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An Analysis on the Impact of Childhood Adversity, Anxiety, and C-reactive Protein on Adult Chronic Pain in the Midlife in the United States (MIDUS) study.

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Abstract

Objectives: This study used the Midlife-Development in the United States (MIDUS) dataset to: 1) examine relationships between reported childhood-adversity (CA), anxiety, and pain; 2) assess associations between CAs, anxiety, C-reactive protein (CRP) levels, and pain; and 3) explore how CAs, anxiety, and CRP are associated with pain medication consumption.

Methods: Data were from Project-4 of MIDUS-II (n-1225), which utilized Project-1 demographics and supplemental chart review. For objectives 1–2, structural equational-modeling (SEM) followed by general linear-modeling (GLM) regression were conducted. For objective 3, all variables from the objectives 1–2 dataset were used as possible independent variables for the exploratory regression.

Results: For objectives 1–2, CRP was significantly correlated with anxiety, emotional-abuse, physical-neglect, and chronic pain (n=1173). The SEM (n=1173) indicated CAs, anxiety, and CRP all played a role in predicting chronic pain. Regression results (n=1173) indicated gender, total-income, and highest-education were significant predictors of chronic pain. Significant interactions to explain chronic pain included physical-abuse/emotional-neglect, emotional-abuse/physical-abuse, physical-abuse/minimization, physical-neglect/education, CRP/income, and CRP/education. For objective 3 (n=600), there were no significant main-effects, but a large variety of interactions contributed to predicting pain-medication consumption. CAs interacting significantly to explain this included emotional-abuse/physical-abuse, physical-abuse/emotional-neglect, physical-abuse/minimization, and sexual-abuse/minimization. There were also significant interactions between CRP/income and CRP/education.

Conclusions: Based on a large US-sample, socio-demographics played a meaningful role in predicting chronic pain in adults, and CRP was significantly correlated with anxiety, emotional-abuse, physical-neglect, multiple socio-demographic variables, and chronic pain. The influence of CAs on predicting long term medication use for chronic pain were complex and warrant further study.

Keywords: Childhood adversity, childhood trauma, anxiety, chronic pain, inflammation, inflammatory biomarker, C-reactive protein.

Abbreviations

ACE, adverse childhood experience

CRP, C-reactive protein

CTQ, childhood trauma questionnaire

GLM, general linear modeling

ICD9, International Classification of Diseases, Ninth Revision

ICPSR, Inter-university Consortium for Political and Social Research

MIDUS, Midlife Development in the United States

NA, not available

SEM, structural equational modeling

STAI, State-Trait Anxiety Inventory

UK, United Kingdom

US, United States

Background

In recent years, there have been advances in research regarding the prevalence of adverse childhood experiences (ACEs) and resulting poor health outcomes for adults who have a history of experiencing childhood adversity (CA). The first ACE study, for example, found a strong relationship between exposure to abuse or household dysfunction during childhood and multiple health risk factors for the leading causes of death in adulthood (1–2). Due to this expanding field of research, CA is no longer perceived as solely a social issue, as it affects overall health and development throughout the entire lifetime of an individual.

Stress-related physiological alterations, influenced by potentially traumatic events and experiences such as ACEs, are linked with affective and physiological states including depression, inflammation, and shortened telomeres, which increase morbidity and mortality risks (3). Some of the adult health behaviors potentially linking ACEs and these risks range from smoking and substance misuse (such as overuse of pain medication). There is increasing evidence that ACEs are associated with persistent pain in adults, which may in turn influence self-medicating to avoid or relieve pain. For example, a 30-year prospective follow-up of a cohort of individuals with court-documented ACEs and a demographically matched control sample showed a small (partial eta squared (η^2) = .01), but statistically significant increase in the risk of pain in adulthood (4). Further, a recent systematic review documented high levels of CAs in adults with chronic pain, and showed that CAs impacted the form, presence, severity, and extent of chronic pain in adults (5). A 2020 US-based analysis tested the associations between ACEs and subsequent prescription pain medicine/opioid misuse outcomes in adults, and results indicated that the presence of ACEs was positively associated with prescription opioid misuse across the two state samples assessed (6). Adults that reported three or more ACEs had increased odds of taking opioids more than prescribed and without a prescription (6).

However, findings from recent longitudinal studies investigating the association between types of ACEs and pain have yielded inconsistent findings in the strength and direction of associations (4), warranting more examination into the potential relationships, associations, and pathways involved. Prior reviews have also highlighted the negative impact of ACEs on psychological (anxiety, depression, self-harming), behavioral (risk taking, smoking, substance misuse, violence), and physical health (obesity, diabetes, cancer, heart, and respiratory disease) (7). However, the impact of CAs on persistent adult outcomes is less clear and may involve other factors such as inflammatory biomarkers and anxiety, which have received less research attention than depression. In chronic pain populations, in particular it has been shown that anxiety disorders are second only to depression as a psychological comorbidity. Clinical or pathological anxiety involves increased feelings of dread that interfere with standard functioning and may be influencing hypervigilance, potentially contributing to or exacerbating pain experiences (8). Further, elevated levels of acute-phase proteins like C-reactive protein (CRP) and proinflammatory cytokines such as interleukins, a downstream product of CRP signaling, have been observed in the plasma of individuals who have experienced CAs or trauma (9). Meta-analyses of cross-sectional studies have also confirmed the association of higher inflammation with traumatic experiences (9). CRP is a protein that responds to inflammatory stimuli by triggering cellular reactions, making it of relevance in the biological impact of childhood trauma. A better understanding of these relationships has important implications for public health.

Aims & Hypotheses

Consequently, the overarching aim of this study was to utilize the Midlife Development in the United States (MIDUS) dataset to identify biopsychosocial pathways that may link CAs with adult chronic pain. The specific objectives are: 1) to examine the relationships between reported CAs, anxiety, and pain; 2) to assess the associations between CAs, anxiety, inflammation (measured through CRP levels), and pain; and 3) to explore how CAs, anxiety, and CRP may be associated with pain medication consumption in

the United States as a proxy for chronic pain as a health outcome. To date, little evidence is available in large, representative samples that address all these associations together rather than looking at one association separately in smaller samples. This study offered a uniquely large dataset and novel analyses including all variables of interest to explore their distinctive associations. The conceptual model, based on the scattered evidence available to date, underpinning the present research questions is that CAs positively relate to adult chronic pain, with anxiety and inflammation (indexed by CRP) potentially influencing this association. It was hypothesized that CAs relate to chronic pain experience in adulthood, and that there would be positive associations between 1) CAs and anxiety, 2) CAs and CRP levels, 3) CAs and pain, and that the link between CAs and pain would be influenced by anxiety and/or CRP. Although objective 3 is exploratory, it is hypothesized that CAs, anxiety, and CRP would all be positively associated with increased pain medication consumption in the United States.

The corresponding null hypotheses (H0) are 1) there will be no significant positive association between CAs and anxiety, 2) there will be no significant positive association between CAs and CRP levels, and 3) there will be no significant positive association between CAs and pain. Further, any CAs and pain association will not be influenced by anxiety and/or CRP. For exploratory objective 3 the H0 is that CAs, anxiety, and CRP will not be associated with increased pain medication consumption in the United States.

Methods

Transparency Statement

All MIDUS datasets, materials, and documentation are archived at the ICPSR (http://www.icpsr.umich.edu) repository at the University of Michigan and are publicly available in a variety of formats and statistical packages. In the sections that follow, we report all measures, manipulations, and exclusions.

Dataset and Participants

The dataset used for this secondary analysis was the publicly available MIDUS longitudinal study, a national survey of more than 7,000 Americans (aged 25 to 74) that started in 1994 (10). The purpose of the MIDUS study was to investigate the role of behavioral, psychological, and social factors in understanding age-related differences in physical and mental health. With support from the National Institute on Aging, a longitudinal follow-up of the original MIDUS samples was conducted in 2004-2006. The Biomarker study aiming to facilitate analyses that integrate behavioral and psychosocial factors with biology is Project 4 of the MIDUS 2 (M2P4), containing data from 1,255 respondents, and is the focus sample of these analyses. Respondents include two distinct subsamples: the longitudinal survey sample (n = 1,054) and the Milwaukee sample (n = 201), all of whom completed the Project 1 Survey. The Milwaukee group contained individuals who participated in the baseline MIDUS Milwaukee study initiated in 2005. All research participants were admitted to or studied at the University of Wisconsin-Clinical and Translational Research Core. Biomarker data was collected at three General Clinical Research Centers (at UCLA, University of Wisconsin, and Georgetown University). Finally, to augment the self-reported data collected in Project 1, participants completed a medical history and self-administered questionnaire. Participants were excluded if they did not respond to the Child Trauma Questionnaire (CTQ) and STAI questionnaires, had not met at least one of the chronic pain criteria, or if CRP was outside of the acceptable ranges (>10% inter-assay variability). Low anxiety score or lack of ACEs was not excluded.

Measures

Childhood adversity: Within the MIDUS database, CA measures included the CTQ (11): 25 items about adverse experiences split into several categories (physical abuse, emotional abuse, sexual abuse, emotional neglect, physical neglect, minimization/denial) which comprise the 5 subscales of this measure. This was completed by participants at the biomarker collection stage. The scale ranged from 1

Never true to 5 Very often true. Unless otherwise indicated, scale scores were computed by summing across all items for which there were no missing data, with higher scores reflecting more experiences of trauma. Mean substitution was used in cases with only one missing value. For all subscales except Minimization/Denial, items marked with (R) were reverse-coded so that high scores reflect higher standing in the scale. For Minimization/Denial, the responses were coded as follows: 5 was coded as 1, 1–4 were coded as 0. This scoring reflected the tendency of the respondent to give exaggerated, desirable responses. The new scores were then added to derive the Minimization/Denial Scale Total Score.

Although the name of the CTQ includes the term "trauma", it does not refer to all experiences that necessarily qualify as "traumatic" (12). In order to avoid potential confusion and to consider the broadness and diversity of the ACEs concept, we referred to the experiences assessed by the CTQ as "childhood adversity" (CA), not ACEs or trauma exclusively.

Anxiety: Anxiety was captured with the State-Trait Anxiety Inventory Form Y (STAI), a comprehensive 20-item instrument for measuring anxiety in adults that differentiates between the temporary condition of "state anxiety" and the more general and long-standing quality of "trait anxiety." The essential qualities evaluated by the STAI-S Anxiety scale are feelings of apprehension, tension, nervousness, and worry (13). Participants responded how each item applied to them by using a range from 1 Almost never to 4 Almost always, and scores were computed by summing across all items for which there was no missing data. Higher scores reflected a higher level of anxiety. Mean substitution was used in cases with only one missing value.

Pain: Most of the pain-related information was captured via general questions about experiences with a range of different chronic condition items rather than a pain specific measure or conditions. These condition-orientated questions did not always reflect a timepoint and hence would be more difficult to

include as a sign of chronic pain. Consequently, the item: “Do you have chronic pain, that is do you have pain that persists beyond the time of normal healing and has lasted anywhere from a few months to many years?” was selected as the key item to reflect chronic pain. In addition, physician-diagnosed pain was also captured and used in the analyses. Chronic pain was modelled as a binary variable that indicates whether the participant had or did not have chronic pain (1=yes, 0=no). A person was considered to have chronic pain if they met any of the following criteria: 1) Had any valid chronic pain diagnostic; Reported zero time without feeling pain in the last month; Saw a professional about chronic pain; Indicated having chronic pain; or Physician diagnosed chronic back/neck problems.

CRP: CRP was a continuous variable captured in ug/mL. The CRP bioassays were performed on blood samples (frozen serum and citrated plasma) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT) using the BNII nephelometer from Dade Behring utilizing a particle enhanced immunonepholometric assay. Polystyrene particles were coated with monoclonal antibodies to CRP, which, in the presence of antigen (CRP) agglutinate causes an increase in the intensity of scattered light. The increase in scattered light is proportional to the amount of CRP in the sample (14). At biomarker collection, 12-hour urine sample and fasting blood samples were collected from each participant after an overnight stay at the research site, and to ensure consistency, all samples were collected and processed using standardized procedures and then fresh and frozen samples were shipped to the MIDUS Biocore Lab for assay. Any samples falling below the assay range for CRP were re-assayed by immunoelectrochemiluminescence using a high-sensitivity assay kit (Meso Scale Diagnostics #K151STG) (15). For citrated plasma, the assay range was 0.175–1100 ug/mL (inter-assay variability: 2.1–5.7%; reference range: ≤3 ug/mL), and for serum the assay range was 0.014–216ug/mL (inter-assay variability: 4.72–5.16%; reference range: <3 ug/mL). The coefficients of variance for all CRP assays were in acceptable ranges (<10%). While CRP values in excess of 10 mg/L are thought to indicate acute infectious illness (16), CRP has gained traction in the last decade to be examined as a potential

biomarker for chronic pain (17–18). Since our study involves both chronic pain whether generally self-reported (and/or defined by a particular pain disease, potentially), we did not feel it would be appropriate to exclude the cases over 10 mg/L as they may have been due to acute infection but importantly may also have been confounded by cooccurring with chronic pain.

Socio-demographics were of interest as potential confounders and were included as additional control variables in the regression. Ethical approval for this study was provided by the General University Ethics Panel, University of Stirling, Stirling, UK (#GUEP 2023 13945 9460).

Variables

Analysis plans

Objectives 1 and 2

Structural equational modeling (SEM) to develop a preliminary understanding of relationships between variables was conducted, followed by general linear modeling (GLM) regression using the variables in **Supplemental Table A1**. All scale variables had their missing values recoded to be "NA" in R (19). For the overall scale variables such as the CTQ scale variables, a value > 97 was recoded to missing, as per the MIDUS data dictionary (20). For subscale variables, e.g., on a 1 to 5 Likert scale, a value > 7 was recoded to missing as per the data dictionary. Control variables for income had values 9999998 and -1 and racial origins had value 7 recoded as "NA" as per the MIDUS data dictionary (20).

The relationships among CAs, anxiety, inflammation, socio-economic factors, and chronic pain were viewed under three methodological lenses to gain insight into different aspects of their relationships. The correlation analysis computed Spearman correlation coefficients on each possible pair of variables to show how strongly and in what direction each pair was related. This provided initial insight into variable relationships and can be used to inform and cross-check the structural equation model-building process and results and the regressions. The Structural Equation Model (SEM) explored and visualised hypothetical relationships among observed and unobserved (latent) variables. It shows how observed

and latent variables for CAs, anxiety, inflammation, and chronic pain, and observed socioeconomic variables directionally affected each other, something not possible with correlation or regression methods (21–22) and is why it was selected over more standard mediation and moderation modelling. The regression model used independent variables for and specified interactions among CAs, anxiety, inflammation, and socio-economic factors (controls) to predict chronic pain presence. This allowed for the identification of significant factors which predicted chronic pain presence. An additional exploratory regression on the subset of respondents who experienced chronic pain explored how CAs, anxiety, and inflammation predicted pain medication use for chronic pain. These three methods overall provided complementary insights. Correlations showed how pairs of variables related to each other, the SEM visualized how all observed and unobserved variables related to each other, and the regression models identified significant variables and interactions, which predicted chronic pain presence and medication use for chronic pain. An additional sensitivity analysis was conducted excluding those with CRP levels >10 to test the validity of our model. Further detailed information outlining how the analyses addressed the objectives are detailed in **Supplemental Tables B1-B3**. The path diagram of the planned SEM and associated Methodology as outline in the Registered Report are detailed in **Supplement B.**

Briefly, the SEM was built with the 'lavaan' package version 0.6 (23) in the R programming language, version 4.3 (19). Missing data in the control and measured variables was coded according to the method detailed in the Measures and Variables sections (p7–11). The entire MIDUS sample of 1,255 participants as detailed in the Dataset and Participants section was used, with cases missing any indicator or control variables dropped from the sample. The maximum likelihood parameter estimation method built into the 'lavaan' package was used, as it is suitable for all-numerical data (including binary and Likert-scaled variables which will be coded numerically as integers) with complete cases (24). The maximum likelihood method assumes data is multivariate normally distributed, and this assumption was tested on the MIDUS data. As the data were found to not be normally distributed, the 'robust' version of the

maximum likelihood parameter estimation method was used, which does not rely on the normality assumption and provides robust standard errors and a scaled test statistic (25).

Exploratory objective

All variables imported into the primary objectives analysis dataset was used as possible independent variables for the pain medication regression. All scale and subscales variables were recoded per the data dictionary as previously described in the analysis plans for objective 1 and 2. Gender was recoded to a factor variable with levels Male and Female instead of numeric values. The chronic pain presence variable was derived as per the primary dataset.

The dependent variable ("did the person use medication for more than 3 months for chronic pain?") was derived from several medication chart variables. Specifically, a person met criteria as having taken long term medication for chronic pain: if a person had taken any prescription, alternative, or over the counter medicine; or if the medicine was taken with a duration for > 3 months, and taken for ICD9 code 338 ("pain, not elsewhere classified").

The final exploratory dataset was constructed by merging the independent and dependent variables by MIDUS-ID and taking the subset that had chronic pain (chronic pain presence variable = 1), as this was the population of interest. A logistic regression was used to predict the presence of long-term medication use for chronic pain in the subset of the study population which was identified as having chronic pain. Any records where one or more parameters were missing was dropped from the regression model. Model accuracy can be broken into sensitivity ("true positives", how many people with chronic pain are correctly identified as taking long term medication for chronic pain) and specificity ("true negatives", how many people with chronic pain are correctly identified as not taking long term medication for chronic pain). The dependent variable may be imbalanced, as 89% of the 651 available records did not take medication for chronic pain. To address this, model performance results were also

presented in the form of a confusion matrix (true positives, true negatives, false positives, false negatives) with the sensitivity and specificity statistics reported. The regression model was tuned to maximizing sensitivity (true positives) to ensure that the model correctly predicted people taking long term medication for chronic pain. The rationale for the Methodology as initially proposed in the Registered Report is detailed in **Supplement B**.

Results

The specific sample sizes for the three different types of analyses conducted, as described above, and socio-demographics within each sample are displayed in **Table 1**.

Objectives 1–2

Correlations

Relationships were initially assessed using non-parametric Spearman correlations (**Figure 1**). The correlation indicated that CAs (aside from minimization), anxiety and CRP were all significantly positively associated with chronic pain presence. Further, CRP was significantly correlated with anxiety (r = 0.07, gender (male: r = -0.16, female: r = 0.16), income (total household: r = -0.11, total: r = -0.11), highest education (r = -0.15), race (white: r = -0.15, Black: r = 0.15), and the presence of chronic pain (r = 0.13). Additionally, CRP was significantly correlated with two of the CTQ subscales; emotional abuse (r = 0.07) and physical neglect (r = 0.06). Relationships among these variables were explored further with the SEM and logistic regressions.

SEM results

The best fitting SEM model that was achieved is displayed in **Figure 2.** The "Mardia's multivariate normality test" in the R package MVN (https://cran.r-project.org/web/packages/MVN/vignettes/MVN.html) was used to calculate Mardia's multivariate

skewness and kurtosis coefficients and the corresponding significance (H0 being the data are multivariate normally distributed). Mardia's skewness was $p < 0.001$ (statistic = 148020) and Mardia's kurtosis was $p < 0.001$ (statistic = 469), thus, the data were not multivariate normally distributed. Therefore, the lavaan 'robust' version of the maximum likelihood parameter estimation method (MLM), which does not assume multivariate normality was used. Based on this model, CAs, anxiety, and CRP all played a role in predicting chronic pain presence.

Regressions predicting chronic pain presence

A general linear model (GLM) with logit link function (logistic regression) was used to predict the binary, dependent variable of chronic pain presence. When conducting modeling against all variables of interest, the margin for error on the race variables was very large, to the extent that the interaction coefficients with race variables were not defined. Therefore, race was removed from the analyses. The results of model 1 (n = 1173) examining the effect of ACEs and anxiety on chronic pain, as well as CRP, are detailed in **Table 2** and visualized in **Figure 3**.

None of the CAs, anxiety, or CRP significantly predicted chronic pain presence as main effects independently. However, female gender, total income, and highest education all independently contributed significantly to predicting chronic pain presence. For the socio-demographic control variables, every one-unit increase in highest education (education scale where 1 is lowest level, 12 is highest), the log odds of having chronic pain (vs not having chronic pain) decreased by 0.68. For every one-unit decrease in total income, the log odds of having chronic pain (vs not having chronic pain) increased by 0.00007. Reported female gender vs male decreased the log odds of having chronic pain by 3.06.

Many significant interactions predicting chronic pain were also found. For instance, CRP levels showed a significant interaction with female gender in determining chronic pain presence. Moreover, there were various interactions between different types of CAs determining the presence of chronic pain, such as emotional abuse and emotional neglect, emotional abuse and physical neglect, and physical abuse and emotional neglect. The partial regression plots (**Figure 3**) indicate how these significant interactions (from **Table 2**) influence the likelihood of chronic pain presence. The impact of emotional abuse depended on levels of emotional and physical neglect and income. At higher frequency of emotional neglect, increasing rates of emotional abuse increased the likelihood of chronic pain, whereas with lower levels of emotional neglect, increasing emotional abuse decreased the likelihood of chronic pain (**Figure 3A**). For increasing levels of physical neglect, increasing levels of emotional abuse decreased the likelihood of chronic pain but at lower levels of physical neglect, increasing emotional abuse had little impact on the risk of chronic pain (**Figure 3B**). Lastly, for high levels of annual income, increasing levels of emotional abuse were related to increased chronic pain likelihood (**Figure 3C**). The interaction between physical abuse and emotional neglect also had a non-linear effect on chronic pain (**Figure 3D**). At low rates of emotional neglect, increasing levels of physical abuse increased the likelihood of chronic pain, but at higher frequency of emotional neglect, the opposite is observed: with increasing levels of physical abuse the likelihood of chronic pain decreased. For the socio-demographic control variable interactions, with increasing levels of education, increased levels of physical abuse were associated with increased likelihood of chronic pain (**Figure 3E**), and the opposite occurred for the lowest education levels, with the impact appearing to switch around at middle education level. An interesting contrast appeared when looking at the interactions between emotional neglect and the entire household income (**Figure 3F**) compared to only the participant's total income (**Figure 3G**). For increasing levels of household income, an increased rate of emotional neglect was related to more chronic pain incidence. However, for increasing levels of high personal

income, high levels of emotional neglect were related to lesser chronic pain incidence. The opposite was found for the lowest level of income, with no impact of emotional neglect found at the second-to-lowest income level ($50,000). Finally, for female participants, increasing CRP increased the likelihood of chronic pain whereas CRP made no difference to chronic pain prediction among males (**Figure 3H**).

To help validate the results, a sensitivity analysis was also conducted in a subset of participants (n=1121) excluding 52 participants with a CRP level ≥ 10, which is sometimes associated with acute infection (**Supplemental Table A3**); however, no major differences arose.

Objective 3

Exploratory pain medication analysis

The regression confusion matrix sensitivity ("true positives") was 45.8% and specificity ("true negatives") was 98.5%. For comparison, a model was run with only the significant predictors and pairwise interactions (including corresponding predictors for the significant pairwise interactions), with a sensitivity of 15.3% and specificity of 98.9%. The confusion matrix for both models is presented in **Supplemental Table A3**. From this, we can infer that the influence of CAs on long-term medication use for chronic pain is complex. Selected interactions relevant to the objectives overall are shown in **Table 3** and the eight significant interactions are visualized in **Figure 4.** The full table of all interactions is in **Supplemental Table A4**.

Emotional abuse, female gender, total household and total (personal) income independently significantly predicted medication use for chronic pain. For emotional abuse, with each one unit increase the log odds of taking medication for chronic pain increased by 0.275. For every one-unit

change in total income, the log odds of medication use for chronic pain increased by 0.00004 for total household income but decreased by 0.0001 for total personal income. Female gender vs male decreased the log odds of medication use for chronic pain by 4.208.

The main CAs interacting with each other significantly to predict pain medication use included emotional abuse and physical abuse, physical abuse and emotional neglect, and physical abuse and minimization. Significant interactions between CAs and the control variables included sexual abuse and total household income, and physical neglect and total income. CRP interactions with control variables were CRP and total household income, and CRP and highest education. Finally, the control variables significantly interacting with each other were gender and income total household income. These interactions are explained in more detail below (**Figure 4**).

For the visualized regressions, lower rates of physical abuse paired with increased occurrence of emotional abuse led to a moderate increase in pain medication use, but there was no impact at other rates of physical abuse (**Figure 4A**). At the highest rates of emotional neglect and increasing physical abuse, the likelihood of taking pain medication for chronic pain greatly increased (**Figure 4B**), however, this gradually lost impact at lower emotional neglect rates. Interestingly, only the highest rate of minimization, interacting with the lowest rates of physical abuse, had a slight increase in pain medication for chronic pain use (**Figure 4C**), with all other rates showing little impact and no impact at physical abuse levels above 7.5. At the lowest level of household income, an increasing frequency of sexual abuse increased the likelihood of taking pain medication for chronic pain (**Figure 4D**); but at all other household income levels there was little influence of sexual abuse. At the lowest level of total personal income, there was no impact of increasing physical neglect on the likelihood of taking pain medication, while for all other levels of income, higher levels of physical neglect were related with an increased chance of taking pain medication (**Figure 4E**). At the lowest household income, increasing CRP level slightly decreased the likelihood of taking pain medication for chronic pain (**Figure 4F**), while for all

other income levels there was little influence of CRP on medication intake. At the highest education level, increasing CRP increased the likelihood of taking pain medication, but at the other education levels, only an increase in CRP from 0 to 5 made any difference, and this was in the form of a decrease in medication for pain usage (**Figure 4G**). Finally, male gender at the lowest total household income level meant a slightly increased likelihood of pain medication usage compared to reported female gender (**Figure 4H**), but this impact gradually disappeared as total household income increased.

Discussion

Using the MIDUS dataset, this study examined the relationships between reported CAs, anxiety, and pain; assessed the associations between CAs, anxiety, inflammation via CRP levels, and pain; and explored how CAs, anxiety, and CRP were potentially associated with pain-medication consumption. None of the CAs, anxiety, or CRP significantly predicted chronic pain presence independently, but the several interactions were significant and offer unique insight into previously held assumptions surrounding ACEs, mental health, and whether socio-demographic variables significantly impact on the effects of these.

For the primary objective analysis, a number of variables were significant, including control variables gender (female), total income, and highest education. While none of the CAs or anxiety significantly predicted chronic pain presence independently, various significant interactions predicting chronic pain were found. Of the main predictors, those that did not interact with each other or any of the socio-demographic control variables in predicting pain presence were sexual abuse, physical neglect, minimization, and trait anxiety. These findings illustrate the complexity around how CAs and socio-demographic variables impact the likelihood of developing chronic pain, where it is not a simple equation of more CAs and/or lower socioeconomic status leading to more pain. A possible explanation

for the deviations with previous literature is that CAs may not be predictors of chronic pain beyond socio-demographic factors. However, if validated in future studies, our results are rather positive in that the complex set of interactions identified provides several opportunities for buffering associations between CA and pain. This highlights the need in clinical practice to gather detailed insights on CA history and socio-demographic situation when assessing a patient with chronic pain, particularly as the present results contradicted some prior research.

Although the findings did match with previous evidence showing how ACEs impact the presence of chronic pain, the lack of an interaction with anxiety or direct impact of anxiety on chronic pain presence was surprising and contrasted with existing literature (28–29). For example, in one study, mediation analyses demonstrated that ACEs (verbal and sexual abuse, parental psychopathology, and early parental loss) were linked to increased anxiety and mood disorders (28). Another study demonstrated that four types of CAs were associated with higher prevalence rates of six different mood and anxiety-related disorders, and self-reported generalized anxiety disorder was specifically associated with physical abuse, emotional abuse, and maternal battering (29). As shown by various studies (both basic and clinical), ACEs have a profound impact on the development and function of the nervous system (30), which we have yet to fully comprehend in terms of adult mental health outcomes such as anxiety. A potential explanation for the lack of anxiety significance in the present results (outside of correlations) may be due to whether ACE history is dependent on the type of anxiety disorder. Indeed, a recent study showed that panic disorder was significantly associated with ACEs but not social phobia (31). This indicates that perhaps we need to investigate the differences between different types of anxieties and anxiety disorders in future research in this field. These results indicate that although some physiological and behavioral adaptations may start to show earlier in life, the outcomes for psychological and physical health may not arise until decades later for adults with a history of CAs, making it even harder to properly account for all variables potentially playing a role, such as in their co-occurring chronic pain and

anxiety. Previous research has also shown that anxiety is associated with chronic pain (32), and that ACEs relate directly to chronic pain or indirectly via anxiety (33). This also contrasts with the present findings, which showed that CAs and chronic pain interactions with anxiety were not significant. This suggests the mental health outcomes of individuals with a history of CAs and chronic pain are indeed complex and may not always interact as previously assumed.

For the secondary objective analysis of how CRP may be an important underlying factor in the association between ACEs and pain, CRP was indeed significantly correlated with two of the CTQ subscales; emotional abuse and physical neglect. The regression results indicated gender, total-income, and highest-education were also significant predictors of chronic pain. Significant interactions to explain chronic pain included CAs interacting with each other and CRP with socio-demographic variables such as income and education level. These findings differ from those of a Denmark cross-sectional and prospective study of 73,131 individuals, where higher CRP level predicted greater psychological distress, depression symptoms, or risk of hospitalization (with depression) 4 to 12 years later in young, middle-aged, or older adults (34). Contrary to previous CRP research, it did not find that the association disappeared when adjusting for confounding variables such as BMI and chronic disease (34). In this way, the present results differed in that anxiety did not have an impact in any of the regression interactions, while socio-demographic variables did play a substantial role. Although the correlations had indicated CRP, CAs (aside from minimization), and anxiety were all significantly positively associated with chronic pain presence, this does not imply a causal relationship nor accounts for the complex interactions that can be identified with linear regressions, and hence should be interpreted with caution. These results highlight the complexity of studying how CRP may be associated with, influencing, or interacting with mental health and/or chronic pain outcomes, and how socio-demographic factors need to be included as well.

Lastly, regarding the third objective, our results on the influence of CAs on long term medication use for chronic pain were also complex. The only variables with a direct impact on predicting medication for chronic pain usage were emotional abuse, male gender, and income (both household and personal income). Again, as seen for the primary objective, the impact of individual CAs was dependent on other CAs and participants' socio-demographics. The finding of those with higher incomes being more likely to be on pain medication is likely intuitive and may represent issues with access to care in the US. Further, pain may be one form of distress that men are more likely to seek treatment for, but relevant literature interpreting such socio-demographic findings remains scarce and the available evidence for pain care in men versus women is mixed and inconsistent (35). A recent study found that for adults with chronic pain, ACEs were associated with more pain complications and pain catastrophizing, with both independently increasing the risk of early treatment attrition (33). Historical epidemiology research has shown that ACEs increase the risk for an adult to develop substance use/abuse disorders (36–37). Of note, beyond opiate dependence—a prevalent issue in the US (38)—ACEs were also more prevalent among cocaine-dependent adults (39) as compared with the general population. In addition, a recent systematic review found that all 20 studies included showed statistical associations between ACEs and either lifetime or current opioid use-related behaviors, but only five demonstrated a significant gradient effect of the number of ACEs increasing with increasing risk of opioid use-related behaviors (40). The present significant interactions between various CAs further highlights the complexity of this issue as the interactions revealed that the impact goes beyond an additive effect of more CAs leading to more pain medication use. These results reinforce how complex CA outcomes are in regard to adult pain, and how pain management and ultimately, pain prevention, needs to account for more trauma-informed approaches to care. Although our understanding of these associations remains obscured by complexities, the need for CA history or ACE screening to be implemented into pain treatment decisions, pain screening, and pain assessment as an important consideration remains warranted.

Finally, it is worth noting that across all analyses, the CA of neglect in some form (emotional or physical) was often significant, highlighting its importance in being more substantially acknowledged and screened for as a type of childhood trauma. While neglect is on the official ACEs list, there remains a paucity of research on the prevalence of neglect in general populations. In a meta-analysis by Stoltenborgh et al. (2013), only 13 studies about emotional neglect were identified, which is drastically low compared to other ACE domains such as childhood sexual abuse, which yielded over 200 publications. (41). Additionally, to date, there is no established questionnaire to measure emotional neglect consistently, which has likely influenced the lack of data on neglect prevalence overall, and past research has shown that a low number of overall suspected cases of child abuse or neglect are actually reported by healthcare providers (42). Thus, the results of the present analyses may help to inform clinical efforts to better predict the potential burden of CAs on adult outcomes across the lifespan and offers insights into the assumptions that are currently held around the relationship between ACEs and anxiety, such as an increased number of ACEs previously being associated with likelihood of anxiety or depression (43), as well as indicating a need to more consistently capture the prevalence and impact of neglect.

Taken together, this study adds to the continuously developing body of research examining the lasting effects of CAs or childhood trauma exposure on health outcomes and adult behaviors across the lifespan, and added some surprising insight into how socio-demographic variables may be involved and thus need to be more strongly considered as potentially contributing factors in both research and clinical settings. These findings have important clinical implications by stressing the need for a history of CAs should be considered in public health policies and decision-making and connect CAs more directly to interventional and preventative programs, including pain management and treatment algorithms. There remains an unmet need for research that better specifies the pathways through which CAs influence later health outcomes and pain medicine consumption, which could be explored more in future studies.

In particular, CA or ACE-informed care should be implemented into pain management considerations such that CRP levels could be examined as part of this treatment selection and decision-making process.

Limitations

Although a dominant theme of the MIDUS biomarker project was to investigate protective or harmful roles that behavioral and psychosocial factors may have in resilience and recovery from health challenges, the research was not targeted towards any specific diseases or conditions, given that psychosocial factors have relevance across multiple health endpoints. Additionally, even though the MIDUS sample was based on a probability sample, minorities and those with lower income levels and less educational attainment are underrepresented in the sample. However, this study offered value as a large, longitudinal US-based sample with consideration of multiple socio-demographic variables. While a variety of intersections between race, gender, class, and income may be associated with higher risks of fair or poor self-rated health, they are usually inconsistent (44). Such interactions make firm conclusions difficult and were too broad for the scope of this study but should be considered in future research. It is also important to note the smaller sample analyzed due to capturing CA in Project 4 compared to the overall MIDUS II population of (N=4963). However, we felt a sample of 1173 was still of value and had enough power to test our hypothesized associations, and added to this growing body of research, even with a low prevalence of CA. Additionally, for patient data captured from MIDUS Project 4, it is a limitation that there would be, by default, a lack of clear temporal precedence in the associations assessed, which SEM cannot address, especially when the analyses use variables mainly collected in Project 4. Finally, there are a small number of participants in the MIDUS II project 4 dataset with HIV/AIDs and histories of cancer who may have been included in the analysis population which has the potential to impact on CRP levels, and therefore any present associations with CRP. However, we conducted sensitivity analysis excluding all patients with CRP above 10 mg/L to account for this possibility as well as potential acute infection.

Conclusions

Based on a large US sample of adults, the results showed that socio-demographic variables played a substantial role in predicting chronic pain experience in adults, with female gender, total income, and highest education all significant. Significant interactions for predicting chronic pain experience included CAs interacting with each other, CAs with income and education; and CRP with income and education levels. The influence of CAs on predicting long term medication use for chronic pain was complex, with significant interactions between a number of CAs, CRP with total household income and highest education, and various CAs and socio-demographics. Across all analyses, the CA of neglect in some form was significant, highlighting its importance in being acknowledged as a type of childhood trauma as well as indicating a need to more consistently capture its prevalence and impact. Although the results warrant further study, these analyses may help to inform clinical efforts and improve screening practices to reduce the burden of CAs on adult outcomes across the lifespan.

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Ethics

Ethical approval for this study was provided by the General University Ethics Panel, University of Stirling, Stirling, UK (reference review #: GUEP 2023 13945 9460).

Data availability and transparency

Midlife in the United States (MIDUS) is a national longitudinal study of health and well-being (http://midus.wisc.edu/). It was conceived by a multidisciplinary team of scholars interested in understanding aging as an integrated bio-psycho-social process, and as such it includes data collected in a wide array of research protocols using a variety of survey and non-survey instruments. The data captured by these different protocols (comprising around 20,000 variables) represent survey measures, cognitive assessments, daily stress diaries, clinical, biomarker and neuroscience data which are contained in separate flat or stacked data files with a common ID system that allows easy data merges among them. All MIDUS datasets and documentation are archived at the ICPSR

(http://www.icpsr.umich.edu/) repository at the University of Michigan and are publicly available in a variety of formats and statistical packages.

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Table 1: Sample sizes and socio-demographics for each type of analysis

Objective	**1–2**	**1–2**	**1–2**	**3**
Type of association	Unstructured	Structured	Predictive	Predictive
Analysis type	Correlation	Structural Equation Model	Regression predicting chronic pain presence	Regression predicting medication use for chronic pain
Variables type	-	Latent and observed	Dependent and independent	Dependent and independent
n	1173	1173	1173	600
			Mean (SD) / %	
Race White	79.0	79.0	79.0	64.7
Black	17.0	17.0	17.0	31.3
Asian	0.2	0.2	0.2	0.0
Native-American	1.4	1.4	1.4	1.5
Other	2.4	2.4	2.4	2.5
Gender Female	56.2	56.2	56.2	60
Male	43.8	43.8	43.8	40
Total income (USD$)	42,194 (39,446)	42,194 (39,446)	42,194 (39,446)	36,152(34,562)
Total household income (USD$)	72,177 (59,161)	72,177 (59,161)	72,177 (59,161)	61,105 (53,972)
Highest education				
None/some grade school	0.2	0.2	0.2	0.2
Eighth grade/junior high school	0.9	0.9	0.9	1.5
Some high school	4.6	4.6	4.6	7.3
GED	1.4	1.4	1.4	2.3
Graduated from high school	20.6	20.6	20.6	21.7
1-2 years of college, no degree	17.4	17.4	17.4	19.8
3+ years of college, no degree	4.9	4.9	4.9	5.3
2-year/vocational college graduate	7.1	7.1	7.1	6.8
4-year/bachelor's college graduate	21.0	21.0	21.0	17.0
Some graduate school	4.0	4.0	4.0	3.2
Master's degree	14.0	14.0	14.0	12.2
PhD/other professional degree	4.1	4.1	4.1	2.7
Age at interview	54 (12)	54 (12)	54 (12)	55 (12)

Table 2: CA, Anxiety, and CRP and interactions as a predictors

Variable	Estimate'	Std. Error	z-value	p-value
(Constant)	0.563	3.528	0.160	0.873
CTQ Emotional Abuse	-0.128	0.261	-0.490	0.624
CTQ Physical Abuse	-0.054	0.327	-0.166	0.868
CTQ Sexual Abuse	0.237	0.206	1.149	0.251
CTQ Emotional Neglect	-0.238	0.240	-0.992	0.321
CTQ Physical Neglect	0.664	0.344	1.929	0.054
CTQ Minimization	0.853	0.839	1.016	0.310
Trait Anxiety	0.130	0.069	1.884	0.060
C-Reactive Protein	-0.353	0.185	-1.912	0.056
Gender (Female)	-3.067	1.371	-2.237	**0.025**
Age At Interview	-0.034	0.045	-0.742	0.458
Total Household Income	0.00002	0.00002	1.177	0.239
Total Income	-0.00007	0.00003	-2.162	**0.031**
Highest Education	-0.680	0.243	-2.799	**0.005**
Interactions				
CTQ Emotional Abuse * CTQ Physical Abuse	0.010	0.008	1.127	0.260
CTQ Emotional Abuse * CTQ Sexual Abuse	0.009	0.008	1.138	0.255
CTQ Emotional Abuse * CTQ Emotional Neglect	0.018	0.007	2.365	**0.018**
CTQ Emotional Abuse * CTQ Physical Neglect	-0.024	0.012	-2.042	**0.041**
CTQ Emotional Abuse * CTQ Minimization	0.021	0.065	0.318	0.750
CTQ Emotional Abuse * Trait Anxiety	0.001	0.003	0.230	0.818
CTQ Emotional Abuse * C-Reactive Protein	0.008	0.010	0.737	0.461
CTQ Emotional Abuse * Gender (Female)	0.037	0.065	0.564	0.573
CTQ Emotional Abuse * Age At Interview	-0.0002	0.003	-0.081	0.935
CTQ Emotional Abuse * Total Household Income	-0.000002	0.000001	-1.742	0.082
CTQ Emotional Abuse * Total Income	0.000003	0.000001	2.132	**0.033**
CTQ Emotional Abuse * Highest Education	-0.015	0.013	-1.182	0.237
CTQ Physical Abuse * CTQ Sexual Abuse	-0.002	0.008	-0.300	0.765
CTQ Physical Abuse * CTQ Emotional Neglect	-0.023	0.011	-2.074	**0.038**
CTQ Physical Abuse * CTQ Physical Neglect	0.010	0.014	0.704	0.481
CTQ Physical Abuse * CTQ Minimization	-0.010	0.070	-0.148	0.882
CTQ Physical Abuse * Trait Anxiety	-0.004	0.004	-1.087	0.277
CTQ Physical Abuse * C-Reactive Protein	0.012	0.014	0.824	0.410
CTQ Physical Abuse * Gender (Female)	0.053	0.080	0.660	0.509
CTQ Physical Abuse * Age At Interview	0.003	0.004	0.872	0.383
CTQ Physical Abuse * Total Household Income	-0.0000007	0.000001	-0.590	0.556
CTQ Physical Abuse * Total Income	-0.0000005	0.000002	-0.275	0.784
CTQ Physical Abuse * Highest Education	0.032	0.015	2.075	**0.038**

CTQ Sexual Abuse * CTQ Emotional Neglect	-0.003	0.008	-0.460	0.645
CTQ Sexual Abuse * CTQ Physical Neglect	-0.001	0.010	-0.061	0.951
CTQ Sexual Abuse * CTQ Minimization	-0.050	0.041	-1.211	0.226
CTQ Sexual Abuse * Trait Anxiety	-0.003	0.003	-1.260	0.208
CTQ Sexual Abuse * C-Reactive Protein	-0.004	0.006	-0.589	0.556
CTQ Sexual Abuse * Gender (Female)	0.037	0.061	0.602	0.547
CTQ Sexual Abuse * Age At Interview	-0.001	0.002	-0.687	0.492
CTQ Sexual Abuse * Total Household Income	-0.0000007	0.0000007	-0.963	0.335
CTQ Sexual Abuse * Total Income	0.000001	0.000001	0.941	0.347
CTQ Sexual Abuse * Highest Education	-0.008	0.010	-0.806	0.420
CTQ Emotional Neglect * CTQ Physical Neglect	0.010	0.010	1.059	0.289
CTQ Emotional Neglect * CTQ Minimization	0.082	0.044	1.860	0.063
CTQ Emotional Neglect * Trait Anxiety	0.004	0.003	1.249	0.212
CTQ Emotional Neglect * C-Reactive Protein	-0.002	0.008	-0.282	0.778
CTQ Emotional Neglect * Gender (Female)	-0.079	0.055	-1.452	0.147
CTQ Emotional Neglect * Age At Interview	0.001	0.003	0.513	0.608
CTQ Emotional Neglect * Total Household Income	0.000002	0.0000008	2.570	**0.010**
CTQ Emotional Neglect * Total Income	-0.000003	0.000001	-2.461	**0.014**
CTQ Emotional Neglect * Highest Education	0.00003	0.011	0.003	0.998
CTQ Physical Neglect * CTQ Minimization	-0.024	0.070	-0.341	0.733
CTQ Physical Neglect * Trait Anxiety	-0.008	0.004	-1.764	0.078
CTQ Physical Neglect * C-Reactive Protein	0.020	0.012	1.665	0.096
CTQ Physical Neglect * Gender (Female)	-0.014	0.081	-0.172	0.863
CTQ Physical Neglect * Age At Interview	-0.004	0.004	-1.176	0.240
CTQ Physical Neglect * Total Household Income	-0.000002	0.000001	-1.516	0.129
CTQ Physical Neglect * Total Income	0.000001	0.000002	0.834	0.404
CTQ Physical Neglect * Highest Education	-0.004	0.015	-0.297	0.766
CTQ Minimization * Trait Anxiety	0.001	0.013	0.039	0.969
CTQ Minimization * C-Reactive Protein	-0.018	0.024	-0.748	0.454
CTQ Minimization * Gender (Female)	-0.121	0.184	-0.656	0.512
CTQ Minimization * Age At Interview	-0.012	0.007	-1.560	0.119
CTQ Minimization * Total Household Income	-0.000001	0.000003	-0.405	0.686
CTQ Minimization * Total Income	-0.000003	0.000004	-0.797	0.425
CTQ Minimization * Highest Education	-0.003	0.039	-0.079	0.937
Trait Anxiety * C-Reactive Protein	-0.0002	0.003	-0.058	0.954
Trait Anxiety * Gender (Female)	0.002	0.019	0.123	0.902
Trait Anxiety * Age At Interview	-0.001	0.001	-0.704	0.481
Trait Anxiety * Total Household Income	0.0000002	0.0000003	0.686	0.493
Trait Anxiety * Total Income	-0.0000002	0.0000004	-0.455	0.649
Trait Anxiety * Highest Education	0.001	0.004	0.219	0.827
C-Reactive Protein * Gender (Female)	0.108	0.050	2.186	**0.029**

C-Reactive Protein * Age At Interview	0.001	0.002	0.748	0.455
C-Reactive Protein * Total Household Income	-0.0000005	0.0000007	-0.727	0.467
C-Reactive Protein * Total Income	0.000002	0.000001	1.506	0.132
C-Reactive Protein * Highest Education	0.005	0.009	0.542	0.588
Gender (Female) * Age At Interview	0.031	0.013	2.303	**0.021**
Gender (Female) * Total Household Income	-0.00001	0.000005	-2.314	**0.021**
Gender (Female) * Total Income	0.00002	0.000007	3.236	**0.001**
Gender (Female) * Highest Education	0.133	0.063	2.110	**0.035**
Age At Interview * Total Household Income	-0.0000003	0.0000002	-1.601	0.109
Age At Interview * Total Income	0.0000007	0.0000003	2.346	**0.019**
Age At Interview * Highest Education	0.007	0.003	2.575	**0.010**
Total Household Income * Total Income	0.00000000002	0.00000000002	0.713	0.476
Total Household Income * Highest Education	0.0000005	0.0000009	0.502	0.615
Total Income * Highest Education	0.000002	0.000001	1.120	0.263

NOTES: Dependent variable: Probability of having chronic pain. N = 1173. (Dispersion parameter for binomial family taken to be 1). 'Logit function ranging between 0 and 1.

Table 3: Long term medication use for chronic pain (significant regression coefficients only)

Variable	Estimate	Std. Error	z-value	p-value
(Constant)	-3.236	4.231	-0.765	0.444
CTQ Emotional Abuse	0.275	0.126	2.175	**0.030**
CTQ Physical Abuse	-0.529	0.309	-1.710	0.087
CTQ Sexual Abuse	0.349	0.295	1.184	0.236
CTQ Emotional Neglect	-0.186	0.189	-0.985	0.325
CTQ Physical Neglect	-0.336	0.183	-1.836	0.066
CTQ Minimization	0.776	0.689	1.126	0.260
Trait Anxiety	0.109	0.095	1.143	0.253
C-Reactive Protein	-0.308	0.169	-1.815	0.069
Gender (Female)	-4.208	1.461	-2.880	**0.004**
Age At Interview	0.087	0.056	1.537	0.124
Total Household Income	0.00004	0.00002	2.025	**0.043**
Total Income	-0.0001	0.00004	-3.150	**0.002**
CTQ Emotional Abuse * CTQ Physical Abuse	-0.030	0.013	-2.291	**0.022**
CTQ Physical Abuse * CTQ Sexual Abuse	-0.010	0.008	-1.208	0.227
CTQ Physical Abuse * CTQ Emotional Neglect	0.050	0.016	3.197	**0.001**
CTQ Physical Abuse * CTQ Minimization	-0.278	0.128	-2.176	**0.030**
CTQ Physical Abuse * Trait Anxiety	0.009	0.005	1.610	0.107
CTQ Sexual Abuse * CTQ Minimization	0.164	0.088	1.858	0.063
CTQ Sexual Abuse * Trait Anxiety	-0.006	0.004	-1.594	0.111
CTQ Sexual Abuse * Gender (Female)	0.281	0.181	1.554	0.120
CTQ Sexual Abuse * Total Household Income	-0.000007	0.000003	-2.620	**0.009**
CTQ Sexual Abuse * Total Income	0.000006	0.000003	1.838	0.066
CTQ Sexual Abuse * Highest Education	-0.025	0.019	-1.307	0.191
CTQ Emotional Neglect * Highest Education	-0.032	0.018	-1.818	0.069
CTQ Physical Neglect * Total Household Income	-0.000003	0.000002	-1.909	0.056
CTQ Physical Neglect * Total Income	0.000009	0.000003	2.696	**0.007**
CTQ Physical Neglect * Highest Education	0.035	0.026	1.352	0.176
Trait Anxiety * Age At Interview	-0.002	0.002	-1.583	0.113
Trait Anxiety * Total Income	0.000001	0.0000006	1.841	0.066
C-Reactive Protein * Total Household Income	-0.000003	0.000001	-2.083	**0.037**
C-Reactive Protein * Highest Education	0.049	0.022	2.170	**0.030**
Gender (Female) * Total Household Income	0.00003	0.00001	2.172	**0.030**
Gender (Female) * Total Income	-0.00002	0.00002	-0.987	0.323
Gender (Female) * Highest Education	0.261	0.140	1.872	0.061

Dependent variable: Probability of taking long term medication for chronic pain (N = 600). Null deviance: 383.69 on 599 degrees of freedom. Residual deviance: 303.66 on 565 degrees of freedom AIC: 373.66.

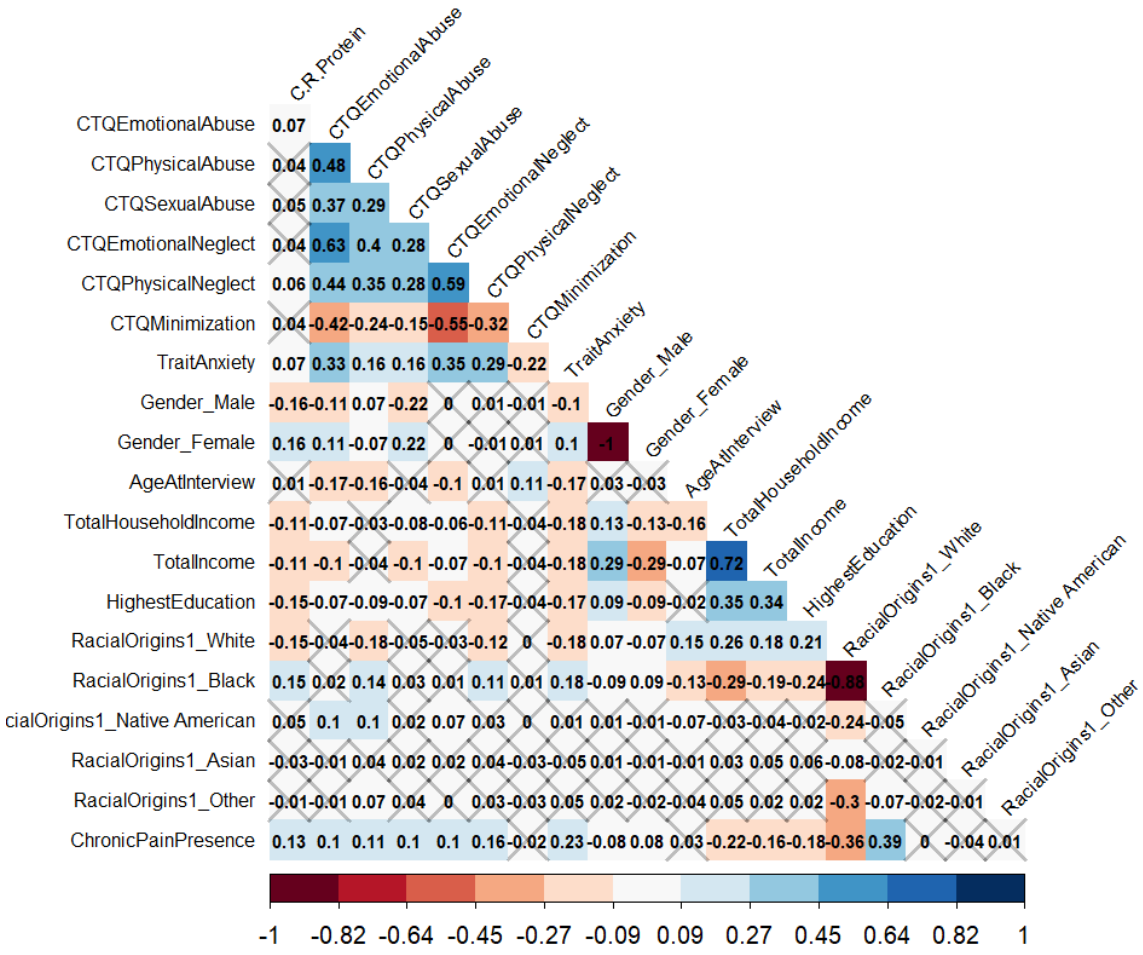

Figure 1. Heatmap of correlations between variables of interest and CRP

The Xs indicate the correlation is insignificant at the 95% level. N = 1173.

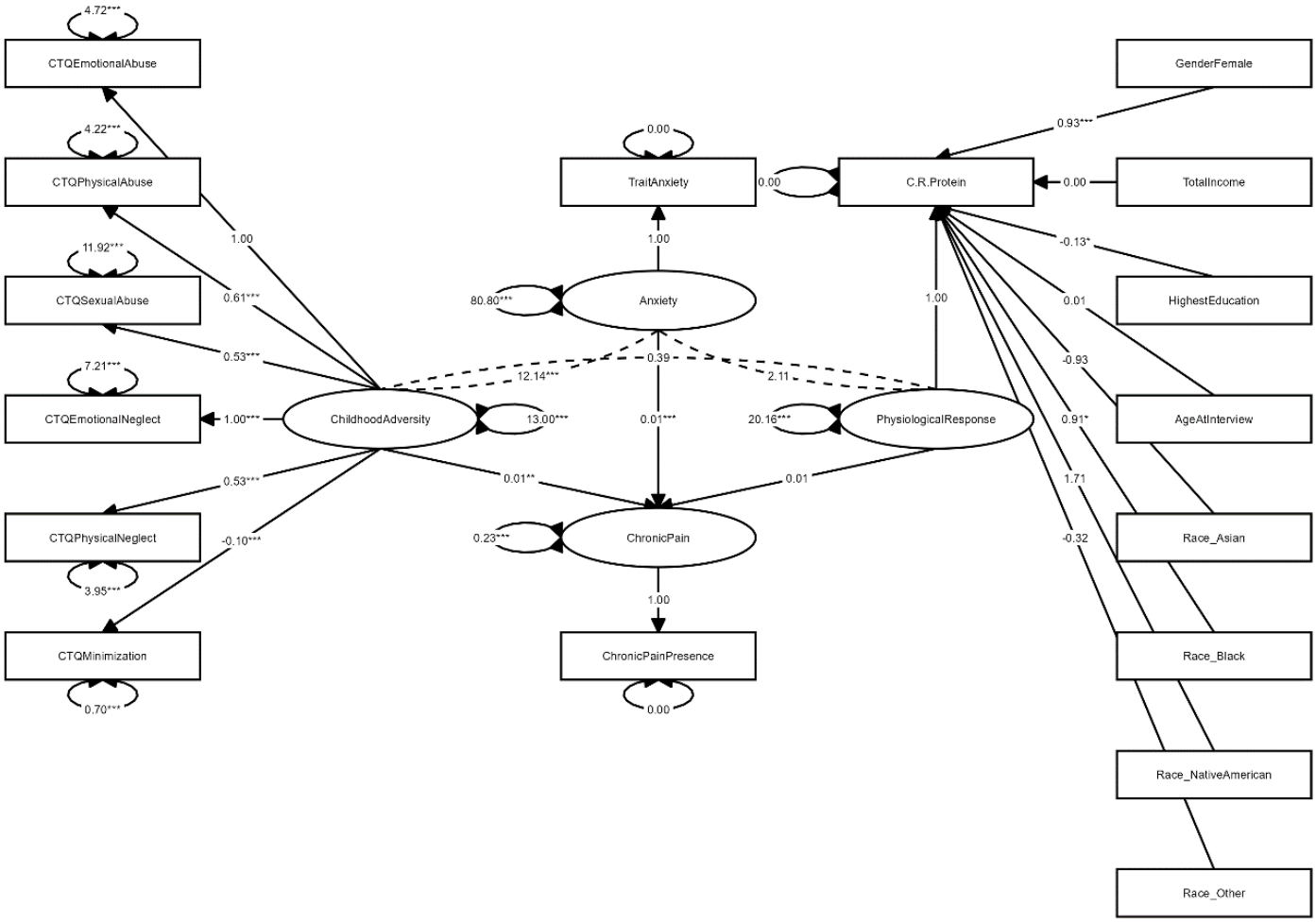

Figure 2. Final SEM

The parameters for this model were CFI: 0.989 (>0.90), RMSEA: 0.087 (<0.05), $\chi^2 = 865$, df = 88, $p < 0.001$.

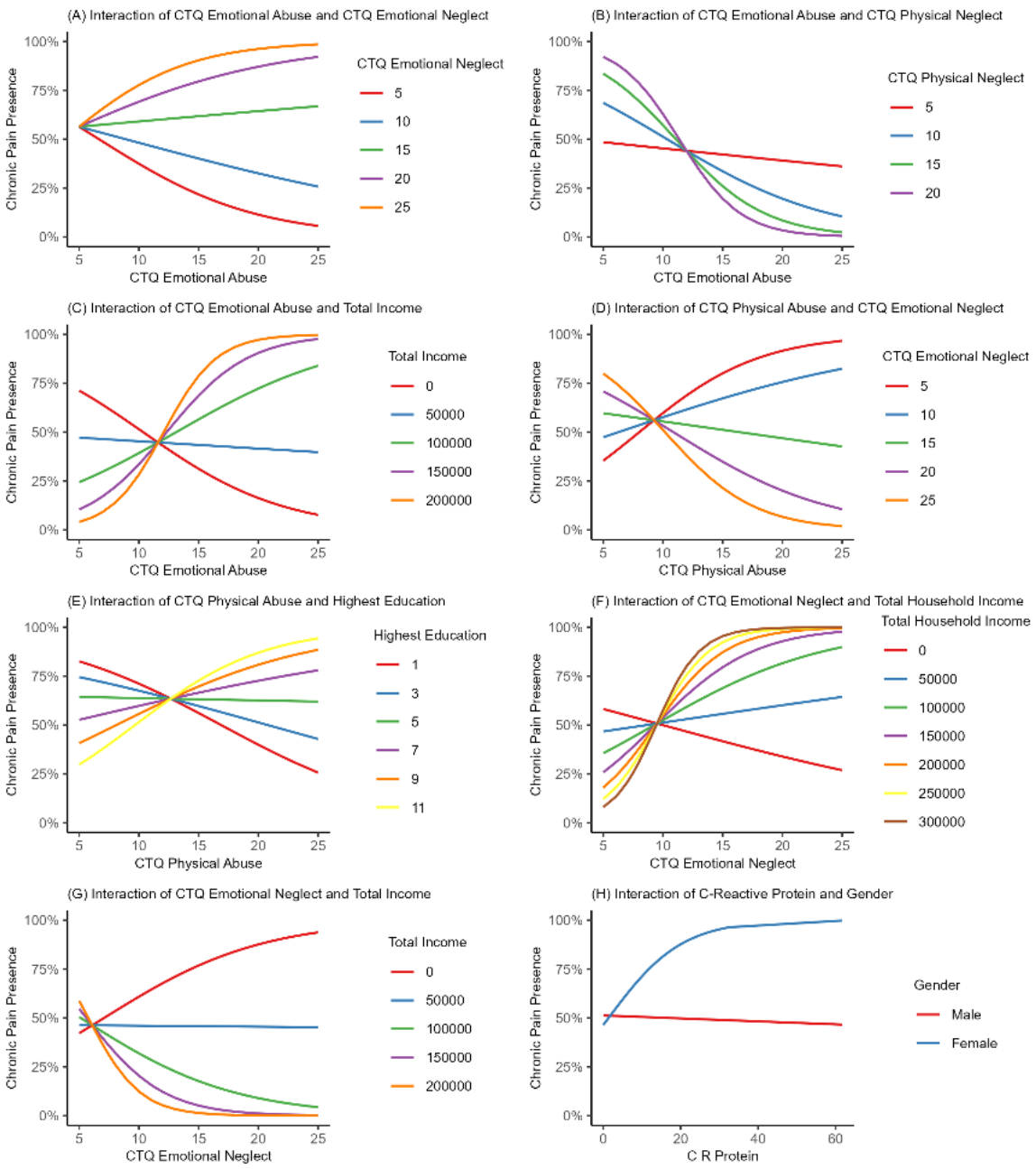

Figure 3. Partial regressions of significant interactions on probability of chronic pain presence
Notes: The likelihood of chronic pain presence increases as the y-axis increases to 100%. Incomes are annual USD ($).

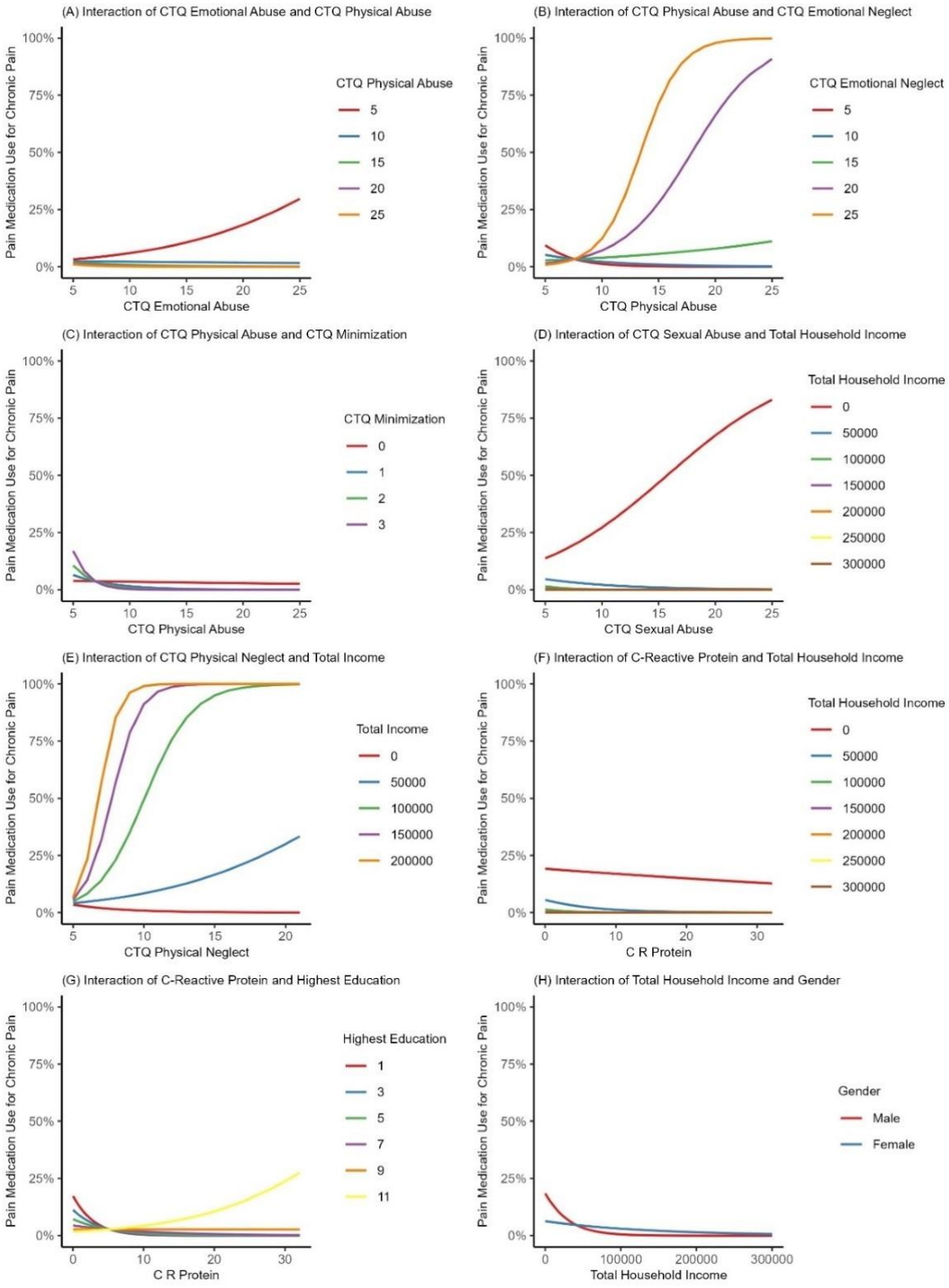

Figure 4. Partial regressions of long-term medication use for chronic pain

Note: The likelihood of medication use for chronic pain presences increase as the y-axis increases to 100%.

Supplemental A. Additional Results

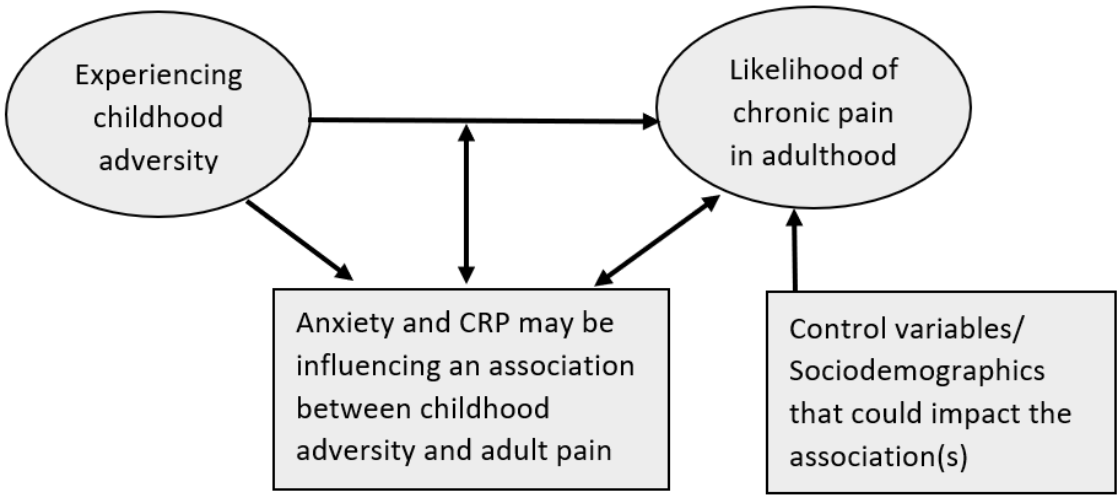

Figure 1A. Conceptual model of how childhood adversity impacts adult chronic pain experience as potentially influenced by anxiety and inflammation (indexed by CRP)

Table A1. MIDUS variables

ID	Variable
Childhood adversity	
B4QCT_EA	CTQ: Emotional Abuse
B4QCT_PA	CTQ: Physical Abuse
B4QCT_SA	CTQ: Sexual Abuse
B4QCT_EN	CTQ: Emotional Neglect
B4QCT_PN	CTQ: Physical Neglect
B4QCT_MD	CTQ: Minimization/Denial
Anxiety	
B4QTA_AX	Spielberger Trait Anxiety Inventory (STAI)
Pain*	
B4HSYMX	Any Symptoms and Chronic Conditions? (Yes/No)
B4HSYMN	Total number of Symptoms and Chronic Conditions
B1SA23A/ B1SA23D	Diagnosis given by physician or other health care professional about pain
B4Q10WW1	Feeling no pain in the last month
BACAS22	Saw physician/professional about pain
K2Q1XD	Physician diagnosed chronic back or neck problems
B1SA15/K2Q17/ BACAS15/RA1SA15	Has chronic pain/persists beyond normal
Inflammatory biomarker	
B4BCRP	Blood C-Reactive Protein (ug/mL)
Control variables	
B1PRSEX	Gender
B1PRAGE_2019/ BACRAGE	Respondent's calculated age at project interview
B1STINC1/ BACTINC1	Household total income from wage, pension, social security, and other sources
B1SRINC1/ BACRINC1	Respondent's personal income from wage, pension, social security, and other sources
B1PB1/BACB1	Highest level of education completed
B1PF7A/BACF7A	Racial origins (#1)

*Many pain measures were duplicated across the series of MIDUS projects and follow-ups, and some control variables were stored separately across the MIDUS projects, which is why some variables have multiple ID numbers for the same variable row.
“Household income” total included different types and different sources, based on sum of original income variables (= [B1SG8AX], [B1SG8BX], [B1SG8CX], [B1SG9AX], [B1SG9BX], [B1SG9CX], [B1SG10AX], [B1SG10BX], [B1SG10CX], AND [B1SG12]). “Total income” personally was for the respondent only, based on original income variables (= sum of [B1SG8AX], [B1SG8BX], AND [B1SG8CX]).

Table A2. Specific diagnosis given by physician (B1SA23A/ B1SA23D)

	Frequency	% of total	% of valid
Fibromyalgia	41	0.83%	3.73%
Migraine/headache	13	0.26%	1.18%
Back/spine/disc/Scoliosis/rib	135	2.72%	12.3%
Carpal Tunnel Syndrome	11	0.22%	1%
Bone spur	9	0.18%	0.82%
Injury from accident	48	0.97%	4.37%
Other	356	7.17%	32.42%
Not diagnosed		0%	0%
Hip problem/Sciatica	21	0.42%	1.91%
Other muscle problem	22	0.44%	2%
Other knee problem	25	0.5%	2.28%
Plantar Fasciitis/foot/ankle problem	6	0.12%	0.55%
Arthritis	335	6.75%	30.51%
Other joint problem/gout	13	0.26%	1.18%
Neck/shoulder problem	22	0.44%	2%
Nerve problem	20	0.4%	1.82%
Cervical problem		0%	0%
Tendonitis	21	0.42%	1.91%
Total	1,098	22.12%	100%

Table A3: CRP as a predictor along with its interactions, sensitivity analysis with participants with CRP ≥ 10.0 excluded

Variable	Estimate	Std. Error	z-value	p-value	Sig
(Constant)	0.563	3.528	0.160	0.873	
CTQ Emotional Abuse	-0.128	0.261	-0.490	0.624	
CTQ Physical Abuse	-0.054	0.327	-0.166	0.868	
CTQ Sexual Abuse	0.237	0.206	1.149	0.251	
CTQ Emotional Neglect	-0.238	0.240	-0.992	0.321	
CTQ Physical Neglect	0.664	0.344	1.929	0.054	.
CTQ Minimization	0.853	0.839	1.016	0.310	
Trait Anxiety	0.130	0.069	1.884	0.060	.
C-Reactive Protein	-0.353	0.185	-1.912	0.056	.
Gender (Female)	-3.067	1.371	-2.237	0.025	*
Age At Interview	-0.034	0.045	-0.742	0.458	
Total Household Income	0.00002	0.00002	1.177	0.239	
Total Income	-0.00007	0.00003	-2.162	0.031	*
Highest Education	-0.680	0.243	-2.799	0.005	**
CTQ Emotional Abuse * CTQ Physical Abuse	0.010	0.008	1.127	0.260	
CTQ Emotional Abuse * CTQ Sexual Abuse	0.009	0.008	1.138	0.255	
CTQ Emotional Abuse * CTQ Emotional Neglect	0.018	0.007	2.365	0.018	*
CTQ Emotional Abuse * CTQ Physical Neglect	-0.024	0.012	-2.042	0.041	*
CTQ Emotional Abuse * CTQ Minimization	0.021	0.065	0.318	0.750	
CTQ Emotional Abuse * Trait Anxiety	0.001	0.003	0.230	0.818	
CTQ Emotional Abuse * C-Reactive Protein	0.008	0.010	0.737	0.461	
CTQ Emotional Abuse * Gender (Female)	0.037	0.065	0.564	0.573	
CTQ Emotional Abuse * Age At Interview	-0.0002	0.003	-0.081	0.935	
CTQ Emotional Abuse * Total Household Income	-0.000002	0.000001	-1.742	0.082	.
CTQ Emotional Abuse * Total Income	0.000003	0.000001	2.132	0.033	*
CTQ Emotional Abuse * Highest Education	-0.015	0.013	-1.182	0.237	
CTQ Physical Abuse * CTQ Sexual Abuse	-0.002	0.008	-0.300	0.765	
CTQ Physical Abuse * CTQ Emotional Neglect	-0.023	0.011	-2.074	0.038	*
CTQ Physical Abuse * CTQ Physical Neglect	0.010	0.014	0.704	0.481	
CTQ Physical Abuse * CTQ Minimization	-0.010	0.070	-0.148	0.882	
CTQ Physical Abuse * Trait Anxiety	-0.004	0.004	-1.087	0.277	
CTQ Physical Abuse * C-Reactive Protein	0.012	0.014	0.824	0.410	
CTQ Physical Abuse * Gender (Female)	0.053	0.080	0.660	0.509	
CTQ Physical Abuse * Age At Interview	0.003	0.004	0.872	0.383	
CTQ Physical Abuse * Total Household Income	-0.0000007	0.000001	-0.590	0.556	
CTQ Physical Abuse * Total Income	-0.0000005	0.000002	-0.275	0.784	
CTQ Physical Abuse * Highest Education	0.032	0.015	2.075	0.038	*
CTQ Sexual Abuse * CTQ Emotional Neglect	-0.003	0.008	-0.460	0.645	
CTQ Sexual Abuse * CTQ Physical Neglect	-0.001	0.010	-0.061	0.951	

Variable	Estimate	Std. Error	z-value	p-value	Sig
CTQ Sexual Abuse * CTQ Minimization	-0.050	0.041	-1.211	0.226	
CTQ Sexual Abuse * Trait Anxiety	-0.003	0.003	-1.260	0.208	
CTQ Sexual Abuse * C-Reactive Protein	-0.004	0.006	-0.589	0.556	
CTQ Sexual Abuse * Gender (Female)	0.037	0.061	0.602	0.547	
CTQ Sexual Abuse * Age At Interview	-0.001	0.002	-0.687	0.492	
CTQ Sexual Abuse * Total Household Income	-0.0000007	0.0000007	-0.963	0.335	
CTQ Sexual Abuse * Total Income	0.000001	0.000001	0.941	0.347	
CTQ Sexual Abuse * Highest Education	-0.008	0.010	-0.806	0.420	
CTQ Emotional Neglect * CTQ Physical Neglect	0.010	0.010	1.059	0.289	
CTQ Emotional Neglect * CTQ Minimization	0.082	0.044	1.860	0.063	.
CTQ Emotional Neglect * Trait Anxiety	0.004	0.003	1.249	0.212	
CTQ Emotional Neglect * C-Reactive Protein	-0.002	0.008	-0.282	0.778	
CTQ Emotional Neglect * Gender (Female)	-0.079	0.055	-1.452	0.147	
CTQ Emotional Neglect * Age At Interview	0.001	0.003	0.513	0.608	
CTQ Emotional Neglect * Total Household Income	0.000002	0.0000008	2.570	0.010	*
CTQ Emotional Neglect * Total Income	-0.000003	0.000001	-2.461	0.014	*
CTQ Emotional Neglect * Highest Education	0.00003	0.011	0.003	0.998	
CTQ Physical Neglect * CTQ Minimization	-0.024	0.070	-0.341	0.733	
CTQ Physical Neglect * Trait Anxiety	-0.008	0.004	-1.764	0.078	.
CTQ Physical Neglect * C-Reactive Protein	0.020	0.012	1.665	0.096	.
CTQ Physical Neglect * Gender (Female)	-0.014	0.081	-0.172	0.863	
CTQ Physical Neglect * Age At Interview	-0.004	0.004	-1.176	0.240	
CTQ Physical Neglect * Total Household Income	-0.000002	0.000001	-1.516	0.129	
CTQ Physical Neglect * Total Income	0.000001	0.000002	0.834	0.404	
CTQ Physical Neglect * Highest Education	-0.004	0.015	-0.297	0.766	
CTQ Minimization * Trait Anxiety	0.001	0.013	0.039	0.969	
CTQ Minimization * C-Reactive Protein	-0.018	0.024	-0.748	0.454	
CTQ Minimization * Gender (Female)	-0.121	0.184	-0.656	0.512	
CTQ Minimization * Age At Interview	-0.012	0.007	-1.560	0.119	
CTQ Minimization * Total Household Income	-0.000001	0.000003	-0.405	0.686	
CTQ Minimization * Total Income	-0.000003	0.000004	-0.797	0.425	
CTQ Minimization * Highest Education	-0.003	0.039	-0.079	0.937	
Trait Anxiety * C-Reactive Protein	-0.0002	0.003	-0.058	0.954	
Trait Anxiety * Gender (Female)	0.002	0.019	0.123	0.902	
Trait Anxiety * Age At Interview	-0.001	0.001	-0.704	0.481	
Trait Anxiety * Total Household Income	0.0000002	0.0000003	0.686	0.493	
Trait Anxiety * Total Income	-0.0000002	0.0000004	-0.455	0.649	
Trait Anxiety * Highest Education	0.001	0.004	0.219	0.827	
C-Reactive Protein * Gender (Female)	0.108	0.050	2.186	0.029	*
C-Reactive Protein * Age At Interview	0.001	0.002	0.748	0.455	

Variable	Estimate	Std. Error	z-value	p-value	Sig
C-Reactive Protein * Total Household Income	-0.0000005	0.0000007	-0.727	0.467	
C-Reactive Protein * Total Income	0.000002	0.000001	1.506	0.132	
C-Reactive Protein * Highest Education	0.005	0.009	0.542	0.588	
Gender (Female) * Age At Interview	0.031	0.013	2.303	0.021	*
Gender (Female) * Total Household Income	-0.00001	0.000005	-2.314	0.021	*
Gender (Female) * Total Income	0.00002	0.000007	3.236	0.001	**
Gender (Female) * Highest Education	0.133	0.063	2.110	0.035	*
Age At Interview * Total Household Income	-0.0000003	0.0000002	-1.601	0.109	
Age At Interview * Total Income	0.0000007	0.0000003	2.346	0.019	*
Age At Interview * Highest Education	0.007	0.003	2.575	0.010	*
Total Household Income * Total Income	0.00000000002	0.00000000002	0.713	0.476	
Total Household Income * Highest Education	0.0000005	0.0000009	0.502	0.615	
Total Income * Highest Education	0.000002	0.000001	1.120	0.263	

NOTES: Dependent variable: Probability of having chronic pain. N = 1121. Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1 (Dispersion parameter for binomial family taken to be 1).

Table A4: **Regression confusion matrix**

Overall regression		**Actual medication use for chronic pain**	
		FALSE	TRUE
Predicted medication use for chronic pain	FALSE	533	32
	TRUE	8	27
Significant interactions only matrix		**Actual medication use for chronic pain**	
		FALSE	TRUE
Predicted medication use for chronic pain	FALSE	535	50
	TRUE	6	9

Table A5. Long-term medication use for chronic pain

Variable	Estimate	Std. Error	z-value	p-value	Sig
(Constant)	-5.886	10.773	-0.546	0.585	
CTQ Emotional Abuse	-0.269	0.764	-0.352	0.725	
CTQ Physical Abuse	-0.540	1.098	-0.492	0.623	
CTQ Sexual Abuse	1.118	0.684	1.634	0.102	
CTQ Emotional Neglect	0.047	0.742	0.063	0.950	
CTQ Physical Neglect	-0.908	0.954	-0.952	0.341	
CTQ Minimization	3.285	2.563	1.282	0.200	
Trait Anxiety	0.166	0.187	0.885	0.376	
C-Reactive Protein	-0.647	0.581	-1.113	0.266	
Gender (Female)	-6.500	4.746	-1.370	0.171	
Age At Interview	0.263	0.123	2.145	0.032	*
Total Household Income	0.0001	0.00007	1.613	0.107	
Total Income	-0.0002	0.0001	-2.082	0.037	*
Highest Education	-0.522	0.840	-0.621	0.534	
CTQ Emotional Abuse * CTQ Physical Abuse	-0.043	0.025	-1.735	0.083	.
CTQ Emotional Abuse * CTQ Sexual Abuse	0.002	0.024	0.064	0.949	
CTQ Emotional Abuse * CTQ Emotional Neglect	0.014	0.018	0.753	0.451	
CTQ Emotional Abuse * CTQ Physical Neglect	0.003	0.032	0.099	0.921	
CTQ Emotional Abuse * CTQ Minimization	0.065	0.180	0.359	0.719	
CTQ Emotional Abuse * Trait Anxiety	0.005	0.008	0.557	0.578	
CTQ Emotional Abuse * C-Reactive Protein	-0.040	0.027	-1.479	0.139	
CTQ Emotional Abuse * Gender (Female)	0.126	0.193	0.654	0.513	
CTQ Emotional Abuse * Age At Interview	0.007	0.008	0.892	0.372	
CTQ Emotional Abuse * Total Household Income	0.000002	0.000003	0.500	0.617	
CTQ Emotional Abuse * Total Income	-0.000001	0.000005	-0.317	0.751	
CTQ Emotional Abuse * Highest Education	-0.039	0.034	-1.150	0.250	
CTQ Physical Abuse * CTQ Sexual Abuse	-0.031	0.020	-1.594	0.111	
CTQ Physical Abuse * CTQ Emotional Neglect	0.076	0.034	2.228	0.026	*
CTQ Physical Abuse * CTQ Physical Neglect	-0.047	0.037	-1.265	0.206	
CTQ Physical Abuse * CTQ Minimization	-0.626	0.244	-2.569	0.010	*
CTQ Physical Abuse * Trait Anxiety	0.019	0.010	1.817	0.069	.
CTQ Physical Abuse * C-Reactive Protein	0.052	0.040	1.282	0.200	
CTQ Physical Abuse * Gender (Female)	-0.239	0.257	-0.930	0.352	
CTQ Physical Abuse * Age At Interview	-0.002	0.012	-0.165	0.869	
CTQ Physical Abuse * Total Household Income	0.000004	0.000004	1.069	0.285	
CTQ Physical Abuse * Total Income	-0.000009	0.000006	-1.414	0.157	
CTQ Physical Abuse * Highest Education	0.047	0.047	1.001	0.317	
CTQ Sexual Abuse * CTQ Emotional Neglect	0.029	0.029	0.996	0.319	
CTQ Sexual Abuse * CTQ Physical Neglect	0.025	0.026	0.982	0.326	
CTQ Sexual Abuse * CTQ Minimization	0.340	0.152	2.239	0.025	*

Variable	Estimate	Std. Error	z-value	p-value	Sig
CTQ Sexual Abuse * Trait Anxiety	-0.018	0.007	-2.445	0.015	*
CTQ Sexual Abuse * C-Reactive Protein	-0.040	0.023	-1.725	0.085	.
CTQ Sexual Abuse * Gender (Female)	0.399	0.235	1.698	0.090	.
CTQ Sexual Abuse * Age At Interview	-0.009	0.005	-1.621	0.105	
CTQ Sexual Abuse * Total Household Income	-0.00001	0.000003	-3.335	0.001	***
CTQ Sexual Abuse * Total Income	0.00001	0.000005	2.597	0.009	**
CTQ Sexual Abuse * Highest Education	-0.056	0.032	-1.731	0.084	.
CTQ Emotional Neglect * CTQ Physical Neglect	-0.006	0.033	-0.197	0.844	
CTQ Emotional Neglect * CTQ Minimization	-0.092	0.172	-0.533	0.594	
CTQ Emotional Neglect * Trait Anxiety	-0.013	0.011	-1.216	0.224	
CTQ Emotional Neglect * C-Reactive Protein	0.054	0.031	1.739	0.082	.
CTQ Emotional Neglect * Gender (Female)	0.197	0.198	0.995	0.320	
CTQ Emotional Neglect * Age At Interview	-0.004	0.008	-0.506	0.613	
CTQ Emotional Neglect * Total Household Income	0.000002	0.000003	0.655	0.513	
CTQ Emotional Neglect * Total Income	-0.000001	0.000004	-0.335	0.737	
CTQ Emotional Neglect * Highest Education	-0.073	0.036	-2.001	0.045	*
CTQ Physical Neglect * CTQ Minimization	0.275	0.237	1.161	0.245	
CTQ Physical Neglect * Trait Anxiety	0.009	0.013	0.718	0.473	
CTQ Physical Neglect * C-Reactive Protein	-0.033	0.031	-1.039	0.299	
CTQ Physical Neglect * Gender (Female)	-0.122	0.255	-0.478	0.632	
CTQ Physical Neglect * Age At Interview	-0.003	0.009	-0.278	0.781	
CTQ Physical Neglect * Total Household Income	-0.000008	0.000003	-2.793	0.005	**
CTQ Physical Neglect * Total Income	0.00002	0.000006	2.719	0.007	**
CTQ Physical Neglect * Highest Education	0.136	0.045	3.054	0.002	**
CTQ Minimization * Trait Anxiety	0.001	0.031	0.020	0.984	
CTQ Minimization * C-Reactive Protein	-0.041	0.084	-0.488	0.626	
CTQ Minimization * Gender (Female)	-0.023	0.592	-0.038	0.970	
CTQ Minimization * Age At Interview	-0.034	0.025	-1.381	0.167	
CTQ Minimization * Total Household Income	0.000004	0.00001	0.371	0.710	
CTQ Minimization * Total Income	-0.00001	0.00002	-0.745	0.456	
CTQ Minimization * Highest Education	-0.137	0.133	-1.030	0.303	
Trait Anxiety * C-Reactive Protein	-0.004	0.007	-0.561	0.575	
Trait Anxiety * Gender (Female)	0.035	0.054	0.647	0.518	
Trait Anxiety * Age At Interview	-0.004	0.002	-1.750	0.080	.
Trait Anxiety * Total Household Income	-0.0000007	0.0000008	-0.866	0.387	
Trait Anxiety * Total Income	0.000003	0.000001	1.867	0.062	.
Trait Anxiety * Highest Education	0.008	0.011	0.727	0.467	
C-Reactive Protein * Gender (Female)	0.023	0.152	0.148	0.882	
C-Reactive Protein * Age At Interview	0.002	0.005	0.489	0.625	

Variable	Estimate	Std. Error	z-value	p-value	Sig
C-Reactive Protein * Total Household Income	-0.000006	0.000003	-2.084	0.037	*
C-Reactive Protein * Total Income	0.000003	0.000004	0.753	0.451	
C-Reactive Protein * Highest Education	0.101	0.034	2.949	0.003	**
Gender (Female) * Age At Interview	-0.038	0.042	-0.892	0.373	
Gender (Female) * Total Household Income	0.00005	0.00002	2.555	0.011	*
Gender (Female) * Total Income	-0.00006	0.00003	-2.133	0.033	*
Gender (Female) * Highest Education	0.622	0.215	2.897	0.004	**
Age At Interview * Total Household Income	-0.0000008	0.0000006	-1.274	0.203	
Age At Interview * Total Income	0.000002	0.000001	1.432	0.152	
Age At Interview * Highest Education	-0.004	0.009	-0.412	0.680	
Total Household Income * Total Income	0.0000000001	0.00000000009	1.359	0.174	
Total Household Income * Highest Education	-0.000002	0.000003	-0.577	0.564	
Total Income * Highest Education	-0.0000008	0.000005	-0.152	0.879	

Dependent variable: Probability of taking long term medication for chronic pain (N = 600). Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1. (Dispersion parameter for binomial family taken to be 1). Null deviance: 385.69 on 599 degrees of freedom. Residual deviance: 242.11 on 508 degrees of freedom AIC:

Supplemental B. Methodology per the accepted Registered Report

The path diagram of the planned SEM is shown in **Figure B1**. In this model the exogenous latent variables for anxiety, physiological response, and CAs predict the endogenous latent variable for chronic pain. Chronic pain was expected to be influenced by anxiety, physiological response, and CAs based on previous studies examining relationships among them (see Background). An individual's physiological response to stress, level of anxiety, experience of CAs, and feeling of chronic pain cannot be directly measured; hence they were latent variables. Though these variables cannot be directly observed or measured (but are approximated through various measures), they were causally related to appropriate indicator variables present in the MIDUS data (**Table 1** of manuscript), which were designed to measure aspects of the trait of interest.

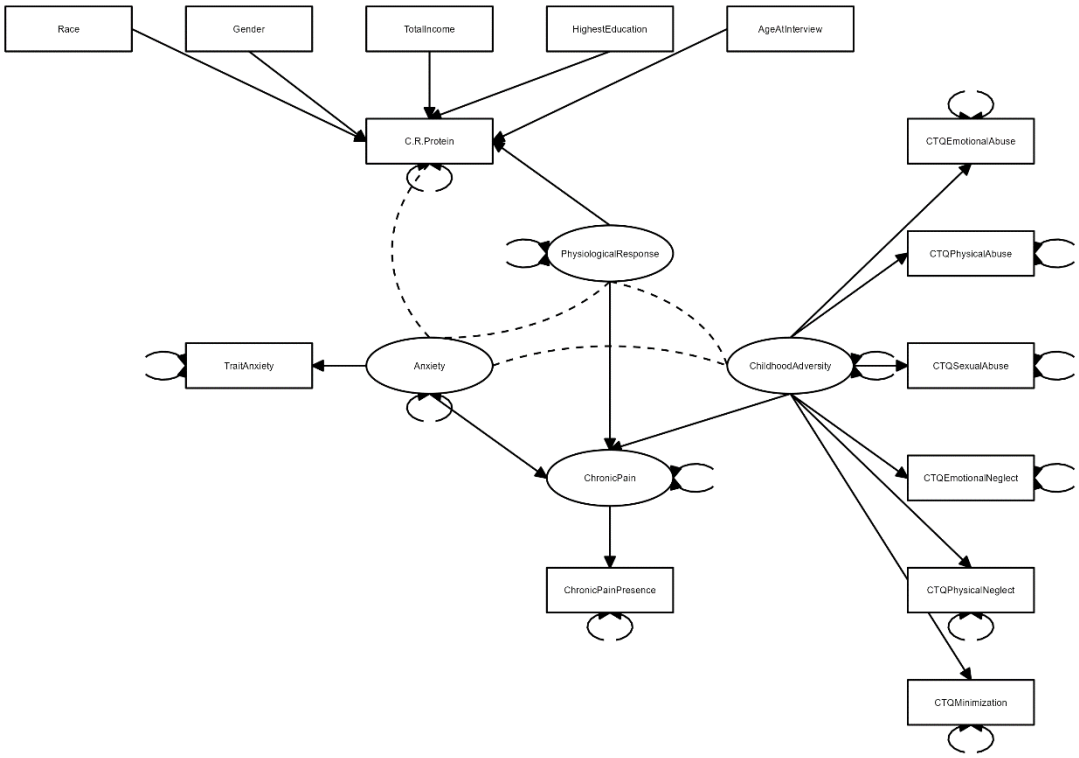

Figure B1: Path diagram of the planned SEM

The MIDUS indicator variable CRP was closely related to the physiological response to stress, the STAI to anxiety, and the reported experience of chronic pain to diagnosed chronic pain or a chronic pain disease/condition, so a single measured variable for each of these latent factors was appropriate. CAs can represent a wide variety of experiences, so a variety of representative measured variables from the MIDUS data were chosen: CTQ: Emotional Abuse, CTQ: Physical Abuse, CTQ: Sexual Abuse, CTQ: Emotional Neglect, CTQ: Physical Neglect, and CTQ: Minimization/Denial. The scale of latent factor variables is assumed and handled to be the same as the scale of the corresponding indicator variables. In the case of more than one indicator variable (such as the CA latent factor), the CTQ indicator variables are all on the same 5-point Likert scale, so this assumption held.

Indicator variables were included in the model as per their MIDUS data dictionary definition, with the exception of the reported experience of chronic pain variable. This variable was derived from the series

of pain variables in **Table 1** of the manuscript. It was modelled as a binary variable that indicated if the participant did or did not have chronic pain, as detailed in the Measures description for pain.
In addition to the latent factors and associated indicator variables, socio-economic control variables available in the MIDUS data (**Table 1** of manuscript) were included as predictors of inflammation (CRP). These control variables were linked to CRP and the physiological response to chronic pain as an individual with worse socioeconomic circumstances was expected to have a higher degree of inflammation. The control variable for race was coded as binary variables (e.g. 'is white race' and 'is black race', the two most common categories in the data), as categorical variables with multiple categories cannot be included easily in an SEM.

Exploratory objective

All variables imported into the primary objectives analysis dataset was used as possible independent variables for the pain medication regression. All scale and subscales variables were recoded per the data dictionary as previously described in the analysis plans for objective 1 and 2. Gender was recoded to a factor variable with levels Male and Female instead of numeric values. The chronic pain presence variable was derived as per the primary dataset.
The dependent variable ("did the person use medication for more than 3 months for chronic pain?") was derived from several medication chart variables. Specifically, a person met criteria as having taken long term medication for chronic pain: if a person had taken any prescription, alternative, or over the counter medicine; or if the medicine was taken with a duration for > 3 months, and taken for ICD9 code 338 ("pain, not elsewhere classified").
The final exploratory dataset was constructed by merging the independent and dependent variables by MIDUS-ID and taking the subset that had chronic pain (chronic pain presence variable = 1), as this was the population of interest. A logistic regression was used to predict the presence of long-term medication use for chronic pain in the subset of the study population which was identified as having chronic pain. Any records where one or more parameters were missing was dropped from the regression model. Model accuracy can be broken into sensitivity ("true positives", how many people with chronic pain are correctly identified as taking long term medication for chronic pain) and specificity ("true negatives", how many people with chronic pain are correctly identified as not taking long term medication for chronic pain). The dependent variable may be imbalanced, as 89% of the 651 available records did not take medication for chronic pain. To address this, model performance results were also presented in the form of a confusion matrix (true positives, true negatives, false positives, false negatives) with the sensitivity and specificity statistics reported. The regression model was tuned to maximizing sensitivity (true positives) to ensure that the model correctly predicted people taking long term medication for chronic pain.
Rationale for proposed methodology
Although SEM is a less common choice in epidemiological and health studies, a paper by Beran and Violato (2010) expressed growing concerns over the paucity of SEM models in epidemiological research, as SEM is able to analyze complex relationships among variables, including posit and testing causal relationships with non-experimental data (allowing researchers to explain the development of phenomena such as disease and health behaviors) (26). The various applications of SEM range from analysis of simple relationships between variables to complex analyses of measurement equivalence for first and higher-order constructs, and SEM also provides a flexible framework for developing and analyzing complex relationships among multiple variables (26). This allows testing the validity of a theory using empirical models with an advantage of managing measurement error, one of the greatest limitations of most health studies. SEM can be used as an exploratory or confirmatory approach within a

research design, and can provide insight into the complex nature of disease and health behaviors by examining both direct, indirect, unidirectional, and bidirectional relationships between measured and latent variables. The combination of these equations is then used to specify the pattern of possible relationships, and these relationships identified in the SEM model will then be further examined in detail via a generalized linear model (GLM). GLM procedures (both univariate and multivariate) are special cases of SEM (27). SEM enables initial testing of multiple hypothesized paths simultaneously (i.e., when your model consists of several independent variables, dependent variables, mediators and/or moderators). However, linear regression provides insight into the amount of variance of criterion is explained by the predictor. For a simplistic model, regression alone would be sufficient, but in the present study of a complex set of relationships, for which their interrelations are unclear from previous evidence, SEM is also needed.

Anticipated outcomes and implications

It was expected that CAs related to pain, with anxiety and inflammation potentially influencing the association. However, to the authors' knowledge no-one has looked at all of these associations together in one large sample before, thus, it is not possible to make detailed predictions of the associations beyond expecting positive associations between all variables. Hence the choice of conducting a SEM to identify the unique relations between all the variables involved, rather than hypothesizing and testing mediation or moderation at this stage. Using SEM also circumvented the problem of some of the assumptions of mediation models not being met e.g., not accounting for one or more relevant variables (21). These proposed analyses may help to inform clinical efforts to reduce the burden of CAs on adult outcomes across the life span. CAs should be considered in public health policies and decision-making and connect them more closely to interventions and prevention programs. There remains an unmet need for research that better specifies the pathways through which CAs influence later health outcomes and pain medicine consumption.

Table B1: Open Science Framework Stage 1 Registered Report questions

1) What is the main question being addressed in your study? Why is it important that we answer this question? What's the big picture?	To identify biopsychosocial pathways that may link childhood adversity with adult chronic pain. The specific objectives are: 1) to examine the relationships between reported childhood adversity, anxiety, and pain; 2) to assess the associations between childhood adversity, anxiety, inflammation (measured through CRP levels), and pain; and 3) to explore how childhood adversity, anxiety, and CRP may be associated with pain medication consumption in the United States.
2) Describe the key independent and dependent variable(s), specifying how they will be measured. Ensure that they are defined precisely	Independent variables: Childhood adversity, anxiety, and CRP Measures of the independent variables: Childhood Trauma Questionnaire (CTQ), State-Trait Anxiety Inventory Form Y (STAI), and blood C-reactive Protein (CRP) Dependent Variables: chronic pain in adulthood, and pain medication use Measures of the dependent variables: Specific pain-related questions designed for the purpose of MIDAS
3) What are your hypotheses?	It is hypothesized that childhood adversity relates to chronic pain experience in adulthood, and that there will be positive associations between 1) childhood adversity and anxiety, 2) childhood adversity and CRP levels, 3) childhood adversity and pain, and that the link between childhood adversity and pain will be influenced by anxiety and/or CRP. Although objective 3 is exploratory, it is hypothesized that childhood adversity, anxiety, and CRP will all be positively associated with increased pain medication consumption in the United States. The corresponding H0 are 1) there will be no significant positive association between childhood adversity and anxiety, 2) there will be no significant positive association between childhood adversity and CRP levels, and 3) there will be no significant positive association between childhood adversity and pain. Furthermore, any childhood adversity and pain association will not be influenced by anxiety and/or CRP. For exploratory objective 3 the H0 is that childhood adversity, anxiety, and CRP will not be associated with increased pain medication consumption in the United States.
4) How many and which conditions will participants/samples be assigned to?	The MIDUS core national sample was based on a nationally representative random-digit dialing (RDD) sample of non-institutionalized, English-speaking adults, aged 25 to 74, selected from working telephone banks in the coterminous United States. City-specific oversamples were also included to increase racial and geographic representativeness. The sampling and selection of participants in the non-survey projects (cognitive, daily stress, biomarker, neuroscience) was contingent upon eligibility criteria specific to each project. For the purposes of our retrospective study, a stratified randomization sample will be taken from the overall MIDUS sampling selection based on which participants have data available for the variables of interest as noted in **Table 1** of the manuscript.

5) How many observations will be collected and what rule will you use to terminate data collection?	Not applicable (as data are secondary).
6) What are your study inclusion criteria? How will participants/samples be recruited/included and under what specific rules?	*Childhood adversity:* Participants had to have responded to the CTQ at the biomarker collection stage sample of MIDUS. Participants reporting no adverse childhood experiences (ACEs) will not be excluded. *Anxiety:* Participants had to have responded to STAI items. Low scores will not be excluded. *Pain*: A person was considered to have chronic pain if they met any of the following criteria: 1) Had any valid chronic pain diagnostic (B1SA23A/B1SA23D); Reported zero time without feeling pain in the last month (B4Q10WW1); Saw a professional about chronic pain (BACAS22); Indicated having chronic pain (B1SA15/K2Q17/BACAS15/RA1SA15); or Physician diagnosed chronic back/neck problems (K2Q1XD). *CRP*: Participants had to have provided plasma and serum samples at the biomarker collection stage. For citrated plasma, the assay range was 0.175–1100 ug/mL (inter-assay variability: 2.1–5.7%; reference range: ≤3 ug/mL), and for serum the assay range was 0.014–216ug/mL (inter-assay variability: 4.72–5.16%; reference range: <3 ug/mL).
7) What are your data exclusion criteria?	Participants will be excluded if they did not respond to the CTQ and STAI questionnaires, have not met chronic pain criteria, and if CRP was outside of the acceptable ranges (>10%). For objective 1 and 2 analyses: Cases missing any indicator (see **Table S4**) or control variables (**Table 1**) will be dropped from the sample. For objective 3 (exploratory): Any records where one or more parameters were missing will be dropped from the regression model. In the overall scale variables such as the CTQ, a value > 97 will be recoded to missing, as per the MIDUS data dictionary (Ryff et al. 2021). For subscale variables, e.g., on a 1 to 5 Likert scale, a value > 7 will be recoded to missing as per the data dictionary. Control variables for income having values 9999998 and -1 and racial origins having value 7 will be recoded as "NA" as per the MIDUS data dictionary (Ryff et al. 2021).
8) What positive controls or quality checks will confirm that the obtained results are able to provide a fair test of the stated hypothesis?	For objective 1 and 2 analyses: If the data is found to not be normally distributed, the 'robust' version of the maximum likelihood parameter estimation method will be used, which does not rely on the normality assumption and provides robust standard errors and a scaled test statistic (Yuan & Bentler 2007). Socio-demographics were of interest as potential confounders and will be included as additional control variables in the regression. For objective 3 (exploratory): If the dependent variable is imbalanced, such as due to a high number of the available records did not including medication data for chronic pain, model performance results will also be presented in the form of a confusion matrix (true positives, true negatives, false positives, false negatives) with the sensitivity and specificity statistics reported to address

	this. For comparison checks for update modeling in this case, a model will also be run with only the significant predictors and pairwise interactions (including corresponding predictors for the significant pairwise interactions).
9) Specify exactly which analyses you will conduct to examine the main question/hypothesis(es)	See **Tables B2 & B3** below. Utilizing SEM analyses allows testing theory validity using empirical models with an advantage of managing measurement error. To additionally address and minimize potential bias in our proposed analysis, robustness testing of the SEM goodness of fit specifically using the root mean square error approximation (RMSEA), comparative fit index (CFI), and Akaike information criterion (AIC) thresholds will be conducted. To account for the possibility the of variable imbalance, model performance results will also be presented in the form of a confusion matrix (true positives, true negatives, false positives, false negatives) with the sensitivity and specificity statistics reported. The regression model will be tuned to maximizing sensitivity (true positives) to ensure that the model correctly predicts the outcomes. Resulting associations will then be tested in General Linear Modeling with logit link function (Logistic regression), such as by first examining the potential effect of ACEs, anxiety, and CRP on chronic pain. If any of the regression models cannot be fitted, then relationships will be assessed using Spearman correlations instead. Finally, additional sensitivity analyses will also be conducted excluding those with CRP levels greater than 10 mg/l from the regression analyses (to test the model validity; $p<0.05$).
10) Are you proposing to collect new data or analyse existing data?	Existing data will be used (see Data verification details p. 20-21).

Table B2: Analyses Planner

Question	Hypothesis	Sampling plan (e.g. power analysis)	Analysis Plan	Interpretation given different outcomes
1) to examine the relationships between reported childhood adversity, anxiety, and pain;	It is hypothesized that childhood adversity relates to chronic pain experience in adulthood, and that there will be positive associations between childhood adversity and anxiety.	Post hoc power analysis, as applicable. Sampling N/A as this is a retrospective study using existing data	Structural equational modeling (SEM) as shown in **Figure B1,** followed by general linear modeling (GLM). The SEM will be built with the 'lavaan' package version 0.6 (Rosseel 2012) in the R. The maximum likelihood parameter estimation method built into the 'lavaan' package will be used, as it is suitable for all-numerical data (including binary and Likert-scaled variables which will be coded numerically as integers) with complete cases (Olsson et al. 2000). IVs: Childhood adversity (CTQ), anxiety (, STAI); DVs: chronic pain in adulthood.	We will use the SEM to develop a preliminary understanding of relationships between variables, followed by GLM regression using the variables in Table 1. If repeated iterations of the best SEM model fit cannot be achieved, controls and other variables will be reconsidered. If any of the regression models cannot be fitted, then relationships will be assessed using Spearman correlations instead.
2) to assess the associations between childhood adversity, anxiety, inflammation (measured through CRP levels), and pain;	There will be positive associations between childhood adversity and CRP levels. The link between childhood adversity and pain will be influenced by anxiety and/or CRP.	Post hoc power analysis, as applicable. Sampling N/A as this is a retrospective study using existing patient records	SEM as noted above and in **Figure B1**, GLM, spearman correlations, and sensitivity analysis. IVs: Childhood adversity (CTQ), anxiety (STAI), CRP (blood CRP); DVs: chronic pain in adulthood (per specific pain questions).	We expect the SEM to help explore and visualize the hypothetical relationships and show how observed and latent variables for childhood adversity, anxiety, inflammation, and chronic pain, and observed socioeconomic variables

				directionally affect each other. We expect the GLM to show the potential effect of ACEs, anxiety, and CRP on predicting chronic pain experience. If Spearman correlation is needed, we expect the coefficients on each possible pair of variables showing how strongly and in what direction each pair is related. Additional sensitivity analyses will be conducted excluding those with CRP levels >10 to test the validity of the model.
3) to explore how childhood adversity, anxiety, and CRP may be associated with pain medication consumption in the United States as a proxy for chronic pain as a health outcome.	Although objective 3 is exploratory, it is hypothesized that childhood adversity, anxiety, and CRP will all be positively associated with increased pain medication consumption in the United States.	Post hoc power analysis, as applicable. Sampling N/A as this is a retrospective study using existing patient records	An additional exploratory regression on the subset of respondents who experience chronic pain. IVs: Childhood adversity (CTQ), anxiety (STAI), CRP (blood CRP); DVs: chronic pain in adulthood, pain medication use (per specific pain questions). All variables will also be tested as possible independent variables for the pain medication regression.	We will conduct exploratory regression and expect it will show how or if childhood adversity, anxiety, and inflammation predict pain medication usage for chronic pain.

Table B3. Desiderata for Structural Equation Modeling

Checklist item	Supporting text from report
1. Substantive theories that led to the model(s) being investigated are synthesized; a set of a priori specified competing models is generally preferred.	Chronic pain is expected to be influenced by anxiety, physiological response, and childhood adversity based on previous studies examining relationships among them (see **Background** section).
2. Path diagrams are presented to facilitate the understanding of the conceptual model(s) and the specification of the statistical model(s).	The path diagram of the planned SEM is shown in Figure 2. In this model the exogenous latent variables for anxiety, physiological response, and childhood adversity predict the endogenous latent variable for chronic pain.
3. If applicable, latent factors are defined and their status as latent (vs. emergent) is justified.	An individual's physiological response to stress, level of anxiety, experience of childhood adversity, and feeling of chronic pain cannot be directly measured; hence they are latent variables. Though these variables cannot be directly observed or measured (but are approximated through various measures), they are causally related to appropriate indicator variables present in the MIDUS data (Table 1), which were designed to measure aspects of the trait of interest.
4. Measured variables are defined and, if applicable, their appropriateness as indicator variables of associated factors is justified.	Though these variables cannot be directly observed or measured (but are approximated through various measures), they are causally related to appropriate indicator variables present in the MIDUS data (Table 1), which were designed to measure aspects of the trait of interest. Indicator variables are included in the model as per their MIDUS data dictionary definition, with the exception of the reported experience of chronic pain variable. This variable is derived from the series of pain variables in Table 1. It is modelled as a binary variable that indicates if the participant did or did not have chronic pain, as detailed in the Measures description for pain.
5. Latent factors are indicated by a sufficient number of appropriate measured variables; how the latent factors are given scale within the model(s) is addressed.	Childhood adversity can represent a wide variety of experiences, so a variety of representative measured variables from the MIDUS data were chosen: CTQ: Emotional Abuse, CTQ: Physical Abuse, CTQ: Sexual Abuse, CTQ: Emotional Neglect, CTQ: Physical Neglect, and CTQ: Minimization/Denial. The scale of latent factor variables is assumed and handled to be the same as the scale of the corresponding indicator variables. In the case of more than one indicator variable (childhood adversity latent factor), the CTQ indicator variables are all on the same 5-point Likert scale, so this assumption holds.
6. How theoretically relevant control variables are integrated into the model is explained.	In addition to the latent factors and associated indicator variables, socio-economic control variables available in the MIDUS data (Table 1) are included as predictors of

	inflammation (CRP). These control variables are linked to CRP and the physiological response to chronic pain as an individual with worse socio-economic circumstances is expected to have a higher degree of inflammation. The control variable for race will be coded as binary variables (e.g. 'is white race' and 'is black race', the two most common categories in the data), as categorical variables with multiple categories cannot be included easily in an SEM.
7. Sampling method(s) and sample size(s) are explicated and justified.	The entire MIDUS sample of 1,255 participants as detailed in the Dataset and Participants section is used, with cases missing any indicator or control variables dropped from the sample. The maximum likelihood parameter estimation method built into the 'lavaan' package will be used, as it is suitable for all-numerical data (including binary and Likert-scaled variables which will be coded numerically as integers) with complete cases (Olsson et al. 2000). The maximum likelihood method assumes data is multivariate normally distributed, and this assumption will be tested on the MIDUS data. If the data is found to not be normally distributed, the 'robust' version of the maximum likelihood parameter estimation method will be used, which does not rely on the normality assumption and provides robust standard errors and a scaled test statistic (Yuan & Bentler 2007).
8. The treatment of missing data and outliers is addressed.	Missing data in the control and measured variables is coded according to the method detailed in the Analysis Plan section. The entire MIDUS sample of 1,255 participants as detailed in the Dataset and Participants section is used, with cases missing any indicator or control variables dropped from the sample. Any records where one or more parameters are missing will be dropped from the regression model. For outliers in the overall scale variables such as the CTQ, a value > 97 will be recoded to missing, as per the MIDUS data dictionary (Ryff et al. 2021). For subscale variables, e.g., on a 1 to 5 Likert scale, a value > 7 will be recoded to missing as per the data dictionary. Control variables for income having values 9999998 and -1 and racial origins having value 7 will be recoded as "NA" as per the MIDUS data dictionary (Ryff et al. 2021).
9. The name and version of the utilized software package is reported; the parameter estimation method is justified and its underlying assumptions are addressed.	The SEM will be built with the 'lavaan' package version 0.6 (Rosseel 2012) in the R programming language, version 4.3 (R Core Team 2021). The maximum likelihood parameter estimation method built into the 'lavaan' package will be used, as it is suitable for all-numerical data (including binary and Likert-scaled variables which will be coded numerically as integers) with complete cases (Olsson et al. 2000).