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Effect of pain on mood affective disorders in adults with cerebral palsy

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ABBREVIATIONS

IRR Incidence rate ratio

MAD Mood affective disorder

AIM To determine if pain is associated with 12-month incidence of mood affective disorders (MAD) in adults with cerebral palsy (CP).

METHOD Data from Optum Clinformatics® Data Mart (2013–2016) were used for this retrospective cohort study. Diagnostic codes were used to identify adults (≥ 18 y) with CP, incident cases of MAD, and covariates (other neurodevelopmental conditions, sleep disorders, arthritis). Pain (any type, location) was identified between 1st October 2014 and 30th September 2015. The pain group was divided into new or consistent pain if they had a history of pain (i.e. consistent) in the 12 months before their first pain claim date. Crude incidence rates of MAD (expressed per 100 person-years) were estimated. Cox regression was used to estimate hazard ratio (95% confidence interval [CI]) of MAD after adjusting for covariates.

RESULTS Adults that had new pain ($n=859$; incidence rate=15.5) or consistent pain ($n=1303$; incidence rate=17.9) had greater crude incidence rate of MAD compared to adults without pain ($n=3726$; incidence rate=5.9). The elevated rate of MAD remained after adjusting for covariates, for new pain (hazard ratio=2.4; 95% CI=1.9–3.0) and consistent pain (hazard ratio=2.1; 95% CI=1.7–2.7).

INTERPRETATION Pain is associated with greater incidence of MAD in adults with CP. This association remained after accounting for potential confounding factors.

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Pain and Mood Affective Disorders in CP *Daniel G Whitney et al.*

What this paper adds

- Pain was associated with higher 12-month incidence of mood affective disorders (MAD).
- The 12-month MAD incidence was similar between new and consistent pain groups.
- The MAD incidence remained higher adjusting for neurodevelopmental comorbidities, sleep disorders, and arthritis.

[main text]

The wide array of complications associated with cerebral palsy (CP) increases risk for developing a variety of physiological changes,^{1,2} including mental health disorders.³ Given that CP is a chronic condition with evidence of accelerated decline in health and function throughout the lifespan,^{4–6} the risk of mental health disorders is likely increased throughout adulthood.⁷ Indeed, emerging evidence has started to shed light on mental health-related risks for individuals with CP.^{3,8–11} In a nationwide study in the US, adults with CP were found to have a higher prevalence of a variety of mental health disorders compared to adults without CP, with mood affective disorder (MAD) the most prevalent mental health disorder for adults with CP.⁹ In a nationwide study from the UK, the incidence of MAD was higher for adults with versus without CP.⁸ This is concerning because mental health disorders, and particularly MAD, are implicated in the pathogenesis of unhealthy aging, and are therefore of great public health concern.¹²

While attention towards understanding the burden of MAD for adults with CP is growing, there is a dearth of evidence identifying longitudinal risk factors for predicting MAD. Recent cross-sectional work suggest a clustering of many commonly reported clinical factors with MAD

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among individuals with CP, including pain, sleep disorders, and arthritis, among other factors (e.g. fatigue, loneliness).^{3,10,13–16} The mechanisms linking these factors are complex and dynamic, and may be driven by unique attributes of the individual, cognitive ability, health history, or a shared neurobiological etiology. Further, the temporal sequence of developing these clinical factors can differ across clinical populations,^{17,18} making clinical diagnosis, prevention, and treatment of MAD challenging.

To date, the temporal sequence of pain, sleep disorders, arthritis, and MAD is unknown for adults with CP. In other populations, there is mixed evidence of bidirectional causal relations between pain and MAD, with evidence to suggest that medical (or biological), psychological, and social factors mediate the association as well as to drive the causal direction.^{19,20} Limited longitudinal studies of the effects of pain treatment suggest positive effects of pain reduction on MAD symptoms.²¹ In the population with CP, the association between pain and MAD may be influenced by the underlying mechanism causing CP and comorbid neurodevelopmental conditions, including intellectual disabilities, autism spectrum disorders, and epilepsy, each associated with mental health disorders.^{22–24}

The objective of this study was to determine the association between pain and 12-month incidence of MAD among adults with CP. We hypothesized that pain would be associated with higher 12-month incidence of MAD, even after accounting for neurodevelopmental conditions, sleep disorders, and arthritis.

METHOD

Data source

Data from 2013 to 2016 were extracted from the Optum Clinformatics® Data Mart Database (OptumInsight™, Eden Prairie, MN, USA), a US nationwide deidentified single private payer administrative claims database.²⁵ This database contains data from beneficiaries who have either commercial or Medicare Advantage health plans, and includes all service utilization (e.g. inpatient, outpatient) throughout their enrolment on the insurance plan. Medicare beneficiaries can opt to enrol in a private Medicare Advantage health plan. These plans can offer additional coverage not available in the public Medicare program (e.g. vision, hearing, dental). To be enrolled in a private payer health plan, beneficiaries of any age, income, or disability status either pay for coverage or are covered through their employer or parents up to the age of 26 years. To

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preserve patient identity, researchers leveraging this database are allowed either the Date of Death or Socioeconomic Status table. The current investigation was developed under a larger project in which the Date of Death table was obtained. Therefore, some information regarding socioeconomic status (i.e. income, education) were not available. Since data are deidentified, the University Institutional Review Board approved this study as non-regulated.

Sample selection

Medical conditions were identified using the International Classification of Diseases, 9th and 10th Revisions (ICD-9 and ICD-10), Clinical Modification codes to account for the shift in reporting codes on 1st October 2015, and are presented in [Table 1](#).

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The period of 1st October 2014 to 30th September 2015 was initially used to identify eligible participants: adults 18 years of age or older with CP with at least one service utilization (to limit detection bias among persons who were not seen by a physician). We defined CP by at least one claim for any CP diagnosis.²⁵ Data regarding severity of CP are not available in claims and more than 70% had 'other' or 'unspecified' CP, thereby preventing stratification of the sample by clinical CP subtypes.

The exposure variable was pain, including, but not limited to, central pain syndrome, chronic pain conditions, dorsalgia, and pain in joints. We defined pain in three steps. First, we identified the first claim for pain during the period of 1st October 2014 and 30th September 2015. Second, individuals had to have at least one more claim for pain on a subsequent day within 12 months after their first pain claim date in step 1, to rule out initial claims that may have been for screening. Third, we categorized our sample based on 'new' or 'consistent' pain using a look-back period of 12 months. Therefore, further eligibility criteria involved continuous enrolment in a health plan and at least one of any service utilization types (e.g. inpatient) in the 12 months before their first pain claim date in step 1: new pain was defined as not having any claim for pain within 12 months before the first pain claim date in step 1; consistent pain was defined as having at least one claim for pain (any type or location) within 12 months before the first pain claim date in step 1. We grouped all pain conditions into a single dichotomous variable (i.e. yes/no) because the majority of diagnosed pain conditions are presumed to come from physicians that have little knowledge on how to adequately treat and/or monitor health for their adult patients with CP. Therefore, the accuracy of diagnosing pain (e.g. etiology, chronicity) in

this database may be lower than the accuracy of identifying the presence/absence of any type of pain. We designated ‘new’ and ‘consistent’ pain as a proxy for new onset versus chronic of any of the included pain conditions.

The comparison group in this study consisted of adults with CP that did not have any claims for pain between 1st October 2014 and 30th September 2015, and that also had at least one service utilization in the look-back period. The start date of follow-up was the date of the first claim for pain or a randomly assigned date for adults without pain by using a uniform distribution to randomly assign a date during the individual’s enrolment period.

Outcome measure

The outcome event was the occurrence of incident MAD up to 12 months after the start date of follow-up, defined by at least one claim.⁹ Individuals were excluded if they had at least one claim for MAD in their 12-month look-back period.

Covariates

Sociodemographic covariates included age, sex, ethnic group, and US region.

Neurodevelopmental conditions included intellectual disabilities, autism spectrum disorders, and epilepsy. Baseline sleep disorders and arthritis and other inflammatory polyarthropathies (hereafter referred to as ‘arthritis’) were identified in the look-back period. Healthcare utilization was determined as the number of all service visits (e.g. inpatient) during the look-back period.

Statistical analysis

Crude incidence rates of MAD were estimated as the number of outcome events divided by the amount of person-years, expressed per 100/year. Crude incidence rate ratios (IRRs) and 95 per cent CIs were estimated using the group without pain as the reference. Individuals were right censored at death, loss to follow-up, or end of study period (12mo after start date of follow-up).

Cox proportional hazard regression models were fitted to adjust for covariates when comparing incidence rate, by estimating hazard ratios (95% CI) of MAD incidence, comparing each exposure group with the reference group. Three sets of covariates were used to explain the difference in crude rates between groups: model 1 – age (continuous), sex, US region, and healthcare utilization (quintiles); model 2 – model 1 covariates plus neurodevelopmental

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conditions; and model 3 – model 2 covariates plus baseline sleep disorders and arthritis. Possible interactions between exposure status and age or sex were assessed by conducting separate analyses for age or sex strata and including product terms in the Cox models. Proportional hazards assumption was visually inspected and was met.

Sensitivity analysis

Ethnic group was not adjusted for in the Cox regression models to limit potential bias because of missing ethnic group data. We conducted two sensitivity analyses to assess for possible confounding and selection bias in the main analysis. Sensitivity analysis #1 was a complete case analysis that did not adjust for ethnic group; sensitivity analysis #2 was a complete case analysis that adjusted for ethnic group. Results were compared from sensitivity analyses #1 and #2 to assess possible confounding by ethnic group. Results were also compared from sensitivity analysis #1 and the main analysis to assess for possible selection bias attributable to exclusion of adults without ethnic group data.

We excluded individuals from the main analysis that had one claim for pain between 1st October 2014 and 30th September 2015 and without a subsequent claim for pain 12 months after that met other inclusion criteria ($n=349$). We conducted a sensitivity analysis using the procedures described above after adding these individuals to the respective pain group, to assess for possible selection bias.

Because of the observational design and lack of medication information (e.g. anti-epileptic drugs, pain medication), which is a limitation to the current study, results are subject to bias from unmeasured confounding. We estimated the extent of unmeasured confounding by computing e-values, which measures the minimum strength of association needed to explain a specific exposure-outcome association, conditional on the set of covariates.²⁶

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Baseline descriptive characteristics of adults without pain ($n=3726$), new pain ($n=859$), and consistent pain ($n=1303$) are presented in Table 2.

Incidence rate of MAD

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Commented [SF5]: Typesetter: insert Table 2 near here

The crude incidence rate was 5.86 for adults without pain, 15.52 for new pain, and 17.92 for consistent pain (Table 3). Compared to adults without pain, the crude IRR was elevated for adults with new pain (IRR=2.65; 95% CI=2.10–3.34) and consistent pain (IRR=3.06; 95% CI=2.51–3.73). Compared to adults with consistent pain, the crude IRR was similar for adults with new pain (IRR=0.87; 95% CI=0.69–1.09) (data not shown).

Commented [SF6]: Typesetter: insert Table 3 near here

Cox regression analysis of MAD

Compared to adults without pain, the hazard ratio (95% CI) adjusting for demographic variables and healthcare utilization (model 1) was 2.35 (1.86–2.97) for adults with new pain and 2.22 (1.79–2.76) for adults with consistent pain (Table 3). The hazard ratios were not largely affected when further adjusting for comorbid neurodevelopmental conditions (model 2). After further adjustment for sleep disorders and arthritis (model 3), the hazard ratio was unaffected compared to model 1 for adults with new pain (hazard ratio=2.35; 95% CI=1.86–2.97) and decreased slightly from model 1 for adults with consistent pain, but remained elevated (hazard ratio=2.13; 95% CI=1.71–2.67). The adjusted rate of MAD was not different for adults with new versus consistent pain when adjusting for covariates in model 1 (hazard ratio=1.06; 95% CI=0.83–1.35), model 2 (hazard ratio=1.07; 95% CI=0.84–1.37), and model 3 (hazard ratio=1.10; 95% CI=0.86–1.41) (data not shown).

Sensitivity analysis

For individuals with complete data on ethnic group ($n=5075$), the MAD cases, incidence rate, and IRR (reference: without pain) were 161 and 5.63 for adults without pain, 102 and 15.58 for new pain (IRR=2.77; 95% CI=2.16–3.55), and 160 and 17.67 for consistent pain (IRR=3.14; 95% CI=2.52–3.91). Adjusted hazard ratios of MAD are presented in Table 4. Crude incidence rate and IRR were similar to the main analysis. A comparison of hazard ratio estimates from sensitivity analysis #1 and #2 show similar results, suggesting that ethnic group is not a confounder in the main analysis. A comparison of hazard ratio estimates from sensitivity analysis #1 and the main analysis show similar results, providing no evidence to suggest selection bias.

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The results of the sensitivity analysis that included individuals with at least one claim for pain ($n=1080$ new pain; $n=1431$ consistent pain) were in accordance with the main analysis for the new pain group (incidence rate=13.93; IRR=2.38, 95% CI=1.90–2.97; model 3 hazard

ratio=2.13, 95% CI=1.70–2.66) and consistent pain group (incidence rate=17.02; IRR=2.91, 95% CI=2.39–3.54; model 3 hazard ratio=2.00, 95% CI=1.61–2.48), providing no evidence to suggest selection bias.

The e-value (lower 95% CI) was 4.13 (3.12) for new pain versus no pain and 3.68 (2.81) for consistent pain versus no pain. Given the large e-values, it appears unlikely that unmeasured confounding or lack of medication information largely biased effect estimates for the exposure variables.

DISCUSSION

The main finding of this study is that pain, whether new onset or consistent, was associated with greater 12-month incidence of MAD among adults with CP, which was largely unaffected by comorbid neurodevelopmental conditions, sleep disorders, and arthritis. Mental health disorders, and particularly MAD, are a primary driver of the burden of disease for adults¹² and can be prevented or treated if adequate clinical knowledge is established leading to detection and response. Knowing that pain increases risk of MAD suggests the need for improved screening strategies and opportunities for intervention to mitigate risk of both pain and MAD specific to the heterogeneous and medically complex nature of CP.

In the current study, the prevalence of pain was approximately 37%, consistent with the range of 33% to 75% previously reported for individuals with CP.^{10,27} The 12-month incidence of MAD for the entire CP cohort was approximately 9%, which is lower than the 18% for depression previously reported.⁸ However, the study by Smith et al.⁸ examined incidence over a 28-year period. In the current study, there were considerable differences in age and healthcare utilization. We therefore used Cox regression to adjust for age, sex, US region, and healthcare utilization. The adjusted hazard ratios were more than twofold higher compared to adults without pain. Further adjustment for comorbid neurodevelopmental conditions, sleep disorders, and arthritis, which are all implicated in the pathogenesis of pain and MAD, had little-to-no impact on hazard ratios for both pain groups. After adjusting for all covariates, pain was associated with a 2.1- to 2.4-fold higher rate of MAD compared to no pain among adults with CP, with no difference between the pain groups.

The link between pain, sleep disorders, arthritis, and MAD is complex, especially for CP, and may be affected by patient (e.g. comorbidities, resilience, loneliness) and environmental (e.g.

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socioeconomic status, adverse events) characteristics. This study was designed to investigate the pathway of pain to incident MAD, and we found a robust association; however, this study does not rule out the possibility that sleep disorders or other factors may be involved early in the pathogenic pathway leading to pain (or pain exacerbation) and/or MAD for a different sector of the CP population, or that MAD leads to these factors. Studies in different clinical populations suggest unique pathways where pain impedes sleep, with a subsequent effect on depressive symptoms.¹⁷ On the other hand, sleep disorders may contribute to exacerbating pain and, consequently, heighten depressive symptoms.²⁸ Also, depressive symptoms have been suggested as a mediator of the sleep-pain association.¹⁸ Further longitudinal investigation of the temporal sequence of pain, sleep disorders, arthritis, and MAD will be essential in establishing causal arguments and developing an understanding of the possible mechanisms that link these factors among adults with CP.

There are a number of limitations of this study. First, data were from a private payer claims database, which likely reflects the higher-functioning segment of the CP population. This speculation is based on differences in enrolment criteria between private and public insurance types, medical needs of individuals with CP based on insurance coverage, and prevalent chronic diseases for adults with pediatric-onset disabilities (higher among publicly vs privately insured), including CP.^{25,29} It is important to note that while the prevalence estimates of the exposure and outcome may reflect the higher-functioning segment of the CP population, it is plausible that the direction, and even the strength, of the exposure-outcome association observed in this study is representative of what occurs in the general CP population. Nevertheless, study conclusions should be considered within the scope of this particular population of privately insured adults with CP.

Second, in order to be identified as having pain in claims data, the individual must be aware of their pain levels and communicate this to their healthcare provider. Some individuals with more severe forms of CP, cognitive or communication impairments, or who have become desensitized to their chronic pain condition may not have communicated their pain. Same holds true for MAD, which often goes unrecognized in CP.

Third, we did not stratify the pain group by pain type. Pain can be driven by peripheral or central mechanisms, or a combination of both. Historically, pain is not well assessed or characterized for the CP population. Pain may be assumed to be more peripherally driven from

muscles and joints because of altered mechanical loading patterns, a history of orthopedic abnormalities and surgical interventions, or higher prevalence of arthritis.³⁰ Therefore, a medical professional with little experience treating adults with CP may be more likely to incorrectly diagnose pain, and thus be incorrectly reflected in claims data. In addition, consistent pain was defined as a claim for any pain condition, not necessarily the same pain condition, in the 12 months before the first pain claim. Future studies are warranted to identify which pain conditions are associated with MAD incidence.

Fourth, although we were following traditional claims-based methods, the relatively short time period may have missed those that had MAD before pain.

Fifth, MAD based on ICD codes instead of the Diagnostic and Statistical Manual of Mental Disorders may either underscore or overrate MAD.

Sixth, we did not adjust for other mental health disorders (e.g. anxiety) or substance abuse. Future studies are needed to investigate how these conditions factor into the association between pain and MAD, which could assist in clinical monitoring and treatment of mental health disorders for adults with CP.

In conclusion, pain is associated with greater 12-month incidence of MAD among privately insured adults with CP. The pain-MAD association was largely unaffected by the presence of neurodevelopmental conditions, sleep disorders, and arthritis. Future studies are needed to determine whether effective pain management reduces the risk of onset of MAD.

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Table 1: Diagnostic codes for all medical conditions using the International Classification of Diseases, 9th or 10th revision (ICD-9/ICD-10), Clinical Modification system

Medical conditions	ICD-9 family or individuals codes	ICD-10 family or individuals codes
Neurodevelopmental conditions		
Cerebral palsy	333.71, 343 family	G80 family
Intellectual disabilities	317–19 families, 758.0–2, 758.31	F70–73 families, F78, F79
Autism spectrum disorders	299.00, 299.01, 299.10, 299.11, 299.80, 299.81, 299.90, 299.91	F84.0, F84.3, F84.5, F84.8, F84.9
Epilepsy	345 family	G40 family
Pain		
Central pain syndrome; other chronic pain; chronic pain syndrome; abdominal pain; dorsalgia, including panniculitis affecting regions of the neck and back, radiculopathy, cervicalgia, sciatica, lumbago with sciatica, low back pain, pain in thoracic spine, other or unspecified dorsalgia; pain in joint, including shoulder, elbow, wrist, hand, hip, knee, ankle/foot; other or unspecified pain	338.0, 338.29, 338.4, 719.4 family, 724.1–5, 729.5, 780.96, 789.0 family	G89.0, G89.29, G89.4, M54 family, M25.5 family, R10 family, R52 family
Mood (affective) disorders		
Manic episode; bipolar disorder; major depressive disorder, single episode and recurrent; persistent mood (affective) disorders; unspecified mood (affective) disorders	296 family, 300.4, 301.12, 311 family	F30–34 families, F39
Sleep disorders		

Insomnia; hypersomnia; circadian rhythm sleep disorders; sleep apnea; narcolepsy and cataplexy; parasomnia; sleep related movement disorders; other or unspecified sleep disorders; sleep disorders not due to a substance or known physiological condition, including insomnia, hypersomnia, sleepwalking, sleep terrors, nightmare disorder, other or unspecified sleep disorder	307.4 family, 327.0–5 families, 347.00, 347.01, 347.10, 347.11, 327.8, 780.51–54, 780.57–59	^a
Arthritis		
Rheumatoid arthritis and other inflammatory polyarthropathies; osteoarthritis and allied disorders	714 family, 715 family	^a

^aICD-9 version was used only.

Table 2: Baseline descriptive characteristics of adults with cerebral palsy by pain status

	Without pain (n=3726)	New pain (n=859)	Consistent pain (n=1303)
Age, y:mo mean (SD)	44:9 (19:4)	52:8 (19:0)	56:8 (17:2)
18–40y	45.5 (1697)	29.3 (252)	18.6 (242)
41–64y	35.1 (1309)	39.6 (340)	47.4 (618)
≥65y	19.3 (720)	31.1 (267)	34 (443)
Sex			
Females	44.7 (1667)	50.4 (433)	50.3 (655)
Males	55.3 (2059)	49.6 (426)	49.7 (648)
Ethnic group			
White	64.0 (2385)	67.5 (580)	61.2 (798)
Black	9.2 (344)	10.5 (90)	11.4 (148)
Hispanic	10.0 (372)	8.4 (72)	8.4 (110)
Asian	3.6 (135)	2.3 (20)	1.6 (21)

Unknown/missing	13.2 (490)	11.3 (97)	17.3 (226)
US region			
West	27.7 (1031)	28.1 (241)	25.1 (327)
Midwest	24.0 (896)	23.4 (201)	23.4 (305)
South	38.7 (1441)	37.1 (319)	37.2 (485)
Northeast	9.2 (342)	10.9 (94)	14.0 (183)
Unknown/missing	0.4 (16)	0.5 (4)	0.2 (3)
Intellectual disabilities	22.4 (836)	16.6 (143)	12.3 (160)
Autism spectrum disorders	4.6 (173)	2.4 (21)	1.6 (21)
Epilepsy	29.1 (1083)	22.4 (192)	21.6 (281)
Sleep disorders	4.5 (169)	6.1 (52)	10.1 (131)
Arthritis	4.1 (152)	5.7 (49)	20.3 (265)
Healthcare utilization (# of visits)			
Median (IQR)	8 (4–19)	11 (5–22)	24 (13–42)
Quintiles			
1–4	29.3 (1093)	22.2 (191)	3.6 (47)
>4–8	22.7 (846)	17.1 (147)	10.0 (130)
>8–15	18.6 (694)	24.2 (208)	17.4 (227)
>15–31	15.2 (566)	20.0 (172)	30.5 (397)
>31	14.1 (527)	16.4 (141)	38.5 (502)

Data are % (*n*) unless otherwise stated. SD, standard deviation; IQR, interquartile range.

Table 3: Crude incidence rate and rate ratio and adjusted hazard ratio of mood affective disorders (MAD) among adults with cerebral palsy by pain status

MAD cases	Crude IR	Crude IRR	Model 1	Model 2	Model 3
<i>n</i>	<i>n</i> per 100/years	IRR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)

	Without pain	IRR	Model 1	Model 2	Model 3	Model 3 + ethnic group
	193	5.86	Reference	Reference	Reference	Reference
New pain	114	15.52	2.65 (2.10–3.34)	2.35 (1.86–2.97)	2.34 (1.85–2.96)	2.35 (1.86–2.97)
Consistent pain	196	17.92	3.06 (2.51–3.73)	2.22 (1.79–2.76)	2.18 (1.75–2.72)	2.13 (1.71–2.67)

IR incidence rate; IRR incidence rate ratio; Model 1 age sex US region healthcare utilization; Model 2 model 1 variables and intellectual disabilities autism spectrum disorders epilepsy; Model 3 model 2 variables and baseline sleep disorders baseline arthritis; HR hazard ratio; CI confidence interval.

Table 4: Adjusted hazard ratio and 95% confidence interval of mood affective disorders among adults with cerebral palsy by pain status with complete data on ethnic group ($n=5075$)

	Model 1	Model 1 + ethnic group	Model 2	Model 2 + ethnic group	Model 3	Model 3 + ethnic group
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Without pain	Reference	Reference	Reference	Reference	Reference	Reference
Consistent pain	2.27 (1.79–2.88)	2.21 (1.74–2.81)	2.18 (1.71–2.78)	2.24 (1.76–2.84)	2.19 (1.72–2.78)	2.16 (1.69–2.75)
New pain	2.42 (1.88–3.11)	2.40 (1.87–3.09)	2.39 (1.86–3.08)	2.41 (1.87–3.10)	2.39 (1.86–3.07)	2.38 (1.85–3.07)

HR hazard ratio; CI confidence interval; Model 1 age sex US region healthcare utilization; Model 2 model 1 variables and intellectual disabilities autism spectrum disorders epilepsy; Model 3 model 2 variables and baseline sleep disorders baseline arthritis.