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Frailty and Depression: A Latent Trait Analysis

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A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University

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Abstract

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Background: Frailty, a state indicating vulnerability to poor health outcomes, is a common condition in later life. However, research and intervention progress is hindered by the current lack of a consensus frailty definition and poor understanding of relationships between frailty and depression.

Objectives: The goal of this research is to understand the interrelationships between frailty and depression among older adults. Specifically, this project aims 1) to examine the construct overlap between depression and three definitions of frailty (biological syndrome, medical burdens, and functional domains), 2) to determine the degree to which this overlap varies by age, gender, race/ethnicity and other individual characteristics, 3) to evaluate how the association between frailty and depression influences prediction of adverse health outcomes.

Methods: This project uses data from the 2004-2012 Health and Retirement Study (HRS), an ongoing, nationally-representative cohort study of adults over the age of 55. Frailty was indexed by three alternative conceptual models: 1) biological syndrome, 2) cumulative medical burdens, and 3) functional domains. Depressive symptoms were indexed by the 8-item Center for Epidemiologic Studies Depression (CESD) scale. Latent class analysis and confirmatory factor analysis were used to assess the construct overlap between depressive symptoms and frailty. Latent growth curve modeling were used to evaluate associations between frailty and depression, and to estimate their joint influence on two adverse health outcomes: nursing home admission and falls.

Results: The measurement overlap of frailty and depression was high using a categorical latent variable approach. Approximately 73% of individuals with severe depressive symptoms, and 85% of individuals with primarily somatic depressive symptoms, were categorized as concurrently frail. When modeled as continuous latent factors, each of the three frailty latent factors was significantly correlated with depression: biological syndrome ($\rho = .67$, $p < .01$); functional domains ($\rho = .70$, $p < .01$); and medical burdens ($\rho = .62$, $p < .01$). Higher latent frailty trajectories were associated with higher likelihood of experiencing nursing home admission and serious falls. This association with adverse health outcomes was attenuated after adjustment for depression as a time-varying covariate.

Conclusions: Findings suggest that frailty and frailty trajectories are potentially important indicators of vulnerability to adverse health outcomes. Future investigations of frailty syndrome,

however it is operationalized, should account for its substantial association with depression in order to develop more accurate measurement and effective treatment.

Chapter 1: Background

The proportion of older adults in the US population is growing, and by 2030, approximately one in five Americans will be age 65 or older. The prevention of disability and unintentional injuries among older adults is a key objective for promoting health and well-being as part of the National Prevention Plan and Healthy People 2020 (1, 2). For example, falls affect one in three adults age 65 and older each year and are the leading cause of death due to unintentional injury among this age group (1, 3). There is increasing concern that acquired functional limitations and disabilities will increase the demand for long-term healthcare services in later life (1). As a result, increased emphasis is being placed on reducing the need for future formal and informal healthcare by promoting healthy lifestyles, strengthening physiologic reserve, and addressing vulnerability to adverse health outcomes before they occur (1, 2).

Frailty as a geriatric syndrome

Preventive approaches which target risk factors and or promote resiliency to physical challenges are thus primary means to prevent disability for older adults. *Frailty* is a geriatric syndrome that indicates multi-system susceptibilities to preventable injury and health decline and may be useful for targeting prevention efforts and allocating health resources. The identification and measurement of geriatric syndromes that indicate at-risk individuals are critical to prevention efforts because they are believed to be modifiable targets for timely intervention (4). Several approaches to reducing the prevalence and severity of frailty among older adults have been investigated with varying degrees of success (5). In clinical settings, care management of frail older adults is associated with lower mortality relative to usual care (6). Exercise training and nutrition interventions aimed at improving muscle strength and balance have had mixed success

at improving mobility and functional abilities among frail older adults in both institutional and home-based settings (7, 8). There is even suggestion that some pharmacologic agents may be viable treatments for addressing frailty symptoms. For instance angiotensin-converting enzyme inhibitors may be effective at slowing age-related muscle loss; however there is little clinical evidence to support the effectiveness of such treatments among frail individuals (9, 10). In sum, frailty may be an important tool for directing public health and clinical approaches to care among older adults and is a practical concept with broad applicability.

Apart from being a treatable condition itself, frailty may be informative for determining other healthcare interventions. For instance, frailty has been used as a measure of suitability for surgery, medication, and transplantation (11-14). Frailty in this context may help vulnerable (frail) individuals avoid potentially harmful interventions, and at the same time, help ensure that healthy (non-frail) older adults receive beneficial care from which they might otherwise be excluded due to age. Frailty then can be seen as a more refined measure of physiological age that is not adequately captured by chronological age alone. However, adoption of frailty, whether as a screening tool or as a sign of poor physiologic reserve, is contingent on the validity and reliability of its measurement.

The potential benefits of frailty as a marker of vulnerability are predicated on the ability to correctly and reliably identify older adults as frail. However, in practice, numerous distinct definitions and operationalizations of frailty are invoked depending on the context. Conceptual differences determine which domains, symptoms and dimensions are incorporated into the various proposed definitions (4, 15, 16). Frailty has been conceptualized as both distinct from and synonymous with comorbidity, disability, and functional limitations (17, 18). Indeed, the various existing definitions of frailty include symptoms that tap into psychological (19, 20),

cognitive (21-23), sensory (24), and even social domains (25-27). Still others suggest that a universally applicable definition of frailty is not possible and that frailty is simply a socially constructed entity (13, 28). It is clear from these contradictions that frailty is a concept still in development.

Frailty and depression in later life

It is unclear how the aforementioned concerns regarding the validity and reliability of current operationalizations of frailty impact the relationship between this syndrome and other health conditions in later life, particularly depression. Depression is an important example of a condition which shares many features and correlates with frailty. First, depression, like frailty, is a common disorder in late life. While the prevalence of major depressive episodes may be relatively low among older adults, the prevalence of clinically significant depressive symptoms is high and is highest among the oldest old (aged 85 years or older) (29, 30). This is often attributed to a greater prevalence of physical disability and cognitive impairment in later life (31). Second, frailty and depression may share common symptoms and predictors, and may predict similar vulnerability to poor health outcomes and mortality. Third, it has been argued that because of a high degree of comorbidity and conceptual similarity, that frailty and depression may be considered causes of each other, forms of each other, or even interchangeable clinical entities (32-39). Research has demonstrated that existing models of frailty and depression identify concordant populations more than expected by chance or by definitional overlap alone (33, 40). Older adults are more likely to report 'somatic' symptoms of depression such as sleep disturbance and fatigue (41), suggesting that frailty and depression may be forms of a similar vulnerability which increases with age. Antidepressant use is also associated with higher risk of

frailty incidence, suggesting that adverse effects of pharmacotherapy may contribute to risk of frailty, or that older adults with more severe depression are at higher risk of frailty (42).

The complex and uncertain nature of the association between frailty and depression indicates the need for focused investigation of these constructs and how they jointly influence aging and health. There are many practical reasons to distinguish between and measure these two concepts. First, frailty may influence effectiveness of and adherence to treatments for depression or vice versa (43, 44). Second, comorbidity of frailty and depression may signal more complex health concerns that may not be adequately addressed by treatments focused on only one condition (15). Prior research has suggested that individuals with comorbid frailty and depression would benefit from more holistic care strategies that address both psychosocial and physiological vulnerabilities (45). Third, comorbid frailty and depression may be premorbid indicators of a more fundamental process of decline such as cardiovascular disorder or dementia, and so the co-occurrence of the two disorders may be of clinical value. Fourth, from a research standpoint, the investigation of these constructs may serve to bridge the gap between two parallel lines of research in frailty and late-life depression. Consideration of both constructs thus provides generative information for future research.

This project aims to investigate the associations between frailty and depression and to describe their combined role in predicting and influencing health in later life using various latent variable techniques. Latent variable techniques are well-suited to investigating these questions because they help to account for measurement error inherent in studying syndromes which cannot be directly observed, like frailty and depression. Explaining the relationships and boundaries between these constructs is an important goal, because without these advances, a consensus frailty definition is less likely to emerge. By providing clarity about frailty as a

diagnostic entity we will aid future efforts to identify and intervene on frailty syndrome. Although frailty is a promising diagnostic and organizational construct for geriatrics, the real-world benefits of being able to predict and prevent injury and disability among older adults will not be realized until conceptual and definitional issues are resolved.

Chapter 2: Gender Differences in the Construct Overlap of Frailty and Depression: Evidence from the Health and Retirement Study

ABSTRACT

Objectives: To determine the measurement overlap of common definitions of frailty and depression and to investigate whether gender differences in symptom endorsement influence the degree of construct overlap.

Design: Cross-sectional latent class analysis.

Setting: Data come from the 2008 wave of the Health and Retirement Study, a nationally-representative longitudinal survey of health characteristics among older adults.

Participants: Community-dwelling adults aged 65 and older completing a general health questionnaire and consenting to physical measurements (N=3,665).

Measurements: Frailty was measured using criteria developed in the Cardiovascular Health Study and depression was measured using items from the 8-item Centers for Epidemiologic Studies Depression (CESD) scale.

Results: Frailty and depression were best modelled as two distinct but highly correlated constructs with 3-classes and 4-classes of symptom response respectively. Measurement overlap was high among both men and women. Approximately 73% of individuals with severe depressive symptoms, and 85% of individuals with primarily somatic depressive symptoms, were categorized as concurrently frail. The degree of construct overlap between depression and frailty did not significantly vary by gender, but women were significantly more likely to endorse all frailty and depressive symptoms.

Conclusion: Findings suggest that common operational definitions of depression and frailty identify substantially overlapping populations of older men and women. More frequent endorsement of depressive symptoms, but not differential endorsement of somatic symptoms in particular, may contribute to the higher prevalence of frailty among women. Future research should

further describe the relationship between frailty and depression and focus on developing better means to discriminate between these constructs.

INTRODUCTION

Frailty, a syndrome characterized by greater vulnerability to morbidity and mortality in later life, affects approximately one in 10 older adults (46-48). Frailty is increasingly recognized as an important predictor of disability and other poor health outcomes, including falls, hospitalization and mortality (4, 15, 18). One principal justification for distinguishing frailty as an independent health state is the potential to identify older adults prior to adverse events and to intervene to delay or prevent disability (4, 15, 18). However, conceptual disagreements about the components and symptoms that define frailty limit the ability of this syndrome to accurately identify affected individuals and to develop meaningful approaches to treatment (26, 48).

The construct proposed by Fried and colleagues defines frailty as a syndrome of five biologic deficits distinct from comorbidity, disability, or a particular disease process (18, 26, 49). Previous research supports the existence of a phenotype characterized by co-occurrence of these deficits (50); however, the existence of this biologically-rooted phenotype does not preclude the predictive utility of additional non-biological criteria. Indeed, alternative definitions of frailty include symptoms that tap into psychological (19, 20), cognitive (21, 22), and sensory (24) domains (25, 26). These symptoms capture elements of biological age, psychosocial vulnerability, and medical morbidity, and, as might be expected with such a range of indicators, the different conceptual interpretations of frailty identify markedly different vulnerable individuals (48, 51); this in turn suggests that there may be distinct methods of effective intervention for these groups (48, 51).

The frailty concept is additionally complicated by the potential inability of current operational schema to discriminate frailty from other geriatric syndromes such as depression (40). Like frailty, depression is a common condition among older adults and shares symptoms,

putative causes and possible outcomes with frailty (30, 32, 36). Predictably, the two conditions are highly comorbid among older adult populations, but the reasons for their co-occurrence are unclear (23, 33). Older adults with depression are more likely than younger adults to endorse somatic depressive symptoms such as sleep disturbances and fatigue (41), suggesting that frailty and depression may be correlated due to shared symptom profiles (akin to the acknowledged symptom overlap between depression and generalized anxiety disorder) (52). These two conditions may also represent alternate manifestations of a more general vulnerability to functional decline which increases with age (53). Despite purportedly measuring conceptually distinct constructs, emerging research has indicated that common operational definitions of frailty and depression identify highly concordant populations of afflicted older adults (40), and thus inferences about these conditions drawn from epidemiologic studies may be biased due to lack of measurement discrimination.

Research exploring whether factors such as gender influence the degree of measurement overlap between frailty and depression is limited but warranted. Women are more likely than men to be identified as frail, regardless of the specific definition of frailty used, and tend to accumulate more physiological deficits with age (46, 54). Likewise, depression and depressive symptoms are consistently more common among women (55). Some attribute the gender difference in depression to the greater prevalence among women of 'somatic depression,' characterized by frequent endorsement of somatic, rather than cognitive or mood-related symptoms (56). The construct overlap of frailty and depression may therefore differ by gender due to differential endorsement of frailty and depression criteria.

The purpose of this study is two-fold: 1) To confirm the extent of diagnostic overlap between established indices of frailty and depression among a nationally representative sample

of older adults; and 2) To explore gender differences in the joint distribution of frailty and depression symptoms. We hypothesize that common indices of frailty and depression will identify highly overlapping populations, and predict that the degree of overlap and the types of symptoms endorsed will differ substantially between men and women.

METHODS

Data and Sample Characteristics

Data for this study come from the 2008 wave of The Health and Retirement Study (HRS), an ongoing prospective survey of adults aged 51 and over, designed to assess the health, demographic, and financial characteristics of the aging population (57). As described in detail elsewhere, the HRS is a nationally-representative multi-stage probability sample (57). HRS respondents are interviewed every two years, and beginning in 2004, a subset of respondents was selected at each wave to participate in enhanced face-to-face interviews. The enhanced interviews include objective measures of physical characteristics such as height, weight, gait speed, strength, and other indicators of physical functioning (58).

A total of 17,217 respondents were interviewed in the 2008 wave. Respondents were ineligible to participate in enhanced physical measurement interviews if they were currently residing in a nursing home (n=460) or interviewed by proxy (n=1,140). Of the 6,931 respondents who consented to enhanced interviews, 4,552 were aged 65 and over. The current study is restricted to the 3,665 respondents aged 65 and over who completed physical performance measures required to determine frailty status. Respondents who completed the physical performance measures were more likely to be women ($t=3.44$, $p<.001$), white ($t=8.36$, $p<.001$, currently married ($t=6.50$, $p<.001$) and to have more years of education ($t=5.68$, $p<.001$)

compared to those who were not included, but did not differ significantly with respect to age or employment status.

Measures

Frailty

Frailty was modeled using criteria derived from the Cardiovascular Health Study (CHS), including deficits in five areas: low weight, physical inactivity, exhaustion, weakness, and slowness (49). To the extent possible, operationalization of these criteria approximated or replicated CHS criteria. *Low weight* was defined as a self-reported or calculated loss of 10% or more in BMI since the previous (2006) wave or as a current BMI <18.5 kg/m^2. Physical activity was calculated as the weighted average of self-reported frequency of three intensities of activity (mild, moderate, and vigorous); *physical inactivity* was defined as being in the lowest 20% on the physical activity score stratified by gender. In the CHS, exhaustion was indicated by endorsement of one of two items from the Center for Epidemiologic Studies – Depression (CESD) scale. Because the goal of this study is to examine the degree of diagnostic overlap between depression and frailty, we did not use items from the CESD to indicate frailty. We instead defined *exhaustion* as report of persistent or troublesome fatigue or exhaustion within the past two years. Grip strength of the dominant hand was measured using a dynamometer, and this value was then averaged across two measurements. *Weakness* was defined as being in the lowest quartile of grip strength stratified by gender. Although grip strength was not further stratified by BMI (as in the CHS) the gender-specific cut-points for weakness (male <29.5 kg; female <17.5 kg) are consistent with CHS stratified measures and conservatively low (49). Gait speed was assessed using a 2.5-meter course; *slowness* was defined as a speed <.762 meters/sec for

individuals >159 cm in height, and as <.653 meters/sec for individuals ≤159 cm tall (49, 50). All frailty indicators were considered as binary (present/absent) symptoms.

Depression

Depressive symptoms were ascertained using the 8-item version of the Center for Epidemiological Studies Depression Scale (CESD-8) (59, 60). The CESD-8 assesses the presence or absence of eight depressive symptoms over the previous week; positive items were reverse-coded (see footnote of Figure 2.1). Although the CESD-8 is not a substitute for diagnosis of major depressive disorder (MD), the CESD-8 has moderate agreement with the Composite International Diagnostic Interview (CIDI), a fully-structured diagnostic interview to assess presence of MD. In the HRS specifically, the CESD-8 has a sensitivity of .71 and specificity of .79 compared to the CIDI-assessed MD using a cut-point of CESD-8 ≥ 4 symptoms to indicate depression (59, 60).

Covariates

Gender, race (categorized as non-Hispanic White, Black, or other), age (years), education (years), marital status (currently married vs. single/widowed/divorced), current employment status (full- or part-time vs. no employment), self-rated health (bad/fair vs. good/very good/excellent), and disability status (presence of any difficulties with activities of daily living (ADL) or instrumental activities of daily living (IADL)) were assessed by self-report. Cognitive functioning was assessed using number of correct responses (range: 0 to 10) to selected items from the Modified Telephone Interview for Cognitive Status (m-TICS) (61, 62).

Analysis

The bivariate associations between depressive symptoms and demographic characteristics, health indicators, disability status, and the five frailty indicators were examined using t-tests for continuous variables and Fisher's exact tests for categorical variables.

Latent class analysis (LCA) was used to investigate the construct overlap between frailty and depression. LCA assumes the existence of an underlying categorical latent variable (i.e. frailty and/or depression) which explains the association between a set of observed variables (i.e. the respective indicator symptoms of frailty and depression) (63, 64). The purpose of LCA is to identify discrete subpopulations (classes) of individuals who share similar symptom endorsement patterns. LCA is appropriate for identifying syndromes, particularly in instances where there is no consensus as to scope of relevant symptomology. Given a specified number of latent classes and the values of observed symptoms, LCA uses an iterative maximum-likelihood method to obtain estimates of two types of parameters: 1) the proportion of the population belonging to a particular class (unconditional probabilities); and 2) the conditional probabilities of symptom endorsement given membership in a class. The set of unconditional and conditional probabilities for a given class describe the features of the class members. To account for the complex sampling design of the HRS, observations in all LCA models were weighted according to HRS sample weights indicating probability of selection into the HRS physical measures subsample (58).

We compared two general types of latent class model in order to determine whether the association between observed symptoms was best explained by a single latent construct or by two distinct constructs: 1) a single latent variable model in which all observed variables indicated a single latent construct (which would be consistent with frailty and depression being alternate forms of the same underlying syndrome), and 2) a model in which two separate latent variables

representing frailty and depression were indicated by symptoms from the CHS criteria and CESD-8 respectively (Figure 2.1). Within the second type of model, a series of additional models was fit, each specifying different numbers of classes for both depression and frailty. The explanatory strengths of these models were compared using goodness-of-fit statistics including Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample-size adjusted Bayesian Information Criterion (BIC_N), for which smaller numbers indicate better relative fit. Goodness-of-fit statistics and interpretability of class features were used to determine the most likely model.

To examine differences in the joint distribution of frailty and depression symptoms by gender, we performed a multiple group LCA, comparing a series of models under different parametric assumptions. The procedure used for multi-group latent class analysis is described in detail elsewhere (65, 66). To summarize, first, the analytic steps described above were repeated independently among males and females to ascertain whether the appropriate number of latent classes was similar across gender. Second, in gender-pooled data, we evaluated the item-level measurement invariance of the model with respect to gender by comparing the fit of a heterogeneous (unconstrained) model to a homogenous model in which item-level conditional probabilities were constrained to be equal across gender. Third, we compared class proportions from item-level invariant and unconstrained models in order to evaluate whether class membership varied significantly by gender. The final, best-fitting measurement model was used to interpret latent class profiles and to compare class sizes across gender.

RESULTS

The characteristics of the analytic sample stratified by gender and depression status are shown in Table 2.1. Individuals who reported experiencing at least 4 CESD symptoms were significantly more likely to be women, to have less years of education and to be currently unmarried. Elevated depressive symptoms were also associated with presence of functional disability, lower cognitive performance scores, poorer self-rated health, and higher likelihood of endorsing all frailty criteria. Women did not differ significantly with men in presence of ADL disability, self-rated health, or cognitive performance scores; however, women were more likely to endorse all frailty criteria.

Measurement Invariance by Gender

Table 2.2 displays fit statistics from selected LCA models assuming different numbers of classes for both frailty and depression. Models which treated frailty and depression as distinct but correlated latent variables defined by their respective indicator criteria (Figure 2.1) collectively achieved better fit to the data (indicated by lower fit-statistic values) than the single-latent-variable model. In overall and gender-specific analyses, the model achieving the best fit to the data was one in which depression and frailty were represented by separate but correlated latent variables, with depression described by four latent classes (low, moderate, somatic, and severe depression) and frailty described by three latent classes (not frail, moderate frailty, and frailty with exhaustion).

To evaluate item-level measurement invariance by gender, we compared heterogeneous and constrained models as described above. The homogenous and heterogeneous models produced comparable fit to the data (BIC_N = 39486.439 and BIC_N = 39493.567 respectively),

indicating that conditional probabilities of symptom endorsement were similar by gender given membership in a particular class. Unlike conditional probabilities, unconditional class proportions varied significantly by gender (see Figures 2.2a and 2.2b), indicating that likelihood of membership in a particular class differed significantly by gender.

Class Characteristics

Figures 2.2a and 2.2b present class proportions and conditional probabilities of frailty and depression produced by the best-fitting model separately by gender. Conditional probabilities of the four depression classes were similar by gender (Figure 2.2a). Among both men and women, three distinct classes of depression characterized by low, moderate and high endorsement of all criteria were apparent. The fourth class, *somatic depression*, was characterized by endorsement of restless sleep, lack of motivation, and feeling activities were an effort. Women were more likely than men to be in the moderate or severe depression classes. Frailty class conditional probabilities were also similar by gender (Figure 2.2b). The criterion of *exhaustion* distinguished the two classes with the greatest symptom endorsement; the criterion of low BMI did not discriminate between frailty classes among either men or women, as shown by similar conditional probabilities for all three classes. Women were more likely than men to be classified as moderately frail or frail with exhaustion.

Table 2.3 illustrates class overlap of frailty and depression. It is apparent from the table that membership in particular depression classes is associated with membership in the frailty classes. For example, among those in the low depression class, only 12.0% were classified in the moderate frailty class, and 0% were in the frailty with exhaustion class. Among those in the somatic depression class, 23.1% were classified as moderately frail and 62.1% were classified in

the frailty with exhaustion class. Similarly those classified in the high depressive symptom endorsement class (8.6%) were likely to endorse frailty symptoms, with approximately 73% classified as likely to endorse at least three frailty symptoms.

DISCUSSION

The primary finding of this study is that commonly used criteria for frailty and depression identify highly-overlapping populations of older adults. Despite the fact that both frailty and depression are more common among women, there was no evidence that the measurement of these constructs differs by gender. We found that a substantial proportion of individuals categorized in the somatic or severe depression classes were also highly likely to meet criteria for frailty. This indicates that current measurement schema for frailty and depression syndrome may be poor at discriminating between these syndromes among older populations. The opportunity for misclassification and misattribution of symptoms given this substantial measurement overlap implies a need for considering frailty and depression jointly in epidemiologic study rather than as isolated conditions.

This study replicates recent work from our group that demonstrated substantial construct overlap between frailty, as defined by CHS criteria, and depression syndrome, as defined by the Diagnostic Interview Schedule (DIS) (40). In the present study nearly three-quarters of the individuals in the severe depression class were categorized in either the moderately frail or frail with exhaustion classes, compared to only 12% of individuals in the low symptom class. The consistency of overlap between CHS defined frailty and two different operationalizations of depression syndrome (DIS and CESD-8) suggests that the association between these two constructs may be explained in part by an underlying conceptual overlap or a common

underlying factor, rather than features of the measurement tool. For instance, Hajjar and colleagues have identified a potentially novel geriatric phenotype characterized by concurrent depressive symptoms, slow gait speed and impaired executive function (67). Similarly, our findings are consistent with the hypothesis that the co-occurrence of frailty and depression may be indicative of some common pathology, such as vascular damage to the brain. Vascular depression, a subtype of depression common among older adults and characterized by slowness, fatigue and muscular weakness, has been suggested as a prodromal state or early warning sign of frailty (38). In support of this hypothesis, we found that individuals in the somatic depression class were also highly likely to be considered frail, with 85% of individuals categorized in the moderate or frail with exhaustion classes.

In addition to shared pathology, several hypotheses regarding a potential causal relationship between these conditions have been proposed. For instance, Lakey and colleagues found that anti-depressant use predicted incident frailty among older women independent of the association between depressive symptoms and frailty (42). However, as our findings suggest, even with longitudinal data the attribution of a causal relationship between depression and frailty is difficult due to measurement overlap. Though the CHS definition of frailty is primarily biological, excluding cognitive and mood-related symptoms present in other frailty definitions, it is nevertheless difficult to distinguish between this operationalization of frailty and depression (40).

Overall, our findings indicate that analytic efforts to treat depression and frailty as independent constructs, or to exclude individuals with depression from studies of frailty is misleading and may bias the relationship between frailty and poor health outcomes. Given calls for a unified approach to conceptualizing and preventing geriatric syndromes (15), an alternative

approach toward the epidemiologic study of frailty would be to consider frailty and depression jointly as indicators of a more general vulnerability. For instance, recent evidence supporting the inclusion of cognitive impairment within the CHS frailty model demonstrates that the biological syndrome model of frailty is strongly correlated with criteria beyond those currently used (68).

Consistent with previous research, we found that women were more likely than men to be classified as likely frail or depressed (46, 54, 55). Conditional item responses and class characteristics were similar across gender-specific analyses, suggesting that classes had similar meaning for men and women, and that gender differences are primarily due to the proportion of individuals in each class. We did not find that a substantially greater proportion of women belonged to a somatic depression class, in contrast to previous research (56). Instead, women were twice as likely as men to be classified in the severe (10.4 vs. 5.7%) or moderate (13.3 vs. 6.8%) depression classes. Most previous studies regarding gender differences in somatic depression have used samples of younger adults (69-71), and thus differences between our findings and these prior studies may suggest that gender differences in the features of depression decrease with age. However, longitudinal data is needed to examine this hypothesis more directly.

Our findings should be interpreted in light of study limitations. First, while the CESD-8 asks respondents to report depressive symptoms in the previous week, some frailty criteria describe changes (e.g., weight loss) or represent average measures (e.g. physical activity). These differences in symptom time scale may have inflated the concurrence of depression and frailty syndromes; however, these results are consistent with prior work using the DIS in which the time scale of depressive symptoms was over a 6-month, rather than 1 week, period, and thus we believe our findings are not substantially influenced by differences in symptom time scale.

Second, the resulting classes from LCA are dependent on the specific metrics used to operationalize frailty and depression syndromes. The CESD-8, a short symptom inventory, may not evaluate all the depressive symptoms that are relevant to identify all meaningful classes. Our results are, however, consistent with previous studies using the DIS, a fully-structured interview. Strengths of this study include the large, nationally representative sample and use of LCA to empirically determine syndrome classes, rather than relying on *a priori* cut-points to define frailty and depression. With the large sample size, we were also able to examine whether gender differences in the prevalence of depression and frailty were due to measurement inconsistencies.

Our study demonstrates that common epidemiologic instruments for measuring frailty and depression identify highly overlapping subgroups of affected individuals among both men and women. These findings have implications for the epidemiologic study of the predictors and consequences of frailty in late life, as well as the translation of research on this construct into clinical care. Future research should examine whether the co-occurrence of depression and frailty is due to a shared pathology, and whether this comorbidity has implications for poor health outcomes, including risk of disability, institutionalization, and mortality.

Table 2.1. Weighted sample characteristics by depression status and sex

	Overall	Elevated Depressive Symptoms[a]	Non-Elevated Depressive Symptoms	Women	Men
	(N = 3665)	(N = 403)	(N = 3262)	(N=2,093)	(N=1,572)
	Weighted % or Mean (SD)[b]				
Demographics					
Female	55.52	67.01	54.03	---	---
Race					
White	90.77	88.26	91.1	89.84	91.92
Black	6.21	7.4	6.06	7.06	5.15
Other	3.02	4.33	2.85	3.09	2.92
Age (years)	74.69 (0.14)	75.07 (0.45)	74.64 (0.15)	75.22 (0.19)	74.04 (0.20)
Education (years)	12.63 (0.05)	11.33 (0.17)	12.8 (0.06)	12.39 (0.07)	12.93 (0.09)
Married	56.02	41.82	57.85	41.91	73.63
Currently Employed (PT/FT)	10.18	6.83	10.61	7.49	13.53
Health Indicators					
TICS (≤ 8 correct items)	15.95	27.63	14.43	16.1	15.75
Any IADL disability	12.44	32.09	9.9	13.57	11.02
Any ADL disability	14.91	40.41	11.62	15.63	14.02
Self-rated health (poor/fair)	25.78	63.46	20.91	25.65	25.94
CES-D ≥ 4 Symptoms		---	---	13.81	8.49
Frailty Criteria (present)					
Low BMI	6.71	9.07	6.41	8.28	4.76
Exhaustion	15.91	46.42	11.97	18.7	12.43

Slow movement	30.92	48.80	28.61	35.86	24.76
Weakness	27.46	39.01	25.97	29.72	24.64
Low energy expenditure	21.91	40.95	19.44	23.66	19.71
Intermediate frail[c]	45.83	47.85	45.57	47.46	43.79
Frail[c]	12.35	32.91	9.62	15.47	8.46

[a]Observations are weighted according to HRS physical measures sample weight

[b]Elevated depressive symptoms are defined as ≥ 4 symptoms on the CESD-8.

[c]Based on Fried et al. (2001) criteria. Subjects classified as frail if they endorsed 3 or more symptoms and intermediately frail if endorsing 1 or 2 criteria.

Table 2.2. Model fit indices from selected latent class models overall and by gender

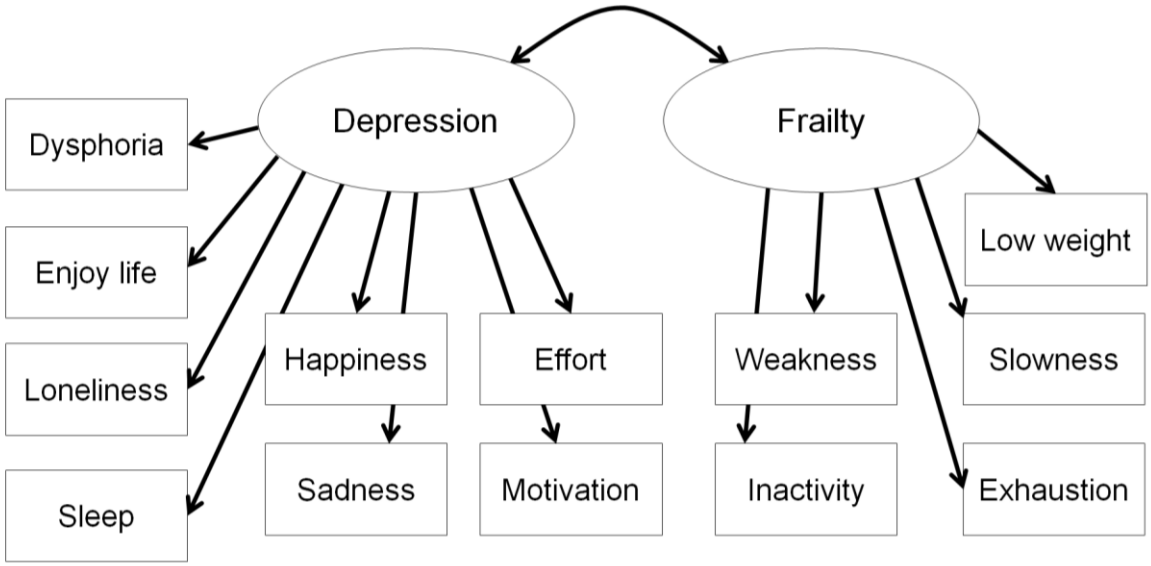
		Two latent variable models				
	Model 1: Single latent variable with 2 classes	**Model 2: Depression 3 class; Frail 3 class**	**Model 3: Depression 3 class; Frail 4 class**	**Model 4: Depression 4 class; Frail 3 class**	**Model 5: Depression 4 class; Frail 4 class**	**Model 6: Depression 5 class; Frail 4 class**
Model Fit Statistics						
AIC	37310.46	36319.13	36269.19	**36044.04**	35993.64	36035.86
BIC	37478.04	36610.83	36610.55	**36404.02**	36409.48	36526.19
BIC_N	37392.24	36461.49	36435.79	**36219.73**	36226.59	36275.16
Women						
AIC	23090.75	22443.18	22411.57	**22246.76**	22204.59	22162.38
BIC	23243.20	22708.56	22722.12	**22574.25**	22582.89	22608.44
BIC_N	23157.42	22559.24	22547.38	**22389.98**	22390.03	22397.45
Men						
AIC	14201.17	13865.67	13851.27	**13810.95**	13796.71	13771.33
BIC	14345.90	14117.60	14146.07	**14121.83**	14155.83	14194.78
BIC_N	14260.12	13968.29	13971.35	**13937.58**	13942.99	13943.81

AIC: Akaike Information Criterion; BIC: Bayesian Information criterion; BIC_N: sample-size adjusted BIC; Smaller values indicate better model fit

Table 2.3. Overlap of class proportions from joint model of depression and frailty (Table 2.2, Model 4)

	Total	Women	Men
	3,665	2,093	1,572
Depressive symptom class			
Frailty class			
Low	**66.5%**	**61.0%**	**75.0%**
Not frail	88.0%	89.6%	88.0%
Moderate Frail	12.0%	10.4%	12.0%
Frail w/exhaustion	0.0%	0.0%	0.0%
Moderate	**11.2%**	**13.3%**	**6.8%**
Not frail	57.8%	58.7%	80.5%
Moderate Frail	37.5%	38.6%	11.5%
Frail w/exhaustion	4.7%	2.7%	8.0%
Somatic	**13.7%**	**15.3%**	**12.5%**
Not frail	14.9%	16.6%	11.4%
Moderate Frail	23.0%	27.4%	21.6%
Frail w/exhaustion	62.1%	56.0%	67.0%
Severe	**8.6%**	**10.4%**	**5.7%**
Not frail	27.1%	20.6%	44.4%
Moderate Frail	2.8%	7.2%	0.0%
Frail w/exhaustion	70.1%	72.2%	57.6%

Figure 2.1. Conceptual model of correlated latent constructs – frailty and depression



Depressive symptoms include presence of the following symptoms much of the time within the past week: 1) felt depressed, 2) enjoyed life (reverse coded), 3) felt lonely, 4) experienced restless sleep, 5) felt happy (reverse coded), 6) felt sad, 7) felt everything was an effort, and 8) could not get going.

Figure 2.2a. Depressive class proportions and conditional probabilities of symptom endorsement

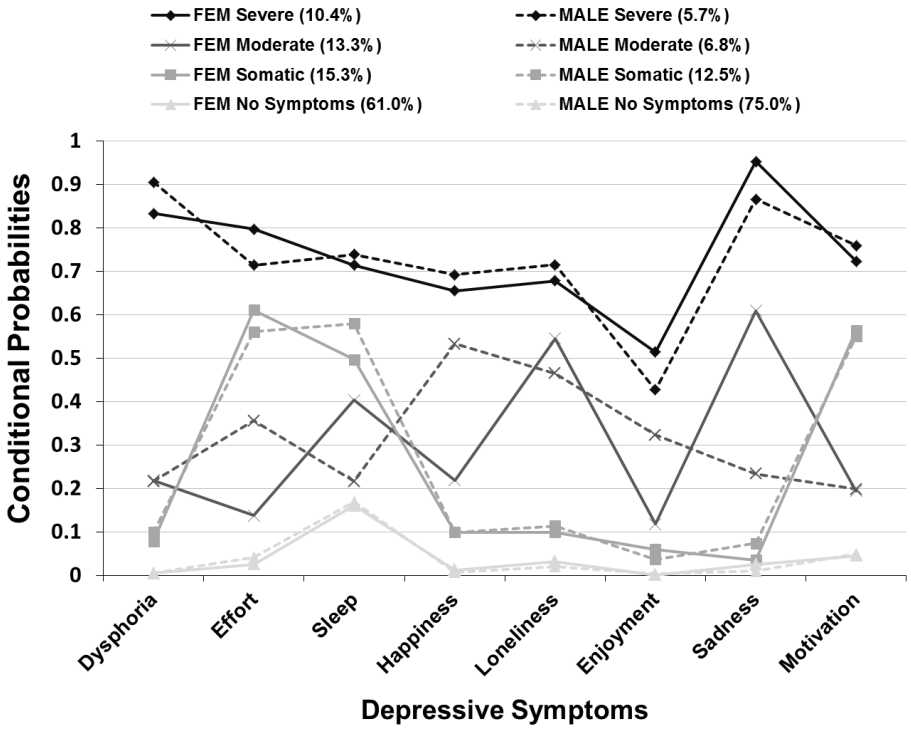
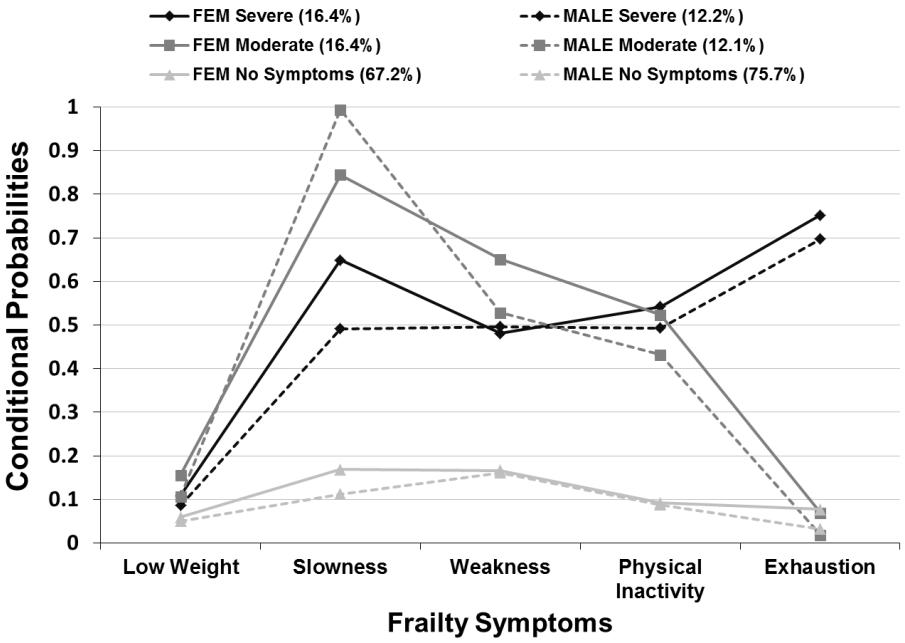


Figure 2.2b. Frailty class proportions and conditional probabilities of symptom endorsement



Conditional probabilities and class proportions estimated from the joint modeling of depression and frailty (Table 3.2, Model 4).

Chapter 3: Depression and Frailty in Late Life: Evidence for a Common Vulnerability

ABSTRACT

Objectives: The purpose of this study is to estimate the correlation between depression and competing models of frailty syndrome and to determine to what degree the comorbidity of these syndromes is determined by shared symptomology.

Methods: Data come from the 2010 Health and Retirement Study. Analysis was limited to community-dwelling participants 65 and older (N=3,453). Depressive symptoms were indexed by the 8-item Centers for Epidemiologic Studies Depression (CESD) scale. Frailty was indexed by three alternative conceptual models: 1) biological syndrome, 2) cumulative medical burden, and 3) functional domains. Confirmatory factor analysis (CFA) was used to estimate the correlation between depression and each model of frailty.

Results: Each of the three frailty latent factors was significantly correlated with depression: *biological syndrome* ($\rho = .67$, $p < .01$); *functional domains* ($\rho = .70$, $p < .01$); and cumulative *medical burden* ($\rho = .62$, $p < .01$). Substantial correlation remained when accounting for shared symptoms between depression and the *biological syndrome* ($\rho = .43$) and *medical burdens* ($\rho = .55$) models.

Discussion: Results indicate that the correlation of frailty and depression in late life is substantial. The association between the two constructs cannot be fully explained by symptom overlap, suggesting that a shared liability to both syndromes may determine their frequent comorbidity.

INTRODUCTION

Aging is often accompanied by declines and deficits in multiple bodily systems. When deficits are significant or numerous enough, physiological reserve may be compromised, rendering older adults vulnerable to adverse health outcomes as a result of stressors or minor perturbations to physical health (5). Frailty syndrome is considered to be a marker of such vulnerability. Frailty is associated with higher incidence of adverse health outcomes such as falls, hospitalizations and mortality (16, 49, 72), and may be an important predictor of complications from surgery, medication use, and other common interventions (11-14). The prevalence of frailty in community-dwelling older adult populations is approximately 11%; however this estimate varies considerably depending on how frailty is defined, with estimates ranging from 4% to 59% (46). Among those age 85 and older, the estimated prevalence of frailty is approximately 26% to 44% (49, 54). The wide ranges reflect fundamental conceptual disagreements regarding the operationalization of this syndrome. These estimates also suggest that frailty, while common, is not an inevitable consequence of advanced age, leading to speculation about how it might be prevented or how it might inform health-related decisions and interventions.

Despite promise as a tool for prevention, frailty's utility remains limited by conceptual and operational differences. Though there is implicit agreement that frailty is a condition conferring vulnerability, diverging explanations of how to define frailty result in substantially different empirical answers to the question "Who is frail?". In a community-based sample of older adults, Cigolle and colleagues compared the diagnostic overlap of three frailty models representing three distinct conceptual approaches: 1) a *biological syndrome* model comprised of five specific physiological symptoms (49), 2) a *cumulative medical burden index*, characterizing

frailty as a state produced by accumulated medical burdens (72), and 3) a *functional domains* model, emphasizing deficits in specific functional abilities (24). Of the older adults found to be frail by at least one model, only 44% were designated as frail by at least two models and only 10% by all three (48). The clear conceptual and diagnostic discordance between frailty models highlights uncertainty regarding the features that should be used to define it. Consequently, a range of potential symptoms, including physiological, cognitive, psychiatric, and sensory deficits have been incorporated into extant frailty definitions (19, 26, 68).

Another challenge to defining frailty is distinguishing it from other common conditions of later life, particularly depression. Like frailty, depression among older adults has been described in terms of diminished reserve capacity, representing a lack of coping resources to respond to mental or physical stressors (32, 73). For example, de Jonge and colleagues hypothesized that poor adjustment following somatic insult among depressed older adults may reflect inadequate psychological and social coping mechanisms, referring to depression as a form of "psychosocial frailty" (74). Depression and frailty are associated with similar outcomes, have similar risk factors, and, depending on the definition of frailty, share similar sympotomology (32, 33). The two concepts are likewise difficult to disentangle in operational terms. Our previous work has shown that frailty and depression produced highly overlapping classification of afflicted individuals, even when correcting for chance categorical overlap (40, 75).

The operational discrimination of frailty and depression is of both conceptual and practical concern. First, the validity of a measurement instrument is tied to its ability to discriminate distinct conditions from one another (76). The inability of frailty models to discriminate between frail and depressed individuals would indicate that current models are poor at measuring construct differences or, alternatively, that distinction between these constructs is

unwarranted. Second, treatment and prevention approaches for vulnerable older adults would differ based on the putative underlying nature of vulnerability, whether it is primarily psychological, physiological, or both. For example, adherence and pharmacodynamic response to anti-depressant medications may be worse among frail older adults (43, 44). When frailty and depression are comorbid, multimodal interventions targeting both depressive illness and physiological deficits concurrently would potentially be more effective than focus on a single area (45).

Arguably, the comorbidity of frailty and depression is similar to the comorbidity between common mental disorders (e.g. depression and anxiety) and presents similar challenges to research design. In epidemiologic studies of frailty, typical strategies for addressing this comorbidity are: 1) excluding individuals who meet criteria for depression, or 2) including individuals without regard for comorbid depression. Both strategies are problematic and may potentially lead to incorrect inferences regarding frailty and depression (77, 78). For instance, excluding depressed individuals from a study of frailty would yield a sample of frail individuals who are non-representative of frail older adults and, importantly, who are less severely impaired (77, 79). On the other hand, ignoring comorbidity in this context would make it difficult to distinguish whether outcomes were related to frailty, depression or the interaction of the two (77-79). As the validity of frailty models is often tied to model prediction of outcomes like falls, hospitalization and mortality (21, 49), this problem would conceivably impact the comparative effectiveness of alternative frailty definitions.

Reflecting these limitations in the extant literature, in this study we aim to determine the correlation between depression and frailty conceived as latent dimensional factors using confirmatory factor analysis (CFA). By using a dimensional approach, we address limitations

introduced by viewing frailty and depression as dichotomous or categorical conditions. Instead, frailty and depression are conceived as extreme points on continua of physical and psychological functioning. Substantial correlation between the two constructs is indicative of a higher order factor (or liability) which influences likelihood of both frailty and depression. Such a finding would provide clarity to the discussion of comorbidity and would help inform future attempts to refine the definition of frailty. To investigate whether operational differences play a role in the relationship between frailty and depression, separate analyses will be performed for each of the three frailty models identified by Cigolle and colleagues. We expect that the correlation of frailty and depression will be substantial but will vary considerably based on different specifications of frailty criteria.

METHODS

SAMPLE

This study is based on data from the 2010 wave of the Health and Retirement Study (HRS), a prospective survey of older adults begun in 1992, designed to collect longitudinal information on the health and finances of older Americans. The HRS employs a multi-stage probability sample of US households to produce a nationally-representative sample of adults age 51 or over (57). Self-reported information regarding demographics, chronic health conditions, daily activities, disability status, health insurance and other determinants of health are collected at baseline and at subsequent two-year intervals. Beginning in 2004, a randomly-selected subset of HRS respondents participated in enhanced face-to-face interviews which included objective assessment of walking speed, hand strength, weight, height and other physical measures (58).

Respondents aged 65 or older at the time of interview were considered eligible for the study. Respondents were considered ineligible if they were interviewed via a proxy or if they

resided in a nursing home at the time of interview. The primary analytical sample was restricted to respondents who were selected for the enhanced face-to-face interviews and completed or attempted physical measures tasks (grip strength and walking speed) used in the calculation of frailty scores. Sensitivity analyses were conducted to evaluate potential influence of excluding individuals with missing physical measures data.

The HRS is approved by the Institutional Review Board (IRB) at the University of Michigan, and this analysis received exempt status from the IRB at Virginia Commonwealth University. All participants provided informed consent.

MEASURES

Frailty

Biological Syndrome

The biological syndrome model of frailty was operationalized using five criteria proposed by Fried and colleagues in the Cardiovascular Health Study (CHS): low weight, physical inactivity, exhaustion, weakness, and slowness (49). Low weight was defined as a loss of 10% or more in BMI since the previous (2008) wave or a current BMI <18.5 kg/m^2. Physical activity was calculated as the average frequency of three activity intensities weighted by average metabolic equivalency of task (MET) scores: mild (1-3 MET), moderate (3-6 MET), and vigorous (6-10 MET). Participants were considered physically inactive if they scored in the lowest 20% of average physical activity. Exhaustion was specified in two ways: 1) using items from the Center for Epidemiologic Studies – Depression (CESD), as in the original CHS operationalization, and 2) as self-reported persistent or troublesome fatigue or exhaustion within the past two years. The separate specifications of exhaustion were compared to assess the role of shared criteria in the overlap of biological syndrome frailty and depression. Weakness was

assessed using the average of two measurements of dominant hand grip strength as measured by dynamometer. Weakness was defined as strength below BMI- and gender-specific thresholds established in the CHS. Slowness was defined as having a walking speed measured over a 2.5-meter distance below gender- and height-specific cut-points established in the CHS (49). Participants were considered as meeting criteria for weakness or slowness if they attempted the corresponding physical measures but were unable to complete due to physical limitation. Participants who did not attempt physical measures due to lack of appropriate facilities or equipment or recent surgery were considered as missing on these physical measures.

Frailty Index

As originally conceived, the Medical Burdens Frailty Index (FI) is a count of 70 clinical deficits, including presence of diseases, difficulties in daily activities, and other physical and neurological signs and symptoms (72). A FI score is calculated as the ratio of present deficits to total possible deficits (e.g. FI = 20/70 = .29). Subsequent analyses have demonstrated that frailty indices composed of 30 – 40 deficits have comparable predictive validity to the full index when deficits are selected based on pre-determined criteria (80, 81). Selection criteria for deficit inclusion are: 1) a deficit must generally accumulate with age, 2) a deficit must be related to health status in a biologically plausible way, 3) a deficit must not become saturated (i.e. universally prevalent) at an early age, and 4) the deficits together must represent a range of bodily systems (80). Using variables available in the HRS, the current study reproduced 35 of the original 70 deficits satisfying these selection criteria (Appendix 3.1). Although presence of depression may itself be considered an indicator in the FI, self-reported and study-determined depression diagnosis was excluded as an indicator in this study in order to address key study

questions of syndrome correlation. Each deficit was considered as either present (1) or absent (0) and no variable contained more than 5% missing cases within the analytic sample.

Functional domains

Strawbridge and colleagues define frailty as functional impairment in at least two of four domains: physical, nutritive, cognitive and sensory (24). In the current study, impairment in each domain was designated as present (1) or absent (0) according to operational criteria defined by Cigolle and colleagues using HRS data (48). Impairment in physical functioning was defined as having persistent dizziness or lightheadedness, experiencing at least one fall in the prior two years, or having difficulty lifting or carrying weights over 10 pounds. Impairment in nutritive functioning was defined as a loss of 10% or more in BMI since the previous (2008) wave or a current BMI <18.5 kg/m^2. Cognitive functioning was assessed using a 35-point composite measure of mental status, reasoning and memory task performance developed in the HRS (62, 82). Impairment in cognitive functioning was defined as a score of 10 or less (corresponding with lowest 10% of HRS respondents) on the HRS cognitive performance measure. Sensory impairment was defined as having fair/poor self-rated vision despite use of corrective lenses or fair/poor hearing despite use of a hearing aid.

Depressive Symptoms

Current depressive symptoms (referred to hereafter as "depression") were measured using the 8-item Center for Epidemiological Studies–Depression scale (CESD) (59). Respondents are asked to indicate whether they have experienced any of the following symptoms much of the time during the previous week: 1) felt depressed, 2) felt activities were efforts, 3) had restless sleep, 4) felt happy, 5) felt lonely, 6) enjoyed life, 7) felt sad, 8) felt unmotivated. Positive symptoms (i.e. feeling happy and enjoying life) were reverse-coded. Although the CESD is not

intended to be a diagnostic tool for major depression, it has been shown to have moderate agreement with the Composite International Diagnostic Interview (CIDI), a structured instrument for assessment of major depression (59, 60).

Sociodemoographic Covariates

Other variables included in the analysis were sex (male=0; female=1), race (dummy variables for white, black, and other), years of education (12 or more years=0; fewer than 12 years=1), primary health insurance provider (dummy variables indicating private, Medicare, and Medicaid insurance), marital status (dummy variables for currently married/partnered, separated/divorced/never married, and widowed), and household poverty-to-income ratio (0=above poverty threshold; below poverty threshold=1). Age was treated as a continuous variable or in 10-year categories (65-75 years, 75-85 years, and greater than 85 years).

A*NALYSIS*

First, exploratory factor analyses (EFA) were performed for each of the latent constructs (three frailty models: biological syndrome, medical burden frailty index, and functional domains, and depression) separately to determine whether the factors, as specified, represented uni-dimensional constructs.

Figure 3.1a – c illustrates the confirmatory factory analysis (CFA) models used to evaluate the correlations between depression and frailty. CFA is an appropriate method for assessing correlation between latent factors that are not directly observable and which are imperfectly measured by the presence of observable symptoms (83). In CFA, constraints are imposed *a priori* on the number of latent factors, the variables used to indicate the factors, and the relationships between variables in the model (83, 84). In CFA latent factors are conceived as dimensional traits, existing on a continuum rather than as categorical diagnoses. In the current

study, indicators of the latent frailty factor were determined by the dichotomous symptoms from each of the three models described above, while depression was indicated by items from the CESD. Two types of CFA model were fit to the data: 1) single-factor models in which a single latent factor was indicated by both frailty items and depression items from the CESD (Figure 3.1a); 2) correlated two-factor models in which separate frailty and depression factors were each defined by their respective indicator variables (Figure 3.1b). In cases where frailty and depression share symptoms by definition (i.e., the symptom "exhaustion" in the biological syndrome model of frailty, as described above), indicator variables were allowed to cross-load on each factor (Figure 3.1c). Models allowing cross-factor loading were compared with models in which shared symptoms indicated only depression in order to evaluate the role of shared symptoms in the correlation between frailty and depression.

The influence of sociodemographic characteristics on latent factors was estimated using multiple indicator, multiple cause (MIMIC) structural equation models. MIMIC models allow for estimation of the influence of covariate characteristics such as age, sex, and race on latent variables. MIMIC models contain at least two components: 1) a measurement component relating the indicator symptoms to the latent variables of frailty and depression (equivalent to CFA models), and 2) a regression component, regressing latent variables on the covariates (Figure 3.2a). When the correlation between frailty and depression was high (that is > 0.60), correlated factor models were equivalently re-expressed as second-order factor models in which a higher order factor is postulated to explain the correlation between frailty and depression. MIMIC models were used in these cases to estimate the influence of covariate factors on the second-order 'vulnerability' factor, indicated by frailty and depression sub-factors (Figure 3.2b).

Model Estimation

Models were estimated using weighted least squares means and variance adjusted (WLSMV) and full-information maximum-likelihood (MLR) estimators as implemented in Mplus software for categorical variables. MLR estimation was used in models which included data from participants who were missing physical measures data, under a missing at random (MAR) assumption. Model fit was assessed using standard fit criteria: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and root mean square error of approximation (RMSEA). As recommended in previous research, pre-specified values of CFI >.90, TLI >.90, and RMSEA <.06 were taken to indicate adequate model fit (85).

Analyses were performed using MPlus (Version 7) and all p-values refer to two-tailed tests.

RESULTS

Sample Characteristics

Figure 3.3 illustrates the selection of the analytic sample. A total of 22,034 respondents participated in the 2010 HRS wave of whom 10,938 were 65 or older at the time of interview and were considered eligible for the study; 1,211 respondents were excluded because they were interviewed by proxy or resided in a nursing home. Of the community-dwelling, non-proxy respondents, 4,035 were selected for and consented to enhanced face-to-face interviews and physical measures. The primary analytical sample was restricted to 3,453 respondents who completed or attempted physical measures tasks (grip strength and walking speed). Primary reasons for incomplete physical measures were absence of a suitable space for testing (N=137), recent surgery or health condition preventing testing (N=98), and respondent thinking the task would not be safe (N=128).

Table 3.1 shows the demographic and health characteristics of the analytic sample. Participants with a self-reported history of depression were more likely to be female, white, to have a household income below the poverty threshold, and to be Medicaid beneficiaries. Participants with a history of depression were significantly more likely to be frail according to diagnostic criteria proposed by the original authors of each of the three frailty models. Comparing individuals with a history of depression to those without, the odds of being considered frail at the time of interview were approximately twice as high according to the biological syndrome and functional domains models. According to the medical burdens FI model, the odds of being frail at time of interview were approximately four times as high for those with a history of depression.

CFA models of depression and frailty

CFA models of the individual latent frailty variables as uni-dimensional factors produced good fit to the data, with all model fit indices satisfying pre-specified criteria (Appendix 3.2). Results using only data from the analytic sample (N=3,453) were similar to those using data for individuals with missing data under MLR estimation (N=4,035), and so only results from the analytic sample are reported (data not shown

Results from CFA models of depression and the three models of frailty are shown in Table 3.2. When depression and frailty were conceived as a single latent factor (indicated by symptoms of both depression and frailty), the biological syndrome and functional domains definitions fit the data adequately, while the medical burdens frailty index fit the data poorly according to pre-specified model fit criteria. Correlated two-factor models provided better fit to the data than single factor models according to all three definitions; however, fit indices indicated poor fit overall for the medical burdens frailty index definition. Correlation between

frailty and depression latent variables was substantial for each of the three frailty definitions with correlations of 0.67 (95% CI: 0.63 - 0.71) for the biological syndrome, 0.61 (95% CI: 0.59 - 0.63) for the frailty index, and .70 (95% CI: 0.66 - 0.74) for the functional domains definitions.

Because the biological syndrome and medical burdens frailty index models share items with the CESD (i.e., exhaustion), a third set of CFA models was estimated allowing cross-loading of items to indicate both frailty and depression factors. Allowing shared symptoms to cross-load on both frailty and depression significantly improved the fit of both models. Correlation between frailty and depression decreased in the shared-symptom models for the biological syndrome (from .67 to .43) and for the frailty index (from .61 to 56) definitions, suggesting that shared symptoms determine some, but not all of, the correlation between the constructs.

MIMIC models

The size of correlations between depression and the three frailty models suggested that frailty and depression could be instead specified as sub-factors of a higher order "vulnerability" latent factor. To further explore the influence of sociodemographic covariates on the correlation between frailty and depression, MIMIC models were fit to estimate the influence of sociodemographic covariates on the hypothesized higher order latent factor. Regression coefficients from MIMIC models are displayed in Table 3.3. Compared to men, women had significantly higher average factor level for each of the three frailty definitions (Biologic Syndrome: $\beta = 0.12$, 95% Confidence Interval (CI) 0.09 – 0.15; Medical burdens: $\beta = 0.17$, 95% CI 0.13 – 0.20; Functional domains: $\beta = 0.09$, 95% CI 0.06 – 0.12). Likewise, older age, lower education, not being married, having a household income below the poverty threshold, and being a Medicaid beneficiary were associated with higher levels of the second order latent factors for

each frailty definition. The influence of coefficients on the higher order latent factor suggest that these covariates predict greater levels of frailty, depression, and comorbid disorder. No significant differences in factor level were found among different races or among widows.

DISCUSSION

This study examined the correlation between frailty and depression using three conceptually distinct definitions of frailty and a latent variable approach. Regardless of definition, frailty was substantially associated with depression, with correlation coefficients ranging from 0.61 to 0.70 in two-factor models. When accounting for the influence of shared symptomology and covariate predictors of the latent variables, correlation remained substantial. These results suggested the existence of a second-order "vulnerability" factor which influences levels of both frailty and depression. Our findings provide evidence that frailty and depression, as commonly defined in epidemiologic research, are not only associated concepts, but may be expressions of a shared underlying vulnerability construct. This underlying construct, which subsumes physiological, functional, and psychological aspects of vulnerability, provides a sensible organizational structure to explain the frequent comorbidity of frailty and depression in the population.

These findings should be interpreted in light of study strengths and limitations. First, the HRS is among the largest, most well-characterized samples of older adults in existence. Because of the breadth of this data source we were able to operationalize and compare multiple definitions of frailty. This study is among the first, to our knowledge, to investigate the association between depression and multiple models of frailty using a common data source. Consistency of results across multiple definitions of frailty indicates that our inferences

regarding the nature of the relationship between depression and frailty are analytically and conceptually robust. Also, we explicitly accounted for the measurement error inherent in the study of syndromes like depression and frailty using latent variable modeling. This approach is important in the analysis of the discriminant properties of frailty for which there is no consensus definition.

We also note study limitations. First, our operationalizations of frailty were approximate, but not exact replications, of the measurement schema proposed by their original developers. Although care was taken to reproduce the elements of each definition as closely as possible, the extent to which the indicators do not capture the intended construct may introduce error in the results. Nevertheless, these operationalizations of frailty have been successfully applied in past studies of frailty in the HRS and were found to be consistent with the original definitions (48). Second, the analytic sample was restricted to those who were selected for and completed physical measures. While the physical measures subsample was selected at random from the HRS population, missing data on these measures may introduce bias. However, we believe this bias is minimal because models estimated using ML which included all participants eligible for physical measures regardless of missing values (N=4,035) produced similar results to models using only the analytic sample. Lastly, the measure of depression used in this study, the CESD, is not designed to approximate clinician diagnosis of major depression but is, rather, a catalog of current depressive symptoms. The extent to which the CESD does not capture the underlying construct of depression may have biased the results of the study; however, the CESD is among the most widely used scales for the measurement of depressive symptoms in epidemiologic research, and therefore its association with frailty has significance for research. Furthermore, the

CESD has been shown to produce moderate diagnostic agreement with more structured instruments for the assessment of major depression such as the CIDI (59, 60).

This study provides valuable insights into the measurement and definition of frailty and helps to synthesize disconnected lines of research in gerontology and psychiatry. One key finding is that the strong correlation exhibited between frailty and depression is not unique to a single definition of frailty and cannot be fully explained by shared symptomology. Indeed, the functional domains model, which shares no symptoms with the CESD, was the most highly correlated with depression. While model comparisons indicate that frailty and depression are distinct syndromes, the consistency of the relationship between these two constructs suggests the possible role of shared underlying vulnerability processes in determining frailty, depression and their comorbidity. Consistent with this hypothesis, studies have suggested that vascular disease and vascular ageing are important predictors in the development of frailty, sarcopenia, and other geriatric syndromes (67, 86, 87). The plausibility of this hypothesis is supported by findings that angiotensin-converting enzyme inhibitors, medications typically used in the treatment of hypertension and congestive heart failure, may help to prevent or slow decline in physical function and muscle strength (9, 10). Likewise, cerebrovascular diseases, particularly those leading to subcortical ischemic lesions, are thought to cause or to facilitate the expression of depression in late life (88). The specific nature of the underlying vulnerability processes proposed in this study remains to be explored.

We note that alternative explanations of comorbidity between depression and frailty can also not be excluded. For instance, frailty and depression may be related through causal mechanisms, or vascular depression may be a prodromal state of frailty (38). However, the hypothesized processes determining comorbidity of frailty and depression provide a target for

future research and serve to merge and organize evidence from studies of frailty and late-life depression.

Although this comorbidity can be viewed as a methodological nuisance to be avoided or addressed in studies aimed at predicting disability and decline, the confluence of frailty and depression may have important clinical implications. For instance, recent studies have demonstrated that frail older adults with depression have higher risk of mortality than non-depressed frail elders, suggesting that depression may exacerbate or hasten the development of frailty symptoms (45). Individuals with both frailty and depression may thus benefit from more comprehensive interventions that assess and target both frailty and depressive symptoms, for instance, by combining anti-depressant treatment with exercise and nutritional interventions (45). Likewise, frailty status may be an important consideration in choosing between treatment options for depression, as some therapies may increase risk of falls among vulnerable older adults.

In conclusion, our results demonstrated a significant and consistent correlation between frailty and depression among older adults, which is not be fully explained by definitional differences, symptom overlap, or sociodemographic covariates. Given that comorbidity of physical and mental disorders is common in late life, future research should continue to explore reasons for comorbidity and the combined implications of frailty and depression in predicting adverse health outcomes among older adults.

Table 3.1. Sample characteristics by lifetime history of depression

	Overall (n=3,453)	Lifetime Depression (n=462)	No Lifetime Depression (n=2,991)	p-Value
	% or Mean (sd)			
Demographics				
Age (yrs)	75.0 (6.8)	73.5 (6.5)	75.2 (6.8)	<.001
Female	56.2	72.9	53.6	<.001
Race				0.051
White	84.7	88.3	84.1	
Black	11.9	8.7	12.4	
Other	3.4	3.0	3.4	
Education (>12 yrs)	43.7	42.2	43.9	0.512
Household Poverty	7.6	10.4	7.1	0.018
Marital Status				<.001
Married/partnered	64.1	52.0	66.0	
Separated/divorced	11.6	15.4	11.1	
Widowed	24.3	32.7	23.0	
Health Insurance				
Medicare	96.8	97.4	96.7	0.568
Medicaid	6.0	9.2	5.5	0.004
Private	24.7	22.2	25.1	0.182
Frailty				
Biological syndrome1				
Frail	11.7	20.8	10.3	<.001
Intermediate	53.2	58.7	52.4	
Frailty Index2				
Frail	25.4	51.7	21.3	<.001
Intermediate	27.7	27.3	27.7	
Funtional domains3				
Frail	22.2	35.7	20.4	<.001
Intermediate	38.3	42.0	37.7	

[1] Biological syndrome: frail = 3 or more symptoms; intermediate = 1 or 2 symptoms
[2] Frailty index: frail = index score >.25; intermediate = index score >.15
[3] Functional domains: frail = 2 or more symptoms; intermediate = 1 symptom

Table 3.2. Model fit statistics and latent variable correlations

	Frailty definition		
	Biological syndrome	Frailty index	Functional domains
Frailty and depression as single factor			
CFI	0.950	0.836	0.957
TLI	0.940	0.828	0.947
RMSEA	0.054	0.051	0.055
Frailty and depression as separate but correlated latent factors			
CFI	0.944	0.854	0.952
TLI	0.959	0.909	0.962
RMSEA	0.054	0.049	0.053
Correlation w/depression	**0.67**	**0.61**	**0.70**
95% CI	**(0.63 - 0.71)**	**(.59 - 0.63)**	**(.66 - .74)**
Correlation accounting for shared symptoms			
CFI	0.980	0.933	---
TLI	0.974	0.929	---
RMSEA	0.038	0.041	---
Correlation w/depression	**0.43**	**0.56**	---
95% CI	**(0.37 - 0.49)**	**(.54 - .58)**	---

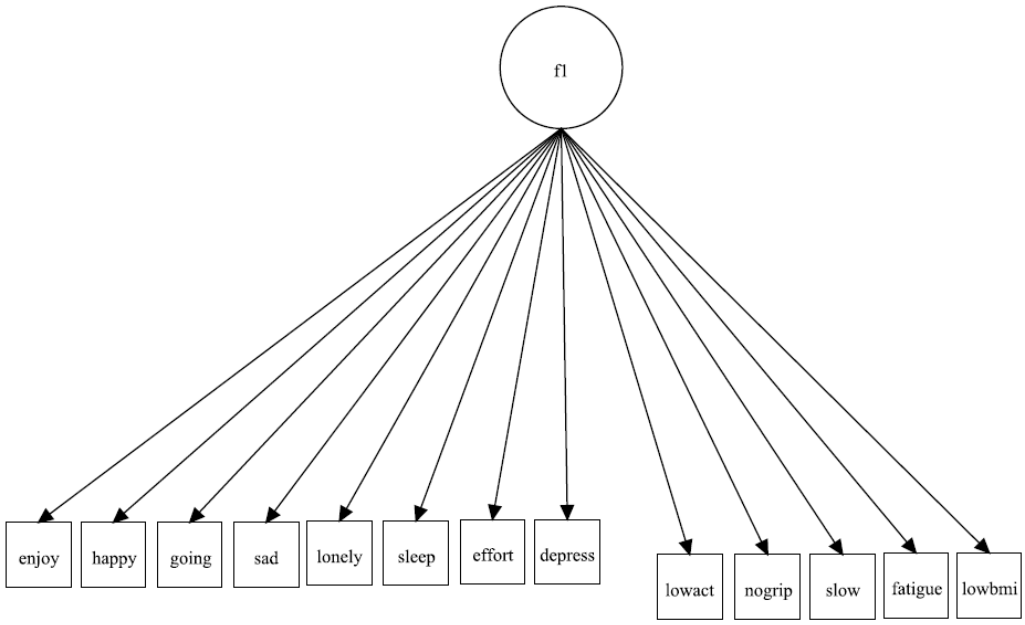
[1]For the biological syndrome definition, shared symptoms were items for not feeling motivated and feeling activities were an effort from the CESD

[2]For the frailty index, the shared symptom from the CESD was feeling depressed much of the time in the past week

Table 3.3. MIMIC model regression coefficients of covariate influence on second-order latent variables

	Frailty definition					
	Biological syndrome		Frailty index		Functional domains	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
Characteristics						
Female	0.12	(0.09, 0.15)	0.17	(0.13, 0.20)	0.09	(0.06, 0.12)
Age						
65-75	---	---	---	---	---	---
75-85	0.08	(0.05, 0.11)	0.15	(0.11, 0.19)	0.08	(0.05, 0.11)
85 or greater	0.17	(0.12, 0.22)	0.39	(0.33, 0.45)	0.21	(0.16, 0.26)
Race						
White	---	---	---	---	---	---
Black	-0.01	(-0.05, 0.03)	-0.02	(-0.07, 0.03)	0.01	(-0.03, 0.04)
Other	0.07	(-0.01, 0.14)	0.00	(-0.09, 0.09)	0.07	(-0.01, 0.15)
Marital Status						
Married	---	---	---	---	---	---
Separated/divorced	0.17	(0.12, .22)	0.19	(0.13, 0.25)	0.14	(0.10, 0.18)
Widowed	0.01	(-0.04, 0.06)	0.01	(-0.05, 0.07)	0.02	(-0.02, 0.06)
Education < 12 years	0.24	(0.20, 0.28)	0.32	(0.28, 0.36)	0.26	(0.22, 0.30)
Income (below poverty threshold)	0.13	(0.08, 0.18)	0.15	(0.11, 0.19)	0.16	(0.11, 0.21)
Health Insurance						
Medicaid	0.20	(0.14, 0.26)	0.34	(0.28, 0.41)	0.19	(0.14, 0.24)
Medicare	-0.01	(-0.09, 0.07)	0.05	(-0.05, 0.15)	0.00	(-0.07, 0.07)
Private insurance	-0.01	(-0.04, 0.03)	-0.02	(-0.06, 0.03)	-0.03	(-0.06, 0.01)

Figure 3.1a. Single latent factor model of frailty and depressive symptoms



Symptoms of frailty and depression indicate a single latent factor implying that a single underlying condition explains variance among both frailty and depressive symptoms.

Figure 3.1b. Two-factor model without symptom overlap

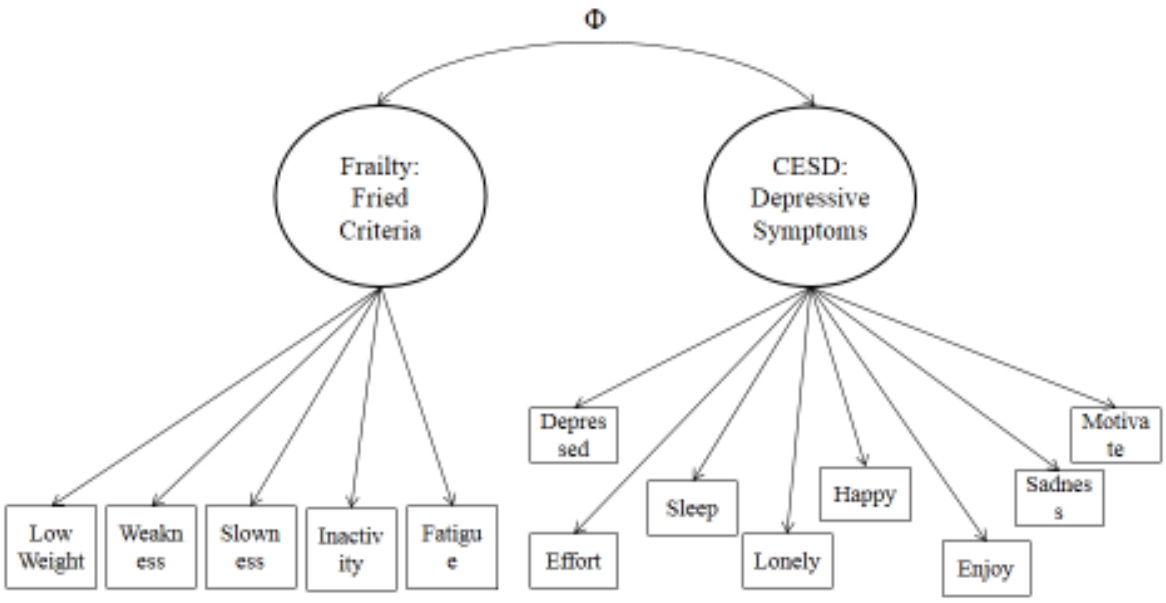


Figure 3.1c. Two-factor model assuming shared symptoms and cross loading

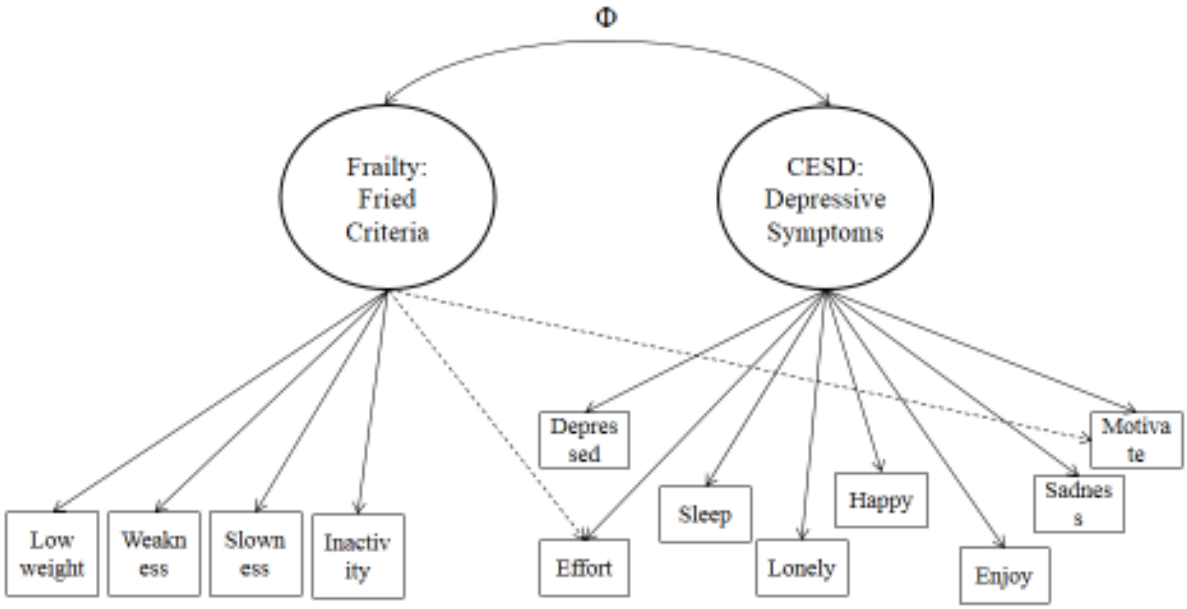


Figure 3.2a. Example of MIMIC model adjusting for sociodemographic covariates

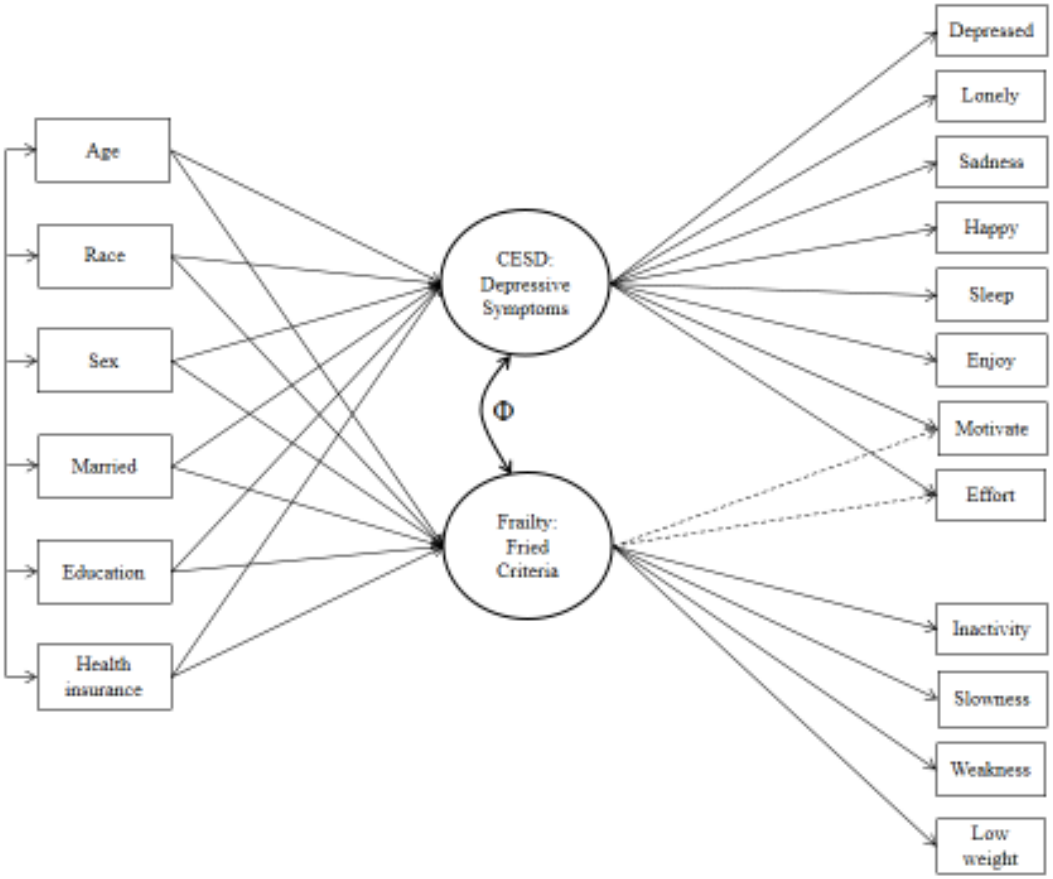
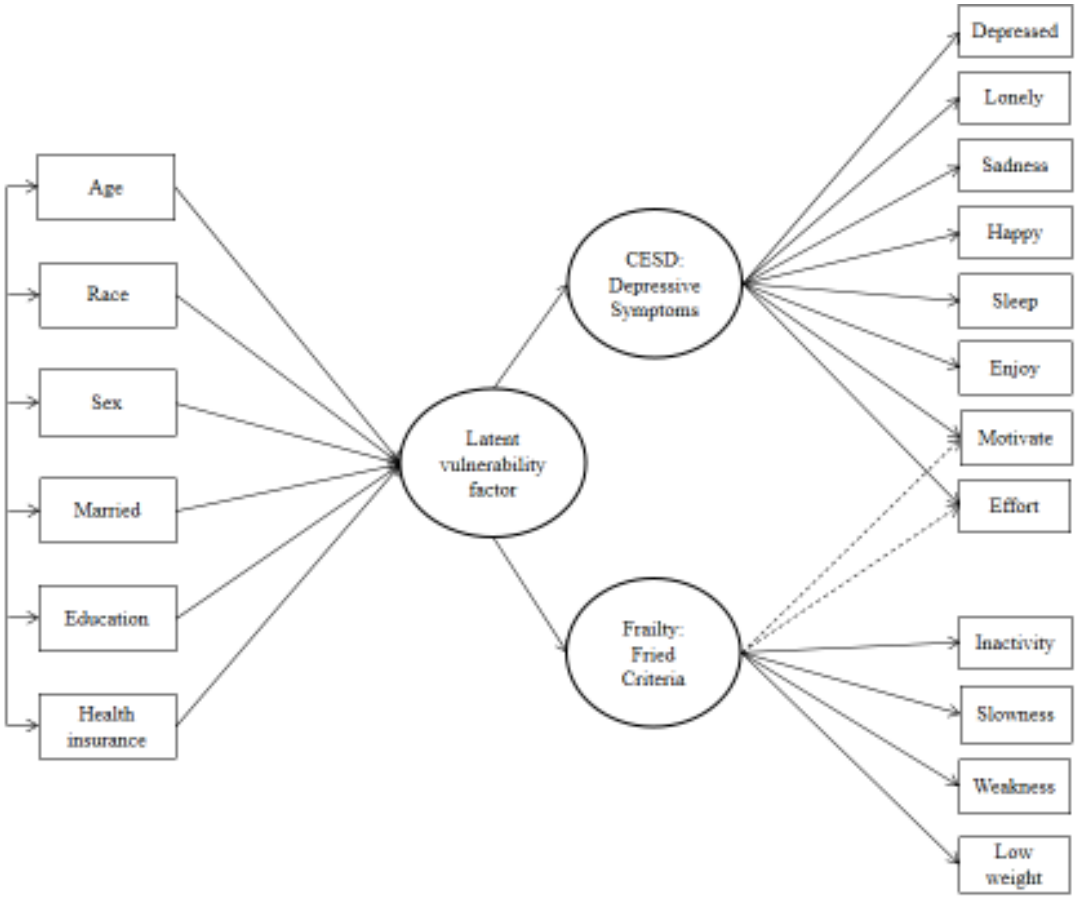
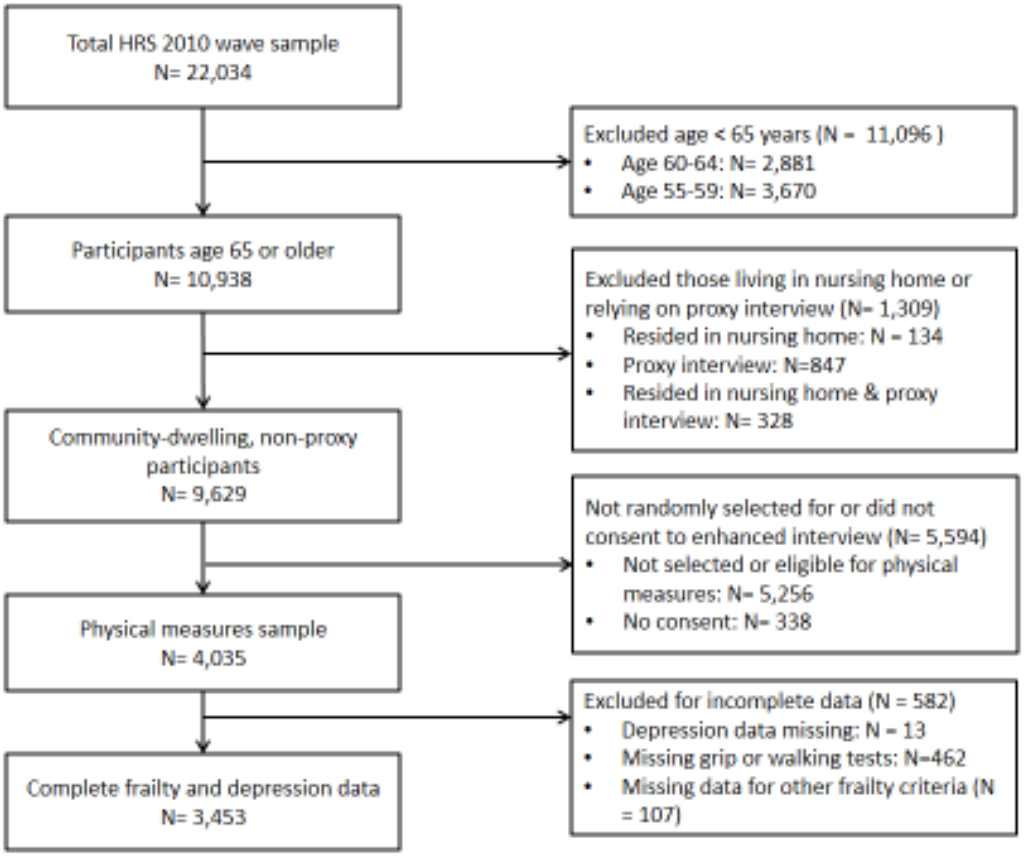


Figure 3.2b. Example of MIMIC model with second-order latent factor



Note: Similar models were fit for each of three frailty definitions. Not all covariates included in analyses are depicted in figure.

Figure 3.3. Sample inclusion/exclusion flowchart



Chapter 4: Frailty, Adverse Health Outcomes and Influence of Depression: A Latent Growth Curve Analysis

ABSTRACT

Objectives: This study used latent growth curve modeling (LGCM) to estimate trajectories of frailty and association between frailty trajectories and propensity for nursing home admission and falls. The time-varying influence of depression on the association of frailty and adverse health outcomes was also evaluated.

Methods: This study used data from five waves (2004-2012) of the Health and Retirement Study. A total of 10,611 community-dwelling individuals age 55 and older who participated in all waves were included in analysis. Frailty was measured using three alternative models: 1) functional domains, 2) medical burdens, and 3) biological syndrome. Depressive symptoms were measured using the 8-item Centers for Epidemiologic Studies Depression (CESD) scale. Adverse health outcomes included any nursing home stay within the previous two years and or injury from falls requiring medical treatment. Latent growth curves were used to estimate frailty trajectories and propensity to experience adverse health outcomes.

Results: The proportion of participants considered frail increased over the study period, and LGC models showed that average frailty trajectories were positive for all three frailty definitions (Functional domains: β=.182, p<.001; Medical Burdens: β=.078, p<.001; Biological Syndrome: β=.375, p<.001). Socio-demographic characteristics predicting steeper growth differed based on frailty definition. Parallel growth process models showed that steeper increases in frailty were associated with higher likelihood of both nursing home admission and serious falls (Functional Domains: $\beta_{NursingHome}$=.594, p<.001; β_{Fall}=1.759, p<.001; Medical Burdens: $\beta_{NursingHome}$=.889, p<.001; β_{Fall}=1.782, p<.001; Biological Syndrome: $\beta_{NursingHome}$=.333, p<.001; β_{Fall}=1.306, p<.001). However, these associations were attenuated, and in some cases were no longer statistically significant, after accounting for depressive symptoms.

Discussion: Developmental trajectories of frailty may be important indicators of risk for nursing home admissions and falls, independent of baseline frailty status. Targeted interventions focused on slowing development or progression of frailty symptoms may provide benefits in helping older adults maintain functional independence. Future studies of frailty must account for concurrent depression status as an important and highly correlated condition.

INTRODUCTION

Epidemiologic studies indicate that frailty, a syndrome purported to represent vulnerability to poor health outcomes, is common in late life. The likelihood of being frail increases with age, with 10% of adults age 65 and older and over 30% of adults age 85 and older considered frail (46). The prevalence of frailty varies considerably by sociodemographic characteristics. Women, racial minorities, and individuals with less education have higher risk of frailty (46, 89, 90). Epidemiologic evidence has linked frailty to higher risk of outcomes such as falls, nursing home entry, hospitalization, and earlier mortality (49, 72, 91). Frailty has also been used as a clinical measure to determine eligibility for treatment approaches such as surgery and pharmacologic intervention (11-14).

Despite frequent use of frailty in epidemiologic and clinical research, there is no consensus regarding its operationalization. Various competing conceptual and operational models have emerged, yielding significantly different estimations of frailty (19, 48, 51, 92). At least three conceptually distinct models have been used extensively in research literature: 1) a biological syndrome model (49), 2) a medical burdens model (21), and 3) a functional domains model (24). The biological syndrome and medical burdens models are the two most widely cited and validated measures of frailty (26, 93); however, these three models offer conflicting views regarding the underlying nature of the frailty construct. Whereas the biological syndrome model conceives of frailty as a syndrome of five specific physiological symptoms, distinct from the concept of comorbidity (18, 50), the medical burdens model posits that frailty is indexed as a sum of accumulated disorders and deficits, similar to comorbidity (17, 81). While the functional domains model is cited less frequently in the research literature, its focus on frailty as measured by functional limitations provides a third distinct conceptual basis for measuring frailty (26). To

varying degrees, each of the three frailty models has been validated in terms of their ability to predict adverse health outcomes; however, few studies have compared the longitudinal relationship of all three models to such outcomes (16, 21, 24, 49).

An important consideration in the study of frailty is its relationship to late-life depression. Evidence from multiple fields suggests that frailty and depression are highly related, both as comorbid conditions and as conceptually similar conditions (32, 33, 38, 42, 45). First, frailty and depression share symptoms (i.e., weight loss, fatigue) and increase risk of similar adverse health outcomes over time. For instance, both frailty and depression have been found to increase risk of earlier mortality among older adults (49, 91, 94, 95). Second, common instruments used for case ascertainment of frailty and depression lead to similar categorization of afflicted individuals. For instance, previous work by our group has shown that operationalizations of frailty and depression produce highly concordant estimates of individuals who are frail and depressed (40, 75). Lohman et al. (Chapter 3) further showed that, when modeled as dimensional traits, depression and frailty were substantially correlated after adjusting for sociodemographic covariates related to prevalence of both conditions. Third, depression among older adults is often characterized by a relative lack of mood symptoms and greater number of neurovegetative symptoms, in what has been termed "depression without sadness" or "masked depression" (41, 96, 97). This alternate presentation of depression among older adults may lead to further difficulties in discriminating depression from frailty in late life. The substantial comorbidity and common symptomology between frailty and depression indicate the need for approaches which incorporate rather than exclude depression as a consideration in studies of frailty.

Frailty, like depression, is a dynamic condition in which symptoms may manifest and remit over time (98). Accordingly, the risk of poor health outcomes conferred by frailty likely

also changes over time. Despite this, research on frailty rarely accounts for temporal changes in frailty status, instead focusing on whether an individual is categorized as frail or not frail at a given point in time and whether this status predicts future outcomes (19, 21, 24, 47, 49). Failure to account for temporal changes and dynamic nature of frailty may lead to incorrect inferences about the frailty construct and its relationship with poor health.

There are two primary aims of the current study. First, we will use latent growth curve models to estimate the trajectories of frailty using the three definitions (biological syndrome, medical burdens, and functional domains) outlined above. We will assess whether these frailty growth trajectories are associated with two adverse outcomes in later life: likelihood of nursing home admission and likelihood of falling. Although previous research has linked baseline frailty status with risk of future adverse health outcomes, to date none have assessed whether trajectories of frailty are associated with the likelihood of experiencing adverse health events. As part of this aim, conditional latent growth models will be used to determine whether frailty trajectories are influenced by characteristics such as gender, race, and education. The second aim is to determine the extent to which depression, treated as a time-varying covariate, influences the relationship between frailty and adverse health outcomes. We expect that, given the strong association between frailty and depression indicated by prior research, incorporation of depression will substantially diminish the relationship between frailty and adverse health outcomes.

METHODS

Data for the current investigation come from the Health and Retirement Study (HRS), an ongoing household survey initiated in 1992 in order to study the health and financial dynamics of older Americans. The HRS is a multi-stage area probability sample of household units designed

to be representative of the non-institutionalized U.S. population of adults over the age of 50 (57). New cohorts of participants are added every three waves (six years) in order to maintain the steady-state and representativeness of the sample. The latest wave of interviews was completed in 2012. The primary HRS questionnaire is administered by telephone at study entry and at subsequent two-year intervals. The questionnaire asks respondents to report information regarding demographics, health conditions, functional limitations, health insurance and other determinants of health. Beginning in 2004, a random half-sample of HRS respondents was asked to complete an enhanced face-to-face interview including objective physical measurements of gait speed, strength, balance and other aspects of physical health (58). The enhanced face-to-face interview was completed on the remaining half of the sample in alternate years.

The 2004 HRS wave had 19,750 respondents, of whom 66% (N=13,054) remained in the study as of the 2012 wave. Respondents were selected for this analysis if they met several selection criteria: first, participants were included in analysis if they were at least 55 years of age in 2004 ensuring that all study participants would be 65 years or older during the last interview wave. Since nursing home stay was a primary outcome of interest, participants were excluded from analysis if they resided in a nursing home at the time of study entry (n=93) or if they were interviewed via a proxy respondent (n=625). These selection criteria resulted in a final analytic sample of N=10,611 respondents. Information for these respondents from waves 2004, 2006, 2008, 2010, and 2012 was used in the current study.

The HRS is approved by the Institutional Review Board (IRB) at the University of Michigan, and this analysis received exempt status from the IRB at Virginia Commonwealth University. All participants provided informed consent.

MEASURES

Frailty

Biological Syndrome

Fried and colleagues define frailty as a biological syndrome represented by five specific symptoms derived from the Cardiovascular Health Study (CHS): slow gait speed, muscle weakness, low physical activity, exhaustion, and low of body weight (49). In the current study, gait speed was measured by time to complete a 2.5-meter walking course and stratified by sex and height. Slowness was defined according to sex- and height- specific cutoff values proposed in the CHS (Appendix 4.1). Strength was defined as the average of two grip-strength measurements of the respondent's dominant hand by dynamometer. Weakness was defined as grip strength below gender- and BMI- specific thresholds established in the CHS (Appendix 4.1). Participants were considered as meeting criteria for weakness or slowness if they attempted the corresponding physical measures but were unable to complete due to physical limitation. Physical activity was measured as the average frequency of self-reported mild, moderate, and vigorous activity weighted according to metabolic equivalency of task (MET) scores (Appendix 4.1). Participants in the lowest 20% of physical activity were considered to have low physical activity. Exhaustion was defined as self-reported persistent or troublesome fatigue or exhaustion within the past two years. Low weight was defined as a loss of 10% or more in BMI in the past two years or a current BMI < 18.5 kg/m^2. Participants were considered frail according to the biological syndrome model if they endorsed or exhibited at least three of the symptoms described above and intermediately frail if they endorsed one or two symptoms (49).

Medical Burdens

The medical burdens model, conceived by Rockwood and colleagues, defines frailty as an accumulated burden of diseases, functional disabilities and other health-related deficits and symptoms. The primary metric used to determine presence of frailty in the medical burdens model, the frailty index (FI), is calculated as the ratio of present deficits to the number of total possible deficits considered in the study (e.g. FI=10/30=.33). The medical burdens model is designed to provide a flexible measure of frailty that may be utilized and compared across multiple surveys (17, 80). Therefore, the deficits included in the FI calculation are non-specific provided they satisfy certain inclusion criteria: 1) a deficit must accumulate with age, 2) a deficit must not become universally prevalent at an early age (e.g. presbyopia), 3) a deficit must be related to health status in a biologically plausible way, and 4) the deficits considered together must represent a range of bodily systems, and 5) the deficits making up a FI must be consistent across time (80). While there is no maximum or minimum number of deficits which may be included in a FI, prior studies suggest that frailty indices composed of 30 to 40 deficits have sufficient specificity to predict adverse health outcomes (17, 80). The current study used a FI consisting of 30 deficits satisfying the inclusion criteria outlined here (Appendix 4.2). Frailty status was determined using cutoff criteria established in prior studies: participants with a FI score $\geq$ 0.25 were considered to be frail while those with a score between 0.15 and .25 were considered intermediately frail (21, 48).

Functional domains

Strawbridge and colleagues define frailty as functional impairment in at least two of four domains: physical, nutritive, cognitive, and sensory (24). Consistent with prior operationalizations of this model, participants were considered to have impairment in physical functioning if they reported persistent dizziness or lightheadedness, experienced at least one fall

within the past two years, or have difficulty lifting or carrying weights over 10 pounds. Impairment in nutritive functioning was defined as a loss of 10% or more in BMI since the previous (2008) wave or a current BMI <18.5 kg/m^2. Cognitive functioning was assessed using a 35-point composite measure of mental status, reasoning and memory task performance developed in the HRS (62, 82). Cognitive impairment was defined as a score of 10 or less on the HRS cognitive performance measure. Sensory impairment was defined as having fair/poor self-rated vision despite use of corrective lenses or fair/poor hearing despite use of a hearing aid. Participants with impairment in at least two domains were considered frail whereas participants with impairment in a single domain were considered intermediately frail.

Depressive Symptoms

Depressive symptoms were indexed using the 8-item Center for Epidemiological Studies – Depression scale (CESD) (59). The CESD asks respondents to report whether they experienced eight symptoms much of the time during the past week: 1) felt depressed 2) felt activities were efforts, 3) had restless sleep, 4) felt happy, 5) felt lonely, 6) enjoyed life, 7) felt sad, 8) felt unmotivated (could not get going). Positive symptoms of feeling happy and enjoying life were reverse-coded, so that their absence indicated a depressive symptom. The CESD is not a structured interview meant to emulate clinician diagnosis of major depression; however, prior studies have shown that when used as a diagnostic substitute (using a cutoff of four or more symptoms to indicate depression), the CESD has moderate agreement with structured diagnostic instruments such as the Composite International Diagnostic Interview (CIDI) (59, 60). In the current study, participants who endorsed four or more symptoms were considered to be depressed. Depression was assessed using a dichotomous variable (1=depressed, 0=not

depressed) at each wave of the HRS, allowing the presence of depression for individuals to vary over time.

Outcome Measures

The current study considered frailty trajectories in relation to two adverse health outcomes: nursing home admission and serious falls. Nursing home admission was assessed using a dichotomous variable (1=any nursing home stay, 0=no nursing home stay) indicating whether a respondent had been a patient overnight in a nursing home, convalescent home, or other long-term health care facility in the preceding two years. This variable encompassed both short stays (e.g., for rehabilitation after a hospital discharge) as well as longer stays. Analysis was repeated considering only those respondents whose nursing home stays were longer than 30 days as experiencing a nursing home stay. We considered 'serious falls' as any fall within the past two years which resulted in injury requiring medical treatment as reported by the respondent. Respondents who experienced a fall which did not result in injury were considered not to have experienced a serious fall. A dichotomous variable (1=experienced a serious fall, 0=did not experience a serious fall) was used in analysis.

Time-invariant Covariates

Sociodemographic characteristics and other health related variables were chosen for inclusion as time-invariant covariates in analysis through a forward selection change-in-estimate procedure: First, bivariate logistic regression of frailty status and each of the adverse health outcomes (nursing home stays, falls) at baseline were fit; second, covariates were added individually to the logistic regression and variables producing the largest change in estimate of the frailty/outcome relationship were included as potential confounders; third, addition of

covariates to the logistic regression continued until individual covariates no longer produced a substantial change in estimate ($\geq$ 10%) (99).

Based on the change-in-estimate selection procedure, time-invariant covariates considered in analysis were sex (male=0; female=1), race (dummy variables for white, black, and other), years of education (12 or more years=0; fewer than 12 years=1), primary health insurance provider (dummy variables indicating private, Medicare, and Medicaid insurance), marital status (dummy variables for currently married/partnered, separated/divorced/never married, and widowed), smoking status (1=current smoker, 0=not current smoker), and household poverty-to-income ratio (0=above poverty threshold; below poverty threshold=1). Age was assessed in 10-year categories (65-75 years, 75-85 years, and greater than 85 years).

ANALYSIS

Growth of frailty and adverse health outcomes over time was modeled using latent growth curve modeling (LGCM). LGCM is a statistical procedure built on confirmatory factor analysis (CFA) approaches (83) used to estimate underlying latent (unobserved) growth parameters that give rise to estimates and interrelations among a set of observed repeated measures. In a LGCM framework, the growth parameters are used to describe average latent linear or non-linear trajectories of change over time, as well as individual variability in those growth trajectories (100). LGCM is an appropriate approach to for modeling longitudinal change for four reasons: 1) it allows for tests of overall model fit, 2) it allows for regression of intercept and slope estimates on other explanatory variables and growth parameters while accounting for imperfect measurement, 3) it can be used to model growth in categorical observed measures, and 4) it allows straightforward incorporation of time-varying explanatory covariates (100). More

detailed discussions of the theoretical and mathematical bases of LGCM are available elsewhere (100).

Unconditional and Conditional Latent Growth Models

In the current study, LGC models were built in a hierarchy of increasing complexity. First, unconditional models of each of the three frailty models and two primary outcomes were fit to assess overall growth in these constructs over time, unadjusted for influence of covariates. Two types of growth, linear and quadratic, were modeled for each outcome and compared in terms of overall model fit and parsimony. Linear growth was specified by constraining the loadings of the latent growth parameters on the observed outcomes to assume incremental change per increase in unit time (Figure 4.1). That is, the factor loading for slope was fixed to 0 for Wave 1 frailty status, to 1 for Wave 2 frailty status, to 2 for Wave 3 frailty status, and so on. Quadratic growth was modeled by the addition of a quadratic latent growth parameter and by fixing factor loadings of the quadratic term to assume exponential change. Because outcomes were modeled as dichotomous variables, the growth factors were interpreted as describing the change in underlying latent propensity of the outcome under a continuous threshold model. That is, increasing levels of latent propensity toward frailty predict the likelihood of reaching a threshold distinguishing frail and not frail individuals.

Time-invariant covariates were subsequently added to the unconditional models to assess influence of these variables on the growth parameters (Figure 4.2). The growth parameters represent continuous variables, and thus estimates were interpreted as linear regression coefficients explaining the change in growth parameter (e.g. intercept), associated with each change in unit of the covariate. Growth parameters and model fit statistics from conditional

models were compared with those from unconditional models to assess influence and explanatory significance of the covariates.

Parallel Process Models and Time-varying Depression

Building on conditional growth models, the next set of models addressed the relationship between trajectories of frailty and change in the propensity to experience adverse health outcomes. In these models, two growth processes (e.g. growth of frailty and expected change in the propensity to be admitted to a nursing home stay), were related through the regression (correlation) of their growth parameters (Figure 4.3). The intercept (initial level) and the slope of change of each adverse health outcome propensity were regressed on the intercept and slope of change in frailty for each of the frailty models. The growth parameters for each process were conditioned upon the time-invariant covariates introduced in preceding models.

Next, to address the secondary aim of the current study, depression status was introduced into the parallel process models as a time-varying predictor of frailty at each corresponding wave. Relationships between the dichotomous variables of depression and frailty were estimated in terms of log odds of being frail comparing depressed and non-depressed respondents. The influence of frailty growth parameters on growth parameters of adverse health outcomes were re-estimated and compared to estimates unadjusted for depression status.

Model estimation and fit criteria

All LGCMs were estimated using maximum likelihood and weighted least squares means and variance adjusted (WLSMV) estimation as implemented in Mplus software version 7 (Muthén & Muthén, Los Angeles, CA). Model fit was assessed using standard fit criteria: Comparative Fit Index (CFI), Tucker-Lewis Index (TLI), and root mean square error of

approximation (RMSEA). Values of CFI >.95, TLI >.95, and RMSEA <.05 were taken to indicate close model fit to the data (85). All p-values refer to two-tailed tests.

RESULTS

At the 2004 HRS interview (baseline for this analysis), all 10,611 respondents in the analytic sample were between 55 to 95 years old. Approximately 61% were female, 84% white, and 70% were married, with a range of other sociodemographic and health related characteristics described in Table 4.1. The three frailty models produced substantially different estimates of the number of frail individuals in the sample at baseline, ranging from approximately 8.4% according to the biological syndrome model to 27.4% according to the medical burdens model. The characteristics of frail older adults for each definition were similar (Table 4.1): frail respondents were older and were more likely to be female, had less education, were more likely to be widowed or divorced/separated, and were more likely to have a household income below the poverty threshold. Notably, the functional domains model identified a higher proportion of black respondents as frail compared to the other two definitions (21.4% vs. 14.4% for the biological syndrome and 16.0% for the medical burdens models). The proportion of frail older adults in the sample increased over the study period for all frailty definition (Table 4.2). In the final wave of analysis, the point prevalence of frailty was approximately 44% according to the medical burdens model, 34% according to the functional domains model, and approximately 21% according to the biological syndrome model.

Unconditional Latent Growth Models

Parameter estimates from unconditional latent growth models of frailty and risk of nursing home entry or falls are displayed in Table 4.3. Compared to linear growth models, quadratic growth models did not provide significantly better model fit for any of the frailty definitions or adverse health outcomes, and so only results from linear growth models are hereafter reported (data not shown). As shown in Table 4.3, the mean slope of frailty propensity was significantly positive for each of the three frailty definitions over time (Functional Domains: β=.182, p<.001; Medical Burdens: β=.078, p<.00; Biological Syndrome: β=.375, p=.01), reflecting an increasing expected likelihood of being considered frail over the study period. The variances of each of the frailty intercept and slope parameters were also statistically significant, suggesting that there is significant variability in initial level of frailty and in the change of frailty propensity between individuals over time. As seen in Figures 4.5-4.7, model estimated probabilities of frailty accurately predicted the observed sample proportions of frailty in the study population and model fit criteria reflect close model fit for each definition. This indicates that the specified linear growth model is appropriate for describing change of frailty over time.

The mean and variance of slope for nursing home stay was not significantly different from zero, suggesting that, unconditioned on predictors, the propensity of needing a nursing home stay did not increase or decrease over time and was not significantly different among individuals. The slope of change for experiencing a serious fall was also not significantly different from zero and moderately negative, suggesting that the mean likelihood of experiencing a serious fall did not change over time.

Conditional Latent Growth Curve Models

Parameter estimates and covariate regressions from conditional growth models of frailty are displayed in Tables 4.4 and 4.5. Model fit improved moderately with the addition of

explanatory covariates according to RMSEA and remained similar according to CFI and TLI. Slope and intercept growth factors remained significantly greater than zero, suggesting that even after adjusting for the influence of time-invariant covariates, the mean likelihood of frailty increased over the study period. Similarly, the significant variances of slope and intercept for each frailty definition suggest that there was significant heterogeneity in trajectories of frailty over time not explained by these fixed characteristics. Regression of intercept growth parameters on covariates indicated that being female, divorced, having less education, being a current smoker, and having low income were significantly associated with higher baseline levels of frailty. Each 10 year increase in age above 55 was also associated with higher initial levels of frailty. While initial level of functional domains frailty was significantly greater among widows and among black and other race participants (compared to whites), widowhood and race were not significantly associated with baseline levels of frailty according to the other definitions.

Regressions of slope parameters on time-invariant covariates revealed further differences in growth of frailty according to the three definitions. Being female, divorced, and of black race was associated with increasing frailty over time according to the biological syndrome model only. Whereas lower educational attainment and income were associated with higher initial levels of medical burdens frailty, these characteristics did not have significant influence on rate of change in medical burdens frailty over time. Older age and current smoking were associated with higher rates of growth in all three definitions of frailty. Results from conditional growth models of adverse health outcomes are presented in Appendix 4.3-4.4.

Parallel Process Models

Further analysis explored the association between frailty growth and the propensity to experience adverse health outcomes. Table 4.6 details the results from regressions and

covariances relating the growth parameters of each frailty definition with growth parameters for nursing home stay for models both unadjusted and adjusted for depression. Not accounting for the influence of depression, initial level of frailty was correlated with greater baseline likelihood of requiring a nursing home stay for all frailty definitions. Initial level of frailty was not, however, directly related to change in nursing home propensity over time. For all frailty definitions, greater slope of change for frailty was associated with greater slope in nursing home probability (Functional Domains: β=.594, p<.001; Medical Burdens: β=.771, p<.001; Biological Syndrome: β=.333, p<.001), suggesting that growth in frailty was significantly associated with propensity to needing nursing home care. That is, higher rates of frailty change were significantly associated with more rapid increase in the likelihood of experiencing nursing home admission.

When depression status was incorporated into parallel process models as a time-varying covariate, concurrent depression was a significant predictor of frailty at each wave and for each frailty definition. Participants with depression had on average between 50% and 140% higher odds of frailty depending on the wave and definition of frailty, as seen in Table 4.6. The inclusion of depression into parallel process models also significantly changed estimates of associations between growth parameters. Regression coefficients describing the relationship between frailty slope and slope in nursing home propensity were diminished and non-significant after accounting for depression (Functional Domains: $\beta_{\text{conditional on time-invariant covariates}}$= 0.594, p<.001 vs. $\beta_{\text{accounting for time-varying depression}}$=0.476, p=.857; Medical Burdens: $\beta_{\text{conditional on time-invariant covariates}}$= 0.889, p<.001 vs. $\beta_{\text{accounting for time-varying depression}}$=0.771, p=.853; Biological Syndrome: $\beta_{\text{conditional on time-invariant covariates}}$= 0.333, p<.001 vs. $\beta_{\text{accounting for time-varying depression}}$=0.251, p=.832),

suggesting that depression status explained a significant portion of the variation in nursing home propensity over time.

Parallel process models with serious falls as the adverse health outcome are displayed in Table 4.7. Unlike nursing home stay, initial frailty level (intercept) was significantly associated with both initial propensity for experiencing a serious fall and higher rate of change in this propensity over time (Functional Domains: β=1.759, p<.001; Medical Burdens: β=1.782, p<.001; Biological Syndrome: β=1.306, p<.001). As with nursing home stays, addition of depression as a time-varying covariate reduced the association between frailty slope and slope of propensity for fall; however, these estimates remained significant depression (Functional Domains: $\beta_{\text{conditional on time-invariant covariates}}$= 1.759, p<.001 vs. $\beta_{\text{accounting for time-varying depression}}$=1.193, p=.001; Medical Burdens: $\beta_{\text{conditional on time-invariant covariates}}$= 1.782, p<.001 vs. $\beta_{\text{accounting for time-varying depression}}$=1.366, p<.001; Biological Syndrome: $\beta_{\text{conditional on time-invariant covariates}}$= 1.306, p<.001 vs. $\beta_{\text{accounting for time-varying depression}}$=0.977, p=.001)

DISCUSSION

There were two primary aims to the current study. First, we used LGCM to model frailty change over time and to assess whether both initial level of frailty and change in frailty over time was associated with experience of adverse health outcomes using three competing definitions of frailty. We accounted for the influence of time-invariant covariates on frailty trajectories using conditional LGCM. The second aim was to evaluate the influence of depression as a time-varying covariate on the relationship between frailty and adverse health outcomes. Our results indicate that, regardless of the operationalization of frailty employed, the predictive relationship between frailty and risk of nursing home entry and serious falls is substantially reduced (and in

the case of nursing home admission, essentially null) after accounting for depression status. Results of these aims provide valuable insights into the dynamic nature of frailty syndrome in later life and its relationship with depressive symptoms.

Frailty growth and adverse health outcomes

Building on prior frailty research, analysis showed that frailty is a dynamic condition and that the influence of this condition on adverse health outcomes extends beyond frailty status at a single time-point. Unconditional LGCM showed that, on average, the expected level of frailty increased over the study period and that there was significant inter-individual variability in both the initial level and rate of change of frailty over time. Regardless of the conceptual basis and operationalization of frailty, the probability of being frail approximately doubled over the study period. This finding highlights the importance of modeling initial frailty status in conjunction with change in frailty status over time, as our findings indicate that both have independent relationships with adverse health outcomes over time. Indeed, parallel process models showed that greater rates of change in frailty were significantly associated with more rapid increase in the likelihood of experiencing serious falls as well as nursing home admission. The reliability of these findings across multiple definitions of frailty indicates that frailty development is an important consideration which is not reserved for any particular conceptual orientation.

These results supplement what is currently known about frailty and its development over the life course. While there is an implicit acknowledgement that the signs of frailty may arise over long periods of time (54), few studies have incorporated frailty change explicitly in analysis. Many studies have assessed the role of frailty as a static predictor of poor health (21, 49), but the current results extend this research by providing evidence that developmental trajectories of frailty are themselves important predictors of poor outcomes. The distinction

between baseline frailty and frailty trajectories is valuable as it may lead to more refined identification of vulnerable older adults. The more rapid accumulation of frailty symptoms and indicators over time may signal increased vulnerability to poor health outcomes and higher health service utilization, even among individuals who would not meet standard criteria for frailty. Future research in frailty would benefit from focus on trajectories of frailty symptom accumulation, as slowing the progression of frailty symptoms might provide therapeutic targets independent of frailty status.

Predictors of frailty levels and trajectories

The time-invariant conditional LGCM of frailty provide further insights into potentially important differences between competing definitions of this syndrome. For example, more education and higher income were associated with lower initial probability and lower rate of change in frailty for the functional domains and biological syndrome definitions, consistent with literature on social disparities in disability (101, 102). However, these factors did not significantly influence change in medical burdens frailty over time. This difference might reflect the medical burden definition's emphasis on chronic disease states which may be less malleable to the influence of compensatory resources (e.g. education and wealth) over time. Likewise, female gender was significantly associated with rate of change of frailty only according to the biological syndrome definition. A potential explanation for this difference is that the biological syndrome definition emphasizes sarcopenia and muscle weakness which may be more common among women (19, 47). Taken together, these findings are in accordance with prior research demonstrating marked differences in the identification of frail individuals produced by competing definitions (48). This study builds on this research by showing that competing frailty definitions may also lead to different conclusions about the factors and characteristics which

determine the presence of and predict the development of frailty. The choice of frailty definition can therefore have considerable impact on how frailty is studied and treated, and who is considered "high risk."

The longitudinal relationship between frailty and depression

These results provide evidence for the hypothesis that frailty and depression are two highly interrelated conditions in late-life. When depression status was introduced into models as a time-varying covariate, the association between frailty and serious falls was substantially diminished and the association with nursing home entry became non-significant. This indicates that depression status and frailty status explain much of the same variation in determining which individuals experience adverse health outcomes over time. There are a number of potential explanations for these findings. One possibility is that frailty and depression independently lead to similar poor health outcomes. While frailty and depression are both associated with poor health (49, 94), it is unlikely, given their pervasive comorbidity and established diagnostic overlap (40, 75), that they are wholly independent of one another. A more likely explanation is that frailty and depression are comparable, but distinct, expressions of a more general underlying process of physiological and psychosocial decline. For example, age-associated cardiovascular changes play a role in development of both frailty and depression (67, 86-88), and may help to explain comorbidity and common consequences of the two conditions. Consistent with this hypothesis, Hajjar and colleagues have identified an age-related phenotype characterized by depressive symptoms and features of frailty such as slow gait speed and poor executive functioning (67); hypertension, diabetes and other cardiovascular disorders were independently associated with this phenotype (67).

Other explanations, for instance that depression is a cause of or prodromal state of frailty (38), cannot be discounted based on the current analysis. Nonetheless, findings regarding the joint influence of frailty and depression on poor health outcomes signal the need for more comprehensive investigations of geriatric syndromes like frailty. Incorporating, rather than excluding, depression as a primary measure in frailty research will help to merge two separate lines of investigation from frailty and late-life depression. Joint consideration of frailty and depression may also help to identify older adults at higher risk and to tailor treatment to address both physiological and psychosocial vulnerabilities (45).

The primary strength of this study lies in the use of LGCM in a population-based sample. To our knowledge, this is among the first applications of LGCM to understanding change in frailty over time. LGCM allows us to address the question of whether frailty trajectories are associated with poor health outcomes independently of baseline frailty status and allows straightforward inclusion of time-varying covariates in analysis. Furthermore, the robustness of the findings is strengthened by replication across multiple definitions of frailty and multiple adverse health outcomes. Comprehensive analysis is possible because of the extensive collection of longitudinal health information and large sample size available in the HRS.

This study also has several limitations. First, while the parameters describing growth of frailty propensity over time were represented as latent factors, frailty itself was considered as a dichotomous, observed variable. To the extent that definitional criteria imperfectly measure the underlying frailty construct, our model results may misrepresent the relationship between frailty and other variables. However, frailty status for each of the three definitions was dichotomized according to standard criteria used extensively in previous research (21, 24, 48-50). Also, categorization of frailty as a discrete condition renders it clinically sensible as a basis for

treatment and intervention. Second, the measure of depression used in this study, the CESD, is not designed as a substitute for clinician diagnosis of major depression, and may not accurately distinguish depressed from non-depressed individuals. Nonetheless, the CESD is among the most widely used measures for depressive symptoms in the general community and thus its relationship with common measures of frailty is of research significance. Furthermore, the CESD has moderate diagnostic agreement with structured instruments for the assessment of major depression such as the CIDI (36, 37) and elevated depressive symptoms indicated by this scale have been associated with a host of adverse health outcomes that are also predicted by more clinically-validated metrics of depression (103, 104). Finally, the analytical sample was restricted to participants who were interviewed in each wave of the HRS from 2004 to 2012. By excluding participants lost to follow-up, it is possible that the study sample was healthier and less frail than individuals in the general population. Because both frailty status and adverse health outcomes are associated with increased likelihood of mortality, conditioning analysis on study retention may introduce bias by diminishing the observed relationship between frailty, depression, and adverse health outcomes. Despite this, the current study found a robust association between frailty and adverse health outcomes across multiple definitions of frailty. A more comprehensive understanding of this relationship could be gained by future studies accounting for competing risks such as mortality (105).

In summary, these results provide another step in understanding frailty's role as a measure of vulnerability in older adults. LGCM showed that more rapid development of frailty, as measured by three common definitions, was associated with propensity for falls and nursing home stays. Furthermore, models suggest that depression plays a substantial role in explaining the risk of poor health conferred by frailty, regardless of how it is operationalized. Results

indicate the need for interdisciplinary research, and inter-professional collaboration, to promote health and well-being in later life.

Table 4.1. Baseline (Wave 2004) sample characteristics by frailty definition

Characteristic	Total	Characteristics among Frail Older Adults		
		Functional Domains	Medical Burdens	Biological Syndrome
	N=10,611	Frail N = 1,768	Frail N = 2,903	Frail N = 864
	% or Mean (sd)	% or Mean (sd)	% or Mean (sd)	% or Mean (sd)
Age (yrs)	67.3 (7.9)	69.5 (8.7)	68.1 (8.2)	69.5 (9.2)
Female	60.7	66.7	72.8	70.1
Race				
White	84.0	75.3	81.1	83.7
Black	13.5	21.4	16.0	14.1
Other	2.4	3.2	3.0	2.2
Education (>12 yrs)	43.0	27.2	32.6	30.6
Household Poverty	7.7	16.6	12.8	16.2
Marital Status				
Married/partnered	69.2	57.3	61.9	59.6
Separated/divorced	10.8	13.8	13.5	14.4
Widowed	17.3	25.2	21.6	22.6
Health Insurance				
Medicare	60.8	75.4	69.3	73.1
Medicaid	6.4	17.4	13.3	17.2
Private	19.6	19.0	20.2	19.4
Current smoker	12.4	15.3	14.4	15.5

[1] Biological syndrome: frail = 3 or more symptoms

[2] Medical burdens: frail = index score >.25

[3] Functional domains: frail = 2 or more symptoms

Table 4.2. Proportion frail by frailty definition and wave

	Frailty Definition		
	Functional Domains	Medical Burdens	Biological Syndrome
Characteristic	N (%)	N (%)	N (%)
Wave 1 (2004)			
Frail	1,768 (17.1)	2,903 (27.4)	864 (8.4)
Intermediate	3,510 (33.1)	2,605 (24.5)	3,397 (32.0)
Wave 2 (2006)			
Frail	1,978 (19.0)	3,337 (31.5)	1,331 (12.5)
Intermediate	3,612 (34.0)	2,839 (26.8)	4,061 (38.3)
Wave 3 (2008)			
Frail	2,231 (21.4)	3,857 (36.4)	1,649 (15.8)
Intermediate	3,790 (35.7)	2824 (26.6)	4,171 (39.3)
Wave 4 (2010)			
Frail	2,906 (27.9)	4,159 (39.2)	2,043 (19.3)
Intermediate	3,705 (34.9)	2,756 (26.0)	4,795 (45.2)
Wave 5 (2012)			
Frail	3,482 (33.8)	4,697 (44.3)	2,130 (20.7)
Intermediate	3,629 (34.2)	2,566 (24.2)	4,669 (44.0)

[1] Biological syndrome: frail = 3 or more symptoms; intermediate = 1 or 2 symptoms

[2] Frailty index: frail = index score >.25; intermediate = index score >.15

[3] Functional domains: frail = 2 or more symptoms; intermediate = 1 symptom

Table 4.3. Unconditional latent growth models of frailty and adverse health outcomes

	Functional Domains		Medical Burdens		Biological Syndrome		Nursing Home Stay		Serious Falls	
	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value
Model Fit Statistics										
CFI	0.995	---	0.999	---	0.955	---	0.995	---	0.982	---
TLI	0.992	---	0.999	---	0.925	---	0.991	---	0.971	---
RMSEA	0.042	---	0.036	---	0.069	---	0.019	---	0.023	---
Means										
Slope	0.182	<.001	0.078	<.001	0.375	0.010	-0.032	0.763	-0.362	0.169
Intercept	0	---	0	---	0	---	0	---	0	---
Variances										
Slope	0.019	<.001	0.031	<.001	0.036	0.049	0.809	<.001	0.733	<.001
Intercept	0.666	<.001	0.887	<.001	0.880	<.001	0.098	0.003	0.141	0.063
Covariances										
Slope with Intercept	-0.096	<.001	0.015	0.361	0.166	0.041	-0.016	0.578	-0.044	0.169

CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root-mean-square error of approximation
All p-values are two-tailed

Table 4.4. Growth parameter estimates, model fit criteria from conditional latent growth models with time-invariant predictors

	Functional Domains		Medical Burdens		Biological Syndrome	
Model Fit Criteria	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value
CFI	0.990	---	0.999	---	0.953	---
TLI	0.983	---	0.998	---	0.923	---
RMSEA	0.020	---	0.015	---	0.028	---
Growth Parameters						
Random effect mean						
Slope	0.195	<.001	0.117	<.001	0.060	<.001
Intercept	0.162	<.001	0.119	<.001	0.271	<.001
Variances						
Slope	0.076	<.001	0.048	<.001	0.774	0.049
Intercept	0.735	<.001	0.904	<.001	1.154	<.001
Covariances						
Slope with Intercept	0.039	<.001	0.045	0.361	0.268	0.012

CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root-mean-square error of approximation; All p-values are two-tailed

Table 4.5. Relationship between time-invariant predictors and initial level of and change in level of frailty

	Functional Domains		Medical Burdens		Biological Syndrome	
Covariates	β	p-Value	β	p-Value	β	p-Value
Intercept on covariate						
Gender	0.079	0.003	0.401	<.001	0.201	<.001
Race (ref: white)						
Black	0.278	<.001	0.032	0.321	0.026	0.558
Other	0.336	<.001	0.051	0.430	0.050	0.546
Divorced (ref: married)	0.130	0.001	0.203	<.001	0.178	<.001
Widow (ref: married)	0.091	0.012	0.043	0.214	-0.043	0.353
Age (ref: 55-65 yrs)						
65 to 75 yrs	0.240	<.001	0.188	<.001	-0.062	0.094
75 to 85 yrs	0.472	<.001	0.317	<.001	0.301	<.001
85+ yrs	0.643	<.001	0.505	<.001	0.563	<.001
Education (ref: HS or less)	-0.381	<.001	-0.296	<.001	-0.230	<.001
Current smoker	0.198	<.001	0.151	<.001	0.157	<.001
Poverty	0.531	<.001	0.433	<.001	0.449	<.001
Slope on covariate						
Gender	-0.007	0.539	0.022	0.209	0.276	0.001
Race (ref: white)						
Black	0.040	0.100	-0.003	0.775	0.107	0.024
Other	0.042	0.231	-0.041	0.040	0.072	0.361
Divorced (ref: married)	0.008	0.667	0.021	0.155	0.179	0.010
Widow (ref: married)	0.028	0.110	0.034	0.007	0.163	<.001
Age (ref: 55-65 yrs)						
65 to 75 yrs	0.087	0.002	0.095	<.001	0.626	<.001
75 to 85 yrs	0.290	<.001	0.201	<.001	1.117	<.001
85+ yrs	0.448	<.001	0.191	<.001	1.151	<.001
Education (ref: HS or less)	-0.100	0.004	-0.018	0.197	-0.368	<.001
Current smoker	0.036	<.001	0.032	0.015	0.277	0.001
Poverty	0.132	0.007	0.026	0.237	0.265	0.012

CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root-mean-square error of approximation; All p-values are two-tailed

Table 4.6. Parallel process models adjusting for time invariant covariates and time-varying depression (Outcome: nursing home admission)

	Functional Domains		Medical Burdens		Biological Syndrome	
	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value
Model Fit Statistics						
CFI	0.993	---	0.998	---	0.970	---
TLI	0.989	---	0.997	---	0.952	---
RMSEA	0.012	---	0.012	---	0.018	---
Parameter	β	p-Value	β	p-Value	β	p-Value
Growth parameter regressions unadjusted for depression						
Frailty Intercept on NH Slope	0.036	0.227	-0.011	0.620	0.002	0.933
Frailty Slope on NH Slope	0.594	<.001	0.889	<.001	0.333	<.001
Frailty Intercept with NH Intercept	0.200	<.001	0.331	<.001	0.311	<.001
Growth parameter regressions adjusted for depression						
Frailty Intercept on NH Slope	0.009	0.986	0.002	0.998	-0.011	0.982
Frailty Slope on NH Slope	0.476	0.857	0.771	0.853	0.251	0.832
Frailty Intercept with NH Intercept	0.170	<.001	0.350	<.001	0.299	0.002
Parameter	log odds	p-Value	log odds	p-Value	log odds	p-Value
Frailty regression on time-varying depression						
Time 1	0.510	<.001	0.581	<.001	0.522	<.001
Time 2	0.405	<.001	0.580	<.001	0.545	<.001
Time 3	0.568	<.001	0.635	<.001	0.721	<.001
Time 4	0.566	<.001	0.655	<.001	0.611	<.001
Time 5	0.791	<.001	0.894	<.001	0.723	<.001

CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root-mean-square error of approximation

Table 4.7. Parallel process models adjusting for time invariant covariates and time-varying depression (Outcome: serious fall)

	Functional Domains		Medical Burdens		Biological Syndrome	
	Estimate	p-Value	Estimate	p-Value	Estimate	p-Value
Model Fit Statistics						
CFI	0.988	---	0.996	---	0.962	---
TLI	0.981	---	0.994	---	0.942	---
RMSEA	0.015	---	0.016	---	0.020	---
Parameter	β	p-Value	β	p-Value	β	p-Value
Growth parameter regressions unadjusted for depression						
Frailty Intercept on Fall Slope	0.403	0.002	0.281	0.001	0.192	0.007
Frailty Slope on Fall Slope	1.759	<.001	1.782	<.001	1.306	<.001
Frailty Intercept with Fall Intercept	0.161	<.001	0.221	<.001	0.164	<.001
Growth parameter regressions adjusted for depression						
Frailty Intercept on Fall Slope	0.211	0.021	0.192	0.009	0.093	0.085
Frailty Slope on Fall Slope	1.193	0.001	1.366	<.001	0.977	0.001
Frailty Intercept with Fall Intercept	0.149	<.001	0.200	<.001	0.120	0.001
Parameter	log odds	p-Value	log odds	p-Value	log odds	p-Value
Frailty regression on time-varying depression						
Time 1	0.510	<.001	0.582	<.001	0.522	<.001
Time 2	0.410	<.001	0.582	<.001	0.563	<.001
Time 3	0.581	<.001	0.640	<.001	0.746	<.001
Time 4	0.585	<.001	0.661	<.001	0.638	<.001
Time 5	0.827	<.001	0.905	<.001	1.800	<.001

CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root-mean-square error of approximation

Figure 4.1. Heuristic example of unconditional latent growth curve model for functional domains frailty

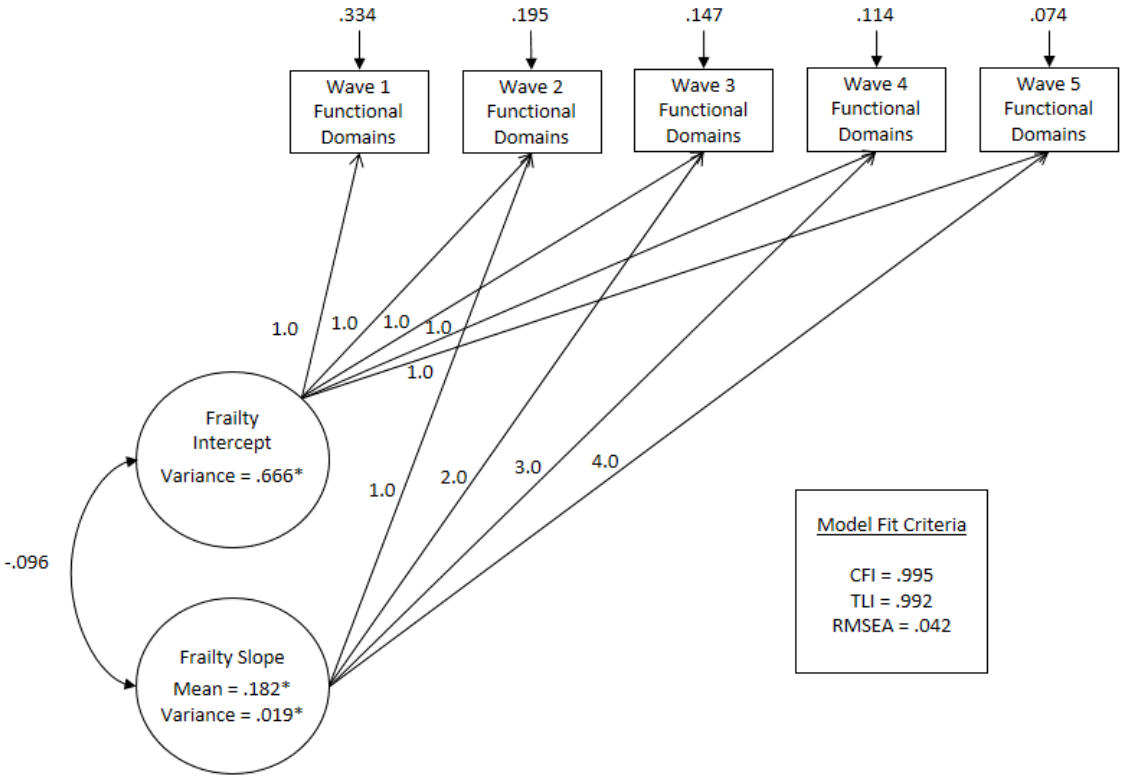


Figure 4.2. Heuristic example of conditional latent growth curve model for functional domains frailty

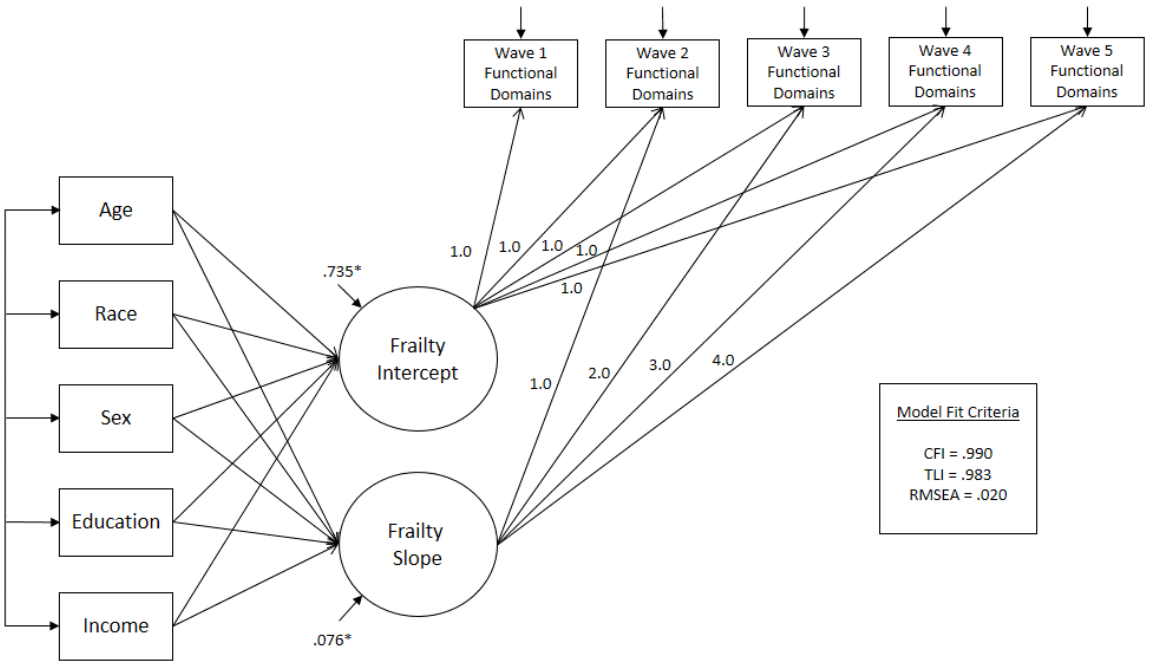


Figure 4.3. Parallel process model of functional domains frailty and nursing home stays

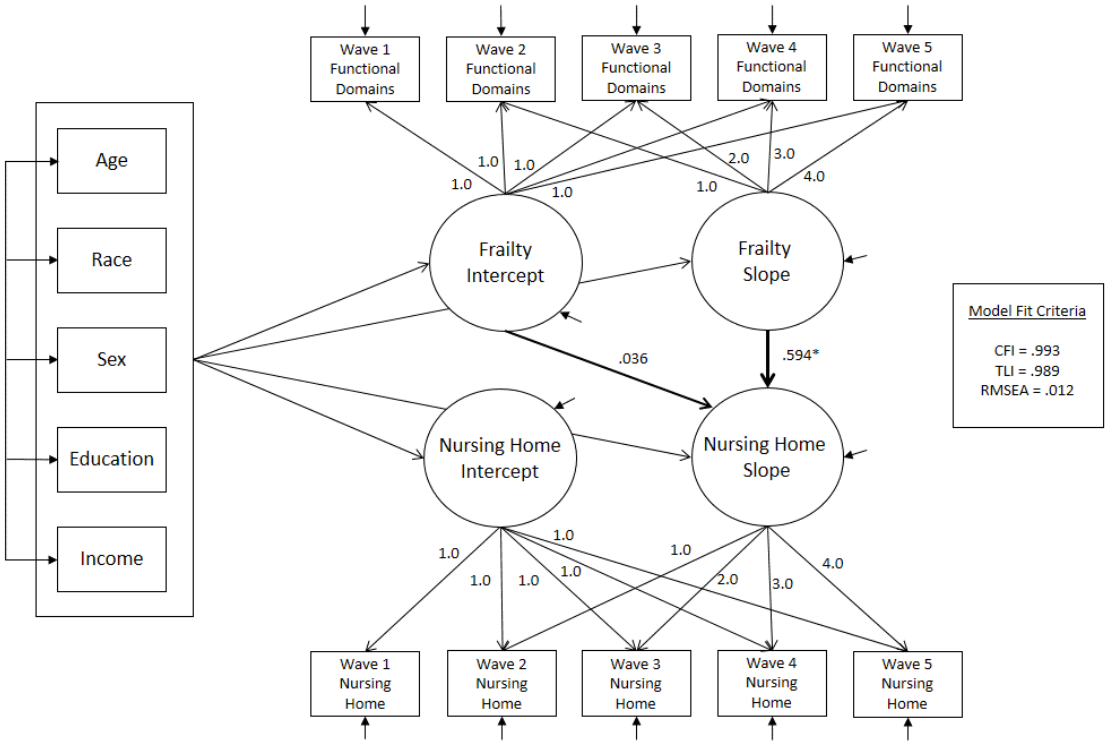


Figure 4.4. Parallel process model adjusted for time-varying depression

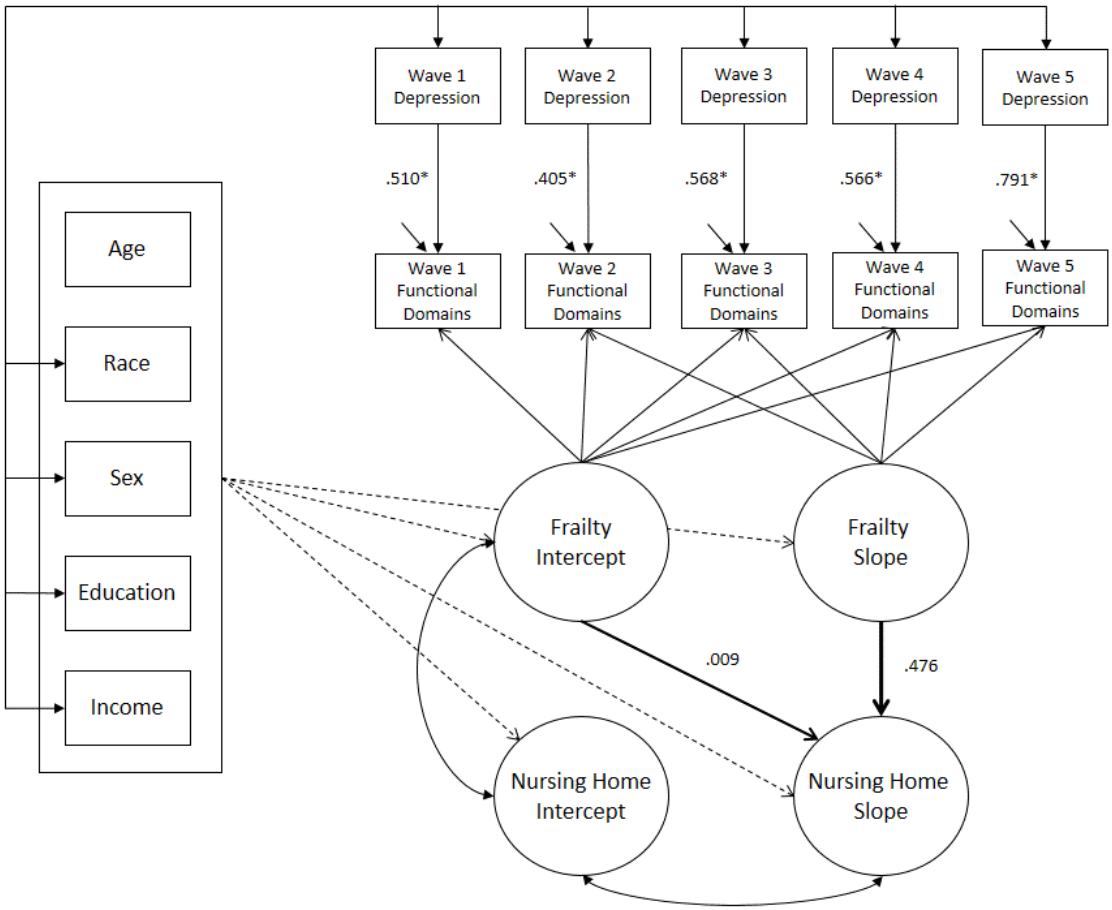


Figure 4.5. Sample proportions and model estimated probabilities for functional domains frailty

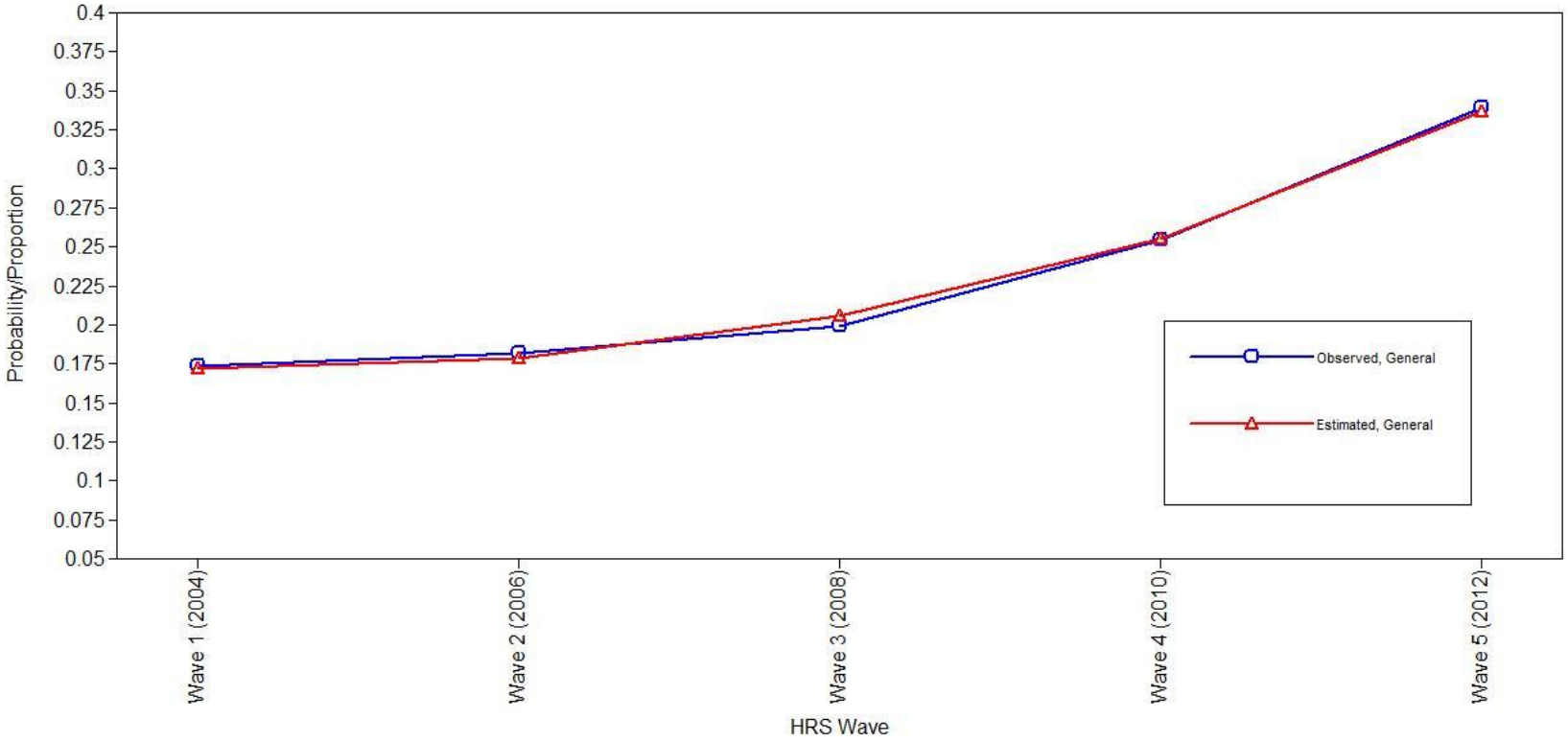


Figure 4.6. Sample proportions and model estimated probabilities for medical burdens frailty

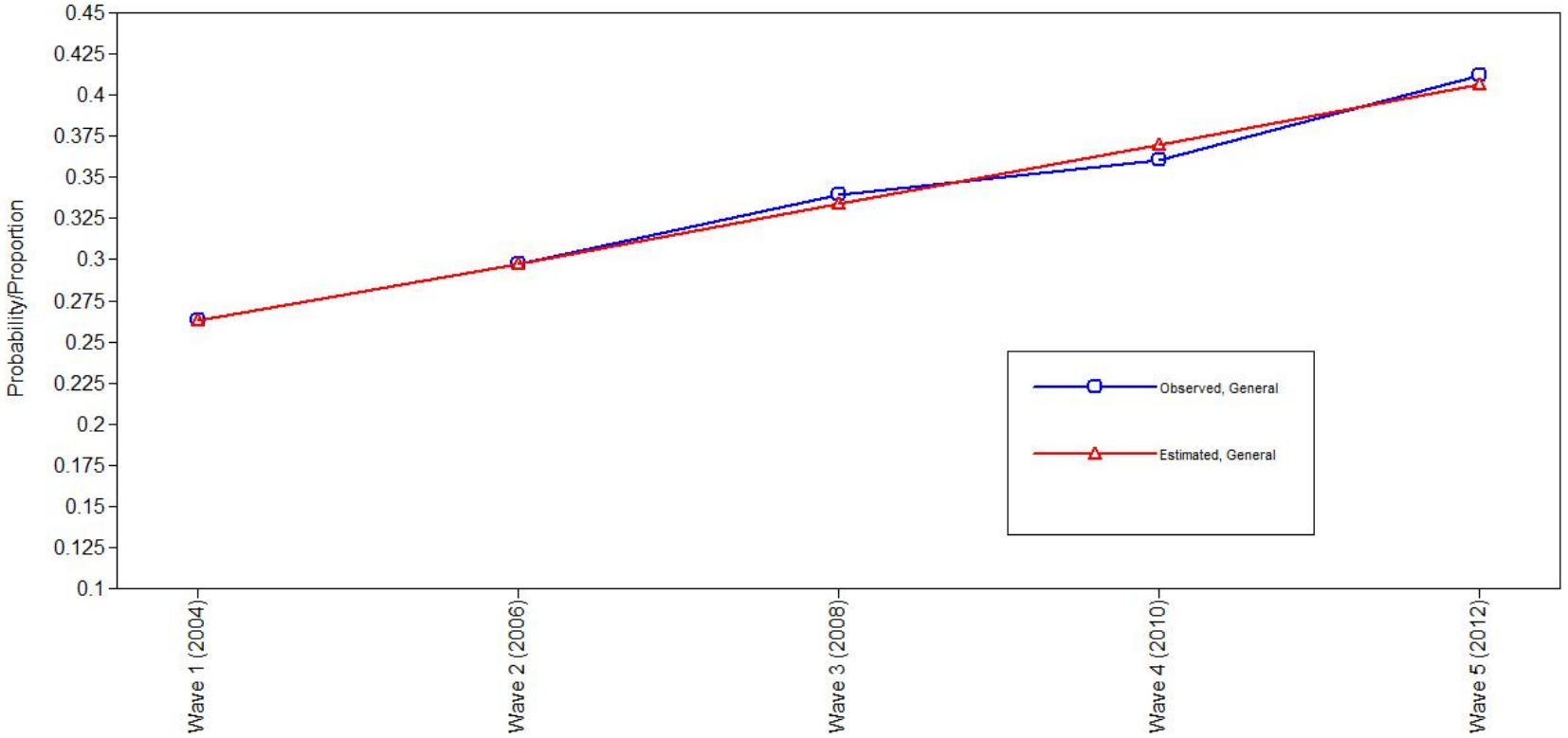
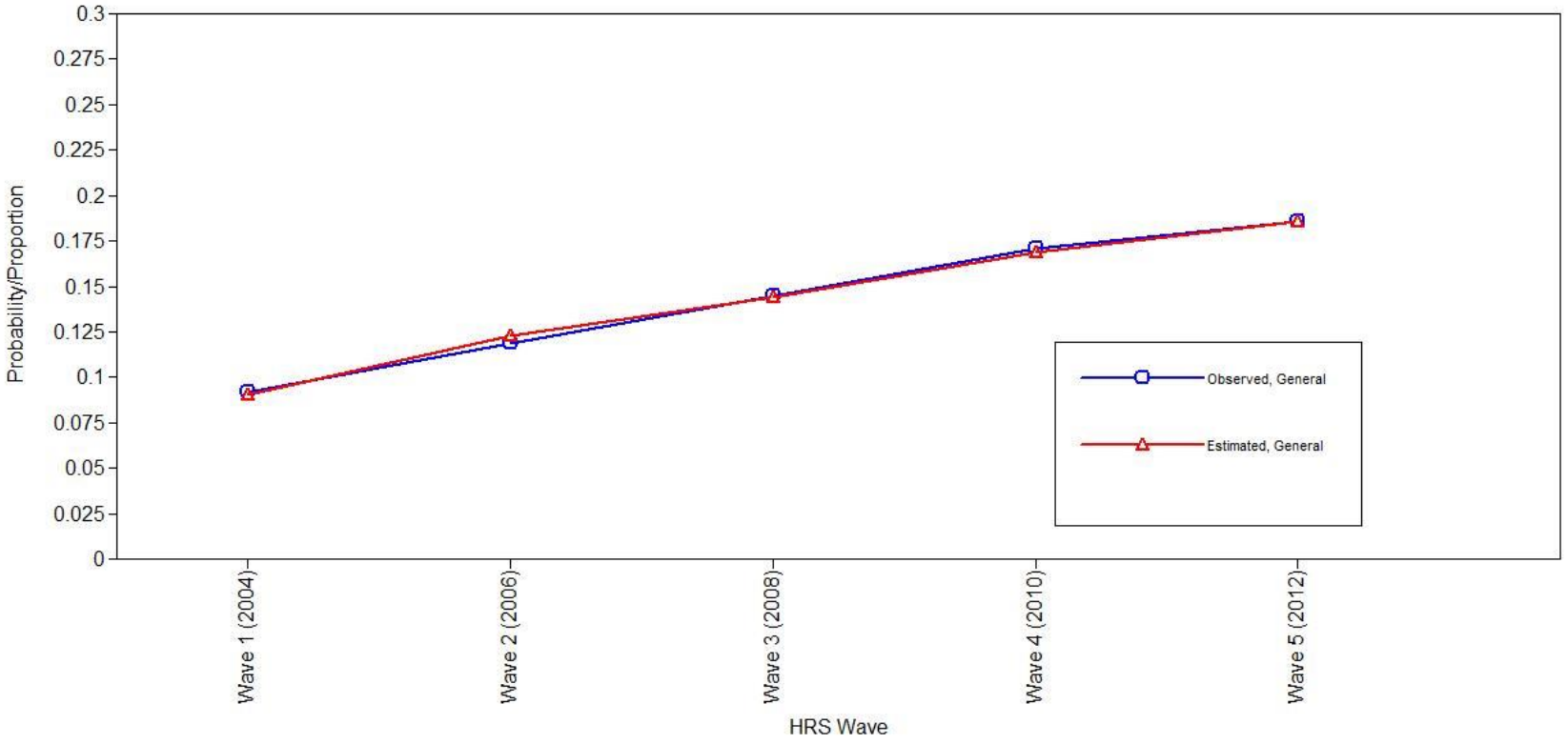


Figure 4.7. Sample proportions and model estimated probabilities for biological syndrome frailty



Afterword

Findings from this project have important implications for promoting health and well-being among older adults. By clarifying the associations between frailty and depression, this project informs design of preventive approaches to addressing physiological and psychosocial vulnerability. This project also highlights important connections between geriatric and psychiatric research. Bridging these lines of investigation will provide a richer understanding of the causes and correlates of adverse health events in late life.

Consistent across the three studies that constitute this project, frailty and depression were found to be highly interrelated syndromes. These findings suggest that frailty and depression should not be viewed as distinct syndromes but as overlapping and fundamentally linked conditions. A common approach to research related to frailty definition is to exclude individuals with depression from analysis; however, studies that aim to examine frailty independently from depression may imply an artificial distinction between these two syndromes and may draw incorrect inferences regarding the consequences and causes of frailty (Chapter 4). A more promising approach to research is to investigate frailty and depression as joint expressions of underlying decline. This approach is reflected in Hajjar et al. (2009), which identified an age-related syndrome characterized by symptoms of frailty and depression that was independently related to cardiovascular disorders (67). The second-order factors detailed in Chapter 3 of this project provide similar implications of an underlying process influencing both frailty and

depression. Therefore this project supplements current literature by organizing key findings within an explanatory structural model that serves as a target for future investigation. The robustness of findings using three conceptually distinct definitions of frailty offers rationale for refocusing the study of frailty and depression on their putative substrates. Study of the mechanisms and biologically plausible explanations of comorbidity of frailty and depression may lead to more effective ways to prevent and or treat these conditions jointly and independently.

This project likewise serves to unite research in frailty with guiding principles from geriatric psychiatry. In geriatric psychiatry, generative hypotheses regarding the causes of and alternate presentations of depression among older adults have led to important advances in understanding of depression. For instance, the 'vascular depression hypothesis,' which proposes that vascular mechanisms underlie many cases of late-onset depression, has guided search for causal explanations of depression among older adults (88, 106). Likewise, evidence suggests that depression among older adults is often characterized by a relative lack of mood-related symptoms and a preponderance of vegetative or somatic symptoms such as sleep disturbance and fatigue (41, 96). This phenomenon, termed 'depression without sadness,' has informed the development of more accurate survey measurements of depression among older adults and has provided avenues for future investigations of age differences in depression (41, 96). Though these findings from geriatric psychiatry may signal potential connections between frailty and depression, research on frailty has progressed, for the most part, independent of input from this related field. By presenting a basis for comparison between frailty and depression research, the current project may help to encourage refinement of the frailty concept and therefore more accurate identification of frail older adults. More accurate identification of frailty would

ostensibly improve recommendations for care and allocation of limited health resources for older adults.

The current project has implications for clinicians seeking to provide effective therapy for frail older adults. Comorbidity of frailty and depression may signal an elevated risk of adverse health outcomes (45). Frail older adults with depression may benefit from more holistic approaches to care which address not only physiological vulnerability but also the psychosocial vulnerabilities represented by depression (45). In support of this idea, the current project found that both depression and frailty were independently associated with risk of adverse health outcomes and that both conditions explained variations in who did and did not experience adverse health outcomes over time. Furthermore, frailty may limit effectiveness of or adherence to depression treatment, suggesting again that frailty and depression must not be considered independently of one another in clinical settings (43, 44). To our knowledge, no studies have investigated treatment approaches specifically aimed at addressing frailty and depression concurrently. A second implication of the current project is that greater rates of change in frailty were significantly associated with more rapid increase in the likelihood of experiencing adverse health outcomes. Thus, frailty trajectories are themselves important predictors of poor health apart from frailty status. More rapid accumulation of frailty symptoms over time may signal greater risk of adverse health outcomes. This suggests that delaying or preventing frailty symptoms may help to prevent adverse health outcomes, even among those who would not be considered frail by standard cut-off criteria. Tracking longitudinal changes in symptoms of frailty may then provide more nuanced measures of vulnerability.

Much is still unknown about how to best identify and to care for frail older adults. Future research should continue to seek the development of a unified frailty definition and to evaluate

approaches to caring for frail older adults. The current project provides a foundation for future research by elucidating frailty's relationship with depression and describing the joint role of these syndromes in determining poor health among older adults. The potential public health benefit of frailty will only be realized when conceptual issues are resolved.

List of References

List of References

1. U.S. Department of Health and Human Services. Office of Disease Prevention and Health Promotion. Healthy people 2020. Washington, DC. Available at [http://www.healthypeople.gov/2020/topicsobjectives2020/default.aspx]. Accessed [June 6, 2012].

2. National Prevention Council. National prevention strategy. Washington, D.C.: U.S. Department of Health and Human Services, Office of the Surgeon General; 2011.

3. Hornbrook MC, Stevens VJ, Wingfield DJ, Hollis JF, Greenlick MR, Ory MG. Preventing falls among community-dwelling older persons: results from a randomized trial. Gerontologist. 1994;34:16-23.

4. Inouye S, Studenski S, Tinetti M, Kuchel G. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55:780-791.

5. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381:752-762.

6. Rubenstein LZ, Stuck AE, Siu AL, Wieland D. Impacts of geriatric evaluation and management programs on defined outcomes: overview of the evidence. J Am Geriatr Soc. 1991;39:8S-16S; discussion 17S-18S.

7. Fiatarone MA, O'Neill EF, Ryan ND, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med. 1994;330:1769-1775.

8. Forster A, Lambley R, Young JB. Is physical rehabilitation for older people in long-term care effective? Findings from a systematic review. Age Ageing. 2010;39:169-175.

9. Sumukadas D, Struthers AD, McMurdo ME. Sarcopenia--a potential target for Angiotensin-converting enzyme inhibition? Gerontology. 2006;52:237-242.

10. Onder G, Penninx BW, Balkrishnan R, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. The Lancet. 2002;359:926-930.

11. Makary MA, Segev DL, Pronovost PJ, et al. Frailty as a Predictor of Surgical Outcomes in Older Patients. J Am Coll Surg. 2010;210:901-908.

12. Hubbard RE, O'Mahony MS, Woodhouse KW. Medication prescribing in frail older people. Eur J Clin Pharmacol. 2013;69:319-326.

13. Freiheit E, Hogan D, Eliasziw M, et al. Development of a frailty index for patients with coronary artery disease. J Am Geriatr Soc. 2010;58:1526-1531.

14. McAdams-DeMarco MA, Law A, Salter ML, et al. Frailty and early hospital readmission after kidney transplantation. Am J Transplant. 2013;13:2091-2095.

15. Tinetti ME, Inouye SK, Gill TM, Doucette JT. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. JAMA. 1995;273:1348-53.

16. Ensrud KE, Ewing SK, Taylor BC, et al. Comparison of 2 frailty indexes for prediction of falls, disability, fractures, and death in older women. Arch Intern Med. 2008;168:382-389.

17. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62:722-727.

18. Fried L, Ferrucci L, Darer J, Williamson J, Anderson G. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci. 2004;59:255-263.

19. Rothman MD, Leo-Summers L, Gill TM. Prognostic significance of potential frailty criteria. J Am Geriatr Soc. 2008;56:2211-2216.

20. Raphael D, Cava M, Brown I, et al. Frailty: a public health perspective. Can J Public Health. 1995;86:224-227.

21. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol B Psychol Sci Soc Sci. 2007;62:738-743.

22. Amici A, Baratta A, Linguanti A, et al. The Marigliano–Cacciafesta polypathological scale: A tool for assessing fragility. Arch Gerontol Geriatr. 2008;46:327-334.

23. Andrew MK, Rockwood K. Psychiatric Illness in Relation to Frailty in Community-Dwelling Elderly People without Dementia: A Report from the Canadian Study of Health and Aging. Can J Aging. 2007;26:33-38.

24. Strawbridge WJ, Shema SJ, Balfour JL, Higby HR, Kaplan GA. Antecedents of frailty over three decades in an older cohort. J Gerontol B Psychol Sci Soc Sci. 1998;53:S9-S16.

25. Markle-Reid M, Browne G. Conceptualizations of frailty in relation to older adults. J Adv Nurs. 2003;44:58-68.

26. Sternberg S, Wershof Schwartz A, Karunananthan S, Bergman H, Mark Clarfield A. The identification of frailty: a systematic literature review. J Am Geriatr Soc. 2011;59:2129-2138.

27. Brown I, Renwick R, Raphael D. Frailty: constructing a common meaning, definition, and conceptual framework. Int J Rehabil Res. 1995;18:93-102.

28. de Souto Barreto P. One operational definition by population: the need for local evaluations of frailty. Journal of Physiological Anthropology. 2011;30:259-262.

29. Hybels CF, Blazer DG. Epidemiology of late-life mental disorders. Clinics in Geriatric Medicine. 2003;19:663-96.

30. Blazer D. Depression in late life: review and commentary. J Gerontol A Biol Sci Med Sci. 2003;58:249-65.

31. Blazer D, Burchett B, Service C, George LK. The association of age and depression among the elderly: an epidemiologic exploration. J Gerontol. 1991;46:M210-5.

32. Katz I. Depression and frailty: the need for multidisciplinary research. Am J Geriatr Psychiatry. 2004;12:1-6.

33. Mezuk B, Edwards L, Lohman M, Choi M, Lapane K. Depression and frailty in later life: a synthetic review. Int J Geriatr Psychiatry. 2011;27:879-892.

34. Fiske A, Wetherell J, Gatz M. Depression in older adults. Annu Rev Clin Psychol. 2009;5:363-389.

35. Gabryelewicz T, Styczynska M, Luczywek E, et al. The rate of conversion of mild cognitive impairment to dementia: predictive role of depression. Int J Geriatr Psychiatry. 2007;22:563-567.

36. Alexopoulos GS. Depression in the elderly. Lancet. 2005;365:1961-1970.

37. Rovner B, German P, Brant L, Clark R, Burton L, Folstein M. Depression and Mortality in Nursing-Homes. JAMA. 1991;265:993-996.

38. Paulson D, Lichtenberg PA. Vascular depression: An early warning sign of frailty. Aging Ment Health. 2013;17:85-93.

39. Mezuk B, Eaton WW, Golden SH. Depression and osteoporosis: epidemiology and potential mediating pathways. Osteoporosis Int. 2008;19:1-12.

40. Mezuk B, Lohman M, Dumenci L, Lapane K. Are depression and frailty overlapping syndromes in mid- and late-life? A latent variable analysis. Am J Geriat Psychiat. 2012;21:560-569.

41. Gallo JJ, Anthony JC, Muthén BO. Age differences in the symptoms of depression: a latent trait analysis. J Gerontol. 1994;49:251-264.

42. Lakey S, LaCroix A, Gray S, et al. Antidepressant use, depressive symptoms, and incident frailty in women aged 65 and older from the Women's Health Initiative Observational Study. J Am Geriatr Soc. 2012;60:854-861.

43. Oslin DW, Ten Have TR, Streim JE, et al. Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. J Clin Psychiatry. 2003;64:875-882.

44. Streim JE, Oslin DW, Katz IR, et al. Drug treatment of depression in frail elderly nursing home residents. Am J Geriatr Psychiatry. 2000;8:150-159.

45. Brown PJ, Roose SP, Fieo R, et al. Frailty and Depression in Older Adults: A High-Risk Clinical Population. Am J Geriatr Psychiatry. 2013.

46. Collard R, Boter H, Schoevers R, Oude Voshaar R. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60:1487-1492.

47. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the women's health initiative observational study. J Am Geriatr Soc. 2005;53:1321-1330.

48. Cigolle C, Ofstedal M, Tian Z, Blaum C. Comparing models of frailty: the Health and Retirement Study. J Am Geriatr Soc. 2009;57:830-839.

49. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-M157.

50. Bandeen Roche K, Xue Q, Ferrucci L, et al. Phenotype of frailty: characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci. 2006;61:262-266.

51. Pijpers E, Ferreira I, Stehouwer CDA, Nieuwenhuijzen Kruseman A. The frailty dilemma. Review of the predictive accuracy of major frailty scores. Eur J Intern Med. 2012;23:118-123.

52. Zbozinek TD, Rose RD, Wolitzky-Taylor KB, et al. Diagnostic overlap of generalized anxiety disorder and major depressive disorder in a primary care sample. Depress Anxiety. 2012;29:1065-1071.

53. Gallo JJ, Rabins PV. Depression without sadness: alternative presentations of depression in late life. Am Fam Physician. 1999;60:820-826.

54. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ. 2011:E487-494.

55. Piccinelli M, Wilkinson G. Gender differences in depression: Critical review. Brit J Psychiat. 2000;177:486-492.

56. Silverstein B, Edwards T, Gamma A, Ajdacic-Gross V, Rossler W, Angst J. The role played by depression associated with somatic symptomatology in accounting for the gender difference in the prevalence of depression. Soc Psychiatry Psychiatr Epidemiol. 2013;48:257-263.

57. Heeringa SG, Connor J. Technical description of the health and retirement study sample design. Ann Arbor, MI: Institute for Social Research, University of Michigan; 1995;DR-0021995.

58. Crimmins E, Guyer H, Langa K, Ofstedal MB, Wallace R, Weir D. Documentation of physical measures, anthropometrics and blood pressure in the health and retirement study. Ann Arbor, MI: Institute for Social Research, University of Michigan; 2008;DR-011.

59. Turvey CL, Wallace RB, Herzog R. A revised CES-D measure of depressive symptoms and a DSM-based measure of major depressive episodes in the elderly. Int Psychogeriatr. 1999;11:139-148.

60. Steffick DE. Documentation of affective functioning measures in the health and retirement study. Ann Arbor, MI: Survey Research Center; 2000;DR-005.

61. Breitner JS, Welsh KA, Gau BA,et al. Alzheimer's disease in the national academy of sciences—national research council registry of aging twin veterans: Iii. detection of cases, longitudinal results, and observations on twin concordance. Archives of Neurology. 1995;52:763-771.

62. Ofstedal MB, Fisher GG, Herzog AR. Documentation of cognitive functioning measures in the health and retirement study. Ann Arbor, MI: Survey Research Center, University of Michigan; 2005;DR-006.

63. Goodman L. Exploratory latent structure-analysis using both indentifiable and unidentifiable models. Biometrika. 1974;61:215-231.

64. McCutcheon AL. *Latent Class Analysis.* Newbury Park: Sage Publications; 1987.

65. Clogg CC, Goodman LA. Latent Structure Analysis of a Set of Multidimensional Contingency Tables. Journal of the American Statistical Association. 1984;79:762-771.

66. Kankaras M, Moors G, Vermunt JK. Testing for measurement invariance with latent class analysis. In: Davidov E, Schmidt P, Billiet J, eds. *Cross-Cultural Analysis: Methods and Applications.* Illustrated ed. New York, NY: Taylor & Francis; 2012:359-384.

67. Hajjar I, Yang F, Sorond F, et al. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. J Gerontol A Biol Sci Med Sci. 2009;64:994-1001.

68. Cigolle C, Liang J, Ha J, et al. Can cognitive impairment be a frailty-defining criterion in the syndromic model of frailty? Annual Meeting of the Gerontological Society of America, San Diego, CA: 2012.

69. Silverstein B. Gender difference in the prevalence of clinical depression: the role played by depression associated with somatic symptoms; Am J Psychiatry. 1999;156:480-2.

70. Bennett DS, Ambrosini PJ, Kudes D, Metz C, Rabinovich H. Gender differences in adolescent depression: Do symptoms differ for boys and girls? J Affect Disord. 2005;89:35-44.

71. Lai CH. Major depressive disorder: gender differences in symptoms, life quality, and sexual function; Journal of clinical psychopharmacology. J Clin Psychopharmacol. 2011;31:39-44.

72. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173:489-495.

73. Szanton SL, Allen JK, Seplaki CL, Bandeen-Roche K, Fried LP. Allostatic load and frailty in the women's health and aging studies. Biol Res Nurs. 2009;10:248-256.

74. de Jonge P, Ormel J, Slaets JP, et al. Depressive symptoms in elderly patients predict poor adjustment after somatic events. Am J Geriatr Psychiatry. 2004;12:57-64.

75. Lohman M, Dumenci L, Mezuk B. Sex Differences in the Construct Overlap of Frailty and Depression: Evidence from the Health and Retirement Study. J Am Geriatr Soc. 2014;62:500-5.

76. Campbell DT, Fiske DW. Convergent and discriminant validation by the multitrait-multimethod matrix. Psychol Bull. 1959;56:81-105.

77. Krueger RF. The structure of common mental disorders. Arch Gen Psychiatry. 1999;56:921-926.

78. Krueger R, Markon K. Reinterpreting comorbidity: a model-based approach to understanding and classifying psychopathology. Annu Rev Clin Psycho. 2006;2:111-133.

79. Clark LA, Watson D, Reynolds S. Diagnosis and Classification of Psychopathology: Challenges to the Current System and Future Directions. Annu Rev Psychol. 1995;46:121-153.

80. Searle S, Mitnitski A, Gahbauer E, Gill T, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatrics. 2008;8:24.

81. Song X, Mitnitski A, Rockwood K. Prevalence and 10-Year Outcomes of Frailty in Older Adults in Relation to Deficit Accumulation. J Am Geriatr Soc. 2010;58:681-687.

82. Blaum CS, Ofstedal MB, Liang J. Low Cognitive Performance, Comorbid Disease, and Task-Specific Disability: Findings From a Nationally Representative Survey. J Gerontol A Biol Sci Med Sci. 2002;57:M523-M531.

83. Joreskog KG. A general approach to confirmatory maximum likelihood factor analysis. Psychometrika. 1969;34:183-202.

84. Mulaik SA. *Linear Causal Modeling with Structural Equations.* Boca Raton: CRC Press; 2009.

85. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: Conventional criteria versus new alternatives. Struct Equ Modeling. 1999;6:1-55.

86. Newman AB, Gottdiener JS, McBurnie MA, et al. Associations of Subclinical Cardiovascular Disease With Frailty. J Gerontol A Biol Sci Med Sci. 2001;56:M158-M166.

87. Strandberg TE, Pitkälä KH, Tilvis RS, O'Neill D, Erkinjuntti TJ. Geriatric syndromes—vascular disorders? Ann Med. 2013;45:265-273.

88. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. 'Vascular depression' hypothesis. Arch Gen Psychiatry. 1997;54:915-922.

89. Hubbard R, Rockwood K. Frailty in older women. Maturitas. 2011;69:203-207.

90. Woo J, Goggins W, Sham A, Ho SC. Social determinants of frailty. Gerontology. 2005;51:402-408.

91. Klein BEK, Klein R, Knudtson MD, Lee KE. Frailty, morbidity and survival. Arch Gerontol Geriatr. 2005;41:141-149.

92. Gobbens RJJ, Luijkx K, Wijnen Sponselee M, Schols JMGA. In search of an integral conceptual definition of frailty: opinions of experts. JAMDA. 2010;11:338-343.

93. Xue Q. The frailty syndrome: definition and natural history. Clin Geriatr Med. 2011;27:1-15.

94. Schulz R, Beach SR, Ives DG, Martire LM, Ariyo AA, Kop WJ. Association between depression and mortality in older adults: the Cardiovascular Health Study. Arch Intern Med. 2000;160:1761-1768.

95. Hybels CF, Pieper CF, Blazer DG. Sex differences in the relationship between subthreshold depression and mortality in a community sample of older adults. Am J Geriatr Psychiatry. 2002;10:283-291.

96. Gallo JJ, Rabins PV. Depression without sadness: Alternative presentations of depression in late life. Am Fam Physician. 1999;60:820-826.

97. Fisch RZ. Masked depression: its interrelations with somatization, hypochondriasis and conversion. Int J Psychiatry Med. 1987;17:367-379.

98. Campbell AJ, Buchner DM. Unstable disability and the fluctuations of frailty. Age Ageing. 1997;26:315-318.

99. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993;138:923-936.

100. Bollen KA, Curran PJ. *Latent Curve Models: A Structural Equation Perspective.* Hoboken, New Jersey: John Wiley & Sons; 2006.

101. Ament BH, de Vugt ME, Koomen FM, Jansen MW, Verhey FR, Kempen GI. Resources as a protective factor for negative outcomes of frailty in elderly people. Gerontology. 2012;58:391-397.

102. Ramsay SE, Whincup PH, Morris RW, Lennon LT, Wannamethee SG. Extent of social inequalities in disability in the elderly: results from a population-based study of British men. Ann Epidemiol. 2008;18:896-903.

103. Stellato RK, Feldman HA, Hamdy O, Horton ES, McKinlay JB. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts male aging study. Diabetes Care. 2000;23:490-494.

104. Carnethon MR, Kinder LS, Fair JM, Stafford RS, Fortmann SP. Symptoms of depression as a risk factor for incident diabetes: findings from the National Health and Nutrition Examination Epidemiologic Follow-up Study, 1971-1992. Am J Epidemiol. 2003;158:416-423.

105. Xue QL, Fried LP, Glass TA, Laffan A, Chaves PH. Life-space constriction, development of frailty, and the competing risk of mortality: the Women's Health And Aging Study I. Am J Epidemiol. 2008;167:240-248.

106. Alexopoulos G. Clinical and biological interactions in affective and cognitive geriatric syndromes. Am J Psychiatry. 2003;160:811-814.

Appendix

Appendix 3.1. Deficits used to define the frailty index (Chapter 3)	
Variable name	Operationalization in HRS
Problems getting dressed	Some difficulty dressing self
Problems with bathing	Some difficulty bathing, shower
Toileting problems	Some difficulty using toilet
Problems cooking	Some difficulty preparing hot meals
Problems going out alone	Difficullty shopping for groceries
Change in everyday activities	Change in activities of daily living
Impaired mobility	Some difficulty walking across room, walking several blocks, climbing stairs
Falls	Any reported falls past 2 years
Poor muscle tone limbs	Difficulty in large muscle activities (e.g. stooping, chair stand, kneeling, pushing large object)
Poor limb coordination	Difficulty in fine motor skills such as picking up a dime, eating and dressing
Bradykinesia of limbs	Slow walking speed
Musculoskeletal problems	Arthritis, hernia, rheumatism, paralysis, etc.
Hypertension	Reported high blood pressure
Myocardial infarction	Ever had heart attack
Congestive heart failure	Ever had heart failure
Arrhythmia	Ever had abnormal heart rhythm
Other cardiac problems	Ever had angina
History of stroke	Ever had a stroke
History of diabetes mellitus	Ever had diabetes
Long-term memory impairment	Problem with dementia
Memory changes	Memory worse than two years ago
History of Parkinson's disease	Ever have Parkinson's disease
Headache	Persistent headache
Trouble sleeping	Trouble falling asleep or waking up during night
Tiredness all the time	Persistent or troublesome fatigue or exhaustion
Syncope or blackouts	Dizziness, blackouts, meningitis, other neurological problems
Lung problems	Ever have lung disease

Respiratory problems	Persistent couch/wheeze/flem or asthma, emphysema, chronic bronchitis
Other psychiatric condition	Psychiatric conditions not including depression and GAD
Feeling sad, blue, depressed	Felt depressed in past year
Gastrointestinal problems	E.g ulcers, colitis, gastritis, diverticulosis
Skin condition	E.g. dermatitis, eczema, rashes
Thyroid trouble	Any thyroid problem
Incontinence	Any reported incontinence past 12 months
Malignant disease	Ever had cancer

Appendix 3.2. Model fit indices from uni-dimensional factor analyses

	Biological syndrome	Frailty index	Functional domains	CESD
CFI	0.991	0.953	0.97	0.953
TLI	0.984	0.95	0.91	0.962
RMSEA	0.013	0.029	0.036	0.082

Exploratory analysis found that the model fit of the medical burdens frailty model was significantly improved when modeled as a second order factor with three sub-dimensions generally corresponding to activities of daily living, cardiovascular and neurological symptoms (Appendix 3.1); however, because frailty is commonly used as a uni-dimensional factor in practice, the frailty index was modeled as such in subsequent analyses.

Appendix 4.1. Criteria used to define physical measures symptoms of biological syndrome model frailty

Grip strength, stratified by gender and body mass index (BMI)	
Men	*Cutoff for grip strength (kg) criterion*
BMI $\leq$ 24	$\leq$ 29
BMI 24.1-26	$\leq$ 30
BMI 26.1-28	$\leq$ 30
BMI > 28	$\leq$ 32
Women	
BMI $\leq$ 23	$\leq$ 29
BMI 23.1-26	$\leq$ 30
BMI 26.1-29	$\leq$ 30
BMI > 29	$\leq$ 32

Walking speed, stratified by gender and height	
Men	*Cutoff time for 15 feet walking course (scaled to 2.5 meter for HRS)*
Height $\leq$ 173 cm	$\geq$ 7 seconds
Height > 173 cm	$\geq$ 6 seconds
Women	
Height $\leq$ 159 cm	$\geq$ 7 seconds
Height > 159 cm	$\geq$ 6 seconds

All cutoff criteria are derived from Fried et al. (2001)

Appendix 4.2. Deficits used to define the frailty index, medical burdens model (Chapter 4)

Variable name	Operationalization in HRS
Problems getting dressed	Some difficulty dressing self
Problems with bathing	Some difficulty bathing, shower
Toileting problems	Some difficulty using toilet
Problems cooking	Some difficulty preparing hot meals
Problems going out alone	Difficullty shopping for groceries
Change in everyday activities	Change in activities of daily living
Impaired mobility	Some difficulty walking across room, walking several blocks, climbing stairs
Falls	Any reported falls past 2 years
Poor muscle tone limbs	Difficulty in large muscle activities (e.g. stooping, chair stand, kneeling, pushing large object)
Poor limb coordination	Difficulty in fine motor skills such as picking up a dime, eating and dressing
Hypertension	Reported high blood pressure
Myocardial infarction	Ever had heart attack
Congestive heart failure	Ever had heart failure
Other cardiac problems	Ever had angina
History of stroke	Ever had a stroke
History of diabetes mellitus	Ever had diabetes
Long-term memory impairment	Problem with dementia
Memory changes	Memory worse than two years ago
Headache	Persistent headache
Trouble sleeping	Trouble falling asleep or waking up during night
Tiredness all the time	Persistent or troublesome fatigue or exhaustion
Lung problems	Ever have lung disease
Respiratory problems	Persistent couch/wheeze/flem or asthma, emphysema, chronic bronchitis
Other psychiatric condition	Psychiatric conditions not including depression and GAD
Feeling sad, blue, depressed	Felt depressed in past year
Incontinence	Any reported incontinence past 12 months
Malignant disease	Ever had cancer
Arthritis	Reported arthritis this wave
Trouble with pain	Often troubled with pain
Back pain or back problems	Back pain or problems

Appendix 4.3. Growth parameter estimates, model fit criteria from conditional latent growth models with time-invariant predictors

	Nursing Home Stay		Serious Fall	
Model Fit Criteria	Estimate	p-Value	Estimate	p-Value
CFI	0.997	---	0.978	---
TLI	0.995	---	0.963	---
RMSEA	0.005	---	0.013	---
Growth Parameters				
Random effect mean				
Slope	-0.125	0.545	-3.233	0.003
Intercept	0.132	<.001	1.413	<.001
Variances				
Slope	0.109	0.029	1.459	0.039
Intercept	0.646	<.001	1.215	<.001
Covariance				
Slope with Intercept	-0.044	0.080	-0.087	0.261

CFI: Comparative Fit Index; TLI: Tucker-Lewis Index; RMSEA: Root-mean-square error of approximation

Appendix 4.4. Growth parameter estimates, model fit criteria from conditional latent growth models with time-invariant predictors

	Nursing Home Stay		Serious Fall	
Covariate Effects	β	p-Value	β	p-Value
Intercept on covariate				
Gender	0.243	0.001	0.284	<.001
Race (ref: white)				
Black	-0.037	0.677	-0.126	0.083
Other	-0.558	0.042	-0.194	0.27
Divorced (ref: married)	0.253	0.006	0.045	0.601
Widow (ref: married)	0.178	0.013	0.095	0.106
Age (ref: 55-65 yrs)				
65 to 75 yrs	0.365	<.001	1.909	<.001
75 to 85 yrs	0.563	<.001	2.013	<.001
85+ yrs	0.762	<.001	2.377	<.001
Education (ref: HS or less)	-0.016	0.791	0.034	0.481
Current smoker	0.056	0.579	0.041	0.612
Poverty	-0.034	0.755	0.153	0.065
Slope on covariate				
Gender	-0.029	0.240	0.416	0.002
Race (ref: white)				
Black	0.001	0.982	-0.399	0.002
Other	0.065	0.479	-0.439	0.030
Divorced (ref: married)	0.011	0.763	0.151	0.087
Widow (ref: married)	0.026	0.425	0.118	0.105
Age (ref: 55-65 yrs)				
65 to 75 yrs	0.136	0.025	0.545	0.042
75 to 85 yrs	0.323	0.006	0.908	0.014
85+ yrs	0.464	0.006	1.179	0.013
Education (ref: HS or less)	-0.025	0.297	-0.041	0.405
Current smoker	0.018	0.600	-0.218	0.015
Poverty	0.129	0.010	0.109	0.269

Vita

Matthew Christopher Lohman was born April 14, 1983, in Norfolk, Virginia and he is an American citizen. He graduated from East Grand Rapids High School, East Grand Rapids, Michigan in 2001. He received his Bachelor of Arts in Psychology from Johns Hopkins University, Baltimore, Maryland in 2005. He received a Master of Health Sciences from Johns Hopkins School of Public Health in 2010.

Honors and Awards

2014, American Association of Geriatric Psychiatry, Best Early Investigator Poster Award
2013, Ruth L. Kirchstein National Research Service Award (NRSA), Fellowship
2012, Phi Kappa Phi Scholarship Nominee Award
2011, VCU Student Travel Grant Award
2011, Phi Kappa Phi Honor Society Induction

Professional and Research Positions

2010-14 Graduate Research Assistantship, Virginia Commonwealth University, Division of Epidemiology, Department of Family Medicine and Population Health
Mentor: Briana Mezuk, Ph.D.

2013 Teaching Assistant, Virginia Commonwealth University, Division of Epidemiology, Department of Family Medicine and Population Health
Professor: Briana Mezuk, Ph.D.

2012 Research Assistantship, Virginia Department of Behavioral Health and Developmental Services
Supervisor: Michael Olsen

2010 Graduate Researcher, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health
Mentor: George Rebok, Ph.D.

2006 Admissions Coordinator, Department of Admissions, Johns Hopkins Bloomberg School of Public Health

Publications

Lohman, M., Rebok, G., Spira, A., Parisi, J., Gross, A., Kueider, A. Depressive symptoms and memory performance among older adults: results from the ACTIVE memory training intervention. 2013 Dec; 25(8S):147S-162S. *Journal of Aging and Health.* [PMID: 23006426]

Mezuk, B., Edwards, L., Lohman, M., Choi, M., Lapane, K. Depression and frailty in later life: a synthetic review. *International Journal of Geriatric Psychiatry.* 2012 Sep; 27(9):879-92. [PMID: 21984056]

Choi, M., Mezuk, B., Lohman, M., Edwards, J., Rebok, G. Gender and racial disparities in driving cessation among older adults. *Journal of Aging and Health.* 2012 Dec; 24(8): 1364-79. [PMID: 22992714]

Mezuk, B., Lohman, M., Dumenci, L., Lapane, K. Are depression and frailty overlapping syndromes in mid- and late-life? A latent variable analysis. *American Journal of Geriatric Psychiatry.* 2013 Jun; 21(6):560-9. [PMID: 23567406]

Lohman, M., Mezuk, B. Frailty and depression: Comorbidity in the context of imperfect measurement. [Letter to the editor]. *Journal of the American Geriatrics Society*. 2013 Mar; 61(3):474. [PMID: 23496193]

Choi, M., Lohman, M., Mezuk, B. Trajectories of Cognitive Function by Driving Mobility in Later Life. *International Journal of Geriatric Psychiatry*. [Published online ahead of print, Sep 10, 2013]. [PMID: 24022894]

Lohman, M., Mezuk, B., Dumenci, L. Sex Differences in the Construct Overlap of Frailty and Depression: Evidence from the Health and Retirement Study. *Journal of the American Geriatrics Society.* 2014 Mar; 62 (3): 500-5. [PMID: 24576097]

Presentations

The Effect of Depression on Memory and Memory Training Intervention in Older Adults: Results from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE)

Study. Gerontological Society of America (November, 2011), Boston MA [Oral, Presenting author]

Are depression and frailty overlapping syndromes in mid- and late-life? Gerontological Society of America (Nov, 2011), Boston MA. [Oral, Contributing author with B. Mezuk, L. Dumenci, and K. Lapane]

Gender and racial disparities in driving cessation among older adults. Gerontological Society of America (Nov, 2011), Boston MA. [Oral, Contributing author with M. Choi, B. Mezuk, J. Edwards, and G. Rebok]

Trajectories of Cognitive Decline by Driving Mobility: Evidence from the Health and Retirement Study. Markesbery Symposium on Aging and Dementia (Nov, 2012), Lexington KY. [Oral, Contributing author with M. Choi and B. Mezuk]

Construct overlap between depression and frailty in later life: Evidence from the Health and Retirement Study. The American Psychopathological Association (March, 2012), New York NY [Poster, Presenting author]

Suicide in Long-term Care: A Qualitative Review of Narratives from the Virginia Violent Death Reporting System. Gerontological Society of America (November, 2013), New Orleans LA [Poster, Presenting author]

Suicide Risk Among Older Adults: Identifying Points of Engagement. Gerontological Society of America (November, 2013), New Orleans LA [Oral, Contributing author with B. Mezuk]

Depression and Frailty in Late Life: Evidence for a Common Vulnerability. American Association for Geriatric Psychiatry (March, 2014), Orlando FL [Poster, Presenting author]

Suicide in long-term care and assisted-living facilities from 2003–2011. American Association for Geriatric Psychiatry (March, 2014), Orlando FL [Poster, Contributing author with B. Mezuk]