain. Later in a multi-center study, Rodríguez-Pascual et al.[328] showed that frailty, assessed by the PFP scale, was associated with increased risk of mortality, hospital readmission, and ADL disability over one year among 497 patients with stable HF in six hospitals in Spain. In addition, prior studies have identified single-item measures of frailty—such as slow gait speed, weak grip strength, and low physical activity—as risk factors for post-HF adverse outcomes, including hospital readmission, disability, and mortality.[328,330,331] In contrast with prior studies that examined short-term recovery outcomes after HF, I showed that frailty, measured by two PFP framework-guided frailty assessments, was associated with long-term mortality among patients hospitalized for HF. Moreover, this study was among the first to reveal a relationship between frailty and risk of post-HF mortality in the U.S.

In addition to two cardiac conditions—MI and HF, I found that frailty was associated with higher risk of long-term mortality among older patients with pneumonia. Several risk score models, such as the Pneumonia Severity Index,[332] have been proposed and validated for predicting unfavorable health outcomes among adult patients diagnosed with pneumonia. These prognostic tools, however, are not tailored specifically to elderly patients, leading to less accurate prediction in the elderly population.[333,334] In a small study of 99 patients aged ≥65 years diagnosed with pneumonia and seen in a hospital in Spain, Torres et al.[333] found that ADL disability was associated with higher risk of 30-day and 18-month mortality. Pieralli et al.[334] showed that delirium was a risk factor for in-hospital death among 443 patients aged ≥65 years hospitalized for pneumonia in a hospital in Italy. To my knowledge, this study was the first to report an association of frailty with long-term mortality among elderly patients hospitalized for pneumonia in the U.S. Findings from this study suggest that an evaluation of frailty of older patients with pneumonia seen in hospitals could provide information about post-pneumonia mortality risk.

Findings from the present study with regard to the association of frailty with increased risk of prolonged LOS and all-cause mortality among elderly patients undergoing CABG were consistent with several prior studies.[335-340] Lee et al.[336] showed that frailty, as defined as ADL disability, ambulation dependency, or dementia, was associated with higher risk of in-hospital mortality and institutional discharge among 3,826 patients undergoing cardiac surgery (including CABG) at a single health center in Canada. In a series of two reports, Sündermann and colleagues[335,340] found that frailty, assessed by 35 criteria, was associated with 30-day and 1-year mortality, respectively, among patients aged ≥74 years that were admitted to cardiac surgery. In a more recent study, Ad et al.[338] showed that frailty, defined as meeting ≥3 out of five PFP

criteria, was associated with longer intensive care unit stays, longer LOS, and greater risk of surgical complications and discharge to an intermediate-care facility among 167 older CABG and/or valve surgery patients at a single center. Findings of this study provided additional evidence supporting the use of frailty assessment in cardiac surgery decision-making.

This present study is not without limitation. First of all, sample size for each stressor is relatively small, which may undermine the reliability and validity of study findings. In addition, although I restricted the analyses to participants who experienced the same medical event or surgery, it is possible that levels of frailty are associated with severity of medical events and burden of surgeries, which, in turn, contributes to the observed differences in recovery. Studies in which comprehensive evaluation of severity for these events may provide more definite evidence. Moreover, the relationship between frailty and medical events and surgical procedures may be bidirectional, experiencing these stressors may therefore alter patients' underlying frailty status, leading to misclassification. Future research needs to elucidate the complex relationship between frailty, medical events and surgical procedures, and recovery outcomes using advanced methodological approaches (e.g., marginal structural modeling).

In this chapter, I found that frailty was associated with LOS after undergoing MI and CABG, respectively. I also showed that frailty was associated with all-cause mortality after experiencing MI, HF, pneumonia, and CABG, respectively. These findings corroborate that both the continuous frailty scale and the PFP scale are valid measures of frailty, characterized by reduced resilience to stressors.

Table 6–1. International Classification of Diseases, Ninth Edition (ICD-9) code for acute medical events and surgical procedures.

Description	Diagnosis	Procedure
MI	410.x	
HF	428.x	
Pneumonia	480.x 481 483.x 484.x 485 486	
Sepsis	995.91 995.92	
CABG		36.1x 36.31
Hip replacement (total, partial, revision)		81.51 81.52 81.53
PTCA		36.0x
Knee replacement (total; revision)		81.54 81.55
Heart valve procedures		35.1x 35.2x
Peripheral Vascular Bypass		38.43 38.48 39.25 39.29
Procedures on spleen (total splenectomy, repair of spleen)		41.43 41.50 41.95
Gastrectomy		43.50 43.60 43.70 43.89 43.99

Abbreviations: MI, myocardial infarction. HF, heart failure; CABG, Coronary artery bypass grafting; PTCA, percutaneous coronary angioplasty.

Table 6–2. Analytic sample size of each event, Cardiovascular Health Study.

	MI	HF	Pneumonia	CABG
ICD-9	410.x	428.x	480.x, 481, 483.x, 484.x, 485, 486	36.1x, 36.31
Original number of events	1,602	7,072	1,468	302
Exclusion criteria:				
1. Frailty was not measured	383	2,072	402	59
2. Not in the primary diagnosis position	455	3,625	587	NA
3. Recurrent events	177	636	200	2
4. Events occurred before frailty measure	73	52	20	49
5. Events occurred >5 years after when frailty was measured	324	482	262	101
Analytic sample size	190	205	105	91

Abbreviations: MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass grafting; ICD-9, International Classification of Diseases, Ninth Edition.
Notes: Only event or procedure with a sample size ≥50 was included.

Table 6–3. Characteristics of participants who had incident event, Cardiovascular Health Study.

Characteristics	MI n = 190	HF n = 205	Pneumonia n = 105	CABG n = 91
Age, years, mean (SD)	75.9 (5.5)	77.1 (5.3)	78.6 (6.4)	73.6 (3.7)
Male, No. (%)	106 (55.8%)	121 (59.0%)	61 (58.1%)	59 (64.8%)
White (vs. Black), No. (%)	161 (84.7%)	183 (89.3%)	86 (81.9%)	85 (93.4%)
Education				
< High school, No. (%)	66 (34.7%)	68 (33.2%)	33 (31.4%)	23 (25.3%)
= High school, No. (%)	51 (26.8%)	62 (30.2%)	23 (21.9%)	30 (33.0%)
> High school, No. (%)	73 (38.4%)	75 (36.6%)	49 (46.7%)	38 (41.8%)
Smoking status				
Never, No. (%)	77 (40.7%)	74 (36.5%)	38 (36.9%)	44 (48.9%)
Former, No. (%)	98 (51.9%)	107 (52.7%)	53 (51.5%)	38 (42.2%)
Current, No. (%)	14 (7.4%)	22 (10.8%)	12 (11.7%)	8 (8.9%)
Body mass index, kg/m^2				
Underweight/normal[a], No. (%)	62 (32.6%)	80 (39.0%)	45 (42.9%)	25 (27.5%)
Overweight, No. (%)	82 (43.2%)	78 (38.1%)	40 (38.1%)	42 (46.2%)
Obese, No. (%)	46 (24.2%)	47 (22.9%)	20 (19.1%)	24 (26.4%)
Coronary heart disease, No. (%)	66 (34.7%)	91 (44.4%)	45 (42.9%)	35 (38.5%)
Heart Failure, No. (%)	15 (7.9%)	NA	22 (21.0%)	17 (18.7%)
Stroke, No. (%)	16 (8.4%)	17 (8.3%)	11 (10.5%)	4 (4.4%)
Hypertension				
Borderline, No. (%)	26 (13.8%)	29 (14.2%)	11 (10.6%)	10 (11.0%)
Hypertensive, No. (%)	103 (54.5%)	103 (50.2%)	56 (53.9%)	43 (47.3%)
Diabetes				
Prediabetes, No. (%)	21 (11.2%)	13 (6.5%)	14 (14.0%)	11 (12.4%)
Diabetes, No. (%)	52 (27.8%)	66 (33.0%)	29 (29.0%)	20 (22.5%)
Arthritis, No. (%)	83 (45.6%)	95 (47.5%)	48 (45.7%)	39 (43.8%)
3MS[b], mean (SD)	89.7 (9.8)	89.1 (7.8)	87.5 (10.7)	92.3 (7.1)
CRP, µg/L, mean (SD)	5.9 (8.4)	7.2 (13.2)	9.8 (17.4)	5.2 (5.6)
Cystatin C, mg/L, mean (SD)	1.2 (0.3)	1.3 (0.4)	1.3 (0.3)	1.2 (0.3)
Systolic BP, mmHg, mean (SD)	140.5 (20.5)	139.0 (22.1)	139.4 (22.3)	135.2 (20.9)
Diastolic BP, mmHg, mean (SD)	70.8 (10.8)	69.6 (12.1)	66.7 (17.2)	71.2 (10.5)

Abbreviations: MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass grafting; SD, standard deviation; 3MS, Modified Mini-Mental State Examination; BP, blood pressure; CRP, C-reactive protein.

[a] Underweight and normal were collapsed due to small cell size in the underweight category.

[b] Ranging from 0 to 100 with higher score indicating a better cognitive function.

Notes: Descriptive statistics for individual measures may not be available for all participants.

Table 6–4. Association of frailty with prolonged length of hospital stay after incident event, Cardiovascular Health Study.

	MI n = 190		HF n = 205		Pneumonia n = 105		CABG n = 91	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[a]
	Relative risk (95% confidence interval)							
Frailty score	1.21 (1.08, 1.37)	1.19 (1.03, 1.38)	0.99 (.86, 1.14)	1.00 (0.87, 1.17)	0.97 (0.82, 1.16)	0.90 (0.70, 1.14)	1.82 (1.41, 2.34)	1.79 (1.33, 2.40)
Categories								
1st tertile	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2nd tertile	1.17 (0.79, 1.74)	1.10 (0.70, 1.72)	1.19 (.85, 1.66)	1.28 (0.91, 1.80)	0.94 (0.55, 1.59)	0.88 (0.50, 1.39)	2.00 (0.94, 4.26)	2.14 (0.99, 4.63)
3rd tertile	1.78 (1.28, 2.48)	1.70 (1.15, 2.51)	0.94 (0.65, 1.36)	1.05 (0.71, 1.57)	1.06 (0.65, 1.75)	0.91 (0.52, 1.62)	3.18 (1.60, 6.31)	3.21 (1.56, 6.61)
PFP scale								
Robust	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Prefrail	2.08 (1.45, 2.99)	2.25 (1.46, 3.46)	0.91 (.67, 1.24)	1.06 (0.78, 1.42)	1.02 (0.62, 1.68)	0.72 (0.44, 1.19)	2.16 (1.35, 3.45)	3.58 (1.91, 6.71)
Frail	2.23 (1.49, 3.35)	2.26 (1.36, 3.74)	0.82 (0.52, 1.28)	0.83 (0.52, 1.35)	0.99 (0.57, 1.71)	0.81 (0.40, 1.61)	2.66 (1.54, 4.58)	1.57 (0.77, 3.21)

Abbreviations: MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass grafting; PFP, physical frailty phenotype.
Notes: only incident surgical procedures and medical events identified by International Classification of Diseases, Ninth Revision, in the primary diagnosis position were included. Participants who died in the hospital were considered having a prolonged LOS (n = 30 for MI; n = 8 for HF; n = 0 for pneumonia; n = 4 for CABG).
[a] Adjusted for clinical site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (black, others), education (<, =, >high school), body mass index (<25.0, 25.0-30.0, >30.0), smoking status (current, former, never), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, and arthritis, cognition measured by modified mini-mental status examination, C-reactive protein, cystatin C, systolic and diastolic blood pressure, and years between when frailty was measured and the occurrence of event.

Table 6–5. Cross-tabulation of frailty and death rates over 16 years of follow-up after incident event, Cardiovascular Health Study.

	MI n = 190	HF n = 205	Pneumonia n = 105	CABG n = 91
	Death rates per 1000 person-years			
Total	147.7	248.2	243.2	80.0
Continuous frailty score				
1st tertile	n = 64	n = 69	n = 35	n = 30
	110.6	204.7	168.0	54.5
2nd tertile	n = 61	n = 67	n = 35	n = 30
	131.0	231.9	296.4	74.3
3rd tertile	n = 65	n = 69	n = 35	n = 31
	236.6	337.4	323.1	118.2
PFP scale				
Robust	n = 75	n = 65	n = 33	n = 51
	100.1	206.3	145.1	67.3
Prefrail	n = 87	n = 105	n = 43	n = 34
	180.2	238.3	276.0	98.4
Frail	n = 28	n = 35	n = 29	n = 6
	305.6	484.3	545.5	121.3

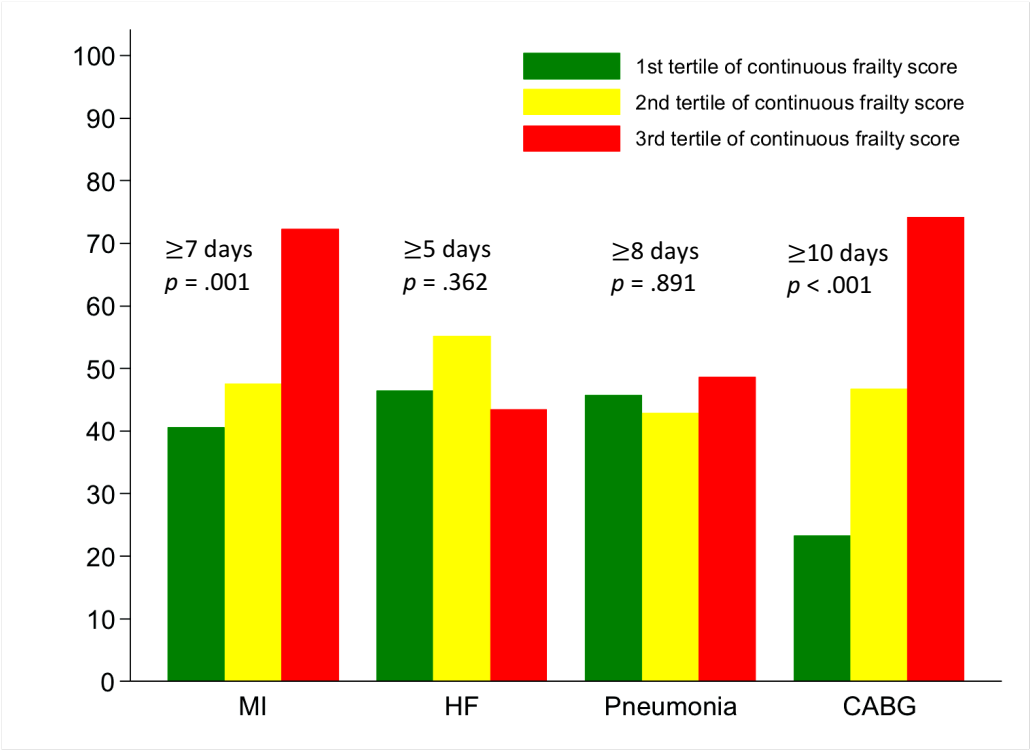
Abbreviations: MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass grafting; PFP, physical frailty phenotype.
Notes: only incident surgical procedures and medical events identified by International Classification of Diseases, Ninth Edition, in the primary diagnosis position were included. All medical events and surgical procedures occurred within five years after frailty was measured.

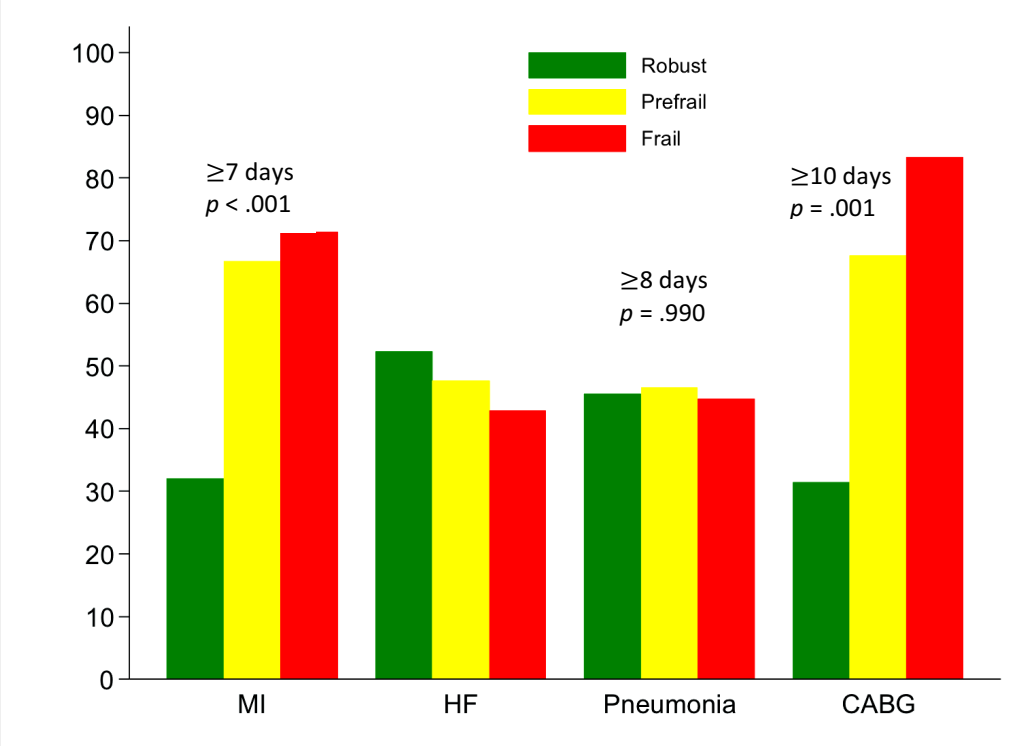
Table 6–6. Association of frailty with all-cause mortality over 16 years of follow-up after incident event, Cardiovascular Health Study.

	MI n = 190		HF n = 205		Pneumonia n = 105		CABG n = 91	
	Unadjusted	Adjusted[a]	Unadjusted	Adjusted[b]	Unadjusted	Adjusted[c]	Unadjusted	Adjusted[d]
	Hazard ratio (95% confidence interval)							
Frailty score	1.25 (1.08, 1.44)	1.18 (0.99, 1.41)	1.20 (1.04, 1.39)	1.20 (0.98, 1.47)	1.17 (0.99, 1.39)	1.14 (0.87, 1.48)	1.35 (0.99, 1.85)	1.22 (0.77, 1.92)
1st tertile	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
2nd tertile	1.17 (0.78, 1.75)	1.20 (0.74, 1.95)	1.13 (0.79, 1.61)	1.19 (0.79, 1.80)	1.62 (0.98, 2.67)	2.08 (1.05, 4.14)	1.21 (0.64, 2.32)	0.65 (0.28, 1.54)
3rd tertile	1.90 (1.29, 2.79)	1.99 (1.21, 3.27)	1.55 (1.10, 2.20)	1.50 (0.94, 2.41)	1.81 (1.09, 2.98)	1.69 (0.77, 3.68)	2.28 (1.23, 4.22)	2.64 (1.10, 6.32)
PFP scale								
Robust	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Prefrail	1.68 (1.19, 2.39)	1.43 (0.94, 2.20)	1.14 (0.83, 1.58)	1.26 (0.86, 1.84)	1.77 (1.09, 2.88)	2.08 (1.09, 3.96)	1.50 (0.88, 2.54)	0.97 (0.44, 2.15)
Frail	2.54 (1.58, 4.07)	2.01 (1.06, 3.81)	2.11 (1.36, 3.26)	2.29 (1.38, 3.68)	2.84 (1.62, 5.00)	2.33 (1.03, 5.29)	1.86 (0.72, 4.79)	3.35 (0.92, 12.25)

Abbreviations: MI, myocardial infarction; HF, heart failure; CABG, coronary artery bypass grafting; PFP, physical frailty phenotype.
Notes: only incident surgical procedures and medical events identified by International Classification of Diseases, Ninth Edition, in the primary diagnosis position were included. All events occurred within five years after frailty was measured. Persons who died immediately after experiencing the incident medical event or surgical procedure were assigned a survival time of 0.1 days to allow for their inclusion in the Cox model.
[a] Adjusted for clinical site (Bowman Gray, Johns Hopkins, Davis, Pittsburgh), age, sex, race (black, others), education (<, =, >high school), body mass index (<25.0, 25.0-30.0, >30.0), smoking status (current, former, never), history of coronary heart disease, heart failure, stroke, hypertension, diabetes, and arthritis, cognition measured by modified mini-mental status examination, C-reactive protein, cystatin C, systolic and diastolic blood pressure, and years between and the occurrence of event.

Figure 6–1. Proportion of prolonged hospital stay after stressors, Cardiovascular Health Study.





Notes: Participants who died in the hospital were considered having a prolonged hospital stay (n = 30 for MI; n = 8 for HF; n = 0 for pneumonia; n = 4 for CABG). *P* values were taken from the χ^2 test. Prolonged hospital stay, greater than sample mean, separate for each stressor; MI, myocardial infarction; HF, heart failure, CABG, coronary artery bypass grafting.

CHAPTER 7: GENETIC BASIS OF FRAILTY IN OLDER ADULTS

7.1. Introduction

Over the past decade, research examining the risk factors of onset and progression of frailty has proliferated. A wide range of socio-demographic,[7] behavioral,[8] health,[13-15,191] clinical,[11] and nutritional[341] characteristics have been associated with frailty from both cross-sectional and prospective studies. However, little attention has been given to the genetic risk factors of frailty. Using data from two large Danish studies, Dato et al.[135] reported a heritability estimate of 43% for frailty, measured by activities of daily living (ADLs), grip strength, body mass index (BMI), self-rated health, and cognition. Murabito et al.[136] showed that frailty, assessed by the PFP scale, was modestly heritable (19%) in the Framingham Heart Study. Recently, Sanders et al.[137] reported a heritability estimate of 23% for a rescaled PFP model (i.e., Scale of Aging Vigor in Epidemiology) using data from the Long Life Family Study. Taken together, these results suggest that frailty is moderately heritable and it is valid to identify genetic variants associated with frailty.

To date, researchers have examined only a very limited number of genes for frailty in small cohorts of older adults (Table 7–1), with no genetic variant being consistently found to be associated with frailty.[138-141,228] The predominant pattern for complex phenotypes is that many genetic variants exist with small effects.[342] The largest cohort used in previous research included slightly over 3,000 participants,[228] which may be underpowered to identify genetic variants for frailty. Therefore, there is a pressing need to explore a wider range of genetic variants in larger cohorts to have a better understanding of the genetic underpinnings of frailty. One approach to serve this purpose is to conduct a genome-wide association study (GWAS), which tests the

associations of genetic variants with diseases and traits across the entire human genome, considering one genetic variant at a time. Since its emergence about a decade ago, GWAS has been successful for identifying genetic variants involved in the development of common diseases and complex traits, such as breast cancer,[145] longevity,[144] and grip strength.[146]

In this chapter, I sought to identify genetic variants that underlie frailty among adults aged ≥65 years, using both phenotype and genotype data from the Health and Retirement Study (HRS) and the Framingham Heart Study (FHS). Over six thousand participants from the two cohorts were eligible for the GWAS. Frailty was measured in two ways: the original physical frailty phenotype (PFP) scale and the continuous frailty scale, which was developed and validated in Chapters 3-6, and. Identification of genetic underpinnings of frailty may improve our understanding of the pathophysiology of frailty and serve as an essential component of patient-tailored prevention and treatment of frailty.

7.2. Methods

7.2.1. Data Source

Health and Retirement Study (HRS)

Description of the HRS cohort was detailed in Section 3.2.1.

Framingham Heart Study (FHS)

The FHS is an on-going, family-based longitudinal study aiming to identify risk factors of cardiovascular disease. The FHS was initiated in 1949 and includes three generations. The original cohort enrolled 5,209 participants aged between 28 to 74 years old; participants were

examined every two years. The offspring cohort was recruited in 1971 and consisted of 5,124 offspring of the original cohort members and their spouses aged between 5 and 70 years. Participants have been examined every 4 to 8 years. The third generation, which was recruited in 2002, consists of 4,095 children of offspring aged between 19 to 72 years. In the present study, Exam 8 of offspring generation were used; 1,300 participants who had all five frailty indicators were included in the present study. All participants provided informed consent for all assessments through the Boston University Medical Center Institutional Review Board (IRB).

7.2.2. Analytic Sample

For both cohorts, the analytic sample was restricted to participants who (i) were ≥65 years, (ii) had complete data on all five frailty indicators: gait speed, grip strength, exhaustion, physical activity, and weight loss, (iii) had genotype data, and (iv) had European ancestry.

7.2.3. Phenotyping

Frailty was measured in two ways: the PFP scale and the continuous frailty scale. For the PFP scale, individuals were classified as robust, prefrail, and frail. Five criteria of the PFP scale for the HRS cohort were provided in Chapter 3. For the continuous frailty scale, standardized score for each frailty indicator was first calculated by dividing the difference between observed value and the sample mean by the standard deviation. Then, five standardized indicator scores were summed to create the continuous frailty score, weighted by the standardized factor loadings identified using confirmatory factor analysis (CFA; Table 3–4).

In the FHS, gait speed, grip strength, exhaustion, and weight loss were measured in the same way as in the Cardiovascular Health Study (CHS; Section 3.2.3.1). Physical activity was assessed by the physical activity index (PAI), calculated by summing up the products of the hours at each level of activity a day times a weight based on the oxygen consumption required for that activity. The dichotomized PAI was created using 20% percentile of sex-specific standardized residuals adjusting for BMI as cutoff.

7.2.4. Genotyping

In 2006-07 and 2008-09 Waves, HRS participants were invited to provide DNA from buccal swabs. A total of 12,507 participants were genotyped for over 2.5 million SNPs at the Center for Inherited Disease Research using the Illimina HumanOmm2.5-4v1 array and the calling algorithm GenomeStudio version 2011.2, Genotyping Module 1.9.4 and GenTrain version 1.0.[343] Genetic information, which is publicly accessible upon request, for all 12,507 participants was uploaded to the Database for Genotypes and Phenotypes (dbGaP; study access number: phs000428.v1.p1) in April, 2012.

FHS participants were genotyped for 549,781 SNPs using the Affymetrix Gene Chip 500K Array Set & 50K Human Gene Focused Panel and the calling algorithm Bayesian Robust Linear Model with Mahalanobis distance classifier (BRLMM).

7.2.5. Quality Control

For the HRS, standard quality control (QC) procedures were performed by the Genetic Coordinating Center of the University of Washington, including gender identify, chromosomal

anomalies, unexpected relatedness, population structure, missing call rates, batch effects, sample contamination, genotyping error rates, Mendelian errors, Hardy-Weinberg equilibrium, and minor allele frequency. Details of the QC procedures in the HRS have been provided elsewhere.[343] For the FHS, standard QCs were performed by analysts from Boston University.

For the HRS, filtering of SNPs and participants in the present study were implemented using PLINK 1.07,[344] a command-line program widely used in GWAS. In the HRS, individuals were filtered for unresolved identity issues, missing call rates >0.02, and unidentified ancestry. As suggested by the HRS Quality Control Report for Genotypic Data, SNPs were filtered if any of the following applied: minor allele frequency <0.01, missing call rates >0.02, >1 Mendelian error per SNP, and Hardy-Weinberg equilibrium *p* value <.0001. I used only genotyped SNPs in chromosomes 1-22 (autosomal chromosomes). Minor allele frequency represents the frequency of the less common allele at a given locus in a given population. Missing call rates indicate the proportion of missing participants per SNP. Mendelian error refers an allele that is impossible to be received from either of its biological parents by Mendelian law of inheritance. The Hardy-Weinberg equilibrium states that allele and genotype frequencies in a population of infinite size will remain constant from generation to generation in the absence of other evolutionary forces (e.g., mate choice, mutation, selection).[345] The *p* value for each SNP indicates the extent of difference between observed and expected genotype frequencies. After the QCs, a final set of 1,635,543 SNPs were available for analysis. A similar QC protocol was used for the FHS genotype data.

SNP data that were genotyped in the HRS, but in the FHS were imputed using MACH.[346] For the FHS, a total of 412,053 SNPs were used as input in the MACH program for phasing and subsequent imputation. A total of 137,728 genotyped SNPs were removed based on the following filtering criteria: 22,018 SNPs for Hardy-Weinberg Equilibrium *p* value of <.000001, 48,285 SNPs for a call rate of <96.9%, 66,063 SNPs for a minor allele frequency of <0.01, 82 SNPs due to not mapping correctly from Build 36 to Build 37 locations, 428 SNPs missing a physical location, 25 SNPs for number of Mendelian errors greater than 1000, 786 SNPs due to not being on chromosomes 1-22 or X and 41 SNPs because they were duplicates. Only SNPs with imputation quality measure $r^2 > 0.3$ were used.

7.2.6. Analytic Approaches

Physical Frailty Phenotype Scale

Multiple linear regression models were fit for genotyped SNPs in chromosomes 1-22 on frailty measured by the PFP scale (score: 0, 1, 2, 3, 4, or 5). Covariates included age in years when frailty was assessed, sex, and top six genome-wide principle components, as suggested by the HRS Quality Control Report for Genotypic Data,[343] to adjust for population stratification. An additive genetic model was assumed, in which each of the SNPs were coded as the number of minor alleles (0, 1, or 2). In addition, because the frailty phenotype measured by the PFP scale is a count variable, I repeated the analyses using negative binomial regression. I compared the *p* values obtained from two models to determine whether it was necessary to use negative binomial regression.

Continuous Frailty Scale

I fit multiple linear regression to identify the association of each SNP with frailty measured by the continuous frailty scale. I assumed an additive genetic model and included age in years when frailty was assessed, sex, and top six genome-wide principle components as covariates.

For both frailty phenotypes, a genome-wide significance threshold of 5×10^{-8} and a suggestive significance threshold of 1×10^{-5} were used to correct for multiple testing.[347] I used Manhattan plot and quantile-quantile (Q-Q) plot to visually summarize the findings. The Manhattan plot is a scatterplot showing the negative $\log_{10}$-transformed *p* values of all SNPs (Y-axis) against their genomic coordinates (X-axis). The Q-Q plot displays the expected distribution of test statistics (X-axis) across all SNPs against the observed values (Y-axis), and it is commonly used to evaluate whether the *p* values are systematically inflated (e.g., due to exclusion of important confounders). Genomic inflation factors (λ) were calculated to evaluate whether the test statistic is overestimated.

Data management, descriptive statistics, and construction of frailty assessments were performed in Stata 13.1 (StataCorp, College Station, TX).[253] Negative binomial regressions and summary of GWAS results and data visualization were conducted in R 3.2.3. Linear regressions were conducted in PLINK 1.07.[344]

Meta-Analysis

For both frailty phenotypes (analyzed separately), test statistics for GWAS in the HRS cohort were combined with those from the FHS cohort (results were available in an ongoing project using GWAS to identify genetic variants associated with frailty in the Cohorts for Heart and

Aging Research in Genomic Epidemiology [CHARGE] Consortium). Results from two cohorts were subsequently meta-analyzed using METAL.[348] I performed an inverse variance-weighted meta-analysis with a fixed-effects model of beta estimates and standard errors from each cohort. Between-study heterogeneity was tested using the Cochran's Q test available in METAL. A threshold of *p*-value $<5\times10^{-8}$ was considered genome-wide statistical significance, and SNPs with *p*-values $<1\times10^{-5}$ were considered suggestive. Suggestively significant SNPs with MAF ≥0.01 were used for subsequent analyses that aimed to annotate their potential regulatory functions.

Functional Annotation

I annotated potential regulatory functions of suggestively significant SNPs and their proxies (i.e., $r^2 >0.8$ in the 1000 Genomes EUR reference panel) using the HaploReg v4.1[349] to annotate potential regulatory functions of non-coding genome based on experimental epigenetic data. r^2, which ranges from 0 to 1, measures correlation between pairs of loci; a value of 1 indicates two markers provide identical information (i.e., perfect linkage disequilibrium [LD]). HaploReg is a free web-tool designed for researchers to generate hypotheses about the functional roles of non-coding genetic variants and has been successfully applied for enrichment analysis[350,351] and haplotype fine-mapping.[351,352] Because the majority of genetic variants for complex phenotypes do not have direct effects on proteins (i.e., located in non-coding regions),[353] HaploReg has been extensively used to understand the regulatory roles of non-coding genetic variation, which in turn provides new mechanistic insights. Detailed description of the HaploReg has been published elsewhere.[349,354]

Expression Quantitative Trait Loci (eQTL) Analysis

I used the publically available eQTL data from the Genotype-Tissue Expression (GTEx) project[355] to explore the biological and functional relevance of suggestively significant SNPs along with their proxy SNPs. The GTEx project was designed to establish a resource database for researchers to identify the relationship among genetic variation, gene expression, and other molecular phenotypes in multiple human tissues (e.g., brain, aorta),[356] which helps understand the functional roles of genetic variation. The GTEx project collects and analyzes multiple human tissues from postmortem donors who are densely genotyped; a total of 7,051 tissues samples spanning 54 distinct body sites from 449 donors were included.[355] Gene expression levels are considered quantitative traits, and those highly correlated with correlated with genetic variants (SNPs) are considered eQTLs. I queried these SNPs in the GTEx dataset (http://www.gtexportal.org/home/) to examine the effects of these SNPs on expression levels of genes across multiple human tissues.

7.3. Results

Description of Participants and Phenotypes

A total of 4,872 HRS participants were analyzed in the GWAS. The average age was 75.0 years (SD = 7.0); 2,165 (45.0%) were men. For the FHS cohort, 1,300 participants were included. The average age was 72.7 years (SD = 5.6); 596 (45.7%) were men. For the count frailty phenotype, 48.4%, 29.7%, 13.4%, 6.1%, 2.2%, and 0.3% of the HRS participants scored 0, 1, 2, 3, 4, and 5, respectively (Figure 7–1). The relative frequency of count frailty phenotype was similar in the FHS cohort; 43.1%, 30.7%, 17.0%, 6.8%, 2.2%, and 0.3% of the participants having a score of 0,

1, 2, 3, 4, and 5, respectively (Figure 7–2). The distribution of the continuous frailty phenotype was approximately normal in both cohorts (Figures 7–3 & 7–4).

Genome-Wide Association Study for the Count Frailty Phenotype

Comparison of *p*-values of SNPs between linear regressions and negative binomial regressions for the count frailty phenotype was displayed in Figure 7–5. For 29 SNPs that reached the suggestive significance in linear regressions, 22 (75.9%) had smaller *p*-values in linear regressions than in negative binomial regressions. For 16 SNPs that reached the suggestive significance in negative binomial regressions, nine SNPs (56.3%) had smaller *p*-values in linear regressions than in negative binomial regressions. The *p*-values for the other seven SNPs were similar between linear regressions and negative binomial regressions. These results suggest that negative binomial regression did not have substantial advantages over the linear regression in identifying potentially important SNPs. Hereafter, I only presented results from linear regressions.

The Q-Q plots did not provide evidence of inflation of test statistics in either cohorts (Figures 7–6 & 7–7); the genomic inflation factor was 1.019 for the HRS cohort and 1.020 for the FHS cohort. The Manhattan plot for the meta-analysis of 6,172 participants from two cohorts was displayed in Figure 7–8. I did not find SNPs that reached genome-wide significance level ($p < 5\times10^{-8}$; Table 7–2); however, 12 SNPs (seven SNPs were independent [LD, $r^2 < 0.80$] based on HaploReg v4.1[349]) had a *p*-value $<1\times10^{-5}$ (suggestively significant) and two SNPs attained a *p*-value of 1×10^{-6}. For all 12 suggestively significant SNPs, directions of the estimates were consistent between the two cohorts. For the seven independent loci that remained suggestive, two

are intergenic, two are intronic, two are in the three prime untranslated region (3'-UTR), and one is missense.

Genome-Wide Association Study for the Continuous Frailty Phenotype

The Q-Q plots of the GWAS for the continuous frailty phenotype in the HRS and FHS cohorts were shown in Figures 7–9 and 7–10, respectively. Both Q-Q plots showed a close match to test statistics expected under the null distribution, indicating minimal overall inflation of genome-wide statistical results due to population stratification (genomic inflation factor $\lambda = 1.017$ for the HRS cohort and 1.028 for the FHS cohort). The Manhattan plot for the meta-analysis of 6,172 participants from two cohorts was displayed in Figure 7–11. I did not find SNPs that reached genome-wide significance level ($p < 5\times10^{-8}$; Table 7–3); however, 10 SNPs (7 loci were independent [LD, $r^2 < 0.5$] based on HaploReg v4.1[349]) had a *p*-value $<1\times10^{-5}$ (suggestively significant) and one SNP attained a p-value of 1×10^{-6}. For all 10 suggestively significant SNPs, directions of the estimates were consistent between the two cohorts. For the seven regions (seven independent SNPs) that remained suggestive, four are intergenic and three are intronic.

Comparisons of Top Hits for the Two Frailty Phenotypes

I examined the *p*-values of SNPs that were suggestively significant for the continuous frailty phenotype in the analyses for the count frailty phenotype and vice versa. All suggestively significant SNPs for the continuous frailty phenotype had a *p*-value <0.05 for the count frailty phenotype (Table 7–4). Similarly, all suggestively significant SNPs for the continuous frailty phenotype had a *p*-value <0.05 for the continuous frailty phenotype. Two SNPs, *rs10842966* and *rs10771354* (LD; $r^2 < 0.97$), had a *p*-value $<1\times10^{-5}$ for both frailty phenotypes.

Functional Annotation

Results from the functional annotation analysis for the count frailty phenotype were shown in Table 7–5. SNP *rs1048889* (chromosome 12) was predicted to alter regulatory motifs in the pair box 5 (*PAX5*). SNP *rs16950822* (chromosome 17) was predicted to alter regulatory motifs in the activator protein 1 (*AP-1*). SNP rs1373185 (chromosome 18) was predicted to alter regulatory motifs in the serum response factor (*SRF*). In addition, *rs1373185* is in a region predicted to be an enhancer in primary B cells from peripheral blood.

Results from the functional annotation analysis for the continuous frailty phenotype were shown in Table 7–6. According to CHIP-seq and DNase-seq data, SNP *rs17084933* (chromosome 5) is in a region predicted to be a promoter in primary T helper memory cells from peripheral blood; SNP *rs10842966* (chromosome 12; smallest *p*-value for both phenotypes) is in a region predicted to be an enhancer in aorta; SNPs *rs135702* and *rs6008957* (in LD) are in a region predicted to be an enhancer in T cells and cardiac muscle cells. In addition, SNP *rs10771354*—one of the two SNPs that were suggestively significant for both phenotypes—was predicted to alter regulatory motifs in the E26 transformation-specific proto-oncogene 1 (*ETS1*). SNP *rs6008957* (chromosome 22) was predicted to alter regulatory motifs in the RAR related orphan receptor A (*RORA*).

Expression Quantitative Trait Loci Analysis

By querying suggestively significant SNPs for either of the two frailty phenotypes, I obtained possible effects of these SNPs on gene expression in human tissues (Tables 7–7 & 7–8). SNP

rs1048889 (chromosome 12) was significantly associated with gene RBPJ-interacting and tubulin-associated 1 (*RITA1*) in multiple tissues, including adipose, esophagus, stomach, skeletal muscle, pancreas, cortex, lung, liver, and whole blood. Researchers have proposed that tubulin-binding protein acts like a negative regulator of the Notch signaling pathway and may play an important role in neurogenesis by reversing Notch-induced loss of neurogenesis.[357]

7.4. Discussion

In this chapter, I performed a meta-analysis of GWAS for frailty in adults aged 65 years or older from two large U.S. cohorts. Although I did not find any genome-wide significant association with frailty, through functional annotation and eQTL analyses, the present study revealed some potentially frailty-related SNPs that could be further explored in larger samples.

SNP *rs10842966*, the most significant SNP for both frailty phenotypes, is an intron variant of gene *PPFIBP1*. The protein coded by *PPFIBP1* is a member of the LAR protein-tyrosine phosphatase-interacting protein (liprin) family; this protein was showed to interact with *S100A4*—a calcium-binding protein involved in tumor invasiveness and metastasis.[358] In addition, *rs10842966* is in a region predicted to be an enhancer in aorta. Located in the same region, SNP *rs10771354* (in LD with *rs10842966*) was predicted to change regulatory motifs in the *ETS1*, which is a transcription factor that regulates genes involved in cell senescence and death.[359] In addition to *rs10842966* and *rs10771354*, *rs1048889*, which is a downstream variant of gene *CFAP13* on chromosome 12, was significantly associated with *RITA1* in multiple tissues, such as skeletal muscle, pancreas, cortex, lung, liver, and whole blood. The tubulin-binding

protein, coded by *RITA1*, acts like a negative regulator of the Notch signaling pathway and may play an important role in neurogenesis by reversing Notch-induced loss of neurogenesis.[357]

SNP *rs1373185* (chromosome 18) was predicted to alter regulatory motifs in the *SRF*, a transcription factor protein that has been shown important for the growth of skeletal muscle.[360] *SRF* also interacts with other proteins—e.g., steroid hormone receptors—that are involved in regulation of muscle growth.[361] In addition, SNP *rs1373185* is in a region predicted to be an enhancer in primary B cells from peripheral blood.

Lastly, SNPs *rs135702* and *rs6008957* (in LD; chromosome 22) are located in a region predicted to be an enhancer in T cells and cardiac muscle cells. Both immune and cardiovascular systems are involved in the development frailty—a complex syndrome resulted from dysregulations across multiple physiological systems.[362-364] In addition, *rs6008957* was predicted to alter regulatory motifs in the *RORA*, which aids in the transcriptional regulation genes involved in circadian rhythm.[365] A growing body of research show that there is potential connection between frailty and sleep disturbances; interventions over circadian rhythm may have clinical implications among frail older adults.[366-368]

One limitation of the present study is that many assessments of frailty exist and there is no consensus among researchers and clinicians regarding what is the best frailty measure. I used two PFP framework-guided frailty assessments—the PFP scale and the continuous frailty scale. The continuous frailty scale is essentially a rescaled, continuous version of the PFP scale, and both scales were guided by the PFP framework. The correlation between the continuous frailty

phenotype and the count frailty phenotype was 0.78 in the HRS cohort, suggesting that both assessments measure the same construct of frailty. SNPs found important for both frailty phenotypes may be less prone to false-positives than those found important for only one phenotype.

In summary, I conducted a meta-analysis of GWAS for frailty using data from 6,172 community-dwelling older men and women of European ancestry from two U.S. cohorts. Although no genome-wide significant genetic variants were revealed, functional annotation and eQTL results suggest biological plausibility of genetic variants with sub-genome-wide significance. One potential explanation why I did not identify genome-wide significant associations is that frailty is an exceedingly complex phenotype with many physiological systems and biological pathways being involved. This complexity adds a layer of difficulty for detecting SNP-based signals. In addition, gene-gene interaction and gene-environment interaction may play an important role in the development of frailty, which deserves future investigations. Moreover, as researchers have performed numerous GWAS for various complex traits and common diseases over the past 12 years, the predominant pattern for these complex phenotypes is that many genetic variants exist with small to modest effects.[342] Nowadays, it is not uncommon to conduct a meta-analysis of multiple GWASs from a large-scale consortium, which often comprises of 100,000 or more individuals.[369,370] Larger samples are therefore needed to detect SNP-based associations for these complex polygenic traits. I am currently leading a meta-analysis of GWAS for frailty using nearly 20 longitudinal cohort studies affiliated with the CHARGE Consortium; both HRS and FHS cohorts serve as discovery sets. This larger meta-analysis will be more powerful for

identifying genetic variations of frailty and provide us a clearer understanding of the genetic architecture of frailty.

Table 7–1. Summary of prior genetic research of frailty.

Study	N	Participants	Definition of frailty	Candidate SNPs	Covariates	Results
Walston et al. (2005)[140]	463	Caucasian and African American women aged 70-79 years from the Women's Health and Aging Studies I and II	PFP scale: Modeled categorically	120 SNPs on the IL-6 gene (MAF ≥0.05)	Age Race BMI	No significant associations (all *p*'s >0.01)
Arking et al. (2006)[141]	363	Caucasian women aged 70-79 years from the Women's Health and Aging Studies I and II	PFP scale: Modeled categorically	8 SNPs on the ciliary neurotrophic factor gene	Age BMI	No significant associations (all *p*'s >0.05)
Mekli et al. (2015a)[139]	3,160	Caucasians aged ≥50 years from Wave 2 of the English Longitudinal Study of Ageing	FI: 62 items Modeled continuously	620 SNPs involved in steroid hormone or inflammatory pathways (e.g., IL-6, CRP, tumor necrosis factor)	Age Sex	rs360722 (*p* = .0021) rs4679868 (*p* = .0062) rs1799986 (*p* = .0065) rs9852519 (*p* = .0077) rs6131 (*p* = .0097) No associations were significant after Bonferroni correction (*p*'s >8.474E-05)
Mekli et al. (2015b)[228]	3,160	Caucasians aged ≥50 years from Wave 2 of the English Longitudinal Study of Aging	PFP scale: Modeled continuously	620 SNPs involved in steroid hormone or inflammatory pathways (e.g., IL-6, CRP, tumor necrosis factor)	Age Sex	rs1800629 (*p* = .0012) rs1566729 (*p* = .0014) rs1566728 (*p* = .0021) rs2047812 (*p* = .0025) rs611646 (*p* = .0039) rs4646316 (*p* = .0155) No associations were significant after Bonferroni correction (*p*'s >8.474E-05)
Liu et al. (2016)[138]	1,723	Chinese aged 70-84 years from the Rugao Longevity and Aging study	FI: 45 items Modeled categorically A FI ≥0.25 was frail	Two common CRP-related SNPs (rs1205, rs3093059)	Age Sex	No significant associations (*p*'s >0.01)

Abbreviations: PFP, physical frailty phenotype; SNP, single nucleotide polymorphism; IL-6, interleukin-6; MAF, minor allele frequency; BMI, body mass index; FI, frailty index; CRP, C-reactive protein.

Table 7–2. GWAS results for the count frailty phenotype (modeled using linear regression).

				Health and Retirement Study			Framingham Heart Study			Meta-analysis		
SNP	Chr	Base pair	Effect allele	Effect allele (%)	Beta	*p* value	Effect allele (%)	Beta	*p* value	Beta	*p* value	Direction
rs79653482	6	15805428	A	0.0243	0.25	1.05E-04	0.0222	0.41	2.01E-02	0.27	8.79E-06	++
rs75221088	8	12880538	A	0.8511	0.13	2.14E-06	0.8563	0.07	2.20E-01	0.12	1.53E-06	++
rs3739303	8	12879940	A	0.1491	-0.13	2.75E-06	0.1437	-0.07	2.21E-01	-0.12	1.95E-06	--
rs1550442	11	116118049	A	0.4742	-0.07	1.82E-04	0.4569	-0.13	4.80E-03	-0.08	5.41E-06	--
rs10842966	12	27810765	A	0.1896	0.12	2.12E-06	0.1868	0.12	2.57E-02	0.12	1.57E-07	++
rs34594391	12	27802490	A	0.7628	-0.09	7.54E-05	0.7657	-0.10	4.61E-02	-0.09	9.22E-06	--
rs10771354	12	27811649	A	0.8160	-0.12	2.87E-06	0.8207	-0.09	1.01E-01	-0.12	8.14E-07	--
rs1048889	12	113596866	A	0.0641	0.16	1.01E-04	0.0754	0.19	3.50E-02	0.16	9.99E-06	++
rs8078818	17	50017724	A	0.1506	0.11	6.00E-05	0.1421	0.12	3.62E-02	0.11	6.00E-06	++
rs16950822	17	50006005	A	0.1505	0.11	5.95E-05	0.1445	0.12	4.16E-02	0.11	6.71E-06	++
rs8068740	17	50003626	A	0.8491	-0.11	6.72E-05	0.8545	-0.12	4.16E-02	-0.11	7.57E-06	--
rs1373185	18	47745851	A	0.7315	-0.10	1.20E-05	0.7447	-0.06	2.64E-01	-0.09	8.39E-06	--

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome.

Notes: only SNPs that had *p*-values $<1\times10^{-5}$ and minor allele frequency ≥1% were shown.

Table 7–3. GWAS results for the continuous frailty phenotype.

				Health and Retirement Study			Framingham Heart Study			Meta-analysis		
SNP	Chr	Base pair	Effect allele	Effect allele (%)	Beta	*p* value	Effect allele (%)	Beta	*p* value	Beta	*p* value	Direction
rs2601634	1	215165933	A	0.4839	-0.09	1.70E-04	0.4936	-0.10	4.12E-03	-0.09	2.35E-06	--
rs2841622	1	215165487	A	0.5189	0.08	2.97E-04	0.5034	0.10	3.90E-03	0.09	3.99E-06	++
rs62332091	4	154866646	A	0.0864	-0.16	1.26E-04	0.0864	-0.15	1.62E-02	-0.16	6.04E-06	--
rs4862613	4	186929068	A	0.2432	-0.13	3.46E-06	0.2243	-0.05	4.05E-01	-0.11	6.14E-06	--
rs17084933	5	94942780	A	0.9603	-0.20	8.49E-04	0.9500	-0.26	1.54E-03	-0.22	4.96E-06	--
rs9642880	8	128718068	A	0.5339	0.09	8.38E-05	0.4600	0.12	1.79E-02	0.10	5.08E-06	++
rs10842966	12	27810765	A	0.1896	0.13	7.12E-06	0.1868	0.12	7.76E-03	0.13	1.81E-07	++
rs10771354	12	27811649	A	0.8160	-0.13	1.15E-05	0.8207	-0.09	5.04E-02	-0.12	2.12E-06	--
rs135702	22	47109525	A	0.2324	0.14	6.02E-07	0.2391	0.03	4.04E-01	0.10	4.51E-06	++
rs6008957	22	47108669	A	0.7663	-0.14	8.33E-07	0.7595	-0.03	4.06E-01	-0.10	5.55E-06	--

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome.

Notes: only SNPs that had *p*-values $<1\times10^{-5}$ and minor allele frequency ≥1% were shown.

Table 7–4. Comparisons of top hits for the two frailty phenotypes.

SNP	Chr	Continuous frailty phenotype		Count frailty phenotype	
		Meta beta	Meta *p* value	Meta beta	Meta *p* value
		Suggestively significant SNPs for the continuous frailty phenotype			
rs2601634	1	-0.09	2.35E-06	-0.04	2.88E-02
rs2841622	1	0.09	3.99E-06	0.04	3.29E-02
rs62332091	4	-0.16	6.04E-06	-0.09	4.48E-03
rs4862613	4	-0.11	6.14E-06	-0.08	2.16E-04
rs17084933	5	-0.22	4.96E-06	-0.18	9.30E-05
rs9642880	8	0.10	5.08E-06	0.07	6.45E-04
rs10842966	12	0.13	1.81E-07	0.12	1.57E-07
rs10771354	12	-0.12	2.12E-06	-0.12	8.14E-07
rs135702	22	0.10	4.51E-06	0.05	2.18E-02
rs6008957	22	-0.10	5.55E-06	-0.05	2.34E-02
		Suggestively significant SNPs for the count frailty phenotype			
rs79653482	6	0.17	1.05E-02	0.27	8.79E-06
rs75221088	8	0.09	1.31E-03	0.12	1.53E-06
rs3739303	8	-0.09	1.64E-03	-0.12	1.95E-06
rs1550442	11	-0.07	7.51E-04	-0.08	5.41E-06
rs10842966	12	0.13	1.81E-07	0.12	1.57E-07
rs34594391	12	-0.10	1.88E-05	-0.09	9.22E-06
rs1048889	12	0.12	2.17E-03	0.16	9.99E-06
rs10771354	12	-0.12	2.12E-06	-0.12	8.14E-07
rs8078818	17	0.07	8.54E-03	0.11	6.00E-06
rs16950822	17	0.07	8.20E-03	0.11	6.71E-06
rs8068740	17	-0.07	8.67E-03	-0.11	7.57E-06
rs1373185	18	-0.09	1.46E-04	-0.09	8.39E-06

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome.

Notes: only SNPs that had *p*-values $<1\times10^{-5}$ for either of the two frailty phenotypes and minor allele frequency ≥1% were shown.

Table 7–5. Functional annotation of suggestively significant SNPs for the count frailty phenotype.

SNP	Chr	Position (bp)	Gene structure	Closest gene	Functional annotation results		# SNPs in LD[b]
					Regulatory motifs altered[a]	regulatory chromatin states	
rs79653482	6	15805428	intergenic	DTNBP1	ATF4		0
rs75221088	8	12880538	3'-UTR	KIAA1456			5
rs3739303	8	12879940	3'-UTR	KIAA1456			5
rs1550442	11	116118049		snoU13 LOC283143	Pou2f2, Sin3Ak-20		9
rs10842966	12	27810765	intronic	PPFIBP1		Enhancer in aorta	5
rs34594391	12	27802490	intronic	PPFIBP1	Evi-1, HDAC2, Hoxa9, Hoxa10, Hoxd10, Pax-4, Zfp105, p300		8
rs10771354	12	27811649	intronic	PPFIBP1	ETS1		4
rs1048889	12	113596866	missense	CCDC42B	Pax5		68
rs8078818	17	50017724	intronic	CA10			34
rs16950822	17	50006005	intronic	CA10	AP1		32
rs8068740	17	50003626	intronic	CA10			32
rs1373185	18	47745851	intergenic		SRF	Enhancer in primary B cells from peripheral blood	2

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome; bp, base pair; LD, linkage disequilibrium.

[a] The change in log-odds (LOD) scores of regulatory motifs larger than 10 were reported.

[b] $r^2 \geq 0.8$

Table 7–6. Functional annotation of suggestively significant SNPs for the continuous frailty phenotype.

SNP	Chr	Position (bp)	Gene structure	Closest gene	Functional annotation results		# SNPs in LD[b]
					Regulatory motifs altered[a]	regulatory chromatin states	
rs2601634	1	15805428	intergenic	KCNK2	Irf		4
rs2841622	1	12880538	intergenic	KCNK2			4
rs62332091	4	12879940	intergenic	AC020703.1 SFRP2	Hsf		11
rs4862613	4	116118049	intergenic	U4 SORBS2	DMRT1, DMRT3, DMRT5, DMRT7, Gfi1		0
rs17084933	5	27810765	intergenic	ARSK		Promoter in primary T helper memory cells from peripheral blood	31
rs9642880	8	27802490	intergenic	RP11-1136L8.1 MYC	COMP1,Pbx-1,Roaz		1
rs10842966	12	27657832	intronic	PPFIBP1		Enhancer in aorta	5
rs10771354	12	27811649	intronic	PPFIBP1	ETS1		4
rs135702	22	50017724	intronic	CERK		Enhancer in primary T regulatory cells from peripheral blood Enhancer in primary T helper naive cells from peripheral blood Enhancer in primary T helper 17 cells Enhancer in right atrium Enhancer in left ventricle Enhancer in right ventricle	7
rs6008957	22	50006005	intronic	CERK	RORA	Enhancer in primary T regulatory cells from peripheral blood Enhancer in primary T helper 17 cells Enhancer in right ventricle Enhancer in duodenum smooth muscle	7

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome; bp, base pair; LD, linkage disequilibrium.

[a] The change in log-odds (LOD) scores of regulatory motifs larger than 10 were reported.

[b] $r^2 \geq 0.8$

Table 7–7. Expression quantitative trait loci (eQTL) results of suggestively significant SNPs for the count frailty phenotype.

SNP	Chr	Gene	p value	Effect size	Tissue
rs12582113	12	RP11-1060J15.4	3.90E-05	0.39	Skin - Sun Exposed (Lower leg)
rs34594391	12	RP11-1060J15.4	5.40E-05	0.40	Skin - Sun Exposed (Lower leg)
rs7974209	12	RP11-1060J15.4	8.50E-09	-0.51	Skin - Sun Exposed (Lower leg)
rs7974209	12	RP11-1060J15.4	2.00E-07	-0.53	Esophagus - Muscularis
rs7974209	12	RP11-1060J15.4	1.10E-05	-0.40	Adipose - Subcutaneous
rs7974209	12	RP11-1060J15.4	1.90E-05	-0.50	Stomach
rs7974209	12	RP11-1060J15.4	4.70E-05	-0.31	Muscle - Skeletal
rs4931235	12	RP11-1060J15.4	4.40E-09	-0.52	Skin - Sun Exposed (Lower leg)
rs4931235	12	RP11-1060J15.4	8.10E-08	-0.55	Esophagus - Muscularis
rs4931235	12	RP11-1060J15.4	3.90E-06	-0.42	Adipose - Subcutaneous
rs4931235	12	RP11-1060J15.4	1.90E-05	-0.49	Stomach
rs4931235	12	RP11-1060J15.4	4.80E-05	-0.31	Muscle - Skeletal
rs4931247	12	RP11-1060J15.4	5.00E-08	-0.51	Skin - Sun Exposed (Lower leg)
rs4931247	12	RP11-1060J15.4	3.30E-07	-0.56	Esophagus - Muscularis
rs4931247	12	RP11-1060J15.4	4.10E-06	-0.44	Adipose - Subcutaneous
rs4931247	12	RP11-1060J15.4	2.70E-05	-0.49	Stomach
rs4931247	12	RP11-1060J15.4	2.80E-05	-0.39	Cells - Transformed fibroblasts
rs4931247	12	RP11-1060J15.4	5.50E-05	-0.43	Esophagus - Mucosa
rs2113875	12	RP11-1060J15.4	1.20E-08	-0.53	Skin - Sun Exposed (Lower leg)
rs2113875	12	RP11-1060J15.4	3.60E-07	-0.56	Esophagus - Muscularis
rs2113875	12	RP11-1060J15.4	2.50E-06	-0.45	Adipose - Subcutaneous
rs2113875	12	RP11-1060J15.4	5.60E-06	-0.54	Stomach
rs2113875	12	RP11-1060J15.4	6.90E-06	-0.42	Cells - Transformed fibroblasts
rs2113875	12	RP11-1060J15.4	7.00E-05	-0.43	Esophagus - Mucosa
rs34982186	12	RP11-1060J15.4	1.50E-08	0.54	Skin - Sun Exposed (Lower leg)
rs34982186	12	RP11-1060J15.4	4.00E-06	0.45	Adipose - Subcutaneous
rs34982186	12	RP11-1060J15.4	6.60E-06	0.43	Cells - Transformed fibroblasts
rs34982186	12	RP11-1060J15.4	8.10E-06	0.51	Esophagus - Muscularis
rs12826974	12	RP11-1060J15.4	6.10E-08	0.48	Skin - Sun Exposed (Lower leg)
rs12826974	12	RP11-1060J15.4	2.40E-06	0.51	Esophagus - Muscularis
rs12826974	12	RP11-1060J15.4	2.80E-06	0.43	Adipose - Subcutaneous
rs1048889	12	RITA	1.30E-11	-0.67	Nerve - Tibial
rs1048889	12	RITA	2.30E-11	-0.48	Skin - Sun Exposed (Lower leg)
rs1048889	12	RITA	1.90E-10	-0.86	Colon - Transverse
rs1048889	12	RITA	6.50E-10	-0.51	Skin - Not Sun Exposed (Suprapubic)
rs1048889	12	RITA	9.60E-10	-0.42	Thyroid
rs1048889	12	RITA	1.60E-09	-0.74	Breast - Mammary Tissue
rs1048889	12	RITA	2.40E-08	-0.54	Adipose - Subcutaneous
rs1048889	12	RITA	4.80E-08	-0.57	Esophagus - Muscularis
rs1048889	12	RITA	7.60E-08	-0.88	Stomach
rs1048889	12	RITA	5.70E-07	-0.32	Muscle - Skeletal
rs1048889	12	RITA	2.00E-06	-0.89	Pancreas
rs1048889	12	RITA	3.40E-06	-0.57	Brain - Cortex
rs1048889	12	RITA	8.30E-06	-0.32	Lung
rs1048889	12	RITA	1.30E-05	-0.66	Liver
rs1048889	12	RITA	2.30E-05	-0.38	Esophagus - Mucosa
rs1048889	12	RITA	4.50E-05	-0.33	Whole Blood
rs1048889	12	IQCD	2.10E-07	0.92	Artery - Aorta
rs1048889	12	IQCD	2.30E-05	0.54	Artery - Tibial
rs1048889	12	RASAL1	1.90E-10	-0.52	Skin - Sun Exposed (Lower leg)
rs1048889	12	DDX54	3.40E-05	0.30	Adipose - Subcutaneous

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome.

Notes: rs12582113 is in linkage disequilibrium (LD; r^2=0.82) with rs10842966; rs7974209 is in LD (r^2=0.81) with rs34594391; rs4931235 is in LD (r^2=0.83) with rs34594391; rs2113875is in LD (r^2=0.81) with rs34594391; rs4931247 is in LD (r^2=0.84) with rs34594391; rs34982186is in LD (r^2=0.81) with rs34594391; rs12826974is in LD (r^2=0.82) with rs34594391.

Table 7–8. Expression quantitative trait loci (eQTL) results of suggestively significant SNPs for the continuous frailty phenotype.

SNP	Chr	Gene	p value	Effect size	Tissue
rs10055673	5	RHOBTB3	3.60E-05	0.45	Adipose - Subcutaneous
rs13355280	5	RHOBTB3	1.00E-05	0.47	Adipose - Subcutaneous
rs12582113	12	RP11-1060J15.4	3.90E-05	0.39	Skin - Sun Exposed (Lower leg)

Abbreviations: SNP, single nucleotide polymorphism; Chr, chromosome.
Notes: rs10055673 and rs13355280 are in linkage disequilibrium (r^2= 0.82 for both) with rs17084933; rs12582113 is in linkage disequilibrium (r^2= 0.82) with rs10842966.

Figure 7–1. Distribution of count frailty phenotype in the Health and Retirement Study.

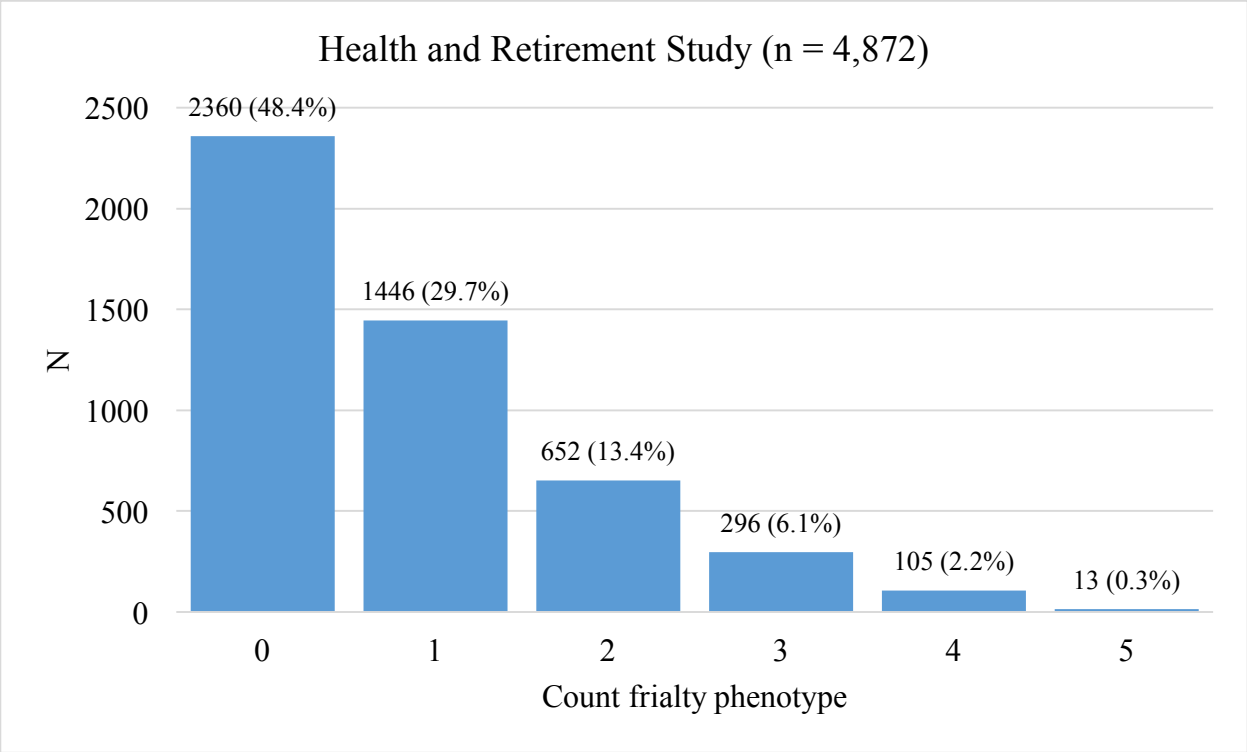


Figure 7–2. Distribution of count frailty phenotype in the Framingham Heart Study.

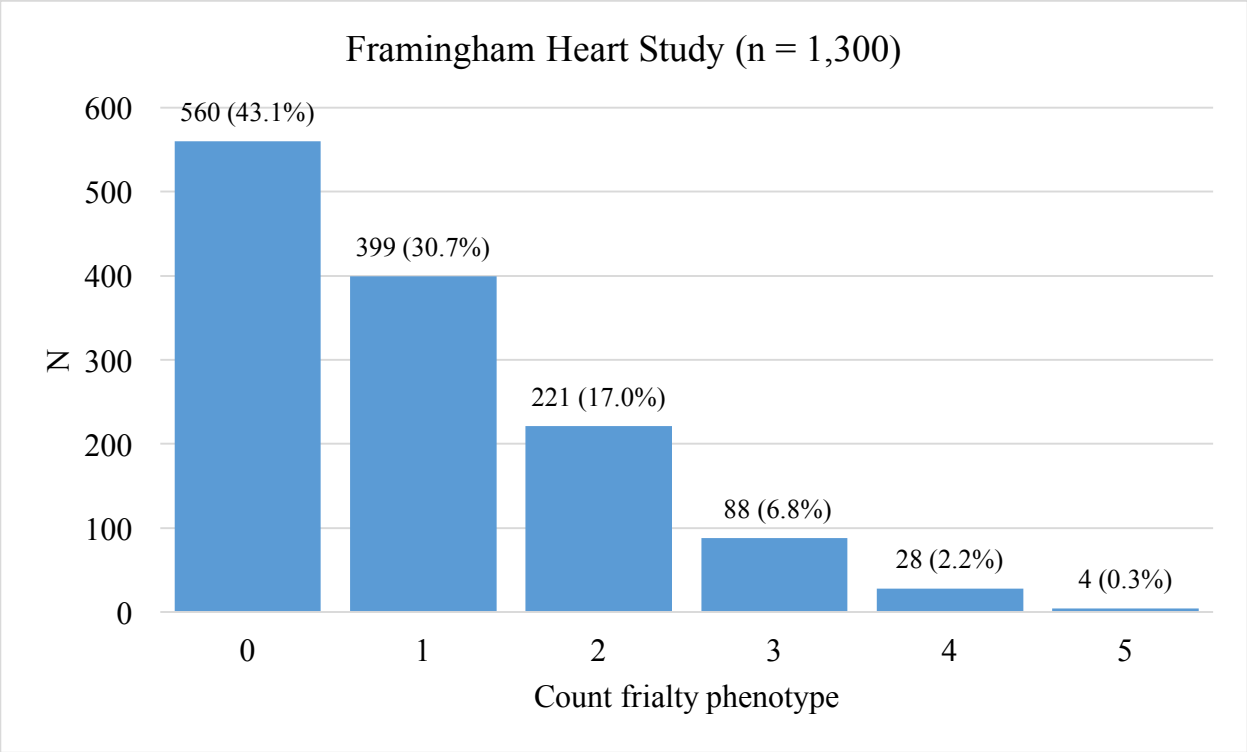


Figure 7–3. Distribution of continuous frailty phenotype in the Health and Retirement Study.

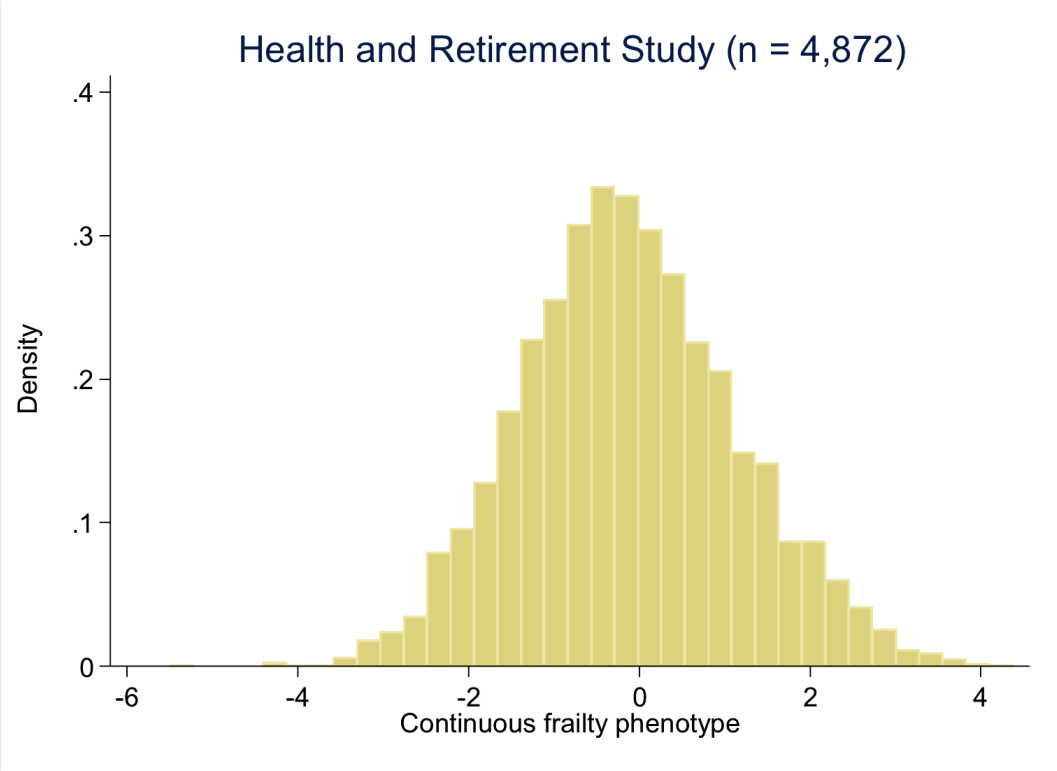


Figure 7–4. Distribution of continuous frailty phenotype in the Framingham Heart Study.

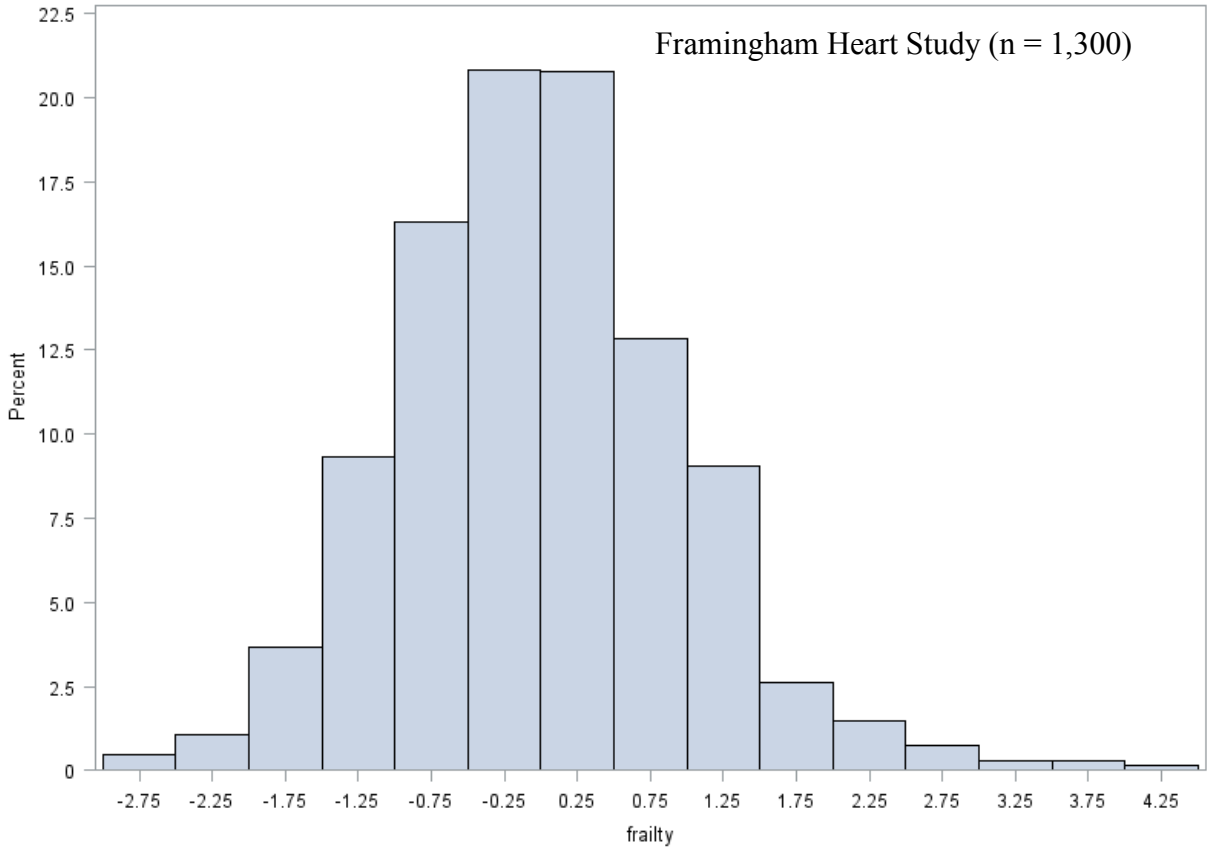
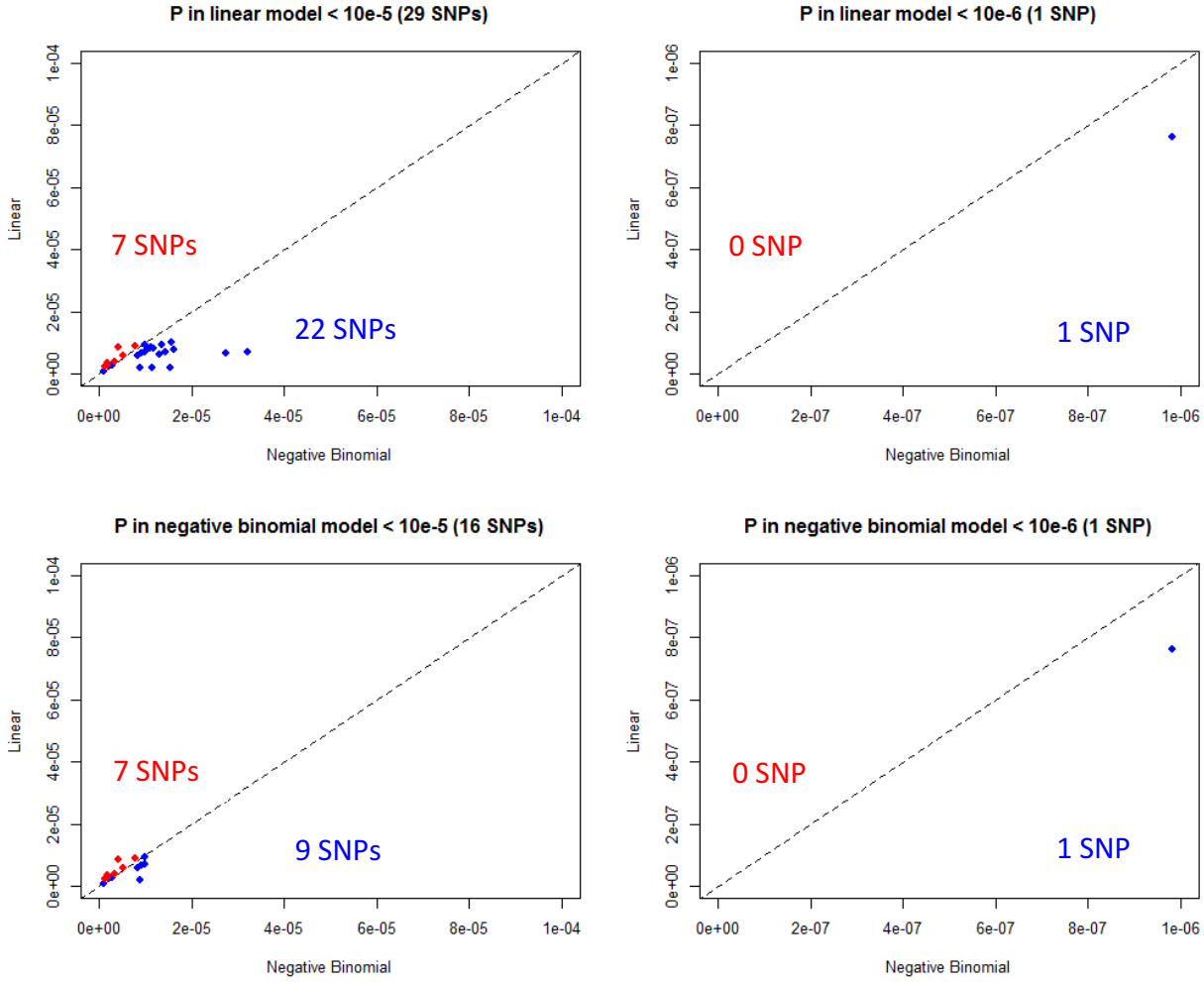
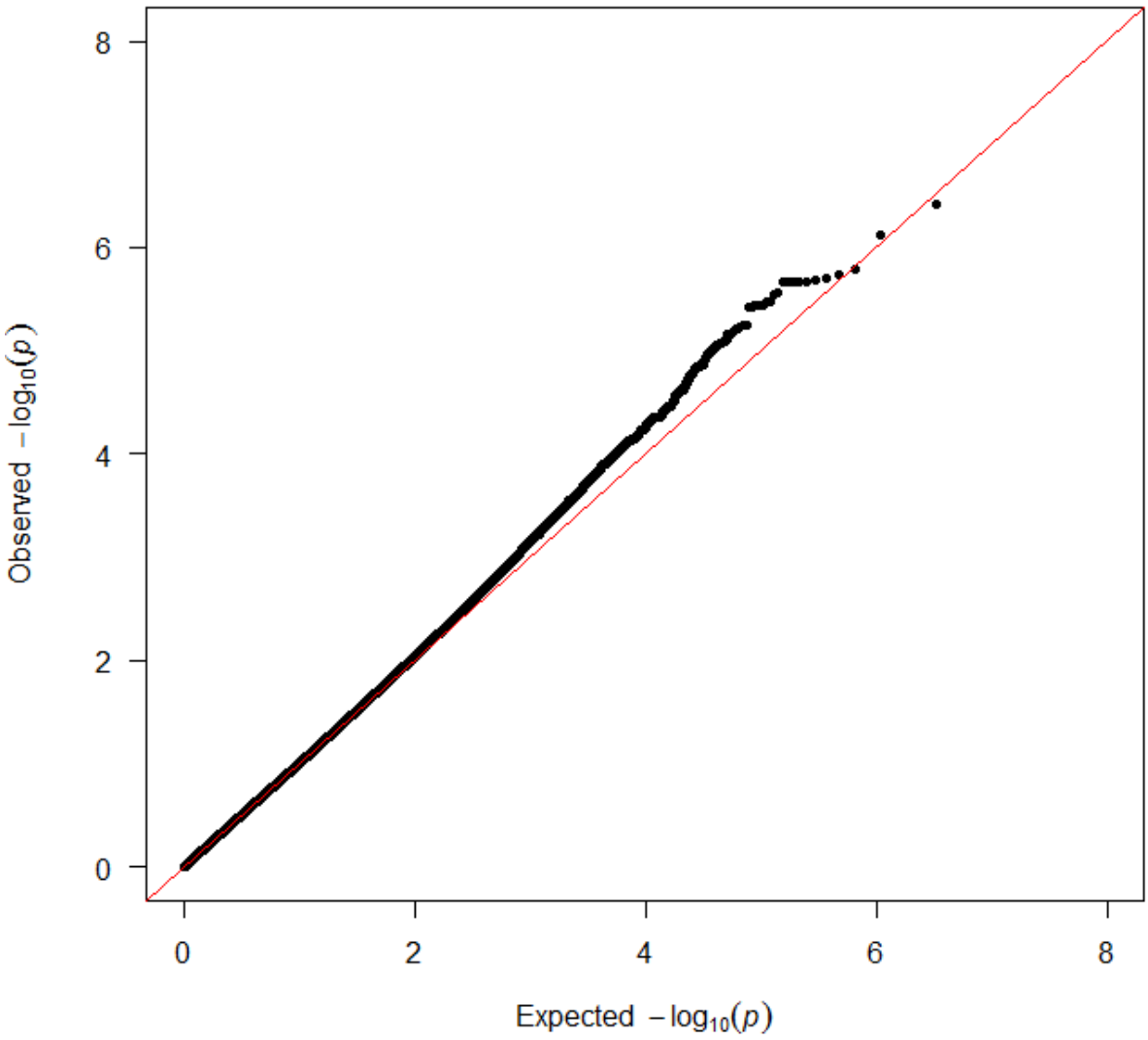


Figure 7–5. Comparison of p-values of SNPs between linear and negative binomial models for the count frailty phenotype (constructed using the physical frailty phenotype scale).



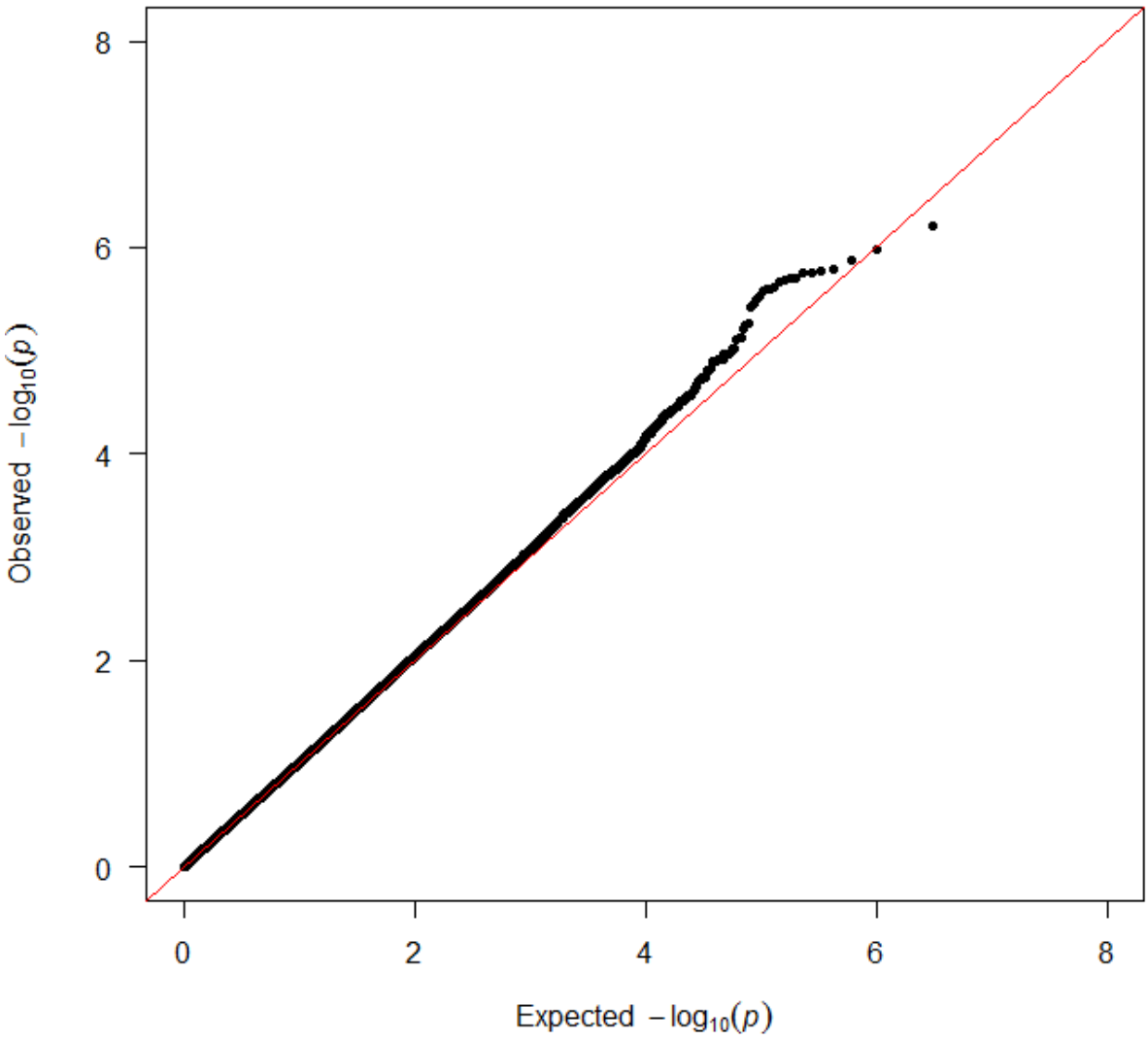
Notes: All SNPs had minor allele frequency greater than or equal to 0.05. Red dots indicate *p*-values that were smaller in negative binomial than in linear models; blue dots represent *p*-values that were smaller in linear than in negative binomial models. Results were derived from the Health and Retirement Study.

Figure 7–6. Quintile-quintile (Q-Q) plot for the count frailty phenotype (modeled using linear regression) in the Health and Retirement Study.



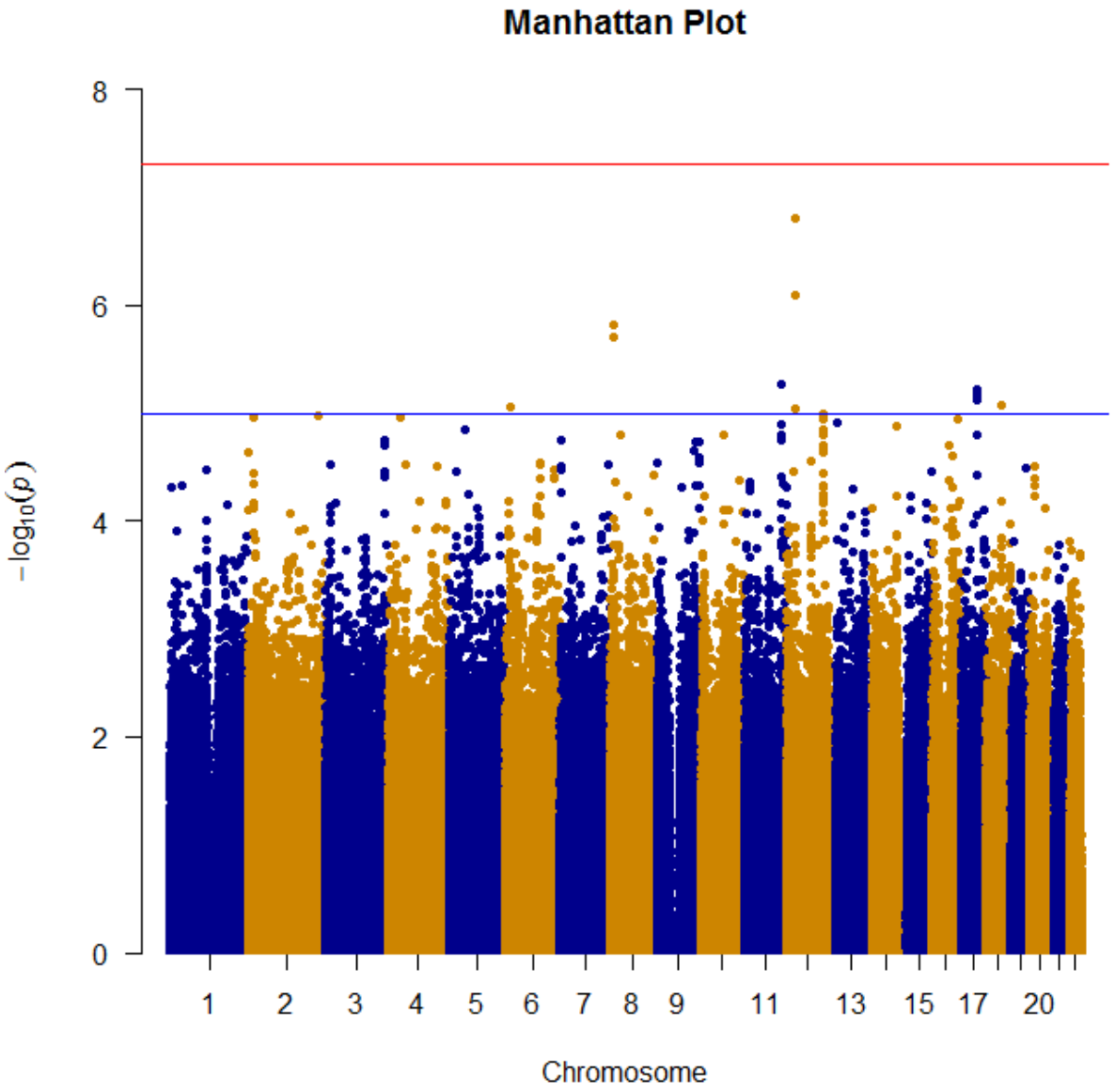
Notes: The y-axis is the quintiles of observed negative $\log_{10}$-transformed p-values and x-axis is the quintiles from the expected distribution of negative $\log_{10}$-transformed p-values.

Figure 7–7. Quintile-quintile (Q-Q) plot for the count frailty phenotype (modeled using linear regression) in the Framingham Heart Study.



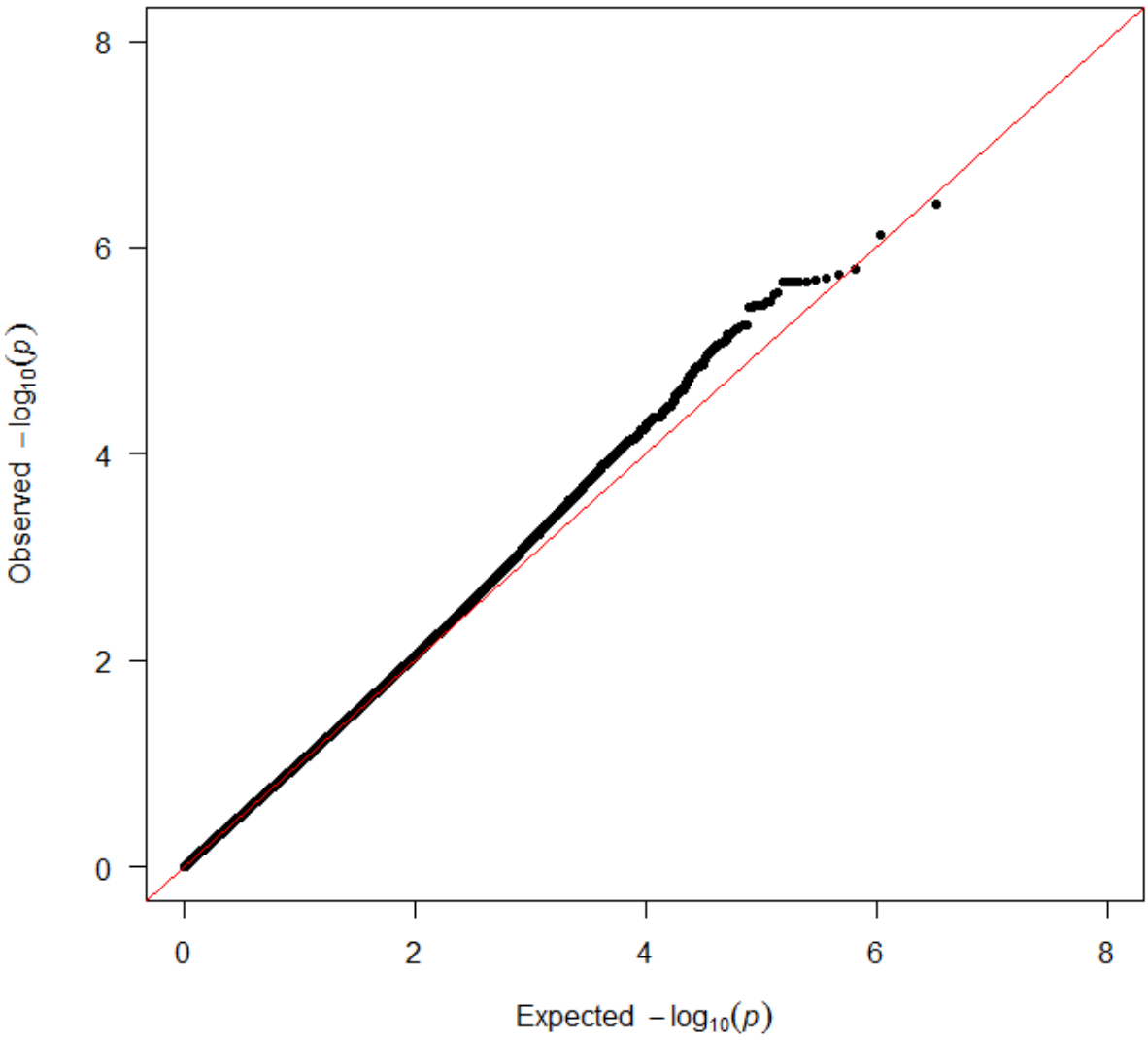
Notes: The y-axis is the quintiles of observed negative $\log_{10}$-transformed p-values and x-axis is the quintiles from the expected distribution of negative $\log_{10}$-transformed p-values.

Figure 7–8. Manhattan plot for the count frailty phenotype (modeled using linear regression) in the meta-analysis of genome-wide association studies of frailty.



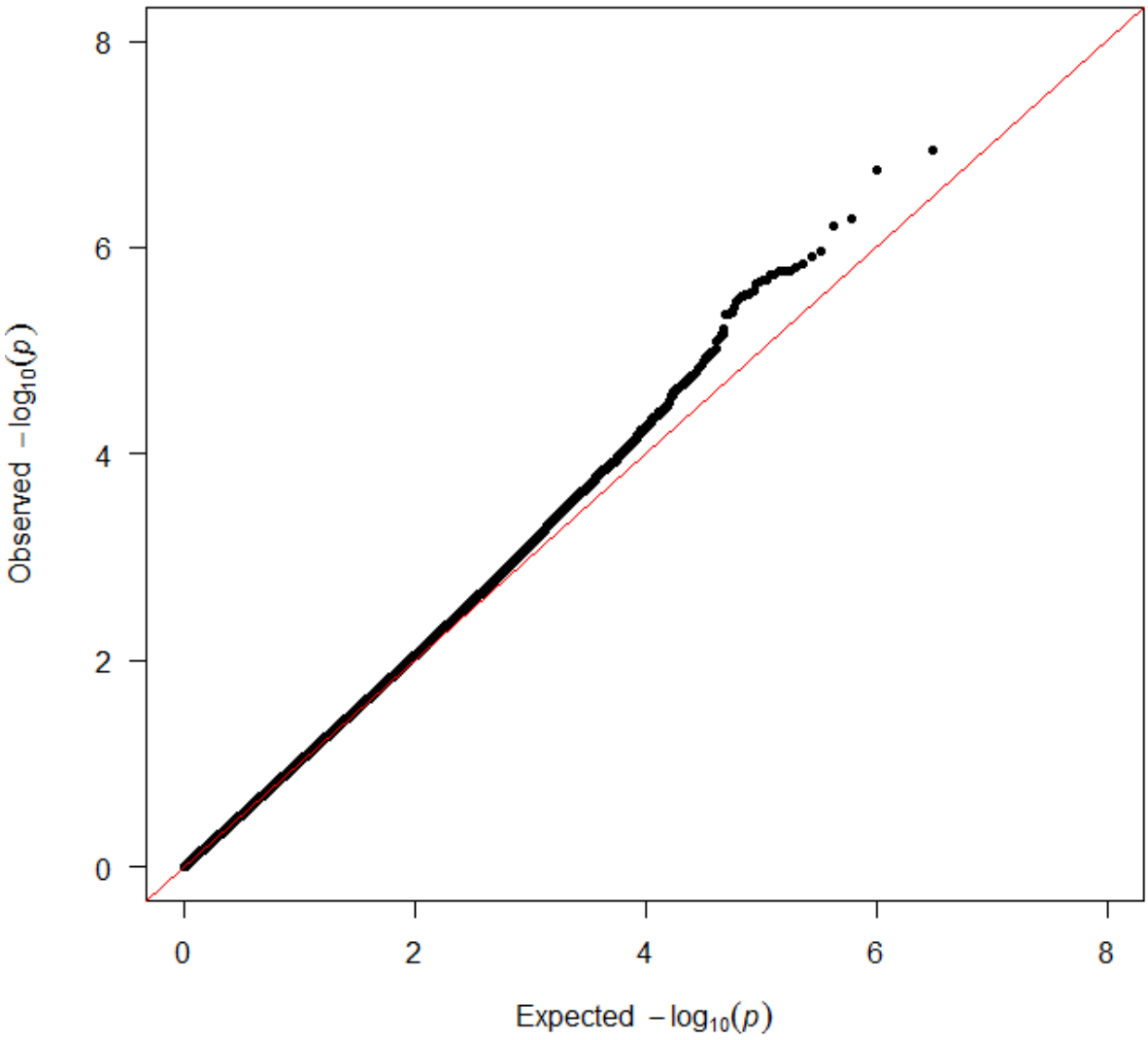
Notes: The y-axis is the quintiles of observed negative $\log_{10}$-transformed p-values and x-axis is the genomic locations for each SNP ordered by chromosome and base pair positions. Dots above solid red line indicate SNPs with *p*-values less than 5×10^{-8}; dots above blue solid line indicate SNPs with *p*-values less than 1×10^{-5}. All SNPs with minor allele frequency greater or equal to 0.05 were displayed.

Figure 7–9. Quintile-quintile (Q-Q) plot for the continuous frailty phenotype in the Health and Retirement Study.



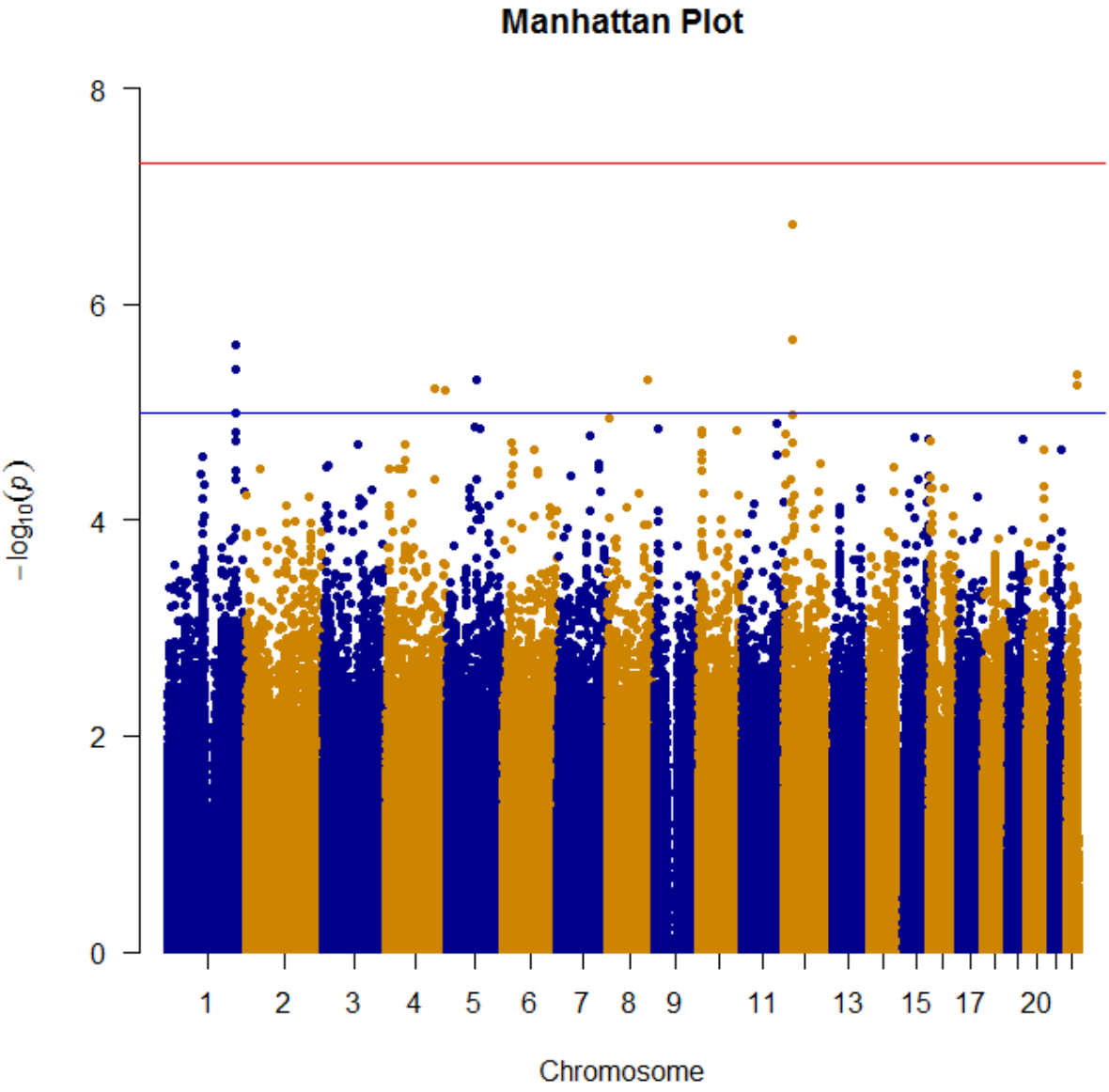
Notes: The y-axis is the quintiles of observed negative $\log_{10}$-transformed p-values and x-axis is the quintiles from the expected distribution of negative $\log_{10}$-transformed p-values.

Figure 7–10. Quintile-quintile (Q-Q) plot for the continuous frailty phenotype in the Framingham Heart Study.



Notes: The y-axis is the quintiles of observed negative $\log_{10}$-transformed p-values and x-axis is the quintiles from the expected distribution of negative $\log_{10}$-transformed p-values.

Figure 7–11. Manhattan plot for the continuous frailty phenotype in the meta-analysis of genome-wide association studies of frailty.



Note: The y-axis is the quintiles of observed negative $\log_{10}$-transformed p-values and x-axis is the genomic locations for each SNP ordered by chromosome and base pair positions. Dots above solid red line indicate SNPs with *p*-values less than 5×10^{-8}; dots above blue solid line indicate SNPs with *p*-values less than 1×10^{-5}. All SNPs with minor allele frequency greater or equal to 0.05 were displayed.

CHAPTER 8: SUMMARY, CONCLUSIONS, AND FUTURE RESEARCH

8.1. Summary and Conclusions

The overarching goal of this dissertation was two-fold. The first was to create a new continuous scale for assessing frailty and to comprehensively evaluate its construct and predictive validity and measurement properties. The second was to identify genetic variants that were associated with frailty. I conducted five empirical studies to achieve these two goals (Chapters 3-7).

The first study of my dissertation (Chapter 3) aimed to create and validate a continuous frailty scale; three major findings warrant comment. First, I created a continuous frailty scale using five measures—gait speed, grip strength, exhaustion, physical activity, and weight loss—and demonstrated that not all five measures were equally important for assessing frailty. Gait speed was the strongest indicator for measuring frailty, weight loss was the weakest, and grip strength, exhaustion, and physical activity had similar strength. Second, the factor structure of five observed measures and the latent frailty construct was unidimensional and the relationship between five measures and the latent frailty construct (i.e., factor structure) was similar across study population, age, and sex. These results were consistent with previous work showing that a one-factor model had a satisfactory fit with qualitatively similar factor structure across 12 European countries.[255] Finally, participants who were identified as robust and prefrail in the PFP scale had different scores on the new continuous frailty scale, suggesting that robust and prefrail persons were two heterogeneous groups with different levels of frailty.

Taken together, results from the first study of my dissertation suggest that it may be valid and feasible to construct a continuous frailty scale based on five measures originally used to

construct the PFP scale. In addition, the new continuous frailty scale had a unidimensional factor structure robust to nuanced differences in measurement of indicators and invariant across cohorts and demographics including age and sex. Moreover, by explicitly examining the relationship between each observed measure and the latent frailty construct, this study is among the first to identify that not all measures had equal importance for assessing frailty, with gait speed being the strongest indicator. Gait speed—a quick, easy, and inexpensive physical performance measure—is an integrative measure of health and a well-documented indicator for mortality, disability, and other adverse outcomes among older adults.[258-263] Many geriatricians have advocated that gait speed, a key component in many frailty assessments (e.g., PFP scale, Fatigue, Resistance, Ambulation, Illness, and Loss [FRAIL] scale), is the most suitable single-item measure of frailty in clinical practice.[70,264] The current work provided additional evidence to support this claim. Furthermore, there were huge variations in levels of frailty among robust and prefrail persons, both of which were considered homogeneous subgroups in the PFP scale. Further stratifying individuals' frailty levels may remove the ceiling effect of the original categorical PFP scale and improve accuracy for early identification of frailty, which would guide implementation of interventions.

In addition to construct validity and measurement property, predictive validity is another important feature in assessing the validity of a scale. The second study of my dissertation (Chapter 4) aimed to evaluate the predictive value of the new continuous frailty scale for adverse health outcomes. I showed that the continuous frailty scale was strongly associated with death, disability, hip fracture, and falls among older adults, respectively, providing evidence that the new scale is a valid assessment of frailty and is a useful measure for stratifying risk of outcomes.

I compared the predictive ability between the new continuous frailty scale and the original PFP scale and showed that the new scale had better performance for predicting all four outcomes—death, disability, hip fracture, and falls—than the PFP scale. It is not surprising that the continuous frailty scale only had slightly better prediction performance than the PFP scale; both frailty assessments have the same five items, and the continuous frailty scale is essentially a weighted, continuous version of the PFP scale, with weights determined by the strength of associations between five observed measures and the underlying frailty construct.

More importantly, I found that the continuous frailty scale was able to further stratify risk of outcomes among robust and prefrail persons identified by the PFP scale. These results suggest that both robust and prefrail individuals, who had different scores on the new continuous frailty scale (as shown in the first study), are two heterogeneous groups with different risks of developing unfavorable outcomes. This study, to my knowledge, was among the first to show that individuals classified as robust and prefrail had different frailty-related risk of adverse outcomes. Previous research has shown that the frailty index (FI) scores (based on 46 deficits) were associated with poor self-rated health and high healthcare utilization among robust persons identified by a modified version of the PFP scale.[275] The authors concluded that the FI might be a more sensitive frailty measure because the FI can stratify risk of outcomes into a broader spectrum than the PFP scale. I extended this work by showing that the continuous frailty scale, developed under the PFP framework, could achieve the same purpose—removing the ceiling effect of the original PFP scale. Additionally, the present study extended upon previous research by demonstrating that not only robust persons but also those who were prefrail had different risks of developing unfavorable outcomes. The FI usually involves a long checklist of comorbidities,

disability, and clinical conditions; the continuous frailty scale, in contrast, only includes five measures and differentiates frailty from disability and comorbidity. In this sense, the continuous frailty scale—a recalibration of the PFP scale—can improve risk stratification while not sacrificing specificity, which offers benefits to elucidate the physiological etiology of frailty and is essential for designing targeted interventions for frailty.[276]

In the third study of my dissertation (Chapter 5), I examined the association between frailty and resilience after disability among older adults. I showed that frailty, as assessed by both the continuous frailty scale and the PFP scale, was strongly associated with recovery of and improvement in activities of daily living (ADL) function after experiencing disability. I also found suggestive evidence that the new continuous frailty scale could capture the risk gradient in recovery of and improvement in ADL function among robust and prefrail elders identified by the PFP scale. This work was among the first identifying relationship between multi-component measures of frailty and recovery from disability among non-hospitalized elders. Prior studies have demonstrated associations between single-component measures of frailty—e.g., gait speed, physical activity, and weight loss—with recovery from disability.[291,303,304] The current study extended previous research in several important ways. First, I measured frailty comprehensively using two multi-component frailty instruments. Second, because participants in this study were from two large, population-based cohorts with heterogeneous samples, findings are readily generalizable.

Taken together, results from the third study suggest that assessing frailty is useful for stratifying risk of poor recovery from disability and could help clinicians, healthcare professionals, and

researchers better identify at-risk elders after experiencing disability. Because reduced physiological reserves and resilience to stressors (e.g., poor recovery) is one of the defining features of frailty, results from this work also corroborated the validity of two PFP framework-guided assessments of frailty. Given the number of adults living with disability in the U.S. is expected to increase due to population aging, having a better understanding of the role of frailty in the recovery process of disability is of significant interest to public health and has important implications for geriatric practice. In addition, knowledge of association between frailty and resilience after disability may offer new opportunities for interventions and geriatric care targeted at promoting recovery from disability, maintaining the duration of recovery, and preventing recurrent disability.

In the fourth study of my dissertation (Chapter 6), I examined whether frailty was associated with older adults' ability to recover from common acute medical events and surgeries in old age. I found that older persons with higher levels of frailty were more likely to have prolonged length of stay (LOS) after undergoing myocardial infarction (MI) and coronary artery bypass grafting (CABG), respectively. I also showed that frailer elders had higher risk of all-cause mortality after experiencing MI, heart failure (HF), pneumonia, and CABG, respectively. Findings from the third and fourth study, taken together, provided strong evidence supporting that both the continuous frailty scale and the PFP scale could capture older persons' ability to recovery from stressors, which is considered one of the defining features of frailty.

Finally, I conducted a meta-analysis of genome-wide association study (GWAS) among older adults to explore the genetic basis of frailty (Chapter 7). Although I did not reveal clear findings

(i.e., no genome-wide significant associations), I found several potentially frailty-related genetic variants (single nucleotide polymorphisms [SNPs]) that worth exploring in larger samples in future research. Functional annotation and expression quantitative trait loci (eQTL) results suggest biological plausibility of genetic variants with sub-genome-wide significance. One of the strengths of this work is I measured frailty using two PFP framework-guided frailty assessments—the PFP scale and the continuous frailty scale. The continuous frailty scale is essentially a rescaled, continuous version of the PFP scale, and the correlation between the two measures was high. SNPs found important for both frailty phenotypes may be less prone to false-positives than those found important for only one phenotype.

In conclusion, the five empirical studies presented in this dissertation contribute to the field of frailty by developing and validating a new continuous frailty scale and demonstrating the utility of this new scale for predicting adverse health outcomes and recovery from disability, medical events, and surgeries. From a measurement standpoint, the new continuous frailty scale frailty is a valid continuous construct with a unidimensional factor structure robust to nuanced differences in measurements and invariant across cohorts and demographics including age and sex. In addition, the new frailty scale has high predictive validity for multiple health outcomes including death, disability, hip fracture, and falls among community-dwelling older adults. Moreover, the new frailty scale could capture elders' ability to recover from stressors (disability, medical events and surgeries), which is considered one of the defining features of frailty. Compared with the categorical PFP scale, the new continuous frailty scale, due to its sensitive and continuous nature, may be more suitable for evaluating the effectiveness of preventive or therapeutic interventions for frailty and depicting the trajectories of frailty over time.

From public health and clinical perspectives, the newly developed continuous frailty scale was useful for predicting adverse outcomes, had slightly better prediction performance than the original PFP scale, and could stratify risk of outcomes among robust and prefrail persons. The new frailty scale, constructed by the same five measures used in the PFP scale, was able to remove the ceiling effect of the PFP scale and stratify frailty-related risk of outcomes into a broader spectrum. Pinpointing frailty level in the early stage may be valuable for identifying at-risk persons who are not frail yet and offers opportunities for interventions that prevent the progression of frailty and maintain health and function. In addition, both the continuous frailty scale and the PFP scale could capture older adults' ability to recover from disability, medical events, and surgeries. Assessment of frailty may help clinicians, public health professionals, and researchers better identify at-risk elders after experiencing disability and acute diseases, and provide useful information in making informed decisions about surgical procedures.

8.2. Directions for Future Research

I created and validated a continuous frailty scale in this dissertation. This new scale is a rescaled, continuous version of the PFP scale; however, these two similar assessments may serve different purposes. The PFP scale classifies persons into three categories: robust, prefrail, and frail. This discrete nature is practitioner-friendly and may facilitate the implementation of frailty assessment into clinical practice.[277] Discrete classifications of frailty may also expedite risk stratification at a population level (i.e., prevalence), which helps evaluate the public health significance of frailty. On the other hand, the continuous frailty scale due to its continuous and sensitive nature may have higher ability to capture small but clinically meaningful changes in frailty levels and may be more suitable to evaluate the effectiveness of interventions for frailty. I

showed that elders who were identified as robust and prefrail by the PFP scale had different frailty scores on the new continuous scale and these differences were related to different risks of adverse outcomes. Therefore, the continuous frailty scale would be useful for future interventions that target individuals who are at lower end of frailty. In addition, the continuous frailty scale, which does not discard useful information by dichotomizing continuous measures, is a potentially more powerful assessment for identifying risk factors for frailty. Future research could use both the continuous frailty scale and the categorical PFP scale to examine whether the new scale is able to identify biomarkers that are missed by the PFP scale.

In Chapter 5, I found frailty, as assessed by both the new continuous frailty scale and the categorical PFP scale, was able to capture older adults' recovery ability after experiencing disability. Individuals with higher levels of frailty were less likely to recover ADL function after being disabled. Little is known about how frailty affects duration of disability (i.e., time to recovery) and the ability to maintain independence after recovery. This work extended previous research examining risk factors for disability recovery and opened up a new area of research regarding the role of frailty in the disabling process among older adults. However, one major challenge while using cohort studies that often have assessment intervals of 12 months or more is the lack of accurate ascertainment of onset and duration of recovery from disability because recovery from disability within 12 months is frequent and duration of recovery is often short-lasting (several months).[291,296] The Yale Precipitating Events Project (PEP Study), which has monthly assessment of ADL disability for almost 20 years and remarkably low attrition rate (<1%),[371] is one of the most notable data sources that can appropriately address these research questions. In addition, I only focused on the relationship between frailty and recovery from

incident disability. Previous work has shown that recurrent disability is not rare among community-dwelling older adults.[291,296] Recovery from recurrent disability might have different risk factor profiles, which deserves consideration for future research.

In Chapter 6, I examined the associations of frailty with recovery from acute medical events and surgeries. Although I restricted the analyses to participants who experienced the same medical event or surgery, it is possible that levels of frailty are associated with severity of medical events and burden of surgeries, which, in turn, contributes to the observed differences in recovery. In this sense, cohort studies, which often lack comprehensive information on diseases, may not be the most suitable data source to answer these research questions; studies (e.g., hospital-based data, electronic medical records) in which comprehensive evaluation of severity for these events may provide more definite evidence. In addition, the relationship between frailty and medical events and surgical procedures may be bidirectional, experiencing these stressors may therefore alter patients' underlying frailty status, leading to misclassification. Future research needs to disentangle the complex relationship between frailty, medical events and surgeries, and recovery outcomes using advanced methodological approaches (e.g., marginal structural modeling).

Although frailty is moderately heritable,[135-137] researchers have only examined only a very limited number of genes for frailty in small cohorts of older adults using the candidate gene approach. GWAS, which tests the associations of genetic variants with diseases and traits across the entire human genome, is an ideal approach to explore a wider range of genetic variants. Identification of genetic underpinnings of frailty may improve our understanding of the pathophysiology of frailty and serve as an essential component of patient-tailored prevention and treatment of frailty. In the current meta-analysis of GWAS among 6,172 community-dwelling

older men and women of European ancestry from two U.S. cohorts, I did not reveal any genome-wide significant genetic variants for frailty. One potential explanation is that frailty is an exceedingly complex phenotype with many physiological systems and biological pathways being involved. This complexity adds a layer of difficulty for detecting SNP-based signals. In addition, gene-gene interaction and gene-environment interaction may play an important role in the development of frailty, which deserves future investigations. Moreover, as researchers have performed numerous GWAS for various complex traits and common diseases over the past 12 years, the predominant pattern for these complex phenotypes is that many genetic variants exist with small to modest effects.[342] Nowadays, it is not uncommon to conduct a meta-analysis of multiple GWASs from a large-scale consortium, which often comprises of 100,000 or more individuals.[369,370] Larger samples are therefore needed to detect SNP-based associations for these complex polygenic traits. I am currently leading a meta-analysis of GWAS for frailty using nearly 20 longitudinal cohort studies affiliated with the Cohorts for Heart & Aging Research in Genomic Epidemiology (CHARGE) Consortium. This larger meta-analysis will be more powerful for identifying genetic variations of frailty and provide us a clearer understanding of the genetic architecture of frailty.

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