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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Objective: This study used the Midlife-Development in the United States (MIDUS) dataset to a) examine relationships between reported childhood adversity (CA), anxiety, and pain; b) assess associations between CAs, anxiety, C-reactive protein (CRP) levels, and pain; and c) 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 was conducted. For objective 3, all variables from the objective 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 that CAs, anxiety, and CRP all played a role in predicting chronic pain. Regression results (n = 1173) indicated that 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, sociodemographics played a meaningful role in predicting chronic pain in adults, and CRP was significantly correlated with anxiety, emotional abuse, physical neglect, multiple sociodemographic variables, and chronic pain. The influence of CAs on predicting long-term medication use for chronic pain was complex and warrants further study.

Key words: 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, **ICD-9** = 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

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INTRODUCTION

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] = 0.01) 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 who 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

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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 and 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 as follows: a) to examine the relationships between reported CAs, anxiety, and pain; b) to assess the associations between CAs, anxiety, inflammation (measured through CRP levels), and pain; and c) 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 a) CAs and anxiety, b) CAs and CRP levels, c) 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 as follows: a) there will be no significant positive association between CAs and anxiety, b) there will be no significant positive association between CAs and CRP levels, and c) 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. The stage 1 registered report for our analysis plan was accepted in principle on March 11, 2024, and can be found in the Supplemental Digital Content, http://links.lww.com/PSYMED/B68.

Dataset and Participants

The dataset used for this secondary analysis was the publicly available MIDUS longitudinal study, a national survey of more than 7000 Americans (aged 25 to 74 years) 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 1255 respondents, and is the focus sample of these analyses. Respondents include two distinct subsamples: the longitudinal survey sample ($n = 1054$) 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 were 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 State-Trait Anxiety Inventory Form Y (STAI) questionnaires, if they had not met at least one of the chronic pain criteria, or if CRP was outside of the acceptable ranges (>10% interassay 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 five 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, and 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 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 were 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 modeled 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: 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 μg/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 μg/ml (interassay variability: 2.1%–5.7%; reference range: ≤3 μg/ml), and for serum, the assay range was 0.014–216 μg/ml (interassay variability: 4.72%–5.16%; reference range: <3 μg/ml). The coefficients of variance for all CRP assays were in acceptable ranges (<10%). Although 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). Because 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.

Sociodemographics 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) was conducted to develop a preliminary understanding of relationships between variables, followed by general linear modeling (GLM) regression using the variables in Table A1 (Supplemental Digital Content, http://links.lww.com/PSYMED/B54). 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 9,999,998 and −1, and racial origins had value 7 recoded as "NA" as per the MIDUS data dictionary (20).

The relationships among CAs, anxiety, inflammation, socioeconomic 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 visualized

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 it is why it was selected over more standard mediation and moderation modeling. The regression model used independent variables for specified interactions among CAs, anxiety, inflammation, and socioeconomic factors (controls) to predict chronic pain presence. This allowed for the identification of significant factors that 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 is detailed in Tables B1–B3, Supplemental Digital Content, http://links.lww.com/PSYMED/B54. The path diagram of the planned SEM and associated methodology as outlined in the Registered Report are detailed in Section B of the Supplemental Digital Content.

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 were coded according to the method detailed in the Measures and Variables sections. The entire MIDUS sample of 1255 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 that data are 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 objectives 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 the 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 *ICD-9* 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 were 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, http://links.lww.com/PSYMED/B54.

RESULTS

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

Objectives 1–2

Correlations

Relationships were initially assessed using nonparametric 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 $p < .001$

TABLE 1. Sample Sizes and Sociodemographics 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, US $	42,194 (39,446)	42,194 (39,446)	42,194 (39,446)	36,152 (34,562)
Total household income, US $	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 y of college, no degree	17.4	17.4	17.4	19.8
3+ y of college, no degree	4.9	4.9	4.9	5.3
2-y/vocational college graduate	7.1	7.1	7.1	6.8
4-y/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, y	54 (12)	54 (12)	54 (12)	55 (12)

(statistic = 148,020), and Mardia's kurtosis was $p < .001$ (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 sociodemographic control variables, every 1-unit increase in highest education (education scale, where 1 is the lowest level and 12 is the highest), the log odds of having chronic pain (versus not having chronic pain) decreased by 0.68. For every 1-unit decrease in total income, the log odds of having chronic pain (versus not having chronic pain) increased by 0.00007. Reported female gender versus 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

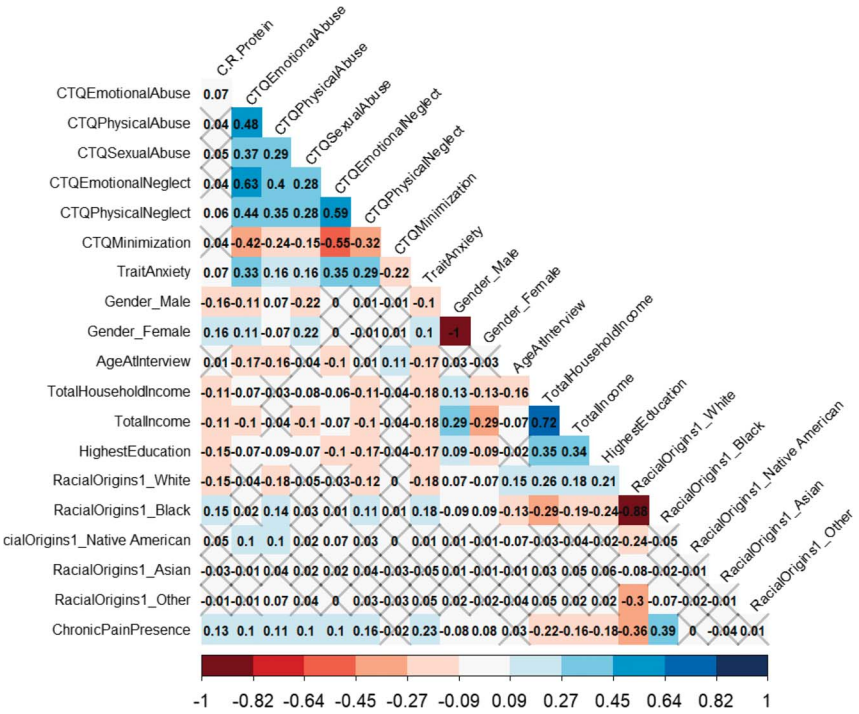

FIGURE 1. Heatmap of correlations between variables of interest and CRP. The Xs indicate the correlation is insignificant at the 95% level. *N* = 1173. CRP = C-reactive protein. Color image is available online only at the journal website.

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 nonlinear effect on chronic pain (Figure 3D). At low rates of

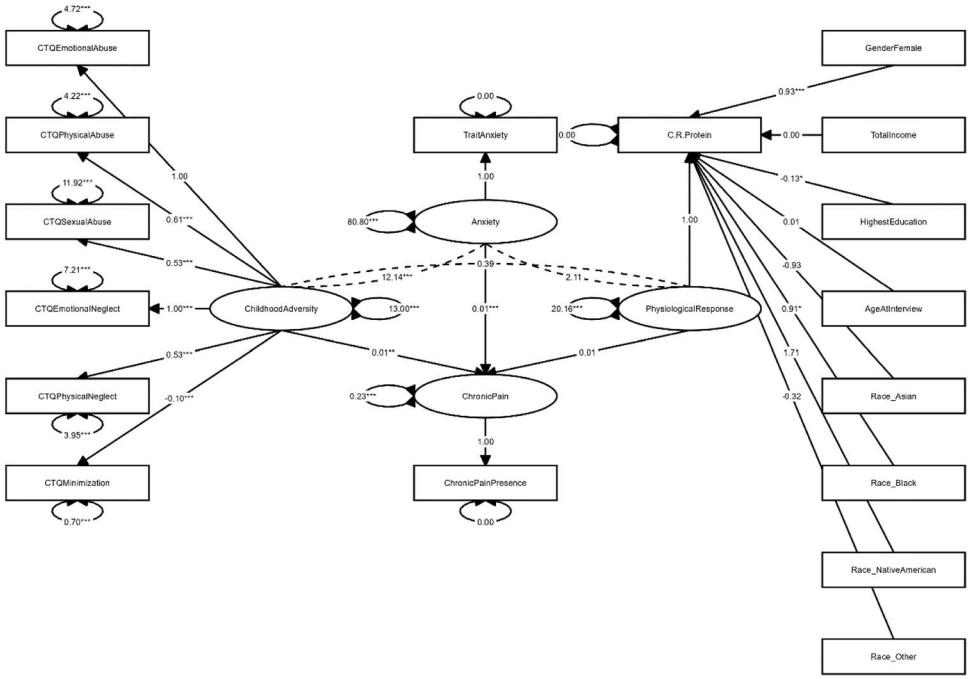

FIGURE 2. Final SEM. The parameters for this model were CFI: 0.989 (>0.90), RMSEA: 0.087 (<0.05), $\chi^2 = 865$, $df = 88$, $p < .001$. CFI = comparative fit index; RMSEA = root mean square error of approximation; SEM = structural equational modeling.

TABLE 2. CA, Anxiety, and CRP and Interactions as a Predictors

Variable	Estimate	Std. Error	*z* Value	*p*
(Constant)	0.563	3.528	0.160	.873
CTQ emotional abuse	−0.128	0.261	−0.490	.624
CTQ physical abuse	−0.054	0.327	−0.166	.868
CTQ sexual abuse	0.237	0.206	1.149	.251
CTQ emotional neglect	−0.238	0.240	−0.992	.321
CTQ physical neglect	0.664	0.344	1.929	.054
CTQ minimization	0.853	0.839	1.016	.310
Trait anxiety	0.130	0.069	1.884	.060
C-reactive protein	−0.353	0.185	−1.912	.056
Gender (female)	−3.067	1.371	−2.237	**.025**
Age at interview	−0.034	0.045	−0.742	.458
Total household income	0.00002	0.00002	1.177	.239
Total income	−0.00007	0.00003	−2.162	**.031**
Highest education	−0.680	0.243	−2.799	**.005**
Interactions				
CTQ emotional abuse by CTQ physical abuse	0.010	0.008	1.127	.260
CTQ emotional abuse by CTQ sexual abuse	0.009	0.008	1.138	.255
CTQ emotional abuse by CTQ emotional neglect	0.018	0.007	2.365	**.018**
CTQ emotional abuse by CTQ physical neglect	−0.024	0.012	−2.042	**.041**
CTQ emotional abuse by CTQ minimization	0.021	0.065	0.318	.750
CTQ emotional abuse by trait anxiety	0.001	0.003	0.230	.818
CTQ emotional abuse by C-reactive protein	0.008	0.010	0.737	.461
CTQ emotional abuse by gender (female)	0.037	0.065	0.564	.573
CTQ emotional abuse by age at interview	−0.0002	0.003	−0.081	.935
CTQ emotional abuse by total household income	−0.000002	0.000001	−1.742	.082
CTQ emotional abuse by total income	0.000003	0.000001	2.132	**.033**
CTQ emotional abuse by highest education	−0.015	0.013	−1.182	.237
CTQ physical abuse by CTQ sexual abuse	−0.002	0.008	−0.300	.765
CTQ physical abuse by CTQ emotional neglect	−0.023	0.011	−2.074	**.038**
CTQ physical abuse by CTQ physical neglect	0.010	0.014	0.704	.481
CTQ physical abuse by CTQ minimization	−0.010	0.070	−0.148	.882
CTQ physical abuse by trait anxiety	−0.004	0.004	−1.087	.277
CTQ physical abuse by C-reactive protein	0.012	0.014	0.824	.410
CTQ physical abuse by gender (female)	0.053	0.080	0.660	.509
CTQ physical abuse by age at interview	0.003	0.004	0.872	.383
CTQ physical abuse by total household income	−0.0000007	0.000001	−0.590	.556
CTQ physical abuse by total income	−0.0000005	0.000002	−0.275	.784
CTQ physical abuse by highest education	0.032	0.015	2.075	**.038**
CTQ sexual abuse by CTQ emotional neglect	−0.003	0.008	−0.460	.645
CTQ sexual abuse by CTQ physical neglect	−0.001	0.010	−0.061	.951
CTQ sexual abuse by CTQ minimization	−0.050	0.041	−1.211	.226
CTQ sexual abuse by trait anxiety	−0.003	0.003	−1.260	.208
CTQ sexual abuse by C-reactive protein	−0.004	0.006	−0.589	.556
CTQ sexual abuse by gender (female)	0.037	0.061	0.602	.547
CTQ sexual abuse by age at interview	−0.001	0.002	−0.687	.492
CTQ sexual abuse by total household income	−0.0000007	0.0000007	−0.963	.335
CTQ sexual abuse by total income	0.000001	0.000001	0.941	.347
CTQ sexual abuse by highest education	−0.008	0.010	−0.806	.420
CTQ emotional neglect by CTQ physical neglect	0.010	0.010	1.059	.289
CTQ emotional neglect by CTQ minimization	0.082	0.044	1.860	.063
CTQ emotional neglect by trait anxiety	0.004	0.003	1.249	.212
CTQ emotional neglect by C-reactive protein	−0.002	0.008	−0.282	.778
CTQ emotional neglect by gender (female)	−0.079	0.055	−1.452	.147
CTQ emotional neglect by age at interview	0.001	0.003	0.513	.608

(Continued on next page)

TABLE 2. *(Continued)*

Variable	Estimate	Std. Error	*z* Value	*p*
CTQ emotional neglect by total household income	0.000002	0.0000008	2.570	**.010**
CTQ emotional neglect by total income	−0.000003	0.000001	−2.461	**.014**
CTQ emotional neglect by highest education	0.00003	0.011	0.003	.998
CTQ physical neglect by CTQ minimization	−0.024	0.070	−0.341	.733
CTQ physical neglect by trait anxiety	−0.008	0.004	−1.764	.078
CTQ physical neglect by C-reactive protein	0.020	0.012	1.665	.096
CTQ physical neglect by gender (female)	−0.014	0.081	−0.172	.863
CTQ physical neglect by age at interview	−0.004	0.004	−1.176	.240
CTQ physical neglect by total household income	−0.000002	0.000001	−1.516	.129
CTQ physical neglect by total income	0.000001	0.000002	0.834	.404
CTQ physical neglect by highest education	−0.004	0.015	−0.297	.766
CTQ minimization by trait anxiety	0.001	0.013	0.039	.969
CTQ minimization by C-reactive protein	−0.018	0.024	−0.748	.454
CTQ minimization by gender (female)	−0.121	0.184	−0.656	.512
CTQ minimization by age at interview	−0.012	0.007	−1.560	.119
CTQ minimization by total household income	−0.000001	0.000003	−0.405	.686
CTQ minimization by total income	−0.000003	0.000004	−0.797	.425
CTQ minimization by highest education	−0.003	0.039	−0.079	.937
Trait anxiety by C-reactive protein	−0.0002	0.003	−0.058	.954
Trait anxiety by gender (female)	0.002	0.019	0.123	.902
Trait anxiety by age at interview	−0.001	0.001	−0.704	.481
Trait anxiety by total household income	0.0000002	0.0000003	0.686	.493
Trait anxiety by total income	−0.0000002	0.0000004	−0.455	.649
Trait anxiety by highest education	0.001	0.004	0.219	.827
C-reactive protein by gender (female)	0.108	0.050	2.186	**.029**
C-reactive protein by age at interview	0.001	0.002	0.748	.455
C-reactive protein by total household income	−0.0000005	0.0000007	−0.727	.467
C-reactive protein by total income	0.000002	0.000001	1.506	.132
C-reactive protein by highest education	0.005	0.009	0.542	.588
Gender (female) by age at interview	0.031	0.013	2.303	**.021**
Gender (female) by total household income	−0.00001	0.000005	−2.314	**.021**
Gender (female) by total income	0.00002	0.000007	3.236	**.001**
Gender (female) by highest education	0.133	0.063	2.110	**.035**
Age at interview by total household income	−0.0000003	0.0000002	−1.601	.109
Age at interview by total income	0.0000007	0.0000003	2.346	**.019**
Age at interview by highest education	0.007	0.003	2.575	**.010**
Total household income by total income	0.00000000002	0.00000000002	0.713	.476
Total household income by highest education	0.0000005	0.0000009	0.502	.615
Total Income by highest education	0.000002	0.000001	1.120	.263

CA = childhood adversity; CRP = C-reactive protein; CTQ = Childhood Trauma Questionnaire

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.

CA = childhood adversity; CRP = C-reactive protein; CTQ = Childhood Trauma Questionnaire.

Significant interactions are in bold.

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 sociodemographic 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

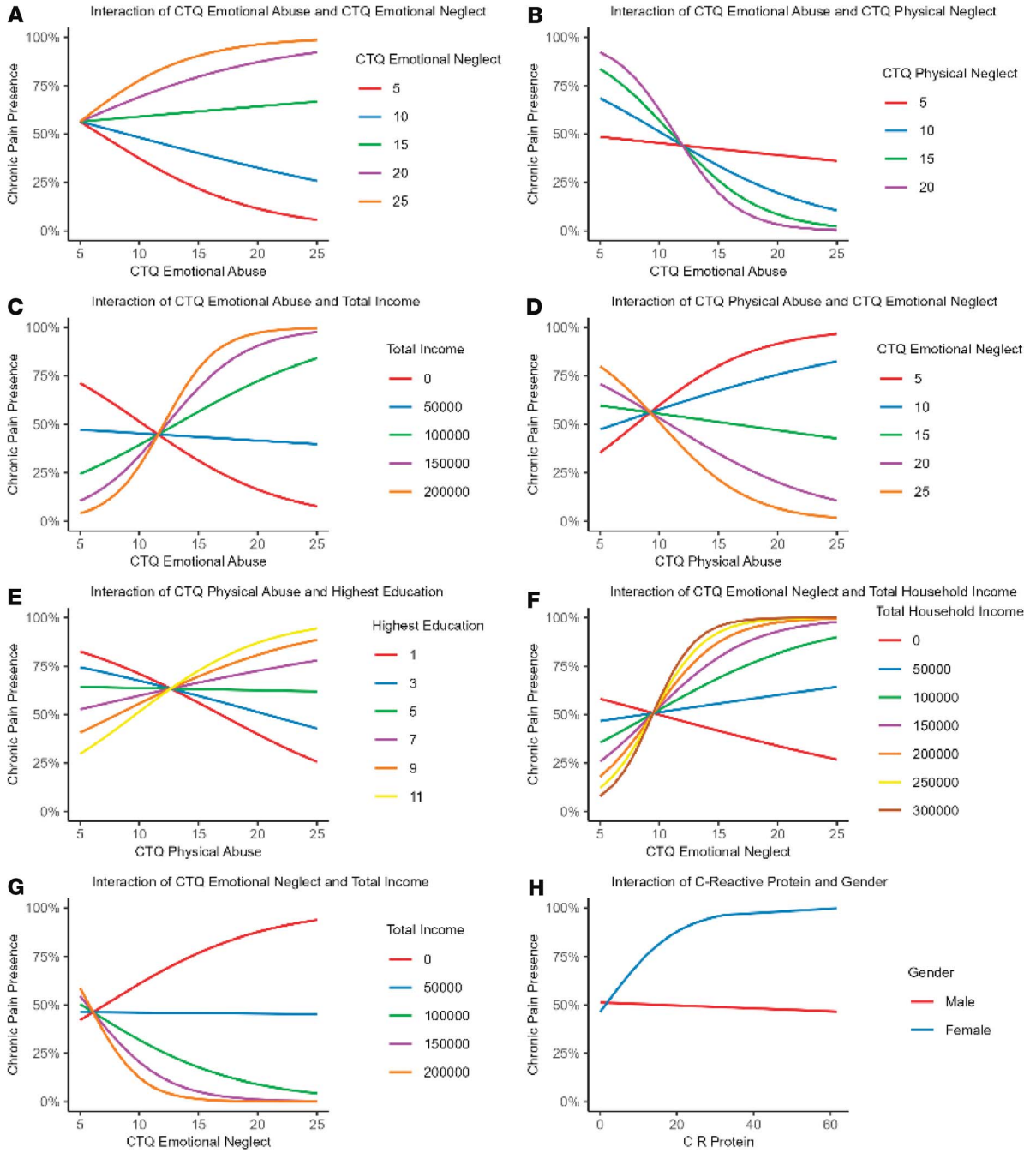

FIGURE 3. Partial regressions of significant interactions on probability of chronic pain presence. Note: The likelihood of chronic pain presence increases as the *y* axis increases to 100%. Incomes are annual USD ($). Color image is available online only at the journal website.

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 (Table A3, Supplemental Digital Content, http://links.lww.com/PSYMED/B54); 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 Table A3, Supplemental Digital Content, http://links.lww.com/PSYMED/B54. 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 1-unit increase, the log odds of taking medication for chronic pain increased by 0.275. For every 1-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 versus 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

TABLE 3. Long-Term Medication Use for Chronic Pain (Significant Regression Coefficients Only)

Variable	Estimate	Std. Error	*z* Value	*p*
(Constant)	−3.236	4.231	−0.765	.444
CTQ emotional abuse	0.275	0.126	2.175	**.030**
CTQ physical abuse	−0.529	0.309	−1.710	.087
CTQ sexual abuse	0.349	0.295	1.184	.236
CTQ emotional neglect	−0.186	0.189	−0.985	.325
CTQ physical neglect	−0.336	0.183	−1.836	.066
CTQ minimization	0.776	0.689	1.126	.260
Trait anxiety	0.109	0.095	1.143	.253
C-reactive protein	−0.308	0.169	−1.815	.069
Gender (female)	−4.208	1.461	−2.880	**.004**
Age at interview	0.087	0.056	1.537	.124
Total household income	0.00004	0.00002	2.025	**.043**
Total income	−0.0001	0.00004	−3.150	**.002**
CTQ emotional abuse by CTQ physical abuse	−0.030	0.013	−2.291	**.022**
CTQ physical abuse by CTQ sexual abuse	−0.010	0.008	−1.208	.227
CTQ physical abuse by CTQ emotional neglect	0.050	0.016	3.197	**.001**
CTQ physical abuse by CTQ minimization	−0.278	0.128	−2.176	**.030**
CTQ physical abuse by trait anxiety	0.009	0.005	1.610	.107
CTQ sexual abuse by CTQ minimization	0.164	0.088	1.858	.063
CTQ sexual abuse by trait anxiety	−0.006	0.004	−1.594	.111
CTQ sexual abuse by gender (female)	0.281	0.181	1.554	.120
CTQ sexual abuse by total household income	−0.000007	0.000003	−2.620	**.009**
CTQ sexual abuse by total income	0.000006	0.000003	1.838	.066
CTQ sexual abuse by highest education	−0.025	0.019	−1.307	.191
CTQ emotional neglect by highest education	−0.032	0.018	−1.818	.069
CTQ physical neglect by total household income	−0.000003	0.000002	−1.909	.056
CTQ physical neglect by total income	0.000009	0.000003	2.696	**.007**
CTQ physical neglect by highest education	0.035	0.026	1.352	.176
Trait anxiety by age at interview	−0.002	0.002	−1.583	.113
Trait anxiety by total income	0.000001	0.0000006	1.841	.066
C-reactive protein by total household income	−0.000003	0.000001	−2.083	**.037**
C-reactive protein by highest education	0.049	0.022	2.170	**.030**
Gender (female) by total household income	0.00003	0.00001	2.172	**.030**
Gender (female) by total income	−0.00002	0.00002	−0.987	.323
Gender (female) by highest education	0.261	0.140	1.872	.061

CTQ = Childhood Trauma Questionnaire.

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.

Significant interactions are in bold.

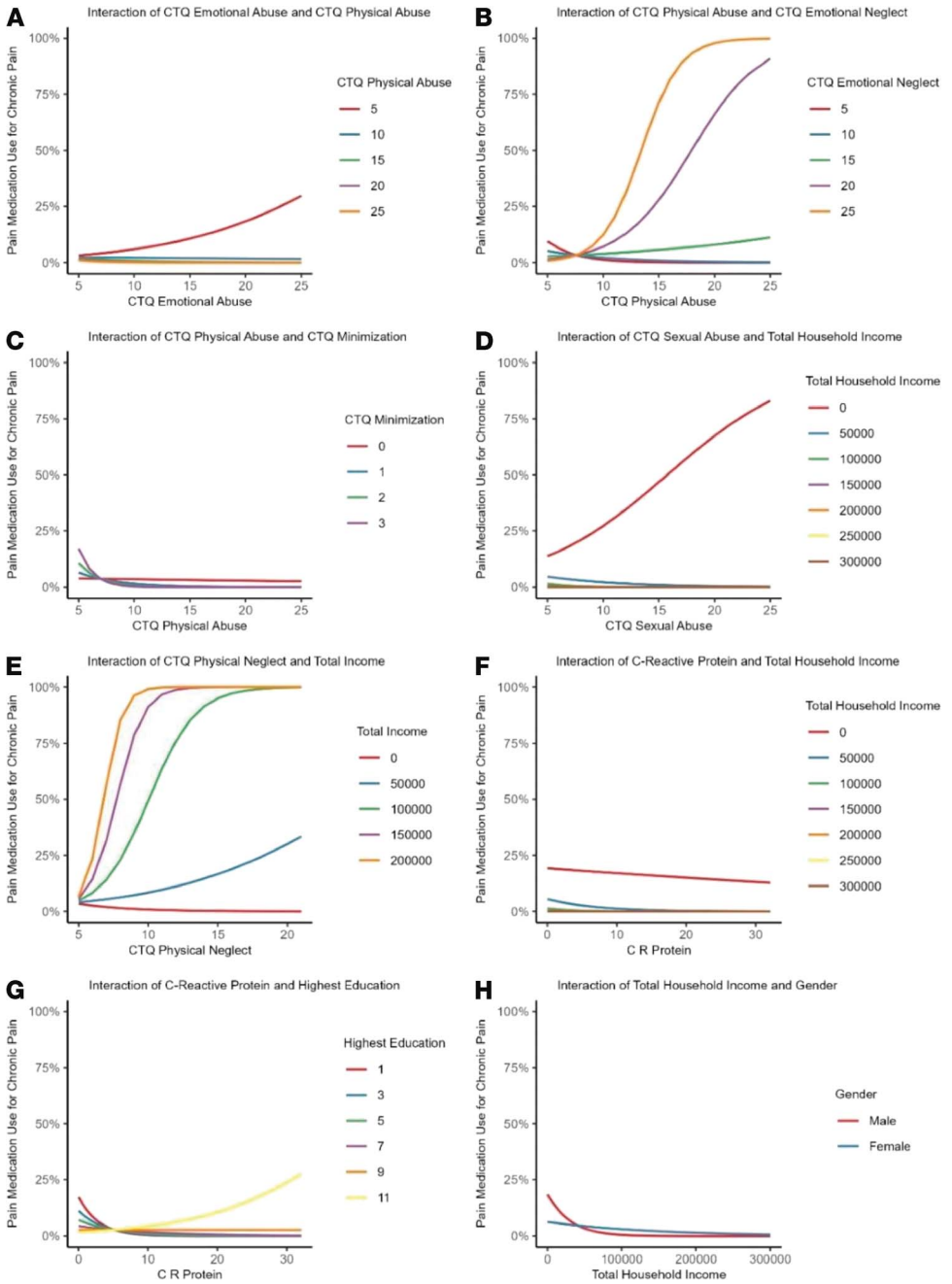

FIGURE 4. Partial regressions of long-term medication use for chronic pain. Note: The likelihood of medication use for chronic pain presences increase as the *y* axis increases to 100%. Color image is available online only at the journal website.

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, whereas 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), whereas 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 several interactions were significant and offer unique insight into previously held assumptions surrounding ACEs, mental health, and whether sociodemographic 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. Although 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 sociodemographic control variables in predicting pain presence were sexual abuse, physical neglect, minimization, and trait anxiety. These findings illustrate the complexity around how CAs and sociodemographic 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 sociodemographic 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 sociodemographic 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 (26,27). 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 (26). 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 (27). As shown by various studies (both basic and clinical), ACEs have a profound impact on the development and function of the nervous system (28), 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 (29). 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 (30), and that ACEs relate directly to chronic pain or indirectly via anxiety (31). This also contrasts with the present findings, which showed that CAs and chronic pain interactions with anxiety were not significant. This suggests that 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 that 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 sociodemographic 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 (32). Contrary to previous CRP research, it did not find that the association disappeared when adjusting for confounding variables such as BMI and chronic disease (32). In this way, the present results differed in that anxiety did not have an impact in any of the regression interactions, whereas sociodemographic variables did play a substantial role. Although the correlations had indicated that CRP, CAs (aside from minimization), and anxiety were all significantly positively associated with chronic pain presence, this does not imply a causal relationship or 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 sociodemographic 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' sociodemographics. 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 United States. Further, pain may be one form of distress that men are more likely to seek treatment for, but relevant literature interpreting such sociodemographic findings remains scarce and the available evidence for pain care in men versus women is mixed and inconsistent (33). 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 (31). Historical epidemiology research has shown that ACEs increase the risk for an adult to develop substance use disorders (34,35). Of note, beyond opioid dependence—a prevalent issue in the United States (36)—ACEs were also more prevalent among cocaine-dependent adults (37) 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 5 demonstrated a significant gradient effect of the number of ACEs increasing with increasing risk of opioid use–related behaviors (38). The present significant interactions between various CAs further highlight 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 need 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. Although 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., 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. (39). 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 health care providers (40). 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 (41), 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 sociodemographic 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 that 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 toward 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 sociodemographic variables. Although 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 (42). 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 that 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 sociodemographic 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 sociodemographics. 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 no.: 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 biopsychosocial process, and as such, it includes data collected in a wide array of research protocols using a variety of survey and nonsurvey instruments. The data captured by these different protocols (comprising around 20,000 variables) represent survey measures, cognitive assessments, daily stress diaries, and 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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