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Item Type	Doctoral Dissertation
Authors	Yuan, Yiyang
DOI	10.13028/r7w2-p162
Publisher	UMass Chan Medical School
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Download date	2025-04-30 01:30:55
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Physical Frailty and Cognitive Impairment in Older U.S. Nursing Home Residents

Yiyang Yuan
University of Massachusetts Chan Medical School

PHYSICAL FRAILTY AND COGNITIVE IMPAIRMENT IN OLDER U.S. NURSING HOME RESIDENTS

A Dissertation Presented

By

YIYANG YUAN

Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Sciences, Worcester

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

FEBRUARY 28, 2022

CLINICAL AND POPULATION HEALTH RESEARCH

PHYSICAL FRAILTY AND COGNITIVE IMPAIRMENT IN OLDER U.S. NURSING HOME RESIDENTS

A Dissertation Presented

By

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This work was undertaken in the Graduate School of Biomedical Sciences

Clinical and Population Health Research Program

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DEDICATION

To my parents Liu Qun and Yuan Decheng,

and my husband Li Mingli

ACKNOWLEDGEMENTS

I still remember that 7 A.M. drive exactly five years ago for my interview with the CPHR doctoral program. The signature New England winter chill remains still, but I have grown so much both as a person and as an aspiring researcher ever since that day because I am fortunate to have experienced this most rewarding journey with everyone here.

I am beyond thankful for my mentors Drs. Christine Ulbricht and Kate Lapane, from introducing the CPHR program to and giving a clueless student your name card back in the APHA conference in 2016, to providing all the resources and opportunities that a mentee can ever dream of during the doctoral studies. Never would I ever imagine that one day, I, too, am qualified and capable to pursue a career as an independent researcher. And that day is today, and it is you that made it possible.

I would like to extend my absolute gratitude to my thesis research advisory committee, Drs. Jennifer Tjia, Jonggyu Baek, and Shao-Hsien Liu, for your thought-provoking questions during every meeting, constructive feedback for each paper revision, and the encouragement all the way through. I want to also send my sincere appreciation to Drs. Stephenie Lemon, Sarah Forrester, and Andrea Gruneir for serving on my dissertation exam committee along with Drs. Tjia and Baek. This dissertation will not be what it is today without all of your wisdom and guidance.

I deeply appreciate the professors, friends, and staff in our department who have always supported me. To Drs. Anthony Nunes, Bill Jesdale, Bruce Barton, Catherine Dube, Jeroan Allison, Matthew Alcusky, Rob Goldberg, and Sharina Person, for sharing your knowledge and expertise so I can confidently conduct my own research. To everyone in our CPHR family, especially Ariel Beccia, Eric Ding, Eric Romo, Danni Zhao, Deb Mack, Grace Masters, Julie Hugunin, Maira Castaneda-Avila, NienChen Li, and Qiaoxi Chen, for all the joy we shared and the challenges we fought through together. To the staff in our department, especially Ms. Kelley Baron and Mandy O'Reilly, for your patience and assistance, without which I can never navigate through the administrative side of things.

I am grateful for the support from people outside of our department as well, including Dr. Jeffery Burr and Changmin Peng from UMass Boston, and my past mentors Dr. Angela Walter from UMass Lowell and Dr. Lewis Kazis from Boston University.

I want to thank the National Institutes on Aging F99 Award to conduct this dissertation research. I also want to thank all the nursing home residents, whom I will never know personally, for sharing perhaps the most vulnerable times of your life with a student.

Last but not the least, I could never do this alone without the unwavering love from my parents and husband, my friends, and my lovely cats. Thank you all for being my inspiration and my motivation.

ABSTRACT

Background

For the 1.2 million older adults residing in U.S. nursing homes, little is known about their experience with physical frailty and cognitive impairment, two critical interrelated aging conditions.

Methods

Minimum Data Set 3.0 was used. Physical frailty was measured by FRAIL-NH and cognitive impairment by Brief Interview for Mental Status and Cognitive Performance Scale. Demographic and clinical characteristics were adjusted accordingly. Aim 1 described the prevalence of physical frailty and cognitive impairment and longitudinally examined the association between two conditions with the non-proportional odds model. Aim 2 used latent class analysis to identify physical frailty subgroups and estimated their association with cognitive impairment using multinomial logistic regression. Aim 3 fitted group-based trajectory models to identify physical frailty trajectories and cognitive impairment trajectories and quantified the association between the two sets of trajectories.

Main Results

Around 60% of older residents were physically frail and 68% had moderate/severe cognitive impairment, with improvement and worsening observed in both conditions, particularly in the first three months. Older residents with moderate/severe cognitive impairment were consistently and increasingly more likely to be frail.

Three physical frailty subgroups were identified at admission. Greater cognitive impairment was associated with higher odds to belong to “severe physical frailty”.

Five physical frailty trajectories and three cognitive impairment trajectories were identified over the first six months. One in five older residents were “Consistently Frail” and “Consistently Severe Cognitive Impairment”.

Conclusion

Findings emphasized the need for care management tailored to the heterogeneous presentations and progression trajectories of physical frailty and cognitive impairment.

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LIST OF ABBREVIATIONS

(In Alphabetic Order)

ACRONYM	MEANING
AIC	Akaike Information Criterion
AvePP	Group average posterior probability
BIC	Bayesian Information Criterion
BIMS	Brief Interview for Mental Status
CMS	Centers for Medicare & Medicaid Services
COPD	Chronic obstructive pulmonary disease
CPS	Cognitive Performance Scale
GBTM	Group-based trajectory model
IAGG	International Association of Gerontology and Geriatrics
IANA	International Academy on Nutrition and Aging
ID/DD facility	Facilities for individuals with intellectual or developmental disabilities
LCA	Latent class analysis
MDS 3.0	Minimum Data Set 3.0
MI	Measurement invariance
MLR	Maximum likelihood with robust standard error
NPOM	Non-proportional odds model
OCC	Odds of correct classification
PHQ-9	Patient Health Questionnaire-9
SNF	Skilled nursing facility
TIA	Transient ischemic attack
TV	Time-varying

LIST OF COPYRIGHTED MATERIALS PRODUCED BY THE AUTHOR*

As of February 2022, the following dissertation papers have been published in peer-reviewed journals:

1. Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. Physical Frailty and Cognitive Impairment in Older Adults in United States Nursing Homes. Dement Geriatr Cogn Disord. 2021;50(1):60-67. doi: 10.1159/000515140. Epub 2021 Apr 22. PMID: 33887723; PMCID: PMC8243819.

2. Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. Physical frailty and cognitive impairment in older nursing home residents: a latent class analysis. BMC Geriatr. 2021 Sep 7;21(1):487. doi: 10.1186/s12877-021-02433-1. PMID: 34493211; PMCID: PMC8425049.

*See **PREFACE** for detailed information on all publications by chapter, including peer-reviewed publications accepted *and*/or under review in addition to accepted abstracts for presentations.

PREFACE

The work presented in this dissertation, including texts, tables and figures, have been presented at conferences and published (or is currently under review) in peer-review journals. Presentation and publication citations by chapter as of February 2022 are summarized below.

Chapter III: Prevalence of Physical Frailty and Cognitive Impairment in Older Nursing Home Residents

Presentation:

Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. (2020 December) Physical Frailty and Cognitive Impairment in Older Nursing Home Residents in the United States: A Longitudinal Study. Poster presentation. Society for Epidemiologic Research (SER) Conference.

Publication:

Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. Physical Frailty and Cognitive Impairment in Older Adults in United States Nursing Homes. Dement Geriatr Cogn Disord. 2021 Apr 22:1-8. doi: 10.1159/000515140. Epub ahead of print. PMID: 33887723.

Chapter IV: Presentation of Physical frailty by Cognitive Impairment in Older Nursing Home Residents

Presentation:

Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. (2021 November) Physical frailty and cognitive impairment in older nursing home residents: a latent class analysis. Gerontological Society of America (GSA) Annual Scientific Meeting.

Publication:

Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. Physical frailty and cognitive impairment in older nursing home residents: a latent class analysis. BMC Geriatr. 2021 Sep 7;21(1):487. doi: 10.1186/s12877-021-02433-1. PMID: 34493211; PMCID: PMC8425049

Chapter V: Progression of Physical frailty and Cognitive Impairment in Older Nursing Home Residents

Presentation:

Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. (2021 September-October) Physical frailty trajectories in older U.S. nursing home residents. Oral presentation. 11th International Conference on Frailty and Sarcopenia Research (ICFSR).

Publication:

Yuan Y, Lapane KL, Tjia J, Baek J, Liu SH, Ulbricht CM. Trajectories of physical frailty and cognitive impairment in older adults in United States nursing homes (*Under review at BMC Geriatrics*)

CHAPTER I.

INTRODUCTION

I. Overview

As the aging population continues to grow globally, the demand for long-term care is expected to increase. Although older adults prefer "aging in place" with home- or community-based services[1], older adults with extensive functional decline and unable to live independently may need to rely on facility-based care, such as from nursing homes, an important healthcare sector providing long-term residence and services to older adults. In the U.S., nursing homes provide services to about 1.2 million older adults[2]. However, despite being an integral part of the aging population, older U.S. nursing home residents are often neglected in research, compared to their community-dwelling counterparts.

Of particular interest are two aging-related conditions: physical frailty and cognitive impairment. Physical frailty is characterized by decreased physiologic reserve and increased vulnerability to stressors[3]. About 15% of U.S. community-dwelling older adults above the age of 65 experience physical frailty[4]. Cognitive impairment ranges from mild cognitive impairment to dementia with progressive loss in cognitive function[5], which respectively affects 22%[5] and 15%[6] of older adults aged 70 years or older. Physical frailty and cognitive impairment share many risk factors, often co-occur, and are shown to predict the future onset of each other[5,7–14]. Although the underlying mechanism has not yet been clarified, their close interrelationship may reflect a shared neuropathology[15], concomitant yet separate outcomes of the aging process, or "cognitive frailty", defined as the co-existence of both conditions without overt dementia and other neurological

conditions[16,17]. Physical frailty and cognitive impairment are associated with numerous adverse health-related outcomes, including decreased functional independence[18–22] and mortality[23], as well as high healthcare costs[24–28] and substantial caregiver burden[29,30]. Not surprisingly, both conditions also predict older adults' admission to nursing homes[31,32], but little is known about the experience of those who reside in nursing homes for an extended period of time.

II. Prevalence of Physical Frailty and Cognitive Impairment in U.S. Nursing Home Residents

There is a lack of consistent, longitudinal estimates of the prevalence of physical frailty and cognitive impairment during older adults' nursing home residence. Previous studies estimated that 30-85% of nursing home residents were physically frail[33,34]. This wide range of prevalence estimates may be attributed to the variations in the operationalization of physical frailty, clinical profiles of the samples, and nursing home settings. For cognitive impairment, the Centers for Medicare & Medicaid Services (CMS) reported that on a given day, 26% of older residents would experience moderate and 39% severe impairment[2]. However, all of these estimates were cross-sectional. The average length of nursing home stay is 835 days, with 56.4% older residents living in nursing homes for over a year[35]. During this prolonged stay, changes in physical and cognitive functions may occur, which may not be captured by the cross-sectional estimates[36]. As such, research examining the prevalence of physical frailty and cognitive impairment and resident characteristics associated with these two conditions in

nursing homes using standardized metrics on the national level with a longitudinal study design is warranted.

III. Presentation of Physical Frailty and Cognitive Impairment in U.S. Nursing Home Residents

Physical frailty can encompass weakness, slowness, low level of physical activity, weight loss, and exhaustion[3]. Multifaceted clinical presentations of physical frailty have been observed in community older adult cohorts[37,38]. For example, three physical frailty subgroups were identified in community-dwelling older adults in Taiwan, with one group characterized by slowness and weakness, one by weight loss and exhaustion, and one by low physical activity[37]. It is unknown if such heterogeneity is consistent in older adults in nursing homes, and if it would be influenced by the frequently co-occurring cognitive impairment[18]. The presentations of physical frailty may largely vary across residents with different levels of cognitive impairment. Residents with severe cognitive impairment may be more likely to experience a particular subgroup of physical frailty symptoms than those with less severe impairment. Findings on how specific subgroups of physical frailty interact with cognitive impairment could provide insight into mechanisms underlying the two conditions in nursing home residents.

On the other hand, intervention studies have shown success in improving physical frailty in community older adults[39,40], but it is unknown if these interventions can translate to older nursing home residents without understanding the clinical profiles of physical frailty in this population. Some interventions have

been effective in specific physical domains like muscle strength, aerobic capacity, gait speed, and energy[41–45]. If physical frailty manifests predominantly as limited mobility in one subgroup of residents and low activity in another, interventions that improve mobility may not effectively apply to the other subgroup. Results could inform future work to tailor care and manage physical frailty domains by cognitive impairment in nursing home settings.

IV. Progression of Physical Frailty and Cognitive Impairment in U.S. Nursing Home Residents

In a cohort of community-dwelling older adults in New Haven, CT, four trajectory groups of physical frailty and cognitive impairment were identified, including one “cognitive frailty” group marked by the simultaneously accelerated worsening of both conditions[46]. For older nursing home residents, the trajectories might differ due to their complex clinical profiles. Identifying the trajectories of physical frailty and cognitive impairment over time could expand our knowledge on how these conditions progress in this population.

Physical frailty has been recognized as a dynamic syndrome. Older adults can experience a decline in physical frailty but with proper care management and intervention, there is the potential to improve physical frailty[47–50], leading to the consensus that physical frailty could act as a promising target for intervention to address the functional decline in older adults[51]. Given the close interrelationship between physical frailty and cognitive impairment and that the progression of physical frailty is potentially reversible[47–49], effectively slowing the progression of

physical frailty through the comprehensive clinical management[50,51] may also have the potential to reduce cognitive decline. Evaluating the extent to which trajectories of physical frailty are associated with the trajectories of cognitive impairment in older nursing home residents could help identify older residents more likely to improve or who may be at risk for accelerated worsening for either or both conditions to inform timely and proper treatment in the nursing home setting.

V. Specific Aims

This dissertation thus sought to examine the prevalence, presentation, and progression of physical frailty and cognitive impairment in older U.S. nursing home residents to provide a fundamental understanding of older adults' experience of these two conditions while residing in a U.S. nursing home. Explicitly, the study intended to answer three research questions:

Research Question 1: In older nursing home residents, what are the prevalence of physical frailty and cognitive impairment, and how are these two conditions associated over time?

Research Question 2: In older nursing home residents, how do their clinical presentations of physical frailty vary, and to what extent are such variations impacted by cognitive impairment?

Research Questions 3: In older nursing home residents, how do physical frailty and cognitive impairment progress over time, and how are these progressions associated?

To answer these questions, this study was conducted with three respective specific aims that would be addressed by each chapter:

Aim 1 (Chapter III): To examine the prevalence of physical frailty and its association with cognitive impairment in older adults' first six months in a nursing home

Aim 2 (Chapter IV): To identify the subgroups of physical frailty in older nursing home residents and examine if the subgroups vary by cognitive impairment at nursing home admission

Aim 3 (Chapter V): To describe the trajectories of physical frailty and cognitive impairment and examine the associations between the two sets of trajectories over older adults' first six months in a nursing home

CHAPTER II.

DATA SOURCE AND MAIN MEASURES

This chapter introduces the data source and instruments used to measure physical frailty and cognitive impairment that were used across all three aims. Methodological details specific to each aim will be presented in later chapters.

I. Data Source

The national nursing home database, Minimum Data Set (MDS) 3.0 (2014-2016), was used. MDS 3.0 is federally mandated for all residents in Medicaid-/Medicare-certified nursing homes. It is conducted at nursing home admission, quarterly, annually, and when significant changes in residents' health occur, collecting data on residents' demographics, physical functioning, cognitive functioning, mood, bladder and bowel conditions, nutritional status, diagnoses, pain, and receipt of medications and other treatment[52].

II. Main Measures

Physical frailty

The FRAIL-NH scale was used (**Table 2.1**). This scale was used developed to measure physical frailty in nursing homes using MDS 3.0 items on *Fatigue*, *Resistance*, *Ambulation*, *Incontinence*, *Loss of weight*, *Nutritional approach* and *Help with dressing*[53,54]. As shown in **Table 2.1**, each item is scored and the total summary score ranges from 0 to 13[53]. FRAIL-NH was shown to comparable performance in identifying residents with physical frailty as other well-established metrics such as the Frailty Phenotype and the Frailty Index in assessing physical frailty in nursing home residents[33,54–60]; physical frailty as assessed by FRAIL-NH was consistently predictive of adverse health outcomes[33,54–59].

Table 2.1. Items in the FRAIL-NH scale

Items	Item Score			Items in MDS 3.0
	0	1	2	
Fatigue[1]	No (never or 1 day)	Yes (several days or everyday)	PHQ-9 ≥ 10	Section D Mood: D0300/D0600; D0200-D/D0500-D
Resistance[2]	Independent	With set-up only	Need physical assistance	Section G Functional Status: G0110B2
Ambulation[3]	Independent	With assistive device (walker/cane)	Cannot walk	Section G Functional Status: G0110E1; G0110F1; G0600A; G0600B; G0600C
Incontinence	None	Urinary incontinence only	Bowel incontinence	Section H Bladder and Bowel: H0300; H0400
Loss of weight	None	≥ 5% in the past 3 months or ≥ 10% in the past 6 months	n/a [4]	Section K Swallowing/Nutritional Status: K0300
Nutritional approach	Regular diet	Mechanically altered diet	Require feeding tube	Section K Swallowing/Nutritional Status: K0500
Help with dressing	Independent	Need help with set up only	Need physical help	Section G Functional Status: G0110G2

Notes.
[1] Based on residents' response to the Patient Health Questionnaire (PHQ-9; MDS 3.0 Section D: Mood).
[2] Measures if the resident needs assistance to be transferred from one location to another.
[3] Measures if the resident can walk in a room.
[4] This item will only receive a score of 0 or 1. A score of 2 is not applicable.

Cognitive impairment

In MDS 3.0, cognitive impairment can be measured either by the Brief Interview for Mental Status (BIMS; total score: 0-15; MDS 3.0 Section C)[61], which is administered when residents can self-report their cognitive status, or the Cognitive Performance Scale (CPS; score range: 0-6; MDS 3.0 Section C), which is completed by staff when residents cannot participate in BIMS[62,63]. The BIMS focuses on temporal orientation and ability to recall, while the CPS focuses on short-term memory, cognitive skills for decision making, ability to make themselves

understood, eating, and comatose state. Both were shown to be highly correlated with the widely-used clinical tools for cognitive function, such as the Mini-Mental State Examination and the Modified Mini-Mental State Examination[61–64], and deemed feasible for the nursing home population.

CHAPTER III.

PRESENTATION OF PHYSICAL FRAILTY BY COGNITIVE IMPAIRMENT IN OLDER NURSING HOME RESIDENTS

(Note: The texts, tables, and figures in this chapter are based on the manuscript published on *Dementia and Geriatric Cognitive Disorders*. Refer to the **LIST OF COPYRIGHTED MATERIAL PRODUCED BY THE AUTHOR** and **PREFACE** for the publication citation for Chapter III.)

I. Introduction

Physical frailty is characterized by decreased physiologic reserve and increased vulnerability to exogenous stressors[3] and affects 15% of U.S. community-dwelling older adults[4]. Older adults with physical frailty are at elevated risks for falls, functional dependency, lowered quality of life, decreased life expectancy, and mortality[65–67]. Physical frailty also predicts older adults' admission to nursing homes[31]. U.S. nursing homes provide care to over 1.2 million older adults[2]. However, there is limited national-level research examining the burden of physical frailty and its associated characteristics after older adults entered nursing homes.

The early period of nursing home stay is not only a critical window for older residents to adjust to the changes in clinical care and living environment but also a time when functional impairment could impact those adjustments and their long-term health outcomes[36,68]. Physical frailty is a dynamic condition and older adults may improve or decline across its spectrum[47,49,69]. Understanding the "natural history" of physical frailty over the early course of nursing home stay is important, as it may be a promising, potentially modifiable, target for intervention[51].

Nearly two-thirds of older nursing home residents experience moderate to severe cognitive impairment[2]. Yet, little is known about the extent to which cognitive impairment impacts physical frailty during older adults' nursing home residence. Given the strong correlation between physical frailty and cognitive impairment in community-dwelling older adults[18,70,71], it is likely that older nursing

home residents with more severe cognitive impairment would experience greater physical frailty. However, no studies have quantified this association in older nursing home residents.

To address these gaps, we conducted this longitudinal study using national nursing home data MDS 3.0. The objectives were to (1) estimate the prevalence of physical frailty at admission, 3 months and 6 months, (2) describe the changes in the prevalence of physical frailty over time; and (3) examine the association between physical frailty and cognitive impairment during older adults' first six months in nursing homes.

II. Methods

The University of Massachusetts Chan Medical School Institutional Review Board approved this study as exempt from federal regulations (09/20/2019).

Sample

Using the MDS 3.0, nursing home residents were eligible if they were (1) newly admitted between 01/01/2014 and 06/30/2016, (2) aged 65 years and over with a life expectancy of six months or greater at admission, (3) stayed in the nursing home for 6 months or longer, and (4) had MDS 3.0 assessments at admission, 3 months and 6 months of nursing home residence.

"Newly-admitted" was defined as having no nursing home episodes during a 90-day look-back period before the given nursing home admission. MDS 3.0 admission assessment was used to determine residents' age and life expectancy. Explicitly, the question "Does the resident have a condition or chronic disease that

may result in a life expectancy of less than 6 months? (yes/no)" requires physician documentation and was shown to be a strong indicator for 6-month mortality[72,73]. Focusing on the first 6 months of residence, we identified residents' 3-month and 6-month MDS 3.0 assessments as the ones respectively completed closest to 90 and 180 days after admission within a +/-31-day window. For the purpose of longitudinal follow-up, only those who had the 3-month and 6-month assessments were included. Finally, between 01/01/2014 and 06/30/2016, residents may have multiple nursing home episodes that met the aforementioned criteria. In such a case, only the first episode was selected. The final sample included 571,139 older residents. (**Figure 3.1**)

Measures

Physical frailty

Using MDS 3.0 assessments at admission, 3 months, and 6 months, we scored each FRAIL-NH item and obtained the total FRAIL-NH score (**Table 2.1**; total score: 0-13), which was categorized using previously validated thresholds: robust (score: 0-5), pre-frail (score: 6-7), and frail (score: ≥8)[33].

Cognitive impairment

The BIMS (total score: 0-15)[61] and the CPS (total score: 0-6) were combined and categorized in accordance with the measurement of cognitive impairment used in CMS Nursing Home Data Compendium: none/mild impairment (score: BIMS 13-15/CPS 0-2), moderate impairment (score: BIMS 8-12/CPS 3-4), and

severe impairment (score: BIMS 0-7/CPS 5-6)[2]. Cognitive impairment was measured at admission, 3 months, and 6 months as a time-varying variable.

Demographic and clinical characteristics

Demographic characteristics were assessed at admission: age groups, sex (male; female), race/ethnicity (non-Hispanic White; racial/ethnic minority, including American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, multi-racial, and Hispanic or Latino of any race), nursing home location (urban; rural), admission sources [community; acute hospital; other, including another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, facility for the individuals with intellectual or developmental disabilities (ID/DD facility), hospice, and other unspecified facilities].

For clinical characteristics, we examined at admission if older residents were diagnosed with cancer, asthma/chronic obstructive pulmonary disease (COPD)/chronic lung disease, heart failure, hypertension, diabetes mellitus, cerebrovascular accident/transient ischemic attack (TIA)/stroke, Alzheimer's disease, Non-Alzheimer's/other dementia (including non-Alzheimer's dementia such as vascular or multi-infarct dementia, mixed dementia; frontotemporal dementia such as Pick's disease, and dementia related to stroke, Parkinson's or Creutzfeldt-Jakob disease), multiple sclerosis, Parkinson's disease, seizure disorder/epilepsy, arthritis, osteoporosis, hip fracture, other fracture, anxiety disorder, or depression. We measured any presence of pain (yes/no) and receipt of psychotropic medications (antipsychotics; antianxiety medications;

antidepressants; hypnotics) at admission, 3 months, and 6 months to capture the potential time-varying experience of pain and receipt of medications.

Analysis

Distributions of sample demographic and clinical characteristics at admission were presented. Prevalence of physical frailty at admission, 3 months, and 6 months were shown, followed by its changes over time. As a trivial difference would be statistically significant with the large sample size, a 5% difference was considered noteworthy.

To examine the longitudinal association between physical frailty and cognitive impairment, a non-proportional odds model (NPOM) was fitted. Physical frailty was operationalized as an ordinal variable with three levels (robust/pre-frail/frail) measured repeatedly at admission, 3 months, and 6 months. Independent variables included assessment times, cognitive impairment and its interaction with assessment times, and demographic and clinical variables and their respective interactions with the assessment times. The associations between the independent variables and physical frailty may not be necessarily uniform across different levels of physical frailty. NPOM was thus used to capture this variation, because it does not assume proportional odds and estimates separate sets of log odds for frail versus pre-frail/robust and frail/pre-frail versus robust with respect to every independent variable[74]. Additionally, to capture the potential different correlations between repeated measures, NPOM was fitted with the generalized estimation equation with the unstructured working covariance matrix.

Results were presented in adjusted odds ratios (aORs) with 95% confidence intervals (CIs) to show the concurrent associations between different levels of physical frailty and cognitive impairment at admission, 3 months, and 6 months, adjusting for all other independent variables.

All analyses were conducted in SAS 9.4[75] with GEEORD macro for NPOM[74]. Figure was created in R with ggplot2[76].

III. Results

Sample characteristics at admission

Nearly half of the older residents (n = 571,139) were ≥85 years, two-thirds were female, over 80% were non-Hispanic White, and one-fourth resided in a rural nursing home. The majority entered nursing homes from acute hospitals, while 20.4% were admitted from the community. The top five diagnoses were hypertension (76.0%), dementia (41.8%), depression (37.2%), diabetes (30.2%), and arthritis (26.7%). The presence of pain was documented in 39% of older adults. One in five older residents received antipsychotics, and almost 45% received antidepressants. (**Table 3.1**)

Prevalence of physical frailty over time

The prevalence of physical frailty was 63.6% at admission, and similar at 3 months and 6 months around 60%. Improvement and decline across the levels of physical frailty were observed, especially in older adults who were pre-frail and during the first 3 months. Explicitly, 22.8% of older residents who were pre-frail at admission became robust by 3 months; later, 15.3% of those who were pre-frail at

3-month stay became robust by 6 months. About 30.5% of those who were pre-frail at admission were frail by 3 months, and 31.2% of those who were pre-frail at 3 months transitioned to frail at 6 months. (**Table 3.2**)

Prevalence of physical frailty over time by cognitive impairment

At admission, 30.5% of older adults had moderate cognitive impairment and 37.2% severe impairment, and similarly at 3 and 6 months. At all assessment times, physical frailty was less prevalent in older adults with none/mild cognitive impairment, and more prevalent in those with severe impairment. The prevalence of physical frailty appeared to decrease by almost 10% in those with none/mild impairment over time, with the most decrease occurring in the first 3 months. The prevalence did not show a considerable decrease among those with moderate or severe cognitive impairment. (**Table 3.3**)

Association between physical frailty and cognitive impairment

Cognitive impairment was shown to be associated with physical frailty (**Figure 3.2**; **Supplement Table S3.1**). At admission, those with moderate impairment were 35% more likely to be frail (aOR: 1.35, 95% CI: 1.33-1.37) and those with severe impairment were 74% more likely to be frail (aOR: 1.74, 95% CI: 1.72-1.77) than pre-frail or robust. Moreover, these associations remained consistent and appeared to increase over time: at 3 months, older residents with moderate cognitive impairment were 42% more likely (aOR: 1.42, 95% CI: 1.40-1.43) and those with severe impairment were almost twice as likely (aOR: 1.96, 95% CI: 1.94-1.99) to be frail than pre-frail or robust; at 6 months, those with

moderate impairment were 50% more likely (aOR: 1.50, 95% CI: 1.48-1.51) and those with severe impairment were over twice as likely (aOR: 2.24, 95% CI: 2.21-2.27) to be frail than pre-frail or robust. The odds of being frail/pre-frail vs. robust were slightly lower but followed a similar increasing trend over time.

For demographic and clinical characteristics, younger age and residing in a rural nursing home were associated with lower odds to be frail vs. pre-frail/robust as well as frail/pre-frail vs. robust, while being female, racial/ethnic minority, and admitted from acute hospitals or other sources were associated with higher odds. These associations remained consistent over time, with the only exception being admission from acute hospitals. At admission, older residents who entered nursing homes from acute hospitals were almost 3 times as likely to be frail than pre-frail/robust (aOR: 2.87, 95% CI: 2.83-2.91), and about 4.6 times as likely to be frail/pre-frail than robust (aOR: 4.62, 95% CI: 4.52-4.73), compared to those from the community. These associations remained positive but decreased over time.

At-admission diagnoses consistently associated with higher odds of physical frailty included cancer, heart failure, diabetes mellitus, cerebrovascular accident/TIA/stroke, multiple sclerosis, Parkinson's disease, seizure disorder/epilepsy, arthritis, hip fracture, other fracture, and depression. Residents with a documented presence of pain at admission, 3 months, or 6 months were at greater odds to be physically frail vs. pre-frail/robust at respective times. Those who received antianxiety medications or antidepressants consistently had greater odds of being frail vs. prefrail/robust, while those who received hypnotics

consistently had lower odds. In contrast, residents who received antipsychotics at admission were less likely to be physically frail vs. pre-frail/robust, but those who received antipsychotics at 3 months and 6 months were more likely to be physically frail.

IV. Discussion

This is the first national-level study to longitudinally estimate the prevalence of physical frailty and its association with cognitive impairment over older adults' first six months of residence in U.S. nursing homes. Nearly two in every three older nursing home residents were physically frail at admission, 3 months and 6 months. Improvement and decline in physical frailty were observed in substantial proportions of residents who were pre-frail and during the first 3 months. Greater levels of cognitive impairment were associated with higher levels of physical frailty at all assessment times, and this association consistently increased over time.

Clinical trials of interventions to improve physical frailty in older nursing home residents are rarely conducted and none in the U.S. In Spain, a 12-week multi-component exercise intervention in nursing home residents aged ≥85 years with frailty was found effective in improving physical functioning, but the change in frailty was not one of the outcomes[43]. Whether the physical, cognitive, nutritional, or multi-pronged interventions that effectively improved physical frailty and other health outcomes in community-dwelling older adults[39,40] could be implemented in older nursing home residents remains unclear. The nursing home setting poses additional barriers. Staff's priority might be given to essential tasks to maintain

basic living[77], leaving limited time and efforts to implement interventions that involve various physical activities. Nonetheless, interventions to address physical frailty are necessary, given that physical frailty is associated with numerous adverse health outcomes and that it is possible to reverse its progression. Cognitive impairment, several demographic and clinical characteristics, were found to be consistently associated with physical frailty over time, which could be informative in identifying older residents with greater odds of experiencing physical frailty. More importantly, this study found that improvements in the physical frailty status were more often observed in older adults who were pre-frail and during the first 3 months of stay, which may represent a population and optimal window that have greater potential to benefit from intervention.

Findings provided evidence on the positive association between physical frailty and cognitive impairment in older nursing home residents, which was expected given the close interrelationship between these conditions[16,18,78,79], but missing in previous research that mainly focused on community-dwelling older adults. This study examined the concurrent association between the two conditions at each assessment time, so findings cannot attest to the potential bi-directional relationship between physical frailty and cognitive impairment in longitudinal studies of community older adults[7–14]. However, the strong and increasing association between the two conditions found in this study indicated the necessity to consider intervention methods to improve physical frailty involving cognitive components, such as cognitive training[40]. Future investigation is needed on if

physical frailty could predict later changes in cognitive impairment and vice versa in older nursing home residents, to develop more effective intervention efforts.

We note a few limitations. We focused on older adults' first six months of nursing home residence. As such, only those who had a length of stay greater than six months were included. Yet, older residents with more severe physical frailty and/or cognitive impairment may be less likely to remain in the nursing home for over 6 months. Although we limited the sample to older residents with a life expectancy greater than 6 months at admission, selection bias is still possible, if the length of stay was differential with regards to physical frailty and cognitive impairment, and other demographic and clinical characteristics. MDS 3.0 allowed us to conduct this national-level analysis, but we were limited by the availability of validated instruments and other clinical measures in it. FRAIL-NH is a relatively new instrument; therefore, more studies are needed to confirm our findings. The combined BIMS/CPS metric captures broad cognitive impairment levels. Further research on the association between specific cognitive domains and physical frailty in older nursing home residents may offer additional insight into their interrelationship. We were not able to examine if non-pharmacotherapy would influence physical frailty over time. While MDS 3.0 documents broad categories including occupational therapy, physical therapy, and psychotherapy, the content of and residents' participation in these therapies may largely vary across nursing homes. Due to the complexity of multilevel NPOM in a large sample, we could not

address the impact of nursing home facility-level factors such as staffing and quality of care, warranting future work.

V. Conclusion

Physical frailty was highly prevalent in older U.S. nursing home residents at admission and during the first six months of stay, with improvement more frequently occurring in those with pre-frail status and during the first three months. Cognitive impairment was shown to be strongly associated with physical frailty over time. Describing the dynamic nature of physical frailty over time in older nursing home residents is an essential first step towards the development of intervention strategies to modify physical frailty. By longitudinally addressing the association between physical frailty and cognitive impairment, findings have implications for future work on the mechanisms underlying the interrelationship between two conditions and physical frailty intervention efforts to include efforts to address cognitive impairment.

Table 3.1. Demographic and clinical characteristics of newly-admitted, long-stay older adults at nursing home admission (n = 571,139)

	All (n=571,139)
	(*column percent*)
Age (years)	
65 - <75	20.3
75 - <85	34.2
≥ 85	45.5
Sex	
Male	33.1
Female	66.9
Race/Ethnicity	
Non-Hispanic White	81.9
Racial/ethnic minority [1]	18.1
Nursing home location	
Urban	75.6
Rural	24.4
Admission source	
Community	20.4
Acute hospital	59.6
Other sources [2]	20.1
Diagnosis	
Cancer	5.9
Asthma/COPD/chronic lung disease	18.5
Cardiovascular/metabolic	
Heart failure	17.6
Hypertension	76.0
Diabetes mellitus	30.2
Neurological	
Cerebrovascular accident/TIA/stroke	13.8
Alzheimer's disease	13.2
Multiple sclerosis	0.5
Non-Alzheimer's/other dementia [3]	41.8
Parkinson's disease	6.0
Seizure disorder/Epilepsy	5.8
Musculoskeletal	
Arthritis	26.7
Osteoporosis	12.2
Hip fracture	5.0
Other fracture	7.4
Mental health	
Anxiety disorder	22.1
Depression	37.2
Any presence of pain	38.7
Receipt of psychotropic medications [4]	
Antipsychotics	20.0
Antianxiety medications	18.4
Antidepressants	44.8
Hypnotics	4.0

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

[1] Racial/ethnic minority includes American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian/Other Pacific Islander, multi-racial, and Hispanic or Latino of any race.

[2] Other admission sources include another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, hospice, long-term care hospital, and other unspecified sources.
[3] Included non-Alzheimer's dementia (e.g., vascular or multi-infarct dementia), mixed dementia; frontotemporal dementia (e.g., Pick's disease), and dementia related to stroke, Parkinson's, or Creutzfeldt-Jakob diseases.
[4] Receipt of psychotropic medications in the past 7 days or since admission.

Table 3.2. Prevalence and changes of physical frailty over older adults' first six months in a nursing home

		Physical frailty		
		Robust	Pre-frail	Frail
			(row percent)	
Prevalence at each time				
Admission		11.0	25.4	63.6
3 months		17.0	23.5	59.5
6 months		17.5	21.9	60.5
Changes in physical frailty over time				
			3 months	
Admission	Robust	75.9	17.1	7.0
	Pre-frail	22.8	46.8	30.5
	Frail	4.7	15.7	79.7
			6 months	
3 months	Robust	75.7	17.2	7.1
	Pre-frail	15.3	53.5	31.2
	Frail	1.8	11.0	87.2

Table 3.3. Levels of physical frailty at admission, 3 months, and 6 months in older residents' first six months in a nursing home by cognitive impairment at each respective time

	All	Physical frailty [1]		
		Robust	Pre-frail	Frail
	(column percent)	*(row percent)*		
		Admission		
Cognitive impairment [2]				
None/Mild impairment	32.3	12.6	30.5	56.9
Moderate impairment	30.5	11.1	25.1	63.8
Severe impairment	37.2	9.5	21.1	69.3
		3-month		
Cognitive impairment [2]				
None/Mild impairment	32.0	22.8	28.6	48.7
Moderate impairment	30.1	17.0	23.6	59.4
Severe impairment	37.9	12.1	19.2	68.7
		6-month		
Cognitive impairment [2]				
None/Mild impairment	31.3	25.2	27.5	47.3
Moderate impairment	29.4	17.5	22.3	60.2
Severe impairment	39.3	11.4	17.3	71.3

Notes.
[1] Physical frailty was measured at admission, 3-month, and 6-month.
[2] Cognitive impairment was measured concurrently with physical frailty at admission, 3-month, and 6-month.

Figure 3.1. Sample selection flowchart

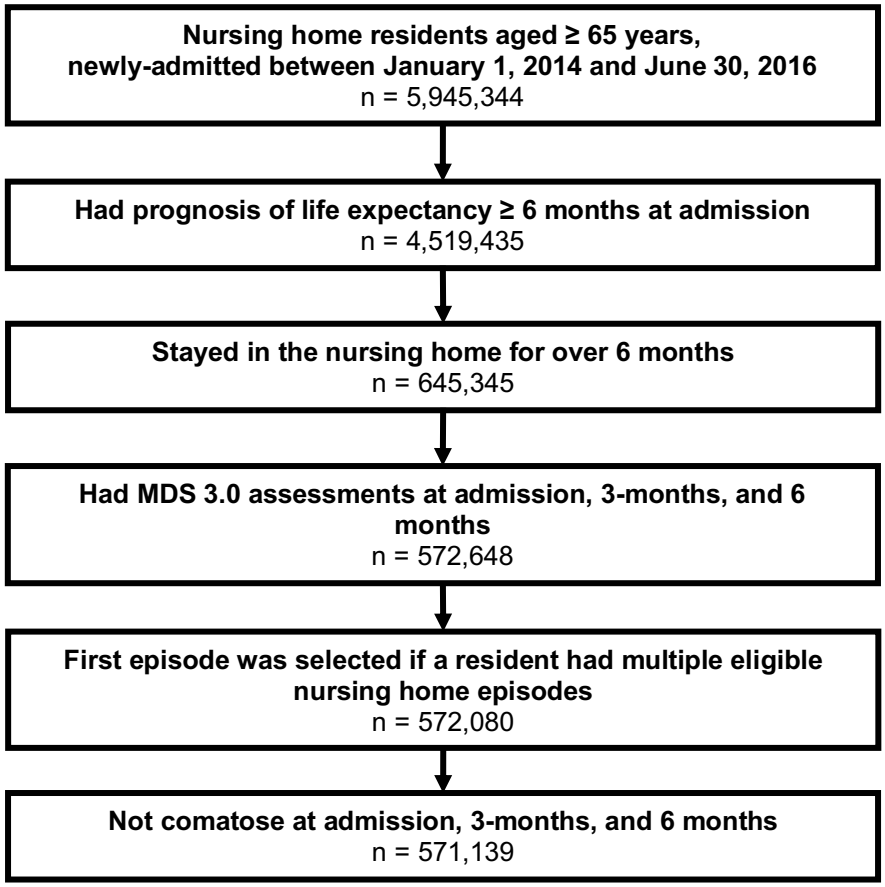
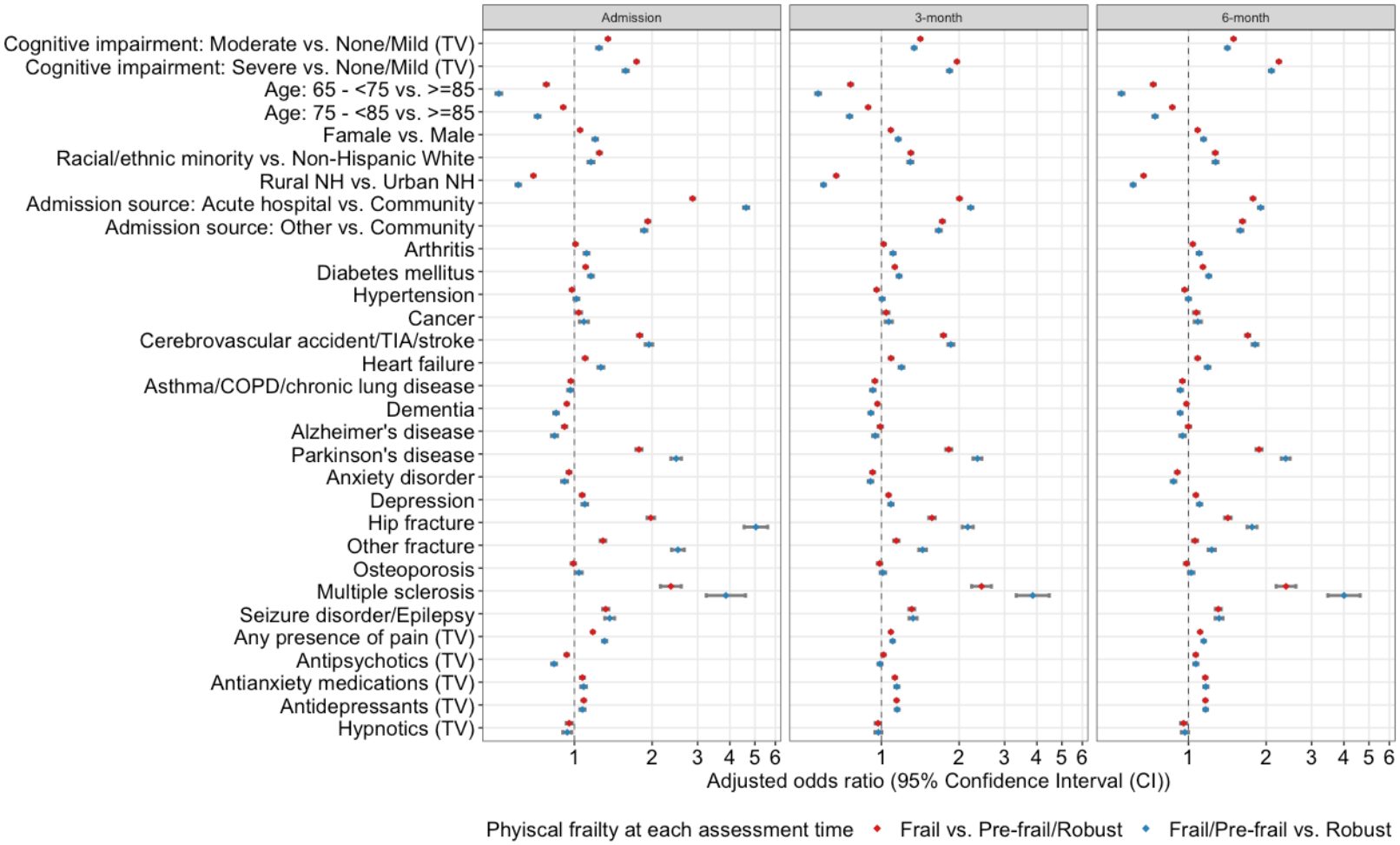


Figure 3.2. Concurrent associations between physical frailty and cognitive impairment, demographic and clinical characteristics over older residents' first six months in a nursing home



Notes. TV = time-varying.
Physical frailty and all TV variables were measured at admission, 3-month, and 6-month. All other variables were time-invariant measured at admission. Independent variables in the NPOM included assessment times, cognitive impairment and its interaction with time, demographic and clinical variables with their respective interactions with time. The association estimates in aOR and 95% CI were summarized in Supplement Table S3.1.

CHAPTER IV.

PRESENTATION OF PHYSICAL FRAILTY BY COGNITIVE IMPAIRMENT IN OLDER NURSING HOME RESIDENTS

(Note: The texts, tables, and figures in this chapter are based on the manuscript published on BMC Geriatrics. Refer to the **LIST OF COPYRIGHTED MATERIAL PRODUCED BY THE AUTHOR** and **PREFACE** for the publication citation for Chapter IV.)

I. Introduction

Over 1.2 million U.S. older adults aged ≥65 years reside in a nursing home[2]. Physical frailty, characterized by decreased physiologic reserve and increased vulnerability to exogenous stressors[3], and cognitive impairment, ranging from mild cognitive impairment to fully-developed dementia[5], are two prominent conditions in this population. Both are highly prevalent, with 30-85% of older nursing home residents experiencing physical frailty[33,34,80] and 65% moderate to severe cognitive impairment[2]. Both are associated with adverse health outcomes, including lowered quality of life and elevated risks for hospitalization and mortality[33,81–83].

Physical frailty may encompass weakness, slowness, low level of physical activity, weight loss, and exhaustion[3], and older adults may experience the heterogeneous symptoms[37,38]. Latent class analysis (LCA) can help identify subgroups of older adults with distinct clinical profiles of physical frailty. For example, in a cohort of community-dwelling older adults in Taiwan, three physical frailty subgroups were identified with LCA: one characterized by slowness and weakness, one weight loss and exhaustion, and one low physical activity[37]. For older U.S. nursing home residents, whether physical frailty has similar heterogeneous clinical presentations remains unknown.

A better understanding of the multifaceted presentations of physical frailty can inform its management. Studies have demonstrated improvements in physical frailty in community-dwelling older adults with exercise-based interventions[39,40]. However, interventions shown to be effective for specific physical frailty domains,

such as muscle strength, physical activity, gait speed, and energy[41–43,84], may not be as effective for other domains. Research on the heterogeneous profile of physical frailty in older nursing home residents can contribute to the development of tailored planning of care.

Physical frailty and cognitive impairment share many risk factors, often co-occur, and predict the onset of each other[7,8,10,14,18]. Given this interrelationship between these two conditions, older adults' physical frailty symptoms may be associated with levels of cognitive impairment. Physical frailty may have distinct clinical manifestations in older residents with different cognitive impairment levels. Or, physical frailty may have consistent symptom profiles, but older adults with severe cognitive impairment may have higher odds of experiencing a particular profile. However, no studies have quantified this interrelationship. Additionally, the construct "cognitive frailty" has been proposed by the International Academy on Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) to capture the co-existence of physical frailty and mild cognitive impairment in the absence of overt dementia and other neurological conditions[16]. However, to date, there is no consensus on the operationalization of "cognitive frailty"[85], leading to discrepancies in the estimates of its prevalence and associations with adverse health outcomes in community-based studies[78]. Treating two conditions as separate constructs with LCA to examine whether and to what extent the heterogeneity of physical frailty is associated with the severity of cognitive impairment could provide insight into the underlying mechanisms

behind the observed interrelationship between the two conditions, as well as implications to have the personalized management for specific physical frailty subgroups by the level of cognitive impairment.

This study thus sought to use LCA to explore the heterogeneity of physical frailty and its association with cognitive impairment in older U.S. nursing home residents. The objectives were to identify subgroups of physical frailty and examine if these subgroups varied by cognitive impairment in newly-admitted, long-stay older nursing home residents.

II. Methods

The University of Massachusetts Chan Medical School Institutional Review Board approved this study as exempt from Federal regulations (09/20/2019).

Sample

Using MDS 3.0, we first identified residents who were newly admitted between 01/01/2014 and 12/31/2016 and aged ≥65 years at admission. "Newly-admitted" was defined as no nursing home stays in ≥90 days prior to the given admission. We excluded those who stayed in the nursing homes for ≤100 days to focus on the "long-stay" older residents[86], and those with a physician-documented prognosis of life expectancy of less than 6 months at admission (MDS 3.0 Section J), as they may be terminally ill and need special care from hospice or palliative services. Older residents who were comatose were also excluded. If a resident had multiple nursing home stays meeting these criteria, the first one was selected.

(**Figure 4.1**) The final sample included 871,801 older residents. The admission MDS 3.0 assessments of the final sample were used in the analysis.

Measures

Physical frailty

To describe the prevalence of physical frailty, each FRAIL-NH item was scored (**Table 2.1**; score range: 0-13) and the summary score was categorized as robust (score: 0-5), pre-frail (score: 6-7), and frail (score: ≥8)[33]. In fitting LCA models to identify physical frailty subgroups, each FRAIL-NH item was used individually as an observed indicator.

Cognitive impairment

Combining BIMS and CPS, cognitive impairment was measured in three levels per the CMS Nursing Home Data Compendium[2]: none/mild (score: BIMS 13-15/CPS 0-2), moderate (score: BIMS 8-12/CPS 3-4), and severe (score: BIMS 0-7/CPS 5-6) cognitive impairment.

Demographic and clinical characteristics

We examined age, sex, race/ethnicity, urban/rural nursing home, admission sources, active diagnoses, any presence of pain, and receipt of antipsychotics, antianxiety medications, and antidepressants in the past 7 days or since admission. Admission sources included community, acute hospital, or other (including another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospitals, or hospice). Active diagnoses were physician-documented diagnoses deemed relevant to residents' current health status and

care management, including cancer, asthma/COPD/chronic lung disease, heart failure, hypertension, diabetes mellitus, cerebrovascular accident/TIA/stroke, Alzheimer's disease, Non-Alzheimer's/other dementia (including non-Alzheimer's dementia such as vascular or multi-infarct dementia, mixed dementia; frontotemporal dementia such as Pick's disease, and dementia related to stroke, Parkinson's or Creutzfeldt-Jakob disease), multiple sclerosis, Parkinson's disease, seizure disorder/epilepsy, arthritis, osteoporosis, hip fracture, other fracture, anxiety disorder, and depression.

Statistical analysis

Analyses were conducted in SAS 9.4[75] and Mplus 8.4[87].

Main analysis

We described the sample demographic and clinical characteristics at nursing home admission. We then showed the frequencies of each FRAIL-NH item for all residents and by cognitive impairment levels.

We used LCA to identify latent subgroups of physical frailty at admission using FRAIL-NH items as the observed indicators. LCA models with 2 to 6 subgroups were fitted and compared to determine the optimal number of physical frailty subgroups. For each model, we obtained (1) fit statistics: entropy, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and sample-size adjusted BIC; (2) subgroup prevalence: the proportion of residents with higher probabilities of belonging to the given subgroup; (3) item-response probability for each indicator by subgroup. After considering model fit, parsimony, and clinical

relevance, the best-fitting model was selected, and the optimal number of physical frailty subgroups was identified. We assigned qualitative labels to describe each subgroup based on the overall patterns of the item-response probabilities[88].

We then examined if and how the subgroups differed by the severity of cognitive impairment. First, we fit LCA models within subsets of residents by their cognitive impairment levels; then, in the entire sample, we examined the measurement invariance (MI) assumption by evaluating cognitive impairment as a grouping variable. As detailed later in Results, the subgroups of physical frailty did not vary across cognitive impairment levels, so we included cognitive impairment as a covariate[88] to assess its association with the identified physical frailty subgroups using the multinomial logistic model, adjusting for demographic and clinical characteristics. The associations were presented in aORs and 95% CIs.

Sensitivity Analysis

Consistent with the "cognitive frailty" concept by IANA and IAGG, we created three subsamples respectively by (A) excluding older residents with Alzheimer's disease (n = 767,034); (B) excluding older residents with non-Alzheimer's/other dementia (n = 529,832); (C) excluding older residents with Alzheimer's disease and those with non- Alzheimer's/other dementia (n = 460,612), for sensitivity analysis. In each subsample, LCA models were fit to identify the physical frailty subgroup, and the association between cognitive impairment and the identified subgroups were assessed following the same steps as the main analysis.

III. Results

Sample characteristics at admission

Of the 871,801 newly-admitted older residents, 44.3% were ≥85 years old, 65.3% women, and 18.8% racial/ethnic minority. Approximately three-quarters of residents entered urban nursing homes. Nearly two-thirds were admitted from acute hospitals and less than one in five from the community. At admission, nearly two-thirds of residents were physically frail, one in four was pre-frail, and over a third had severe cognitive impairment. About 45% of older residents had more than two physician-documented active diagnoses. Two in five had documented any presence of pain. Receipt of antidepressants (43.9%), antipsychotics (19.2%), and antianxiety medications (18.4%) were common. (**Table 4.1**)

Indicators of physical frailty

Of all residents, 62.1% did not experience fatigue, 91.5% needed physical assistance to transfer between surfaces, 85.7% could not walk between locations in a room, 57.5% experienced bowel incontinence, 3.0% lost weight (for at least 5% in the past 3 months or 10% in the past 6 months), 67.8% were on a regular diet, and 95.2% needed help with dressing. Similar distributions were observed across cognitive impairment levels except for a few items. There were higher proportions of older adults with severe cognitive impairment who did not experience fatigue, had bowel incontinence, and needed the mechanically altered diet. (**Table 4.2**)

Subgroups of physical frailty

For model selection, although entropy favored the 2-subgroup model, a clinically relevant subgroup emerged in the 3-subgroup model based on the item response probabilities. While AIC, BIC, and adjusted BIC values favored models with more subgroups, for models with 4-6 subgroups, at least two of the identified subgroups largely overlapped and lacked sufficient separation. With these considerations, we chose the 3-subgroup model to represent physical frailty subgroups in nursing home residents at admission. (**Supplement Table S4.1**)

Based on the item-response probabilities, we assigned qualitative labels to the three subgroups: “mild physical frailty”, “moderate physical frailty” and “severe physical frailty”. (**Table 4.3**) About 7.6% of older residents had higher probabilities to belong to the “mild physical frailty” subgroup, 44.5% to the “moderate physical frailty” subgroup, and 47.9% to the “severe physical frailty” subgroup. The major difference between the “mild physical frailty” subgroup and the other two subgroups were reflected in the probabilities for resistance and ambulation: older adults that were likely to be in the “moderate physical frailty” or the “severe physical frailty” subgroups had high probabilities of needing physical assistance to transfer between locations and inability to walk in a room. The “moderate physical frailty” subgroup and the “severe physical frailty” subgroup were mainly distinguished by the item-response probability for the incontinence item: residents belonging to the “moderate physical frailty” subgroup had about an equal probability of having no urinary incontinence, urinary incontinence only, or urinary and bowel incontinence,

while the “severe physical frailty” subgroup had a high probability of both urinary and bowel incontinence.

In sensitivity analysis when older residents with Alzheimer’s disease and/or those with non-Alzheimer’s/other dementia were excluded, the three-subgroup model appeared to best fit all three subpopulations. (**Supplement Table S4.2**) The overall patterns of the item-response probabilities and the respective prevalence of the physical frailty subgroups were similar and consistent with the full sample: “mild physical frailty” (prevalence range: 6.4%-7.2%), “moderate physical frailty” (45.0%-47.4%), and “severe physical frailty” (46.1%-47.7%). (**Supplement Table S4.3**)

Association between physical frailty subgroups and cognitive impairment

We first examined if and how the subgroups of physical frailty would differ by cognitive impairment levels. First, residents were stratified into subsets by cognitive impairment level at admission. Basic LCA models with 2-6 subgroups were fitted separately within each subset to evaluate if the number of physical frailty subgroups was identical across cognitive impairment levels. After considering the fit statistics, latent class prevalence, and patterns of response probabilities, the classes appeared to be similar across all three cognitive impairment levels. (**Supplement Table S4.4**)

So, we included cognitive impairment as a grouping variable in a multiple-group LCA model for the entire sample to test the MI assumption, essentially, whether residents with different cognitive impairment levels have the same

physical frailty subgroups as represented by consistent patterns of item-response probabilities. Two sets of multiple-group models, one with MI in item-response probabilities imposed (nested models) and the other without (full models), were fit and compared using the log-likelihood ratio test. Results from the log-likelihood difference test (**Supplement Table S4.5**) showed a statistically significant difference between the full models and the nested models, which suggested that the full model would better fit the data. As such test statistics tend to be significant when the sample size is large, we also examined the patterns of the item-response probabilities of each subgroup, which were shown to be consistent between the full and nested models, supporting the MI assumption. Therefore, there appeared to be three physical frailty subgroups ("severe physical frailty", "moderate physical frailty", and "mild physical frailty") in older nursing home residents, regardless of their level of cognitive impairment. Cognitive impairment was thus included as a covariate in the 3-subgroup LCA model to examine its association with physical frailty subgroups, with the "mild physical frailty" subgroup as the reference, adjusting for demographic and clinical characteristics. (**Table 4.4**)

Compared to those with none/mild cognitive impairment, older residents with moderate impairment had similar odds to belong to the moderate physical frailty" subgroup (aOR: 1.01, 95% CI: 0.99-1.03), while over twice as likely (aOR: 2.41, 95% CI: 2.35-2.47) to belong to the "severe physical frailty" subgroup; older residents with severe impairment had slightly higher odds to belong to the "moderate physical frailty" subgroup (aOR: 1.03, 95% CI: 1.01-1.05), and were

close to 6 times as likely (aOR: 5.74; 95% CI: 5.58-5.90) to belong to the “severe physical frailty” subgroup.

For demographic and clinical characteristics, older age and being female were associated with higher odds of belonging to the “moderate physical frailty” or “severe physical frailty” subgroups, compared to their respective counterparts. Older residents who were racial/ethnic minorities were less likely to belong to the “moderate physical frailty” subgroup, but more likely to belong to the “severe physical frailty” subgroup. Older residents in rural nursing homes were less likely to be in the “moderate physical frailty” or “severe physical frailty” subgroups than those in urban nursing homes. Older residents admitted from acute hospitals had much higher probabilities of belonging to the “moderate physical frailty” and “severe physical frailty” subgroups than those admitted from the community.

Older residents with cancer, heart failure, diabetes mellitus, cerebrovascular accident/TIA/stroke, multiple sclerosis, Parkinson’s disease, seizure disorder/epilepsy, hip fracture, other facture, or depression had higher odds of belonging to the “moderate physical frailty” or “severe physical frailty” subgroups, while those with the anxiety disorder had lower odds. Older residents with hypertension, arthritis, or osteoporosis were more likely to belong to the “moderate physical frailty” subgroup, but less likely to be in the “severe physical frailty” subgroup. Older residents with any pain presence at admission were more likely to be in the “moderate physical frailty” or “severe physical frailty” subgroups. Older residents who received antipsychotics were less likely to be in the “moderate

physical frailty" or "severe physical frailty" subgroups, while those who received antianxiety medications or antidepressants were more likely to do so.

Findings from sensitivity analysis suggested consistent positive associations between cognitive impairment and physical frailty subgroups, but the magnitude of these associations increased. (**Supplement Table S4.6**) Particularly, in the absence of Alzheimer's disease and non-Alzheimer's/other dementia, older residents with severe cognitive impairment were 8.55 times (95% CI: 8.18-8.92) as likely to be in the "severe physical frailty" subgroup, compared to those with none/mild cognition.

IV. Discussion

In older adults in U.S. nursing homes, we identified three subgroups of physical frailty at nursing home admission, namely, "mild physical frailty", "moderate physical frailty" and "severe physical frailty". Physical frailty subgroups did not appear to differ across cognitive impairment levels. Older residents with greater levels of cognitive impairment were more likely to belong to the "moderate physical frailty" or "severe physical frailty" subgroups. Recent research has shown the possibility to reduce the prevalence or even reverse the progress of physical frailty through physical activity programs, cognitive training, nutritional supplementation, and interventions individualized to older adults' clinical conditions[39,40,51]. However, these studies were conducted in community-dwelling older adults. Whether physical frailty could also serve as an intervention target for older nursing home residents warrants further exploration. This is the first study to

provide evidence for the heterogeneity of physical frailty in older nursing home residents and its association with cognitive impairment, which can inform the development of interventions tailored to specific clinical profiles of physical frailty and cognitive impairment, while also considering the potential impact from other demographic and clinical characteristics.

The majority of the older nursing home residents in this study had high probabilities of belonging to either “moderate physical frailty” or “severe physical frailty” subgroups. This was expected as nearly two-thirds of the older nursing home residents were admitted post-hospitalization, indicating a more clinically complex group. The use of LCA allowed us to examine the heterogeneity of physical frailty by identifying three distinct subgroups. Regardless of the subgroups they were more likely to belong to, all residents had a high probability of requiring assistance with dressing. Besides the high probabilities of limited mobility that older residents belonging to the “moderate physical frailty” or the “severe physical frailty” subgroups were shown to have, those in the “severe physical frailty” subgroup also had a particularly greater probability of bowel incontinence. Such distinctive experiences would be masked when physical frailty is measured by categorizing a total score into robust/pre-frail/frail levels. Using the LCA person-centered approach, findings not only reflected the increasing levels of physical frailty severity but also provided a more nuanced picture of the physical frailty experience in older nursing home residents.

We note one important caveat that the characteristics of the subgroups to be identified by LCA are determined by the observed indicators, namely, the FRAIL-NH items in the context of this study. Unique experiences of physical frailty in older nursing home residents that were not captured by FRAIL-NH would not be reflected in the identified subgroups. Therefore, other distinct subgroups of physical frailty may exist in older nursing home residents and future studies should consider additional metrics to provide a more comprehensive picture of the heterogeneity of physical frailty in this population.

The finding that greater levels of cognitive impairment were associated with increasingly higher odds to be in the "moderate physical frailty" and "severe physical frailty" subgroups provided additional evidence on the frequent co-occurrence of physical frailty and cognitive impairment, which has been established in older adults in the community[70,71], but not in nursing homes. Further, in the sensitivity analysis when older residents with Alzheimer's disease and those with non-Alzheimer's/other dementia were excluded, the magnitude of the association between cognitive impairment and the "severe physical frailty" subgroup substantially increased, which could be indicative of "cognitive frailty".

Regardless of older residents' cognitive impairment levels, the characteristics of the identified physical frailty subgroups appeared to be similar, without notable differences in the patterns of the item-response probabilities. The consistent patterns of physical frailty subgroups were also observed in the sensitivity analysis. These findings should be interpreted in light of the potential

limitation of the instruments used to measure physical frailty and cognitive impairment. Despite several studies to validate FRAIL-NH[33,54–59], it is admittedly a relatively new scale. Additionally, BIMS/CPS may not be informative for certain cognitive domains, such as executive functioning[61]. To further our understanding of the underlying mechanism between these two conditions in older adults in nursing homes, additional instruments that could provide a more granular, domain-specific measurement of both conditions are warranted.

Several demographic and clinical variables were also found to be associated with physical frailty subgroups, which may be helpful for care planning and triaging intervention efforts upon nursing home admission. Older age, being female, and entering nursing homes from acute hospitals were associated with greater odds of belonging to the "moderate physical frailty" or "severe physical frailty" subgroups. It was unexpected that racial/ethnic minority older adults had lower odds of belonging to the "moderate physical frailty" subgroup and higher odds of belonging to the "severe physical frailty" subgroup. Future studies should attempt to elucidate and properly address the causes for the observed racial differences.

Consistent with prior studies that found pain[89], cancer[90], heart failure[91], diabetes[92], and depression[93] as risk factors for physical frailty in community-dwelling older adults, we provided additional information that older nursing home residents with these conditions would be more likely to belong to the "moderate physical frailty" or "severe physical frailty" subgroups. Although prior studies have

demonstrated a strong positive relationship between frailty and Alzheimer's and vascular dementia[94,95], we did not include Alzheimer's disease or non-Alzheimer's/other dementia in the final model, as our preliminary findings suggested that a considerable extent of the impact on physical frailty subgroups from either of these two diagnoses would be through cognitive impairment.

Older adults who receive antipsychotics were less likely to be in the "moderate physical frailty" and "severe physical frailty" subgroups. Antipsychotics could be less prescribed to older residents in these two subgroups because they were more physically impaired, and thus less likely to have challenging behaviors that would need to be been handled using chemical restraints. The concerns that the use of antipsychotics may increase risks for hospitalization and mortality in older adults who were frail[96,97] may also play a role. Conversely, older residents who are more active and less frail may be more likely to receive antipsychotics because they have a greater propensity to present behavioral management issues. Receipt of antidepressants was associated with higher odds of being in the "moderate physical frailty" or "severe physical frailty" subgroups. This may be attributed to the higher risks of functional limitations associated with antidepressant use[98]. On the other hand, the overlapping characteristics between depression and physical frailty may lead to an erroneous diagnosis of depression in those who were physically frail and not depressed, resulting in a wrong indication for antidepressant[99]. Given that MDS 3.0 only documents the receipt of psychotropic medications in the past 7 days or since nursing home admission and the cross-

sectional nature of the current study, we could not ascertain the clinical indications for these prescriptions and the length of time that the older adults have been using them, nor could we establish a causal relationship between psychotropic medications and physical frailty subgroups, explicitly, whether it was the concerns for physical frailty that had influenced the prescription of these medications, or the use of these medications that had led to a higher probability to belong to a certain physical frailty subgroup. However, considering that physical frailty may increase older adults' vulnerability to adverse drug effects[96], additional research to examine their long-term impact on physical frailty could further inform the consideration of psychotropic medications in managing physical frailty in this population.

Limitations should be noted. Our analysis focused on older residents who stayed for longer than 100 days in nursing homes with a life expectancy at admission longer than 6 months. If residents' length of stay and/or life expectancy were differential with regards to symptoms of physical frailty, cognitive impairment levels, or other demographic and clinical characteristics, selection bias cannot be ruled out. This was a cross-sectional study at nursing home admission. As physical frailty and cognitive impairment could change during residents' stay, longitudinal studies may be informative in exploring if and how physical frailty subgroups and cognitive impairment change over time.

V. Conclusion

Three subgroups of physical frailty were identified in older U.S. nursing home residents at admission, and older residents with greater levels of cognitive

impairment were increasingly more likely to belong to the “moderate physical frailty” and “severe physical frailty” subgroups. Findings have implications for future efforts to tailor interventions to specific symptom profiles of physical frailty and cognitive impairment and provide new evidence for the interrelationship between these two prominent conditions in older nursing home residents.

Table 4.1. Demographic and clinical characteristics of newly-admitted older residents at nursing home admission (n = 871,801)

	All (n = 871,801)
	Percentage
Age (years)	
65 - <75	21.4
75-<85	34.3
≥ 85	44.3
Female	65.3
Racial/ethnic minority	18.8
Nursing home location	
Rural	23.5
Urban	76.5
Admission source	
Community	17.8
Acute hospital	63.8
Other [1]	18.4
Physical frailty	
Robust	9.6
Pre-frail	25.0
Frail	65.4
Cognitive impairment	
None/Mild	33.6
Moderate	30.1
Severe	36.4
Active diagnosis	
Cancer	6.8
Asthma/COPD/Chronic lung disease	19.6
Cardiovascular/metabolic	
Heart failure	18.9
Hypertension	76.3
Diabetes mellitus	31.3
Neurological	
Alzheimer's disease	12.0
Cerebrovascular accident/TIA/Stroke	13.9
Non-Alzheimer's/other dementia [2]	39.2
Multiple sclerosis	0.5
Parkinson's disease	5.8
Seizure disorder/Epilepsy	5.8
Musculoskeletal	
Arthritis	26.1
Osteoporosis	11.7
Hip fracture	5.4
Other fracture	8.2
Mental health	
Anxiety disorder	21.8
Depression	36.3
Any presence of pain	40.9
Receipt of psychotropic medications[3]	
Antipsychotics	19.2
Antianxiety medications	18.4
Antidepressant	43.9

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease.
[1] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.
[2] Included non-Alzheimer's dementia (e.g. vascular or multi-infarct dementia), mixed dementia; frontotemporal dementia (e.g. Pick's disease), and dementia related to stroke, Parkinson's, or Creutzfeldt-Jakob diseases.
[3] Receipt of psychotropic medications in the past 7 days or since admission.

Table 4.2. Physical frailty indicators by cognitive impairment in newly-admitted older residents at nursing home admission

	All	Cognitive impairment		
		None/Mild	Moderate	Severe
	(n=871,801)	(n=292,548)	(n=262,307)	(n=316,946)
	Percentage	*Percentage*	*Percentage*	*Percentage*
FRAIL-NH Items				
Fatigue				
0 No (never or 1 day)	62.1	59.4	59.5	67.1
1 Yes (several days/everyday)	31.7	34.5	33.8	27.2
2 PHQ-9 ≥ 10	6.2	6.1	6.8	5.7
Resistance [1]				
0 Independent	4.5	4.5	4.5	4.5
1 With set-up only	4.0	3.9	4.0	4.1
2 Need physical assistance	91.5	91.6	91.5	91.4
Ambulation [2]				
0 Independent	6.5	7.9	6.4	5.3
1 With assistive device	7.8	7.3	8.3	7.8
2 Cannot walk	85.7	84.8	85.4	86.8
Incontinence				
0 None	19.8	27.3	19.6	13.2
1 Urinary incontinence only	22.7	26.1	23.5	19.0
2 Bowel incontinence	57.5	46.6	57.0	67.9
Loss of weight				
0 None	97.0	96.9	97	97.1
1 ≥5% past 3 mo./ ≥10% past 6 mo.	3.0	3.2	3.0	2.9
Nutritional approach				
0 Regular diet	67.8	76.7	67.6	59.7
1 Mechanically altered diet	26.9	19.4	27.6	33.2
2 Require feeding tube	5.3	3.9	4.8	7.1
Help with dressing				
0 Independent	1.8	2.6	1.8	1.1
1 Need help with set up only	3.0	3.5	3.1	2.4
2 Need physical help	95.2	93.9	95.0	96.5

Notes. PHQ-9 = Patient Health Questionnaire.
[1] Measures if the resident needs assistance to be transferred from one location to another.
[2] Measures if the resident can walk in a room.

Table 4.3. Physical frailty 3-class latent class model: subgroup prevalence and item-response probabilities of indicators

	Mild physical frailty subgroup	Moderate physical frailty subgroup	Severe physical frailty subgroup
Subgroup prevalence	7.6%	44.5%	47.9%
Item-response probabilities			
Fatigue			
0 No (never or 1 day)	**0.74 ***	**0.61 ***	**0.62 ***
1 Yes (several days/everyday)	0.22	0.34	0.31
2 PHQ-9 ≥ 10	0.04	0.06	0.07
Resistance [1]			
0 Independent	**0.56 ***	0.00	0.00
1 With set-up only	0.33	0.03	0.00
2 Need physical assistance	0.11	**0.96 ***	**1.00 ***
Ambulation [2]			
0 Independent	**0.53 ***	0.05	0.01
1 With assistive device	0.18	0.13	0.01
2 Cannot walk	0.29	**0.82 ***	**0.98 ***
Incontinence			
0 None	**0.67 ***	0.30	0.03
1 Urinary incontinence only	0.22	**0.38 ***	0.08
2 Bowel incontinence	0.11	0.32	**0.89 ***
Loss of weight			
0 None	**0.98 ***	**0.98 ***	**0.96 ***
1 ≥ 5% past 3 mo./ ≥10% past 6 mo.	0.02	0.02	0.04
Nutritional approach			
0 Regular diet	**0.90 ***	**0.85 ***	**0.49 ***
1 Mechanically altered diet	0.10	0.15	0.41
2 Require feeding tube	0.01	0.01	0.11
Help with dressing			
0 Independent	0.24	0.00	0.00
1 Need help with set up only	0.34	0.01	0.00
2 Need physical help	**0.42 ***	**0.99 ***	**1.00 ***

Notes. PHQ-9 = Patient Health Questionnaire.

* The level of the given indicator with the highest item-response probability. Residents belonging to the given subgroup had the highest probability of experiencing this level of the indicator.

[1] Measures if the resident needs assistance to be transferred from one location to another.

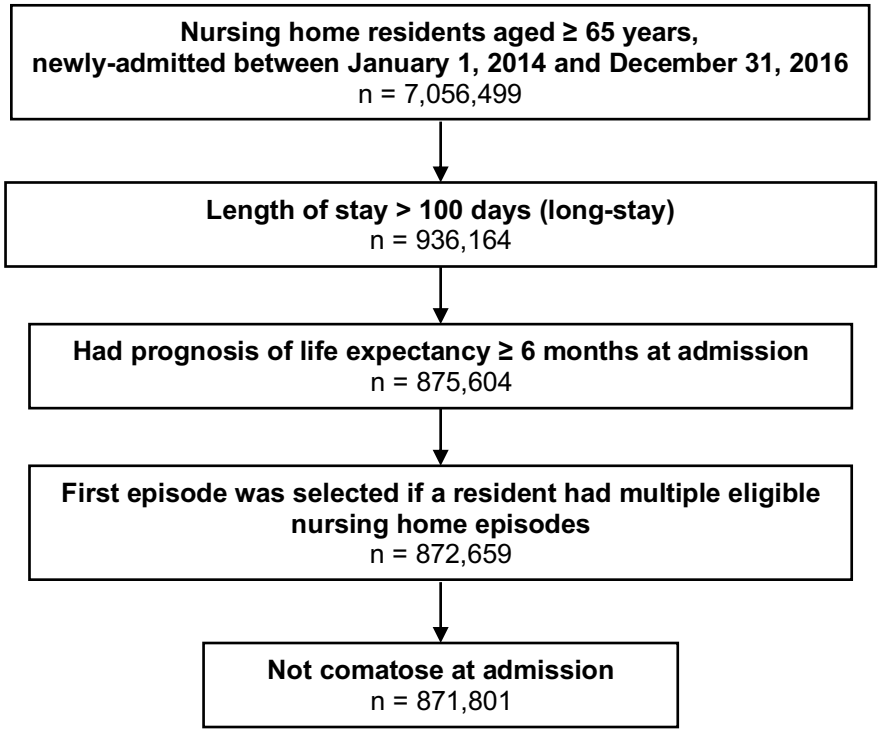
[2] Measures if the resident can walk in a room.

Table 4.4. Association between physical frailty subgroups and cognitive impairment in newly-admitted older nursing home residents[1]

	Moderate physical frailty subgroup *(vs. Mild physical frailty subgroup)*		**Severe physical frailty subgroup** *(vs. Mild physical frailty subgroup)*	
	aOR	95% CI	aOR	95% CI
Cognitive impairment *(ref: none/mild)*				
Moderate	1.01	(0.99-1.03)	2.41	(2.35-2.47)
Severe	1.03	(1.01-1.05)	5.74	(5.58-5.90)
Age *(ref: 65 - <75 years)*				
75 - <85 years	1.55	(1.52-1.58)	1.51	(1.47-1.54)
85 and over years	2.53	(2.48-2.59)	2.45	(2.38-2.51)
Female *(ref: male)*	1.35	(1.32-1.37)	1.10	(1.08-1.13)
Racial/ethnic minority *(ref: non-Hispanic white)*	0.76	(0.74-0.78)	1.84	(1.80-1.89)
Rural nursing homes *(ref: urban)*	0.66	(0.65-0.67)	0.34	(0.33-0.35)
Admission source *(ref: community)*				
Acute hospital	4.39	(4.31-4.48)	23.46	(23.62-25.33)
Other [2]	1.34	(1.31-1.37)	6.82	(6.58-7.06)
Diagnosis (*ref: without the diagnosis)*				
Cancer	1.11	(1.07-1.14)	1.12	(1.08-1.16)
Asthma/COPD/Chronic Lung Disease	0.96	(0.94-0.97)	1.00	(0.98-1.02)
Cardiovascular/metabolic				
Heart failure	1.46	(1.43-1.50)	1.35	(1.31-1.38)
Hypertension	1.06	(1.04-1.08)	0.96	(0.94-0.98)
Diabetes Mellitus	1.30	(1.28-1.33)	1.28	(1.26-1.31)
Neurological				
Cerebrovascular Accident/TIA/Stroke	1.47	(1.42-1.51)	4.97	(4.81-5.13)
Multiple Sclerosis	6.60	(5.41-8.05)	12.45	(10.09-15.36)
Parkinson's Disease	2.57	(2.46-2.68)	4.87	(4.65-5.10)
Seizure disorder or Epilepsy	1.12	(1.08-1.16)	2.02	(1.94-2.11)
Musculoskeletal				
Arthritis	1.26	(1.24-1.28)	0.95	(0.93-0.99)
Osteoporosis	1.06	(1.04-1.09)	0.97	(0.93-1.00)
Hip fracture	8.20	(7.29-9.22)	13.35	(11.87-15.01)
Other fracture	3.87	(3.67-4.09)	3.24	(3.06-3.44)
Mental health				
Anxiety disorder	0.91	(0.89-0.93)	0.87	(0.84-0.89)
Depression	1.04	(1.02-1.07)	1.04	(1.01-1.07)
Any presence of pain *(ref: no presence)*	1.74	(1.71-1.77)	1.57	(1.54-1.60)
Receipt of psychotropic medications[3] *(ref: did not receive)*				
Antipsychotics	0.64	(0.63-0.66)	0.61	(0.60-0.62)
Antianxiety	1.05	(1.02-1.07)	1.20	(1.17-1.23)
Antidepressant	1.14	(1.12-1.16)	1.10	(1.07-1.12)

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease.
[1] Multinomial logistic regression model adjusted for all demographic and clinical characteristics listed in this table.
[2] Other admission sources included another nursing home or swing bed, psychiatric hospital, inpatient rehabilitation facility, MR/DD facility, long-term care hospitals, hospice, and other sources.
[3] Receipt of psychotropic medications in the past 7 days or since admission.

Figure 4.1. Sample flowchart (n = 871,801)



CHAPTER V.

PROGRESSION OF PHYSICAL FRAILTY BY COGNITIVE IMPAIRMENT IN OLDER NURSING HOME RESIDENTS

(Note: The texts, tables, and figures in this chapter are based on the manuscript currently under review at BMC Geriatrics. Refer to the **LIST OF COPYRIGHTED MATERIAL PRODUCED BY THE AUTHOR** and **PREFACE** for the publication citation for Chapter V.)

I. Introduction

Physical frailty, characterized by decreased physical reserve and increased vulnerability to external stressors, and cognitive impairment, manifested as dysfunctions on at least one cognitive domain, are common geriatric conditions. In community-dwelling older adults in the U.S., 6% have physical frailty only, 26% have cognitive impairment only, and 9% have both conditions[100]. Physical frailty and cognitive impairment are more prevalent in nursing home residents[2]. Between 30-85% of older nursing home residents experience physical frailty[33,34,80], and over 60% have moderate to severe cognitive impairment[2,80]. Despite the high prevalence and the increased risk for hospitalization, lower quality of life, and mortality associated with physical frailty and cognitive impairment[65–67], limited research has examined the longitudinal experience of these two conditions among older nursing home residents.

Changes in the prevalence of both conditions were observed particularly in the first three months of nursing home residence[80]: 23% of older residents who were pre-frail at admission became physically robust while 31% became frail after three months; 20% of those with moderate cognitive impairment at admission were found to experience intact/mild impairment while 23% were found to be severely impaired after three months[80]. While informative on the overall burden of both conditions and their potential changes over time in nursing home residents, such population-level prevalence may not reflect how residents progress on the individual level, as older adults may experience distinctive trajectories of physical

frailty[101–103] and cognitive impairment[104]. Furthermore, categorizing residents as robust vs. prefrail vs. frail and intact/mild vs. moderate vs. severe cognitive impairment while having clinical value, may not adequately capture the dynamic continuum of these conditions[105,106]. Therefore, exploring older residents' physical frailty trajectories and cognitive impairment trajectories using continuous measures and quantifying factors associated with these trajectories could provide insight into the "natural history" of frailty and cognitive decline. Such information could help identify older residents who may be more likely to improve or at risk for accelerated worsening to inform appropriate treatments in the nursing home setting.

Physical frailty and cognitive impairment are highly correlated[18,70,71,80,107]. About 70% of nursing home residents who were physically frail had severe cognitive impairment[80] and those with greater levels of cognitive impairment experience more indicators of physical frailty[107]. This close interrelationship may reflect a shared neuropathology[15,18], concomitant yet separate outcomes of the aging process, or "cognitive frailty", defined as the co-existence of both conditions without overt dementia and other neurological conditions[16,17], but the underlying mechanism has not yet been clarified[108]. There are limited evidence-based treatment options available to modify the progression of cognitive impairment[108], but physical frailty is potentially reversible[47–49] and could serve as a promising target for intervention[51,109]. Reducing the progression of physical frailty through comprehensive clinical management with physical activity and nutritional

approaches[50,51] may help improve the trajectories of cognitive decline. Evaluating the extent to which trajectories of physical frailty are associated with the trajectories of cognitive impairment in older nursing home residents would further our understanding of the interrelationship between these two conditions and provide foundational knowledge to develop tailored care for residents to address both conditions.

This study examined the trajectories of physical frailty and cognitive impairment in a national cohort of U.S. older adults over the first six months in a nursing home, as this early period is a critical window during which older residents adjust to clinical care and living environment changes[36,68]. The objectives were to: (1) identify the trajectories of physical frailty and estimate the association between cognitive impairment, demographic and clinical characteristics at admission and the identified physical frailty trajectories; (2) identify the trajectories of cognitive impairment and estimate the association between physical frailty, demographic and clinical characteristics at admission and the identified cognitive impairment trajectories; (3) quantify the association between the physical frailty trajectories and cognitive impairment trajectories.

II. Methods

The University of Massachusetts Chan Medical School Institutional Review Board approved this study as exempt from Federal regulations (09/20/2019).

Sample

We included residents who were (1) aged ≥65 years at admission; (2) newly admitted (defined as no previous stay in a nursing home in the 90 days before the current admission) between 01/01/2014 and 06/30/2016; (3) had a prognosis of life expectancy ≥6 months at admission, determined by answering "no" to the MDS 3.0 question, "Does the resident have a condition or chronic disease that may result in a life expectancy of less than 6 months?"[72,73]; (4) resided in the nursing home for at least six months; (5) had MDS 3.0 assessments at admission, 3 months (closest assessment to 90 days ± 31 days), and 6 months (closest assessment to 180 days ± 31 days); (6) participated in the Brief Interview for Mental Status (BIMS) on each MDS 3.0 assessment; (7) did not enter as a skilled nursing facility (SNF) resident. We excluded residents admitted for a SNF stay because they were not expected to reside in the nursing home for a prolonged period of time. The final sample included 266,001 older residents. (**Figure 5.1**) Their admission, 3-month, and 6-month assessments were used in the analysis.

Measures

Physical frailty

Each FRAIL-NH item was scored and the total score was summed up with a range from 0 to 13[33]. (**Table 2.1**) The continuous total FRAIL-NH score was used in the primary trajectory analysis. The previously validated cutoffs as robust (score: 0-5), pre-frail (score: 6-7), and frail (score: ≥8)[33] were used as a guide to interpreting the trajectories as well to assess physical frailty levels at admission.

Cognitive impairment

The BIMS was used to assess the level of cognitive impairment in residents that could participate in the interview, with the total score ranging from 0 to 15[61]. The continuous BIMS score was used in the primary trajectory analysis. To describe cognitive impairment level at admission, the total score was categorized into intact/mild impairment (score: 13-15), moderate impairment (8-12), and severe impairment (0-7) using previously validated cutoffs[61].

Demographic and clinical characteristics

The following characteristics were drawn from the admission assessment: age (65-<75 years; 75-<85 years; ≥85 years), sex (male; female), race/ethnicity (non-Hispanic White; racial/ethnic minority, including American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, multi-racial, and Hispanic or Latino of any race), location of the nursing homes (urban; rural), sources of admission [community; acute hospital; other sources, including another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facilities, hospice, and other unspecified facilities]; active diagnoses, any presence of pain (yes/no), and receipt of medications in the 7 days before the MDS 3.0 assessment [antipsychotics (yes/no), antianxiety medications (yes/no), antidepressants (yes/no), or hypnotics (yes/no)]. Active diagnoses included cancer, asthma/COPD/chronic lung disease, heart failure, hypertension, diabetes mellitus, Alzheimer's disease, cerebrovascular accident/ TIA/stroke, non-Alzheimer's/other dementia [vascular or multi-infarct dementia, mixed dementia, frontotemporal dementia (e.g. Pick's disease), and dementia

related to stroke, Parkinson's or Creutzfeldt-Jakob diseases], multiple sclerosis, Parkinson's disease, seizure disorder/epilepsy, arthritis, osteoporosis, hip fracture, other fracture, anxiety disorder, and depression.

Statistical analysis

Sample characteristics at admission were first described in percentages.

To address the first two study objectives, two sets of group-based trajectory models (GBTM) were fitted respectively for 1) physical frailty (using the continuous total FRAIL-NH score in the censored normal distribution at admission, 3 months, and 6 months), and 2) cognitive impairment (using the continuous BIMS score in the censored normal distribution at admission, 3 months, and 6 months), with time measured by the length of stay (in days) when each of the respective assessments occurred. We then estimated the association between sample characteristics at admission and the identified trajectories. We followed the three-step model building process recommended by Nagin[110] and reported the results according to the GRoLTS-Checklist[111].

Step 1: We first identified the trajectories. We used the same approach for physical frailty and cognitive impairment. GBTM with two to six trajectory groups were fitted to the data with all groups in quadratic shape, the highest possible order for three assessment time points. We compared the fit statistics and graphic depictions of these models to see if adding another trajectory identified a new unique experience or if it overlapped with the existing ones. Fit statistics included (1) Bayesian information criterion (BIC):

the model with the greater BIC was preferred; (2) Group average posterior probability (AvePP) of assignment: An AvePP >0.7 for all trajectory groups was indicative of good certainty of group assignments; (3) Odds of correct classification (OCC): A model was considered to have high assignment accuracy with OCC>5 for all trajectory groups. From these models, predicted values of FRAIL-NH (or BIMS) scores were graphed as solid lines to depict the trajectories with 95% confidence bands (shown with dashed lines). After we determined the optimal number of trajectories, we optimized the shapes of each trajectory (quadratic or linear) to further improve the model fit. The model that best fit the data was identified to represent the trajectories of physical frailty or the trajectories of cognitive impairment. We assigned qualitative labels to each trajectory guided by the aforementioned cutoffs. The prevalence of each trajectory was reported for physical frailty trajectories and cognitive impairment trajectories.

Step 2: We then selected the residents' characteristics to be included in each trajectory model. We first "hard-assigned" residents into the trajectory to which they had the highest posterior probability of belonging. The distributions of demographic and clinical characteristics were calculated by the assigned trajectory groups. Then, we used multinomial logistic regression models to estimate and compare the crude and adjusted associations between demographic and clinical characteristics and the assigned trajectory groups. These models helped us identify the final set of

characteristics to be included in the GBTMs in *Step 3*. Although it is possible to identify covariates directly using GBTMs, Nagin[110] recommends using the conventional multinomial logistic model because it is less computationally demanding. Given our large sample size, we heeded Nagin's advice.

Step 3: We then estimated the association between demographic and clinical characteristics and the trajectories. We included cognitive impairment at admission and the selected demographic and clinical characteristics (*Step 2*) in the final physical frailty GBTM model (*Step 1*) to estimate the association between the characteristics and the identified physical frailty trajectories. Similarly, physical frailty at admission and the selected demographic and clinical characteristics (*Step 2*) were included in the final cognitive impairment GBTM (*Step 1*) to estimate the association between the characteristics and the identified cognitive impairment trajectories. From these models, we derived aORs and 95% CIs.

To address the third study objective, a dual trajectory model was used. This model allowed us to examine the association between the identified physical frailty trajectories and the identified cognitive impairment trajectories. Three sets of conditional probabilities linked membership across the physical frailty and cognitive impairment trajectory groups[110]. Explicitly, the conditional probabilities were: 1) probability of following each of the physical frailty trajectories conditional on each cognitive impairment trajectory, 2) the probability of following each of the cognitive impairment trajectories conditional on each physical frailty trajectory, and

3) the probability of jointly following a given physical frailty trajectory and a given cognitive impairment trajectory.

The analysis used SAS 9.4[75] with PROC TRAJ for GBTM[112]. Figures were created in R with *ggplot2*[76].

III. Results

Sample characteristics

Of the 266,001 eligible older residents, nearly half were aged ≥85 years, two-thirds were women, less than one in five belonged to a racial/ethnic minority group, three quarters entered nursing homes located in urban settings, 35.7% were admitted from the community, and 38.8% from acute hospitals. At admission, 54.1% of older adults were frail as measured by the FRAIL-NH scale, and 36.7% had severe cognitive impairment according to BIMS. The top five diagnoses were hypertension (75.9%), Non-Alzheimer's/Other dementia (42.5%), depression (39.8%), diabetes mellitus (30.2%), and arthritis (29.3%). The presence of pain was documented in over one-third of residents. In the past seven days, 19.0% received antipsychotics and 46.9% received antidepressants. (**Table 5.1**)

Physical frailty trajectories in the first six months of nursing home residence and associated characteristics

We first examined the GBTMs with two to six trajectory groups where all trajectories were estimated as quadratic (*Step 1*). All models showed good certainty and accuracy of group assignment. (**Supplement Table S5.1a**) The model with five groups captured distinctive trajectories that were not identified in

models with two to four groups; it was also more parsimonious than the six-group model, which, despite a greater BIC, identified several overlapping trajectories. (**Figure 5.2**) Therefore, the five-group model was selected for further adjustment in the shape parameters to improve model fit. For this five-group GBTM, 32 models with each trajectory set to either linear or quadratic shape were compared. The final model identified had a quadratic trajectory for groups 1 to 4 and a linear trajectory for group 5.

As shown in **Figure 5.3**, in the first six months post-admission, 5.2% of older residents were consistently physically robust ("Consistently Robust"), 5.5% showed an improvement over time ("Improving Frailty"), 7.6% showed a tendency to be worsening ("Worsening Frailty"), 29.0% consistently following a pre-frail trajectory ("Consistency Pre-frail"), and 53.0% consistently followed a frail trajectory ("Consistently Frail").

Next, in *Step 2*, each resident was assigned to the physical frailty trajectory group to which they had the highest posterior probability of belonging. As shown in **Supplement Table S5.2a**, about one in every four older residents assigned to the "Consistently Robust" and the "Improving Frailty" trajectories had severe cognitive impairment at admission, but this prevalence was much higher in those assigned to the other three trajectories. Other characteristics that showed notable differences in the prevalence across trajectory groups included admission sources and presence of pain. After "hard-assigning" each resident to their highest probability trajectory, we used multinomial logistic regression models to select the

demographic and clinical characteristics to include in the final GBTM. For each demographic characteristic, we examined its crude associations with the assigned trajectories, which were all statistically significant; and then the adjusted associations when all demographic characteristics were adjusted for, which showed minimal changes and remained significant. Hence, all demographic characteristics were selected. For all clinical characteristics, the crude and adjusted associations controlling for all demographic characteristics were statistically significant with the assigned physical frailty trajectories. However, given the study objective, cognitive impairment at admission would be included in the model. So, we further compared the adjusted associations adjusting for demographic characteristics only and the adjusted associations adjusting for demographic characteristics and cognitive impairment at admission, to explore if and how cognitive impairment would impact the association between each clinical characteristic and the physical frailty trajectories. We used the 10% change in the odds ratios and identified three clinical characteristics that showed substantial changes: Alzheimer's disease, Non-Alzheimer's/Other dementia, and any presence of pain. Moreover, the direction of the associations between Alzheimer's disease or Non-Alzheimer's/Other dementia with assigned consistently pre-frail trajectory and the assigned consistently frailty trajectory flipped. Based on clinical knowledge, for Alzheimer's disease or Non-Alzheimer's/Other dementia, it was likely that cognitive impairment acted as a mediator between these two conditions and physical frailty trajectories, so adjusting for it would bias their association. For

pain, on the other hand, it would be more likely that the presence of cognitive impairment influenced older residents' assessment of pain, making cognitive impairment a confounder, and adjusting for it would not bias the association between pain and physical frailty trajectories. Therefore, in the *Step 3* GBTM model to assess the association between resident characteristics at admission and the identified physical frailty trajectories over the first six months, the final covariate set included cognitive impairment level at admission, demographic characteristics, and all clinical characteristics except Alzheimer's disease or non-Alzheimer's/other dementia. The "Consistently Robust" trajectory was chosen as the reference to highlight the characteristics associated with higher risks to be in the "Improving Frailty", "Worsening Frailty", "Consistently Pre-frail", or "Consistently Frail" trajectories, despite it being the less frequent experience in older nursing home residents.

As shown in **Supplement Table S5.3a**, older residents with worse cognitive impairment at admission had increased odds to follow any of the four trajectories. Notably, those with severe cognitive impairment were 37% more likely to follow the "Improving Frailty" trajectory (aOR: 1.37, 95% CI: 1.27-1.48), twice as likely to follow the "Worsening Frailty" trajectory (aOR: 2.06, 95% CI: 1.93-2.20) and "Consistently Pre-frail" trajectory (aOR: 1.96, 95% CI: 1.85-2.07), and four times as likely to follow the "Consistently Frail" trajectory (aOR: 4.02, 95% CI: 3.81-4.25).

Advancing age and female sex were associated with greater odds of belonging to any of the four trajectories, while those in rural nursing homes had

lower odds. Racial/ethnic minority residents had similar odds as their non-Hispanic White counterparts to follow the “Improving Frailty” trajectory and higher odds for the other three trajectories. Compared to those admitted from the community, older adults admitted from acute hospitals had increased odds of belonging to the “Consistently Pre-frail” trajectory (aOR: 2.63, 95% CI: 2.49-2.79), the “Improving Frailty” trajectory (aOR: 4.24, 95% CI: 3.94-4.55) and the “Consistently Frail” trajectory (aOR: 5.48, 95% CI: 5.18-5.80).

Most diagnoses were consistently associated with higher odds of the four trajectories relative to the “Consistently Robust” trajectory. Notably, the aORs for the “Consistently Frail” trajectory were higher than the other three trajectories for cerebrovascular accident/TIA/stroke (aOR: 2.89, 95% CI: 2.67-3.13), multiple sclerosis (aOR: 20.26, 95% CI: 11.39-36.04), Parkinson’s Disease (aOR: 4.91, 95% CI: 4.38-5.50), and hip fracture (aOR: 6.09, 95% CI: 4.36-8.51). Older residents with the documented presence of pain had greater odds of being in the “Consistently Frail” (aOR: 1.80, 95% CI: 1.72-1.89), “Improving Frailty” (aOR: 1.65, 95% CI: 1.55-1.76), and “Consistently Pre-frail” (aOR:1.43, 95% CI: 1.36-1.50) trajectories. Older residents who received antipsychotics or hypnotics in the seven days were less likely to follow the “Improving Frailty”, “Consistently Pre-frail” or “Consistently Frail” trajectories, while those who received antidepressants were more likely to do so.

<u>Cognitive impairment trajectories in the first six months of nursing home residence and associated characteristics</u>

Following a similar model building and selection process (**Supplement Table S5.1b**; **Figure 5.4**), we identified the GBTM with three groups as the optimal model for cognitive impairment trajectories. As shown in **Figure 5.5**, for the first six months of post-admission, older residents appeared to follow three distinctive but very consistent trajectories: “Consistently Severe Cognitive Impairment” (35.5%), “Consistently Moderate Cognitive Impairment” (31.8%), and “Consistently Intact/Mild Cognitive Impairment” (32.7%).

Older residents were then assigned to the cognitive impairment trajectory group to which they had the highest posterior probability of belonging (*Step 2*). At admission, about 57.8% of the older residents assigned to the “Consistently Severe Cognitive Impairment Trajectory” were frail, which was 8% higher than those assigned to the “Consistently Intact/Mild Cognitive Impairment Trajectory”. The distribution of demographic and clinical characteristics are summarized in **Supplement Table S5.2b**.

A very similar process for *Step 2* was carried out to select the demographic and clinical characteristics for cognitive impairment trajectories, the only difference being that cognitive impairment at admission was replaced by physical frailty at admission. All demographic and clinical characteristics were significantly associated with the assigned cognitive impairment trajectories. When comparing the adjusted associations between each clinical characteristic with the assigned cognitive impairment trajectories adjusting for demographic characteristics only versus adjusting for demographic characteristics and physical frailty at admission,

no characteristic showed a >10% change, so all demographic and clinical characteristics were selected into the *Step 3* GBTM model to examine how physical frailty levels and demographic and clinical characteristics at admission were associated with the identified cognitive impairment trajectories ("Consistently Intact/Mild Cognitive Impairment" as the reference trajectory) over the first six months.

As shown in **Supplement Table S5.3b**, older adults who were pre-frail or frail at admission had greater odds of following the "Consistently Moderate Cognitive Impairment" trajectory (pre-frail - aOR: 1.18, 95% CI: 1.14-1.22; frail - aOR: 1.68, 95% CI: 1.62-1.74) and the "Consistently Severe Cognitive Impairment" trajectory (pre-frail - aOR: 1.43, 95% CI: 1.37-1.48; frail - aOR: 2.69, 95% CI: 2.59-2.80).

Older adults with advancing age, from racial/ethnic minority groups, or who were residing in rural nursing homes had greater odds of being in the "Consistently Moderate Cognitive Impairment" or "Consistently Severe Cognitive Impairment" trajectories, while those admitted from acute hospitals or other non-community sources were less likely to do so. Female residents were less likely than males to belong to the "Consistently Moderate Cognitive Impairment" trajectory. There were no sex differences for the "Consistently Severe Cognitive Impairment" trajectory.

Alzheimer's disease, cerebrovascular accident/TIA/stroke, non-Alzheimer's/other dementia, seizure disorder/epilepsy, or hip fracture were associated with greater odds for the "Consistently Moderate Cognitive Impairment"

or “Consistently Severe Cognitive Impairment” trajectories. Conversely, cancer, heart failure, hypertension, diabetes mellitus, multiple sclerosis, Parkinson’s disease, arthritis, osteoporosis, asthma/COPD/chronic lung disease, anxiety disorder, depression, or presence of pain were consistently associated with lower odds. Older residents who received antipsychotics or antidepressants were more likely to follow the “Consistently Moderate Cognitive Impairment” or “Consistently Severe Cognitive Impairment” trajectories.

Dual trajectory of physical frailty and cognitive impairment

The conditional probabilities linking trajectories of physical frailty and trajectories of cognitive impairment are shown in **Figure 5.6**.

In older residents following a “Consistently Intact/Mild Cognitive Impairment” trajectory, over a third followed the “Consistently Pre-frail” trajectory. The probability of following a “Consistently Frail” trajectory was highest (60.9%) in those with a “Consistently Severe Cognitive Impairment” trajectory. In residents who followed a “Consistently Robust” or “Improving Frailty” physical frailty trajectory, around half followed a “Consistently Intact/Mild Cognitive Impairment” trajectory. Over 40% of those in the “Consistently Frail” trajectory followed a “Consistently Severe Cognitive Impairment” trajectory. In their six months after nursing home admission, 21.5% of older residents followed “Consistently Frail” and “Consistently Severely Cognitive Impairment” trajectories.

IV. Discussion

To the best of our knowledge, this is the first study to quantify the trajectories of physical frailty and cognitive impairment in U.S. nursing home residents on the national level. The use of GBTM with continuous measures of physical frailty and cognitive impairment enabled us to describe the "natural history" of these two prominent conditions, identify the demographic and clinical characteristics associated with the respective trajectories, as well as examine the relationship between the trajectories of physical frailty and trajectories of cognitive impairment in older adults' first six months of nursing home residence.

Consistent with prior studies that found heterogeneous progression trajectories in community-dwelling older adults[105], five distinct physical frailty trajectories were identified in older nursing home residents. While most older adults' experience of physical frailty did not appear to change, 1 in 18 residents showed improvement and 1 in 13 showed worsening over time. With the growing body of studies that have effectively improved older adults' physical frailty through physical and nutritional interventions[47–51], clinical management individualized to older residents' respective trajectories may be helpful to maintain their physical robustness, help them improve more steadily, reduce the rate of worsening, or address the factors that contributed to their consistently pre-frail or frail status in the nursing home setting. The demographic and clinical characteristics that were found to be associated with the physical frailty trajectories may help identify and triage distinct subgroups of older residents to proper care.

Several diagnoses were associated with higher odds to follow the "Worsening Frailty", "Consistently Pre-frail" and "Consistently Frail" trajectories but also the "Improving Frailty" trajectory. This seemingly contradictory finding may have several plausible explanations. The predicted score for older residents following the "Improving Frailty" trajectory at admission was higher than those following the "Consistently Robust" trajectory. The positive association between at-admission comorbidities and the "Improving Frailty" trajectory may be mainly attributed to this greater baseline physical frailty level. On the other hand, the baseline physical frailty level was comparable between the "Improving Frailty" trajectory and the "Consistently Pre-frail" trajectory. Clinical characteristics including seizure disorder/epilepsy, other fracture, and presence of pain were associated with higher odds to be in the "Improving Frailty" trajectory than the "Consistently Pre-frail" trajectory, which may help distinguish the two. But perhaps the strongest factors to differentiate these two trajectories would be severe cognitive impairment and demographic characteristics, namely, admission from acute hospitals and age 85 years and above.

Older residents' experience during nursing home residence may also influence the physical frailty trajectories. Social isolation and loneliness are notable risk factors for physical frailty[113,114] as well as nursing home admission[115,116] in older adults. The improving trajectory may reflect some older adults' experience of adjusting to communal living, becoming more engaged in social activities, and having support from other residents and staff. Physical frailty may improve as a

result. Our data did not allow us to evaluate the extent to which this possible explanation could be empirically supported. Alternatively, given the medical supervision provided in the nursing home setting, some older residents may experience fewer issues related to access and/or adherence to medications and other non-pharmacological therapies to manage their chronic conditions, which may, in turn, be reflected in the improving trajectory. Future research is needed to evaluate how such post-admission factors can be associated with physical frailty trajectories to optimize care management for potential improvements in physical frailty in this setting.

The “Intact/Mild Cognitive Impairment” trajectory was consistent with prior research that mostly identified a subgroup of older adults who started with a high cognitive function and remained relatively stable over time[104]. However, unlike previous studies that commonly found trajectories of cognitive decline to various degrees[104,117], older nursing home residents with moderate and severe cognitive impairment at nursing home admission showed minimal changes during the six months post-admission. Aside from the differences in population and setting, this could be attributed to the fact that change in cognitive function is a slow process[104], and therefore six months may not be adequate to capture substantial changes on the trajectories. Additionally, our eligibility criteria excluded those who were unable to participate in the BIMS at all three times. As a result, older residents who may have their cognition function measured by the staff through the CPS[63] due to extensive cognitive decline were not included in our study. Although the Cognitive

Function Scale[118] combines both the BIMS and the CPS, the combined categories may not capture the continuous changes over time as adequately as a continuous score from one scale. Potential floor effects from the assessment tools in terms of not being able to detect cognitive changes below a certain threshold could also have played a role[104], but there is limited research to thoroughly examine if BIMS suffered from such a disadvantage in the nursing home population.

Comorbid conditions were associated with reduced odds to follow the "Consistently Moderate Cognitive Impairment" or "Consistently Severe Cognitive Impairment" trajectories. However, this finding does not suggest that older adults with greater comorbidities were less likely to follow the more adverse cognitive impairment trajectories. Instead, residents with comorbid conditions likely entered nursing homes for care needs related to dependencies related to activities of daily living and other physical functions and physical illnesses[119,120], rather than impairment in cognitive function. Older residents who received antipsychotics or antidepressants were more likely to belong to the "Consistently Moderate Cognitive Impairment" or "Consistently Severe Cognitive Impairment" trajectories. Antipsychotics and antidepressants are frequently prescribed for older residents with Alzheimer's disease or other dementia to address the behavioral and psychologic symptoms[121,122]. However, exposure to these medications could accelerate cognitive decline[123], although the trajectories identified in our study did not show substantial changes. Because we examined the receipt of psychotropic medications at nursing home admission, future research should consider

medication use before and after nursing home admission to evaluate how psychotropic medications could impact cognitive impairment trajectories.

Regarding the relationship between the two sets of trajectories, one previous study in community-dwelling older adults identified four trajectory groups of physical frailty and cognitive impairment, including one trajectory marked by the simultaneously accelerated worsening of both conditions, which was named "cognitive frailty"[46]. Another study found that in older adults with mild cognitive impairment and mild-moderate Alzheimer's disease, the progression of physical frailty may be independent of cognitive impairment at its earlier stages and only became positively associated at its later stages[124]. Our study treated physical frailty and cognitive impairment as two separate constructs. This allowed us to focus on the progression trajectories of individual conditions and then describe the correlation between them in nursing home residents. Our study provides longitudinal evidence that the two sets of trajectories were highly correlated. In older nursing home residents who were consistently severely cognitive impaired, three in five were consistently physically frail. This was almost 1.5 times that of those who were consistently cognitively intact or mildly cognitively impaired. For those who were "Consistently Robust", "Improving Frailty", and "Consistently Pre-frail", the majority followed the "Intact/Mild Cognitive Impairment" trajectory. For residents who experienced "Worsening Frailty" or were "Consistently Frail", the majority followed the "Consistently Severe Cognitive Impairment" trajectory. These findings were similar to a study in older Mexican American community-dwelling

adults[125]. However, due to modeling convergence constraints, we were not able to identify relevant resident characteristics associated with both sets of trajectories. Future studies should attempt to incorporate resident characteristics into dual trajectory models, as such analyses would provide further insight on how the progression of physical frailty and cognitive impairment are interrelated over time. As more than 1 in 5 residents remained consistently frail and severely cognitively impaired during the first six months after nursing home admission, more research is needed to examine the risk profiles of these older residents to develop tailored care to address both conditions.

We note a few limitations. Only the first six months post older adults' nursing home admission were analyzed, but this early period is a critical window when functional impairment could impact older adults' adjustments to changes in the care setting and living environment, as well as long-term health outcomes[36,126]. We included older adults who resided in nursing homes for 6 months or longer so that we would have sufficient follow-up time. We acknowledge that selection bias may have been introduced. We examined sample characteristics at admission, but some of these characteristics may change over time. Additional research is needed to examine how such changes during older adults' nursing home residence could alter the identified physical frailty trajectories and cognitive impairment trajectories. We used a validated scale for physical frailty. Nevertheless, the FRAIL-NH is a relatively new scale. The BIMS may not be informative for executive functioning. Items for FRAIL-NH and BIMS were readily available in MDS 3.0,

which enabled this work to examine physical frailty at the national level. However, to further our understanding of the trajectories of these two conditions in older adults in nursing homes, studies using additional instruments that could provide a more granular, domain-specific measurement of both conditions in the nursing home setting are warranted.

V. Conclusion

In older adults' first six months in a U.S. nursing home, five physical frailty trajectories were identified. While half of older residents were consistently frail, some showed improvement or decline in their physical frailty. Three cognitive impairment trajectories were identified with minimal changes over time. Trajectories of physical frailty were strongly associated with trajectories of cognitive impairment. More than 1 in 5 residents followed the trajectories of being consistently frail and severely cognitively impaired. Older residents may benefit from comprehensive care management approaches tailored to the distinctive trajectories that they were following. The identified sociodemographic and clinical characteristics that were associated with the identified physical frailty and cognitive impairment trajectories can inform our efforts to triage older residents upon admission for proper care.

Table 5.1. Characteristics of older adults who were newly admitted to nursing homes as non-skilled nursing facility residents at admission (n = 266,001)

	All (n=266,001) (%)
Age (years)	
65 - <75	20.3
75 - <85	33.9
≥ 85	45.8
Female	67.3
Race/ethnic minority	17.5
Rural nursing home	25.6
Admission source	
Community	35.7
Acute hospital	38.8
Other sources[1]	25.6
Physical frailty[2]	
Robust	17.2
Pre-frail	28.7
Frail	54.1
Cognitive impairment[3]	
Intact/Mild impairment	33.1
Moderate impairment	30.2
Severe impairment	36.7
Diagnosis	
Cancer	5.8
Asthma/COPD/Chronic lung disease	18.2
Cardiovascular/metabolic	
Heart failure	16.5
Hypertension	75.9
Diabetes Mellitus	30.2
Neurological	
Alzheimer's Disease	13.8
Cerebrovascular accident/TIA/Stroke	11.8
Non-Alzheimer's/Other dementia [4]	42.5
Multiple Sclerosis	0.6
Parkinson's Disease	6.3
Seizure disorder/Epilepsy	5.3
Musculoskeletal	
Arthritis	29.3
Osteoporosis	13.6
Hip fracture	2.6
Other fracture	5.8
Mental health	
Anxiety disorder	23.3
Depression	39.8
Any presence of pain	36.6
Receipt of psychotropic medications [5]	
Antipsychotics	19.0
Antianxiety	18.4
Antidepressant	46.9
Hypnotic	4.0

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

[1] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.
[2] Measured by FRAIL-NH using previously validated cutoffs: robust (0-5), pre-frail (6-7), and frail (≥8).
[3] Measured by BIMS using previously validated cutoffs: intact/mild impairment (13-15), moderate impairment (8-12), and severe impairment (0-7).
[4] Included non-Alzheimer's dementia (e.g., vascular or multi-infarct dementia), mixed dementia; frontotemporal dementia (e.g., Pick's disease), and dementia related to stroke, Parkinson's, or Creutzfeldt-Jakob disease.
[5] Receipt of psychotropic medications in the past 7 days or since admission.

Figure 5.1. Sample flowchart (n = 266,001)

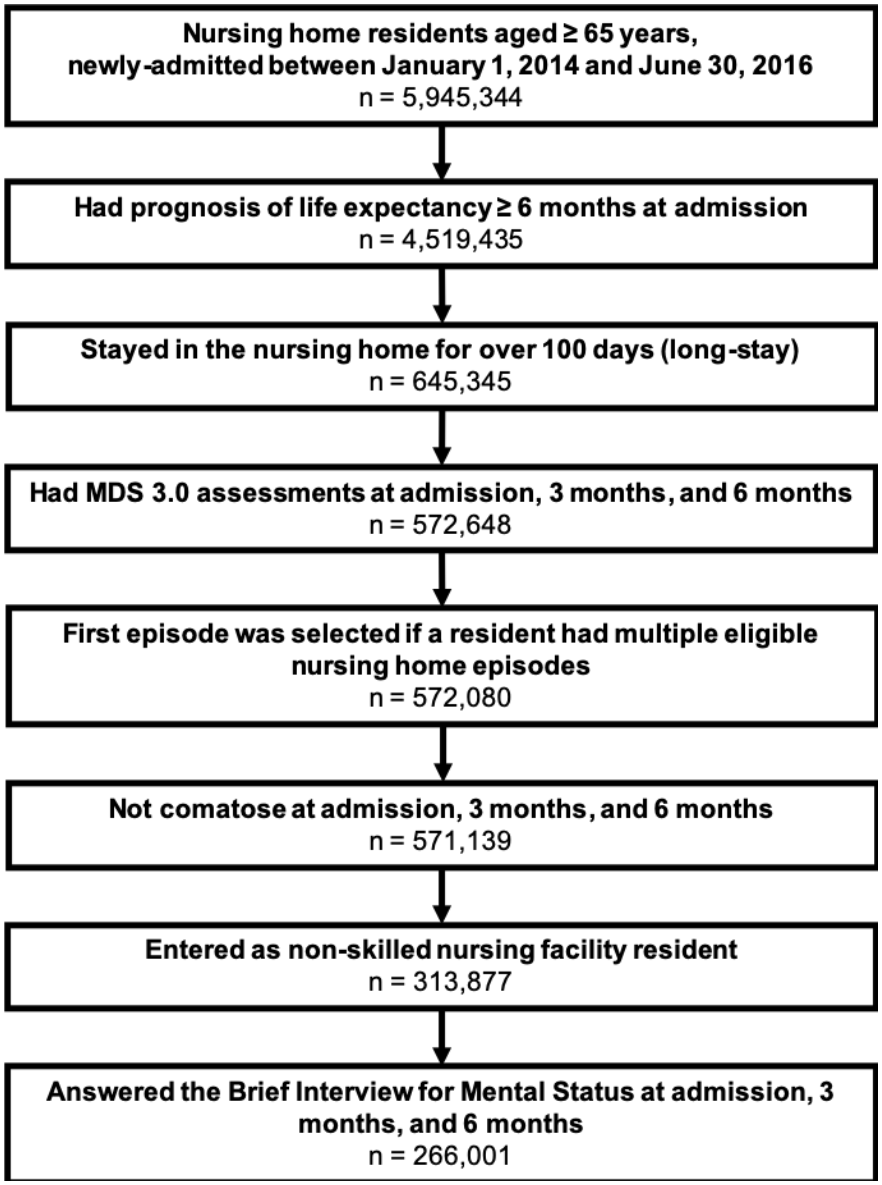


Figure 5.2. Graphic depictions of group-based trajectory model with two to six groups for physical frailty

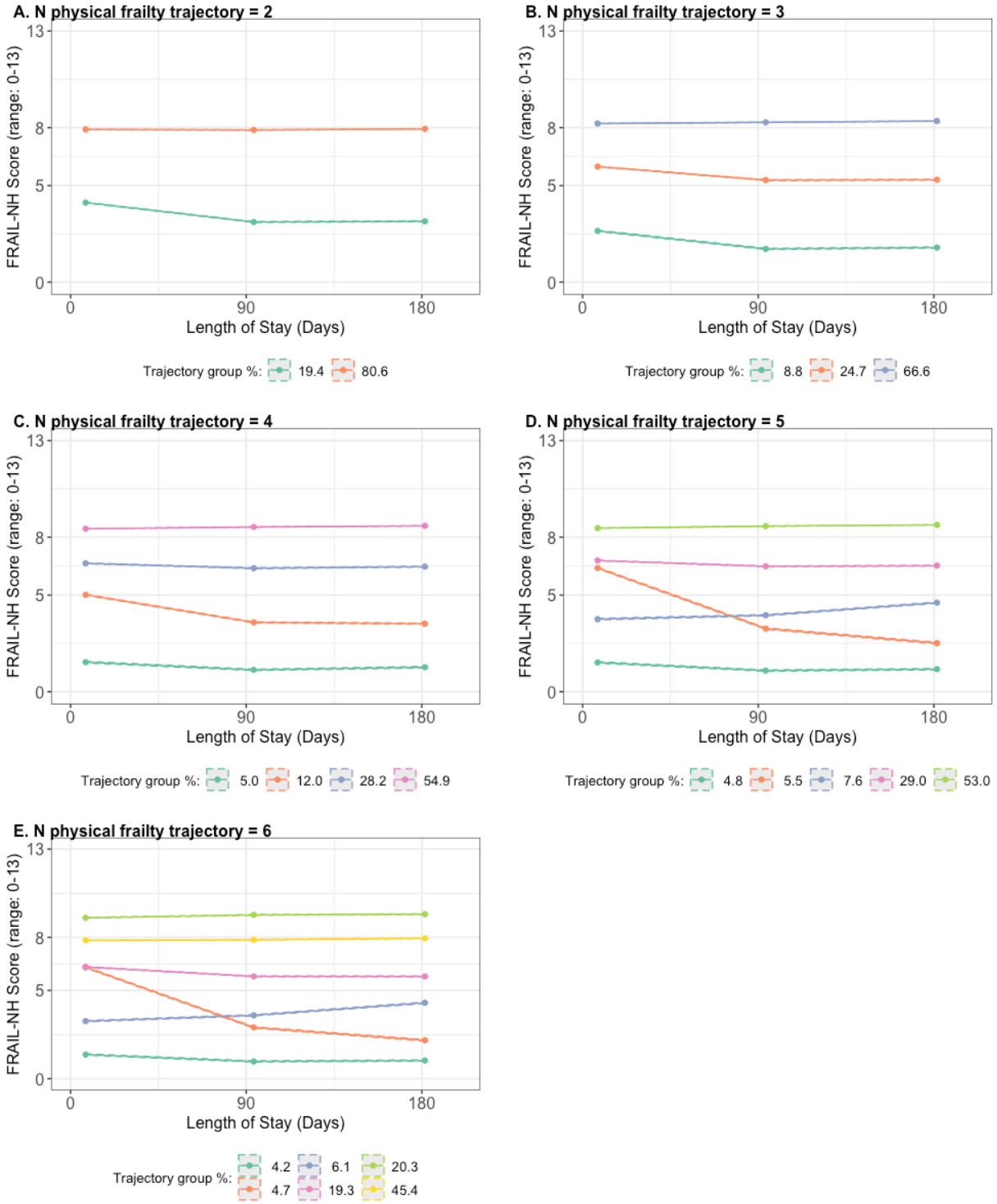
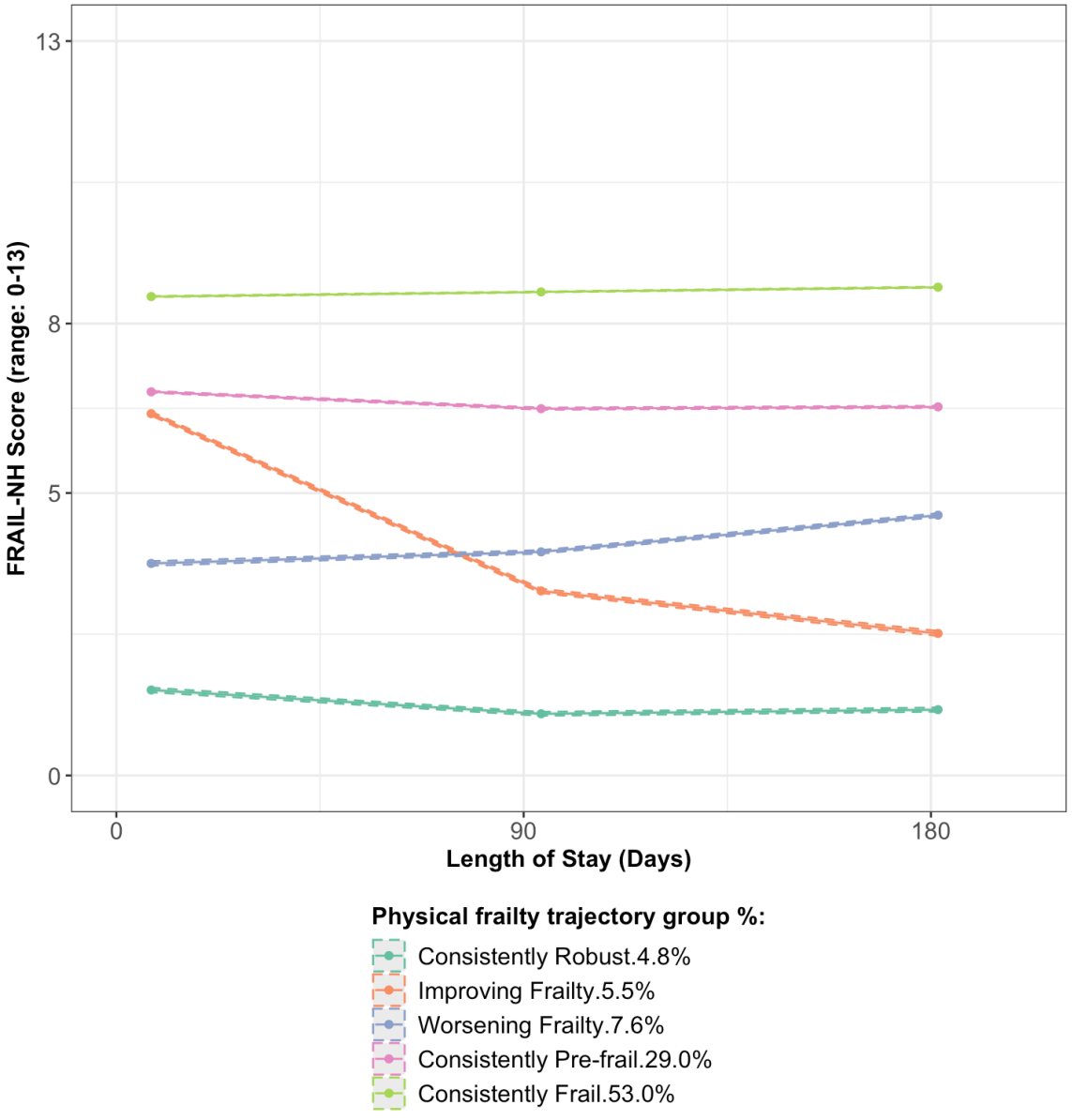


Figure 5.3. Physical frailty trajectories in the first six months of nursing home stay in older adults newly admitted to nursing homes as non-skilled nursing facility residents in 2014-2016.



Solid lines: trajectories of model predicted scores. Dash lines: 95% confidence bands.

Figure 5.4. Graphic depictions of group-based trajectory model with two to six groups for cognitive impairment

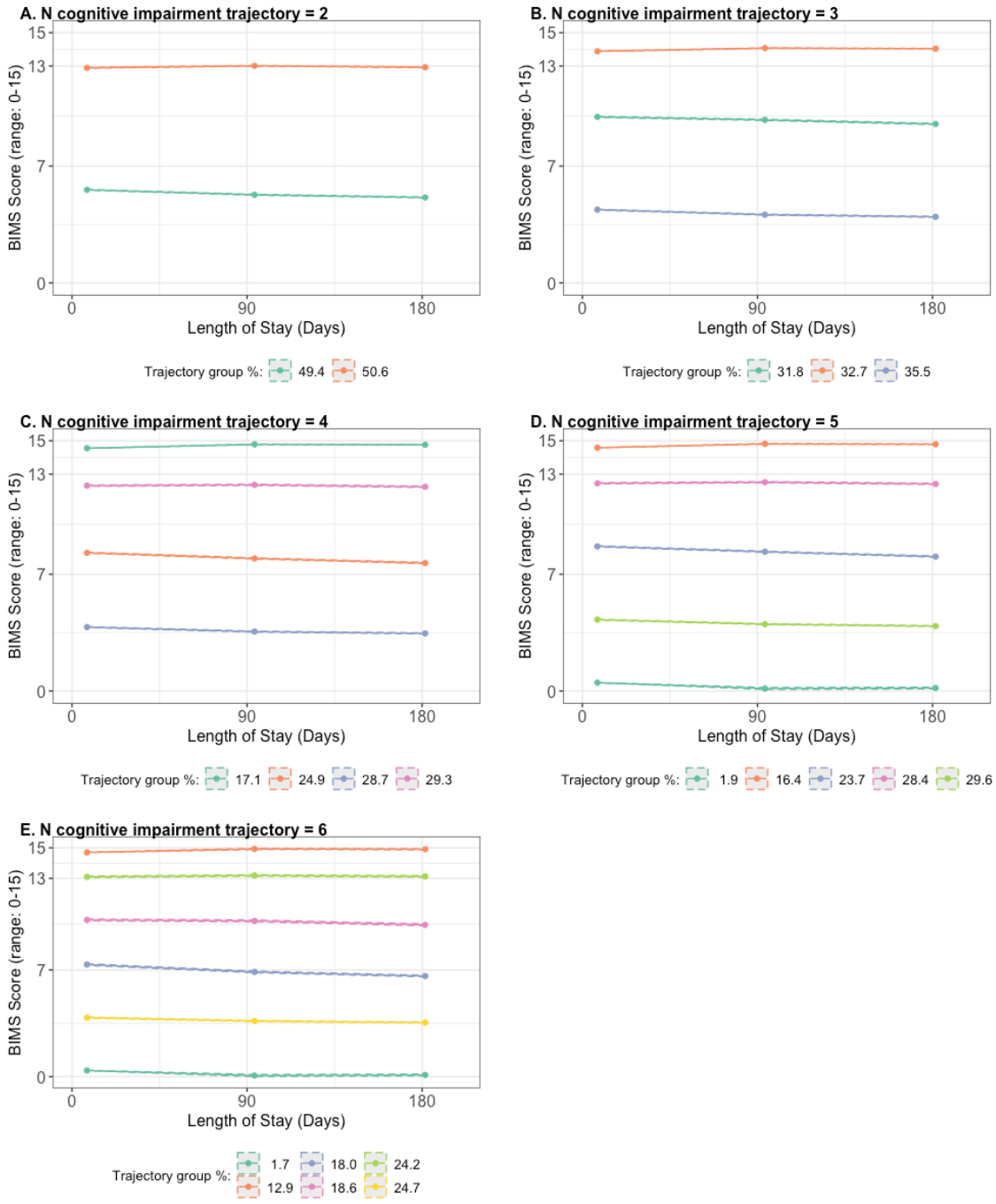
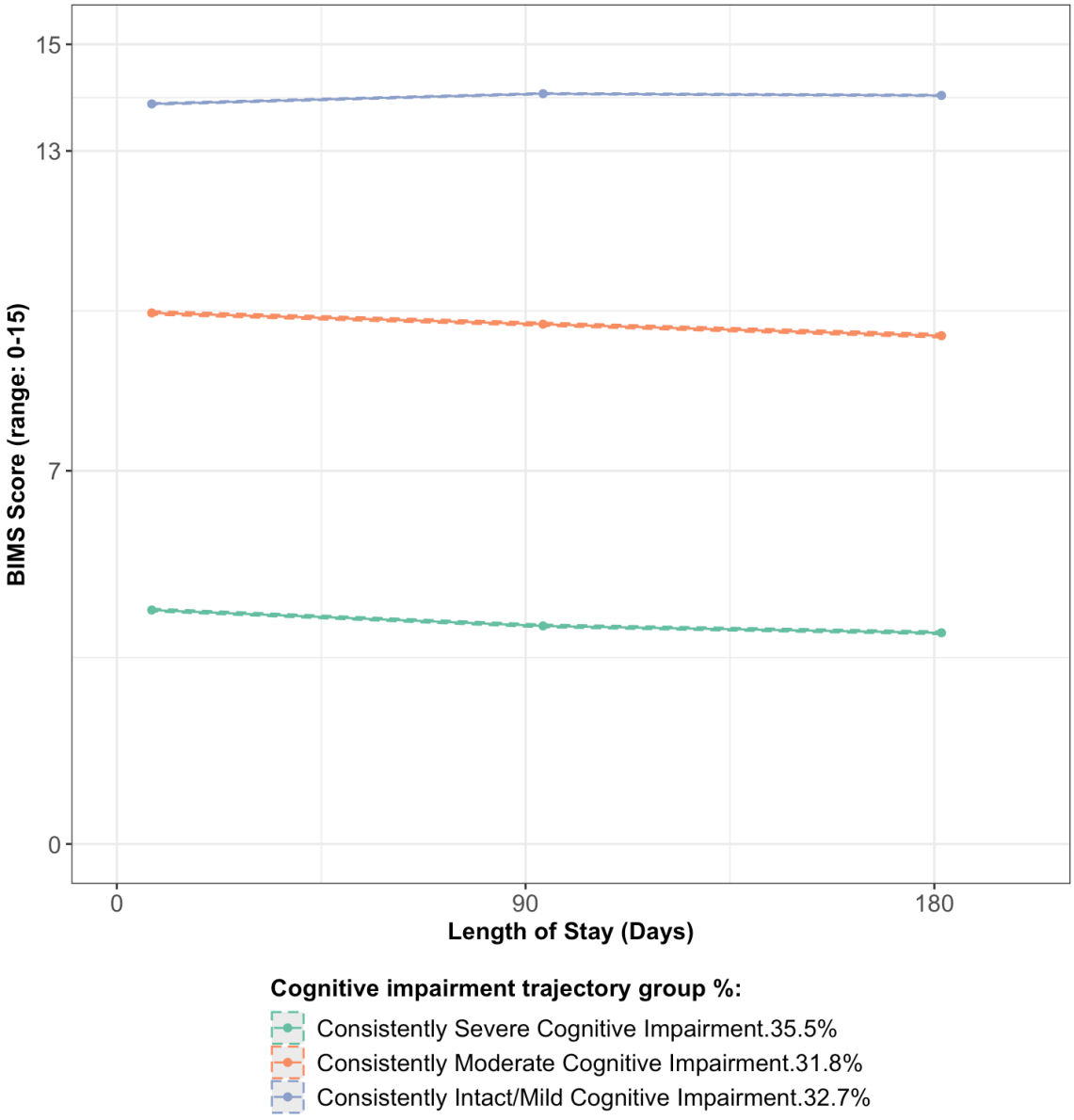
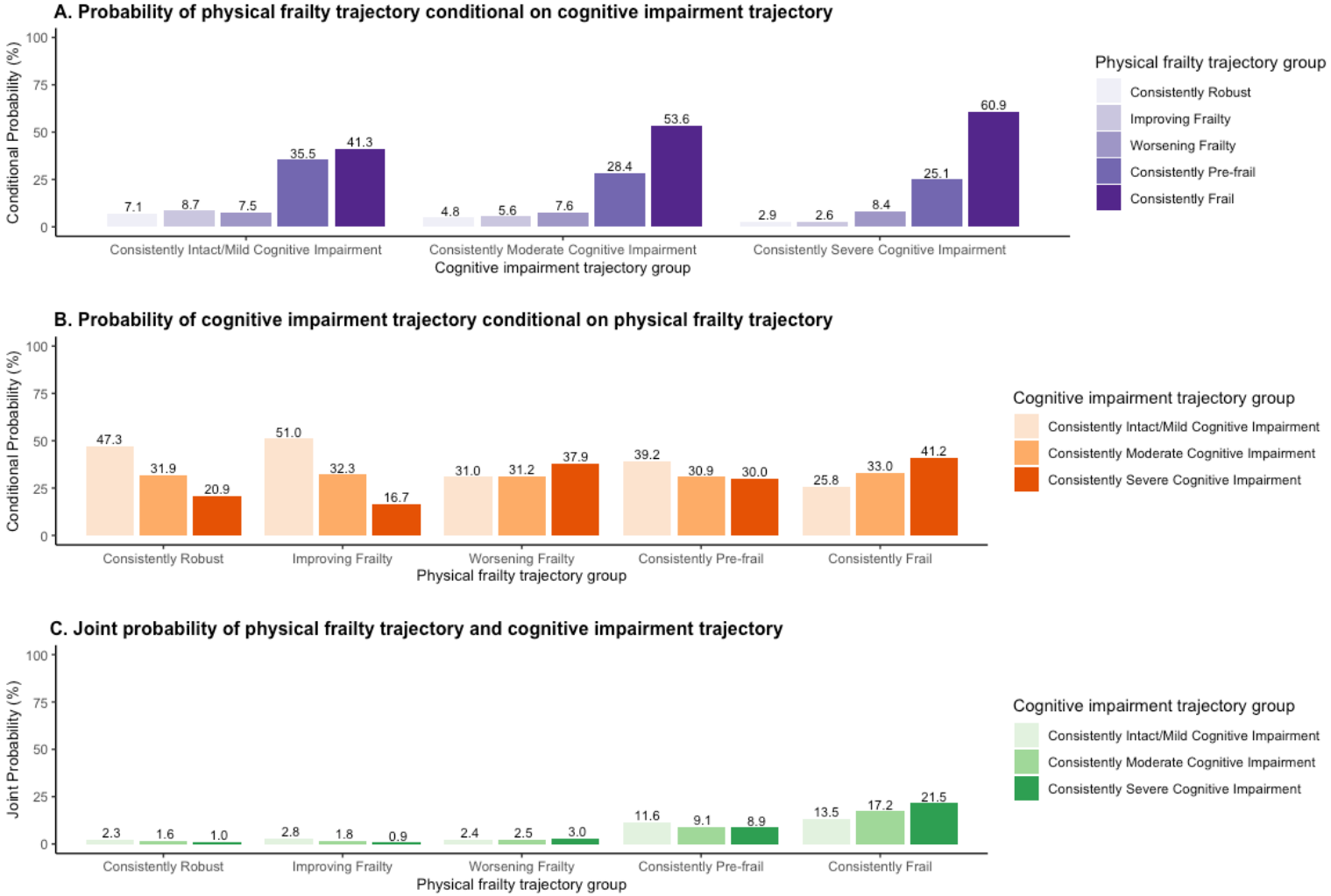


Figure 5.5. Cognitive impairment trajectories in the first six months of nursing home stay in older adults newly admitted to nursing homes as non-skilled nursing facility residents in 2014-2016



Solid lines: trajectories of model predicted scores. Dash lines: 95% confidence bands.

Figure 5.6. Unadjusted dual trajectory model of physical frailty and cognitive impairment in the first six months of nursing home stay in older adults newly admitted to nursing homes as non-skilled nursing facility residents in 2014-2016



CHAPTER VI.

DISCUSSION

(Note: Findings presented and discussed in this chapter are based on three manuscripts, two of which have been published and one is under review in peer-reviewed journals. Refer to the **LIST OF COPYRIGHTED MATERIAL PRODUCED BY THE AUTHOR** and **PREFACE** for publication citations.)

I. Review of Study Objective, Research Questions, and Specific Aims

The objective of this study was to provide a fundamental understanding of older adults' experience of physical frailty and cognitive impairment while residing in a U.S. nursing home. Essentially, the study intended to answer three main research questions, each of which was addressed by one specific aim:

Research Question 1: In older nursing home residents, what are the prevalence of physical frailty and cognitive impairment, and how are these two conditions associated over time?

Aim 1: To examine the prevalence of physical frailty and its association with cognitive impairment in older adults' first six months in a nursing home

Research Question 2: In older nursing home residents, how do their clinical presentations of physical frailty vary, and to what extent are such variations impacted by cognitive impairment?

Aim 2: To identify the subgroups of physical frailty in older nursing home residents and examine if the subgroups vary by cognitive impairment at nursing home admission

Research Questions 3: In older nursing home residents, how do physical frailty and cognitive impairment progress over time, and how are these progressions associated?

Aim 3: To describe the trajectories of physical frailty and cognitive impairment and examine the associations between the two sets of trajectories over older adults' first six months in a nursing home

II. Summary of Main Results

Aim 1:

Around 60% of older residents were physically frail and 68% had moderate/severe cognitive impairment in the first 6 months. Improvement and worsening across physical frailty levels and across cognitive impairment levels were both observed, particularly in the first three months. Older residents with moderate cognitive impairment were 35% more likely (aOR: 1.35, 95% CI: 1.33-1.37) and those with severe impairment were 74% more likely (aOR: 1.74, 95% CI: 1.72-1.77) to be physically frail than pre-frail/robust. The magnitude of the association between the two conditions consistently increased over time.

Aim 2:

At admission, three physical frailty subgroups [“mild physical frailty” (prevalence: 7.6%); “moderate physical frailty” (44.5%); “severe physical frailty” (47.9%)] were identified. Older residents in the "moderate physical frailty" or "severe physical frailty" had high probabilities of needing assistance in transferring between locations and inability to walk in a room; additionally, those in "severe physical frailty" had a greater probability of bowel incontinence. Compared to those with none/mild cognitive impairment, older adults with moderate and severe cognitive impairment were only slightly more likely to belong to the "moderate physical frailty" subgroup, while respectively over twice (aOR: 2.41, 95% CI: 2.35-2.47) and nearly six times (aOR: 5.74, 95% CI: 5.58-5.90) as likely to belong to the "severe physical frailty" subgroup.

Aim 3:

During the first six months, five physical frailty trajectories ["Consistently Frail" (53.0%), "Consistently Pre-frail" (29.0%), "Worsening Frailty" (7.6%), "Improving Frailty" (5.5%), "Consistently Robust" (4.8%)] and three cognitive impairment trajectories ["Consistently Severe Cognitive Impairment" (35.5%), "Consistently Moderate Cognitive Impairment" (31.8%), "Consistently Intact/Mild Cognitive Impairment" (32.7%)] were identified over the first six months. At-admission levels of physical frailty were associated with the identified trajectories of cognitive impairment, and at-admission levels of cognitive impairment were associated with the identified trajectories of physical frailty. Over 21% of older residents followed the trajectories of "Consistently Frail" and "Consistently Severe Cognitive Impairment".

III. Implications and Future Directions

The past few years have seen a growing number of interventions in the nursing home setting that effectively improved older adults' physical functioning in a variety of aspects, many of which were related to frailty. One systematic review of thirteen randomized clinical trials indicated significant improvements in muscle strength and functional performance, such as gait speed and chair to stand time, in institutionalized older adults through progressive resistance training[127]. Another systematic review of ten chair-based interventions in nursing home residents also indicated effectiveness in multiple areas of physical functioning, including grip strength, even in those who were frail[128]. Given the substantial burden of physical

frailty in older residents in U.S. nursing homes, it would be crucial to examine and implement interventions as such to address this prominent condition in this vulnerable population. Findings from this study have important implications for this.

Firstly, this study suggested a potential optimal window for such interventions. On the population level, *Aim 1* highlighted the notable changes in both physical frailty and cognitive impairment during the first three months. On the individual level, *Aim 3* showed that one in eighteen older residents experienced an improvement in physical frailty, with more changes observed during the first three months. These findings are in parallel with a previous study that examined changes in health instability, measured by the Changes in Health, End-Stage Disease, Signs, and Symptoms (CHESS) scale, in a cohort of Canadian older nursing home residents, where researchers found that the first 90 days after entering a nursing home were associated with the highest odds for changes in health instability[129]. Taken together, the first three months post nursing home admission appears to be an active transition phase and therefore might be a potential window for intervention to address physical frailty for older nursing home residents. Research with a crossover design comparing the effectiveness of intervention for physical frailty during the first three months versus later is needed to further confirm this.

On the other hand, a third systematic review of randomized clinical trials of exercise programs in older adults with frailty suggested that exercise training may not be effective in older adults who were very frail, indicating that the level of frailty

was critical in designing and evaluating such interventions[130]. Linking this to the findings from *Aim 2* and *Aim 3* regarding older residents' distinctive experiences of physical frailty, it would be essential to identify older residents with differential presentations and progressions and to individualize treatment options to their physical frailty subgroups or physical frailty trajectories better address the symptoms of most concern, and to maintain their physical robustness, help them improve more steadily, reduce the rate of worsening, or address the factors that contributed to their consistent pre-frail or frail status in the nursing home setting.

This study also contributed to the understanding of how physical frailty was associated with cognitive impairment in the older nursing home population, which was missing from previous research. At admission, older residents with greater levels of cognitive impairment were increasingly more likely to belong to the more severe physical frailty subgroups. Over the first six months, there was also salient longitudinal evidence on the interrelationship between these two conditions in terms of both population prevalence and individual trajectories. These findings may be indicative of the presence of "cognitive frailty", although research with more granular, domain-specific instruments to measure physical frailty and cognitive impairment is warranted to further inform the underlying mechanism behind these two conditions. To date, evidence-based treatment options that modify the progression of cognitive impairment are limited[108]. Given that physical frailty could be modified and the close interrelationship between their progression shown in this study, future intervention research on physical frailty may consider incorporating

cognitive function as an outcome to examine whether it would be possible to improve the trajectories of cognitive decline through effectively reducing the progression of physical frailty.

Last but not the least, several demographic and clinical characteristics were found to be associated with physical frailty subgroups and/or physical frailty trajectories, which may be helpful for care planning and triaging intervention efforts upon nursing home admission. One caveat is that the demographic and clinical characteristics analyzed in this study were drawn from the MDS 3.0. Factors that are not documented in the MDS 3.0 may also affect residents' experience. Greater self-efficacy, positive perception of the conception of moving into a nursing home, adequate social and emotional support from various sources, and satisfaction with the care from nursing homes could help older adults' adjustment to life in nursing homes[131–133]. On the facility level, inadequate staffing level and provision of care that did not consider older residents' individual preferences and unique needs were shown to inhibit older adults' adjustment to nursing homes[131–133]. More research is needed to examine how such intrinsic psychosocial factors and extrinsic contextual factors would influence residents' experience of physical frailty and cognitive impairment. Lastly, what would happen after the first six months? Given that the median length of stay in nursing homes (471 days[35]; for those who deceased, 5 months[134]) and that the initial period is associated with the highest likelihood for health changes[129], the progression of physical frailty and cognitive impairment after six months may remain rather stable. But additional research is needed to

delineate the “full picture” of these conditions, which would be of great value to our understanding of their “natural history” throughout the nursing home residence. Previous research found that both the number and the accumulation rate of physical frailty symptoms could predict mortality in community-dwelling older adults[135]. As such, worse at-admission physical frailty subgroup and six-month trajectories would likely further elevate older residents’ risks for adverse health outcomes. Quantifying such associations in future studies could underscore the importance of providing timely and tailored care to the relevant subgroups and trajectories with the hope to reduce such risks and improve quality of life in nursing homes.

IV. Strengths and limitations

To the best of my knowledge, this was the first study to examine on the national level the longitudinal prevalence, clinical presentation, and progression trajectories of physical frailty and cognitive impairment in older nursing home residents in the U.S. Findings provided fundamental knowledge regarding these two prominent aging-related conditions in this vulnerable population.

Several limitations should be noted. Only the first six months of nursing home residence were analyzed. This was because this early period was found to be a critical window when functional impairment could impact older adults’ adjustments to changes in clinical care and living environment, as well as long-term health outcomes[36,68]. However, physical frailty and cognitive impairment can further develop past six months. Additional research that explores beyond the first

six months would inform a more comprehensive picture of older adults' experience of these conditions in nursing homes. Despite several studies to validate FRAIL-NH[33,53,56,60], it is a relatively new scale, and studies using other scales for physical frailty in the nursing home setting are needed to confirm our findings. Additionally, BIMS and CPS may not be informative for certain cognitive domains, such as executive functioning[61]. Items for FRAIL-NH, BIMS, and CPS are readily available in MDS 3.0, which enabled this work to examine physical frailty at the national level and allowed future efforts to replicate the findings. However, to further our understanding of the underlying mechanism between these two conditions in older adults in nursing homes, additional instruments that could provide a more granular, domain-specific measurement of both conditions are warranted. Lastly, the majority of the demographic and clinical characteristics included in the study were only examined sample characteristics at admission, but they may change over time. More work is needed to examine how such changes could alter their associations with physical frailty and cognitive impairment. Additional limitations specific to each aim have been discussed in earlier chapters.

V. Conclusions

In older U.S. nursing home residents, physical frailty and cognitive impairment are highly prevalent, but notable improvements were observed during the first three months post-admission. Older residents had heterogeneous experiences with physical frailty at admission and distinctive progression over the first six months. Greater cognitive impairment was associated with higher odds to

be in the more severe physical frailty subgroups as well as the more adverse physical frailty trajectories. Findings from this dissertation contributed to the knowledge on the prevalence, presentation, and progression of physical frailty and cognitive impairment and how these two conditions were interrelated in older nursing home residents in the U.S., an imperative part of the aging population often neglected in research. Findings have implications for future intervention efforts to be tailored specific symptom profiles of physical frailty and cognitive impairment levels. The identified sociodemographic and clinical characteristics associated with the trajectories of physical frailty and trajectories of cognitive impairment can also inform efforts to triage older residents upon admission for proper care.

APPENDICES

SUPPLEMENT TABLES BY CHAPTER

- **CHAPTER III Supplement Tables (Page 99-101)**
- **CHAPTER IV Supplement Tables (Page 102-112)**
- **CHAPTER V Supplement Tables (Page 113-122)**

Supplement Table S3.1. Concurrent associations between physical frailty and cognitive impairment, demographic and clinical characteristics over older residents' first six months of nursing home stay [1]

	Physical frailty at admission		Physical frailty at 3-month		Physical frailty at 6-month	
	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Cognitive impairment [2] *(ref: none/mild impairment)*						
Moderate impairment	1.35 (1.33-1.37)	1.25 (1.22-1.27)	1.42 (1.40-1.43)	1.34 (1.32-1.36)	1.50 (1.48-1.51)	1.42 (1.39-1.44)
Severe impairment	1.74 (1.72-1.77)	1.58 (1.54-1.62)	1.96 (1.94-1.99)	1.84 (1.80-1.87)	2.24 (2.21-2.27)	2.10 (2.06-2.13)
Age (ref: ≥ 85 years)						
65 - <75 years	0.78 (0.77-0.79)	0.51 (0.50-0.52)	0.76 (0.75-0.77)	0.57 (0.56-0.58)	0.73 (0.72-0.74)	0.55 (0.54-0.56)
75 - <85 years	0.91 (0.89-0.92)	0.72 (0.71-0.74)	0.89 (0.88-0.90)	0.75 (0.74-0.77)	0.87 (0.85-0.88)	0.74 (0.73-0.76)
Female *(ref: Male)*	1.05 (1.04-1.07)	1.20 (1.18-1.23)	1.09 (1.07-1.10)	1.16 (1.14-1.18)	1.09 (1.07-1.10)	1.14 (1.13-1.16)
Racial/ethnic minority *(ref: Non-Hispanic White)*	1.25 (1.23-1.27)	1.16 (1.13-1.19)	1.30 (1.28-1.32)	1.29 (1.27-1.32)	1.27 (1.25-1.29)	1.27 (1.25-1.30)
Rural nursing home *(ref: urban)*	0.69 (0.68-0.70)	0.61 (0.59-0.62)	0.67 (0.66-0.68)	0.60 (0.59-0.61)	0.67 (0.66-0.68)	0.61 (0.60-0.62)
Admission source *(ref: community)*						
Acute hospital	2.87 (2.83-2.91)	4.62 (4.52-4.73)	2.01 (1.98-2.04)	2.22 (2.18-2.26)	1.78 (1.75-1.80)	1.90 (1.87-1.94)
Other	1.92 (1.89-1.96)	1.86 (1.82-1.91)	1.72 (1.69-1.75)	1.67 (1.63-1.70)	1.62 (1.59-1.65)	1.59 (1.55-1.62)

Supplement Table S3.1. Concurrent associations between physical frailty and cognitive impairment, demographic and clinical characteristics over older residents' first six months of nursing home stay [1] (Cont'd)

	Physical frailty at admission		Physical frailty at 3-month		Physical frailty at 6-month	
	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Diagnosis *(ref: without the given condition)*						
Cancer	1.04 (1.01-1.07)	1.09 (1.05-1.13)	1.04 (1.02-1.07)	1.07 (1.03-1.10)	1.07 (1.05-1.10)	1.09 (1.05-1.12)
Asthma/COPD/chronic lung disease	0.97 (0.95-0.98)	0.96 (0.94-0.99)	0.94 (0.93-0.96)	0.93 (0.91-0.94)	0.95 (0.93-0.96)	0.93 (0.91-0.95)
Cardiovascular/metabolic						
Heart failure	1.10 (1.08-1.12)	1.27 (1.23-1.30)	1.09 (1.07-1.11)	1.20 (1.17-1.22)	1.09 (1.07-1.10)	1.19 (1.16-1.21)
Hypertension	0.98 (0.96-0.99)	1.02 (1.00-1.04)	0.96 (0.94-0.97)	1.01 (0.99-1.02)	0.97 (0.95-0.98)	1.00 (0.98-1.02)
Diabetes mellitus	1.11 (1.09-1.12)	1.16 (1.14-1.18)	1.13 (1.11-1.14)	1.17 (1.15-1.19)	1.14 (1.12-1.15)	1.20 (1.18-1.22)
Neurological						
Alzheimer's disease	0.92 (0.90-0.93)	0.84 (0.82-0.86)	0.99 (0.97-1.01)	0.95 (0.92-0.97)	1.00 (0.98-1.02)	0.95 (0.93-0.97)
Cerebrovascular accident/TIA/stroke	1.79 (1.76-1.82)	1.94 (1.88-2.01)	1.74 (1.71-1.77)	1.86 (1.81-1.91)	1.70 (1.67-1.73)	1.81 (1.77-1.86)
Non-Alzheimer's/other dementia	0.93 (0.92-0.95)	0.85 (0.83-0.87)	0.96 (0.95-0.98)	0.91 (0.90-0.93)	0.98 (0.97-0.99)	0.93 (0.91-0.94)
Multiple sclerosis	2.36 (2.15-2.59)	3.86 (3.24-4.60)	2.44 (2.24-2.67)	3.86 (3.33-4.47)	2.39 (2.19-2.61)	4.00 (3.47-4.63)
Parkinson's disease	1.78 (1.73-1.83)	2.48 (2.36-2.60)	1.82 (1.78-1.87)	2.35 (2.26-2.45)	1.88 (1.83-1.93)	2.38 (2.29-2.48)
Seizure disorder/Epilepsy	1.32 (1.29-1.36)	1.37 (1.31-1.43)	1.31 (1.28-1.34)	1.33 (1.28-1.37)	1.31 (1.27-1.34)	1.31 (1.27-1.36)
Musculoskeletal						
Arthritis	1.01 (1.00-1.02)	1.11 (1.09-1.14)	1.02 (1.01-1.03)	1.11 (1.09-1.13)	1.04 (1.03-1.05)	1.10 (1.08-1.12)
Osteoporosis	0.99 (0.97-1.01)	1.04 (1.01-1.07)	0.98 (0.97-1.00)	1.01 (0.99-1.04)	0.98 (0.97-1.00)	1.02 (1.00-1.05)
Hip fracture	1.98 (1.91-2.04)	5.05 (4.54-5.61)	1.57 (1.52-1.62)	2.16 (2.06-2.27)	1.42 (1.38-1.46)	1.76 (1.69-1.84)
Other fracture	1.29 (1.26-1.32)	2.52 (2.38-2.67)	1.14 (1.12-1.17)	1.44 (1.40-1.49)	1.06 (1.04-1.08)	1.23 (1.19-1.27)
Mental health						
Anxiety disorder	0.95 (0.94-0.97)	0.92 (0.89-0.94)	0.92 (0.91-0.94)	0.91 (0.89-0.92)	0.91 (0.89-0.92)	0.88 (0.86-0.89)
Depression	1.07 (1.05-1.09)	1.10 (1.07-1.12)	1.07 (1.05-1.08)	1.09 (1.07-1.11)	1.07 (1.05-1.08)	1.10 (1.08-1.12)

Supplement Table S3.1. Concurrent associations between physical frailty and cognitive impairment, demographic and clinical characteristics over older residents' first six months of nursing home stay [1] (Cont'd)

	Physical frailty at admission		Physical frailty at 3-month		Physical frailty at 6-month	
	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust	Frail vs. Pre-frail/Robust	Frail/Pre-frail vs. Robust
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Any presence of pain [2] *(ref: no presence)*	1.18 (1.17-1.19)	1.31 (1.29-1.33)	1.09 (1.08-1.10)	1.11 (1.09-1.12)	1.11 (1.10-1.12)	1.15 (1.13-1.16)
Psychotropics received [2,3] *(ref: did not receive)*						
Antipsychotics	0.93 (0.92-0.95)	0.83 (0.82-0.85)	1.02 (1.01-1.03)	0.99 (0.97-1.00)	1.07 (1.05-1.08)	1.07 (1.05-1.09)
Antianxiety medications	1.07 (1.06-1.09)	1.09 (1.06-1.11)	1.13 (1.11-1.14)	1.15 (1.13-1.17)	1.16 (1.15-1.18)	1.17 (1.15-1.19)
Antidepressants	1.09 (1.07-1.10)	1.07 (1.05-1.10)	1.14 (1.13-1.16)	1.15 (1.13-1.17)	1.16 (1.15-1.18)	1.17 (1.15-1.18)
Hypnotics	0.95 (0.93-0.98)	0.94 (0.90-0.98)	0.97 (0.95-0.99)	0.97 (0.94-1.00)	0.96 (0.93-0.98)	0.97 (0.94-1.00)

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

[1] This supplement table summarizes the estimates in Figure 3.2. NPOM was used to examine the association between physical frailty and cognitive impairment, adjusting for covariates age group, sex, race/ethnicity, nursing home location, admission source, each diagnosis, presence of pain, and receipt of each psychotropic medications.

[2] Time-varying variables (cognitive impairment, any presence of pain, receipt of psychotropic medications) were measured at admission, 3-month and 6-month. All other variables were time-invariant and measured at admission.

[3] Receipt of psychotropic medications in the past 7 days or since admission.

Supplement Table S4.1. Fit statistics of basic LCA models of physical frailty subgroups

Class	Entropy	AIC	BIC	adjusted BIC	Latent class prevalence
2	0.900	6113225.3	6113540.6	6113454.8	10.6% 89.4%
3	0.621	6041188.5	6041667.3	6041537.0	7.6% 44.5% 47.9%
4	0.664	6016312.5	6016954.9	6016780.1	3.7% 5.6% 43.6% 47.1%
5	0.591	6012530.3	6013336.1	6013116.8	3.1% 3.6% 13.3% 38.5% 41.5%
6	0.617	6010409.1	6011378.4	6011114.6	2.4% 2.9% 3.3% 11.8% 31.5% 48.1%

Supplement Table S4.2. Fit statistics of LCA models of physical frailty subgroups (Sensitivity Analysis)

(A) Excluding older residents with diagnosis of Alzheimer's disease (n=767,034)

Class	Entropy	AIC	BIC	adjusted BIC	Latent class prevalence
2	0.906	5370229.657	5370541.514	5370455.707	10.0% 90.0%
3	0.625	5306746.331	5307219.893	5307089.593	7.2% 47.7% 45.0%
4	0.669	5284870.135	5285505.401	5285330.608	43.8% 5.4% 47.3% 3.5%
5	0.591	5281820.349	5282617.318	5282398.033	3.0% 3.3% 12.8% 39.6% 41.3%
6	0.640	5280238.572	5281197.246	5280933.468	3.3% 52.4% 28.7% 2.4% 2.8% 10.3%

(B) Excluding older residents with diagnosis of non- Alzheimer's/other dementia (n=529,832)

Class	Entropy	AIC	BIC	adjusted BIC	Latent class prevalence
2	0.914	3723735.482	3724037.350	3723951.543	90.6% 9.4%
3	0.628	3680137.863	3680596.256	3680465.956	46.1% 7.0% 46.9%
4	0.674	3664860.141	3665475.059	3665300.266	42.2% 5.1% 3.5% 49.2%
5	0.602	3662777.881	3663549.322	3663330.037	2.9% 41.8% 11.8% 3.3% 40.1%
6	0.642	3661592.379	3662520.345	3662256.567	10.5% 3.0% 27.7% 2.9% 53.5% 2.4%

Supplement Table S4.2. Fit statistics of LCA models of physical frailty subgroups (Sensitivity Analysis) (Cont'd)

(C) Excluding older residents with diagnosis of Alzheimer's disease and those with non-Alzheimer's/other dementia (n=460,612)

Class	Entropy	AIC	BIC	adjusted BIC	Latent class prevalence
2	0.924	3222967.344	3223265.432	3223179.625	91.5% 8.5%
3	0.641	3184427.659	3184880.312	3184750.012	6.4% 47.4% 46.2%
4	0.684	3171050.680	3171657.897	3171483.104	42.9% 4.7% 49.2% 3.1%
5	0.655	3169277.351	3170039.132	3169819.847	3.1% 12.5% 3.1% 24.5% 56.8%
6	0.531	3168377.070	3169293.416	3169029.638	3.1% 24.4% 3.0% 12.1% 13.3% 44.1%

Supplement Table S4.3. Physical frailty 3-class latent class model: subgroup prevalence and item-response probabilities of indicators (Sensitivity Analysis)

(A) Excluding older residents with diagnosis of Alzheimer's disease (n=767,034)

	Mild physical frailty subgroup	Moderate physical frailty subgroup	Severe physical frailty subgroup
Subgroup prevalence	7.2%	45.0%	47.7%
Item-response probabilities			
Fatigue			
0 No (never or 1 day)	**0.72 ***	**0.60 ***	**0.61 ***
1 Yes (several days/everyday)	0.23	0.35	0.32
2 PHQ-9 ≥ 10	0.05	0.06	0.07
Resistance [1]			
0 Independent	**0.55 ***	0.00	0.01
1 With set-up only	0.34	0.03	0.00
2 Need physical assistance	0.12	**0.97 ***	**1.00 ***
Ambulation [2]			
0 Independent	**0.53 ***	0.05	0.01
1 With assistive device	0.19	0.13	0.01
2 Cannot walk	0.28	**0.83 ***	**0.98 ***
Incontinence			
0 None	**0.68 ***	0.31	0.03
1 Urinary incontinence only	0.22	**0.39 ***	0.08
2 Bowel incontinence	0.10	0.30	**0.89 ***
Loss of weight			
0 None	**0.98 ***	**0.98 ***	**0.96 ***
1 ≥ 5% past 3 mo./ ≥10% past 6 mo.	0.02	0.02	0.04
Nutritional approach			
0 Regular diet	**0.89 ***	**0.84 ***	**0.49 ***
1 Mechanically altered diet	0.10	0.15	0.40
2 Require feeding tube	0.01	0.01	0.11
Help with dressing			
0 Independent	0.25	0.00	0.00
1 Need help with set up only	0.35	0.01	0.00
2 Need physical help	**0.41 ***	**0.99 ***	**1.00 ***

Supplement Table S4.3. Physical frailty 3-class latent class model: subgroup prevalence and item-response probabilities of indicators (Sensitivity Analysis) (Cont'd)

(B) Excluding older residents with diagnosis of non- Alzheimer's/other dementia (n=529,832)

	Mild physical frailty subgroup	Moderate physical frailty subgroup	Severe physical frailty subgroup
Subgroup prevalence	7.0%	46.9%	46.1%
Item-response probabilities			
Fatigue			
0 No (never or 1 day)	**0.71 ***	**0.58 ***	**0.60 ***
1 Yes (several days/everyday)	0.24	0.36	0.33
2 PHQ-9 ≥ 10	0.05	0.06	0.07
Resistance [1]			
0 Independent	**0.55 ***	0.00	0.01
1 With set-up only	0.33	0.02	0.00
2 Need physical assistance	0.12	**0.98 ***	**1.00 ***
Ambulation [2]			
0 Independent	**0.55 ***	0.05	0.01
1 With assistive device	0.19	0.11	0.01
2 Cannot walk	0.26	**0.84 ***	**0.99 ***
Incontinence			
0 None	**0.69 ***	0.33	0.03
1 Urinary incontinence only	0.22	**0.39 ***	0.08
2 Bowel incontinence	0.10	0.2	**0.89 ***
Loss of weight			
0 None	**0.98 ***	**0.97 ***	**0.96 ***
1 ≥ 5% past 3 mo./ ≥10% past 6 mo.	0.02	0.03	0.04
Nutritional approach			
0 Regular diet	**0.90 ***	**0.84 ***	**0.50 ***
1 Mechanically altered diet	0.10	0.15	0.37
2 Require feeding tube	0.01	0.01	0.13
Help with dressing			
0 Independent	0.27	0.00	0.00
1 Need help with set up only	0.34	0.01	0.00
2 Need physical help	**0.39 ***	**0.99 ***	**1.00 ***

Supplement Table S4.3. Physical frailty 3-class latent class model: subgroup prevalence and item-response probabilities of indicators (Sensitivity Analysis) (Cont'd)

(C) Excluding older residents with diagnosis of Alzheimer's disease and those with non-Alzheimer's/other dementia (n=460,612)

	Mild physical frailty subgroup	Moderate physical frailty subgroup	Severe physical frailty subgroup
Subgroup prevalence	6.4%	47.4%	46.2%
Item-response probabilities			
Fatigue			
0 No (never or 1 day)	**0.69 ***	**0.57 ***	**0.59 ***
1 Yes (several days/everyday)	0.26	0.37	0.34
2 PHQ-9 ≥ 10	0.05	0.06	0.07
Resistance [1]			
0 Independent	**0.54 ***	0.00	0.00
1 With set-up only	0.34	0.02	0.00
2 Need physical assistance	0.12	**0.98 ***	**1.00 ***
Ambulation [2]			
0 Independent	**0.55 ***	0.05	0.01
1 With assistive device	0.20	0.10	0.01
2 Cannot walk	0.25	**0.85 ***	**0.99 ***
Incontinence			
0 None	**0.71 ***	0.35	0.03
1 Urinary incontinence only	0.21	**0.39 ***	0.08
2 Bowel incontinence	0.08	0.26	**0.90 ***
Loss of weight			
0 None	**0.98 ***	**0.97 ***	**0.96 ***
1 ≥ 5% past 3 mo./ ≥10% past 6 mo.	0.02	0.03	0.04
Nutritional approach			
0 Regular diet	**0.89 ***	**0.84 ***	**0.51 ***
1 Mechanically altered diet	0.10	0.15	0.35
2 Require feeding tube	0.01	0.01	0.14
Help with dressing			
0 Independent	0.29	0.00	0.00
1 Need help with set up only	0.34	0.01	0.00
2 Need physical help	**0.36 ***	**0.99 ***	**1.00 ***

Notes. PHQ-9 = Patient Health Questionnaire-9.

* The level of the given indicator with the highest item-response probability. Residents belonging to the given subgroup had the highest probability of experiencing this level of the indicator.

[1] Measures if the resident needs assistance to be transferred from one location to another.

[2] Measures if the resident can walk in a room.

Supplement Table S4.4. Fit statistics of LCA models of physical frailty subgroups by cognitive impairment levels

Class	Entropy	AIC	BIC	adjusted BIC	Latent class prevalence
Cognitively intact (n = 292,548)					
2	0.932	2080430.7	2080716.6	2080630.8	9.0%; 90.2%
3	0.595	2065296.9	2065730.9	2065600.6	8.1%; 43.0%; 48.9%
4	0.648	2054145.3	2054727.5	2054552.7	4.1%; 5.8%; 41.3%; 48.8%
5	0.668	2052883.1	2053613.6	2053394.3	3.7%; 4.1%; 13.6%; 17.0%; 61.5%
6	0.567	2052426.9	2053305.5	2053041.7	3.6%; 4.1%; 7.4%; 13.1%; 20.0%; 51.8%
Moderate cognitive impairment (n = 262,307)					
2	0.904	1851917.2	1852200.0	1852114.2	10.7%; 89.3%
3	0.618	1831981.8	1832411.4	1832281.1	7.8%; 41.2%; 51.0%
4	0.660	1824164.7	1824740.9	1824566.2	3.7%; 5.9%; 43.6%; 46.7%
5	0.591	1822984.5	1823707.4	1823488.1	3.2%; 3.7%; 13.0%; 35.4%; 44.7%
6	0.708	1822382.8	1823252.4	1822988.6	2.2%; 3.0%; 3.8%; 11.6%; 19.8%; 59.7%
Severe cognitive impairment (n = 316,946)					
2	0.849	2113054.8	2113342.7	2113256.9	12.8%; 87.2%
3	0.635	2082990.3	2083427.6	2083297.3	7.2%; 40.1%; 52.7%
4	0.672	2076901.8	2077488.4	2077313.6	3.5%; 5.1%; 42.4%; 48.9%
5	0.682	2075411.1	2076147.1	2075927.8	2.4%; 4.2%; 4.4%; 39.6%; 49.4%
6	0.582	2074387.6	2075273.0	2075009.2	2.3%; 3.1%; 3.2%; 15.4%; 38.0%; 38.0%

Supplement Table S4.5. Fit statistics of LCA models of physical frailty subgroups with cognitive impairment as a grouping variable and test of measurement invariance

LCA model	Entropy	AIC	BIC	adjusted BIC	Log-likelihood	Scaling correction factor for MLR	Number of free parameters	Log-likelihood ratio test p-value
2-class without MI	0.959	7955768.08	7956737.38	7956473.60	-3977801.04 (a)	1.0459 (c)	83 (e)	<0.0001
2-class with MI	0.960	8022526.91	8022888.94	8022790.42	-4011232.46 (b)	1.0395 (d)	31 (f)	
3-class without MI	0.808	7890634.37	7892094.16	7891696.90	-3945192.18	1.0240	125	<0.0001
3-class with MI	0.827	7917163.80	7917712.68	7917563.32	-3958534.90	1.0243	47	
4-class without MI	0.811	7865577.24	7867527.52	7866996.79	-3932621.62	1.0135	167	<0.0001
4-class with MI	0.829	7888986.17	7889721.90	7889521.69	-3944430.08	1.0252	63	
5-class without MI	0.767	7861856.79	7864297.56	7863633.34	-3930719.39	1.0279	209	<0.0001
5-class with MI	0.799	7874810.16	7875732.75	7875481.68	-3937326.08	1.0256	79	
6-class without MI	0.761	7859558.05	7862489.31	7861691.62	-3929528.03	1.0449	251	<0.0001
6-class with MI	0.724	7869727.16	7870836.60	7870534.68	-3934768.58	1.0388	95	

Notes. MI = Measurement invariance across cognitive impairment levels. MLR = Maximum likelihood with robust standard error.
Log-likelihood ratio test p-value calculation: Cd = [(c*e)-(d*f)]/(e-f); LR = 2*(b-a)/Cd; Df = e-f; then use chi-square distribution to determine the p-value for LR with Df degrees of freedom.

Supplement Table S4.6. Association between physical frailty subgroups and cognitive impairment in newly-admitted older nursing home residents[1] (Sensitivity Analysis)

(A) Excluding older residents with diagnosis of Alzheimer's disease (n=767,034)

	Moderate physical frailty subgroup *(vs. Mild physical frailty subgroup)*		**Severe physical frailty subgroup** *(vs. Mild physical frailty subgroup)*	
	aOR	95% CI	aOR	95% CI
Cognitive impairment *(ref: none/mild)*				
Moderate	1.04	(1.02-1.06)	2.51	(2.44-2.57)
Severe	1.07	(1.05-1.10)	6.14	(5.96-6.32)
Age *(ref: 65 - <75 years)*				
75 - <85 years	1.57	(1.53-1.60)	1.53	(1.49-1.57)
85 and over years	2.48	(2.42-2.53)	2.33	(2.26-2.40)
Female *(ref: male)*	1.37	(1.35-1.40)	1.12	(1.10-1.15)
Racial/ethnic minority *(ref: non-Hispanic white)*	0.77	(0.75-0.79)	1.84	(1.79-1.89)
Rural nursing homes *(ref: urban)*	0.65	(0.64-0.66)	0.32	(0.32-0.33)
Admission source *(ref: community)*				
Acute hospital	4.72	(4.62-4.83)	28.50	(27.40-29.65)
Other [2]	1.42	(1.39-1.46)	7.76	(7.46-8.08)
Active diagnosis (*ref: without the diagnosis)*				
Cancer	1.11	(1.07-1.14)	1.13	(1.08-1.17)
Asthma/COPD/Chronic Lung Disease	0.94	(0.92-0.96)	0.99	(0.96-1.01)
Cardiovascular/metabolic				
Heart failure	1.45	(1.41-1.48)	1.31	(1.27-1.34)
Hypertension	1.06	(1.04-1.08)	0.98	(0.95-1.00)
Diabetes Mellitus	1.30	(1.28-1.33)	1.28	(1.25-1.31)
Neurological				
Cerebrovascular Accident/TIA/Stroke	1.49	(1.44-1.54)	5.24	(5.07-5.43)
Multiple Sclerosis	6.77	(5.52-8.32)	12.71	(10.22-15.80)
Parkinson's Disease	2.58	(2.46-2.70)	4.80	(4.56-5.04)
Seizure disorder or Epilepsy	1.11	(1.06-1.16)	1.99	(1.90-2.07)
Musculoskeletal				
Arthritis	1.26	(1.23-1.28)	0.92	(0.90-0.95)
Osteoporosis	1.06	(1.03-1.09)	0.93	(0.90-0.96)
Hip fracture	7.91	(7.00-8.94)	11.86	(10.49-13.41)
Other fracture	3.77	(3.56-4.00)	3.07	(2.89-3.27)
Mental health				
Anxiety disorder	0.91	(0.89-0.94)	0.85	(0.83-0.88)
Depression	1.04	(1.02-1.07)	1.04	(1.01-1.07)
Any presence of pain *(ref: no presence)*	1.74	(1.71-1.78)	1.57	(1.53-1.60)
Psychotropics received [3] *(ref: did not receive)*				
Antipsychotics	0.60	(0.58-0.61)	0.57	(0.56-0.59)
Antianxiety	1.01	(0.99-1.04)	1.17	(1.14-1.21)
Antidepressant	1.16	(1.13-1.19)	1.13	(1.10-1.16)

Supplement Table S4.6. Association between physical frailty subgroups and cognitive impairment in newly-admitted older nursing home residents[1] (Sensitivity Analysis) (Cont'd)
(B) Excluding older residents with diagnosis of non- Alzheimer's/other dementia (n=529,832)

	Moderate physical frailty subgroup *(vs. Mild physical frailty subgroup)*		**Severe physical frailty subgroup** *(vs. Mild physical frailty subgroup)*	
	aOR	95% CI	aOR	95% CI
Cognitive impairment *(ref: none/mild)*				
Moderate	1.08	(1.05-1.11)	2.77	(2.68-2.86)
Severe	1.06	(1.03-1.09)	6.90	(6.64-7.16)
Age *(ref: 65 - <75 years)*				
75 - <85 years	1.55	(1.51-1.59)	1.51	(1.46-1.56)
85 and over years	2.29	(2.23-2.36)	1.94	(1.87-2.01)
Female *(ref: male)*	1.39	(1.36-1.42)	1.15	(1.12-1.18)
Racial/ethnic minority *(ref: non-Hispanic white)*	0.83	(0.80-0.85)	1.89	(1.83-1.95)
Rural nursing homes *(ref: urban)*	0.63	(0.62-0.65)	0.32	(0.31-0.33)
Admission source *(ref: community)*				
Acute hospital	5.46	(5.32-5.61)	33.40	(31.75-35.12)
Other [2]	1.51	(1.47-1.56)	8.68	(8.24-9.14)
Active diagnosis (*ref: without the diagnosis)*				
Cancer	1.09	(1.04-1.13)	1.14	(1.08-1.19)
Asthma/COPD/Chronic Lung Disease	0.90	(0.88-0.93)	0.94	(0.91-0.97)
Cardiovascular/metabolic				
Heart failure	1.41	(1.37-1.45)	1.19	(1.15-1.23)
Hypertension	1.07	(1.05-1.10)	0.98	(0.95-1.00)
Diabetes Mellitus	1.30	(1.27-1.33)	1.23	(1.20-1.27)
Neurological				
Cerebrovascular Accident/TIA/Stroke	1.56	(1.50-1.63)	6.19	(5.92-6.46)
Multiple Sclerosis	6.87	(5.45-8.65)	11.63	(9.07-14.91)
Parkinson's Disease	2.38	(2.24-2.52)	4.06	(3.80-4.33)
Seizure disorder or Epilepsy	1.16	(1.10-1.22)	2.04	(1.93-2.15)
Musculoskeletal				
Arthritis	1.25	(1.22-1.28)	0.88	(0.86-0.91)
Osteoporosis	1.05	(1.02-1.09)	0.90	(0.87-0.95)
Hip fracture	7.10	(6.18-8.14)	8.81	(7.66-10.14)
Other fracture	3.94	(3.68-4.22)	2.90	(2.68-3.13)
Mental health				
Anxiety disorder	0.92	(0.89-0.95)	0.87	(0.83-0.90)
Depression	1.04	(1.01-1.07)	1.04	(1.00-1.08)
Any presence of pain *(ref: no presence)*	1.74	(1.70-1.78)	1.53	(1.49-1.57)
Psychotropics received [3] *(ref: did not receive)*				
Antipsychotics	0.55	(0.54-0.57)	0.52	(0.50-0.54)
Antianxiety	1.01	(0.98-1.05)	1.16	(1.11-1.20)
Antidepressant	1.13	(1.10-1.16)	1.09	(1.05-1.13)

Supplement Table S4.6. Association between physical frailty subgroups and cognitive impairment in newly-admitted older nursing home residents[1] (Sensitivity Analysis) (Cont'd)
(C) Excluding older residents with diagnosis of Alzheimer's disease and those with non-Alzheimer's/other dementia (n=460,612)

	Moderate physical frailty subgroup *(vs. Mild physical frailty subgroup)*		**Severe physical frailty subgroup** *(vs. Mild physical frailty subgroup)*	
	aOR	95% CI	aOR	95% CI
Cognitive impairment *(ref: none/mild)*				
Moderate	1.17	(1.14-1.20)	3.00	(2.90-3.10)
Severe	1.22	(1.17-1.26)	8.55	(8.18-8.92)
Age *(ref: 65 - <75 years)*				
75 - <85 years	1.60	(1.55-1.64)	1.58	(1.52-1.63)
85 and over years	2.15	(2.01-2.22)	1.70	(1.63-1.76)
Female *(ref: male)*	1.45	(1.42-1.48)	1.17	(1.14-1.21)
Racial/ethnic minority *(ref: non-Hispanic white)*	0.84	(0.82-0.87)	1.87	(1.81-1.94)
Rural nursing homes *(ref: urban)*	0.63	(0.61-0.64)	0.31	(0.30-0.32)
Admission source *(ref: community)*				
Acute hospital	5.70	(5.54-5.86)	39.75	(37.41-42.24)
Other [2]	1.65	(1.60-1.71)	11.01	(10.34-11.73)
Active diagnosis (*ref: without the diagnosis)*				
Cancer	1.05	(1.01-1.09)	1.12	(1.07-1.18)
Asthma/COPD/Chronic Lung Disease	0.87	(0.84-0.89)	0.91	(0.88-0.94)
Cardiovascular/metabolic				
Heart failure	1.35	(1.31-1.39)	1.09	(1.05-1.13)
Hypertension	1.08	(1.05-1.11)	1.00	(0.97-1.04)
Diabetes Mellitus	1.27	(1.24-1.30)	1.18	(1.14-1.21)
Neurological				
Cerebrovascular Accident/TIA/Stroke	1.53	(1.46-1.59)	6.37	(6.08-6.66)
Multiple Sclerosis	6.09	(4.89-7.57)	9.43	(7.42-11.99)
Parkinson's Disease	2.26	(2.13-2.40)	3.64	(3.40-3.90)
Seizure disorder or Epilepsy	1.13	(1.07-1.19)	1.95	(1.84-2.07)
Musculoskeletal				
Arthritis	1.25	(1.22-1.28)	0.84	(0.81-0.87)
Osteoporosis	1.03	(1.00-1.07)	0.85	(0.81-0.89)
Hip fracture	6.31	(5.53-7.20)	6.47	(5.64-7.42)
Other fracture	3.56	(3.33-3.81)	2.43	(2.25-2.62)
Mental health				
Anxiety disorder	0.93	(0.90-0.96)	0.87	(0.83-0.91)
Depression	1.04	(1.01-1.08)	1.04	(1.00-1.08)
Any presence of pain *(ref: no presence)*	1.71	(1.67-1.75)	1.46	(1.42-1.50)
Psychotropics received [3] *(ref: did not receive)*				
Antipsychotics	0.48	(0.47-0.49)	0.49	(0.47-0.51)
Antianxiety	0.95	(0.92-0.99)	1.11	(1.07-1.16)
Antidepressant	1.16	(1.12-1.19)	1.13	(1.09-1.18)

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; aOR = adjusted odds ratio; 95% CI = 95% confidence interval.
[1] Measured by FRAIL-NH using previously validated cutoffs: robust (0-5), pre-frail (6-7), and frail (≥8).
[2] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.
[3] Receipt of psychotropic medications in the past 7 days or since admission.

Supplement Table S5.1a. Fit statistics for trajectory models for physical frailty over the first six months of nursing home stay

# Trajectory groups	Trajectory shape parameter [1]	BIC	Group membership	Group AvePP [2]	OCC [3]
2	(2 2)	-1525679	0.194 (a)	0.942 (b)	67.07
			0.806	0.981	12.55
3	(2 2 2)	-1472788	0.088	0.958	235.53
			0.247	0.882	22.59
			0.666	0.951	9.71
4	(2 2 2 2)	-1453213	0.050	0.936	275.87
			0.120	0.888	60.44
			0.282	0.832	12.60
			0.549	0.902	7.52
5	**(2 2 2 2 2)**	**-1441341**	**0.048**	**0.943**	**334.50**
			0.055	**0.838**	**87.48**
			0.076	**0.818**	**54.65**
			0.290	**0.835**	**12.52**
			0.530	**0.908**	**8.61**
6	(2 2 2 2 2 2)	-1431466	0.042	0.931	307.66
			0.047	0.868	134.09
			0.061	0.838	79.70
			0.193	0.837	21.65
			0.454	0.803	4.88
			0.203	0.780	13.96

Notes. BIC = Bayesian information criterion; AvePP = Average posterior probability; OCC = Odds of correct classification.

[1] Defines the shape parameters of the trajectory groups: 0 = intercept only, 1 = linear, 2 = quadratic, 3 = cubic.

[2] Group AvePP of assignment: Based on the maximum probability assignment rule, each individual will be assigned to a group according to the largest posterior probability. For all the individuals assigned to a certain group, an AvePP will be calculated. For each trajectory group, an AvePP of assignment > 0.7 is indicative of good certainty of group assignments.

[3] OCC: The numerator is the odds of a correct classification into a certain group based on the model, and the denominator is the correct classification into that group based on random assignment, essentially, OCC = [b/(1-b)]/[a/(1-a)]. For each trajectory group, OCC ≥ 5 suggests high assignment accuracy.

Supplement Table S5.1b. Fit statistics for trajectory models for cognitive impairment over the first six months of nursing home stay

# Trajectory groups	Trajectory shape parameter [1]	BIC	Group membership	Group AvePP	OCC
2	(2 2)	-1836008	0.494 (a)	0.965 (b)	27.99
			0.506	0.949	18.14
3	**(2 2 2)**	**-1774126**	**0.355**	**0.920**	**20.76**
			0.318	**0.881**	**15.85**
			0.327	**0.945**	**35.10**
4	(2 2 2 2)	-1751091	0.287	0.934	35.06
			0.249	0.858	18.10
			0.293	0.838	12.49
			0.171	0.905	46.04
5	(2 2 2 2 2)	-1739468	0.019	0.872	358.15
			0.296	0.885	18.25
			0.237	0.851	18.48
			0.284	0.889	19.77
			0.164	0.897	47.01
6	(2 2 2 2 2 2)	-1734898	0.017	0.867	389.20
			0.247	0.835	15.42
			0.180	0.780	16.16
			0.186	0.780	15.57
			0.242	0.859	18.19
			0.129	0.852	42.03

Notes. BIC = Bayesian information criterion; AvePP = Average posterior probability; OCC = Odds of correct classification.

[1] Defines the shape parameters of the trajectory groups: 0 = intercept only, 1 = linear, 2 = quadratic, 3 = cubic.

[2] Group AvePP of assignment: Based on the maximum probability assignment rule, each resident will be assigned to a group according to the largest posterior probability. For all the individuals assigned to a certain group, an AvePP will be calculated. For each trajectory group, an AvePP of assignment > 0.7 is indicative of good certainty of group assignments.

[3] OCC: The numerator is the odds of a correct classification into a certain group based on the model, and the denominator is the correct classification into that group based on random assignment, essentially, OCC = [b/(1-b)]/[a/(1-a)]. For each trajectory group, OCC ≥ 5 suggests high assignment accuracy.

Supplement Table S5.2a. At-admission cognitive impairment, demographic and clinical characteristics by assigned physical frailty trajectories

	Assigned trajectory [1]				
	Consistently Robust	**Improving Frailty**	**Worsening Frailty**	**Consistently Pre-frail**	**Consistently Frail**
Characteristics at admission	(%)	(%)	(%)	(%)	(%)
Cognitive impairment [2]					
Intact/Mild impairment	44.7	44.4	35.0	37.3	28.6
Moderate impairment	30.9	31.0	30.0	29.6	30.4
Severe impairment	24.5	24.6	34.9	33.1	41.0
Age (years)					
65-<75	28.8	24.0	24.1	19.8	19.1
75 - <85	35.6	35.0	35.3	33.2	33.8
≥ 85	35.6	41.0	40.6	47.0	47.1
Female	61.1	66.4	63.8	68.1	68.0
Racial/ethnic minority	12.7	13.3	15.7	15.6	19.6
Rural nursing home	44.0	34.7	34.8	27.2	21.1
Admission source					
Community	54.0	38.2	53.5	40.8	28.8
Acute hospital	18.6	42.8	19.7	36.0	44.1
Other [3]	27.4	19.0	26.8	23.2	27.1

Supplement Table S5.2a. At-admission cognitive impairment, demographic and clinical characteristics by assigned physical frailty trajectories (Cont'd)

	Assigned trajectory [1]				
	Consistently Robust	**Improving Frailty**	**Worsening Frailty**	**Consistently Pre-frail**	**Consistentl y Frail**
Characteristics at admission	(%)	(%)	(%)	(%)	(%)
Diagnosis					
Cancer	5.1	6.1	5.5	5.7	5.9
Asthma/COPD/Chronic Lung Disease	19.0	21.3	18.0	18.4	17.8
Cardiovascular/metabolic					
Heart failure	11.9	16.0	13.2	16.5	17.4
Hypertension	73.3	75.4	73.6	76.4	76.2
Diabetes Mellitus	27.0	29.1	27.6	29.4	31.3
Neurological					
Alzheimer's Disease	14.1	11.1	17.8	13.7	13.5
Cerebrovascular Accident/TIA/Stroke	6.4	7.9	7.2	9.6	14.4
Non-Alzheimer's/other dementia [4]	39.4	37.6	45.3	40.6	43.8
Multiple Sclerosis	0.1	0.2	0.2	0.6	0.8
Parkinson's Disease	2.9	3.9	3.2	5.4	7.7
Seizure disorder/Epilepsy	4.3	4.9	4.2	4.5	5.9
Musculoskeletal					
Arthritis	26.3	29.5	27.0	30.4	29.3
Osteoporosis	11.8	13.1	12.8	14.2	13.7
Hip fracture	0.3	1.8	0.5	2.0	3.5
Other fracture	1.5	6.6	1.8	5.9	6.5
Mental health					
Anxiety disorder	23.4	24.1	23.8	22.9	23.4
Depression	35.6	35.6	38.0	38.5	41.5
Any presence of pain	28.7	41.0	27.2	36.3	38.2
Psychotropics received [5]					
Antipsychotics	21.8	16.4	22.3	17.7	19.3
Antianxiety medications	18.1	18.5	18.0	17.9	18.8
Antidepressants	41.8	42.7	45.1	45.2	48.9
Hypnotics	4.9	4.5	4.3	4.1	3.8

Note: TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

[1] Older nursing home residents were assigned to the physical frailty trajectories they had the highest posterior probability of belonging to.

[2] Measured by BIMS using previously validated cutoffs: intact/mild impairment (13-15), moderate impairment (8-12), and severe impairment (0-7).

[3] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.

[4] Included non-Alzheimer's dementia (e.g., vascular or multi-infarct dementia), mixed dementia; frontotemporal dementia (e.g., Pick's disease), and dementia related to stroke, Parkinson's or Creutzfeldt-Jakob diseases.

[5] Receipt of psychotropic medications in the past 7 days or since admission.

Supplement Table S5.2b. At-admission physical frailty, demographic and clinical characteristics by assigned cognitive impairment trajectories

	Assigned trajectory [1]		
	Consistently Intact/Mild Cognitive Impairment	**Consistently Moderate Cognitive Impairment**	**Consistently Severe Cognitive Impairment**
Characteristics at admission	(%)	(%)	(%)
Physical Frailty [2]			
Robust	19.0	16.9	15.7
Pre-frail	31.2	28.4	26.5
Frail	49.8	54.7	57.8
Age (years)			
65-<75	31.2	18.4	12.6
75 - <85	33.6	33.7	34.3
≥ 85	35.2	47.9	53.1
Female	66.0	65.3	70.1
Racial/ethnic minority	15.3	17.7	19.3
Rural nursing home	25.6	25.8	25.4
Admission source			
Community	30.8	34.5	10.9
Acute hospital	42.6	41.1	33.4
Other [3]	26.6	24.4	25.7

Supplement Table S5.2b. At-admission physical frailty, demographic and clinical characteristics by assigned cognitive impairment trajectories (Cont'd)

	Assigned trajectory [1]		
	Consistently Intact/Mild Cognitive Impairment	**Consistently Moderate Cognitive Impairment**	**Consistently Severe Cognitive Impairment**
Characteristics at admission	(%)	(%)	(%)
Comorbidities			
Cancer	6.7	6.0	4.8
Asthma/COPD/Chronic Lung Disease	24.2	18.4	12.9
Cardiovascular/metabolic			
Heart failure	21.0	17.3	11.9
Hypertension	78.0	77.2	72.9
Diabetes Mellitus	36.4	30.9	24.2
Neurological			
Alzheimer's Disease	3.4	10.7	25.5
Cerebrovascular Accident/TIA/Stroke	12.4	12.9	10.3
Non-Alzheimer's/other dementia [4]	19.3	43.7	61.5
Multiple Sclerosis	1.1	0.5	0.2
Parkinson's Disease	7.2	7.0	4.9
Seizure disorder/Epilepsy	5.6	5.6	4.8
Musculoskeletal			
Arthritis	32.4	29.2	26.8
Osteoporosis	13.2	13.5	14.1
Hip fracture	2.4	2.8	2.6
Other fracture	6.7	6.1	4.7
Mental health			
Anxiety disorder	23.6	21.8	24.4
Depression	40.5	39.9	39.1
Any presence of pain	52.2	36.9	21.0
Psychotropics received [5]			
Antipsychotics	13.0	17.0	25.9
Antianxiety medications	18.5	16.6	20.0
Antidepressants	46.4	46.6	47.6
Hypnotics	5.7	3.7	2.8

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease

[1] Older nursing home residents were assigned to the physical frailty trajectories they had the highest posterior probability of belonging to.

[2] Measured by FRAIL-NH using previously validated cutoffs: robust (0-5), pre-frail (6-7), and frail (≥8).

[3] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.

[4] Included non-Alzheimer's dementia (e.g., vascular or multi-infarct dementia), mixed dementia; frontotemporal dementia (e.g., Pick's disease), and dementia related to stroke, Parkinson's or Creutzfeldt-Jakob diseases.

[5] Receipt of psychotropic medications in the past 7 days or since admission.

Supplement Table S5.3a. Association between demographic and clinical characteristics at admission and physical frailty trajectories [1]

Characteristics at admission	**Physical frailty trajectories *(ref: Consistently Robust)***							
	Improving Frailty		**Worsening Frailty**		**Consistently Pre-frail**		**Consistently Frail**	
	aOR	95% CI	aOR	95% CI	aOR	95% CI	aOR	95% CI
Cognitive impairment[2] *(ref: Intact/Mild impairment)*								
Moderate impairment	1.17	(1.09-1.25)	1.29	(1.21-1.37)	1.21	(1.15-1.27)	1.81	(1.72-1.90)
Severe impairment	1.37	(1.27-1.48)	2.06	(1.93-2.20)	1.96	(1.85-2.07)	4.02	(3.81-4.25)
Age *(ref: 65-<75 years)*								
75 - <85	1.28	(1.19-1.38)	1.16	(1.08-1.24)	1.42	(1.35-1.50)	1.62	(1.53-1.71)
≥ 85	1.66	(1.53-1.79)	1.34	(1.25-1.44)	2.24	(2.11-2.37)	2.82	(2.66-2.98)
Female *(vs. Male)*	1.19	(1.12-1.27)	1.07	(1.02-1.13)	1.25	(1.20-1.31)	1.30	(1.24-1.36)
Racial/ethnic minority *(ref: Non-Hispanic White)*	0.95	(0.87-1.03)	1.29	(1.20-1.39)	1.15	(1.08-1.23)	1.46	(1.37-1.55)
Rural nursing home *(ref: Urban nursing home)*	0.74	(0.70-0.79)	0.66	(0.63-0.69)	0.50	(0.48-0.52)	0.36	(0.34-0.37)
Admission source *(ref: Community)*								
Acute hospital	4.24	(3.94-4.55)	0.97	(0.90-1.04)	2.63	(2.49-2.79)	5.48	(5.18-5.80)
Other [3]	1.05	(0.97-1.13)	1.01	(0.96-1.08)	1.13	(1.08-1.19)	2.21	(2.10-2.32)

Supplement Table S5.3a. Association between demographic and clinical characteristics at admission and physical frailty trajectories [1] (Cont'd)

Characteristics at admission	**Physical frailty trajectories** *(ref: Consistently Robust)*			
	Improving Frailty	**Worsening Frailty**	**Consistently Pre-frail**	**Consistently Frail**
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Diagnosis *(ref: without the diagnosis)*				
Cancer	1.19 (1.06-1.35)	1.13 (1.01-1.27)	1.14 (1.04-1.25)	1.26 (1.15-1.39)
Asthma/COPD/Chronic Lung Disease	1.12 (1.05-1.21)	1.00 (0.93-1.06)	0.99 (0.94-1.04)	1.00 (0.95-1.06)
Cardiovascular/metabolic				
Heart failure	1.28 (1.18-1.39)	1.15 (1.07-1.25)	1.40 (1.31-1.49)	1.58 (1.49-1.69)
Hypertension	1.02 (0.95-1.09)	1.01 (0.95-1.07)	1.07 (1.02-1.12)	0.99 (0.95-1.04)
Diabetes Mellitus	1.15 (1.08-1.23)	1.11 (1.04-1.17)	1.26 (1.20-1.32)	1.45 (1.38-1.52)
Neurological				
Cerebrovascular Accident/TIA/Stroke	1.32 (1.18-1.47)	1.17 (1.06-1.30)	1.62 (1.49-1.76)	2.89 (2.67-3.13)
Multiple Sclerosis	3.20 (1.58-6.50)	2.74 (1.39-5.41)	9.81 (5.49-17.53)	20.26 (11.39-36.04)
Parkinson's Disease	1.87 (1.61-2.17)	1.13 (0.97-1.32)	2.56 (2.28-2.87)	4.91 (4.38-5.50)
Seizure disorder/Epilepsy	1.41 (1.24-1.61)	0.99 (0.87-1.12)	1.19 (1.07-1.31)	1.56 (1.41-1.72)
Musculoskeletal				
Arthritis	1.16 (1.08-1.23)	1.02 (0.96-1.08)	1.20 (1.14-1.26)	1.19 (1.14-1.25)
Osteoporosis	1.03 (0.95-1.13)	1.04 (0.96-1.12)	1.08 (1.01-1.15)	1.06 (0.99-1.13)
Hip fracture	3.30 (2.31-4.73)	0.94 (0.59-1.52)	3.61 (2.58-5.07)	6.09 (4.36-8.51)
Other fracture	3.34 (2.80-3.97)	0.87 (0.69-1.10)	3.03 (2.58-3.56)	3.14 (2.67-3.68)
Mental health				
Anxiety disorder	1.08 (1.00-1.18)	0.99 (0.92-1.07)	0.95 (0.90-1.01)	0.90 (0.85-0.96)
Depression	1.00 (0.92-1.08)	1.07 (1.00-1.15)	1.12 (1.06-1.19)	1.23 (1.16-1.30)
Any presence of pain *(ref: no presence of pain)*	1.65 (1.55-1.76)	1.00 (0.94-1.06)	1.43 (1.36-1.50)	1.80 (1.72-1.89)
Psychotropics received [4] *(ref: did not receive)*				
Antipsychotics	0.72 (0.66-0.77)	0.99 (0.93-1.05)	0.78 (0.74-0.82)	0.75 (0.72-0.79)
Antianxiety medication	1.07 (0.98-1.17)	0.98 (0.91-1.06)	1.05 (0.98-1.12)	1.13 (1.06-1.21)
Antidepressant	1.17 (1.08-1.26)	1.14 (1.06-1.22)	1.19 (1.13-1.27)	1.40 (1.32-1.48)
Hypnotic	0.85 (0.75-0.97)	0.90 (0.80-1.01)	0.85 (0.77-0.93)	0.81 (0.73-0.89)

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; aOR = adjusted odds ratio; CI = confidence interval.

[1] Multinomial logistic model with physical frailty trajectories as dependent variable, cognitive impairment as main independent variable, adjusting for all covariates in this table.

[2] Measured by BIMS using previously validated cutoffs: intact/mild impairment (13-15), moderate impairment (8-12), and severe impairment (0-7).

[3] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.

[4] Receipt of psychotropic medications in the past 7 days or since admission.

Supplement Table S5.3b. Association between demographic and clinical characteristics at admission and cognitive impairment trajectory groups [1]

Characteristics at admission	Cognitive impairment trajectories *(ref: Consistently intact/mild cognitive impairment)*			
	Consistently Moderate Cognitive Impairment		Consistently Severe Cognitive Impairment	
	aOR	95% CI	aOR	95% CI
Physical frailty *(ref: Robust)* [2]				
Pre-Frail	1.18	(1.14-1.22)	1.43	(1.37-1.48)
Frail	1.68	(1.62-1.74)	2.69	(2.59-2.80)
Age *(ref: 65-<75 years)*				
75 - <85	1.71	(1.66-1.77)	2.37	(2.28-2.46)
≥ 85	2.75	(2.65-2.84)	4.42	(4.25-4.59)
Female *(vs. Male)*	0.86	(0.83-0.88)	1.03	(1.00-1.06)
Racial/ethnic minority *(ref: Non-Hispanic White)*	1.43	(1.39-1.48)	1.80	(1.74-1.87)
Rural nursing home *(ref: Urban nursing home)*	1.14	(1.11-1.17)	1.19	(1.16-1.23)
Admission source *(ref: Community)*				
Acute hospital	0.96	(0.93-0.99)	0.68	(0.65-0.70)
Other [3]	0.79	(0.76-0.81)	0.65	(0.63-0.67)

Supplement Table S5.3b. Association between demographic and clinical characteristics at admission and cognitive impairment trajectory groups [1] (Cont'd)

Characteristics at admission	Cognitive impairment trajectories *(ref: Consistently intact/mild cognitive impairment)*			
	Consistently Moderate Cognitive Impairment		Consistently Severe Cognitive Impairment	
	aOR	95% CI	aOR	95% CI
Diagnoses *(ref: without the comorbid condition)*				
Cancer	0.92	(0.88-0.97)	0.78	(0.74-0.83)
Asthma/COPD/Chronic Lung Disease	0.82	(0.80-0.85)	0.62	(0.60-0.64)
Cardiovascular/metabolic				
Heart failure	0.85	(0.83-0.88)	0.63	(0.61-0.66)
Hypertension	0.94	(0.91-0.97)	0.79	(0.77-0.81)
Diabetes Mellitus	0.90	(0.88-0.92)	0.71	(0.69-0.73)
Neurological				
Alzheimer's Disease	4.97	(4.68-5.27)	17.66	(16.70-18.67)
Cerebrovascular Accident/TIA/Stroke	1.21	(1.17-1.26)	1.05	(1.01-1.10)
Non-Alzheimer's/other dementia [4]	4.00	(3.88-4.11)	9.88	(9.59-10.17)
Multiple Sclerosis	0.62	(0.53-0.71)	0.35	(0.29-0.43)
Parkinson's Disease	0.86	(0.81-0.90)	0.49	(0.46-0.52)
Seizure disorder/Epilepsy	1.19	(1.13-1.26)	1.06	(1.00-1.12)
Musculoskeletal				
Arthritis	0.82	(0.79-0.84)	0.70	(0.68-0.72)
Osteoporosis	0.96	(0.92-0.99)	0.92	(0.88-0.95)
Hip fracture	1.27	(1.18-1.37)	1.50	(1.38-1.63)
Other fracture	1.04	(0.99-1.09)	1.00	(0.94-1.06)
Mental health				
Anxiety disorder	0.92	(0.89-0.95)	0.92	(0.89-0.96)
Depression	0.95	(0.92-0.98)	0.78	(0.75-0.81)
Any presence of pain *(ref: no presence of pain)*	0.60	(0.59-0.62)	0.32	(0.31-0.32)
Psychotropics received [5] *(ref: did not receive)*				
Antipsychotics	1.37	(1.32-1.42)	1.99	(1.92-2.07)
Antianxiety	1.01	(0.97-1.05)	1.22	(1.17-1.27)
Antidepressant	1.12	(1.08-1.16)	1.21	(1.17-1.25)
Hypnotic	0.71	(0.67-0.75)	0.52	(0.48-0.56)

Notes. TIA = transient ischemic attack; COPD = chronic obstructive pulmonary disease; aOR = adjusted odds ratio; CI = confidence interval.

[1] Multinomial logistic model with cognitive impairment trajectories as dependent variable, cognitive impairment as main independent variable, adjusting for all covariates in this table.

[2] Measured by FRAIL-NH using previously validated cutoffs: robust (0-5), pre-frail (6-7), and frail (≥8).

[3] Included another nursing home/swing bed, psychiatric hospital, inpatient rehabilitation facility, ID/DD facility, long-term care hospital, hospice, and other unspecified admission sources.

[4] Included non-Alzheimer's dementia (e.g., vascular or multi-infarct dementia), mixed dementia; frontotemporal dementia (e.g., Pick's disease), and dementia related to stroke, Parkinson's or Creutzfeldt-Jakob diseases.

[5] Receipt of psychotropic medications in the past 7 days or since admission.

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