CURRICULUM VITAE

Heather Lee Mutchie, Ph.D.

Contact Information: Hmutchie27@gmail.com

Education

Aug 2011-Dec 2013	B.A., Psychology, University of West Florida (Summa Cum Laude), Minors: Aging Studies, Spanish
Aug 2015-May 2021	M.S., Epidemiology & Preventive Medicine, University of Maryland Baltimore
Aug 2015-May 2021	Ph.D., Gerontology, University of Maryland Baltimore,

Employment History

2014-2015	Research Assistant, University of Florida, Institute on Aging
2015-2020	Graduate Research Assistant, University of Maryland School of Medicine, Department of Epidemiology & Public Health
2016-2020	Veterans Administration (VA) Without Compensation Appointment, Baltimore MD VA Hospital
2018-2020	Epidemiology of Aging Graduate Training Fellow (T32), Department of Epidemiology & Public Health, UMB
2020-2021	Graduate Research Assistant, University of Maryland Baltimore County

Research Training

2014	Volunteer Research Assistant, Claude D. Pepper Older Americans Independence Center, University of Florida Institute on Aging, Gainesville, FL
2017-2019	IPEC- Statistician for Advanced Care Planning Project Grant, University of Maryland School of Medicine
2018-2020	Journal Article Review with Supervision *JAG*, *Journal of Gerontology: Medical Sciences* Supervisor: Ann Gruber-Baldini
Nov 2019	Forming Science-Industry Research Collaborations, Gerontological Society of America Annual Scientific Meeting, Austin, TX

Professional Society Memberships

2016-present	The Gerontological Society of America
2017-2018	International Society of Advanced Alzheimer's Research and Treatment
2017-2020	Sigma Phi Omega – Gerontology Honor Society
2018, 2020, 2021	Society of Epidemiological Research
2021	National Postdoctoral Association

Honors and Awards

2019	Gerontology and Geriatrics Education And Research Program Award for oral presentation of "The Feasibility of the Four Square Step Test"
2020	Dorothy and Morris Magaziner Endowment Award
2021	Patricia Langenberg Endowment in Women's Health and Epidemiology
2021	University of Maryland Baltimore Graduate Student Association Work from Home Award
2021	2021 Society for Epidemiologic Research Conference Scholarship

Institutional Service

Gerontology Doctoral Program

2016-2018	Student Member, Steering Committee, University of Maryland Doctoral Program in Gerontology
2016-2017	Junior Student Leader, Aging Forum, University of Maryland Doctoral Program in Gerontology
2017-2018	Senior Student Leader, Aging Forum, University of Maryland Doctoral Program in Gerontology
2018-2019	Graduate Student Association Program Representative, University of Maryland Doctoral Program in Gerontology
2018-2020	Co-led and Organized Student Comprehensive Exam Prep Session, University of Maryland Doctoral Program in Gerontology

University of Maryland Baltimore

2018-2021	Member, Graduate Student Association Finance Committee
2018-2020	Voting Member, Graduate Program in Life Sciences and OPS Awards Committee
2019-2021	Graduate Program in Life Sciences Student Advisory Committee
2019-2020	Treasurer, Graduate Student Association

University of Maryland Baltimore County

2018-2019	President of UMBC Sigma Phi Omega Delta Lambda Chapter
2018-2019	Voting Member, Institutional Review Board

Teaching Service

Undergraduate

2012-2013	Undergraduate Honors Mentor, University of West Florida Honors Program, Pensacola, FL

Graduate

2015	Teaching Assistant, <u>Special Topics in Health Psychology: Health Promotion</u>, University of Florida, Gainesville, FL Graduate level students
2017-2019	Student Big, Mentoring incoming first year student, University of Maryland Doctoral Program in Gerontology
Jan-May 2018	Teaching Assistant, <u>PREV 803: Clinical Trials & Experimental Epidemiology</u>, University of Maryland Baltimore, Graduate level students
Jan 2018-Jan 2019	Statistics Assistance for Medical Resident, University of Maryland Baltimore, University of Maryland Medical Center
Aug 2020-Dec 2020	Co-Instructor & Guest Lecturer, <u>PSYC/GERO 786 Psychological Aspects of Aging</u>, University of Maryland Baltimore County

Grant Support

2015-2017	CAP-MP Grant PI: Jay Magaziner, National Institute on Aging R01 AG035009, Project Dates: 07/01/10-5/31/18 (Total Direct Costs: $11,675,384)
Aug 2017-Aug 2020	T32 Epidemiology of Aging Trainee Grant P.I.: Jay Magaziner; National Institute on Aging T32 AG00262-21, Project dates: 05/01/18—04/30/23 (Total costs: $1,709,305)

Publications

<u>Peer-reviewed journal articles</u>

1. Anton SD, Woods AJ, Ashizawa T, Barb D, Buford TW, Carter CS, Clark DJ, Cohen RA, Corbett DB, Cruz-Almeida Y, Dotson V, Ebner N, Efron PA, Fillingim RB, Foster TC, Gundermann DM, Joseph AM, Karabetian C, Leeuwenburgh C, Manini TM, Marsiske M, Mankowski RT, **Mutchie HL**, Perri MG, Ranka S, Rashidi P, Sandesara B, Scarpace PJ, Sibille KT, Solberg LM, Someya S, Uphold C, Wohlgemuth S, Wu SS, Pahor M. 2015. "Successful aging: Advancing the science of physical independence in older adults". *Ageing Research Reviews*, 24(B): 304-327. [PMID: 26462882]

2. Hausenblas HA, Heekin K, **Mutchie HL**, Anton S. 2015. "A systematic review of randomized controlled trials examining the effectiveness of saffron (Crocus sativus L.) on psychological and behavioral outcomes. *J Integr Med*; 13(4):231-40. [PMID:26165367]

3. Anton SA, Azumi H, Heekin K, Sowalsky K, Karabetian C, **Mutchie HL**, Leeuwenburgh C, Manini T, Barnett TE. 2017. "Effects of Popular Diets without Specific Calorie Targets on Weight Loss Outcomes: Systematic Review of Findings from Clinical Trials". *Nutrients,* 9(822). [PMCID: PMC5579615]

4. Millstein LS, Allen J, Bellin M, Eveland SR, Baek D, Agarwal A, Hill T, **Mutchie H**, Cagle J. 2020. An interprofessional training to improve advanced care planning skills among medicine, nursing, and social work students. *Journal of Interprofessional Education & Practice*. 22:100382.

5. Beck BM, Coda C, Gerges J, Allen J, Agarwal A, **Mutchie HL**, Baek D, Millstein LS. 2020. Advanced Care Planning: An Interprofessional Approach to Resident Education. *JAGS. 68(11),* E66-E68.

6. **Mutchie HL**, Orwig DL, Beamer B, Conroy V, Guralnik J, Magaziner J, Gruber-Baldini AL. 2021. Four Square Step Test Performance in Hip Fracture Patients. *Journal of Geriatric Physical Therapy*. Accepted

Abstracts and Presentations
1. **Mutchie H**, Durkin DW. Comparison of MMSE and ACTIVE Methods for the Identification of MCI. Presented at the 25th Annual Southeastern Student Mentoring Conference in Geriatrics and Gerontology. Athens, GA April 11-12, 2014.
2. **Mutchie HL**, Gruber-Baldini AL. Detecting Cognitive Impairment after Hip Fracture to Predict Dementia-Related Cause of Death. Presented at the University of Maryland Baltimore 39th Annual Graduate Research Conference. Baltimore, MD March 12, 2017.

3. **Mutchie HL**, Gruber-Baldini AL. Detecting Cognitive Impairment after Hip Fracture to Predict Dementia-Related Cause of Death. (Poster)Presented at the University of Maryland Baltimore County 39th Annual Graduate Research Conference. Baltimore, MD March 29, 2017.

4. **Mutchie HL**, Orwig D, Beamer B, Conroy V, Guralnik J, Magaziner J, Gruber-Baldini A. Feasibility of Four Square Step Test in Hip Fracture Patients. Presented at the Johns Hopkins University 12th Annual Research on Aging Conference, April 20th, 2018.

5. Millstein LS, Agarwal A, Allen J, Baek D, Bellin M, Eveland SR, Hill T, Wiegand D, **Mutchie H**, Cagle J. An Interdisciplinary Approach to Advanced Care Planning. Nexus Summit Meeting. July 30, 2018.

6. **Mutchie HL**, Orwig D, Beamer B, Conroy V, Guralnik J, Magaziner J, Gruber-Baldini A. Feasibility of Four Square Step Test in Hip Fracture Patients. Poster presentation at The Gerontological Society of America's 70th Annual Scientific Meeting, Boston, MA, November 14-18, 2018. Abstract ID: 467894.

7. **Mutchie HL**, Orwig DL, Hochberg M, Magaziner J, Gruber-Baldini A. Detecting Cognitive Impairment After Hip Fracture to Predict Dementia-Related Cause of Death. Poster presentation at The Gerontological Society of America's 70th Annual Scientific Meeting, Boston, MA, November 14-18, 2018. Abstract ID: 468020.

8. **Mutchie HL**, Orwig D, Gruber-Baldini A. Distinct Trajectories for Cognitive Performance within the First Year After Hip Fracture. Johns Hopkins Aging Showcase. Baltimore, MD, March 24, 2020. Submitted Abstract for poster. Conference canceled.

9. **Mutchie HL**, Orwig D, Gruber-Baldini A. Distinct Trajectories for Cognitive Performance within the First Year After Hip Fracture. Center for Research and Aging 2nd Annual Aging Research Symposium. Baltimore, MD, April 24, 2020. Abstract Accepted.

10. **Mutchie HL**, Orwig D, Gruber-Baldini A. Distinct Trajectories of Recovery within the First Year After Hip Fracture. Gerontological Society of America 71st Annual Conference, Philadelphia, PA November 2020.

11. **Mutchie HL,** Orwig DL, Gruber-Baldini AL. Joint Cognitive and Physical Function Recovery Trajectories After Hip Fracture. University of Maryland Baltimore Graduate Research Conference. Online. March 26th, 2021.

12. **Mutchie HL,** Orwig DL, Gruber-Baldini AL. Joint Cognitive and Physical Function Recovery Trajectories After Hip Fracture. Johns Hopkins Aging Showcase. Online. April 16th, 2021.

Invited Speeches

Local

1. The Impact of Sex and Cognition on Recovery and Mortality Post Hip Fracture, University of Maryland Doctoral Program in Gerontology Aging Forum, Online, 2021

Abstract

Title of Dissertation: The Impact of Sex and Cognition on Recovery and Mortality Post Hip Fracture

Heather Mutchie, Doctor of Philosophy, 2021

Dissertation Directed by:

> Ann Gruber-Baldini, PhD
> Professor, Division of Gerontology, Department of Epidemiology and Public Health
> Director, Doctoral Program in Epidemiology and Human Genetics

Introduction

The overall objective of this work was to estimate misclassification of cognitive impairment (CI) by sex among hip fracture patients. The effects of sex and identified CI on hip fracture recovery outcomes, including trajectories of cognitive and physical function and mortality (all-cause and cognition-specific), were subsequently examined.

Methods

This study used secondary data from a cohort of hip fracture patients recruited from 8 Baltimore-area hospitals between 2006-2011 (N=339), with frequency matched enrollment of females (n=171) and males (n=168), tested within 22 days of hip fracture admission and at 2, 6, and 12 months. Death data were derived from the National Death Index 2006-2018 (n=260; females=113, females=147). Analyses differentiated source of CI identification (SCI, n=330) between clinical diagnosis/documentation and direct testing [Modified Mini Mental State Examination (3MS)] of cognition at baseline by patient sex. Analyses identified cognitive and functional recovery using group-based trajectory modeling (GBTM) and joint trajectory models; and estimated time to death for all-cause and cognition-related cause of death (CR-COD) by SCI and sex.

Results

Males had increased odds of CI identified by both hospital record and 3MS after adjusting for age, education, and comorbidities. There were 2-4 distinct groups of recovery for cognitive and functional recovery. In joint models of recovery, high levels of cognitive function were only seen in high physical functioning groups. Significantly more men died than women (147 vs 113, p<.0001) and died sooner from all-cause mortality (41 vs 54 months, p=0.001) but not CR-COD. Males and those with SCI Both were independently at increased risk for all-cause mortality but there was not a significant interaction. Those with SCI Both were 14 times more likely to die of CR-COD (p<.0001).

Conclusions

There is clinical underdiagnosis of active CI in males. Additional CI ascertainment can identify a sub-population of patients at excess risk for mortality and CR-COD. Cognitive testing after hip fracture should be instituted as standard practice to avoid sex bias in identification of CI. Cognition changes little over 12 months post fracture. Pre-fracture functional status informs pattern of physical function recovery. Sex and CI increase mortality risk, and to some extent cause-specific mortality.

The Impact of Sex and Cognition on Recovery and Mortality Post Hip Fracture

by
Heather L. Mutchie

Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, Baltimore in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2021

Dedication

To my parents, Bill and Diane Mutchie, my grandparents, Kevin and Shirley Macdonald,

and belated grandparents, Randy and Pat Mutchie, for their unyielding support and faith,

for all that I do.

Acknowledgements

Table of Contents

List of Tables

xiv

List of Figures

List of Abbreviations

Abbreviation	Terminology
CI	Cognitive Impairment
OR	Odds Ratio
MCI	Mild Cognitive Impairment
ADRD	Alzheimer's disease and Related Dementia
HRS	Health and Retirement Study
BHS7	Baltimore Hip Studies 7th Cohort
NDI	National Death Index
3MS	Modified Mini-Mental State Examination
SCI	Source of Cognitive Impairment Identification
GBTM	Group Based Trajectory Modeling
CR-COD	Cognition-Related Cause of Death
BMD	Bone Mineral Density
DXA	Dual X-ray Absorptiometry
ASA	American Society of Anesthesiologists Physical Status
ADL	Physical Activities of Daily Living
AD	Alzheimer's Disease
NIA	National Institute on Aging
APOe-4	Apolipoprotein E ε4
MMSE	Mini-Mental State Examination
BMI	Body Mass Index [weight (kg)/height (m)^2]
ICD	International Classification of Disease
IRB	Institutional Review Board
BIC	Bayesian Information Criterion
CCI	Charlson Comorbidity Index
LPADL	Lower Extremity Physical Activities of Daily Living
SPPB	Short Physical Performance Battery
TMT	Trail Making Task
HVOT	Hooper Visual Organization Test

CHAPTER 1. INTRODUCTION

1.1 Statement of Problem

Hip fractures are a prevalent geriatric condition, resulting in chronic pain, disability, and early mortality. There are currently approximately 300,000 hip fractures annually among U.S. adults 65 years and older, and the absolute number is expected to rise as the global population ages.[1,2] Hip fracture rates double each decade after the age of 50.[3,4] Most geriatric hip fractures (95%) result from low-trauma falls from standing height and require surgical fixation.[5] The relationship between cognitive impairment (CI) and hip fracture is a multi-factored problem as CI is a risk factor, outcome, and moderator of other outcomes. Pre-existing global CI increases risk of falls with serious injuries [Odds Ratio (OR) 2.13 (1.56, 2.90)] in older adults and is therefore related to the event history. CI, including acute delirium and previously undetected dementia, can be a result of the hip fracture and required medical care,[6,7] making CI an outcome of hip fracture. Finally, impaired cognition has been shown to negatively impact recovery,[6–9] thereby mediating hip fracture outcomes.

Detecting and differentiating CI and delirium in hip fracture populations is challenging. CI could be due to multiple etiologies (normal cognitive decline, mild cognitive impairment (MCI), delirium, dementia, etc.), requiring testing and medical history to differentiate.[10,11] This is a diagnostic burden in general clinical practice and specifically in hip fracture. Hip fractures are acute events; therefore, it is unlikely for a large sample of hip fracture patients to have pre-fracture cognitive screenings. CI has

been shown to inhibit functional recovery after hip fracture increasing the morbidity of patients. Additionally, CI has been associated with higher mortality in hip fracture patients; a population with an already higher one-year mortality risk (30%).[12,13]

Older adults as a population are very heterogeneous, and this is no different among a subpopulation of hip fracture patients. Although many hip fracture patients do have pre-existing CI, this is not always diagnosed or indicated prior to the fracture. Previous analyses of hip fracture outcomes (i.e., functional recovery and mortality) have undervalued the innate differences between hip fracture patients prior to the fracture, including CI, and how these differences may impact the recovery process. These studies have relied on linear models to demonstrate patterns of recovery. One of the weaknesses of this approach is that the researcher specifies what covariates may be important to the recovery process and will often dichotomize based on cut-points that have been validated in non-geriatric or non-hip fracture older adults. These outcomes produce an overly specified model of recovery (e.g., controlling for comorbidities, sex, age, etc.) that may hide the unique patterns and trajectories of recovery within the hip fracture population by regressing outcomes to the mean.

Hip fracture risk due to prevalence of osteoporosis and osteopenia, CI, functional recovery, and mortality after hip fracture are all important topics that research has primarily focused on in older women. However; men are beginning to make up a substantial proportion of the hip fracture population (one-third)[7] and seem to have worse pre-fracture morbidities and worse outcomes including increased and earlier mortality and likelihood to be discharged to a nursing home with CI after hip fracture.[14] Currently two-thirds of U.S. Alzheimer's disease and related dementia (ADRD) cases are

women.[11,15,16] From a Health and Retirement Study (HRS) subset focusing on cognition; 16% of women and 11% of men had ADRD.[11,17] It has been suggested that this difference is largely attributable to sex differences in longevity.[11,18] Studies focusing on age-specific ADRD risk between sexes have found null results. This could be reflective of survival bias in which healthier men live longer, or at least as long as women.[11,19] Alternative theories for sex differences in ADRD incidence propose cohort differences in educational attainment for men and women born before compulsory education, such that aging women had less education, increasing their ADRD risk.[11,20] Previous studies have looked at the sensitivity of clinical diagnosis of dementia and found that using clinical evaluation alone only captured one-third of cases.[21] Although more recent research from Zhu et al. (2020), using a 20% Medicare sample linked to the HRS, has suggested that the discrepancies between prevalence of dementia diagnostic codes and cognitive testing have narrowed over time through 2012.[22] Neither sample focused specifically on hip fracture patients, nor did they find discrepancies between sex and age groups.[21,23] Additionally, Medicare algorithms use a two-year lookback to determine ADRD. In a clinical setting the only indication available may be in the medical record.

It is not currently known how sex differences affect hip fracture risk and the recovery process, though it is understood that despite having previously been older women's issues, hip fracture and ADRD are negatively impacting more men. There is very little published research on sex as a biasing factor for diagnosis of CI in U.S populations as previous work has focused primarily on patient age, severity of dementia, and education as potential sources of diagnostic bias. Given the historic sex disparity in hip fracture populations (more women than men), and current observations of men

experiencing worse outcomes, sex should be a rising concern for pre-fracture risks outside of osteoporosis. A critical barrier to addressing this problem is the underrepresentation of men in hip fracture research and the systematic exclusion of cognitively impaired individuals in research studies.

The central hypothesis of this work was that pre-fracture CI diagnosis is biased by patient sex and the results of biased diagnosis are associated with worse functional recovery and earlier mortality.

The objective of this study is to investigate whether hip fracture patients with impaired cognition, regardless of the time or method of clinical identification, have similarly poor health outcomes, including recovery, time to death, and cause-of-death.

1.2 Specific Aims

These research aims address these issues utilizing the Baltimore Hip Studies 7th Cohort (BHS7; 2006-2011) supplemented by data from the National Death Index (NDI), 2006-2018).

1.2.1 Aim 1

Aim 1a: Estimate whether there is under-diagnosis and documentation of CI among hip fracture patients and evaluate if under-diagnosis differs by sex.

Hypothesis 1.a: Additional screening of hip fracture patients using the Modified Mini-Mental State Examination (3MS) will result in detecting previously undocumented CI (including ADRD, MCI, and delirium) cases.

Rationale 1: Clinical diagnosis of CI (ADRD) is known to miss at least one-third of impaired individuals.[21,23] Women in the general population have had a higher ADRD incidence than men.[11,15] Given the associations between and injury, specifically hip fracture, it is expected that many of the individuals who were not previously diagnosed with CI will present with CI (ADRD, MCI, delirium) upon screening after the acute injury event (hip fracture). In a non-research setting, clinical determination of CI is likely the sole determination of cognitive status. However, in research studies a more thorough examination of cognition may find additional underdiagnosed cases.

Methods 1.a: This study will use secondary data from BHS7 to perform a retrospective cohort study of hip fracture patients of older adults, 65 years and older, who had a hip fracture repair surgery. It will compare presence of CI (ADRD, MCI, delirium) at baseline from the medical chart to the 3MS administered within 22 days of hospitalization for hip fracture.

Aim 1.b: Evaluate if the proportion of under-diagnosis is different by sex in hip fracture patients.

Hypothesis 1.b: The proportion of documented CI diagnosis will differ by patient sex; such that the proportion of documented CI in men is not equal to the proportion of documented CI in women.

1.2.2 Aim 2

Identify trajectories of functional and cognitive recovery and group membership characteristics associated with distinct trajectory groups, particularly patient sex and source of cognitive impairment identification (SCI).

Aim 2.a. Identify trajectories of functional recovery and group membership characteristics associated with distinct trajectory groups, focusing on patient sex as a risk factor.

Hypothesis 2.a.1: There are multiple distinct trajectory groups that may vary in shape, amplitude, and direction.

Hypothesis 2.a.2: Individuals in similar recovery groups will be more likely to also have similar sex and SCI.

Rational 2.a: This aim will examine the distinct recovery groups that make up a population of hip fracture patients and determine key recovery time points in the distinct groups. This differs and builds upon aim 1 in that it is data-driven and the groups are therefore not pre-specified. A recent study from the Baltimore Hip Studies (Colón-Emeric et al. 2019)[24] used latent class profile analysis, a type of growth mixture model, to illustrate physical resiliency trajectories among hip fracture patients by combining three studies from 1998-2011. This work was novel in this population. However, as part of the analysis the group combined at least 10 separate physical outcome measures to create domains of recovery. This complex analysis had limitations such as ignoring potential age/period/cohort effects between the study enrollment groups of older adults with hip fracture. The team did not assess for significant differences in outcomes based on

6

enrollment group. The contribution of the two studies besides BHS7 overrepresented women in the total sample and were also intervention trials.

Aim 2.b. Identify trajectories of cognitive recovery and group membership characteristics associated with distinct trajectory groups, focusing on patient sex as a risk factor.

Hypothesis 2.b.1: There are multiple distinct trajectory groups that may vary in shape, amplitude, and direction.

Hypothesis 2.b.2: Individuals in similar recovery groups will be more likely to also have similar sex.

Rational 2.b: Few studies observe cognition as its own longitudinal outcome in the context of hip fracture. Those that have use regression models which may be hiding the variability within hip fracture patients. Colón-Emeric et al. (2019)[24] study did not assess cognitive measures over time for recovery or patterns of cognition.

Aim 2.c. Identify joint trajectories of cognitive and functional recovery and the group membership characteristics associated with trajectory group membership focusing on patient sex as a risk factor.

Methods 2: The analyses will use secondary data from BHS7, a cohort study of hip fracture patients of older adults, 65+years, who had a hip fracture repair surgery. Main analyses will utilize Group Based Trajectory Modeling (GBTM).

7

1.2.3 Aim 3

Establish if time to death and the proportion of individuals with Cognition-Related Cause of Death (CR-COD) are comparable for individuals with undiagnosed/documented CI; and if these associations are different by patient sex.

Hypothesis 3.a: Unrecognized CI is a contributing factor to the poor outcomes of otherwise heterogeneous subgroups. Those identified from cognitive testing will have similar poor outcomes as those with a dementia diagnosis.

Hypothesis 3.b: CI differentially misclassified by patient sex, will result in increased mortality in the underdiagnosed group compared to those identified with medical records and those found to not have CI on medical records nor 3MS.

Rational 3. Sex bias in clinical diagnosis of CI may contribute to disparities in outcomes by sex. If males are underdiagnosed, the observed effect of male sex on early/increased mortality may be due to CI.

Methods 3. Estimate the hazard of mortality and CR-COD in the BHS7 cohort supplemented by data from NDI for date and cause of death. Conduct survival analysis using Cox proportional hazards to estimate survival time for all-cause mortality and CR-COD by sex and SCI.

CHAPTER 2. LITERATURE REVIEW

2.1 Etiology of Hip Fractures

Hip fractures, acute injuries resulting in a fracture to the femoral head, neck, trochanter, or femoral shaft,[1] have been identified as one of the most serious healthcare problems for geriatric patients[2-4] due to subsequent functional decline, increased morbidity, and premature mortality.[2,3,5] Femoral neck and intertrochanteric fractures are the most common fracture types among older adults[25], accounting for 37% and 49% respectively of all U.S hip fractures.[5]

Anatomy of a hip fracture differs slightly from conventional considerations for anatomy of the hip. The iliac fossa or 'hip bone' is a large bilateral structure. The superior connection is fused to the sacrum at the base of the spine and the inferior bone is connected to the pubic symphysis. This structure covers the hip that is felt below the iliac crest (i.e., waist), to the coccyx (i.e., tail bone) upon which a person sits. The iliac crest flows down into the anterior superior iliac spine, a ridge along the large bone of the hip. The iliac spine meets the acetabular rim which is the socket in which the femur sits.

The anatomy of a hip fracture is primarily focused on the fracture along the femur at and around the pelvic girdle. A fracture of the larger structure would be considered a fractured pelvis. Within the socket of the pelvic girdle there is the acetabulum and the acetabular labrum, which nest the femoral head securely and freely within the socket structure. This entire system is held together by ligaments and muscle, but the bone involved in a hip fracture is the femur. The femur is comprised of the femoral head, neck,

and trochanter. The femoral head is a knob that fits in the round socket of the girdle becoming narrow at the femoral neck and largest at the greater trochanter, which faces laterally. At the base of the trochanter is the proximal lesser trochanter - the meeting point of the greater and lesser forms the intertrochanteric line – followed by the main shaft of the femur.

2.1.1 Fracture Types

Femoral neck fractures are considered either displaced or non-displaced depending on the location of the fractured hip segments.[5] Non-displaced femoral neck fractures present with dull or aching pain in the groin, mid-thigh or knee, which is increased by moving.[5] Displaced femoral neck fractures are typified by severe pain in the entirety of the hip.[5] Patients with displaced femoral neck fracture are usually unable to walk.[5] Femoral neck fractures risk osteonecrosis as blood supply to the femoral head can be disrupted during the fracture. Displaced fractures have a 40% avascular necrosis risk.[5,26,27] There is little soft tissue surrounding the bone, delaying the healing process.[5]

Intertrochanteric fractures are either stable or non-stable based on fracture segments and severity of comminution.[5] These fractures present painfully above the hip, and with severe pain in the hip upon weight bearing or moving.[5] Weight-bearing pain may inhibit mobility in these fracture patients, and they may often limp.[5] Due to the large hip muscles that attach around the trochanters, in intertrochanteric fractures, there is often leg shortening and some deformity in regard to leg alignment. However, in older adults, pain in the hip may either be minimal or only painful with movement and is not necessary

in the presence of a fracture. Morbidity after intertrochanteric fractures is higher than
after femoral neck fractures, often due to comminution of bone fragments.[28]

2.1.2 Underlying Biology

Hip fractures most often occur from low trauma falls at standing height indicating
suboptimal bone strength. Osteoporosis and osteopenia are disease conditions in which
the bone is very porous and does not rebuild quickly or with integrity. Osteopenia is a
precursor indicator to osteoporosis, the diagnosis of both are based on test of bone
mineral density (BMD) and quality.[29] Only BMD has satisfactory clinical measures and
is therefore the central determinant of bone mineral health.[29] Bone mineral content
divided by area measured is the BMD value. Bone mineral content is most often captured
using single or dual X-ray absorptiometry (DXA). DXA produces area-adjusted results
and is over 90% accurate for the hip.[29] Broad-band ultrasound attenuation and velocity at
the heel can be used to assess fracture risk but not osteoporosis in elderly women.[29]
Quantitative computed tomography produces true volumetric density, allowing for
assessment of change in cancellous bone, spongy bone found at the end of long bones,
which is more responsive to interventions than cortical bone. However it has higher
radiation exposure and is more costly than DXA.[29] BMD is measured against population
means at the measured site (i.e. femoral neck). BMD $\leq$2.5 standard deviations for a
young person of the same sex indicates osteoporosis, reported as T-score.[30] As of 2016,
Medicare reimbursed BMD screening for patients 70+ years old who had not already had
a fracture.[30] Both osteoporosis (T-score -2.5 and below) and osteopenia (T-score -1 to -

2.5),[30–32] are more prevalent in, and seen at an earlier age among women. The U.S

Preventive Task Force still does not recommended that men without prior fractures

undergo screening for osteoporosis.[33] Further evidence includes increased risk of hip

fractures in older women who have had a previous fracture other than a hip fracture,

indicating system wide vulnerability and fragility.[3] However, this risk is highest in the

early years subsequent to the non-hip fracture.[3]

Osteoporosis is degenerative and should therefore increase fracture risk over time.

Thus, it is thought that poor balance may contribute more to early increased fracture risk

than osteoporosis in the case of secondary fractures.[3] Estrogen and testosterone levels

have been proposed as essential protective factors to BMD loss, with mixed results in

clinical trials.[34,35] Osteoporosis has been associated with reduced estrogen following

menopause in women, and depleted testosterone in aging men.[36] Probability of

osteoporotic hip fracture is 23% higher in women when accounting for age and femoral

neck bone mineral density.[37]

2.2 Epidemiology of Hip Fracture

2.2.1 Globally and in the U.S

At the turn of the 21st Century, there were 1.6 million osteoporotic hip fractures

globally.[38] Given current population trends, it is estimated that by 2050 the global

incidence will be closed to 6.3 million.[4,38,39] In the late 1990's, 17.5% of all hip fractures

occurred in the U.S.[4] despite moderate risk in the population, with black and Hispanic

populations having very low risk.[37] Northwest European nations (Scandinavia) and those

of northwestern European decent have had the highest incidence of hip fracture for many

decades.[4,37] Presently, Europe and North American populations compose 50% of all

geriatric hip fractures. This number is expected to decline to as low as 25% by 2050 as

other currently low incidence countries begin to see more hip fractures.[39]

2.2.2 Historical, Current, and Future Trends

In the U.S., 1995 was a seminal year for hip fracture incidence. Incidence in both

men and women has been in a substantial downward trend compared to the marginal

increases in hip fracture rates seen since the late 1980's to 1995[12] until 2012 after which

there was a plateau at increased rates.[40] However, the increase in numbers of older people

will lead to an increased number of hip fractures, even as incidence rates decrease or

plateau. Other changes have been seen in the treatment of hip fracture over time,

including reduced median length of hospital stays from 12 to five days.[12] Additionally,

discharge procedures have changed. From 1986-1988, 34.3% of patients went home at

discharge while 29% went to a skilled nursing facility. From 2003-2005, 6.5% of patients

were discharged to home, 53% went to a skilled nursing facility.[12]

Low-energy falls from standing height are responsible for 53% of hip fractures in

adults 50+, 85% in those 75+, and over 90% of all hip fractures among older adults.[5,41,42]

In the U.S., there were 3.2 million non-fatal falls by adults 65 years and older in 2012 and

over 1.75 million resulted in emergency department visits.[43] While environmental

obstacles are common inciting factors, less than half (47%) of the falls resulting in

femoral neck fractures among lucid adults age 65+years studied in Nyberg 1996[44] cited external factors. Individual health conditions are also known to contribute to the risk of falls and hip fracture. Primary non-environmental causes of falls include recent hospitalization, inability to walk unassisted, peripheral neuropathy, neurological disease or gait disorders, drug effects and interactions, syncope, and vitamin deficiencies. Many of these cause impaired walking ability, or impair instinctive fall and balance recovery mechanisms.[5,44,45]

2.2.3 Age

Adults aged 65-69 years were projected to be the largest proportion of the U.S older population in 2016. As they age, by 2042 they will be 80 to 84 years old and still make up the largest population proportion of older adults.[46] By 2050,the US population 65 years and older is predicted to be composed of 42% minorities.[46] It is unknown how this aging cohort will effect hip fracture incidence or the absolute number of geriatric hip fractures. Black and Hispanic individuals have been at low risk, but that may not be true for this rising cohort of older adults.

Mean age at hip fracture in the U.S. is 76 years of age, 79 years globally.[47] From 1986 to 2005, the number of adults 85 and older with hip fractures in the US has increased from 38% to 43.6%.[12] A review of studies on hip fracture from MEDLINE identified a one-year increase in age of fracture for every five years forward in time from 1959 to 1998 (mean age 73 to 79).[47] Functional, psychological, and other health

outcomes are all worse for hip fracture patients compared to age- and sex-matched older adults.[6]

2.2.4 Sex

Osteoporosis and osteopenia, degenerative bone diseases that increase fracture risk after low-trauma falls, are more prevalent in women to due biological factors. Overall age-standardized hip fracture risk is two-times greater in women than in men.[37]

Femoral neck fractures are estimated to occur among 17.5% of women (mean age 77) and 6% of men (mean age 72 years).[11, 12] Men currently account for 25-30% of U.S hip fractures.[13] Between 1985-2005, mean annual hip fracture incidence in women was 957.3 per 100,000 compared to 414.4 per 100,000 in men.[12] Lifetime risk of hip fracture in Caucasian women is 16-18% compare to 5-6% in Caucasian men.[4] In age-adjusted analysis of hip fracture from 1970 to 1991, men had an 80% increase in incidence while women had a 51% increase.[4] By 2025, men are expected to present with as many hip fractures as were seen in women 20 years ago.[14] The sex disparity in the U.S of the proportion of older women to older men is expected to close by 2050 especially among the oldest old (age 85 and up).[5] Among this oldest group, by 2050, women are expected to make up 61% of the age bracket, a reduction from 67% in 2010.[46] Overall, it is expected that in adults 65 years and older, by 2050, there will be 82 men per 100 women. These changes have been attributed to increased life expectancy among men.[46]

In a MEDLINE review paper, the proportion of women in hip fracture studies (80%-90%) has changed very little in the past 40 years.[47] Women had better outcomes

than men with hip fractures, despite being less likely to be married and having lower

education on average. Males who fracture their hip tended to have more comorbid

conditions prior to fracture than their female counterparts (mean 3.3:2.9,

males:females).[14] Men have also been shown to have higher American Society of

Anesthesiologists (ASA) pre-operative risk (2.4:2.1, Males:Females).[14,48]

Despite higher risk factors in men, the average cost per fall (2012) in an

emergency department costs $1,000 more for women 65-74 years, and almost $4,000

more for women 85 and older compared to men of the same age.[43] This pattern was

maintained in 2015, where emergency department visits and hospitalizations for falls cost

women $1,500+ more than men on average.[43] The cost disparities by sex increase for

non-fatal falls ($8,462 : $10,441, Men: Women).[43]

2.3 Cognitive Impairment in Older Adults

2.3.1 Types of Cognitive Impairment

2.3.1.1 Delirium

Delirium is a characterized by the sudden onset of cognitive difficulty in a

previously lucid person, usually lasting anywhere from a few hours to days but no more

than 6 months. Cognitive function fluctuates in and out, notably disorienting the patient

to time, shot-term recall and impaired attention are hallmarks of delirium.[49] Delirious

patients may experience visual hallucinations.[49] Risk factors for delirium include older

age, history of delirium, dementia, polypharmacy, catheter use, vision or auditory

impairment, and malnutrition.[49] Managing delirium is accomplished by treating

underlying medical problems, reducing the number of medications particularly the

cessation of anticholinergic medication, access to bright lighting, normalizing patient's

sleep cycle.[49] Isolation is not recommended.

2.3.1.2 <u>Alzheimer's Disease and Related Dementia (ADRD)</u>

Chronic CI in multiple domains (e.g., language, vision, problem-solving,

attention, memory) is indicative of dementia rather than delirium. The onset of dementia

can take many years but is predicated by mood changes such as experiencing depression

or anxiety in early stages, and agitation with more progressive dementia. Due to this slow

onset and progression the range of dementia symptoms and experiences is vast, from mild

forgetfulness (more than is normal for aging) to complete Activity of Daily Living

(ADL) dependence.[50] The main risk factors are age, and family history or genetics. The

patient with dementia will likely have unaltered consciousness (except with Lewy

bodies). Medication therapy for dementia currently treats for the behavioral symptoms

(e.g. depression) or works to prevent cerebrovascular dementia. Some neurotransmitter

regulating products approved by the U.S Food and Drug Administration can be used to

treat symptoms of moderate to severe Alzheimer's Disease (AD), but will not cure AD.[50]

AD is the 6th leading cause of death in the U.S, but may be rising to 3rd as the

proportion of older adults grows.[50] ADRD affects 15 to 20% of adults 75+years.[51] The

National Institute on Aging (NIA) currently recognizes the following forms of age-

related dementias for which there are currently no cures: Alzheimer's disease (50-70% of

cases of dementia), frontotemporal disorders (12-25%), Lewy body dementia (5-10%),

progressive brain diseases from vascular causes (10-20%), and mixed dementia.[49,52,53]

Mixed dementias are a combination of any of the above and constitute 10-30% of cases.

Other conditions or exposures can lead to dementia-like symptoms.[52] These are

differentiated in that some are revisable after stopping exposure (ex. medication side

effects, psychosomatic symptoms of anxiety or depression, effects of alcohol, blood clots

or brain infections, thyroid or liver problems), others are side effects of other disease

conditions (e.g.,. Argyrophilic grain disease, Creutzfeldt-Jakob disease, Huntington's

disease, chronic traumatic encephalopathy from repeated traumatic brain injury, HIV-

associated dementia).[52]

Risk factors for ADRD include older age, female sex, head trauma, and the

presence of apolipoprotein E ε4 (APOe-4) allele. In individuals with homozygous APOe4

alleles the OR of ADRD ranges from 7 to 19.3. Over 40% of sporadic AD cases have at

least one APOe-4 allele, making it a more valuable predictor than familial AD (5% of

cases).[49]

Differentiating AD, Lewy bodies, cerebrovascular dementia, and frontotemporal

dementia can be clinically hallmarked by time and rate of onset and domains of

impairment or change.[49] Mid-stage AD is very dangerous to the individual as they may

still have physical independence but could be experiencing delusions, paranoia, or

hallucinations and have difficulty reacting to novel stimuli.[50]

2.3.1.3 Mild Cognitive Impairment (MCI)

MCI has been previously called preclinical AD. This is a misnomer, in that not all

MCI will progress to ADRD. Some patients who experience MCI do develop ADRD.[50]

Reduced olfactory abilities have been associated with MCI and MCI to AD progression, though the nature of this relationship is unclear.[50,54,55] However, current dementia diagnosis acknowledge MCI as a pre-clinical stage of AD.[10]

2.3.2 Tests

2.3.2.1 <u>Clinical Diagnosis</u>

Medical assessment of dementia in a non-emergency setting generally consists of patient's personal and family medical history, physical exam to rule out other causes, and neurological tests. Upon inability to rule out other causes a patient may receive neuropsychological/cognitive tests of mental functioning, brain scans, psychiatric evaluations, and/or genetic testing.[52] Prior to AD diagnosis a patient may be diagnosed with all-cause dementia.[56] Dementia, resulting in cognitive or behavioral symptoms that disrupt the patients' daily functioning, is corroborated by medical history and bedside mental status examination. AD can only be definitively diagnosed post-mortem. However, the NIA and Alzheimer's Association have core clinical criteria for probable AD: insidious onset over months to years, clear history of worsening cognition, most prominent deficits are evidenced upon examination of recall of new information (amnestic) or word-finding difficulties, impaired spatial cognition or problem solving (non-amnestic). These criteria should not be applied in the presence of cerebrovascular disease, core Lewy body dementia markers besides dementia, or evidence of other core criteria for other dementis.[10]

2.3.2.2 <u>Screening Tests</u>

      Dementia screening tests can be divided into brief screening instruments, comprehensive assessments, special situation tools, and informant-based assessments. These can use solely patient input or patient input supplemented by proxy. The most common brief instruments are the Mini-Mental State Examination (MMSE)[57,58] and the Mini-Cog.[59] The MMSE can be administered in 7 to 10 minutes, but has specific age and education adjustments and has limited sensitivity for detecting MCI.[53] More comprehensive exams include the 3MS, which is similar to the MMSE but has several other domains included and as a result takes 10-15 miuntes.[53,60] The 3MS is scored from 0-100, with higher scores indicating better cognition. Conventional cut-off scores for CI indication are score $\leq$78.[61,62] Scores <95 have been considered as indicative of MCI.[63] Many other tests exist and are in use but the MMSE, Mini-Cog and 3MS are widely accepted. While these are powerful screening tools, poor performance is not enough to warrant a clinical dementia diagnosis.

      There are many delirium screening tests but the Confusion Assessment Method (CAM) derived from Diagnostic and Statistical Manual III-R has over 90% sensitivity and specificity, takes 5 to 7 minutes to administer by a trained clinician, and is one of the most common delirium assessments.[64,65]

20

2.3.3 Cognitive Impairment and Hip Fracture

2.3.3.1 Pre-existing Cognitive Impairment

CI in older adults increases the risk for acute injury, specifically hip fracture, by as much as 2.7-fold compared to those without CI.[66] It has been estimated that 20% of older adults have dementia prior to a hip fracture and are increasingly likely to suffer from hospital-acquired delirium than older adults hospitalized with other conditions.[16] CI reduces the level of physical function recovery and time to mortality after acute injury.[18,19] Delirium has been independently associated with onset of dementia and mortality in geriatric hip fracture patients.[20,21] Studies have shown these effects may be moderated by participation in rehabilitation after hip fracture.[22]

2.3.3.2 Post-operative Cognitive Impairment

After hip fracture, 35-61% of patients are estimated to have CI and/or delirium.[17] Delirium incidence in hip fracture has been found to be significantly higher in patients with pre-existing dementia.[67] In patients without dementia, versus those with dementia, 25% vs 57% respectively had post-operative delerium.[67] Older adults 80 years and over were significantly more likely than those 70-79 to experience delirium [OR 2.64, 95% CI (1.71-4.10)].[67] Recent studies on hip fracture patients revealed that AD biomarkers in cerebrospinal fluid (Aβ42/40 ratio, p-tau, t-tau) of cognitively normal patients was comparable to that of patients with MCI (88.6%:98.8%).[68] While the comparable AD biomarker findings could indicate a lack of sensitivity in the biomarkers, this is unlikely. There is existing evidence on the associations with the presence of these markers and

dementia outcomes.[10,69] Therefore, it is more likely that hip fracture patients, even those who are cognitively normal at presentation, may be in the dementia progression timeline (early non-memory or attention symptom phases). These biomarker findings highlight the need for cognitive monitoring after discharge of all hip fracture patients, particularly given the known associations between cognition deficiency (ADRD and/or delirium), functional dependence, and mortality.[70,71]

2.3.4 Sex and Cognitive Impairment

2.3.4.1 <u>General Population</u>

Older age, severity of dementia, and female sex demonstrated bias towards reduced efforts to diagnose dementia in a Swedish study.[72] Despite health risks and consequences, MCI is largely under-reported in medical charts, and patients with MCI or dementia are systematically excluded from research studies.[73]

U.S.-based studies have focused more on age, education, or severity of CI biases in CI diagnosis, leaving sex under-explored.[24,25] The Swedish study attributed the sex differences in dementia diagnosis to strong age differences between men and women. There are known sex differences in how medical professionals diagnose patients, particularly women, with conditions that cannot be corroborated by lab tests;[27] conversely, men are much less likely to be diagnosed and treated for mental disorders such as depression.[28] Delirium is underdiagnosed in up to 70% of patients.[74,75] Potential sex differences in delirium diagnosis may stem from sex differences in delirium phenotype. Men tend to display more behavioral symptoms such as motor agitation and

affective lability, where women more frequently have hypoactive delirium.[76] However, history of traumatic brain injury and age were most correlated to delirium phenotype, not sex.[76] How these sex differences impact dementia diagnosis is unclear.

2.3.4.2 <u>In Hip Fracture</u>

Among hip fracture cases, it is difficult to isolate the effects of sex on outcomes (CI, recovery, mortality) due to the large proportion of women.[10] Traditionally, men with hip fractures have been sicker than non-fractured men and sicker than women with hip fracture.[29] Upon admission to a rehabilitation center and at discharge from geriatric rehabilitation, men have significantly higher incidence of CI.[14] Changing demographics in the population of hip fracture patients create a critical need to understand if current practices leave cognitively vulnerable subgroups at heightened risk for morbidity and mortality, and to what extent CI impacts health outcomes (e.g., functional recovery, cognitive recovery, mortality) for the different sexes.

2.4 Outcomes

2.4.1 Cognitive Recovery

The terminal decline hypothesis posits that as an individual approaches end of life their rate cognitive decline accelerates in the last few years.[77] Given the known associations between CI and hip fracture incidence as well as CI and mortality, it is possible the hip fracture can be an injury accrued during this decline process. To capture

23

this, cognition of hip fracture patients needs to be studied over time. It is particularly important to differentiate delirium from ADRD. However very few studies examine improvement or change of cognition over time in a hip fracture population. Most assessments of cognitive recovery are concerned with delirium post-operatively and only measured until hospital discharge. Alternatively, CI was collected at baseline and used as a predictor of other outcomes. Rarely has cognitive performance been followed as its own outcome. Some exceptions include work from Beishuizen et al. (2017)[61] and Gruber-Baldini et al. (2003)[6].

Beishuizen[61] assessed cognitive trajectories in the first year after hip fracture among 302 patients age 65+. Participants were part of a larger multi-center randomized controlled trial. Using GBTM they found three distinct trajectories of MMSE performance: improvement (n=175), stable (n=85), and rapid decline (n=42).

Gruber-Baldini et al. (2003), looked at CI over time in 804 hip fracture patients in Baltimore, Maryland (1990-1991).[6] MMSE scores <17 marked severe impairment, 17-23 moderate impairment, and ≥24 were cognitively normal. Pre-fracture MMSE was estimated by patient proxy.[6] CI was noted in 50% of the sample, 30% was incident impairment (11% pre-surgery, 22% post-surgery).[6] CI in the hospital was predictive of 2 and 12 month CI and persisted in 40% of patients.[6] There was little change in the level of impairment (mean MMSE score).

All of these studies focused on CI captured by the MMSE. The MMSE, as discussed in Section 2.3.2.2, is a good brief assessment for dementia but is not sensitive to MCI and additionally is limited to certain domains of cognition. More measures should

be assessed over time to capture different domains of recovery or decline in cognition within a hip fracture population.

2.4.2 Functional Recovery

Functional recovery was one of the primary outcomes of interest for most studies of hip fracture patients. After hip fracture, 44-60% of patients did not recover to their pre-fracture level of physical function, functional independence, or ambulation.[13,78] What recovery is seen takes place predominantly within the first 6 months after fracture.[78] In that time, equal proportions (approximately 13.5%) of a hip fracture cohort were seen to have divergent recovery patterns with one group improving and the other deterioraiting.[79,80] A 2016 study of HRS participants found that among hip fracture patients (n=773) approximately 1/3 regained their pre-fracture ADL function, 1/3 regained mobility, and 41% could climb stairs as well as before the fracture at 6 month to 2.5 years (mean 12.5 ± 8 months) post fracture .[81] Among adults who were ADL independent prior to fracture, 27% saw functional decline after hip fracture with new difficulties in ADL dependency, mobility, or stair climbing.[81] Regaining ADL independence was seen less often if the patient was >85 years old, had dementia, or >2 comorbid conditions.

Factors known to decrease mobility at discharge include CI, limited pre-fracture functioning and ADLs, male sex, older age, high or very low body mass index (BMI), polypharmacy, and surgery type.[71] Early functional recovery (walking 4 days after surgical repair) has been shown to be predicted by ASA score, pre-fracture function

(Barthel Index), number of comorbidities, and depression; while age, cognition, and surgery factors were more predictive of functions like early stair climbing ability.[82]

Evidence on the recovery of individuals with CI is conflicting.[22] Outcomes for those with CI were often worse than for those who were not impaired. There were often significantly more complications (25.1:48%, p <.001), increased mortality (11:30%, p <.001), and increased likelihood of going to a nursing home after surgery (77.6:91.8%, p<.001) in non-delirious versus delirious hip fracture patients respectively.[67,83] Recent studies have illustrated that when controlling for fracture type, age, and sex, those with CI recover more slowly than hip fracture patients without CI at 6 months post-fracture.[84]

When a non-traumatic fall results in a hip fracture, there are underlying weaknesses that create a negative feedback loop for decline. There is evidence that pre-fracture CI is not as strongly associated with poor outcomes like rate of improvement or decline as pre-fracture functional impairment, although both impairments resulted in worse long term outcomes at 6 months.[85] In the previously mentioned HRS study, there was no association between patient race, income, or marital status with recovery. This study did support associations between low education (less than high school) and male sex, with nursing home residency and worse recovery outcomes.

Some of the barriers to assessing functional recovery outcomes across the literature include different follow-up periods post fracture. Follow-up of functional recovery has varied from hours after surgery, to patient discharge, as well as length of follow-up months and years after discharge.[86,87] Additional problems arise when different measures are used to assess functional recovery. Some measures capture different components of function, others measure the same components but use different methods

26

or follow-up time points. Finally, many high quality studies focusing on functional recovery come from various countries with heterogeneous populations such as Germany[82], Canada[84,85], Israel[88], and Japan[89]. The ability to generalize findings from one of these populations to another is limited given race/ethnicity, different cultures around lifetime health, healthcare utilization, and post-injury care.

2.4.3 Mortality

Mortality rates post-hip fracture have unfortunately remained unchanged despite increased research for rehabilitation after hip fracture and reduced rates of hip fracture.[90] Among adults 65 years and older in the U.S in 2012, 24,190 had fatal falls, with an average cost of $25,487 per fall, resulting in an annual cost of almost $616.5million in direct medical costs in the U.S.[43] Almost 30% of hip fracture patients die within one year of surgery.[30,31] In femoral neck fractures, a dose response has been observed between perioperative vitamin D deficiency (<10 ng/ml, 10-20 ng/ml, >20 ng/ml: 29%, 13%, 9%) and C-reactive protein (≥40 mg/l, 10-33.9 mg/l, <10 mg/l: 40%, 33%, 15%) with one-year mortality.[91] Among those studied (164 women 50+ years old, 45 men 60+ years old), perioperative levels of C-reactive protein, but not vitamin D, was an independent predictor of one-year mortality, while the inverse was true of postoperative complications.[91]

A review published in 2014 compiled results from 70 randomized clinical trials on surgical fixation of intertrochanteric or femoral neck fractures published between 1981 and 2012.[90] One-year mortality rate from studies in the 1980s to after 1999 were not

significantly different (23% to 21% respectively). When stratified by fracture type, one-year mortality in intertrochanteric fractures decreased in this time period, 34% to 23%. Femoral neck fracture mortality rate increased though not significantly, from 19% to 20%.[90] In U.S.-specific data, Brauer et al. (2009)[12], used a 20% sample of Medicare claims data from 1986 to 2005 for patients 65 years and older with a hip fracture (n=786,717). Men were more likely to die than women. The 30 day mortality rate (adjusted for age, race, comorbidities, and geographic region) for both sexes was found to have been steady, although men's mortality rate was an order of magnitude higher.[12] The relative hazard of mortality among men during the first three months after hip fracture surgery has been estimated as 7.95 (95% CI: 6.13-10.30) compared to 5.75 (95% CI: 4.94-6.67) among women after hip fracture.[17,32,33]

Common causes of death among hip fracture patients include circulatory diseases, ADRD[34], and infections.[33] In a Finish study of sex-specific cause of death after hip fracture,[83] preoperatively 62.1% and 69.9% of men and women had circulatory disease, while 14.6% and 28.6% of men and women had ADRD. Circulatory disease was the underlying cause of death in 37.9% and 33.9% of men and women respectively, ADRD was the underlying cause of death in 9.7% and 13.2% of patients.[83]

Mortality still presents a conundrum for hip fracture research. As the aging population increases, the anticipated impact of ADRD is expected to increase.[35] As rehabilitation efforts aim to reduce premature mortality, it should be anticipated that the burden of ADRD among hip fracture patients, which was previously masked by early mortality, will increase. Using standardized annual mortality for the hip fracture patients

observed from 1999-2007, the relative risk of mortality in hip fracture compared to the general population for circulatory system diseases was 2.76. It was 3.05 for ADRD.[83]

2.4.3.1 Comorbid Conditions Related to Mortality

Congestive heart failure, chronic obstructive pulmonary disease, and diabetes were the most prevalent comorbidities among U.S. Medicare hip fracture patients (1985-2005). In both men and women with hip fracture, the absolute number of comorbidities increased for all comorbid conditions expect paralysis from the late 80s to the early 2000s.[12] Predictive factors for post-fracture mortality include use of diuretics, history of coronary heart disease, male sex, low heart rate (>100) at admission, and low BMI (<20). Use of statins was found to be protective in this population of Norwegian hip fracture patients (mean age 83.4 years).[92] Use of diuretics increased the risk for all causes of death [Hazard ratio 4.02,(95% CI, 2.13-7.64)].[92]

2.5 Summary of Research

It is known that hip fractures are a pervasive global geriatric condition exacerbated by CI, which often results in long term functional disability and early mortality. Hip fractures have predominantly affected women in the past, but in more recent years more men are experiencing hip fracture. CI has been demonstrated to impact recovery and mortality, and it has been shown that men have worse outcomes in the short- and long-term recovery process following hip fracture. The discrepancy between sexes regarding CI has not been explored sufficiently. Part of this logical gap includes

examining if there are sex differences in CI diagnosis prior to hip fracture that may have long term effects on patient outcomes. There may be bias resulting in under or over diagnosis of one sex.

Furthermore, it is known that functional recovery is often poor in hip fracture patients, who seldom recover to pre-fracture status. There has been very little examination of long-term recovery and the different patterns this may take. If there are multiple pathways that recovery follows, and patient baseline characteristics that can reasonably predict these patterns, then there may also be time points in the recovery process that are more crucial to some patients than others. Additionally, there is scant research on the progress of cognitive recovery in hip fracture patients beyond hospital discharge. CI increases the risk of complications, use of long-term care, and greatly increases demands on caregivers. Change in this integral function over the recovery process should not be undervalued.

Finally, mortality has not improved in this population over the last few decades. However, it is the hope of medicine to change this fact. With more adults living longer and the known risks of CI in hip fracture populations there could be an unexpectedly large increase in ADRD populations as the number of older adults and hip fractures increase. It is unclear how much ADRD is being misclassified and if misclassified ADRD has similar mortality rates to clinically recognized ADRD.

CHAPTER 3. RESEARCH METHODS AND STUDY DESIGN

3.1 Study Design

This was a secondary analyses of data from the BHS7 (2006-2011), an observational cohort study of hip fracture [International Classification of Disease (ICD)-9 codes 820.00-820.9] patients in the greater Baltimore, Maryland area. Study assessments were performed at baseline, 2, 6, and 12 months post-fracture.[93] Baseline data were collected within 22 days of hospital admission for hip fracture.[93] Physical performance was assessed only at follow-up visits, surveys of physical functional were assessed at all time-points.[93] Demographic and descriptive information were abstracted from the patient medical chart as well as through conversations with the patient and proxy.[93] The BHS7 frequency-matched recruitment of females with the recruitment of males to achieve a balanced sample.[93] Aim 3 follow-up mortality data is derived from the National Death Index (NDI) as of Dec. 31st 2018. The study was reviewed and approved by the University of Maryland Baltimore Institutional Review Board (IRB).

3.2 Sample

The total sample of BHS7[93] comprised 339 hip fracture patients from eight hospitals in within the BHS network. The importance of the BHS7 cohort is that it over-sampled males such that the sample was approximately 50% male, which is novel for hip fracture research due to the large proportion of females that fill aging research and hip

fracture in particular. Descriptive sample characteristics are listed in Table 1 of each Aim.

Subjects were all 65+ years old and were approached for the study within 15 days of admission to the hospital for hip fracture. Hip fracture patients were excluded from the study if the fracture was pathological, they were not community-dwelling when they fractured their hip, were non-English speaking, bedbound before the fracture, lived >70 miles from the hospital from which they were recruited, weighed >300 pounds, did not have surgical fixation of the hip, or had hardware in both hips.[93] Cognitively impaired individuals were included in the study. For participants scoring <36 on 3MS, proxies provided data on the participant's behalf.

3.2.1 Aim 1 Analytic Sample

All enrolled participants were eligible to be in the analytic sample. Participants were excluded if they were missing a baseline 3MS score (n=8; 4 male, 4 female) or a medical record abstraction items related to ADRD and delirium (n=1 male). Final analytic sample was 330 (163 male, 167 female).

3.2.2 Aim 2 Analytic Sample

The total available sample size was 339 (168 male, 171 female) as CI status by SCI was not required. To be included in the analysis, participants needed at least 2 timepoints of follow-up data. Missingness in measures by timepoint is displayed in

Supplemental Figure S2.2. Given at least 2 timepoints, GBTM accepts dropout within the models. Model fit is established through Bayesian Information Criterion (BIC) which accounts for the number of groups (complexity), sample size, and goodness of fit based on maximized likelihood estimation.[61] Because of the BIC, power analyses are not commonly done a priori for GBTM analyses. Based on previous studies of hip fracture using GBTM, our sample size was estimated to be sufficient to identify 3 or 4 unique trajectory groups.[61,84,94]

3.2.3 Aim 3 Analytic Sample

The sample was separated by those who were alive or deceased as of December 31, 2018. The total available sample size was 339 (168 male, 171 female), 260 died (147 male, 113 female) as of December 31, 2018. To measure impact of sex and SCI, the Aim 1 analytic sample was used, removing 8 from the study sample from these 6 were removed from the death sample. The final sample for Aim 3 was 330 hip fracture patients (163 male, 167 female), 260 died (147 male, 113 female), 67 died of CR-COD (33 male, 34 female).

Power calculations were based on sex stratified groups of males (n=124) who died and females (n=80) who died (all-cause) vs. those who died of CR-COD [(Died all-cause: Died CR-COD)(males 102:22) (females 55:25)] comparing group proportions at α=.05 found sufficient power for this aim (1-$\beta\geq$.80).

3.3 Measures

3.3.1 Demographic and Clinical Variables

Demographic information: age (years, 65+); sex (male/female); race; education (years of education); BMI; Charlson Comorbidity Index (CCI) was derived from medical record abstraction or patient interviews. CCI is totaled with -1 if dementia was positive as it was captured in SCI. Race was combined to make a binary variable of White and Non-White/Mixed. Non-white mixed is made up of American Indian/Alaskan Native, Black/African American, or anyone who indicated a mixed racial ethnic background (no participants identified as Native Hawaiian/Pacific Islander or Asian).

Clinical and health related information such as fracture, surgery, and post-surgery related information were also derived from medical record abstraction. Fracture related information included: site of fracture (femoral neck, intertrochanteric, and other); American Society of Anesthesiologists Physical Status Rating (ASA, 1-4). Surgery related information included: length of surgery (minutes); surgical approach (fixation, arthroplasty, other). Post-surgery information included: length of stay (days); number of physical therapy sessions, time from hospital admission to initiation of physical therapy (days). See Table M1.1 for BHS7 variable information.

3.3.2 Aim 1 Independent and Dependent Variables

The independent variable assessed was source of CI indication (SCI), a

categorical representation of a hospital chart review and 3MS score within 22 days of

hospital admission for hip fracture. Source of impairment is either Hospital Chart Only,

3MS Only, Both (3MS and Hospital Chart), or No CI (Neither Hospital Chart nor 3MS).

Due to mechanistic differences in the role of CI, patients with Parkinson's disease were

not considered cognitively impaired in the analysis (n=6; 5 male, 1 female). See Methods

Figure M1.1 for SCI Category Designation.

Medical Record Abstraction

		ADRD in medical record or delirium as a post-operative complication	No ADRD in medical record nor delirium as a post-operative complication
3MS	≤ 78	Both	3MS Only
	>78	Hospital Record Only	No CI

Figure M1.1 SCI Category Designation
 Note: Grey boxes are discordant pairs. All categories were mutually exclusive. SCI: No
CI was a concordant category for patients without medical record abstraction indication
of ADRD or delirium as a post-operative complication; and with a 3MS score > 78. This
group serves as the referent category for all analyses.

3.3.3 Aim 2 Independent and Dependent Variables

Key outcome data on functional recovery used multiple functional tests including:

lower extremity physical activities of daily living (LPADL),[95] The Short Physical

Performance Battery (SPPB),[96,97] gait speed,[98] and Yale physical activity scales (YALE).

LPADL[95] was assessed using the Functional Status Index modified to address functions specifically related to hip fracture.[93] LPADL is scored from 0 to 12, with high scores indicating more dependence on the 11 lower extremity activities: walking 10ft, 1 block; climbing 5 stairs, getting into (out of) a car, bed, shower/bath; standing from a chair without arms, dressing (putting on pants, sock and shoes), bathing, and getting on/off a toilet.

SPPB[96,97] was collected a 2, 6, and 12 months. SPPB is scored from 0 to 12, scores <9 indicate functional impairment. The SPPB components include balance, gait speed, and lower extremity strength.[96,97]

Gait speed[98,99] (a subcomponent of the SPPB) was measured in meters per second, with <.8m/s being the convention for slow walking speed. Walking slower than .8m/s has been associated with limited community ambulation; mortality, morbidity, and ADL disability, hospitalization, and falls.[98,99]

Yale Physical Activity scale[100,101] was specifically designed for assessing physical activity in older adults. The Yale utilizes a seven day physical activity recall of household, recreational, and a variety of exercise activities recording both form and intensity of activity.[101] Baseline Yale were asked for pre-fracture activities.

Key outcome data on cognitive recovery used multiple assessments including Trails A&B Trail Making Task (TMT)[102], Hooper Visual Organization Test (HVOT)[103], and 3MS[60]. Prevalent CI was derived from medical chart review.

3MS is scored from 0 to 100, <78 is considered impaired.[60] MMSE can be

derived from 3MS scores.[6] Scores of <95 are considered indicative of MCI.[63] More about

3MS is discussed in Section 2.3.2.2. Screening Tests.

TMT (Trails A, Trails B; 0-301s), was modified for older adults and extended the

maximum time allowed for completion to 5 minutes, participants taking longer were

scored as 301 seconds.[104–106] TMT are frequently used in older adult populations.[107] TMT

measures attention (complex and divided), executive function, mental flexibility, and

visual tracking.[102,108,109] These cognitive domains have also been linked to ability to

remain community dwelling.[110] TMT is scored in seconds; longer times to completion, or

higher scores, are indicative of worse performance. The cut off scores for impaired

performance are $\leq$ 78 seconds for Trails A and $\leq$ 273 seconds for Trails B.[104,105,111] These

cut points are based on the original 3-minute test, validated cut points for the 5-minute

test have not yet been established.

HVOT[103] measures spatial analytic skills, general and specific cognition, and is

related to "visual-perceptual-construction skills".[6,112] These skills have been associated

with walking function and falls avoidance.[113] HVOT is scored out of 30, $\leq$20 is

considered impaired.[112]

3.3.4 Aim 3 Independent and Dependent Variables

The variables of interest for this analysis were SCI at baseline, participant sex

(male/female), cause of death (ICD code from NDI for CI), and date of death as of

December 31, 2018.

The dependent variables being assessed are dichotomous mortality a) all-cause, b) CR-COD; survival time in months a) all-cause b) CR-COD. Mortality information includes date of death, cause of death or contributing cause of death using ICD-10 codes and date of death as listed in the NDI. Applicable CI ICD codes are listed in Table M1.2 and include F01 (Vascular Dementia), F02 (Dementia), F03 (Unspecified Dementia), F05 (Delirium), and G30 (Alzheimer's disease).[23] Time to death was calculated as date of death minus date of hospital admission. CR-COD could be indicated in any place among the list of contributing cause of death to be considered CR-COD.

3.4 Analyses

3.4.1 Aim 1 Analyses

Aim 1: Estimate whether there is under-diagnosis and documentation of CI among hip fracture patients and evaluate if under-diagnosis differs by sex or other patient characteristics.

> Hypothesis 1.a: Additional screening of hip fracture patients using the 3MS will result in detecting a substantial number of previously undocumented CI (including ADRD, MCI, and delirium) cases.

> Hypothesis 1.b: The proportion of documented CI diagnosis will differ by patient sex; such that the proportion of documented CI in males is not equal to the proportion of documented CI in females.

> Hypothesis 1.c: The proportion of documented CI diagnosis will differ by other patient characteristics, such as age, comorbidity, and education. such that

older, more clinically complex, and less educated cases will be more likely to be identified and documented with CI.

3.4.1.1 Primary Analyses

Descriptive analyses of the study sample used Chi-square (χ^2, Fisher's exact tests as applicable) to assess sex differences within categorical variables, and Student's t-test for continuous variables.

A χ^2 of the dichotomous 3MS and hospital record indication was used to examine the significance of the proportion of the under-diagnosed group (3MS), such that the two sources should not be significantly different if there is accurate diagnosis of impairment. The SCI group proportions were established via crosstabulation of 3MS and hospital record indication. Continuous sample characteristics were compared across SCI categories using ANOVA with a Tukey correction.

To determine if there was differential misclassification of CI by patient sex, an unordered multinomial logistic regression model was used to assess the association of patient sex with SCI. Covariates were included in adjusted models using forward selection at $p \leq 0.2$. The covariates were also assessed for potential interactions to address collinearity. Each of the covariates was also assessed for a potential interaction with patient sex.

3.4.1.2 Supplementary Analyses

The main analyses were run using an alternative definition of hospital record indication of CI which included post-operative confusion as a sensitivity analysis. Ordered multinomial regressions of SCI were performed as supplementary sensitivity analyses.

3.4.2 Aim 2 Analyses

Aim 2.a: Identify trajectories of functional recovery and cognitive recovery and determine the group membership characteristics associated with distinct trajectory groups, particularly those related to patient sex and SCI.

> Hypothesis 2.a.1: There are multiple distinct trajectory groups that will vary in shape, amplitude, and/or direction.
>
> Hypothesis 2.a.2: Individuals in similar recovery groups will be more likely to also have similar sex and SCI.

Aim 2.b: Identify joint trajectories of cognitive and functional recovery and determine the group membership characteristics associated with similar trajectory group patterns, including patients' sex and cognitive identification source.

> Hypothesis 2.b.1: Male sex and CI, regardless of the source, will be risk factors significantly associated with the posterior probability of group membership in the worst recovery groups for joint trajectories of cognitive and functional outcomes.

Aim 2.c: Evaluate death as non-random source of truncation within recovery groups identified in Aims 2 a-b.

> Hypothesis 2.c.1: One group in each outcome model will experience a higher proportion of earlier truncation by death than other groups.

3.4.2.1 Aim 2 Primary

The primary outcome measures were separated as cognitive and physical function measures. Cognitive measures included baseline; 2, 6, and 12 months assessments of 3MS, HVOT, and TMT. Physical function surveys including the YALE and LPADL were administered at all 4 time points. The SPPB was only assessed at 2, 6, and 12 months. Initial models were run as independent trajectories for each type of cognitive and physical function recovery outcome. Analyses utilized PROC TRAJ in SAS 9.4.

Model selection was achieved using methods documented in Haviland et al. (2011).[114] comparing the BIC, estimated log Bayes factor, and estimated group proportions for various models. The estimated log Bayes factor can be approximated as 2*[(BIC more complex model) – (BIC simpler model)]. A log Bayes factor can be categorized as weak (0-2), moderate (2-6), strong (6-10), or very strong (>10) evidence for the more complex model.

First each measure was run as a cubic censored normal unadjusted model for one trajectory (no separation). Then the number of trajectories (or groups) was increased by 1 sequentially until the log bayes factor of the more complex model (the one with more groups) was smaller than that of the simpler model, the log bayes factor was >10, and/or the estimated group size was less than 5% of the total sample.

Each functional test, cognitive and physical function, was modeled to illustrate similar patterns. Posterior probability characteristic describes the percent probability or likelihood of belonging to one trajectory group based on the specified characteristic. Group membership probability as a function of covariates collected at baseline and treated as time-stable such as Sex (male/female), age, race (white/black and non-white), years of education, record of dementia or delirium in the hospital chart (yes/no), ASA physical status rating (2-4), CCI, BMI, side of fracture (left/right), fracture type (femoral neck/other), surgery type (fixation, arthroplasty), length of surgery (minutes), length of hospital stay (days), day to initiation of physical therapy, and number of physical therapy sessions. The outcome was interpreted as the log odds of risk factor (covariate) on probability of trajectory group membership relative to other (reference) group. Reference groups were either the largest percentage of the sample, or the best performing group.

3.4.2.2 Aim 2 Supplementary and Sensitivity Analyses

3.4.2.2.1 Preliminary Analysis

Descriptive statistics for means and standard deviations of all measures at each available time point were run (See Tables 2.1 and S2.2a-c), as well as identifying the number and percent who passed or failed a measure at each time point. Functional recovery outcomes and cognitive recovery outcomes were stratified by sex at each timepoint using repeated measures ANOVA to identify between or within subject differences. It was anticipated that this result would hide the unique changes different groups undergo during recovery. Additional posterior probability characteristic analyses

were run on risk factors using alterative refence groups to understand more about the relationships between the different groups.

3.4.2.2.2 Joint Trajectories

As part of secondary analysis, group-based multi-trajectory modeling allows for latent cluster analysis of subjects who follow similar trajectories over multiple outcomes of interest.[115] The best fitting models from the individual trajectories will be used in the joint trajectory.

3.4.2.2.3 Dropout by Mortality

Finally, death was modeled as a non-random source of truncation for each independent measure. Due to other sources of missingness and restraints in sample size to only exclude those with missingness due to death the sample size became too small to provide substantial analyses. Joint modeling with mortality is secondary to the initial identification of finite trajectory groups and may not have a large enough remaining sample to successfully model.

3.4.3. Aim 3 Analyses

3.4.3.1 Aim 3 Primary Analyses

Aim 3: Establish if time to death and the proportion of individuals with CR-COD are comparable for individuals with undiagnosed and document CI, and if these associations are moderated by patient sex.

Hypothesis 3.a: Those identified from cognitive testing only will have similar

poor outcomes as those with a dementia diagnosis only, or by both, compared to

those identified with no CI.

Hypothesis 3.b: CI differentially misclassified by patient sex, will result in

increased mortality in the underdiagnosed group compared to those identified

with medical records and those found to not have CI on medical records nor

3MS.

Hypothesis 3.c: Patient sex and CI differentially misclassified by patient

sex (interaction), will result in reduced time to mortality and cause-specific

mortality in the underdiagnosed group and those identified with medical

records compared to those identified with no CI.

Aim 3 analyses compared the proportion of hip fracture patients who died by

December 31, 2018 to those who survive, focusing on SCI as an independent variable.

Additionally, the proportion of hip fracture patients who died of CR-COD were

compared to those who died of other causes of death. This main analysis was stratified by

patient sex to identify if sex was modifying or confounding the observed relationships.

Preliminary analyses included descriptive statistics of the sample and cross-

tabulation of SCI, mortality, cause of death, and gender. The second analyses assessed

time to all-cause mortality and CR-COD, stratifying these results by sex, such that it will

identify the hazard of all cause-mortality and CR-COD by SCI across both sexes. See

Table 3.1 for sample statistics regarding key variables, mortality status, CR-COD, sex,

and cognition identification source.

Survival analysis utilized cox proportional hazards models. Time to event analysis was conducted for time to death in all-cause mortality (all those who died, including CR-COD). This analysis was then be stratified by patient sex. A subsequent time to event analysis was conducted for time to death in CR-COD. This analysis was stratified by patient sex. A comparative time to event analysis assessed time to death stratifying based on CR-COD, and then subsequently by patient sex.

3.4.3.2 Aim 3 Supplementary and Sensitivity Analyses

Logistic regressions were used to determine odds of death and cause specific mortality as function of SCI and sex. Model building relied on forward selection of key variables including age, education, comorbidities, ASA status at admission $p \leq .2$. Trajectory group membership from Aim 2 was used as a categorical covariate to predict and time to death and cause-specific mortality in a supplemental cox proportional hazards model. Each measure was used independently.

CHAPTER 4. AIM 1 RESULTS

4.1 Aim 1 Main Analysis and Manuscript

Under-Diagnosis and Differential Misclassification of Cognitive Impairment by Sex in Hip Fracture Patients

4.1.1 Introduction

Cognitive impairment, including delirium and Alzheimer's disease and related dementias (ADRD), is severely underdiagnosed in the U.S. It has been estimated that hospital records capture only a third of existing age-related cognitive impairment.[21] Cognitive impairment could be due to multiple etiologies, which require testing and medical history review to differentiate.[10,11] This diagnostic burden in general clinical practice can be more difficult in hip fracture cases. Hip fracture patients have a high prevalence of cognitive impairment, much of which is likely underdiagnosed.[21,116] Cognitive impairment increases an older adult's risk of hip fracture. An estimated 20% of hip fracture patients have dementia prior to their fracture, and 35%-61% have prevalent cognitive impairment and/or delirium after hip fracture.[18,19] Studies assessing biomarkers related to ADRD show that hip fracture patients with normal cognitive function have comparable levels of biomarkers compared to hip fracture patients with mild cognitive impairment. These results suggest that changes at the physiological level are occurring before manifestation of cognitive impairment.[10,68,69] Given the associations between cognitive impairment and hip fracture,

it is expected that many individuals who were not previously diagnosed with cognitive impairment will present with cognitive impairment (mild cognitive impairment, dementia, delirium) upon screening after the acute injury event (hip fracture).

Our understanding of cognition in hip fracture patients is further complicated by differences by sex. Men with hip fractures have been shown to be more likely to have cognitive impairment at discharge and geriatric rehabilitation after hip fracture.[14] Patient sex is largely under explored in U.S research with regard to potential biases in cognitive impairment diagnoses. Men currently represent 25-30% of the hip fracture population, but the number of hip fractures in men is expected to increase 51% from 2010 to 2030.[2] To date, two-thirds of ADRD cases in the U.S. and two-thirds of hip fracture cases are women who have comprised 80-90% of the hip fracture research subjects.[11,15,16,47] In a non-research setting, clinical determination of cognitive impairment is likely the sole determination of cognitive status. However, in research studies, a more thorough and equitable examination of cognition may find additional cases.

Research has shown the deleterious effects of a hip fracture can be worse in individuals with cognitive impairment.[6,61,71,117,118] Hip fracture patients with dementia are more likely to suffer delirium during hospitalization than other hip fracture patients and other hospitalized older adults.[67] Functional recovery and mortality in hip fracture patients with cognitive impairment due to ADRD and/or delirium have been shown to be worse compared to non-impaired counterparts.[6,61,71,117,118] It is necessary to understand whether under-diagnosed cognitive impairment may be contributing to the sex differences seen in recovery and mortality after hip fracture. The first step to

understanding these sex differences is to assess for differential misclassification of cognitive impairment by patient sex.

This study aims to 1) examine the degree to which cognitive impairment is under-diagnosed in hip fracture patients, and 2) determine if cognitive impairment is under-diagnosed differentially by sex in hip fracture patients. We hypothesized that additional screening of hip fracture patients using the Modified Mini-Mental State Examination (3MS) would result in detecting previously undocumented cognitive impairment (including ADRD, mild cognitive impairment, and delirium) cases, and that the proportion of documented cognitive impairment in males is not equal to the proportion of documented cognitive impairment in females.

4.1.2 Methods

4.1.2.1 Study Design

This study was a retrospective analysis of the Baltimore Hip Studies 7th Cohort (BHS7), a longitudinal observational cohort study of community-dwelling geriatric hip fracture patients recruited from eight hospitals in the greater Baltimore area from 2006-2011. Participants were recruited and consented (self or proxy) by trained research nurses within 15 days of admission for hip fracture repair surgery. Baseline assessments were conducted within 22 days of the admission and clinical information was abstracted from the medical record. The original study was approved by the institutional review boards of the University of Maryland, Baltimore and participating hospitals.

4.1.2.2 Sample

The BHS7 study sample comprised 339 hip fracture patients (ICD-9 codes 820.00-820.9) age 65 and older. Study subjects were hospitalized for non-pathological, non-traumatic hip fracture. Patients were excluded if they were not community-dwelling at the time of fracture, were non-English speaking, had been bedbound for 6 months or more prior to fracture, lived >70 miles from the hospital, weighed >300 pounds, did not have surgical hip repair, or had hardware in the contralateral hip (from prior hip fracture or replacement).[93] BHS7 oversampled males by frequency matching the enrollment of females to males by hospital and time of admission, such that the sample was approximately 50% male (male=168; female =171). Proxies provided data on the patient's behalf if patients scored <36 on the Modified Mini Mental State Examination (3MS).

Nine participants were excluded due to missing medical record abstraction information or a baseline 3MS. Of these nine participants, four females and four males were missing a baseline 3MS, and one male was missing baseline medical record abstraction information. Thus, the analytic sample was 330 (163 male, 167 female).

4.1.2.3 Measurements

4.1.2.3.1 Cognitive Status

Cognitive status was assessed within 22 days post-admission, using the 3MS.[1,2] The 3MS is based on the most common brief cognitive screening instrument, the Mini-Mental State Examination.[53,57,58,60] The 3MS is scored from 0 to 100, with a score of ≤78 indicative of cognitive impairment.[119]

Medical record abstraction provided cognitive information on patients' ADRD diagnosis, delirium at admission, confusion or disorientation at admission, confusion or disorientation as a post-operative complication, and/or delirium as a post-operative complication. Date of diagnosis was not indicated in the medical record abstraction. An existing diagnosis of ADRD and/or delirium as a post-operative complication was used to indicate cognitive impairment from medical history.

Source of cognitive impairment identification (SCI) was coded as a mutually exclusive categorical representation of cognitive impairment determined by two distinct sources: 1) medical record abstraction indication of ADRD and/or delirium and 2) 3MS score ≤78. SCI category determinations are shown in Figure 1. These two sources can be concordant or discordant. No CI was used as the referent SCI category throughout. The category of 3MS represents a clinically under-diagnosed sub-population.

4.1.2.3.2 Demographics and Clinical Information

Demographics and clinical information were collected from a medical record abstraction or patient interview. Demographic information included: age, sex, race (White/non-white), and education. Clinical characteristics included body mass index (BMI), site of fracture, type of surgery, length of surgery (minutes), time from hospital admission to surgery (minutes), American Society of Anesthesiologists Physical Status Rating (ASA, 1-4); length of stay (days, date discharge-date admission); number of physical therapy sessions, and time from hospital admission to initiation of physical therapy (days, date of first physical therapy visit – date of admission). A modified

Charlson Comorbidity Index (CCI) was calculated in which only moderate or severe (not mild) liver disease was recorded.[120] Dementia was not included in the CCI count because it was a dependent variable. These were used as potential covariates, as they are indicators of health, well-being, the severity of the hip fracture, the hospital experience, or are previously indicated as being related to hip fracture outcomes.

4.1.2.4 <u>Analyses</u>

Descriptive analyses of the study sample used Chi-square (χ^2, Fisher's exact tests as applicable) to assess sex differences within categorical variables, and Student's t-test for continuous variables.

A χ^2 of the dichotomous 3MS and hospital record indication was used to examine the significance of the proportion of the under-diagnosed group (3MS), such that the two sources should not be significantly different if there is accurate diagnosis of impairment. The SCI group proportions were established via crosstabulation of 3MS and hospital record indication. Continuous sample characteristics were compared across SCI categories using ANOVA with a Tukey correction.

To determine if there was differential misclassification of cognitive impairment by patient sex, an unordered multinomial logistic regression model was used to assess the association of patient sex with SCI. Covariates were included in adjusted models using forward selection at $p \leq 0.2$. The covariates were also assessed for potential interactions to address collinearity. Each of the covariate was also assessed for a potential interaction with patient sex.

4.1.3 Results

4.1.3.1 Sample Characteristics

       Table 1.1 shows the sample characteristics with the mean age of 81 (7.8) years. On average, participants had 13.1 years of education, 1.9 comorbid conditions (not including dementia), and a BMI of 25.2. The modal ASA rating was 3 for 66% of participants. Most participants were admitted with a femoral neck fracture (50.3%) and were treated using surgical fixation (54.6%). Participants had similar hospitalization experiences: the average length of surgery was 84.5 minutes, mean hospital stay was 5.3 days, and physical therapy was initiated on average 2.6 days after admission.

       Males and females were not significantly different in age, years of education, BMI, fracture type, or surgery type (Table 1.1). Males had significantly more comorbidities than females at baseline ($p<.001$) and higher ASA ratings ($p<.001$) and failed the 3MS ($p= 0.004$). Males started physical therapy later than females (2.8 vs. 2.3 days; $p<.001$).

Table 1.1 Characteristics of BHS7 Analytic Sample by Sex				
	Total N=330	Male N=163	Female N=167	p-value
Age (years, 65+)	81.0 ± 7.8	80.6 ± 7.7	81.4 ± 7.9	0.32
Education (years, n=319)	13.1 ± 3.4	13.2 ± 3.8	13.1 ± 3.0	0.09
Race (White; n=321), n (%)	291 (90.7)	142 (48.8)	149 (51.2)	0.41
Charlson Comorbidity Index	1.9 ± 1.7	2.3 ± 1.8	1.5 ± 1.5	<.001
Body Mass Index	25.2 ± 5.0	25.5 ± 4.4	24.9 ± 5.6	0.27
Length of Surgery (minutes)	84.5 ± 44.4	86.0 ± 44.9	82.9 ± 44.1	0.53
Admission to Physical Therapy (days)	2.6 ± 1.2	2.8 ± 1.4	2.3 ± 1.0	<.001
Length of Hospital Stay (days)	5.3 ± 2.6	5.5 ± 2.5	5.2 ± 2.8	0.31
Admission to 3MS (days)	18.5 ± 49.6	15.8 ± 4.9	21.1 ± 10.5	0.33
Number of PT Sessions	3.4 ± 1.8	3.4 ± 1.6	3.5 ± 2.0	0.58
Site of Fracture, n (%)				0.30
Intertrochanteric	129 (39.1)	69 (42.3)	60 (35.9)	
Femoral Neck	166 (50.3)	75 (46.0)	91 (54.5)	
Other	35 (10.6)	19 (11.7)	16 (9.6)	
Surgery Type, n (%)				0.20
Fixation	180 (54.6)	95 (59.5)	83 (49.7)	
Arthroplasty	139 (42.1)	61 (37.4)	78 (46.7)	
Other	11 (3.3)	5 (3.1)	6 (3.6)	
ASA Physical Status Rating, n (%)				<.001
2	65 (19.7)	20 (12.3)	45 (26.9)	
3	218 (66.1)	107 (65.6)	111 (66.5)	
4	47 (14.2)	36 (22.1)	11 (6.6)	
Baseline 3MS Score (0-100)	84.2 ± 16.5	82.19 ± 16.4	86.2 ± 16.4	0.03
ADRD in Medical Chart	46 (13.9)	28 (17.2)	18 (10.8)	0.09
Post-operative Delirium	30 (9.1)	16 (9.8)	14 (8.4)	0.65
ADRD and Post-operative Delirium	7 (2.1)	4 (2.5)	3 (1.8)	0.72
Cognitive Impairment Source				
SCI: No CI	219 (66.3)	96 (58.9)	123 (73.7)	0.004
SCI: 3MS	42 (12.7)	27 (16.6)	15 (9.0)	0.04
SCI: Hospital Record	38 (11.5)	20 (12.3)	18 (10.8)	0.67
SCI: Both	31 (9.4)	20 (12.3)	11 (6.6)	0.08

*Note: Alzheimer's Disease and Related Dementia (ADRD), Modified Mini-Mental State Examination (3MS),Cognitive Impairment (CI);p-value is χ^2*Cochran, Pooled as applicable, Charlson Comorbidity Index -1 if ADRD indicated in Medical Chart ; Notation: N (%), Mean ± SD*

4.1.3.2 SCI Category Allocation

The four non-overlapping SCI categories for the sample are shown in Figure 1.1:

3MS (n=42, 12.7%), Hospital Record (n=38, 11.5%), Both (n=31, 9.4%), or No CI

(n=219, 66.4%).

Medical Record Abstraction

		ADRD in medical record or delirium as a post-operative complication	No ADRD in medical record nor delirium as a post-operative complication
3MS	≤ 78	Both n=31 (9.39%)	3MS n=42 (12.73%)
	>78	Hospital Record n=38 (11.52%)	No CI n=219 (66.36%)

Figure 1.1 SCI Category Designation
Note: Grey boxes are discordant pairs. All categories were mutually exclusive.
SCI: 3MS was a discordant category for the source of identification of cognitive
impairment in the sample, in which there is no record of cognitive impairment from
medical chart abstraction, but the patient tested as impaired on the baselines 3MS.
SCI: Hospital Record was a discordant category in which the two sources of cognitive
impairment identification did not agree on the presence of cognitive impairment, such
that only medical chart abstraction had an indication of cognitive impairment.
SCI: Both represents the concordance of 3MS and hospital record indication of cognitive
impairment such that both positively indicate the presence of cognitive impairment.
SCI: No CI represents the concordance of 3MS and hospital record indication cognitive
impairment such that neither indicate the presence of cognitive impairment. This group
serves as the referent category for all analyses.

The χ^2 of 3MS and hospital indication was significant at p=0.0007 indicating that

the proportions are unequal between those identified by 3MS and the hospital record.

This results in an under-diagnosed sub-group (indication only on the 3MS). The SCI

category differences between males and females are shown in Table 1.1. Among those

with complete record abstraction and cognitive testing there were significantly more

females with no indication of cognitive impairment (96 males and 123 females,

p<0.01), and significantly more males identified as cognitively impaired only with

the 3MS (27 males and 15 females; p= 0.04). There were not significant sex differences for indication by hospital record only or by both hospital record and 3MS.

Table 1.2. shows the results for sample characteristics stratified by SCI category. The main differences between the SCI categories included age, education, hospital stay, ASA rating, sex, and race. Those in the No CI category were the youngest (79.8 years) while those in the Both category were among the oldest participants (85.6 years). The No CI group started physical therapy soonest (2.4 days), while those in Both started latest (3.1 days). The 3MS group has the fewest years of education (11.1 years), while Hospital Record group had the most education (14.0 years). Participants in Both had the longest hospital stays (7.1 days) while 3MS group had the shortest hospital stays (5.2 days).

Table 1.2 Characteristics of BHS7 Analytic Sample by SCI					
			SCI		
	3MS N=42	Hospital Record N=38	Both N=31	No CI N=219	P-value
Age (years, 65+)	81.6 ± 8.2	83.3 ± 6.8	85.6 ± 5.8	79.8 ± 7.8	<0.01[a]
Education (years, n=319)	11.1 ± 4.1	14.0 ± 3.2	12.4 ± 3.6	13.4 ± 3.1	<0.01[b,c]
Charlson Comorbidity Index	2.0 ± 1.7	2.4 ± 1.9	2.0 ± 1.4	1.7 ± 1.7	0.14
Body Mass Index	25.6 ± 5.3	24.8 ± 4.8	24.6 ± 5.0	25.3 ± 5.0	0.81
Length of Surgery (minutes)	88.8 ± 44.1	98.0 ± 45.4	73.7 ± 45.4	82.8 ± 43.9	0.11
Admission to PT (days)	2.9 ± 1.3	2.7 ± 1.2	3.2 ± 1.7	2.4 ± 1.1	<0.01[d]
Length of Hospital Stay (days)	5.3 ± 2.1	6.4 ± 2.8	7.2 ± 5.2	4.8 ± 1.9	<0.01[d]
Admission to 3MS (days)	15.4 ± 4.8	16.5 ± 4.4	16.7 ± 4.1	15.5 ± 5.3	0.45
Number of PT Sessions	3.0 ± 1.6	3.8 ± 2.1	3.7 ± 3.0	3.4 ± 1.5	0.15
Site of Fracture, n (%)					0.68
Intertrochanteric	17 (40.48)	13 (34.21)	15 (48.39)	84 (38.36)	
Femoral Neck	23 (54.76)	21 (55.26)	14 (45.16)	108 (49.32)	
Other	2 (4.76)	4 (10.53)	2 (6.45)	27 (12.33)	
Surgery Type, n (%)					0.34
Fixation	21 (50.00)	16 (42.11)	20 (64.52)	123 (56.16)	
Arthroplasty	19 (45.24)	19 (50.00)	11 (35.48)	90 (41.10)	
Other	2 (4.76)	3 (7.89)	0 (0)	6 (2.74)	
ASA Physical Status Rating					0.01
2	4 (9.5)	4 (10.5)	3 (9.7)	54 (24.7)	
3	30 (71.4)	24 (63.2)	21 (67.7)	143 (65.3)	
4	8 (19.0)	10 (26.3)	7 (22.6)	22 (10.0)	
Sex					0.02
Male	27 (64.3)	20 (52.6)	20 (64.5)	96 (43.8)	
Female	15 (35.7)	18 (47.4)	11 (35.5)	123 (56.2)	
Race					<0.01
White	30 (75.0)	37 (97.4)	28 (90.3)	196 (92.5)	
Non-white, mixed	10 (20.0)	1 (2.6)	3 (9.7)	16 (7.6)	

Table 1.2 Continued
Note: Physical Therapy (PT), Modified Mini-Mental State Examination (3MS),cognitive impairment (CI); p-value is based on F-test and chi-square (Fisher's exact as needed)*, Charlson Comorbidity Index -1 if ADRD indicated in Medical Chart* ; Notation: N (%), Mean ± SD , difference significant at p ≤ 0.05: a: No CI vs Hospital Record, b: Hospital Record vs 3MS, c: No CI vs 3MS, d: No CI vs Both

4.1.3.3 Associations of SCI Category Allocation and Patient Sex

The unadjusted multinomial logistic regression of cognitive impairment identification (reference No CI) modeled for patient sex (refence females) was significant (Type 3 p=0.03, likelihood ratio of Global Null P=0.02). It showed significantly greater relative log odds for males identified by 3MS (2.33, 1.07-5.10) or Both (2.31, 1.16-4.58) but not hospital record (1.42, 0.71-2.84). The adjusted model included age, education, and CCI. There were no significant interactions between the covariates. Older age was associated with a significant (p<.05) increase in the relative log odds of SCI identified by Both or Hospital Record. Higher levels of education were associated with a significant (p<.05) decrease in the relative log odds of 3MS indication. The other SCI groups were not significant and had varying directionality. Increased comorbidities on the CCI was associated a significant increase (p<.05) in the relative log odds of cognitive impairment indicated by Hospital Record. Adjusting for age, education, and CCI, the 3MS association with increased odds for males was reduced to non-significance (Figure 1.2). After adjustment, males still had significantly greater odds of having Both indications than females.
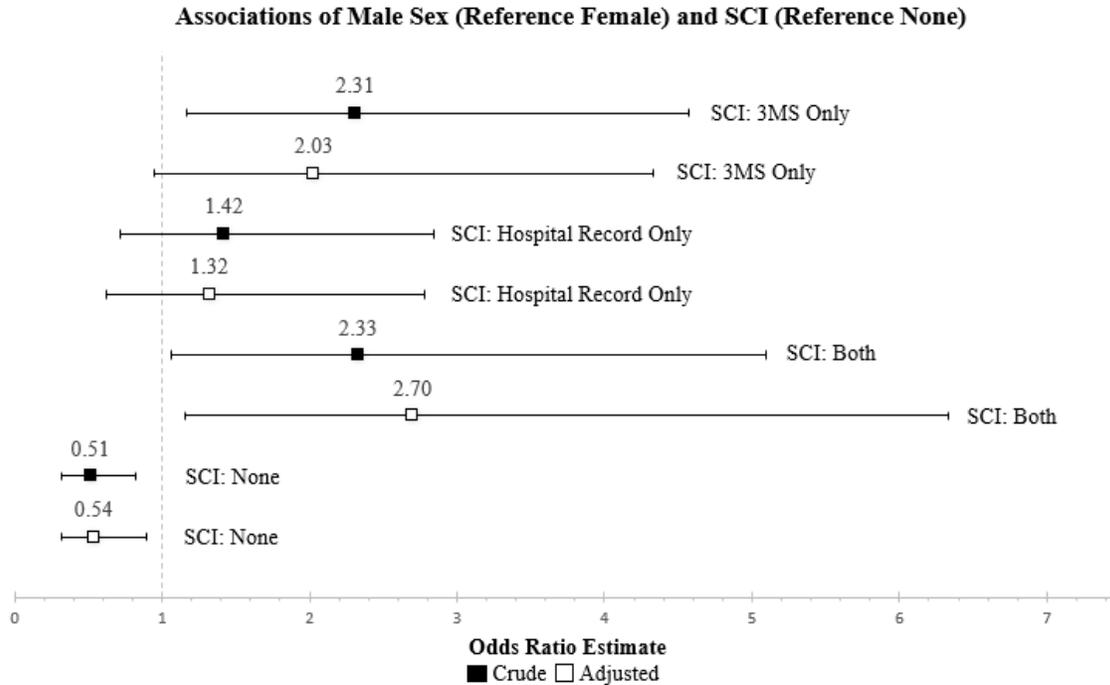
Figure 1.2 Associations of Male Sex with SCI
Crude and adjusted odds ratio estimates of SCI (reference No CI) for Males (reference Females). Adjusted odds are adjusted for age, education, CCI.

4.1.4 Discussion

4.1.4.1 Underdiagnosis of Cognitive Impairment

Thirty-three percent of hip fracture patients in the BHS7 had cognitive impairment in the hospital or within 22 days of admission, including a low 3MS score, ADRD, MCI, and/or delirium. 3MS testing identified cognitive impairment in 12.7% of the sample that was not identified in the patient medical record, revealing potential underdiagnosis. On the other hand, 11.5% of those with a diagnosis of cognitive impairment did not actively demonstrate impairment based on the baseline 3MS. In standard clinical practice, those identified by Hospital Record and Both would be treated as cognitively impaired. Separating SCI into four distinct categories illustrated a sub-

58

population with cognitive impairment who were not identified in their medical charts. This sub-population accounted for a third of the impaired cases.

In contrast to our findings, new research from Zhu et al. (2020), using a 20% Medicare sample linked to the HRS has suggested that the discrepancies between prevalence of dementia diagnostic codes and cognitive testing have narrowed over time through 2012.[22] However, Medicare files use an algorithm for ADRD with a two-year lookback, whereas in a clinical setting the only indication available may be a medical record held in the institution network. Zhu's analysis also found no difference in discrepancies between sex and age groups.

Older adults with cognitive impairment have been shown to require more conscientious effort to benefit from rehabilitation therapy.[121] The discrepancy identified in this research may inform future clinical practices to improve rehabilitation after hip fracture by using additional screening for cognitive impairment to better guide rehabilitation efforts. A systematic review of the cognitive impairment in rehabilitation after hip fracture found that characteristics of dementia including severity and the domain of impairment were prognostic of rehabilitation outcomes, but patients with cognitive impairment were amenable to as intense physical therapy as non-impaired hip fracture patients.[122] Rehabilitation should not rely solely on intake diagnosis for estimating the degree of effort needed by patients as 12% may be under-diagnosed based on our findings.

4.1.4.2 Source of Cognitive Impairment Identification and Patient Sex

Odds of identification by both 3MS and Hospital Record for males were still greater than females after adjusting for age, education, and CCI. Males were therefore more likely to have a history of ADRD coupled with active presentation of impairment after hip fracture surgery. Although both sexes had similar medical record documentation for ADRD, males presented with poorer health at baseline. It's possible that underlying, yet undiagnosed, cognitive impairment in males may have been exacerbated by the hospitalization experience. Males with hip fractures are more disabled pre-fracture, more impaired after fracture, and more likely to die in the year subsequent to the fracture than their female counterparts.[14,48] The under-diagnosis of cognitive impairment could be contributing to the degree to which males fail to recover after hip fracture.

4.1.4.3 Strengths and Limitations

Hip fractures are acute events; it is therefore unlikely for a large sample of hip fracture patients to have pre-fracture cognitive screenings to measure pre-existing cognitive impairment. Date of diagnosis of ADRD was not available through medical record abstraction, and it is therefore unknown how long cognitive impairment may have been present. The severity of the cognitive impairment was also not indicated in the medical chart nor was it clear what practices delineated a diagnosis of confusion and disorientation from delirium. While we found a sizeable number who had a $3MS \leq 78$ at about 3 weeks after admission, we do not have a measure of what their cognitive function was pre-fracture, or even during their hospital stay. Thus, we have no indication whether these participants had previous cognitive impairment that was not

detected. Generalizability of these findings may be limited by the racial and geographic homogeneity of the sample.

The BHS7's balanced recruitment of males and females with hip fracture was a novel research design in this population that allowed for comparison of SCI based on sex. BHS7 also included patients with poor cognition: these patients are often excluded from research.

4.1.4.4 Conclusions

This research has illustrated that a significant proportion of cognitive impairment cases go undocumented during standard care of hip-fracture. Additionally, males are more likely to be under diagnosed compared to females. Research has shown the deleterious effects of a hip fracture can be worse in individuals with cognitive impairment, such as lowered functional recovery and earlier mortality.[6,123,124] These results identify males as a vulnerable subgroup within the hip fracture population. Future research should incorporate additional screening for cognitive impairment, focusing on patient sex, to follow up on longitudinal outcomes such as functional recovery and mortality. Such information could guide future clinical practice and improve indication of cognitive impairment in older patients and particularly older males, who have more negative experiences after hip fracture.

4.2 Aim 1 Supplementary Analysis and Results

As a sensitivity analysis for the main paper supplementary analyses were done on how hospital record identification was quantified, and the analytic method used to determine differential misclassification. Below are the results and arguments for these methods not being used in the main paper.

4.2.1 Alternate Definition of SCI Hospital Record Indication

On average, the 3MS was administered 18.5 days after hospital admission for hip fracture (range 1-37 days). Days to cognitive battery was not significantly different between males and females. Males scored significantly lower than females on average [82.2 vs 86.2, p=0.03]. In our sample, 73 (22.1%) of the participants were cognitively impaired on the baseline 3MS (3MS ≤78).

Medical chart abstraction revealed 46 (13.9%) participants with ADRD in their medical records and 30 (9.1%) with delirium as a post-operative complication. There was moderate overlap between the two indications, 7 individuals had both ADRD and post-operative delirium, 23 of the 30 (76.7%) participants with post-operative delirium had other noted delirium but not ADRD.

Other medical record abstraction items were considered for positive hospital record indication such as delirium at admission (n<5), confusion or disorientation at admission (n=23), and confusion or disorientation as a post-operative complication (n=90). Many of the individuals had multiple indications of CI in the medical charts. All the individuals with delirium at admission, 17 of the 23 (36.96%) patients with confusion

or disorientation at admission, and 23 of the 90 (25.6%) of those with confusion or disorientation as a post-operative complication also had ADRD indicated in the medical chart. Using ADRD and/or delirium as a post-operative complication to define hospital record indication of CI captures 100% of the delirium at admission cases and 97.9% of the confusion or disorientation at admission cases (6 not captured). ADRD or post-operative dementia did not capture 47 of 90 (52.2%) of the confusion or disorientation as a post-operative complication cases. The alternative SCI definition of Hospital Record identification includes ADRD, delirium and/or confusion or disorientation as a post-operative complication. See Figure S1.1 for SCI Categories using the alternative definition of positive hospital record. The overall direction and significance of associations between sex and SCI did not change with using this alternative definition. More covariates remained significant at p<.02 and were included during model building. However, 3MS only was no longer significant when unadjusted. ANOVA (with a Tukey correction) of SCI using the alternative definition was still significantly different on the same covariates as the original definition. See Table S1.1 for Sample Characteristics by Alternative SCI Definition.

Medical Record Abstraction

	ADRD in medical record or delirium as a post-operative complication	No ADRD in medical record nor delirium as a post-operative complication
3MS ≤ 78	Both n=45 (13.64%)	3MS n=28 (8.48%)
>78	Hospital Record n=71 (21.52%)	No CI n=186 (56.36%)

Figure S1.1 SCI Category Designation Where ADRD in Medical Record Includes Confusion or Disorientation as a Post-operative Complication; N=330

Note: Grey boxes are discordant pairs. All categories were mutually exclusive.

SCI: 3MS was a discordant category for the SCI in the sample, in which there is no record of cognitive impairment from medical chart abstraction, but the patient tested as impaired on the baseline 3MS.

SCI: Hospital Record was a discordant category in which the two SCI did not agree on the presence of CI, such that only medical chart abstraction had an indication of CI .

SCI: Both represents the concordance of 3MS and hospital record indication of CI such that both positively indicate the presence of CI.

SCI: No CI represents the concordance of 3MS and hospital record indication CI such that neither indicate the presence of CI. This group serves as the referent category for all analyses.
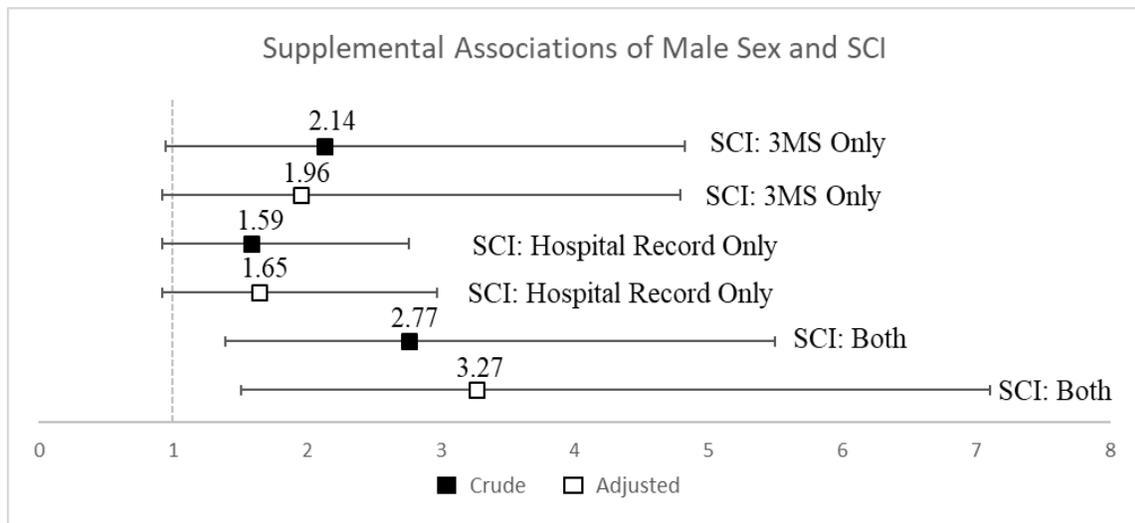
Figure S1.2 Associations of Male Sex with SCI (Alternative Definition)

Note: Adjusted for age, education, race, and length of hospital stay

Table S1.1 Sample Characteristics of BHS7 by SCI (Alternative Definition)					
	SCI				
	3MS N=28	Hospital Record N=71	Both N=45	No CI N=71	P-value
Age (years, 65+)	81.9 ± 7.7	82.8 ± 6.8	84.2 ± 7.4	79.4 ± 7.9	$<0.01^{a,\ d}$
Education	11.0 ± 4.0	13.6 ± 3.1	12.1 ± 3.8	13.4 ± 3.2	$<0.01^{b,\ c}$
CCI	1.6 ± 1.7	2.2 ± 1.8	2.2 ± 1.5	1.7 ± 1.7	0.12
Body Mass Index	25.0 ± 4.4	24.9 ± 4.6	25.3 ± 5.7	25.4 ± 5.1	0.92
Length of Surgery	80.4 ± 37.7	88.1 ± 45.1	83.6 ± 49.7	83.9 ± 44.1	0.86
Admission to PT (days)	2.8 ± 1.3	2.8 ± 1.3	3.2 ± 1.6	2.3 ± 1.0	$<0.01^{d}$
Hospital Stay (days)	4.9 ± 1.9	6.2 ± 2.7	6.8 ± 4.5	4.7 ± 1.7	$<0.01^{a,d,e}$
Time to 3MS (days)	15.1 ± 5.1	16.3 ± 4.7	16.5 ± 4.1	15.4 ± 5.3	0.40
Number of PT Sessions	3.1 ± 1.5	3.8 ± 1.9	3.5 ± 2.7	3.3 ± 1.5	0.17
Site of Fracture, n (%)					0.37
Intertrochanteric	11 (39.3%)	33 (46.5%)	21 (46.7%)	64 (34.4%)	
Femoral Neck	15 (53.6%)	32 (45.1%)	22 (48.9%)	97 (52.2%)	
Other	2 (7.1%)	6 (8.5%)	2 (4.4%)	25 (13.4%)	
Surgery Type, n (%)					0.58
Fixation	13 (46.4%)	41 (57.8%)	28 (62.2%)	98 (52.7%)	
Arthroplasty	13 (46.4%)	27 (38.0%)	17 (37.8%)	82 (44.1%)	
Other	2 (7.1%)	3 (4.2%)	0 (0.0%)	6 (3.2%)	
ASA Physical Status Rating					<0.01
2	4 (14.3%)	10 (14.0%)	3 (6.7%)	48 (25.8%)	
3	19 (67.9%)	46 (64.8%)	32 (71.1%)	121 (65.1%)	
4	5 (17.9%)	15 (21.1%)	10 (22.2%)	17 (9.1%)	
Sex					<0.01
Male	17 (60.7%)	38 (53.5%)	30 (66.7%)	78 (41.9%)	
Female	11 (39.3%)	33 (46.5%)	15 (33.3%)	108 (58.1%)	
Race					<0.01
White	22 (81.5%)	70 (98.6%)	36 (81.8%)	163 (91.1%)	
Non-white, mixed	5 (18.5%)	1 (1.4%)	8 (18.2%)	16 (8.9%)	

Note: Physical Therapy (PT), Modified Mini-Mental State Examination (3MS), p-value is based on F-test and chi-square (Fisher's exact as needed)*, CCI= Charlson Comorbidity Index -1 if ADRD indicated in Medical Chart* , Length of surgery is in minutes, total sample values available in Table 1.1; Notation: N (%), Mean $\pm$ SD. Difference significant at $p \leq 0.05$: a: No CI vs Hospital Record, b: Hospital Record vs 3MS, c: No CI vs 3MS, d: No CI vs Both, e: 3MS vs Both

4.2.2 Ordered Multinomial Regression

A subsequent sensitivity analysis was done implementing ordered logistic regressions. SCI was ordered such that 0 = No CI, 1 = 3MS, 2 = Hospital Record, 3 = Both. Ordered logistic regressions were implemented because they preserve power in the calculations compared to multinomial regressions. However, ordered regression was not the primary analytic method as it puts an implicit hierarchy on the categories that has not yet been confirmed and assumes proportional odds of outcomes between the sexes.

The adjusted ordered logistic regressions included age, education, and CCI (p<.001); there were no significant interactions between the covariates. Ordered logistic regression differed from un-ordered regarding the role of education. In the unordered regression more education was protective against 3MS as SCI and this association was not seen in the ordered regression. Sex was added to the adjusted ordered logistic regressions. The final model of ordered SCI included sex, age, and education (p<.001) and there were no significant interactions between the covariates. When SCI is assessed as an unordered categorical variable, older age is significantly associated with any clinical identification and the relative log odds was increased with the addition of a comorbid condition. Ordering SCI such that 3MS was below hospital record only in severity of impairment the protective effect of increased education for 3MS only was no longer seen, but the models were otherwise similar.

CHAPTER 5. AIM 2 RESULTS

5.1 Aim 2 Main Analyses and Manuscript

Latent Trajectories of Cognitive and Functional Recovery After Hip Fracture

5.1.1 Introduction

Older adults who fall and fracture their hip often experience sudden and sometimes permanent declines in independence and physical functioning.[8] Recovery responses vary depending on older adults' history, expectations, and circumstances.[125] While there is considerable variability in recovery of physical functioning, many patients remain impaired. In a nationally representative sample of hip fracture patients with data on self-reported Instrumental Activities of Daily Living (IADLs) and Activities of Daily Living (ADLs) prior to the fracture, less than half returned to pre-fracture functioning irrespective of pre-fracture function level.[79,126] Less than one-third returned to baseline function if they were 85+, had multiple comorbidities, or had dementia. Most research and clinical work have focused on restoring physical functional ability in older adults after hip fracture. While this is important, recovery following hip fracture has multiple distinct domains, including upper and lower extremity Activities of Daily Living (ADLs), Instrumental ADLs (IADLs), as well as cognition, that may vary in recovery patterns.[78]

Cognitive impairment after hip fracture is common. It has been estimated that 20% of patients have pre-fracture impairment and 35%-61% develop delirium during hospitalization after hip fracture.[6,7,78] Cognitive impairment, including delirium and

dementia, after hip fracture has been shown to negatively impact the rehabilitation and subsequent functional recovery process.[127–129] To date, research has focused on cognitive impairment after hip fracture as a risk factor for other outcomes like nursing home placement,[123] functional recovery,[117,128–131] and secondary fracture[132] or as a long-term risk for subsequent dementia. Prior work on functional improvement after hip fracture has used dichotomized cognitive groups (usually from baseline) or baseline cognitive means as predictors of function.[117,133] Few studies have considered cognition over time as part of the longitudinal recovery process. Beishuizen et al. (2017), identified three distinct trajectories of cognitive recovery: improvement, stable, and rapid decline in 302 hip fracture patients up to one-year after fracture using the Mini Mental State Examination (MMSE) measured at hospital admission, discharge, 3 months, and 12 months.[131] However, different domains of cognition may recover at a different pace or demonstrate varying patterns over time and may have a distinct impact on physical functioning.

Magaziner et al. (2000) illustrated that the recovery process for different domains (including functional and cognitive) occurs at varied rates over the year after hip fracture, with global cognitive recovery peaking at 3 months post-fracture, but functional recovery happening later.[78] However, this work did not model the impact of joint patterns of recovery across cognitive and functional domains. We hypothesized that as people recover functional ability after hip fracture, recovery of cognition is happening at the same time (or slightly prior) and that each impacts the recovery of the other. However, there is little to no work available on the joint recovery patterns of functional and cognitive recovery after hip fracture.

To better understand patterns of recovery after hip fracture, this study utilized group-based trajectory modeling (GBTM) to identify patterns of functional and cognitive recovery and determine the group membership characteristics associated with distinct trajectory groups. Additionally, we considered functional trajectories and cognitive trajectories as joint occurrences and examined the relationship between co-occurring recovery in one domain with that of the other.

5.1.2 Methods

5.1.2.1 Study Design and Sample

This is a secondary analysis of data from the Baltimore Hip Studies 7th Cohort (BHS7; 2006-2011), described in Orwig et al, 2018.[93] Participants were age 65 and older living in the community with a surgical fixation for a non-pathological hip fracture who were enrolled (consent provided by self or proxy) within 15 days of admission. Participants could not be bed bound in the 6 months prior to fracture or weigh over 300 pounds, but no other strict functional inclusion/exclusion criteria were used for enrollment. BHS7 is a unique cohort as enrollment of females was frequency matched to males at eight study hospitals on timing of fracture within each hospital resulting in an almost equal distribution by patient sex (males=168, females =171). The BHS7 study was approved by the University of Maryland Baltimore Institutional Review Board (IRB) and participating hospitals. Proxy information on baseline characteristics and functional outcomes was provided for participants scoring ≤ 36 on the Modified Mini-Mental State Examination (3MS).[93] Participants were followed for 12 months after enrollment with

69

measures administered at baseline, and at 2, 6, and 12 months including observed

mortality within the study period.

5.1.2.2 Measures

Baseline cognitive testing was performed within 22 days of admission for hip

fracture. Modified Mini Mental State Examination (3MS) and Hooper Visual

Organization Task (HVOT) measures were collected at all time points.

Modified Mini-Mental State Examination (scoring range 0-100) tests

working memory, attention, verbal recall and fluency, reasoning, and judgement

among other constructs.[62,111] 3MS scores have been shown to be predictive of

functional outcomes.[62,134] Higher scores are indicative of better performance and

scores ≤78 have been accepted as indicative of cognitive impairment.[131] 3MS cut

points as high as 95 have been identified for mild cognitive impairment (MCI).[63]

Hooper Visual Organization Task (0-30)[103], higher scores indicate better

performance and scores ≤19 are considered cognitively impaired.[112,135,136] HVOT

scores are related to visual-spatial abilities which have been shown to be related

walking function and fall avoidance.[113]

Physical functioning was measured using the *Lower Extremity Physical*

Activities of Daily Living (LPADLs; 0-12) which was derived from a modified

Functional Status Index and administered at all four timepoints to capture self-

report of lower extremity physical function.[95] The baseline assessment asks

about function in the week prior to the hip fracture. Higher scores mean more

disability.

Risk factors considered for posterior probability of group membership included patient sex, age, race, years of education, medical record indication of dementia and/or delirium, American Society of Anesthesiology (ASA) Physical Status Rating (1-4), Charlson Comorbidity Index (-1 if dementia was positive as it was captured in a separate measure; CCI), body mass index (BMI), fracture type (intertrochanteric, vs. femoral neck, other including trochanteric), surgery type (fixation, vs arthroplasty or other), length of surgery (minutes), length of hospital stay (days), days to initiation of physical therapy, and number of physical therapy sessions.

Source of Cognitive Impairment Identification (SCI) was also included as a risk factor of for LPADL trajectory groups. SCI in this population is detailed in Aim 1 Chapter 4. SCI comprised four mutually exclusive categories describing diagnosed versus undiagnosed cognitive impairment, such that groups were: 1) baseline medical record abstraction identified Alzheimer's disease or related dementia (ADRD) or delirium, 2) 3MS-identified cognitive impairment, 3) both sources, or 4) neither source identified cognitive impairment.

5.1.2.3 Analysis

Descriptive statistics of all outcome measures, study sample, and risk factors were performed preliminary to the trajectory analysis. Model optimization utilized techniques described in Andruff et al. (2009).[137] Model selection was accomplished comparing the Bayesian Information Criterion (BIC), estimated log Bayes factor, and estimated group proportions (≥5%) for various models. The estimated log Bayes factor can be approximated as 2*[(BIC more complex model) – (BIC simpler model)]. A log Bayes

factor can be categorized as weak (0-2), moderate (2-6), strong (6-10), or very strong (>10) evidence for the more complex model. First the cubic censored normal unadjusted model for a single trajectory was performed for each outcome. Then the number of trajectory groups was increased sequentially until the BIC of a more complex model (more groups) was smaller than that of a simpler model but greater than 10, the log Bayes factors was not sufficient, and/or the estimated group membership was less than 5% of the total sample.

Prior to joint modeling, outcome measures were optimized individually. Risk factors modeled for association with group membership were included after the optimum model was derived. Then each cognitive measure was jointly modeled with LPADL to examine the conditional probability of group membership in cognitive recovery given functional recovery group membership. Analyses were performing using Proc Traj in SAS, developed by B.L. Jones.[115,138] The entire sample of 339 participants were eligible for analysis. Participants needed at least 2 responses to a measure to be included in the pool. As GBTM uses Bayesian methodology, the model accepts dropout by assuming the drop out is independent of the response.

5.1.3 Results

Participants mean age was 80.9 ± 7.8 years old, with a range of 65 to 99. The sample was majority white and had an average of 13 years of education (approximately high school graduate level). Other sample characteristics are described in Table 2.1.

Table 2.1 BHS7 (2006-2011) Sample Characteristics	
Demographics	**Mean (SD), N (%)**
Sex	
Female	167 (50.6)
Male	163 (49.4)
SCI	
3MS Only	42 (12.7)
Hospital Record Only	38 (11.5)
Both	31 (9.4)
No CI	219 (66.4)
Age (years)	80.93 (7.8)
Race	
White	291 (90.7)
Black/American Indian/Other	30 (9.3)
Education (years)	13.10 (3.4)
Clinical Information	
BMI	25.21 (5.03)
CCI	1.87 (1.7)
ASA Rating	
2	65 (19.7)
3	218 (66.1)
4	47 (14.2)
Site of Fracture	
Intertrochanteric	129 (39.1)
Femoral Neck	166 (50.3)
Other	35 (10.6)
Surgical Approach	
Fixation	180 (54.6)
Arthroplasty	139 (42.1)
Other	11 (3.3)
Length of Surgery (minutes)	84.46 (44.43)
Length of Hospital Stay (days)	5.32 (2.62)
Days to Initiation of Physical Therapy	2.57 (1.23)
Number of Physical Therapy Sessions	3.41 (1.79)

Notes: BHS7=Baltimore Hip Studies 7th Cohort, SCI= Source of Cognitive Impairment, CI= Cognitive Impairment, BMI = Body Mass Index, CCI = Charlson Comorbidities Index, ASA Rating = American Society of Anesthesiology

5.1.3.1 Optimum Models and Risk Factors for Trajectory Group Membership

Model selection for each measure is described in supplemental online only Table S2.1. Group trajectories and group percentages are shown for individual outcomes in Figure 2.1 and means for those outcomes across timepoints are in Table 2.2. All models used a censored normal distribution.

Figure 2.1 Trajectory Groups for a) 3MS, b) HVOT, and c) LPADL

Figure 2.1a

4 GROUP TRAJECTORY OF HVOT OVER 12 MONTHS
UNADJUSTED CNORM MODEL
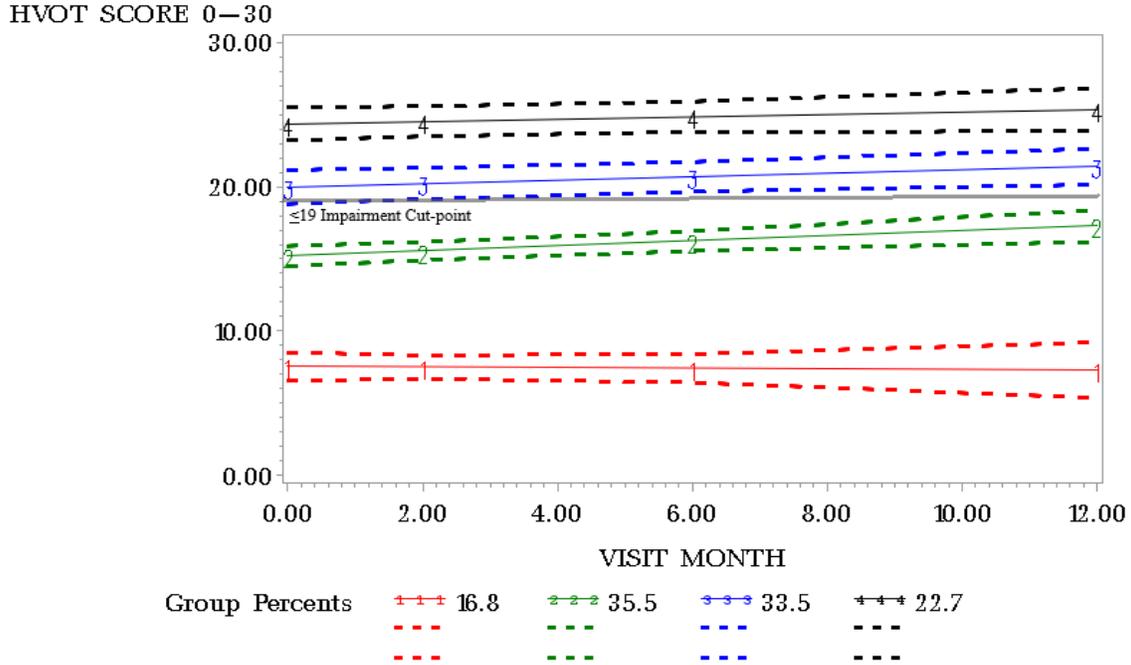
Figure 2.1b

4 GROUP TRAJECTORY OF LPADL 0—12 MONTHS
UNADJUSTED CNORM MODEL

Figure 2.1c

	Group %	Baseline	2 Month	6 Month	12 Month
LPADL (0-12)					
Total	100	2.59 (2.58)	7.47 (3.28)	5.56 (3.38)	5.28 (3.37)
Group 1	26.25	0.61 (0.90)	3.62 (2.07)	1.94 (1.41)	1.80 (1.21)
Group 2	53.10	2.83 (2.00)	7.54 (1.79)	5.38 (1.78)	5.24 (1.96)
Group 3	15.04	2.83 (2.00)	11.32 (0.93)	10.17 (1.44)	10.17 (1.44)
Group 4	5.60	9.05 (2.04)	12.00 (0.00)	11.23 (1.17)	11.78 (0.44)
3MS (0-100)					
Total	100	84.25 (16.49)	83.35 (17.74)	84.57 (17.62)	84.67 (17.34)
Group 1	6.7	37.00 (19.04)	29.14 (17.15)	28.7 (20.17)	17.0 (17.23)
Group 2	19.0	68.70 (11.01)	66.61 (9.93)	65.62 (11.05)	61.0 (12.03)
Group 3	74.3	91.05 (6.57)	90.65 (6.51)	91.07 (6.62)	91.06 (6.34)
HVOT (0-30)					
Total	100	17.68 (6.00)	18.15 (6.52)	19.04 (5.93)	20.27 (5.50)
Group 1	12.98	7.54 (3.45)	6.87 (4.15)	7.68 (4.14)	7.45 (3.36)
Group 2	29.79	15.08 (2.74)	15.05 (3.76)	16.33 (2.96)	17.62 (3.08)
Group 3	39.53	20.41 (2.02)	20.47 (2.60)	20.86 (2.53)	21.66 (2.47)
Group 4	17.70	24.91 (1.97)	25.07 (1.79)	25.41 (1.87)	25.75 (1.82)

Note: Lower Extremity Physical Activities of Daily Living (LPADL), Modified Mini-Mental State Examination (3MS), Hooper Visual Organization Task (HVOT). Totals are derived from means at each timepoint. Group means are derived from each time point in grouped by trajectory group membership

3MS*:* The mean 3MS score at baseline was 84.3 ± 16.7 and remained around this point through the 12 months of follow up. Based on 3MS cut point values, most of this sample has some degree of MCI. A mixed polynomial function (1,1,2) 3-group model of low scoring cognitive impairment (5.7%), moderate scoring mild cognitive impairment

(18.6%), and high scoring cognitively intact (74.5%) groups was the optimal model for 3MS based on selection criteria. All groups had little to no change in 3MS scores over time although slight declines were observed particularly in the low scoring cognitive impairment group. See Figure 1.a for trajectory patterns and relationship to <78 cognitive impairment cut point. For 3MS trajectory group membership probabilities, log odds of membership in Group 1 (impaired) were significantly increased for older, non-white, and less educated participants compared with Group 3 (high performing).

HVOT: Overall mean HVOT at baseline was 17.7 ± 6.0 and improved moderately over time, but this improvement did bring the overall mean above the 19-cut point for impairment by the end of the study period. A linear polynomial function (1,1,1,1) 4-group model of severely impaired (14.2%), moderately impaired (31.9%), mildly impaired (32.5%), and cognitively intact (21.4%) groups was the optimal model for HVOT based on selection criteria. All the group trajectories were well differentiated from baseline and remained mostly consistent with some improvement. See Figure 1.b for trajectory patterns and standard cognitive impairment cut point. Compared to Group 4 (the best performing group), members of Group 1 (severely impaired) were more likely to be older and less educated; log odd of being in Group 2 (moderately impaired) were increased for males, older, and non-white participant; Group 3 (mildly impaired) were more likely to have longer time until the initiation of physical therapy, more comorbid conditions, and less education.

LPADLs was optimized with a 4-group cubic polynomial function (3,3,3,3). The groups all experienced increased LPADL difficulties at 2 months post-fracture compared to reported pre-fracture levels and then subsequently recovered some function. Group 1

77

(27.1%) was very functionally independent at baseline and regained most of their LPADL functionality by 12 months. Group 2 (50.1%) had mild LPADL impairment at baseline and retained some new impairment at 12 months. Group 3 (17.1%) started with mild LPADL impairment at baseline that is almost indiscernible from Group 2. However, Group 3 had a dramatic increase in LPADL disability at 2 months and remained very impaired out to 12 months. Group 4 (5.7%) began very impaired and had almost no recovery from the 2-month spike in impairment. See Figure 1.c for trajectory groups and patterns. Risk factors associated with LPADL group membership in Group 4 (very dependent) and Group 2 (some dependence) included older age, higher ASA rating, greater BMI, and being identified by 3MS only for cognitive impairment (SCI) compared to Group 1 membership probability (functionally independent) (p<.05). Using the risk factors specified in this study there were no factors significantly associated with Group 3 (newly dependent) membership. Additional analysis using Group 3 as the referent showed that Group 2 (some dependance) had significantly longer surgeries.

5.1.3.2 <u>Joint Trajectory of LPADL and Cognitive Measures</u>

3MS and HVOT successfully jointly modeled with LPADL to produce group membership in cognitive groups, given membership in LPADL groups (conditional probabilities) as shown in Table 2.3.

Table 2.3 Conditional Probability of Cognitive Function Trajectory in 3MS and HVOT Given LPADL Group Membership

	LPADL Group			
	1	**2**	**3**	**4**
3MS Group	**Functionally Independent**	**Some Disability**	**Acquired Disability**	**Functionally Dependent**
1 (Impaired Cognition)	2.86	0.00	16.52[**]	34.03[*]
2 (Mild Cognitive Impaired)	5.62	15.47[**]	42.76[***]	30.78[**]
3 (Cognitively Intact)	91.52[***]	84.53[***]	40.71[***]	35.19[**]
HVOT Group				
1 (Severe Impairment)	4.31	14.59[*]	20.87[*]	40.67[**]
2 (Moderately Impaired)	0.00	0.00	40.28[**]	20.58
3 (Some Impairment)	63.02[***]	47.70[***]	19.75	21.86
4 (Intact Cognition)	32.66[***]	37.71[***]	19.10[*]	16.89

Note: P<.05*, p<.01 **, p<.001***

This directionality was selected because of the temporality of the data presented, such that LPADL asks about pre-fracture functioning at baseline while 3MS and HVOT test current cognitive status at baseline.

Most of the group members in LPADL Group 1 (functionally independent) were jointly in 3MS Group 3 (high performing) (91.52%, p<.0001). LPADL Group 2 membership had the most distinct joint membership with 3MS Groups, such that 0% were in 3MS Group 1 (impaired), 15.47% were in 3MS Group 2 (MCI), and 84.53% were in Group 3 (intact). Among the LPADL newly dependent group (Group 3), few were also in the 3MS impaired group (16.52%, p=.0082), while membership in the other groups was approximately equal (MCI 42.76 vs high performing 40.71; p<.0001). Conditional group membership probabilities for those in very dependent LPADL group (Group 4) were evenly distributed across the 3MS Groups.

5.1.4 Discussion

This study identified cognitive trajectories post hip fracture for four cognitive measures (3MS, HVOT) that found between 2-4 groups of recovery that were mainly determined by baseline performance. These groups were similar to Beishuizen's three cognitive recovery groups, but the trajectories were less well defined in their direction as many were linear or even constant.[61] Beishuizen saw three distinct patterns as well as groups: stable, improvement, and decline. In general, the three 3MS groups from this sample were stable with some decline over time. The low scoring cognitive impairment (Group 3) had more decline. This decline may be attributable to terminal decline[77] coupled with selective attrition.[139] The most cognitively impaired individuals are more likely to die during the course of the study leaving slightly less ill participants to provide information.(Chapter 6 Aim 3) Additionally, though they may not have died during the course of the study, those with the most advanced cognitive impairment may be declining more than the other groups as they approach death. Future work should explore mortality as a non-random source of attrition and time to death among the different trajectory groups to better understand the source of decline in the low scoring 3MS group.

The LPADL analyses revealed 4 groups and all experienced an initial increase in lower extremity ADL limitations from their pre-fracture ability and then had recovery in functioning over time. Two groups (Group 2 and 3) were very similar pre-fracture, but their recovery dramatically diverged, resulting in significant impairment in one group and only minor additional impairment in another. There were no risk factors identified that significantly predicted the probability in being in one group versus the other. Few

patients returned to their previous level of functioning by 12 months, which is consistent with the literature on functional recovery after hip fracture.[78,140]

In individual measure trajectories, the worst performing trajectory group was a smaller percentage of the sample for 3MS (5.3%), HVOT (13%), and LPADL (5.1%). The continuity in differences between groups starting from baseline suggests that seemingly more transient conditions, like delirium, may be symptomatic of larger problems that persist when exacerbated by the hip fracture experience.

Interpreting the joint trajectories of LPADL with 3MS and HVOT was difficult due to the acquired disability LPADL Group 3, that experienced a high degree of change in functional dependence. The acquired disability LPADL group was similar to other LPADL groups at different points over time; reducing the ability to differentiate the group membership characteristics. In joint trajectory analysis, 3MS had the best conditional probability of group membership identification with LPADLs, potentially because the 3MS groups themselves were well-differentiated and because of less missing data for 3MS. Moderate functional ability allowed for distinct identification of cognitive groups for HVOT and 3MS including low to high performance. Acquired disability LPADL Group 3, which had mild pre-fracture lower extremity ADL impairment but became significantly worse post fracture, was the most interesting group for future research.

This analysis illustrated the existence of distinct latent groups of recovery over time as seen in Table 2.2 and group trajectories displayed in Figures 1a-c. Mean overall performance summaries did not adequately capture the pattens of poor-performers. This was because the poor performing groups tended to be a smaller sub-section of the sample.

81

Overall mean 3MS performance scores, an average of 85 at each time point, did not adequately capture the 24% of the sample who never performed above 78 (the threshold for impairment). Similarly, in the other measures, regression to the mean would have hidden the extent of impairment in the sample. While this kind of observation could be differentiated using cut-points, it still may not have been clear that early poor performers never improved in cognition or functional outcomes without doing trajectory analyses. Each measure had at least 2 groups which performed below the standard cut-points for that measure.

Next steps should explore if the degree of cognitive or functional impairment among the trajectory groups, particularly those in the groups well below standard cut-points, is indicative of other negative outcomes. In some ways, this is highlighted in our joint trajectory analyses. For example, the 3MS cognitive impairment group were not in any of the low impairment ADL groups in the joint trajectory with LPADL.

Our work supports the finding from Beloosesky et al. (2012) that cognitive performance and functional recovery are inter-related.[117] Physical function improvements in LPADLs were lower in cognitively impaired patients. Pre-fracture functional levels largely determined the potential for functional recovery, even in patients with cognitive impairment. Many common risk factors for group membership in the worst performing cognitive and functional groups were consistent: older age, male sex, lower education, and non-white race. These factors are also among the most common factors adjusted for in models of recovery after hip fracture.

5.1.4.1 Strengths and Limitations

Key limitations to the findings from this study include mortality-related missingness, the older age of participants, and limited racial and geographic diversity which may limit generalizability of findings. This study was unable to estimate pre-fracture cognition. Thus future studies should include pre-fracture estimates of cognition. It is likely that death is a non-random source of truncation in this population and may be more prevalent in one trajectory than another. This work could not support such analyses due to missingness from other causes limiting the sample size available for a death-only missingness analysis. Though sex did not present as a significant risk factor in most measures, the balanced sample in a hip fracture population allowed for the consideration of sex without too much concern about sample size effects. The sample was older at 81 years of age. This is 4 years older than the national average age of hip fracture.[47] However, the average age of onset for dementia in the U.S is 83 years old.[141] Therefore we believe that participants older age is more reflective of cognitive change than in a potentially younger population of adults 65 and older.

This work illustrates that recovery is not best modeled by mean values alone, and even when using cut-points there are tiers of impairment which impact multiple domains of recovery. LPADL used self-report approximation but the value of pre-fracture data should not be understated. Estimates of pre-fracture functioning illuminated a group of hip fracture patients at critical need for intervention to prevent the development of new functional dependence. Future work, to the extent possible, should try to ascertain pre-fracture functioning as it provides a more meaningful picture of recovery after hip fracture especially to patients.

5.1.5 Conclusion

Using GBTM, distinct patterns of recovery in cognition and LPADLs among hip fracture patients were revealed. There was little to no overlap between the trajectories such that one group pattern did not cross another. In most cognitive measures, baseline performance was the most significant indicator of 12-month performance. This study highlights the importance of understanding baseline levels of cognition for hip fracture patients as it is likely to be a consistent challenge to other recovery efforts. Baseline performance alone was not enough to determine the pattern of functional recovery in LPADLs for over 65% of the sample.

The differentiation between those who begin with mild LPADL impairments (Groups 2 and 3) is a key focal point for future research. Patients with acquired disability in LPADLs (Group 3) had mild pre-fracture impairment but subsequently had marked increase and sustained LPADL impairment over 12 months. This contrasts with a group with similar levels pre-fracture that had better recovery over time. It is possible that this group might benefit from some focused therapy or intervention. This also highlights the importance of understanding pre-fracture function in hip fracture patients. LPADL limitation at 2 months is highly differentiated between these two initially similar groups. Without pre-fracture function, this divergence would not have been identified. Other functional measures should be assessed with cognitive recovery as function and cognition are inter-related. Future work should consider depression and biomarkers in the LPADL acquired disability group as a moderating factor on functional recovery that could inhibit their recovery participation.

Table S2.1 Online Only Table Model Selection			
Number of Groups	Order	Log bayes factor	Smallest group percentage
3MS			
1	3		100
2	33	633.56	10.15
3	333	272.56	5.89
4	3333	98.70	2.38
3	222	284.74	5.8
3	112	11.50	5.66
3	111	5.68	5.66
HVOT			
1	3		100
2	33	271.54	29.07
3	333	174.16	15.94
4	3333	14.56	14.58
5	33333	-12.54	14.06
4	2222	19.32	14.42
4	1111	21.4	14.24
4	1112	-5.46	14.24
LPADL			
1	3		100
2	33	244.9	24.58
3	333	95.96	19.74
4	3333	32.5	5.75
5	33333	-12.5	3.85
4	3332	-25.34	2.81
4	3313	-17.92	4.23
Note: 3MS: Modified Mini Mental State Examination, HVOT: Hooper Visual Organization Task, LPADL: Lower Extremity Physical Activities of Daily Living. Smallest group should not be less than 5, log bayes factor is approximately 2*(Complex BIC- Null BIC), Order refers to polynomial shape and after the group number is defined is modified.			

5.2 Aim 2 Supplementary Analysis and Results

There were many supplementary analyses done on measures not included in the main Aim 2 paper that are described below. The measures are described on page 34 in Section 3.3.3. The outcomes for cognitive and functional measures generally follow similar trends seen in the main paper. Trajectory group plots for all measures not in main analyses are in Supplemental Figure S2.1a-e, overall mean and group means over time for each measure are in Table S2.1

5.2.1 Trajectories for Cognitive Measures

3MS

The 3MS was optimized in a 3-group polynomial function (liner, liner, quadratic) with a censored normal distribution. Mean baseline 3MS was 84.3 (16.7), and this was still reflective of 12-month mean 3MS. The three 3MS groups patterns can be described as stable, while the trajectory itself is best described by its relative position to the cognitive cut scores: Cognitive Impairment (Group 1, 5.7%), Mild Cognitive Impairment (Group 2, 18.6%), and Cognitively Intact (Group 3, 74.5%). Each group was well differentiated in their scores. Group 1 (Cognitive Impairment) showed a pattern of consistently poor performance over time that was well below the standardized cut-point of 78 some notable decline after the 2-month follow-up. Group 2 (MCI) also had consistently poor performance with decline after the 2-month visit. Group 2 (MCI) mean scores were much closer to, although still below, the standardized CI cut point of ≤ 78.

Group 3 (Cognitively Intact) can be described as consistently high performing with little variation in performance overtime. This group's performance pattern was well above 78.

In 3MS, probability of membership in the Cognitive Impairment group (Group 1) groups (reference group 3, Cognitively Intact) was significantly associated with being non-white, having less education, and dementia/delirium in the hospital record. Factors significantly associated with the probability of membership in the MCI group (Group 2) were older age, black or non-white race, fewer years of education, and a positive hospital record of dementia/delirium.

Comparing characteristics for likelihood to be in the Cognitive Impairment versus MCI group (Group 1 vs Group 2); those who had more years of education and did not have a hospital record of dementia were significantly more likely to be in the mildly impaired group compared to the severely impaired group. The parameter estimate for the education difference was small, indicating that the difference in number of years was not large.

HVOT

The HVOT had four groups described in a linear polynomial function. The groups all remained distinct over time, but group 3 and 4 were very similar. The model could have been defined by a 5-group model but the distinction separated group 4 which was already high performing and provides little information as group 4 was cognitively intact using HVOT 19 cut-pint and group 5 was also intact. Group 1 (Severe Impairment) scored well below 19 at baseline and continued to perform poorly, with an increase in the spread of scores by 12 months with some improving and some worsening marginally.

87

Group 2 (Moderately Impaired) improves the most dramatically over time, but this is still only a small improvement and not enough of an improvement to overcome the threshold of 19. Group 3's (Some Impairment) recovery pattern is interesting in that the pattern itself closely mimics that of Group 2 (Moderately Impaired) and 4 (Intact Cognition), but with mild improvement over time, the scores hover on and around the CI cut point for HVOT. Group 4 (Intact Cognition) was the best performing group whose pattern over the 12-month study period was consistently high above the 19-cut point and whose baseline scores were also well above the overall mean.

Being older and having fewer years of education were associated with the probability of being in Group 1 (Severe Impairment) rather than Group 4 (Intact Cognition, reference). Older age alone was significantly associated with Group 2 (Moderately Impaired) membership. Membership in Group 3 (Some Impairment) was only significantly different as the number of days to PT initiation went up. More days to PT more likely to be in group 3(Some Impairment; Group 4 Intact Cognition, reference). The scores of Group 3 (Some Impairment) and 4 (Intact Cognition) were very close, this may make sense as an indicator of some additional level of impairment that is not substantial enough to warrant lifestyle differences.

Trails A

Overall mean performance of Trails A fluctuated over time improving some (m= 88.8$\pm$63.3 at baseline to 76.1$\pm$50.6 at 2 months), worsening (m= 82.9$\pm$65.4 at 6 months), and improving again (m= 76.4$\pm$60.4 at 12 months) with wide standard deviations for performance time. This unusual patten becomes clearer after the application of GBTM

where two very well differentiated patterns become evident. A mixed polynomial

function (1,3) 2-group model of passing speed (85.4%) and very slow (14.6%) groups

was the optimal model for Trails A based on selection criteria. The typical cut-off score

for poor performance on Trails A is 78 seconds. Passing Speed (Group 1) begins around

this threshold and always performed well improving over time to some degree. The Very

Slow group (Group 2) begins with very poor scores (over 2 minutes) improves after

baseline but then as more time goes on between observations substantially worsens. The

group trajectories were well differentiated throughout, and older age as well as a history

of delirium or dementia were significant risk factors for membership in Group 2. Those

with membership in the Very Slow group (Group 2) (reference group 1; 87.91%) were

more likely to be older and have a hospital record of dementia/delirium.
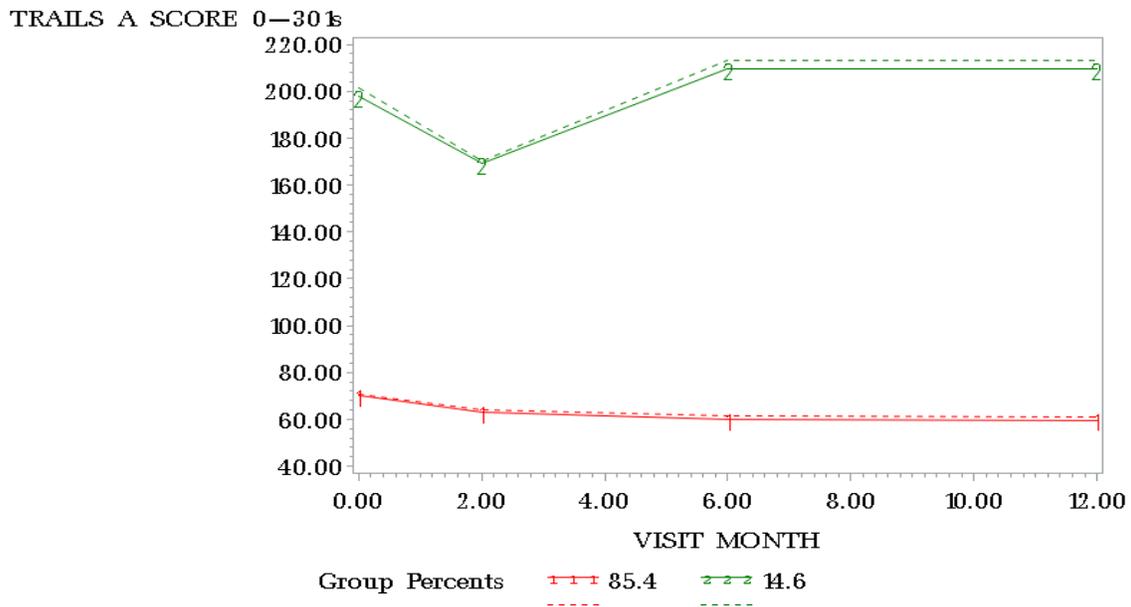
Figure S2.1a Supplemental Trajectory Groups; Trails A

Trails B

Overall performance of Trails B improved over time (from 209.45±84.2 at baseline to 176.0 ±84.5 at 12 months). A mixed polynomial function (1,2,2,1) 4-group model of fast (40.2%), Impaired and Improved (18.1%), Impaired and Worsened (17.4%), and Unable to Complete (24.2%) groups was the optimal model for Trails B based on selection criteria. When separated into groups, Group 1 (Passing Speed) and 4 (Unable to Complete) were consistent across time and Groups 2 (Impaired and Improved) and 3 (Impaired and Worsened) experienced marginal improvement, with Group 3 experiencing the most improvement. Unable to Complete (Group 4) never achieved the 273 second cut point with a mean of 300 seconds, indicating they could not complete the Trails B within 5 minutes at any time point. Male sex, older age, less education, non-white race, femoral neck fractures, shorter surgery time, longer hospital stays, and fewer PT sessions were significant risk factors for all Group's membership compared to membership in Group 1 (Passing Speed).
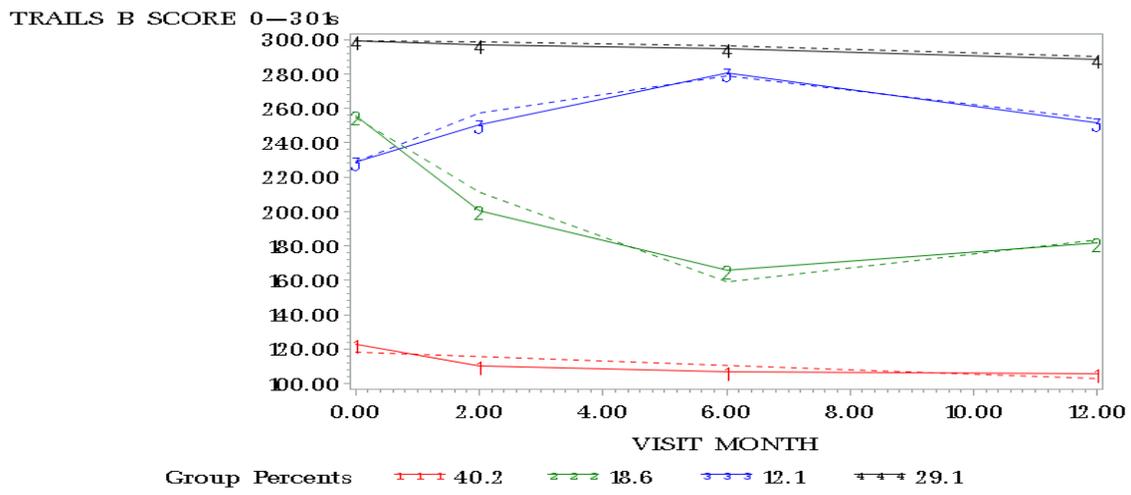
Figure S2.1b Supplemental Trajectory Groups; Trails B

90

	Group %	Baseline	2 Month	6 Month	12 Month
Table S2.2a Mean Performance by Trajectory Group for Supplemental Cognitive Measures Across Study Timepoints					
Trails A (0-301s)					
Total	100	88.78 (63.27)	76.10 (50.61)	82.91 (65.42)	76.43 (60.38)
Group 1	87.91	70.63 (34.77)	62.71 (30.10)	59.73 (26.66)	59.50 (31.43)
Group 2	12.09	200.49 (82.44)	172.67 (63.00)	209.91 (69.39)	207.63 (70.37)
Trails B (0-301s)					
Total	100	209.45 (84.16)	187.65 (87.79)	174.97 (86.26)	176.01 (84.51)
Group 1	52.51	124.35 (39.39)	110.78 (37.06)	106.65 (34.84)	106.29 (34.40)
Group 2	14.75	257.71 (40.50)	200.03 (54.07)	165.42 (32.91)	180.52 (52.15)
Group 3	7.96	224.88 (39.81)	253.29 (52.49)	284.06 (21.86)	254.14 (50.40)
Group 4	24.78	300.66 (1.60)	296.85 (18.10)	291.43 (29.56)	287.81 (23.40)

5.2.2 Trajectories for Functional Measures

LPADL

The LPADL baseline asks for an estimate of pre-fracture functioning, which differentiates it from the SPPB (as described in Section 3.3.3). A four-group cubic model best described the LPADL trajectory patterns. From the baseline estimate of pre-fracture ADL difficulty all groups experienced an increase in ADL disability at 2 months. The groups are best described by their overall level of ADL dependance and disability over time: Functionally independent (Group 1, 27.1%); Some Disability (Group 2, 50.1%); Acquired Disability (Group 3, 17.1%); and Functionally Dependent (Group 4; 5.7%). Mean LPADL performance was most closely reflected in Group 2 (Some Disability). While this group represents a majority of the sample, there are still important sub-groups that this analysis differentiated, particularly the Acquired Disability group (Group 3). SCI was considered for LPADL as a risk factor for group membership, as well as baseline 3MS and HVOT in separate models. Group 2 (Some Disability) was the largest group, but given the intersection with Group 3 (Acquired Disability) at baseline the Functionally

Independent group was used as the reference (Group 1, 27.1%). Compared to Group 1(Functionally Independent), factors significantly more likely to be in associated with members in Group 2 (Some Disability) include older age, higher ASA rating, more comorbid conditions (not including dementia), and higher BMI. There are not significant characteristics differentiation Group 1 (Functionally Independent) and Group 3 (Acquired Disability) membership. Characteristics more likely to be associated with the Functionally Dependent group (Group 4) include older age, higher ASA rating, grater BMI, shorter surgery time, and CI indicated on the 3MS only.

Group 3 (Acquired Disability) was the most clinically interesting group. They started with as much functional dependance as Group 2 (Some Disability), very mild and likely to still be living independently. However, by 2 months they sustained severe functional limitations and remained very impaired. Using this group as a reference group, the only significant difference for group membership characteristics was that the other groups were more likely to have had longer surgery times.

Supplemental trajectories of functional measures included the Yale (exercise and active minutes) and SPPB (balance, gait, chair stand). The SPPB groups were difficult to differentiate due to a large group being unable to ever perform the chair stand. SPPB was not included in the main analyses of GBTM due to the sub-categories very differentiated groups and lack of cohesion between total SPPB and floor effects seen with chair stand.

SPPB (Total, Balance, Gait Speed, Chair Stand)

Total SPPB was best defined in a 3-group quadratic polynomial model (2,2,2). Trajectory pattens and group percentages are shown in Figure S2.1c.

3 GROUP TRAJECTORY OF SPPB 2—12 MONTHS
UNADJUSTED CNORM MODEL
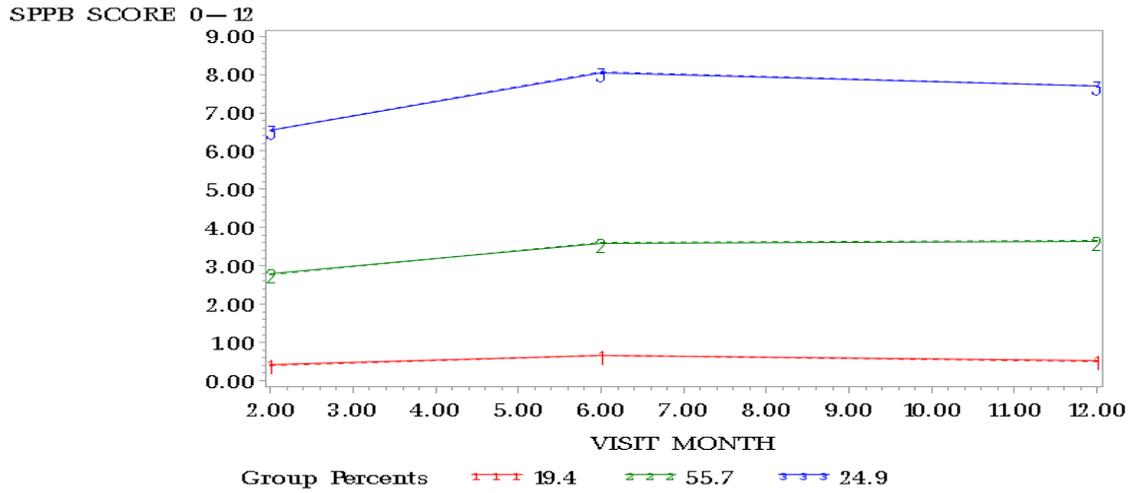
Figure S2.1c Supplemental Trajectory Groups; SPPB Total

Group 1 (Severe Functional Limitation, 19.4%), Group 2 (Very Limited, 55.7%), and

Group 3 (Mild Limitation, 24.9%) comprise the trajectories of SPPB recovery from 2 to

12 months. Group 1 (Severe Functional Limitation) is never able to perform well at any

timepoint and could be considered very disabled likely requiring a lot of human aid to

move around in the world. Group 2 (Very Limited) are still considered to be very

functionally limited but may be able to stand unassisted or walk across a room slowly

without human assistance. Group 3 (Mild Limitation) may still have compromised

balance, or struggle to stand from an armless chair, but are otherwise likely to move

around in the world without need for human help.

SPPB Balance was also best defined in a 3-group quadratic polynomial model

(2,2,2). Group 1 (No Balance, 39.6%), Group 2 (Some Balance, 73.3%), and Group 3

(Good Balance, 12.9%) comprise the trajectories of SPPB Balance recovery from 2 to 12

months. The Good Balance group (Group 3) did not necessarily demonstrate good

balance at 2 months, but from 6 months onward scored well. Compared to likelihood of

membership in Group 3 (Good Balance), members of Group 1 (No Balance) and Group 2 (Some Balance) were more likely to be older, have worse ASA ratings and greater BMIs. Those in Group 1 (No Balance) were also more likely to have longer hospital stays and fewer PT sessions.

SPPB Gait Speed was again best defined in a 3-group quadratic polynomial model (2,2,2). Group 1 (Immobile, 19.8%), Group 2 (Slow Gait, 49.2%), and Group 3 (Adequate Gait, 31.0%) comprise the trajectories of SPPB Gait recovery from 2 to 12 months. The gait trajectories were much more consistent than the balance trajectories with very tight confidence intervals. Almost 20% of the recovery patterns were unable to walk the 4 meters and never were able to do so out to 12 months. Almost 50% were able to walk the 4 meters and were slow but capable. This group did not experience enough improvement to comment on. The remaining 31% of a walking patterns from 2 to 12 months were satisfactory and would likely be able to walk across a small room with little difficulty.

	Group %	Baseline	2 Month	6 Month	12 Month
Table S2.2b Mean Performance by Trajectory Group for Supplemental Physical Function Measures Across Study Timepoints					
SPPB (0-12)					
Total	100		3.23 (2.65)	4.24 (2.98)	4.31 (2.89)
Group 1	19.38		0.28 (0.60)	0.52 (0.70)	0.29 (0.46)
Group 2	55.72		2.8 (1.52)	3.66 (1.66)	3.70 (1.74)
Group 3	24.90		6.72 (2.03)	8.28 (1.83)	7.85 (1.75)
SPPB: Balance (0-4)					
Total	100		1.61 (1.47)	2.00 (1.52)	1.95 (1.44)
Group 1	20.01		0.21 (0.45)	0.03 (0.16)	0.21 (0.50)
Group 2	63.14		1.63 (1.18)	2.12 (1.17)	1.94 (1.19)
Group 3	16.85		3.65 (0.70)	3.97 (0.18)	3.71 (0.60)
SPPB: Gait Speed (0-4)					
Total	100		1.25 (0.97)	1.27 (0.92)	1.34 (0.89)
Group 1	19.79		0.00	0.00	0.00
Group 2	49.23		0.99 (0.10)	1.00 (0.00)	1.00 (0.00)
Group 3	30.98		2.47 (0.66)	2.44 (0.66)	2.38 (0.61)
SPPB: Chair Stand (0-4)					
Total	100		0.31 (0.76)	0.59 (1.06)	0.62 (0.97)
Group 1	66.16		0.00	0.00	0.08 (0.28)
Group 2	33.84		1.01 (1.08)	1.84 (1.10)	1.51 (1.04)

The SPPB Total, SPPB Balance, and SPPB Gait sub-scale patterns looked similar. However, the balance subscale had wider confidence intervals particularly at 2 months and the percentage of group membership in the different patterns was not the same as Total SPPB and Gait.

Chair stand trajectories seem very differentiated until confidence intervals are included. With the inclusion of confidence intervals, 2-month chair stand is either fully successful or unattempted within the same trajectory group of poor future performance. This may be due to patients still being enrolled in rehabilitation at 2 months. Those who were able to the chair stand were more likely to be younger and less likely to have 3MS only SCI indication. Group 1 (Cannot Stand, 66.2%) and Group 2 (Slow to Stand, 33.8%)

comprise the chair stand trajectories. Most participants will never successfully complete the chair stand.

Yale: exercise hours/week; activity hours/week

Yale results were similar to expectations of the population in which a large percentage were not active, for activity or exercise and the small active group became less active over time. Both Yale scales were best described by a 2-group cubic polynomial model (3,3); resulting in one inactive and one active group. Group membership percentages and patterns are seen in Figures S2.1 d and e. Probability of membership in the Yale Exercise active group (Group 2) increased with lower ASA Rating and more years of education. Membership in the Yale Activity active group (Group 2) was more likely for females and those with lower ASA ratings.

Table S2.2c Mean Performance by Trajectory Group for Supplemental Physical Function Measures Across Study Timepoints						
		Group %	Baseline	2 Month	6 Month	12 Month
Yale Exercise (0-30; hrs/wk)						
Total		100	1.23 (2.84)	3.31 (3.70)	1.89 (2.38)	1.76 (2.89)
Group	1	94.91	0.87 (1.74)	3.12 (3.44)	1.60 (2.04)	1.29 (1.91)
	2	5.09	10.08 (7.05)	8.03 (5.44)	7.16 (2.24)	9.18 95.03)
Yale Activity (0-30; hrs/wk)						
Total		100	15.78 (12.90)	9.01 (10.07)	12.06 (11.12)	13.27 (13.52)
Group	1	82.08	11.80 (8.72)	6.15 (5.85)	8.10 (7.36)	9.22 (8.53)
	2	17.92	35.38 (11.83)	22.65 (14.00)	27.57 (9.72)	29.14 (17.40)
Note: Totals are derived from means at each timepoint. Group means are derived from each time point in grouped by trajectory group membership						

2 GROUP TRAJECTORY OF YALE Activity 0—12 MONTHS
UNADJUSTED CNORM MODEL
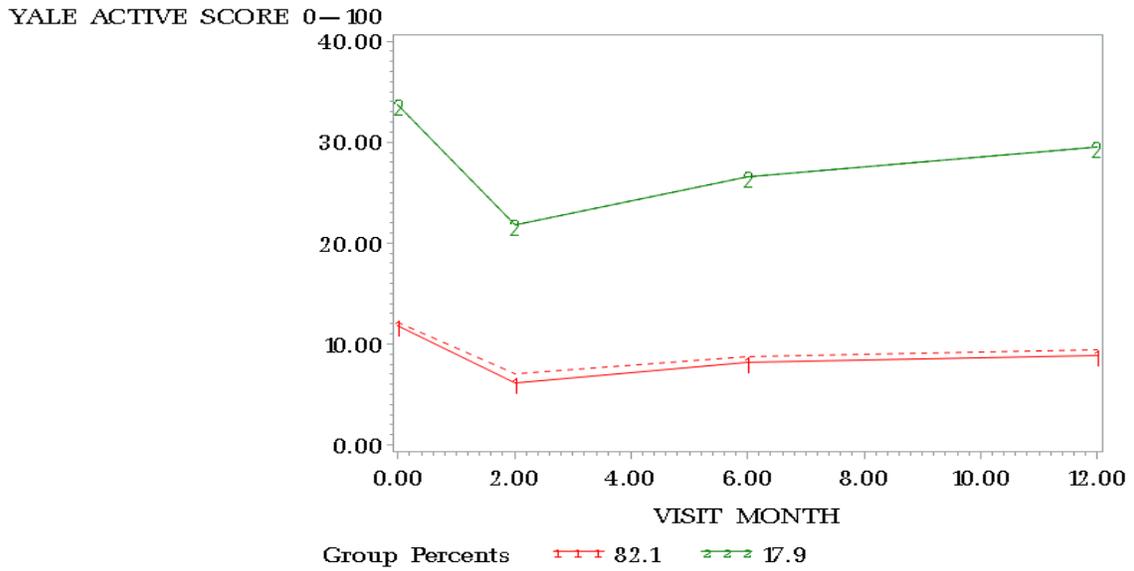
Figure S2.1d Supplemental Trajectory Groups; Yale Activity

2 GROUP TRAJECTORY OF YALE Exercise 0—12 MONTHS
UNADJUSTED CNORM MODEL
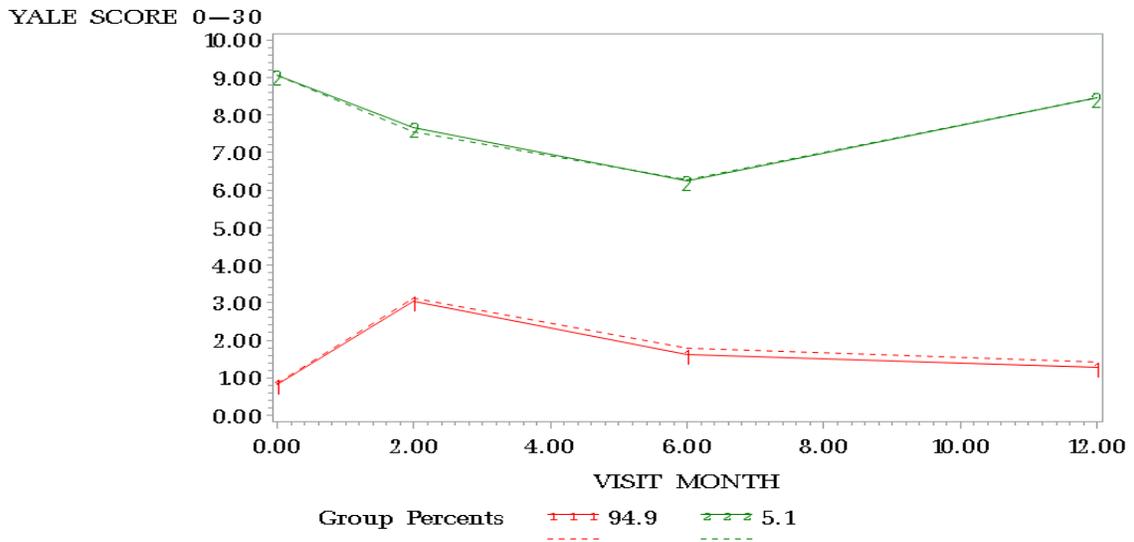
Figure S2.1e Supplemental Trajectory Groups; Yale Exercise

97

5.2.3 Joint Trajectories

Analytically joint trajectories were difficult to run for outcomes that were not well differentiated in their individual trajectories. In joint analysis of cognitive measures with LPADL trajectory patterns, Trails A and B did not successfully model. For Trails A, there was not enough differentiation to output joint models and for Trails B, 122 subjects had no trajectory data in one or more of the joint models. Very few of the conditional probabilities for HVOT membership given LPADL group membership were significant.

Only 3MS and HVOT successfully ran jointly with LPADL. These trajectories were modeled as cognitive trajectory give functional, the conditional probability of membership in a 3MS group given membership in a particular LPADL group, for temporality. Although both measures were taken at baseline, LPADL baseline asks about estimates of pre-fracture function while 3MS and HVOT measure cognition at time of administration. Therefore, when interpreting the applicability of joint models, it makes more sense to consider joint future membership based on knowledge that is potentially available pre-fracture. For example, prior to fracture the patient was functionally independent, then the joint trajectory predicts probability of cognitive recovery after fracture. Those who were functionally dependent in LPADL were equally distributed among the 3MS groups (approximately 30% in each 3MS trajectory group). Among the Acquired Disability LPADL group (LPADL Group 3) larger proportions were in the Cognitively Intact (3MS Group 1, 40.7%) and MCI group (3MS Group 2, 42.7%) compared to the Impaired Cognition group (3MS Group 3, 16.5%). However, all the joint groups were significant. Considering the LPDAL group with Some disability (LPADL Group 2), they were predominantly in the Cognitively Intact group (3MS Group 3,

84.5%) and the MCI group (3MS Group 2, 15.4%). None of the LPADL Some Disability group (LPADL Group 2) also was in the Impaired Cognition group (3MS Group 1). Among the Functionally Dependent group (LPADL Group 4, 7.4% single model), the only significant joint trajectory was with the Cognitively Intact group (3MS Group 4, 91.5% joint). This grouping suffers from the small sample proportions.

Among those likely to be Functionally Independent (LPADL Group 1), 63% were likely to be in HVOT Group 3 (Some Impairment) who began borderline impaired but marginally improved over the course of the study. A remaining 32% were in HVOT Group 4 (Intact Cognition), who were consistently high performing, leaving 4% non-significantly assigned across the groups. Among LPADL Group 2 (Some Disability), 14% were in HVOT Group 1 (Intact Cognition), 47% in HVOT Group 3 (Moderately Impaired) and 37% in HVOT Group 4 (Severe Impairment), 0% were identified in HVOT Group 2 (Moderately Impaired). Given membership in Acquired Disability LPADL (Group 3) membership was identified in HVOT Group 1 (Severe Impairment, 20%), Group 2 (Moderately Impaired 40%), and Group 4 (Intact Cognition 19%). Although 19% were identified in HVOT Group 3 (Some Impairment), this was not a significant conditional probability. LPADL Group 4 (Functionally Dependent), the most functionally limited group, was only significantly likely to be in the HVOT group 1 (Severe Impairment, 40%), the most impaired group.

See Table S2.2 for other joint trajectories with SPPB and Yale and TMT. There were many modeling errors between the other measures that reduced the number of produced joint trajectories. Models either had convergence or floating-point errors making them unable to produce joint trajectories. 3MS with SPPB Balance, SPPB Chair

99

Stand, or Yale exercise. HVOT did not jointly model with SPPB Gait, SPPB Chair stand, or Yale Exercise; Trails A did not jointly model LPADL, SPPB Total, or Yale Activity. Trails B did not jointly model with LPADL, SPPB Balance, SPPB Gait, SPPB Chair Stand, or Yale exercise. Similar to the main analysis, when there was a clear temporality between the measures, the measure with pre-fracture information was used as the primary model (secondary|primary), otherwise if only one measure had baseline data that measure was the primary model, if both measures were taken at baseline the model least based on self-report was used. Thus, in all models with SPPB and it's sub-scales SPPB is the secondary model. In all cognitive models with Yale, Yale is the secondary model.

Given 3MS Cognitively Intact Trajectory group (3MS Group 3) 33% were also likely to be in SPPB Group 3 (Mild Limitation). This was the only joint trajectory that significantly predicted membership in this SPPB Group. Given 3MS Group 3 (Cognitively Intact), 55% were likely also Very Limited (SPPB Group 2). If in the Impaired Cognition group (3MS Group 1) the joint model could only significantly predict membership in the Severe Functional Limitation group (SPPB Group 1, 76%).

When jointly modeling 3MS and SPPB Gait, given Cognitively Intact (3MS Group 3) recovery patters 56% will also have Slow Gait (SPPB: Gait Group 2) and 31% will have Adequate Gait (SPPB: Gait Group 3). However, almost 12% will still be immobile (SPPB: Gait Group 1) despite being Cognitively Intact (3MS Group 3) throughout the study period. It stands to reason that if there is a trajectory of Impaired Cognition (3MS Group 1), 64% will also follow an Immobile trajectory (SPPB: Gait Group 1). In this pairing, 31% will have slow gait. A similar joint pairing are seen among those with MCI (3MS Group 2) however the proportion in each is closer (43% Immobile

100

vs. 51% Slow Gait). The inability of being Cognitively Intact (3MS Group 3) to preclude from immobility is a concerning result from this set of analyses.

In the joint trajectory of 3MS and Yale Activity, 90% or more are likely to be Inactive (Yale Activity Group 1) given any impairment (3MS Group 1 or 2). Given Intact Cognition (3MS Group 3) 73.41% were also Inactive (Yale Activity Group 1), and 26% were Active (Yale Active Group 2). Even though there are more cognitively intact in the Inactive (Yale Activity Group 1), they were the only group to also comprise the Active (Yale Activity Group 2). This may be due to the wide spread in group proportions in Yale Activity.

Table S2.3a Conditional Probability of Functional Recovery Given Cognitive Function Trajectory (3MS) Group Membership			
SPPB Group			
	1	**2**	**3**
3MS Group	**Severe Functional Limitation**	**Very Limited**	**Mild Limitation**
1 (Impaired Cognition)	76.23***	23.77	0.00
2 (MCI)	43.25***	56.74***	0.00
3 (Cognitively Intact)	11.23**	55.70***	33.07***
SPPB Gait			
3MS Group	**1**	**2**	**3**
	Immobile	**Slow Gait**	**Adequate Gait**
1 (Impaired Cognition)	64.78***	31.26*	3.96
2 (MCI)	43.71***	51.39***	4.91
3 (Intact cognition)	11.83***	56.62***	31.55***
YALE Activity			
3MS Group	**1**	**2**	
	Inactive	**Active**	
1 (Impaired Cognition)	90.99***	9.00	
2 (MCI)	92.16***	7.84	
3 (Intact cognition)	73.41***	26.59***	
MCI= Mild cognitive impairment, SPPB= Short Physical Performance Battery, 3MS= Modified Mini Mental State Examination. 3MS and: SPPB Balance, SPPB Chair Stand, YALE exercise had convergence/modeling errors. Unable to produce joint trajectories. Rows are primary models and columns are secondary models. P<.05*, p<.01 **, p<.001***			

Unlike in 3MS, the extreme HVOT performance groups were not significantly related to membership in the opposing functional trajectories. For example, in the Severe Impairment Group (HVOT Group 1), 54% were also in the Sever Functional Limitation group (SPPB Group 1), and 45% were Very Limited (SPPB Group 2); but there was not a significant proportion also in the Mild Limitation group (SPPB Group 3). Conversely, among those with a pattern of Intact Cognition (HVOT Group 4) 55% were Very Limited (SPPB Group 2) and 37% were in the Mild Limitation group (SPPB Group 3); but there was not a significantly predicted proportion in the Severe Functional Limitation group (SPPB Group 1). HVOT Group 3 (Some Impairment) had the same patterns as the Intact Cognition group (HVOT Group 4) though the proportions were less favorable to Mild Limitation (SPPB Group 3). Interestingly, Moderately Impaired (HVOT Group 2) patterns were predicted to be in the Severe Functional Limitation group (SPPB Group 1, 54%) and the Mild Limitation Group (SPPB Group 1, 31%), but were not significantly likely to also be in the middle Very Limited group (SPPB Group 2). Other HVOT joint trajectories can be seen in Table S2.3b.

Table S2.3b Conditional Probability of Cognitive Function Trajectory (HVOT) Given Functional Recovery Group Membership

	SPPB Group		
	1	**2**	**3**
HVOT Group	**Severe Functional Limitation**	**Very Limited**	**Mild Limitation**
1 (Severe Impairment)	54.94***	45.06**	0.00
2 (Moderately Impaired)	52.56**	15.85	31.58***
3 (Some Impairment)	3.58	70.93***	25.50**
4 (Intact cognition)	6.86	55.15***	37.99***
	SPPB Balance		
HVOT Group	**1**	**2**	**3**
	No Balance	**Some Balance**	**Good Balance**
1 (Severe Impairment)	39.57**	60.43***	0.00
2 (Moderately Impaired)	51.36**	26.93	21.71
3 (Some Impairment)	3.60	76.24***	20.16*
4 (Intact cognition)	7.89	78.20***	13.91
	YALE Activity		
	1	**2**	
HVOT Group	**Inactive**	**Active**	
1 (Severe Impairment)	88.42***	11.58	
2 (Moderately Impaired)	89.29***	10.71*	
3 (Some Impairment)	70.71***	29.29***	
4 (Intact cognition)	53.24**	46.76**	

Note: SPPB= Short Physical Performance Battery, HVOT= Hooper Visual Organization Task. HVOT and: SPPB Gait, SPPB Chair stand, YALE Exercise; had convergence/modeling errors. Unable to produce joint trajectories. Rows are primary models and columns are secondary models. P<.05*, p<.01 **, p<.001***

Interesting joint trajectories of Trails A were between Trails A and SPPB Gait Speed. Trails A measures processing speed and Gait Speed measures walking speed which requires a lot of simultaneous mental processes. Among the Trails A group who were Very Slow (Group 2), none had Adequate Gait (SPPB: Gait Group 3) speed patterns, 57% had slow walking speed and 42% were Immobile (SPPB: Gait Group 1). From the group with Passing Speed (Trails A Group 1) at all time points, 33% were in Adequate Gait (SPPB: Gait 3) and 54% were in Slow Gait (SPPB: Gait 2). Only 11%

were Immobile (SPPB: Gait Group 1). This may be highlighting some interplay between the different types of processing speed.

From Trails B there are a few join trajectories of note, particularly between Trails B and Yale Activity. Among those Unable to Complete (Trails B Group 4) 100.00 were Inactive (Yale Activity Group 1). However even among those with Passing Speed (Trails B Group 1), 60% were Inactive (Yale Activity Group 1) and 39% were Active (Yale Activity Group 2). Among the Impaired and the Worsened (Trails B Group 3) 40% were in the Active group (Yale Activity Group 2), which is counter to what one would presume about the relationship between activity and cognition. Again, there was a wide distribution spread between the proportions of the sample in the Inactive vs Active Yale Activity Groups that may be contributing to some of these patterns.

Table S2.3c Conditional Probability of Cognitive Function Trajectory (Trails A and B) Given Functional Recovery Group Membership			
SPPB Group			
	1	**2**	**3**
Trails A Group	**Severe Functional Limitation**	**Very Limited**	**Mild Limitation**
1 (Passing Speed)	12.54**	71.72***	15.73**
2 (Very Slow)	57.37***	42.63***	0.00
SPPB Gait			
	1	**2**	**3**
Trails A Group	**Immobile**	**Slow Gait**	**Adequate Gait**
1 (Passing Speed)	11.76***	54.84***	33.40***
2 (Very Slow)	42.68***	57.32***	0.00
SPPB Chair Stand			
	1	**2**	
Trails A Group	**Cannot Stand**	**Improve to Stand**	
1 (Passing Speed)	57.29***	42.71***	
2 (Very Slow)	93.37***	6.63	
YALE Activity			
	1	**2**	
Trails A Group	**Inactive**	**Active**	
1 (Passing Speed)	76.40***	23.60***	
2 (Very Slow)	89.28***	10.72	
SPPB			
	1	**2**	**3**
Trails B Group	**Severe Functional Limitation**	**Very Limited**	**Mild Limitation**
1 (Passing Speed)	0.00	50.22***	49.78***
2 (Impaired and Improved)	0.00	99.99***	0.00
3 (Impaired and Worsened)	20.26**	48.23***	31.51***
4 (Unable to Complete)	45.97***	54.03***	0.00
YALE Activity			
	1	**2**	
Trails B Group	**Inactive**	**Active**	
1 (Passing Speed)	60.26***	39.73***	
2 (Impaired and Improved)	71.05***	28.95***	
3 (Impaired and Worsened)	59.02**	40.98***	
4 (Unable to Complete)	100.00***	0.00	

Note: SPPB= Short Physical Performance Battery. Trails A and: LPADL, SPPB Total, Yale Activity, Trails B and: LPADL, SPPB Balance, SPPB Gait, SPPB Chair Stand, Yale exercise had convergence/modeling errors. Unable to produce joint trajectories. Rows are primary models and columns are secondary models. P<.05*, p<.01 **, p<.001***

5.2.4 Death as a Non-random Source of Truncation in Groups

Proc Traj requires at least 2 time points for analysis. To conduct the drop out due to death analysis, only missingness due to death could be maintained. Missingness for this analysis is displaying in Figure S2.2. Only 33 of the 339 participants had no missing data. All missing datapoints that were missing not due to death used last value carried forward replacement for assessment of dropout due to death. Drop out probabilities by group for each main outcome are listed in Table S2.4. As hypothesized, the lowest performing trajectory groups had the highest dropout probability. For example, in Impaired Cognition 3MS group (3MS Group 1) there was a 16% probability of dropout due to death compared to 9% and 4% in the MCI (3MS Group 2) and Cognitively intact (3MS Group 1) respectively. An interesting derivation from this trend is among the LPADL groups. The LPADL Group 3 (Acquired Disability) who began with mild limitation then developed and maintained severe functional limitation had a 17% probability of drop out due to death. However, LPADL Group 4 (Functionally Dependent), which started with and maintained severe functional limitation only had a 3.2% chance of drop out due to death.

Table S2.4 Drop Out Probability by Trajectory Group				
	Trajectory Group			
	Group 1	**Group 2**	**Group 3**	**Group 4**
Cognitive Tests				
3MS	16.69%	9.46%	3.63%	
HVOT	8.72%	5.56%	5.17%	0.90%
Trails A	3.62%	8.74%		
Trails B	1.27%	6.47%	0.00%	9.96%
Physical Function Tests				
LPADL	4.39%	2.14%	16.85%	3.20%
YALE Activity	19.88%	11.82%		
YALE Exercise	2.69%	1.75%		
Note: SPPB and sub-scales would not run in drop out model.				

CHAPTER 6. AIM 3 RESULTS

6.1 Aim 3 Main Analyses and Manuscript

Associations of Male Sex and Cognitive Impairment on Time to Death, All-Cause Mortality, and Cause-Specific Mortality After Hip Fracture

6.1.1 Introduction

Recovery after hip fracture is a long process and outcomes are often poor.[81,142] Approximately 30% of all hip fracture patients will die within one year of their fracture.[30,31] In the last 30 years of hip fracture research, the 1-year mortality rate for hip fracture patients has changed very little.[90] The most common causes of death among hip fracture patients include circulatory diseases, cardiovascular disease, pneumonia, and Alzheimer's disease and related dementias (ADRD).[83,143]

Cognitive impairment (CI) predisposes an individual to increased hip fracture risk and also increases the patient's risk of hospital-acquired delirium.[18,66] There is an overall underdiagnosis of CI due to ADRD in the community, and of that due to delirium in hospital settings.[7,21,23] Research has shown that at hip-fracture rehabilitation admission and discharge, men have higher CI.[29] CI, such as ADRD and acute-onset delirium, have been shown to increase mortality risk in hip fracture patients.[12,13,144,145] Because ADRD is associated with poor outcomes, such as mortality, it has been recommended that additional attention be paid to patient cognitive status.[146] Yet, our previous work (Aim 1 Chapter 4) showed that following discharge from hip fracture, a sizeable number of

patients experience CI that was not noted in the hospital chart, suggesting the presence of undocumented delirium or pre-fracture CI. Males demonstrated increased odds of having concurrent clinical history of ADRD and active impairment observed through direct testing.

Although females make up 80-90% of all hip fracture research participants, males who fracture their hip tend to be sicker pre-fracture, with more comorbid conditions and higher American Society of Anesthesiologists (ASA) pre-operative risk compared to females.[14,48] They also have worse post-hip fracture outcomes.[46] In hip fracture populations, male sex plays an exacerbating role on mortality outcomes.[12,14] The existing research has shown that males are more likely to die within one year of hip fracture, and they die sooner than female counterparts.[147,148]

It is possible that higher mortality risk among males may be partially attributable to unrecognized CI. The objective of this study was to estimate the contribution of CI (both diagnosed and undiagnosed) to overall mortality and cause-specific mortality following hip-fracture and whether that contribution varies by patient sex. We hypothesized that unrecognized CI is a contributing factor to mortality following hip fracture and that patient sex will continue to contribute to mortality.

6.1.2 Methods

6.1.2.1 Study Design

This study was a secondary analysis of the Baltimore Hip Studies 7th Cohort (BHS7). The BHS7 was a longitudinal observational cohort study of community-dwelling geriatric hip fracture patients recruited from eight hospitals in the greater

Baltimore area in Maryland from 2006-2011. Date and cause of death were obtained from the National Death Index (NDI) 2006-2018. The BHS7 was approved by Institutional Review Boards (IRB) at the University of Maryland Baltimore and each recruitment hospital. This study was granted continued approval by the University of Maryland Baltimore IRB.

6.1.2.2 Sample

The BHS7 sample comprised 339 hip fracture patients (ICD-9 codes 820.xx) 65 years and older.[93] BHS7 frequency-matched the enrollment of females to males into the study, such that the sample was approximately 50% male (N=339; female =171, male =168). See Orwig et al. 2018 for full enrollment criteria.[93] Participants were consented and enrolled by trained research nurses within 15 days of admission for hip fracture repair surgery and received baseline assessments within 22 days of the admission. In home follow-up assessments were performed at 2, 6 and 12 months after hospital admission. An NDI search from 2006 through 2018 identified 266 (N=260 with baseline SCI) deceased participants an additional 56 participants who had died. The analytic sample size for this analysis was 330 (163 male, 167 female). The sample is further separated by mortality as of December 31, 2018; 260 died (147 male, 113 female).

6.1.2.3 Measurements

6.1.2.3.1 Cognitive Status

Cognitively impaired individuals were included in BHS7 and cognitive status was assessed using the Modified Mini Mental State Examination 3MS (score range 0-100)

within 22 days of hospital admission.[1,2] A score of ≤78 is considered cognitively impaired.[3] Participants scoring <36 on the 3MS had a proxy provide data on their behalf for interviews assessing functional status and other appropriate data.[93] Notation of ADRD and/or delirium as a post-operative complication in the medical record was used to indicate medical history positive for CI. Source of CI identification (SCI) is a categorical representation of CI determined by medical record abstraction and/or a 3MS score ≤78 at baseline. SCI is defined as being identified by 3MS only, Hospital record only, Both hospital record and 3MS, or No CI. SCI in BHS7 is described in Aim1 Chapter 4. 3MS only represents undiagnosed CI, as these patients would not be treated as cognitively impaired in standard clinical practice.

6.1.2.3.2 Death

Mortality was the key outcome of interest. Survival time was calculated as the difference between date of admission for hip fracture and death in months (assessed for all-cause mortality and for cause-specific mortality). Cause of death derived from NDI was listed in ICD-10 codes. Cognition-related cause of death (CR-COD) was defined by ICD-10-CM codes related to ADRD (G13, G18, G30, G31, G91, G94, F01, F03, F04, F05, F06, R41, R54) in any position derived from Taylor et al. (2009).[23,149] All other causes of death were grouped as 'other'.

6.1.2.3.3 Demographics and Health Information

Participant characteristics such as age (years, 65+); sex (male/female); race (White/non-white); education (years of education); body mass index (BMI); and the

Charlson Comorbidity Index (CCI) was derived from medical record abstraction or

patient interviews. Dementia was not included in this modified CCI count because it is

being used as an independent variable. Other variables abstracted include type of

fracture; surgical procedure; American Society of Anesthesiologists Physical Status

Rating (ASA, 1-4); length of surgery (minutes); length of stay (days); number of physical

therapy sessions; and time from hospital admission to initiation of physical therapy

(days).

6.1.2.4 Analyses

6.1.2.4.1 Descriptive

Descriptive analysis of the study sample to assess sex differences in participant

characteristics used chi-square (χ^2; Fisher's exact tests as applicable) for categorical

variables, and Student's t-test for continuous variables. ANOVA was used to assess

sample characteristic differences across SCI categories, with a Tukey correction.[150] Each

SCI category (binary) was assessed using χ^2 (Fisher's exact tests as applicable) for

significant differences by survivor status as of December 31, 2018, CR-COD, and

participant sex.

6.1.2.4.2 Time-to-Event

Cox proportional hazards models assessed the relationship between a sex by SCI

interaction (Sex|SCI) and time to a) all-cause mortality and b) CR-COD. A Sex|SCI

(reference: female, reference: No CI) model was assessed. Given no interaction effect;

main effects were assessed. The models were adjusted by additional covariates using

forward selection at p <0.2. These produced hazard ratios (HR) and Confidence Limits (CL) for time to a) all-cause mortality and b) CR-COD. Survival curves for Sex|SCI were produced using a lifetest. Sidak p-values, which are slightly less conservative than Bonferroni corrections, were used to adjust for multiple testing between the different levels of sex and SCI.

6.1.3 Results

6.1.3.1 Sample Characteristics

The study sample of 339 hip fracture patients (168 males, 171 female) had a mean age of 80.9 [Standard Deviation (SD) 7.9] years, a mean of 13.1 (SD 3.4) years of education, mean modified CCI (not including dementia) of 1.9 (1.7), and a mean BMI of 25.26 (5.1). The modal ASA Physical Status Rating was 3 for 223 (66%) patients. Participants had similar hospitalization experiences: mean length of surgery was 84.46 (44.43) minutes, mean hospital stay of 5.3 (2.6) days, physical therapy was initiated on average 2.6 (1.2) days after admission.

Sample characteristics by sex are identified in Table 3.1 and by SCI in Table 3.2. Males and females were not significantly different on any pre-surgery baseline characteristics, except that males had significantly higher modified CCI (p=0.0001) and ASA level IV (Patient has incapacitating disease that is a constant threat to life) ratings compared to females (36 (76.6%) vs. 11 (23.4%); p <.0001). Males started physical therapy slightly later than women (2.80 vs. 2.34 days, p=0.0009).

Table 3.1 Baseline Demographic and Clinical Characteristics and Mortality of BHS7 Sample by Sex				
	Total N=330	Male N=163	Female N=167	p-value
Age (years, 65+)	80.99 ± 7.79	80.57 ± 7.71	81.41 ± 7.88	0.33
Education (years, n=319)	13.10 ± 3.39	13.15 ± 3.75	13.06 ± 3.02	0.09
Charlson Comorbidity Index	1.87 ± 1.69	2.26 ± 1.77	1.49 ± 1.51	<.001
Body Mass Index	25.21 ± 5.03	25.52 ± 4.43	24.91 ± 5.56	0.27
Number of PT Sessions	3.41 ± 1.79	3.35 ± 1.56	3.46 ± 1.99	0.58
Length of Surgery (minutes)	84.46 ± 44.43	86.03 ± 44.93	82.93 ± 44.10	0.53
Admission to PT (days)	2.57 ± 1.23	2.80 ± 1.36	2.34 ± 1.03	<.001
Length of Hospital Stay (days)	5.32 ± 2.62	5.47 ± 2.47	5.17 ± 2.77	0.31
Admission to 3MS (days)	18.47 ± 49.64	15.79 ± 4.94	21.10 ± 10.46	0.33
Race				0.41
White	291 (90.65)	142 (89.31)	149 (91.98)	
Non-White, Mixed	30 (9.35)	17 (10.69)	13 (8.02)	
Site of Fracture				0.30
Intertrochanteric	129 (39.09)	69 (42.33)	60 (35.93)	
Femoral Neck	166 (50.30)	75 (46.01)	91 (54.49)	
Other	35 (10.61)	19 (11.66)	16 (9.58)	
Surgical Approach				0.19
Fixation	180 (54.55)	97 (59.51)	83 (49.70)	
Arthroplasty	139 (42.12)	61 (37.42)	78 (46.71)	
Other	11 (3.33)	5 (3.07)	6 (3.59)	
ASA Physical Status Rating				<.0001
2	65 (19.70)	20 (12.27)	45 (26.95)	
3	218 (66.06)	107 (65.64)	111 (66.47)	
4	47 (14.24)	36 (22.09)	11 (6.59)	
Mortality				
All Cause (n=330)	260 (78.79)	147 (56.54)	113 (43.46)	<.0001
CR-COD (n=260)	67 (25.87)	33 (49.25)	34 (50.75)	0.17
Time to Death				
All Cause (n=330)	46.91 (32.76)	41.13 (31.81)	54.42 (32.60)	0.001
CR-COD (n=260)	51.07 (33.33)	43.71 (31.87)	58.22 (33.61)	0.07

*Note: Physical Therapy (PT), Cognition-related cause of death (CR-COD), Alzheimer's Disease (AD), Modified Mini-Mental State Examination (3MS),*p-value is χ^2*Cochran, Pooled or Fisher's Exact as applicable, Charlson Comorbidity Index -1 if ADRD indicated in Medical Chart* ; Notation: Mean ± SD, N (%); % = column percent

SCI was available for 330 participants: 163(97.0%) males and 167 (97.7%) females. No CI was identified in 219 (66.4%) participants, identification by both hospital record and 3MS in 31 (9.39%) participants, identification by hospital record only in 42 (12.7%), and identification by 3MS only in 38 (11.5%). In unadjusted analyses significantly more females did not have CI [p=0.005; 123 (73.7%) female vs. 96 (58.9%) male] and significantly more males than females were identified by 3MS only [p=0.039; 27 (16.6%) male vs. 15 (9.0%) female]. There were not significant sex differences by hospital record only or both hospital record and 3MS.

Table 3.2 Sample Characteristics by SCI Category with Mortality				
	3MS Only N=42	Hospital Record N=38	Both N=31	No CI N=219	p-value
Age (years, 65+)	81.57 ± 8.23	83.29 ± 6.78	85.61 ± 5.78	79.84 ± 7.83	<.001
Education (years, n=319)	11.13 ± 4.06	14.00 ± 3.24	12.39 ± 3.57	13.41 ± 3.14	<.001
CCI	1.95 ± 1.72	2.42 ± 1.85	2.00 ± 1.44	1.75 ± 1.68	0.14
Body Mass Index	25.60 ± 5.30	24.83 ± 4.82	24.61 ± 5.04	25.30 ± 5.05	0.81
Number of PT Sessions	3.02 ± 1.63	3.84 ± 2.09	3.74 ± 2.98	3.37 ± 1.52	0.15
Length of Surgery (min)	88.79 ± 44.14	98.02 ± 45.37	73.72 ± 45.43	82.75 ± 43.87	0.11
Admission to PT (days)	2.90 ± 1.26	2.68 ± 1.23	3.19 ± 1.70	2.40 ± 1.11	<.01
Hospital Stay (days)	5.26 ± 2.07	6.37 ± 2.76	7.16 ± 5.24	4.89 ± 1.92	<.0001
Admission to 3MS (days)	15.38 ± 4.81	16.50 ± 4.40	16.71 ± 4.11	15.51 ± 5.29	0.45
Sex					0.02
Male	27 (16.56)	20 (12.27)	20 (12.27)	96 (58.9)	
Female	15 (8.98)	18 (10.78)	11 (6.59)	123 (73.65)	
Race					<0.01
White	30 (10.31)	37 (12.71)	28 (9.62)	196 (67.35)	
Non-white, mixed	10 (33.33)	1 (3.33)	3 (10.00)	16 (53.33)	

Table 3.2 Continued					
Site of Fracture					0.73
Intertrochanteric	17 (40.48)	13 (34.21)	15 (48.39)	84 (38.36)	
Femoral Neck	23 (54.76)	21 (55.26)	14 (45.16)	108 (49.32)	
Other	2 (4.76)	4 (10.53)	2 (6.45)	27 (12.33)	
Surgical Approach					<.0001
Fixation	21 (50.00)	16 (42.11)	20 (64.52)	123 (56.16)	
Arthroplasty	19 (45.24)	19 (50.00)	11 (35.48)	90 (41.10)	
Other	2 (4.76)	3 (7.89)	0 (0.00)	6 (2.74)	
ASA Rating					<0.01
2	4 (6.15)	4 (6.15)	3 (4.62)	54 (83.08)	
3	30 (13.76)	24 (11.01)	21 (9.63)	143 (65.60)	
4	8 (17.02)	10 (21.28)	7 (14.89)	22 (46.81)	
All-Cause Mortality	36 (85.71)	35 (92.10)	29 (93.52)	160 (73.06)	<0.01
CR-COD Mortality	15 (35.71)	10 (26.32)	19 (61.90)	23 (10.50)	<.0001
Time to Death (months)					
All Cause n=260	40.32 ± 32.28	44.78 ± 37.44	22.03 ± 22.32	53.36 ± 31.08	<.0001
CR-COD n=67	52.43 ± 27.91	63.69 ± 36.23	27.39 ± 23.56	64.26 ± 33.25	<0.01

Notes: Hospital chart includes medical record abstraction of diagnosis of Alzheimer Disease and Related Dementias and/or delirium as a post-operative complication, CI=Cognitive impairment, CCI= Charlson Comorbidity Index, ASA= American Society of Anesthesiologists 3MS= Modified Mini Mental State Examination, CR-COD = cognition-related cause of death. Total Sample = 330, Reported statistics are Mean±SD or N (%), %=row percent rounded to the tenth place; Fisher's exact used if cell size ≤ 5.

6.1.3.2 Mortality

Of 330 participants with baseline cognition information, there was a significant proportion of overall death n=260 (78.8%) in the sample. More males than females (p<.0001) had died as of December 31st, 2018 [(147 (90.2%) male, 113 (67.7%) female]. There were significantly more deaths among those with identified CI compared to No CI (p=.0028) described in Table 2.

In regards to cause-specific mortality, as of December 31st, 2018, of the 260 participants who died, 67 (25.8%) died from CR-COD: 48 from unspecified dementia

(F03), 11 with Alzheimer's disease (G30), and 13 from other specific causes. None of these were significantly different across participant sex. Proportion of CR-COD was not significantly different by patient sex [33 (19.6%) male, 34 (19.9%) female], nor were the types of CR-COD different by sex.

6.1.3.3 Time to Death

The mean time to death was 46.90 months (SD 32.76). Of those who died, the 25th-percentile survived up to 15.65 months (95% CI:11.60, 23.41), and the 75th-percentile survived 73.37 months (95% CI: 66.71, 77.75). Females' mean survival time (months) was significantly longer than males after hip fracture (54.42 ± 32.60 vs 41.13 ± 31.81, p=0.0047). The months to death for when SCI was identified by 3MS only were not significantly different from Hospital Record nor Both. Those identified by 3MS died significantly sooner than No CI (p=0.0317). The SCI Both group died significantly sooner than Hospital Record alone (p=0.0295). In SCI and sex models only Female: Both vs. No CI (p=0.0101), Female, No CI vs. Male, 3MS (p=0.0154), and Female, No CI vs. Male, Both (p=0.0052) were significantly different Figure 2a. shows time to death for all-cause mortality by patient sex and SCI.

The risk for mortality among males was greater than for females 1.43 (CI: 1.11, 1.83). Age, ASA physical status rating, and CCI were included in the adjusted model. Sex was significantly related to the risk of all-cause mortality (HR: 1.39; 95% CL: 1.08, 1.81). Identification by SCI Both had significantly increased risk of death compared to No CI (2.55; 95% CL 1.68, 3.89). The relationship was not significant for those identified by 3MS (HR: 1.39, 95% CL 0.97, 2.00) or Hospital Record (HR: 1.07; 95% CL 0.74,

1.54). See Figure 1 a and b for hazard of all-cause mortality and CR-COD. The

interaction of sex and SCI was not statistically significant.
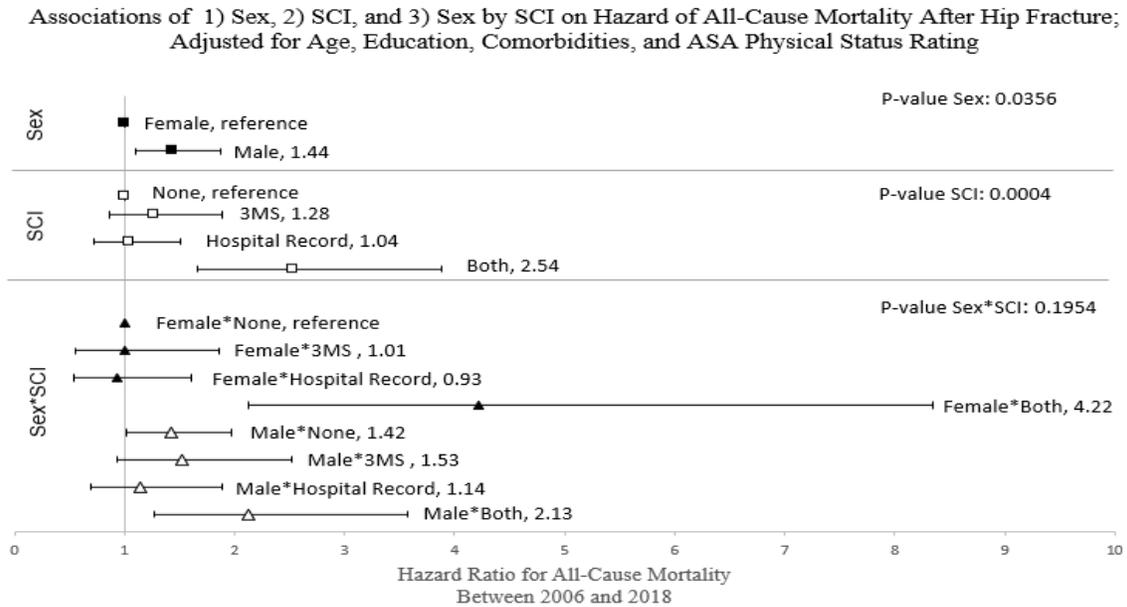
Figure 3.1a Associations of Patient Sex and SCI on Hazard of All-Cause Mortality

After Hip Fracture
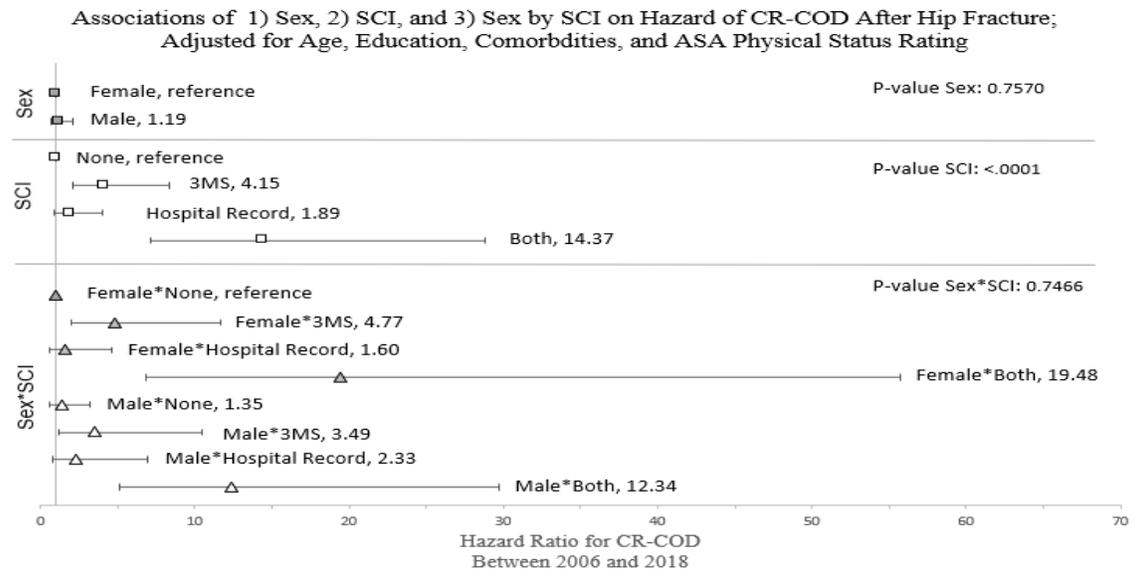
Figure 3.1b Associations of Patient Sex and SCI on Hazard of CR-COD Mortality

After Hip Fracture

118

Figure 2b. shows time to death for CR-COD by patient sex and SCI. The adjusted Cox model contained terms for age, ASA physical status rating, side of fracture, and length of hospital stay. Sex was not significantly related to risk of CR-COD (HR: 0.89; 0.51, 1.56). 3MS only (HR: 5.01; 95% CL: 2.55, 9.84) and Both (16.82; 95% CL: 8.06, 35.12) had significantly increased risk of earlier mortality by CR-COD compared to those with no identified CI.
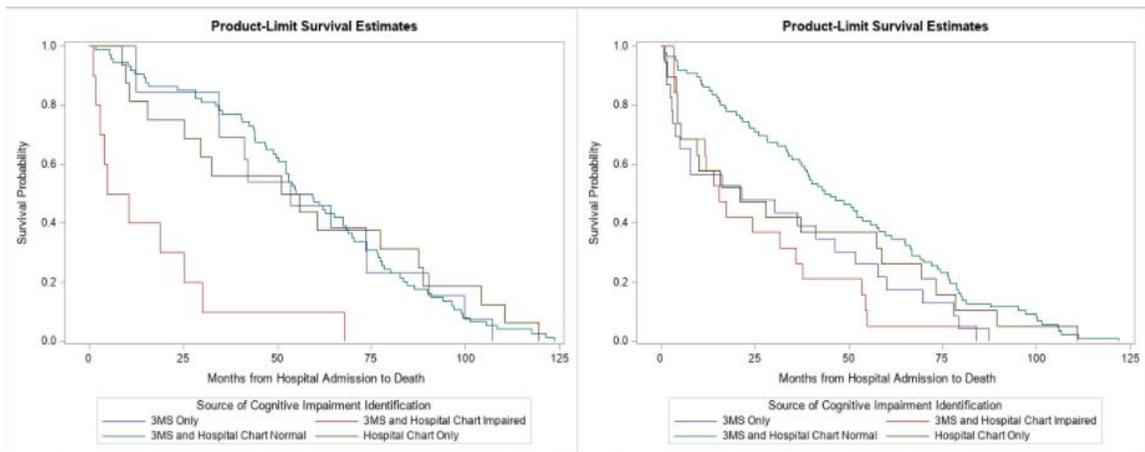
Figure 3.2a All-Cause Mortality Kaplan Meir Plot by Sex and SCI; Left: Female Right: Male
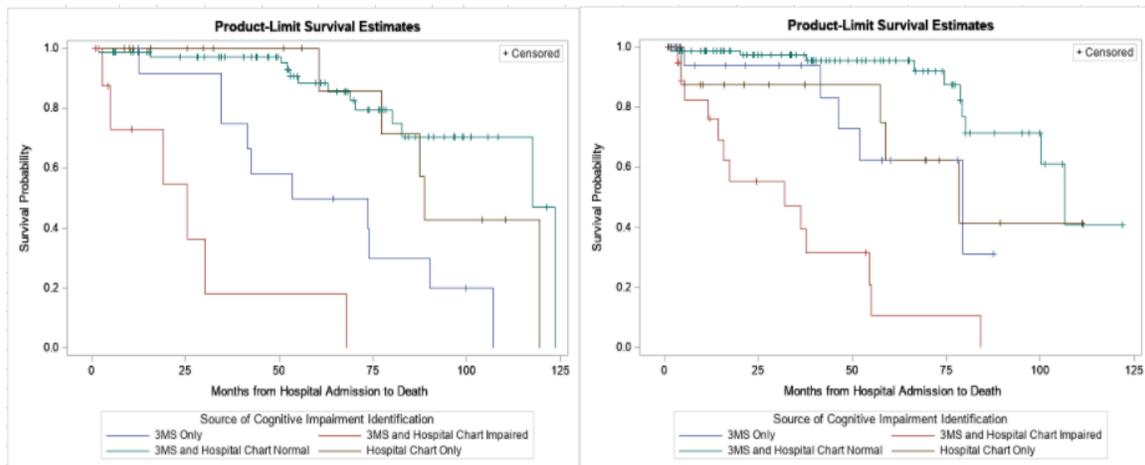
Figure 3.2b CR-COD Mortality Kaplan Meir Plot by Sex and SCI; Left: Female Right: Male

6.1.4 Discussion

Unique to this work is the identification of mortality risk according to the SCI. The SCI categories represent the concordance between cognitive testing within 22 days after hip fracture using the 3MS and any ADRD and/or delirium identified during the hip fracture hospitalization from medical record abstraction. Our previous work showed that a significant proportion of the hip fracture sample was clinically under-diagnosed for ADRD and/or delirium (12.7%). Clinically, the SCI groups Both (9.4%) and Hospital Record (11.5%) are identified ADRD cases. Although neither 3MS only nor Hospital Record only identification were significantly associated with mortality after controlling for age, education, CCI, and ASA rating, these two groups had similar survival times as hypothesized. This suggests that while clinically under recognized, the 3MS only group has similarly poor outcomes to those with previously identified CI.

Consistent with previous research findings, males who experienced a hip fracture had 4.39 times greater odds of all-cause mortality than females with a hip fracture.[147] However, the associations of sex and all-cause mortality in our study sample were stronger than those found in a multi-national meta-analysis of hip fracture and mortality.[147] The lack of Hospital Record only differences (those who have a history of dementia but have normal to mild impairment on testing) between males and females across forms of SCI may suggest that: 1) there was either unmeasured bias regressing outcomes to the null or 2) that the prevalence of CI in the two sexes are associated with truly equitable mortality risk. The latter is unlikely given the known associations between cognition and mortality in hip fracture[83,144,145] and the exacerbating effect of male sex on

survival time after hip fracture. Therefore, future work should continue to explore potential sources of bias in diagnosis between males and females. The addition of direct testing in BHS7 revealed that more males have active cognitive impairment, thus something is missing from the CI documentation process. This is additionally important given the increased mortality risk associated with having CI identified.

These analyses revealed that there was not a significant interaction between sex and SCI on: 1) all-cause or 2) CR-COD mortality hazard. However, male sex and identification of cognitive impairment by both 3MS and hospital record together were associated with increased risk of all-cause mortality. Underdiagnosis of CI (3MS only) was not associated with increased all-cause mortality risk compared to no identification of impairment. The underdiagnosed group are clinically classified as the No CI group, which would not support additional cognitive testing. However, with the addition of 3MS testing a 'Both' group was revealed, and this group would clinically be recognized as the hospital record only group. The strong association between SCI by both 3MS and hospital record together and all-cause mortality risk indicates a clinical rational to implement additional cognitive testing after hip fracture to identify extremely vulnerable individuals who had either more severe dementia or persistent delirium.

There were not significant sex differences in CR-COD hazard, but SCI by 3MS only or by both 3MS and hospital record were significantly associated with increased CR-COD hazard. Any positive 3MS indication of CI, or actively demonstrating impairment after hip fracture, was associated with increased risk of CR-COD. This finding in addition with findings from all-cause mortality support the use of additional

121

cognitive testing after hip fracture to identify vulnerable sub-groups who may have been misclassified as unimpaired.

This suggests that a hospital chart indication of dementia and/or delirium did not necessarily capture the severity of CI or active symptomology. Those identified by 3MS are actively presenting with CI at the time of testing after hip fracture. Given that time to death was similar for participants with only a chart history and those with impairment only during direct testing after fracture, there may not be a temporal relationship between CI symptomology and mortality risk. This similarity does however highlight the importance of identifying the misclassified 3MS only group, those only recognized as impaired through direct cognitive testing, as they would clinically be treated as those without a CI.

Participants who were not identified as having CI during baseline still had records of CR-COD in their cause-of death. Among those who died of cause-specific mortality 34% had no indication of baseline CI. Those with any indication of CI had greater odds of CR-COD than those without. Still, among those without baseline CI, 23 (10.5%) died of CR-COD. Survival time in the 3MS only group was significantly shorter compared to those with no CI. Because patients identified by either source experienced significantly shorter survival times than patients with no impairment, it appears that any CI is associated with earlier cause-specific mortality. Thus, undiagnosed CI contributes to increased cognition-related mortality, and this effect is similar between males and females with hip fracture.

There may be compounding effects of a history of ADRD and active CI, as those identified by both sources had shortest survival times after fracture that were significantly

122

shorter than those who were not actively displaying impaired cognition despite a history of ADRD. Cognitive testing, such as the 3MS, may be useful in identifying persistent impairment, such as delirium superimposed on dementia. This persisting impairment could be a factor for further assessment as those whose CI in hospital persisted through 22 days were most at risk for death.

6.1.4.1 Strengths & Limitations

This study is one of the first to examine CR-COD among a U.S. hip fracture population and the impact of misclassification of CI by patient sex. The strengths of this study include its balanced recruitment of males and females in a population whose research sample is typically over-representative of females despite males suffering worse outcomes. Additionally, this study utilized over 12 years of follow-up for mortality making it among the longest observational study for post-hip fracture survival. While the balanced sample is a plus, the overall enrollment size was not large and thus there are limited number of events of CR-COD. Future studies could use a nationally representative sample with multiple years of follow-up data to capture more CR-COD events and generalize to a racially and geographically diverse sample. This study did not capture time varying cognitive status, which is likely to deteriorate before death as described in terminal decline. Additionally, more cases may have been recorded after the 12-month study period, but this study was unable to capture updated medical record information.

6.1.5 Conclusions

Underdiagnosed CI (3MS only) increased participants' risk of CR-COD but not all-cause mortality. Clinically documented ADRD in concert with direct testing revealed a subset of clinically identified patients who were more likely to die, die of CR-COD, and die sooner across both sexes. Direct testing of cognitive status after hip fracture revealed at risk populations including those who were misclassified and among the clinically documented. This works supports implementation of cognitive testing among hip fracture patients within 22 days of fracture to predict risk of mortality and direct clinician attention.

6.2 Aim 3 Supplementary Analysis and Results

Interactions of covariates with sex and or SCI were assessed for the adjusted models.

6.2.1 Trajectory Group Membership and Mortality Risk

This analysis is limited by the sample size of the group over time and missingness of data not attributable to participant death. As such it was not included in the primary analyses. Figure S3.1a and b shows the hazard of all-cause mortality for each trajectory group. Figures S3.2a and b shows the hazard of CR-COD mortality.

In the cognitive trajectory groups, any impaired 3MS Group (1 or 2) were at increased risk of death from all-cause mortality. This is somewhat different from the main results of SCI in which 3MS only was not at increased risk for mortality. However, the SCI group with both a hospital record and 3MS impairment were consistently at increased risk of mortality. This may be reflected in the trajectory group hazard of mortality. Among other cognitive measures, only the Severe Impairment group (HVOT Group 1), and Very Slow group (Trails A Group 2) had an increased hazard of mortality. Interestingly none of the Trails B trajectories were associated with increased or reduced mortality risk.

Figure S3.1a Hazard of Mortality by Cognitive Function Trajectory
Group; Adjusted for Patient Sex

Figure S3.1a Hazard of Mortality by Cognitive Function Trajectory Group;

Adjusted for Patient Sex

Figure S3.2a Hazard of CR-COD by Cognitive Function Trajectory Group;
Adjusted for Patient Sex
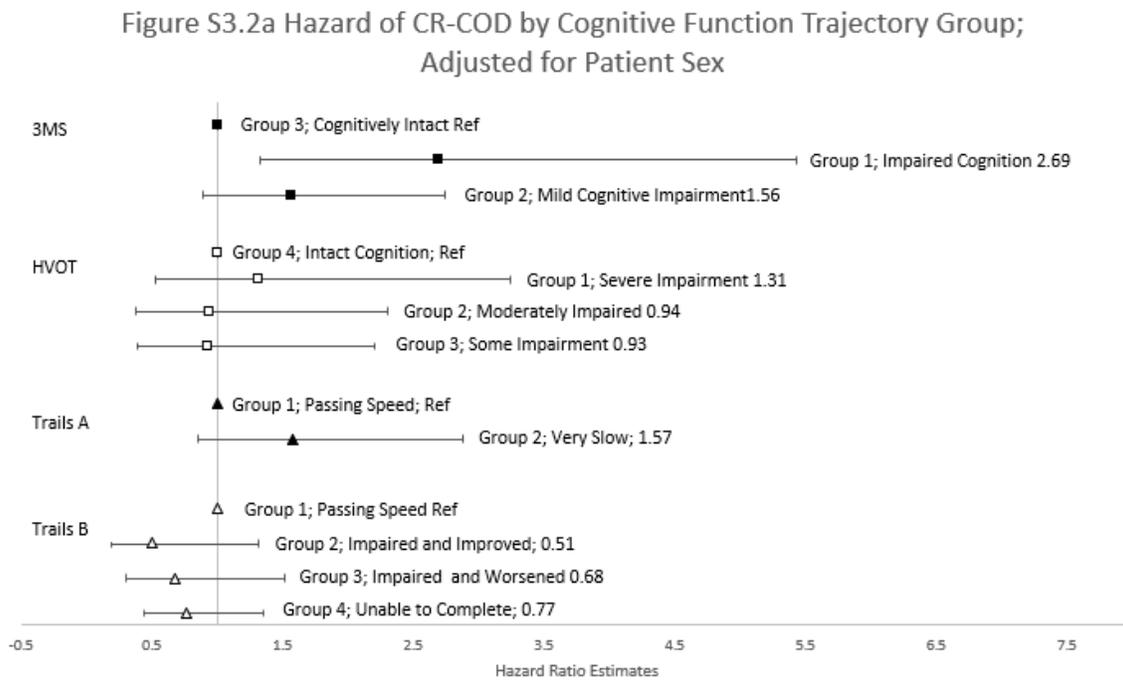
Figure S3.2a Hazard of CR-COD for Cognitive Function Trajectory Group;

Adjusted for Patient Sex

All-cause mortality risk by functional trajectory group uniformly showed increased risk of mortality for any level of impaired function regardless of the measure. This effect was somewhat muted in CR-COD hazard. SPPB Gait and Chair stand trajectories were not associated with CR-COD time to death. The worst SPPB Balance and Total SPPB groups, No balance (SPPB Balance Group 1) and Severe Limitation (SPPB Group 1) respectively, were at increased risk of CR-COD, but not the more mild limitations in either measure. Yale Activity and Exercise groups were not associated with CR-COD risk. LPADL was the only functional measure with two groups at increased risk of CR-COD. Acquired Disability (LPADL Group 3) comes to resemble Functional Dependence (LPADL Group 4) by 6 months. This large shift in ability over a relatively short period of time could have been thought to lead to increased risk of mortality compared to more stable states of disability. However, this is not seen in either all-cause or CR-COD mortality risk.
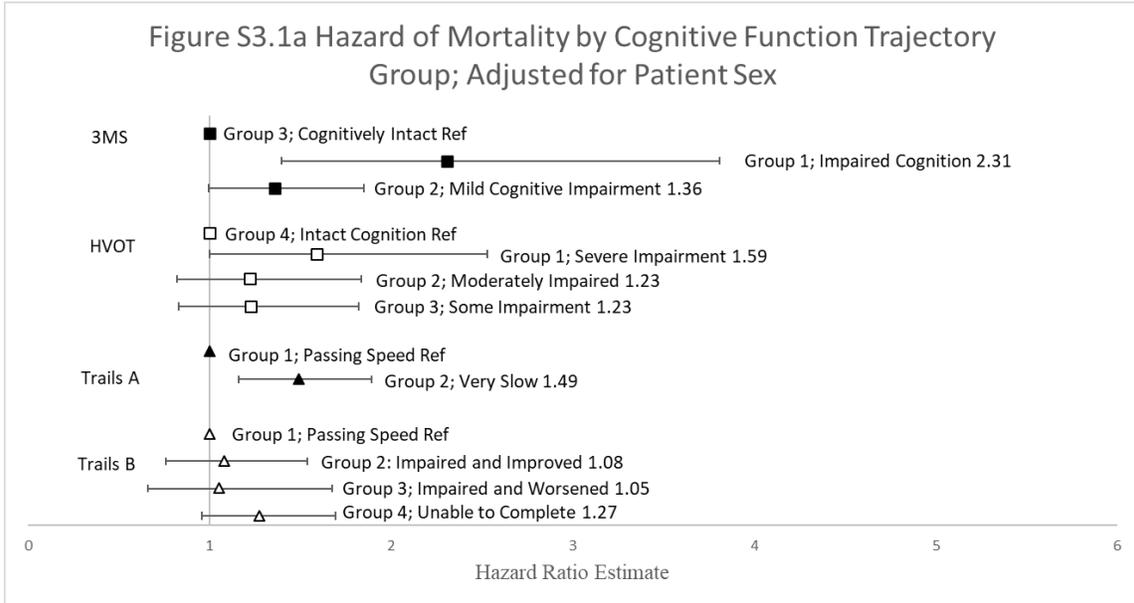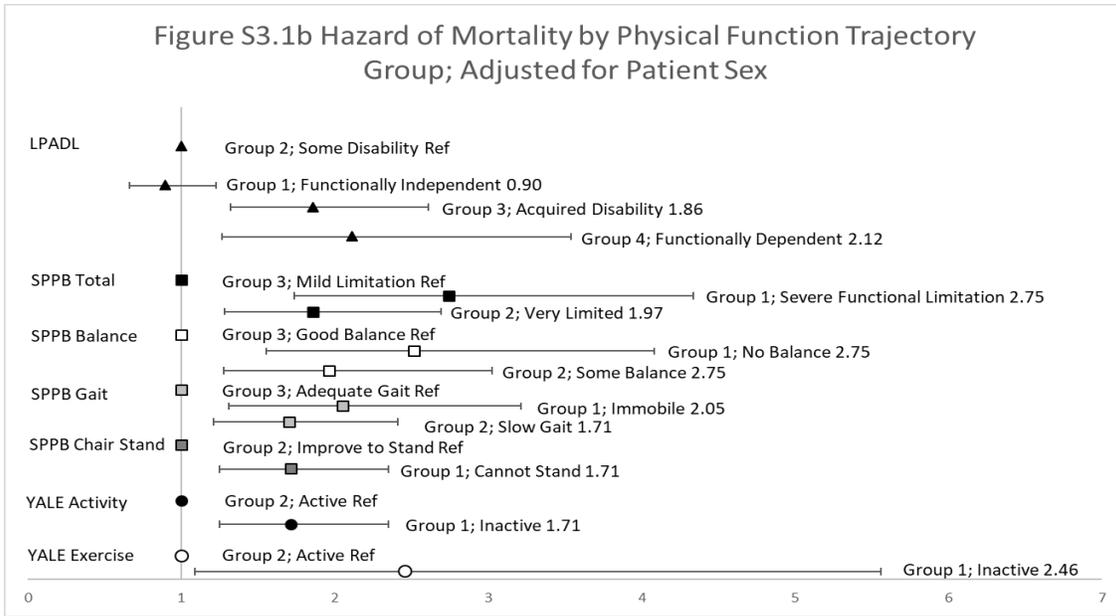
Figure S3.1b Hazard of Mortality by Physical Function Trajectory Group; Adjusted for Patient Sex
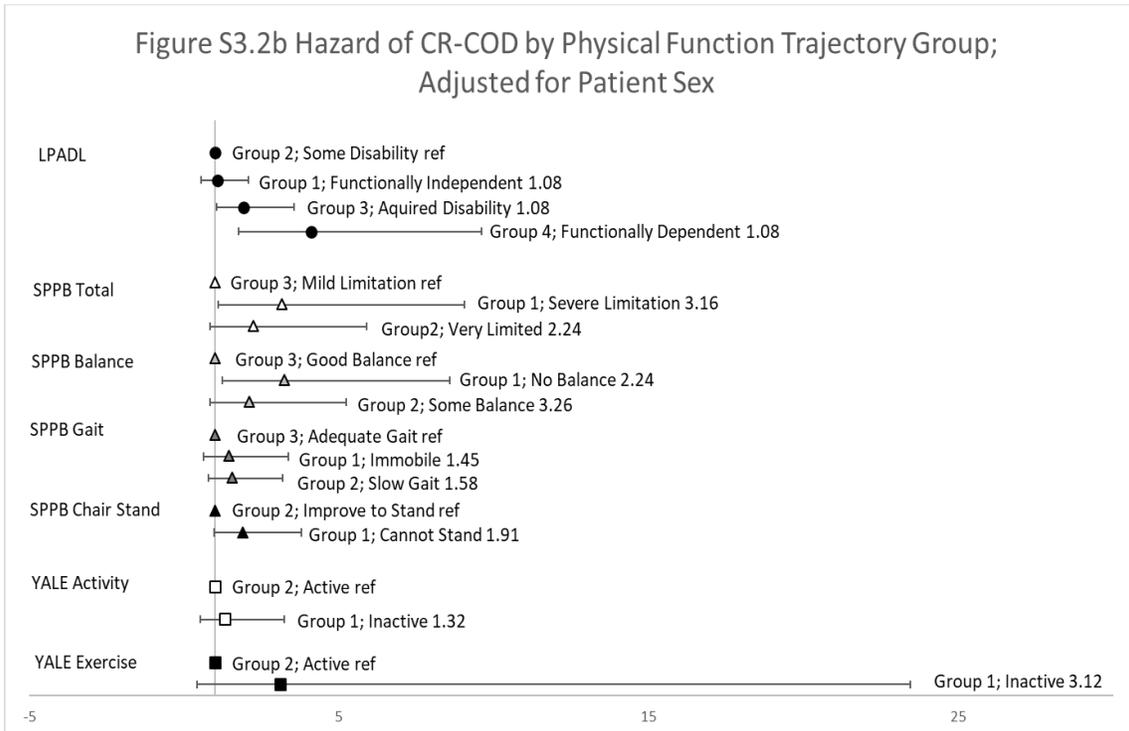
Figure S3.2b Hazard of CR-COD by Physical Function Trajectory Group; Adjusted for Patient Sex

128

CHAPTER 7. DISCUSSION

The main analyses were discussed in the papers included in Chapters 4, 5, and 6. In this chapter, I present a global summary and integration of the main findings from this work.

7.1 Sex Differences in Cognitive Impairment, Recovery and Mortality in Hip Fracture

The mean age of the BHS7 sample was older at 80 (7.8) years old, this is congruent with similar study populations.[151] However, in the U.S the average hip fracture patient in the emergency department during this study time period was a 76-year-old woman who fell.[1,47,152] This may be due to the fact that the BHS7 sample excluded those who fractured before age 65 and was majority white, while national averages include more population heterogeneity. Age was not significantly different by patient sex.

Studies assessing hip fracture in men have found them to arrive at the hospital with more comorbid conditions despite their younger age compared to female counterparts.[153] Additionally, men have shown more CI in the early phase of recovery (first 22 days).[7] These trends were largely echoed in this balanced recruitment cohort of men and women in the Baltimore area with hip fractures between 2006 and 2011.

As seen in Aim 1, men and women who fractured their hip had very similar hospital experiences including type of fracture and surgery, length of surgery and hospital length of stay. Most patients arrived with at least one comorbid condition (excluding dementia), but men had significantly more comorbidities than women. Men also had a

significantly longer time from hospital admission to initiation of physical therapy, but the difference may not be clinically significant as it was a less than a day (0.78). This trend could be related to the degree of CI seen in men, the increase in medical complexity for men, or women being treated as less frail in medicine.

In Aim 2 results, sex was not a risk factor for membership in a particular trajectory group for 3MS, HVOT, Trails A, or LPADL. In Trails B trajectories, male sex was associated with increased log odds of being in the Unable to Complete group (Trails B: Group 4) compared to the Impaired and Worsened (Trails B: Group 3). This supports the idea the at the time of baseline testing, males are already displaying more active CI.

In the BHS7 sample Aim 3 analyses, 260 (78%) of the 330 participants had died over 10 years; the mean time to death was about 3.8 years (46 months). Men had 5 times greater odds of all-cause mortality than women in the study. Women's survival time was significantly longer than men's by approximately 1 year.

7.2 Cognitive Differences in Hip Fracture Patients

7.2.1 Source of Cognitive Impairment Identification

The goal of Aim 1 was to estimate whether there was under-diagnosis and documentation of CI among hip fracture patients and evaluate if under-diagnosis differs by sex or other patient characteristics. We hypothesized that additional screening of hip fracture patients using the Modified Mini-Mental State Examination (3MS) would result in detecting previously undocumented CI (including ADRD, MCI, and delirium) cases. This was supported in the 12.7% (n=42) identified who failed direct

cognitive testing within 22 days after hip fracture but had no clinically documented indications of CI at admission or post-operatively in the medical chart. This is similar to rates of incident post-operative CI found in U.K. hip fracture populations.[154] While most patients did not have a history of CI, nor did they demonstrate impairment when directly tested for CI (n=219, 66.4%), 20.9% (n=69) of the sample had an indication of ADRD and/or delirium on their medical charts. This is similar to other estimates of pre-existing dementia in hip fracture populations.[155] Among those with clinically identified impairment, 11.5% (n=38) did not fail direct testing, which indicates they were not actively demonstrating symptoms of CI within 22 days after their admission for hip fracture event. The two sources were concordant in only 9.4% (n=31) of patients.

Postmortem examination is the only current gold standard for ADRD diagnosis, otherwise extensive tests and review of medical history are documented in the hospital records making them a clinical standard for establishing existing impairment.[156] Therefore, a lack of concordance between clinical identification and direct testing may not seem too concerning for identification of impairment. However, a significant proportion of the cognitively impaired sample was misclassified as unimpaired when only using clinical identification. Additionally, there were differences between the sub-groups identified by the different sources. Patients not identified as having CI by either source were significantly younger than those identified by medical records alone. Those identified by 3MS but not hospital records had significantly fewer years of education than those identified by hospital record only and those without an indication of impairment. Days to physical therapy initiation were also significantly different for those identified by both 3MS and Hospital Record compared to those with no CI identification, such that

131

those with documented impairment had delayed physical therapy initiation despite no differences in physical factors such as comorbid conditions or BMI. Previous work by Kenyon-Smith et al. (2019)[27] has shown that a difference of 9 hours in mobilization initiation can result in increased delirium. Their findings were impacted by premorbid health in which earlier mobilizers had better premorbid health. Though our study did not use proximal measures of post-surgery mobilization, we did have time to physical therapy initiation which may serve as a proxy for mobilization. The difference in time to physical therapy initiation between men and women could be associated with CI at 22 days after hip fracture. The role of this association to mediate sex difference in CI such as those seen in this study should be explored further in future work.

Odds of CI identification for men compared to women in BHS7 were greater for 3MS only identification (direct testing of active impairment) and agreement between clinical diagnosis and direct testing. After adjusting for age, education, and CCI, men no longer had significantly increased odds of identification using direct testing. The loss of significance after adjusting for education and the significant difference in levels of education by SCI group may highlight the language demands of the 3MS.

7.2.2 Trajectories of Recovery

7.2.2.1 Cognitive Recovery Trajectories

Previous studies have examined physical function recovery and recovery trajectories in hip fracture patients.[8,78,79,81,89,93,97,142] A select few studies have assessed cognitive recovery trajectories in hip fracture patients.[61,157,158] All trajectories from our sample were shown in Figure 2.1 and S2.1. The following observations emerged from the

Aim 2 analyses: the existence of multiple trajectories of cognition, which differed from the mean scores overtime, baseline cognition scores were predictive of 12-month cognition, and group membership size (%) was not equally distributed between the groups across cognition measures.

Across the cognitive measures there were multiple distinct trajectory groups, but relatively few change patterns. The general grouping of the patterns is similar to Beishuizen's three cognitive trajectory groups (improvement, stable, and decline), but the largely linear or constant state of cognition over time differentiates the samples.[61] The recovery of cognition at 12 months was largely determined by baseline cognitive status, in which those with worse baseline cognition remained low at 12 months and those with better baseline cognition had better cognition after one year. These differences may have been driven by attrition due to mortality in this sample, but it is interesting that this trend was seen across multiple cognitive tests. The trajectory analysis illustrated clearly that modelling the mean score over time was hiding sub-groups who performed consistently differently from the mean. Even using accepted cut-points, there were still groups who did not perform within those parameters, such that at least one group consistently was above the cut-point, another group was consistently close to the cut-point, and at least one other group was consistently performing much worse than the cut-point.

Finally, for the 3MS (5.7%) and HVOT (13%) trajectories, the smallest group (that with the smallest percentage group membership) was also the worst performing group. This was not seen in either of the TMT (Trails A: 89%; Trails B: 41%) in which the inverse was true and the worst performing groups had the largest membership percentage. The implications of this difference should be explored in future work,

133

focusing on what this could mean about the cognitive domains tested. The large proportion of poor performance over time on TMT might have implications for functional recovery related to areas of executive function and psychomotor speed, such as fall prevention.[159]

The improvement in Trails A Group 2 performance from baseline to 2 months could be due to practice effects (or delirium recovery), but the cause for subsequent worsening in performance is unclear. This pattern is not well explained by practice effects nor by survival bias. Practice effects would presume that the scores overtime would improve or at least be somewhat maintained as seen in Trails B, particularly in Group 2 where the scores become more like the best performing Group 1 over time due to improved scores. Survival bias would suggest that healthier patients would stay in the study biasing outcomes towards better responses over time. Neither of these two patterns were observed for Trails A Group 2. Participants may have still been undergoing rehabilitation for their hip fracture between baseline and two months. Increased scores may be attributable to participation in physical activity. The decline seen from 2 months onward may be a reversion to baseline after conclusion of rehabilitation or a natural decline due to aging. The latter is less likely given the large change over a one-year period despite consistent one-year cognitive trajectories on other measures. A notable limitation of cognitive measure analysis was the lack of pre-fracture performance information. Having pre-fracture information, such as the informant-based IQCODE[160] may have provided more context particularly about the observed increase and maintained impairment of Trails B Group 3.

7.2.2.2 Functional and Joint Recovery Trajectories

The newly acquired disability group (LPADL Group 3) remains an important focal point for analysis. Using pre-fracture function estimates, members of this group were indistinguishable from those who did not get worse functionally by 6 months. Using risk factors to predict probability of membership in Group 3 did not yield any identifiable factors to explain the dramatic functional loss. Using continuous cognitive scores as risk factors did not differentiate the groups, despite outcomes from joint trajectories revealing a relationship between recovery of functional trajectory and cognition.

Joint trajectories of LPADL and cognitive measures (Aim 2) showed that those who have few LPADL limitations tended to be those with good 3MS scores. However, among the very limited mobility group, it was almost impossible to predict cognition as the conditional probabilities were evenly distributed. This effect may not be seen in a larger sample, as the impaired LPADL group was a relatively small group. In a community-dwelling sample of adults age 70 and older assessing joint trajectory of cognition and frailty yielded 4 trajectories: no frailty, slow cognitive decline with progressive frailty, rapid cognitive decline and progressive frailty, and cognitive frailty.[157] This distinction in the directionality of the trajectory patterns was not seen in our hip fracture sample and may be due to the increased level of impairment, both cognitive and functional, in a hip fracture sample.

Supplemental measures were largely similar in that there were distinct groups whose baseline performance best predicted 12-month performance. Only LPADL had the divergence from a previously healthy group. Yale did also ask for pre-fracture estimates,

but there was not an intermediate group as seen in LPADL. This means that there was not a sub-group who were active prior to fracture and became extremely inactive.

7.2.3 Mortality and Cognitive Impairment

SCI identification by Both sources (hospital record and 3MS) was associated with 2.5 times greater risk of all-cause mortality and 16 times greater risk of CR-COD, after adjusting for age, education, CCI, and ASA rating. Identification by 3MS only was associated with increased odds of all-cause mortality before adjustment and 5 times greater odds of CR-COD. These findings further highlight how the under-diagnosed group is at risk for poor outcomes. If these individuals had not been in the BHS7 study, they would not have been identified as having CI at the time of hip fracture.

7.3 Sex and Cognitive Impairment in Hip Fracture Patients

It was hypothesized (Aim 1b) that odds of CI identification would not be equal across the sexes. The hypothesis was intentionally two-tailed as there was a rationale for either sex being more likely to be missed in clinical practice. Before SCI was separated into distinct categories, men had worse baseline 3MS scores, but ADRD and/or post-operative delirium in the medical chart was not significantly different by patient sex. In unadjusted analyses, women were significantly more likely to have no impairment identified and significantly more men were diagnosed by 3MS only. There were not sex differences for other impairment sources, which included identification by hospital record. This is somewhat counter to the original hypothesis. It was hypothesized that

136

clinical identification would be significantly lower in men due to underreporting by men and potentially underdiagnosed in women due to dismissive biases about women's complaints of pain and other mental discomforts. The lack of distinction between sexes in hospital record identification may be an artifact of regression to the null. Men present much more poorly than women at hospital admission. The similar proportion in identification could be evidence of the hospitalization experience exacerbating men's underlying impairments. It could also be that the greater prevalence of ADRD in women may have been counter-balanced by men having a spouse and perhaps a better reported history at admission to the hospital with a fracture. This is something that could be assessed with linkages to claims diagnoses.

After adjusting for age, education, and number of comorbid conditions, men's odds of identification by both 3MS and hospital record remained over 2 times higher compared to women. The sex difference in 3MS was no longer significant. This is likely due to the education adjustment. Education was not significantly different between men and women in this cohort. 3MS has a large language emphasis for cognition and working memory. Literature on the effects of endogenous sex and memory hormones are mixed, but have suggested that estradiol is protective of memory in females for episodic, sematic, and verbal memory.[161] Testosterone in either sex has mixed results.[161] After adjusting for other factors and comorbidities, the 3MS level has been shown to be similar by both sex.[162] There were no significant interactions between SCI and patient sex.

When considering the impact of patient sex on mortality through the lens of SCI; males had shorter survival times than female counterparts, but females identified by both sources died significantly sooner than females with no identified impairment. Males

137

identified by 3MS only or by both sources died significantly sooner than males with no identified impairment. The other combinations were not significantly different. The lack of Hospital Record only differences between males and females may suggest that there was either unmeasured bias regressing outcomes to the null or that CI in the two sexes was associated with truly equitable mortality risk. The latter, equitable risk of mortality between the sexes given CI, is unlikely given the known associations between cognition and mortality in hip fracture[83,144,145] and the exacerbating effect of male sex on survival time after hip fracture. CI may be contributing more to female mortality creating the equality that is not seen when looking at sex differences without CI. Overall, there were effects of sex and SCI on mortality, but no significant interactions.

7.4 Strengths and Limitations

The BHS7 data have many strengths, but like a lot of research on older adults and research on hip fracture, it suffers from a lack of racial diversity. The most affected population is currently Caucasian older adults, but there is still a large risk of hip fracture among adults of Asian descent. Studies have shown that mobilization in the hospital within 48 hours can be more important than guided rehabilitation efforts to improve hip fracture outcomes.[163] Unfortunately, BHS7 did not asses specifically for early mobilization or delirium in the hospital, but did include chart abstraction to account for documented delirium upon admission and post-operatively. There was baseline data within 22 days of hip fracture admission, but physical performance tests were only collected at follow-up visits (2, 6, and 12 months post admission). However, there is

longitudinal data (baseline over one year) for a comprehensive set cognitive and physical function surveys allowing for observation of the timeframe of rehabilitation, and analysis of early progress and long-term outcomes.

The BHS7 cohort, by design, had an approximately equal numbers of men and women, but due to oversampling men, the overall rate of mortality may be higher and could result in fewer observed long-term outcomes. Mortality is an important outcome and should, therefore, be weighted as part of the recovery process, particularly when looking at sex differences in recovery. Patients were only enrolled from the greater Baltimore, Maryland area. In 2014, Maryland had 934 deaths due to ADRD, or a cause-specific morality rate of 15.6 per 100,000.[11] While this is not the lowest ADRD representation among U.S states it is still comparatively low, as the U.S 2014 ADRD mortality rate was 29 per 100,000.[11,164] This is a limitation related to the anticipated number of events in the study sample, but a strength with respect to the implications for the strong relationships between ADRD and hip fracture given the limited sub-population being represented.

ADRD has been historically underdiagnosed in claims data. Previous studies of Medicare claims for ADRD have found that at least 3 consecutive years of claims data are needed to identify ADRD using Medicare.[21] Furthermore, Medicare claims capture longitudinal information from outpatient settings in addition to hospital claims. Therefore, Medicare claims are more likely to capture ADRD than hospital records alone. Thus, relying strictly on hospital record for ADRD diagnosis would introduce information bias into the analyses. Aim 1 provided a sensitivity analysis for existing CI compared to diagnosed impairment in the sample.

One of the strengths of this research is the use of a unique dataset to capture previously under-studied subsamples, such as men with hip fracture and underdiagnosed CI. The results of this study will be meaningful to the population at risk. Findings from Aim 1 provided evidence for the implementation of CI testing, Aim 2 results provided distinct patterns of recovery and sensitive timepoints for intervention. Aim 3 findings emphasized the importance of addressing ADRD underdiagnosis as underdiagnosed groups perform similarly poor to the diagnosed groups. Our work continues to support previous findings on the risk for worse outcomes among men with hip fracture including CI and mortality. Additional testing, as recommended from this work, differentiates a sub-group within the diagnosed patients who are at greatest risk for mortality and CR-COD regardless of sex.

7.5 Future Research Directions

Based on the results and limitations of this work, future research directions should include cognitive testing at time of fracture. Future transportation of this work should utilize cognitive status testing as a metric in planning rehabilitation intensity or duration. Measures that may provide additional information for future research include pre-fracture cognitive estimates, as well as pre-fracture functional estimates of ADLs for focused therapy. Since cognitive status did not predict functional decline between LPADL group 2 and 3 whose pre-fracture ADL levels were comparable, other possible mechanisms such as depression, inflammation and resilience biomarkers should be explored. Mortality attrition in groups of recovery trajectories should be assessed for impact of non-random

truncation on trends estimates as this may be an important source of bias in a population that has a high one-year mortality rate. Aarden et al. (2017)[165] has made preliminary efforts by assessing proportion deceased in ADL trajectory groups after hip fracture, but this does not address how death impacts the group size or over-all shape. The goal of future rehabilitation work should seek to target LPADL Group 3 (Acquired Disability) to prevent the new and sustained disability.

Use of claims data for prevalent pre-fracture diagnoses of ADRD in comparison to incident hospital chart documentation during hip fracture versus direct testing implemented after hip fracture can further enhance generalizability of findings from this work. Additionally, it could provide time to event information not currently available in this study based on time from ADRD diagnosis pre-fracture to hip fracture and subsequent outcomes, particularly mortality. Semi-competing risks of ADRD and mortality in a hip fracture sample given the known under recognition of CI may be one way to utilize the claims data. Some similar work has been done using competing risks,[166,167] but few use semi-competing risks which allows for a non-terminal event such as ADRD diagnosis. Semi-competing risks analyses after hip fracture has been done in the U.K.[168], Australia[169], and other non-US countries, but given differences in healthcare systems, population homogeneity, and lifetime approaches to health it will be important to conduct this work in the U.S.

CHAPTER 8. CONCLUSION

Men and women experience hip fracture differently. It is well established that men arrive more impaired and are discharged in poorer condition despite otherwise similar hospitalization experiences compared to women. There are no sex differences in hospital record diagnosis of ADRD despite these differences in known pre-fracture comorbidity and outcomes between men and women. While women still comprise the majority of ADRD cases in the U.S., this work has highlighted that men experience CI at the time of hip fracture and it may be underdiagnosis. These findings not only impact the course of care but have very real implications for recognizing at risk sub-groups for functional limitation and mortality.

Cognitive recovery is less dynamic than previously hypothesized. This work has provided foundational evidence for future work in clinical practice, rehabilitation, and research to more closely examine the impact of patient sex and cognition on outcomes among U.S. hip fracture patients. The two concepts cannot be extricated from the hip fracture experience.

Finally, this research supports the implementation of a test of CI after hip fracture to provide clinical information about the individuals risk for negative outcomes such as reduced mobility and early mortality.

APPENDIX

Table M1.1 BHS7 Variable Information			
Variable	Label	Type	Other information
Id	Participant ID	Continuous	
cs00q9	3MS Score	Continuous	0-100
Test	3MS Category	Categorical	Cs00q9 <78, Test =1; else =0
medabq14a	Dementia or Alzheimer's in Medical Chart	Binary	If dementia or AD in chart = 1, else =0
medabq14b	Parkinson's in Medical Chart	Binary	If PD in chart = 1, else =0
medabq96e	Delirium in Medical Chart	Binary	Post-operative delirium
Medabq96d		Binary	Post-operative confusion/disorientation
		Binary	
Medabq26a		Binary	Confusion/Disorientation at admission
Medabq26b		Binary	Delirium at admission
hx	Hospital Chart	Binary	If medabq14A and/or medabq96E =1 then HX=1, else =0
HxOrig	Original Hospital Chart	Binary	
SCI	Source of Cognitive Impairment Identification	Categorical	if Test=0 AND Hx=0 then SCI=3; else if Test=0 AND Hx=1 then SCI=1; else if Test=1 AND Hx=0 then SCI=0; else if Test=1 AND Hx=1 then SCI=2; else if Test=. OR Hx=. then SCI=.;
Medrec	CI on Medical Record Only	Binary	Identify dummy variable for Hx=1 test=0
Both	CI on Medical Record and 3MS	Binary	Identify dummy variable for Hx and test =1
Msonly	CI on 3MS Only	Binary	Identify dummy variable for Hx=0 test=1

Table M1.1 Continued			
None	CI on Neither Medical Record nor 3MS	Binary	Identify dummy variable for hx and test=0
medabq4	Sex	Binary	1= female, 0= male
medabq5	Date of Admission	Date	
blq11	Years of Education	Continuous	
Medabq45	ASA Physical Status Rating	Categorical	1-4, higher scores worse
age	Age	Continuous	Floor 65 years of age
Race	Blq8	Categorical	Asian, Native Hawaiian/Pacific Islander, Black/African American, White, Don't Know, Refused, Other
Race	Race	Binary	0= White, 1=Black, American Indian, Other
Rfractype	Fracture Type	Categorical	1= Intertrochanteric, 2= Femoral Neck, 3=Other
surgtype	Surgical Approach	Categorical	1= Fixation, 2= Arthroplasty, 3= Other
losmin	Length of Surgery (MinuteS)	Continuous	Lengthsurg*60
bmi	bmi	Continuous	
comorbidity	Comorbid Conditions	Discrete	Does not include liver disease (exclusion for study)
Charlson	Comorbid Conditions without Dementia	Discrete	Number of conditions on CCI (excluding liver disease and dementia)
Medabq80	Date physical therapy start	Date	
dayspt	Days to Initiation of Physical Therapy	Continuous	daysPT=(Medabq80-medabq5)
Medabq81	Number PT Sessions	Continuous	
Medabq83	Date Discharge	Date	
dayslos	Days from Hospital Admission to Discharge		daysLOS=(Medabq83-medabq5)
DATEOFDEATH	Date of Death	Date	
Dead	Deceased with a Date of Death	Binary	

Table M1.1 Continued			
DeathCheck	Any Cause of Death Listed on National Death Index	Binary	
Condition1	Primary Cause of Death	Nominal	
Condition2	Secondary Cause of Death	Nominal	
Condition3	Tertiary Cause of Death	Nominal	
Condition4	Quaternary Cause of Death	Nominal	
Condition5	5th Contributing Cause of Death	Nominal	
Condition6	6th Contributing Cause of Death	Nominal	
Condition7	7th Contributing Cause of Death	Nominal	
Condition8	8th Contributing Cause of Death	Nominal	
Condition9	9th Contributing Cause of Death	Nominal	
Condition11	10th Contributing Cause of Death	Nominal	
RACondition1	Primary Cause of Death Recoded	Nominal	
RACondition2	Secondary Cause of Death Recoded	Nominal	
RACondition3	Tertiary Cause of Death Recoded	Nominal	
RACondition4	Quaternary Cause of Death Recoded	Nominal	
RACondition5	5th Cause of Death Recoded	Nominal	
RACondition6	6th Cause of Death Recoded	Nominal	
RACondition7	7th Cause of Death Recoded	Nominal	
RACondition8	8th Cause of Death Recoded	Nominal	
RACondition9	9th Cause of Death Recoded	Nominal	
RACondition10	10th Cause of Death Recoded	Nominal	

Table M1.1 Continued			
F01	Vascular Dementia	Binary	If condition1-11 or RAconditon1-10 = F01, then F01=1, else F01=0
F02	Dementia	Binary	If condition1-11 or RAconditon1-10 = F02, then F02=1, else F02=0
F03	Unspecified Dementia	Binary	If condition1-11 or RAconditon1-10 = F03, then F03=1, else F03=0
F05	Delirium	Binary	If condition1-11 or RAconditon1-10 = F05, then F05=1, else F05=0
F01_RA	Vascular Dementia Recoded	Binary	If condition1-11 or RAconditon1-10 = F01_RA, then F01_RA=1, else F01_RA=0
F02_RA	Dementia Recoded	Binary	If condition1-11 or RAconditon1-10 = F02_RA, then F02_RA=1, else F02_RA=0
F03_RA	Unspecified Dementia Recoded	Binary	If condition1-11 or RAconditon1-10 = F03_RA, then F03_RA=1, else F03_RA=0
F05_RA	Delirium Recoded	Binary	If condition1-11 or RAconditon1-10 = F05_RA, then F05_RA=1, else F05_RA=0
G20	Parkinson's Disease	Binary	If condition1-11 or RAconditon1-10 = G20, then G20=1, else G20=0
G30	Alzheimer's Disease	Binary	If condition1-11 or RAconditon1-10 = G30, then G30=1, else G30=0
G20_RA	Parkinson's Disease Recoded	Binary	If condition1-11 or RAconditon1-10 = G20_RA, then G20_RA=1, else G20_RA=0
G30_RA	Alzheimer's Disease Recoded	Binary	If condition1-11 or RAconditon1-10 = G30_RA, then G30_RA=1, else G30_RA=0

Table M1.1 Continued			
R41	Senility	Binary	If condition1-11 or RAconditon1-10 = R41, then R41=1, else R41=0
CRCOD	Cognition-Related Cause of Death	Binary	Any indication of 1 in the ICD-10 Cognition related codes
Months	Months from Hospital Admission to Date of Death	Continuous	(DATEOFDEATH-medabq5)/**30.25**;
CMonths	Months from Hospital Admission to Date of Death CR-COD	Continuous	(DATEOFDEATH-medabq5)/**30.25**; where CRCOD=1
Cs00dt	Date of Baseline Cognitive Battery	Date	
dayscog	Days from Hospital Admission to Baseline Cognitive Battery	Continuous	daysCOG=(cs00dt-medabq5)
Cs02q16	FU Period	Number	Follow up period, 2 month
Cs06q16	FU Period	Number	Follow up period, 6 month
Cs12q16	FU Period	Number	Follow up period, 12 month
Cs02q9	3MS Score	Continuous	100 max score, 2 month
CS06q9	3MS Score	Continuous	6 month
Cs12q9	3MS Score	Continuous	12 month
Cs00q11	Hooper Score	Continuous	30 max score, Baseline
Cs02q11	Hooper Score	Continuous	2 month
Cs06q11	Hooper Score	Continuous	6 month
Cs12q11	Hooper Score	Continuous	12 month
TrailA00	Baseline Trails A	Continuous	301 max score, Baseline
TrailA02	2 Month Trails A	Continuous	2 Month
TrailA06	6 Month Trails A	Continuous	6 Month
TrailA12	12 Month Trails A	Continuous	12 Month
TrailB00	Baseline Trails B	Continuous	301 max score, Baseline
TrailB02	2 Month Trails B	Continuous	2 Month
TrailB06	6 Month Trails B	Continuous	6 Month
TrailB12	12 Month Trails B	Continuous	12 Month
Lpadl00	LPADL	Continuous	12 max score, Baseline Asks for pre-fracture function self-estimate
Lpadl02	LPADL	Continuous	2 Month

Table M1.1 Continued			
Lpadl06	LPADL	Continuous	6 Month
Lpadl12	LPADL	Continuous	12 Month
SPPB02	SPPB score at 2 month, ranges 0-12, higher is better	Continuous	2 month, no baseline assessment done
SPPB06	SPPB score at 6 month, ranges 0-12, higher is better	Continuous	6 month
SPPB12	SPPB score at 12 month, ranges 0-12, higher is better	Continuous	12 month
TtlBal02	Total Balance Score at 2 months	Continuous	2 Month; 0-4 range
TtlBal06	Total Balance Score at 6 months	Continuous	6 Month
TtlBal12	Total Balance Score at 12 months	Continuous	12 Month
Gaitspd02	SPPB Gait speed	Continuous	2 Month
Gaitspd06	SPPB Gait speed	Continuous	6 Month
Gaitspd12	SPPB Gait speed	Continuous	12 Month
chairstnd02	SPPB Chair Stand	Continuous	2 Month
Chairstnd06	SPPB Chair Stand	Continuous	6 Month
Chairstnd12	SPPB Chair Stand	Continuous	12 Month
extim00	Yale: total exercise time baseline, hrs/wk	Continuous	Baseline
extim02	Yale: total exercise time 2 mo., hrs/wk	Continuous	2 Month
extim06	Yale: total exercise time 6 mo., hrs/wk	Continuous	6 Month
Extim12	Yale: total exercise time 12 mo., hrs/wk	Continuous	12 Month
Ytime00	Yale:Total activity time at baseline mo, hrs/wk	Continuous	
Ytime02	Yale:Total activity time at 2 mo, hrs/wk	Continuous	
Ytime06	Yale:Total activity time at 6 mo, hrs/wk	Continuous	
Ytime12	Yale:Total activity time at 12 mo, hrs/wk	Continuous	
T0		Number	Observation Period: Baseline

Table M1.1 continued		
T1	Number	Observation Period: 2 Month
T2	Number	Observation Period: 6 Month
T3	Number	Observation Period: 12 Month
Note: Tables title with M are Methods tables. Non-shaded cells are variables created for analysis, Cells shaded in light grey are original data from BHS7 data sets, cells shaded in dark grey are original data from NDI.		

ICD-9-CM	Diagnosis	ICD-10-CM	Diagnosis
331.0	Alzheimer's Disease	G30.0	Alzheimer's disease with early onset
		G30.1	Alzheimer's disease with late onset
		G30.8	Other Alzheimer's disease
		G30.9	Alzheimer's disease, unspecified
331.1	Pick's disease		
331.7	Senile degeneration of the brain	G13.2	Systemic atrophy primarily affecting the central nervous system in myxedema
		G13.8	Systemic atrophy primarily affecting central nervous system in other diseases classified elsewhere
		G31.2	Degeneration of nervous system due to alcohol
		G91.4	Hydrocephalus in diseases classified elsewhere
		G94	Other disorders of brain in diseases classified elsewhere
290.0	Cerebral degeneration in diseases classified elsewhere	F03.90	Unspecified dementia without behavioral disturbance
290.1	Senile dementia, uncomplicated	F03.90	
290.10	Presenile dementia, uncomplicated	F03.90	
290.11	Presenile dementia, w/ delirium	F03.90	
290.12	Presenile dementia, w/ delusional features	F03.90	
		F05	Delirium due to known physiological condition
290.13	Presenile dementia, w/ depressive features	F03.90	
290.20	Senile dementia, w/ delusional features	F03.90	
		F05	

Table M1.2 continued			
290.21	Senile dementia, w/ depressive features	F03.90	
290.3	Senile dementia, w/ delirium	F03.90 F05	
290.40	Arteriosclerotic dementia, uncomplicated	F01.50	Vascular dementia without behavioral disturbance
290.41	Arteriosclerotic dementia, w/ delirium	F01.51	Vascular dementia with behavioral disturbance
290.42	Arteriosclerotic dementia, w/ delusional features	F01.51	
290.43	Arteriosclerotic dementia, w/ depressive features	F01.51	
294.0	Amnestic syndrome (Korsakoff's psychosis or syndrome, nonalcoholic)	F04	Amnestic disorder due to known physiological condition
294.1	Dementia in conditions classified elsewhere		
294.8	Other specified organ brain syndrome (chronic)	F06.1	Catatonic disorder due to known physiological condition
		F06.0	Psychotic disorder with hallucinations due to known physiological condition
		F06.8	Other specified mental disorders due to known physiological condition
797	Senility without mention of psychosis	R54	Age-related physical debility
		R41.81	Age-related cognitive decline
Note: Tables title with M are Methods tables. Crossover utilizes: https://www.aapc.com/icd-10/codes/			

151

Figure S2.2 Missingness of Measures

BHS 7 Sample
N=339

↓

Baseline (Missing)		Reason Missing Baseline
Overall N=339		Death = 0
3MS (8)		IRB Audit = 0
HVOT (45)	→	Refused = 0
Trails A (60)		Scheduling = 0
Trails B (83)		Other = 2
LPADL (13)		Some but not all missing N = 103
YALE (44)		

↓

2 Month (Missing)		Reason Missing 2 Month
Overall N=257		Death = 12
3MS (86)	→	IRB Audit = 5
HVOT (132)		Refused = 39
Trails A (142)		Scheduling = 39
Trails B (83)		Other = 39
SPPB (135)		Some but not all missing N = 93
LPADL (88)		
YALE (109)		

↓

6 Month (Missing)		Reason Missing 6 Month
Overall N=199		Death = 23
3MS (141)	→	IRB Audit = 5
HVOT (191)		Refused = 26
Trails A (190)		Scheduling = 26
Trails B (83)		Other = 39
SPPB (175)		Some but not all missing N = 39
LPADL (144)		
YALE (162)		

↓

12 Month (Missing)		Reason Missing 12 Month
Overall N=187		Death = 16
3MS (154)	→	IRB Audit = 5
HVOT (199)		Refused = 4
Trails A (199)		Scheduling = 6
Trails B (83)		Other = 39
SPPB (185)		Some but not all missing N = 22
LPADL (155)		
YALE (172)		

REFERENCES

1. Hip fractures among older adults | Home and recreational safety | CDC injury center. Published February 4, 2019. Accessed April 22, 2019. https://www.cdc.gov/homeandrecreationalsafety/falls/adulthipfx.html

2. Stevens JA, Rudd RA. The impact of decreasing U.S. hip fracture rates on future hip fracture estimates. *Osteoporos Int*. 2013;24(10):2725-2728. doi:10.1007/s00198-013-2375-9

3. Lauritzen JB. Hip fractures: incidence, risk factors, energy absorption, and prevention. *Proceedings of the International Symposium on Physical Loading, Exercise, and Bone*. 1996;18(1, Supplement 1):S65-S75. doi:10.1016/8756-3282(95)00382-7

4. Kannus P, Parkkari J, Sievänen H, Heinonen A, Vuori I, Järvinen M. Epidemiology of hip fractures. *Proceedings of the International Symposium on Physical Loading, Exercise, and Bone*. 1996;18(1, Supplement 1):S57-S63. doi:10.1016/8756-3282(95)00381-9

5. Hip Fracture. In: *IBM Micromedex® Disease General Medicine (Electronic Version)*. IBM Watson Health. Accessed September 5, 2019. https://www.micromedexsolutions.com/micromedex2/librarian/CS/273536/ND_PR/evidencexpert/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/D54161/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=CP3653C&contentSetId=135&title=Alzheimer%27s+disease%3B+Dementia&servicesTitle=Alzheimer%27s+disease%3B+Dementia#

6. Gruber-Baldini AL, Zimmerman S, Morrison RS, et al. Cognitive impairment in hip fracture patients: timing of detection and longitudinal follow-up. *JAmGeriatrSoc*. 2003;51(9):1227-1236. doi:10.1046/j.1532-5415.2003.51406.x

7. Gruber-Baldini A, Hosseini M, Orwig D, et al. Cognitive differences between men and women who fracture their hip and impact on six-month survival. *JAmGeriatrSoc*. 2017;65(3):e64-e69. doi:10.1111/jgs.14674

8. Beaupre LA, Binder EF, Cameron ID, et al. Maximising functional recovery following hip fracture in frail seniors. *Bailliere's Best Practice & Research in Clinical Rheumatology*. 2013;27(6):771-788. doi:10.1016/j.berh.2014.01.001

9. Muir SW, Gopaul K, Montero Odasso MM. The role of cognitive impairment in fall risk among older adults: a systematic review and meta-analysis. *Age Ageing*. 2012;41(3):299-308. doi:10.1093/ageing/afs012

10. McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-

Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. 2011;7(3):263-269. doi:10.1016/j.jalz.2011.03.005

11. Alzheimer's Association. 2017 Alzheimer's disease facts and figures. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*. 2017;13(4):325-373. doi:10.1016/j.jalz.2017.02.001

12. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the united states. *JAMA*. 2009;302(14):1573-1579.

13. Abrahamsen B, van Staa T, Ariely R, Olson M, Cooper C. Excess mortality following hip fracture: a systematic epidemiological review. *Osteoporos Int*. 2009;20(10):1633-1650. doi:10.1007/s00198-009-0920-3

14. Arinzon Z, Shabat S, Peisakh A, Gepstein R, Berner YN. Gender differences influence the outcome of geriatric rehabilitation following hip fracture. *Archives of Gerontology and Geriatrics*. 2010;50(1):86-91. doi:10.1016/j.archger.2009.02.004

15. Hebert LE, Weuve J, Scherr PA, Evans DA. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*. 2013;80(19):1778. doi:10.1212/WNL.0b013e31828726f5

16. Mielke MM. Sex and gender differences in Alzheimer's disease dementia. *Psychiatr Times*. 2018;35(11):14-17.

17. Plassman BL, Langa KM, Fisher GG, et al. Prevalence of dementia in the United States: The Aging, Demographics, and Memory Study. *Neuroepidemiology*. 2007;29(1-2):125-132. doi:10.1159/000109998

18. Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. *Neurology*. 1997;49(6):1498. doi:10.1212/WNL.49.6.1498

19. Tom SE, Hubbard RA, Crane PK, et al. Characterization of dementia and Alzheimer's disease in an older population: Updated incidence and life expectancy with and without dementia. *Am J Public Health*. 2014;105(2):408-413. doi:10.2105/AJPH.2014.301935

20. Rocca WA. Time, sex, gender, history, and dementia. *Alzheimer Dis Assoc Disord*. 2017;31(1):76-79. doi:10.1097/WAD.0000000000000187

21. Taylor DH, Fillenbaum GG, Ezell ME. The accuracy of Medicare claims data in identifying Alzheimer's disease. *J Clin Epidemiol*. 2002;55(9):929-937. doi:10.1016/s0895-4356(02)00452-3

22. Zhu Y, Chen Y, Crimmins EM, Zissimopoulos JM. Sex, race, and age differences in prevalence of dementia in medicare claims and survey data. *J Gerontol B Psychol Sci Soc Sci*. Published online June 26, 2020. doi:10.1093/geronb/gbaa083

23. Taylor DH, Østbye T, Langa KM, Weir D, Plassman BL. The accuracy of Medicare claims as an epidemiological tool: The case of dementia revisited. *J Alzheimers Dis*. 2009;17(4):807-815. doi:10.3233/JAD-2009-1099

24. Colón-Emeric C, Whitson HE, Pieper CF, et al. Resiliency groups following hip fracture in older adults. *J Am Geriatr Soc*. Published online August 30, 2019. doi:10.1111/jgs.16152

25. University of Rochester Medical Center. Health encyclopedia: Hip fracture. https://www.urmc.rochester.edu/encyclopedia/content.aspx?ContentTypeID=85&ContentID=P08957

26. Manninger J, Kazar G, Fekete G, Nagy E, Zolczer L, Frenyo S. Avoidance of avascular necrosis of the femoral head, following fractures of the femoral neck, by early reduction and internal fixation. *Injury*. 1985;16(7):437-448. doi:10.1016/0020-1383(85)90162-7

27. Rudman N, McIlmail D. Emergency department evaluation and treatment of hip and thigh injuries. *Emerg Med Clin North Am*. 2000;18(1):29-66, v.

28. Bratzler DW, Houck PM, Surgical Infection Prevention Guidelines Writers Workgroup, et al. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. *Clin Infect Dis*. 2004;38(12):1706-1715. doi:10.1086/421095

29. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. *The Lancet*. 2002;359(9321):1929-1936. doi:10.1016/S0140-6736(02)08761-5

30. Sheu A, Diamond T. Bone mineral density: testing for osteoporosis. *Aust Prescr*. 2016;39(2):35-39. doi:10.18773/austprescr.2016.020

31. Cummings SR, Bates D, Black DM. Clinical use of bone densitometry: Scientific review. *JAMA*. 2002;288(15):1889-1897. doi:10.1001/jama.288.15.1889

32. Bone Density Test, Osteoporosis Screening & T-score Interpretation. National Osteoporosis Foundation. Accessed August 20, 2019. https://www.nof.org/patients/diagnosis-information/bone-density-examtesting/

33. U.S. Preventive Services Task Force. Screening for osteoporosis: Recommendation statement. *AFP*. 2011;83(10):1197.

34. Barrett-Connor E, Stuenkel CA. Hormone replacement therapy (HRT)— risks and benefits. *Int J Epidemiol*. 2001;30(3):423-426. doi:10.1093/ije/30.3.423

35. Ho-Pham LT, Nguyen ND, Nguyen TV. Quantification of the relative contribution of estrogen to bone mineral density in men and women. *BMC Musculoskelet Disord*. 2013;14:366. doi:10.1186/1471-2474-14-366

36. Mohamad N-V, Soelaiman I-N, Chin K-Y. A concise review of testosterone and bone health. *Clin Interv Aging*. 2016;11:1317-1324. doi:10.2147/CIA.S115472

37. Kanis JA, Oden A, McCloskey EV, et al. A systematic review of hip fracture incidence and probability of fracture worldwide. *Osteoporosis Int*. 2012;23(9):2239-2256. doi:10.1007/s00198-012-1964-3

38. The IOF CSA Working Group on Fracture Epidemiology, Cooper C, Cole ZA, et al. Secular trends in the incidence of hip and other osteoporotic fractures. *Osteoporosis International*. 2011;22(5):1277-1288. doi:10.1007/s00198-011-1601-6

39. Cooper C, Campion G, Melton LJ. Hip fractures in the elderly: a world-wide projection. *OsteoporosInt*. 1992;2(Journal Article). doi:10.1007/BF01623184

40. Lewiecki EM, Wright NC, Curtis JR, et al. Hip fracture trends in the United States, 2002 to 2015. *Osteoporos Int*. 2018;29(3):717-722. doi:10.1007/s00198-017-4345-0

41. Greenspan SL, Myers ER, Kiel DP, Parker RA, Hayes WC, Resnick NM. Fall direction, bone mineral density, and function: risk factors for hip fracture in frail nursing home elderly. *Am J Med*. 1998;104(6):539-545.

42. Butler M, Forte M, Kane RL, et al. Treatment of common hip fractures. *Evidence Report/Technology Assessment*. 2009;(184):1-v.

43. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults — United States. *JSafRes*. 2016;58(Journal Article):99-103. doi:10.1016/j.jsr.2016.05.001

44. Nyberg L, Gustafson Y, Berggren D, Brännström B, Bucht G. Falls leading to femoral neck fractures in lucid older people. *Journal of the American Geriatrics Society*. 1996;44(2):156-160. doi:10.1111/j.1532-5415.1996.tb02432.x

45. Dargent-Molina P, Favier F, Grandjean H, et al. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet*. 1996;348(9021):145-149. doi:10.1016/s0140-6736(96)01440-7

46. Vincent GK, Velkoff VA. *The Next Four Decades: The Older Population in the United States: 2010 to 2050*. US Census Bureau; 2010. https://www.census.gov/library/publications/2010/demo/p25-1138.html

47. Haleem S, Lutchman L, Mayahi R, Grice JE, Parker MJ. Mortality following hip fracture: Trends and geographical variations over the last 40 years. *Injury*. 2008;39(10):1157-1163. doi:10.1016/j.injury.2008.03.022

48. Doyle DJ, Garmon EH. *American Society of Anesthesiologists Classification (ASA Class)*. StatPearls Publishing; 2019. Accessed August 18, 2019. https://www.ncbi.nlm.nih.gov/books/NBK441940/

49. Mukaetova-Ladinska E, McKeith I. Delirium and dementia. *Medicine*. 2004;32(8):44-47. doi:10.1383/medc.32.8.44.43171

50. Alzheimer's Disease Fact Sheet. National Institute on Aging. Accessed September 4, 2019. https://www.nia.nih.gov/health/alzheimers-disease-fact-sheet

51. APA Work Group on Alzheimer's Disease and other Dementias, Rabins PV, Blacker D, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry*. 2007;164(12 Suppl):5-56.

52. What is dementia? Symptoms, types, and diagnosis. National Institute on Aging. Accessed September 4, 2019. https://www.nia.nih.gov/health/what-dementia-symptoms-types-and-diagnosis

53. Holsinger T, Deveau J, Boustani M, Williams JW. Does this patient have dementia? *JAMA*. 2007;297(21):2391-2404. doi:10.1001/jama.297.21.2391

54. Roberts RO, Christianson TJH, Kremers WK, et al. Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. *JAMA Neurol*. 2016;73(1):93-101. doi:10.1001/jamaneurol.2015.2952

55. Tonacci A, Bruno RM, Ghiadoni L, et al. Olfactory evaluation in mild cognitive impairment: correlation with neurocognitive performance and endothelial function. *Eur J Neurosci*. 2017;45(10):1279-1288. doi:10.1111/ejn.13565

56. Lauriello J, Bustillo J, Horan WP, Keith SJ. The patient with first episode psychosis. *J Psychiatr Pract*. 2001;7(2):123-132.

57. Boustani M, Peterson B, Hanson L, Harris R, Lohr KN, U.S. Preventive Services Task Force. Screening for dementia in primary care: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2003;138(11):927-937. doi:10.7326/0003-4819-138-11-200306030-00015

58. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *JPsychiatrRes*. 1975;12(3):189-198. doi:10.1016/0022-3956(75)90026-6

59. Scanlan J, Borson S. The Mini-Cog: receiver operating characteristics with expert and naïve raters. *Int J Geriatr Psychiatry*. 2001;16(2):216-222.

60. Teng EL, Chui HC. The Modified Mini-Mental State (3MS) examination. *JClinPsychiatry*. 1987;48(8):314-318.

61. Beishuizen SJE, Munster BC, Jonghe A, Abu-Hanna A, Buurman BM, Rooij SE. Distinct cognitive trajectories in the first year after hip fracture. *JAmGeriatrSoc*. 2017;65(5):1034-1042. doi:10.1111/jgs.14754

62. Grace J, Nadler JD, White DA, et al. Folstein vs Modified Mini-Mental State Examination in geriatric stroke: Stability, validity, and screening utility. *Arch Neurol*. 1995;52(5):477-484. doi:10.1001/archneur.1995.00540290067019

63. Van Patten R, Britton K, Tremont G. Comparing the Mini Mental State Examination and the Modified Mini Mental State Examination in the detection of mild cognitive impairment in older adults. *International Psychogeriatrics*. 2018;31. doi:10.1017/S1041610218001023

64. De J, Wand APF. Delirium screening: A systematic review of delirium screening tools in hospitalized patients. *The Gerontologist*. 2015;55(6):1079-1099. doi:10.1093/geront/gnv100

65. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948. doi:10.7326/0003-4819-113-12-941

66. Friedman SM, Menzies IB, Bukata SV, Mendelson DA, Kates SL. Dementia and hip fractures: Development of a pathogenic framework for understanding and studying risk. *Geriatric Orthopaedic Surgery & Rehabilitation*. 2010;1(2):52-62. doi:10.1177/2151458510389463

67. Mosk CA, Mus M, Vroemen JP, et al. Dementia and delirium, the outcomes in elderly hip fracture patients. *Clin Interv Aging*. 2017;12:421-430. doi:10.2147/CIA.S115945

68. Oh ES, Blennow K, Bigelow GE, et al. Abnormal CSF amyloid-β42 and tau levels in hip fracture patients without dementia. *PLOS ONE*. 2018;13(9):e0204695. doi:10.1371/journal.pone.0204695

69. Hugo J, Ganguli M. Dementia and cognitive impairment: Epidemiology, diagnosis, and treatment. *Clin Geriatr Med*. 2014;30(3):421-442. doi:10.1016/j.cger.2014.04.001

70. Yaffe K, Lindquist K, Vittinghoff E, et al. The effect of maintaining cognition on risk of disability and death. *JAmGeriatrSoc*. 2010;58(5):889-894.

71. Givens JL, Sanft TB, Marcantonio ER. Functional recovery after hip fracture: The combined effects of depressive symptoms, cognitive impairment, and delirium. *JAmGeriatrSoc*. 2008;56(6):1075-1079. doi:10.1111/j.1532-5415.2008.01711.x

72. Beam CR, Kaneshiro C, Jang JY, Reynolds CA, Pedersen NL, Gatz M. Differences between women and men in incidence rates of dementia and Alzheimer's disease. *J Alzheimers Dis*. 2018;64(4):1077-1083. doi:10.3233/JAD-180141

73. Mundi S, Chaudhry H, Bhandari M. Systematic review on the inclusion of patients with cognitive impairment in hip fracture trials: a missed opportunity? *Canadian Journal of Surgery*. 2014;57(4):E141-E145. doi:10.1503/cjs.023413

74. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Arch Intern Med*. 2001;161(20):2467-2473. doi:10.1001/archinte.161.20.2467

75. Chin Y, Koh G, Tay Y, Tan C, Merchant R. Underdiagnosis of delirium on admission and prediction of patients who will develop delirium during their inpatient stay: a pilot study. *smedj*. 2016;57(01):18-21. doi:10.11622/smedj.2016007

76. Trzepacz PT, Franco JG, Meagher DJ, et al. Delirium phenotype by age and sex in a pooled data set of adult patients. *JNP*. 2018;30(4):294-301. doi:10.1176/appi.neuropsych.18020024

77. Wilson RS, Yu L, Leurgans SE, Bennett DA, Boyle PA. Proportion of cognitive loss attributable to terminal decline. *Neurology*. 2020;94(1):e42-e50. doi:10.1212/WNL.0000000000008671

78. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. *The Journals of Gerontology: Series A: Biological Sciences and Medical Sciences*. 2000;55(9):M498-M507. doi:10.1093/gerona/55.9.M498

79. Magaziner J, Simonsick EM, Kashner TM, Hebel JR, Kenzora JE. Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. *J Gerontol*. 1990;45(3):M101-107.

80. Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in White women aged 70 years and older. *AmJPublic Health*. 1997;87(10):1630-1636.

81. Tang VL, Sudore R, Cenzer IS, et al. Rates of recovery to pre-fracture function in older persons with hip fracture: an observational study. *J Gen Intern Med*. 2017;32(2):153-158. doi:10.1007/s11606-016-3848-2

82. Buecking B, Bohl K, Eschbach D, et al. Factors influencing the progress of mobilization in hip fracture patients during the early postsurgical period?—A prospective observational study. *Archives of Gerontology and Geriatrics*. 2015;60(3):457-463. doi:10.1016/j.archger.2015.01.017

83. Panula J, Pihlajamaki H, Mattila VM. Mortality and cause of death in hip fracture patients aged 65 or older: a population-based study. *BMC MusculoskeletDisord*. 2011;12(Journal Article). doi:10.1186/1471-2474-12-105

84. Jones CA, Jhangri GS, Feeny DH, Beaupre LA. Cognitive status at hospital admission: Postoperative trajectory of functional recovery for hip fracture. *GERONA*. 2017;72(1):61-67. doi:10.1093/gerona/glv138

85. McGilton KS, Chu CH, Naglie G, Wyk PM, Stewart S, Davis AM. Factors influencing outcomes of older adults after undergoing rehabilitation for hip fracture. *JAmGeriatrSoc*. 2016;64(8):1601-1609. doi:10.1111/jgs.14297

86. Lee SY, Yoon B-H, Beom J, Ha Y-C, Lim J-Y. Effect of lower-limb progressive resistance exercise after hip fracture surgery: A systematic review and meta-analysis of randomized controlled studies. *Journal of the American Medical Directors Association*. 2017;18(12):1096.e19-1096.e26. doi:10.1016/j.jamda.2017.08.021

87. Lima CA, Sherrington C, Guaraldo A, et al. Effectiveness of a physical exercise intervention program in improving functional mobility in older adults after hip fracture in later stage rehabilitation: protocol of a randomized clinical trial (REATIVE Study). *BMC Geriatr*. 2016;16. doi:10.1186/s12877-016-0370-7

88. Mizrahi EH, Harel N, Heymann AD, et al. The relation between gain in cognition during rehabilitation on functional outcome among hip fracture adult patients with and without pre- hip fracture dementia. *Archives of Gerontology and Geriatrics*. 2018;78(Generic):177-180. doi:10.1016/j.archger.2018.06.016

89. Ishidou Y, Koriyama C, Kakoi H, et al. Predictive factors of mortality and deterioration in performance of activities of daily living after hip fracture surgery in Kagoshima, Japan: Mortality and function after hip fracture. *Geriatrics & Gerontology International*. 2017;17(3):391-401. doi:10.1111/ggi.12718

90. Mundi S, Pindiprolu B, Simunovic N, Bhandari M. Similar mortality rates in hip fracture patients over the past 31 years: A systematic review of RCTs. *Acta Orthopaedica*. 2014;85(1):54-59. doi:10.3109/17453674.2013.878831

91. Fakler JKM, Grafe A, Dinger J, Josten C, Aust G. Perioperative risk factors in patients with a femoral neck fracture - influence of 25-hydroxyvitamin D and C-reactive protein on postoperative medical complications and 1-year mortality. *BMC Musculoskeletal Disorders*. 2016;17:51-51. doi:10.1186/s12891-016-0906-1

92. Juliebo V, Krogseth M, Skovlund E. Medical treatment predicts mortality after hip fracture. *JGerontolA BiolSciMedSci*. 2010;65(Journal Article). doi:10.1093/gerona/glp199

93. Orwig D, Hochberg MC, Gruber-Baldini AL, et al. Examining differences in recovery outcomes between male and female hip fracture patients: Design and baseline results of a prospective cohort study from the Baltimore Hip Studies. *J Frailty Aging*. 2018;7(3):162-169. doi:10.14283/jfa.2018.15

94. Cristancho P, Lenze EJ, Avidan MS, Rawson KS. Trajectories of depressive symptoms after hip fracture. *Psychological Medicine*. 2016;46(7):1413-1425. doi:10.1017/S0033291715002974

95. Jette AM. Functional Status Index: reliability of a chronic disease evaluation instrument. *Arch Phys Med Rehabil*. 1980;61(9):395-401.

96. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol*. 1994;49(2):M85-M94. doi:10.1093/geronj/49.2.M85

97. Guralnik JM, Ferrucci L, Pieper CF, et al. Lower extremity function and subsequent disability: Consistency across studies, predictive models, and value of gait speed alone compared with the Short Physical Performance Battery. *J Gerontol A Biol Sci Med Sci*. 2000;55(4):M221-M231. doi:10.1093/gerona/55.4.M221

98. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-58. doi:10.1001/jama.2010.1923

99. Middleton A, Fritz SL, Lusardi M. Walking speed: The functional vital sign. *J Aging Phys Act*. 2015;23(2):314-322. doi:10.1123/japa.2013-0236

100. Dipietro L, Caspersen CJ, Ostfeld AM, Nadel ER. A survey for assessing physical activity among older adults. *Med Sci Sports Exerc*. 1993;25(5):628-642.

101. Rohm Young D, Ha Jee S, Appel LJ. A comparison of the Yale Physical Activity Survey with other physical activity measures. *Medicine & Science in Sports & Exercise*. 2001;33(6):955.

102. Bornstein RA, Suga LJ. Educational level and neuropsychological performance in healthy elderly subjects. *Developmental Neuropsychology*. 1988;4(1):17-22. doi:10.1080/87565648809540386

103. Hooper H E. The Hooper Visual Organization Test (VOT) manual. Published online 1958.

104. Ashendorf L, Jefferson AL, O'Connor MK, Chaisson C, Green RC, Stern RA. Trail Making Test errors in normal aging, Mild cognitive impairment, and dementia. *Arch Clin Neuropsychol*. 2008;23(2):129-137. doi:10.1016/j.acn.2007.11.005

105. Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*. 2004;19(2):203-214. doi:10.1016/S0887-6177(03)00039-8

106. Reitan RM. Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*. 1958;(8):271-276.

107. Richardson ED, Marottoli RA. Education-specific normative data on common neuropsychological indices for individuals older than 75 years. *Clinical Neuropsychologist*. 1996;10(4):375-381. doi:10.1080/13854049608406698

108. Bornstein RA. Normative data on selected neuropsychological measures from a nonclinical sample. *Journal of Clinical Psychology*. 1985;41(5):651-659. doi:10.1002/1097-4679(198509)41:5<651::AID-JCLP2270410511>3.0.CO;2-C

109. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological tests' norms above age 55: COWAT, BNT, MAE token, WRAT-R reading, AMNART, STROOP, TMT, and JLO. *The Clinical Neuropsychologist*. 1996;10(3):262-278. doi:10.1080/13854049608406689

110. Ble A, Volpato S, Zuliani G, et al. Executive function correlates with walking speed in older persons: the InCHIANTI study. *J Am Geriatr Soc*. 2005;53(3):410-415. doi:10.1111/j.1532-5415.2005.53157.x

111. Salthouse TA. What cognitive abilities are involved in trail-making performance? *Intelligence*. 2011;39(4):222-232. doi:10.1016/j.intell.2011.03.001

112. Lopez MN, Lazar MD, Oh S. Psychometric properties of the Hooper Visual Organization Test. *Assessment*. 2003;10(1):66-70. doi:10.1177/1073191102250183

113. DeVries MR. Analysis of group differences and predictors of Hooper Visual Organization Test scores. :157.

114. Haviland AM, Jones BL, Nagin DS. Group-based Trajectory Modeling extended to account for nonrandom participant attrition. *Sociological Methods & Research*. 2011;40(2):367-390. doi:10.1177/0049124111400041

115. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2018;27(7):2015-2023. doi:10.1177/0962280216673085

116. Olofsson B, Persson M, Bellelli G, Morandi A, Gustafson Y, Stenvall M. Development of dementia in patients with femoral neck fracture who experience postoperative delirium—a three-year follow-up study. *IntJGeriatrPsychiatry*. 2018;(Journal Article). doi:10.1002/gps.4832

117. Beloosesky Y, Grinblat J, Epelboym B, Weiss A, Grosman B, Hendel D. Functional gain of hip fracture patients in different cognitive and functional groups. *Clinical Rehabilitation*. 2002;16(3):321-328.

118. Mitchell R, Harvey L, Brodaty H, Draper B, Close J. Hip fracture and the influence of dementia on health outcomes and access to hospital-based rehabilitation for older individuals. *Disability & Rehabilitation*. 2016;38(23):2286-2295. doi:10.3109/09638288.2015.1123306

119. Jones TG, Schinka JA, Vanderploeg RD, Small BJ, Graves AB, Mortimer JA. 3MS normative data for the elderly. *Archives of Clinical Neuropsychology*. 2002;17(2):171-177. doi:10.1016/S0887-6177(00)00108-6

120. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383. doi:10.1016/0021-9681(87)90171-8

121. Haneuse S, Lee KH. Semi-competing risks data analysis: Accounting for death as a competing risk when the outcome of interest is non-terminal. *CirculationCardiovascular quality and outcomes*. 2017;9(3):322-331. doi:10.1161/CIRCOUTCOMES.115.001841

122. Thomas K, Christine L. Rehabilitation care after hip fracture in older patients with cognitive impairment: Systematic review. *Int J Phys Med Rehabil*. 2016;04(03). doi:10.4172/2329-9096.1000336

123. Abraham DS, Barr E, Ostir GV, et al. Residual disability, mortality, and nursing home placement after hip fracture over 2 decades. *Archives of Physical Medicine and Rehabilitation*. 2019;100(5):874-882. doi:10.1016/j.apmr.2018.10.008

124. Baker NL, Cook MN, Arrighi HM. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. *Age Ageing*. 2011;40(Journal Article). doi:10.1093/ageing/afq146

125. Healee DJ, McCallin A, Jones M. Restoring: How older adults manage their recovery from hip fracture. *International Journal of Orthopaedic and Trauma Nursing*. 2017;26:30-35. doi:10.1016/j.ijotn.2017.03.001

126. Magaziner J, Fredman L, Hawkes W, et al. Changes in functional status attributable to hip fracture: a comparison of hip fracture patients to community-dwelling aged. *Am J Epidemiol*. 2003;157(11):1023-1031.

127. Ariza-Vega P, Lozano-Lozano M, Olmedo-Requena R, Martín-Martín L, Jiménez-Moleón JJ. Influence of cognitive impairment on mobility recovery of patients with hip fracture. *American Journal of Physical Medicine & Rehabilitation*. 2017;96(2):109-115. doi:10.1097/PHM.0000000000000550

128. Seematter-Bagnoud L, Frascarolo S, Büla CJ. How much do combined affective and cognitive impairments worsen rehabilitation outcomes after hip fracture ? *BMC Geriatr*. 2018;18(1):71. doi:10.1186/s12877-018-0763-x

129. Söderqvist A, Miedel R, Ponzer S, et al. The influence of cognitive function on outcome after a hip fracture. *Journal of Bone & Joint Surgery, American Volume*. 2006;88(10):2115-2123.

130. Morghen S, Gentile S, Ricci E, Guerini F, Bellelli G, Trabucchi M. Rehabilitation of older adults with hip fracture: Cognitive function and walking abilities: Dementia

and hip fracture rehabilitation. *Journal of the American Geriatrics Society*. 2011;59(8):1497-1502. doi:10.1111/j.1532-5415.2011.03496.x

131. Beishuizen SJE, Scholtens RM, Munster BC, Rooij SE. Unraveling the relationship between delirium, brain damage, and subsequent cognitive decline in a cohort of individuals undergoing surgery for hip fracture. *JAmGeriatrSoc*. 2017;65(1):130-136. doi:10.1111/jgs.14470

132. Berry SD, Samelson EJ, Ngo L, Bordes M, Broe KE, Kiel DP. Subsequent fracture in nursing home residents with a hip fracture: A competing risks approach. *J Am Geriatr Soc*. 2008;56(10):1887-1892. doi:10.1111/j.1532-5415.2008.01918.x

133. Liu H-Y, Wang H-P, Chen C-Y, et al. Subjective memory complaints predict poorer functional recovery during the first year following hip-fracture surgery among elderly adults. *Int J Geriatr Psychiatry*. Published online June 8, 2020. doi:10.1002/gps.5358

134. Weeks DL, Ambrose SB, Tindall AG. The utility of the Modified Mini-Mental State Examination in inpatient rehabilitation for traumatic brain injury: preliminary findings. *Brain Injury*. 2020;34(7):881-888. doi:10.1080/02699052.2020.1761564

135. Tamkin AS, Jacobsen R. Age-related norms for the Hooper Visual Organization Test. *J Clin Psychol*. 1984;40(6):1459-1463. doi:10.1002/1097-4679(198411)40:6<1459::aid-jclp2270400633>3.0.co;2-3

136. Pavasini R, Guralnik J, Brown JC, et al. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. *BMC Medicine*. 2016;14(1):215. doi:10.1186/s12916-016-0763-7

137. Andruff H, Carraro N, Thompson A, Gaudreau P, Louvet B. Latent Class Growth Modelling: A tutorial. *TQMP*. 2009;5(1):11-24. doi:10.20982/tqmp.05.1.p011

138. Jones BL, Nagin DS. Advances in Group-Based Trajectory Modeling and an SAS procedure for estimating them. *Sociological Methods & Research*. 2007;35(4):542-571. doi:10.1177/0049124106292364

139. Salthouse TA. Selectivity of attrition in longitudinal studies of cognitive functioning. *J Gerontol B Psychol Sci Soc Sci*. 2014;69(4):567-574. doi:10.1093/geronb/gbt046

140. Burns A, Younger J, Morris J, et al. Outcomes following hip fracture surgery: A 2-year prospective study. *The American Journal of Geriatric Psychiatry*. 2014;22(8):838-844. doi:10.1016/j.jagp.2013.01.047

141. Fishman E. Risk of developing dementia at older ages in the United States. *Demography*. 2017;54(5):1897-1919. doi:10.1007/s13524-017-0598-7

142. Fischer K, Trombik M, Freystätter G, Egli A, Theiler R, Bischoff-Ferrari HA. Timeline of functional recovery after hip fracture in seniors aged 65 and older: a prospective observational analysis. *Osteoporos Int*. 2019;30(7):1371-1381. doi:10.1007/s00198-019-04944-5

143. von Friesendorff M, McGuigan FE, Wizert A, et al. Hip fracture, mortality risk, and cause of death over two decades. *Osteoporos Int*. 2016;27(10):2945-2953. doi:10.1007/s00198-016-3616-5

144. Ruggiero C, Bonamassa L, Pelini L, et al. Early post-surgical cognitive dysfunction is a risk factor for mortality among hip fracture hospitalized older persons. *Osteoporos Int*. 2017;28(2):667-675. doi:10.1007/s00198-016-3784-3

145. Tarazona-Santabalbina FJ, Belenguer-Varea Á, Daudi ER, et al. Severity of cognitive impairment as a prognostic factor for mortality and functional recovery of geriatric patients with hip fracture. *Geriatrics & Gerontology International*. 2015;15(3):289-295. doi:10.1111/ggi.12271

146. Witlox J, Eurelings LM, de Jonghe JM, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis. *JAMA*. 2010;304(4):443-451.

147. Katsoulis M, Benetou V, Karapetyan T, et al. Excess mortality after hip fracture in elderly persons from Europe and the USA: the CHANCES project. *JInternMed*. 2017;281(3):300-310. doi:10.1111/joim.12586

148. Barceló M, Torres OH, Mascaró J, Casademont J. Hip fracture and mortality: study of specific causes of death and risk factors. *Arch Osteoporos*. 2021;16(1):15. doi:10.1007/s11657-020-00873-7

149. ICD-10 Codes, ICD-10 Converter, ICD-9 to ICD-10 Codes Online Coding Translator Tool. Accessed October 7, 2019. https://www.aapc.com/icd-10/codes/

150. Lee S, Lee DK. What is the proper way to apply the multiple comparison test? *Korean J Anesthesiol*. 2018;71(5):353-360. doi:10.4097/kja.d.18.00242

151. Parker M, Johansen A. Hip fracture. *BMJ*. 2006;333(7557):27-30.

152. Solomon DH, Johnston SS, Boytsov NN, McMorrow D, Lane JM, Krohn KD. Osteoporosis medication use after hip fracture in U.S. patients between 2002 and 2011. *J Bone Miner Res*. 2014;29(9):1929-1937. doi:10.1002/jbmr.2202

153. Löfman O, Berglund K, Larsson L, Toss G. Changes in hip fracture epidemiology: redistribution between ages, genders and fracture types. *Osteoporos Int*. 2002;13(1):18-25. doi:10.1007/s198-002-8333-x

154. Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: what we need to know and do. *BJA: British Journal of Anaesthesia*. 2017;119(suppl_1):i115-i125. doi:10.1093/bja/aex354

155. Seitz DP, Gill SS, Gruneir A, et al. Effects of dementia on postoperative outcomes of older adults with hip fractures: a population-based study. *J Am Med Dir Assoc*. 2014;15(5):334-341. doi:10.1016/j.jamda.2013.12.011

156. Scheltens P, Rockwood K. How golden is the gold standard of neuropathology in dementia? *Alzheimers Dement*. 2011;7(4):486-489. doi:10.1016/j.jalz.2011.04.011

157. Liu H-Y, Yang C-T, Tseng M-Y, et al. Trajectories in postoperative recovery of elderly hip-fracture patients at risk for depression: A follow-up study. *Rehabilitation Psychology*. 2018;63(3):438-446. doi:10.1037/rep0000130

158. Jones CA, Jhangri GS, Feeny DH, Beaupre LA. Cognitive status at hospital admission: Postoperative trajectory of functional recovery for hip fracture. *J Gerontol A Biol Sci Med Sci*. 2017;72(1):61-67. doi:10.1093/gerona/glv138

159. Chen TY, Peronto CL, Edwards JD. Cognitive function as a prospective predictor of falls. *J Gerontol B Psychol Sci Soc Sci*. 2012;67(6):720-728. doi:10.1093/geronb/gbs052

160. Jorm AF. A short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE): development and cross-validation. *Psychol Med*. 1994;24(1):145-153. doi:10.1017/s003329170002691x

161. Boss L, Kang D-H, Marcus M, Bergstrom N. Endogenous sex hormones and cognitive function in older adults: A systematic review. *West J Nurs Res*. 2014;36(3):388-426. doi:10.1177/0193945913500566

162. Garrett SL, Sawyer P, Kennedy RE, et al. Racial and sex differences in associations between activities of daily living and cognition in community-dwelling older adults. *Journal of the American Geriatrics Society*. 2013;61(12):2174-2180. doi:https://doi.org/10.1111/jgs.12543

163. Mattisson L, Bojan A, Enocson A. Epidemiology, treatment and mortality of trochanteric and subtrochanteric hip fractures: data from the Swedish fracture register. *BMC Musculoskeletal Disorders*. 2018;19(1):369-369. doi:10.1186/s12891-018-2276-3

164. Xu J, Kochanek KD, Murphy SL, Tejada-Vera B. Deaths: final data for 2014. National Center for Health Statistics (U.S.). Division of Vital Statistics., ed. *National vital statistics reports*. 2016;65(4). https://stacks.cdc.gov/view/cdc/40133

165. Aarden JJ, van der Esch M, Engelbert RHH, van der Schaaf M, de Rooij SE, Buurman BM. Hip fractures in older patients: Trajectories of disability after surgery. *J Nutr Health Aging*. 2017;21(7):837-842. doi:10.1007/s12603-016-0830-y

166. Diem SJ, Vo TN, Langsetmo L, et al. Impact of Competing Risk of Mortality on Association of Cognitive Impairment With Risk of Hip Fracture in Older Women. *J Bone Miner Res*. 2018;33(9):1595-1602. doi:10.1002/jbmr.3462

167. Proust-Lima C, Dartigues J-F, Jacqmin-Gadda H. Joint modeling of repeated multivariate cognitive measures and competing risks of dementia and death: a latent process and latent class approach. *Statistics in Medicine*. 2016;35(3):382-398. doi:https://doi.org/10.1002/sim.6731

168. Barrett JK, Siannis F, Farewell VT. A semi-competing risks model for data with interval-censoring and informative observation: An application to the MRC cognitive function and ageing study. *StatMed*. 2010;30(1):1-10. doi:10.1002/sim.4071

169. Mitchell R, Ting HP, Draper B, et al. Frailty and risk of re-hospitalisation and mortality for aged care residents following a fall injury hospitalisation. *Australas J Ageing*. Published online September 3, 2020. doi:10.1111/ajag.12847