Traumatic Spinal Cord Injury and Risk of Early and Late Onset Alzheimer's Disease and related Dementia: Large Longitudinal Study

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Abstract

Objective: Traumatic spinal cord injury (TSCI) is a life altering event most often causing permanent physical disability. Little is known about the risk of developing Alzheimer's disease and related dementia (ADRD) among middle-aged and older adults living with TSCI. Time to diagnosis of and adjusted hazard for ADRD was assessed.

Design: Cohort Study

Setting: Using 2007–2017 claims data from the Optum Clinformatics Data Mart, we identified adults (45+) with diagnosis of TSCI (n=7,019). Adults without TSCI diagnosis were included as comparators (n=916,516). Using age, sex, race/ethnicity, cardiometabolic, psychologic, and musculoskeletal chronic conditions, U.S. Census Division, and socioeconomic variables, we propensity score matched persons with and without TSCI (n=6,083). Incidence estimates of ADRD was compared at 4-years of enrollment. Survival models were used to quantify unadjusted, fully adjusted, and propensity-matched unadjusted and adjusted hazard ratios for incident ADRD.

Participants: Adults with and without TSCI.

Intervention: Not applicable.

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Main Outcomes Measures: Diagnosis of ADRD

Results: Both middle-aged and older adults with TSCI had higher incident ADRD compared to those without TSCI [(0.5% vs. 0.2% and 11.7% vs. 3.3% among 45–64 and 65+ years old unmatched cohorts, respectively) (0.5% vs. 0.3% and 10.6% vs. 6.2% among 45–64 and 65+ years old matched cohorts, respectively)]. Fully adjusted survival models indicated that adults with TSCI had a greater hazard for ADRD (among 45–64 years old: unmatched HR: 3.19 (95% CI: 2.30–4.44), matched HR: 1.93 (95% CI:1.06–3.51); among 65+ years old: unmatched HR: 1.90 (95% CI: 1.77, 2.04), matched HR: 1.77 (1.55, 2.02)).

Conclusions: Adults with TSCI are at a heightened risk for ADRD. Improved clinical screening and early interventions aiming to preserve cognitive function are of paramount importance for this patient cohort.

Introduction

Traumatic spinal cord injury (TSCI) is associated with life-long debilitating consequences that negatively impact physical functioning and secondary morbidities.[1,2] Some evidence suggests that TSCI may exacerbate certain biological mechanisms due to neuronal damage that elevate the risk for Alzheimer's disease and related dementia (ADRD).[3,4] It is important to identify risk factors for ADRD because early identification of ADRD risk factors may not only elucidate better understanding of pathophysiology of ADRD but also help to identify potential preventative mechanisms or targeted treatment.[5,6]

Following a TSCI, a higher level of tau protein may accumulate in the cerebrospinal fluid.[7] Furthermore, TSCI causes chronic inflammation,[8] which triggers the accumulation of amyloid precursor protein (APP) throughout the spinal cord. This may lead to increased production and subsequent transmission of beta amyloid to different regions of the brain not only causing further inflammation but also resulting in neuronal degeneration.[9] Moreover, adults with TSCI have higher prevalence of cardiometabolic[10] and psychological[11] conditions; all of which are considered risk factors for ADRD. To date, no large-scale study in the U.S. has examined the association between TSCI and ADRD.

In this study, we examined a national administrative claims database to quantify time to diagnosis of and adjusted hazard ratios for ADRD after TSCI. Our study underscores an urgent need for understanding the risk factors for ADRD among people with TSCI. Our main hypothesis is that adults with TSCI have shorter ADRD-free survival compared with their matched cohort of adults without TSCI.

Methods

Data Source

We used national, private administrative claims from the Clinformatics DataMart Database (OptumInsight, Eden Prairie, MN). OptumInsight is a de-identified claims database

capturing inpatient, outpatient, and emergency department use of over 80 million privately insured people throughout their enrollment. This study was deemed exempt by the University of Michigan Institutional Review Board.

Sample Selection

All adults aged 45 years or older at the time of enrollment starting from 2007 to 2017 were deemed potentially eligible for this analysis. We excluded individuals with less than 12 months of continuous enrollment such that there was a sufficient history of service utilization for comorbidity history. The schematic flow diagram is presented in Supplement Figure 1.

Identification of Patients with a TSCI—Our cut-off date among our cohort of people with TSCI was January 2014 to ensure at least 4 years of follow up. Thus, all enrolled members with a diagnosis of TSCI were identified using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) (Supplementary Table S1). To allow sufficient longitudinal follow up for individuals with TSCI, we retained those with four or more continuous years of enrollment following their first diagnosis of TSCI.

We identified a comparison cohort of controls without TSCI using the same aforementioned inclusion criteria. The additional exclusion criteria for identifying the control cohort included removal of any individual with other physically disabling neurological disorders. Among remaining individuals without TSCI, a 20% simple random sample of members was selected to represent the control group. Post-hoc analyses of demographic characteristics were compared between the 20% random sample of controls and all controls to ensure no unintentional bias in the sampled control cohort attributable to random selection.

Outcome—The primary outcome was time in days to first diagnosis of ADRD following index TSCI. Due to inappropriate coding practice in administrative data, underdiagnosis for the disease, and misdiagnosis of the specific type of dementia, we combined ADRD into one umbrella term.[12–14] ADRD was identified in the follow-up period using ICD-9-CM or ICD-10-CM diagnosis codes on any single claim (Supplemental Table 2). If multiple claims were identified, the first claims after TSCI was considered the incident date of ADRD.

Covariates and Comorbidities—Independent variables included age (split into two categories: 45–64, 65 or older), sex, race/ethnicity, Elixhauser comorbidity index, U.S. Census Divisions, educational attainment, and net worth. We also identified psychological, cardiometabolic, and musculoskeletal diseases that were prevalent in the one-year lookback period before index TSCI diagnosis to develop a matched cohort. The aforementioned conditions were identified based on a single healthcare encounter of at least one of the pertinent ICD-9 codes (Supplement Table 3). For psychological morbidity, we included: (1) insomnia, (2) adjustment disorders, (3) anxiety disorders and post-traumatic stress disorder (PTSD), (4) impulse control disorders, (5) mood disorders, (6) personality disorders, (7) alcohol-related disorders, (8) substance-related disorders, and (9) central pain syndrome. Cardiometabolic morbidity included: (1) cardiac dysrhythmias, (2) heart failure, (3) peripheral and visceral atherosclerosis, (4) non-alcoholic fatty liver disease, (5)

chronic kidney disease, (6) type 2 diabetes, (7) hypercholesterolemia, and (8) hypertension. Musculoskeletal morbidity included: (1) rheumatoid arthritis and related disease, (2) osteoarthritis, (3) osteoporosis, (4) pathological fracture, (5) other connective tissue disease, (6) muscle atrophy weakness, and (7) myalgia.

Statistical Analysis

Bivariate analyses of baseline demographic characteristics between TSCI patients and general population controls were examined for differences between groups. For categorical variables, column percentages were compared between both groups using effect size calculations.[15] For large sample studies such as those using administrative claims, the effect size calculation is used since these studies are typically statistically overpowered and do not provide clinically meaningful differences in proportions between groups. For continuous variables, means and standard deviations were calculated. Standardized mean differences were calculated for continuous variables to ascertain clinically meaningful differences between groups.

For individuals with TSCI, we captured full comorbidity history in the one year of enrollment on their insurance plan prior to the index diagnosis. Individuals with TSCI must be adults aged 45 years or older at the time of the start of their first diagnosis. For randomly sampled controls, all patients with sufficient continuous enrollment within the study period of five years were randomly assigned a time zero to begin follow-up. The selection of the randomly assigned date required one year of enrollment to collect comorbidity history, and four years of post-index date follow-up to measure the first diagnosis of TSCI. The random assignment of the dates was determined assuming a uniform distribution across a specified interval of candidate dates that meet pre- and post-index date criteria and age criteria. This approach was used to address potential bias of selecting patients who were systematically younger during their enrollment on the plan for the sampled control group.

To examine disease-free ADRD survival of TSCI patients compared to general population controls, those patients that have no evidence of ADRD in each group in the one-year lookback period were graphed with Kaplan-Meier product limit survival curves for a four-year period post-index SCI diagnosis. To establish incidence in claims, we used a one-year lookback period from the index date in each group to obtain evidence of any service utilization with a diagnosis of any ADRD. Patients with ADRD in the one-year lookback period were excluded from the product-limit survival curves and other subsequent analyses.

To estimate the risk of incident ADRD, we constructed three analytic approaches. First, we used a bivariate regression to estimate the crude, unadjusted hazard ratio for ADRD comparing TSCI to the general population representing the exposure variable. Second, to estimate the adjusted hazard ratio, we performed multivariable regression to adjust for demographics, socioeconomic, and composite Elixhauser comorbidity index (Supplement Table 4). Since age is the most significant predictor of ADRD, we included an interaction term between TSCI (binary variable) and age (categorical variable) to examine the risk of TSCI between those 45–64 years of age and those 65 or older.

Finally, in order to account for selection bias attributable to TSCI patients, we performed propensity score matching. To achieve these ends, we estimated the propensity to be in the case (TSCI) group using multivariable logistic regression adjusting for demographics, individual comorbidities, and socioeconomic variables. We used a one-to-one caliper matching algorithm with caliper size of 0.0001 without replacement. To assess covariate balance, post-matched analyses of effect sizes were compared between the case (TSCI) and control groups. In order to quantify the risk of ADRD in the follow-up period, bivariate and multivariable Weibull regression were used to calculate the hazard ratio (Supplement Table 5). All patients were right censored if they did not experience ADRD in the follow-up period or disenrolled from the plan.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). All hazard ratios included a calculation of the 95% confidence interval. Statistical testing was two-tailed with a significance level of 0.05 and effect sizes used a 0.2 meaningful difference cutoff. Interaction term analysis was conducted using PROC LIFETEST and LSMEANS for marginal hazard ratios.

Sensitivity Analysis—Since incident TSCI is usually discovered in the hospital setting, we conducted a sensitivity analysis that restricted our cohort to the first TSCI diagnosed in the inpatient setting. This was due to baseline differences being sufficiently noteworthy between those diagnosed with SCI in any setting compared to the general population. Therefore, after restricting the analysis to those whose inpatient facility and professional claims indicate a diagnosis for a hospitalization with SCI, we found baseline differences to be similar between the case and the general population. Therefore, our results reflect the full cohort of SCI patients discovered in any setting at the index diagnosis.

Due to large incident of traumatic brain injury (TBI) at the time of TSCI and high prevalence of cardiovascular disease among TSCI patients, we conducted a sensitivity analysis that included fitting models that assess within-group effects (marginal hazard ratios) for incident ADRD by interacting TSCI and TBI as well as TSCI and cardiovascular disease, respectively. The predicted marginal hazard ratios for our unmatched and matched cohorts are reported in Supplemental Tables 6 and 7, respectively. The results did not confer increased risk of ADRD. While literature has suggested that mild TBI might be associated with increased risk of ADRD, due to low prevalence of TBI (3.12% among cases and 0.18% among controls), further investigation on this topic is warranted.

Results

Table 1 represents unadjusted characteristics of individuals with and without TSCI within our unmatched and matched cohorts during the 1-year lookback period. Average number of enrollment years for those with and without TSCI was 10.9 (standard deviation (SD)=3.4) and 8.7 (SD=3.3) years, respectively. Majority of people with TSCI, 4,545 (64.8%), were 65 years or older, which represent primarily Medicare Advantage Part C patients. Females represent 59.3% (n=4,163) and 53.6% (n=491,029) of adults with and without TSCI, respectively. There were no significant differences in race/ethnicity between individuals with and without TSCI, with White being the majority in both groups (case=4,505 (64.2%);

control=586,624 (64.0%)). We did not find any significant differences between our case and control groups in their educational attainment and net worth. For example, about 54.8% (n=3,847) of those with TSCI vs. 53.2% (n=487,526) of those without had fewer than 4-year college degree; and, 9.9% (n=694) of people with TSCI vs. 10.5% (n=96,323) of those without had a net worth of $150K–$249K. There was no difference in basic demographic characteristics between case and control groups after matching.

In Table 2, we compared a set of psychological, cardiometabolic, and musculoskeletal conditions between adults with and without TSCI. In our unmatched cohorts, prevalence of all conditions including any psychological (36.0% vs. 16.4%), cardiometabolic (77.0% vs. 53.1%), and musculoskeletal (70.1% vs. 33.6%) conditions were substantially higher among people with TSCI compared with those without. There was no significant difference in listed chronic conditions between case and control groups after matching.

Unadjusted and unmatched average incidences of ADRD among individuals with and without TSCI were 0.5% (n=36) and 0.2% (n=1,837) among the 45–64 age group and 11.7% (n=819) and 3.3% (n=30,226) among the 65+ age group, respectively (Figure 1). After matching, average incident ADRD among persons with and without TSCI were 0.5% (n=33) and 0.2% (n==16) among 45–64 age group and 10.6% (n=644) and 6.2% (n=375) among 65+ age group, respectively.

Figure 2 displays the Kaplan-Meier curve of the unmatched cohorts of adults with (case) and without (control) TSCI for ADRD-free survival. Among the unmatched cohorts of adults, at the end of a 4-year period, 13% of adults with TSCI compared with 4% of those without had ADRD. Among the matched cohorts, the difference between the two groups reduced to about 5% (12% of adults with TSCI compared with 7% of those without had incident ADRD).

Table 3 represents various hazard ratios between unmatched and matched cohorts. Adjusted unmatched and matched hazard ratios (HR) of TSCI for incident ADRD among 45–64 age group were HR=3.19 (95% CI: 2.30, 4.44; $P < 0.001$) and HR=1.93 (95% CI: 1.06, 3.51), respectively; and, adjusted unmatched and matched hazard ratios (HR) of TSCI for incident ADRD among 65+ age group were HR=1.90 (95% CI: 1.77, 2.04; $P < 0.001$) and HR=1.77 (95% CI: 1.55, 2.02), respectively (regression results are presented in Supplemental Tables 4 and 5).

Discussion

This study examined the risk of TSCI on incident ADRD, comparing unmatched and matched cohorts of adults with and without TSCI among two different age groups of 45–64 and 65+. Three main findings emerge: (1) risk of incident ADRD is substantially and significantly higher among persons with TSCI compared to those without; (2) TSCI approximately doubles the risk of early onset ADRD (among people 45–64 years old); (3) secondary comorbid conditions that are more prevalent among people with TSCI may also increase the risk of incident ADRD. These findings are of prominent importance because they denote the need for early detection and targeted interventions using preventative,

rehabilitative, and therapeutic services that may preserve cognitive function among persons with TSCI.

Our findings are in concordance with other emerging evidence indicative of association between TSCI and ADRD.[3,10,16–18] There is a neurodegenerative mechanism that manifest after sustaining TSCI.[8] This may enable biological mechanisms related to neural dysfunction, neuroinflammation, and toxicity which are potential risk factors driving incident ADRD.[7,9,19] For example, prior clinical studies showed that 40–60% of TSCI patients have some cognitive and emotional deficits.[20] Roth et al. stated that TSCI patients show declines in attention span, concentration, and memory function.[21] These evidence suggests that potential neurodegenerative consequences of TSCI may evolve over time and affect both the spine and brain.[20]

Furthermore, our findings suggest that TSCI increases the risk of early-onset ADRD more than it increases the risk among older people. Hazard of early onset ADRD is approximately twice among middle-aged persons with TSCI (45–64 years old) compared to their counterparts without TSCI. This plausibly can be explained by the risk associated directly with aforementioned pathophysiologic impact of TSCI on spine and brain.

Moreover, higher levels of anxiety, depression, and other chronic conditions among people with TSCI may further raise their risk for cognitive decline and ADRD.[22–24] People with TSCI compared with adults without disability have a more sedentary lifestyle and lower level of physical and social activities.[25,26] Living with TSCI places individuals at a greater risk of chronic comorbidities.[1,17,27,28,29] After matching our case and control groups in psychological, cardiometabolic, and musculoskeletal conditions, risk of TSCI for incident ADRD declined. This suggest that portion of this additional risk may go back to higher prevalence of secondary conditions among people with TSCI and thus is potentially preventable.

ADRD is one of the most devastating neurodegenerative conditions.[30] Appropriate preventative and rehabilitative services are central to improvement in neurological recovery.[31–34] Further research on healthy lifestyle emphasizing on cognitive leisure activities,[35] social engagement and community living,[36] and use of preventative services that may reduce the risk of ADRD and other chronic conditions among this patient population is imperative.

Study Limitations

This study had several limitations. First, using claims data we were unable to distinguish between incident and prevalent TSCI. Although we used a one-year lookback period to ensure no prior SCI, it is plausible that diagnosis of SCI has not been recorded over the prior year's healthcare encounters. Accordingly, with only limited enrollment periods on an insurance plan, we did not have visibility to the length of time a person has lived with TSCI since they could have acquired it before our one-year lookback period. To address this limitation, knowing that certain chronic conditions that are also risk factors for ADRD had much higher prevalence among people with SCI, we matched our SCI population to those without SCI on all our observable confounders. Although matching revealed a

reduction in the risk difference between SCI and non-SCI individuals for ADRD, the risk remained substantially higher. Second, due to errors in administrative claims' diagnostic codes, confirmatory identification of TSCI may not always be accurate. While our estimates of TSCI and other reported chronic conditions may not be 100% accurate, prior research indicates that claim-based estimates have high sensitivity and specificity.[37,38] Having said this, it is also well known that for a broad set of reasons, certain conditions such as ADRD are underdiagnosed.[12,39] Thus, it is conceivable and likely that our measures for incident ADRD diagnosis is underestimated. Third, using diagnosis codes to define TSCI, we had no measure of the neurological classification. Inclusion of various functional measures in future studies on this topic will serve as an appropriate adjunctive to existing data and will enrich and inform severity of injury and other unobserved factors related to the TSCI patient which may influence incident ADRD. Fourth, while literature has suggested that TBI might be associated with increased risk of ADRD,[40] due to potential under-coding of TBI using administrative claims,[41] our sensitivity analysis did not show incremental risk. Finally, although we adjusted/matched for some socioeconomic variables, we had no information on lifestyle choices and level of cognitive engagements.

The strengths of our study can be captured in two primary aspects. First, this is the largest study to date examining the trajectory course of ADRD among privately insured people with TSCI in the U.S. Second, while randomized clinical trials may be pondered as the gold standard in clinical research, large observational studies are increasingly proving to be practical and valuable in research.[42]

Conclusions

To summarize, this study used large national private claims data to examine the hazard of TSCI in association with incident ADRD. Adults with TSCI are at a heightened risk for incident ADRD. Further efforts are required to develop recommendations for healthy life choices, leisure cognitive activities and clinical guidelines with emphasis on preserving cognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Abbreviations:

ADRD	Alzheimer's Disease and Related Dementia
APP	Amyloid Precursor Protein
AIC	Akaiki Information Criterion
CI	Confidence Interval

ICD	International Classification of Diseases
HR	Hazard Ratio
PTSD	post-traumatic stress disorder
TSCI	Traumatic Spinal Cord Injury

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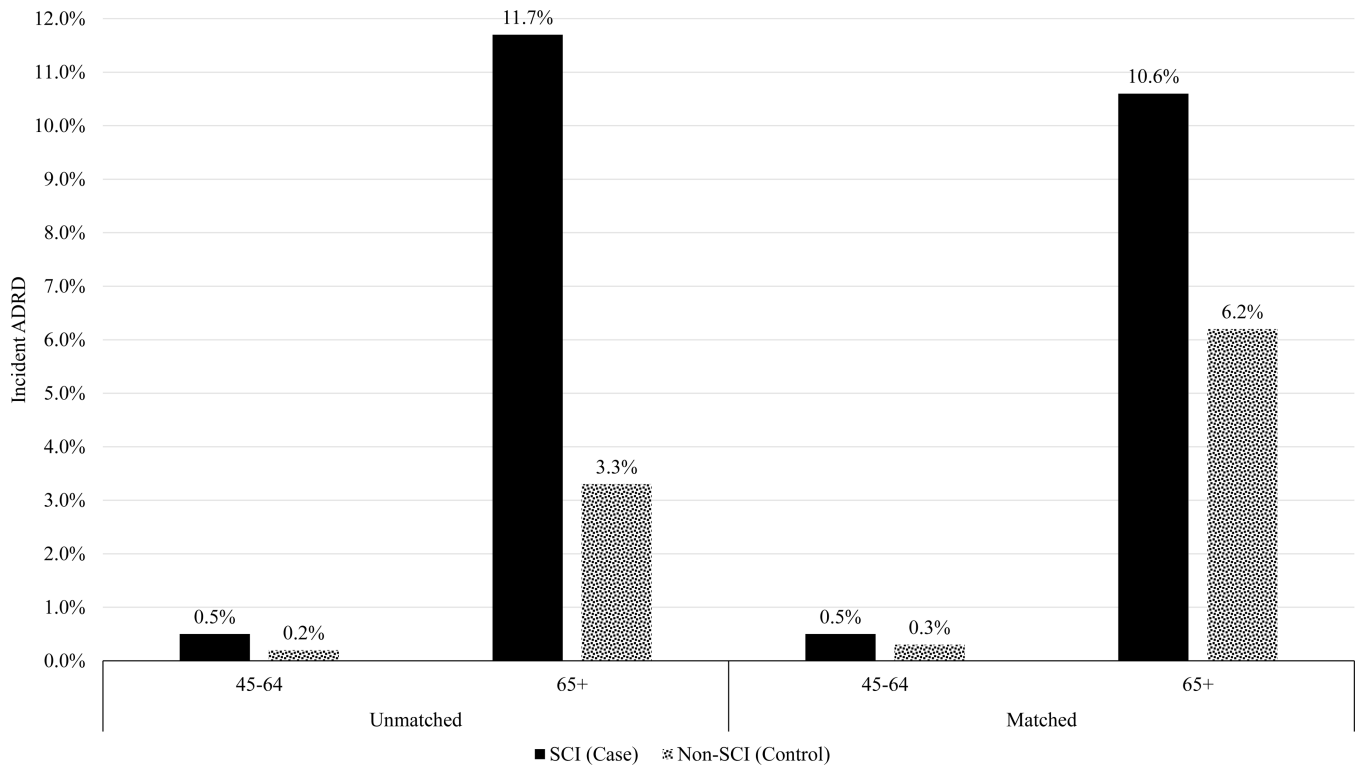
Figure 1.
Unmatched and matched average incidences of ADRD among individuals with and without TSCI

A. Unmatched 45-64-year-old cohorts

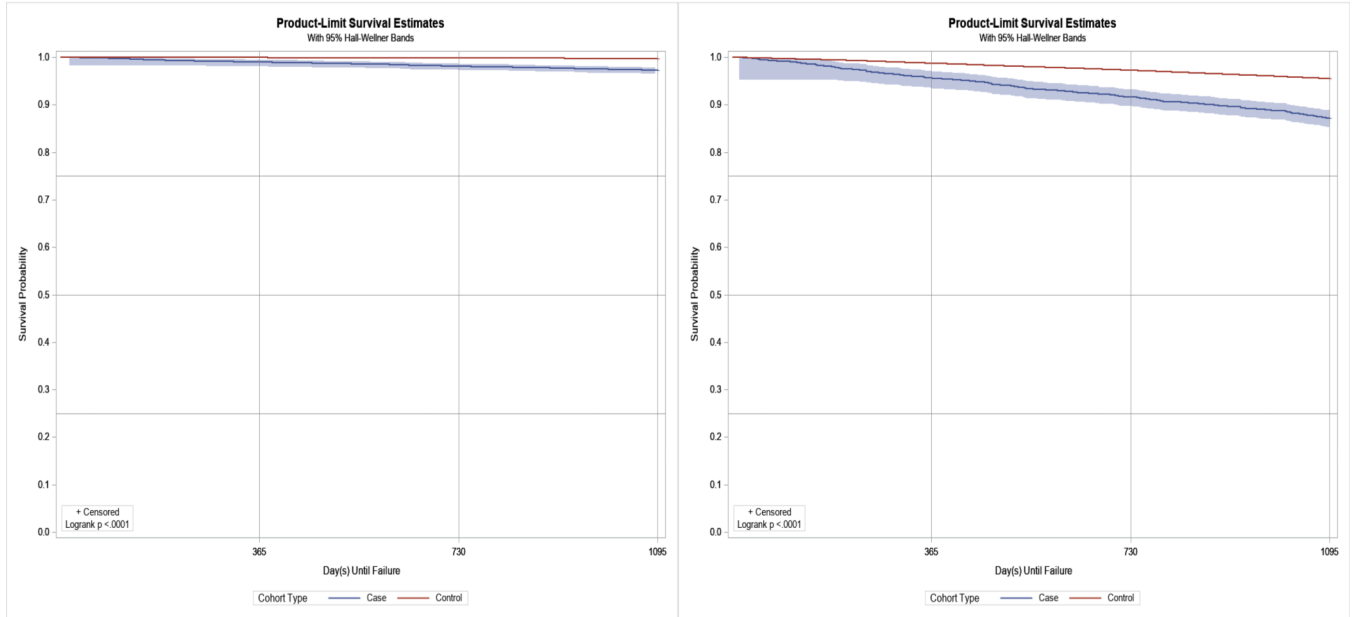B. Unmatched 65-and-older cohorts

Figure 2.
Unmatched and matched Kaplan-Meier product-limit survival curves (4-year) for adults with and without TSCI

Table 1.

Descriptive Characteristics of Adults with (Case) and Without (Control) Traumatic SCI

Spinal Cord Injury	PREMATCHED			POSTMATCHED		
	Case	Control	ES	Case	Control	ES
Overall	7019 (100%)	916516 (100%)		6083 (100%)	6083 (100%)	
Full Enrollment Length						
Mean (StD)	10.9 (3.4)	8.7 (3.3)		10.9 (3.4)	8.6 (3.3)	
Median (Q1-Q3)	10.6 (8.0–13.2)	7.8 (6.0–10.7)		10.5 (8.0–13.1)	7.5 (6.0–10.6)	
Years Post Eligibility Start Date†						
Mean (StD)	6.1 (1.7)	5.3 (1.5)		6.1 (1.7)	5.3 (1.5)	
Median (Q1-Q3)	5.6 (4.7–7.0)	4.8 (4.2–5.9)		5.6 (4.7–7.1)	4.7 (4.2–5.8)	
Age Group						
45–64	2474 (35.2%)	511120 (55.8%)	0.42	2317 (38.1%)	2227 (36.6%)	0.03
65 or Older	4545 (64.8%)	405396 (44.2%)	0.42	3766 (61.9%)	3856 (63.4%)	0.03
Gender						
Female	4163 (59.3%)	491029 (53.6%)	0.12	3479 (57.2%)	3514 (57.8%)	0.01
Male	2856 (40.7%)	425487 (46.4%)	0.12	2604 (42.8%)	2569 (42.2%)	0.01
Race/Ethnicity						
Asian	206 (2.9%)	28114 (3.1%)	0.01	170 (2.8%)	169 (2.8%)	0.00
Black	494 (7.0%)	73822 (8.1%)	0.04	447 (7.3%)	423 (7.0%)	0.01
Hispanic	542 (7.7%)	72777 (7.9%)	0.01	471 (7.7%)	458 (7.5%)	0.01
Unknown	1272 (18.1%)	155179 (16.9%)	0.03	1070 (17.6%)	1052 (17.3%)	0.01
White	4505 (64.2%)	586624 (64.0%)	0.00	3925 (64.5%)	3981 (65.4%)	0.02
Education						
Less than 12th Grade	48 (0.7%)	5376 (0.6%)	0.01	42 (0.7%)	42 (0.7%)	0.00
High School Diploma	1873 (26.7%)	231118 (25.2%)	0.03	1621 (26.6%)	1632 (26.8%)	0.00
Less than Bachelor	3847 (54.8%)	487526 (53.2%)	0.03	3339 (54.9%)	3362 (55.3%)	0.01
Bachelor Degree Plus	1091 (15.5%)	156476 (17.1%)	0.04	942 (15.5%)	923 (15.2%)	0.01
Unknown	160 (2.3%)	36020 (3.9%)	0.09	139 (2.3%)	124 (2.0%)	0.02
Net Worth						
Unknown	1095 (15.6%)	135560 (14.8%)	0.02	926 (15.2%)	918 (15.1%)	0.00
<$25K	1119 (15.9%)	120560 (13.2%)	0.08	968 (15.9%)	988 (16.2%)	0.01
$25K–$149K	1247 (17.8%)	147804 (16.1%)	0.05	1073 (17.6%)	1080 (17.8%)	0.01
$150K–$249K	694 (9.9%)	96323 (10.5%)	0.02	608 (10.0%)	628 (10.3%)	0.01
$250K–$499K	1070 (15.2%)	167313 (18.3%)	0.08	939 (15.4%)	925 (15.2%)	0.01
$500K+	1794 (25.6%)	248956 (27.2%)	0.04	1569 (25.8%)	1544 (25.4%)	0.01

Source: The 2007–2017 OptumInsight

Abbreviations: StD: Standard Deviation; ES: Effect Size; Q1-Q3: Quartile 1 and Quartile 3.

*
Effect size equal to or greater than 0.20 considered significant.

Table 2.

Incident of Chronic Conditions among Adults with (Case) and Without (Control) Traumatic SCI

Spinal Cord Injury	PREMATCHED			POSTMATCHED		
	Case	Control	ES	Case	Control	ES
Overall	7019 (100%)	916516 (100%)		6083 (100%)	6083 (100%)	
Psychological						
Any Psychological	2530 (36.0%)	149925 (16.4%)	0.45	1985 (32.6%)	1899 (31.2%)	0.03
Insomnia	425 (6.1%)	29587 (3.2%)	0.14	336 (5.5%)	334 (5.5%)	0.00
Adjustment disorders	144 (2.1%)	11357 (1.2%)	0.07	117 (1.9%)	102 (1.7%)	0.02
Anxiety disorders	892 (12.7%)	56461 (6.2%)	0.23	690 (11.3%)	664 (10.9%)	0.01
PTSD	27 (0.4%)	1894 (0.2%)	0.04	23 (0.4%)	19 (0.3%)	0.02
Impulse control	3 (0.0%)	217 (0.0%)	0.00	2 (0.0%)	3 (0.0%)	0.00
Mood disorders	1242 (17.7%)	72191 (7.9%)	0.30	948 (15.6%)	951 (15.6%)	0.00
Personality disorders	21 (0.3%)	883 (0.1%)	0.05	15 (0.2%)	17 (0.3%)	0.02
Alcohol-related dis.	206 (2.9%)	6869 (0.7%)	0.17	155 (2.5%)	141 (2.3%)	0.01
Substance-related dis.	202 (2.9%)	5455 (0.6%)	0.19	132 (2.2%)	110 (1.8%)	0.03
Central Pain	901 (12.8%)	22276 (2.4%)	0.42	605 (9.9%)	590 (9.7%)	0.01
Cardiometabolic						
Any Cardiometabolic	5405 (77.0%)	487055 (53.1%)	0.45	4539 (74.6%)	4540 (74.6%)	0.00
Cardiac dysrhythmias	1606 (22.9%)	88072 (9.6%)	0.44	1228 (20.2%)	1263 (20.8%)	0.01
Heart Failure	671 (9.6%)	26163 (2.9%)	0.42	483 (7.9%)	457 (7.5%)	0.02
Peripheral and visceral atherosclerosis	818 (11.7%)	40467 (4.4%)	0.44	605 (9.9%)	626 (10.3%)	0.01
Liver; Non-Alcohol	120 (1.7%)	9506 (1.0%)	0.06	98 (1.6%)	77 (1.3%)	0.03
Chronic kidney disease	682 (9.7%)	37242 (4.1%)	0.31	537 (8.8%)	542 (8.9%)	0.00
Diabetes Type II	1731 (24.7%)	150414 (16.4%)	0.21	1481 (24.3%)	1442 (23.7%)	0.01
Hypercholesterolemia	1703 (24.3%)	152123 (16.6%)	0.18	1401 (23.0%)	1435 (23.6%)	0.01
Hypertension	4561 (65.0%)	395374 (43.1%)	0.44	3791 (62.3%)	3871 (63.6%)	0.03
Musculoskeletal						
Any Musculoskeletal	4923 (70.1%)	307891 (33.6%)	0.73	3990 (65.6%)	3986 (65.5%)	0.00
Rheumatoid arthritis	311 (4.4%)	15546 (1.7%)	0.19	236 (3.9%)	193 (3.2%)	0.04
Osteoarthritis	2146 (30.6%)	119632 (13.1%)	0.48	1687 (27.7%)	1753 (28.8%)	0.02
Osteoporosis	1500 (21.4%)	49193 (5.4%)	0.63	986 (16.2%)	1011 (16.6%)	0.01
Pathological fracture	1213 (17.3%)	4088 (0.4%)	0.87	401 (6.6%)	371 (6.1%)	0.02
Other connective tissue	3750 (53.4%)	228676 (25.0%)	0.66	3042 (50.0%)	3099 (50.9%)	0.02
Muscle Atrophy	679 (9.7%)	13505 (1.5%)	0.69	445 (7.3%)	420 (6.9%)	0.02
Myalgia	610 (8.7%)	36268 (4.0%)	0.23	469 (7.7%)	456 (7.5%)	0.01

Source: The 2007–2017 OptumInsight

Abbreviations: StD: Standard Deviation; ES: Effect Size.

[*]
Effect size equal to or greater than 0.20 considered significant.

Table 3.

Hazard Ratios of SCI for ADRD

	Unmatched Cohort		Matched Cohort	
	Unadjusted	Adjusted	Unadjusted	Adjusted
Among those 45 to 64 years of age	4.08 (2.93, 5.67) ***	3.19 (2.30, 4.44) ***	1.99 (1.09, 3.62) ***	1.93 (1.06, 3.51) ***
Among those 65+ years of age	2.51 (2.34, 2.70) ***	1.90 (1.77, 2.04) ***	1.79 (1.56, 2.04) ***	1.77 (1.55, 2.02) ***

Note: As with incidence estimates (Tables 1 and 2), all survival models used case (SCI) and control cohorts, which required a one-year clean period with no evidence of the ADRD. To estimate the hazard ratios (HRs) of SCI among each age group, we interacted categorical age group (45–64 and 65+) with SCI.

Regression models for fully adjusted unmatched and matched cohorts are reported in Supplementary Tables 4 and 5.

***
P-value < 0.001