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Psychological morbidity among adults with cerebral palsy and spina bifida

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Abstract

Background: Very little is known about the risk of developing psychological morbidities among adults living with cerebral palsy (CP) or spina bifida (SB). The objective of this study was to compare the incidence of and adjusted hazards for psychological morbidities among adults with and without CP or SB.

Methods: Privately-insured beneficiaries were included if they had an ICD-9-CM diagnostic code for CP or SB (n=15,302). Adults without CP or SB were also included (n=1,935,480). Incidence estimates of common psychological morbidities were compared at 4-years of enrollment. Survival models were used to quantify unadjusted and adjusted hazard ratios for incident psychological morbidities.

Results: Adults living with CP or SB had a higher 4-year incidence of *any* psychological morbidity (38.8% vs. 24.2%) as compared to adults without CP or SB, and differences were to a clinically meaningful extent. Fully adjusted survival models demonstrated that adults with CP or SB had a greater hazard for *any* psychological morbidity (Hazard Ratio [HR]: 1.60; 95%CI: 1.55,

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1.65), and all but one psychological disorder (alcohol-related disorders), and ranged from HR: 1.32 (1.23, 1.42) for substance disorders, to HR: 4.12 (3.24, 5.25) for impulse control disorders.

Conclusions: Adults with CP or SB have a significantly higher incidence of and risk for common psychological morbidities, as compared to adults without CP or SB. Efforts are needed to facilitate the development of improved clinical screening algorithms and early interventions to reduce risk of disease onset/progression in these higher risk populations.

Introduction

Cerebral Palsy (CP) is the most common pediatric-onset physical disability with an estimated prevalence ranging from 2.6–3.1 cases per 1,000 live births in the U.S (Maenner et al., 2016). CP is caused by an insult or malformation of the developing brain which affects motor control centers, and causes alterations in growth, development, and overall health throughout the lifespan (Christensen et al., 2014). The population of adults with CP is expanding because of the steady or marginally increased prevalence (Paneth, Hong, & Korzeniewski, 2006) and increases in the childhood survival rate (Brooks et al., 2014) in recent decades. Despite being considered a neurological syndrome caused by a non-progressive insult, the hallmark features of CP represent a highly progressive phenotype of “early aging” (Peterson, Gordon, & Hurvitz, 2013; Peterson, Gordon, Hurvitz, & Burant, 2012; Verschuren et al., 2018).

Spina bifida (SB) is another congenital birth defect that occurs in approximately 3.5 cases per 10,000 live births in the U.S. (Prevention., 2011), and encompasses a spectrum of birth defects (meningomyelocele, myelomeningocele, myelocele, meningocele, and rachischisis), which are the result of an incomplete closure of the spinal column and lead to exposure of or herniation to the spinal cord/meninges (Atta et al., 2016). Although SB has a lower case fatality rate than other neural tube defects, it often results in severe life-long disability and morbidity. Moreover, now that the oldest cohort with SB is nearly 60 years of age, better understanding of age-related changes across the lifespan is critical to inform and improve clinical care for this population (Dennis, Spiegler, & Hetherington, 2000; Ware, Kulesz, Juranek, Cirino, & Fletcher, 2017).

The clinical framework that encompasses healthcare for patients with CP and SB has been largely confined to issues that arise during childhood and adolescence. Despite the shortage of surveillance research to evaluate lifespan health and developmental trajectories in both of these populations, there is ample indication that adults living with CP and SB have significant and progressive functional decline, inadequate muscle and bone development, increased obesity, and risk for secondary chronic disease (Dosa NP, Foley JT, Eckrich M, Woodall-Ruff D, & GS., 2009; Lampe, Grassl, Mitternacht, Gerdesmeyer, & Gradinger, 2006; Lidal, Lundberg Larsen, & Hoff, 2019; Marreiros, Monteiro, Loff, & Calado, 2010; Moreau, Li, Geaghan, & Damiano, 2008; Peterson, Zhang, Haapala, Wang, & Hurvitz, 2015; Polfuss, Bandini, & Sawin, 2017; Trinh et al., 2017; D. Whitney et al., In Press; D. G. Whitney et al., 2018). However, there have been very few studies to examine psychological morbidity among adults living with CP or SB (Bellin et al., 2010; Dicianno et al., 2015; Smith et al., 2018; D. G. Whitney, Warschausky, et al., 2019), and no current studies

have examined the longitudinal trends of a broad array of mental health disorders in these populations. The purpose of this study was therefore to examine the incidence of and risk for common psychological morbidities in a large sample of adults with CP or SB, as compared to adults without CP or SB.

Methods

Data Source

This is a retrospective cohort study of adults with congenital CP or SB whose diagnosis could have existed across any patient care setting. This study used a national, private insurance claims database, Clinformatics DataMart Database (OptumInsight, Eden Prairie, MN). This is a de-identified administrative claims database of over 80 million adults and children with commercial insurance representing those on a single, large U.S. private payer who had both medical and pharmacy coverage throughout the enrollment. Enrolled beneficiaries' emergency department, outpatient, and inpatient encounters are captured. This study was deemed exempt by the University of Michigan Institutional Review Board at the researchers' institution.

Sample Selection

All individuals 18 years of age and older at the time of their enrollment which could start from 2007 to 2017 were potentially eligible for this analysis. We excluded individuals with less than 12 months of continuous enrollment to require sufficient claim history. All medical claims excluding laboratory and outpatient pharmacy was considered to identify prevalence or treatment for these conditions during the enrollment period.

Identification of Patients with CP and SB—All members with a diagnosis of CP or SB were identified using International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) (Supplementary Table S1). Members that had CP or SB prior to 2007 were excluded due to poorer coverage of diagnosis codes during 2001 to 2006 in the database. Members without a diagnosis code in any position when they were 18 years or older during enrollment were excluded. Due to lack of clinical feasibility and different disease etiologies, a small number of members were excluded who had both CP *and* SB during enrollment. To allow adequate longitudinal follow up for all patients with CP or SB, only those that had four or more continuous years of enrollment following their starting date of enrollment within the study period were included.

A comparison cohort of controls without CP or SB were also identified using the same aforementioned inclusion criteria. Additional exclusion criteria for identifying the control cohort included removal of any individual with other physically disabling neurological disorders (e.g., paraplegia, quadriplegia, hemiplegia, traumatic spinal cord injury, and multiple sclerosis). Among remaining members without CP or SB, a 20% simple random sample of members was selected to represent the control group. We performed simple random sampling of the set of controls that had no evidence of CP or SB throughout their enrollment on the insurance plan during the study period. Post-hoc analyses of demographic

characteristics were compared between the 20% sample of controls and all controls to ensure no bias in control cohort attributable to random selection (Figure 1).

Psychological Morbidities—Physician-diagnosed psychological health disorders were identified based on a single encounter that included at least one of pertinent ICD-9 or ICD-10 codes (in any position) (see Supplementary Table S1). The primary outcome was time in days to incident psychological morbidity as a composite outcome following enrollment on the plan. Secondary outcomes were component incident psychological morbidity, including: (1) insomnia, (2) adjustment disorders, (3) anxiety disorders and post-traumatic stress disorder (PTSD), (4) delirium/dementia/amnestic or other cognitive disorder, (5) dementias, (6) impulse control disorders, (7) mood disorders, (8) personality disorders, (9) alcohol-related disorders, (10) substance-related disorders, and (11) central pain syndrome.

Covariates—Explanatory covariates included age group split into three categories (18–44, 45–64, 65 or older), sex, race, educational attainment, household net worth, and a modified Elixhauser comorbidity index. The Elixhauser comorbidity index was modified to removed four conditions that would be correlated with incident psychological morbidity: alcohol abuse, drug abuse, psychoses, and depression. Therefore, the revised index only considers 27 comorbidities (Supplemental Table S2).

Statistical Analysis

Bivariate analyses of baseline demographic characteristics between patients with CP or SB and controls were examined. For categorical variables, column percentages were compared between both groups using effect size calculations with Cohen's h. The Cohen's h effect size calculation was used since, due to large sample sizes, being statistically overpowered would not provide clinically meaningful differences in proportions between groups. For continuous variables, means and standard deviations as well as medians with upper and lower bounds on interquartile ranges were calculated. Cohen's d standardized mean differences were calculated for continuous variables to ascertain clinically meaningful differences between groups.

Since CP and SB are congenital conditions, it is assumed that all adults already have the condition at the time of their enrollment by age 18. To capture full comorbidity history within the study period, all patients with sufficient continuous enrollment within the study period of four years were retained to enable sufficient follow-up. The CP/SB cohort, use the first year of enrollment out of the four-year enrollment to capture comorbidity history and to examine if any prevalent psychological outcomes existed.

To examine disease-free survival of individuals with CP or SB compared to controls, those patients that had no evidence of composite psychological morbidity in each group were plotted using Kaplan-Meier product limit survival curves for a three-year period. 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 psychological morbidity. These patients were excluded from the product-limit survival curves and other subsequent analyses.

To estimate the unadjusted and adjusted hazard of the composite and each psychological morbidity, a series of survival models were developed. For each psychological morbidity, all patients that had evidence of the specific psychological morbidity were excluded from the model. For example, if insomnia was being considered as the incident outcome, all patients with prevalent insomnia in the one year prior to the index date would be excluded from the model. Therefore, sample sizes of patients included for each outcome varied based on evidence of prevalent disease in the one year prior to the index date. Survival models were then used to quantify unadjusted and adjusted hazard ratios for each incident psychological morbidity. Appropriate survival models were based on distributional assumptions that included testing Weibull, lognormal, exponential, gamma, logistic, loglog, and Normal distribution with respect to the follow-up in days by minimizing critical model fit statistics. Critical assessment of Akaiki Information Criterion (AIC) was used as a basis for minimization amongst all candidate distributions. Use of the parametric Weibull regression for incident psychological outcome was applied stepwise. To examine the effects of incremental adjustment on the exposure variable (CP or SB), a series of models for each psychological outcome was evaluated. All patients were right censored if they did not experience the outcome in the follow-up period or disenrolled from the plan. Both unadjusted and all adjusted hazard ratios and 95% confidence intervals for the exposure to CP/SB were calculated.

All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC). Statistical testing was two-tailed with a significance level of 0.05 and effect sizes used a 0.2 meaningful difference cutoff.

Results

The median time in the plan for eligible enrollees was 7.0 (25th Percentile: 5.1; 75th Percentile: 9.7) and 6.7 (25th Percentile: 5.0; 75th Percentile: 9.3) years for patients with CP or SB vs controls respectively. Adults living with CP or SB had a higher 4-year incidence of any psychological morbidity (38.8% vs. 24.2%) as compared to adults without CP or SB, and differences were to a clinically meaningful extent. Moreover, adults with CP or SB had significantly higher incidence of all of the psychological outcomes, including insomnia (9.6% vs. 5.6%), adjustment disorders (5.2% vs. 3.3%), anxiety disorders (18.9% vs. 11.2%) and PTSD (1.1% vs. 0.4%), delirium/dementia/amnestic or other cognitive disorder (6.7% vs. 2.2%), dementia (2.3% vs. 1.0%), impulse control disorders (0.5% vs. 0.1%), mood disorders (19.6% vs. 10.0%), personality disorders (1.0% vs. 0.2%), alcohol-related disorders (2.3% vs. 1.8%), substance-related disorders (4.9% vs. 2.7%), and central pain syndrome (13.9% vs. 6.1%), as compared to adults without CP or SB (all $P<.01$ and $SMD \geq 0.2$) (Table 2).

A Kaplan-Meier curve for the unadjusted disease-free survival for any psychological morbidity in adults with CP or SB and controls are demonstrated in Figure 2. Unadjusted survival models demonstrated a robust increased hazard ratio (HR) for each of the incident psychological morbidities among adults with CP or SB, and ranged from HR: 1.29 (1.16, 1.43) for alcohol-related disorders to HR: 6.32 (4.96, 8.05) (all $p<0.001$). Fully adjusted survival models demonstrated that adults with CP or SB had a greater hazard for *any*

psychological morbidity (HR: 1.60; 95%CI: 1.55, 1.65) (Supplemental Table S3), and all but one psychological disorder (alcohol-related disorders), and ranged from HR: 1.32 (1.23, 1.42) for substance disorders to HR: 4.12 (3.24, 5.25) for impulse control disorders (Table 3).

Discussion

The principal finding of this study was that adults living with CP or SB had a higher incidence of and adjusted hazard for *any* and all psychological morbidities than adults without CP or SB. This is the first and largest study to date to examine longitudinal trajectories of psychological morbidity among adults living with CP or SB. Future research and clinical efforts are needed to not only better understand the healthcare burden associated with mental health disorders in the CP and SB populations, as well as across other subpopulations with other neurodevelopmental disabilities, but also to understand the disparities in healthcare access between privately- and federally-insured beneficiaries living with disabilities. Importantly, these findings bolster the need for improved clinical screening and design of early behavioral interventions to reduce risk of psychological disease onset/progression in the CP and SB populations.

Our findings support previous research indicating a higher risk of various psychological morbidities in adults with CP and SB. Adults with CP often experience depression and anxiety at higher prevalence and incidence than the general population (Smith et al., 2018; D. G. Whitney, Warschausky, et al., 2019). In a population representative sample from the UK, more than 16% of younger adults with CP under 30 years of age were found to have depression compared to less than 7% of the general population (Fortuna, Holub, Turk, Meccarello, & Davidson, 2018). Depression and anxiety are also considered to be factors of concern for adults with SB (Mukherjee & Pasulka, 2017). In fact, in a recent cohort study, approximately 26% of adults with SB experienced depressive symptomatology, 36% were on antidepressants to treat depressive symptoms, and 63% of those with clinical symptoms of depression were on antidepressants (Dicianno et al., 2015). The pathophysiology underlying CP and SB consist of insults to or malformations of the central nervous system that may include the frontal cortex, the prefrontal cortex, cerebellum, the limbic system and other brain centers that control behavior, self-regulation, working memory, and executive function may be disrupted, thus predisposing individuals with CP or SB to higher risk of poor cognitive health than typically-developing peers.

In addition to the findings that adults living with CP or SB had higher risk for developing conventional psychological morbidities (e.g., depression and anxiety), we found that risk for central pain was also significantly greater in adults with CP or SB. Indeed, chronic pain is the most commonly reported physical symptomology of CP and SB throughout the lifespan, and yet pain is perhaps the least understood, emphasized, and studied physical comorbidity of these conditions (Alriksson-Schmidt, Josenby, Lindquist, & Westbom, 2018; Blackman, Svensson, & Marchand, 2018; Fehlings, 2017; Wagner et al., 2015). There exists robust literature linking pain and psychological morbidity in the general population (Goesling, Lin, & Clauw, 2018; Tsang et al., 2008); however, there have been virtually no investigations to understand pain phenotype distributions (e.g., including nociceptive,

nociplastic, neuropathic) in CP or SB and how they contribute to psychological morbidity onset/progression. Pain is experienced by adults with CP and SB when completing normal tasks, such as dressing and transferring, or other activities that require medical interventions (Fox et al., 2019; Morley CP et al., 2019). Prior research has found that nearly 40% of adults with CP and 45% of those diagnosed with SB commonly experienced pain and severe fatigue (Benner et al., 2017; van Gorp et al., 2019). When compared to individuals without CP, about 70–75% of adults with CP report chronic pain (Fox et al., 2019; van der Slot et al., 2020). Individuals with SB are likely to have pain in all regions of their bodies, with pain in legs (thigh, hip, knee, shin, and ankle) reported most often (Morley CP et al., 2019). Assessment of putative pain mechanisms could provide new insight into the pain experience in adults with CP and SB and inform interventions to address pain and psychological morbidity.

Strengths and Weaknesses

A major strength of this study is the large and longitudinal sample of adults with CP or SB. It can be challenging to gather data on these clinical sub-populations, and very little is known about health outcomes among individuals with CP or SB as they transition throughout adulthood. Moreover, most large administrative claims databases do not contain some socioeconomic indicators such as net worth, race, and location (division). Herein, we provide incidence estimates and adjusted hazards for psychological morbidity while considering numerous sociodemographic variables from samples representing all states in the US. Lastly, while clinical trials may be considered the “gold standard” in clinical research, cohort studies are less expensive, include broader patient populations, and are more efficient. In fact, there is little evidence to support the superiority of clinical trials over observational studies (Benson & Hartz, 2000).

Our study also has several limitations that should be acknowledged. First, we were unable to determine the severity of CP or SB through claims-based data. However, we suspect that our sample may be more reflective of a healthier, higher functioning segment of the CP or SB population (D. G. Whitney, Alford, et al., 2019), because they had to be enrolled in private insurance, either by purchasing their own insurance, or by being covered through employment or marriage to someone who had private insurance. Therefore, results and comparisons to adults without CP or SB are likely conservative estimates, and the true extent of psychological morbidity may be underestimated in this study. Importantly, administrative claims data may be prone to inaccurate coding of medical diagnoses, such as CP or SB, as well as chronic diseases, which may have an effect on our incidence estimates. While validation studies have shown that using >1 claim for a medical condition improves the ability to identify beneficiaries with that medical condition (Kerr, McGlynn, Van Vorst, & Wickstrom, 2000; Reeves et al., 2014), single claim-based algorithms have been reported to have moderate-to-high positive predictive value (~80%) or specificity (up to 96%) (Doktorchik et al., 2019; Leslie, Lix, & Yogendran, 2011; Reeves et al., 2014). However, the accuracy of identifying medical conditions using claims data depends on the number of years for the study period (Leslie et al., 2011) and the medical condition examined (Doktorchik et al., 2019; Leslie et al., 2011; Noyes, Liu, Lyness, & Friedman, 2011; Reeves et al., 2014). Finally, we cannot rule out time-varying confounding since

baseline measurements of all covariates were included in our final models. Thus, whether having CP or SB "causes" an elevated risk for earlier-onset psychological morbidity, or if changes in other health parameters (e.g., diabetes, a known predictor of psychological morbidity) themselves, are a cause of poor mental health, is an interesting topic. Thus, we were unable to determine if other competing risks or unmeasured confounding (i.e., other risk factors [e.g., family history of mental health disorders, lack of physical activity, loss of functional independence, etc.]) may have influenced the observed findings. Indeed, unmeasured confounding could also be within proxy variables of appropriate care (PT, OT, etc.) which might mitigate psychological morbidity risk (and were not considered). This would lend credence to additional follow-up work to understand the care pathway to success for these patients.

Conclusion

In conclusion, adults with CP or SB have an elevated risk of developing a variety of psychological morbidities compared to the general adult population of privately insured beneficiaries without CP or SB. Individuals with CP and SB frequently utilize healthcare services as part of their routine clinical care. Therefore, increasing clinical awareness of the mental health disorders experienced and risks among adults with CP and SB, improving clinical screening strategies, and developing efficient referral resources for coordinated care may help reduce the burden of mental health disorders in these population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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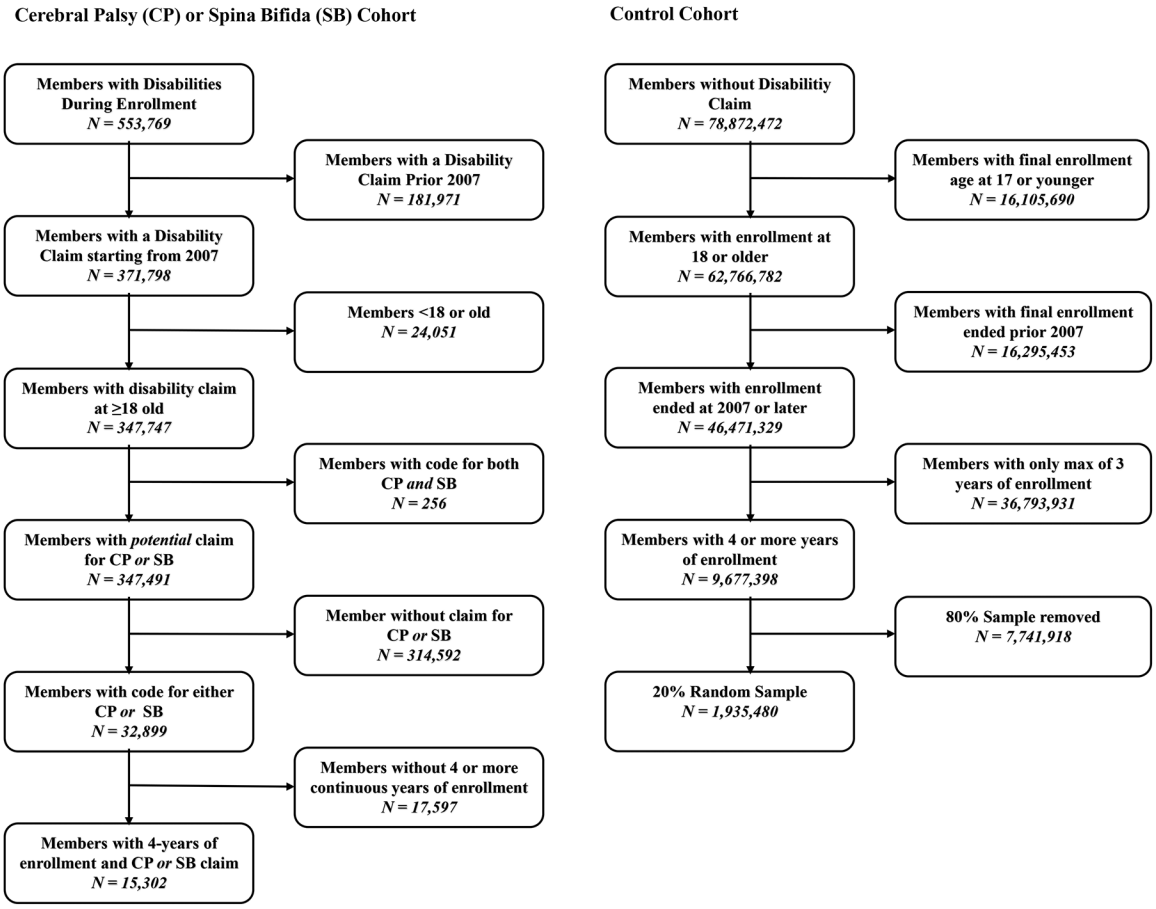

Figure 1.
Flow chart of subject inclusion and exclusion for final case and control cohorts.

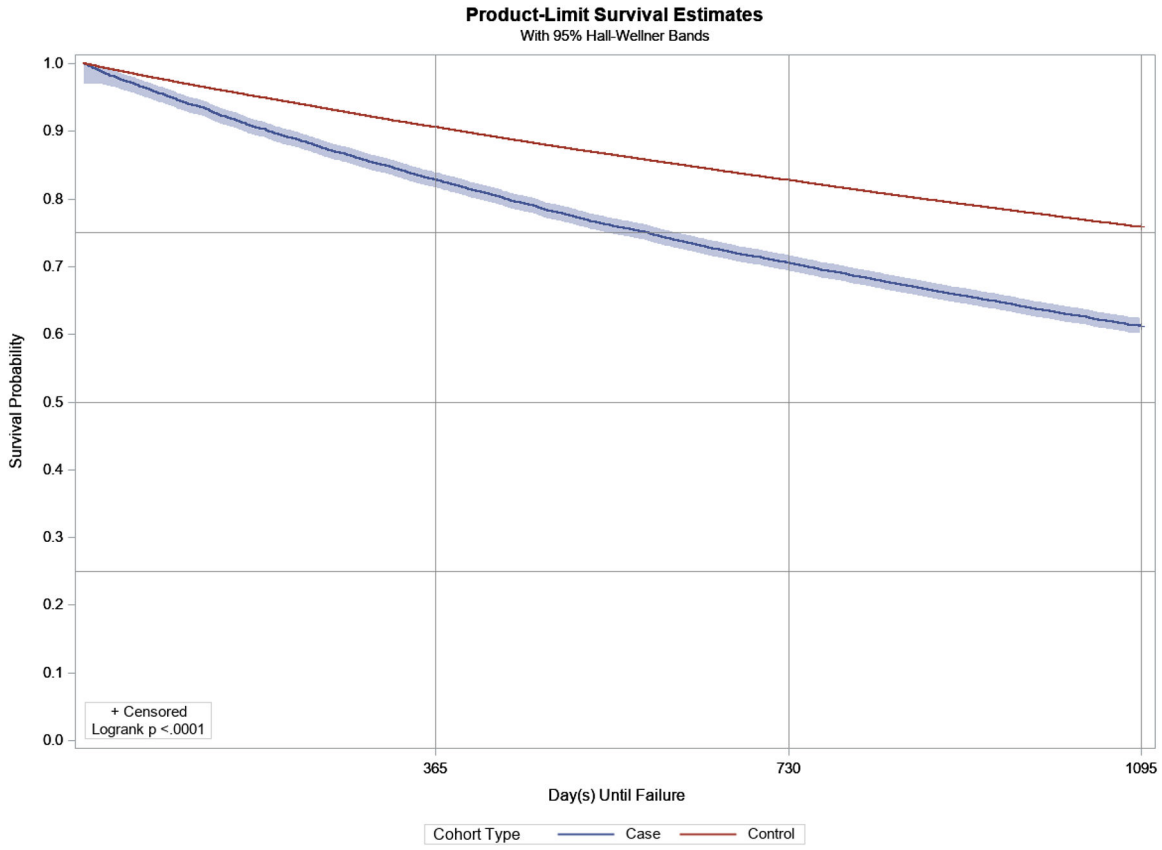

Figure 2.

Disease-free survival and Kaplan-Meier product-limit survival curves (3-year) for adults with CP or SB (blue) and without CP or SB (red), for *any* psychological morbidity.

Table 1.

Descriptive characteristics among adults with CP or SB (case) or without CP or SB (control).

	Case	Control
Overall	15,302 (100%)	1,935,480 (100%)
Full Enrollment Length		
Mean (SD)	7.8 (3.3)	7.6 (3.3)
Median (Q1-Q3)	7.0 (5.1–9.7)	6.7 (5.0–9.3)
Years Post Eligibility Start Date[†]		
Mean (SD)	5.8 (2.2)	5.5 (2.2)
Median (Q1-Q3)	5.3 (4.0–7.3)	5.0 (3.7–6.8)
Age Group		
18–44	7055 (46.1%)	798257 (41.2%)
45–64	5255 (34.3%)	617997 (31.9%)
65 or Older	2992 (19.6%)	519226 (26.8%)
Gender		
Female	8666 (56.6%)	1012200 (52.3%)
Male	6636 (43.4%)	923280 (47.7%)
Race		
Asian	300 (2.0%)	75437 (3.9%)
Black	1496 (9.8%)	155609 (8.0%)
Hispanic	1268 (8.3%)	175966 (9.1%)
Unknown/Missing	3161 (20.7%)	379802 (19.6%)
White	9077 (59.3%)	1148666 (59.3%)
Education		
<High School Diploma	86 (0.6%)	10761 (0.6%)
High School Diploma	4465 (29.2%)	469829 (24.3%)
<Bachelor Degree	8107 (53.0%)	1021803 (52.8%)
Bachelor Degree	2238 (14.6%)	371346 (19.2%)
Unknown/Missing	406 (2.7%)	61741 (3.2%)
Net Worth		
Unknown	3334 (21.8%)	346012 (17.9%)
<$25K	3234 (21.1%)	302790 (15.6%)
$25K-$149K	2695 (17.6%)	340966 (17.6%)
$150K-$249K	1379 (9.0%)	196032 (10.1%)
$250K-$499K	2088 (13.6%)	313883 (16.2%)
≥$500K	2572 (16.8%)	435797 (22.5%)

[†]All adults with CP and SB have their Index Date set the same as start of eligibility date (start of 2007, year when turned 18, or enrollment start date, whichever was the latest)

Table 2.

Incidence of any and all psychological morbidities among adults with and without CP or SB with one-year clean enrollment period.

	[†] No Outcome at Baseline	
	Case/Denominator	**Control/Denominator**
Any Psychological Morbidity	4205/10848 (38.8%) [*]	395275/1635348 (24.2%)
Insomnia	1402/14655 (9.6%) [*]	105331/1884216 (5.6%)
Adjustment disorders	767/14891 (5.2%) [*]	63017/1905421 (3.3%)
Anxiety disorders	2568/13560 (18.9%) [*]	204060/1819089 (11.2%)
PTSD	163/15193 (1.1%) [*]	8416/1931162 (0.4%)
Delirium/Dementia/Amnestic/Other Cognitive Disorder	990/14826 (6.7%) [*]	41606/1916260 (2.2%)
Dementias	351/15150 (2.3%) [*]	19773/1929124 (1.0%)
Impulse control disorders NEC	79/15236 (0.5%)	1592/1934754 (0.1%)
Mood disorders	2524/12898 (19.6%) [*]	179935/1794787 (10.0%)
Personality disorders	157/15229 (1.0%) [*]	4790/1933048 (0.2%)
Alcohol-related disorders	341/15112 (2.3%) [*]	33777/1921455 (1.8%)
Substance-related disorders	731/15043 (4.9%) [*]	51119/1923254 (2.7%)
Central Pain	1996/14391 (13.9%) [*]	115911/1898453 (6.1%)

[*] **P<.01** *and* standard mean difference (SMD) ≥0.2

[†] Denominators for both cases and controls reflect a one-year clean period during their enrollment for the specific condition. For instance, among cases (CP/SB), there exist 14,655 patients whose first year of enrollment had no evidence of insomnia; therefore, inferred incident insomnia could be estimated for this subset of the full CP/SB cohort. As a result, all patient cohorts' denominators dynamically change conditional on the incident outcome being measured to ensure a clean period in the first year of enrollment

Table 3.

Survival models with parametric Weibull regression was completed stepwise for each incident psychological outcome to examine the effects of incremental adjustment on the exposure variable (CP or SB).

	Model 1	Model 2	Model 3	Model 4
Any Psychological	1.79 (1.74, 1.85)***	1.81 (1.76, 1.87)***	1.62 (1.57, 1.67)***	1.60 (1.55, 1.65)***
Insomnia	1.75 (1.66, 1.84)***	1.78 (1.69, 1.87)***	1.51 (1.44, 1.60)***	1.50 (1.43, 1.58)***
Adjustment disorders	1.57 (1.47, 1.69)***	1.46 (1.36, 1.57)***	1.30 (1.21, 1.40)***	1.32 (1.23, 1.42)***
Anxiety disorders	1.77 (1.70, 1.84)***	1.71 (1.65, 1.78)***	1.48 (1.43, 1.54)***	1.47 (1.42, 1.53)***
PTSD	2.47 (2.11, 2.89)***	2.26 (1.93, 2.64)***	1.71 (1.46, 2.00)***	1.68 (1.44, 1.97)***
Delirium/Dementia/Amnestic/Other Cognitive Disorder	3.15 (2.96, 3.36)***	4.15 (3.89, 4.43)***	3.57 (3.35, 3.81)***	3.34 (3.13, 3.56)***
Dementias	2.28 (2.05, 2.53)***	3.34 (3.00, 3.72)***	2.84 (2.55, 3.16)***	2.56 (2.30, 2.85)***
Impulse control disorders NEC	6.32 (4.96, 8.05)***	6.00 (4.71, 7.64)***	4.23 (3.32, 5.39)***	4.12 (3.24, 5.25)***
Mood disorders	2.07 (1.99, 2.15)***	2.05 (1.97, 2.13)***	1.74 (1.68, 1.81)***	1.72 (1.65, 1.79)***
Personality disorders	4.18 (3.55, 4.92)***	3.92 (3.32, 4.61)***	2.76 (2.34, 3.25)***	2.70 (2.29, 3.18)***
Alcohol-related disorders	1.29 (1.16, 1.43)***	1.30 (1.17, 1.45)***	1.11 (1.00, 1.24)	1.09 (0.98, 1.21)
Substance-related disorders	1.85 (1.72, 1.99)***	1.85 (1.72, 1.99)***	1.38 (1.28, 1.49)***	1.32 (1.22, 1.42)***
Central Pain	2.38 (2.27, 2.49)***	2.46 (2.36, 2.57)***	1.92 (1.83, 2.01)***	1.88 (1.80, 1.97)***

Model 1: Unadjusted

Model 2: Model 1 + Demographic variables (age, sex, race, geographic region).

Model 3: Model 1 + Model 2 + Modified Elixhauser Comorbidity Index

Model 4: Model 1 + Model 2 + Model 3 + Education + Income

*As with incidence estimates (Table 2), all survival models used cases (CP/SB) and control cohorts consistent with Table 2, which required a one-year clean period with no evidence of the condition being measured