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Pain phenotypes among adults living with cerebral palsy and spina bifida

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Abstract

Chronic pain is the most commonly reported physical symptomology of cerebral palsy (CP) and spina bifida (SB) throughout the lifespan, and yet pain is perhaps the least understood comorbidity in these populations. The objective of this study was to compare the prevalence and types of pain diagnosed among adults living with and without CP or SB. In this retrospective cohort study, we analyzed data from a nation-wide commercial insurance claims database. Beneficiaries were included if they had an ICD-9-CM diagnosis code for CP or SB (n= 22,648). Adults without CP or SB were also included as controls (n= 931,623). Pain phenotypes (nociceptive, nociplastic, and neuropathic pain) and pain multimorbidity (≥2 conditions) were compared. We found that adults living with CP or SB had a higher prevalence of *any* pain disorders (55.9% vs. 35.2%), nociceptive pain (44.0% vs. 26.7%), nociplastic pain (26.1% vs. 11.9%), neuropathic pain (9.6% vs. 5.6%), and pain multimorbidity (21.1% vs 8.4%), as compared to adults without CP or SB, and differences were to a clinically meaningful extent. Adjusted odds ratios (OR) of nociceptive pain (OR: 2.20; 95%CI: 2.15, 2.24), nociplastic pain (OR: 2.47; 95%CI: 2.41, 2.53), neuropathic pain (OR: 2.71; 95%CI: 2.54, 2.89), and other pain (OR: 3.92; 95%CI: 3.67, 4.19) were significantly higher for adults living with CP or SB. In conclusion, adults with CP or SB have a significantly higher prevalence and odds of common peripheral, central, and neuropathic pain disorders and pain multimorbidity, as compared to adults without CP or SB.

Keywords

cerebral palsy; spina bifida; chronic pain; nociceptive pain; nociplastic pain; neuropathic pain

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Introduction

Cerebral palsy (CP) and spina bifida (SB) are two pediatric-onset disabilities that result in lifelong impaired mobility and function. Individuals with CP and SB can have a near-normal life expectancies, but experience higher risk for developing secondary conditions [31], which can exacerbate underlying impaired functional status leading to continued functional decline and early mortality [4, 11, 24]. 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 chronic disease and multimorbidity [7, 8, 22, 24–26, 33, 34, 38, 43]. In addition to multimorbidity, a significantly higher incidence of psychological morbidity has been documented in adults with CP and SB [32].

Recent evidence has linked chronic pain and mood affective disorders among adults living with CP and other neurodevelopmental disorder [46]; and yet, very little is known about the natural history of pain subtypes in these populations. Most studies on pain in CP or SB have focused on general pain prevalence, with some studies documenting pain intensity, location and presence of co-occurring mood disorders and fatigue [2, 39, 41]. Although chronic pain has been documented as a significant problem in both CP and SB, there has been very little further evaluation of pain by etiology or phenotype. Many studies have documented the presence of musculoskeletal pain, and the links between mobility impairments in both CP and SB with musculoskeletal pain [37, 39]. Some evidence suggests a concern for pain centralization secondary to chronic musculoskeletal pain, or the role that periventricular leukomalacia (PVL) may play in the development of neuropathic pain [2, 3, 39]. There is an excellent review of the assessment and treatment of pain among children with significant impairment of the central nervous system [17]; however, there have been virtually no investigations to understand the pain phenotype among adults living with CP or SB. Thus, understanding the type and mechanisms of pain for adults living with CP or SB can help with diagnosis and aid in more targeted pain treatments. This study aimed to evaluate the number of pain diagnoses, pain multimorbidity, and pain phenotype in individuals with CP or SB from a large nationwide insurance claims database, with the goal of improving understanding of the pain experience in CP and SB.

Methods

Data Source

This was 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 2009 to 2014 were potentially eligible for this analysis. We chose these specific enrollment years for two reasons, including: (1) the ICD-9 Coordination and Maintenance Committee expanded pain diagnoses codes in 2006 [5], which took several years to see uptake and stabilization in the claims (e.g., Supplemental File 1 demonstrates the trajectory of diagnosis for "Any Pain" among cases [CP or SB] and controls); and (2) in 2015 ICD-10 codes were implemented which dramatically altered classification of pain as well as the prevalence estimates. We excluded individuals with less than 12 months of continuous enrollment to ensure sufficient claim history. All medical claims excluding outpatient pharmacy were considered to identify prevalence for these pain 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 File 2). 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 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) using ICD-9-CM codes. Among remaining members without CP or SB, we obtained a 20% simple random sample of general population controls, using a fixed randomization seed. The fixed randomization seed was used such that the exact sample of controls would be reproducible using the specific statistical software package. We further examined that no unintentional bias was introduced due to random sampling by conducting post-hoc effect size (ES) calculations between the full general population control cohort and the 20% sample on baseline covariates such as demographics and prevalent comorbidities. We considered an unbiased random sample if post-hoc effect sizes indicated no meaningful differences. The use of effect sizes is especially important in large administrative claims studies due to being statistically overpowered; therefore, Cohen's d and h ES calculations provides meaningful differences and addresses drawbacks of conventional statistical significance in high power studies.

Pain Phenotypes—The chronic pain literature describes different pain subtypes, depending on pain etiology: nociceptive pain, or pain due to direct tissue damage; neuropathic pain, or pain due to damage to the somatosensory system and nociplastic pain,

or pain due to central sensitization [13, 15]. The category of nociplastic pain has been developed more recently than nociceptive or neuropathic pain and has had other names, more specifically centralized pain or central hyperalgesia, where there is amplification of the pain processing or pain experience in the CNS [1]. Musculoskeletal pain is a common cause of nociceptive pain. Radiculopathy or peripheral neuropathy are common examples of possible etiologies leading to neuropathic pain. Fibromyalgia, chronic migraine headaches, IBS and interstitial cystitis are examples of nociplastic pain conditions. In the case of nociplastic pain conditions, many of the conditions co-occur (either simultaneously or sequentially) and the term chronic overlapping pain conditions has been developed to categorize the grouping of nociplastic diagnoses [36]. Describing the pain phenotype allows for improved diagnosis and more targeted treatment of pain.

Physician-diagnosed pain disorders were identified based on a single encounter that included at least one of pertinent ICD-9 codes (see Supplemental File 2 for list). The pain disorders were grouped into 4 categories: (1) Nociceptive Pain (e.g., pain in limb, joint pain-shoulder, joint pain-upper arm, joint pain-lower leg, joint pain-ankle and foot, etc.); (2) Nociplastic Pain (e.g., chronic pain, central pain syndrome, chronic pain syndrome, psychogenic pain, fibromyalgia, bladder pain syndrome, headache [including migraines], etc.); (3) Neuropathic Pain (e.g., neuralgia and neuritis); and (4) Other/Unspecified Pain. We defined pain multimorbidity as the onset of at least two of the aforementioned pain morbidities.

Statistical Analysis

Patient characteristics were summarized using means and standard deviations (SDs) for continuous variables and frequencies and percentages for categorical variables. The primary analysis was carried out to compare the prevalence estimates of each of the primary pain morbidities, pain morbidity combinations, as well as pain multimorbidity, between adults with CP or SB, as compared to adults without CP or SB. Standardized mean differences (SMD) via effect size (ES) calculations using Cohen's h were used in conjunction with formal p-value determination of significance to better understand a clinically meaningful effect size, with SMD≥0.2 determined to be a clinically meaningful difference, as previously described [6].

Since CP and SB are congenital conditions, all adults already have the condition at the time of their enrollment by age 18. To capture full pain morbidity 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.

To estimate the unadjusted and adjusted odds ratios for pain morbidities, a series of multivariable logistic regression with repeated measures for patients were developed. Since patients could be enrolled across multiple calendar years, a repeated measures analysis was used. Specifically, these models were used to quantify unadjusted and adjusted odds for each pain morbidity category comparing those with and without CP as the main exposure variable. Explanatory covariates for the adjusted models included age, sex, race, educational attainment, and household net worth. Several covariance structures were tested and the models that minimized the Akaike Information Criterion (AIC) was used as the most appropriate model fit. All analyses were conducted using SAS 9.4 (SAS Institute, Cary,

NC). All models were fit using PROC GENMOD with binomial distribution and log link with repeated measures on patient. Statistical testing was two-tailed with a significance level of 0.01 or 0.05 and effect sizes used a 0.2 meaningful difference cutoff.

Results

The mean time in the plan for eligible enrollees was 7.8±3.3 and 7.6±3.3 years for patients with CP or SB and controls respectively, and ranged from one year (inclusion criterion) to 11 years (Table 1).

Adults with CP or SB had a higher prevalence of *any* pain morbidity (55.9% vs. 35.2%), as well as nociceptive pain *only* (24.0% vs. 18.9%) and nociplastic pain *only* (8.4% vs. 5.5%) as compared to adults without CP or SB (Table 2). Adults with CP or SB had a higher prevalence of pain multimorbidity (21.1% vs 8.4%) as compared to adults without CP or SB, as well as a higher prevalence of *any* nociceptive pain combination (44.0% vs. 26.7%), *any* nociplastic pain combination (26.1% vs. 11.9%), *any* neuropathic pain combination (9.6% vs. 5.6%), and *any* "other/unspecified" pain combination (1.7% vs. 0.4%), as compared to adults without CP or SB (Table 2). Adults with CP or SB had a higher prevalence of the two most common pain multimorbidity combinations: (1) nociceptive pain + nociplastic pain (12.6% vs. 5.0%), and (2) nociceptive pain + nociplastic pain + neuropathic pain (3.1% vs. 0.9%), as compared to adults without CP or SB (Table 2).

Unadjusted logistic models demonstrated robust odds ratios (OR) for each of the incident pain morbidities among adults with CP or SB, and ranged from OR: 2.04 (95%CI: 2.00, 2.09) for nociceptive pain to OR: 3.74 (95%CI: 3.50, 4.00) for other/unspecified pain (all $p<0.001$). Fully adjusted logistic models demonstrated that adults with CP or SB had a greater odds ratio for all pain morbidities, including: (1) OR: 2.20 (95%CI: 2.15, 2.24) for nociceptive pain; (2) OR: 2.47 (95%CI: 2.41, 2.53) for nociplastic pain; (3) OR: 2.71 (95%CI: 2.54, 2.89) for neuropathic pain; and (4) OR: 3.92 (95%CI: 3.67, 4.19) for other/unspecified pain (Table 3).

Discussion

The principal finding of this study was that adults living with CP or SB had a higher prevalence of any and all pain morbidities and pain multimorbidity as compared to adults without CP or SB. This is the first and largest study to date examining pain morbidities across multiple etiologies in adults living with CP or SB. Future research and clinical efforts are needed to not only better understand the healthcare burden associated with these distinct pain conditions in adults with CP and SB, as well as across other subpopulations with neurodevelopmental and acquired physical disabilities, but also to understand the health disparities in access to appropriate pain management options between privately- and federally-insured beneficiaries living with these disabilities. Moreover, this is the first study to document the elevated burden of nociplastic and neuropathic pain experienced by adults living with CP or SB. In 2017, the International Association for the Study of Pain (IASP) defined "nociplastic pain" as "Pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral

nociceptors or evidence for disease or lesion of the somatosensory system causing the pain [18]" following the 2016 proposition of Kosek et al [21]. These findings support the need for improved clinical screening algorithms and design of targeted pain treatments specific to the etiology in order to reduce risk of pain progression and associated psychological morbidity [32] in these higher risk populations.

This study represents an important contribution to the current literature by distinguishing the pain phenotypes among adults living with CP or SB. Overall pain prevalence, pain multimorbidity and all three specific pain subtypes (nociceptive, nociplastic, and neuropathic pain) had a substantially higher risk of occurrence in adults living with CP or SB, as compared to the control population. Any pain prevalence was nearly 60% among the adults with CP or SB, which is slightly lower than many studies involving adults with neurodevelopmental disabilities [2, 19, 20, 37, 40]. For example, when compared to individuals without CP, previous studies have shown that about 70-75% of adults with CP have reported chronic musculoskeletal pain [12, 40]. It is plausible this study underestimated the true pain experience in these population, due to poor clinical diagnostic practice of pain among patients with CP and SB. Indeed, the patterns of any pain diagnoses in the claim has changed dramatically from 2002 to 2014 (Supplemental File 1). Thus, future clinical research is desperately needed to determine the true pain experience and phenotype in these populations, through comprehensive pain screening inventories. This could include use of questionnaires to evaluate for nociplastic and neuropathic pain, as well as assessments of pain processing with quantitative sensory testing with advanced imaging techniques such as fMRI. Future studies are also needed to examine outpatient pharmacy claims and inferred opioid and non-opioid medication prescribing patterns. Although opioids are well known for high risk of addiction and morbidity, many non-opioid pain medications also present risks for morbidity. In fact, two of the most commonly utilized non-opioid pain medication categories, NSAIDs and acetaminophen, can affect renal and liver function, depending on dosing and baseline comorbidities. This is particularly important when considering individuals with CP and SB, as recent reports have noted a high level of polypharmacy in adults with CP, with CKD and liver disease contributing extensively to morbidity and mortality [44, 48]. In addition to concerns regarding polypharmacy, chronic opioid use has many adverse long-term consequences, including tolerance or addiction, central hyperalgesia and risk of respiratory depression [16]. Many individuals with CP or SB may be prescribed benzodiazepines or gabapentinoids for comorbid medical conditions. The combination of benzodiazepines and opioids represents a particularly scary combination with elevated risk of all-cause mortality [51]. Thus, understanding the pain phenotype facilitates improved treatment of pain by targeting medications appropriately and avoiding high risk prescribing patterns and polypharmacy.

When separating out by pain phenotype, all three subtypes of pain had substantially higher adjusted odds for adults with CP or SB, with nociceptive pain having a 2.2 times higher odds, nociplastic pain conditions with a nearly 2.5 times higher odds, and neuropathic pain conditions with a 2.7 times higher odds of diagnosis. Pain multimorbidity was also significantly higher in CP or SB (21.1% vs. 8.4%), and the most frequent combination of pain subtypes were nociceptive pain + nociplastic pain, and nociceptive pain + nociplastic pain + neuropathic pain. Most studies evaluating pain in CP or SB have described the

presence of nociceptive (or “musculoskeletal”) pain, with lower extremity and back pain being the most common pain location [27, 37, 41]. The risk for developing neuropathic pain conditions may be secondary to the underlying damage to the central nervous system, potentially to the lemniscal and extraleminscal tracts due to damage from PVL [3] or alterations in somatosensory processing described in individuals with CP [35]. Nociplastic pain also had substantially higher odds among adults with CP or SB in this study than in the general population. The nociplastic pain subtype has not been well documented or studied in CP or SB, but some experts have described the potential for central sensitization and/or hyperalgesia secondary to chronic peripheral nociceptive pain, particularly among children with impairment of the central nervous system [17]. Ultimately, understanding the mechanisms of pain is vital, as response to pain treatment varies depending on pain etiology. Better identifying pain phenotypes will allow for more focused/specific treatment. In addition, some treatments for pure nociceptive pain, such as narcotics, have been demonstrated to be harmful in nociplastic pain conditions, such as fibromyalgia [14]. As an important example, long-term opioid use in fibromyalgia has been associated with poorer outcomes than in individuals who are not receiving opioids [29].

In addition to chronic pain, there is a high burden of mental health disorders and fatigue in both children and adults with CP [9, 47, 49, 50]. Central sensitization includes the joint contributions of mental health, sleep disorders, and other pain conditions to a centralized processing. Sleep disorders are common in persons with CP and SB [23, 28], as are depression, anxiety and other mental health disorders [30, 46, 50]. Nociplastic pain assessments evaluate the intersection of sleep, mental health and pain. One such tool is the fibromyalgia (FM) survey questionnaire. The FM questionnaire is split into the Widespread Pain Index, which assesses number of pain areas, and the Symptom Severity Scale. The Symptom Severity Scale assesses problems with sleep, mood, other pain conditions like chronic headaches and abdominal pain to assess for constellation of symptoms noted in centralized pain states. The Central Sensitization Inventory also assesses for the presence of central sensitization, not only in individual pain states but also for chronic overlapping pain conditions. The Central Sensitization Inventory includes questions about sleep, mood/anxiety and bladder and bowel symptoms along with diagnoses of other central pain conditions like irritable bowel syndrome, FM, etc. Future research should consider incorporating these tools when attempting to understand the intersection between chronic pain, sleep disorders and psychological morbidity among adults living with CP or SB, as well for informing the appropriate clinical interventions to treat pain.

Strengths and Weaknesses

A major strength of this study is the number of pain morbidities from different etiologies that were investigated. Our comprehensive assessment of medically-diagnosed pain phenotypes among individuals with CP or SB throughout the adult lifespan may prompt the development of improved screening strategies and identification of individuals for risk of nociceptive, nociplastic, and neuropathic pain. Given that chronic pain has also been noted to negatively impact quality of life and function in both CP and SB [2, 10, 24, 42], the ability to accurately identify and specifically tailor pain management/treatments

by understanding etiology may also prevent early functional loss and lack of independence among adults living with CP and SB.

Our study also has several limitations that should be acknowledged. First, the sample with CP or SB may not be entirely representative of the U.S. population of adults with CP or SB, attributable to a varied market penetration across states. 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 population of adults with CP or SB [45], because they had to be enrolled in private insurance, either by purchasing their own insurance, by being covered through employment or marriage to someone who had private insurance, or by receiving insurance on parent's insurance up to age 26. Individuals with more severe forms of CP or SB may be more likely to be on federally-subsidized health insurance, Medicare, or Medicaid state-sponsored programs. Therefore, results and comparisons to adults without CP or SB are likely conservative estimates, and the true extent of chronic pain may be underestimated in this study. Another limitation was that chronic low back pain could not be separated out in this study from acute back pain for the analysis of pain phenotypes. As a result, all back pain codes were included in the nociceptive pain group, potentially reducing the prevalence of nociplastic pain and elevating the prevalence of nociceptive pain diagnoses. Further research is needed to more closely evaluate pain phenotypes, in particular nociplastic pain, neuropathic pain, and pain multimorbidity (i.e., chronic overlapping pain conditions) among individuals living with CP or SB, as well as other neurodevelopmental disabilities. Moreover, we were unable to determine or account for the pathological etiologies of the CP or SB diagnoses (e.g., extent of white matter damage). It is possible that the extent, severity, and compensatory mechanisms for recovery from the initial brain damage leading to CP, or extent of myelomeningocele leading to SB, may interfere with development in early life, and accelerate decline with age. Future studies are needed to disentangle the pathological features of CP and SB with the development of secondary disorders in this population. Finally, our study included only adults living with CP and SB, both of which have high rates of pain in childhood. Since we are only studying prevalent pain conditions/phenotypes in adults using administrative data, we were unable to determine the age at pain commencement, and/or the impact of living with pain in terms of both the lived experience (e.g., links with quality of life, depression, etc.) and also the burden to healthcare (e.g., healthcare utilization, hospitalization, etc.). Indeed, it is very likely that these pain outcomes would have been present long before their enrollment period in the claim began, and that they may have an enormous impact on both the lived experience and healthcare burden. Future work is needed to include prospective data collection of patients being seen in clinic, which will allow for determining a self-reported approximate age at pain commencement and potential links with health related quality of life.

Conclusion

Adults with CP or SB have an elevated risk of a variety of pain subtypes and pain multimorbidity, as 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 pain phenotype among adults with CP and SB, improving clinical pain screening strategies, and developing efficient referral resources for appropriate pain management may help reduce the burden of physical and mental health disorders in these population. Future studies are needed to better understand how the impact of chronic overlapping pain may influence the lived experience for adults with CP and SB, as well as to understand the burden to health systems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Descriptive characteristics among adults with (Case) and without (Control) CP/SB.

	Case	Control
Overall	22,648 (100%)	931,623 (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)
Age Group		
18-30	5,060 (22.3%)	142,861 (15.3%)
31-54	10,182 (45.0%)	397,909 (42.7%)
55-64	3,239 (14.3%)	149,841 (16.1%)
65 or Older	4,167 (18.4%)	241,012 (25.9%)
Gender		
Female	12,948 (57.2%)	488,160 (52.4)
Male	9,699 (42.8%)	443,368 (47.6)
Race		
White	15,473 (68.3%)	627,918 (67.4%)
Black	2,511 (11.1%)	84,431 (9.1%)
Hispanic	2,059 (9.1%)	94,709 (10.2%)
Asian	506 (2.2%)	40,233 (4.3%)
Unknown	2,099 (9.3%)	84,332 (9.1%)
Geographic Region		
East North Central	3,402 (15.0%)	124,811 (13.4%)
East South Central	784 (3.5%)	29,943 (3.2%)
Middle Atlantic	1,638 (7.2%)	64,014 (6.9%)
Mountain	2,286 (10.1%)	89,431 (9.6%)
New England	944 (4.2%)	33,353 (3.6%)
Pacific	2,873 (12.7%)	133,804 (14.4%)
South Atlantic	5,620 (24.8%)	228,711 (24.6%)
West North Central	1,918 (8.5%)	95,420 (10.2%)
West South Central	3,063 (13.5%)	124,948 (13.4%)
Unknown or Missing	120 (0.5%)	7,188 (0.8%)

Table 2.

Prevalence of any and all pain morbidities and multimorbidity among adults with (case) and without (control) CP or SB

Pain Combinations	Cases *n=22,648*	Controls *n=931,623*
Any Pain	12,661 (55.9%) *	328,150 (35.2%)
Pain Multimorbidity	4,769 (21.1%) *	78,380 (8.4%)
Any Nociceptive Pain Combination	9,964 (44.0%) *	248,944 (26.7%)
Nociceptive Pain Only	5,439 (24.0%) *	175,622 (18.9%)
Nociceptive Pain and Other Pain	106 (0.5%)	1,161 (0.1%)
Nociceptive Pain and Neuropathic Pain	642 (2.8%)	16,731 (1.8%)
Nociceptive Pain, Neuropathic Pain, and Other Pain	21 (0.1%)	194 (0.02%)
Nociceptive Pain and Nociplastic Pain	2,860 (12.6%) *	46,183 (5.0%)
Nociceptive Pain, Nociplastic Pain, and Other Pain	127 (0.6%)	756 (0.1%)
Nociceptive Pain, Nociplastic Pain, and Neuropathic Pain	706 (3.1%) *	8,060 (0.9%)
Nociceptive Pain, Nociplastic Pain, Neuropathic Pain, and Other Pain	63 (0.3%)	237 (0.03%)
Any Nociplastic Pain Combination	5,905 (26.1%) *	111,209 (11.9%)
Nociplastic Pain Only	1,906 (8.4%) *	50,970 (5.5%)
Nociplastic Pain and Other Pain	15 (0.1%)	276 (0.03%)
Nociplastic Pain and Neuropathic Pain	223 (1.0%)	4,690 (0.5%)
Nociplastic Pain, Neuropathic Pain, and Other Pain	5 (0.02%)	37 (<0.01%)
Nociplastic Pain and Nociceptive Pain	2,860 (12.6%) *	46,183 (5.0%)
Nociplastic Pain, Nociceptive Pain, and Other Pain	127 (0.6%)	756 (0.1%)
Nociplastic Pain, Nociceptive Pain, and Neuropathic Pain	706 (3.1%) *	8,060 (0.9%)
Nociplastic Pain, Nociceptive Pain, Neuropathic Pain, and Other Pain	63 (0.3%)	237 (0.03%)
Any Neuropathic Pain Combination	2,171 (9.6%) *	52,506 (5.6%)
Neuropathic Pain Only	510 (2.3%)	22,502 (2.4%)
Neuropathic Pain and Other Pain	1 (<0.01%)	55 (0.01%)
Neuropathic Pain and Nociceptive Pain	642 (2.8%)	16,731 (1.8%)
Neuropathic Pain, Nociceptive Pain, and Other Pain	21 (0.1%)	194 (0.02%)
Neuropathic Pain and Nociplastic Pain	223 (1.0%)	4,690 (0.5%)
Neuropathic Pain, Nociplastic Pain, and Other Pain	5 (0.02%)	37 (<0.01%)
Neuropathic Pain, Nociplastic Pain, and Nociceptive Pain	706 (3.1%) *	8,060 (0.9%)
Neuropathic Pain, Nociplastic Pain, Nociceptive Pain, and Other Pain	63 (0.3%)	237 (0.03%)
Any Other Pain Combination	375 (1.7%) *	3,392 (0.4%)
Other Pain Only	37 (0.2%)	676 (0.1%)
Other Pain and Neuropathic Pain	1 (<0.01%)	55 (0.01%)
Other Pain, Nociceptive Pain, and Neuropathic Pain	21 (0.1%)	194 (0.02%)
Other Pain, Nociplastic Pain, and Neuropathic Pain	5 (0.02%)	37 (<0.01%)
Other Pain, Nociplastic Pain, Nociceptive Pain, and Neuropathic Pain	63 (0.3%)	237 (0.03%)

Pain Combinations	**Cases** ***n=22,648***	**Controls** ***n=931,623***
Other Pain and Nociplastic Pain	15 (0.1%)	276 (0.03%)
Other Pain and Nociceptive Pain	106 (0.5%)	1,161 (0.1%)
Other Pain, Nociplastic Pain, and Nociceptive Pain	127 (0.6%)	756 (0.1%)

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

Table 3.

Unadjusted and adjusted odds for pain morbidity comparing CP or SB to the general population of controls.

	Model 1	Model 2
Pain Morbidity		
Nociceptive Pain	2.04 (2.00, 2.09)***	2.20 (2.15, 2.24)***
Nociplastic Pain	2.52 (2.46, 2.58)***	2.47 (2.41, 2.53)***
Neuropathic Pain	2.63 (2.47, 2.818)***	2.71 (2.54, 2.89)***
Other/Unspecified Pain	3.74 (3.50, 4.00)***	3.92 (3.67, 4.19)***

Model 1: Unadjusted

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

*** P-value < 0.001