

Curriculum Vitae

Miriam Doyinsola Bailey, MPH, PhD
Graduate Research Assistant, Department of Epidemiology and Public Health
University of Maryland School of Medicine

Contact Information

Department of Epidemiology and Public Health
School of Medicine
University of Maryland, Baltimore
MSTF Suite 257
10 S. Pine St.
Baltimore, Maryland, 21201
Phone: 410-706-0074
doyinsola.bailey@gmail.com

Education

Sept 2015 – May 2022	Ph.D. Molecular Epidemiology University of Maryland School of Medicine Baltimore, MD
Sept 2012 - May 2014	M.P.H. Hospital and Molecular Epidemiology University of Michigan School of Public Health Ann Arbor, MI
Sept 2007 - May 2010	B.Sc. Biochemistry University of Ghana (Legon) Accra, Ghana

Employment History

2015 - current	Graduate Research Assistant University of Maryland School of Medicine Department of Epidemiology and Public Health Baltimore, MD
2013 - 2015	Research Assistant Center for Molecular and Clinical Epidemiology of Infectious Diseases University of Michigan School of Public Health Ann Arbor, MI
2013	Research Intern International Centre of Excellence for Malaria Research Blantyre, Malawi

2011 - 2012
Research Assistant
Malaria Research Laboratory
Nigerian Institute of Medical Research
Lagos, Nigeria

Teaching Service

2016 (Fall) Teaching Assistant, PREV 780, Molecular Epidemiology, 9 students, 3 hour/week, 4 months/year
2017 (Fall) Teaching Assistant, PREV 600, Principles of Epidemiology, 20 students, 3 hour/week, 4 months/year
2018 (Fall) Teaching Assistant, PREV 780, Molecular Epidemiology, 9 students, 3 hour/week, 4 months/year

Student Service

2019 - 2021 Student Representative, Graduate Program Committee
Department of Epidemiology and Public Health
University of Maryland, Baltimore
2013 - 2014 Epidemiology Student Representative,
Epidemiology Section, Michigan Public Health Association
2009 - 2010 Member, Planning Committee
Ghana Biochemistry Students' Association
University of Ghana, Legon

Grants and Contract Support

Active Grants

7/7/2021-present
Role: Graduate Research Assistant, 100%
Title: "Impact of Treated and Untreated OSA on 30-Day Hospital Readmission among Medical Beneficiaries with Pre-existing Cardiovascular Disease"
American Academy of Sleep Medicine Foundation
Diversity Supplement (PI Albrecht)
Grant Number: #193-SR-18
Annual Direct Costs: \$28,650

Peer-reviewed Publications

1. **Ismail MD**, Luo T, McNamara S, Lansing B, Koo E, Mody L, Foxman B. Long-Term Carriage of Ciprofloxacin-Resistant Escherichia coli Isolates in High-Risk Nursing Home Residents. *Infect Control Hosp Epidemiol*. 2016 Apr. Epub 2016 Jan 19. PMID: 26782632.
2. Graham SE, Zhang L, Ali I, Cho YK, **Ismail MD**, Carlson HA, Foxman B. Prevalence of CTX-M extended-spectrum beta-lactamases and sequence type 131 in Korean blood, urine, and rectal Escherichia coli isolates. *Infect Genet Evol*. 2016 Jul. Epub 2016 Apr 19. PMID: 27101781.
3. Coalson JE, Walldorf JA, Cohee LM, **Ismail MD**, Mathanga D, Cordy RJ, Marti M, Taylor TE, Seydel KB, Laufer MK, Wilson ML. High prevalence of Plasmodium falciparum gametocyte infections in school-age children using molecular detection: patterns and predictors of risk from a cross-sectional study in southern Malawi. *Malar J*. 2016 Nov 4. PMID: 27809907
4. **Ismail MD**, Ali I, Hatt S, Salzman EA, Cronenwett AW, Marrs CF, Rickard, AH, Foxman, B. Association of Escherichia coli ST131 Lineage with risk of Urinary Tract Infection Recurrence among young women. *J Glob Antimicrob Resist*. 2018 Jun 16. PMID: 29258889.
5. Wickwire EM, **Bailey MD**, Somers VK, Srivastava MC, Scharf SM, Johnson AM, Albrecht JS. CPAP adherence reduces cardiovascular risk among older adults with obstructive sleep apnea. *Sleep Breath*. 2020 Nov 3. PMID: 33141315.
6. Wickwire EM, **Bailey MD**, Somers VK, Srivastava MC, Scharf SM, Johnson AM, Albrecht JS. CPAP adherence is associated with reduced risk for stroke among older adult Medicare beneficiaries with obstructive sleep apnea. *J Clin Sleep Med*. 2021 Jun 1. PMID: 33612161.
7. Wickwire EM, Jobe SL, Martin JL, Williams SG, Capaldi VF, Collen J, **Bailey MD**, Scharf SM, Johnson AM, Albrecht JS. Diagnosed or prescribed only? A national analysis of initial evaluation and management of insomnia among older adult Medicare beneficiaries. *Sleep Adv*. 2021 Oct 15.
8. Wickwire EM, **Bailey MD**, Somers VK, Oldstone LM, Srivastava MC, Johnson AM, Scharf SM, Albrecht JS. CPAP adherence is associated with reduced inpatient utilization among older adult Medicare beneficiaries with pre-existing cardiovascular disease. *J Clin Sleep Med*. 2022 Jan 1.

Non-Peer-reviewed Publications

1. Levin-Sparenberg E, Gicquelais R, Blanco N, **Ismail MD**, Lee KH, Foxman B. Ebola: The Natural and Human History of a Deadly Virus. *Am J Epidemiol*. 2014 Dec 17

Abstracts

1. Coalson JE, Walldorf JA, Marti MJ, Joice R, Seydel KB, **Ismail MD**, Mathanga DP, Kapito-Tembo AP, Taylor TE, Laufer MK, Wilson ML. "Submicroscopic Gametocytemia and Malaria in Malawi: Molecular identification and implications for transmission." American Society of Hygiene and Tropical Medicine. ASTMH 62nd Annual Meeting, Washington, DC. 13-17 Nov 2013. Poster presentation.
2. Coalson JE, Walldorf JA, Marti MJ, Joice R, Seydel KB, **Ismail MD**, Mathanga DP, Kapito-Tembo AP, Taylor TE, Laufer MK, Wilson ML. "Submicroscopic Gametocytemia and Malaria in Malawi: Molecular identification and implications for transmission." 16th International Congress on Infectious Diseases, Cape Town, South Africa. 2-5 April 2014. Poster presentation.
3. **Ismail MD**, Luo TL, Srinivasan U, McNamara SE, Lansing BJ, Koo E, Mody LR, Foxman B. "Long-term Carriage of Ciprofloxacin-Resistant *E. coli* isolates among Nursing Home (NH) Residents." IDWeek 2014: A joint meeting of IDSA, SHEA, HIVMA and PIDS. Philadelphia, PA. 8-12 Oct 2014. Poster presentation.
4. Coalson JE, Walldorf JA, Marti MJ, Joice R, Seydel KB, **Ismail MD**, Mathanga DP, Kapito-Tembo AP, Taylor TE, Laufer MK, Wilson ML. "Submicroscopic Gametocytemia and Malaria in Malawi: Molecular identification and implications for transmission." American Society of Hygiene and Tropical Medicine. ASTMH 63rd Annual Meeting, New Orleans, LA. 2-6 Nov 2014. Oral presentation.
5. Buchwald A, **Ismail MD**, Aceto C, Halbach A, Sixpence A, Chimenya M, Damson M, Sorkin J, Seydel K, Mathanga D, Taylor T, Laufer MK. "Clinical Implications of Asymptomatic Plasmodium falciparum Infections in Malawi." Open Forum Infectious Disease, October 2017. Oral Presentation.
6. **Ismail, MD**, Wickwire, E, Somers, V, Albrecht, J. "Risk of subsequent cardiovascular events among Medicare Beneficiaries diagnosed with Obstructive Sleep Apnea, treated with Continuous Positive Airway Pressure." 42nd Annual Graduate Research Conference, University of Maryland, Baltimore. Baltimore, MD. March 6, 2020. Poster presentation.
7. **Ismail, MD**, Albrecht, J. "Receipt of Treatment for Depression following Traumatic Brain Injury in Older Adults is Associated with Decreased Health Care Utilization." 42nd Annual Graduate Research Conference, University of Maryland, Baltimore. Baltimore, MD. March 6, 2020. Oral presentation.
8. **Ismail, D**, Wickwire, E, Somers, V, Albrecht, J. "Risk of subsequent cardiovascular events among Medicare Beneficiaries diagnosed with Obstructive Sleep Apnea, treated with Continuous Positive Airway Pressure." American Thoracic Society Annual Meeting. May 2020, Philadelphia, PA. Poster presentation.

9. **Bailey, MD**, Gambert, S, Gruber-Baldini, A, Guralnik, J, Kozar, R, Qato, DM, Shardell, M, Albrecht, JS “Traumatic Brain Injury and Risk of Long-Term Nursing Home Entry among Older Adults: An Analysis of Medicare Administrative Claims Data.” 15th Annual Aging Showcase, Johns Hopkins School of Public Health. Baltimore, MD. April 8, 2022. Poster presentation.
10. **Bailey, MD**, Wickwire, E, Albrecht, J. “Continuous Positive Airway Pressure Adherence and the Risk of 30-day Hospital Readmission in Older Adults with Obstructive Sleep Apnea and Cardiovascular Disease”. SLEEP 2022, 36th Annual Meeting of the Associated Professional Sleep Societies, LLC (APSS). June 2022, Charlotte, NC. Poster presentation.

Abstract

Title of Dissertation: **Long-term Recovery following Traumatic Brain Injury in Older Adults: A Retrospective Cohort Study of Medicare Administrative Claims Data**

Miriam Doyinsola Bailey, Doctor of Philosophy, 2022

Dissertation Directed By: Jennifer S. Albrecht, PhD

Associate Professor

Department of Epidemiology and Public Health

Background: Traumatic brain injury (TBI) is a leading cause of injury-related disability among older adults and there is increasing interest in long-term post-discharge management as this population grows. There is currently a lack of information on the long-term impact of having a TBI among older adults, and this is essential for informing post-injury interventions and policies directed at maintaining their independence and quality of life.

Objective: This study evaluated the effect of an isolated TBI on the long-term development of physical and psychological health outcomes in a nationally representative sample of older adult Medicare beneficiaries. Specifically, I evaluated the association between TBI and incident frailty, disability, nursing home (NH) entry, chronic pain, insomnia, depression, anxiety/PTSD.

Methods: I conducted a retrospective study of a 5% random sample of U.S. Medicare beneficiaries ≥ 65 years of age for years 2007-2015. I used cumulative logit regression

models with stabilized inverse probability weights to estimate the odds associated with an increase in frailty and disability as a function of injury status over 5 years. I also used Cox proportional hazards models with stabilized inverse probability of exposure weights to model time to nursing entry, chronic pain, insomnia, depression, anxiety/PTSD as a function of injury in the presence of death as a competing risk and generated hazard ratios (HR) and 95% confidence intervals (CI).

Results: I identified 207,355 adults aged ≥ 65 years, diagnosed with either a TBI, non-TBI trauma, or were uninjured between January 2008 and June 2015. The mean age was 77 ± 9 years, 86% were white ($n=177,419$), and 70% were female ($n=144,670$). I found that TBI increased the risk of all examined outcomes compared to the general population of Medicare beneficiaries. In addition, TBI increased the risk of frailty, NH placement, depression, and anxiety/PTSD compared to those with non-TBI trauma.

Conclusions: Among older adults, TBI was associated with a higher risk of adverse physical and psychological functioning outcomes. My findings suggest that older adults with TBI may benefit from targeted rehabilitation interventions to reduce the occurrence of these outcomes.

Long-term Recovery Following Traumatic Brain Injury in Older Adults:
A Retrospective Cohort Study of Medicare Administrative Claims Data

by
Miriam Doyinsola Bailey

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
2022

©Copyright 2022 by Miriam Doyinsola Bailey

All rights Reserved

DEDICATION

To myself for being naïve enough to start but stubborn enough to finish.

To my mother for the invaluable educational opportunities.

To the memory of my father whose excitement at the prospect of his daughter with a Ph.D. still rings in my ears.

To my amazing husband, daughter and pup who sacrificed so much.

To my siblings for keeping me financially and emotionally secure.

To true friends. May we all find a few!

Funlayo David
Yomi Ismail
Gerald Bailey
Tiwalayo Bailey
Riley Bailey
Ladi Ismail
Bimbo Dawodu
DeeJay Ismail
Precious Ismail

ACKNOWLEDGMENTS

First, I would also like to thank the American Academy of Sleep Medicine Foundation for their financial contribution towards my graduate research assistantship. I would also like to express my deep and sincere gratitude to my advisor and committee chair, Dr. Jennifer S. Albrecht. I appreciate the effort you put into rescuing me, sharing your research with me, mentoring me and, quite literally, dragging me to the finish line. Thank you for everything you taught me that I could not have learned elsewhere. I will carry that knowledge with me for the rest of my career.

I would like to thank the members of my dissertation committee, Dr. Steven Gambert, Dr. Ann Gruber-Baldini, Dr. Jack Guralnik, Dr. Rosemary Kozar, Dr. Michelle Shardell, and Dr. Danya Qato, for sharing their wealth of knowledge with me. I am so thankful for your willingness to give freely of your time and support. My appreciation also goes to the past and present faculty and staff of the Department of Epidemiology and Public Health for supporting my growth on this journey. A special thanks to Dr. Laura Hungerford, Dr. John Sorkin, and Mr. Jonathan Shinnick.

To my colleagues, now dear friends, Dr. Rotana Alsaggaf, Dr. Aparna Chauhan, Dr. O'Mareen Spence, Dr. Maya Lloyd, Dr. Jenna Coalson, Abigail Strane, MPH, Dr. Rachael Bush, Heather Olden, MPH, Dr. Rachel Sinicola, Dr. Chani Hodonsky, and Dr. Huajun Liang, I am so thankful for all the moments you shared your expertise with me. From epidemiology methods to SAS coding, venting sessions, hiking get-aways and everything in-between, thank you. To Ana Salas, José López Cobano, Celeste Doaks, and Laura Clayton. Your love, friendship, support, and perspective along this journey has been invaluable. Thank you.

Finally, I am extremely thankful to my family. Especially to my mother whose entire life has led me to this point. Mom, I thank you for creating invaluable educational opportunities for me, for instilling in me a strong passion for learning, for pushing me to think big, and for believing in my abilities to achieve my goals even when I did not. You are for sure my number one fan and you have given me the greatest gift. My dad, while he was alive, never failed to remind me how proud he was of me for taking this step. Dad, if tears could bring you back, you would be here to celebrate this milestone with me. I know, because I have cried so hard that you planted a seed and were not able to see it blossom. To my siblings, Ladi, Bimbo, DeeJay and Precious, thank you for the care packages, for always listening to me when I needed to talk and for reminding me that things will always work out. You are truly the best support system I could have asked for. To my godmother, Dr. Yemisi Abebe, who has been a pillar of love, guidance, and support since the day I was born. I love you and cannot express sufficiently just how important your presence has been in my life. To Joan Abebe, thank you for loving me unconditionally, for helping me decide what to eat, what to wear, which workout to do, what TV show to watch and for keeping my life balanced throughout this journey. Thank you for always cheering me up in challenging times. You are my ray of light.

And lastly, to my daughter Tiwalayo, I hope that you might be as proud to be my daughter as I am as proud to be your mother. To my husband Gerald, your love and support carried me through the times I considered giving up, and together we persevered! The joy in your eyes is my reassurance that I have made you proud. I love you.

TABLE OF CONTENTS

PREFACE.....	iii
DEDICATION.....	iii
ACKNOWLEDGMENTS.....	iv
LIST OF TABLES.....	x
LIST OF FIGURES.....	xii
LIST OF ABBREVIATIONS.....	xiii
CHAPTER I: INTRODUCTION AND SPECIFIC AIMS.....	1
A. Introduction.....	1
B. Specific Aims.....	2
CHAPTER II: BACKGROUND AND SIGNIFICANCE.....	4
A. Neuropathology of TBI.....	6
B. Sequelae of TBI.....	8
1. TBI and Frailty.....	9
2. TBI and Disability.....	11
3. TBI and Nursing Home Placement.....	11
4. TBI and Chronic Pain.....	12
5. TBI and Insomnia.....	13
6. TBI and Depression.....	14
7. TBI and Anxiety/PTSD.....	14
C. Significance.....	16

D. Innovation	17
CHAPTER III: METHODS	19
A. Study Design	19
B. Data Sources	19
C. Index Date	20
D. Coverage Criteria	21
E. Study Participants	22
F. Measures	22
1. Exposure Variable	22
2. Outcome Variables	26
3. Covariates	29
G. Sample Size and Power	30
1. Aims 1.1 – 1.2	30
2. Aims 1.3 – 2.2	30
H. Data Analysis	31
1. Aim 1.1	32
2. Aim 1.2	32
3. Aims 1.3-2.2	32
CHAPTER IV: RESULTS	34
A. AIM 1.1 MANUSCRIPT	35
B. AIM 1.3 MANUSCRIPT	49

CHAPTER V: ADDITIONAL RESULTS	66
A. Study Sample	66
B. Disability.....	67
C. Chronic Pain.....	70
D. Insomnia.....	73
E. Depression.....	76
F. Anxiety/PTSD.....	79
CHAPTER VI: DISCUSSION.....	82
A. Physical Health and Functioning Outcomes.....	83
1. Frailty.....	83
2. Disability.....	85
3. Nursing Home Placement.....	87
4. Chronic Pain.....	89
5. Insomnia.....	90
B. Psychological Health Outcomes.....	92
1. Depression.....	92
2. Anxiety/PTSD.....	93
C. Strengths	94
D. Limitations	95
E. Summary and Implications	100

APPENDIX A: Table of Relevant Codes for Identification of Measures from Medicare

Data 106

REFERENCES 114

LIST OF TABLES

Table 1. Baseline Characteristics of Medicare Beneficiaries ≥ 65 years, by Injury Type (2008-2015), (n=207,355).....	47
Table 2. Cumulative Logit Regression Analyses of Frailty, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=186,604)	48
Table 3. Baseline Characteristics of Community-Dwelling Medicare Beneficiaries ≥ 65 years, by Injury Type (2008-2015), (n=194,225)	64
Table 4. Outcomes of Medicare Beneficiaries ≥ 65 years, by Injury Type (2008-2015), (n=207,355).....	65
Table 5. Cox Regression Analyses of Time to Nursing Home Entry with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=194,255).....	65
Table 6. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥ 65 years, in the analysis of Risk of Disability (2008-2015) (n=207,355)	68
Table 7. Cumulative Logit Regression Analyses of Disability, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=207,355).....	69
Table 8. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥ 65 years, in the analysis of Risk of Chronic Pain (2008-2015) (n=162,752).....	71
Table 9. Cox Regression Analyses of Time to Chronic Pain with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=162,752).....	72
Table 10. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥ 65 years, in the analysis of Risk of Insomnia (2008-2015) (n=199,486).....	74
Table 11. Cox Regression Analyses of Time to Insomnia with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=199,486).....	75
Table 12. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥ 65 years, in the analysis of Risk of Depression (2008-2015) (n=174,452).....	77
Table 13. Cox Regression Analyses of Time to Depression with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=174,452).....	78
Table 14. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥ 65 years, in the analysis of Risk of Anxiety/PTSD (2008-2015) (n=184,580)	80

Table 15. Cox Regression Analyses of Time to Anxiety/PTSD with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=184,580).....	81
---	----

LIST OF FIGURES

Figure 1: Study Timeline	21
Figure 2: Flowchart detailing participant selection by injury group.....	66

LIST OF ABBREVIATIONS

ADRD	Alzheimer’s disease and related dementias
ANOVA	Analysis of Variance
CDC	Centers for Disease Control and Prevention
CCW	Chronic Conditions Warehouse
CFI	Claims-based Frailty Index
CI	Confidence Interval
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic Obstructive Pulmonary Disease
CTE	Chronic Traumatic Encephalopathy
DIB	Disability Insurance Benefits
ESRD	End-stage Renal Disease
FRI	Functioning-related Indicator
GAD	Generalized Anxiety Disorder
GCS	Glasgow Coma Scale
HR	Hazard Ratio
HrQOL	Health-related Quality of Life
ICD	International Classification of Disease
ICD-9-CM	International Classification of Disease, 9 th Revision, Clinical Modification
IPTW	Inverse Probability of Treatment Weights
IPW	Inverse Probability Weights
MS-DRG	Medicare Severity Diagnosis Related Groups
MDS	Minimum Data Set

NH	Nursing home
OASI	Old Age and Survivor's Insurance
OR	Odds Ratio
OREC	Original Reason for Entitlement Code
PTSD	Post-Traumatic Stress Disorder
RA	Rheumatoid Arthritis
RR	Risk/Rate Ratio
SD	Standard Deviation
SNF	Skilled Nursing Facility
TIA	Transient Ischemic Attack
TBI	Traumatic Brain Injury

CHAPTER I: INTRODUCTION AND SPECIFIC AIMS

A. Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States.^{1,2} Each year, approximately 1.7 million people sustain a TBI³ and, as of 2013, adults aged 75 years and older had the highest incidence of TBI.² From 2006 to 2014, the number of TBI-related emergency department visits, hospitalizations, and deaths increased by 53%,³ with the highest increases observed among older adults aged \geq 75 years.² Though the population is aging, the rapid rise in TBI-related hospital visits among the elderly U.S. population exceeded population growth in the same time frame.⁴ While improvements in trauma care have increased the chances of surviving a serious TBI,⁵⁻⁸ the prognosis among older adults has remained relatively unchanged.⁹ Little is known about post-discharge recovery after a TBI, especially among older adults who typically have higher death rates, slower rates of functional recovery, and experience worse functional outcomes compared to younger adults. Physical and psychological outcomes are commonly reported among younger adults who survive a TBI; however, less is known about these outcomes in older adults and when available, are estimated short-term. Physical functioning outcomes such as incident frailty and nursing home placement are especially important in older adults with TBI, but these outcomes have not yet been examined. Studies of psychological outcomes following TBI among older adults have reported increased rates of rates of depression,¹⁰ anxiety, and posttraumatic stress disorder (PTSD)¹¹ in the year following TBI compared to the pre-TBI period. However, these studies did not include control groups with other traumatic injuries to determine whether the higher risk is specifically due the brain injury or to general trauma. A better

understanding of long-term physical and psychological recovery can inform clinical guidelines and restructure injury care protocols, rehabilitation programs, and resource allocation for geriatric TBI care.

B. Specific Aims

The objective of this dissertation was to assess long-term recovery defined by physical and psychological functioning among older adults with TBI compared to older adults with non-TBI trauma (orthopedic fractures in other body regions) and to older adults with no injuries. I proposed to achieve this objective through the following specific aims:

Aim 1: Determine the association between TBI and physical functioning among older adults. Specifically, to examine the association between TBI and five measures of physical functioning that can be assessed in administrative claims data, in the following sub-aims:

- 1.1 Determine the association between TBI and incident frailty.
- 1.2 Determine the association between TBI and disability.
- 1.3 Determine the association between TBI and incident nursing home placement.
- 1.4 Determine the association between TBI and incident chronic pain.
- 1.5 Determine the association between TBI and incident insomnia.

Hypothesis: For each physical functioning measure, individuals who sustained a TBI will have a higher risk of the outcome compared to older adults with non-TBI trauma and older adults with no injuries.

Aim 2: Determine the association between TBI and psychological health among older adults. Specifically, to examine the association between TBI and two measures of psychological health that can be assessed using administrative claims data in the following sub-aims:

- 2.1 Determine the association between TBI and depression.
- 2.2 Determine the association between TBI and anxiety/post-traumatic stress disorder.

Hypothesis: For each psychological health measure, individuals who sustained a TBI will have a higher risk of the outcome compared to older adults with non-TBI trauma and older adults with no injuries.

CHAPTER II: BACKGROUND AND SIGNIFICANCE

Traumatic brain injury (TBI) is a leading cause of death and disability in the United States.^{1,2} Each year, approximately 1.7 million people sustain a TBI³ and, as of 2013, adults aged 75 years and older had the highest incidence of TBI.² From 2006 to 2014, the number of TBI-related emergency department visits, hospitalizations, and deaths increased by 53%,³ with the highest increases observed among older adults aged \geq 75 years.² Though the population is aging, the rapid rise in TBI-related hospital visits among the elderly U.S. population exceeded population growth in the same time frame.⁴ While improvements in trauma care have increased the chances of surviving a serious TBI,⁵⁻⁸ the prognosis among the elderly population has remained relatively unchanged.⁹

Older adult survivors of TBI typically have slower recovery periods, slower rates of functional recovery, and experience worse functional outcomes compared to younger patients with similar injury severity.¹²⁻¹⁵ Aging results in a progressive decline in molecular and cellular function¹⁶ that leads to a limited physiologic reserve and a higher number of comorbidities.¹⁷ This puts the older adult trauma population at high risk for poorer outcomes such as severe disability, functional decline, reduced ability to perform activities of daily living^{18,19} and death.^{19,20} As many as 48% of young adult survivors of TBI experience moderate to severe disability after injury,²¹⁻²⁴ and 52% experience chronic pain,²⁵ however little is known about these outcomes in older adults. Physical outcomes such as incident frailty and nursing home placement may especially be important in older adults with TBI, but these outcomes have not been examined, even in younger populations. TBI also results in psychological sequelae that impede return to normal functioning.²⁶⁻²⁸ Studies of psychological outcomes following TBI among older

adults have reported increased rates of rates of depression,²⁹ anxiety,¹¹ and posttraumatic stress disorder (PTSD)¹¹ in the year following TBI compared to the pre-TBI period, but these studies did not compare to a non-TBI trauma group to tease out the independent impact of trauma from that of TBI.

Longitudinal studies on recovery following TBI among older adults are few and limited. When available, these studies either track short-term outcomes (e.g., 30-day mortality and morbidity) or have limited follow-up post injury. Though meaningful, these studies fail to capture longer-term function and quality of life beyond survival.

Administrative claims-based studies provide an opportunity to follow large numbers of older adults with TBI over time. Existing claims-based studies have investigated health outcomes such as incidence of stroke or depression post-TBI among older adults^{11,29} but these studies focus only on short-term (up to 1 year) outcomes and do not include control groups with other traumatic injuries to help isolate the effect of TBI from the general effect of trauma. There have been few studies of long-term recovery outcomes (up to 5 years) among older adult TBI patients. A national analysis of functional and psychological outcomes following TBI will inform goals of care discussions between healthcare providers and families, support evidence-based clinical guideline development, and help in structuring injury care protocols, rehabilitation programs, and resource allocation for geriatric TBI care.

The objective of this dissertation was to assess long-term recovery in physical and psychological functioning among older adults with TBI compared to older adults with non-TBI moderate to severe injuries and to older adults with no injuries using Medicare administrative claims data from 2007-2015.

A. Neuropathology of TBI

Traumatic Brain Injury (TBI) is a broad term describing a wide range of injuries to the brain from an external, physical assault. It usually occurs when a blow or jolt to the head, or penetration of the skull leads to a disruption in normal brain function.³⁰ The degree of damage can depend on several factors, including the nature of the injury, the location and force of impact, as well as the depth and amount of brain penetration.³¹ The damage can either be confined to one area of the brain (focal) or in more than one area of the brain (diffuse), closed (non-penetrating) or open (penetrating), resulting in severity that ranges from a mild concussion to a severe injury, potentially leading to coma or death. Fall-related TBIs more commonly result in mass lesions, such as subdural hemorrhage, while motor vehicle accident–related TBIs more commonly result in diffuse axonal injury.³² The mechanism of a TBI is biologically important because it results in differences in the type of brain damage which may result in different clinical manifestations.

From a neuropathologic standpoint, TBI is characterized by changes in diverse cortical areas, subcortical structures, and the white matter tracts that connect them.³³ After a violent jolt or blow to the head, the soft brain hits the intracranial surface of the skull, which may damage the contact area. Any additional rotational movement to the brain following this impact may stretch or tear axons within white matter tracts, leading to diffuse axonal injury.^{34–37} Using rodent models, there is recent evidence to suggest this type of injury may impair neuronal function,³⁸ although the reason why remains unclear. Some research suggests diffuse axonal injury may induce neuronal degeneration³⁹ which could explain the pathological correlations between TBI and chronic neurodegenerative

diseases.⁴⁰ Other research suggests it may only induce neuronal atrophy due to axotomy of the axon initial segment.^{38,41} Any penetration of the brain structure can mechanically tear apart neurons and shear their axons to disrupt neuronal circuitry as well as damage the vasculature, allowing movement of blood and leukocytes⁴²⁻⁴⁴ which may induce necrotic cell loss and apoptosis of the surrounding cells.^{42,45,46} Soon after, proinflammatory cytokines are secreted into the perilesional region,⁴⁷⁻⁴⁹ causing further inflammation associated with gliosis, demyelination and continued apoptosis.³¹

In a healthy brain, cerebral blood flow provides an adequate supply of oxygen and nutrients through a dense network of arteries and capillaries.⁵⁰ Following a traumatic injury, there is an initial reduction in cerebral blood flow (within hours of the injury), which can remain low for days, depending on injury severity.⁵¹ Over the next few days to weeks there is usually a return of normal cerebral blood flow, which coincides with an increase in blood vessel density in the affected region.^{52,53} Similar to the uninjured brain, the constant supply of blood then needs to be maintained, and this occurs by cerebral vessels undergoing vasodilation in response to dilatory stimuli, termed cerebrovascular reactivity. Unfortunately, following a brain injury, cerebral blood vessels may be less able to respond to dilatory stimuli⁵⁴⁻⁵⁶ and this can lead to poor prognosis, including death.⁵⁷ In addition to these neuronal morphologic and functional alterations, TBI may also induce other pathophysiologic responses such as sustained proinflammatory cytokine upregulation, reduction in oligodendrocyte cell numbers, and glial reactivity.⁵⁸⁻⁶⁰

A TBI is usually diagnosed based on clinical observations and patient history such as duration of loss of consciousness and post traumatic amnesia.⁶¹ The severity of TBI can be classified as mild, moderate, or severe based on clinical presentation of a patient's

neurologic signs and symptoms. The most common measure of these symptoms is the Glasgow Coma Scale (GCS) which ranks functional ability from 1 (worst outcome) to 15 (best outcome), with a mild injury defined between 13 and 15 and moderate to severe TBI defined as $GCS < 13$.⁶²

In the acute period following a mild TBI, an individual may experience a brief loss of consciousness, transient confusion, disorientation or amnesia, and other neurologic and neuropsychological dysfunctions, such as seizures, headaches, dizziness, irritability, fatigue, and poor concentration.³¹ Subsequently, these symptoms may evolve into persistent low-grade headaches, pain, poor attention and concentration, fatigue, anxiety, and depression, some or all of which may continue for months to years.^{10,25,29,63,64}

Moderate TBIs are characterized by loss of consciousness lasting up to a few hours, confusion lasting from days to weeks, and physical, cognitive or behavioral impairments lasting for months, or permanently.⁶² In comparison, a severe brain injury can sometimes result in a prolonged unconscious or a vegetative state that can last for days to months.⁶² Following a severe injury, patients may experience physical limitations (headaches, nausea/vomiting, pupil dilation, slurred speech, aphasia, sensory deficits), along with cognitive (memory, attention, concentration) and emotional (motivation, irritability, aggression) dysfunctions or even death.³¹

B. Sequelae of TBI

In the past decade, TBI has been recognized as a chronic health condition⁶⁵ with consequences that can have lasting effects on recovery and overall quality of life. This

has increased interest in identifying and managing outcomes that could potentially develop or deteriorate over time in order to optimize recovery outcomes. Corrigan *et al.*⁶⁶ found that more than half of individuals who receive inpatient rehabilitation for TBI will deteriorate or die within 5 years post-injury. Several studies have also found that pre-existing^{67,68} and incident conditions^{10,11,29,69,70} are quite common among older individuals who seek medical care for TBI, complicating management and recovery. Some commonly studied conditions resulting from TBI include sleep disturbances, depression, cognitive deficits, and psychiatric illnesses.^{10,63,70-76} Lesser studied conditions include neuroendocrine dysregulation and metabolic dysregulation.^{46,77,78} The focus of the following sections will be on the primary outcomes of this dissertation: frailty, nursing home placement, disability, chronic pain, insomnia, depression, anxiety/PTSD.

1. TBI and Frailty

Frailty is an emerging global health burden among the aging population⁷⁹ that may be linked to TBI.⁷⁸ It is described as a clinical syndrome resulting in functional declines across multiple physiological systems, characterized by decreased homeostatic reserves and increased vulnerability to important adverse health outcomes including death, hospitalization and disability and admission to long-term care.^{80,81} From a neuropathological perspective, this reduced physiological reserve may increase the susceptibility of the central nervous system to insults from TBI.^{80,82} Though little is known about how TBI influences frailty, it has become increasingly evident that chronic disorders can exacerbate risk of frailty in older individuals. Such associations have been reported between frailty and chronic kidney disease,⁸³ atrial fibrillation,⁸⁴ chronic

obstructive pulmonary disease,⁸⁵ anemia,⁸⁶ hypertension, cardiovascular disease and stroke.⁸⁷⁻⁹¹ These comorbidities share common pathophysiological determinants like neuroendocrine disturbances and chronic inflammation which are also common consequences of TBI.⁷⁸

In the United States, a single study from 2001 estimated the prevalence of frailty in community-dwelling adults to be 7-11% among individuals over 65 years of age and 25-40% among individuals over 80 years.⁸¹ Prevalence estimates can vary based on the type of evaluation tool used,⁹² demographic characteristics of the study population and regional variation.⁹³ The prevalence of frailty is known to increase with age,⁸¹ but in recent years frailty has emerged as an independent predictor of adverse outcomes⁹⁴ in older trauma patients,⁹⁵ independent of age and irrespective of the associated comorbidities that could be present.⁹⁶

Although research suggests that older adults have lower levels of physical functioning following TBI^{13,15,97,98} compared to younger adults following TBI, no studies have investigated the impact of TBI on the development of frailty among older adults. Frailty in older adults has major implications for independence, quality of life and health-care costs. It is relevant when considering financial health care planning and as such is an important concept for caregivers, clinical practitioners, and policy makers. The objective of this study was to estimate the risk of frailty associated with TBI over 5 years of follow-up in a nationally representative sample of older Medicare beneficiaries.

From a clinical perspective, frailty is important because it is associated with a greater risk of adverse health outcomes,⁹⁴ falls (which could result in recurrent TBI and other trauma), reduced mobility, less independence, hospitalization, disability, and death.

It is also important from a societal perspective because it identifies groups of people in need of additional medical attention. Frailty is relevant when considering financial health care planning and as such is an important concept for caregivers, clinical practitioners, and policymakers.

2. TBI and Disability

TBI is associated with functional impairments and disability^{13,99,100} which have an impact on independence, and reintegration into society. Previous population-based studies have documented worse functional status^{101,102} and higher rates of disability^{103–105} in adults of all ages with a history of TBI compared to those without TBI. Among adults receiving inpatient rehabilitation after TBI, 57% were moderately or severely disabled 5 years postinjury.⁶⁶ Lewin *et al.*, 1979 reported that 18% of a sample of 291 individuals was either totally or severely disabled 10 to 25 years after severe head injury.¹⁰⁶ A study of 306 individuals with moderate to severe TBI showed that 22% were not independent in activities of daily living even 14-years post-injury.¹⁰⁷ Taken together, these studies indicate that many people with moderate-severe TBI are disabled in activities of daily functioning, even a decade after injury. However, there is limited research on long-term disability after TBI among older adults, including those with mild TBI who form the majority of TBI cases.²

3. TBI and Nursing Home Placement

Poor functional recovery following an acute insult to the brain can signal the end of independent living,^{108,109} particularly among older adults who may have decreased

physiologic reserve.^{17,80} Among survivors of acute TBI, older age is associated with a lower likelihood of being discharged home,⁴ and reduced community participation post-injury.¹¹⁰ However, to date, no studies have examined the association between TBI and nursing home (NH) entry among older adults. The exceedingly high financial, personal, and social costs of nursing home care have motivated interest in identifying risk factors that are associated with long-term nursing home entry.

4. TBI and Chronic Pain

Chronic pain is a recognized sequela of TBI,¹¹¹ even among patients with mild injury. While there are many potential mechanisms, there is still no clear understanding of which contribute to chronic pain. One study showed that TBI disrupts pain signaling in the brainstem and spinal cord.¹¹² It is also unclear whether pain that persists long after a TBI represents an activation of brainstem structures or a medical problem separate from brain injury mediated by posttraumatic stress disorder (PTSD), sleep disturbances, or depression.^{113–115} A systematic review of 23 studies involving 4206 patients with traumatic brain injury (TBI) revealed that, while 51.5% of included patients experienced chronic pain, its frequency in those with mild TBIs was twice that in those with more severe injuries, even after adjusting for PTSD.^{25,115,116} To date, there has been little research devoted to understanding the development of pain in older adult TBI populations. In view of the high incidence of TBI among older adults, chronic and persistent pain may be common or exacerbated following TBI and might impede recovery progress and compromise optimal daily functioning.

5. TBI and Insomnia

Sleep disturbances such as insomnia, sleep apnea, post-traumatic hypersomnia and narcolepsy are common complaints, reported by 30-85% of people with TBI across the full range of severity.^{72,73,117-119} Although the exact mechanisms through which TBI affects sleep and circadian health are not yet fully understood, it is clear that sleep disturbances can impair the brain injury recovery process,⁷⁴ eventually leading to physical¹²⁰ and psychological consequences¹²¹ in a person. After a mild TBI, insufficient sleep causes more neurodegeneration and also likely independently contributes to morbidity and long-term sequelae.¹¹⁹ Evidence from non-TBI studies have shown that insufficient and disturbed sleep can worsen outcomes in depression,¹²² post-traumatic stress disorder,¹²³ and chronic pain,¹²⁴ and impairs cognitive and functional performance.¹²⁵ Poor sleep can precede, exacerbate, and prolong each of these conditions, with a profound negative impact on neurocognitive function,¹²⁶ health-related quality of life (HrQOL)¹²⁷ and increased economic costs, including health-care utilization and disability.^{74,128}

Previous research on sleep disturbances following TBI has mostly focused on children, adolescents, and young adults.^{127,129,130} However, among older adults, Albrecht and Wickwire recently reported that when compared with older adults without TBI, those with TBI experienced a higher rate of insomnia (rate ratio (RR) 1.17; 95% confidence interval (CI) 1.08, 1.26).⁷⁵ In this study however, there was no comparison to a non-TBI trauma group to tease out the effect of TBI from trauma more generally.

6. TBI and Depression

Depression is common following TBI, with an annual incidence rate of 123.9 per 1,000 older adults in the year after injury.¹⁰ It is associated with increased morbidity^{131,132} and decreased patient adherence to treatment¹³³ which may further worsen patient outcomes. Psychosocial¹³⁴ and biological factors^{135,136} (such as the disruption of frontal brain networks) are believed to predispose individuals to the development of depression post-TBI. There is evidence for both acute and chronic inflammatory cytokine changes after a TBI^{137,138} and inflammatory pathways may contribute to the development of depression post-TBI.¹³⁹

Most studies have focused on reporting prevalent and not incident depression post-TBI¹⁴⁰ which overestimates the risk of depression associated with TBI. Previous work by Albrecht *et al.* addressed this limitation by excluding those with a previous diagnosis of depression in a nationally representative sample²⁹ and also specifically among older adults.¹⁰ However, these studies focused on the short-term risk of depression and were also not designed to tease out the separate effects of general trauma and TBI with the addition of a non-TBI traumatic injury control group. This dissertation attempts to address those limitations to present a more accurate estimation of risk.

7. TBI and Anxiety/PTSD

Anxiety disorders following a traumatic brain injury (TBI) are common problems, with generalized anxiety disorder (GAD) and posttraumatic stress disorder (PTSD) being the most common diagnoses among adults 16-80 years.¹⁴¹ Currently, there is insufficient

research on the epidemiology of anxiety disorders post-TBI among older adults and PTSD is the more researched of the two.

When a brain injury occurs in the context of a traumatic event, symptoms of PTSD may appear. Post-traumatic stress disorder (PTSD) is characterized by re-experiencing an extremely traumatic event, usually by way of nightmares and intrusive thoughts of the incident. In addition, symptoms of heightened arousal and avoidance of stimuli associated with the trauma must be present for more than one month and cause significant distress or impair the individual's functioning.¹⁴² Research into the epidemiology of PTSD has focused largely on combat veteran populations, but civilian populations with TBIs can experience PTSD because injury occurs to the same neural networks that communicate via long axonal pathways through white matter tracts.⁷⁶ Though there are concerns about the ability to diagnose PTSD after TBI, one literature review has concluded that PTSD can occur after TBI even in the absence of explicit memories of trauma.¹⁴³ Some authors have argued that damage to the brain may directly contribute to PTSD by compromising neural circuitry required to regulate fear.^{144,145} Alternatively, TBI may increase the risk of PTSD by depleting the cognitive resources required to cope with stressors.¹⁴⁴

The term "anxiety" in this dissertation refers to GAD for which there are accepted international classification of disease (ICD) diagnostic criteria. The prevalence of anxiety and PTSD post-TBI varies in the literature and is likely due to inconsistent diagnostic criteria and differences in methodology. Prior studies estimate a prevalence of anxiety of 37% (range 4–83%)¹⁴⁶, and PTSD 16% (range 2.6–36%)¹⁴⁷ among TBI survivors of mixed ages and TBI severity. These studies were not amongst older adults and focused

largely on estimating prevalence, which could overestimate risk by including pre-existing cases. One study of older adult Medicare beneficiaries hospitalized with TBI reports that TBI was associated with a slightly higher rate of anxiety diagnoses (rate ratio (RR) 1.04; 95% CI 1.02, 1.06) and an higher rate of PTSD diagnoses (RR 1.24; 95% CI 1.05, 1.48).¹¹ The same study concluded that the incidence of post-TBI anxiety was 18% and post-TBI PTSD less than <1%.¹¹ However, this study focused on the short-term (one year) risk and was also not designed to isolate the separate effects of trauma and TBI.

The first few months after TBI are a crucial period and the presence of anxiety disorders can interfere with rehabilitation¹⁴⁸ and decrease quality of life. Elevated levels of suicidality are additionally reported to be associated with anxiety following a TBI,^{149,150} further highlighting its importance. In the community, general anxiety disorders are associated with relationship breakdowns, increased reliance on disability benefits, and lower annual incomes.¹⁵¹ These findings may likely be mirrored in a TBI setting; thus, the evidence of negative outcomes associated with anxiety disorders underline the need for more studies, especially among older TBI patients.

C. Significance

Older adults are more likely to experience negative outcomes after injury yet continue to be underrepresented in clinical research despite their burgeoning population in the United States. Due to the lack of research, physicians often propose treatment plans for older adults based on data from studies involving younger, healthier, and more-functional, participants. Results from this dissertation provide essential information on

several outcomes of importance to older adult TBI patients, their caregivers, and their care providers.

This is the first study to characterize frailty, disability, NH placement and chronic pain among older adults following TBI. It is also the first study among older TBI survivors to attempt to isolate the effect of TBI on recovery outcomes from the effect of trauma. Thus, it can serve as a baseline reference for future studies and inform post-discharge care services and policies and guidelines for structuring injury care protocols, rehabilitation programs, and resource allocation for geriatric TBI care for patients, caregivers, and providers.

D. Innovation

This study is novel in that it will be the first to assess long-term (up to 5 years) recovery outcomes (physical and psychological) after a TBI in older adults and thus provide novel information on a problem of public health importance in an understudied population. In addition, our sample was selected from a nationally representative sample of Medicare beneficiaries, ensuring a high degree of generalizability to most older adults in the United States.

Further, the study design is unique in that it will use two comparison cohorts (a non-TBI trauma and a non-injured group). Together, they enable the evaluation of brain- vs general-injury effects. Comparison to the non-TBI trauma group was made to disentangle the effect of TBI from the effect of traumatic injury and minimize residual confounding due to comorbidity burden and health behavior. Comparison to the

uninjured group provides an estimate of the overall impact of TBI on frailty compared to the general population of Medicare beneficiaries.

CHAPTER III: METHODS

A. Study Design

I conducted a retrospective cohort study using administrative claims data from a 5% sample of de-identified Medicare beneficiaries from January 2007-September 2015.

B. Data Sources

A 5% random sample of Medicare administrative claims data for years 2007-2015 was obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse (CCW). These data contain longitudinal health encounter information on beneficiaries ≥ 65 years and select individuals <65 years with end-stage renal disease (ESRD) or recognized Social Security disabilities. The data source is representative of the Medicare-covered U.S. population,¹⁵² a diverse mixture of race, ethnicities, and geographical regions across the United States.

The data comprises Medicare files for fee-for-service institutional and non-institutional claims, enrollment/eligibility, assessment data, costs, and diagnosis and procedure codes using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). The CCW data contain detailed claims data for all Medicare part A (hospital inpatient and outpatient or skilled nursing facility (SNF) encounters) and part B (physician/supplier). Additionally, it contains files for part D prescription drug event data which includes plan, pharmacy, and prescriber characteristics, as well as formulary data and costs.

The CCW includes date of first diagnosis and annual flags for 27 chronic conditions identified using an algorithm based on Medicare Severity Diagnosis Related Groups

(MS-DRG) or procedure codes.¹⁵³ The 27 common chronic conditions include: acquired hypothyroidism, acute myocardial infarction, Alzheimer’s disease, Alzheimer’s disease and related dementias (ADRD), anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, colorectal cancer, endometrial cancer, breast cancer, lung cancer, prostate cancer, cataract, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, heart failure, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, and stroke/transient ischemic attack.¹⁵⁴

To identify beneficiaries residing in NHs, Medicare Part A data were linked to the Minimum Data Set 2.0 and 3.0 (MDS 2.0 and 3.0). The MDS is a federally mandated health status assessment of all Medicare/Medicaid certified NH residents. It provides a comprehensive assessment of each resident’s functional capabilities and includes clinical assessments for residents at admission, discharge, quarterly, and annually, and upon any significant change in health status. It also includes dates of all the assessments, admissions, and discharges with or without a return anticipated.¹⁵⁵ The merged file of Medicare claims with MDS consists of detailed date-specific information, which allows for tracking NH status on a monthly basis.

C. Index Date

In this study, the term “index date” refers to the date of TBI in the TBI cohort, the date of injury in the non-TBI injury cohort and a randomly assigned date in the uninjured group (groups described below). Baseline refers to the 12-month period prior to the index date.

D. Coverage Criteria

Requiring continuous coverage ensured that all claims were captured, and no exposure or outcome events were missed. For all aims, continuous Medicare coverage was defined as having full, uninterrupted Medicare Parts A, B but no C (Medicare Advantage) coverage. Claims are not consistently available for beneficiaries with Medicare Part C (Medicare Advantage), thus beneficiaries with this coverage were not included. Participants were required to have 12 months of continuous coverage before the index date (the date of TBI, non-TBI trauma, or date of inpatient/outpatient visit in the uninjured group) and a minimum of 3 months of continuous coverage after the index date (Figure 1). This permitted a 12-month period in which to collect information on comorbid conditions prior to the start of follow-up, and a minimum of 3 months of follow-up for outcome ascertainment (Figure 1). Thus, the minimum amount of continuous coverage required was 15 months, but participants could contribute follow-up time until the sooner of discontinued coverage, outcome occurrence, death, September 30, 2015, or 5 years.

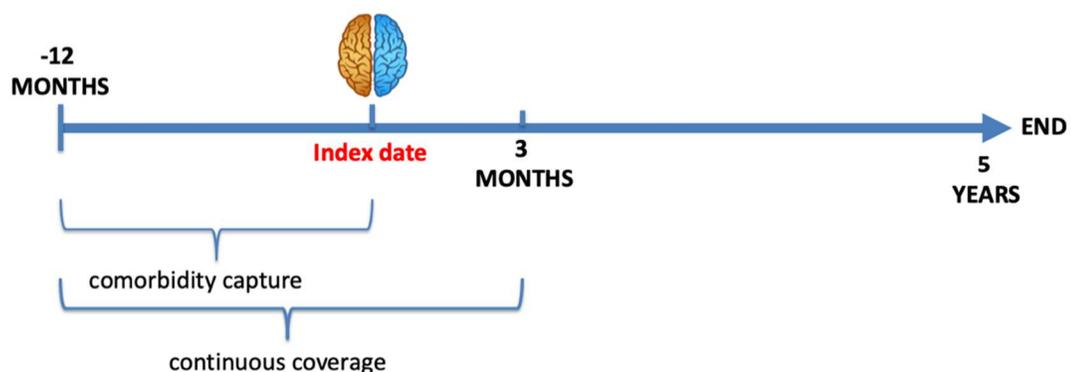


Figure 1: Study Timeline

E. Study Participants

Participants included beneficiaries ≥ 65 years of age, meeting coverage criteria, and diagnosed with either a TBI, a non-TBI injury, or were uninjured between January 2008 and June 2015.

F. Measures

1. Exposure Variable

The independent variable in this study was injury status, classified into three mutually exclusive levels: TBI, non-TBI trauma and uninjured. I ensured that the injury groups were independent by excluding people who could have appeared in more than one cohort.

a. TBI Group

The TBI group included beneficiaries with at least one TBI diagnosis between January 2008 and June 2015. A TBI diagnosis was operationalized using the Centers for Disease Control and Prevention (CDC) case definition International Classification of Disease (ICD) codes often used in epidemiologic studies.^{156,157} I searched for the first claim for at least one of the following ICD version 9, clinical modification (ICD-9-CM) codes for concussion (850.xx), non-specific TBIs (853.xx-854.1x) and other TBIs (800.xx, 801.xx, 803.xx, 804.xx, 851.xx-852.xx, 950.1-950.3, 959.0) between January 2008 and June 2015 in the first position of inpatient and outpatient claims.

b. Non-TBI Trauma Group

This exposure category consisted of comparison beneficiaries with a traumatic injury, not involving the head. Adopting codes from the Barell Injury Diagnosis Matrix,¹⁵⁸ I searched for the first claim for at least one of the following ICD-9-CM codes for any of injury diagnoses (listed below) between January 2008 and June 2015 in the first position of inpatient and outpatient claims. I randomly selected and frequency-matched with the TBI group on index dates and inpatient and outpatient claims.

Torso fractures:

1. Ribs and sternum: 807.0x, 807.1x, 807.2x, 807.3x, 807.4x
2. Pelvis: 808.xx
3. Other unspecified fractures of the bones of trunk: 809.xx

Upper extremity fractures:

1. Shoulder and upper arm: 810.xx, 811.xx, 812.xx
2. Forearm and elbow: 813.xx
3. Wrist, hand, and fingers: 814.xx, 815.xx, 816.xx, 817.xx
4. Other unspecified fractures of the upper limb: 818.xx

Hip fractures: 820.xx ICD-9-CM codes.

Lower extremity fractures:

1. Upper leg and thigh: 821.xx
2. Knee: 822.xx
3. Lower leg and ankle: 823.xx, 824.xx
4. Foot and toes: 825.xx, 826.xx
5. Other unspecified fractures of the lower limb: 827.xx

c. Uninjured Cohort

The uninjured exposure category included a random sample of inpatient and outpatient claims of beneficiaries aged ≥ 65 years of age, meeting continuous coverage criteria, and without a TBI or a non-TBI injury between January 2008 and June 2015. Beneficiaries in this group were randomly selected to have a frequency-matched sample of the same size and with the same distribution of inpatient and outpatient claims as the TBI group, resulting in an equivalent distribution of index dates.

d. Injury Severity

Current severity scoring systems available in claims data are inadequate for predicting non-fatal outcomes (e.g., functional impairment and disability), especially across multiple injury populations. This leads to a reliance on proxies for injury severity which can have limitations.

- i. Point of service codes: two-digit codes placed on claims to indicate in which setting a service was provided (i.e., inpatient, outpatient, or emergency setting). This assumes that more severe injuries are typically seen in inpatient versus outpatient settings.
- ii. Hospital length of stay (LOS): defined as the number of days from the date of admission to date of hospital discharge. This has been validated as a reasonable proxy for important injury outcomes in younger populations,¹⁵⁹ when more detailed measures are not available. The discriminatory value among older adults is questionable. In older patients, with a higher prevalence of comorbidities and lower physical resilience, the injury admission and resulting hospital stay may not

- be driven primarily by the injury itself. Thus, hospital LOS may be associated with TBI severity, but may also reflect the severity of other injuries, lack of social supports type of insurance coverage or current standards of care. This reduces the utility of this surrogate in an older adult population.
- iii. Discharge destination: whether a patient was discharged to the community versus skilled nursing facility. This assumes that the extended recovery required by patients discharge to a skilled nursing facility is indicative of a more severe injury. Similar to the limitations with hospital LOS, the discriminatory value among older adults is questionable. Discharge destination may also reflect the severity of other injuries, lack of social supports type of insurance coverage or current standards of care. This reduces the utility of this surrogate in an older adult population.
 - iv. ICD-9 Injury Severity Score (ICISS): This is based on the calculation of survival risk ratios (SRRs) for each ICD-9 CM code. The SRR's are derived by dividing the number of patients that survive a given ICD-9 CM injury diagnosis code by the number of patients with that diagnosis code. The ICISS is the product of the SRRs corresponding to a patient's set of injuries. Though the ICISS has been shown to outperform several injury severity measures in predicting mortality, healthcare costs, and length of stay, they are unfortunately database specific. Therefore, SRRs from one source may not accurately predict injury severity in other sets of patients. The development of this approach to injury severity assessment is on-going and shows great promise for use across several injury populations.

Typically, less severe injuries are diagnosed in an outpatient setting while more severe injuries are likely diagnosed in an inpatient setting. Using stratified random sampling, I attempted to balance the groups on injury severity by frequency matching on inpatient and outpatient claims to ensure a similar distribution of hospitalized and non-hospitalized cases and ultimately, injury or health problem severity.

2. Outcome Variables

All outcomes were based on ICD-9-CM codes in any position on inpatient or outpatient claims. I searched for the first documented claim containing the code of interest in the study period. Outcomes occurring prior to the index date were considered present at baseline. For all aims, excluding aim 1.2 (the disability outcome), only beneficiaries without the outcome at baseline were analyzed.

Aim 1: The primary outcomes of physical functioning were frailty, disability, nursing home placement, chronic pain, and insomnia.

1.1 Frailty: Using an algorithm developed by Kim *et al.*,¹⁶⁰ based on the Rockwood and Mitnitski conceptualization of frailty,¹⁷ a claims-based frailty index (CFI) was calculated for each beneficiary, using claims for any of the pertinent ICD-9-CM, CPT and HCPCS codes (appendix A), in any position on inpatient and outpatient claims. This algorithm has been previously validated internally¹⁶⁰ and externally.¹⁶¹ The CFI was calculated as the weighted sum of health deficit variables present, assuming lack of codes during the entire year would represent the absence of the deficit. Although the CFI is a continuous measure, frailty is typically categorized into robust (<0.15),

prefrail (0.15–0.24), mildly frail (0.25–0.34), and moderately-to-severely frail (≥ 0.35).¹⁶¹ A cut point of ≥ 0.25 ¹⁶² was used to exclude participants who were frail at baseline.

1.2 Disability was defined using a set of claims-based functioning-related indicators (FRIs) as described by Chrischilles *et al.*¹⁶³ Each patient's FRI is a summary score from 0-13 for each of the following conditions: mobility limitations (defined by claims for cane, walker, wheel chair, hospital bed, etc.), blood transfusion, use of oxygen, supplemental nutrition, hip or pelvic fracture, chronic skin ulcer, pneumonia, delirium/dementia/Alzheimer disease, bone marrow failure/agranulocytosis, depression, use of urinary catheter, respiratory failure/insufficiency/arrest, sepsis, and malnutrition/unintentional weight loss, fall-related injury, and syncope. This algorithm has been previously validated internally¹⁶³ and performs well (c-statistic 0.71-0.77).¹⁶³

1.3 Nursing-home stays were identified based on the method described by Intrator *et al.*¹⁶⁴ and modified by Goodwin *et al.*,¹⁶⁵ using Part A claims plus the MDS. I defined long-term NH entry as the first nursing-home admission that resulted in a stay of ≥ 100 days to distinguish admissions for long-term care from admissions for short-term stays that typically occur for rehabilitation. Time to NH entry was calculated as the difference between the index date and the date of the NH admission that resulted in a stay ≥ 100 days. Beneficiaries were right censored at NH entry, death, disenrollment, or at the end of follow-up.

1.4 Consistent with prior work, I defined chronic pain as non-cancer pain that is continuous and persistent and lasting for more than 90 days.¹⁶⁶ I operationalized this

outcome as two claims at least 4 weeks apart in any position on inpatient and outpatient claims during the study period for any of the following ICD-9-CM diagnostic codes: 307.80, 307.89, 338.0, 338.2, 338.4, 719.41, 719.45–719.47, 719.49, 720.0, 720.2, 720.9, 721.0–721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3–723.9, 724.0–724.6, 724.70, 724.79, 724.8, 724.9, 729.0–729.2, 729.4, 729.5 338.21, 338.22, 338.28, 338.29. These codes are based on a validated algorithm for chronic pain with sensitivity, specificity and positive predictive values of 70%, 99% and 95% respectively.¹⁶⁷ The date of the first of these two claims was considered the event date for analyses.

1.5 Insomnia was operationalized as the first claim for the listed diagnostic codes in any position on inpatient and outpatient claims during the study period.¹⁶⁸

ICD-9-CM codes: 307.41, 307.42, 307.49, 327.00, 327.01, 327.09, 780.52, V69.4.

Aim 2: The primary outcomes of psychological functioning were depression and anxiety/PTSD.

2.1 Depression was defined as the first claim in any position on inpatient and outpatient claims during the study period for any of the following ICD-9-CM diagnostic codes: 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, or 311. These codes are based on validated case definitions for depression.^{169,170}

2.2 Anxiety/PTSD was defined as the first claim in any position on inpatient and outpatient claims during the study period for any of the following ICD-9-CM codes identified from previous literature as well as input from healthcare providers.

- a. Generalized anxiety and panic disorders: 300.0x, 300.21, 300.22
- b. Post-traumatic stress disorder: 309.81

3. Covariates

Based on my literature search, I identified variables available in claims data and associated with TBI as well as each of the outcomes of interest. These include age, sex, race, original reason for entitlement code (OREC), and comorbid conditions.

Demographic, clinical characteristics, and original reason for entitlement code (OREC) were obtained from administrative claims files. The CCW data also contains information on 27 common chronic comorbid conditions, with an annual flag for each condition as well as the date of the first diagnosis for that condition, based on validated algorithms that search for specific diagnostic codes within the CMS administrative claims.¹⁷¹ We combined the five cancer flags to create an ‘any cancer’ variable and selected to report the Alzheimer’s disease and related dementias flag rather than the Alzheimer’s disease (only) flag. We used the date of the first diagnosis to determine if a condition was present at the index date.

G. Sample Size and Power

1. Aims 1.1 – 1.2

I used frailty as an example to calculate the power for this aim. Given a fixed sample size of $\cong 30,000$ beneficiaries per injury group and taking into account the repeated measures of frailty for each patient, GLIMMPSE v3.0.0 (a freely available online software¹⁷²) was used to estimate the power to detect a clinically significant difference in frailty between three injury groups, based on a two-tailed significance of level of 0.05. Assuming a mean frailty score of 0.14 and standard deviation of 0.11 in a population-based sample of community-dwelling older adults¹⁷³ and a conservative clinically meaningful difference of 0.019 using a 43-item frailty index,¹⁷³ the expected power for this analysis was >0.99 .

2. Aims 1.3 – 2.2

I used depression as an example to calculate the minimum detectable hazard ratio based on a two-tailed significance level of 0.05, a sample size of $\cong 30,000$ beneficiaries per injury group, and a desired power of 0.99. Using an incidence rate of post-TBI depression in a population-based sample of community-dwelling adults (79.5 per 1,000 person-years),²⁹ the minimum detectable hazard ratio between two injury groups was 1.02. Assuming the incidence rates for the other outcomes are as high as the incidence of depression in the TBI group, the analyses for these aims are sufficiently powered due to the large sample size.

H. Data Analysis

After excluding beneficiaries with the outcome of interest at baseline, for all aims I compared the baseline distribution of demographic and clinical variables by injury status, using either Chi-square goodness of fit for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables, as appropriate. I used stabilized inverse probability of treatment weights (IPTW) to balance the distribution of covariates across groups prior to modelling. I generated the IPTW using a multinomial logistic regression in which the outcome variable was injury group and included the following as covariates in the model: demographic variables such as age, sex, and race, twenty-seven common chronic conditions from the CCW and original reason for Medicare entitlement. I examined the balance of observed covariates in the weighted sample by computing standardized mean differences (the difference in means between TBI and no-TBI (non-TBI trauma and uninjured) groups divided by the overall standard deviation) on pre- and post-matched samples, following published guidelines.¹⁷⁴ We used a cutoff of ± 0.03 for standardized differences to identify covariates that should be further adjusted for in the regression model.^{175,176} Because there were three injury groups, I selected TBI as the reference to avoid comparing two non-TBI groups to each other. Thus, the estimates reported are for the non-TBI trauma group and the uninjured group compared to TBI. All analyses were performed using SAS Enterprise Guide 7.1 using a two-sided significance level of < 0.001 due to the large sample size.

1. Aim 1.1

To estimate the effect of TBI on frailty, I excluded those with pre-existing frailty ($CFI \geq 0.25$) at baseline and estimated the odds associated with injury status, using a proportional odds cumulative logit model with stabilized inverse probability weights. I computed stabilized inverse probability of survival weights (to balance differential death rates between injury groups) and stabilized inverse probability of treatment weights (to balance observed covariates), then multiplied both weights to generate the final weights used in the models.

2. Aim 1.2

The objective of this aim was to evaluate the association between TBI and incident disability. I modeled the effect of TBI on monthly counts of the FRI, using a proportional odds cumulative logit model with stabilized inverse probability weights to estimate the odds ratio (OR) associated with a one-unit increase in FRI score, with 95% confidence intervals (CIs).

3. Aims 1.3-2.2

The objectives of Aims 1.3, 1.4, 1.5, 2.1 and 2.2 were to evaluate the association between injury status and the risk of NH placement, chronic pain, insomnia, depression, and anxiety/PTSD, respectively. The analytic approach for these aims were identical given I wanted to determine when the outcomes occurred and not only whether they occurred. I quantified the effect of TBI on the risk of developing each outcome, in the presence of death as a competing risk by conducting time-to-event analyses, using cause-

specific Cox proportional hazards models with stabilized inverse probability weights to estimate the hazard ratio (HR) of developing the outcome, with 95% confidence intervals (CIs).

CHAPTER IV: RESULTS

The following manuscripts present the findings of this dissertation by aim. The manuscript for Aim 1.1 reports on the increased risk of frailty post-TBI among older adult Medicare beneficiaries. The manuscript for Aim 1.3 reports on the increased risk of NH placement following TBI among community dwelling older-adult Medicare beneficiaries. Following these two manuscripts, additional results are reported for Aims 1.2, 1.4, 1.5, 2.1 and 2.2 on the risk of disability, and the incidence of chronic pain, insomnia, depression, and anxiety/PTSD following TBI.

A. AIM 1.1 MANUSCRIPT

Traumatic Brain Injury is Associated with Higher Frailty Risk among Older Adults¹

Abstract

Objective: Traumatic brain injury's (TBI) systemic effects among older adults may result in decreased physiologic reserve. This study evaluated the effect of TBI on the development of frailty in a nationally representative sample of older adult Medicare beneficiaries.

Design: Retrospective cohort study.

Setting: Medical claims data from a 5% sample of Medicare beneficiaries for years 2007-2015.

Participants: We included 207,355 adults aged ≥ 65 years, diagnosed with either a TBI, non-TBI trauma, or were uninjured between January 2008 and June 2015.

Main Measures: Frailty was operationalized based on the Frailty Index (FI), a deficit-accumulation approach using a validated claims-based algorithm to generate a summary frailty score (range: 0-1; higher values indicate greater frailty). We used a proportional odds cumulative logit model with stabilized inverse probability weights to estimate the odds ratio (OR) associated with injury status over 5 years.

Results: A total of 55,345 TBI, 61,492 non-TBI trauma, and 69,767 uninjured beneficiaries were included in our final analysis. We observed that, relative to the uninjured and non-TBI trauma beneficiaries, those with TBI had a higher odds of frailty in weighted models; OR 1.66 (95% CI 1.61, 1.71) and OR 1.12 (95% CI 1.10, 1.14) respectively.

¹ *Traumatic Brain Injury is Associated with Higher Frailty Risk among Older Adults.* Bailey, M. Doyinsola; Gambert, Steven; Gruber-Baldini Ann; Guralnik, Jack; Kozar, Rosemary; Qato, Danya M.; Shardell, Michelle; Albrecht, Jennifer S. In preparation for submission.

Conclusions: Among older adults, TBI is associated with a higher odds of frailty, even when compared to individuals with non-TBI trauma and adjusting for shared risk factors. Our findings highlight the need to evaluate frailty among older adults with TBI and suggests that older adults with TBI may benefit from rehabilitation interventions.

Keywords: Frailty; Older adults; Aging; Traumatic brain injury.

Background

Traumatic brain injury (TBI) is a major cause of death and disability and a growing public health problem among adults aged 65 years and older in the United States.^{1,2,177} Older adults have high rates of TBI-related emergency department visits, hospitalizations, and deaths,²⁻⁴ and these rates have increased significantly over the last decade. Importantly, older adults with TBI experience higher morbidity and mortality,¹⁷⁸ especially compared to younger adults with similar injury severity.^{69,179-182} In addition, they have slower recovery trajectories¹³⁻¹⁵ and have, on average, worse functional, cognitive, and psychosocial outcomes months or years post-injury.^{12,15,101,183}

Frailty is an emerging global health burden among the aging population⁷⁹ that may be linked to TBI.⁷⁸ It is described as a clinical syndrome resulting in functional declines across multiple physiological systems, characterized by decreased homeostatic reserves and increased vulnerability to important adverse health outcomes including death, hospitalization and disability and admission to long-term care.^{80,81} It has become increasingly evident that chronic disorders can exacerbate risk of frailty in older individuals. Such associations have been reported between frailty and chronic kidney disease,⁸³ atrial fibrillation,⁸⁴ chronic obstructive pulmonary disease,⁸⁵ anemia,⁸⁶ hypertension, cardiovascular disease and stroke.⁸⁷⁻⁹¹ These comorbidities share common pathophysiological determinants like neuroendocrine disturbances and chronic inflammation, common consequences of TBI.⁷⁸

Although research suggests that older adults have lower levels of physical functioning following TBI^{13,15,97,98} compared to younger adults, no studies have investigated the impact of TBI on the development of frailty. Frailty in older adults has major implications for independence, quality of life and health-care costs. It is relevant when considering financial

health care planning and as such is an important concept for caregivers, clinical practitioners, and policy makers. The objective of this study was to estimate the odds of frailty associated with TBI over 5 years of follow-up in a nationally representative sample of older Medicare beneficiaries.

Methods

Data Sources and Study Design

The data source for this retrospective cohort study was a 5% random sample of Medicare administrative claims data obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse (CCW) for years 2007-2015. These data contain longitudinal health encounter information on beneficiaries ≥ 65 years and select individuals <65 years with end-stage renal disease (ESRD) or recognized Social Security disabilities. There are over 55 million beneficiaries¹⁸⁴ (>98% of adults aged 65 and over)^{152,185} enrolled in the Medicare program today, making claims data nationally representative and one of the richest sources of utilization information in the country. It represents the Medicare-covered US population,¹⁵² a diverse mixture of ethnicities, and geographical regions across the United States.

Coverage Criteria

Continuous Medicare coverage was defined as having full, uninterrupted Medicare Parts A, B but no C (Medicare Advantage) coverage. Participants were required to have 12 months of continuous coverage before the index date (the date of TBI, non-TBI trauma, or date of inpatient/outpatient visit in the uninjured group and a minimum of 3 months of continuous coverage after the index date.

Study Participants

Participants included community-dwelling beneficiaries ≥ 65 years of age, meeting coverage criteria, and diagnosed with either a TBI, a non-TBI injury, or were uninjured between January 2008 and June 2015. Participants contributed follow-up time until the sooner of September 30, 2015, or 5 years.

Exposure

The exposure in this study was injury status, classified into three mutually exclusive categories: TBI, non-TBI trauma and uninjured. Comparison to the non-TBI trauma group was made to disentangle the effect of TBI from the effect of traumatic injury. Comparison to the uninjured group provides an estimate of the overall impact of TBI on frailty compared to the general population of Medicare beneficiaries.

TBI Group

TBI was operationalized using the Centers for Disease Control and Prevention (CDC) case definition International Classification of Disease (ICD) codes often used in epidemiologic studies.^{156,157} We searched for the first claim for at least one of the following ICD version 9, clinical modification (ICD-9-CM) codes for concussion (850.xx), non-specific TBIs (853.xx-854.1x) and other TBIs (800.xx, 801.xx, 803.xx, 804.xx, 851.xx-852.xx, 950.1-950.3, 959.0) between January 2008 and June 2015 in the first position (primary diagnosis) of inpatient and outpatient claims. We excluded anyone with a non-TBI trauma during the entire study period.

Non-TBI Trauma Group

This group comprised beneficiaries with a traumatic injury, excluding TBI. Adopting codes from the Barell Injury Diagnosis Matrix,¹⁵⁸ we searched for the first claim for at least one of the following ICD-9-CM codes for any of the four major injury diagnoses: torso fractures (807.0x-4x, 808.xx, 809.xx) upper extremity fractures (810.xx-818.xx), hip fractures (820.xx) and lower extremity fractures (821.xx-827.xx) between January 2008 and June 2015 in the first position of inpatient and outpatient claims. We frequency-matched the number of inpatient and outpatient claims to the TBI group, resulting in an equivalent distribution of index dates, and randomly selected a sample that was the same size as the TBI group. We excluded anyone with a TBI at any time during the study period.

Uninjured Group

The uninjured group included a random sample of inpatient and outpatient claims of beneficiaries aged ≥ 65 years of age, meeting continuous coverage criteria, and without a TBI or a non-TBI injury between January 2008 and June 2015. As described for the non-TBI trauma group, we frequency-matched this group to the TBI group.

Outcome

The primary outcome was frailty. We used a claims-based frailty index¹⁶⁰ to calculate a frailty score for each beneficiary using inpatient, outpatient, skilled nursing facility, home health agency, carrier, and durable medical equipment claims in the 12-month period prior to the index date. The score contains groups of International Classification of Diseases 9th Revision, Current Procedural Terminology, and Healthcare Common Procedure Coding System codes that are

theoretically associated or congruent with frailty. The full model, including codes, can be found in Table 2 of the published manuscript detailing the development and validation of the algorithm.¹⁶⁰ Each beneficiary's frailty score was a proportion from 0-1 (higher values indicate greater frailty), calculated as the weighted sum of the ratio of the number of deficits accumulated to the total number of deficits considered. Beneficiaries were categorized as robust (<0.15), prefrail (0.15–0.24), mildly frail (0.25–0.34), and moderately-to-severely frail (≥ 0.35) for descriptive purposes¹⁶¹ and a cut point of ≥ 0.25 ¹⁶² was used to define frail beneficiaries for exclusion at baseline (index date).

Covariates

Demographic, clinical characteristics, and original reason for entitlement code (OREC) were obtained from administrative claims files. The CCW data also contains information on 27 common chronic comorbid conditions, with an annual flag for each condition as well as the date of the first diagnosis for that condition, based on validated algorithms that search for specific diagnostic codes within the CMS administrative claims.¹⁷¹ We combined the five cancer flags to create an 'any cancer' variable. We used the date of the first diagnosis to determine if a condition was present at baseline.

Statistical Analysis

We compared the baseline distribution of demographic and clinical variables by injury status, using Chi-square goodness of fit for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables, as appropriate.

We used stabilized inverse probability of treatment weights (IPTW) to balance the distribution of covariates across groups. We generated the IPTW using a multinomial logistic regression in which the outcome variable was injury group and included the following as covariates in the model: demographic variables such as age, sex, and race; twenty-seven common chronic conditions from the CCW, original reason for Medicare entitlement. We then examined the balance of observed covariates in the weighted sample by computing standardized mean differences (the difference in means between TBI and no-TBI (non-TBI trauma and uninjured) groups divided by the overall standard deviation) on pre- and post-matched samples, following published guidelines.¹⁷⁴ We used a cutoff of ± 0.03 for standardized differences to identify covariates that could be further adjusted for in the regression model.^{175,176}

To estimate the effect of TBI on frailty we excluded those with pre-existing frailty (FI ≥ 0.25) at baseline and estimated the odds associated with injury status, using a proportional odds cumulative logit model with stabilized inverse probability weights. We computed stabilized inverse probability of survival weights (to balance differential death rates between injury groups) and stabilized inverse probability of treatment weights (to balance observed covariates), then multiplied both weights to generate the final weights used in the models. Odds ratios are reported with 95% confidence intervals (CIs). All analyses were performed with SAS Studio Enterprise Edition 3.71 (SAS Institute, Cary, NC). This study was approved by the Institutional Review Board at the University of Maryland, Baltimore.

RESULTS

Study Cohort

Our final cohort contained 207,355 beneficiaries (68,203 with TBI, 67,679 with trauma, and 71,473 uninjured) that were predominantly female (70%) and white (89%) with an average age of 77.0 years (standard deviation [SD] 8.8; Table 1). As presented in Table 1, those with TBI were older (80.8 years (SD 8.2) vs 78.4 (SD 8.3) for non-TBI trauma and 72.1 (SD 7.5) years in the uninjured, $p < 0.001$), more likely to have originally received Medicare benefits because of a disability (11% vs 10% and 6%, $p < 0.001$). Beneficiaries in the TBI group also had a higher burden of comorbidities. For example, they were significantly more likely to have hypertension (90% vs 84% and 65%), hyperlipidemia (82% vs 78% and 62%), rheumatoid arthritis (71% vs 63% and 34%), ischemic heart disease (66% vs 54% and 29%), and diabetes (43% vs 36% and 26%) ($p < 0.001$ for all).

Frailty

The average frailty score in the study cohort was 0.16 (SD 0.06), (0.19 (SD 0.06) among those with TBI, 0.16 (SD 0.05) for non-TBI trauma and 0.13 (SD 0.04) among the uninjured. Among these beneficiaries, 51% ($n = 105,415$) were robust ($FI < 0.15$), 39% ($n = 81,189$) were pre-frail ($FI 0.15-0.24$), 9% ($n = 19,316$) were mildly frail ($FI 0.25-0.34$), and $< 1\%$ ($n = 1,435$) were moderately to severely frail ($FI \geq 0.35$) (Table 1). Beneficiaries with a $FI \geq 0.25$ were considered frail and excluded from our final analysis.

After excluding beneficiaries who were frail at baseline (19% with TBI, 9% with trauma, and 2% uninjured, $p < 0.001$), our final cohort contained 186,604 beneficiaries (55,345 with TBI, 61,492 with trauma, and 69,767 uninjured). Table 2 presents the results of our weighted

proportional odds cumulative logit model. In the unadjusted model, we observed a significantly higher odds of frailty comparing the TBI to the uninjured (OR 3.76; 95% CI 3.69, 3.82) and non-TBI trauma (OR 1.38; 95% CI 1.35, 1.40) groups. Weighting and adjusting for covariates with standardized differences exceeding |0.03|, resulted in a change to results but did not change our conclusions (non-TBI trauma (OR 1.12; 95% CI 1.10, 1.14) and uninjured (OR 1.66; 95% CI 1.61, 1.71) groups), compared to the TBI group.

DISCUSSION

In this large, nationally representative study of Medicare beneficiaries, TBI was associated with more severe frailty compared to both beneficiaries with non-TBI trauma and the general population of Medicare beneficiaries. Results from this study provide a new and important insight for clinicians to consider when managing an older adult with TBI. The overall prevalence of frailty at baseline was 10%, which is higher than reported by Fried (6.9% in a study of cardiovascular health),⁸¹ but lower than reported in a nationally representative sample of community-dwelling older adults (15%).¹⁸⁶ The differences may depend on the conceptual framework and diagnostic criteria that were used to define frailty and the populations being studied. Our study utilized the deficit accumulation criteria,^{17,187} as opposed to the more commonly used frailty phenotype criteria.⁸¹ Additionally, differences in the study populations and ultimately, the demographic characteristics of study subjects could also have led to different estimates.

Our study demonstrated that TBI was associated with a higher prevalence of frailty at baseline (19% vs 9% and 2%, $p < 0.001$). The risk of frailty increases with age, comorbidities, low socioeconomic position, poor diet, and sedentary lifestyles. In our study sample, beneficiaries

with TBI were more likely to have a higher comorbidity burden and be on disability insurance benefits (a proxy for lower socioeconomic position) before their injury, which may have predisposed them to being more frail. Even after excluding those who were frail at baseline, those with TBI may have been at higher risk of becoming frail even before the injury.

Although the development of frailty has not been previously studied among older adults with TBI, chronic disorders that share common pathophysiological determinants, have been reported to increase the risk of frailty in older individuals.⁸³⁻⁹¹ TBI could increase the risk of frailty through the hypothalamo-pituitary (HP) axis¹⁸⁸ which links the brain to the endocrine system. Longitudinal studies have shown hypothalamic-pituitary hormone deficiencies among long-term survivors of TBI.⁷⁷ Additionally, inflammation has been argued to be important in the processes of accelerated aging and frailty.^{80,189,190} Thus, the significant inflammatory burden that results after a TBI could also predispose older adults to frailty.¹⁹¹

Older people living with frailty are at an increased risk of important adverse outcomes^{80,94} which have considerable importance from an individual, societal and health service perspective. Frailty could increase the risk of falls (resulting in recurrent TBI or other trauma), less mobility, less independence, hospitalization, disability, and death. It is also important from a societal perspective because it identifies groups of people in need of extra medical attention. Studies have shown a clear pattern of increased health-care costs and use associated with frailty. Frailty is relevant when considering financial health care planning and as such is an important concept for caregivers, clinical practitioners, and policy makers. Clinically it may be important for clinicians to communicate the potential risk of frailty in relevant patients, to possibly include frailty assessment in follow-up visits, and to consider frailty in any care planning. Given that

frailty has been associated with adverse health outcomes, our results highlight a high-risk population that could benefit from intervention.

This study has various strengths. This is the first study to examine the development of frailty among older adults following TBI and as such, it can serve as a baseline reference for future studies and inform post-discharge care services and policies. Next, our sample was large enough to ensure adequate statistical power and was selected from a nationally representative sample of Medicare beneficiaries, ensuring a high degree of generalizability to older adults with TBI. Additionally, we evaluated frailty using a validated claims-based algorithm, used two unexposed categories to isolate the effects of TBI beyond general trauma, and applied IPTW to balance covariates between exposure groups. Nonetheless, there are some limitations to this study. Although we adjusted for available confounders, there is the potential for residual confounding due to an unequal distribution of unmeasured confounders between groups. This study did not use the traditional clinical measurement of frailty,⁸¹ however we used a claims-based measure¹⁶⁰ that has been validated against the Rockwood frailty index^{17,187} and can be modelled continuously, which is arguably more useful for analysis purposes. Administrative claims data lack documentation of traditional measures of TBI severity (Glasgow Coma Scale Score, Abbreviated Injury Score), and the occurrence of previous head injuries which would be important factors to control for in future studies. Lastly, administrative claims data are collected for billing and reimbursement purposes. Therefore, the assessment of all measures is dependent on documentation.

In this study, TBI resulted in an increased odds of frailty among older adult Medicare beneficiaries. Additional studies are required to further clarify the role of TBI in frailty and to determine how frailty interacts with recovery in older adults.

Table 1. Baseline Characteristics of Medicare Beneficiaries ≥65 years, by Injury Type (2008-2015), (n=207,355)

	Total n=207,355	TBI n=68,203	Trauma n=67,679	Uninjured n=71,473	p-value
Patient Characteristics					
Age (years), mean(SD)	77.0 (8.8)	80.8 (8.2)	78.4 (8.3)	72.1 (7.5)	<0.001
Sex, n (%)					<0.001
Female	144,670 (70)	46,248 (68)	49,789 (74)	48,633 (68)	
Male	62,685 (30)	21,955 (32)	17,890 (26)	22,840 (32)	
Race, n (%)					<0.001
White, non-Hispanic	177,419 (86)	58,885 (86)	59,987 (89)	58,547 (82)	
Black	12,831 (6)	4,028 (6)	3,134 (5)	5,669 (8)	
Hispanic	10,000 (5)	3,224 (5)	2,837 (4)	3,939 (6)	
Asian/Pacific Islander	4,053 (2)	1,298 (2)	366 (<1)	1,827 (3)	
American Indian/Alaska Native	1,012 (<1)	337 (<1)	928 (1)	309 (<1)	
Other	1,134 (<1)	323 (<1)	294 (<1)	517 (<1)	
Unknown	906 (<1)	108 (<1)	133 (<1)	665 (<1)	
OREC ^a , n (%)					<0.001
Old Age	188,658 (91)	60,739 (89)	60,667 (90)	67,252 (94)	
Disability	18,281 (9)	7,302 (11)	6,840 (10)	4,139 (6)	
Other	416 (<1)	162 (<1)	172 (<1)	82 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	43,375 (21)	24,252 (36)	14,028 (21)	5,095 (7)	<0.001
Acute Myocardial Infarction	10,361 (5)	5,302 (8)	3,835 (6)	1,224 (2)	<0.001
Anemia	111,346 (54)	48,658 (71)	40,462 (60)	22,226 (31)	<0.001
Asthma	26,278 (13)	11,311 (17)	9,804 (14)	5,163 (7)	<0.001
Atrial Fibrillation	35,312 (17)	18,071 (27)	12,213 (18)	5,028 (7)	<0.001
Cataracts	138,834 (67)	54,454 (80)	50,440 (75)	33,940 (47)	<0.001
Congestive Heart Failure	61,012 (29)	29,713 (44)	22,072 (33)	9,227 (13)	<0.001
Chronic Kidney Disease	46,781 (23)	22,772 (33)	16,684 (25)	7,325 (10)	<0.001
All cancers	32,672 (16)	13,169 (19)	11,757 (17)	7,746 (11)	<0.001
COPD ^c	55,234 (27)	24,371 (36)	21,132 (31)	9,731 (14)	<0.001
Depression	69,496 (34)	32,139 (47)	24,712 (37)	12,645 (18)	<0.001
Diabetes	71,973 (36)	29,279 (43)	24,436 (36)	18,258 (26)	<0.001
Glaucoma	48,204 (23)	19,530 (29)	16,876 (25)	11,798 (17)	<0.001
Hip/Pelvic Fracture	9,886 (5)	5,895 (9)	2,694 (4)	1,297 (2)	<0.001
Hyperlipidemia	153,622 (74)	56,415 (82)	52,746 (78)	44,461 (62)	<0.001
Benign Prostatic Hyperplasia	27,944 (13)	12,697 (19)	8,754 (13)	6,493 (9)	<0.001
Hypertension	164,787 (79)	61,626 (90)	56,579 (84)	46,582 (65)	<0.001
Acquired Hypothyroidism	57,206 (28)	23,432 (34)	20,421 (30)	13,353 (19)	<0.001
Ischemic Heart Disease	101,754 (49)	44,785 (66)	36,236 (54)	20,733 (29)	<0.001
Osteoporosis	56,746 (27)	23,188 (34)	23,251 (34)	10,307 (14)	<0.001
RA ^d /Osteoarthritis	115,452 (56)	48,478 (71)	42,524 (63)	24,450 (34)	<0.001
Stroke/TIA ^e	38,117 (18)	20,113 (29)	13,133 (19)	4,871 (7)	<0.001
Frailty Status					<0.001
Moderate/Severe (FI > 0.35)	1,435 (<1)	951 (1)	378 (<1)	106 (<1)	
Mild (FI 0.25-0.34)	19,316 (9)	11,907 (17)	5,809 (9)	1,600 (2)	
Pre-frail (FI 0.15-0.24)	81,189 (39)	35,042 (51)	29,350 (43)	16,797 (24)	
Not Frail (FI <0.15)	105,415 (51)	20,303 (30)	32,142 (47)	52,970 (74)	

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack.

Table 2. Cumulative Logit Regression Analyses of Frailty, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=186,604)

	Odds Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted ^a	Weighted ^b	Weighted ^c
Uninjured	Reference	Reference	Reference	Reference
TBI	3.76 (3.69, 3.82)	1.48 (1.43, 1.52)	1.66 (1.61, 1.71)	1.66 (1.61, 1.71)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	1.38 (1.35, 1.40)	1.12 (1.10, 1.15)	1.12 (1.10, 1.14)	1.12 (1.10, 1.14)

^aNo adjustment for additional covariates.

^bAdjusted for age, baseline frailty score (covariates with standardized differences ± 0.03).

^cAdjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

B. AIM 1.3 MANUSCRIPT

Traumatic Brain Injury and Risk of Long-Term Nursing Home Entry among Older Adults: An Analysis of Medicare Administrative Claims Data²

Traumatic brain injury (TBI) is a leading cause of injury-related disability among older adults and there is increasing interest in post-discharge management as this population grows. We evaluated the association between TBI and long-term nursing home (NH) entry among a nationally representative sample of older adults. We identified 207,355 adults aged ≥ 65 years who were diagnosed with either a TBI, non-TBI trauma, or were uninjured between January 2008 and June 2015 from a 5% sample of Medicare beneficiaries. NH entry was operationalized as the first NH admission that resulted in a stay ≥ 100 days. Time to NH entry was calculated as the difference between the NH entry date and the index date (the date of TBI, non-TBI trauma, or inpatient/outpatient visit in the uninjured group). We used cause specific Cox proportional hazards models with stabilized inverse probability of exposure weights to model time to NH entry as a function of injury in the presence of death as a competing risk and generated hazard ratios (HR) and 95% confidence intervals (CI). After excluding beneficiaries living in a NH at index, there were 60,600 TBI, 63,762 non-TBI trauma, and 69,893 uninjured beneficiaries in the sample. In weighted models, beneficiaries with TBI entered NHs at higher rates relative to the non-TBI trauma (HR 1.15; 95% CI 1.10, 1.20) and uninjured (HR 1.67; 95% CI 1.60, 1.74)

² *Traumatic Brain Injury and Risk of Long-Term Nursing Home Entry among Older Adults: An Analysis of Medicare Administrative Claims Data.* Bailey, M. Doyinsola; Gambert, Steven; Gruber-Baldini Ann; Guralnik, Jack; Kozar, Rosemary; Qato, Danya M.; Shardell, Michelle; Albrecht, Jennifer S. In preparation for submission.

groups. Future research should focus on interventions to retain older adult TBI survivors within the community.

Keywords: nursing home entry, nursing home placement, older adult, head injury, traumatic brain injury.

Background

Traumatic brain injury (TBI) is a major cause of death and disability in the United States among older adults aged 65 years and older,^{1,2,177} with over 600,000 sustaining a TBI in 2013 alone.² As a result of these injuries, over 123,000 older adults were hospitalized, and 21,000 died.² The incidence of TBI-related emergency department visits, hospitalizations, and deaths is highest among older adults^{2,3} and is increasing faster than any other age group,^{2,4} at a rate that exceeds their population growth.³ In addition to being at greater risk of TBI, older adults experience higher morbidity and mortality¹⁷⁸ compared to younger adults with similar injury severity.^{69,179–182}

Following a TBI, older adults have slower recovery trajectories^{13–15} and worse functional, cognitive, and psychosocial outcomes post-injury.^{12,15,101,183} Among older adults, a study of the year following TBI found that functional capacity declined steadily following injury, reaching a loss of one activity of daily living (ADL) at 12 months.¹⁹ In addition, older adults with TBI have a heavier burden of comorbid illness compared to those without TBI,^{11,29,75} which may complicate or impede recovery.

Poor functional recovery following an acute insult to the brain can signal the end of independent living,^{108,109} particularly among older adults who may have decreased physiologic reserve.^{17,80} Among survivors of acute TBI, older age is associated with a lower likelihood of being discharged home,⁴ and reduced community participation post-injury.¹¹⁰ However, to date, no studies have examined the association between TBI and nursing home (NH) entry among older adults. The exceedingly high financial, personal, and social costs of nursing home care have motivated interest in identifying risk factors that

are associated with long-term nursing home entry. Given the increased emphasis on aging in place, such information could inform rehabilitation and home health policies. Thus, the objective of this study was to estimate the risk of long-term nursing-home placement associated with an isolated TBI in a nationally representative sample of community-dwelling older Medicare beneficiaries.

Methods

Data Sources and Study Design

The data source for this retrospective cohort study was a 5% random sample of Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Warehouse (CCW) for years 2007-2015. These data contain longitudinal health encounter information on beneficiaries ≥ 65 years and individuals <65 years with end-stage renal disease (ESRD) or recognized Social Security disabilities. There are over 55 million beneficiaries¹⁸⁴ ($>98\%$ of adults aged 65 and over^{152,185}) enrolled in the Medicare program today, making claims data nationally representative and one of the richest sources of utilization information in the country. It represents the Medicare-covered US population,¹⁵² a diverse mixture of race, ethnicities, and geographical regions across the United States.

To identify beneficiaries residing in NHs, Medicare Part A data was linked to the Minimum Data Set 2.0 and 3.0 (MDS 2.0 and 3.0). The MDS is a federally mandated health status assessment of all Medicare/Medicaid certified NH residents. It provides a comprehensive assessment of each resident's functional capabilities and includes clinical

assessments for residents at admission, discharge, quarterly, annually, and upon any significant change in health status. It also includes dates of all assessments, admissions, and discharges.¹⁵⁵ The merged file of Medicare claims with the MDS consists of detailed date-specific information, which allows for tracking NH status monthly.

Coverage Criteria

Continuous Medicare coverage was defined as having full, uninterrupted Medicare Parts A, B but no C (health maintenance organization (HMO)) coverage. Participants were required to have 12 months of continuous coverage before the index date (the date of TBI, non-TBI trauma, or date of inpatient/outpatient visit in the uninjured group) and a minimum of 3 months of continuous coverage after the index date. Participant follow-up time continued if the continuous coverage criterion was met, up to five years post-index date.

Study Participants

Participants included community-dwelling beneficiaries ≥ 65 years of age, meeting coverage criteria, and diagnosed with either a TBI, a non-TBI injury, or were uninjured between January 2008 and June 2015. Beneficiaries already living in a nursing home were excluded. Participants contributed follow-up time until the sooner of discontinued enrollment, nursing home placement, death, September 30, 2015, or 5 years.

Exposure

The exposure in this study was injury status, classified into three mutually exclusive levels: TBI, non-TBI trauma and uninjured. We ensured that the injury groups were independent by excluding people who appeared in more than one group. We chose to use only diagnoses codes in the primary position of a claim, to eliminate beneficiaries who may have had other more severe health problems that could have altered their risk of NH placement. Typically the location of claims can be indicative of the severity of injury or health problem (in the uninjured cohort). Comparison to the non-TBI trauma beneficiaries will help disentangle the effect of an isolated TBI from the effect of traumatic injury in general while comparison to uninjured beneficiaries will provide an estimate of the overall impact of TBI on NH entry compared to the general population of Medicare beneficiaries.

TBI

This exposure category consisted of beneficiaries with an isolated traumatic injury to the head. TBI was operationalized using the Centers for Disease Control and Prevention (CDC) case definition International Classification of Disease (ICD) codes often used in epidemiologic studies.^{156,157} We searched for the first claim for at least one of the following ICD version 9, clinical modification (ICD-9-CM) codes for concussion (850.xx), non-specific TBIs (853.xx-854.1x) and other TBIs (800.xx, 801.xx, 803.xx, 804.xx, 851.xx-852.xx, 950.1-950.3, 959.0) between January 2008 and June 2015 in the first position of inpatient and outpatient claims.

Non-TBI Trauma

This exposure category consisted of comparison beneficiaries with a traumatic injury, not involving the head. Adopting codes from the Barell Injury Diagnosis Matrix,¹⁵⁸ we searched for the first claim for at least one of the following ICD-9-CM codes for any of the four major injury diagnoses: torso fractures (807.0x-4x, 808.xx, 809.xx) upper extremity fractures (810.xx-818.xx), hip fractures (820.xx) and lower extremity fractures (821.xx-827.xx) between January 2008 and June 2015 in the first position of inpatient and outpatient claims. We randomly selected and frequency-matched with the TBI group on index dates and inpatient and outpatient claims. Typically, less severe injuries are diagnosed in an outpatient setting while more severe injuries are likely diagnosed in an inpatient setting. By matching on the distribution of inpatient and outpatient claims we attempted to ensure a similar distribution of hospitalized and non-hospitalized cases and ultimately, injury or health problem severity. Our random sampling was conducted in a stratified manner to ensure this.

Uninjured

The uninjured exposure category included a random sample of inpatient and outpatient claims of beneficiaries aged ≥ 65 years of age, meeting continuous coverage criteria, and without a TBI or a non-TBI injury between January 2008 and June 2015. Beneficiaries in this group were randomly selected to have a frequency-matched sample of the same size and with the same distribution of inpatient and outpatient claims as the TBI group, resulting in an equivalent distribution of index dates.

Outcome

The primary outcome was long-term NH entry. Nursing-home stays were identified based on the method described by Intrator *et al.*¹⁶⁴ and modified by Goodwin *et al.*,¹⁶⁵ using Part A claims plus the MDS. We defined long-term NH entry as the first nursing-home admission that resulted in a stay of ≥ 100 days to distinguish admissions for long-term care from admissions for short-term stays that typically occur for rehabilitation (detailed in the appendix). This definition is based on Medicare's policy for reimbursement (short nursing home stays < 100 days where skilled nursing care is needed are covered by Medicare. However, long stays ≥ 100 days where the purpose is primarily custodial care are not covered). Time to NH entry was calculated as the difference between the index date and the date of NH admission. Beneficiaries were right censored at the time of death, at the end of follow-up, or study termination.

Covariates

Demographic, clinical characteristics, and original reason for entitlement code (OREC) were obtained from administrative claims files. The CCW data also contains information on 27 common chronic comorbid conditions, with an annual flag for each condition as well as the date of the first diagnosis for that condition, based on validated algorithms that search for specific diagnostic codes within the CMS administrative claims.¹⁷¹ We combined the five cancer flags to create an 'any cancer' variable and selected to report the Alzheimer's disease and related dementias flag rather than the Alzheimer's disease (only) flag. We used the date of the first diagnosis to determine if a condition was present at the index date.

Statistical Analysis

We compared the baseline distribution of demographic and clinical variables by injury status, using either Chi-square goodness of fit for categorical variables and ANOVA or Kruskal-Wallis tests for continuous variables, as appropriate. We excluded all individuals who were NH-dwelling pre-injury and used stabilized inverse probability of treatment weights (IPTW) to balance covariates between exposure groups. We used a multinomial logistic regression in which the outcome variable was injury group and included the following as covariates in the model: demographic variables such as age, sex, and race; 27 common chronic conditions and other variables such as length of follow-up and original reason for Medicare entitlement. Given our large sample size, all covariates differed significantly across injury groups. We examined the balance of observed covariates in the weighted sample by computing standardized mean differences (the difference in means between TBI and no-TBI (non-TBI trauma and uninjured) groups divided by the overall standard deviation) on pre- and post-matched samples, following published guidelines.¹⁷⁴ We used a cutoff of ± 0.03 for standardized differences to identify covariates that could be further adjusted for in the regression model as a form of doubly robust estimation.^{175,176}

We quantified the effect of TBI on the risk of NH entry in the presence of death as a competing risk using cause-specific Cox proportional hazards models with stabilized inverse probability weights to estimate the hazard ratio (HR) of entering a NH, with 95% confidence intervals (CIs). All analyses were performed with SAS Studio Enterprise

Edition 3.71 (SAS Institute, Cary, NC). This study was approved by the Institutional Review Board at the University of Maryland, Baltimore.

RESULTS

Study Cohort

Between January 2008 and June 2015, we identified 76,539 beneficiaries aged 65 years and older who were diagnosed with TBI and met continuous coverage criteria. In the same period, we identified 201,698 trauma and 1,893,700 uninjured beneficiaries and randomly selected 76,539 from each group. To ensure the groups were mutually exclusive, we excluded 9,514 (12%) of the TBI group with a trauma diagnosis, 8,860 (12%) of the trauma group with a TBI diagnosis, and 5,066 (7%) of the uninjured group with a TBI/trauma diagnosis. At baseline, 13,100 (6%) of the sample, (11% of those with TBI, 6% of those with trauma, and 2% of the uninjured group) were living in a NH and were excluded from analyses.

Our final cohort contained 194,225 beneficiaries (60,600 with TBI, 63,762 with trauma, and 69,893 uninjured) that were predominantly female (69%) and white (86%) with an average age of 77.0 years (standard deviation [SD] 8.6; Table 3). As presented in Table 3, those with TBI were older (80.4 years (SD 8.1) vs 78.1 (SD 8.2) for non-TBI trauma and 71.8 (SD 7.2) years in the uninjured, $p < 0.001$), and had a higher burden of comorbidities. For example, those with TBI were significantly more likely to have hypertension (90% vs 83% and 65%), hyperlipidemia (83% vs 78% and 62%), ischemic heart disease (64% vs 52% and 28%), and diabetes (42% vs 35% and 25%) ($p < 0.001$ for all).

Nursing Home Entry

Of those in the TBI group that were community-dwelling at baseline, 19,064 (35%) were censored due to death, compared to 13,957 (24%) and 7,615 (11%) of the trauma and uninjured groups, respectively ($p < 0.001$). Those with a TBI were more likely to enter a NH during the 5-year follow-up (9% vs 7% and 2%, $p < 0.001$). The median time to NH entry was shorter for the trauma group, 159 days (IQR 763 days), than for the TBI and uninjured groups, 274 days (IQR 709 days) and 388 days (IQR 1011 days) (Table 4). Median follow-up time was shorter in the TBI group vs the control groups ($p < 0.001$).

Table 5 presents the results of Cox proportional hazard models to evaluate the relation of TBI with NH entry. In the unadjusted model, we observed a higher risk of NH entry in the TBI group compared to the trauma (HR 1.47; 95% CI 1.42, 1.53) and uninjured groups (HR 5.91; 95% CI 5.57, 6.26). After adjusting for covariates, we still observed a significantly higher risk of NH entry compared to both the trauma (HR 1.15; 95% CI 1.10, 1.20) and uninjured (HR 1.67; 95% CI 1.60, 1.74) groups compared to the TBI group. (Table 5).

DISCUSSION

This is the first study to report on long-term NH home placement after TBI in a large, nationally representative sample of community-dwelling older adults enrolled in Medicare. In our study, TBI was associated with an increased risk of nursing home entry among community-dwelling Medicare beneficiaries compared to those with non-TBI

trauma and to uninjured beneficiaries. Among those with TBI, the 5-year cumulative incidence of NH entry was 9%, which was higher than those with non-TBI trauma and the uninjured. Among beneficiaries with TBI, the median time to NH placement was 274 days (Table 2) suggesting that individuals with TBI were community-dwelling for a period of time prior to entering the nursing home.

Aging results in a progressive decline in molecular and cellular function¹⁹² that leads to a limited physiologic reserve and a higher comorbidity burden.^{17,68} Consistent with other research,^{15,67,193} our findings indicated that those with TBI had a higher comorbidity burden before their injury, even when compared to older adults with non-TBI trauma. In our study sample, those with TBI were more likely to have diabetes, high blood pressure, cancer, and stroke, risk factors for NH admission.¹⁹⁴ Although the three exposure groups were balanced on these covariates in weighted regression analyses, residual confounding due to unequal burden of comorbidity between groups was still possible. Time to NH entry was also much shorter in the trauma cohort, suggesting that that NH admissions after a TBI come after a period of declining health while admissions after trauma may be more immediate. This could potentially be because most cases of TBI among those over 65 are mild,¹⁹⁵ but without the documentation of injury severity in claims data, we were unable to assess this further.

The long-term sequelae of TBI include both cognitive and functional impairment, some of the strongest predictors of NH admission among older adults.¹⁹⁴ Although the association between TBI and NH placement has not been well studied among older adults, falls have been reported to result in declines in function, both from physical injury and the loss of confidence in the ability to perform functional activities,¹⁹⁶ ultimately

increasing the risk of NH admission.^{194,197} Falls are the most prevalent mechanism of TBI² and also the primary cause of hip fractures among the elderly (95%)¹⁹⁸ Hip fracture results in significant increases in disability and nursing home admission compared to age-matched controls.^{199,200} In 2008, one study reported that 35% of older adult hip fracture patients were placed in long-term NH care within 1 year post-fracture.²⁰¹ Another study of older adult hip fracture patients reports that 33% became permanent SNF residents.²⁰² The findings from this our study, which are specific to older adult TBI survivors, report a 5-year cumulative incidence of NH placement of 9%, much lower than that reported following hip fracture. Hip fracture usually requires surgery and causes an immediate drop in mobility whereas TBI generally does not.

Older adults with stroke are perhaps most similar to those with TBI with regards to cognitive impairment. In 2018, Blackburn *et al.* characterized long-term NH placement after stroke among older adult Medicare beneficiaries. They reported that within 5 years of stroke, 119 (21.3%) participants had been placed in a nursing home.²⁰³ Lifestyle-related factors such as diabetes and hypertension have also been reported as important predictors of long-term NH admission among middle-aged and older adults.²⁰⁴ In our study, those with TBI were significantly more likely than the other groups to have diabetes and hypertension at baseline, increasing their risk of NH placement even before the TBI. Though imbalances in the distribution of these comorbidities and covariates were accounted for using IPTW, there still remains a potential for residual confounding.

There are limitations to the current study. This was a secondary analysis of administrative claims data from 2008-2015. Though we had data for years 2016 and 2017 available to us, we chose to only use data prior to the switch from ICD-9 to ICD10

coding. Though more recent data are preferable, given the lack of literature on this topic, we believe the data can still provide an estimate of the risk of long-term nursing-home placement associated with having a TBI. At the very least, estimates from this study can serve as a historical reference for comparison when current data becomes available. Administrative claims data lack documentation of the occurrence of previous head injuries or of traditional measures of TBI severity (Glasgow Coma Scale Score, Abbreviated Injury Score), which likely have a large impact on NH placement. These are certainly important factors that impact NH placement and which would be important factors to control for in future studies. Additionally, this study lacks contextual factors such as social/family support which have been associated with a 10–50% decreased likelihood of NH admission among older adults in the general population.²⁰⁵ Prior studies in younger populations suggest that home- and community-based services can substitute for long-term NH for some individuals.²⁰⁶ For example, the availability of home- and community-based services is negatively associated with the rate of NH admissions among young adults and the presence of NH residents with low-care needs.^{206,207} The extent to which home- and community-based services can reduce NH placement among older survivors of TBI should be explored in future studies. However, it is unlikely that social/family support and home- and community-based services are distributed so differently in the 3 groups studied that they can explain differential nursing home admissions. It is worth noting that we excluded beneficiaries with multiple injuries, which may under-estimate the true effect size. Though, this is less of a concern among older adults who are less likely to have multiple injuries than younger persons. Lastly,

administrative claims data is collected for billing and reimbursement purposes. Therefore, the assessment of all measures is dependent on documentation.

This is the largest study of which we are aware reporting estimates of long-term NH placement following TBI among older adults. As such, it can serve as a baseline reference for future studies and inform the development and improvement of post-discharge care services and policies. This is significant because it provides critical information on an important recovery outcome after TBI. Additionally, our nationally representative dataset had an average follow-up duration of 3.3 years and the use of a non-TBI trauma injury and an uninjured control group allowed us to disentangle the separate effects of trauma and TBI. Finally, data on nursing home admission was collected monthly, allowing us to determine dates of admission and length of stay more accurately.

Older adults with a TBI have a significantly increased risk of NH entry. Future research is needed to understand the rehabilitation needs of older adults with TBI so that resources can be directed toward keeping older adults in community settings.

Table 3. Baseline Characteristics of Community-Dwelling Medicare Beneficiaries ≥65 years, by Injury Type (2008-2015), (n=194,225)

	Total n=194,225	TBI n=60,600	Trauma n=63,762	Uninjured n=69,893	p-value
Patient Characteristics					
Age (years), mean(SD)	76.5 (8.6)	80.4 (8.1)	78.1 (8.2)	71.8 (7.2)	<0.001
Sex, n (%)					<0.001
Female	134,575 (69)	20,007 (33)	17,167 (27)	22,506 (32)	
Male	59,680 (31)	40,593 (67)	46,595 (73)	47,387 (68)	
Race, n (%)					<0.001
White, non-Hispanic	166,152 (86)	52,366 (86)	56,525 (89)	57,261 (82)	
Black	11,785 (6)	3,404 (6)	2,890 (5)	5,491 (8)	
Hispanic	9,450 (5)	2,906 (5)	2,685 (4)	3,859 (6)	
Asian/Pacific Islander	3,920 (2)	1,216 (2)	894 (1)	1,810 (3)	
American Indian/Alaska Native	951 (<1)	303 (<1)	350 (<1)	298 (<1)	
Other	1,112 (<1)	308 (<1)	290 (<1)	514 (<1)	
Unknown	885 (<1)	97 (<1)	128 (<1)	660 (<1)	
OREC ^a , n (%)					<0.001
Old Age	177,440 (91)	54,234 (90)	57,332 (90)	65,874 (94)	
Disability	16,430 (8)	6,222 (10)	6,269 (10)	3,939 (6)	
Other	385 (<1)	144 (<1)	161 (<1)	80 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	33,323 (17)	18,203 (30)	11,193 (18)	3,927 (6)	<0.001
Acute Myocardial Infarction	9,042 (5)	4,465 (7)	3,437 (5)	1,140 (2)	<0.001
Anemia	100,096 (52)	42,005 (69)	37,108 (58)	20,983 (30)	<0.001
Asthma	24,078 (12)	9,972 (16)	9,127 (14)	4,979 (7)	<0.001
Atrial Fibrillation	31,332 (16)	15,610 (26)	11,057 (17)	4,665 (7)	<0.001
Cataracts	128,299 (66)	48,143 (79)	47,277 (74)	32,879 (47)	<0.001
Congestive Heart Failure	52,943 (27)	24,889 (41)	19,634 (31)	8,420 (12)	<0.001
Chronic Kidney Disease	41,079 (21)	19,215 (32)	15,049 (24)	6,815 (10)	<0.001
All cancers	30,297 (16)	11,740 (19)	11,017 (17)	7,540 (11)	<0.001
COPD ^c	49,164 (25)	20,721 (34)	19,261 (30)	9,182 (13)	<0.001
Depression	60,318 (31)	26,607 (44)	22,024 (35)	11,687 (17)	<0.001
Diabetes	65,517 (34)	25,459 (42)	22,509 (35)	17,549 (25)	<0.001
Glaucoma	44,536 (23)	17,264 (29)	15,829 (25)	11,443 (16)	<0.001
Hip/Pelvic Fracture	7,443 (4)	4,304 (7)	2,140 (3)	999 (1)	<0.001
Hyperlipidemia	143,843 (74)	50,477 (83)	49,870 (78)	43,496 (62)	<0.001
Benign Prostatic Hyperplasia	26,150 (13)	11,480 (19)	8,333 (13)	6,337 (9)	<0.001
Hypertension	152,338 (78)	54,330 (90)	52,857 (83)	45,151 (65)	<0.001
Acquired Hypothyroidism	52,240 (27)	20,475 (34)	18,912 (30)	12,853 (18)	<0.001
Ischemic Heart Disease	92,325 (48)	39,065 (64)	33,469 (52)	19,791 (28)	<0.001
Osteoporosis	51,031 (26)	19,832 (33)	21,413 (34)	9,786 (14)	<0.001
RA ^d /Osteoarthritis	105,366 (54)	42,487 (70)	39,453 (62)	23,426 (34)	<0.001
Stroke/TIA ^e	32,493 (17)	16,628 (27)	11,509 (18)	4,356 (6)	<0.001

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack.

	Total n=207,355	TBI n=68,203	Trauma n=67,679	Uninjured n=71,473	p-value
Nursing Home Entry					
Pre-existing NH-dwelling, n (%)	13,100 (6)	7,603 (11)	3,917 (6)	1,580 (2)	<0.001
Deaths before NH entry, n (%)	33,021 (16)	19,064 (35)	13,957 (24)	7,615 (11)	<0.001
Incident NH Entry, n (%)	12,276 (6)	6,108 (9)	4,740 (7)	1,428 (2)	<0.001
Time to NH Entry (days), median (IQR)	246 (769)	274 (709)	159 (763)	388 (1011)	<0.001
Follow Up (months), mean (SD)	39 (25)	34 (24)	38 (25)	44 (25)	<0.001

	Hazard Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted^a	Weighted^b	Weighted^c
Uninjured	Reference	Reference	Reference	Reference
TBI	5.91 (5.57, 6.26)	1.40 (1.34, 1.46)	1.67 (1.60, 1.74)	2.21 (2.08, 2.36)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	1.47 (1.42, 1.53)	1.18 (1.13, 1.23)	1.15 (1.10, 1.20)	1.15 (1.10, 1.20)

^aNo adjustment for additional covariates.

^bAdjusted for age, Alzheimer's disease and related dementias, atrial fibrillation, congestive heart failure, stroke/transient ischemic attack (covariates with standardized differences ±0.03).

^cAdjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

CHAPTER V: ADDITIONAL RESULTS

A. Study Sample

These results report the association between TBI and risk of disability, chronic pain, insomnia, depression, and anxiety/PTSD in a cohort of older adult Medicare beneficiaries. Exclusion of those not at risk of the outcome at the start of follow-up resulted in different cohorts for each analysis. The final study sample prior to exclusion contained 207,355 beneficiaries (68,203 with TBI, 67,679 with trauma, and 71,473 uninjured; Figure 2) that were predominantly female (70%) and white (89%) with an average age of 77.0 years (standard deviation [SD] 8.8; Table 1). As presented in Table 1, those with TBI were older (80.8 years (SD 8.2) vs 78.4 (SD 8.3) for non-TBI trauma and 72.1 (SD 7.5) years in the uninjured, $p < 0.001$), more likely to have originally received Medicare benefits because of a disability (11% vs 10% and 6%, $p < 0.001$). Beneficiaries in the TBI group also had a higher burden of comorbidities. For example, they were significantly more likely to have hypertension (90% vs 84% and 65%), hyperlipidemia (82% vs 78% and 62%), rheumatoid arthritis (71% vs 63% and 34%), ischemic heart disease (66% vs 54% and 29%), and diabetes (43% vs 36% and 26%) ($p < 0.001$ for all).

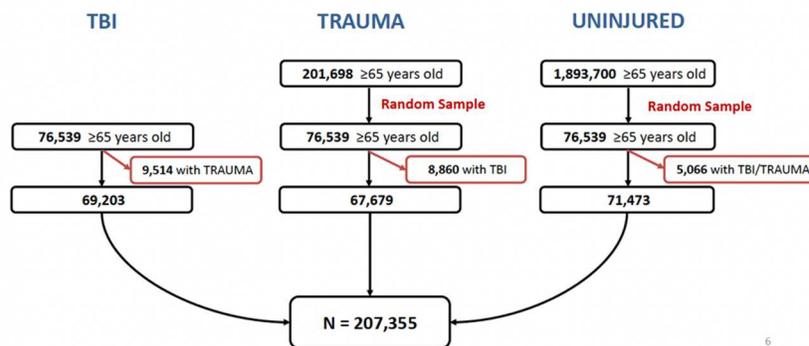


Figure 2: Flowchart detailing participant selection by injury group

B. Disability

At baseline, 53% of the entire cohort had at least one disability (70% with TBI, 57% with trauma, and 32% uninjured, $p < 0.001$). The mean disability score was greater in the TBI compared to the trauma and uninjured groups (1.9 vs 1.3 and 0.6, $p < 0.001$). Table 7 presents the results of the proportional-odds cumulative logit regression to evaluate the association of TBI with disability. In the unadjusted model, I observed a significantly higher odds of disability comparing the TBI to the non-TBI trauma (OR 1.49, 95% CI 1.40, 1.41) and uninjured groups (OR 6.66, 95% CI 6.64, 6.68) compared to the TBI group. Weighting and adjusting for covariates with standardized differences exceeding $|0.03|$, resulted in a slight change to results but did not change the conclusions (non-TBI trauma (OR 0.94; 95% CI 0.94, 0.95) and uninjured (OR 2.17; 95% CI 2.17, 2.18) groups compared to the TBI group).

Table 6. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥65 years, in the analysis of Risk of Disability (2008-2015) (n=207,355)

	Total n=207,355	TBI n=68,203	Trauma n=67,679	Uninjured n=71,473	p-value
Patient Characteristics					
Age (years), mean(SD)	77.0 (8.8)	80.8 (8.2)	78.4 (8.3)	72.1 (7.5)	<0.001
Sex, n (%)					<0.001
Female	144,670 (70)	46,248 (68)	49,789 (74)	48,633 (68)	
Male	62,685 (30)	21,955 (32)	17,890 (26)	22,840 (32)	
Race, n (%)					<0.001
White, non-Hispanic	177,419 (86)	58,885 (86)	59,987 (89)	58,547 (82)	
Black	12,831 (6)	4,028 (6)	3,134 (5)	5,669 (8)	
Hispanic	10,000 (5)	3,224 (5)	2,837 (4)	3,939 (6)	
Asian/Pacific Islander	4,053 (2)	1,298 (2)	366 (<1)	1,827 (3)	
American Indian/Alaska Native	1,012 (<1)	337 (<1)	928 (1)	309 (<1)	
Other	1,134 (<1)	323 (<1)	294 (<1)	517 (<1)	
Unknown	906 (<1)	108 (<1)	133 (<1)	665 (<1)	
OREC ^a , n (%)					<0.001
Old Age	188,658 (91)	60,739 (89)	60,667 (90)	67,252 (94)	
Disability	18,281 (9)	7,302 (11)	6,840 (10)	4,139 (6)	
Other	416 (<1)	162 (<1)	172 (<1)	82 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	43,375 (21)	24,252 (36)	14,028 (21)	5,095 (7)	<0.001
Acute Myocardial Infarction	10,361 (5)	5,302 (8)	3,835 (6)	1,224 (2)	<0.001
Anemia	111,346 (54)	48,658 (71)	40,462 (60)	22,226 (31)	<0.001
Asthma	26,278 (13)	11,311 (17)	9,804 (14)	5,163 (7)	<0.001
Atrial Fibrillation	35,312 (17)	18,071 (27)	12,213 (18)	5,028 (7)	<0.001
Cataracts	138,834 (67)	54,454 (80)	50,440 (75)	33,940 (47)	<0.001
Congestive Heart Failure	61,012 (29)	29,713 (44)	22,072 (33)	9,227 (13)	<0.001
Chronic Kidney Disease	46,781 (23)	22,772 (33)	16,684 (25)	7,325 (10)	<0.001
All cancers	32,672 (16)	13,169 (19)	11,757 (17)	7,746 (11)	<0.001
COPD ^c	55,234 (27)	24,371 (36)	21,132 (31)	9,731 (14)	<0.001
Depression	69,496 (34)	32,139 (47)	24,712 (37)	12,645 (18)	<0.001
Diabetes	71,973 (36)	29,279 (43)	24,436 (36)	18,258 (26)	<0.001
Glaucoma	48,204 (23)	19,530 (29)	16,876 (25)	11,798 (17)	<0.001
Hip/Pelvic Fracture	9,886 (5)	5,895 (9)	2,694 (4)	1,297 (2)	<0.001
Hyperlipidemia	153,622 (74)	56,415 (82)	52,746 (78)	44,461 (62)	<0.001
Benign Prostatic Hyperplasia	27,944 (13)	12,697 (19)	8,754 (13)	6,493 (9)	<0.001
Hypertension	164,787 (79)	61,626 (90)	56,579 (84)	46,582 (65)	<0.001
Acquired Hypothyroidism	57,206 (28)	23,432 (34)	20,421 (30)	13,353 (19)	<0.001
Ischemic Heart Disease	101,754 (49)	44,785 (66)	36,236 (54)	20,733 (29)	<0.001
Osteoporosis	56,746 (27)	23,188 (34)	23,251 (34)	10,307 (14)	<0.001
RA ^d /Osteoarthritis	115,452 (56)	48,478 (71)	42,524 (63)	24,450 (34)	<0.001
Stroke/TIA ^e	38,117 (18)	20,113 (29)	13,133 (19)	4,871 (7)	<0.001

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack.

Table 7. Cumulative Logit Regression Analyses of Disability, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=207,355)

	Odds Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted ^a	Weighted ^b	Weighted ^c
Uninjured	Reference	Reference	Reference	Reference
TBI	6.66 (6.64, 6.68)	1.92 (1.91, 1.93)	2.17 (2.17, 2.18)	2.33 (2.32, 2.33)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	1.49 (1.40, 1.41)	1.00 (0.99,1.00)	0.94 (0.94, 0.95)	0.95 (0.94, 0.95)

^a No adjustment for additional covariates.

^b Adjusted for age, Alzheimer's disease and related dementias, stroke/transient ischemic attack (covariates with standardized differences ± 0.03).

^c Adjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

C. Chronic Pain

After excluding beneficiaries with chronic pain at baseline (29% with TBI, 27% with trauma, and 10% uninjured, $p < 0.001$), the final cohort contained 162,752 beneficiaries (48,532 with TBI, 49,556 with trauma, and 64,665 uninjured; Table 8). Of those remaining, 42% were censored due to death in the TBI group, compared to 28% and 13% of the trauma and uninjured groups respectively ($p < 0.001$). Over the follow-up period, the overall cumulative incidence of chronic pain was 7.9% (8% in the TBI, 10% in the trauma and 7% in the uninjured group).

Table 9 presents the results of cause-specific Cox proportional hazard models to evaluate the relation of TBI with incident chronic pain. In the unadjusted models, I observed a lower risk of incident chronic pain comparing the TBI to the non-TBI trauma group (HR 0.94; 95% CI 0.90, 0.98) but a higher risk compared to the uninjured group (HR 1.50; 95% CI 1.44, 1.57). Weighting and adjusting for covariates with standardized differences exceeding $|0.03|$, resulted in a higher risk of chronic pain compared to both the non-TBI trauma (HR 1.01; 95% CI 0.97, 1.05) and uninjured (HR 1.47; 95% CI 1.41, 1.54) groups, however the result was not statistically significant compared to the non-TBI trauma group. A sensitivity analysis that involved IPTW and adjusting for all covariates in the regression model (not just those with standardized differences exceeding $|0.03|$) did not significantly change the results (Table 9).

Table 8. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥65 years, in the analysis of Risk of Chronic Pain (2008-2015) (n=162,752)

	Total n=162,752	TBI n=48,532	Trauma n=49,556	Uninjured n=64,664	p- value
Patient Characteristics					
Age (years), mean(SD)	76.7 (8.9)	81.0 (8.3)	78.5 (8.5)	72.0 (7.5)	<0.001
Sex, n (%)					<0.001
Female	111,055 (68)	31,696 (65)	35,732 (72)	43,627 (67)	
Male	51,697 (32)	16,836 (35)	13,824 (28)	21,037 (33)	
Race, n (%)					<0.001
White, non-Hispanic	138,499 (85)	41,680 (86)	43,861 (89)	52,958 (82)	
Black	10,145 (6)	2,837 (6)	2,222 (4)	5,086 (8)	
Hispanic	8,061 (5)	2,369 (5)	2,132 (4)	3,560 (6)	
Asian/Pacific Islander	3,594 (2)	1,110 (2)	776 (2)	1,708 (3)	
American Indian/Alaska Native	690 (<1)	198 (<1)	228 (<1)	264 (<1)	
Other	956 (<1)	252 (<1)	226 (<1)	478 (<1)	
Unknown	807 (<1)	86 (<1)	111 (<1)	610 (<1)	
OREC ^a , n (%)					<0.001
Old Age	150,541 (93)	44,131 (91)	45,275 (91)	61,135 (95)	
Disability	11,909 (7)	4,296 (9)	4,160 (8)	3,453 (5)	
Other	302 (<1)	105 (<1)	121 (<1)	76 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	32,330 (20)	17,567 (36)	10,253 (21)	4,510 (7)	<0.001
Acute Myocardial Infarction	7,326 (5)	3,646 (8)	2,616 (5)	1,064 (2)	<0.001
Anemia	80,679 (50)	33,307 (69)	28,003 (57)	19,369 (30)	<0.001
Asthma	17,508 (11)	7,006 (14)	6,179 (12)	4,323 (7)	<0.001
Atrial Fibrillation	25,573 (16)	12,578 (26)	8,573 (17)	4,422 (7)	<0.001
Cataracts	103,829 (64)	37,827 (78)	35,839 (72)	30,163 (47)	<0.001
Congestive Heart Failure	43,207 (27)	20,084 (41)	15,136 (31)	7,987 (12)	<0.001
Chronic Kidney Disease	32,603 (20)	15,195 (31)	11,105 (22)	6,303 (10)	<0.001
All cancers	24,507 (15)	9,288 (19)	8,344 (17)	6,875 (11)	<0.001
COPD ^c	38,159 (23)	15,912 (33)	13,990 (28)	8,257 (13)	<0.001
Depression	47,051 (29)	20,665 (43)	15,859 (32)	10,527 (16)	<0.001
Diabetes	53,508 (33)	20,147 (42)	17,189 (35)	16,172 (25)	<0.001
Glaucoma	36,198 (22)	13,608 (28)	12,071 (24)	10,519 (16)	<0.001
Hip/Pelvic Fracture	6,973 (4)	3,912 (8)	1,948 (4)	1,113 (2)	<0.001
Hyperlipidemia	116,399 (72)	39,223 (81)	37,578 (76)	39,638 (61)	<0.001
Benign Prostatic Hyperplasia	21,558 (13)	9,377 (19)	6,397 (13)	5,784 (9)	<0.001
Hypertension	125,007 (77)	43,180 (89)	40,396 (82)	41,431 (64)	<0.001
Acquired Hypothyroidism	41,546 (26)	15,750 (32)	14,072 (28)	11,724 (18)	<0.001
Ischemic Heart Disease	73,811 (45)	30,721 (63)	25,018 (51)	18,072 (28)	<0.001
Osteoporosis	39,573 (24)	15,064 (31)	15,654 (32)	8,855 (14)	<0.001
RA ^d /Osteoarthritis	78,245 (48)	31,092 (64)	27,226 (55)	19,927 (31)	<0.001
Stroke/TIA ^e	27,040 (17)	13,770 (28)	9,066 (18)	4,204 (7)	<0.001

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack

Table 9. Cox Regression Analyses of Time to Chronic Pain with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=162,752)

	Hazard Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted ^a	Weighted ^b	Weighted ^c
Uninjured	Reference	Reference	Reference	Reference
TBI	1.50 (1.44, 1.57)	1.53 (1.46, 1.59)	1.47 (1.41, 1.54)	1.53 (1.47, 1.60)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	0.94 (0.90, 0.98)	1.02 (0.98, 1.07)	1.01 (0.97, 1.05)	1.01 (0.97, 1.06)

^a No adjustment for additional covariates.

^b Adjusted for age, Alzheimer's disease and related dementias, atrial Fibrillation, congestive heart failure, stroke/transient ischemic attack (covariates with standardized differences ± 0.03).

^c Adjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

D. Insomnia

After excluding beneficiaries who with insomnia at baseline (5% with TBI, 4% with trauma, and 2% uninjured, $p < 0.001$), the final cohort contained 199,486 beneficiaries (64,660 with TBI, 64,655 with trauma, and 70,189 uninjured; Table 10). Of those remaining, 40% were censored due to death in the TBI group, compared to 28% and 13% of the trauma and uninjured groups respectively ($p < 0.001$). Over the follow-up period, the overall cumulative incidence of Insomnia was 2.9% (3% in the TBI, 3% in the trauma and 2% in the uninjured group).

Table 11 presents the results of cause-specific Cox proportional hazard models to evaluate the relation of TBI with incident insomnia. In the unadjusted model, I observed a higher risk of incident insomnia comparing the TBI to the non-TBI trauma (HR 1.08; 95% CI 1.02, 1.15) and uninjured groups (HR 1.91; 95% CI 1.81, 2.07). After weighting and adjusting for covariates with standardized differences exceeding $|0.03|$, the effect was no longer significant compared to the non-TBI trauma group (HR 1.05; 95% CI 0.99, 1.12), but remained significant in the uninjured group (HR 1.53; 95% CI 1.44, 1.63). A sensitivity analysis that involved IPTW and adjusting for all covariates in the regression model (not just those with standardized differences exceeding $|0.03|$) did not significantly change the results (Table 11).

Table 10. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥65 years, in the analysis of Risk of Insomnia (2008-2015) (n=199,486)

	Total n=199,486	TBI n=64,660	Trauma n=64,637	Uninjured n=70,189	p-value
Patient Characteristics					
Age (years), mean(SD)	76.9 (8.8)	80.8 (8.2)	78.4 (8.3)	72.1 (7.5)	<0.001
Sex, n (%)					<0.001
Female	138,726 (70)	21,037 (33)	17,230 (27)	22,493 (32)	
Male	60,760 (30)	43,623 (67)	47,407 (73)	47,696 (68)	
Race, n (%)					<0.001
White, non-Hispanic	170,599 (86)	55,822 (86)	57,286 (89)	57,491 (82)	
Black	12,455 (6)	3,866 (6)	3,009 (5)	5,580 (8)	
Hispanic	9,598 (5)	3,040 (5)	2,694 (4)	3,864 (6)	
Asian/Pacific Islander	3,932 (2)	1,234 (2)	900 (1)	1,798 (3)	
American Indian/Alaska Native	928 (<1)	296 (<1)	337 (<1)	295 (<1)	
Other	1,092 (<1)	303 (<1)	281 (<1)	508 (<1)	
Unknown	882 (<1)	99 (<1)	130 (<1)	653 (<1)	
OREC ^a , n (%)					<0.001
Old Age	182,038 (91)	57,781 (89)	58,143 (90)	66,114 (94)	
Disability	17,052 (9)	6,727 (10)	6,330 (10)	3,995 (6)	
Other	396 (<1)	152 (<1)	164 (<1)	80 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	40,849 (20)	22,727 (35)	13,181 (20)	4,941 (7)	<0.001
Acute Myocardial Infarction	9,845 (5)	5,014 (8)	3,645 (6)	1,186 (2)	<0.001
Anemia	105,922 (53)	45,880 (71)	38,351 (59)	21,691 (31)	<0.001
Asthma	24,651 (12)	10,488 (16)	9,160 (14)	5,003 (7)	<0.001
Atrial Fibrillation	33,542 (17)	17,103 (26)	11,553 (18)	4,886 (7)	<0.001
Cataracts	132,701 (67)	51,470 (80)	47,995 (74)	33,236 (47)	<0.001
Congestive Heart Failure	57,828 (29)	27,976 (43)	20,854 (32)	8,998 (13)	<0.001
Chronic Kidney Disease	44,229 (22)	21,359 (33)	15,725 (24)	7,145 (10)	<0.001
All cancers	31,286 (16)	12,515 (19)	11,180 (17)	7,591 (11)	<0.001
COPD ^c	52,004 (26)	22,770 (35)	19,804 (31)	9,430 (13)	<0.001
Depression	64,397 (32)	29,536 (46)	22,769 (35)	12,092 (17)	<0.001
Diabetes	68,944 (35)	27,725 (43)	23,289 (36)	17,930 (26)	<0.001
Glaucoma	46,217 (23)	18,542 (29)	16,071 (25)	11,604 (17)	<0.001
Hip/Pelvic Fracture	9,325 (5)	5,505 (9)	2,561 (4)	1,259 (2)	<0.001
Hyperlipidemia	147,227 (74)	53,408 (83)	50,224 (78)	43,595 (62)	<0.001
Benign Prostatic Hyperplasia	26,804 (13)	12,083 (19)	8,370 (13)	6,351 (9)	<0.001
Hypertension	157,851 (79)	58,319 (90)	53,871 (83)	45,661 (65)	<0.001
Acquired Hypothyroidism	54,460 (27)	22,059 (34)	19,349 (30)	13,052 (19)	<0.001
Ischemic Heart Disease	96,943 (49)	42,332 (65)	34,375 (53)	20,236 (29)	<0.001
Osteoporosis	53,782 (27)	21,760 (34)	21,987 (34)	10,035 (14)	<0.001
RA ^d /Osteoarthritis	109,596 (55)	45,581 (70)	40,210 (62)	23,805 (34)	<0.001
Stroke/TIA ^e	36,074 (18)	18,934 (29)	12,392 (19)	4,748 (7)	<0.001

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack.

Table 11. Cox Regression Analyses of Time to Insomnia with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=199,486)

	Hazard Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted ^a	Weighted ^b	Weighted ^c
Uninjured	Reference	Reference	Reference	Reference
TBI	1.91 (1.81, 2.07)	1.52 (1.43, 1.62)	1.53 (1.44, 1.63)	1.52 (1.43, 1.63)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	1.08 (1.02, 1.15)	1.05 (0.99, 1.12)	1.05 (0.99, 1.12)	1.04 (0.98, 1.11)

^a No adjustment for additional covariates.

^b Adjusted for age, Alzheimer's disease and related dementias, Atrial Fibrillation, congestive heart failure, stroke/transient ischemic attack (covariates with standardized differences ± 0.03).

^c Adjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

E. Depression

After excluding beneficiaries who were depressed at baseline (24% with TBI, 18% with trauma, and 7% uninjured, $p < 0.001$), the final cohort contained 174,452 beneficiaries (51,971 with TBI, 55,776 with trauma, and 66,705 uninjured; Table 12). Of those remaining, 33% were censored due to death in the TBI group, compared to 23% and 11% of the trauma and uninjured groups respectively ($p < 0.001$). Over the follow-up period, the overall cumulative incidence of depression was 9.5% (14% in the TBI, 11% in the trauma and 6% in the uninjured group).

Table 13 presents the results of cause-specific Cox proportional hazard models to evaluate the relation of TBI with incident depression. In the unadjusted model, I observed a higher risk of incident depression comparing the TBI to the non-TBI trauma (HR 1.42; 95% CI 1.37, 1.47) and uninjured groups (HR 3.10; 95% CI 2.98, 3.23). Weighting and adjusting for covariates with standardized differences exceeding $|0.03|$, resulted in a change in the results but did not change the conclusions (non-TBI trauma (HR 1.27; 95% CI 1.23, 1.32) and uninjured (HR 1.86; 95% CI 1.79, 1.93) groups compared to the TBI group). A sensitivity analysis that involved IPTW and adjusting for all covariates in the regression model (not just those with standardized differences exceeding $|0.03|$) did not significantly change the results (Table 13).

Table 12. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥65 years, in the analysis of Risk of Depression (2008-2015) (n=174,452)

	Total n=174,452	TBI n=51,971	Trauma n=55,776	Uninjured n=66,705	p-value
Patient Characteristics					
Age (years), mean(SD)	76.7 (8.8)	80.9 (8.2)	78.5 (8.3)	72.0 (7.4)	<0.001
Sex, n (%)					<0.001
Female	118,998 (68)	33,916 (65)	40,179 (72)	44,903 (67)	
Male	55,454 (32)	18,055 (35)	15,597 (28)	21,802 (33)	
Race, n (%)					<0.001
White, non-Hispanic	148,128 (85)	44,470 (86)	49,183 (88)	54,475 (82)	
Black	11,457 (7)	3,302 (6)	2,743 (5)	5,412 (8)	
Hispanic	8,459 (5)	2,466 (5)	2,341 (4)	3,652 (5)	
Asian/Pacific Islander	3,744 (2)	1,138 (2)	842 (2)	1,764 (3)	
American Indian/Alaska Native	818 (<1)	244 (<1)	292 (<1)	282 (<1)	
Other	1,021 (<1)	261 (<1)	264 (<1)	496 (<1)	
Unknown	825 (<1)	90 (<1)	111 (<1)	624 (<1)	
OREC ^a , n (%)					<0.001
Old Age	161,189 (92)	47,236 (91)	50,906 (91)	63,047 (95)	
Disability	12,935 (7)	4,614 (9)	4,736 (9)	3,585 (5)	
Other	328 (<1)	121 (<1)	134 (<1)	73 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	29,568 (17)	15,770 (30)	9,681 (17)	4,117 (6)	<0.001
Acute Myocardial Infarction	8,012 (5)	3,882 (7)	3,032 (5)	1,098 (2)	<0.001
Anemia	87,375 (50)	35,560 (68)	31,833 (57)	19,982 (30)	<0.001
Asthma	19,473 (11)	7,640 (15)	7,282 (13)	4,551 (7)	<0.001
Atrial Fibrillation	28,004 (16)	13,673 (26)	9,805 (18)	4,526 (8)	<0.001
Cataracts	113,527 (65)	41,009 (79)	41,095 (74)	31,423 (47)	<0.001
Congestive Heart Failure	46,576 (27)	21,433 (41)	16,978 (30)	8,165 (12)	<0.001
Chronic Kidney Disease	35,514 (20)	16,225 (31)	12,774 (23)	6,515 (10)	<0.001
All cancers	26,587 (15)	9,961 (19)	9,510 (17)	7,116 (11)	<0.001
COPD ^c	41,336 (24)	16,922 (33)	15,944 (29)	8,470 (13)	<0.001
Depression	37,649 (22)	16,186 (31)	13,138 (24)	8,325 (12)	<0.001
Diabetes	57,842 (33)	21,596 (42)	19,522 (35)	16,724 (25)	<0.001
Glaucoma	39,696 (23)	14,839 (29)	13,889 (25)	10,968 (16)	<0.001
Hip/Pelvic Fracture	6,977 (4)	3,824 (7)	2,079 (4)	1,074 (2)	<0.001
Hyperlipidemia	126,493 (73)	42,487 (82)	42,905 (77)	41,101 (62)	<0.001
Benign Prostatic Hyperplasia	23,726 (14)	10,192 (20)	7,453 (13)	6,081 (9)	<0.001
Hypertension	135,054 (77)	46,323 (89)	45,855 (82)	42,876 (64)	<0.001
Acquired Hypothyroidism	44,827 (26)	16,844 (32)	15,955 (29)	12,028 (18)	<0.001
Ischemic Heart Disease	80,624 (46)	33,102 (64)	28,754 (52)	18,768 (28)	<0.001
Osteoporosis	44,090 (25)	16,462 (32)	18,343 (33)	9,285 (14)	<0.001
RA ^d /Osteoarthritis	90,761 (52)	35,308 (68)	33,532 (60)	21,921 (33)	<0.001
Stroke/TIA ^e	28,149 (16)	14,102 (27)	9,828 (18)	4,219 (6)	<0.001

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack.

Table 13. Cox Regression Analyses of Time to Depression with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=174,452)

	Hazard Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted ^a	Weighted ^b	Weighted ^c
Uninjured	Reference	Reference	Reference	Reference
TBI	3.10 (2.98, 3.23)	1.80 (1.73, 1.87)	1.86 (1.79, 1.93)	1.88 (1.81, 1.95)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	1.42 (1.37, 1.47)	1.28 (1.23, 1.32)	1.27 (1.23, 1.32)	1.26 (1.22, 1.31)

^a No adjustment for additional covariates.

^b Adjusted for age, Alzheimer's disease and related dementias, stroke/transient ischemic attack (covariates with standardized differences ± 0.03).

^c Adjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

F. Anxiety/PTSD

After excluding beneficiaries with either anxiety or PTSD at baseline (16% with TBI, 13% with trauma, and 5% uninjured, $p < 0.001$), our final cohort contained 184,580 beneficiaries (57,489 with TBI, 59,180 with trauma, and 67,865 uninjured; Table 14). Of those remaining, 37% were censored due to death in the TBI group, compared to 9% and 12% of the trauma and uninjured groups respectively ($p < 0.001$). Over the follow-up period, the overall cumulative incidence of anxiety/PTSD was 7.9% (10% in the TBI, 9% in the trauma and 5% in the uninjured group).

Table 15 presents the results of cause-specific Cox proportional hazard models to evaluate the relation of TBI with incident Anxiety/PTSD. In the unadjusted model, I observed a higher risk of incident Anxiety/PTSD comparing the TBI to the non-TBI trauma (HR 1.20; 95% CI 1.16, 1.25) and uninjured groups (HR 2.32; 95% CI 2.22, 2.42). Weighting and adjusting for covariates with standardized differences exceeding $|0.03|$, resulted in a change in the results but did not change the conclusions (non-TBI trauma (HR 1.15; 95% CI 1.10, 1.19) and uninjured (HR 1.62; 95% CI 1.15, 1.68) groups compared to the TBI group). A sensitivity analysis that involved IPTW and adjusting for all covariates in the regression model (not just those with standardized differences exceeding $|0.03|$) did not significantly change the results (Table 15).

Table 14. Baseline Characteristics by Injury Type of Medicare Beneficiaries ≥65 years, in the analysis of Risk of Anxiety/PTSD (2008-2015) (n=184,580)

	Total n=184,580	TBI n=57,516	Trauma n=59,192	Uninjured n=67,872	p-value
Patient Characteristics					
Age (years), mean(SD)	76.9 (8.8)	89.9 (8.1)	78.4 (8.3)	72.1 (7.5)	<0.001
Sex, n (%)					<0.001
Female	126,247 (68)	37,761 (66)	42,666 (72)	45,820 (68)	
Male	58,333 (32)	19,755 (34)	16,526 (28)	22,052 (32)	
Race, n (%)					<0.001
White, non-Hispanic	157,084 (85)	49,360 (86)	52,232 (88)	55,492 (82)	
Black	11,881 (6)	3,564 (6)	2,875 (5)	5,442 (8)	
Hispanic	8,960 (5)	2,728 (5)	2,506 (4)	3,726 (5)	
Asian/Pacific Islander	3,853 (2)	1,207 (2)	868 (1)	1,778 (3)	
American Indian/Alaska Native	889 (<1)	283 (<1)	318 (<1)	288 (<1)	
Other	1,052 (<1)	280 (<1)	274 (<1)	498 (<1)	
Unknown	861 (<1)	94 (<1)	119 (<1)	648 (<1)	
OREC ^a , n (%)					<0.001
Old Age	169,493 (92)	51,848 (90)	53,604 (91)	64,041 (94)	
Disability	14,719 (8)	5,529 (10)	5,436 (9)	3,754 (6)	
Other	368 (<1)	139 (<1)	152 (<1)	77 (<1)	
Clinical Characteristics & Comorbidities, n (%)					
ADRD ^b	35,424 (19)	19,368 (34)	11,437 (19)	4,619 (7)	<0.001
Acute Myocardial Infarction	8,713 (5)	4,355 (8)	3,226 (5)	1,132 (2)	<0.001
Anemia	95,473 (52)	40,271 (70)	34,501 (58)	20,701 (31)	<0.001
Asthma	21,425 (12)	8,785 (15)	7,955 (13)	4,685 (7)	<0.001
Atrial Fibrillation	30,321 (16)	15,187 (26)	10,425 (18)	4,709 (7)	<0.001
Cataracts	121,408 (66)	45,629 (79)	43,763 (74)	32,016 (47)	<0.001
Congestive Heart Failure	51,498 (28)	24,399 (42)	18,585 (31)	8,514 (13)	<0.001
Chronic Kidney Disease	39,470 (21)	18,656 (32)	14,051 (24)	6,763 (10)	<0.001
All cancers	26,646 (16)	11,163 (19)	10,188 (17)	7,295 (11)	<0.001
COPD ^c	45,519 (25)	19,329 (34)	17,342 (29)	8,848 (13)	<0.001
Depression	53,315 (29)	23,868 (42)	18,647 (32)	10,800 (16)	<0.001
Diabetes	62,956 (34)	24,523 (43)	21,167 (36)	17,275 (25)	<0.001
Glaucoma	42,350 (23)	16,420 (29)	14,734 (25)	11,196 (17)	<0.001
Hip/Pelvic Fracture	8,170 (4)	4,648 (8)	2,340 (4)	1,182 (2)	<0.001
Hyperlipidemia	134,816 (73)	47,187 (82)	45,680 (77)	41,949 (62)	<0.001
Benign Prostatic Hyperplasia	25,442 (14)	11,261 (20)	7,979 (13)	6,202 (9)	<0.001
Hypertension	144,301 (78)	51,553 (90)	48,926 (83)	43,822 (65)	<0.001
Acquired Hypothyroidism	48,948 (27)	19,114 (33)	17,346 (29)	12,488 (18)	<0.001
Ischemic Heart Disease	87,164 (47)	37,035 (64)	30,870 (52)	19,259 (28)	<0.001
Osteoporosis	47,912 (26)	18,699 (35)	19,657 (33)	9,556 (14)	<0.001
RA ^d /Osteoarthritis	98,634 (53)	39,811 (69)	36,150 (61)	22,673 (33)	<0.001
Stroke/TIA ^e	31,862 (17)	16,398 (29)	11,011 (19)	4,453 (7)	<0.001

^aOREC: Original Reason for Entitlement Code. ^bADRD: Alzheimer's disease and related dementias.

^cCOPD: Chronic Obstructive Pulmonary Disease. ^dRA: Rheumatoid Arthritis. ^eTIA: Transient Ischemic Attack.

Table 15. Cox Regression Analyses of Time to Anxiety/PTSD with Death as a Competing Event, among Medicare Beneficiaries ≥ 65 years (2008-2015), (n=184,580)

	Hazard Ratio (95% CI)			
	Unadjusted	Adjusted		
		Weighted ^a	Weighted ^b	Weighted ^c
Uninjured	Reference	Reference	Reference	Reference
TBI	2.32 (2.22, 2.42)	1.59 (1.52, 1.65)	1.62 (1.55, 1.68)	1.61 (1.55, 1.68)
Non-TBI Trauma	Reference	Reference	Reference	Reference
TBI	1.20 (1.16, 1.25)	1.14 (1.10, 1.18)	1.15 (1.10, 1.19)	1.14 (1.09, 1.18)

^a No adjustment for additional covariates.

^b Adjusted for age, Alzheimer's disease and related dementias, stroke/transient ischemic attack (covariates with standardized differences ± 0.03).

^c Adjusted for all available covariates: age, sex, race, original reason for Medicare entitlement, months of follow up, acquired hypothyroidism, Alzheimer's disease and related dementias, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, cataracts, congestive heart failure, chronic kidney disease, cancer, chronic obstructive pulmonary disease, depression, diabetes, glaucoma, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack.

CHAPTER VI: DISCUSSION

Traumatic brain injury is a growing public health concern among older adults that should be considered the beginning of an ongoing disease process rather than an isolated event. Among older adults, there is currently a lack of information on the long-term impact of having a TBI, which is essential for informing post-injury interventions and policies directed at maintaining the independence and quality of life. The goal of this dissertation was to better understand the impact of an isolated TBI on physical and psychological health outcomes among older adults with up to five years of follow-up. By comparing to non-TBI trauma and uninjured individuals, I attempted to disentangle the effects of TBI from the effects of other trauma and provide an estimate of the overall impact of TBI relative to the general population of Medicare beneficiaries.

At the time of the injury (or medical appointment in the uninjured group), those with TBI were older and had a greater burden of comorbidities which potentially increased their risk of worse outcomes, thus inverse probability weighted models were employed to balance covariates across comparison groups. In inverse probability weighted models, I reported greater risks of frailty, NH placement, depression, and anxiety/PTSD among older adults with TBI compared to those with non-TBI trauma and to the uninjured. TBI was not significantly associated with greater risk of chronic pain or insomnia compared to those with a non-TBI trauma but was associated with greater risk compared to those who were uninjured. As well, I reported a lower risk of disability among those with TBI compared to those with trauma, but a greater risk compared to the uninjured. What follows is a more detailed discussion of my findings.

A. Physical Health and Functioning Outcomes

Physical functioning is the ability to perform both basic and instrumental activities of daily living. The ability of older adults to remain in the community depends to a large extent on their level of physical function. This dissertation investigated the effect of TBI on physical functioning using measures of frailty, nursing home placement, disability, chronic pain, and insomnia.

1. Frailty

TBI was associated with a higher risk of frailty compared to Medicare beneficiaries with non-TBI trauma and those who were uninjured. Results from this analysis provide a new and important insight for clinicians to consider when managing older adults with TBI.

In the combined cohort, the overall prevalence of frailty at baseline was 10%, which is higher than reported by Fried (6.9% in a study of cardiovascular health),⁸¹ but lower than reported in a nationally representative sample of community-dwelling older adults (15%).¹⁸⁶ These differences may relate to the diagnostic criteria that were used to define frailty and the populations being studied. In this analysis I utilized a frailty index, defined by the deficit accumulation criteria,^{17,187} as opposed to the more commonly used frailty phenotype criteria.⁸¹ The identification of frailty is conceptually different for each of these criteria. While the frailty phenotype is explicit about being distinct from disability and comorbidity, the frailty index includes these items as part of the definition which could result in a higher estimate. Additionally, differences in the study populations and

the demographic characteristics of study subjects could also have led to different estimates.

This work found that people who sustained TBI had a higher prevalence of frailty at baseline compared to those with non-TBI trauma and the uninjured (19% vs 9% and 2%, $p < 0.001$). Prior research suggests that the risk of frailty is higher with older age, greater comorbidity burden, lower socioeconomic position, poor diet, and sedentary lifestyles.⁷⁹ In the study sample, beneficiaries with TBI were more likely to have a higher comorbidity burden and be eligible for Medicare due to disability (a proxy for lower socioeconomic position) before their injury, which may have predisposed them to frailty, even after excluding those who were frail at baseline.

Although, the development of frailty has not been previously studied among older adults with TBI, other chronic disorders with similar pathophysiological determinants to TBI have been reported to increase the risk of frailty in older individuals.⁸³⁻⁹¹ TBI could increase the risk of frailty through the hypothalamo-pituitary (HP) axis¹⁸⁸ which links the brain to the endocrine system. Longitudinal studies have shown hypothalamic-pituitary hormone deficiencies among long-term survivors of TBI.⁷⁷ Additionally, inflammation has been argued to be important in the processes of accelerated aging and frailty.^{80,189,190} Thus, the significant inflammatory burden that results after a TBI could predispose older adults to frailty, providing a biological mechanism for the observed association.¹⁹¹

Older people living with frailty are at an increased risk of adverse outcomes,^{80,94} which have considerable importance from an individual, societal and health services perspective. Frailty increases the risk of falls,^{80,208} which could result in recurrent TBI or other trauma,^{209,210} decreased mobility,²¹¹ loss of independence,²¹² hospitalization,²¹³

disability,²¹¹ and death.²¹³ It is also important from a societal perspective because it identifies groups of people in need of additional medical attention. Studies have also shown a clear pattern of increased health-care utilization and costs and use associated with frailty.^{80,214-216} It may be important for clinicians to communicate the potential risk of frailty to patients, to include frailty assessments in follow-up visits, and to consider frailty in care planning after a TBI.

2. Disability

In this large, nationally representative study of Medicare beneficiaries, my results show a reduced risk of disability in the TBI group compared to those with non-TBI trauma. However, having a TBI was associated with an increased risk of disability compared to the general population of Medicare beneficiaries.

Overall, the results of this analysis support the hypothesis that TBI increases the risk of disability among older adults. This is consistent with findings from studies of younger adults documenting impaired functional status²⁴ and high rates of disability^{217,218} following TBI. For example, in a population-based study of individuals hospitalized after TBI in the US, 43% continued to experience disability one year after the injury.²¹⁷ Similarly, among adults receiving inpatient rehabilitation after TBI, 57% were moderately or severely disabled 5 years post-injury.⁶⁶ A study from Glasgow, UK, reported that 53% of persons with mild-to-severe TBI remained disabled 5-7 years after injury as assessed by the Glasgow Outcome Scale extended (GOSE).²¹⁹ Another study of 306 individuals with moderate to severe TBI showed that 22% were dependent in activities of daily living even 14-years post-injury.¹⁰⁷ In contrast, a longitudinal study of

301 patients with TBI demonstrated no meaningful functional changes in 76% of patients while 7% declined from 1 to 5 years post-injury.²²⁰ Variations in the data collected, the populations studied, and a lack of consistency in methodology make comparisons between these studies difficult. However, taken together, most of these studies show an association between TBI and disability.

By comparing to a non-TBI trauma control group, this study attempted to account for the unique characteristics of being a TBI patient (i.e., risk-taking behavior, higher burden of medical and psychological comorbidities) that could increase the risk of disability beyond that of having general trauma. Contrary to expectation, my hypothesis that those with a TBI would have a greater risk of disability than those with a non-TBI trauma was not supported. As age increases,^{221,222} comorbidities,^{221–224} drug therapies, reduced visual acuity, postural instability, deterioration of reflexes and/or slowing of reaction time can increase the risk of trauma in the elderly,²²⁵ leading to head injuries, fractures and/or other traumatic events.^{226–228} In this study, the non-TBI trauma group comprised beneficiaries with fractures. Although most fractures heal without permanent injury, multiple complications can lead to neurovascular damage, loss of skeletal function, restricted range of motion, and associated soft tissue injuries, which can severely compromise function and performance. Hip fractures, one of the most debilitating traumatic events, were the second most frequent type of fracture in the non-TBI trauma group. Hip fractures are reported to be associated with disability, mortality, and nursing home admission among older adult survivors^{199,200} In contrast, the majority of TBI cases among older adults are mild and perhaps less likely to result in disability, providing a possible explanation for study results.

I did not exclude those already living with a disability because there is not a validated cut-point for the disability index and therefore could not report the incidence of TBI-related disability among older adults. Future studies estimating TBI-related disability would be useful to ensure adequate planning and resource-allocation for rehabilitation programs to meet the long-term needs of this population.

3. Nursing Home Placement

This is the first study to report on long-term NH home placement after TBI in a large, nationally representative sample of community-dwelling older adults enrolled in Medicare. In this study, TBI was associated with an increased risk of nursing home entry compared to those with non-TBI trauma and to uninjured beneficiaries. Among those with TBI, the 5-year cumulative incidence of NH entry was 9%, which was higher than that observed in the non-TBI trauma and uninjured groups.

Aging results in a progressive decline in molecular and cellular function¹⁹² that leads to a limited physiologic reserve and a higher comorbidity burden.^{17,68} Consistent with other research,^{15,67,193} those with TBI had a higher comorbidity burden before their injury, even when compared to older adults with non-TBI trauma. In our study sample, those with TBI were more likely to have diabetes, high blood pressure, cancer, and stroke, risk factors for NH admission.¹⁹⁴ Although the three exposure groups were balanced on these covariates in weighted regression analyses, residual confounding due to unequal burden of comorbidity and unmeasured confounders between groups was still possible. Time to NH entry was also much shorter in the trauma cohort, suggesting that

that NH admissions after a TBI come after a period of declining health while admissions after trauma may be more immediate. Most cases of TBI among those over 65 years are mild and may not result in an immediate loss of independence.¹⁹⁵

Falls have been reported to result in declines in function, both from physical injury and the loss of confidence in the ability to perform functional activities,¹⁹⁶ ultimately increasing the risk of NH admission.^{194,197} An estimated 18% of TBIs in older adults are as a result of falls.² Although the association between TBI and NH placement has not been well studied among older adults, falls are also the primary cause of hip fractures among the elderly (95%)¹⁹⁸. Hip fracture results in significant increases in disability and nursing home admission compared to age-matched controls.^{199,200} In 2008, one study reported that 35% of older adult hip fracture patients were placed in a NH within 1 year post-fracture.²⁰¹ Another study of older adult hip fracture patients reports that 33% became permanent SNF residents.²⁰² The findings from this dissertation, which are specific to older adult TBI survivors, report a 5-year cumulative incidence of NH placement of 9%, much lower than that reported following hip fracture. Hip fracture usually requires surgery and causes an immediate drop in mobility whereas TBI generally does not.

The long-term sequelae of TBI include both cognitive and functional impairment, some of the strongest predictors of NH admission among older adults.¹⁹⁴ Older adults with stroke are perhaps most similar to those with TBI in this regard. In 2018, Blackburn *et al.* characterized NH placement after stroke among older adult Medicare beneficiaries. They reported that within 5 years of stroke, 119 (21.3%) participants had been placed in a nursing home.²⁰³ Lifestyle-related factors such as diabetes and hypertension have also

been reported as important predictors of long-term NH admission among middle-aged and older adults.²⁰⁴ In my study, those with TBI were significantly more likely than the other groups to have diabetes and hypertension at baseline, increasing their risk of NH placement even before the TBI. Though imbalances in the distribution of these comorbidities and covariates were accounted for using IPTW, there still remains a potential for residual confounding.

4. Chronic Pain

This study confirmed that TBI is associated with incident chronic pain in a nationally representative sample of older adults. At baseline, the prevalence of chronic pain in this study sample was 22% (29% in TBI, 27% in trauma, and 10% among the uninjured). Our estimates are lower than estimates from the National Health Interview Survey (NHIS) which reported the prevalence of chronic pain as 30.8% among adults 65 years and older.^{229,230} Similarly, estimates from this study are lower than those reported among older adults (50% among community-dwelling and >80% among nursing home-dwelling older adults).²³¹ Most prevalence estimates of chronic pain are derived from self-report surveys which do not require a diagnosis. This study identified chronic pain using administrative claims which captures information obtained through physician and hospital encounters, likely underestimating the true prevalence. Poor kappa agreement between survey and administrative claims data for identifying cases of a pain condition has been previously reported and may influence the observed discrepancies.²³² The use of prescription pain medications as a proxy for chronic pain could have improved estimates slightly, but there is not a way to capture over the counter analgesic use.

Compared to the uninjured group, TBI was associated with higher risk of chronic pain. However, I did not find that TBI was associated with risk of chronic pain compared to the non-TBI trauma group. Chronic pain often arises in response to an acutely painful experience, with proposed mechanisms involving inflammatory and stress responses including microglia priming, ionic imbalances, altered blood flow, and inflammation, all of which result in sensitization.^{233–237} Studies on chronic pain after trauma or fractures are scarce, but a few report that the majority of trauma patients have moderately severe pain from their injuries or the surgery 1 year later^{238,239}

5. Insomnia

This study provides evidence that TBI is associated with incident insomnia in a nationally representative sample of older adults.

Compared to the uninjured group, TBI was associated with higher risk of insomnia. However, compared to the non-TBI trauma group, TBI was not associated with higher risk of insomnia. The association between TBI and risk of insomnia compared to the uninjured group is consistent with reports from prior studies.^{119,240} These results provide additional insight by comparing to those with non-TBI trauma. Though different types of sleep disturbances can occur in individuals with TBI and trauma depending on the type of injury and the location of damage, insomnia is one of the most common sleep disorders.²⁴¹ Existing theories on the etiology of trauma-induced insomnia substantiate the premise that traumatic events can lead to a state of heightened arousal that can induce immediate symptoms of insomnia.^{242–244} Trauma may generate an intense, sustained

hyperarousal state by activating the amygdala, which is known to be critical in reducing stress and fear responses.²⁴⁵ Amygdala activation, creates a heightened arousal in the brainstem, promoting activation and alertness, as well as more complex cognitive and emotional hyperarousal²⁴⁶ that may function to develop and maintain clinically significant insomnia after trauma. Thus, both TBI and trauma may result in insomnia via similar mechanisms, helping to explain the similar risk estimates in the two groups.

At baseline, the prevalence of insomnia in this study sample was 4% (5% in TBI, 4% in trauma, and 2% among the uninjured). This is lower than estimates of the annual prevalence of insomnia in older adults which range from 25–40% in studies based on survey assessments²⁴⁷ but is consistent with prior estimates of studies utilizing administrative claims data¹⁶⁸ and studies utilizing ICD codes.²⁴⁸ In a study comparing prevalence estimates of insomnia based on ascertainment methods, Roth et al reported population prevalence of insomnia in 2009 to be 3.9% based ICD-10-CM criteria, 14.7% based on International Classification of Sleep Disorders – Second Edition criteria, and 22.1% based on Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition. This suggests that insomnia diagnoses are underestimated when relying on ICD codes. To ascertain insomnia disorders more accurately from claims data, consideration should be given to medication use as well. Prior studies have shown a discrepancy between insomnia diagnosis and treatment, reporting a prevalence of insomnia medication use up to four-times higher than insomnia diagnoses.¹⁶⁸

B. Psychological Health Outcomes

1. Depression

Compared to the uninjured group and to those with non-TBI trauma, TBI was associated with higher risk of depression. Few studies have assessed the risk of depression compared to non-TBI traumas in older adults. However, previous estimates of depression post-TBI adults ≥ 18 years also report an increased risk of depression compared to non-TBI controls (HR 1.83; 95% CI, 1.79,1.86). Similarly, another study among older adults found that the risk of depression is doubled post-TBI. (HR in men 1.95; 95% CI, 1.84, 2.06 and 1.69; 95% CI, 1.62,1.77 in women). Comparing to the non-TBI trauma group resulted in a lower estimate than when compared to controls potentially because this group also suffer from injuries that may endanger their independence. Older people who sustain fall-related injuries typically do not regain their pre-injury levels of physical functioning.^{249–252} Some studies examining the association of depression with physical functioning have found that worse physical functioning was related to more severe depressive symptoms.^{253,254} Compared with trauma control groups at 1–2 years post-injury, individuals with TBI have been reported as having more symptoms of depression.²⁵⁵ In contrast, one comparative study found no differences in levels of depression between TBI and trauma controls. It has been suggested that impaired self-awareness, which can reduce the likelihood of depression following TBI, may contribute to the lack of differences in depression levels reported by trauma control and TBI groups at 1–2 years post-injury.^{256,257}

2. Anxiety/PTSD

Compared to the uninjured group and to those with non-TBI trauma, TBI was associated with higher risk of anxiety/PTSD. Few studies have assessed the risk of Anxiety/PTSD compared to non-TBI traumas in older adults. However, previous studies of Anxiety and PTSD among Medicare beneficiaries 65 years and older also report higher risk in the compared to non-TBI controls.^{11,70} TBI was associated with higher risk of anxiety (rate ratio [RR] = 1.08; 95% confidence interval [CI], 1.05-1.12) and PTSD (RR = 1.41; 95% CI, 1.24-1.60) diagnoses.⁷⁰

A useful way of analyzing the uniqueness of TBI sequelae is to compare to those who have traumatic orthopedic injuries without any TBI. This is especially relevant for an outcome such as PTSD given both the TBI, and non-TBI trauma groups experienced an isolated stressor (the injury). One study comparing individuals with TBI to those with only orthopedic traumas found that individuals with TBI reported greater anxiety as measured on the Hospital Anxiety and Depression Scale (34% vs 20%) and also PTSD as measured on the PTSD Checklist-Specific (17% vs 5%), leading to greater psychosocial difficulties in those with TBI.²⁵⁸

Cognitive impairments associated with TBI may contribute to the development of PTSD²⁵⁹ and explain the greater risk compared to those with general trauma. Disruption to prefrontal circuitry, which is common following TBI, may lead to heightened amygdala activation, resulting in reduced control over emotional responses—especially fear, anxiety and panic.^{260,261} One study investigating PTSD following traumatic injury, reported that PTSD symptoms endorsed by participants with TBI are more reflective of brain injury symptoms, such as loss of interest, feeling distant or cut-off from people,

feeling emotionally numb, sleep difficulties, irritability, and difficulty concentrating.²⁵⁸

While symptoms related to recalling or reliving the accident were reported at similar levels by both injury groups.²⁵⁸ This study highlights the need to understand more about impact of anxiety disorders in individuals with TBI.

C. Strengths

Understanding the impact of a TBI on physical and psychological functioning in older adults is essential because of the implications for maintenance of independence and quality of life. Although many studies have investigated outcomes following TBI among younger adults, fewer have focused on older adults. This is the first study to report incidence estimates of frailty, NH placement, and chronic pain following TBI among older adults. This is significant as it provides critical information on important recovery outcomes that can inform post-discharge care services and policies. It also serves as a baseline reference for future studies.

This was the first study among older adults to make comparisons to two non-TBI control groups to isolate the effect of TBI from trauma and examine risk compared to the general population. I also used IPTW to minimize confounding and obtain unbiased estimates. Participants with TBI were more likely to die and therefore had less time to experience their outcomes. To improve the accuracy of TBI-associated risk estimates, this study treated death as a competing risk. Lastly, the large and robust dataset used in this study permitted the comparison of multiple injury groups with multiple clinical and demographic characteristics without the loss of statistical power. Using this unique dataset allowed for continuous long-term follow-up both before and after the index date

and the monthly-level structure of the data allowed incident diagnoses to be captured over up to 60 months of follow-up post index TBI.

D. Limitations

The focus of this dissertation work was on examining physical and psychological outcomes of TBI that could effectively be measured using administrative claims data. There are currently questions about whether the outcomes observed post-TBI are brain-injury specific, or whether they represent more general injury effects that may also be present in other traumatically injured patients. Finding a suitable comparison group to determine how much TBI increases the risk of these adverse outcomes post-injury required a consideration of issues that may have pre-dated their injuries as well as the medical experiences after injury (presentation to the emergency department, radiological exams, medical interventions, medication for pain, stress, rehabilitation etc.) that may have mediated the effect of injury on the examined outcomes.

An uninjured group was used as a comparison because they are thought to be representative of general population-level functioning (physical and psychological) and they also faced fewer medical processes that are associated with the examined outcomes. Unfortunately, this group of beneficiaries are not like the TBI group in pre-injury characteristics (demographic, behavior, medical history). Non-TBI trauma patients on the other hand are thought to have similar pre-existing characteristics that put them at a similar risk for sustaining injury as those who incur a TBI, and they are often victims of traumatic incidents that can result in psychologic issues. Unfortunately, they are

comparable to the TBI group in post-injury experiences which implies that comparing to this group inadvertently controlled for processes that occurred after injury.

To isolate the effect of TBI from trauma, I excluded participants with both TBI and trauma. Having multiple injuries may be related to injury severity; for instance, those with a severe TBI could potentially have fractures in other body regions. Hence, the exclusion of participants in multiple injury groups could lead to the differential exclusion of those with more severe injuries from the TBI and non-TBI trauma groups. This would have the effect decreasing the overall injury severity in both groups, but whether these exclusions would be differential by TBI status is not known. In this study 40% of the non-TBI trauma group had lower extremity fractures (mainly upper leg and thigh, knee, lower leg, ankle, foot, and toe fractures). Lower extremity fractures are serious and potentially life-changing injuries, with literature documenting poor functional outcomes in the months and years after injury. Previous studies have shown lower extremity fractures to be associated with persistent limitations in activities of daily living, recreation, and social interaction;²⁶² factors that have a bearing on the outcomes examined in this work. The composition of the non-TBI trauma group could contribute to observed outcomes such as higher disability compared to the TBI group. Despite this, I observed that TBI was significantly associated with a higher risk of frailty and nursing home placement but could have underestimated the magnitude of the risk observed by having a comparison group with a high proportion of functionally debilitating injuries.

In this study the trauma group comprised individuals with lower, upper, torso and hip fractures but the sub-groups were not mutually exclusive. This resulted in some beneficiaries having multiple types of fractures. Multiple injuries can be indicative of a

more severe injury mechanism and consequently a more severe injury to recover from, increasing the potential for higher rates of poor outcomes in this group. There is evidence suggesting increased risk of poorer functional and health status outcomes at 12-months with increasing number of injuries sustained.²⁶³ This may explain why the trauma group had a higher risk of disability than the TBI group. For outcomes where TBI was associated with a higher risk of occurrence, it is also possible to have underestimated the magnitude of risk by comparing to a non-TBI trauma group with co-occurring injuries.

This study did not use the traditional clinical measures of frailty⁸¹ and disability (IADLs). However it used a claims-based measure of frailty¹⁶⁰ that has been validated against the Rockwood frailty index.^{17,187} Additionally, both the frailty and disability indices have been previously validated^{160,161,163} and perform well (c-statistic frailty index 0.62-0.77; disability index 0.71-0.77). Further, these indices can be modelled continuously, which is arguably more useful for analysis purposes. A few limitations should be considered when interpreting results using the frailty and disability algorithms. In developing these algorithms, assumptions were made that the diagnosis and procedure codes and health care services claims used to construct the scores can serve as proxies of a beneficiary's health status. Health status may be transiently impaired and could potentially improve as a result of health care services. In addition, the severity of the conditions was not considered. It remains to be determined whether specifically coding the severity of the score components could result in more sensitive scores. Though the indices are not disease specific, they were both developed for the purpose of generating point in time scores for confounding adjustment in studies predicting adverse patient outcomes. Neither of the indices have been validated for ascertaining frailty and

disability as outcomes to be monitored longitudinally. In addition, survey data was used as the reference standard for calculating the frailty score. Objective measures of frailty (e.g., walking speed) may be more sensitive than a frailty definition based on self-reported data in identifying those who are truly frail.

Although I tried to balance the three exposure groups on age and available comorbidities in inverse probability weighted regression analyses, the potential for residual confounding still exists because the balance is never perfect. In addition, though twenty-seven of the most common chronic conditions were used in generating the weights, there may still be an unequal distribution of other unconsidered comorbidities which may also be related to physical and psychological health. For example, pneumonia, Parkinson's disease, and cancers are other comorbidities that were not considered and are associated with impaired functioning and could potentially be differentially distributed among the three exposure groups. While the chronic conditions warehouse provides information on the diagnosis of five types of cancers (breast, colorectal, endometrial, lung and prostate), there are over one hundred types of cancers that affect humans which were not considered.

Additionally, one of the limitations of ascertaining comorbid conditions from claims databases is the reliance on ICD-9-CM codes. Beneficiaries must first seek care to receive a diagnosis implying that the presence of comorbidities could be under-ascertained. Also, claims databases typically are constructed for administrative rather than research purposes so the assignment of diagnosis codes is primarily to obtain reimbursement. Given the limited number of fields that are available for recording diagnoses and procedures, conditions such as complications that provide more lucrative

reimbursement tend to receive priority over comorbid conditions. Validation studies comparing administrative claims and medical records as sources of comorbidity data have shown that comorbid conditions are under-ascertained in claims databases.²⁶⁴⁻²⁶⁷

In summary, it is difficult to completely account for differences in patients' underlying health status. Despite this, strong associations were observed for most of the outcomes and it can be argued that such strong associations are unlikely to be completely attributable to residual confounding.^{268,269}

Administrative claims data also lack documentation of traditional measures of TBI severity (Glasgow Coma Scale Score, Abbreviated Injury Score). Future studies should try to incorporate these measures, potentially through linkages with the electronic health record. Depression, anxiety, and insomnia require expert assessment and must meet the DSM criteria before a diagnosis is given. However, situations may arise where the DSM criteria are not met but a diagnosis is given based on the opinion of the primary care physician, potentially leading to overdiagnosis.

Finally, administrative claims data is collected for billing and reimbursement purposes. Therefore, assessment of all measures is dependent on documentation: patients must seek care for documentation of a diagnosis, service, or procedure and only those that will get reimbursed, get documented on a claim. As a result, outcomes may be underdiagnosed and under recorded in billing records, which could have resulted in an underestimate of incident outcomes. However, this should not differ by injury status. Requiring 12 months of continuous Part A and B but no Part C coverage prior to the index date ensured a 12-month baseline period in which all claims were captured, and no events could be missed, thus increasing the ability to capture comorbid conditions prior to

the start of follow-up. For the TBI and non-TBI trauma groups, it also ensured that their injuries were incident and had not been ongoing in the year prior. Extending the baseline period beyond 12 months would have increased the requirement for continuous coverage and thus the potential for selection bias by including only those beneficiaries that were able to maintain coverage beyond 12 months.

E. Summary and Implications

TBI is a major cause of death and disability in the United States among an aging population already at high risk of poor outcomes. While the number of TBIs among older adults tops 600,000 annually in the US, research on long-term recovery outcomes following TBI in this population remains limited. Given the lack of information, this dissertation sought to address an important gap by estimating the association between TBI and incident measures of physical and psychological functioning. TBI increased the risk of all examined outcomes compared to the general population of Medicare beneficiaries. In addition, the risk of frailty, NH placement, depression and anxiety/PTSD associated with TBI was greater than that associated with non-TBI trauma.

Although the majority of TBIs among older adults are mild, negative consequences may continue to persist even up to 5 years post-injury. These include physical and psychological consequences that impact their behavior, quality of life and the ability to function in their everyday life, adding costs and burden to the patients, their families and society. These issues can also co-occur, compounding the effect of the injury and interacting to impede recovery. Among older adults, there is evidence of associations between frailty and disability, NH placement,²⁷⁰ and insomnia²⁷¹⁻²⁷³. Pain is also

associated with impairments in balance and gait,^{274,275} functional disability,^{276,277} mobility limitations^{278–281} and with frailty,^{278,282–296} suggesting a cumulative or ‘snowball’ effect of these sequelae. In individuals with mild TBI, insomnia is reportedly associated with PTSD, depression, and chronic pain.⁷⁴ A longitudinal study observed an association between sleep disturbances and functional impairment in adults with mild TBI.²⁹⁷ These relationships are complex and potentially bidirectional. For example, frailty is a risk factor for insomnia and insomnia is also a risk factor for frailty. The association between sleep quality and global functioning is also reported to be bidirectional, with greater sleep disturbance predicting greater functional impairment and vice versa, months later.²⁹⁷

This work generated the first estimates of the incidence of frailty, NH placement, and chronic pain following TBI, in a nationally representative sample of older adults. By using two non-TBI groups as comparisons, I also sought to improve the accuracy of TBI associated-risk estimates and provide some insight on the interpretation of results depending on the control group. These risk estimates can serve as a baseline for continued monitoring of these outcomes which will be useful when investigating the impact of care management interventions. Given a proper recognition of the limitations, this work also substantiates the use of administrative claims data to study diverse issues in healthcare research.

In this study, the non-TBI trauma group comprised beneficiaries with lower, upper, torso and hip fractures. Although most fractures heal without permanent injury, multiple complications can lead to neurovascular damage, loss of skeletal function, restricted range of motion, and associated soft tissue injuries, which can severely compromise function and performance. As described earlier, 40% of the non-TBI trauma group had

lower extremity fractures which are known to be associated with disability. Hip fractures, one of the most debilitating traumatic events, were the second most frequent type of fracture (15%) in the non-TBI trauma group and is also reported to be associated with disability among older adult survivors. In contrast, the majority of TBI cases among older adults are mild and potentially less likely to result in disability, providing a plausible explanation for study results.

In this study, Frailty was assessed according to a regression-based deficit-accumulation¹⁶⁰ approach based on the Rockwood and Mitnitski¹⁷ conceptualization of frailty, rather than the Fried conceptualization.^{81,96} While the Fried conceptualization is explicit about being distinct from disability and comorbidity, the frailty index includes these items as part of the definition. Although it considers claims for some function related indicators (walking aids and attachments, wheelchair or transport chair and related accessories), a greater proportion of the indicators (92 in total) making up the frailty index focus on clinical diagnoses, and hospital encounters with the assumption that an individual will be more frail when more things are wrong. In this study, having a TBI was consistently associated with a higher comorbidity burden (and potentially a higher frequency of hospital visits) than the non-TBI group which consequently be reflected in the summary frailty measure. This likely contributes to why TBI was associated with more frailty.

On the other hand, disability was specifically operationalized using a set of 13 claims-based functioning related indicators to generate a summary score from claims for **mobility limitations (defined by claims for canes, walkers, wheelchairs, hospital beds, etc.)**, blood transfusion, use of oxygen, supplemental nutrition, **hip or pelvic**

fracture, chronic skin ulcer, pneumonia, delirium/dementia/Alzheimer disease, bone marrow failure/agranulocytosis, depression, use of urinary catheter, respiratory failure/insufficiency/arrest, sepsis, and malnutrition/unintentional weight loss, fall-related injury, and syncope.¹⁶³ This risk measure reflects conditions that are associated with the non-TBI trauma group. First, a 15% of this group consisted of beneficiaries with hip fractures and additionally, fracture patients are generally more likely to use mobility assistance such as walkers, canes, crutches, and wheelchairs. This likely contributes to why non-TBI trauma was associated with more disability.

Maintaining health and functioning is an important component of independent living for older adults. To extend the impact of this work, future research should focus on evaluating the potential for mediation or interaction to better assess the risk of poor health outcomes in the long-term recovery of older adult survivors of TBI. Stratified analyses on sex, race and injury severity have shown that certain subgroups are at higher risk for developing poor outcomes following TBI. For example, studies of functional outcomes post-TBI among whites, blacks, and Hispanics report worse outcomes for minorities compared to whites potentially due to lower social integration and thus a lack of social support necessary to provide care for them at home. As a result, they may be discharged to inpatient rehabilitation facilities at higher rates than whites.

There is also evidence from other medical fields of sex/gender differences in receiving medical care that may be translated to the field of neurotrauma. Studies show men are provided with more aggressive treatments in cardiovascular medicine, while women have less access and lower rates of direct transfers to trauma centers, and fewer admissions to intensive care after traumatic injuries. Additionally, some frailty studies

have found that though, on average, females may have higher frailty scores than males (using both phenotypic and cumulative deficit models of frailty), they have lower mortality rates at any given frailty score. However, such studies are limited among older adults with TBI, and it would be useful to investigate sex/gender differences in recovery outcome measures.

Generally, studies of sex/gender differences tend to report worse psychological outcomes in women following a mild TBI. Whereas studies of moderate to severe TBI showed either similar or better functional outcomes in women, compared to men. This indicates that there may also be differences by injury severity. In fact, multiple studies confirm that PTSD is less likely to develop in victims of accidents if trauma had resulted in a prolonged period of unconsciousness (more severe), potentially due to memory loss of the trauma event.

Following a TBI, participation in social activities is often significantly reduced, leaving individuals less integrated in their communities. As a result, individuals may spend more time at home, often beyond the acute recovery period, straining family and other relationships and potentially impacting their mental health and general well-being. For example, depression and PTSD are reported to mediate the effects of pain and functional impairment on health-related quality of life.

Sleep disturbances may also mediate the effect of a TBI on the development of PTSD and depression. A longitudinal study of sleep and PTSD in veteran TBI populations have found that initial sleep problems predict increased PTSD and depression at 6-month follow-up, whereas initial PTSD and depression did not predict increased sleep problems.

In addition, future studies should incorporate try to ensure a similar range of severities across injury group and accounting for either having multiple injuries at once or additional injuries over the follow-up period. There are also additional opportunities to investigate predictors of these outcomes in a TBI population and examine the role of social support in mitigating the effects of a TBI on the studied outcomes. Future studies could try to ensure that the TBI and non-TBI trauma groups had injuries across a similar range of severities and that the non-TBI trauma injuries were isolated and not co-occurring injuries.

Recovery from TBI is influenced by individual patient characteristics (e.g., age and pre-injury functioning), greater disease comorbidity and social-environmental factors (e.g., socioeconomic status, family support systems), and barriers to rehabilitation access. Greater disease comorbidity at the time of TBI has been found to be associated with reduced functional independence at rehabilitation admission, at discharge, and up to 4 years post-injury, as well as with increased 1-year mortality. Older adults affected by TBI have a higher risk for mortality and worse functional outcomes following injury than younger patients with similar injuries. The costs of TBI are also more extensive for older adults than younger patients. When compared with younger patients, older adults tend to have longer hospital stays and slower rates of functional improvement during inpatient rehabilitation.

This dissertation also confirms that, at baseline, older adults with TBI are older, more likely to be female and have more comorbidities than the average older adult without a TBI which likely influences the observed occurrence of poorer physical and psychological outcomes.

APPENDIX A: Table of Relevant Codes for Identification of Measures from Medicare Data

APPENDIX A: Table of Relevant Codes for Identification of Measures from Medicare Data	
Condition	Codes
Traumatic Brain Injury	ICD9: 800.xx, 801.xx, 803.xx, 804.xx, 850.xx-854.1x, 950.1-950.3, 959.0
Chronic Pain	ICD9: 307.80, 307.89, 338.0, 338.2, 338.4, 719.41, 719.45–719.47, 719.49, 720.0, 720.2, 720.9, 721.0–721.4, 721.6, 721.8, 721.9, 722, 723.0, 723.1, 723.3–723.9, 724.0–724.6, 724.70, 724.79, 724.8, 724.9, 729.0–729.2, 729.4, 729.5 338.21, 338.22, 338.28, 338.29
Insomnia	ICD9: 307.41, 307.42, 307.49, 327.00, 327.01, 327.09, 780.52, V69.4
Depression	ICD9: 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, or 311
Anxiety	ICD9: 300.0x, 300.21, 300.22
PTSD	ICD9: 309.81

Torso Fractures	<ul style="list-style-type: none"> a. Ribs and sternum: ICD9: 807.0x, 807.1x, 807.2x, 807.3x, 807.4x b. Pelvis: ICD9: 808.xx c. Other unspecified fractures of the bones of trunk: ICD9: 809.xx
Upper Extremity Fractures	<ul style="list-style-type: none"> a. Shoulder and upper arm: ICD9: 810.xx, 811.xx, 812.xx b. Forearm and elbow: ICD9: 813.xx c. Wrist, hand, and fingers: ICD9: 814.xx, 815.xx, 816.xx, 817.xx d. Other unspecified fractures of the upper limb: ICD 818.xx
Hip Fractures	ICD9: 820.xx
Lower Extremity Fractures	<ul style="list-style-type: none"> a. Upper leg and thigh: ICD9: 821.xx b. Knee: ICD9: 822.xx c. Lower leg and ankle: ICD9: 823.xx, 824.xx d. Foot and toes: ICD9: 825.xx, 826.xx e. Other unspecified fractures of the lower limb: ICD 827.xx
Frailty Index	<p>ICD-9-CM codes: 001-009, 030-041, 110-118, 190-199, 210-229, 235-238, 240-246, 250-259, 270-279, 285, 287, 288, 290-294, 295-299, 300-316, 330-338, 340-349, 350-359, 360-379, 401-405, 410-414, 420-429, 430-438, 440-448, 451-459, 470-478, 480-487, 490-496, 520-529, 530-537, 550-553, 580-589, 590-599, 600-608, 680-686, 690-698, 710-719, 720-724, 725-729, 730-739, 753, 754-756, 780-789, 790-796, 797-799, 890-897, 920-924, 990-995, V01-V09, V40-V49, V50-V59, V70-V82.</p>

	<p>CPT-4 codes: 99214, 99222, 99242, 99245, 99308, 99381-99429, 00100-00222, 00300-00352, 00500-00580, 00800-00882, 01320-01444, 30000-32999, 56405-58999, 61000-64999, 78000-79999, 80150-80299, 88104-88199, 88300-88399, 92002-92499, 92950-93799, 93875-93990, 95004-95199, 97001-97799, 98940-98943, 99000-99091.</p> <p>HCPCS codes: A0021-A0999, A4244-A4290, A5500-A5513, A7000-A7046, A9150-A9999, E0100-E0159, E0250-E0373, E0424-E0486, E0550-E0601, E0950-E1298, E2201-E2294, E2300-E2399, E2601-E2621, E1353-E1406, G0008-G0010, G0101-G0124, J0120-J7130, J7608-J7684, K0001-K0462, K0669.</p>
Disability Algorithm	<p>Canes: HCPCS Codes E0100, E0105 Walkers: HCPCS Codes E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0153, E0154, E0155, E0156, E0157, E0158, E0159 Commodities: HCPCS Codes E0163, E0165, E0167, E0168, E0170, E0171, E0172, E0175 Bedpans: HCPCS Codes E0275, E0276 Urinals: HCPCS Codes E0325, E0326</p>

	<p>Shower/tub/toilet-assistive devices: HCPCS Codes E0240, E0241, E0242, E0243, E0244, E0245, E0246, E0247, E0248</p> <p>Lifts, transfer boards, safety belt/harness/vest: HCPCS Codes E0621, E0625, E0627, E0628, E0629, E0630, E0635, E0636, E0637, E0638, E0639, E0640, E0641, E0642, E0700, E0705, E0710</p> <p>Hospital beds: HCPCS Codes E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0271, E0272, E0273, E0274, E0277, E0280, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0301, E0302, E0303, E0304, E0305, E0310, E0315, E0316, E0370, E0371, E0372, E0373</p> <p>Wheelchairs: HCPCS Codes E1031, E1035, E1038, E1039, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1092, E1093, E1100, E1110, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1220, E1221, E1222, E1223, E1224, E1230, E1240, E1250, E1260, E1270, E1280, E1285, E1290, E1295, E1296, E1297, E1298, E0950, E0951, E0952, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0966, E0967, E0970, E0971, E0973, E0974, E0978, E0980, E0981, E0982,</p>
--	--

	<p>E0983, E0984, E0985, E0986, E0990, E0992, E0994, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1015, E1016, E1017, E1018, E1020, E1028, E1029, E1030, E1225, E1226, E1227, E1228, E2201, E2202, E2203, E2204, E2205, E2206, E2207, E2208, E2209, E2210, E2211, E2212, E2213, E2214, E2215, E2216, E2217, E2218, E2219, E2220, E2221, E2222, E2223, E2224, E2225, E2226, E2300, E2301, E2310, E2311, E2321, E2322, E2323, E2324, E2325, E2326, E2327, E2328, E2329, E2330, E2331, E2340, E2341, E2342, E2343, E2351, E2360, E2361, E2362, E2363, E2364, E2365, E2366, E2367, E2368, E2369, E2370, E2371, E2372, E2373, E2374, E2375, E2376, E2377, E2381, E2382, E2383, E2384, E2385, E2386, E2387, E2388, E2389, E2390, E2391, E2392, E2393, E2394, E2395, E2396, E2399, E2402, E2601, E2602, E2603, E2604, E2605, E2606, E2607, E2608, E2609, E2610, E2611, E2612, E2613, E2614, E2615, E2616, E2617, E2618, E2619, E2620, E2621 Blood transfusion: Revenue Center codes 0380, 0381, 0382, 0383, 0384, 0384,0385,0386,0387,0389,0391 Oxygen: HCPCS Codes E0424, E0425, E0430,</p>
--	--

	<p>E0431, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E1390, E1391, E1392, E1399, E1405, E1406 Supplemental nutrition: HCPCS Codes B4034, B4035, B4036, B4083, B4086, B4100, B4102, B4104, B4149, B4150, B4152, B4153, B4154, B4155, B4157, B4164, B4168, B4172, B4176, B4178, B4180, B4185, B4189, B4193, B4197, B4199, B4216, B4220, B4222, B4224, B5000, B5100, B5200, B9000, B9002, B9004, B9006, B9998, B9999, E0791, G0270, G0271, V5364 Hip/pelvic fracture: ICD-9 DX Codes 733.98, 808.0, 808.1, 808.2, 808.3, 808.41, 808.42, 808.43, 808.49, 808.51, 808.52, 808.53, 808.59, 808.8, 808.9, 820.00, 820.01, 820.02, 820.03, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19, 820.20, 820.21, 820.22, 820.30, 820.31, 820.32, 820.8, 820.9</p> <p>Urinary catheter: HCPCS Codes Internal—A4310, A4311, A4312, A4313, A4314, A4315, A4316, A4320, A4321, A4322, A4323, A4331, A4332, A4333, A4334, A4338, A4340, A4344, A4346, A4351, A4352, A4353, A4354, A4355, A4357, A4358; External—A4326, A4327, A4328, A4349</p>
--	--

	<p>Chronic ulcer of skin: ICD-9 DX Codes 7070, 70700, 70701, 70702, 70703, 70704, 70705, 70706, 70707, 70709, 7071, 70710, 70711, 70712, 70713, 70714, 70715, 70719, 70720, 70721, 70722, 70723, 70724, 70725, 7078, 7079</p> <p>Pneumonia: ICD-9 DX Codes 00322, 0203, 0204, 0205, 0212, 0221, 0310 0391, 0521, 0551, 0730, 0830, 1124, 1140, 1144, 1145, 11505, 11515, 11595, 1304, 1363, 4800, 4801, 4802, 4803, 4808, 4809, 481, 4820, 4821, 4822, 4823, 48230, 48231, 48232, 48239, 4824, 48240, 48241, 48242, 48249, 4828, 48281, 48282, 48283, 48284, 48289, 4829, 483, 4830, 4831, 4838, 4841, 4843, 4845, 4846, 4847, 4848, 485, 486, 5130, 5171</p> <p>Delirium, dementia, and Alzheimer disease: ICD-9 DX Codes 2900, 29010, 29011, 29012, 29013, 29020, 29021, 2903, 29040, 29041, 29042, 29043, 2908, 2909, 2930, 2931, 2940, 2941, 29410, 29411, 29420, 29421, 2948, 2949, 3100, 3102, 3108, 31081, 31089, 3109, 3310, 3311, 33111, 33119, 3312, 33182, 797 In addition, 3 codes from HCUP #85, which indicate brain damage: 78001, 78003, 78009</p> <p>Bone marrow failure/agranulocytosis: ICD-9 DX</p>
--	--

	<p>Codes 284.8 - 284.9, 288.0, 289.9 Depression: ICD-9 DX Codes 296.20, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.30, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 296.50, 296.51, 296.52, 296.53, 296.54, 296.55, 296.56, 296.60, 296.61, 296.62, 296.63, 296.64, 296.65, 296.66, 296.89, 298.0, 300.4, 309.1, 311 Respiratory failure; insufficiency; arrest (adult): ICD-9 DX Codes 5173, 5185, 51851, 51852, 51853, 51881, 51882, 51883, 51884, 7991, V461, V4611, V4612, V4613, V4614, V462 Sepsis: ICD-9 DX Codes 038.0-038.9, 790.7 Malnutrition and Unintended Weight loss: ICD-9 DX Codes 260, 261, 262, 263, 2631, 2632, 2638, 2639, 7830x, 7832x, 7833x, 7834x, 7994x Fall-related injury: ICD-9 DX Codes 800.xx-908.9 Syncope: ICD-9 DX Code 780.2</p>
--	---

REFERENCES

1. Centers for Disease Control and Prevention. Surveillance Report of Traumatic Brain Injury-related Emergency Department Visits, Hospitalizations, and Deaths—United States, 2014. 24 (2017).
2. Taylor, C. A., Bell, J. M., Breiding, M. J. & Xu, L. Traumatic Brain Injury–Related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2007 and 2013. *MMWR Surveill. Summ.* **66**, 1–16 (2017).
3. Faul, M., Xu, L., Wald, M. & Coronado, V. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002-2006. <https://stacks.cdc.gov/view/cdc/5571> (2010).
4. Dams-O'Connor, K. et al. Traumatic Brain Injury among Older Adults at Level I and II Trauma Centers. *J. Neurotrauma* **30**, 2001–2013 (2013).
5. Nathens, A. B., Jurkovich, G. J., Rivara, F. P. & Maier, R. V. Effectiveness of state trauma systems in reducing injury-related mortality: a national evaluation. *J. Trauma* **48**, 25–30; discussion 30-31 (2000).
6. Nathens, A. B., Jurkovich, G. J., Cummings, P., Rivara, F. P. & Maier, R. V. The Effect of Organized Systems of Trauma Care on Motor Vehicle Crash Mortality. 5 (2000).
7. Lukasiewicz, A. M. et al. Patient factors associated with 30-day morbidity, mortality, and length of stay after surgery for subdural hematoma: a study of the American College of Surgeons National Surgical Quality Improvement Program. *J. Neurosurg.* **124**, 760–766 (2016).
8. Fountain, D. M. et al. Survival Trends After Surgery for Acute Subdural Hematoma in Adults Over a 20-year Period: *Ann. Surg.* **265**, 590–596 (2017).
9. Lee, H. Q. et al. The Utility Of The Modified Frailty Index In Outcome Prediction For Elderly Patients With Acute Traumatic Subdural Haematoma. *J. Neurotrauma* neu.2019.6943 (2020) doi:10.1089/neu.2019.6943.

10. Albrecht, J. S. et al. Depression Among Older Adults After Traumatic Brain Injury: A National Analysis. *Am. J. Geriatr. Psychiatry* **23**, 607–614 (2015).
11. Albrecht, J. S., Peters, M. E., Smith, G. S. & Rao, V. Anxiety and Posttraumatic Stress Disorder Among Medicare Beneficiaries After Traumatic Brain Injury. *J. Head Trauma Rehabil.* **32**, 178–184 (2017).
12. Thompson, H. J., McCormick, W. C. & Kagan, S. H. Traumatic Brain Injury in Older Adults: Epidemiology, Outcomes, and Future Implications. *J. Am. Geriatr. Soc.* **54**, 1590–1595 (2006).
13. Cifu, D. X. et al. Functional outcomes of older adults with traumatic brain injury: A prospective, multicenter analysis. *Arch. Phys. Med. Rehabil.* **77**, 883–888 (1996).
14. Frankel, J. E. et al. A Follow-Up Study of Older Adults With Traumatic Brain Injury: Taking Into Account Decreasing Length of Stay. *Arch. Phys. Med. Rehabil.* **87**, 57–62 (2006).
15. Mosenthal, A. C. et al. The Effect of Age on Functional Outcome in Mild Traumatic Brain Injury: 6-Month Report of a Prospective Multicenter Trial. *J. Trauma Inj. Infect. Crit. Care* **56**, 1042–1048 (2004).
16. Kirkwood, T. B. L. Understanding the Odd Science of Aging. *Cell* **120**, 437–447 (2005).
17. Rockwood, K. & Mitnitski, A. Frailty Defined by Deficit Accumulation and Geriatric Medicine Defined by Frailty. *Clin. Geriatr. Med.* **27**, 17–26 (2011).
18. Important Facts about Falls | Home and Recreational Safety | CDC Injury Center. <https://www.cdc.gov/homeandrecreationalsafety/falls/adultfalls.html> (2019).
19. Kelley-Quon, L. et al. Functional Status After Injury: A Longitudinal Study of Geriatric Trauma. *Am. Surg.* **76**, 1055–1058 (2010).
20. Murphy, S. L. Mortality in the United States, 2017. *8* (2018).

21. Ponsford, J., Draper, K. & Schönberger, M. Functional outcome 10 years after traumatic brain injury: its relationship with demographic, injury severity, and cognitive and emotional status. *J. Int. Neuropsychol. Soc. JINS* **14**, 233–242 (2008).
22. Zaloshnja, E., Miller, T., Langlois, J. A. & Selassie, A. W. Prevalence of Long-Term Disability From Traumatic Brain Injury in the Civilian Population of the United States, 2005: *J. Head Trauma Rehabil.* **23**, 394–400 (2008).
23. McMillan, T. M., Teasdale, G. M. & Stewart, E. Disability in young people and adults after head injury: 12–14 year follow-up of a prospective cohort. *J. Neurol. Neurosurg. Psychiatry* **83**, 1086–1091 (2012).
24. Andelic, N. et al. Functional outcome and health-related quality of life 10 years after moderate-to-severe traumatic brain injury. *Acta Neurol. Scand.* **120**, 16–23 (2009).
25. Nampiaparampil, D. E. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA* **300**, 711–719 (2008).
26. Deb, S. et al. Rate of Psychiatric Illness 1 Year After Traumatic Brain Injury. *Am J Psychiatry* **5** (1999).
27. Fann, J. R. et al. Psychiatric Illness Following Traumatic Brain Injury in an Adult Health Maintenance Organization Population. *Arch. Gen. Psychiatry* **61**, 53 (2004).
28. Bryant, R. A. et al. The Psychiatric Sequelae of Traumatic Injury. *Am J Psychiatry* **9** (2010).
29. Albrecht, J. S., Barbour, L., Abariga, S. A., Rao, V. & Perfetto, E. M. Risk of Depression after Traumatic Brain Injury in a Large National Sample. *J. Neurotrauma* **36**, 300–307 (2019).
30. Menon, D. K., Schwab, K., Wright, D. W., Maas, A. I., & Demographics and Clinical Assessment Working Group of the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and

- Psychological Health. Position statement: definition of traumatic brain injury. *Arch. Phys. Med. Rehabil.* **91**, 1637–1640 (2010).
31. Dixon, K. J. Pathophysiology of Traumatic Brain Injury. *Phys. Med. Rehabil. Clin. N. Am.* **28**, 215–225 (2017).
 32. Alberico, A. M. & Marmarou, A. Outcome after severe head injury. *J Neurosurg* **67**, 9 (1987).
 33. Jorge, R. E. & Starkstein, S. E. Pathophysiologic Aspects of Major Depression Following Traumatic Brain Injury: *J. Head Trauma Rehabil.* **20**, 475–487 (2005).
 34. Hill, C. S., Coleman, M. P. & Menon, D. K. Traumatic Axonal Injury: Mechanisms and Translational Opportunities. *Trends Neurosci.* **39**, 311–324 (2016).
 35. Lafrenaye, A. D., Todani, M., Walker, S. A. & Povlishock, J. T. Microglia processes associate with diffusely injured axons following mild traumatic brain injury in the micro pig. *J. Neuroinflammation* **12**, 186 (2015).
 36. Browne, K. D., Chen, X.-H., Meaney, D. F. & Smith, D. H. Mild Traumatic Brain Injury and Diffuse Axonal Injury in Swine. *J. Neurotrauma* **28**, 1747–1755 (2011).
 37. Topal, N. B. et al. MR imaging in the detection of diffuse axonal injury with mild traumatic brain injury. *Neurol. Res.* **30**, 974–978 (2008).
 38. Greer, J. E., Povlishock, J. T. & Jacobs, K. M. Electrophysiological Abnormalities in Both Axotomized and Nonaxotomized Pyramidal Neurons following Mild Traumatic Brain Injury. *J. Neurosci.* **32**, 6682–6687 (2012).
 39. Rachmany, L. et al. Cognitive Impairments Accompanying Rodent Mild Traumatic Brain Injury Involve p53-Dependent Neuronal Cell Death and Are Ameliorated by the Tetrahydrobenzothiazole PFT- α . *PLoS ONE* **8**, e79837 (2013).

40. Cruz-Haces, M., Tang, J., Acosta, G., Fernandez, J. & Shi, R. Pathological correlations between traumatic brain injury and chronic neurodegenerative diseases. *Transl. Neurodegener.* **6**, 20 (2017).
41. Greer, J. E., McGinn, M. J. & Povlishock, J. T. Diffuse Traumatic Axonal Injury in the Mouse Induces Atrophy, c-Jun Activation, and Axonal Outgrowth in the Axotomized Neuronal Population. *J. Neurosci.* **31**, 5089–5105 (2011).
42. Raghupathi, R. Cell Death Mechanisms Following Traumatic Brain Injury. *Brain Pathol.* **14**, 215–222 (2004).
43. Lotocki, G. et al. Alterations in Blood-Brain Barrier Permeability to Large and Small Molecules and Leukocyte Accumulation after Traumatic Brain Injury: Effects of Post-Traumatic Hypothermia. *J. Neurotrauma* **26**, 1123–1134 (2009).
44. Johnson, V. E., Stewart, W. & Smith, D. H. Axonal pathology in traumatic brain injury. *Exp. Neurol.* **246**, 35–43 (2013).
45. Wang, J.-Y. et al. Pomalidomide mitigates neuronal loss, neuroinflammation, and behavioral impairments induced by traumatic brain injury in rat. *J. Neuroinflammation* **13**, 168 (2016).
46. Moro, N., Ghavim, S. S., Harris, N. G., Hovda, D. A. & Sutton, R. L. Pyruvate treatment attenuates cerebral metabolic depression and neuronal loss after experimental traumatic brain injury. *Brain Res.* **1642**, 270–277 (2016).
47. Ekmark-Lewén, S. et al. Vimentin and GFAP responses in astrocytes after contusion trauma to the murine brain. *Restor. Neurol. Neurosci.* **28**, 311–321 (2010).
48. Morganti-Kossmann, M. C. et al. Production of cytokines following brain injury: beneficial and deleterious for the damaged tissue. *Mol. Psychiatry* **2**, 133–136 (1997).
49. Taupin, P. Adult neurogenesis, neuroinflammation and therapeutic potential of adult neural stem cells. *Int J Med Sci* **6** (2008).

50. Hoiland, R. L., Bain, A. R., Rieger, M. G., Bailey, D. M. & Ainslie, P. N. Hypoxemia, oxygen content, and the regulation of cerebral blood flow. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* **310**, R398–R413 (2016).
51. McQuire, J. C., Sutcliffe, J. C. & Coats, T. J. Early changes in middle cerebral artery blood flow velocity after head injury. *J. Neurosurg.* **89**, 526–532 (1998).
52. Hayward, N. M. E. A. et al. Magnetic Resonance Imaging of Regional Hemodynamic and Cerebrovascular Recovery after Lateral Fluid-Percussion Brain Injury in Rats. *J. Cereb. Blood Flow Metab.* **31**, 166–177 (2011).
53. Park, E., Bell, J. D., Siddiq, I. P. & Baker, A. J. An Analysis of Regional Microvascular Loss and Recovery following Two Grades of Fluid Percussion Trauma: A Role for Hypoxia-Inducible Factors in Traumatic Brain Injury. *J. Cereb. Blood Flow Metab.* **29**, 575–584 (2009).
54. Gao, G., Oda, Y., Wei, E. P. & Povlishock, J. T. The Adverse Pial Arteriolar and Axonal Consequences of Traumatic Brain Injury Complicated by Hypoxia and Their Therapeutic Modulation with Hypothermia in Rat. *J. Cereb. Blood Flow Metab.* **30**, 628–637 (2010).
55. Ueda, Y., Wei, E. P., Kontos, H. A., Suehiro, E. & Povlishock, J. T. Effects of delayed, prolonged hypothermia on the pial vascular response after traumatic brain injury in rats. *J. Neurosurg.* **99**, 899–906 (2003).
56. Baranova, A. I. et al. Cerebral vascular responsiveness after experimental traumatic brain injury: the beneficial effects of delayed hypothermia combined with superoxide dismutase administration. *J. Neurosurg.* **109**, 502–509 (2008).
57. Petkus, V. et al. Association between the outcome of traumatic brain injury patients and cerebrovascular autoregulation, cerebral perfusion pressure, age, and injury grades. *Medicina (Mex.)* **52**, 46–53 (2016).
58. Lotocki, G. et al. Oligodendrocyte vulnerability following traumatic brain injury in rats. *Neurosci. Lett.* **499**, 143–148 (2011).

59. Yang, S. H., Gangidine, M., Pritts, T. A., Goodman, M. D. & Lentsch, A. B. Interleukin 6 Mediates Neuroinflammation and Motor Coordination Deficits After Mild Traumatic Brain Injury and Brief Hypoxia in Mice: *Shock* **40**, 471–475 (2013).
60. Mouzon, B. C. et al. Chronic neuropathological and neurobehavioral changes in a repetitive mild traumatic brain injury model: Chronic Effects of r-mTBI. *Ann. Neurol.* **75**, 241–254 (2014).
61. Malec, J. F. et al. The Mayo Classification System for Traumatic Brain Injury Severity. *J. Neurotrauma* **24**, 1417–1424 (2007).
62. Centers for Disease Control and Prevention. Report to Congress on Traumatic Brain Injury in the United States: Epidemiology and Rehabilitation. https://www.cdc.gov/traumaticbraininjury/pdf/TBI_Report_to_Congress_Epi_and_Rehab-a.pdf (2015).
63. Konrad, C. et al. Long-term cognitive and emotional consequences of mild traumatic brain injury. *Psychol. Med.* **41**, 1197–1211 (2011).
64. Smits, M. et al. Postconcussion syndrome after minor head injury: Brain activation of working memory and attention. *Hum. Brain Mapp.* **30**, 2789–2803 (2009).
65. Masel, B. E. & DeWitt, D. S. Traumatic Brain Injury: A Disease Process, Not an Event. *J. Neurotrauma* **27**, 1529–1540 (2010).
66. Corrigan, J. D. et al. US Population Estimates of Health and Social Outcomes 5 Years After Rehabilitation for Traumatic Brain Injury: *J. Head Trauma Rehabil.* **29**, E1–E9 (2014).
67. Kumar, R. G. et al. The Longitudinal Effects of Comorbid Health Burden on Functional Outcomes for Adults With Moderate to Severe Traumatic Brain Injury. *J. Head Trauma Rehabil.* **Publish Ahead of Print**, (2020).

68. Dams-O'Connor, K., Gibbons, L. E., Landau, A., Larson, E. B. & Crane, P. K. Health Problems Precede Traumatic Brain Injury in Older Adults. *J. Am. Geriatr. Soc.* **64**, 844–848 (2016).
69. Coronado, V. G., Thomas, K. E., Sattin, R. W. & Johnson, R. L. The CDC Traumatic Brain Injury Surveillance System: Characteristics of Persons Aged 65 Years and Older Hospitalized With a TBI. *J. Head Trauma Rehabil.* **20**, 215–228 (2005).
70. Albrecht, J. S., Abariga, S. A., Rao, V. & Wickwire, E. M. Incidence of New Neuropsychiatric Disorder Diagnoses Following Traumatic Brain Injury. *J. Head Trauma Rehabil.* **Publish Ahead of Print**, (2020).
71. Al-Ameri, L., Mohsin, T. & Abdul Wahid, A. Sleep Disorders Following Mild and Moderate Traumatic Brain Injury. *Brain Sci.* **9**, 10 (2019).
72. Wei, L. et al. Sleep Disturbances Following Traumatic Brain Injury in Older Adults: A Comparison Study. *J. Head Trauma Rehabil.* **Publish Ahead of Print**, (2020).
73. Wickwire, E. M. et al. Sleep, Sleep Disorders, and Mild Traumatic Brain Injury. What We Know and What We Need to Know: Findings from a National Working Group. *Neurotherapeutics* **13**, 403–417 (2016).
74. Wickwire, E. M. et al. Sleep, Sleep Disorders, and Circadian Health following Mild Traumatic Brain Injury in Adults: Review and Research Agenda. *J. Neurotrauma* **35**, 2615–2631 (2018).
75. Albrecht, J. S. & Wickwire, E. M. Sleep disturbances among older adults following traumatic brain injury. *Int. Rev. Psychiatry* **32**, 31–38 (2020).
76. Wolf, J. A. & Koch, P. F. Disruption of Network Synchrony and Cognitive Dysfunction After Traumatic Brain Injury. *Front. Syst. Neurosci.* **10**, (2016).
77. Behan, L. A., Phillips, J., Thompson, C. J. & Agha, A. Neuroendocrine disorders after traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* **79**, 753–759 (2008).

78. Molaie, A. M. & Maguire, J. Neuroendocrine Abnormalities Following Traumatic Brain Injury: An Important Contributor to Neuropsychiatric Sequelae. *Front. Endocrinol.* **9**, 176 (2018).
79. Hoogendijk, E. O. et al. Frailty: implications for clinical practice and public health. *The Lancet* **394**, 1365–1375 (2019).
80. Clegg, A., Young, J., Iliffe, S., Rikkert, M. O. & Rockwood, K. Frailty in elderly people. *The Lancet* **381**, 752–762 (2013).
81. Fried, L. P. et al. Frailty in Older Adults: Evidence for a Phenotype. *J. Gerontol. A. Biol. Sci. Med. Sci.* **56**, M146–M157 (2001).
82. Chen, X., Mao, G. & Leng, S. Frailty syndrome: an overview. *Clin. Interv. Aging* **433** (2014) doi:10.2147/CIA.S45300.
83. Chowdhury, R., Peel, N. M., Krosch, M. & Hubbard, R. E. Frailty and chronic kidney disease: A systematic review. *Arch. Gerontol. Geriatr.* **68**, 135–142 (2017).
84. Villani, E. R. et al. Frailty and atrial fibrillation: A systematic review. *Eur. J. Intern. Med.* **56**, 33–38 (2018).
85. Marengoni, A. et al. The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies. *CHEST* **154**, 21–40 (2018).
86. Bouillon, K. et al. Cardiovascular disease risk scores in identifying future frailty: the Whitehall II prospective cohort study. *Heart* **99**, 737–742 (2013).
87. Vetrano, D. L. et al. Hypertension and frailty: a systematic review and meta-analysis. *BMJ Open* **8**, e024406 (2018).
88. Vaingankar, J. A. et al. Prevalence of frailty and its association with sociodemographic and clinical characteristics, and resource utilization in a population of Singaporean older adults. *Geriatr. Gerontol. Int.* **17**, 1444–1454 (2017).

89. Ng, T. P., Feng, L., Nyunt, M. S. Z., Larbi, A. & Yap, K. B. Frailty in Older Persons: Multisystem Risk Factors and the Frailty Risk Index (FRI). *J. Am. Med. Dir. Assoc.* **15**, 635–642 (2014).
90. Rodriguez, J. J. L. et al. The Prevalence and Correlates of Frailty in Urban and Rural Populations in Latin America, China, and India: A 10/66 Population-Based Survey. *J. Am. Med. Dir. Assoc.* **19**, 287-295.e4 (2018).
91. Winovich, D. T. et al. Factors Associated With Ischemic Stroke Survival and Recovery in Older Adults. *Stroke* **48**, 1818–1826 (2017).
92. Van Iersel, M. B. & Olde Rikkert, M. G. M. FRAILITY CRITERIA GIVE HETEROGENEOUS RESULTS WHEN APPLIED IN CLINICAL PRACTICE: LETTERS TO THE EDITOR. *J. Am. Geriatr. Soc.* **54**, 728–729 (2006).
93. Choi, J., Ahn, A., Kim, S. & Won, C. W. Global Prevalence of Physical Frailty by Fried's Criteria in Community-Dwelling Elderly With National Population-Based Surveys. *J. Am. Med. Dir. Assoc.* **16**, 548–550 (2015).
94. Kojima, G., Taniguchi, Y., Iliffe, S. & Walters, K. Frailty as a Predictor of Alzheimer Disease, Vascular Dementia, and All Dementia Among Community-Dwelling Older People: A Systematic Review and Meta-Analysis. *J. Am. Med. Dir. Assoc.* **17**, 881–888 (2016).
95. Abdulle, A. E. et al. Early Predictors for Long-Term Functional Outcome After Mild Traumatic Brain Injury in Frail Elderly Patients: *J. Head Trauma Rehabil.* **1** (2018) doi:10.1097/HTR.0000000000000368.
96. Fried, L. P., Ferrucci, L., Darer, J., Williamson, J. D. & Anderson, G. Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved Targeting and Care. *J. Gerontol. A. Biol. Sci. Med. Sci.* **59**, M255–M263 (2004).
97. Livingston, D. H. et al. Recovery at one year following isolated traumatic brain injury: a Western Trauma Association prospective multicenter trial. *J. Trauma* **59**, 1298–1304; discussion 1304 (2005).

98. Thompson, H. J., Rivara, F. P. & Wang, J. Effect of Age on Longitudinal Changes in Symptoms, Function, and Outcome in the First Year After Mild-Moderate Traumatic Brain Injury. *J. Neurosci. Nurs. J. Am. Assoc. Neurosci. Nurses* **52**, 46–52 (2020).
99. Lewis, F. D. & Horn, G. J. Traumatic Brain Injury: Analysis of Functional Deficits and Posthospital Rehabilitation Outcomes. *Trauma. Brain Inj.* **13**, 6 (2013).
100. Al-Hassani, A. et al. Functional Outcomes in Moderate-to-Severe Traumatic Brain Injury Survivors. *J. Emerg. Trauma Shock* **11**, 197–204 (2018).
101. Kornblith, E. S., Langa, K. M., Yaffe, K. & Gardner, R. C. Physical and Functional Impairment Among Older Adults With a History of Traumatic Brain Injury. *J. Head Trauma Rehabil.* **Publish Ahead of Print**, (2020).
102. Whiteneck, G. G., Cuthbert, J. P., Corrigan, J. D. & Bogner, J. A. Prevalence of Self-Reported Lifetime History of Traumatic Brain Injury and Associated Disability: A Statewide Population-Based Survey. *J. Head Trauma Rehabil.* **31**, E55-62 (2016).
103. Cullen, N. K., Park, Y.-G. & Bayley, M. T. Functional recovery following traumatic vs non-traumatic brain injury: a case-controlled study. *Brain Inj.* **22**, 1013–1020 (2008).
104. Whiteneck, G. G., Cuthbert, J. P., Corrigan, J. D. & Bogner, J. A. Risk of Negative Outcomes After Traumatic Brain Injury: A Statewide Population-Based Survey. *J. Head Trauma Rehabil.* **31**, E43-54 (2016).
105. Yi, H. et al. Lifetime History of Traumatic Brain Injury and Current Disability Among Ohio Adults. *J. Head Trauma Rehabil.* **33**, E24–E32 (2018).
106. Lewin, W., Marshall, T. F. & Roberts, A. H. Long-term outcome after severe head injury. *Br. Med. J.* **2**, 1533–1538 (1979).
107. Colantonio, A. et al. Long-term outcomes after moderate to severe traumatic brain injury. *Disabil. Rehabil.* **26**, 253–261 (2004).

108. Utomo, W. K., Gabbe, B. J., Simpson, P. M. & Cameron, P. A. Predictors of in-hospital mortality and 6-month functional outcomes in older adults after moderate to severe traumatic brain injury. *Injury* **40**, 973–977 (2009).
109. Hukkelhoven, C. W. P. M. et al. Patient age and outcome following severe traumatic brain injury: an analysis of 5600 patients. *J. Neurosurg.* **99**, 666–673 (2003).
110. Erler, K. S. et al. Predicting the Trajectory of Participation After Traumatic Brain Injury: A Longitudinal Analysis. *J. Head Trauma Rehabil.* **33**, 257–265 (2018).
111. Alfano, D. P. Emotional and pain-related factors in neuropsychological assessment following mild traumatic brain injury. *Brain Cogn.* **60**, 194–196 (2006).
112. Irvine, K.-A., Sahbaie, P., Liang, D.-Y. & Clark, J. D. Traumatic Brain Injury Disrupts Pain Signaling in the Brainstem and Spinal Cord. *J. Neurotrauma* **35**, 1495–1509 (2018).
113. Elkind, A. H. Headache and facial pain associated with head injury. *Otolaryngol. Clin. North Am.* **22**, 1251–1271 (1989).
114. Lagarde, E. et al. Association of symptoms following mild traumatic brain injury with posttraumatic stress disorder vs. postconcussion syndrome. *JAMA Psychiatry* **71**, 1032–1040 (2014).
115. Martelli, M. F., Zasler, N. D., Bender, M. C. & Nicholson, K. Psychological, neuropsychological, and medical considerations in assessment and management of pain. *J. Head Trauma Rehabil.* **19**, 10–28 (2004).
116. McCracken, L. M. & Iverson, G. L. Predicting complaints of impaired cognitive functioning in patients with chronic pain. *J. Pain Symptom Manage.* **21**, 392–396 (2001).

117. Kempf, J., Werth, E., Kaiser, P. R., Bassetti, C. L. & Baumann, C. R. Sleep-wake disturbances 3 years after traumatic brain injury. *J. Neurol. Neurosurg. Psychiatry* **81**, 1402–1405 (2010).
118. Aoun, R., Rawal, H., Attarian, H. & Sahni, A. Impact of traumatic brain injury on sleep: an overview. *Nat. Sci. Sleep* **Volume 11**, 131–140 (2019).
119. Mathias, J. L. & Alvaro, P. K. Prevalence of sleep disturbances, disorders, and problems following traumatic brain injury: A meta-analysis. *Sleep Med.* **13**, 898–905 (2012).
120. Helbig, A. K. et al. Association between sleep disturbances and falls among the elderly: results from the German Cooperative Health Research in the Region of Augsburg-Age study. *Sleep Med.* **14**, 1356–1363 (2013).
121. Chiu, H.-Y., Lai, F.-C., Chen, P.-Y. & Tsai, P.-S. Differences Between Men and Women Aged 65 and Older in the Relationship Between Self-Reported Sleep and Cognitive Impairment: A Nationwide Survey in Taiwan. *J. Am. Geriatr. Soc.* **64**, 2051–2058 (2016).
122. Manber, R. et al. Cognitive Behavioral Therapy for Insomnia Enhances Depression Outcome in Patients with Comorbid Major Depressive Disorder and Insomnia. *Sleep* **31**, 489–495 (2008).
123. Germain, A. Sleep Disturbances as the Hallmark of PTSD: Where Are We Now? *Am. J. Psychiatry* **170**, 372–382 (2013).
124. Smith, M. T. & Haythornthwaite, J. A. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. *Sleep Med. Rev.* **8**, 119–132 (2004).
125. Banks, S. & Dinges, D. F. Behavioral and Physiological Consequences of Sleep Restriction. *J. Clin. Sleep Med.* **03**, 519–528 (2007).

126. Mahmood, O., Rapport, L. J., Hanks, R. A. & Fichtenberg, N. L. Neuropsychological Performance and Sleep Disturbance Following Traumatic Brain Injury: *J. Head Trauma Rehabil.* **19**, 378–390 (2004).
127. Baumann, C. R., Werth, E., Stocker, R., Ludwig, S. & Bassetti, C. L. Sleep-wake disturbances 6 months after traumatic brain injury: a prospective study. *Brain* **130**, 1873–1883 (2007).
128. Wickwire, E. M., Shaya, F. T. & Scharf, S. M. Health economics of insomnia treatments: The return on investment for a good night’s sleep. *Sleep Med. Rev.* **30**, 72–82 (2016).
129. Pillar, G. et al. Prevalence and risk of sleep disturbances in adolescents after minor head injury. *Pediatr. Neurol.* **29**, 131–135 (2003).
130. Tham, S. W. et al. The Longitudinal Course, Risk Factors, and Impact of Sleep Disturbances in Children with Traumatic Brain Injury. *J. Neurotrauma* **29**, 154–161 (2012).
131. Fawcett, J. The morbidity and mortality of clinical depression. *Int. Clin. Psychopharmacol.* **8**, 217–220 (1993).
132. Baldessarini, R. J. et al. Morbidity in Depressive Disorders. *Psychother. Psychosom.* **86**, 65–72 (2017).
133. Grenard, J. L. et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. *J. Gen. Intern. Med.* **26**, 1175–1182 (2011).
134. Hibbard, M. R. et al. Relationship between depression and psychosocial functioning after traumatic brain injury | No commercial party having a direct financial interest in the results of the research supporting this article has or will confer benefit upon the author(s) or upon any organization with which the author(s) is/are associated. *Arch. Phys. Med. Rehabil.* **85**, 43–53 (2004).

135. Chen, S., Bowman, F. D. & Mayberg, H. S. A Bayesian hierarchical framework for modeling brain connectivity for neuroimaging data: A Bayesian Hierarchical Framework for Modeling Brain Connectivity for Neuroimaging Data. *Biometrics* **72**, 596–605 (2016).
136. Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D. & Pizzagalli, D. A. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. *JAMA Psychiatry* **72**, 603 (2015).
137. Plesnila, N. The immune system in traumatic brain injury. *Curr. Opin. Pharmacol.* **26**, 110–117 (2016).
138. Sharma, R., Rosenberg, A., Bennett, E. R., Laskowitz, D. T. & Acheson, S. K. A blood-based biomarker panel to risk-stratify mild traumatic brain injury. *PLoS ONE* **12**, e0173798 (2017).
139. Miller, A. H. & Raison, C. L. The role of inflammation in depression: from evolutionary imperative to modern treatment target. *Nat. Rev. Immunol.* **16**, 22–34 (2016).
140. Stein, M. B. et al. Risk of Posttraumatic Stress Disorder and Major Depression in Civilian Patients After Mild Traumatic Brain Injury: A TRACK-TBI Study. *JAMA Psychiatry* **76**, 249 (2019).
141. Gould, K. R., Ponsford, J. L., Johnston, L. & Schönberger, M. The nature, frequency and course of psychiatric disorders in the first year after traumatic brain injury: a prospective study. *Psychol. Med.* **41**, 2099–2109 (2011).
142. Diagnostic and statistical manual of mental disorders: DSM-5. (American Psychiatric Association, 2013).
143. Bryant, R. A. Posttraumatic stress disorder and traumatic brain injury: can they co-exist? *Clin. Psychol. Rev.* **21**, 931–948 (2001).
144. Bryant, R. A. Post-traumatic stress disorder vs. traumatic brain injury. *Dialogues Clin. Neurosci.* **13**, 12 (2011).

145. Vasterling, J. J., Verfaellie, M. & Sullivan, K. D. Mild traumatic brain injury and posttraumatic stress disorder in returning veterans: Perspectives from cognitive neuroscience. *Clin. Psychol. Rev.* **29**, 674–684 (2009).
146. Osborn, A. J., Mathias, J. L. & Fairweather-Schmidt, A. K. Prevalence of anxiety following adult traumatic brain injury: A meta-analysis comparing measures, samples and postinjury intervals. *Neuropsychology* **30**, 247–261 (2016).
147. Van Praag, D. L. G., Cnossen, M. C., Polinder, S., Wilson, L. & Maas, A. I. R. Post-Traumatic Stress Disorder after Civilian Traumatic Brain Injury: A Systematic Review and Meta-Analysis of Prevalence Rates. *J. Neurotrauma* **36**, 3220–3232 (2019).
148. Vanderploeg, R. D., Belanger, H. G. & Curtiss, G. Mild Traumatic Brain Injury and Posttraumatic Stress Disorder and Their Associations With Health Symptoms. *Arch. Phys. Med. Rehabil.* **90**, 1084–1093 (2009).
149. Anstey, K. J. et al. A population survey found an association between self-reports of traumatic brain injury and increased psychiatric symptoms. *J. Clin. Epidemiol.* **57**, 1202–1209 (2004).
150. Tsaousides, T., Cantor, J. B. & Gordon, W. A. Suicidal ideation following traumatic brain injury: prevalence rates and correlates in adults living in the community. *J. Head Trauma Rehabil.* **26**, 265–275 (2011).
151. Mendlowicz, M. V. & Stein, M. B. Quality of life in individuals with anxiety disorders. *Am. J. Psychiatry* **157**, 669–682 (2000).
152. Virnig, B. & Parsons, H. Strengths and Limitations of CMS Administrative Data in Research | ResDAC. <https://www.resdac.org/articles/strengths-and-limitations-cms-administrative-data-research>.
153. Condition Categories. Chronic Conditions Data Warehouse <https://www2.ccwdata.org/condition-categories>.

154. Chronic Conditions. Chronic Conditions Data Warehouse
<https://www2.ccwdata.org/condition-categories-chronic>.
155. MDS 3.0 Frequency Report | CMS. <https://www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/Minimum-Data-Set-3-0-Public-Reports/Minimum-Data-Set-3-0-Frequency-Report>.
156. St Germaine-Smith, C. et al. Recommendations for optimal ICD codes to study neurologic conditions: a systematic review. *Neurology* **79**, 1049–1055 (2012).
157. Carroll, C. P., Cochran, J. A., Guse, C. E. & Wang, M. C. Are we underestimating the burden of traumatic brain injury? Surveillance of severe traumatic brain injury using centers for disease control International classification of disease, ninth revision, clinical modification, traumatic brain injury codes. *Neurosurgery* **71**, 1064–1070; discussion 1070 (2012).
158. Barell, V. et al. An introduction to the Barell body region by nature of injury diagnosis matrix. *Inj. Prev.* **8**, 91–96 (2002).
159. Newgard, C. D. et al. Validation of Length of Hospital Stay as a Surrogate Measure for Injury Severity and Resource Use Among Injury Survivors. *Acad. Emerg. Med. Off. J. Soc. Acad. Emerg. Med.* **17**, 142–150 (2010).
160. Kim, D. H. et al. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index. *J. Gerontol. Ser. A* **73**, 980–987 (2018).
161. Kim, D. H. et al. Validation of a Claims-Based Frailty Index Against Physical Performance and Adverse Health Outcomes in the Health and Retirement Study. *J. Gerontol. Ser. A* **74**, 1271–1276 (2019).
162. Rockwood, K., Andrew, M. & Mitnitski, A. A Comparison of Two Approaches to Measuring Frailty in Elderly People. *J. Gerontol. A. Biol. Sci. Med. Sci.* **62**, 738–743 (2007).

163. Chrischilles, E. et al. Beyond Comorbidity: Expanding the Definition and Measurement of Complexity Among Older Adults Using Administrative Claims Data. *Med. Care* **52**, (2014).
164. Intrator, O., Hiris, J., Berg, K., Miller, S. C. & Mor, V. The Residential History File: Studying Nursing Home Residents' Long-Term Care Histories. *Health Serv. Res.* **46**, 120–137 (2011).
165. Goodwin, J. S. et al. Comparison of methods to identify long term care nursing home residence with administrative data. *BMC Health Serv. Res.* **17**, 376 (2017).
166. Chronic Pain. Spine-health <https://www.spine-health.com/glossary/chronic-pain>.
167. Tian, T. Y., Zlateva, I. & Anderson, D. R. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J. Am. Med. Inform. Assoc. JAMIA* **20**, e275–e280 (2013).
168. Albrecht, J. S., Wickwire, E. M., Vadlamani, A., Scharf, S. M. & Tom, S. E. Trends in Insomnia Diagnosis and Treatment Among Medicare Beneficiaries, 2006–2013. *Am. J. Geriatr. Psychiatry* **27**, 301–309 (2019).
169. Fiest, K. M. et al. Systematic review and assessment of validated case definitions for depression in administrative data. *BMC Psychiatry* **14**, 289 (2014).
170. Albrecht, J. S. et al. Depression among Older Adults Following Traumatic Brain Injury: A National Analysis. *Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry* **23**, 607–614 (2015).
171. About Chronic Condition Data Warehouse - Chronic Conditions Data Warehouse. <https://www2.ccwdata.org/web/guest/about-ccw>.
172. Guo, Y., Logan, H. L., Glueck, D. H. & Muller, K. E. Selecting a sample size for studies with repeated measures. *BMC Med. Res. Methodol.* **13**, 100 (2013).

173. Jang, I.-Y. et al. Evaluation of Clinically Meaningful Changes in Measures of Frailty. *J. Gerontol. Ser. A* **75**, 1143–1147 (2020).
174. Hulbert, E. & Brekke, L. A SAS® Macro to Evaluate Balance after Propensity Score Matching. *12*.
175. Robins, J. M., Rotnitzky, A. & Zhao, L. P. Estimation of Regression Coefficients When Some Regressors are not Always Observed. *J. Am. Stat. Assoc.* **89**, 846–866 (1994).
176. Funk, M. J. et al. Doubly robust estimation of causal effects. *Am. J. Epidemiol.* **173**, 761–767 (2011).
177. Gardner, R. C., Dams-O'Connor, K., Morrissey, M. R. & Manley, G. T. Geriatric Traumatic Brain Injury: Epidemiology, Outcomes, Knowledge Gaps, and Future Directions. *J. Neurotrauma* **35**, 889–906 (2018).
178. Albrecht, J. S., Al Kibria, G. M., Greene, C. R., Dischinger, P. & Ryb, G. E. Post-Discharge Mortality of Older Adults with Traumatic Brain Injury or Other Trauma. *J. Am. Geriatr. Soc.* **67**, 2382–2386 (2019).
179. Dams-O'Connor, K. et al. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. *J. Neurol. Neurosurg. Psychiatry* **84**, 177–182 (2013).
180. Ramanathan, D. M., McWilliams, N., Schatz, P. & Hillary, F. G. Epidemiological Shifts in Elderly Traumatic Brain Injury: 18-Year Trends in Pennsylvania. *J. Neurotrauma* **29**, 1371–1378 (2012).
181. McIntyre, A., Mehta, S., Aubut, J., Dijkers, M. & Teasell, R. W. Mortality among older adults after a traumatic brain injury: a meta-analysis. *Brain Inj.* **27**, 31–40 (2013).
182. Mosenthal, A. C. et al. Isolated Traumatic Brain Injury: Age Is an Independent Predictor of Mortality and Early Outcome. *J. Trauma Inj. Infect. Crit. Care* **52**, 907–911 (2002).

183. Rapoport, M. J. & Feinstein, A. Age and functioning after mild traumatic brain injury: the acute picture. *Brain Inj.* **15**, 857–864 (2001).
184. On its 50th anniversary, more than 55 million Americans covered by Medicare | CMS. <https://www.cms.gov/newsroom/press-releases/its-50th-anniversary-more-55-million-americans-covered-medicare>.
185. Health Care Financing Administration. Medicare 2000: 35 Years of Improving Americans' Health and Security. (2000).
186. Bandeen-Roche, K. et al. Frailty in Older Adults: A Nationally Representative Profile in the United States. *J. Gerontol. A. Biol. Sci. Med. Sci.* **70**, 1427–1434 (2015).
187. Rockwood, K. et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ Can. Med. Assoc. J. J. Assoc. Medicale Can.* **173**, 489–495 (2005).
188. Bishop, N. A., Lu, T. & Yankner, B. A. Neural mechanisms of ageing and cognitive decline. *Nature* **464**, 529–535 (2010).
189. Soysal, P. et al. Inflammation and frailty in the elderly: A systematic review and meta-analysis. *Ageing Res. Rev.* **31**, 1–8 (2016).
190. Franceschi, C., Garagnani, P., Parini, P., Giuliani, C. & Santoro, A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat. Rev. Endocrinol.* **14**, 576–590 (2018).
191. Postolache, T. T. et al. Inflammation in Traumatic Brain Injury. *J. Alzheimers Dis. JAD* **74**, 1–28 (2020).
192. Kirkwood, T. B. L. Understanding the Odd Science of Aging. *Cell* **120**, 437–447 (2005).

193. Selassie, A. W., McCarthy, M. L., Ferguson, P. L., Tian, J. & Langlois, J. A. Risk of Posthospitalization Mortality Among Persons With Traumatic Brain Injury, South Carolina 1999–2001: *J. Head Trauma Rehabil.* **20**, 257–269 (2005).
194. Gaugler, J. E., Duval, S., Anderson, K. A. & Kane, R. L. Predicting nursing home admission in the U.S: a meta-analysis. *BMC Geriatr.* **7**, 13 (2007).
195. Stycke, J., Stålnacke, B.-M., Sojka, P. & Björnstig, U. Traumatic brain injuries in a well-defined population: epidemiological aspects and severity. *J. Neurotrauma* **24**, 1425–1436 (2007).
196. Tinetti, M. E., De Leon, C. F. M., Doucette, J. T. & Baker, D. I. Fear of Falling and Fall-Related Efficacy in Relationship to Functioning Among Community-Living Elders. *J. Gerontol.* **49**, M140–M147 (1994).
197. Tinetti, M. E. & Williams, C. S. Falls, injuries due to falls, and the risk of admission to a nursing home. *N. Engl. J. Med.* **337**, 1279–1284 (1997).
198. Parkkari, J. et al. Majority of hip fractures occur as a result of a fall and impact on the greater trochanter of the femur: a prospective controlled hip fracture study with 206 consecutive patients. *Calcif. Tissue Int.* **65**, 183–187 (1999).
199. Leibson, C. L., Tosteson, A. N. A., Gabriel, S. E., Ransom, J. E. & Melton III, L. J. Mortality, Disability, and Nursing Home Use for Persons with and without Hip Fracture: A Population-Based Study. *J. Am. Geriatr. Soc.* **50**, 1644–1650 (2002).
200. Abraham, D. S. et al. Residual Disability, Mortality, and Nursing Home Placement After Hip Fracture Over 2 Decades. *Arch. Phys. Med. Rehabil.* **100**, 874–882 (2019).
201. Becker, D. J. et al. Trends in the Utilization and Outcomes of Medicare Patients Hospitalized for Hip Fracture, 2000–2008. *J. Aging Health* **26**, 360–379 (2014).
202. Bonar, S. K., Tinetti, M. E., Speechley, M. & Cooney, L. M. Factors Associated with Short- Versus Long-Term Skilled Nursing Facility. *J. Am. Geriatr. Soc.* **38**, 1139–1144 (1990).

203. Blackburn, J. et al. Men Lacking a Caregiver Have Greater Risk of Long-Term Nursing Home Placement After Stroke. *J. Am. Geriatr. Soc.* **66**, 133–139 (2018).
204. Valiyeva, E., Russell, L. B., Miller, J. E. & Safford, M. M. Lifestyle-Related Risk Factors and Risk of Future Nursing Home Admission. *Arch. Intern. Med.* **166**, 985–990 (2006).
205. Luppá, M., Luck, T., Weyerer, S., König, H.-H. & Riedel-Heller, S. G. Gender differences in predictors of nursing home placement in the elderly: a systematic review. *Int. Psychogeriatr.* **21**, 1015–1025 (2009).
206. Thomas, K. S., Keohane, L. & Mor, V. Local Medicaid home- and community-based services spending and nursing home admissions of younger adults. *Am. J. Public Health* **104**, e15-17 (2014).
207. Mor, V. et al. Prospects for transferring nursing home residents to the community. *Health Aff. Proj. Hope* **26**, 1762–1771 (2007).
208. Sattin, R. W. et al. The incidence of fall injury events among the elderly in a defined population. *Am. J. Epidemiol.* **131**, 1028–1037 (1990).
209. Sterling, D. A., O'Connor, J. A. & Bonadies, J. Geriatric Falls: Injury Severity Is High and Disproportionate to Mechanism. *J. TRAUMA* **50**, 4 (2001).
210. Alexander, B. H., Rivara, F. P. & Wolf, M. E. The cost and frequency of hospitalization for fall-related injuries in older adults. *Am. J. Public Health* **82**, 1020–1023 (1992).
211. Tinetti, M. E., Speechley, M. & Ginter, S. F. Risk factors for falls among elderly persons living in the community. *N. Engl. J. Med.* **319**, 1701–1707 (1988).
212. The prevention of falls in later life. A report of the Kellogg International Work Group on the Prevention of Falls by the Elderly. *Dan. Med. Bull.* **34 Suppl 4**, 1–24 (1987).

213. Burns, E. R., Stevens, J. A. & Lee, R. The direct costs of fatal and non-fatal falls among older adults — United States. *J. Safety Res.* **58**, 99–103 (2016).
214. Ensrud, K. E. et al. Frailty Phenotype and Healthcare Costs and Utilization in Older Women. *J. Am. Geriatr. Soc.* **66**, 1276–1283 (2018).
215. Ensrud, K. E. et al. Frailty Phenotype and Healthcare Costs and Utilization in Older Men. *J. Am. Geriatr. Soc.* **68**, 2034–2042 (2020).
216. Fan, L. et al. Frailty Predicts Increased Health Care Utilization Among Community-Dwelling Older Adults: A Longitudinal Study in China. *J. Am. Med. Dir. Assoc.* **22**, 1819–1824 (2021).
217. Selassie, A. W. et al. Incidence of Long-term Disability Following Traumatic Brain Injury Hospitalization, United States, 2003: *J. Head Trauma Rehabil.* **23**, 123–131 (2008).
218. Andelic, N. et al. Disability and quality of life 20 years after traumatic brain injury. *Brain Behav.* **8**, (2018).
219. Whitnall, L. Disability in young people and adults after head injury: 5-7 year follow up of a prospective cohort study. *J. Neurol. Neurosurg. Psychiatry* **77**, 640–645 (2006).
220. Hammond, F. M. et al. Five years after traumatic brain injury: A study of individual outcomes and predictors of change in function. *NeuroRehabilitation* **19**, 25–35 (2004).
221. Kirshenbom, D., Ben-Zaken, Z., Albilya, N., Niyibizi, E. & Bala, M. Older Age, Comorbid Illnesses, and Injury Severity Affect Immediate Outcome in Elderly Trauma Patients. *J. Emerg. Trauma Shock* **10**, 146–150 (2017).
222. Hollis, S., Lecky, F., Yates, D. W. & Woodford, M. The effect of pre-existing medical conditions and age on mortality after injury. *J. Trauma* **61**, 1255–1260 (2006).

223. Niven, D. J., Kirkpatrick, A. W., Ball, C. G. & Laupland, K. B. Effect of comorbid illness on the long-term outcome of adults suffering major traumatic injury: a population-based cohort study. *Am. J. Surg.* **204**, 151–156 (2012).
224. McGwin, G., MacLennan, P. A., Fife, J. B., Davis, G. G. & Rue, L. W. Preexisting conditions and mortality in older trauma patients. *J. Trauma* **56**, 1291–1296 (2004).
225. GIOFFRÈ-FLORIO, M., MURABITO, L. M., VISALLI, C., PERGOLIZZI, F. P. & FAMÀ, F. Trauma in elderly patients: a study of prevalence, comorbidities and gender differences. *Il G. Chir.* **39**, 35–40 (2018).
226. Perdue, P. W., Watts, D. D., Kaufmann, C. R. & Trask, A. L. Differences in mortality between elderly and younger adult trauma patients: geriatric status increases risk of delayed death. *J. Trauma* **45**, 805–810 (1998).
227. Jacobs, D. G. Special considerations in geriatric injury. *Curr. Opin. Crit. Care* **9**, 535–539 (2003).
228. Schoeneberg, C. et al. Mortality in severely injured elderly patients: a retrospective analysis of a German level 1 trauma center (2002-2011). *Scand. J. Trauma Resusc. Emerg. Med.* **22**, 45 (2014).
229. Dahlhamer, J. et al. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *Morb. Mortal. Wkly. Rep.* **67**, 1001–1006 (2018).
230. Zelaya, C. E. Chronic Pain and High-impact Chronic Pain Among U.S. Adults, 2019. *8* (2020).
231. Bicket, M. C. & Mao, J. Chronic Pain in Older Adults. *Anesthesiol. Clin.* **33**, 577–590 (2015).

232. Lix, L. M. et al. Comparing administrative and survey data for ascertaining cases of irritable bowel syndrome: a population-based investigation. *BMC Health Serv. Res.* **10**, 31 (2010).
233. Hains, L. E. et al. Pain intensity and duration can be enhanced by prior challenge: initial evidence suggestive of a role of microglial priming. *J. Pain* **11**, 1004–1014 (2010).
234. Kontos, A. P. et al. Preliminary evidence of reduced brain network activation in patients with post-traumatic migraine following concussion. *Brain Imaging Behav.* **10**, 594–603 (2016).
235. Heyer, G. L., Young, J. A., Rose, S. C., McNally, K. A. & Fischer, A. N. Post-traumatic headaches correlate with migraine symptoms in youth with concussion. *Cephalalgia Int. J. Headache* **36**, 309–316 (2016).
236. Bree, D. & Levy, D. Development of CGRP-dependent pain and headache related behaviours in a rat model of concussion: Implications for mechanisms of post-traumatic headache. *Cephalalgia Int. J. Headache* **38**, 246–258 (2018).
237. Salberg, S., Sgro, M., Brady, R. D., Noel, M. & Mychasiuk, R. The Development of Adolescent Chronic Pain following Traumatic Brain Injury and Surgery: The Role of Diet and Early Life Stress. *Dev. Neurosci.* **42**, 2–11 (2020).
238. Rivara, F. P. et al. Prevalence of Pain in Patients 1 Year After Major Trauma. *Arch. Surg.* **143**, 282–287 (2008).
239. Friesgaard, K. D. et al. Persistent pain is common 1 year after ankle and wrist fracture surgery: a register-based questionnaire study. *Br. J. Anaesth.* **116**, 655–661 (2016).
240. Trajectories of Insomnia in Adults After Traumatic Brain Injury | Traumatic Brain Injury | JAMA Network Open | JAMA Network.
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2788444>.
241. Viola-Saltzman, M. & Watson, N. F. Traumatic Brain Injury and Sleep Disorders. *Neurol. Clin.* **30**, 1299–1312 (2012).

242. Sinha, S. S. Trauma-induced insomnia: A novel model for trauma and sleep research. *Sleep Med. Rev.* **25**, 74–83 (2016).
243. Germain, A., McKeon, A. B. & Campbell, R. L. Sleep in PTSD: Conceptual model and novel directions in brain-based research and interventions. *Curr. Opin. Psychol.* **14**, 84–89 (2017).
244. Germain, A., Buysse, D. J. & Nofzinger, E. Sleep-specific mechanisms underlying posttraumatic stress disorder: Integrative review and neurobiological hypotheses. *Sleep Med. Rev.* **12**, 185–195 (2008).
245. Williams, L. M. et al. Trauma modulates amygdala and medial prefrontal responses to consciously attended fear. *NeuroImage* **29**, 347–357 (2006).
246. Pare, D., Quirk, G. J. & Ledoux, J. New Vistas on Amygdala Networks in Conditioned Fear. <https://journals.physiology.org/doi/epdf/10.1152/jn.00153.2004> (2004) doi:10.1152/jn.00153.2004.
247. Ancoli-Israel, S. Sleep and its disorders in aging populations. *Sleep Med.* **10 Suppl 1**, S7-11 (2009).
248. Roth, T. et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. *Biol. Psychiatry* **69**, 592–600 (2011).
249. Scaf-Klomp, W., van Sonderen, E., Sanderman, R., Ormel, J. & Kempen, G. I. Recovery of physical function after limb injuries in independent older people living at home. *Age Ageing* **30**, 213–219 (2001).
250. Tinetti, M. E. & Williams, C. S. The effect of falls and fall injuries on functioning in community-dwelling older persons. *J. Gerontol. A. Biol. Sci. Med. Sci.* **53**, M112-119 (1998).

251. Magaziner, J., Simonsick, E. M., Kashner, T. M., Hebel, J. R. & Kenzora, J. E. Predictors of functional recovery one year following hospital discharge for hip fracture: a prospective study. *J. Gerontol.* **45**, M101-107 (1990).
252. Mossey, J. M., Mutran, E., Knott, K. & Craik, R. Determinants of recovery 12 months after hip fracture: the importance of psychosocial factors. *Am. J. Public Health* **79**, 279–286 (1989).
253. Lyness, J. M., King, D. A., Cox, C., Yoediono, Z. & Caine, E. D. The importance of subsyndromal depression in older primary care patients: prevalence and associated functional disability. *J. Am. Geriatr. Soc.* **47**, 647–652 (1999).
254. Lenze, E. J. et al. The association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. *Am. J. Geriatr. Psychiatry Off. J. Am. Assoc. Geriatr. Psychiatry* **9**, 113–135 (2001).
255. Testa, J. A., Malec, J. F., Moessner, A. M. & Brown, A. W. Predicting Family Functioning After TBI: Impact of Neurobehavioral Factors. *J. Head Trauma Rehabil.* **21**, 236–247 (2006).
256. Malec, J. F., Testa, J. A., Rush, B. K., Brown, A. W. & Moessner, A. M. Self-assessment of impairment, impaired self-awareness, and depression after traumatic brain injury. *J. Head Trauma Rehabil.* **22**, 156–166 (2007).
257. Hanks, R. A., Temkin, N., Machamer, J. & Dikmen, S. S. Emotional and behavioral adjustment after traumatic brain injury. *Arch. Phys. Med. Rehabil.* **80**, 991–997 (1999).
258. Dahm, J. & Ponsford, J. Comparison of long-term outcomes following traumatic injury: What is the unique experience for those with brain injury compared with orthopaedic injury? *Injury* **46**, 142–149 (2015).
259. Ehlers, A. & Clark, D. M. A cognitive model of posttraumatic stress disorder. *Behav. Res. Ther.* **38**, 319–345 (2000).

260. Bryant, R. A. Disentangling Mild Traumatic Brain Injury and Stress Reactions. *N. Engl. J. Med.* **358**, 525–527 (2008).
261. Ghinassi, C. Anxiety. ABC-CLIO <https://www.abc-clio.com/products/b1494c/>.
262. Butcher, J. L. et al. Long-term outcomes after lower extremity trauma. *J. Trauma* **41**, 4–9 (1996).
263. Gabbe, B. J. et al. Association between the Number of Injuries Sustained and 12-Month Disability Outcomes: Evidence from the Injury-VIBES Study. *PLOS ONE* **9**, e113467 (2014).
264. Malenka, D. J., McLerran, D., Roos, N., Fisher, E. S. & Wennberg, J. E. Using administrative data to describe casemix: a comparison with the medical record. *J. Clin. Epidemiol.* **47**, 1027–1032 (1994).
265. Kieszak, S. M., Flanders, W. D., Kosinski, A. S., Shipp, C. C. & Karp, H. A comparison of the Charlson comorbidity index derived from medical record data and administrative billing data. *J. Clin. Epidemiol.* **52**, 137–142 (1999).
266. Hawker, G. A., Coyte, P. C., Wright, J. G., Paul, J. E. & Bombardier, C. Accuracy of administrative data for assessing outcomes after knee replacement surgery. *J. Clin. Epidemiol.* **50**, 265–273 (1997).
267. van Doorn, C. et al. Risk adjustment for older hospitalized persons: a comparison of two methods of data collection for the Charlson index. *J. Clin. Epidemiol.* **54**, 694–701 (2001).
268. Morabia, A. Poppers, Kaposi’s sarcoma, and HIV infection: empirical example of a strong confounding effect? *Prev. Med.* **24**, 90–95 (1995).
269. Khaw, K.-T., Day, N., Bingham, S. & Wareham, N. Observational versus randomised trial evidence. *Lancet Lond. Engl.* **364**, 753–754; author reply 754-755 (2004).

270. Maxwell, C. J. et al. Variation in the health outcomes associated with frailty among home care clients: relevance of caregiver distress and client sex. *BMC Geriatr.* **18**, 211 (2018).
271. Nemoto, Y. et al. Bidirectional relationship between insomnia and frailty in older adults: A 2-year longitudinal study. *Arch. Gerontol. Geriatr.* **97**, 104519 (2021).
272. Kawada, T. Associations between symptoms of pain, insomnia and depression, and frailty in older adults: Comment on Liu et al. (2021). *Int. J. Nurs. Stud.* **123**, 104068 (2021).
273. Fan, J. et al. Association of insomnia and multidimensional frailty in community-dwelling older adults: A cross-sectional survey. *J. Clin. Nurs.* **31**, 167–173 (2022).
274. Morone, N. E. et al. Impact of chronic musculoskeletal pathology on older adults: a study of differences between knee OA and low back pain. *Pain Med. Malden Mass* **10**, 693–701 (2009).
275. Ling, S. M. et al. Knee osteoarthritis compromises early mobility function: The Women’s Health and Aging Study II. *J. Rheumatol.* **30**, 114–120 (2003).
276. Cecchi, F. et al. Measures of physical performance capture the excess disability associated with hip pain or knee pain in older persons. *J. Gerontol. A. Biol. Sci. Med. Sci.* **64**, 1316–1324 (2009).
277. Kovacs, F. et al. The influence of psychological factors on low back pain-related disability in community dwelling older persons. *Pain Med. Malden Mass* **9**, 871–880 (2008).
278. Thapa, S., Shmerling, R. H., Bean, J. F., Cai, Y. & Leveille, S. G. Chronic multisite pain: evaluation of a new geriatric syndrome. *Aging Clin. Exp. Res.* **31**, 1129–1137 (2019).
279. Cruz-Almeida, Y. et al. Associations of Musculoskeletal Pain With Mobility in Older Adults: Potential Cerebral Mechanisms. *J. Gerontol. Ser. A* **72**, 1270–1276 (2017).

280. Coyle, P. C., Schrack, J. A. & Hicks, G. E. Pain Energy Model of Mobility Limitation in the Older Adult. *Pain Med. Malden Mass* **19**, 1559–1569 (2018).
281. Stubbs, B., Schofield, P. & Patchay, S. Mobility Limitations and Fall-Related Factors Contribute to the Reduced Health-Related Quality of Life in Older Adults With Chronic Musculoskeletal Pain. *Pain Pract. Off. J. World Inst. Pain* **16**, 80–89 (2016).
282. Megale, R. Z. et al. Association between pain and the frailty phenotype in older men: longitudinal results from the Concord Health and Ageing in Men Project (CHAMP). *Age Ageing* **47**, 381–387 (2018).
283. Domenichiello, A. F. & Ramsden, C. E. The silent epidemic of chronic pain in older adults. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **93**, 284–290 (2019).
284. Blyth, F. M. & Noguchi, N. Chronic musculoskeletal pain and its impact on older people. *Best Pract. Res. Clin. Rheumatol.* **31**, 160–168 (2017).
285. Lohman, M. C., Whiteman, K. L., Greenberg, R. L. & Bruce, M. L. Incorporating Persistent Pain in Phenotypic Frailty Measurement and Prediction of Adverse Health Outcomes. *J. Gerontol. A. Biol. Sci. Med. Sci.* **72**, 216–222 (2017).
286. Coelho, T., Paúl, C., Gobbens, R. J. J. & Fernandes, L. Multidimensional Frailty and Pain in Community Dwelling Elderly. *Pain Med. Malden Mass* **18**, 693–701 (2017).
287. Hirase, T. et al. Impact of frailty on chronic pain, activities of daily living and physical activity in community-dwelling older adults: A cross-sectional study. *Geriatr. Gerontol. Int.* **18**, 1079–1084 (2018).
288. Livshits, G. et al. Shared genetic influence on frailty and chronic widespread pain: a study from TwinsUK. *Age Ageing* **47**, 119–125 (2018).

289. Nakai, Y. et al. Association between Chronic Pain and Physical Frailty in Community-Dwelling Older Adults. *Int. J. Environ. Res. Public. Health* **16**, 1330 (2019).
290. O'Brien, M. S. & McDougall, J. J. Age and frailty as risk factors for the development of osteoarthritis. *Mech. Ageing Dev.* **180**, 21–28 (2019).
291. Otones Reyes, P., García Perea, E. & Pedraz Marcos, A. Chronic Pain and Frailty in Community-Dwelling Older Adults: A Systematic Review. *Pain Manag. Nurs. Off. J. Am. Soc. Pain Manag. Nurses* **20**, 309–315 (2019).
292. Tse, M. M. Y., Lai, C., Lui, J. Y. W., Kwong, E. & Yeung, S. Y. Frailty, pain and psychological variables among older adults living in Hong Kong nursing homes: can we do better to address multimorbidities? *J. Psychiatr. Ment. Health Nurs.* **23**, 303–311 (2016).
293. Guerriero, F. & Reid, M. C. Linking Persistent Pain and Frailty in Older Adults. *Pain Med.* **21**, 61–66 (2020).
294. Chen, C., Winterstein, A. G., Fillingim, R. B. & Wei, Y.-J. Body weight, frailty, and chronic pain in older adults: a cross-sectional study. *BMC Geriatr.* **19**, 143 (2019).
295. Rodríguez-Sánchez, I. et al. Frequency, intensity and localization of pain as risk factors for frailty in older adults. *Age Ageing* **48**, 74–80 (2019).
296. Saraiva, M. D. et al. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. *Age Ageing* **47**, 785–793 (2018).
297. Kalmbach, D. A. et al. Poor sleep is linked to impeded recovery from traumatic brain injury. *Sleep* **41**, zsy147 (2018).