Assessing the Role of Depression in Dementia Risk Among Patients with a Traumatic Brain Injury

By

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Dedication

This thesis is dedicated to my parents, who traveled thousands of miles and sacrificed all they could to ensure my siblings and I had better opportunities than they did. I hope we fulfilled the dreams you gave for us.

To my mom, Ignatia Su, your compassion, hard work, and persistence in the face of all challenges is reflected in the accomplishments of your children. You're a certified girl boss and the world's greatest mom.

To my dad, Peter Ashby, who passed before I started my graduate program, thank you for everything, you were the best dad a girl could dream of. I wouldn't the person I am without your patient and loving guidance. I love and miss you endlessly.

Abstract

Nearly 3 million Americans sustain a traumatic brain injury (TBI) annually and 5.3 million are currently living with a TBI-related disability, with depression being the most prevalent consequence.[1] While past studies linked TBI and dementia risk and depression and dementia risk, this is the first study that we know of that investigates the association between depression and dementia post-TBI in a non-military cohort. The objectives of this study are to characterize the incidence of depression and dementia post-TBI in a cohort representative of the U.S., to assess the role of depression in the risk of developing dementia, and to assess the timing of depression post-TBI to dementia to determine if depression is a consequence of a TBI or a prodromal symptom of dementia. This retrospective cohort is comprised of over 55,000 patients diagnosed with a TBI via International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) in Merative Marketscan from January 1, 2000 to December 31, 2019. Dementia diagnosis, medical, and psychiatric comorbidities were identified via ICD-9 and ICD-10 codes. Depression diagnosis was defined via ICD-9 and ICD-10 coding as well as the prescription of common antidepressants. Of those participants, 30737 (56%) individuals were diagnosed with depression post-TBI and 8493 (15%) developed dementia. The adjusted hazard ratio for dementia was 3.021 (95% CI 2.857-3.185) for depressed individuals. In this cohort, depression diagnosis was associated with over a 3-fold increase in the risk of dementia diagnosis. The median (IQR) time from incident TBI to depression diagnosis was 8.86 (1.86-60.86) weeks, while time from depression diagnosis to dementia was 121.5 (65.43 -211.29) weeks, showing that depression is a consequence of TBI rather than a prodrome of dementia. Future research on timing, mechanisms, and treatment of TBI-related depression and dementia is needed.

Assessing the Role of Depression in Dementia Risk among Patients with a Traumatic Brain Injury

Introduction:

Nearly 3 million Americans sustain a traumatic brain injury (TBI) annually and 5.3 million are currently living with a TBI-related disability.[1,2] Over one-third of civilians in the U.S. are living with a TBI and prevalence is higher amongst military personnel and veterans.[3] Older adults are at a higher risk for poor functional and neurological outcomes post-TBI.[4,5] TBIs are a known risk factor for dementia, with past research showing that as TBI severity increases, the risk for dementia also increases.[1,6] Other long term consequences of TBIs vary from physical impairment and neurobehavioral symptoms such as insomnia, chronic pain, and memory loss, however, depression is the most commonly reported disorder post-TBI and is associated with poorer outcomes post-TBI.[7,8] Past research in the U.S. centers around veterans and suggests that TBIs and co-occurring depression may lead to higher dementia incidence.[8–10] However, the cause of TBI in veterans is often from IEDs or gunshot wounds and veterans also have higher rates of PTSD, MDD, and physical and psychiatric disabilities as compared to the general population of the U.S.[8–10] Despite TBI being one of the leading causes of disability among both civilians and veterans, few studies have examined the relationship of depression and dementia post-TBI in civilians alone.

Previous studies report the incidence of depression post-TBI ranging anywhere from 13% to 75%.[11,12] Depression post-TBI is associated with prior psychiatric history, alcohol abuse, increasing TBI severity, female gender, and nonwhite ethnicity.[11,13,14] While the timing of depression post-TBI is still debated, studies generally agree that the majority of individuals are diagnosed with depression within 3 months post-TBI and

there is a decrease in depression prevalence over time.[15] The variation in incidence and timing is a result of differences between the studies in terms of how depression is diagnosed, the sample population, the severity of TBI and depression, and time between incident TBI and incident depression. Post-TBI depression is typically treated via pharmacological interventions like antidepressants and psychological interventions like cognitive behavioral therapy. However, there is insufficient evidence to form conclusions on the long term effectiveness of these treatments.[16,17] As both TBI and depression are associated with an elevated dementia risk, it is vital to disentangle the relationship between the two to understand mechanisms for dementia risk, timing of dementia, and the impact of depression treatment on dementia outcomes post-TBI. The relationship between depression and dementia is still highly debated between depression being a risk factor for dementia, a prodromal symptom of dementia, or depression and dementia occurring coincidentally.[14,16,18] The association of the timing of depression diagnosis and dementia is also highly debated. There is growing evidence that early life depression may be a risk factor for dementia, while later life depression is a prodromal symptom of dementia.[18] Dementia risk is elevated in older individuals with structural brain changes and co-occurring depression.[12] As a result, it can be hypothesized that an adult with a TBI and depression may be at an increased risk for dementia. However, this has yet to be studied in a large diverse cohort of civilians.[19] TBI and depression also share similar changes in white matter disease and the formation of Aβ-plaques, which are thought to increase cognitive impairment and risk for dementia.[19,20] As a result, it can be hypothesized that an adult with a TBI and depression may be at an increased risk for dementia. However, this has yet to be

studied in a large diverse cohort of civilians.[19] Further evidence on the timing of depression and dementia, neurobiological pathways from depression to dementia, and the impact of depression post-TBI is essential to provide recommendations on surveillance, diagnosis, and treatment of depression post-TBI to lower dementia risk. The primary aim of this study is to characterize the incidence of depression and dementia after a TBI in a large, civilian cohort representative of the U.S. population and to assess the role of depression in the risk of developing dementia. The secondary aim of this study is to assess the timing of depression post-TBI to dementia to determine if depression is a consequence of a TBI or a prodromal symptom of dementia. We hypothesized that depression would result in an increased risk of developing dementia following a TBI in a US civilian cohort and that depression is more likely to be a consequence of a TBI.

Methods:

For this retrospective cohort study, we extracted adults, 55 years or older, hospitalized with traumatic brain injury (TBI) and discharged alive from January 1, 2000, and December 31, 2019 from a large claims database. To ensure only incident cases of dementia were included, patients who did not have 1 year of continuous enrollment prior and following the TBI were excluded. To reduce the chance of reverse-causality or post-concussive syndrome medication induced delirium, patients who had a dementia diagnosis within 1 year of a TBI diagnosis were excluded.[21] Individuals who were diagnosed with depression prior to their incident TBI were excluded as this study is focused on post-TBI depression. Dementia diagnosis had to also have a wash out period of one year and all participants had to have continuous enrollment during the

study period. Analysis was conducted on 55,149 patients, 24412 did not have depression, while 30737 had depression.

Data used in this study were extracted from the Merative MarketScan Research Database, Commercial Claims and Encounters and the Medicare Supplemental and Medicaid Databases 2000-2019. These data represent the health services of enrollees including inpatient stays, outpatient visits, medical services, and refill prescribed medication. Over 25 million individuals with neurological conditions nationwide are represented in this 19-year study period. Each individual has a unique identifier which is used to track longitudinal trajectories. Included variables are demographics, medical conditions and treatments tracked with diagnostic and procedure codes (International Classification of Diseases, 9th and 10th Revisions, Clinical Modification [ICD-9-CM prior to October 2015, ICD-10 after October 2015], Current Procedural Terminology, 4th edition [CPT-4]), and other variables. The MarketScan Databases have been used extensively in the medical field since 1990.

TBI was defined using ICD-9-CM and ICD-10-CM guidelines respectively.[5] **(Supplemental: Table 1)**. Patients were classified into 3 severity levels of TBI (mild, moderate, and severe) as defined by the Barrell Matrix and Injury Diagnostic Matrix.[1] The first hospitalization for TBI was considered the beginning of follow-up. Depression was defined by ICD coding, the prescription of common antidepressants, or the combination of both coding and prescription **(Supplemental: Table 2)**. Those who were defined as depressed via ICD coding alone are referred to as depressed via diagnosis and those who were defined as depressed via prescription of antidepressants are

referred to as depressed via treatment in this study. Individuals who were diagnosed with depression prior to TBI were excluded.

Dementia diagnosis was captured from inpatient or outpatient visits with a “wash out” period of one year. Inpatient and outpatient claims of included individuals were screened in the years 2-5 after TBI hospitalization for dementia using ICD-9 codes. Upon the incident TBI hospitalization, demographics including age and sex, trauma characteristics, medical and psychiatric comorbidities, and insurance type was collected. The burden of comorbidities was accounted for by the Elixhauser score[8] using Quan et al. adaptation to ICD-9 and ICD-10 codes present in the TBI hospitalization. Noteworthy psychiatric comorbidities (bipolar disorder, schizophrenia, alcohol disorder, and drug abuse) and other medical comorbidities (hypertension, hyperlipidemia, diabetes, coronary artery disease, and cerebrovascular disease) were also flagged and captured via ICD-9 and ICD-10.

All statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA). All individuals had continuous enrollment in the study, meaning all participants were followed for the entire time period of the study. If participants died during the length of the study, they were censored from time of death. Cumulative incidence of dementia by age and depression diagnosis was calculated, in the presence of death as a competing risk. This approach has been taken by previous studies, however, future estimates of cumulative incidence of dementia by depression diagnosis will be estimated using the Practical Incidence Estimator macro to adjust for the competing risk of death. Unadjusted and adjusted Cox proportional hazards models were used to evaluate associations between depression and dementia risk. Age was assumed as the time

scale in all Cox regression analyses. Adjusted hazard ratios (aHRs) and 95% CIs for dementia risk were calculated. Models were adjusted in steps for (1) demographics; (2) demographics, medical and psychiatric comorbidities, and (3) TBI severity. Multicollinearity and other Cox proportional hazard assumptions were checked at each step. Models were fit by adding each group of variables at each step of the model. Stratified analysis by TBI severity was run for Cox regression analysis of dementia risk by TBI severity and depression status. In this regression, those with mild, moderate, and severe TBI with depression are compared to those without depression with the same TBI severity, rather than the general cohort of non-depressed. The significance level was set to 0.05 and all tests were 2-sided.

Results:

The final cohort was composed of 55149 individuals who had experienced at least 1 TBI **(Appendix: Table 1)**. 30737 (56%) individuals were diagnosed with depression post-TBI and 8493 (15%) developed dementia. The severity of TBIs in the cohort varied; 11567 (21%) had a mild TBI, 29352 (53%) experienced a moderate TBI, and 14230 (26%) experienced a severe TBI. Sex was well distributed in the cohort. 21579 (39%) of the cohort was between the ages of 55-64, followed by 14197 (26%) ages 75-84, 11781 (21%) 65-74, and 7592 (14%) 85 and older. A total of 16079 (29%) individuals had commercial insurance, 9726 (18%) had Medicaid, while 29344 (53%) had Medicare insurance. 22566 (41%) of the cohort had hypertension; 8457 (15%) had diabetes; 6116 (11%) had hyperlipidemia; and 2359 (4%) suffered from alcohol abuse.

7081 participants (23%) were defined as depressed via ICD coding; 9168 (30%) via the prescription of common antidepressants; and 14488 (47%) via ICD coding and

prescription of common antidepressants. Of those with depression, 6404 (21%) had a mild TBI; 16606 (54%) moderate; and 7727 (25%) severe. TBI severity remains consistent across the different coding of depression. There were more females (55%) among the depressed and age characteristics are similar to the general cohort. A total of 8188 (27%) individuals had commercial insurance, 6374 (21%) had Medicaid, while 16175 (53%) had Medicare insurance. 12339 (40%) of the depressed cohort were diagnosed with hypertension; 4862 (16%) diabetes; 3219 (10%) hyperlipidemia; and 1569 (5%) alcohol abuse.

Of the 8497 individuals who developed dementia, 6,771 (80%) were diagnosed with depression, while 1,726 (20%) did not have a depression diagnosis. After adjusting for age, demographics, trauma characteristics, medical comorbidities, and psychiatric comorbidities, the adjusted hazard ratio (aHR) for dementia was 3.021 (95% CI 2.857-3.185) for those with a depression through a diagnosis or treatment; the risk of dementia for those with depression via a diagnosis had a hazard of 2.577 (95% CI, 2.387-2.778); the risk of dementia for those with depression via treatment had a hazard of 2.326 (95% CI, 2.169-2.488); the risk of dementia for those with depression through diagnosis and treatment was 3.704 (95% CI, 3.497- 3.922) **(Appendix: Table 2)**. The cumulative incidence of dementia based on age at TBI diagnosis increased significantly with the presence of a depression diagnosis **(Appendix: Figure 2)**. Among individuals with depression, either through diagnosis, treatment, or both diagnosis and treatment, median (IQR) time from incident TBI to depression diagnosis was 8.86 (1.86-60.86) weeks, while time from depression diagnosis to dementia was 121.5 (65.43 -211.29) weeks.

This study further investigated the association of TBI severity on dementia risk among those with depression. Those with depression and a mild, moderate, or severe TBI were compared to individuals without depression with the same severity of TBI, rather than the whole cohort of nondepressed. After adjusting for age, demographics, trauma characteristics, medical comorbidities, and psychiatric comorbidities, the adjusted hazard ratio (aHR) for dementia was 3.021 (95% CI 2.857-3.185) for all individuals with depression via diagnosis, treatment, or both; 3.344 (95% CI, 2.924-3.817) for mild TBI with depression; 2.825 (95% CI, 2.646-3.021) for moderate TBI with depression; and 3.390 (95% CI, 3.003-3.831) for severe TBI with depression (**Appendix: Table 3**). The cumulative incidence of dementia based on age at TBI diagnosis increased greatly with depression diagnosis and by increasing TBI severity **(Appendix: Figure 2)**.

Discussion:

In a retrospective cohort of over 55000 participants with a TBI, depression is associated with increased dementia risk and is a consequence of a TBI, rather than a prodromal symptom of dementia. Individuals with depression were associated with a 3.02-fold increased risk in dementia after adjusting for demographics, trauma characteristics, medical comorbidities, and psychiatric comorbidities. The median time from TBI to depression was approximately 9 weeks while median time to dementia from depression was 122 weeks, which leads us to conclude that depression is a result of a TBI, rather than a prodrome of dementia. To our knowledge, this study is the first of its kind to study a large civilian cohort of diverse individuals with a traumatic brain injury in the United States to disentangle associations between depression and dementia post-TBI and to investigate if depression is a consequence of TBI or a prodromal symptom of dementia.

Prior to adjustment, those with depression post-TBI have 3.12 times the risk for dementia as compared to individuals without depression. This risk remains even after adjusting for age, demographics, medical and psychiatric comorbidities, and TBI severity (aHR: 3.021, 95% CI: 2.857-3.185). These results fall in the range of other longitudinal cohort studies that examined depression and dementia risk, which found that depression was associated with a 2 to 4-fold increase in dementia risk.[11,14,16,19] However, a majority of these studies looked at veteran and active military populations and did not factor for the influence of an initial TBI. Compared to individuals who were not depressed, those who were depressed based on diagnosis alone had 2.58 (95% CI: 2.39-2.78) increased risk of dementia, those who were depressed via treatment alone had a 2.33 (95% CI: 2.17-2.49) increased risk of dementia, and those were depressed via both diagnosis and treatment had a 3.70 (95% CI, 3.50- 3.92) increased risk of dementia.

Those who were depressed using both diagnosis and treatment may have a more severe form of depression like major depressive disorder as compared to those who are just coded as depressed or given antidepressants.[16,17] If this is the case, our results suggest those with more severe depression are at the highest risk for dementia among the depressed. Past reviews and meta-analysis vary on results of how antidepressants impact depression severity post-TBI, which is most likely due to variation in depression definition and measurement, as well as the type of studies included and excluded in the meta-analysis; however, generally, studies agree that antidepressants reduce depressive symptoms.[17,26–29] The connection between antidepressants and dementia is less well known, with some studies suggesting long term antidepressant use may

increase types of dementia, while others suggest that early antidepressant use decreases risk of dementia.[16,30–33] Given the lack of standard treatment of depression post-TBI and the extremely high rates of depression post-TBI, these results are critically vital to increase surveillance of patients with severe depression post-TBI to study pathways from depression to dementia and to examine potential treatment methods to lower dementia incidence.[27,28] Recent research shows that TBIs accelerate the formation of amyloid (Aβ) plaques and white matter disease that are found in dementia pathologies and severe depression is known to injure neurons and increase amyloid deposition.[19,20,22–25] These mechanisms suggest that TBI and severe depression share similar disease pathways that accelerate dementia development.[20,25]

We also found that TBI severity plays a role in dementia risk in those who were depressed. Among those who were depressed, dementia risk increased by 3.34 times (95% CI, 2.92-3.82) for those with a mild TBI, 2.82 times (95% CI: 2.65-3.02) for a moderate TBI, and 3.39 times (95% CI, 3.00-3.83) for a severe TBI as compared to non-depressed individuals with the same severity of TBI. After adjusting for age, demographics, and medical and psychiatric comorbidities, these risks still remain. Those with a mild or severe TBI had the highest risk for dementia, followed moderate TBI. Severe TBIs having a higher risk for dementia as compared to moderate TBIs is supported by past studies, while the impact of mild TBIs is still debated.[8,11,34–37] Those with moderate TBI and depression consistently had the highest cumulative incidence of dementia, followed by severe TBI and depression, and mild TBI and depression. Among the non-depressed, those with a moderate TBI had the highest incidence of dementia as compared to severe and mild, however, the difference in incidence

between severity groups is less than 0.1. For the non-depressed who are 80 or older, the severity of TBI does not seem to affect dementia outcome for people with mild or severe TBIs. Furthermore, for individuals who are 95 or older with a mild TBI, the incidence of dementia is the same, independent of a depression diagnosis. This finding is critically important in building evidence for the association between mild TBIs and dementia as mild TBIs are the most common type of TBI.[8,38] A past study found similar results of mild TBI association with dementia risk.[8,38]

Understanding the timing of depression onset following a TBI and the timing of dementia following a depression diagnosis is essential to disentangle its role as either a consequence of a TBI or a prodrome symptom of dementia.[16,32] The median (IQR) time from incident TBI to depression diagnosis was 8.86 (1.86-60.86) weeks, while time from depression diagnosis to dementia was 121.5 (65.43 -211.29) weeks. As the timing from depression to TBI is much closer than that of depression to dementia, depression appears to be a consequence of TBI and not a prodrome symptom of dementia in this cohort. Past studies that focus solely on depression and dementia support the idea depression is a risk factor of dementia, however, conclusions on early life depression as compared to late life depression and dementia risk are less conclusive.[8,16,32,39–42] Unfortunately, research on the association of depression and dementia post-TBI and particularly the timing of depression and dementia is minimal and thus this finding is critically important.

This study has several strengths which include the cohort size and an understudied population. To our knowledge, this study is one of the first studies that examines the association of depression and dementia post-TBI all in a single cohort of U.S. civilians.

There is a large cohort, which leads to higher statistical validity as we can adjust for several potential confounding factors and an increased power to see associations. Furthermore, the long follow-up period of 19 years allows the study to establish temporality between TBI, depression, and dementia and lower potential for reverse causality bias. The demographic characteristics of the cohort are well distributed and reflect similar characteristics as past literature. Because depression is known to be highly underdiagnosed in the U.S. population and misclassification bias may be prevalent in this cohort, several definitions of depression were utilized to allow for better coverage of the disease.

There are limitations that need to be considered while analyzing our results. As this is a retrospective study that uses electronic medical records via ICD-coding, it may not represent more common definitions of TBI such as the Glasgow Coma Scale. Furthermore, dementia subtype data was not available. Despite mild TBIs being the most common type of TBI, moderate TBIs made up a majority of the cohort as typically individuals with mild TBIs do not seek in patient or hospitalization care. As the first diagnosis of the TBI is dependent on hospitalization, there is a sampling bias in which moderate TBI's are overrepresented in our cohort. Furthermore, depression was not treated as a time dependent variable which may affect proportionality. Future studies on the timing of depression onset are essential to disentangle its role as either a driver of dementia or a consequence of dementia. Lastly, this cohort study focuses solely on individuals with a traumatic brain injury and does not have a controlled non-TBI population. This was done as the aims of this paper were to investigate the association and timing of depression on dementia post-TBI, however, this may entangle

relationships between TBI, depression, and dementia. Because of this, this study examined the relationship of timing to investigate if depression was more likely to be a consequence of a TBI or if it was an early symptom of dementia. Research investigating the biological rationale behind the association of TBI, depression, and dementia is vital in developing targeted treatment and mitigation roles.

In a large, retrospective cohort of over 55000 U.S. patients with a TBI, we found an increased risk of dementia amongst depressed individuals. This association remained over 3-fold even after adjusting for demographics, trauma characteristics, and medical and physical comorbidities. Depression is a consequence of TBI, rather than a prodromal symptom of dementia. Future research on timing, mechanisms, and treatment of TBI-related depression and dementia is needed.

Appendix

Table 1: Characteristics of 55149 Individuals With or Without Depression

Characteristic	***No Depression (n=24412)***	***Depression (n=30737)***
Dementia	1726 (7%)	6771 (22%)
Age		
55-64	9353 (38%)	12226 (40%)
65-74	5283 (22%)	6498 (21%)
75-84	6297 (26%)	7900 (26%)
85+	3479 (14%)	4113 (13%)
Gender		
Male	13862 (57%)	13946 (45%)
Female	10550 (43%)	16791 (55%)
Insurance		
Commercial	7891 (32%)	8188 (27%)
Medicaid	3352 (14%)	6374 (21%)
Medicare	13169 (54%)	16175 (53%)
TBI Severity		
Mild	5163 (21%)	6404 (21%)
Moderate	12746 (52%)	16606 (54%)
Severe	6503 (27%)	7727 (25%)
Medical Comorbidities		
Hypertension	10227 (42%)	12339 (40%)
Hyperlipidemia	2897 (12%)	3219 (10%)
Diabetes	3595 (15%)	4862 (16%)
Coronary Artery Disease	2091 (9%)	2566 (8%)
Cerebrovascular Disease	1928 (8%)	3028 (10%)
Psychiatric Comorbidity		
Bipolar Disorder	49 (0.2%)	523 (2%)
Schizophrenia	57 (0.2%)	350 (1%)
Alcohol Disorder	790 (3%)	1569 (5%)
Drug Abuse	236 (1%)	608 (2%)

Figure 1: Cumulative Incidence of Dementia With and Without Depression

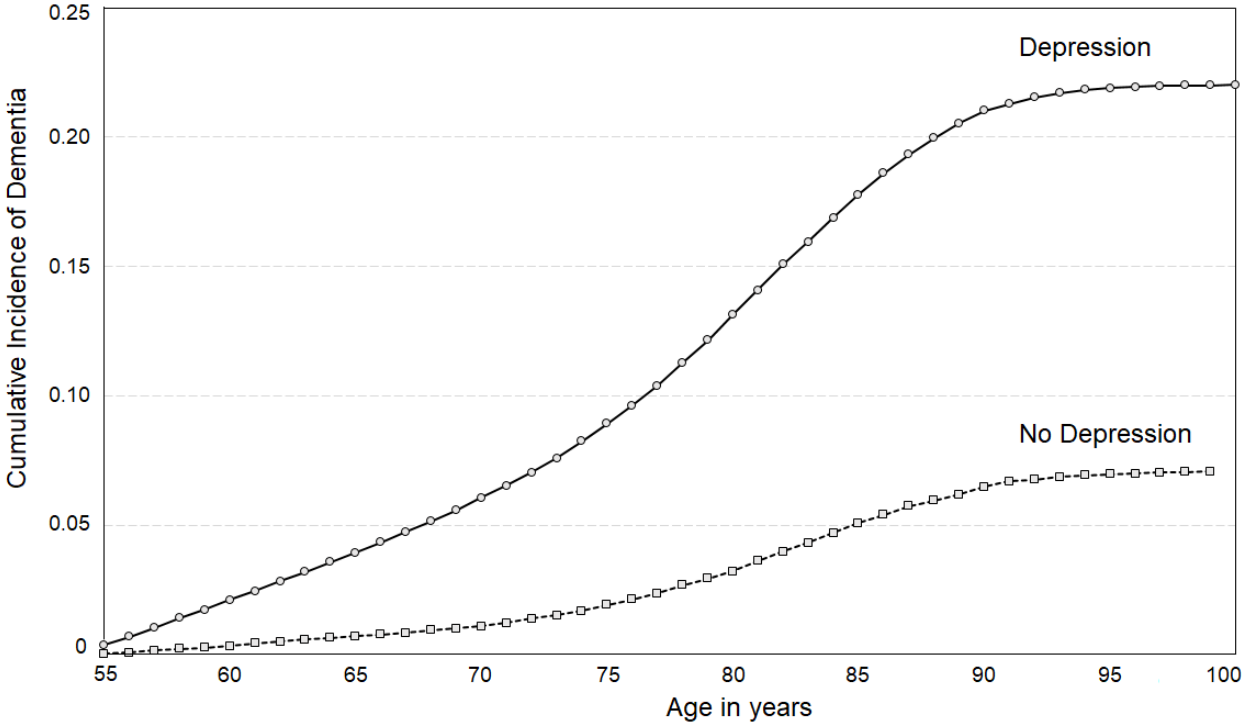

Table 2: Unadjusted and Adjusted Risk of Dementia by Depression Definition

Model	Individuals without Depression (n = 24412)	Depression by Diagnosis Type			
		All (n = 30737)	Diagnosis (n = 7081)	Treatment (n = 9168)	Diagnosis and Treatment (n = 14488)
Unadjusted[a]	1 [Reference]	3.115 (2.950, 3.279)	3.175 (2.959, 3.413)	2.222 (2.079, 2.381)	3.704 (3.509, 3.922)
1[b]	1 [Reference]	3.049 (2.890, 3.215)	2.632 (2.445, 2.841)	2.326 (2.174, 2.488)	3.745 (3.534, 3.968)
2[c]	1 [Reference]	3.021 (2.865, 3.185)	2.577 (2.387, 2.778)	2.331 (2.174, 2.494)	3.704 (3.484, 3.922)
3[d]	1 [Reference]	3.021 (2.857, 3.185)	2.577 (2.387, 2.778)	2.326 (2.169, 2.488)	3.704 (3.497, 3.922)

[a] All models use age as a time-scale
[b] Model 1 is adjusted for demographic characteristics (sex, insurance)
[c] Model 2 is adjusted for demographic characteristics, medical conditions, and psychiatric conditions (hypertension, hyperlipidemia, diabetes, coronary artery disease, cerebrovascular disease, bipolar disorder, schizophrenia, alcohol disorder, and drug abuse)
[d] Model 3 is adjusted for demographic characteristics, medical and psychiatric conditions, and TBI severity (mild, moderate, and severe)

Figure 2: Cumulative Incidence of Dementia With and Without Depression by TBI Severity

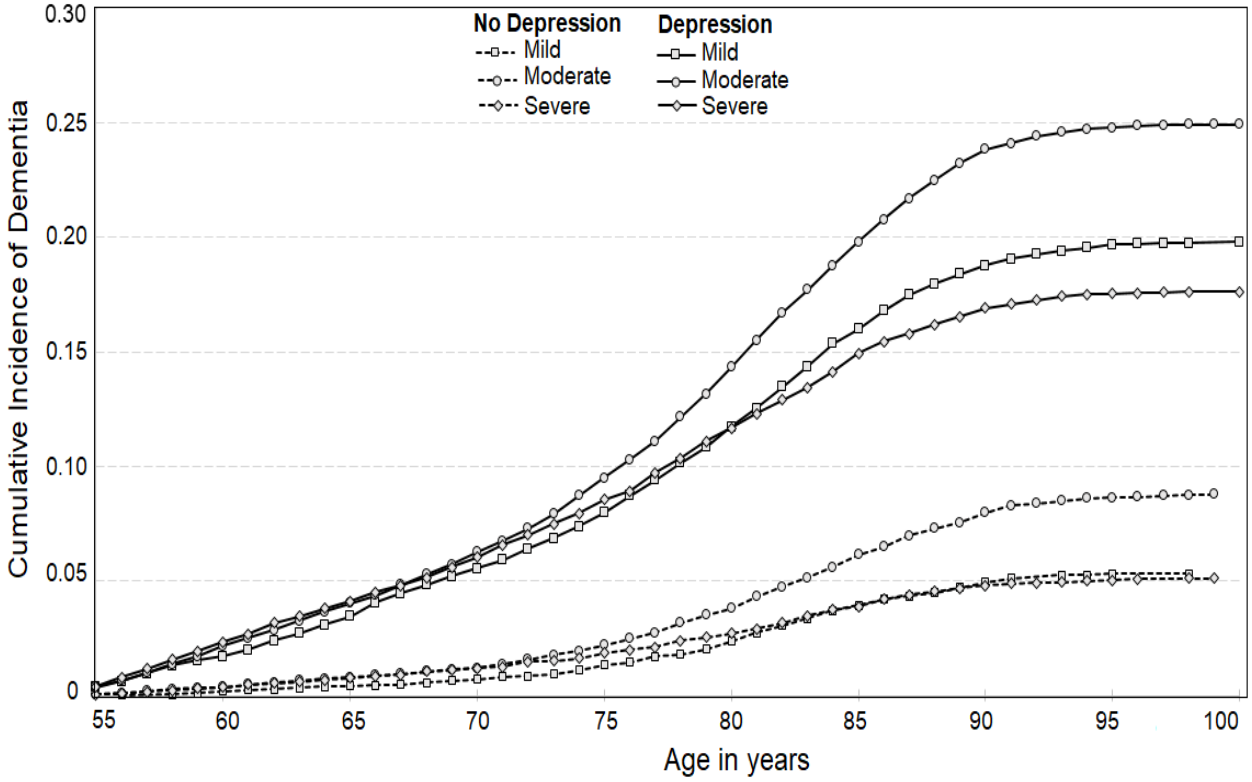

Table 3: Unadjusted and Adjusted Risk of Dementia by Depression and TBI Severity

Model	Individuals without Depression [a]	Depression by TBI Severity Type			
		All TBI Severity	Mild	Moderate	Severe
		(n = 30737)	*(n = 6404)*	*(n = 16606)*	*(n = 7727)*
Unadjusted	1 [Reference]	3.115 (2.950, 3.279)	3.509 (3.077, 3.984)	2.899 (2.717, 3.096)	3.448 (3.058, 3.891)
1[b]	1 [Reference]	3.049 (2.890, 3.215)	3.390 (2.976, 3.861)	2.857 (2.674, 3.049)	3.413 (3.021, 3.846)
2[c]	1 [Reference]	3.021 (2.865, 3.185)	3.344 (2.924, 3.817)	2.825 (2.646, 3.021)	3.390 (3.003, 3.831)

[a] Mild, Moderate, and Severe TBI individuals with depression are compared to those without depression with the same severity. Among those without depression, 5163 had a mild TBI, 12746 moderate TBI, and 6503 severe TBI.

[b] Model 1 is adjusted for demographic characteristics (sex, insurance)

[c] Model 2 is adjusted for demographic characteristics, medical conditions, and psychiatric conditions (hypertension, hyperlipidemia, diabetes, coronary artery disease, cerebrovascular disease, bipolar disorder, schizophrenia, alcohol disorder, and drug abuse)

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Supplemental

Table 1: TBI, Depression, and Dementia Codes

Condition	*Source of Code*	*Code Used*
TBI	ICD-9	800 801 802 803 804 850 851 852 853 854 950.1 950.2 950.3
	ICD-10	S020 S021 S028 S0291 S0402 S0403 S0404 S06 S071
Depression	ICD-9	296.2 296.3 296.5 300.4 309 311
	ICD-10	F313 F314 F315 F32 F33 F341 F412 F432
Dementia	ICD-9	290 294.2
	ICD-10	F015 F039 F05

Table 2: Antidepressants Coding

Class of Antidepressant	***Source of Code***	***Code***	***Antidepressant***
Selective Serotonin Reuptake Inhibitor (SSRI)	RxNorm	485039 664145 4493 42355 36437 32937 321988	Paroxetine Mesylate Citalopram Fluoxetine Fluvoxamine Sertraline Paroxetine Escitalopram
Serotonin and Norepinephrine Reuptake Inhibitor (SNRI)	RxNorm	734064 72625 588250 39786	Desvenlafaxine Duloxetine Milnacipran Venlafaxine
Monoamine Oxidase Inhibitors (MAOI)	RxNorm	6011 7394 8123 9639 10734	Isocarboxazid Nialamide Phenelzine Selegiline Tranylcypromine
Antipsychotic	RxNorm	89013 784649 1658314 1667655 2626 73178 1040028 61381 679314 51272 35636 115698	Aripiprazole Asenapine Brexpiprazole Cariprazine Clozapine Iloperidone Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Ziprasidone
Unclassified Antidepressant	RxNorm	42347 6646 6929 15996 31565 60842 38252 10737 10898 1086769 11196 1455099	Bupropion Maprotiline Mianserin Mirtazapine Nefazodone Reboxetine Tianeptine Trazodone Tryptophan Vilazodone Viloxazine Vortioxetine