Research Paper

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# Child maltreatment elevated the risk of late-life chronic pain: a biopsychosocial framework from the UK Biobank cohort

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**Abstract**

Understanding the development of chronic pain (CP) is challenging due to its multifactorial etiology. Child maltreatment (CM), encompassing various types of neglect and abuse affecting more than one-third of the population, is a critical aspect of early-life adversity with long-lasting impacts. It is increasingly recognized for its role in altering biopsychosocial processes, potentially increasing vulnerability to CP. However, the exact path connecting CM to CP is not fully elucidated, primarily attributable to limitations in prior research, including insufficient sample sizes, inadequate consideration of comprehensive mediative variables, and a lack of longitudinal data. To address these gaps, our study utilizes a large-scale dataset (n = 150,989) comprising both cross-sectional and longitudinal data, along with an extensive range of biopsychosocial variables. Our findings reveal that all types of CMs, except physical neglect, significantly increase the risk of CP, and all types of CPs, except headache, were affected by CM. Furthermore, we demonstrate that individuals with CM histories are more predisposed to comorbid CP conditions. Importantly, biopsychosocial factors are found to explain over 60% of the association between CM and CP, with psychological factors playing a key role. This study not only characterizes the relationship between CM and CP but also underscores the influence of psychosocial elements in this dynamic interplay. These findings offer important insights into the long-term impacts of CM and provide a foundation for developing targeted therapeutic and preventive strategies for CP.

**Keywords:** Chronic pain, Child maltreatment, Biopsychosocial, Epidemiology, UK Biobank

## 1. Introduction

Chronic pain (CP) is a prevalent and debilitating condition that affects approximately 30% of people worldwide.[10] Despite its high prevalence, the underlying causes of CP remain largely unknown,[10,60] primarily due to its complex and multifactorial etiology.[36] Furthermore, the scarcity of long-term and multivariate evidence hampers our understanding of the developmental processes leading to CP.[47]

Child maltreatment (CM), which includes various forms of neglect and abuse, is a profound early-life stressor.[28] With prevalence rates varying between 7.6% and 36.3%,[58] Child maltreatment has enduring consequences,[19] significantly influencing neurodevelopment,[7,62,63] inflammatory responses,[49] and psychosocial health,[28,39,59,62] leading to a spectrum of psychopathology and physical ailments.[8,23,45] Recent studies also suggest that CM plays a critical role in central sensitization syndromes and CP development.[7,9]

While researchers consistently find predictive associations between CM and pain symptoms, specific characteristics of these links remain unclear.[2,8,21,24,25,31,37,43,52,64–68] Many studies suffer from small sample sizes and inadequate adjustment for confounding factors. Although dose–response relationships between CM and various health conditions have been demonstrated,[26,39] this remains unexplored for CP. In addition, the differential impact of CM types on various CP conditions at different body sites lacks clear evidence, hindering comprehensive theoretical understanding and exploration of underlying mechanisms.

Although studies have attempted to understand the link between CM and CP conditions, they have predominantly focused on a limited set of factors, such as depression[5,52] and posttraumatic stress.[2] Recent research has highlighted the biopsychosocial model as a promising framework for understanding CP development and predicting rehabilitation outcomes.[10,12,18,30,36,41,44,47,60] Given the alignment of CM consequences with known causes of CP,[7–9,43] it is crucial to incorporate CM as a pivotal factor within the biopsychosocial framework.[27] The potential link between CM and CP, particularly when considering multiple biopsychosocial factors using longitudinal data, remains largely unexplored.

In this study, we aimed to elucidate the relationship between various types of CMs and different types of CPs, as well as to investigate the biopsychosocial pathways that may underlie these associations. Drawing from a cohort of 150,989 participants from the UK Biobank, our methodology encompassed 3 main steps. Initially, we examined the impact of CM on the likelihood of

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developing CP and characterized the dose–response relationship. We hypothesized that CM significantly impacts late-life CP with a dose–response relationship. We then explored whether specific types of CMs were associated with CP and whether all types of CPs were affected by CM. We hypothesized that the associations uniformly exist across different types of CPs. Finally, we employed both cross-sectional and longitudinal data to study the biopsychosocial mechanisms that might explain the link between CM and CP. This was achieved using category-based models and formal mediation analyses. We hypothesized that biopsychosocial factors play a crucial role in explaining the CM–CP association and expect to reveal the pattern of these factors underlying this association.



## 2. Materials and methods

### 2.1. UK Biobank population

The UK Biobank is a large-scale biomedical database and research resource registered in England and Wales, which contains in-depth, de-identified genetic and health phenotypes from half a million UK participants aged between 40 and 69. It has multiple measurement stages, and the data collection processes are still ongoing.

This study utilized data from the UK Biobank with application ID 71901. All 501,147 participants in the UK Biobank provided written, informed consent, and this study was approved by the North West Multi-centre Research Ethics Committee.

Initially, participants from the UK Biobank were invited to the assessment centre to collect information such as demographics, health status (including pain status), and biological sample data from 2006 to 2010 (initial visit stage). Subsequent to this initial data collection, a proportion of participants were then invited several years later to repeat the assessment, and a subset of participants also performed additional online CM and pain measurements through email invitations in 2016 and 2019 separately. This study mainly used pain and biopsychosocial data collected at the assessment centre during the initial visit and CM and pain data that were measured online. A description of the measurement timeline is provided in **Figure 1A**.

### 2.2. Pain measurement at the initial visit

Pain conditions collected at the assessment centre during the initial visit were measured using a touchscreen questionnaire: "In the last month have you experienced any of the following that interfered with your usual activities." Participants were able to select from the following categories: back pain, facial pain, headaches, knee pain, stomach/abdominal pain, hip pain, neck/shoulder pain, none of the above, prefer not to answer, or pain all over the body. If any of the pain types were selected, the participants were then asked to report whether each selected type of pain lasted for more than 3 months. If the participants reported pain all over the body, information about specific pain sites would not be recorded. Based on their responses, individuals with pain lasting longer than 3 months at more than one body site were classified as having multisite CP, and those with only one body site of pain that lasted longer than 3 months were included in the group of single-site CP. Our primary models were based on these initial pain assessment data, leveraging its largest sample size (n = 501,462) of pain assessments in the current dataset.

### 2.3. Online child maltreatment measurement

Child maltreatment conditions were assessed using the Childhood Trauma Screener[20] online in 2016. Specifically, participants responded to 5 questions regarding emotional or physical neglect and physical, emotional, or sexual abuse experienced during childhood on a 5-point Likert scale. The items were organized as: "When I was growing up…," (1) "I felt loved" (emotional neglect), (2) "There was someone to take me to the doctor if I needed it" (physical neglect), (3) "People in my family hit me so hard that it left me with bruises or marks" (physical abuse), (4) "I felt that someone in my family hated me" (emotional abuse), and (5) "Someone molested me (sexually)" (sexual abuse). Each statement was rated on a 5-point Likert scale ranging from "Never true" (0 points) to "Very often true" (4 points). These responses were then converted into dichotomous variables, representing the presence or absence of each of the 5 types of CMs, as detailed in (Table S1, http://links.lww.com/PAIN/C143).

### 2.4. Online pain measurement

Participants were sent an email in 2019 to complete a pain questionnaire online. For CP conditions, they were asked "Are you troubled by pain or discomfort, either all the time or on and off, that has been present for more than 3 months?" Those responding "yes" were included in the CP group, while those responding "no" were placed in the control group. Ambiguous responses, such as "Prefer not to answer" or "Do not know," were excluded from the analysis. This online assessment was critical in establishing a temporal order between the collected biopsychosocial factors and the CP status. The data thus obtained enabled us to validate and extend the findings of our primary category-based and mediation analyses.

### 2.5. Biopsychosocial factors at the initial visit

Biopsychosocial factors measured at the UK Biobank initial visit stage at the assessment centre were used as covariates to adjust the effect of potential confounders or mediators in the association analyses. These variables were also considered as mediators in the mediation analyses. We included 83 psychosocial factors that were identified by a previous study[60] following the recommendation of the Prognosis Research Strategy (PROGRESS) group[57] and demonstrated to be predictors of CP risk, along with 9 systemic inflammation markers.[53] These factors were classified into 10 distinct biopsychosocial categories as defined by previous research[53,60] and the UK Biobank: (1) mood, (2) neuroticism, (3) traumas, (4) sleep, (5) anthropometric, (6) substance use, (7) physical activity, (8) socioeconomic, (9) social kinship, and (10) inflammation. Specifically, (1) mood includes variables such as self-reported negative mood frequency in the past 2 weeks and whether they visited a GP or psychiatrist for nerves, anxiety, tension, or depression; (2) neuroticism includes variables associated with negative feelings or behaviors; (3) traumas refers to illness, injury, bereavement, and stress events in the last 2 years, such as the death of a person they were close to; (4) sleep is related to questions about duration, habits, or abnormal sleep status; (5) anthropometrics includes blood pressure, body size-related measures, fracture, and pulse rates; (6) substance use are variables that reflect smoking and alcoholic behavior; (7) physical activity includes metabolic equivalent tasks based on the International Physical Activity Questionnaire, hand grip, and whether to join the gym or sports club; (8) socioeconomic comprises education, employment, and economic status; (9) social kinship is based on the status of family members and social support; (10) inflammation markers are based on blood count and blood biochemistry data. Detailed descriptions of these variables and their processing are presented in Table S2, http://links.lww.com/PAIN/C143.

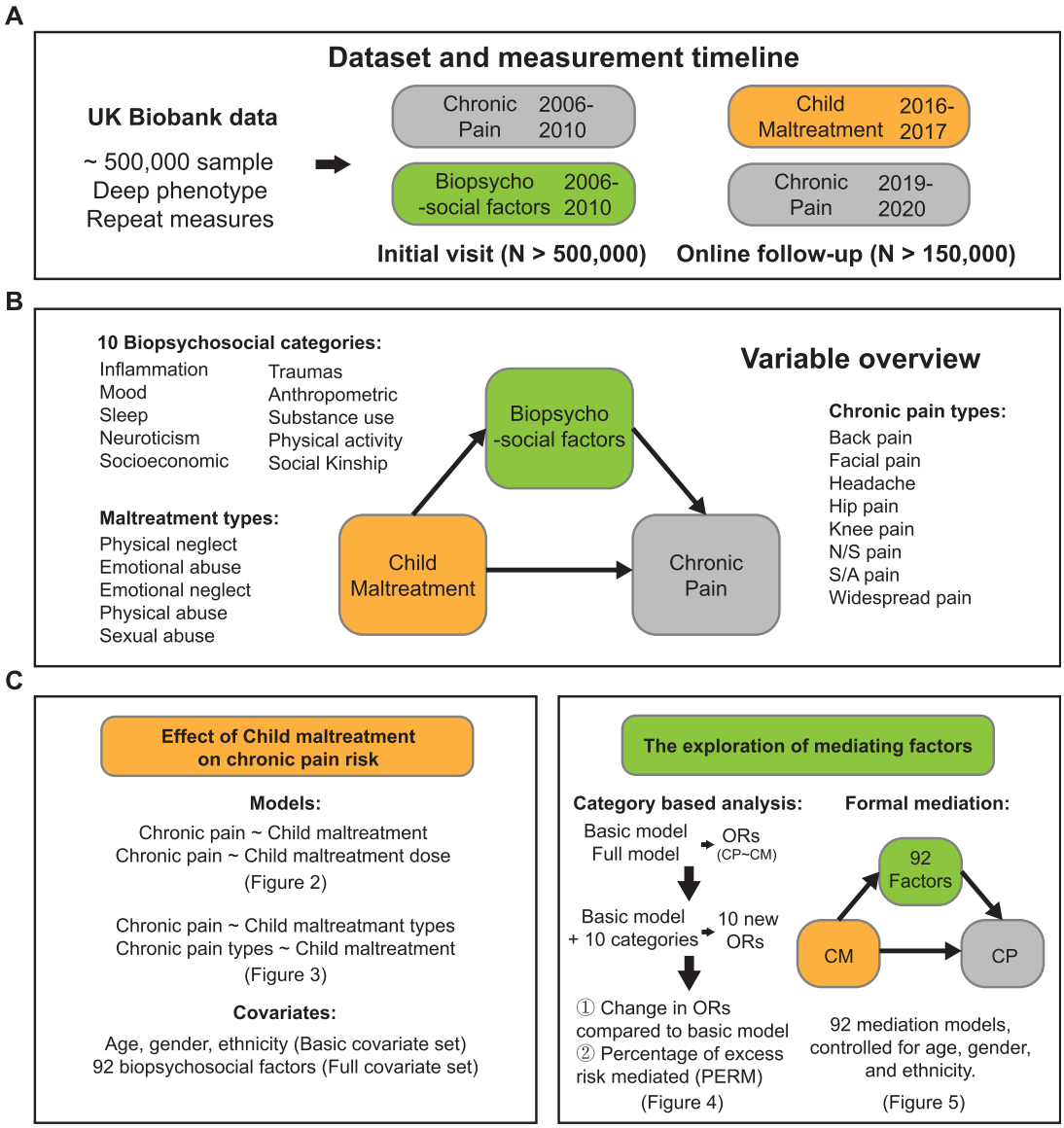


**Figure 1.** Overview of the study design and analyses. (A) Dataset information and measurement timeline. (B) Overview of the study and the variables involved. (C) Description of the key analyses in the study. CM, child maltreatment; CP, chronic pain; N/S, neck/shoulder; ORs, odd ratios; S/A, stomach/abdominal.

### *2.6. Statistical analyses*

All analyses were conducted in R.[61] Graphical processes were performed using the "ggplot2" package.[73]

#### *2.6.1. Association analysis*

To assess the relationship between CM measured online and the late-life CP measured at the initial visit, binary logistic regression models (BLRMs) were applied. Self-reported CP conditions served as the dependent variable. The "glm" function in R, with "binomial" as the link function, was utilized for this analysis. Participants who reported experiencing at least one type of CP were categorized as events (coded as 1), excluding those with widespread CP for a precision quantifying of the pain site. Those with no CP conditions were categorized as nonevents (coded as 0). We calculated odds ratios (ORs) and 95% confidence intervals (CIs) to quantify the strength of this association.

Initially, 2 basic models were established with minimal adjustments for demographical factors (age, sex, and ethnicity). These aimed to elucidate both the summarized and dose–response effects (ie, number of CM experienced) of CM on CP. The summarized model incorporated a binary CM variable: participants who had experienced at least one type of CM were coded as 1 and those who had not were coded as 0. The dose–response model used the number of CM (0-5) conditions as a categorical independent variable, setting 0 CM condition as the reference.

Subsequently, we established models that accounted for 92 potential biopsychosocial confounders or mediators (Table S2, http://links.lww.com/PAIN/C143), along with age, sex, and ethnicity. The model settings were the same as basic models but included additional covariates. To determine the effect of sex, overlapping, and nonoverlapping CP conditions on the association strength, we replicated our association analyses in male, female, single-site CP, and multisite CP participants separately with the same model settings mentioned above.

Last, to characterize the associations between various types of CMs and different types of CPs, we established BLRMs with the adjustment of demographical factors. We first examined the associations between each of the 5 types of CM—emotional neglect, physical neglect, emotional abuse, sexual abuse, and

physical abuse—and the incidence of CP, categorizing individuals reporting at least one type of CP as events. To assess the collinearity among the 5 types of CMs, we established a unified BLRM that incorporated all CM conditions allowing for their cooccurrence. Demographical factors were adjusted in the model. We then calculated the percentage of variance explained by each individual CM condition compared with all terms in the model. We then extended our analysis to examine how early-life CM experiences, defined as individuals reporting at least one type of CM, were associated with each of the 8 specific types of CPs in later life.

#### 2.6.2. Category-based analysis

To dissect the combined effect of underlying biopsychosocial factors that may contribute to the association between CM and CP, we established models that incorporated 10 distinct biopsychosocial categories as additional covariates along with demographic factors. Each category comprises at least 5 variable items (Table S2, http://links.lww.com/PAIN/C143), and participants with any missing covariate data were excluded from the analyses.

Initially, to leverage the maximum sample size for exploratory purposes, we used biopsychosocial factors and CP conditions measured during the initial visit to the UK Biobank. A BLRM with the demographical factors as covariates was first established and served as a baseline model (M1). Subsequent models included each of the 10 biopsychosocial categories separately (M2 to M11), and a fully adjusted model that included all 10 categories was also established (M12). We quantified the impact of experiencing at least one type of CM on developing at least one type of CP with ORs. The percentage of excess risk mediated (PERM) method was used to calculate the extent to which the category factors explained the associations of CM and CP.[35,54]

To provide causal insight into the analysis and replicate our exploratory results, we used pain status data, which were collected online 10.1 years (SD = 0.87) on average after the initial visit, to establish models with temporal-ordered data organized as CM (childhood)—Biopsychosocial (2006-2010)—CP (2019-2020). Participants who reported CP at the initial visit were excluded from this replication analysis.

#### 2.6.3. Formal mediation analysis

To investigate the potential mediating factors between CM and CP, we developed 92 distinct formal mediation models. Each model included one of the 92 biopsychosocial factors as a mediating factor, while demographic factors were controlled for in all models. Mediation analyses were carried out using the "lavaan" package[51] in R, and variables with more than 2 distinct values were scaled. For each model, the indirect effects ($\beta_{a\times b}$) were reported. *P* values were adjusted with the Bonferroni method. Similar to the category-based analysis, the initial mediation models used biopsychosocial and CP data collected during the initial visit. Replication models with temporal order data were also established for mediation analyses.

## 3. Results

### 3.1. Characteristics of sample

This study utilized the UK Biobank cohort comprising pain assessment data collected from 501,147 participants during the initial visit (age range = 37-73 years, Mean ± SD = 56.53 ± 8.10 years) and early-life traumatic events data from 157,300 participants during the online follow-up period (age range = 49-83 years, Mean ± SD = 66.61 ± 7.68 years). After removing those with ambiguous responses (ie, "prefer not to answer"), the remaining sample consisted of 150,989 participants. Among these, 56.3% were women. Nearly half (46.1%) of the participants reported at least one type of CM, and the most frequently reported CM type was emotional neglect (22.0%), and the least was sexual abuse (8.7%).

During an average follow-up duration of 10.1 years (SD = 0.87), a subset of participants from the initial visits completed the online pain questionnaire (n = 167,185, age range = 46-81 years, Mean ± SD = 63.89 ± 7.73 years), 56.8% were women. We utilized the CP status collected online to establish regression and mediation models for variables that were measured with temporal order (ie, CM, biopsychosocial, CP) to replicate the primary category-based and mediation results of this study. The outline of this study is shown in **Figure 1**.

### 3.2. Association between early-life child maltreatment and late-life chronic pain conditions

The association models used retrospective CM data collected online, which is the first follow-up data used in this study, and CP data collected at the initial visit. Overall, in the 2 basic models, individuals who had experienced at least one type of CM were 1.34 times (95% CI: 1.32-1.37) more likely to develop CP conditions in later life (**Fig. 2A**). Furthermore, the likelihood of developing CP increased along with the number of CM types experienced. Specifically, individuals with 1 to 5 CM conditions were 1.18 (95% CI: 1.15-1.21), 1.39 (95% CI: 1.34-1.44), 1.65 (95% CI: 1.57-1.72), 2.05 (95% CI: 1.92-2.18), and 2.58 (95% CI: 2.30-2.89) times more likely to develop CP conditions (**Fig. 2A**).

In the 2 fully adjusted models, individuals who had experienced at least one type of CM were 1.13 times (95% CI: 1.09-1.18) more likely to develop CP (**Fig. 2B**); for individuals with 1 to 5 CM types, the likelihoods of developing CP conditions were 1.11 (95% CI: 1.06-1.16), 1.09 (95% CI: 1.02-1.16), 1.27 (95% CI: 1.16-1.38), 1.33 (95% CI: 1.18-1.51), and 1.76 (95% CI: 1.37-2.27) times (**Fig. 2B**).

Interestingly, in the subgroup analyses, we found a higher OR of multisite CP (OR = 1.58, 95% CI: 1.54-1.63, basic model; OR = 1.24, 95% CI: 1.17-1.31, fully adjusted model) compared with single-site CP (OR = 1.19, 95% CI: 1.16-1.22, basic model; OR = 1.08, 95% CI: 1.03-1.13, fully adjusted model), full results were illustrated in Fig. S1 to Fig. S4, http://links.lww.com/PAIN/C143.

### 3.3. Association between child maltreatment types and chronic pain types

!The association models also used CM data collected at the first follow-up specific to this study and CP data collected at the initial visit.

In the models characterizing the association of CM types and CP development, we found that 4 out of the 5 types of CMs, specifically emotional abuse, emotional neglect, physical abuse, and sexual abuse, were associated with an increased likelihood of developing CP in later life. Physical neglect, however, did not show a significant association (**Fig. 3A**; emotional abuse, OR = 1.24, 95% CI: 1.17-1.32; emotional neglect, OR = 1.13, 95% CI: 1.08-1.18; physical abuse, OR = 1.19, 95% CI: 1.14-1.24; sexual abuse, OR = 1.16, 95% CI: 1.10-1.24; physical neglect, OR = 1.01, 95% CI: 0.97-1.05). When considering all CM types and cooccurrence conditions, emotional abuse explained nearly half of the total variance (41.42%), followed by physical abuse (11.64%), emotional neglect (8.49%), sexual abuse (7.48%), and

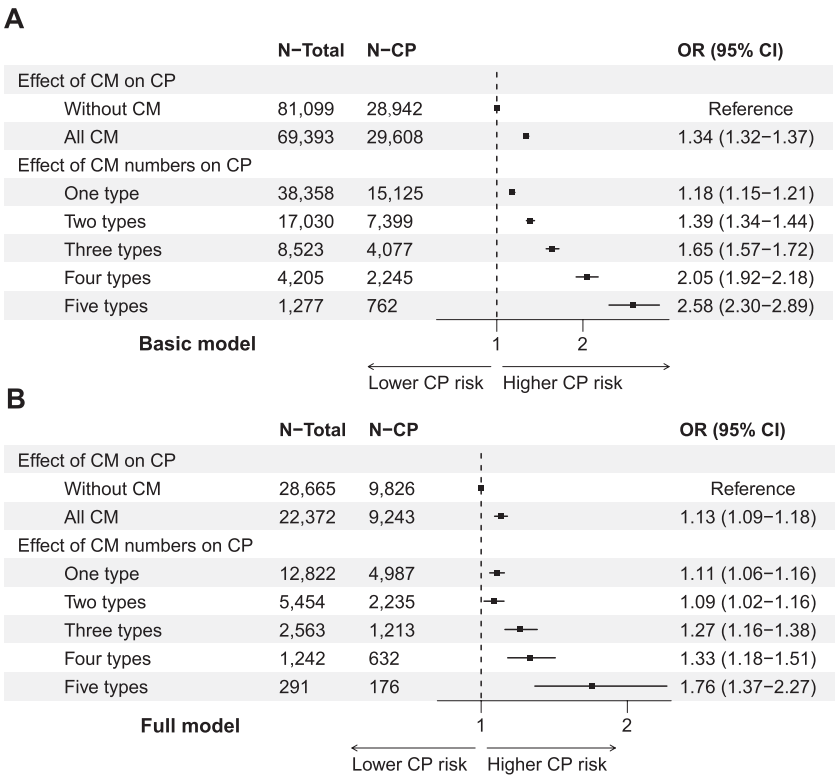


**Figure 2.** Association between CM and late-life CP. Two sets of models were established to explore the combined effects and dose effects of CM on CP separately. Without CM group comprises samples with no self-reported experiences of CM. All CM represents samples with at least one of the 5 types of CM. (A) Models with the adjustment of basic covariates (age, sex, and ethnicity). (B) Models with the adjustment of full covariates (92 biopsychosocial factors). CI, confidence interval; type, child maltreatment type; CM, child maltreatment; CP, chronic pain; N-CP, number of samples with at least one type of chronic pain record in the current group; N-Total, total sample size of the current group; OR, odd ratio.

the lowest explanation ability observed in physical neglect (3.92%) (Fig. S5, http://links.lww.com/PAIN/C143).

In the models characterizing the association between CM and CP types, we observed that CM was significantly linked to a higher likelihood of developing different types of CPs, including chronic back pain, facial pain, hip pain, knee pain, neck/shoulder pain, stomach/abdominal pain, and widespread pain (**Fig. 3B**). However, CM did not show a significant association with the likelihood of developing chronic headache pain (chronic back pain, OR = 1.16, 95% CI: 1.10-1.23; facial pain, OR = 1.44, 95% CI: 1.01-2.05; hip pain, OR = 1.13, 95% CI: 1.03-1.24; knee pain, OR = 1.14, 95% CI: 1.09-1.20; neck/shoulder pain, OR = 1.21, 95% CI: 1.14-1.28; stomach/abdominal pain, OR = 1.34, 95% CI: 1.19-1.51; widespread pain, OR = 2.33, 95% CI: 2.06-2.63; chronic headache pain, OR = 1.00, 95% CI: 0.94-1.06).

### *3.4. Association of child maltreatment with chronic pain and proportions attributable to 10 biopsychosocial categories*

The exploratory category-based analysis used retrospective CM data collected online at the first follow-up of this study and CP data collected at the initial visit. For the temporal order analysis, CP data collected online, which is the second follow-up specific to this study, was used. In the baseline model adjusting for demographic factors, the OR for developing any type of CP among individuals who had experienced any type of CM was 1.35 (95% CI: 1.31-1.40). Additional adjustments for biopsychosocial categories generally attenuated this association (**Fig. 4A**). Notably, the most significant reductions in the strength of the association were observed when adjusting for mood (OR = 1.21, 95% CI: 1.17-1.26; PERM = 39.95%), neuroticism (OR = 1.23, 95% CI: 1.19-1.28; PERM = 34.11%), and sleep (OR = 1.29, 95% CI: 1.24-1.34; PERM = 18.06%) (**Fig. 4B**). The full model, which adjusted for all categories, yielded an OR of 1.13 (95% CI: 1.09-1.18) and a PERM of 62.03%.

Leveraging the model with temporal order, with the event timeline organized as CM (childhood)—Biopsychosocial (2006-2010)—CP (2019-2020), the strength of the CM–CP association remained even when all 10 biopsychosocial categories were included (M1, OR = 1.17, 95% CI: 1.11-1.23; M12, OR = 1.07, 95% CI: 1.01-1.12) (Fig. S6A, http://links.lww.com/PAIN/C143). Similar to the primary category-based analysis, the association was most attenuated when adjusting for mood and neuroticism (OR = 1.12, 95% CI: 1.06-1.18 for both; PERMs = 29.57% and 28.57%, respectively) (Fig. S6B, http://links.lww.com/PAIN/C143). The PERM for the fully adjusted model was 59.91%.

### *3.5. The impact of each of the 92 factors on the association between child maltreatment and chronic pain*

The exploratory mediation analysis used retrospective CM data collected online at the first follow-up of this study and CP data collected at the initial visit. For the temporal order analysis, CP data collected online, which is the second follow-up specific to this study, was used. The results of the mediation analysis, shown in **Figure 5**, revealed significant indirect effects in 45 out of 92 models based on 92 mediators from 10 biopsychosocial categories. The significant indirect effects are denoted by blue bars after the Bonferroni correction. Among the 10 categories, the most prominent indirect effects were observed in mood and

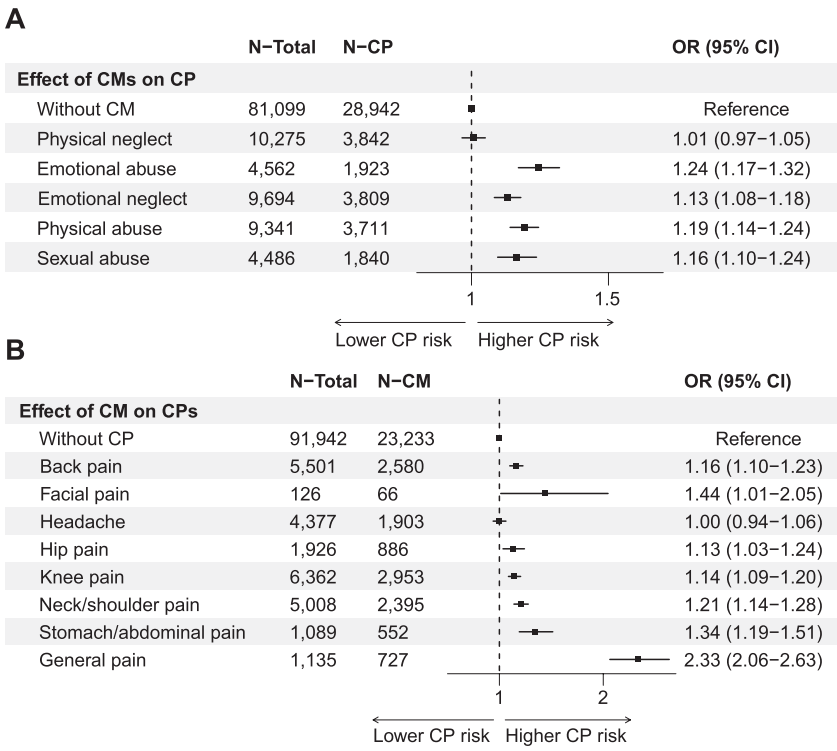


**Figure 3.** Association between CM types and CP types. Models were established to explore the association between different types of CMs and various CP types. Without CM group comprises samples with no self-reported experiences of CM. All models controlled the effect of age, sex, and ethnicity. (A) Effect of individual CM type on the CP risk. Without CM group comprises samples with no self-reported experiences of CM. (B) Effect of CM on the risk of each CP type. Without CP group comprises samples with no self-reported CP. CI, confidence interval; CM, child maltreatment; CP, chronic pain; N-CM, number of samples with at least one type of child maltreatment record in the current group; N-CP, number of samples with at least one type of chronic pain record in the current group; N-Total, total sample size of the current group; OR, odd ratio.

neuroticism. Specifically, the following 8 factors demonstrated significant indirect effects: frequency of tiredness/lethargy in the last 2 weeks ($\beta_{a\times b} = 0.017$, $P < 0.001$), mood swings ($\beta_{a\times b} = 0.013$, $P < 0.001$), miserableness ($\beta_{a\times b} = 0.013$, $P < 0.001$), fed-up feelings ($\beta_{a\times b} = 0.012$, $P < 0.001$), seen doctor (GP) for nerves anxiety, tension, or depression ($\beta_{a\times b} = 0.011$, $P < 0.001$), frequency of tenseness/restlessness in the last 2 weeks ($\beta_{a\times b} = 0.011$, $P < 0.001$), frequency of depressed mood in the last 2 weeks ($\beta_{a\times b} = 0.068$, $P < 0.001$), and frequency of unenthusiasm/disinterest in the last 2 weeks ($\beta_{a\times b} = 0.010$, $P < 0.001$). Sleep also played a significant role, with sleeplessness/insomnia ($\beta_{a\times b} = 0.007$, $P < 0.001$) and getting up in the morning ($\beta_{a\times b} = 0.005$, $P < 0.001$) emerging as the most important factors.

The explanatory powers were similar for anthropometric, substance use, socioeconomic, and traumas. In the anthropometric category, BMI ($\beta_{a\times b}$ 0.006, $P < 0.001$) and weight ($\beta_{a\times b} = 0.005$, $P < 0.001$) were the most important factors. For substance use, alcohol intake frequency ($\beta_{a\times b} = 0.002$, $P < 0.001$) exhibited the most significant indirect effect. The most significant factors for the socioeconomic category were average total household income ($\beta_{a\times b} = 0.003$, $P < 0.001$), unable to work ($\beta_{a\times b} = 0.003$, $P < 0.001$), and college or university degree ($\beta_{a\times b} = 0.003$, $P < 0.001$). In the traumas category, the number of traumas ($\beta_{a\times b} = 0.005$, $P < 0.001$) and financial difficulties ($\beta_{a\times b} = 0.004$, $P < 0.001$) were the leading factors. Physical activity, social kinship, and inflammation generally played a less important role, with gym activity ($\beta_{a\times b} = 0.001$, $P < 0.001$), able to confide ($\beta_{a\times b} = 0.003$, $P < 0.001$), and CRP ($\beta_{a\times b} = 0.003$, $P < 0.001$) becoming the most important factors in their respective categories.

The results for mediation with temporal order are shown in Fig. S7, http://links.lww.com/PAIN/C143. Of the 92 models with the same mediators, 28 demonstrated significant indirect effects after the Bonferroni correction. While the effect magnitudes were reduced due to the up-to-10-year follow-up periods, the effect patterns were generally similar to those found in the exploratory analysis. The most prominent indirect effects were observed in mood and neuroticism, with mood swings ($\beta_{a\times b} = 0.007$, $P < 0.001$), seen doctor (GP) for nerves anxiety, tension, or depression ($\beta_{a\times b} = 0.007$, $P < 0.001$), miserableness ($\beta_{a\times b} = 0.006$, $P < 0.001$), fed-up feelings ($\beta_{a\times b} = 0.006$, $P < 0.001$), and frequency of tiredness/lethargy in the last 2 weeks ($\beta_{a\times b} = 0.005$, $P < 0.001$) emerging as the most influential factors. For sleep, anthropometric, socioeconomic, and traumas categories, the most significant results were sleeplessness/insomnia ($\beta_{a\times b} = 0.003$, $P < 0.001$), BMI ($\beta_{a\times b} = 0.004$, $P < 0.001$), college or university degree ($\beta_{a\times b} = 0.002$, $P < 0.001$), and financial difficulties ($\beta_{a\times b} = 0.002$, $P < 0.001$). The remaining 5 categories did not show any significant indirect effects.

## 4. Discussion

Previous studies have indicated a negative impact of CM on the development of CP.[7,43] However, the characteristics of this association and underlying mechanisms are largely unclear due to sample size limitations and a lack of comprehensive mediation variable searches. Leveraging a large-scale cohort (n = 150,989) from the UK Biobank, our study not only confirms a significant increase in the likelihood of developing CP following early-life CM but also uncovers a dose–response relationship. Furthermore, this study provides the first large-scale evidence revealing that all

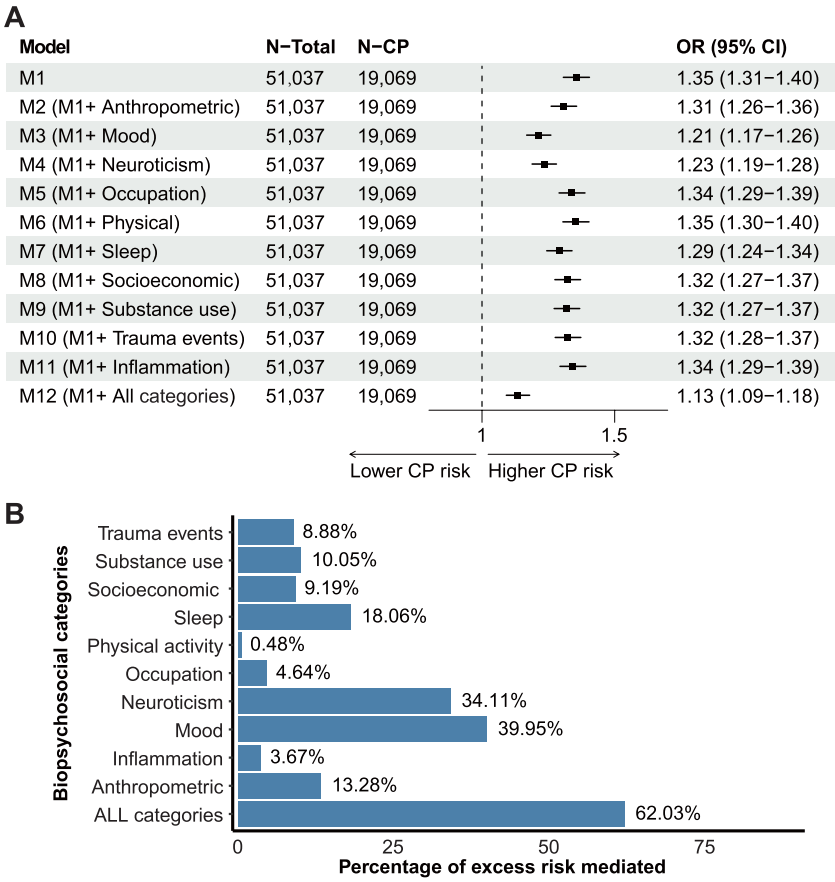


**Figure 4.** Association of CM with CP and proportions attributable to different risk category factors. (A) The models are adjusted for demographical factors along with 10 additional categories. Model M1 adjusted for age, sex, and ethnicity (demographical factors). (B) Percentage of excess risk mediated by each category. CI, confidence interval; CP, chronic pain; N-CP, number of samples with at least one type of chronic pain record in the current model; N-Total, total sample size of the current model; OR, odd ratio.

types of CMs, except physical neglect, significantly increase the likelihood of developing CP, and CM affects the risk of all types of CPs, except headaches. Finally, integrating 92 biopsychosocial factors with cross-sectional and longitudinal data, this study provides a comprehensive understanding of how CM can impact the development of CP and highlights the importance of psychological factors in this relationship.

Since individuals experience one type of CM often combined with another type,[19] confirming the dose–response relationship is important as it may reflect a homogeneity impact across different CMs on CP. Consistent with previous large-scale CM studies showing that a greater number of self-reported CM is associated with a higher risk of cardiovascular diseases, mental disorders, asthma, and multimorbidity,[22,23,26,39] we established a similar dose–response relationship for CP conditions. Building on previous research that observed cumulative CM experiences in women are associated with more severe pain symptoms,[56] we extended such findings to CP conditions in individuals with any type of CM and provided validation evidence across a larger sample size and including single-site CP, multisite CP, male, and female participants, revealing a common impact of CM on CP. It is crucial to note that the measurement limitation of the current dataset does not exclude the possibility that, as individuals experience multiple types of CM conditions, the likelihood of encountering a critical CM type at a critical age also increases.[32] Therefore, the timing of each CM experienced should be considered in future studies.

We also included various types of CMs and CPs in our analyses to provide a comprehensive perspective regarding the heterogeneous characteristics of their relationship that were previously unaddressed.[43] Among the CM types, previous studies found that emotional abuse[17,22,26,39] and neglect[26,39] prove to be associated with more severe outcomes in a wide range of diseases compared with physical maltreatment. Consistent with these findings, our study indicates that individuals who experience emotional abuse demonstrate the highest risk of CP,[17,22,23,26,39] and physical neglect exerts no influence on developing CP in later life. This observation is underscored by recent studies highlighting the role of the medial prefrontal cortex (mPFC), a key neural substrate of CP,[34,70] and emotional regulation.[14] Abnormalities in the mPFC have been documented in individuals subjected to emotional abuse,[50,72] underscoring the pivotal role of emotional factors in the association between CM and CP.

In addition, similar to a previous study,[8] we found that CM is associated with an increased likelihood of all CP types, except chronic headaches. This may indicate the distinct nature of headaches among other CPs, as indicated by their unique classification,[3,69] and the relatively small effect of genetic association with other CP conditions.[75] It is noteworthy that previous studies showed a significant association between migraine and CM.[65–67] On the other hand, these findings do not preclude the possibility of confounding in the context of comorbid pain conditions, as migraineurs with CM have a higher prevalence of comorbid pain conditions in these works.[67]

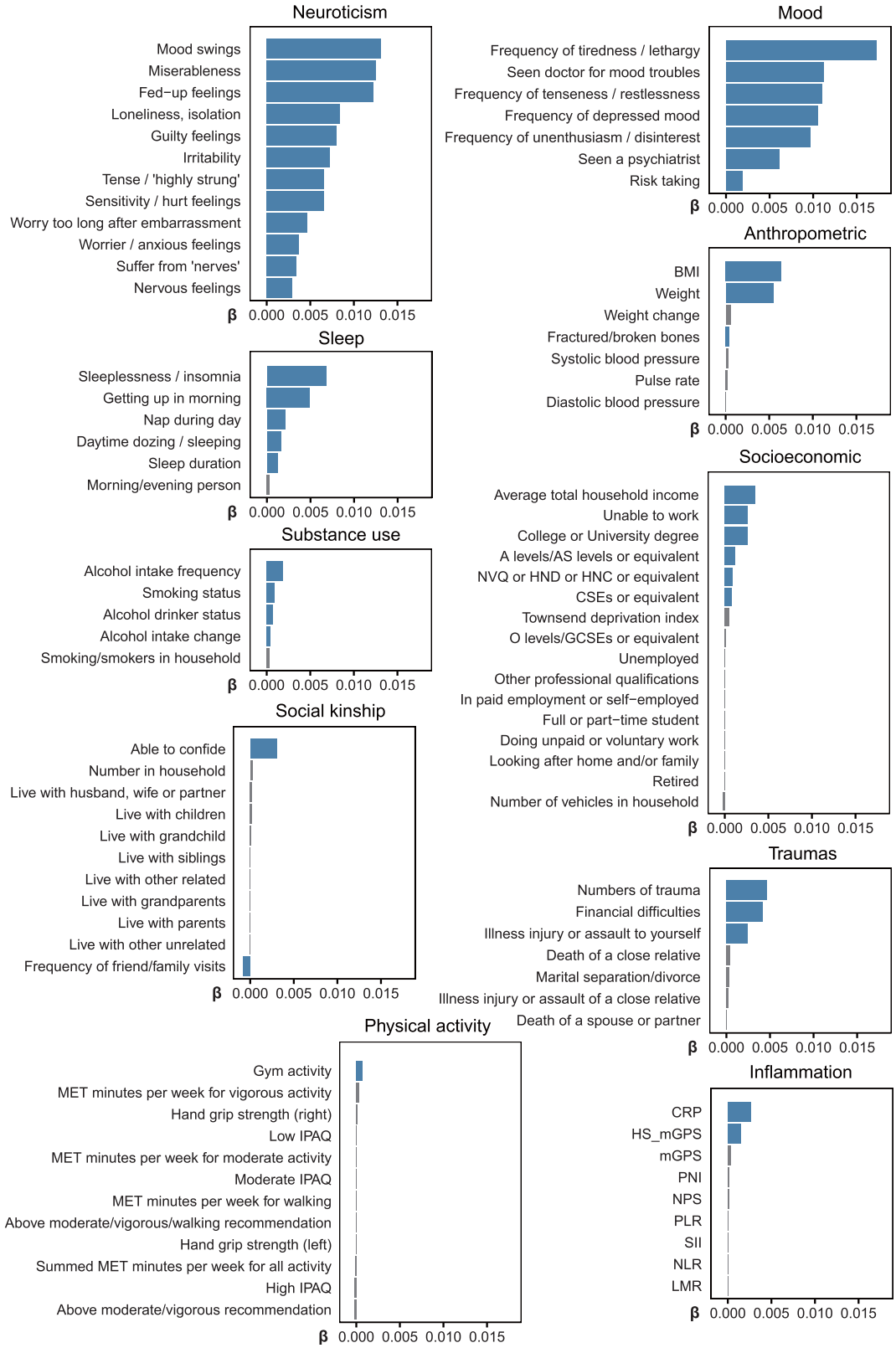


**Figure 5.** Mediation models reveal the impact of each of the 92 factors on the association between CM and CP. The indirect effects of the mediation models are visually represented using bar plots. For each subplot, the x-axes represent the standard β values. Each model has been adjusted for age, sex, and ethnicity to control for potential confounding effects. Blue bars indicate significant indirect effects after the Bonferroni correction, and grey bars indicate nonsignificant results.

Interestingly, we found that CM has a stronger association with comorbid CP conditions, as indicated by higher ORs of developing general and multisite CP compared with other CP conditions. Previous studies suggest a higher biological and psychosocial burden in overlapping CP conditions.[29,41,74] These burdens, known to be caused by CM,[7,28,63] may intensify the tendency of reporting multiple CPs by influencing the cognitive and emotional processes related to pain.[9,71] Indeed, a recent

study found that individuals with higher biopsychosocial burdens tend to develop CP at multiple body sites.[60]

Recognizing that the biopsychosocial framework may serve as a basis for understanding the mechanisms underly CM–CP associations,[46,52] we conducted a comprehensive search for potential biopsychosocial mediative pathways between CM and CP. The overall 60% explanatory power of biopsychosocial factors in the CM–CP association confirmed the effectiveness of the framework. Among those contributing biopsychosocial factors, mood and neuroticism emerged as the most influential categories, which is consistent with findings from a recent large-scale study.[60] Regarding specific factors, while previous research has highlighted the importance of posttraumatic stress[2] and depressive conditions,[5,52] our study found the contributions of depressive and stress-related mood (ie, anxious, nervous, and tense) to be of moderate importance. Instead, factors such as unstable mood, fatigue, and negative thinking profiles appeared more prominent, potentially increasing the risk of maladaptive coping strategies related to pain.[12]

Interestingly, when studying traumas and social kinship categories, we found a dissociative indirect effect pattern between social needs and relationships with others. In the traumas category, stressors had a significant indirect effect when they were directly related to the individuals themselves, such as cumulative stress, financial difficulties, or personal injury. However, stressors originating from the suffering of individuals with close relationships or household-related factors, such as the presence of household members, did not show a significant indirect effect. These findings align with previous evidence indicating that individuals with histories of CM tend to have more distant and strained relationships with family[33,48] and others.[40] As such, those with CM histories may become indifferent to the suffering of others and their living situation, thus not associating these factors with CP outcomes. However, the factor "able to confide" emerged as a significant contributor to the CM–CP association, along with loneliness from the neuroticism category. These findings did not preclude our hypotheses about relationships with others as social interactions are objective human needs, and previous evidence suggested that individuals with histories of CM still require social support.[15] Overall, these results may reveal a different impact pattern of CM on human health through social-related factors.

Categories associated with lifestyle, physical activity, and general health measures had less pronounced effects. Leading factors in these categories, such as sleep problems, overweight, and alcohol intake, are well-documented consequences of CM[6,13,45] and established risk factors for CP.[60] The socioeconomic category also had a moderate role, with significant factors including higher education levels and income, which may contribute to improved cognitive function and access to better medical care. Surprisingly, the inflammation category had a lower impact on the CM–CP association, despite strong links between inflammation and both CM[11,42] and CP.

Overall, individuals who experienced CM were found to be 1.34 times more likely to develop CP in later life. This risk ratio is higher than those reported for developing cardiovascular diseases[26] and asthma,[22] and comparable with those for major mental health conditions like dementia, depressive disorder, and affective disorder[39] in studies with similar scale and covariate adjustments. Although the effect sizes from the single-variable mediation analyses were subtle, a common trend in large-scale studies,[54,74] they remain meaningful in guiding forthcoming intervention studies aimed at targeting these variables to showcase their impact through longitudinal designs.

Our study has several limitations. First, the information on CM and CP status relied on self-reported measures, and formal diagnosis or objective detail measurement was not available. It is important to acknowledge that self-report measures of CM are subject to potential recall bias and subject interpretation.[1,5,55] Future studies should aim to replicate our findings using more rigorous methods. Second, the assessment of CM history in our study was based on a shortened form of the Childhood Trauma Screener. While this tool has been validated in research,[20] it is worth noting that this simplified version may not cover the most clinically meaningful information as compared with the 10-item Adverse Childhood Experience Questionnaire.[16] Third, CP, as well as biopsychosocial factors, was measured in late adulthood, limiting the coverage of the entire lifespan. As brain development[4] and personality[38] are dynamic processes, future studies should replicate our primary findings with different age ranges. Fourth, our longitudinal models were based on CP measurements taken with a 10-year gap, which may introduce unmeasured confounding related to the occurrence of CPs. Future work should consider shorter intervals for repeated measurements.

## 5. Conclusion

In conclusion, this study provides a basic understanding of the relationship between CM and CP, uncovering the underlying biopsychosocial factors involved in this association. These findings offer a foundation for understanding the pathways through which early-life CM translates into long-term health challenges. By identifying key biopsychosocial mediators, our findings also pave the way for developing preventative and therapeutic strategies aimed at mitigating the risk of CP development in those with histories of CM.

## Conflict of interest statement

All authors declare no conflict of interest.

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Code and data availability: Scripts used to conduct the analyses are available at https://github.com/tulab-brain/Child-Maltreatment.

This project corresponds to UK Biobank application ID 71901. Data used in this study are available at https://biobank.ndph.ox.ac.uk/.

## Supplemental digital content

Supplemental digital content associated with this article can be found online at http://links.lww.com/PAIN/C143.

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