Longitudinal Dynamics in Indicators of Frailty: Predictors and Long-Term Outcomes

Oleg Zaslavsky

A dissertation

submitted in partial fulfillment of the

requirements for the degree of

Doctor of Philosophy

University of Washington

2012

Reading Committee:

Barbara B. Cochrane, Chair

Jerald R. Herting

Hilaire Thompson

Nancy F. Woods

Program Authorized to Offer Degree:

School of Nursing

University of Washington

Abstract

Longitudinal Dynamics in Indicators of Frailty: Predictors and Long-Term Outcomes

Oleg Zaslavsky

Chair of the Supervisory Committee:
Barbara B. Cochrane Associate Professor The de Tornyay Endowed Professor for Healthy Aging Family and Child Nursing

Frailty is a common geriatric condition with a wide array of sequelae, including increased risks of mortality, morbidity and disability. Despite its long conceptual and operational history in research and publications, both frailty and mechanisms of frailty development are still poorly understood. A detailed description of trajectories of frailty indicators could offer vital insights on unfolding longitudinal dynamics involved in the development of frailty. Such a longitudinal modeling could also provide researchers and clinicians with a better foundational understanding of the phenomenon and facilitate targeted care approach. The purpose of this study was to:

1. Describe longitudinal (~10 years) trajectories of change in musculoskeletal and neuro-cognitive indicators of frailty in older (>/=65 years) women enrolled in the Women's Health Initiative Clinical Trial.

2. Estimate the extent to which baseline factors (e.g., demographic characteristics, health status and behaviors) conjointly were associated with a likelihood of membership in the derived longitudinal clusters.

3. To determine the extent to which membership in longitudinal trajectories predicts the incidence of clinically relevant geriatric health outcomes (i.e., mortality and hospitalization) over 5-years of follow up (2005-2010 WHI Extension Study) in a model adjusted for all other baseline predictors.

The study findings demonstrated a high degree of heterogeneity in longitudinal dynamics of individual frailty criteria. We also showed that age, socio-demographic variables, health status, health behavior, environmental factors and personality traits are important determinants of individual frailty criteria. However the effect of these determinants on frailty phenotype is complex, presumably due to the multidimensional nature of frailty phenomenon. Thirdly, we found that the magnitude of risk carried by a membership in a certain longitudinal group for each of the defining elements of frailty is closely linked to the distance of that trajectory estimates from the one that represents the most optimal criterion-specific functioning over time. The further the distance between trajectory estimates of an individual who maintained the highest level of performance (specific to that indicator) and those who demonstrated less optimal functioning, the higher the risk of incidence of adverse health events. Finally, we empirically determined that distribution based cross sectional partitioning of frailty criteria seems to be a valid method for defining frailty given that elderly women maintained approximately similar levels of functioning over time without demonstrating clear increasing or decreasing longitudinal patterns.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

I would like to express my appreciation to Professor Barbara B. Cochrane supervisory committee chairperson, who shared her wealth of knowledge, experience and unequalled expertise in research on aging. She had provided invaluable guidance, support, and encouragement throughout the entire program. The opportunity to be a student of Dr. Cochrane has been a great honor.

Special gratitude to the members of my Supervisory Committee, Dr. Jerald Herting, Dr. Andrea LaCroix, Dr.Hilaire Thompson, and Dr. Nancy F. Woods who provided valuable support, guidance, expertise, insightful advises, and comments for the completion of this dissertation.

Sincere thanks are also extended to the Cheryl Spencer Department of Nursing at the University of Haifa, Israel and Aaron and Irma Spencers' who provided financial support for my Doctoral program and to the Hester McLaws Nursing Scholarship Awards who, provided funding for my dissertation.

I also wish to express sincere appreciation to Dr. Rheba deTornyay whose guidance, support and encouragement provided vital source of inspiration and motivation throughout all years of my Doctoral program.

And last by no means least, my deepest gratitude to my parents Alla and Alexander Zaslavsky, for all their love and support.

DEDICATION

To my parents Alla and Alex Zaslavsky,

whose unconditional love, support and inspiration

motivate me to explore new horizons

CHAPTER I

Introduction and Organization of Dissertation Chapters

Introduction

Frailty is a common geriatric condition with a wide array of sequelae, including increased risks of mortality, morbidity, disability, cognitive decline and health care utilization (Bandeen-Roche et al., 2006; Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010; Ensrud et al., 2007; Fried et al., 2001; Rochat et al., 2010; Woods et al., 2005). Despite its long conceptual and operational history in research and publications, frailty and mechanisms of frailty development are still poorly understood. A number of screening models have been proposed to objectively measure the severity of the frailty process and to assess its long-term consequences in clinical and community settings (Fried, et al., 2001; Ensrud, et al., 2009; Rockwood, et al., 2007). Each model incorporates a distinct set of biological dimensions (e.g., musculoskeletal, neuro-cognitive and psycho-emotional) and physiological indicators (Zaslavsky, Demiris, & Thompson, 2012). The most widely used operational definition of frailty includes indicators of sarcopenia, body composition change and energy level impairment (Fried et al., 2001). Of note, in addition to these "conventional" criteria, we have suggested extending Fried's working definition of frailty by also including indicators of neurosensory loss (i.e., cognition, changes in vision) (Zaslavsky et al., in press). Although most frail older adults develop age-related deficits affecting multiple biological systems, their clinical outcomes are not universally poor and fluctuate widely in severity even among individuals sharing the same initial level of frailty (Gill, Gahbauer, Allore, & Han, 2006). In longitudinal studies of frailty to date, investigators have used gender-specific cutoff points for each of the frailty indicators, based on their distributions within a particular sample at baseline, and then applied the cutoffs to determine frailty status at a later time-point (Fried, et al., 2001; Woods, et al., 2005). As a result, frailty indicators have been analyzed as predictors of health outcomes, based on a "snap shot" of their distributions, and defined as the lowest quintile of functioning. Such definitions yield results that are inherently linked to the timing of the measurements and to

the unique characteristics of the sample, which challenges generalization of findings beyond the examined cohort and fails to capture the longitudinal course of indicators during the follow-up period. In addition, a reliance on distribution-based single-occasion thresholds is conceptually misleading, particularly when frailty is defined as a process of gradual decline in resilience over time rather than a static condition which these methods infer.

A detailed description of trajectories of frailty indicators will provide vital insights on unfolding longitudinal dynamics involved in the development of frailty. Furthermore, such longitudinal modeling might help to identify those older adults who experience significant decline in frailty criteria but never cross below a pre-defined threshold that is associated with adverse outcomes. From a clinical perspective, there are a number of benefits to identifying potentially modifiable risk factors that predict the likelihood of belonging to a particular trajectory group. First, given clusters of risk factors often occur, health care providers might more efficiently allocate resources for those older adults at highest risk of adverse outcomes, particularly for those with subtle initial changes in frailty indicators. Secondly, prognostic knowledge might inform the design and application of a tailored care approach to frailty management; that is, to match the intensity of treatment and modalities to the type and stage of this geriatric syndrome. Next, elucidation of modifiable risks for adverse outcomes may yield targets for innovative approaches to treatment, which is important given the modest effect sizes for current therapies (Gray et al., 2009; LaCroix et al., 2008). Finally, trajectory modeling might provide clinically meaningful information on the magnitude of risk associated with membership in a longitudinal cluster with regard to incidence of health outcomes (e.g., mortality, disability, hospitalization, falls). This last set of analyses can also be used as a convenient statistical tool for empirical partitioning of a population curve into a number of distinctly different longitudinal clusters; each of these clusters, in turn, would represent a data-driven threshold for frailty criteria.

Based on the above, the specific aims of this study were to:

1. Describe longitudinal (~10 years) trajectories of change in musculoskeletal and neuro-cognitive indicators of frailty in older (>/=65 years) women enrolled in the Women's Health Initiative Clinical Trial.

2. Estimate the extent to which baseline factors (e.g., demographic characteristics, health status and behaviors) conjointly are associated with a likelihood of membership in the derived longitudinal clusters.

3. To determine the extent to which membership in longitudinal trajectories predicts the incidence of clinically relevant geriatric health outcomes (i.e., mortality and hospitalization) over 5-years of follow up (2005-2010 WHI Extension Study) in a model adjusted for all other baseline predictors.

Organization of Dissertation Chapters

This dissertation has been organized in a way to convey the results of the secondary data analysis as a compilation of three distinct manuscripts. Review of the literature (chapter II) and methodological manuscripts (chapter III) have been designed to meet the established guidelines and criteria for publication in a specific journal (that is listed on a cover sheet) and the results paper (chapter IV) was designed to comprehensively cover the findings of the data analysis. The last manuscript will be turned into publishable format by potentially splitting its content into a number of smaller reports. Each journal was chosen based on the observed research priorities for that particular journal as indicated by articles that were published there. Chapter I contains a brief introduction and specific aims of the proposed study. Chapter II illustrates a consolidated pathophysiological conceptual model of frailty, taking into consideration the large and exponentially growing body of studies regarding predictors, indicators, and outcomes of frailty. Chapter III provides details and step-by-step working example of the statistical approach that has been used to analyze the longitudinal data. Chapter IV contains an overview of the

conducted study, summary of the main findings; study limitations, and suggestions for the future research.

References:

Bandeen-Roche, K., Xue, Q. L., Ferrucci, L., Walston, J., Guralnik, J. M., Chaves, P., et al. (2006). Phenotype of frailty: characterization in the women's health and aging studies. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 61(3), 262-266.

Boyle, P. A., Buchman, A. S., Wilson, R. S., Leurgans, S. E., & Bennett, D. A. (2010). Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *Journal of the American Geriatrics Society,* 58(2), 248-255.

Ensrud, K. E., Blackwell, T. L., Redline, S., Ancoli-Israel, S., Paudel, M. L., Cawthon, P. M., et al. (2009). Sleep disturbances and frailty status in older community-dwelling men. *Journal of the American Geriatrics Society*, 57(11), 2085-2093.

Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Stone, K. L., Cauley, J. A., et al. (2007). Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 744-751.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., et al. (2001). Frailty in older adults: evidence for a phenotype. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 56(3), M146-156.

Gill, T. M., Gahbauer, E. A., Allore, H. G., & Han, L. (2006). Transitions between frailty states among community-living older persons. *Archives of Internal Medicine*, 166(4), 418-423.

Gray, S. L., LaCroix, A. Z., Aragaki, A. K., McDermott, M., Cochrane, B. B., Kooperberg, C. L., et al. (2009). Angiotensin-converting enzyme inhibitor use and incident frailty in women aged 65 and older: prospective findings from the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society*, 57(2), 297-303.

LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Newman, A. B., Kooperberg, C. L., et al. (2008). Statin use and incident frailty in women aged 65 years or older: prospective findings from the Women's Health Initiative Observational Study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 63(4), 369-375.

Rochat, S., Cumming, R. G., Blyth, F., Creasey, H., Handelsman, D., Le Couteur, D. G., et al. (2010). Frailty and use of health and community services by community-

dwelling older men: the Concord Health and Ageing in Men Project. *Age and Ageing*, 39(2), 228-233.

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62(7), 722-727.

Woods, N. F., LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Brunner, R. L., et al. (2005). Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society*, 53(8), 1321-1330.

Zaslavsky, O., Cochrane, B. B., Thompson, H. J., Woods, N. F., Herting, J.R., & LaCroix, A. Z. Frailty: a review of the first decade of research Biological Research for Nursing (in press)

Zaslavsky, O., Demiris, G., & Thompson, H. The role of emerging information technologies in frailty assessment. *Research in Gerontological Nursing*. [Epub ahead of print]

CHAPTER II: Manuscripts # 1

"Frailty: A Review of the First Decade of Research"

The manuscript has been accepted for publication in the Biological Research for Nursing journal

Abstract

Frailty is an emerging geriatric syndrome that refers to a state of increased vulnerability to adverse events including mortality, morbidity, disability, hospitalization and nursing home admission. Despite its long conceptual and operational history in research and publications, frailty and mechanisms of frailty development are still poorly understood. In this review we describe a number of conceptual models – reliability, allostatic load, and complexity – that have been put forward to explain the dynamic nature of frailty. We illustrate a consolidated pathophysiological model of frailty, taking into consideration the large and exponentially growing body of studies regarding predictors, indicators, and outcomes of frailty. The model addresses cellular (e.g., oxidative damage, telomere length) and systemic- mechanisms (e.g., endocrinal, inflammatory, coagulatory and metabolic deficiencies) of frailty, moderating or risk factors (e.g., ethnicity, life style, co-morbidities) and outcomes (morbidity, disability, cognitive decline). Finally we identify the weaknesses of traditional epidemiological approaches for studying complex phenomena related to frailty and propose areas for future methodological and physiological inquiry.

Introduction

There is an inevitable sequence of structural, functional, and physiological changes associated with advanced age (e.g., decreased number of myocardial cells, decreased collagen levels, reduced muscle mass). For some individuals these changes are accentuated and lead to increased morbidity and mortality, whereas other older adults remain physically and functionally robust up to a fairly advanced age. In an attempt to understand the heterogeneous nature of human aging, the concept of frailty has emerged as particularly germane. Frailty, to distinguish it from normal aging, usually refers to a state of increased vulnerability to external and internal stressors resulting from a significant reduction in physiological reserves (Fried et al., 2001; Lang, Michel, & Zekry, 2009). When exposed to environmental challenges, frail individuals demonstrate an increased risk of hospitalization, nursing home placement, and mortality compared with non-frail older adults (Ensrud et al., 2007; Rockwood & Mitnitski, 2007).

This article focuses on conceptual models proposed to explain the dynamics of frailty and its development. We elucidate pathophysiological changes that have been studied as etiological mechanisms of frailty. We also identify risk factors that initiate these pathophysiological changes and the downward spiral of events leading to frailty and its clinically relevant health outcomes. Finally, we graphically illustrate a framework for the development of frailty and its outcomes and point to directions for future research.

Operational Definition

Conceptual and operational definitions of frailty have transformed over time culminating with the scientific recognition of the construct as a medical syndrome with important etiological, symptomatic, and pathophysiological considerations. The concept of frailty first appeared in the research literature in 1968 when O'Brien and colleagues, in a cross-sectional study of 48 community-dwelling older adults, conceptually outlined the gradual development of frailty as an excessive disproportionate reaction of older adults to

adverse events (O'Brien, Roberts, Brackenridge, & Lloyd, 1968). After this first publication, the concept of frailty rarely appeared in the medical literature until the late 1980's when Winograd and colleagues (1988) defined its first quantitative measurement. Frail older adults were operationally defined as having one or more out of 15 common geriatric clinical conditions (Winograd, Gerety, Brown, & Kolodny, 1988).

Considerable progress in understanding and exploring the pathophysiology of frailty can be traced to 2001 when Fried and colleagues (2001) introduced a phenotypical (rule-based) operational definition of frailty based on a large sample of community-dwelling older adults participating in the Cardiovascular Health Study (CHS). In this approach, frailty was defined as meeting three or more out of five physiological deficits (muscle weakness, low gait speed, unintentional weight loss, exhaustion, and low physical activity). Findings from this study showed that frailty was independently associated with incident falls, worsened mobility, activities of daily living (ADL) disability, incident hospitalization, and death. The "Frailty Task Force" of the American Geriatrics Society adopted Fried's working definition of frailty as its conventional operational definition (Lang, Michel, & Zekry, 2009).

Conceptual Models

Since frailty was operationalized, scientific efforts have been directed at uncovering its biological and physiological underpinnings. Reliability, allostatic load, and complexity theories have been proposed to explain the dynamic nature of frailty and its development.

Reliability Theory

Reliability theory argues that all living organisms inherently possess a limited number of redundant biological systems to maintain homeostasis. As one ages, there is an inevitable but gradual process of deficit accumulation (e.g., genetic damages, co-morbidities, stresses), which in turn leads to an exhaustion of available physiological

reserves and increased mortality (Gavrilov & Gavrilova, 2001). This loss of system redundancy (e.g., decline in the number and function of homeostatic mechanisms) and the cumulative effect of cell loss over time have been observed in several biological studies (Andersen, Gundersen, & Pakkenberg, 2003; Leeuwenburgh, 2003; Wallace & Kelsey, 2010). The application of reliability theory in frailty research has been demonstrated by Mitnitski and colleagues (2001), who operationalized frailty as an accumulation of aging-associated deficits across multiple physiological systems. These researchers showed that the frailty index (FI)—based on a set of 20 symptoms, signs and impairments—is a sensitive predictor of 5-year survival. This view of frailty in relation to deficit accumulation has been further validated internationally in several large-scale cohort studies (Goggins, Woo, Sham, & Ho, 2005; Kulminski, Ukraintseva, Akushevich, Arbeev, & Yashin, 2007; Rockwood, Andrew, & Mitnitski, 2007).

Allostatic Load

Allostatic load (AL) theory postulates that a critical mass of wear and tear processes across physiological systems affects biological equilibrium. Beyond a certain critical mass, an individual is at increased risk for adverse health outcomes (Seeman, McEwen, Rowe, & Singer, 2001). An AL index including biomarkers of cardiovascular, metabolic, endocrine, and inflammatory regulatory systems has been suggested as a preclinical marker of frailty (Szanton, Allen, Seplaki, Bandeen-Roche, & Fried, 2009). Findings of an association between AL and the frailty phenotype in longitudinal and cross-sectional studies suggest that the major regulatory systems represented in the AL index are linked to individual indicators of frailty. For example, a decline in muscle strength has been associated with inflammation (Schaap et al., 2009), and low energy levels have been linked to endocrine misbalance (Kop et al., 2002). On the multisystem level, among a large sample of older adults who were high-functioning at baseline in the MacArthur Study of Successful Aging, higher levels of allostatic load were associated with a greater

incidence of frailty after three years of follow-up (Gruenewald, Seeman, Karlamangla, & Sarkisian, 2009). Additional support for the linkage between AL and frailty came from a secondary analysis of a large cohort of aging women participants in the Women's Health and Aging Study (WHAS; Fried, Xue, Cappola et al., 2009). In that study, Fried and colleagues confirmed an association between the phenotype of frailty and a number of abnormal physiological systems, independent of specific system abnormalities. The authors also indicated that three systems functioning at an abnormal level emerged as a potential threshold for a critical mass of wear and tear processes.

Complexity Theory

Complexity theory draws attention to the dynamic interplay across regulatory systems that govern the homeostatic adaptive response to external and internal stressors. This theory focuses on both the quality of interactions among biological systems and the quantity of accumulated physiological abnormalities (Lipsitz, 2004). According to this theory "deterioration of the complex network of interacting physiological signals … may compromise the capacity to mount compensatory physiological adaptations in response to stressors and lead to greater clinical vulnerability –or frailty"(Chaves et al., 2008, p.1699). A number of biological markers have been proposed as surrogate measures for impaired physiological complexity. For example, heart rate variability (HRV), a natural fluctuation in the intervals between normal heartbeats based on autonomic nervous system inputs to the sinus node, reflects a continuous exchange of regulatory signals for maintaining cardiovascular homeostasis. The approximate entropy for a heart rate (ApEnHR), a statistic that quantifies the regularity of heart rate fluctuations over time, has been found to correlate with older age (Beckers, Verheyden, & Aubert, 2006;Pikkujamsa et al., 1999) and greater morbidity and mortality (Makikallio et al., 2004; Tapanainen et al., 2002). Chaves and colleagues (2008) conducted a cross-sectional analysis of WHAS data aimed at testing the link between frailty and loss of physiological complexity, as indicated by low

ApEnHR. They found that individuals who had lower ApEnHR were twice as likely to be diagnosed as frail as those without lower ApEnHR (OR=1.99, 95% CI=1.1-3.7).

Summary of Conceptual Models

Frailty is independently associated with an absolute number of impaired physiological systems; as more systems show abnormal function, frailty increases and a dysregulation in a complex network of interaction occurs between its biological elements. Further research, though, is needed to determine the hierarchical, chronological, and causal sequence of physiological events that initiate the downward spiral of pathophysiological processes terminating with a state of increased vulnerability. An integrative model of frailty -- one that incorporates both quantitative measurements (that estimates the number of systems functioning abnormally) and an assessment of quality of interaction between two or more of its defining elements -- may help close gaps among alternative conceptual models.

Pathophysiological Mechanisms

Level I - Cellular Changes

Although no specific cause for frailty has been identified, efforts to outline its molecular and systemic mechanisms are ongoing. At the cellular level, cumulative oxidative damage has received scientific support as one of the plausible causal pathways leading to frailty (Walston, 2004). The loss of telomeres, with resultant alterations in cell division and protein production, has been strongly associated with physiological decline in older adults. Cawthon and colleagues reported that the mortality rate of aging individuals with shorter telomeres was nearly twice that of those with longer telomeres (Cawthon, Smith, O'Brien, Sivatchenko, & Kerber, 2003). However, a later cross-sectional study found no relationship between a frailty index (defined as the proportion of actual to possible deficits in an individual) and telomere length (Woo, Tang, Suen, Leung, & Leung, 2008). These researchers concluded that although telomere length may be a biomarker of cellular

senescence, this relationship might not extrapolate to a higher level representing frailty. Additional research is needed to further explore the molecular foundations of frailty.

Level II - System Dysregulation

On a higher level (i.e., System Dysregulation), a number of studies have helped to establish inflammation, activation of blood clotting pathways, hormonal dysregulation, and metabolic abnormalities as important correlates of frailty (Cappola, Xue, & Fried, 2009; Reiner et al., 2009; Walston et al., 2006).

Inflammatory Pathway Dysregulation

Previous research has shown that certain inflammatory markers (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], leukocytes) are more elevated in frail individuals than in age-matched counterparts. Cross-sectional data from the CHS cohort revealed that frail vs. non-frail participants had significantly increased levels of C-reactive protein (CRP) (Walston et al., 2006). Longitudinal analyses assessing the risk of frailty after 5 and 9 years of follow-up yielded similar results, demonstrating that CRP levels at baseline were significantly associated with incident frailty (Hazard Ratio [HR]=1.16, 95% CI=1.02-1.32) (Barzilay et al., 2007). Similarly, the Longitudinal Aging Study of Amsterdam (LASA), which aimed to assess predictors and consequences of change in physical, cognitive, emotional and social functioning, found that moderately elevated levels of CRP predicted 3-year incident frailty. In the LASA study frailty was operationalized as the presence of at least three out of nine frailty indicators: low BMI, low peak expiratory flow, impaired cognitive function, poor distant vision, hearing problems, incontinence, low sense of mastery, depressive symptoms, and low physical activity (Puts, Visser, Twisk, Deeg, & Lips, 2005). This evidence suggests that inflammatory pathway alterations play a crucial pathophysiological role in the development of frailty. However, further research is needed to draw definitive conclusions about the effects of inflammatory signals on biological and physiological indicators of frailty. In addition, although anti-inflammatory cytokines such as

IL-4 and IL-10 have been studied extensively in aging research (van den Biggelaar et al., 2004; Walston et al., 2008), effects on the development of frailty in humans has yet to be determined.

Endocrine Dysregulation

Alterations in anabolic hormones are theorized to contribute to aging and frailty. In fact, given the impact of endocrine dysfunction on biological senescence, much of the research on frailty has focused on these hormones. Cappola et al. (2009) showed that Women's Health and Aging (WHAS) participants who had two or more deficiencies in anabolic hormones were significantly more likely to be frail than their counterparts with no hormonal deficiencies. Moreover, the authors demonstrated that the absolute burden of anabolic hormonal deficiencies is a stronger predictor of frailty than the type of hormonal deficiency (Cappola, Xue, & Fried, 2009). Dehydroepiandrosterone sulfate (DHEA-s) levels show a gradual decline throughout the life span, reaching as low as 5-10% of peak values achieved in early adulthood (Heineman, Hamrick-King, & Sewell, 2010). Very low levels of DHEA-s have also been observed in a variety of age-related conditions including Alzheimer's disease, cardiovascular disease, and various cancers. A large cross-sectional study demonstrated a negative correlation between DHEA-s levels and frailty status (Voznesensky, Walsh, Dauser, Brindisi, & Kenny, 2009).

Similar to findings regarding DHEA-s, growth hormone insulin-like growth factor-1 (IGF-1) and sex steroids decline with age (Heineman et al., 2010). Puts et al. (2005) demonstrated a significant cross-sectional association between low serum IGF-1 and the presence of four or more out of nine physical and psychological indicators of frailty in a large sample of older Dutch individuals. Research on steroid hormones in gender-specific cohorts has, however, provided more ambiguous results. A research team from the New England Research Institute found no association between total and free testosterone levels and frailty in a sample of 646 community-dwelling men, aged 50 years and older

(Mohr et al., 2007). Conversely, the longitudinal Australian Health in Men study found that low free testosterone was independently associated with frailty at baseline as well as after a follow-up period of 4-7 years (Hyde et al., 2010). In that study, frailty was operationalized using a FRAIL scale comprised of five physiological indicators: fatigue, difficulty climbing a flight of stairs, difficulty walking more than 100 m, more than five illnesses present, or weight loss greater than 5%. In summary, endocrine studies indicate that lower levels of anabolic hormones are closely linked to a state of multisystem senescence and therefore frailty. Cappola et al. (2009) have suggested that these effects are mediated through musculoskeletal impairment; however, further confirmatory research is needed.

Hemato-Coagulatory Dysregulation

Excessive activation of the coagulation system has been associated with aging (Pieper, Rao, Currie, Harris, & Chen, 2000), functional decline, and increased mortality (Cohen, Harris, & Pieper, 2003). Moreover, age-associated changes in coagulation markers occur earlier than other aging biomarkers (Kanapuru & Ershler, 2009), leading to the hypothesis that biomarkers of coagulation (e.g., D-dimer, factor VIII, fibrinogen) and fibrinolysis (e.g., tissue-type plasminogen activator [t-PA]) signal important physiological mechanisms in the development of frailty. Evidence in support of this idea includes cross-sectional findings by Walston and colleges (2002), who reported that increased mean levels of factor VIII and fibrinogen were associated with frailty status. However, recent prospective studies on the association between inflammation, coagulation and fibrinolysis, and frailty have been inconsistent. A mere borderline association between factor VIII levels and incidence of frailty was demonstrated in the CHS cohort (Barzilay et al., 2007). Conversely, using a nested case-control design with 900 randomly-selected enrollees in the Women's Health Initiative (WHI) who developed frailty cross-matched for age and ethnicity with those who did not, the former showed higher levels of D-dimer and t-PA at

baseline (Reiner et al., 2009). Thus, activation of coagulation and fibrinolytic systems seems to play a role in the pathophysiology of frailty in older adults. Additional prospective studies are needed to further explore possible synergistic biological connections among coagulation system activation, inflammation, and risk of frailty.

Metabolic Dysregulation

There is growing evidence that a rise in insulin resistance occurs as individuals grow older, resulting in impaired uptake of glucose by skeletal muscle (Heineman et al., 2010). Previous research has described a relationship between elevated insulin resistance (IR) and many of the clinical indicators of frailty, such as skeletal muscle weakness, lower extremity mobility problems, physical disability, and cognitive impairment (Abbatecola & Paolisso, 2008). Insulin resistance, therefore, has been suggested as a metabolic disorder likely to have a direct impact on frailty. Gradual replacement of lean tissue with fat is partly responsible for the increased IR and glucose intolerance seen in older individuals (Chevalier et al., 2006). In addition, chronic overproduction of cortisol in response to stress can result in suppressed immune function, increased IR, increased adipose tissue mass, and loss of lean mass (Goulet et al., 2009). Examining the association between impaired metabolic state and frailty in a cross-sectional analysis of WHAS data, Blaum et al. (2009) demonstrated that hyperglycemia itself is associated with greater prevalence of frailty, independent of complications from diabetes mellitus, obesity, and high IL-6. Barzilay and collegues (2007), using data from the CHS cohort, demonstrated similar results by showing an association between IR and a 1.15-increased risk (95% CI=1.02-1.31) of frailty. Thus, future interventions aimed at correcting IR may have a significant role in preventing or at least slowing the downward cascade toward frailty.

Summary of Pathophysiological Mechanisms

In summary, it has become apparent that inflammatory, coagulation, endocrine, and metabolic pathways are increasingly disrupted with advanced age and to a greater extent in those who meet criteria for frailty. The coexistence of these unbalanced factors suggest their synergistic role in pathophysiological mechanisms leading to frailty. For example, it is has been shown that there is bilateral interplay between inflammatory cytokines and procoagulant factors in a wide range of age-related conditions (Kanapuru & Ershler, 2009). Similarly, an interaction between endocrine factors (e.g., IGF-1) and IL-6 in relation to disability and mortality has been previously reported (Cappola et al., 2003). While these findings provide important new insights into the physiological correlates of frailty and indicate that these factors exist simultaneously in aging individuals, more questions about multisystem dysregulation remain to be explored.

Level III - System Impairment

A consideration of high-level or multi-system impairment (i.e., level III) in frailty is consistent with the wide range of studies on different factors associated with its development. Musculoskeletal and neurocognitive changes are key indicators for frailty in the research literature and represent a high level impairment in the chain of pathophysiological events.

Musculoskeletal Impairment

Sarcopenia or loss of muscle mass and functioning occurs with aging and is one of the major components of the frailty phenotype. Sarcopenia is of great consequence to older adults because it is associated with an increased risk of functional impairment and disability (Hairi et al., 2010). The biology of sarcopenia remains elusive; however, a few etiological mechanisms have been proposed to explain this age-related decline in muscle mass (Heineman et al., 2010). In an extensive literature review encompassing several decades of frailty research, most studies were noted to include a functional decline in

muscle mass (e.g., upper muscle strength, gait speed, total physical activity) as a fundamental indicator of frailty (Zaslavsky et al., in press).

The age-related loss of muscle mass may not be an isolated phenomenon, but rather strongly connected with a parallel increase in fat mass. The fat mass increase and muscle mass decrease may act synergistically and lead to sarcopenic obesity. In the Invecchiare in Chianti study of 923 participants aged 65 years and older, frail subjects had lower muscle density and muscle mass and higher fat mass than did their non-frail counterparts (Cesari et al., 2006). This difference was observed in both genders and was independent of the concentration of inflammatory markers such as IL-6, CRP, and tumor necrosis factor-α (TNF-α). Sarcopenic obesity is particularly ominous, being associated with worse functional outcomes (e.g., climbing stairs, rising from a chair or bed, lifting heavy objects) and disability (Baumgartner et al., 2004; Rolland et al., 2009). A prospective study of 3075 well-functioning older adults aged 70-79 years participating in the Health ABC cohort showed that greater fat infiltration into muscle, as measured by computed tomography, was associated with an almost two-fold risk of mobility loss in 2.5 years of follow-up (Visser et al., 2005). Research has also demonstrated a positive correlation between fat infiltration into the muscle and overall body weight, as well as changes in body composition (Ryan & Nicklas, 1999). In fact, body weight can be sustained or increased as a result of the accumulation of adipose tissue, despite a loss of lean body mass (Koster, Ding, Stenholm et al., 2011). In the Koster et al. study excess body fat was a stronger determinant of impaired physical function in older adults than was inadequate lean body mass. More importantly, fat in older adults is preferentially accumulated in a central distribution. This central distribution of adipose tissue mass, similar to relative weight or other measures of obesity, is a major risk factor for many age-related metabolic abnormalities (Hubbard, Lang, Llewellyn, Rockwood, 2010). Impaired nutrition status, as measured by change in body mass index (BMI) or total body weight

over 1 to 3 years, has been used in multiple studies as one of the well-established frailty criteria (Ensrud, Ewing et al., 2009; Fried et al., 2001; Woods et al., 2005). Yet, additional research is needed to clearly establish which indicators will provide the more sensitive measure of these age-related pathophysiological processes in frail elderly: loss of lean mass, change in fat mass as indicated by an increase or decrease in BMI, or alternatively a direct measurement of central obesity (e.g., waist circumference).

Neurocognitive Impairment

The association between neurocognitive impairment and functional decline has been previously reported (Lenze et al., 2001; Spiers et al., 2005). Although these factors have been associated with frailty (Avila-Funes et al., 2009; Rothman, Leo-Summers & Gill, 2008), their pathophysiological role in the process of frailty development has yet to be determined. In frailty research, neurocognitive indicators have included a wide array of measures such as cognition, sensory impairment (e.g., visual or hearing loss), and psychological factors (depression) (Zaslavsky et al., in press). Avila-Funes and colleagues (2009) examined 6030 participants aged 65 to 95 in the French Three-City Study and clearly demonstrated that cognitive impairment, as measured by the Mini-Mental State Examination (MMSE) and the Isaac Set Test, improved the predictive validity of the CHS-based frailty phenotype for adverse health outcomes (e.g., dementia, functional decline, hospitalization). The odds ratio (OR) of incident 4-year hospitalization in frail individuals without cognitive impairment was not statistically significant (OR=1.26, 95% CI=0.91-1.74) compared to a non-frail group without cognitive deficits. However, frail individuals with cognitive impairment had 1.9-times increased risk (95% CI=1.09-3.31) compared to the same reference group. Rothman et al. (2008) had similar findings in their longitudinal analysis of 754 initially nondisabled, community-dwelling persons aged 70 and older. These researchers sought to determine the individual prognostic effect of each of Fried's

five frailty criteria as well as cognitive impairment (measured by the MMSE), and depressive symptoms (measured by the Center for Epidemiological Studies Depression Scale) on clinically relevant geriatric outcomes (e.g., disability, institutionalization, injurious falls, death). Rothman et al. found that cognitive impairment was independently and strongly associated with chronic disability (HR=1.82, 95 % CI=1.4-2.38), long term nursing home stay (HR=2.64, 95% CI=1.75-3.99), and death (HR=1.54, 95% CI=1.13-2.1) over 7.5 years of follow-up.

Sensory loss, such as decline of visual function, has also been linked to increased mortality in older adults (Klein, Klein, Knudtson, & Lee, 2005; Knudtson, Klein, & Klein, 2006). Longitudinal data indicate that older individuals with reduced visual acuity have a 70% increased mortality risk compared to persons without visual impairment (Wang, Mitchell, Simpson, Cumming, & Smith, 2001). Thus, it has been argued that visual impairment may also be a useful indicator of frailty. Testing this hypothesis, Klein and colleagues (Klein, Klein, Knudtson, & Lee, 2005) demonstrated that greater frailty status, as measured by a modified frailty index that included best corrected visual acuity in addition to musculoskeletal indicators, was associated with poorer survival among community-dwelling Midwestern older adults.

Mood disturbance (e.g., depression) is another neurocognitive parameter that predicts functional disability in older adults (Lenze et al., 2001) and has been suggested as an indicator of frailty (Lang et al., 2009). Longitudinal analysis of CHS data showed that persistently depressed older individuals had a 5.3-fold (95% CI=3.03-9.16) increased risk for functional disability compared to non-depressed individuals over 3 years of follow-up (Lenze, Schultz, Martire et al., 2005). However, despite mounting evidence on the effect of mood disorder on aging-related outcomes, findings of an independent effect of depressive symptoms on frailty have been inconsistent (Rothman et al., 2008). For instance, Rothman et al. found that depressive symptoms failed to independently predict

risk of chronic disability, long-term nursing home stay, injurious falls or death, after adjusting for age, sex, race, education, chronic conditions and the presence of other frailty criteria.

Summary of Pathophysiological Mechanisms

Numerous researchers argue that frailty is a multidimensional and multisystem process that cannot be comprehensively captured by applying physical criteria only, as there are other cognitive, neurological and biological domains that ought to be taken into consideration (Lang et al., 2009). This lack of consensus on the definition of the construct of frailty and its components has been discussed in a number of papers (Abellan van Kan et al., 2008; Lang et al., 2009), prompting continued efforts to identify a comprehensive model of frailty. Furthermore, it becomes apparent that no single system impairment characterizes frailty. Instead, an intertwined network of biological abnormalities is likely to be part of the pathophysiological chain of events leading to frailty. Of note, based on multiple studies and literature reviews, we suggest including measures of cognition and sensory loss as defining criteria of frailty, thus, extending Fried's phenotypical definition into the neurocognitive dimension.

Moderating/Risk Factors

Ethnicity, comorbidities, lifestyle, and poor nutrition have been proposed as plausible risk factors of frailty and increased mortality. Numerous studies have shown their independent and synergistic effect on frailty development (Alvarado, Zunzunegui, Beland, & Bamvita, 2008; Newman et al., 2001; Woods et al., 2005).

Ethnicity

Cross-sectional analysis of CHS cohort data has shown that African Americans have a four-fold greater odds of frailty than their white counterparts (Hirsch et al., 2006). The authors hypothesized that race serves as a marker for the differential genetic

polymorphisms that affect the expression of the frailty phenotype. However, it is also likely to suggest that an increased risk for frailty among African Americans closely relates to their experience of cumulative disadvantage (decreased health care access, poorer quality education, fewer employment choices) for the current generation of older African American adults. Addressing the effect of ethnicity on frailty, Espinoza and Hazuda (2008) conducted a secondary analysis of baseline data from a random sample of community-dwelling Mexican Americans (n=394) and European Americans (n=355) aged 65 to 80. The prevalence of frailty among Mexican Americans was 4.3% higher (p=.045) than among European Americans when applying Fried's screening tool for frailty. The authors argued, however, that the observed ethnic differences in frailty might be attributed in part to screening criteria that are inherently biased and do not take into account the unique biological and psychosocial characteristics of ethnically diverse groups. The standardization of frailty indicators according to racially sensitive cutoff points (e.g., that take into consideration the higher incidence of obesity, malnutrition, and comorbidities in some racial/ethnic minority populations) as well as concerns about racial disparities deserve further investigation in gerontological research.

Comorbidities

Comorbidities increase the risk for frailty. In a prospective longitudinal study of 40,657 women aged 65 to 79 years old participating in the Women's Health Initiative observational study, Woods and colleagues (2005) found that history of coronary heart disease (CHD), stroke, hip fracture, chronic obstructive pulmonary disease (COPD), treated diabetes mellitus, and arthritis were significantly related to 3-year incident frailty. Moreover, in a cross-sectional analysis of participants in the CHS, cardiovascular morbidity and vascular abnormalities were independently associated with increased prevalence of frailty (Newman et al., 2001). Thus, it is clear now that subclinical and chronic health conditions are strongly linked to the development and prevalence of frailty.

Lifestyle factors

Lifestyle, health-related behaviors, and socioeconomic status have also been recognized as contributors to the risk of developing frailty. For example, in a Latin American and Caribbean cross-sectional study of 10,661 men and women 60 years and older, poor health, little education, and poor socioeconomic conditions were associated with higher odds of frailty (Alvarado, Zunzunegui, Beland, & Bamvita, 2008).

Impaired nutrition

Finally, various aspects of poor nutritional intake are also considered important biological mechanisms in the development of frailty (Fried et al., 2009; Walston et al., 2006). One sign of impaired nutrition is daily energy intake. Calorie intakes of 21 kcal/kg/day or less were linked to frailty (as defined by Fried et al., 2001) by the Laboratory of Clinical Epidemiology of the Italian National Research Council of Aging (Florence, Italy) in a prospective population-based analysis of 1155 participants aged 65 to 102 years old (Bartali et al., 2006). In that study, a poor nutritional score (low intake of more than three nutrients, such as protein, vitamins A,C and E, calcium, folate and zinc), independent of energy intake, was significantly associated with frailty. Anti-inflammatory effects of dietary antioxidants are proposed as a plausible mechanism linking micronutrient deficiency and frailty (Waltson et al., 2006).

An Integrative Model of Frailty Development

A biological model that integrates the various conceptual models of frailty, as well as research on the multilevel/nested pathophysiological processes leading to frailty and their moderating/risk factors, is illustrated in Figure 1. Although potential interactions among these multiple physiological deficits have been recognized, to date no unifying causal mechanism has been established from which to derive a more mathematical model of frailty. Figure 1 provides an integrative conceptual framework for examining the cascade of pathophysiological events leading to frailty and can help researchers generate

testable hypotheses about the complex intra- and inter-level dynamics involved in its development. Analytic approaches like multilevel modeling (Singer & Willet, 2003) have the capacity to examine and estimate the multilevel, non-linear longitudinal trends that are expected in such complex biological phenomena. For example, one research question that can be derived from the integrative model would be to estimate the extent to which variability in longitudinal dynamics of musculoskeletal indicators (Level III) could be explained by lower level (i.e., Level II) factors (e.g., hemato-coagulatory, metabolic), which in turn could be a function of Level I factors (i.e., oxidative damage, telomere length).

Conclusions and Areas for Future Research

Based on research to date, frailty develops as a result of impairment in musculoskeletal and neurocognitive systems. The etiology of such impairment is multifactorial and includes progressive dysregulation in a number of main physiological systems (e.g., hemato-coagulatory, metabolic, endocrine) and their complex interconnected network. The process of frailty development starts with the prolonged exposure of an individual to a set of behavioral and environmental risk factors such as unhealthy life style, low socioeconomic status and abnormal health conditions that initiate a downward spiral of molecular- and system-level pathological events. Frailty is expressed as an accumulation of musculosketal and neurocognitive limitations. The indicators of frailty include weakness, slowness, low physical activity, low energy, weight loss, cognitive changes and sensory loss, thus representing its multidimensional nature stretching beyond mere physical function.

To date the main focus in frailty research has been to find its ultimate constellation of biological indicators and physiological markers. In addition to “conventional” Fried et al. (2001) criteria, we suggest including indicators of neurosensory loss (i.e., cognition and sensory loss). However, a more complete understanding of biological processes involved

in frailty development requires a deeper examination of its structural components and their unique longitudinal dynamics. In other words, to better understand etiological processes in the development of frailty, it is important to extend uni-level analyses to more comprehensive multilevel models. Given such efforts, we will be able to explicitly model complex structural and longitudinal dynamics involved in the pathophysiology of frailty. As an illustration of one of important ventures for future research we suggest examining the longitudinal patterns of change in frailty indicators and evaluating the effect of aggregate physiological abnormalities on these trajectories. The results of such analyses are likely to explicate the heterogeneous nature of frailty and its development and identify directions for future intervention.

References:

Abbatecola, A. M., & Paolisso, G. (2008). Is there a relationship between insulin resistance and frailty syndrome. *Current Pharmaceutical Design*, *14*(4), 405-410.

Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008;12(1):29-37.

Alvarado, B. E., Zunzunegui, M. V., Beland, F., & Bamvita, J. M. (2008). Life course social and health conditions linked to frailty in Latin American older men and women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 63(12), 1399-1406.

Andersen, B. B., Gundersen, H. J., & Pakkenberg, B. (2003). Aging of the human cerebellum: a stereological study. *Journal of Comparative Neurology*, 466(3), 356-365.

Avila-Funes, J. A., Amieva, H., Barberger-Gateau, P., Le Goff, M., Raoux, N., Ritchie, K., et al. (2009). Cognitive impairment improves the predictive validity of the phenotype of frailty for adverse health outcomes: the three-city study. *Journal of the American Geriatrics Society*, 57(3), 453-461.

Bartali, B., Frongillo, E. A., Bandinelli, S., Lauretani, F., Semba, R. D., Fried, L. P., et al. (2006). Low nutrient intake is an essential component of frailty in older persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 61(6), 589-593

Barzilay, J. I., Blaum, C., Moore, T., Xue, Q. L., Hirsch, C. H., Walston, J. D., et al. (2007). Insulin resistance and inflammation as precursors of frailty: the Cardiovascular Health Study. *Archives of Internal Medicine*, 167(7), 635-641.

Baumgartner, R. N., Wayne, S. J., Waters, D. L., Janssen, I., Gallagher, D., & Morley, J. E. (2004). Sarcopenic obesity predicts instrumental activities of daily living disability in the elderly. *Obesity Research*, 12(12), 1995-2004.

Beckers, F., Verheyden, B., & Aubert, A. E. (2006). Aging and nonlinear heart rate control in a healthy population. *Am J Physiol Heart Circ Physiol*, 290(6), H2560-2570.

Blaum, C. S., Xue, Q. L., Tian, J., Semba, R. D., Fried, L. P., & Walston, J. (2009). Is hyperglycemia associated with frailty status in older women*? Journal of the American Geriatrics Society*, 57(5), 840-847.

Cappola, A. R., Xue, Q. L., Ferrucci, L., Guralnik, J. M., Volpato, S., & Fried, L. P. (2003). Insulin-like growth factor I and interleukin-6 contribute synergistically to disability and mortality in older women. Journal of Clinical Endocrinology and Metabolism, 88(5), 2019-2025.

Cappola, A. R., Xue, Q. L., & Fried, L. P. (2009). Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging studies. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 64(2), 243-248.

Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 years or older. *Lancet,* 361(9355), 393-395.

Cesari, M., Leeuwenburgh, C., Lauretani, F., Onder, G., Bandinelli, S., Maraldi, C., et al. (2006). Frailty syndrome and skeletal muscle: results from the Invecchiare in Chianti study. *American Journal of Clinical Nutrition*, 83(5), 1142-1148.

Chaves, P. H., Varadhan, R., Lipsitz, L. A., Stein, P. K., Windham, B. G., Tian, J., et al. (2008). Physiological complexity underlying heart rate dynamics and frailty status in community-dwelling older women. *Journal of the American Geriatrics Society*, 56(9), 1698-1703.

Chevalier S, Gougeon R, Choong N, Lamarche M, Morais JA. Influence of adiposity in the blunted whole-body protein anabolic response to insulin with aging. *J. Gerontol. A. Biol. Sci. Med. Sci.* 2006;61(2):156-164.

Cohen, H. J., Harris, T., & Pieper, C. F. (2003). Coagulation and activation of inflammatory pathways in the development of functional decline and mortality in the elderly. *American Journal of Medicine,* 114(3), 180-187.

Ensrud, K. E., Blackwell, T. L., Redline, S., Ancoli-Israel, S., Paudel, M. L., Cawthon, P. M., et al. (2009). Sleep disturbances and frailty status in older community-dwelling men. *Journal of the American Geriatrics Society*, 57(11), 2085-2093.

Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Stone, K. L., Cauley, J. A., et al. (2007). Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62(7), 744-751.

Espinoza, S. E., & Hazuda, H. P. (2008). Frailty in older Mexican-American and European-American adults: is there an ethnic disparity? *Journal of the American Geriatrics Society*, 56(9), 1744-1749.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., et al. (2001). Frailty in older adults: evidence for a phenotype. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 56(3), M146-156.

Fried, L. P., Xue, Q. L., Cappola, A. R., Ferrucci, L., Chaves, P., Varadhan, R., et al. (2009). Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 64(10), 1049-1057.

Gavrilov, L. A., & Gavrilova, N. S. (2001). The reliability theory of aging and longevity. *Journal of Theoretical Biology*, 213(4), 527-545.

Goggins, W. B., Woo, J., Sham, A., & Ho, S. C. (2005). Frailty index as a measure of biological age in a Chinese population. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 60(8), 1046-1051.

Goulet ED, Hassaine A, Dionne IJ, et al. Frailty in the elderly is associated with insulin resistance of glucose metabolism in the postabsorptive state only in the presence of increased abdominal fat. *Exp. Gerontol.* 2009;44(11):740-744.

Gruenewald, T. L., Seeman, T. E., Karlamangla, A. S., & Sarkisian, C. A. (2009). Allostatic load and frailty in older adults. *Journal of the American Geriatrics Society*, 57(9), 1525-1531.

Hairi NN, Cumming RG, Naganathan V, et al. Loss of muscle strength, mass (sarcopenia), and quality (specific force) and its relationship with functional limitation and physical disability: the Concord Health and Ageing in Men Project. *J. Am. Geriatr. Soc.* 2010;58(11):2055-2062.

Heineman, J. M., Hamrick-King, J., & Sewell, B., S. (2010). Review of the aging of Physiological Systems In K. L. Mauk (Ed.), *Gerontological Nursing* (2nd ed., pp. 172-177). Sudbury, MA: Jones and Bartlett Publishers

Hirsch, C., Anderson, M. L., Newman, A., Kop, W., Jackson, S., Gottdiener, J., et al. (2006). The association of race with frailty: the cardiovascular health study. *Annals of Epidemiology,* 16(7), 545-553.

Hubbard RE, Lang IA, Llewellyn DJ, Rockwood K. Frailty, body mass index, and abdominal obesity in older people. *J. Gerontol. A. Biol. Sci. Med. Sci.* Apr 2010;65(4):377-381.

Hyde, Z., Flicker, L., Almeida, O. P., Hankey, G. J., McCaul, K. A., Chubb, S. A., et al. (2010). Low free testosterone predicts frailty in older men: the health in men study. *Journal of Clinical Endocrinology and Metabolism*, 95(7), 3165-3172.

Kanapuru, B., & Ershler, W. B. (2009). Inflammation, coagulation, and the pathway to frailty. *American Journal of Medicine*, 122(7), 605-613.

Klein, B. E., Klein, R., Knudtson, M. D., & Lee, K. E. (2005). Frailty, morbidity and survival. *Archives of Gerontology and Geriatrics*, 41(2), 141-149.

Knudtson, M. D., Klein, B. E., & Klein, R. (2006). Age-related eye disease, visual impairment, and survival: the Beaver Dam Eye Study*. Archives of Ophthalmology*, 124(2), 243-249.

Kop, W. J., Gottdiener, J. S., Tangen, C. M., Fried, L. P., McBurnie, M. A., Walston, J., et al. (2002). Inflammation and coagulation factors in persons > 65 years of age with symptoms of depression but without evidence of myocardial ischemia. *American Journal of Cardiology*, 89(4), 419-424.

Koster, A., Ding, J., Stenholm, S., Caserotti, P., Houston, D. K., Nicklas, B. J., et al. (2011). Does the Amount of Fat Mass Predict Age-Related Loss of Lean Mass, Muscle Strength, and Muscle Quality in Older Adults*? Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,*66(8):888-95

Kulminski, A. M., Ukraintseva, S. V., Akushevich, I. V., Arbeev, K. G., & Yashin, A. I. (2007). Cumulative index of health deficiencies as a characteristic of long life*. Journal of the American Geriatrics Society*, 55(6), 935-940.

Lang, P. O., Michel, J. P., & Zekry, D. (2009). Frailty Syndrome: A Transitional State in a Dynamic Process. *Gerontology*, 55(5), 539-549

Leeuwenburgh, C. (2003). Role of apoptosis in sarcopenia. *Journals of Gerontology*. *Series A, Biological Sciences and Medical Sciences,* 58(11), 999-1001.

Lenze, E. J., Rogers, J. C., Martire, L. M., Mulsant, B. H., Rollman, B. L., Dew, M. A., et al. (2001). The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. *American Journal of Geriatric Psychiatry*, 9(2), 113-135.

Lenze, E. J., Schulz, R., Martire, L. M., Zdaniuk, B., Glass, T., Kop, W. J., et al. (2005). The course of functional decline in older people with persistently elevated depressive symptoms: longitudinal findings from the Cardiovascular Health Study. *Journal of the American Geriatrics Society*, 53(4), 569-575.

Lipsitz, L. A. (2004). Physiological complexity, aging, and the path to frailty. *Sci Aging Knowledge Environ*, 2004(16), pe16.

Makikallio, A. M., Makikallio, T. H., Korpelainen, J. T., Sotaniemi, K. A., Huikuri, H. V., & Myllyla, V. V. (2004). Heart rate dynamics predict poststroke mortality. *Neurology*, 62(10), 1822-1826.

Mitnitski, A. B., Mogilner, A. J., & Rockwood, K. (2001). Accumulation of deficits as a proxy measure of aging. *ScientificWorldJournal,* 1, 323-336.

Mohr, B. A., Bhasin, S., Kupelian, V., Araujo, A. B., O'Donnell, A. B., & McKinlay, J. B. (2007). Testosterone, sex hormone-binding globulin, and frailty in older men. *Journal of the American Geriatrics Society*, 55(4), 548-555.

Newman, A. B., Gottdiener, J. S., McBurnie, M. A., Hirsch, C. H., Kop, W. J., Tracy, R., et al. (2001). Associations of subclinical cardiovascular disease with frailty. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 56(3), M158-166.

O'Brien, T. D., Roberts, J., Brackenridge, G. R., & Lloyd, W. H. (1968). Some aspects of community care of the frail and elderly: the need for assessment. *Gerontologia Clinica*, 10(4), 215-227.

Pieper, C. F., Rao, K. M., Currie, M. S., Harris, T. B., & Chen, H. J. (2000). Age, functional status, and racial differences in plasma D-dimer levels in community-dwelling elderly persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 55(11), M649-657.

Pikkujamsa, S. M., Makikallio, T. H., Sourander, L. B., Raiha, I. J., Puukka, P., Skytta, J., et al. (1999). Cardiac interbeat interval dynamics from childhood to senescence : comparison of conventional and new measures based on fractals and chaos theory. *Circulation*, 100(4), 393-399.

Puts, M. T., Visser, M., Twisk, J. W., Deeg, D. J., & Lips, P. (2005). Endocrine and inflammatory markers as predictors of frailty. *Clinical Endocrinology*, 63(4), 403-411.

Reiner, A. P., Aragaki, A. K., Gray, S. L., Wactawski-Wende, J., Cauley, J. A., Cochrane, B. B., et al. (2009). Inflammation and thrombosis biomarkers and incident frailty in postmenopausal women. *American Journal of Medicine*, 122(10), 947-954.

Rockwood, K., Andrew, M., & Mitnitski, A. (2007). A comparison of two approaches to measuring frailty in elderly people. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 738-743.

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 62(7), 722-727.

Rolland, Y., Lauwers-Cances, V., Cristini, C., Abellan van Kan, G., Janssen, I., Morley, J. E., et al. (2009). Difficulties with physical function associated with obesity, sarcopenia, and sarcopenic-obesity in community-dwelling elderly women: the EPIDOS (EPIDemiologie de l'OSteoporose) Study. *American Journal of Clinical Nutrition*, 89(6), 1895-1900.

Rothman, M. D., Leo-Summers, L., & Gill, T. M. (2008). Prognostic significance of potential frailty criteria. *Journal of the American Geriatrics Society*, 56(12), 2211-2116.

Ryan, A. S., & Nicklas, B. J. (1999). Age-related changes in fat deposition in mid-thigh muscle in women: relationships with metabolic cardiovascular disease risk factors. *International Journal of Obesity and Related Metabolic Disorders*, 23(2), 126-132.

Schaap, L. A., Pluijm, S. M., Deeg, D. J., Harris, T. B., Kritchevsky, S. B., Newman, A. B., et al. (2009). Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 64(11), 1183-1189.

Singer, J. D., & Willet, J. B. Applied Longitudinal Data Analysis. Oxford University Press; 2003

Seeman, T. E., McEwen, B. S., Rowe, J. W., & Singer, B. H. (2001). Allostatic load as a marker of cumulative biological risk: MacArthur studies of successful aging. *Proceedings of the National Academy of Sciences of the United States of America*, 98(8), 4770-4775.

Spiers, N. A., Matthews, R. J., Jagger, C., Matthews, F. E., Boult, C., Robinson, T. G., et al. (2005). Diseases and impairments as risk factors for onset of disability in the older population in England and Wales: findings from the Medical Research Council Cognitive Function and Ageing Study. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 60(2), 248-254.

Szanton, S. L., Allen, J. K., Seplaki, C. L., Bandeen-Roche, K., & Fried, L. P. (2009). Allostatic load and frailty in the women's health and aging studies. *Biol Res Nurs*, 10(3), 248-256.

Tapanainen, J. M., Thomsen, P. E., Kober, L., Torp-Pedersen, C., Makikallio, T. H., Still, A. M., et al. (2002). Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *American Journal of Cardiology*, 90(4), 347-352.

van den Biggelaar, A. H., Huizinga, T. W., de Craen, A. J., Gussekloo, J., Heijmans, B. T., Frolich, M., et al. (2004). Impaired innate immunity predicts frailty in old age. The Leiden 85-plus study. Experimental Gerontology, 39(9), 1407-1414.

Visser, M., Goodpaster, B. H., Kritchevsky, S. B., Newman, A. B., Nevitt, M., Rubin, S. M., et al. (2005). Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences,* 60(3), 324-333.

Voznesensky, M., Walsh, S., Dauser, D., Brindisi, J., & Kenny, A. M. (2009). The association between dehydroepiandosterone and frailty in older men and women. *Age and Ageing,* 38(4), 401-406.

Wallace, W. H., & Kelsey, T. W. (2010). Human ovarian reserve from conception to the menopause. *PLoS One*, 5(1), e8772.

Walston, J. (2004). Frailty--the search for underlying causes. *Sci Aging Knowledge Environ,* 2004(4), pe4.

Walston, J., McBurnie, M. A., Newman, A., Tracy, R. P., Kop, W. J., Hirsch, C. H., et al. (2002). Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. *Archives of Internal Medicine*, 162(20), 2333-2341.

Walston, J., Xue, Q., Semba, R. D., Ferrucci, L., Cappola, A. R., Ricks, M., et al. (2006). Serum antioxidants, inflammation, and total mortality in older women. *American Journal of Epidemiology,* 163(1), 18-26.

Walston, J., Fedarko, N., Yang, H., Leng, S., Beamer, B., Espinoza, S., et al. (2008). The physical and biological characterization of a frail mouse model. Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63(4), 391-398.

Wang, J. J., Mitchell, P., Simpson, J. M., Cumming, R. G., & Smith, W. (2001). Visual impairment, age-related cataract, and mortality. *Archives of Ophthalmology*, 119(8), 1186-1190.

Winograd, C. H., Gerety, M. B., Brown, E., & Kolodny, V. (1988). Targeting the hospitalized elderly for geriatric consultation. *Journal of the American Geriatrics Society*, 36(12), 1113-1119.

Woo, J., Tang, N. L., Suen, E., Leung, J. C., & Leung, P. C. (2008). Telomeres and frailty. *Mechanisms of Ageing and Development*, 129(11), 642-648.

Woods, N. F., LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Brunner, R. L., et al. (2005). Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society*, 53(8), 1321-1330.

Zaslavsky, O., Thompson, H., Demiris, G. (In Press). The role of emerging information technologies in frailty assessment. *Research in Gerontological Nursing*

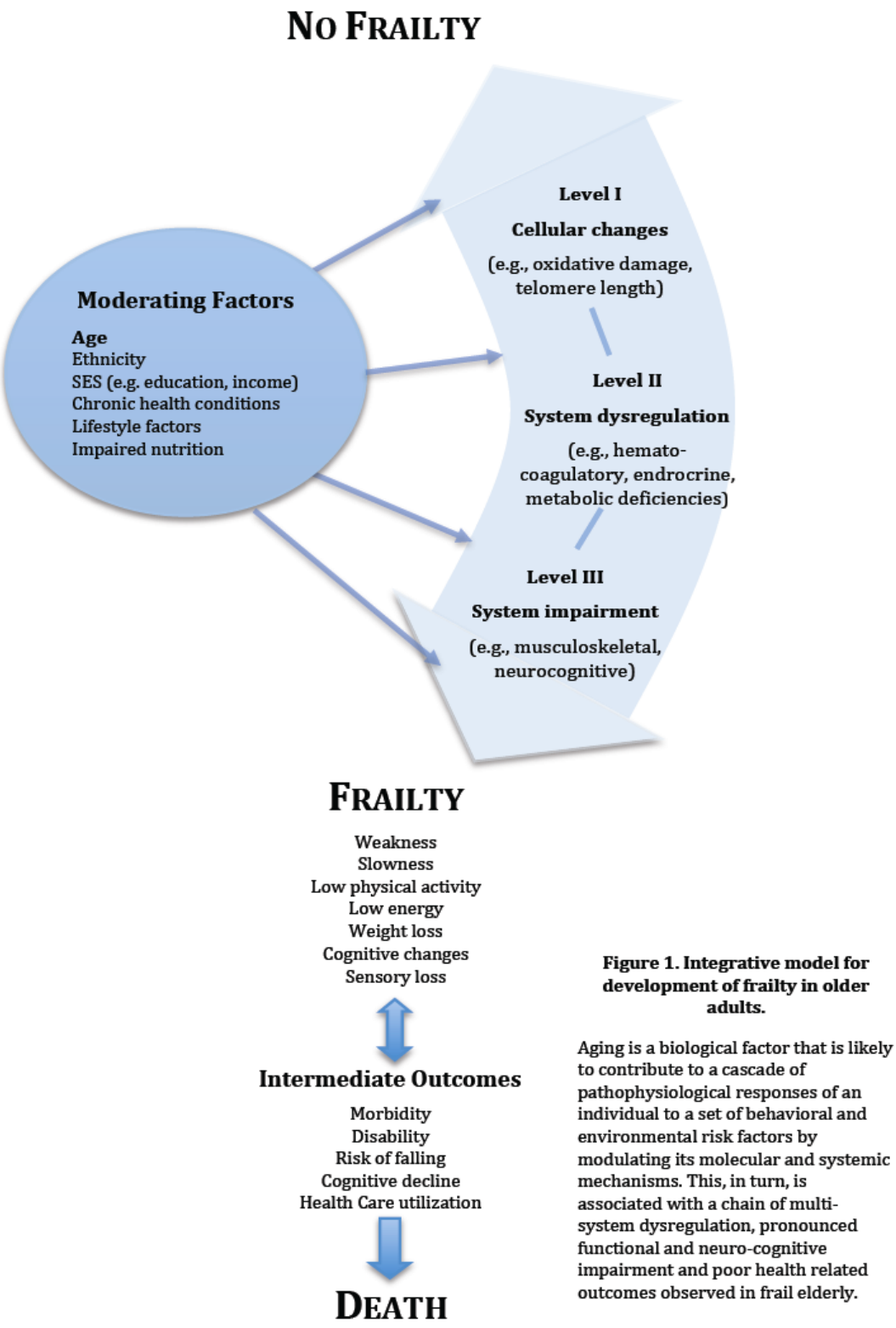

Figure 1. Integrative model for development of frailty in older adults.

Aging is a biological factor that is likely to contribute to a cascade of pathophysiological responses of an individual to a set of behavioral and environmental risk factors by modulating its molecular and systemic mechanisms. This, in turn, is associated with a chain of multi-system dysregulation, pronounced functional and neuro-cognitive impairment and poor health related outcomes observed in frail elderly.

CHAPTER III: Manuscript #2

"Application of Person-Centered Methodology in Nursing Research"

To be submitted to Nursing Research

Introduction

The importance of integrating health trajectory modeling into an arsenal of available methods for researchers in nursing has recently been highlighted (Henly, Wyman & Gaugler, 2011; Wyman & Henly, 2011). Scientists who are interested in modeling the longitudinal patterns of change in health over time, whether to better understand age-related normative dynamics or study unfolding pathophysiological processes, are often faced with a number of available analytical strategies. These strategies include, among others, analysis of variance (ANOVA), variable-centered models (e.g., hierarchical models, random effect models, growth curve models) or person-centered models (e.g., latent class growth modeling [Nagin 2005], growth mixture modeling [Muthen & Shedden, 1999]).

Despite the variety of available methods, current nursing research has been dominated by use of variable-centered approach. Based on the assumption that all individuals in the population follow a similar pattern of change, the variable-centered approach identifies the average longitudinal trajectory, estimates variability about the average, and explains that variability in terms of covariates of interest (Gelman & Hill, 2007; Singer & Willet, 2003). In statistical terms variable-centered methodologies model the population distribution of trajectories of change over time based on continuous distribution functions (Singer & Willet, 2003). However, clinical phenomena with high inter- and intra-individual variability (e.g., depressive symptoms, obesity, disabilities), demonstrate more of a multinomial pattern (Ferro, Avison, Campbell & Speechley, 2011; Gill, Gahbauer, Han & Allore, 2010; Liang, Bennett, Ye & Quinones, 2010; Mustillo et al.,

2003). In such circumstances, person-centered models will likely provide a better fit to the research question and to the data under investigation (Nagin & Odgers, 2010).

A detailed technical and mathematical overview of these models not the intent of this paper and can be found elsewhere (Muthen & Shedden, 1999; Nagin, 2005). Briefly, person-centered models belong to the class of finite mixture models, which were designed to analyze data comprised from a mixture of statistically heterogeneous groups (Nagin & Odgers, 2010). These models assume that the population is composed of a mixture of two or more groups whose longitudinal trajectories could be expressed by a distinct number of polynomial functions of time. Thus, the estimated group trajectories are used as a convenient statistical device to approximate and summarize an unknown but complex population distribution (Bauer & Curran, 2003).

There are some differences between person-centered Latent Class Growth Model (LCGM) and Growth Mixture Model (GMM) with regard to structural assumptions of a population curve. The former does not make any assumptions about a population's distribution, whereas the later assumes a distribution with a heterogeneic nature. That is, GMM assumes that the population curve consists of a mixture of normally distributed subgroups (Nagin & Odgers, 2010). In applied analysis the differences between these two approaches are best expressed as constraining within-class variability to zero among individuals composing a trajectory group in LCGM framework and allowing it to be freely estimated in GMM analysis.

Two important results of person-centered modeling - estimates of the shape of each class's trajectory and the size of the population belonging to each trajectory – can also be used to identify those factors that predict trajectory group membership or to estimate the effect of longitudinal class membership on proximal or distal outcomes. The

association between predictor variables and trajectory group membership is traditionally examined by specifying the probability of trajectory group membership to follow a multinomial logit model (Nagin, 2005). However, as we will further demonstrate, this specification could be easily extended to include ordinal models. The major benefit of using ordinal versus multinomial models is to minimize the proliferation of regression estimates and instead apply a hierarchical or ordered structure to the estimated longitudinal trajectories. Our discussion will focus on latent class growth models, given that their parsimony allows for a clearer interpretation; however, all models presented could be also estimated using GMM framework.

In nursing research, LCGM can be used to address many different types of research questions. First of all, they can identify distinctive and prototypical growth trajectories within target populations in variety of health conditions. These studies might range from distinct trajectories of disability in the last year of life (Gill, Ganbauer, Han, & Allore, 2010) to those concerning multiple patterns of change in physiological and psycho-emotional indicators (Payette, Gueye, Gaudreu, et al., 2011; Smith, Kupper, Jonge & Denollet, 2010; Smolderen, Aquarius, Vries, Smith, Hamming & Denollet, 2008). Secondly, LCGM provides a convenient framework for estimating the effects of interventions or individual-level characteristics (e.g., ethnicity, education, prior or current health behaviors, cognitive status) on the probability of belonging to a given trajectory. For example, Ferro and colleagues (2011) found that a child's cognitive function was the strongest predictor of a moderately-increasing form of depressive symptoms trajectory in mothers of children with newly diagnosed epilepsy. Finally, researchers who are interested in approximating the magnitude of risk carried by members of a cluster over time can use person- centered models to estimate the effect of membership in a growth trajectory on incidence of clinically relevant health outcomes (e.g., mortality, disability, hospitalization, falls).

The purpose of this article is to present the utility and real-data application of basic LCGM and its extensions using a large cohort of aging American women enrolled in the Women's Health Initiative Clinical Trial (WHI CT). The objectives in using this example are to demonstrate how a LCGM framework can describe longitudinal clustering of self-reported energy/fatigue levels in older women, relate membership in these longitudinal clusters to baseline characteristics (e.g., ethnicity, education, health status, behavior) and estimate the effect of their membership in a particular growth trajectory on the first incident hospitalization during five years of WHI Extension Study follow up. Energy/fatigue indicator was selected as a trajectory variable given that fatigue prevalence and incidence appear to increase with advancing age in addition to becoming increasingly recognized as a specific geriatric entity (Avlund, Damsgaard & Schroll, 2001; Moreh, Jacobs & Stessman, 2010; Vestergaard et al., 2009).

Methods

Design and Data

Data for this analysis came from the large WHI study. Details of the design, recruitment strategies, data collection methods, and tabulations of baseline data are available elsewhere (Anderson et al., 2003). In the present study we focused on data from women ages 65 years and older (at baseline) who enrolled in one or more of the WHI clinical trials and also consented to participate in the 2005-2010 Extension Study that followed-up on participants after study interventions were stopped. Of note, denominators of data collected over time changed considerably due to the protocol-defined data collection schedule that varied by measure (see Table1-data collection frequency table). In addition, stratified longitudinal sampling that stretched over five years (i.e., 1993-1998) resulted in delayed enrollment for a large proportion of women, thus limiting the possible

follow-up period. Therefore, among the 19,891 women included in our final sample, 19,645 women had data on energy/fatigue indicators at baseline; 18,750 had non-missing observations in year 1; 1391 women had non-missing data in year 3; 5,463 participants had non-missing data in year 6; and finally 14,228 subjects had non-missing measurements in year 9 (Table 2).

Measures

Energy/Fatigue Indicator (Trajectory variable)

Self-reported energy/fatigue was operationalized using four questions from the Medical Outcomes Study Short Form-36 (SF-36; Ware & Sherbourne, 1992). Participants were asked to consider how much time during the past four weeks they: a) felt full of pep; b) had a lot of energy; c) felt worn out; and d) felt tired. Possible responses ranged from "all the time"=1 to "none of the time"=6. The final index scores were coded on a 0 to 100 scale with higher values reflecting the more favorable health state and a score of 0 the least favorable. Energy/fatigue levels were assessed at baseline, year 1, and closeout in all CT participants, and additionally in years 3, 6, and 9 in a CT subsample (see data collection frequency table). Analyses presented here included a combined cohort of individuals who had energy/fatigue measurements collected during at least one of the data collection occasions.

Baseline Predictors

Comprehensive data on demographic, health behavior, health status, personality and social factors were collected using well-established self-report measures (Matthews, et al., 1997) at baseline (Table 3). Demographic characteristics included age, education and ethnicity. Age was used as a continuous variable in years. Education indicated the highest level of education completed and included three categories: highschool; college and

postgraduate education. Ethnicity was coded as a binary variable with non-white category =1. Health behavior questionnaire items - related to smoking, alcohol consumption, low fat diet, engagement in vigorous exercise at age 50 and leisure walking outside for more than 10 minutes - were assessed by self-report and coded as follows:

- Smoking: never smoker=0; past smoker=1; current smoker=2
- Alcohol Intake: continuous score representing the number of servings per week of beer, wine and/or liquor, based on a medium-serving size (12oz of beer, 6oz of wine and 1½ oz of liquor)
- Low fat diet: yes=1; no=0
- Vigorous exercise at age 50: yes=1; no=0
- Walling outside the home for more than 10 minutes without stopping: incrementally increasing in frequency of walking categorical ordinal scale with levels starting at 0=never or rarely walk outside to 5= walking outside seven or more times each week.

Comorbidities measured included: history of coronary heart disease, heart failure, stroke, diabetes mellitus, hypertension, arthritis, cancer, and hip fracture. Data on these conditions were collected by self-report and coded as 0= absence of a condition; 1= condition present. The codes were then summed up to calculate the total number of chronic conditions present.

General symptoms were assessed using a list of 34 symptom items measuring occurrence and severity of symptoms in the last four weeks. Symptoms included diarrhea, dizziness, hot flashes and tremors, among others. Scores ranged from 0 to 30, with a higher score indicating more symptoms.

Depression symptoms were assessed using a short form of the Center for Epidemiological Studies Depression scale (CES-D; Burnam, Wells, Leake, Landsverk, 1988). Scores ranged from 0 to 10, with a higher score indicating a greater likelihood of depression.

Sleep disturbance was assessed by self-report using the Insomnia Rating Scale (Levine et al., 2003), which included five items with a summary score ranging from 0 to 20. A higher score indicated greater sleep disturbance.

Personal traits included optimism measured using a six-item Life Orientation Test-Revised Scale (Scheier & Carver, 1985), with possible scores ranging from 6 to 30, and a higher score indicating greater optimism.

Environmental factors included negative life events assessed using an 11-item questionnaire from the Alameda County Study (Berkman & Syme, 1979). Scores ranged from 0 to 11 with a higher score indicating a greater number of negative life events.

Social support was assessed using nine items that asked respondents to indicate how often each of nine different types of support was available to them (Sherbourne & Stewart, 1991). Final scores ranged from 9 to 45, with a higher score indicating greater support.

Hospitalization (Outcome variable)

All 2005-2010 Extension Study participants completed annual medical history update forms in which they indicated the occurrence of any overnight hospitalization. This information was then used to obtain medical records for adjudication, first by a trained local physician adjudicator and then by a panel of central adjudicators. Outcomes information is currently available through March 31, 2011, for an average length of 13.01 years of total follow up. As of March 31, 2011, 5,547 out of 19880 women ages 65 and

older at baseline who were enrolled in the CT reported at least one overnight hospitalization during the 2005-2010 WHI Extension Study follow up.

Data Analysis

Defining trajectories

Analytic strategies began with a calculation of descriptive statistics (Tables 2-3). Skewness and kurtosis were calculated for the energy/fatigue index scores in addition to graphical examinations of the data using histograms and normal probability plots. Given that non-normally distributed data increase the probability of an over-extraction of spurious classes in the latent class growth framework, a square-root transformation was applied to improve normality for the trajectory variable (i.e., energy/fatigue) (Bauer & Curran, 2003).

We used person centered LCGM framework to identify relatively homogeneous clusters of individuals who followed similar trajectories of change in energy/fatigue index scores (Nagin, 2005; Nagin & Odgers, 2010). Trajectory parameters were estimated using maximum likelihood methods with the following specifications:

(Eq. 1) $\Upsilon_{it}^{g} = \beta_0^g + \beta_1^g * Time_{it} + \beta_2^g * Time_{it}^2 + \varepsilon_{it}; i = 1, \dots n$

Υ_{it}^{g} is a latent variable representing the underlying energy/fatigue status of the individual (*i*) at time (*t*) given membership in group (*g*). Time (*t*) refers to the time interval for data collection from baseline. $\beta_0^g, \beta_1^g, \beta_2^g$ are the coefficients associated with the intercept, linear and quadratic rate of change in energy/fatigue scores. ε_{it} is a time-specific disturbance term assumed to be normally distributed with a zero mean and constant variance.

Provided that the data were collected at five time points (i.e., baseline, year 1, 3, 6 and 9/closeout), a high-order polynomial function (i.e., quadratic) was fitted to the data. Through a process similar to that of latent class analysis (latent class analysis is a subset of structural equation modeling, used to find groups or subtypes of cases in multivariate categorical data), parameters were estimated to define the shape of the trajectories and the probability of trajectory group membership (Muthen & Shedden, 1999; Nagin, 2005). The number of clusters was chosen based on the following selection criteria: (1) interpretability; (2) theoretical justification; (3) parsimony; (4) lowest Bayesian Information Criteria (BIC) score; (5) non-significant Lo-Mendel-Rubin likelihood ratio test; (6) non-significant parametric bootstrapped likelihood ratio test; (7) Entropy>0.7; (8) average posterior probability in each class >0.75 and no more than 10% overlap/cross-membership between non-contiguous clusters; and (9) at least 2.5% of total count in each cluster. Of note, in the final selection process we preferred the most parsimonious and interpretable model, provided that the models under consideration were not distinctively different on other formal statistical criteria. Given the continuous nature of the energy/fatigue scores, a normal distribution function was fitted to the data. In order to ensure the most statistically efficient model, non-significant higher-order terms (i.e., quadratic) were removed and the model was re-specified until optimal fit was achieved (Table 4).

Estimating effects of the predictors on the trajectory group membership

To test the effect of predictors on trajectory group membership, individuals were assigned to their highest probability group, which was initially treated as a nominal dependent variable to be linked to predictors using multinomial logistic specification (Table 5):

(Eq.2) $\Pr(y_i = j|\, x_i) = \frac{exp^{x_i\beta_j}}{\Sigma_{j=1}^{J} exp^{x_i\beta_J}}$

Where β_j represents the parameter for a multinomial logit model that captures the effects of baseline covariates x_i (i.e., age, life events, sleep disturbances) on $\Pr(y_i = j|\, x_i)$, the probability of membership in trajectory group *j* (Nagin, 2005).

Alternatively, given that visual inspection of trajectory group dynamics (Figure 1) revealed a clearly ordered structure for the estimated longitudinal patterns, without noticeable points of inflection or intersections among trajectories, we recoded trajectory group assignment in an incrementally increasing (i.e., ordered) way so that that the lowest number would represent membership in the most vigorous trajectory group and the highest number would reflect membership in the most frail trajectory. This modification allowed us to use an ordered logit specification to test the effect of predictors on membership in increasingly more frail trajectories (Table 6):

Eq.3 $\Pr(y_i \geq j|\, x_i) = \frac{exp^{-\tau_i}}{1+exp^{-\tau_i}}$

Where $\Pr(y_i \geq j|\, x_i)$, is the probability of membership in trajectory group (*j*) or higher; and $-\tau_i$ represents estimated thresholds on the latent variable that is used to differentiate trajectory groups conditional on the effect of baseline covariates x_i (Long, 1997). It is important to note that the ordered logit model imposes an overly restrictive proportionality assumption that the multiplicative effect of covariates on the odds of being in a category *j* is the same for all *j*=0,1… *j*-1. This assumption is often violated, as was the case here, which is why we proceeded with fitting a less restrictive model, known as a partial proportional-odds model (Table 7). Conceptually speaking, partial proportional-odds models generate one set of estimates for those variables that do not violate parallel line assumptions and other category-specific estimates for those covariates that have distinctively different effects across levels of a categorical outcome (Williams, 2006).

Estimating the effects of a trajectory group membership on hospitalization

Finally, the last set of analyses was implemented using Cox proportional hazard models. Membership assignment served as a predictor of first incident overnight hospitalization during the WHI Extension Study in sequentially fitted models adjusted for the baseline variables (Table 8). In the analyses, the days from enrollment to death (or the last contact if no death occurred) were used as the censoring time for those participants without the target event (i.e., overnight hospitalization).

Partial proportional odds modeling and survival analyses were conducted using Stata 11 Software package (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). LCGM modeling was conducted with MPlus 6 software (Muthén & Muthén, 1998-2011). Full information maximum-likelihood estimation was used to integrate all available information based on missing at random assumptions for the outcome variables (i.e., frailty indicators) and list-wise deletion for the predictors (Muthén & Muthén, 1998-2011). To improve interpretability, all continuous predictors were centered on their means before fitting into regression models.

Results

Longitudinal Characteristics

Tables 2 and 3 include estimates of the mean, standard deviation and number of participants at each measurement occasion (baseline, years 1, 3, 6, and 9) for energy/fatigue scores and baseline distribution of the predictors.

Trajectories of Change

Although model fit scores improved with the addition of groups, we noticed a less dramatic change when going from a four- to five-trajectory model or higher (data not shown). Also, when models contained five or more trajectories, the average posterior probability of one or more of the trajectory groups reached as low as 68%, in addition to a

substantial overlap (i.e., cross-membership) between two or more non-contiguous clusters. Thus, based on an improvement in model selection criteria when comparing two- to three-trajectory models, including an adequate sample size in each of the estimated groups, reasonably good average posterior probabilities of trajectory group membership (range 0.81-0.87, mean 0.85), adequacy of interpretability and non significant likelihood ratio tests, we selected a four-trajectory model to represent the data.

Inspection of parameter estimates for the four-trajectory model revealed significant variation in the intercepts across groups. Three groups were best modeled with inclusion of a quadratic term to capture the slightly concave shape of the trajectory groups. One group *(Mid-Low Decliner)* required the inclusion of simple linear terms only (Table 4).

Figure 1 illustrates estimated longitudinal dynamics in the energy/fatigue index scores. To ease interpretation, we assigned labels to each of the derived trajectory groups such that the first word of a label represented an ordinal ranking of that trajectory's y-intercept relative to other groups (e.g., High, Medium, Low), and the second word indicated a direction of change over time (i.e., Decliner).

Almost a quarter of the sample (n=4725, 24%) fell into the lowest declining trajectory (*Low Decliner*). The second lowest trajectory included 35% (n=6976) of the sample and is described as *Mid-Low Decliner*. These women had a relatively steep rate of decline [Slope=-1.162, 95% CI= (-1.04 -1.26)]. The third and the largest trajectory (n=7206, 36%) described women who had a *Medium Declining* trajectory. The last trajectory included women with a *High Decliner* trajectory (n=985, 5%); these participants had relatively high and stable energy/fatigue levels during the first nine years of follow up with a slight degree of annual decline.

Predictors of Trajectory Group Membership

Predictors of membership in the energy/fatigue trajectories were initially examined with multinomial logistic regression. Odds ratios (OR) using the *High Decliner* group as the reference category are summarized in Table 5.

Briefly, *the Medium Decliner* group was more educated; had a higher number of chronic conditions, general symptoms and sleep disturbances; had lower levels of optimism; and also was less engaged in vigorous exercise at age 50 or leisure walking at WHI baseline. The *Mid-Low Decliner* group was older and predominantly white; had more education; had a higher number of chronic conditions, general and depression symptoms; had a higher prevalence of sleep disturbances; had lower levels of optimism; was less engaged in vigorous exercise at age 50 or leisure walking; had lower alcohol consumption; and also had less social support. Finally, the *Low Decliner* group was older and predominantly white; had more education; had a higher number of chronic conditions, general and depression symptoms; had a higher prevalence of sleep disturbances; had lower levels of optimism; was less engaged in vigorous exercise at age 50 or leisure walking; had lower alcohol consumption; and also had less social support than the reference group (i.e., *High Decliner*).

Table 6 presents the results of the fitted ordered logit regression, explaining the effect of predictors on orderly, structured trajectories of the energy/fatigue index scores. The effects are presented as Odds Ratios (ORs). This means that we compared the women who were in trajectory groups greater than *j* versus those who were in groups less than or equal to *j*, where *j* is the level of the outcome variable. ORs greater than 1 reflected increased odds of being in the frailer trajectories of the energy/fatigue index scores than the comparison category and ORs less than 1 reflected decreased odds. For example, for a 1-unit increase in the general symptoms score, the odds of being in the *Low Decliner* trajectory rather than the combined *High, Medium* and *Mid-Low Decliner* trajectories were 1.51 greater (95% CI=1.48-

1.53) than in those who do not exhibit such a trait, when all other variables were held constant. Given the proportionality assumption, a similar interpretation is valid regardless of the selected reference category. Comparing multinomial and order logit outputs, we observed consistency in estimating directionality of the effects. For instance, having a college degree, a higher number of chronic conditions and general symptoms, presence of sleep disturbances, engagement in leisure walking and exercise at age 50 and a higher optimism scores were consistent and significant predictors of membership in longitudinal trajectories in both models. Of note, the magnitude of the effects tended to be higher in the multinomial model than those used in the proportional odds model, presumably due to a more granular interpretation of the estimates. Further, fitting a partial proportional odds model, as shown in Table 7, provided additional granularity to the specified model, revealing clinically meaningful information that was obscured in the proportional odds model. For example, analyses showed that higher general symptoms scores were consistently associated with membership in frailer trajectories of the energy/fatigue index score, but the greatest effect was in differentiating between the most functionally vigorous trajectory (i.e., *High Decliner*) and the combination of all other more frail trajectories (OR=2.05; 95% CI=1.92-2.19).

Outcomes of Trajectory Group Membership

A total of 5,547 women reported at least one incident hospitalization during the WHI Extension Study follow up: 17.9% of these women were in the *High Decliner* trajectory, 23.0% in the *Medium Decliner* trajectory group, 29.1% in the *Mid-Low Declining* trajectory cluster, and 35.5% in the *Low Declining* trajectory (Table 8). In the partially-adjusted model, those who were in the *Low Declining* trajectory were approximately twice as likely to report a first incident hospitalization during the WHI Extension Study as *High Decliner* group members (HR=2.25; 95% CI=1.92-2.63). Final multivariate adjustment slightly attenuated these results. The fully-adjusted model showed that membership in the

Medium, Mid-Low and *Low Declining* trajectories carried a statistically significant additional risk of hospitalization (28%, 50% and 66%, respectively) compared with the *High Decliner* reference group.

Discussion

The purpose of this article is to provide a step-by-step example of the utility of LCGM framework and its extensions. Four distinct trajectories of energy/fatigue scores were identified during the first nine years of follow up of women 65 years and older in the WHI. The number of trajectories in this sample was similar to several longitudinal patterns identified in other studies (Gill, Gahbauer, Han, Allore, 2010; Liang, Xu, Bennett, Ye & Quinones, 2010) using similar methodology. Although taken together these findings suggest that there is substantial heterogeneity among aging individuals with regard to functional and energy level indicators, a number of major categories of indicators could additionally be distinguished in concordance with related discussions of variability in normal aging, successful aging and pathological aging (Fried et al., 2001; Rowe & Kahn, 1997; Woods et al., 2012). It is also important to acknowledge the prospective nature of these findings; indicating, for example, that the most vigorous individuals (i.e., those in *High Decliner* trajectory) did not merely have elevated energy levels at baseline but sustained fairly high vitality for up to nine years of follow up.

In line with other studies (Avlund, Damsgaard & Schroll, 2001; Moreh, Jacobs & Stessman, 2010; Vestergaard et al., 2009), this analysis showed that fatigue was closely linked to age, socio-demographic factors, comorbidities, health behaviors and poor sleep quality. However, contrary to previous published work, we demonstrated that in fully adjusted models additional factors such as optimism and social support had significant positive and independent effects on the likelihood of membership in vigorous trajectories

of energy/fatigue index scores. These findings were consistent regardless of the methodological framework used, and they hold promise for developing behavioral interventions to help the elderly maintain optimal levels of energy throughout the aging process.

Similar to other studies (Avlund, Damsgaard & Schroll, 2001), we demonstrated that energy/fatigue levels (i.e.,"tiredness") predicted future hospitalization in non-disabled elderly. However, in contrast to other prospective studies that measured the association between such distal outcomes (e.g., hospitalization, mortality) and cross-sectional distribution of predictors, the LCGM framework enabled us to capture subtle longitudinal dynamics in energy/fatigue scores over a relatively long follow up and relate these levels to a clinically relevant outcome. In this way consideration of trajectory groups can be as a tool for empirical partitioning of a population curve into clinically and statistically distinct longitudinal clusters. This application is especially useful, given that investigators frequently use more subjective categorization criteria such as tertiles and quintiles, as well as other *a priori* assumptions to assign individuals into different clinical categories. Although such a subjective categorization is methodologically reasonable, it has one major weakness, in that it provides no basis for calibrating the precision of an individual's classification into a particular category. In other words, when using traditional (i.e., variable-centered) methodology, we cannot quantify a category assignment in terms of probabilities. In contrast, the LCGM-based analysis presented here supports an empirical statement that there is a 24% chance that randomly selected woman age 65 years old and older who participated in WHI CT will demonstrate an energy/fatigue-related longitudinal trend similar to that found in the *Low Decliner* group. Similar claims would be challenging to make using traditional variable-centered framework.

One of the particular limitations of this analysis should be considered. Older women with low energy/fatigue levels presumably were less likely to complete as many occasions of follow up as women who did not exhibit such traits. If that is the case, then the proportion of older women at risk of being in low-energy/fatigue levels trajectories may be misrepresented. However, the main aim of the analyses presented here was to describe the heterogeneity in energy/fatigue scores rather than estimating its prevalence. The LCGM framework can serve as a convenient analytic approach for outlining longitudinal patterns occurring in the population. In addition, LCGM successfully integrates full-information, maximum-likelihood techniques that generate consistent estimates when missing-at-random assumptions hold (Muthén & Muthén, 1998-2011). In the analyses presented here, delayed enrollment, flexible data collection protocol, and sparsely-scheduled measurement occasions resulted in a large proportion of missing observations.

Conclusion

Researchers in nursing can benefit from using person-centered methodologies. The estimates (i.e., trajectory functions and membership probabilities) from these basic analytic techniques could be easily used to identify those factors that predict trajectory group membership and to approximate the magnitude of risk carried by membership in certain longitudinal clusters. The association between predictors and trajectory group membership could be specified using either a traditional multinomial framework or an alternative categorically-ordered specification, provided that the estimated longitudinal patterns show clear ordered structure. Sensible application of either model generates comparable estimates. However, to ensure the most parsimonious and statistically justifiable model (i.e., the model that does not violate parallel-line assumptions), a partial proportional odds model should be used. The latter provides a detailed output that is easily interpreted. Finally, either discrete- or continuous-time survival analyses can be

readily fit to the data to approximate the magnitude of risk that is carried by membership in particular longitudinal clusters.

In summary, person-centered methods provide unique opportunities to explore and statistically model the effects of longitudinal heterogeneity within a population. This methodology needs to be more fully integrated into nursing research analyses.

References:

Anderson, G. L., Manson, J., Wallace, R., Lund, B., Hall, D., Davis, S., et al. (2003). Implementation of the Women's Health Initiative study design. *Annals of Epidemiology, 13*(9 Suppl), S5-17.

Avlund, K., Damsgaard, M. T., & Schroll, M. (2001). Tiredness as determinant of subsequent use of health and social services among nondisabled elderly people. *Journal of Aging and Health, 13*(2), 267-286.

Bauer, D. J., & Curran, P. J. (2003). Distributional assumptions of growth mixture models: implications for overextraction of latent trajectory classes. *Psychol Methods, 8*(3), 338-363.

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology, 109*(2), 186-204.

Burnam, M. A., Wells, K. B., Leake, B., & Landsverk, J. (1988). Development of a brief screening instrument for detecting depressive disorders. *Medical Care, 26*(8), 775-789.

Ferro, M. A., Avison, W. R., Campbell, M. K., & Speechley, K. N. (2011). Prevalence and trajectories of depressive symptoms in mothers of children with newly diagnosed epilepsy. *Epilepsia, 52*(2), 326-336.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., et al. (2001). Frailty in older adults: evidence for a phenotype. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 56*(3), M146-156.

Gelman, A., & Hill, J. (2007). *Data analysis using regression and multilevel/hierarchical models: analytical methods for social research*: Cambridge University Press; New York, USA.

Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2010). Trajectories of disability in the last year of life. *New England Journal of Medicine, 362*(13), 1173-1180.

Henly, S. J., Wyman, J. F., & Gaugler, J. E. (2011). Health trajectory research: a call to action for nursing science. *Nursing Research, 60*(3 Suppl), S79-82.

Levine, D. W., Kripke, D. F., Kaplan, R. M., Lewis, M. A., Naughton, M. J., Bowen, D. J., et al. (2003). Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. *Psychological Assessment, 15*(2), 137-148.

Liang, J., Xu, X., Bennett, J. M., Ye, W., & Quinones, A. R. (2010). Ethnicity and changing functional health in middle and late life: a person-centered approach. *Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 65*(4), 470-481.

Long, J. Scott (1997). *Regression Models for Categorical and Limited Dependent Variables*: Thousand Oaks, CA: Sage.

Matthews, K. A., Shumaker, S. A., Bowen, D. J., Langer, R. D., Hunt, J. R., Kaplan, R. M., ….. (1997). Women's health initiative. Why now? What is it? What's new? *American Psychologist, 52*(2), 101-116.

Moreh, E., Jacobs, J. M., & Stessman, J. (2010). Fatigue, function, and mortality in older adults. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 65*(8), 887-895.

Mustillo, S., Worthman, C., Erkanli, A., Keeler, G., Angold, A., & Costello, E. J. (2003). Obesity and psychiatric disorder: developmental trajectories. *Pediatrics, 111* (4 Pt 1), 851-859.

Muthén, L. K., & Muthén, B. O. (1998-2011). Mplus User's Guide (6th Ed.). Los Angeles, CA: Muthén & Muthén.

Muthen, B., & Shedden, K. (1999). Finite mixture modeling with mixture outcomes using the EM algorithm. *Biometrics, 55*(2), 463-469.

Nagin, D. S. (2005). *Group-Based Modeling of Development* Harvard University Press.

Payette, H., Gueye, N. R., Gaudreau, P., Morais, J. A., Shatenstein, B., & Gray-Donald, K. (2011). Trajectories of Physical Function Decline and Psychological Functioning: The Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge).

Journals of Gerontology. Series B, Psychological Sciences and Social Sciences, 66 Suppl 1, i82-i90.

Rowe, J. W., & Kahn, R. L. (1997). Successful aging. *Gerontologist, 37*(4), 433-440

Scheier, M. F., & Carver, C. S. (1985). Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psychology, 4*(3), 219-247.

Sherbourne, C. D., & Stewart, A. L. (1991). The MOS social support survey. *Social Science and Medicine, 32*(6), 705-714.

Singer, J. D., & Willet, J. B. (2003). *Applied longitudinal data analysis.* Oxford University Press; New York, USA.

Smith, O. R., Kupper, N., de Jonge, P., & Denollet, J. (2010). Distinct trajectories of fatigue in chronic heart failure and their association with prognosis. *European Journal of Heart Failure, 12*(8), 841-848.

Smolderen, K. G., Aquarius, A. E., de Vries, J., Smith, O. R., Hamming, J. F., & Denollet, J. (2008). Depressive symptoms in peripheral arterial disease: a follow-up study on prevalence, stability, and risk factors. *Journal of Affective Disorders, 110*(1-2), 27-35.

Vestergaard, S., Nayfield, S. G., Patel, K. V., Eldadah, B., Cesari, M., Ferrucci, L., et al. (2009). Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 64*(1), 76-82.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care, 30*(6), 473-483.

Williams, R (2006). Generalized Ordered Logit/Partial Proportional Odds Models for Ordinal Dependent Variables. *The Stata Journal 6*(1), 58-82.

Woods, N. F., Cochrane, B. B., Lacroix, A. Z., Seguin, R. A., Zaslavsky, O., Liu, J., et al. (2012). Toward a positive aging phenotype for older women: observations from the

women's health initiative. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*.

Wyman, J. F., & Henly, S. J. (2011). Advancing nursing science through health trajectory research: an introduction. *Nursing Research, 60*(3 Suppl), S1-4.

Table 1. Frequency of data collection occasions of energy/fatigue index in Women's Health Initiative Clinical Trial

	Baseline	**Year 1**	**Year 3**	**Year 6**	**Year 9**	**Closeout**
Measure:						
Energy/fatigue index scores	X	X	%	%	%	X

%- Percentage (subsample) of participants

X - All participants

Table 2. Energy/fatigue indicators at 5-time points in WHI CT Cohort (N=19891): Mean (SD)

Variables	Baseline n=19,645	Year 1 n=18,750	Year 3 n=1,391	Year 6 n= 5,463	Close out / Year 9 n=14,228
Energy/Fatigue[a]	45.38 (21.38)	45.93 (22.4)	43.94 (22.17)	38.98 (22.25)	37.74 (21.86)

Notes: [a] Original variables were transformed by squaring and dividing by 10

Table 3. Descriptive Statistics of Baseline predictors in WHI CT Cohort (N=19891): Data are reported as Mean (SD) for continuous variables; percentage (n) for categorical outcomes.

Variables	**Baseline**
Age	69.5 (3.5)
Ethnicity	
White	88.08% (17,519)
Education	
High school	36.9% (7,346)
College	37.9% (7,538)
Postgraduate	24.7% (4,907)
Health behaviors	
Smoking:	
Never smoked	54.45% (10,831)
Past Smoker	39.8% (7,916)
Current Smoker	4.67% (928)
Alcohol Serving per week	2.25 (4.47)
Low fat diet	33.47% (6,657)
Walking Outside:	
Rarely or never	17.9% (3,567)
1-3 times each month	15.04% (2,991)
1 time each week	10.9% (2,169)
2-3 times each week	27.88% (5,546)
4-6 times each week	20.7% (4,122)
7 or more times each week	7.09% (1,410)
Hard exercise at age 50	37.38% (7,435)

Health Status	
Number of Chronic Conditions	1.52 (1.3)
Severity of General Symptoms	0.4 (0.24)
Severity of Sleep Disturbances	6.73 (4.36)
Severity of Depression symptoms	0.026 (0.097)
Psychological Environmental and Social factors	
Optimism	23.4 (3.2)
Negative Life Event	3 (2.9)
Social Support	36.06 (7.6)

Table 4. Parameter estimates for the 4-group trajectory model of self-reported energy/fatigue index scores[a] at 5 measurement occasions (baseline, years 1, 3, 6 and 9); N=19892

Group	% Sample	Parameter	Estimate	Standard Error
High Decliner	5	Intercept	80.655	1.082
		Linear	1.048	0.391
		Quadratic	-0.207	0.043
Medium Decliner	36	Intercept	61.323	0.525
		Linear	0.127	0.186
		Quadratic	-0.15	0.021
Mid-Low Decliner	35	Intercept	41.72	0.833
		Linear	-1.162	0.062
Low Decliner	24	Intercept	20.665	0.451
		Linear	-1.092	0.171
		Quadratic	0.086	0.019
Residual Variances	Baseline		152.12	2.608
	Year 1		154.189	2.794
	Year 3		161.007	10.122
	Year 6		206.583	6.072
	Year 9		231.191	4.456

[a] Original variables were transformed by squaring and dividing by 10

Figure 1. Estimated trajectories of energy/fatigue index scores during 9 years of follow up

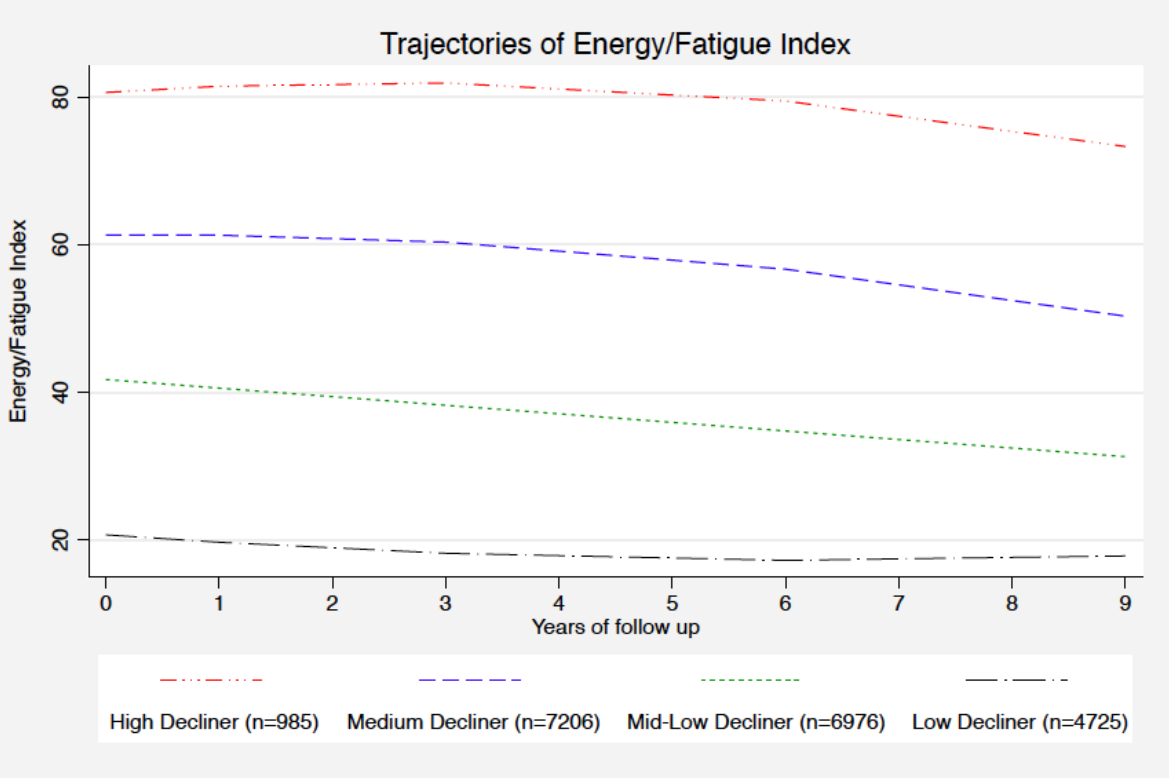

Table 5. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Multinomial Logistic Regression of Energy/Fatigue index scores. The model estimates the effect of predictors on a likelihood of being in High Decliner versus Moderate Decliner, Mid-Low Decliner, and Low Decliner Trajectory Groups, WHI CT cohort (N= 15811)

Baseline Characteristics	High Decliner vs. Medium Decliner OR (95% CI)	High Decliner vs. Mid-Low Decliner OR (95% CI)	High Decliner vs. Low Decliner OR (95% CI)
Age	1.00 (0.98-1.03)	1.03 (1.01-1.06)**	1.05 (1.02-1.07)**
Non-white	0.77 (0.59-1.01)	0.66 (0.49-0.87)**	0.44 (0.33-0.60)***
College[a]	1.24 (1.03-1.49)*	1.28 (1.05-1.56)*	1.39 (1.13-1.72)**
Postgraduate[a]	1.44 (1.17-1.77)***	1.43 (1.16-1.78)**	1.47 (1.17-1.86)**
Number of Chronic Conditions	1.10 (1.02-1.18)*	1.32 (1.23-1.42)***	1.61 (1.48-1.74)***
General Symptoms	1.85 (1.73-1.99)***	2.55 (2.37-2.75)***	3.36 (3.10-3.59)***
Depression Symptoms	1.42 (0.89-2.26)	1.6 (1.01-2.55)*	1.88 (1.18-2.99)**
Sleep Disturbances	1.05 (1.02-1.07)***	1.09 (1.07-1.12)***	1.12 (1.09-1.15)***
Smoking	0.93 (0.81-1.07)	0.98 (0.85-1.13)	0.97 (0.83-1.13)
Alcohol consumption	0.99 (0.97-1.00)	0.97 (0.95-0.99)***	0.96 (0.95-0.98)***
Low fat diet	0.99 (0.83-1.17)	0.94 (0.79-1.13)	0.89 (0.74-1.08)
Walking outside	0.92 (0.87-0.97)**	0.82 (0.77-0.86)***	0.70 (0.66-0.74)***
Exercise at age 50	0.74 (0.63-0.87)***	0.59 (0.50-0.69)***	0.49 (0.41-0.58)***
Negative life events	1.01 (0.97-1.04)	1.02 (0.98-1.05)	0.99 (0.95-1.03)
Optimism	0.90 (0.88-0.93)***	0.84 (0.82-0.87)***	0.79 (0.76-0.81)***
Social support	0.99 (0.98-1.01)	0.98 (0.97-0.99)***	0.95 (0.94-0.97)***

Notes: All variables were entered simultaneously into the multinomial logistic model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi2_{(48)}$ = 7308.51, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables. Reference category: High Decliner

*p < .05; **p < .01; ***p < .001.

[a] – Reference category: high school

Table 6. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from an Ordered Logistic Regression. The model estimates the effect of predictors on ordered trajectories of energy/fatigue index scores. WHI CT cohort (N= 15811)

Baseline Characteristics	OR (95% CI)
Age	1.03 (1.02-1.04)***
Non-white	0.71 (0.64-0.79)***
College[a]	1.10 (1.02-1.18)*
Postgraduate[a]	1.07 (0.99-1.16)
Number of Chronic Conditions	1.28 (1.25-1.32)***
General Symptoms	1.51 (1.48-1.53)***
Depression Symptoms	1.18 (1.13-1.24)***
Sleep Disturbances	1.05 (1.04-1.06)***
Smoking	1.03 (0.97-1.08)
Alcohol consumption	0.98 (0.98-0.99)***
Low fat diet	0.93 (0.88-0.99)*
Walking outside	0.84 (0.82-0.86)***
Exercise at age 50	0.74 (0.69-0.79)***
Negative life events	0.99 (0.98-1.01)
Optimism	0.91 (0.89-0.92)***
Social support	0.98 (0.97-0.98)***
Threshold (1)	-4.38 (-4.50 -4.26)
Threshold (2)	-1.20 (-1.29 -1.11)
Threshold (3)	0.94 (0.85 1.03)

Notes: All variables were entered simultaneously into the ordered logistic model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi2_{(16)}$ = 7074.69, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables. WHI-Women's Health Initiative

*p < .05; **p < .01; ***p < .001.

[a] – Reference category: high school

Table 7. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of energy/fatigue index scores. WHI CT cohort (N= 15811)

Baseline Characteristics	Constant components of odds ratio across trajectories OR (95% CI)	High Decliner vs. Medium, Mid-Low, Low Decliner OR (95% CI)	High, Medium Decliner vs. Mid-Low, Low Decliner OR (95% CI)	High. Medium, Mid-Low Decliner vs. Low Decliner OR (95% CI)
Age	1.03 (1.02-1.04)***			
Non-white	0.72 (0.65-0.80)***			
College[a]	1.09 (1.02-1.18)**			
Postgraduate[a]		1.31 (1.10-1.55)**	1.05 (0.96-1.15)	1.03 (0.93-1.15)
Number of Chronic Conditions	1.28 (1.25-1.31)***			
General Symptoms		2.05 (1.92-2.19)***	1.52 (1.48-1.55)***	1.45 (1.42-1.49)***
Depression Symptoms	1.20 (1.15-1.25)***			
Sleep Disturbances	1.05 (1.04-1.06)***			
Smoking	1.02 (0.97-1.08)			
Alcohol consumption	0.98 (0.97-0.99)***			
Low fat diet	0.93 (0.87-1.00)			
Walking outside	0.84 (0.82-0.86)***			
Exercise at age 50	0.74 (0.70-0.79)***			
Negative life events		1.00 (0.97-1.05)	1.00 (0.99-1.01)	0.98 (0.97-0.99)*
Optimism	0.91 (0.90-0.92)***			
Social support	0.98 (0.97-0.99)***			

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi2_{(22)}$ = 7210.87, $\rho<0.001$. ORs< 1 denotes benefit for continuous and categorical variables. Reference category: High Decliner

*p < .05; **p < .01; ***p < .001. [a] – Reference category: high school

Table 8. Relative hazard of first Incidence of hospitalization by membership in longitudinal trajectory groups of energy/fatigue index scores

		Hazard Ratio (95% CI)	
Trajectory group	Hospitalization n (%)	Model 1[a] (n=19880)	Model 2[b] (n=15811)
High Decliner	177 (17.99)	1.00 (reference)	1.00 (reference)
Medium Decliner	1658 (23.02)	1.31 (1.12-1.53) **	1.28 (1.07-1.53) **
Mid-Low Decliner	2031 (29.13)	1.73 (1.49-2.02) ***	1.50 (1.25-1.80) ***
Low Decliner	1675 (35.48)	2.25 (1.92-2.63) ***	1.66 (1.37-2.01) ***

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic comorbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

** $p < .01$; *** $p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

CHAPTER IV: Manuscript #3

"Longitudinal Dynamics in Frailty Indicators: Predictors and Long-Term Outcomes"

To be submitted to the Journal of Gerontology: Medical Sciences

Introduction

Frailty is a common geriatric condition with a wide array of sequelae, including increased risks of mortality, morbidity, disability, cognitive decline and health care utilization (Bandeen-Roche et al., 2006; Boyle, Buchman, Wilson, Leurgans, & Bennett, 2010; Ensrud et al., 2007; Fried et al., 2001; Rochat et al., 2010; Woods et al., 2005). Despite its long conceptual and operational history in research and publications, frailty and mechanisms of frailty development are still poorly understood. Several screening models have been proposed to objectively measure the severity of the frailty process and to assess its long-term consequences in clinical and community settings (Fried, et al., 2001; Ensrud, et al., 2009; Rockwood, et al., 2007). Each model incorporates a distinct set of biological dimensions (e.g., musculoskeletal, neuro-cognitive and psycho-emotional) and physiological indicators (Zaslavsky, Demiris, & Thompson, 2012). The most widely used operational definition of frailty includes indicators of sarcopenia, body composition change and energy level impairment (Fried et al., 2001). Of note, in addition to these "conventional" criteria, we have suggested extending Fried's working definition of frailty by also including indicators of neurosensory loss (i.e., cognition, changes in vision) (Zaslavsky et al., in press). Although most frail older adults develop age-related deficits affecting multiple biological systems, their clinical outcomes are not universally poor and fluctuate widely in severity even among individuals sharing the same level of frailty initially (Gill, Gahbauer, Allore, & Han, 2006). In longitudinal studies of frailty to date, investigators have used gender-specific cutoff points for each of the frailty indicators, based on their distributions within a particular sample at baseline, and then applied the cutoffs to determine frailty status at a later time-point (Fried, et al., 2001; Woods, et al., 2005). As a result, frailty indicators have been analyzed as predictors of health outcomes, based on a "snap shot" of their distributions, and defined as the lowest quintile of functioning. Such definitions yield results that are inherently linked to the timing of the measurements and to

the unique characteristics of the sample, which challenges generalization of the findings beyond the examined cohort and fails to capture the longitudinal course of indicators during the follow up period. In addition, a reliance on distribution-based single-occasion thresholds is conceptually misleading, particularly when frailty is defined as a process of gradual decline in resilience over time rather than merely a static condition.

A detailed description of trajectories of frailty indicators could provide vital insight on unfolding longitudinal dynamics involved in the development of frailty. Furthermore, such longitudinal modeling might help to identify those older adults who experience significant decline in frailty criteria but never cross below a pre-defined threshold that is associated with adverse outcomes. From a clinical perspective, there are a number of benefits to identifying potentially modifiable risk factors that predict the likelihood of belonging to a particular trajectory group. First, given that clusters of risk factors often occur, health care providers might more efficiently allocate resources for those older adults at highest risk of adverse outcomes, particularly for those with subtle initial changes in frailty indicators. Secondly, prognostic knowledge might inform the design and application of a tailored care approach to frailty management; that is, to match the intensity of treatment and modality to the type and stage of this geriatric syndrome. Next, elucidation of modifiable risk factors for adverse outcomes may yield targets for innovative approaches to treatment, which is important given the modest effect sizes for current therapies (Gray et al., 2009; LaCroix et al., 2008). Finally, trajectory modeling might provide clinically meaningful information on the magnitude of risk associated with membership in a longitudinal cluster with regard to incidence of health outcomes (e.g., mortality, disability, hospitalization, falls). This last set of analyses can also be used as a convenient statistical tool for empirical partitioning of a population curve into a number of distinctly different longitudinal clusters; each of these clusters, in turn, would represent a data-driven threshold for frailty criteria.

Based on the above, the specific aims of this paper are to:

1. Describe longitudinal (~10 years) trajectories of change in musculoskeletal and neuro-cognitive indicators of frailty in older (>/=65 years) women enrolled in the Women's Health Initiative Clinical Trial.
2. Estimate the extent to which baseline factors (e.g., demographic characteristics, health status and behaviors) conjointly are associated with a likelihood of membership in the derived longitudinal clusters.
3. To determine the extent to which membership in longitudinal trajectories predicts the incidence of clinically relevant geriatric health outcomes (i.e., mortality and hospitalization) over 5 years of follow up (2005-2010 WHI Extension Study) in a model adjusted for all other baseline predictors.

Methods

Design and Data

Data for these analyses came from the WHI study, which included three randomized controlled clinical trials (CTs). Details of the design, recruitment strategies, data collection methods, and tabulations of baseline data have been reported elsewhere (Anderson et al., 2003). In the present study we focused on data from women ages 65 years and older (at baseline) who enrolled in one or more of the CTs and also consented to participate in 2005-2010 Extension Study (ES). The final sample included 19,891 women. Of note, the number of available observations at each occasion for each frailty criteria changed considerably mainly due to a protocol-defined data collection schedule that varied by measure (as outlined in Tables 1-2)

Measures

Frailty Indicators

Performance-based tests: Physical performance indicators assessed musculoskeletal capacity at baseline and years 1, 3, 6, and 9 in a 25% subsample of CTs participants. The

tests included grip strength, chair stand, and timed walk, all of which have good validity and reliability (Onder et al., 2002; Ostir et al., 2002). Two trials were conducted for each measure and scored as the average of the two trials. The timed-walk involved using a stopwatch to measure the number of seconds from start to when the first foot completely crossed the end line of a 6-meter course, using a normal walking pace; the analytic variable was calculated in seconds. Participants could use ambulatory aids as needed. The chair-stand test involved counting the number of times in 15 seconds that a participant could stand up from a straight-back, armless chair without using her arms. The grip-strength measure involved use of a handgrip dynamometer (JAMAR, Lafayette Instrument Co., Lafayette, IN) with the dominant arm. Measurement was recorded to the nearest kilogram, rounding up for both trials.

Self-reported energy/fatigue index was operationalized using four questions from the Short Form 36 Health Survey (SF-36; Ware & Sherbourne, 1992). The participants were asked to consider how much time during the past four weeks that they: a) felt full of pep; b) had a lot of energy; c) felt worn out; and d) felt tired. Possible responses ranged from "all the time"=1 to "none of the time"=6. The final scores were coded on a 0-to-100 scale with higher values reflecting the more favorable health state and a score of 0 the least favorable. Energy/fatigue levels were assessed at baseline, year 1, and closeout in all CT participants, and additionally in years 3, 6, and 9 in a subsample of CT participants (see Table 1- data collection frequency table).

Physical activity index was assessed by self-report and collected at baseline, years 1, 3, 6, and 9 in all CT participants. A final calculated score represented total expenditure of energy (in Metabolic Equivalent of Tasks; METs) from recreational physical activity, including walking and mild, moderate, and strenuous physical activity.

Cognitive function index was assessed at baseline and years 1, 3, 6, and 9 only in Hormone Therapy participants (65 years and over), using the 18-item Modified Mini Mental Status Scale (MMMS) (Cockrell and Folstein, 1988).

Vision impairment index was assessed with a self-report symptoms checklist at baseline, year 1, and closeout in all CT and additionally in years 3, 6, and 9 in a CT subsample. Women were asked how bothersome the symptom was during the past four weeks. Each item was coded as symptom did not occur (0) to symptom was severe (3).

Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, measured using standardized techniques and equipment and rounded up to the nearest 0.10 kg and 0.10 cm, respectively. These measurements were collected annually in all CT participants.

Baseline Predictors

Comprehensive data on demographic, health behavior and status, personality and social factors were collected using well-established self-report measures (Matthews, et al., 1997) at baseline, as outlined in Table 3. Demographic characteristics included age, education and ethnicity. Age in years was used as a continuous variable. Education indicated the highest level of education completed and included three categories: high school; college and postgraduate education. Ethnicity was coded as a binary variable with non-white category =1. Health behavior questionnaires included items related to smoking, alcohol consumption, low fat diet, engagement in vigorous exercise at age 50 and leisure walking outside for more than 10 minutes, were assessed by self-report and coded as follows:

- Smoking: never smoker=0; past smoker=1; current smoker=2
- Alcohol Intake: continuous score representing a number of servings per week of beer, wine and/or liquor based on a medium serving size which is 12oz of beer, 6oz of wine and 1½ oz of liquor
- Low fat diet: yes=1; no=0

- Vigorous exercise at age 50: yes=1; no=0
- Walking outside the home for more than 10 minutes without stopping: incrementally increasing in frequency of walking categorical ordered scale with levels starting at 0=never or rarely walk outside to 5= walking outside seven or more times each week.

Comorbidity measures included: history of coronary heart disease, heart failure, stroke, treated diabetes mellitus, hypertension, arthritis, cancer, and hip fracture. Data on these conditions were collected by self-report and coded as 0= absence of a condition; 1= condition present. The codes were then summed to calculate the total number of chronic conditions present at baseline.

General symptoms were assessed using a list of 34 symptom items that measured the occurrence and severity of symptoms in the last four weeks. Symptoms included diarrhea, dizziness, hot flashes and tremors, among others. Scores ranged from 0 to 30, with a higher score indicating more symptoms.

Depression symptoms were assessed using the short form of the Center for Epidemiological Studies Depression scale (CES-D; Burnam, Wells, Leake & Landsverk, 1988). Scores ranged from 0 to 10, with a higher score indicating a greater likelihood of depression.

Sleep disturbance was assessed by self-report on the Insomnia Rating Scale (Levine et al., 2003), which included five items with a summary score ranging from 0 to 20. A higher score indicated greater sleep disturbance.

Personal traits included optimism, which was measured using a six-item Life Orientation Test-Revised Scale (Scheier & Carver, 1985), with possible scores ranging from 6 to 30. A higher score indicated greater optimism.

Environmental factors included negative life events assessed using an 11-item questionnaire from the Alameda County Study (Berkman & Syme, 1979). Scores ranged from 0 to 11 with a higher score indicating a greater number of negative life events. Social support was assessed by asking respondents to indicate how often each of nine different types of support was available to them (Sherbourne & Stewart, 1991). Final scores ranged from 9 to 45, with a higher score indicating greater support.

Outcomes

Hospitalization

All 2005-2010 Extension Study participants completed annual medical history update forms in which they indicated the occurrence of medical events such as overnight hospitalization and newly diagnosed health conditions. This information was then used to obtain medical records for adjudication, first by a local physician adjudicator and then by a panel of central adjudicators. Outcomes information is currently available through March 31, 2011, for an average length of 13.01 (SD=1.4) years of follow up. As of March 31, 2011, 5547 women ages 65 and older at baseline who were enrolled in the CT reported an incident overnight hospitalization during the 2005-2010 follow up period.

Mortality

Time to death was defined as the number of days between enrollment and occurrence of death, censored at the time of the last follow-up contact for which women were still alive. As of March 31, 2011, 2411 of total 19880 women had died during ES follow-up.

Data Analysis

Analytic strategies included a calculation of descriptive statistics (Tables 2 and 3). Skewness and kurtosis of each frailty criteria distribution was calculated in addition to graphically examining the data using histograms and normal probability plots. Transformation was applied to those outcomes that substantially violated normality

assumptions, given that non-normally distributed data increase the probability of over-extraction spurious classes in the latent class growth framework (Bauer & Curran, 2003).

We used latent class growth models (LCGM) to identify relatively homogeneous clusters of individuals following similar longitudinal trajectories of change (Muthen & Shedden, 1999; Nagin, 2005; Nagin & Odgers, 2010). Trajectory parameters were estimated using maximum likelihood methods. Provided that the data were collected at five time points, a high-order polynomial function (i.e., quadratic) was fitted to the data. Through a process similar to that of latent class analysis (latent class analysis is a subset of structural equation modeling, used to find groups or subtypes of cases in multivariate categorical data), parameters were estimated to define the shape of the trajectories and the probability of trajectory group membership (Nagin, 2005). The number of clusters were chosen based on the following selection criteria: (1) interpretability; (2) theoretical justification; (3) parsimony; (4) lowest Bayesian Information Criteria (BIC) score; (5) non-significant Lo-Mendel-Rubin likelihood ratio test; (6) non-significant parametric bootstrapped likelihood ratio test; (7) Entropy>0.7; (8) average posterior probability in each class >0.75 and no more than 10% overlap (i.e., cross-membership) between non-contiguous clusters; and (9) at least 2.5% of the total count in each cluster for continuous variables and 1% for categorical outcomes. Of note, in the final adjudication process we selected the most parsimonious and easily interpreted models, provided that they were not distinctively different on other formal statistical criteria. A normal distribution function was fitted to continuous data and ordinal logit to categorical variables. In order to ensure the most statistically efficient model, non-significant higher order terms (i.e., quadratic) were removed and the model was re specified until optimal fit was achieved (Tables 3 to 10).

To test the effect of predictors on trajectory group membership, highest probability group assignment was initially treated as a nominal dependent variable that was linked to

predictors using multinomial logistic specification. However, given that visual inspection of trajectory group dynamics (Figures 1 to 8) revealed a fairly clear, ordered structure of the estimated longitudinal patterns in most of the frailty criteria, without noticeable points of inflection or intersections between trajectories, we recoded trajectory group assignments in incrementally increasing (i.e., ordered) ways so that that the lowest number would represent membership in the most functionally vigorous trajectory group and the highest number would reflect membership in the most frail. This modification allowed us to use an alternative ordered logit specification to test the effect of predictors on trajectory group membership. It is important to note that the traditional ordered logit model imposes an overly restrictive parallel line assumption, which is often violated, as was the case here (data not shown). Therefore, we proceeded with fitting less restrictive models, known as partial proportional odds models (Tables 12 to 19). Conceptually speaking, a partial proportional odds model generates one set of estimates for those variables that do not violate parallel line assumptions, and other category-specific estimates for those covariates that have distinctively different effects across levels of categorical outcome (Williams, 2006).

Finally, the last set of analyses was implemented using Cox proportional hazard models (Tables 21 to 28). Membership assignment served as a predictor of mortality and the first incident overnight hospitalization in sequentially fitted models adjusted for the baseline predictors. In these analyses, the days from enrollment to death (or the last contact, if no death occurred) were used as the censoring time for those participants without the target event, when the incidence of overnight hospitalization was the event of interest. The time to the last contact was used as the censoring time in time-to-mortality analyses.

Data analysis was conducted using the Stata 11 Software package (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). LCGM

modeling was conducted with Mplus 6 software (Muthén & Muthén, 1998-2011). Full-information maximum-likelihood estimation was used to integrate all available information based on missing-at-random assumptions for the trajectory variables (i.e., frailty indicators) and list-wise deletion for the predictors (Muthén & Muthén, 1998-2011). To improve interpretability, all continuous predictors were centered on their means before fitting into regression models.

Results

Aim 1

Tables 2 and 3 include estimates of the mean and standard deviation, as well as the number of participants at each measurement occasion (baseline, years 1, 3, 6, and 9/closeout) for the eight frailty criteria and the baseline distribution of the predictor variables.

Grip Strength: A four-group model was selected to represent the data. Two groups were best modeled with inclusion of a quadratic term, one group required the inclusion of simple linear term, and the last group was modeled with inclusion of an intercept only (Table 4).

Figures 1 to 8 illustrate estimated longitudinal dynamics in frailty criteria. To simplify interpretation, we assigned labels to each of the derived trajectories in such a way that the first word of a label denoted an ordinal ranking of that trajectory's y-intercept relative to the other trajectories (e.g., High, Medium, Low) and the second word indicated a direction of change over time (e.g., Decliner, Increaser).

Figure 1 graphically depicts the four estimated trajectories of grip strength. Fifteen percent of the sample (n=674) fell into a *Low Declining* trajectory. The second lowest trajectory included almost half of the sample (n=2255) and is described as *Mid-Low*

Decliner. The third trajectory group (n=1343, 31%) described women who had a *Medium Declining* trajectory. The last trajectory included a *High Maintainer* trajectory (n=985, 5%); these participants had stable grip strength levels during all years of follow up.

Timed chair stand: a three-group model was selected to represent the data. One group was modeled with the inclusion of a quadratic term, one group required the inclusion of simple linear term, and one group was modeled with the inclusion of an intercept only (Table 5).

Figure 2 illustrates the three estimated trajectories of the timed chair stand. More than half of the sample (n=2350) fell into a *Low Declining* trajectory. Another 40% (n=1737) were described by a *Medium Declining* trajectory. The last 6% (*High Maintainer*; n=261) had a high and stable number of completed stand ups.

Timed gait speed: A three-group model was selected to represent the data. Two groups were modeled with the inclusion of a quadratic term; one group required the inclusion of simple linear term only (Table 6).

Figure 3 illustrates the three estimated trajectories of the 6-meter walking time. The majority of participants (75%, n=3289) fell into a *Low Increasing* category. These women, on average, had the fastest 6-meter walk times at baseline but then sustained a slight annual increase in time over all years of follow up (Slope=0.019, 95% CI=0.0021-0.0017). The second group included 22% of the women with a *Medium Increasing* trajectory (n=978). This group had a relatively moderate rate of annual increase in time during the first six years of follow up but reached a plateau in the following years. We labeled the third group as *High Curver* (n=124), demonstrating rather volatile longitudinal pattern. These participants were relatively slow on the 6-meter timed walk at baseline, then had steep rate of improvement during the first three years of follow up, followed by a

fairly stable pattern in the next three years and culminating with a sharp increase in time in the last follow up period.

Energy/Fatigue: A four-group model was selected to represent the data. Three groups were best modeled with the inclusion of a quadratic term to capture the slightly concave shape of the trajectories. One trajectory group required the inclusion of a simple linear term only (Table 7).

Figure 4 graphically depicts the four estimated trajectories of the energy/fatigue index. Almost a quarter of the sample (n=4725, 24%) fell into a *Low Decliner* trajectory. The second lowest trajectory included 35% (n=6976) of the sample and is described as *Mid-Low Decliner*. These women had a relatively steep rate of decline [Slope=-1.162, 95% CI= (-1.04 -1.26)]. The third and largest trajectory group (n=7206, 36%) represented women with a *Medium Declining* trajectory. The last trajectory included women with a *High Decliner* trajectory (n=985, 5%), these participants had relatively stable energy/fatigue index scores during nine years of follow up with a slight degree of annual decline.

Physical Activity: A four-group model was selected to represent the data. Three groups were best modeled with inclusion of a quadratic term and one group required the inclusion of an intercept only (Table 8).

Figure 5 illustrates the four estimated trajectories of physical activity indicators. Almost one-fifth of the sample (n=4116, 21%) maintained consistently low levels of physical activity (*Low Maintainers*). The second lowest trajectory included 9% (n=1760) of the sample and is described as *Mid-Low Improvers*. These women had a relatively low level of physical activity at baseline that was followed by a steep increase in energy expenditure in the first six years and reaching a fairly stable plateau in the following years.

The third group (n=5884, 30%) represented women who had a *Medium Declining* trajectory. The last and the largest trajectory group included women in a *High Maintaining* trajectory (n=8136, 41%), these participants had relatively stable high levels of energy expenditure during all nine years of follow up.

Body Mass index: A 5-group trajectory model was selected to represent the data. One group was best modeled with inclusion of a quadratic term; two groups required the inclusion of a simple linear term, and the remaining two groups were represented by intercepts only (Table 9).

Figure 6 illustrates the five estimated trajectories of body mass index. Almost one-quarter of the sample (n=4506, 23%) maintained consistently low-normal levels of body mass index (*Low Maintainers*). The second lowest trajectory included 35% (n=7024) of the sample and is described as *Mid-Low Maintainers*. These women had stable upper-normal levels of body weight. The third group (n=5080, 26%) described women who had a *Medium Maintaining* trajectory and were consistently overweight. The fourth group (*Mid-High Maintainer*) was consistently moderately obese and included 13% of the sample (n=2625). The last and the smallest group (*High Maintainer*) included a mere 3% of the sample and consisted of morbidly obese participants (n=664).

Cognition: A three-group model was selected to represent the data. Two groups were best modeled with the inclusion of a quadratic term; one group required inclusion of a constant term only (Table 10).

Figure 7 illustrates the three estimated trajectories of cognitive changes. The majority of the sample (n=6888) fell into a *High Maintaining* trajectory. Another one-fifth of participants (n=1602) were best described as *Medium Maintainers*. The last and smallest group (*Low Maintainers;* .5%, n=261) had persistently low cognitive performance.

Because vision loss was a categorical variable, we labeled its trajectories in a different way. For vision loss the first word of the label denoted its relevant categorical score at baseline (e.g., Normal, Mild, Medium) and the second word preserved the same interpretation as in continuous models (i.e., representing a direction of change over time).

Vision Loss: A three-group model was selected to represent the data. Two groups were best modeled with inclusion of a quadratic term; one group required inclusion of a simple linear term only (Table 11).

Figure 8 illustrates the three estimated trajectories of vision loss. The majority of the sample (79%; n=15645) fell into a *Normal Maintainer* trajectory. These women did not report vision loss in nine years of follow up. Another fifth of the participants (n=1602) were labeled as *Mild Maintainers*, who experienced non-accelerated mild symptoms of vision loss. The last and smallest group (1%, n=235) reported experiencing moderate symptoms of vision loss (*Moderate Maintainer*).

Aim 2

Tables 12 to 20 present the results of the fitted partially proportional ordered logit regressions, which explain the effect of predictors on the orderly structured longitudinal trajectories of frailty indicators. The effects are presented as Odds Ratios (ORs) and can be interpreted as comparisons between the women who belong to a trajectory group greater than *j* versus those who are the members in groups less than or equal to *j* (where *j* is the ordered level of the trajectory variable). An OR greater than 1 reflects increased odds, and an OR less than 1 reflects decreased odds of being in less vigorous trajectories of frailty indicators than the comparison categories.

Grip strength (Table 12): Partial proportional odds modeling of grip strength demonstrated, for example, that for a 1-unit increase in optimism score, the odds of being in a *Low*

Declining trajectory versus combined *High, Medium* and *Mid-Low Decliner* trajectories were 0.96 times smaller(95% CI=0.94-0.99), when all other variables were held constant. Given proportionality assumptions, a similar interpretation is valid, regardless of the selected reference category, for variables that do not violate parallel line assumptions. However, for those variables that demonstrated differential effects across trajectory groups, the model generated category-specific estimates. For example, the partial proportional odds model showed that higher age was consistently associated with membership in frailer trajectories of grip strength; however, the greatest effect was in differentiating between the most functionally healthy trajectory (i.e., *High Maintainer*) and a combination of other more frailer trajectories (OR=1.23; 95% CI=1.14-1.34). Similarly, an accumulation of general symptoms had a constant and negative effect on the likelihood of membership in functionally vigorous trajectories of grip strength, whereas engagement in vigorous exercise at age 50 provided statistically significant, persistent and positive effects.

Timed chair stands (Table 13): Older age and a higher number of chronic conditions had consistent and negative effects on the odds of membership in higher functioning trajectories of timed chair stand than the reference category, whereas exercise, leisure walking and postgraduate education provided constant protective effects. The accumulation of general symptoms and smoking had category-specific effects; with the strongest detrimental effect differentiating *High Maintainer* versus *Mid- and Low Decliner* group trajectories for general symptoms and *Low Decliner* versus others for smoking.

Timed gait speed (Table 14): Older age, being non-white, smoking, a higher number of chronic conditions, and an accumulation of general symptoms were statistically significant risk factors of membership in sub-optimal trajectories of timed gait speed; conversely

average alcohol consumption and recreational walking were strongly linked to membership in vigorous trajectories of walking speed.

Energy/fatigue (Table 15): Older age, college degree, a higher number of chronic conditions and general symptoms, sleep disturbances, and depression symptoms were significant adverse factors of membership in high functioning trajectories of the energy/fatigue index. Being non-white, average alcohol consumption, recreational walking and engagement in vigorous exercise in addition to higher levels of optimism and social support provided significant protective effects. Furthermore, although the results showed that higher general symptoms were consistently associated with membership in frailer trajectories of the energy/fatigue index, the greatest effect was on differentiating between the most robust trajectory (i.e., *High Decliner*) and a combination of other less robust trajectories (OR=2.05; 95% CI=1.92-2.19).

Physical Activity (Table 16): Older, non-white individuals who had a higher number of chronic conditions and general symptoms had higher odds of having constantly low levels of energy expenditure. However, college and postgraduate education, average alcohol consumption, recreational walking outside, low fat diet, previous vigorous exercise, higher optimism and social support were strongly associated with consistently high levels of energy expenditure.

Body Mass Index (Table 17): Non-white race, a higher number of chronic conditions, general symptoms and negative life events were significant risk factors for membership in heavier weight trajectories of BMI than the reference category. On the other hand, older age, postgraduate education, sleep disturbances, smoking, average alcohol consumption, low fat diet and leisure walking outside were significantly linked with a higher odds of membership in normal weight trajectories.

Cognition (Table 18). Older age, non-white race and higher number of general symptoms were significant factors for belonging to the cognitively impaired trajectory. Conversely, postgraduate or college education, sleep disturbances, smoking, average alcohol consumption and higher levels of optimism increased the odds of membership in a cognitively healthy trajectory. Furthermore, although the results showed that non-white race was consistently associated with a membership in frailer trajectories of cognitive index, the greatest effect was in differentiating between the most cognitively impaired (i.e., *Low Maintainer*) and a combination of all other more cognitively intact trajectories (OR=8.31; 95% CI=5.75-12.02).

Vision Loss (Table 19): Older age, non-white race, postgraduate education, number of chronic conditions, sleep disturbances, depression and negative life events increased the odds of membership in trajectories indicating some degree of visual loss, whereas an average alcohol consumption, recreational walking and social support increased the likelihood of belonging to visually intact trajectories. Age and depression symptoms had category-specific effects, with the strongest detrimental effect when differentiating between *Moderate Maintainer* versus *Normal- and Mild Maintainer* trajectory groups (OR =1.09 95% CI=1.05-1.13; OR=1.18 95% CI=1.08-1.28) respectively.

Tables 20a-20b summarize the baseline predictors of age, socioeconomic status, health status, health behaviors, personality trait, and environmental factors, according to each main latent construct measured.

Older age was consistently linked to higher odds of being in a frailer trajectory than the reference category in most of the estimated models. BMI was the only exception; the reference category denoted a sub-optimal weight category for older women. Race and educational level had opposite effects, with non-white race being a significant detrimental

factor for membership in higher-functioning trajectories than the reference category for most of the frailty criteria, except the energy/fatigue index. In later analysis race had the opposite (i.e., positive) effect. Conversely, postgraduate education provided protective effects for seven of the frailty indicators, but education had an opposite (i.e., adverse) effect on vision loss. The number of chronic conditions and an accumulation of general symptoms were identified as important factors predicting membership in functionally impaired (i.e., frailer) longitudinal groups for all of the frailty criteria. Among health behaviors, leisure walking and engagement in vigorous exercise at age 50 were the most consistent factors that increased the likelihood of membership in higher functioning trajectories of frailty markers. We also found that optimism was strongly linked to higher functioning in longitudinal trajectories of physical activity, energy/fatigue, grip strength and cognitive indexes. Environmental factors offered protective effects for physical activity, energy/fatigue and vision loss criteria when higher levels of social support were present. Environmental factors were associated with adverse effects for BMI and vision loss when an individual had experienced a higher number of negative life events.

Aim 3

During the 2005-2010 Extension Study follow-up, 2411 women died, and 5547 participants reported a first incident hospitalization.

Grip Strength (Table 21)

Among 515 women who died and had complete data on grip strength, 7% were in *High Maintainer*, 9.2% in *Medium Decliner,* 12.3% in *Mid-Low Decliner* and 16.0% in *Low Declining* trajectories. Although not statistically significant, the fully adjusted proportional hazards model demonstrated a consistently increased risk of mortality as a result of

membership in lower functioning trajectories compared to the *High Maintainer* reference category.

Among 1,205 women who reported a first incident hospitalization during the ES and had complete data on grip strength, 15.1% were in *High Maintainer*, 25.6% in *Medium Decliner,* 27.9% in *Mid-Low Decliner* and 31.8% were in *Low Decliner* trajectory groups. In this analysis, we found that membership in the *Low Decliner* trajectory carried an additional 72% risk of hospitalization compared to the *High Maintainer* reference category.

Timed Chair Stands (Table 22)

Among 508 women who died and had complete data on timed chair stands, 8.0% were in *High Maintainer*, 9.6% *Medium Decliner* and 11.7% in *Low Decliner trajectories*. Although the fully-adjusted proportional hazards model was not statistically significant, we could clearly observe an increasing trend of higher mortality with membership in lower functioning trajectories as compared the *High Maintainer* group.

Among 1,183 women who reported a first incident hospitalization during the ES and had complete data for the timed chair stand, 18% were in *High Maintainer*, 23% in *Medium Decliner and* 31.4% in *Low Decliner* trajectories. Although not statistically significant, the model adjusted for all other baseline predictors suggested that membership in *Low* and *Medium Decliner* trajectories carried an additional 21% and 35% risk of hospitalization, respectively, compared to the *High Maintainer* reference group.

Timed Walking Test (Table 23)

Among 516 women who died and had complete data on the 6-meter timed walking test, 10.3% were in *Low Increaser*, 16.4% in *Medium Increaser* and 15.3% were in *High Curver* trajectories. Although not statistically significant, the fully-adjusted proportional hazards

model again demonstrated persistently increased risk of mortality as a result of membership in lower functioning trajectories.

Additionally, among 1,204 women who reported a first incident hospitalization during the ES and had complete data on the timed walking test, 24.3% were in *Low Increaser*, 37.6% in *Medium Increaser* and around 31% in *High Curver trajectorie*s. In this analysis, we found that membership in *the Medium Increaser* trajectory carried an additional 23% odds of incident hospitalization when comparing to the *Low Increaser* trajectory group in the model adjusted for all other baseline predictors.

Energy/Fatigue (Table 24)

Among 2410 women who died and had non-missing available data on the energy/fatigue index, 7.1% were in *High Decliner*, 9.4% in *Medium Decliner,* 12.8% in *Mid-Low Decliner* and finally 16.3% in *Low Decliner* trajectories. The fully-adjusted proportional hazards model demonstrated statistically significant and consistently increased risk of mortality as a result of membership in lower-energy trajectories compared to the *High Decliner* reference category. For example, those who were *Low Decliners* had 2.64 times (95% CI=1.93-3.62) higher risk of mortality than *High Decliners.*

Among 5541 women who reported a first incident hospitalization during the ES and had complete data on energy/fatigue measurements, 18% were *High Decliners*, 23% *Medium Decliners*, 29.1% *Mid-Low Decliners* and finally 35.5% *Low Decliner*s. In the partially-adjusted model, those women who were in the *Low Decliner* trajectory were approximately twice as likely as *High Decliner*s to report a first incident hospitalization (HR=2.25; 95% CI=1.92-2.63). The final multivariate adjustment slightly attenuated these results. The fully adjusted model showed that membership in *Medium, Mid-Low* and *Low*

Decliner trajectories carried a statistically significant additional 28%, 50% and 66% risk of hospitalization, respectively, compared with the *High Decliner* reference group.

Physical Activity (Table 25)

Among 2411 women who died and had complete data on energy expenditure measurements, 9.9% were *High Maintainers*, 10.7% *Mid-Low Improvers,* 13.5% *Medium Decliners* and finally 15.2% *Low Maintainers*. The fully-adjusted proportional hazards model demonstrated a statistically significant increased risk of mortality as a result of membership in lower energy expenditure trajectories compared to the *High Maintainer* reference category. For example, those who were in the *Low Maintainer or Medium Decliner* trajectories had an additional 41% and 33% risks of all case mortality respectively, as compared to members of the *High Maintainer* longitudinal cluster.

Furthermore, among 5,542 women who reported a first incident hospitalization during the ES and had complete physical activity measurements, 24% of the women were in *High Maintainer*, 27 % in *Mid-Low Improver*, 29.2% in *Medium Decliner* and 34% in *High Maintainer* trajectories. The fully-adjusted model showed that the *Medium Decliners and Low Maintainers* carried a statistically significant additional 9% and 26% risk of hospitalization, respectively, as compared with the *High Maintainer* reference category.

Body Mass Index (Table 26)

Among 2411 women who died and had complete data on BMI, 12.6% were *Low Maintainers*, 11.2% *Mid-Low Maintainers,* 12.3% *Medium Maintainers*, 13% *Mid-High Maintainers* and finally 14.2% *High Maintainers.* The fully-adjusted proportional hazards model demonstrated a statistically significant 0.87-times reduced risk of mortality (95% CI=0.77-0.99) as a result of membership in the *Mid-Low Maintainer* trajectory group in comparison with the *Low Maintainer* category.

Furthermore, among 5,543 women who reported a first incident hospitalization during the ES and had complete data on body mass measurements 25.9% were in *Low Maintainer*, 25.7% in *Mid-Low Maintainer,* 29% in *Medium Maintainer*, 33.7% in *Mid-High Maintainer* and 33% in *High Maintainer* trajectories. In this analysis, we found that membership in the *Mid-High Maintainer* trajectory carried a statistically significant additional 12% increased risk of hospitalization when the *Low Maintainer* group served as the reference category.

Cognition (Table 27)

Among 1,131 women who died and had complete data on cognitive tests, 11.7% were *High Maintainers*, 17.3% were *Medium Maintainers* and 23% were *Low Maintainers*. The fully-adjusted proportional hazard model demonstrated a statistically significant additional 35% and 72% risk of mortality as a result of membership in *Medium-* and *Low-Maintaining* trajectories, respectively, using *High Maintainers* as the reference category

Furthermore, among 2,534 women who reported a first incident hospitalization during the ES and had complete cognitive assessment data, 28.7% were in *High Maintainer*, 30.5% in *Medium Maintainer* and 32.1% in *Low Maintainer* trajectories. Although the fully-adjusted proportional hazards model failed to demonstrate statistically significant results, there was a clear trend toward an increased risk of hospitalization as a result of membership in lower cognitive trajectories.

Vision Loss (Table 28)

Among 2,410 women who died and had complete data on self-reported vision loss, 11.6% were *Normal Maintainers*, 13.9% *Mild Maintainers* and 15.4% *Moderate Maintainers*. The fully-adjusted proportional hazards model did not yield statistically significant results.

Among 5,542 women who reported a first incident hospitalization during the ES and had complete data on vision loss 26.8% were *Normal Maintainers,* 31.7% *Mild Maintainers* and 34.2% *Moderate Maintainers*. The fully-adjusted proportional hazard model demonstrated a statistically significant 11% increased risk of hospitalization as a result of membership in the *Mild Maintainer* trajectory comparing to *Normal Maintainer* category.

Discussion

The study findings demonstrated a high degree of heterogeneity in longitudinal dynamics of individual frailty criteria. These dynamics, in turn, might provide partial explanation on the high degree of variability in health related outcomes even among individuals sharing the same level of frailty initially. Furthermore, we showed that age, socio-demographic variables, health status, health behavior, environmental factors and personality traits are important determinants of individual frailty criteria, but their effect on the frailty phenotype is complex, presumably due to the multidimensional nature of frailty. Thirdly, we demonstrated that the magnitude of risk carried by membership in longitudinal trajectories for each of the defining elements of frailty is closely linked to their distance from the trajectory that represents the most optimal functioning over time. That is to say, the further the distance between highest level of indicator function and less optimal functioning, the higher the risk of incident adverse health events. Finally, we empirically determined that distribution-based, cross-sectional partitioning of frailty criteria seems to be a valid method of analyzing frailty given that elderly women maintained similar levels of functioning over time without demonstrating clear accelerated or decelerated longitudinal patterns. Of note, exact thresholds that define sub-optimal functioning were found to be flexible and criterion-specific, as some of the longitudinal dynamics were best represented by three-trajectory models (e.g., chair stand, cognition and vision loss criteria), whereas other criteria needed to include more groups.

In spite of the fact that many physiological systems show steady decline in older adults, the rate of change is highly variable. Many older adults show a pronounced reduction in health status whereas others demonstrate minimal or no decline at all. Those (later) individuals might be viewed as aging successfully (i.e., free from disease or disease-related disability, high cognitive and physical functioning, and active engagement with life), and could be distinguished from normal, non-pathological aging (Rowe & Kahn, 1997). There is also some evidence that functional decline in the last year of life follows five distinct trajectories: a) persistently severe disability, b) progressive disability, c) accelerated disability, d) catastrophic disability, and e) no disability (Gill et al., 2010). Based on these notions and in concordance with successful aging, variability in normal aging and pathological aging discourses, we hypothesized that at least five trajectories exist in patterns of change in frailty criteria. In this study, we found partial support for our hypothesis, as there was a number of indicators that were best modeled by five polynomial functions of time whereas others were best represented by a smaller number of groups. To our surprise; however, we did not see strong longitudinal dynamics in frailty criteria. In most estimated models women maintained approximately similar levels of functioning throughout follow-up without presenting clear increasing or decreasing patterns. This finding might be due to somewhat sparsely-scheduled measurement points, which might not capture subtle changes in frailty indicators but rather provide an averaged trajectory, which in turn could have been heavily influenced by the data starting point (i.e., baseline measurement). Alternatively, women with dramatic changes in functioning might have been less likely to complete more occasions of follow-up compared to women who did not exhibit such changes. This possible bias (e.g., due to loss during follow-up) may underrepresent the proportion of older women at risk of being in declining trajectories. To alleviate the effect of selection bias and rule out attrition due to mortality, our analyses included only those women who consented to participate in the 2005-2010 ES. In other

words, the trajectory analyses were based on data from those older WHI participants who survived at least until the beginning of the ES follow up period.

In line with other published reports (Alvarado et al., 2008; Espinoza & Hasuda, 2008; Hirsch et al., 2006; Woods et al., 2006), the current analyses showed that frailty phenotype was closely linked to age, socio-demographic factors, comorbidities and health behaviors. For example, previous evidence has showen that African Americans have four-fold greater odds of frailty than their white counterparts, based on cross-sectional analyses of the Cardiovascular Health Study (CHS) cohort (Hirsch, et al., 2006). Other ethnic groups have demonstrated similar findings when compared to the white population (Espinoza & Hazuda, 2008). Furthermore, Woods and colleagues (2005) found that a history of coronary heart disease (CHD), stroke, hip fracture, chronic obstructive pulmonary disease (COPD), treated diabetes mellitus, and arthritis were significantly related to 3-year incident frailty in the WHI Observational study. Finally, a Latin American and Caribbean cross-sectional study showed that poor health, little education and poor socioeconomic conditions were associated with higher odds of frailty (Alvarado, Zunzunegui, Beland, & Bamvita, 2008). Unlike other studies we demonstrated that in fully-adjusted models additional factors such as leisure walking, optimism and social support, had significant positive and independent effects on the likelihood of membership in higher functioning trajectories of frailty criteria than the reference category. These results hold promise for developing holistic behavioral interventions to help the elderly maintain a high level of functioning throughout the aging process. However, interventions that focus exclusively on health-related behaviors might have limited potential for promoting frailty-free aging, given that other predictors were closely linked in our study to both musculoskeletal and neurosensory dimensions of the frailty phenotype. For instance, interventions aimed at attaining a disease- and general symptoms- free condition, as well

as fostering the development of higher levels of optimism and social support in addition to promoting positive health behaviors (i.e., low fat diet, physical exercise) would have strong beneficial impact on a number of frailty criteria simultaneously. This possibility is supported by other studies and reviews on frailty (Fried, et al., 2009; Lang, Michel & Zekry, 2009).

Similar to other studies (Abellan, et al., 2009; Sarkisian, et al., 2008), we demonstrated that deficits in individual frailty criteria predict incident adverse health outcomes. However, in contrast to other prospective studies that measured the association between distal outcomes (e.g., hospitalization, mortality) and the cross-sectional distribution of frailty-related indicators, we were able to capture the variability in longitudinal patterns of individual frailty criteria over a relatively long follow up period. We were then able to relate these estimated levels to clinically relevant geriatric outcomes. As a result, the frailest individuals, defined empirically, did not merely demonstrate low criterion-specific functioning at a single occasion but sustained that functioning for up to nine years of follow-up. This finer-grained description of trajectories in frailty indicators provides a fertile ground to further compare their predictive power at any single time point versus prediction on the basis of trajectory group membership. These differences in predictive power of static versus dynamic measurements have been discussed in biomedical literature with inconsistent results. Some researchers indicated that cross sectional measures of functional loss did not predict adverse outcomes nearly as well as longitudinal measures (Xue, Beamer, Chaves, Guralnik & Fried, 2010), whereas others demonstrated opposite results (Hicks, et al., 2012).

Of note, the criterion-specific trajectories of frailty predicted mortality and first incident overnight hospitalization independent of other baseline factors. These findings indicate that individual-level baseline factors and trajectory groups are related constructs,

but their effects on health outcomes occur through different mechanisms. As a next step in research, it would be important to expand this single-parameter trajectory analysis by examining longitudinally two or more interconnected frailty criteria that evolve contemporaneously. Such multi-trajectory modeling can also be extended to estimate the effects of joint trajectories on distal outcomes and relate these combined growth patterns to individual-level characteristics (Nagin, 2005). Such models will likely provide further insight into the interconnected nature of physiological mechanisms that lead to frailty (Zaslavsky et al., in press).

We demonstrated that the magnitude of risk carried by membership in longitudinal groups of frailty's defining elements is proportional to the distance between that trajectory estimates and one that represents the most optimal criterion-specific functioning over time. Analysis of trajectory groups might be considered, thus, as a tool for empirical partitioning of a population curve into clinically and statistically distinct longitudinal groups. This type of application can be especially useful, given that investigators will frequently use subjective categorization criteria (e.g., tertiles, quintiles) and other *a priori* assumptions to assign individuals into different clinical categories. Although such subjective categorization is methodologically justifiable, its major weakness is that it does not provide a basis for detailed calibration the precision of an individual's classification into a category. In other words, using traditional methodology we cannot quantify category assignment into probabilities. However, our analyses allowed us to estimate the likelihood of randomly selected elderly woman (age 65 and older) who participated in Women's Health Initiative Clinical Trial being a member in a given trajectory group, if they had at least one of the frailty-related measurements available.

We found that elderly women maintained similar levels of functioning throughout time without demonstrating clear acceleration or deceleration in longitudinal patterns.

These findings provide partial support for the use of distribution-based cross-sectional partitioning of frailty criteria to define those who have impaired physiological reserves. However, exact cut-off points that distinguish levels of sub-optimal functioning from a high level of functioning were found to be variable and criterion specific as some longitudinal patterns were best modeled by merely three polynomial functions; whereas others required inclusion of up to five trajectory groups.

Several limitations of this study should be considered. As mentioned, women with low musculoskeletal and neurosensory functioning were less likely to complete more occasions of follow-up compared to women who did not exhibit such traits. The proportion of older women at risk of being in frail trajectories, therefore, may have been misrepresented. However, the main aim of the analysis was to describe the heterogeneity in frailty-related criteria rather than estimate their prevalence. To this end, we used a LCGM framework as a convenient analytic approach for outlining longitudinal patterns in an aging sample. In addition, the LCGM technique successfully integrates full information, maximum-likelihood estimation that can generate consistent estimates when a missing-at-random assumptions holds (Muthén & Muthén (1998-2011). In analyses presented here, the prolonged enrollment period and flexible data collection protocol resulted in a large number of missing observations.

Although we measured many traditional risk factors that did predict the odds of membership in a given frailty indicator trajectory, other unmeasured variables, such as biomarkers and/or genetic factors, might have affected this association. Inclusion of these other variables might increase our understanding of frailty mechanisms and deserve consideration in future studies.

Our study did have some unique strengths, including the use of a robust statistical method of LCGM to identify subgroups with distinct trajectories of change within a population over time. Traditional growth curve modeling is generally useful for investigating research questions where the underlying assumption is that, on average, most individuals follow similar patterns of change. However, some phenomena that have strong individual variability, such as depressive symptoms, obesity, and disabilities, demonstrate a multinomial pattern. In such circumstances, traditional growth curve modeling can mask significant differences and lead to erroneous inferences about changes in population over time. Therefore, assuming population heterogeneity in longitudinal trajectories of frailty criteria, we implemented LCGM. To our knowledge, this is the first published study using a data-driven approach in quantifying the heterogeneity of indicators of frailty in an aging population. We also analyzed the association of demographic, personal, social, and health-related baseline variables with longitudinal patterns of change in a large and ethnically diverse sample of aging American women using a prospective design and a relatively long follow-up period. Finally, we were among the first to determine the extent to which membership in longitudinal trajectories predicted incidence of clinically relevant geriatric health outcomes (i.e., mortality and hospitalization) over an average 5 years of follow up.

In summary, future studies are warranted to confirm these findings in other mixed cohorts, given that this was the first study to examine the course of frailty-related indicators among elderly women. The results of the present study might help to identify distinct groups among aging women with potentially modifiable risks of adverse health outcomes and guide future interventions; therefore are valuable for both research and clinical practice.

References:

Abellan van Kan, G., Rolland, Y., Andrieu, S., Bauer, J., Beauchet, O., Bonnefoy, M., et al. (2009). Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. *Journal of Nutrition Health Aging, 13*(10), 881-889.

Alvarado, B. E., Zunzunegui, M. V., Beland, F., & Bamvita, J. M. (2008). Life course social and health conditions linked to frailty in Latin American older men and women. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63*(12), 1399-1406.

Anderson, G. L., Manson, J., Wallace, R., Lund, B., Hall, D., Davis, S., et al. (2003). Implementation of the Women's Health Initiative study design. *Annals of Epidemiology, 13*(9 Suppl), S5-17.

Bandeen-Roche, K., Xue, Q. L., Ferrucci, L., Walston, J., Guralnik, J. M., Chaves, P., et al. (2006). Phenotype of frailty: characterization in the women's health and aging studies. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 61*(3), 262-266.

Bauer, D. J., & Curran, P. J. (2003). Distributional assumptions of growth mixture models: implications for overextraction of latent trajectory classes. *Psychological Methods, 8*(3), 338-363.

Berkman, L. F., & Syme, S. L. (1979). Social networks, host resistance, and mortality: a nine-year follow-up study of Alameda County residents. *American Journal of Epidemiology, 109*(2), 186-204.

Boyle, P. A., Buchman, A. S., Wilson, R. S., Leurgans, S. E., & Bennett, D. A. (2010). Physical frailty is associated with incident mild cognitive impairment in community-based older persons. *Journal of the American Geriatrics Society, 58*(2), 248-255.

Burnam, M. A., Wells, K. B., Leake, B., & Landsverk, J. (1988). Development of a brief screening instrument for detecting depressive disorders. *Medical Care, 26*(8), 775-789.

Cockrell, J. R., & Folstein, M. F. (1988). Mini-Mental State Examination (MMSE). *Psychopharmacology Bulletin, 24*(4), 689-692.

Ensrud, K. E., Ewing, S. K., Taylor, B. C., Fink, H. A., Stone, K. L., Cauley, J. A., et al. (2007). Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62*(7), 744-751.

Ensrud, K. E., Ewing, S. K., Cawthon, P. M., Fink, H. A., Taylor, B. C., Cauley, J. A., et al. (2009). A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. *Journal of the American Geriatrics Society, 57*(3), 492-498.

Espinoza, S. E., & Hazuda, H. P. (2008). Frailty in older Mexican-American and European-American adults: is there an ethnic disparity? *Journal of the American Geriatrics Society, 56*(9), 1744-1749.

Fried, L. P., Tangen, C. M., Walston, J., Newman, A. B., Hirsch, C., Gottdiener, J., et al. (2001). Frailty in older adults: evidence for a phenotype. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 56*(3), M146-156.

Fried, L. P., Xue, Q. L., Cappola, A. R., Ferrucci, L., Chaves, P., Varadhan, R., et al. (2009). Nonlinear multisystem physiological dysregulation associated with frailty in older women: implications for etiology and treatment. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 64*(10), 1049-1057.

Gill, T. M., Gahbauer, E. A., Allore, H. G., & Han, L. (2006). Transitions between frailty states among community-living older persons. *Archives of Internal Medicine, 166*(4), 418-423.

Gill, T. M., Gahbauer, E. A., Han, L., & Allore, H. G. (2010). Trajectories of disability in the last year of life. *New England Journal of Medicine, 362*(13), 1173-1180.

Gray, S. L., LaCroix, A. Z., Aragaki, A. K., McDermott, M., Cochrane, B. B., Kooperberg, C. L., et al. (2009). Angiotensin-converting enzyme inhibitor use and incident frailty in women aged 65 and older: prospective findings from the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society*, 57(2), 297-303.

Hicks, G. E., Shardell, M., Alley, D. E., Miller, R. R., Bandinelli, S., Guralnik, J., et al. (2012). Absolute strength and loss of strength as predictors of mobility decline in older adults: the InCHIANTI study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 67*(1), 66-73.

Hirsch, C., Anderson, M. L., Newman, A., Kop, W., Jackson, S., Gottdiener, J., et al. (2006). The association of race with frailty: the cardiovascular health study. *Annals of Epidemiology, 16*(7), 545-553.

LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Newman, A. B., Kooperberg, C. L., et al. (2008). Statin use and incident frailty in women aged 65 years or older: prospective findings from the Women's Health Initiative Observational Study.

Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 63(4), 369-375.

Lang, P. O., Michel, J. P., & Zekry, D. (2009). Frailty Syndrome: A Transitional State in a Dynamic Process. *Gerontology, 55*(5), 539-549.

Levine, D. W., Kripke, D. F., Kaplan, R. M., Lewis, M. A., Naughton, M. J., Bowen, D. J., et al. (2003). Reliability and validity of the Women's Health Initiative Insomnia Rating Scale. *Psychological Assessment, 15*(2), 137-148.

Matthews, K. A., Shumaker, S. A., Bowen, D. J., Langer, R. D., Hunt, J. R., Kaplan, R. M., et al. (1997). Women's health initiative. Why now? What is it? What's new? *American Psychologist, 52*(2), 101-116.

Muthén, L. K., & Muthén, B. O. (1998-2011). *Mplus user's guide*. Sixth Edition. Los Angeles, CA: Muthén & Muthén.

Muthen, B., & Shedden, K. (1999). Finite mixture modeling with mixture outcomes using the EM algorithm. *Biometrics, 55*(2), 463-469.

Nagin, D. S. (2005). *Group-based modeling of development* Harvard University Press.

Nagin, D. S., & Odgers, C. L. (2010). Group-based trajectory modeling in clinical research. *Annual Review on Clinical Psychology, 6*, 109-138.

Onder, G., Penninx, B. W., Lapuerta, P., Fried, L. P., Ostir, G. V., Guralnik, J. M., et al. (2002). Change in physical performance over time in older women: the Women's Health and Aging Study. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 57*(5), M289-293.

Ostir, G. V., Volpato, S., Fried, L. P., Chaves, P., Guralnik, J. M., Women's, Health, et al. (2002). Reliability and sensitivity to change assessed for a summary measure of lower body function: results from the Women's Health and Aging Study. *Journal of Clinical Epidemiology, 55*(9), 916-921.

Rochat, S., Cumming, R. G., Blyth, F., Creasey, H., Handelsman, D., Le Couteur, D. G., et al. (2010). Frailty and use of health and community services by community-dwelling older men: the Concord Health and Ageing in Men Project. *Age and Ageing, 39*(2), 228-233.

Rockwood, K., & Mitnitski, A. (2007). Frailty in relation to the accumulation of deficits. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 62*(7), 722-727.

Rowe, J. W., & Kahn, R. L. (1997). Successful aging. *Gerontologist, 37*(4), 433-440.

Sarkisian, C. A., Gruenewald, T. L., John Boscardin, W., & Seeman, T. E. (2008). Preliminary evidence for subdimensions of geriatric frailty: the MacArthur study of successful aging. *Journal of the American Geriatrics Society, 56*(12), 2292-2297.

Scheier, M. F., & Carver, C. S. (1985). Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psychology, 4*(3), 219-247.

Sherbourne, C. D., & Stewart, A. L. (1991). The MOS social support survey. *Social Science and Medicine, 32*(6), 705-714.

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). *Medical Care, 30*(6), 473-483.

Woods, N. F., LaCroix, A. Z., Gray, S. L., Aragaki, A., Cochrane, B. B., Brunner, R. L., et al. (2005). Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *Journal of the American Geriatrics Society, 53*(8), 1321-1330.

Williams, R (2006). Generalized Ordered Logit/Partial Proportional Odds Models for Ordinal Dependent Variables. *The Stata Journal 6*(1), 58-82.

Xue, Q. L., Beamer, B. A., Chaves, P. H., Guralnik, J. M., & Fried, L. P. (2010). Heterogeneity in rate of decline in grip, hip, and knee strength and the risk of all-cause mortality: the Women's Health and Aging Study II. *Journal of the American Geriatrics Society, 58*(11), 2076-2084.

Zaslavsky, O., Cochrane, B. B., Thompson, H. J., Woods, N. F., Herting, J.R., & LaCroix, A. Z. *(*in press). Frailty: a review of the first decade of research *Biological Research for Nursing* .

Zaslavsky, O., Thompson, H., & Demiris, G. (2012). The Role of Emerging Information Technologies in Frailty Assessment. *Research in Gerontological Nursing*, 1-13.

Table 1. Frequency of data collection of trajectory variables in Women's Health Initiative Clinical Trial (N= 19891)

	Baseline	**Year 1**	**Year 3**	**Year 6**	**Year 9**	**Closeout**
Measures:						
Grip strength	%	%	%	%	%	
Chair stands	%	%	%	%	%	
Timed walk	%	%	%	%	%	
Energy/fatigue	X	X	%	%	%	X
Physical activity	X	X	X	X	X	
Cognition	@	@	@	@	@	
Visual impairment	X	X	%	%	%	X
Body Mass Index	X	X	X	X	X	X

%- Percentage (subsample) of participants

X - All participants

@ - Subsample of Hormone Therapy participants

Table 2. Frailty indicators at five-time points in WHI Clinical Trial cohort (N=19891): Mean (SD) n for continuous variables; percentage (n) for categorical outcomes.

Variables	**Baseline**	**Year 1**	**Year 3**	**Year 6**	**Close out / Year 9**
Body Mass Index	28.35 (5.36) 19,792	28.06 (5.35) 19,052	28.36 (5.46) 19,361	28.42 (5.41) 18,716	28.04 (5.3) 7004
Physical Activity[a]	1.96 (1.17) 18,533	1.99 (1.18) 12,852	1.98 (1.19) 18,784	1.89 (1.22) 19,563	1.8 (1.23) 3580
Energy/Fatigue[b]	45.38 (21.38) 19,645	45.93 (22.4) 18,750	43.94 (22.17) 1,391	38.98 (22.25) 5,463	37.74 (21.86) 14,228
Timed Chair Stands	6.61 (1.7) 4191	6.65 (1.85) 3715	6.57 (1.93) 3858	6.31 (2.05) 3572	6.36 (2) 276
Grip Strength	23.6 (6.04) 4335	22.9 (5.8) 3884	21.67 (6.3) 4073	20.43 (6.13) 3904	19.8 (5.5) 325
Walking Time[c]	1.7 (0.29) 4321	1.73 (0.27) 3895	1.76 (0.27) 4062	1.81 (0.28) 3870	1.87 (0.31) 326
Cognition	95.34 (4.28) 6431	95.93 (3.98) 7162	95.95 (4.17) 8396	96.11 (4.41) 8179	95.32 (5.69) 2621
Vision loss:					
No vision loss	80.7% (15,880)	79.05% (14,882)	74.68% (1,038)	72.58% (3,991)	70.99% (10,167)
Mild vision loss	14.5% (2,854)	15.56% (2,930)	17.55% (244)	19.29% (1,061)	20.21% (2,895)
Moderate vision Loss	4.03% (793)	4.41% (831)	6.33% (88)	6.15% (338)	6.55% (938)
Severe vision loss	0.81% (159)	0.97% (182)	1.44% (20)	1.98% (109)	2.25% (322)

[a] - Original variable was log transformed

[b]- Original variables was transformed by squaring and divided by 10

[c] - Original variable was log transformed

Table 3. Descriptive statistics of baseline predictors in WHI Clinical Trial cohort (N=19891): Mean (SD) for continuous variables; and percentage (n) for categorical outcomes.

Variables	**Baseline**
Age	69.5 (3.5)
Ethnicity	
White	88.08% (17,519)
Education	
High School	36.9% (7,346)
College	37.9% (7,538)
Postgraduate	24.7% (4,907)
Health behaviors	
Smoking:	
Never smoked	54.45% (10,831)
Past Smoker	39.8% (7,916)
Current Smoker	4.67% (928)
Alcohol Serving per week	2.25 (4.47)
Low fat diet	33.47% (6,657)
Walking Outside:	
Rarely or never	17.9% (3,567)
1-3 times each month	15.04% (2,991)
1 time each week	10.9% (2,169)
2-3 times each week	27.88% (5,546)
4-6 times each week	20.7% (4,122)

7 or more times each week	7.09% (1,410)
Hard exercise at age 50	37.38% (7,435)
Health Status	
Number of Chronic Conditions	1.52 (1.3)
Severity of General Symptoms	0.4 (0.24)
Severity of Sleep Disturbances	6.73 (4.36)
Severity of Depression Symptoms	0.026 (0.097)
Psychological Environmental and Social factors	
Optimism	23.4 (3.2)
Negative Life Event	3 (2.9)
Social Support	36.06 (7.6)

Table 4. Parameter estimates for the four-group trajectory model of grip strength at five measurement occasions (baseline, years 1, 3, 6 and 9) in WHI Clinical Trial (N=4335).

Group	% Sample	Parameter	Estimate	Standard Error
High Maintainer	3	Intercept	34.263	0.630
Medium Decliner	31	Intercept	27.885	0.377
		Linear	-0.539	0.028
Mid-Low Decliner	51	Intercept	22.264	0.382
		Linear	-0.627	0.061
		Quadratic	0.02	0.009
Low Decliner	15	Intercept	17.210	0.348
		Linear	-1.297	0.184
		Quadratic	0.106	0.022
Residual Variances	Baseline		19.412	1.318
	Year 1		15.053	0.878
	Year 3		18.564	1.319
	Year 6		18.504	1.065
	Year 9		13.202	1.974

Table 5. Parameter estimates for the three-group trajectory model of timed chair stands at five measurement occasions (baseline, years 1, 3, 6 and 9) in WHI Clinical Trial (N=4191)

Group	% Sample	Parameter	Estimate	Standard Error
High Maintainer	6	Intercept	10.127	0.259
Medium Decliner	40	Intercept	7.355	0.117
		Linear	0.077	0.022
		Quadratic	-0.017	0.003
Low Decliner	54	Intercept	5.619	0.065
		Linear	-0.083	0.007
Residual Variances	Baseline		1.461	0.065
	Year 1		1.598	0.078
	Year 3		1.841	0.079
	Year 6		2.240	0.106
	Year 9		2.188	0.281

Table 6. Parameter estimates[a] for the three-group trajectory model of 6-meter walking time at five measurement occasions (baseline, years 1, 3, 6 and 9) in WHI Clinical Trial (N=4321).

Group	% Sample	Parameter	Estimate	Standard Error
Low Increaser	75	Intercept	1.621	0.007
		Linear	0.019	0.001
Medium Increaser	22	Intercept	1.861	0.011
		Linear	0.068	0.008
		Quadratic	-0.006	0.001
High Curver	3	Intercept	2.681	0.027
		Linear	-0.456	0.032
		Quadratic	0.048	0.005
Residual Variances	Baseline		0.036	0.001
	Year 1		0.061	0.004
	Year 3		0.053	0.003
	Year 6		0.061	0.003
	Year 9		0.098	0.013

[a] In log scale

Table 7. Parameter estimates for the four-group trajectory model of self-reported energy/fatigue index scores[a] at five measurement occasions (baseline, years 1, 3, 6 and 9/closeout) in WHI Clinical Trial (N=19645)

Group	% Sample	Parameter	Estimate	Standard Error
High Decliner	5	Intercept	80.655	1.082
		Linear	1.048	0.391
		Quadratic	-0.207	0.043
Medium Decliner	36	Intercept	61.323	0.525
		Linear	0.127	0.186
		Quadratic	-0.15	0.021
Mid-Low Decliner	35	Intercept	41.72	0.833
		Linear	-1.162	0.062
Low Decliner	24	Intercept	20.665	0.451
		Linear	-1.092	0.171
		Quadratic	0.086	0.019
Residual Variances	Baseline		152.12	2.608
	Year 1		154.189	2.794
	Year 3		161.007	10.122
	Year 6		206.583	6.072
	Year 9		231.191	4.456

[a] Original values have been transformed by squaring and dividing by 10

Table 8. Parameter estimates[a] for the four-group trajectory model of self-reported physical activity index scores at five measurement occasions (baseline, years 1, 3, 6 and 9) in WHI Clinical Trial (N=19,563)

Group	% Sample	Parameter	Estimate	Standard Error
High Maintainer	41	Intercept	2.916	0.016
		Linear	0.023	0.005
		Quadratic	-0.005	0.001
Mid-Low Improver	9	Intercept	0.886	0.102
		Linear	0.468	0.077
		Quadratic	-0.038	0.01
Medium Decliner	30	Intercept	2.126	0.025
		Linear	-0.163	0.018
		Quadratic	0.007	0.002
Low Maintainer	21	Intercept	0.525	0.01
Residual Variances	Baseline		0.435	0.015
	Year 1		0.546	0.012
	Year 3		0.593	0.014
	Year 6		0.632	0.025
	Year 9		0.796	0.055

[a] in log scale

Table 9. Parameter estimates for the five-group trajectory model of body mass index at five measurement occasions (baseline, years 1, 3, 6 and 9/closeout) in WHI Clinical Trial (N=19,792)

Group	% Sample	Parameter	Estimate	Standard Error
Low Maintainer	23	Intercept	22.29	0.083
Mid-Low Maintainer	35	Intercept	26.33	0.135
		Linear	0.04	0.005
Medium Maintainer	26	Intercept	30.59	0.197
		Linear	0.03	0.007
Mid-High Maintainer	13	Intercept	35.29	0.27
		Linear	0.191	0.032
		Quadratic	-0.02	0.004
High Maintainer	3	Intercept	42.27	0.43
Residual Variances	Baseline		4.984	0.251
	Year 1		4.317	0.241
	Year 3		4.784	0.31
	Year 6		5.16	0.271
	Year 9		6.33	0.605

Table 10. Parameter estimates for the three-group trajectory model of cognitive performance index scores at five measurement occasions (baseline, years 1, 3, 6 and 9) in WHI Clinical Trial (N=8396)

Group	% Sample	Parameter	Estimate	Standard Error
High Maintainer	79	Intercept	96.712	0.062
		Linear	0.335	0.021
		Quadratic	-0.035	0.003
Medium Maintainer	18.5	Intercept	90.681	0.306
		Linear	0.691	0.089
		Quadratic	-0.073	0.012
Low Maintainer	3.5	Intercept	82.669	0.977
Residual Variances	Baseline		10.733	0.456
	Year 1		8.184	0.417
	Year 3		8.067	0.420
	Year 6		10.386	0.815
	Year 9		20.868	2.914

Table 11. Parameter estimate for the three-group trajectory model of vision loss index[a] at five measurement occasions (baseline, years 1, 3, 6 and 9/closeout) in WHI Clinical Trial (N=15880)

Group	% Sample	Parameter	Estimate	Standard Error
Normal Maintainer	79	Intercept	-3.129	0.077
		Linear	0.264	0.041
		Quadratic	0.012	0.004
Mild Maintainer	21	Intercept	0 [b]	- [b]
		Linear	0.092	0.031
Moderate Maintainer	1	Quadratic	-0.008	0.003
		Intercept	2.46	0.25
		Linear	0.123	0.03
Thresholds				
	K_1		-0.145	0.079
	K_2		1.815	0.083
	K_3		3.758	0.089

[a] Ordinal outcome (ordinal logit model applied)

[b] Fixed to 0 by model parameterization

Table 12. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Grip Strength; WHI Clinical Trial cohort (N= 3527)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Maintainer vs. Medium, Mid-Low, Low Decliner OR (95% CI)**	**High Maintainer, Medium Decliner vs. Mid-Low, Low Decliner OR (95% CI)**	**High Maintainer, Medium and Mid-Low Decliner vs. Low Decliner OR (95% CI)**
Age		1.23 (1.14-1.34)***	1.13 (1.11-1.16)*	1.1 (1.08-1.14)***
Non-white	0.94 (0.76-1.17)			
College [a]	0.93 (0.80-1.08)			
Postgraduate[a]	0.89 (0.75-1.05)			
Number of Chronic Conditions	1.03 (0.98-1.09)			
General Symptoms	1.04 (1.01-1.08)**			
Depression symptoms	1.04 (0.96-1.12)			
Sleep Disturbances	0.99 (0.98-1.01)			
Smoking		1.6 (1.08-2.37)*	0.92 (0.82-1.05)	0.99 (0.84-1.17)
Alcohol consumption	1.00 (0.99-1.02)			
Low fat diet	0.9 (0.79-1.04)			
Walking outside	1.01 (0.97-1.05)			
Exercise at age 50	0.84 (0.74-0.96)*			
Negative life events	1.00 (0.98-1.03)			
Optimism	0.96 (0.94-0.99)**			
Social support	0.99 (0.08-1.00)			

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(20)}$ = 239.05, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001

[a]- Reference category: School

Table 13. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Timed Chair Stands. WHI Clinical Trial cohort (N= 3497)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Maintainer vs. Medium, Low Decliner OR (95% CI)**	**High Maintainer, Medium Decliner vs. Low Decliner OR (95% CI)**
Age	1.07 (1.05-1.09)***		
Non-white	0.93 (0.73-1.17)		
College [a]	0.86 (0.73-1.00)		
Postgraduate[a]	0.64 (0.54-0.77)***		
Number of Chronic Conditions	1.17 (1.10-1.23)***		
General Symptoms		1.24 (1.15-1.33)***	1.11 (1.07-1.15)***
Depression symptoms	1.00 (0.93-1.09)		
Sleep Disturbances	0.98 (0.97-0.99)*		
Smoking		1.01 (0.79-1.29)	1.33 (1.17-1.50)***
Alcohol consumption	0.99 (0.98-1.01)		
Low fat diet	0.97 (0.84-1.12)		
Walking outside	0.86 (0.82-0.90)***		
Exercise at age 50	0.80 (0.69-0.92)**		
Negative life events	1.02 (0.99-1.04)		
Optimism	0.99 (0.97-1.01)		
Social support	0.99 (0.99-1.01)		

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(18)}$ = 317.96, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001

[a]- Reference category: School

Table 14. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of 6-Meter Timed Walk. WHI Clinical Trial cohort (N= 3528)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Increaser vs. Medium Increaser, High Curver OR (95% CI)**	**High, Medium Increaser vs. High Curver OR (95% CI)**
Age		1.10 (1.07-1.12) ***	0.99 (0.94-1.05)
Non-white	1.79 (1.40-2.29) ***		
College [a]	0.96 (0.80-1.16)		
Postgraduate [a]	0.84 (0.68-1.04)		
Number of Chronic Conditions		1.27 (1.19-1.35) ***	1.06 (0.90-1.25)
General Symptoms		1.04 (1.00-1.08) *	0.91 (0.83-1.00)
Depression symptoms	0.92 (0.85-1.01)		
Sleep Disturbances		1.00 (0.99-1.03)	1.08 (1.03-1.13) **
Smoking	1.16 (1.01-1.34) *		
Alcohol consumption	0.98 (0.96-0.99) *		
Low fat diet	0.91 (0.77-1.08)		
Walking outside	0.89 (0.84-0.93) ***		
Exercise at age 50	0.97 (0.82-1.14)		
Negative life events	1.01 (0.98-1.04)		
Optimism	0.98 (0.95-1.01)		
Social support	0.99 (0.98-1.00)		

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(xx)}$ = 267.34, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001

[a]- Reference category: School

Table 15. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Energy/Fatigue index. WHI Clinical Trial cohort (N= 15811)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Decliner vs. Medium, Mid-Low, Low Decliner OR (95% CI)**	**High, Medium Decliner vs. Mid-Low, Low Decliner OR (95% CI)**	**High, Medium, Mid-Low Decliner vs. Low Decliner OR (95% CI)**
Age	1.03 (1.02-1.04)***			
Non-white	0.72 (0.65-0.80)***			
College[a]	1.09 (1.02-1.18)**			
Postgraduate[a]		1.31 (1.10-1.55)**	1.05 (0.96-1.15)	1.03 (0.93-1.15)
Number of Chronic Conditions	1.28 (1.25-1.31)***			
General Symptoms		2.05 (1.92-2.19)***	1.52 (1.48-1.55)***	1.45 (1.42-1.49)***
Depression Symptoms	1.20 (1.15-1.25)***			
Sleep Disturbances	1.05 (1.04-1.06)***			
Smoking	1.02 (0.97-1.08)			
Alcohol consumption	0.98 (0.97-0.99)***			
Low fat diet	0.93 (0.87-1.00)			
Walking outside	0.84 (0.82-0.86)***			
Exercise at age 50	0.74 (0.70-0.79)***			
Negative life events		1.00 (0.97-1.05)	1.00 (0.99-1.01)	0.98 (0.97-0.99)*
Optimism	0.91 (0.90-0.92)***			
Social support	0.98 (0.97-0.99)***			

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi2_{(22)}$ = 7210.87, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

*p < .05; **p < .01; ***p < .001.

[a] – Reference category: school

Table 16. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Physical Activity index. WHI Clinical Trial cohort (N= 15813)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Maintainer vs. Mid-Low Improver, Medium Decliner, Low Maintainer OR (95% CI)**	**High Maintainer, Mid-Low Improver vs. Medium Decliner, Low Maintainer OR (95% CI)**	**High Maintainer, Mid-Low Improver, Medium Decliner vs. Low Maintainer OR (95% CI)**
Age		1.02 (1.01-1.03)**	1.03 (1.02-1.04)***	1.01 (1.00-1.03)*
Non-white	1.16 (1.04-1.28)**			
College [a]		0.73 (0.67-0.79)***	0.78 (0.72-0.84)***	0.80 (0.73-0.88)***
Postgraduate[a]		0.55 (0.50-0.60)***	0.59 (0.54-0.64)***	0.60 (0.53-0.67)***
Number of Chronic Conditions	1.16 (1.13-1.19)***			
General Symptoms	1.06 (1.04-1.07)***			
Depression symptoms	1.01 (0.98-1.05)			
Sleep Disturbances	0.99 (0.99-1.01)			
Smoking		1.00 (0.95-1.06)	1.04 (0.98-1.10)	1.03 (0.96-1.10)
Alcohol consumption	0.98 (0.97-0.99)***			
Low fat diet		0.80 (0.74-0.85)***	0.81 (0.75-0.86)***	0.71 (0.65-0.78)***
Walking outside		0.60 (0.59-0.61)***	0.71 (0.69-0.72)***	0.45 (0.44-0.47)***
Exercise at age 50	0.54 (0.51-0.58)***			
Negative life events	1.00 (0.99-1.01)			
Optimism	0.98 (0.97-0.99)***			
Social support	0.99 (0.98-0.99)***			

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(28)}$ = 6054.18, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001; [a]- Reference category: School

Table 17. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Body Mass Index. WHI Clinical Trial cohort (N= 15814)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Maintainer vs. Mid-High, Medium, Mid-Low, Low Maintainer OR (95% CI)**	**High, Mid-High Maintainer vs. Medium, Mid-Low, Low Maintainer OR (95% CI)**	**High, Mid-High, Medium Maintainer vs. Mid-Low, Low Maintainer OR (95% CI)**	**High, Mid-High, Medium, Mid-Low Maintainer vs. Low Maintainer OR (95% CI)**
Age		0.95 (0.94-0.96)***	0.94 (0.94-0.95)***	0.93 (0.91-0.94)***	0.89 (0.87-0.92)***
Non-white	1.12 (1.01-1.23)*				
College [a]	0.97 (0.90-1.03)				
Postgraduate[a]		0.73 (0.67-0.80)***	0.82 (0.75-0.89)***	0.88 (0.79-0.98)*	0.75 (0.59-0.94)*
Number of Chronic Conditions		1.30 (1.26-1.34)***	1.34 (1.30-1.37)***	1.36 (1.32-1.41)***	1.54 (1.44-1.64)***
General Symptoms	1.07 (1.06-1.09)***				
Depression symptoms	0.99 (0.96-1.02)				
Sleep Disturbances		0.99 (0.98-0.99)*	0.98 (0.97-0.99)***	0.99 (0.98-1.00)	0.97 (0.95-0.99)**
Smoking		0.92 (0.86-0.98)*	0.93 (0.88-0.98)**	1.06 (0.98-1.15)	1.09 (0.93-1.27)
Alcohol consumption		0.97 (0.97-0.98)***	0.96 (0.95-0.97)***	0.95 (0.94-0.96)***	0.94 (0.91-0.97)***
Low fat diet		0.98 (0.91-1.07)	0.87 (0.81-0.93)***	0.80 (0.72-0.88)***	0.68 (0.56-0.83)***
Walking outside		0.88 (0.86-0.90)***	0.84 (0.83-0.86)***	0.80 (0.77-0.82)***	0.73 (0.69-0.77)***
Exercise at age 50	0.97 (0.91-1.02)				
Negative life events	1.02 (1.01-1.03)**				
Optimism	1.01 (0.99-1.02)				
Social support	1.00 (0.99-1.00)				

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(40)}$ = 2037.84, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001; [a]- Reference category: School

Table 18. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Cognitive Performance index. WHI Clinical Trial cohort (N= 6858)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**High Maintainer vs. Medium, Low Maintainer OR (95% CI)**	**High, Medium Maintainers vs. Low Maintainer OR (95% CI)**
Age	1.08 (1.06-1.10) ***		
Non-white		4.99 (4.16-5.98)***	8.31 (5.75-12.02)***
College [a]	0.51 (0.44-0.59)***		
Postgraduate[a]	0.32 (0.26-0.39)***		
Number of Chronic Conditions	1.03 (0.98-1.09)		
General Symptoms	1.06 (1.03-1.09)***		
Depression symptoms	1.01 (0.95-1.08)		
Sleep Disturbances	0.98 (0.96-0.99)**		
Smoking	0.89 (0.79-1.00)		
Alcohol consumption	0.96 (0.94-0.98)***		
Low fat diet	1.00 (0.87-1.14)		
Walking outside	1.08 (0.96-1.14)		
Exercise at age 50	1.05 (0.91-1.20)		
Negative life events	1.01 (0.99-1.04)		
Optimism	0.93 (0.91-0.96)***		
Social support	1.00 (0.99-1.00)		

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(17)}$ = 810.04, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001

[a]- Reference category: School

Table 19. Estimated Odd Ratios (OR) and 95% Confidence Intervals (CI) from a Partial Proportional Odds Model. The model estimates the effect of predictors on ordered trajectories of Vision Loss index. WHI Clinical Trial cohort (N= 17061)

Baseline Characteristics	**Constant components of odds ratio across trajectories OR (95% CI)**	**Normal Maintainer vs. Mild, Moderate Maintainer OR (95% CI)**	**Normal, Mild Maintainer vs. Moderate Maintainer OR (95% CI)**
Age		1.05 (1.04-1.06) ***	1.09 (1.05-1.13) ***
Non-white	1.49 (1.32-1.67) ***		
College [a]	1.06 (0.97-1.16)		
Postgraduate[a]	1.24 (1.13-1.37) ***		
Number of Chronic Conditions	1.14 (1.11-1.17) ***		
Depression symptoms		1.03 (0.99-1.07)	1.18 (1.08-1.28) ***
Sleep Disturbances	1.04 (1.04-1.05) ***		
Smoking	1.06 (0.99-1.13)		
Alcohol consumption	0.99 (0.98-0.99) *		
Low fat diet	1.05 (0.97-1.14)		
Walking outside	0.97 (0.94-0.99) **		
Exercise at age 50	1.06 (0.98-1.15)		
Negative life events	1.04 (1.03-1.05) ***		
Optimism	0.97 (0.95-0.98) ***		
Social support	0.98 (0.98-0.99) ***		

Notes: All variables were entered simultaneously into the partial proportional odds model. Model fit statistic: Likelihood Ratio Chi-Square statistic -LR $chi^2_{(17)}$ = 710.93, ρ<0.001. ORs< 1 denotes benefit for continuous and categorical variables.

* p<0.05 ** p<0.01 *** p<0.001

[a]- Reference category: School

Table 20a. Effects of the baseline predictors on trajectory group membership in the WHI Clinical Trial cohort

Latent Construct	**Health Behaviors**					**Personal Traits**	**Environmental Factors**	
Baseline Indicators / **Trajectories**	**Smoking**	**Alcohol Use**	**Low fat diet**	**Walking outside**	**Exercise at age 50**	**Optimism**	**Negative life events**	**Social support**
BMI	NS	(+)	(+)	(+)	NS	NS	(-)	NS
Physical Activity	NS	(+)	(+)	(+)	(+)	(+)	NS	(+)
Energy/Fatigue	NS	(+)	(+)	(+)	(+)	(+)	NS	(+)
Chair Stands	(-)	NS	NS	(+)	(+)	NS	NS	NS
Grip strength	NS	NS	NS	NS	(+)	(+)	NS	NS
Walking Time	(-)	(+)	NS	(+)	NS	NS	NS	NS
Cognition	(+)	NS	NS	NS	NS	(+)	NS	NS
Vision Loss	NS	(+)	NS	(+)	NS	NS	(-)	(+)

Notes: (-) – significantly decrease odds of being a member in higher functioning trajectory than the reference category; (+) - significantly increase odds of being a member in higher functioning trajectory than the reference category; NS - non significant effect; NA- measurement not available

Table 20b. Effect of the baseline predictors on trajectory group membership in the WHI Clinical Trial cohort

Latent Construct	**Age**	**Socio-Economic Factors**			**Health Status**			
Baseline Indicators / **Trajectories**	**Age**	**Non-White**	**Postgraduate**	**College**	**Chronic Conditions**	**Sleep Disturbances**	**General symptoms**	**Depression**
BMI	(+)	(-)	(+)	NS	(-)	(+)	(-)	NS
Physical Activity	(-)	(-)	(+)	(+)	(-)	NS	(-)	NS
Energy/Fatigue	(-)	(+)	NS	(-)	(-)	(-)	(-)	(-)
Chair Stands	(-)	NS	(+)	NS	(-)	(+)	(-)	NS
Grip strength	(-)	NS	NS	NS	NS	NS	(-)	NS
Walking Time	(-)	(-)	NS	NS	(-)	(-)	(-)	NS
Cognition	(-)	(-)	(+)	(+)	(-)	(+)	(-)	NS
Vision Loss	(-)	(-)	(-)	NS	(-)	(-)	NA	NS

Notes: (-) – significantly decrease odds of being a member in more robust trajectory than the reference category; (+) - significantly increase odds of being a member in more robust trajectory than the reference category; NS - non significant effect; NA-measurement not available

Table 21. Relative hazard of mortality and first incidence of hospitalization by membership in longitudinal trajectory groups of Grip Strength Test in WHI Clinical Trial cohort, N=4389

Trajectory group	Mortality n (%)	Mortality Hazard Ratio (95% CI)		Hospitalization n (%)	Hospitalization Hazard Ratio (95% CI)	
		Model 1[a] (n=4389)	Model 2[b] (n=3528)		Model 1[c] (n=4389)	Model 2[d] (n=3528)
High Maintainer	7 (5.9)	1.00 (reference)	1.00 (reference)	18 (15.1)	1.00 (reference)	1.00 (reference)
Medium Decliner	123 (9.2)	1.37 (0.64-2.93)	1.70 (0.62-4.62)	344 (25.6)	1.67 (1.04-2.69)*	1.46 (0.87-2.45)
Mid-Low Decliner	277 (12.3)	1.68 (0.79-3.56)	2.11 (0.78-5.69)	629 (27.9)	1.77 (1.11-2.83)**	1.52 (0.91-2.55)
Low Decliner	108 (16.0)	2.00 (0.93-4.33)	2.67 (0.97-7.31)	214 (31.8)	1.96 (1.21-3.18)**	1.72 (1.01-2.92)*

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

** $p < .01$; *** $p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 22. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of Timed Chair Stands test in WHI Clinical Trial cohort, N=4389

Trajectory group	**Mortality n (%)**	**Mortality Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hospitalization Hazard Ratio (95% CI)**	
		Model 1[a] (n=4389)	Model 2[b] (n=3528)		Model 1[c] (n=4389)	Model 2[d] (n=3528)
High Maintainer	21 (8.0)	1.00 (reference)	1.00 (reference)	47 (18.0)	1.00 (reference)	1.00 (reference)
Medium Decliner	155 (9.6)	1.16 (0.74-1.83)	1.07 (0.65-1.75)	399 (23.0)	1.29 (0.95-1.75)	1.21 (0.86-1.69)
Low Decliner	321 (11.7)	1.57 (1.01-2.45)*	1.22 (0.75-2.00)	737 (31.4)	1.83 (1.36-2.46)***	1.35 (0.97-1.89)

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

**$p < .01$; ***$p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 23. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of 6-Meter Walking Time in WHI Clinical Trial cohort , N= 4389

Trajectory group	**Mortality n (%)**	**Mortality Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hospitalization Hazard Ratio (95% CI)**	
		Model 1[a] (n=4389)	Model 2[b] (n=3528)		Model 1[c] (n=4389)	Model 2[d] (n=3528)
Low Increaser	337 (10.3)	1.00 (reference)	1.00 (reference)	798 (24.3)	1.00 (reference)	1.00 (reference)
Medium Increaser	160 (16.4)	1.44 (1.19-1.74)***	1.16 (0.93-1.45)	368 (37.6)	1.65 (1.45-1.87)***	1.23 (1.06-1.43)**
High Curver	19 (15.3)	1.46 (0.92-2.32)	1.15 (0.64-2.06)	38 (30.7)	1.30 (0.94-1.80)	1.05 (0.72-1.55)

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

**$p < .01$; ***$p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 24. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of Energy/Fatigue Index in WHI Clinical Trial cohort, N=19880

Trajectory group	**Mortality n (%)**	**Mortality Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hospitalization Hazard Ratio (95% CI)**	
		Model 1[a] (n=19880)	Model 2[b] (n=15811)		Model 1[c] (n=19880)	Model 2[d] (n=15811)
High Decliner	70 (7.1)	1.00 (reference)	1.00 (reference)	177 (18.0)	1.00 (reference)	1.00 (reference)
Medium Decliner	679 (9.4)	1.33 (1.04-1.70) *	1.56 (1.16-2.10) **	1,658 (23.0)	1.31 (1.12-1.53) **	1.28 (1.07-1.53) **
Mid-Low Decliner	892 (12.8)	1.75 (1.37-2.23) ***	2.05 (1.52-2.77) ***	2,031 (29.1)	1.73 (1.49-2.02) ***	1.50 (1.25-1.80) ***
Low Decliner	769 (16.3)	2.27 (1.77-2.90) ***	2.64 (1.93-3.62) ***	1,675 (35.5)	2.25 (1.93-2.63) ***	1.66 (1.37-2.01) ***

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

** $p < .01$; *** $p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 25. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of Physical Activity Index in WHI Clinical Trial cohort, N=19884

Trajectory group	**Mortality n (%)**	**Mortality Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hospitalization Hazard Ratio (95% CI)**	
		Model 1[a] (n=19884)	Model 2[b] (n=15812)		Model 1[c] (n=19884)	Model 2[d] (n=15812)
High Maintainer	805 (9.9)	1.00 (reference)	1.00 (reference)	1,955 (24.0)	1.00 (reference)	1.00 (reference)
Mid-Low Improver	188 (10.7)	1.14 (0.97-1.34)	1.06 (0.87-1.28)	475 (27.00)	1.17 (1.06-1.29) **	1.00 (0.88-1.13)
Medium Decliner	793 (13.5)	1.35 (1.23-1.49) ***	1.33 (1.18-1.49) ***	1,715 (29.2)	1.26 (1.18-1.34) ***	1.09 (1.01-1.18) **
Low Maintainer	625 (15.2)	1.55 (1.39-1.72) ***	1.41 (1.22-1.63) ***	1,397 (34.0)	1.54 (1.44-1.65) ***	1.26 (1.15-1.39) ***

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

** $p < .01$; *** $p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 26. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of Body Mass Index in WHI Clinical Trial cohort, N=19887.

Trajectory group	**Mortality n (%)**	**Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hazard Ratio (95% CI)**	
		Model 1[a] (n=19887)	Model 2[b] (n=15813)		Model 1[c] (n=19887)	Model 2[d] (n=15813)
Low Maintainer	567 (12.6)	1.00 (reference)	1.00 (reference)	1,164 (25.9)	1.00 (reference)	1.00 (reference)
Mid-Low Maintainer	786 (11.2)	0.90 (0.80-1.00)	0.87 (0.77-0.99)*	1,807 (25.7)	1.00 (0.93-1.08)	0.93 (0.86-1.02)
Medium Maintainer	625 (12.3)	1.04 (0.93-1.16)	0.96 (0.84-1.10)	1,469 (28.9)	1.17 (1.09-1.27)***	1.01 (0.92-1.10)
Mid-High Maintainer	339 (12.9)	1.15 (1.01-1.32)*	0.97 (0.82-1.14)	883 (33.7)	1.45 (1.33-1.59)***	1.12 (1.01-1.25)*
High Maintainer	94 (14.2)	1.39 (1.12-1.73)**	1.05 (0.81-1.37)	220 (33.1)	1.50 (1.30-1.74)***	1.12 (0.95-1.32)

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

**$p < .01$; ***$p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 27. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of Cognitive Performance index in WHI Clinical Trial cohort, N=8704

Trajectory group	**Mortality n (%)**	**Mortality Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hospitalization Hazard Ratio (95% CI)**	
		Model 1[a] (n=8704)	Model 2[b] (n=6857)		Model 1[c] (n=8704)	Model 2[d] (n=6857)
High Maintainer	803 (11.7)	1.00 (reference)	1.00 (reference)	1,975 (28.7)	1.00 (reference)	1.00 (reference)
Medium Maintainer	278 (17.4)	1.35 (1.18-1.55)***	1.35 (1.13-1.60)**	489 (30.5)	1.05 (0.95-1.16)	1.08 (0.96-1.22)
Low Maintainer	50 (22.9)	1.82 (1.36-2.42)***	1.72 (1.14-2.60)**	70 (32.1)	1.15 (0.91-1.46)	1.02 (0.73-1.42)

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, general symptoms, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

**$p < .01$; ***$p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Table 28. Relative Hazard of Mortality and First Incidence of Hospitalization by Membership in Longitudinal Trajectory Groups of Vision Loss index in WHI Clinical Trial cohort, N=19886

Trajectory group	**Mortality n (%)**	**Mortality Hazard Ratio (95% CI)**		**Hospitalization n (%)**	**Hospitalization Hazard Ratio (95% CI)**	
		Model 1[a] (n=19886)	Model 2[b] (n=15813)		Model 1[c] (n=19886)	Model 2[d] (n=15813)
Normal Maintainer	1,814 (11.6)	1.00 (reference)	1.00 (reference)	4,191 (26.8)	1.00 (reference)	1.00 (reference)
Mild Maintainer	560 (13.9)	1.13 (1.03-1.25)**	1.04 (0.94-1.16)	1,271 (31.7)	1.19 (1.12-1.27)***	1.11 (1.03-1.19)**
Moderate Maintainer	36 (15.4)	1.18 (0.85-1.64)	1.14 (0.79-1.63)	80 (34.2)	1.33 (1.07-1.66)**	1.14 (0.89-1.46)

Note: Follow-up averaged 13.01 years

[a] Adjusted for age and years of follow up in WHI at the start of Extension study

[b] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, optimism, negative life events and social support

[c] Adjusted for age and years of follow up in WHI at the start of Extension study

[d] Adjusted for age, years of follow up in WHI at the start of Extension study, ethnicity, education, health behaviors (i.e., smoking, alcohol consumption, low fat diet, recreational walking and vigorous exercise at age 50), number of chronic co-morbidities, depression symptoms, sleep disturbances, optimism, negative life events, social support and number of hospitalization prior to start of Extension Study.

** $p < .01$; *** $p < .001$.

CI=confidence interval; WHI=Women's Health Initiative

Figure 1. Estimated trajectories of Grip Strength test during 9 years of follow up in WHI Clinical Trial, N=4335

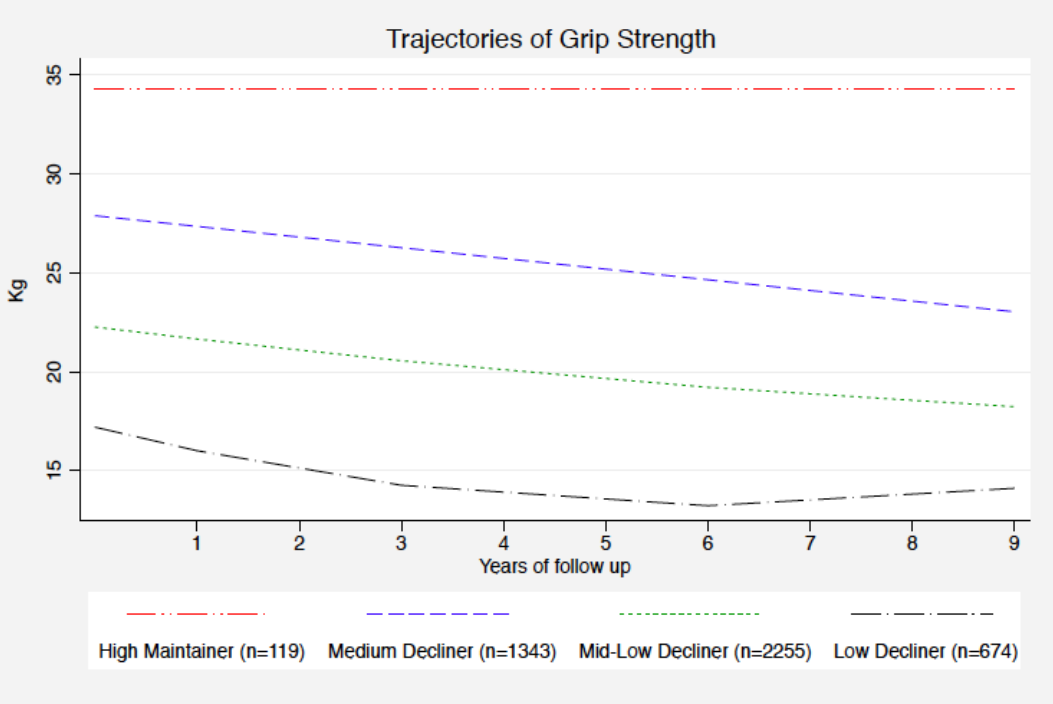

Figure 2. Estimated trajectories of Timed Chair Stand during 9 years of follow up in WHI Clinical Trial, N=4191

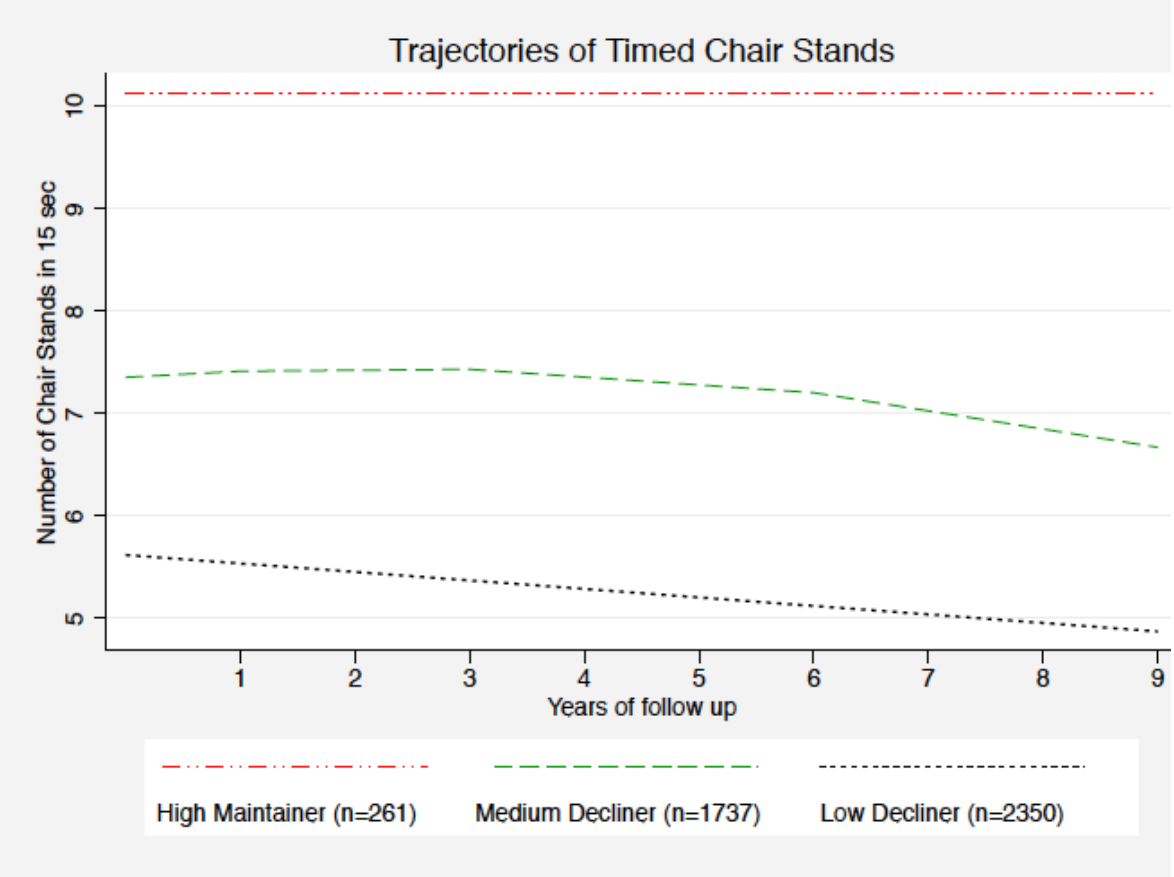

Figure 3. Estimated trajectories of 6-Meter Walking Time during 9 years of follow up in WHI Clinical Trial, N=4321

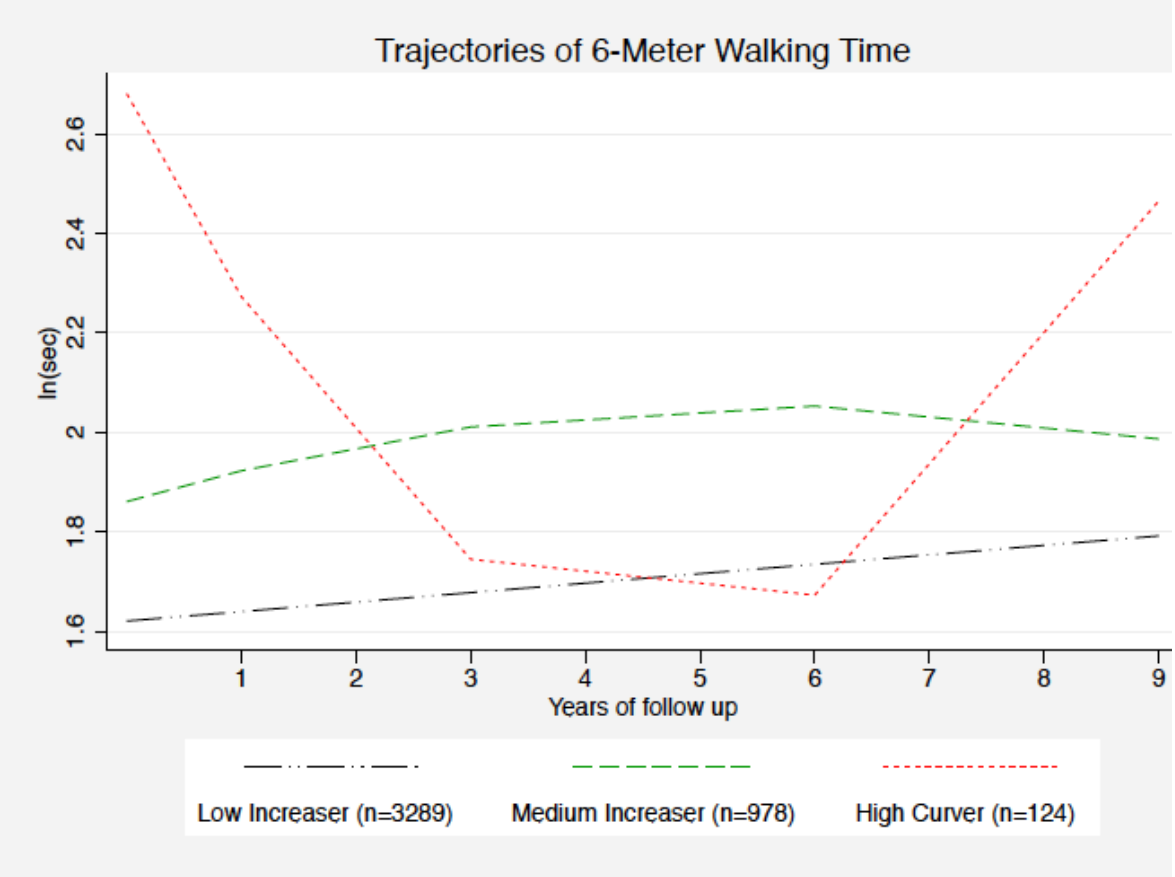

Figure 4. Estimated trajectories of Energy/Fatigue index during 9 years of follow up in WHI Clinical Trial, N=19645

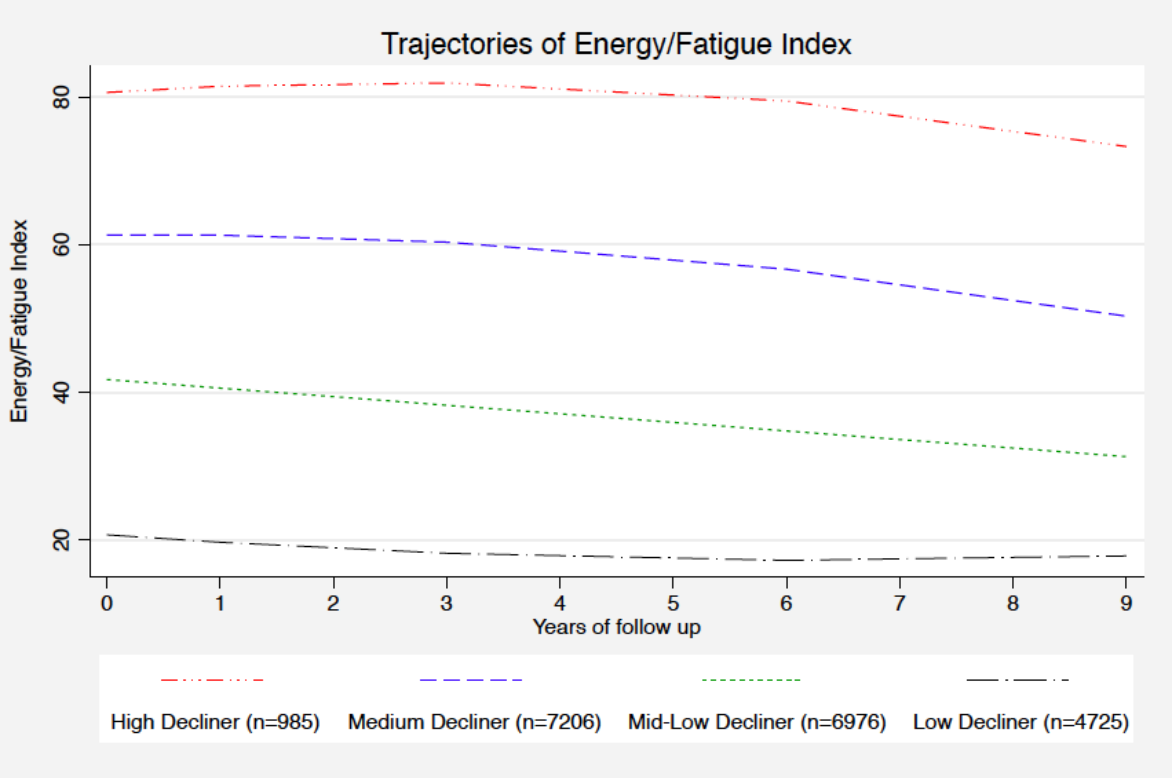

Figure 5. Estimated trajectories of Physical Activity index during 9 years of follow up in WHI Clinical Trial, N= 19563

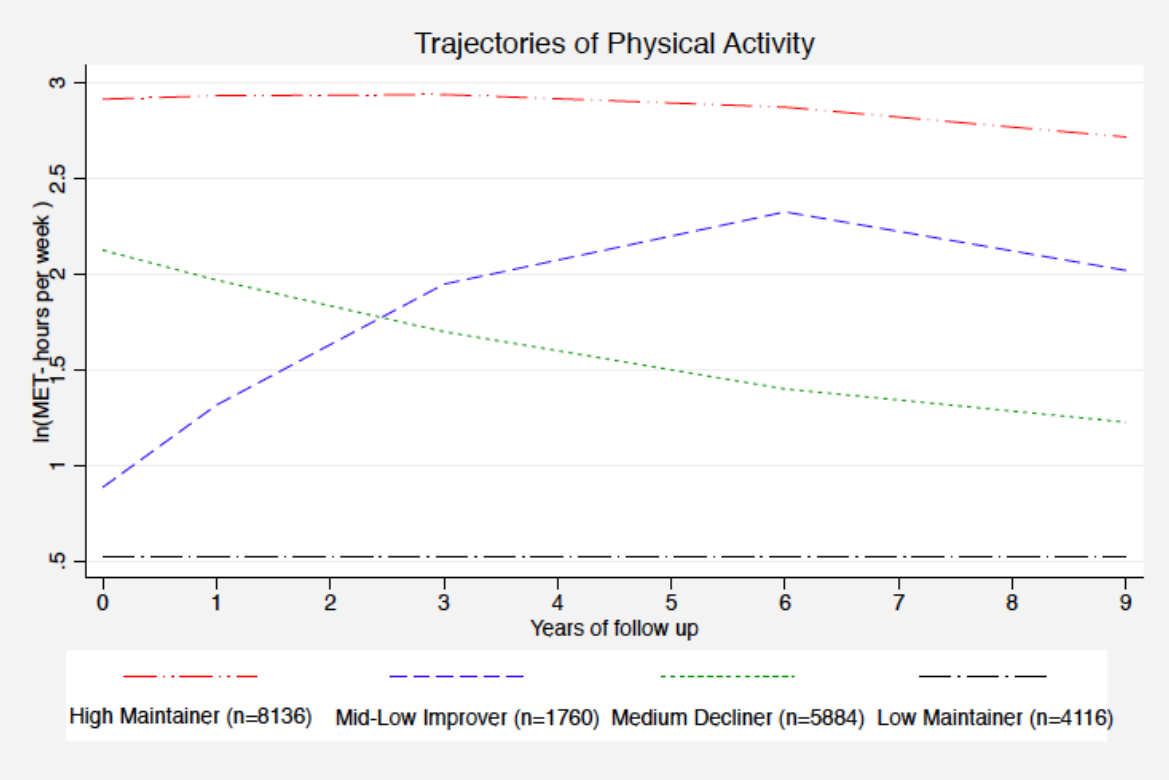

Figure 6. Estimated trajectories of Body Mass index during 9 years of follow up in WHI Clinical Trial, N=19792

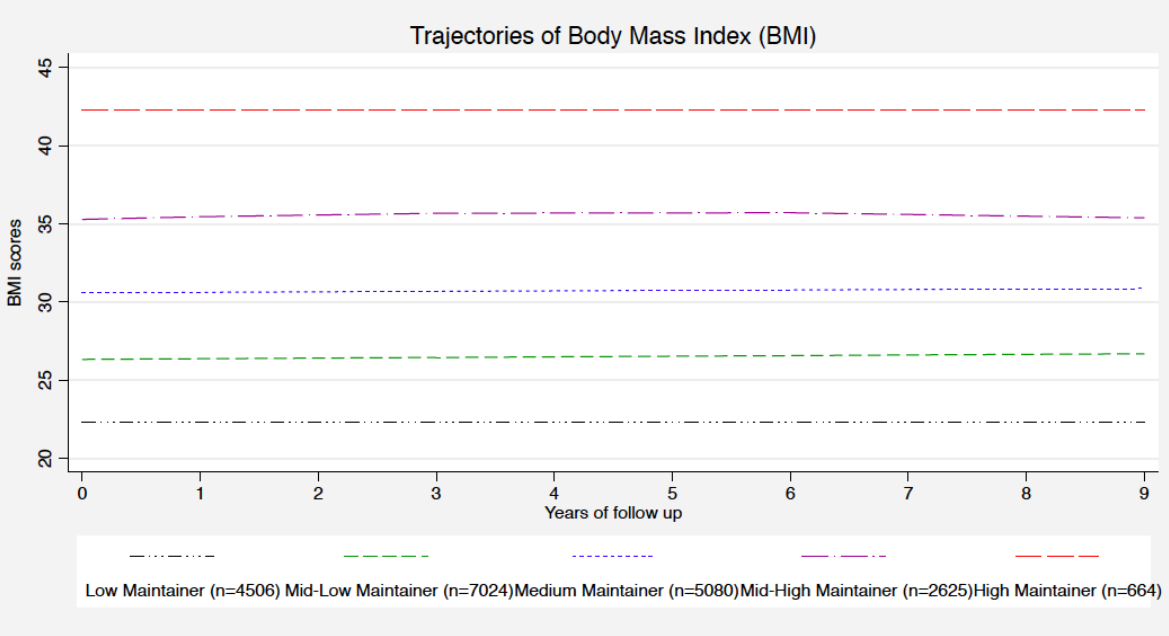

Figure 7. Estimated trajectories of Cognitive Performance index during 9 years of follow up in WHI Clinical Trial, N=8396

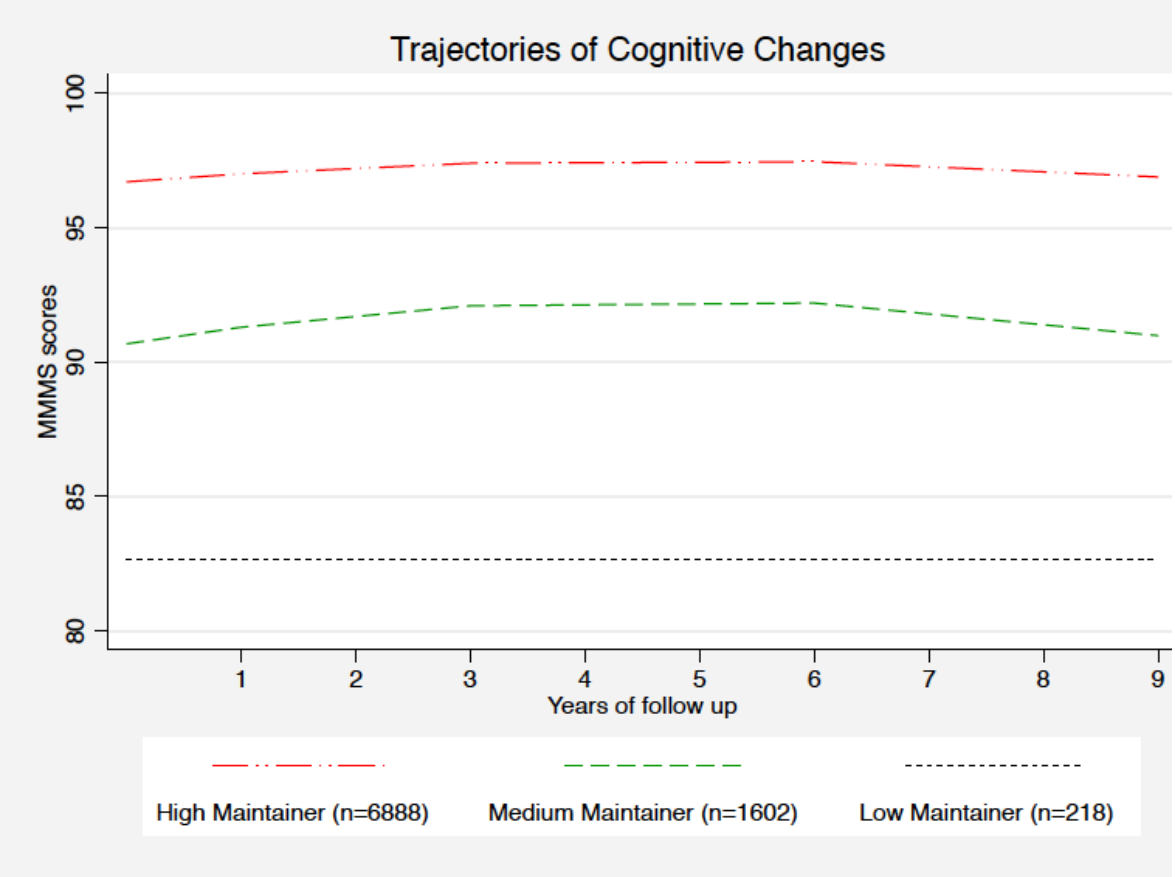

Figure 8. Estimated trajectories of Vision Loss index during 9 years of follow up in WHI Clinical Trial, N=15880