Childhood maltreatment and chronic 'all over' body pain in adulthood: a counterfactual analysis using UK Biobank

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Abstract

Evidence linking adverse childhood experiences (ACEs) and chronic pain in adulthood is largely cross-sectional, potentially subject to recall bias and does not allow exploration of mediating pathways. We analysed a large population-based cohort (UK Biobank) using a causal framework, to determine if childhood maltreatment is related to chronic 'all over' body pain in adulthood. We used doubly-robust estimation with inverse probability weights to estimate the difference in risk of chronic pain 'all over' between those exposed/not exposed to childhood maltreatment (abuse or neglect). Additionally, we looked at interaction with adult stressful life events, and examined mediation using inverse odds weighting in a generalized linear model. Using cases with complete data (n=118,347), the risk of chronic 'all over' body pain was higher in the exposed (6.3%, 95% confidence interval (CI) [6.0%, 6.5%]) than in the unexposed (4.0%;95%CI [3.8%, 4.2%]). This difference remained in analyses stratified by sex. Conversely, when analyses were repeated with a negative control exposure, childhood sunburn, risk differences were 0.8% in women (95% CI [0.3%, 1.3%]); 0.5% in men (95% CI [0.1%, 0.9%]). Childhood maltreatment and adult life events had similar effects, and there was a supra-additive risk (1.2%; 95%CI [0.6, 1.7]) when experiencing both. In mediation analyses, the total effect was a relative risk (RR) of 1.57 (95%CI [1.49, 1.66]), while the estimated indirect effect via all mediators was RR 1.16 (95%CI [1.14, 1.18]). Reducing childhood maltreatment would likely prevent cases of chronic widespread pain in adulthood. Stressful adult events and mediators may offer opportunities for intervention.

Introduction

Adverse childhood experiences (ACEs), including maltreatment (abuse, neglect) and household challenges such as deprivation, have been identified as risk factors for several health conditions in adulthood [9, 16]. A recent review [35] found a consistent association between ACEs and chronic pain in adulthood, with the most common pain outcomes studied being chronic widespread pain and fibromyalgia. The evidence, however, largely comes from cross-sectional studies which suffer several shortcomings, including recall bias [29,41], and a lack of opportunity to explore potential mechanisms or pathways leading from childhood adversity to chronic pain. In prospective studies, a direct effect of maltreatment on chronic pain is not as clear, though study quality is largely poor [26].

Theoretical models of ACEs and chronic pain propose multiple pathways: biological, psychological and social [33]. These imply a cascade of consequences, which ultimately lead to developing chronic pain. Relatively few studies incorporate these concepts in their analyses. Some authors report mediation analyses, implicating, for example, post-traumatic stress disorder [36, 1], or mood disorders [38], but these are typically restricted to single factors.

Additionally, adversity during a sensitive developmental window may cause epigenetic and/or neurobiological changes which affect stress reactivity in later life [21]. Stress is commonly attributed a role in the aetiology of fibromyalgia or chronic widespread pain, both in terms of the presence of life stressors [18] and in observations of perturbations in the hypothalamic-pituitary-adrenal (HPA) axis [5,4]. Only a few studies have analysed the role of both adult life stressors and ACEs on chronic pain [19, 43], but these considered a mediating role, rather than a joint interactive effect

Exposure to ACEs is problematic to measure prospectively (many ACEs are ‘hidden’ and only later disclosed), yet retrospective assessment may introduce recall bias [20]. A negative control exposure (NCE), which is subject to similar recall processes but lacks a plausible causal mechanism linking it to the outcome, may illustrate the presence and extent of recall bias [11].

A ‘potential outcomes’ framework [15] is useful for thinking through causal relationships: it helps identify confounding and mediating variables, and encourages consideration of potential sources of bias. Risk differences between counterfactual scenarios (e.g. where either all participants have been exposed to maltreatment or none have) offer a quantification of causal effect.

As part of the Consortium Against Pain InEquality (CAPE), our overall aim is to analyse a population-based cohort using a causal framework, to determine if childhood maltreatment is causally related to chronic 'all over' body pain in adulthood. Specifically we wished to: quantify the excess risk, if any, associated with childhood maltreatment; determine whether any excess risk differed by sex or ethnic group; contrast this with any risk associated with a negative control exposure; quantify the combined effect on risk, if any, of both exposure to childhood maltreatment and adversity in adulthood; and quantify the extent to which the effect, if any, of childhood maltreatment on chronic "all over" body pain is indirect (mediated).

Methods

The UK Biobank is a population-based cohort that recruited over 500,000 participants aged 40-69 years between 2006-2010 (www.ukbiobank.ac.uk). NHS-registered adults who lived within 25 miles of the 22 assessment centres were invited to take part, with a participation rate of ~5%. Baseline assessment included clinical and questionnaire measures. Repeat assessment of these measures is conducted every few years with a subset of 20,000-25,000. Over 300,000 of the participants were invited to complete follow-up questionnaires online, in 2016 and 2019.

The UK Biobank lends itself to our aim, given its size (around 500,000), design and the data collected, enabling us to look at effect modification and mediation for a relatively rare outcome (around 5%). We focus on chronic pain experienced 'all over the body' as an indicator of the more severe end of the pain spectrum. In 2019, participants were asked "Are you troubled by pain or discomfort, either all the time or on and off, that has been present for more than 3 months?". Those who responded positively were asked additional questions about pain including "In the last 3 months have you experienced pain or discomfort all over the body?". Those who answered positively to both questions were classified as having chronic "all over" body pain.

Childhood maltreatment was derived from responses to 5 items from the Childhood Trauma Screener [14] that were included in the 2016 questionnaire (see Supplementary material). The primary analysis used a binary variable, indicating whether participants had experienced any of the maltreatment types. In addition, for sensitivity analyses we derived a) a binary indicator for each of the 5 items and b) a 3-category variable indicating frequency of maltreatment (never, rarely/sometimes, often/very often).

All covariates were taken from baseline assessment data. Sex (male, female) was taken from health records. Index of multiple deprivation (IMD) [49, 40,46] was derived from postcodes by the study team. IMD is a UK government-issued measure of the relative deprivation of small geographical areas, which incorporates several facets of living

conditions (such as income, crime, housing, and education). We separated the sample into IMD quintiles separately for England, Scotland and Wales (each of which has its own index), but presented results combined as a measure of relative deprivation. Self-reported ethnicity was coded into 6 categories: White, Mixed ethnicity, Black or Black British, Asian or Asian British, Chinese, and Other ethnic group. The age when participants completed full-time education was used as a proxy of childhood socio-economic position [12]. Five categories were created: three categories for completing education at school (aged <15/16 years (minimum UK school leaving age), at 15/16 years, or between 15/16 and 18 years); and two categories for completing education in adulthood (non-degree/college qualification, degree/college qualification). We used binary variables to indicate whether participants reported ever seeing a general practitioner for “nerves, anxiety, tension or depression” (mental health), whether they felt able to confide in someone at least once every few months (social support), and whether they usually have problems falling asleep or waking in the night (sleep problems). Information was available on whether participants had experienced any of the following events in the previous 2 years: serious illness, injury or assault to themselves or someone close to them, death of a close relative or partner, marital separation or divorce, or financial difficulties. For all these variables, a value of 1 was given if these were reported at any assessment timepoint.

We used childhood sunburn as a negative control exposure in sensitivity analysis to examine the potential influence of recall bias (see below). This was chosen as an appropriate control because it was assessed in the same questionnaire as childhood maltreatment and referred to a similar period of recollection, but we could find no plausible mechanism or evidence linking childhood sunburn to chronic pain or fibromyalgia in adulthood. We would therefore not expect to see an effect of sunburn on risk of chronic ‘all over’ body pain, and any observed effect could be interpreted as reflecting bias. Participants were asked: "Before the age of 15, how many times did you suffer sunburn that was painful for at least 2 days or caused blistering?". This was dichotomised to ‘never’ and ≥1 sunburn occasions.

Analysis

We applied g-methods (see [32] for an introduction) to address pre-specified estimands (below). Estimands define the target quantity for estimation in a way that clearly links the aims of the research to the analysis [25]. We ran doubly-robust estimation models [15, 17] to address estimands 1 and 2 (see below). This effectively creates and compares pseudopopulations, for example in which all people are modelled to have been exposed versus one in which all are unexposed. The models are ‘doubly-robust’ in that they are also

weighted by the inverse of the probability of exposure. Further details of the models are described for each estimand below.

Consideration of the assumptions we made in building and interpreting all models is given in the Discussion. We used an *a priori* process model (a directed acyclic graph, or DAG; see Figure 1) to select measured variables and plan analytical models. Childhood socioeconomic position was identified as a confounder; sex and ethnicity as potential moderators; and we hypothesised 4 potential mediators (estimand 3): IMD, mental health, sleep problems, and social support. We used Stata 15.1 [44] for all analyses.

Estimand 1: what is the average causal effect on the risk of chronic 'all over' body pain all over for those reporting ≥1 childhood maltreatment type compared to those with no childhood maltreatment?

We derived inverse probability weights (IPW) using the method described by [15] to account for differential probabilities of exposure. Risk differences were then calculated using the teffects ra command [45], incorporating the (manually derived) IPW. Manual derivation of IPW allowed stratified weights to be calculated for moderated analyses. To examine moderation, analyses were stratified, first by sex and secondly by ethnicity. To examine the potential influence of recall bias, we additionally constructed a parallel model using a negative control exposure, childhood sunburn.

Estimand 2: what is the joint interactive effect of reporting both ≥1 childhood maltreatment type and ≥1 adverse adult experience on the risk of chronic 'all over' body pain?

We derived a 4-category combined exposure variable: reporting both childhood maltreatment and a recent stressful life event; reporting childhood maltreatment but no recent stressful life event; reporting a recent stressful life event but no childhood maltreatment; reporting neither childhood maltreatment nor a recent stressful life event. The teffects ipwra command [45] was used for doubly-robust estimation. Risk differences were compared to assess if there was an effect of experiencing both events that was greater than the sum of each individual event (an interaction on the additive scale).

Estimand 3: what is the indirect effect of childhood maltreatment on the risk of chronic 'all over body pain, mediated by deprivation in adulthood (IMD), mental health, social support, or sleep problems?

We incorporated inverse odds weighting (IOW) in generalized linear models, as suggested by Nguyen *et al* [34]. Direct and total effects (relative risks) were estimated with a log link function assuming a Poisson distribution, the model for the direct effect weighted by the

inverse odds. Simple post-estimation contrast of these models showed the estimated indirect effect, with bootstrapped confidence intervals.

Sensitivity analyses

For quantifying the risk of chronic ‘all over’ body pain with exposure to childhood maltreatment (estimand 1), we undertook sensitivity analyses with the following adjustments: assessing risk differences for each of the five types of maltreatment individually; examining exposure across three categories of frequency; excluding individuals who reported chronic ‘all over’ body pain at baseline; substituting the negative control exposure (childhood sunburn) in place of childhood maltreatment; and using multiple imputation (with chained equations) to gauge the extent of bias from missing data. Data were imputed from baseline values for a sample size of 502,367 in each of 10 imputations. Details of the imputation model can be found in the Supplementary materials.

Patient and public involvement

A Chronic Pain Advisory Group, comprising 5-6 people, has been involved in all stages of CAPE. Group members all have lived experience of chronic pain and childhood adversity. For these analyses, two online meetings and one in-person workshop were held. Advisory group members received compensation for their time, based on NIHR involvement guidelines. The group provided input at the planning stage, when identifying potential mediating and moderating factors, and prioritising analysis objectives, as well as helping to interpret the key findings. In particular, the decision to investigate a potential interaction with adult stressful events was largely driven by conversations with the advisory group. Members also cautioned against the use of a summed ‘score’ of adversity types.

Results

A total of 118,347 people had all data available (complete cases); 57% were female, 97% of white ethnicity, 47% had a university or college qualification, and they had a median age of 57 years at recruitment. Five percent of the sample (n=6,207) reported chronic ‘all over’ body pain and 42% (n=49,485) reported any form of maltreatment: emotional neglect (23%), physical abuse (19%), emotional abuse (16%), sexual abuse (9%) and physical neglect (5%). There were higher proportions of ethnic minorities, those living in the most deprived areas, and people that left education at a young age amongst those who reported childhood maltreatment compared to those who did not (Table 1).

The risk of chronic ‘all over’ body pain was higher in the exposed pseudo-population in which everyone had experienced some form of childhood maltreatment (6.3%, 95% confidence intervals (CI) [6.0%, 6.5%]) than in the unexposed pseudo-population in which no one had experienced childhood maltreatment (4.0%; 95% CI [3.8%, 4.2%]). This difference remained when analyses were stratified by sex: females 8.1% (95% CI [7.7%, 8.4%]) vs 5.0% (95% CI [4.8%, 5.3%]); males 3.9% (95% CI [3.6%, 4.2%]) vs 1.3% (95% CI [0.9%, 1.6%]). When stratified by ethnicity, estimates of risk differences lacked precision (with very wide confidence intervals), making it difficult to discern a moderating effect. Estimates were similar regardless of whether IPW were included (Table 2).

There was evidence of independent (and similar) effects of both childhood maltreatment and recent adult stressful life events on the risk of chronic ‘all over’ body pain (Table 3). There was an additional (supra-additive) risk of 1.2% (95% CI [0.6, 1.7]) of chronic ‘all over’ body pain compared to the individual risks associated with each of childhood and adulthood adversity. In mediation analyses (Table 4), the total effect of exposure to childhood maltreatment was a relative risk of 1.57 (95% CI [1.49, 1.66]), while the estimated indirect effect, via all of the mediators combined, was RR 1.16 (95% CI [1.14, 1.18]). When examined individually, mental health was the mediator with the largest indirect effect: RR 1.09 (95% CI [1.08, 1.11]), as compared to IMD (RR 1.03, 95% CI [1.02, 1.03]), sleep problems (RR 1.04, 95% CI [1.03, 1.05]) and social support (RR 1.01, 95% CI [1.01, 1.02]).

Whilst prevalence of each type of maltreatment varied widely, sensitivity analyses showed an increase in risk of chronic ‘all over’ body pain for each type of maltreatment (Table 5). There was also an increase in risk with increasing frequency of exposure to any maltreatment: rarely/sometimes risk difference 1.4% (95% CI [1.1%, 1.7%]); often/very often 3.4% (95% CI [2.8%, 4.0%]). Excluding those with chronic ‘all over’ body pain at baseline attenuated estimates only slightly (absolute risk difference 2% (95% CI [1.7%, 2.3%])). Results from analyses using imputed data were confirmatory, so we present complete case analyses (see Supplementary material for full details of sensitivity analyses).

When analyses were repeated with the control exposure, sunburn (Table 6), only a small risk difference was found in women (0.8%; 95% CI [0.3%, 1.3%]) and even smaller in men (0.5%; 95% CI [0.1%, 0.9%]). Descriptive statistics for the negative control exposure are found in the Supplementary material.

Discussion

Counterfactual comparisons indicated that childhood maltreatment increases the population risk of chronic ‘all over’ body pain by 2-3%. Increased risk was associated with each type of reported maltreatment and there was additional risk of chronic ‘all over’ body pain associated with the combination of both childhood maltreatment and adversity in adulthood.

These conclusions are based on a set of assumptions, that: exposure to maltreatment was independent between individuals (no interference); whilst the experiences of maltreatment cannot be assumed to be identical across individuals, these variations would not have differential effects (treatment variation irrelevance); all participants had a chance of being exposed or not to childhood maltreatment (positivity); exposed and unexposed groups are exchangeable following the application of IPW, with no unmeasured confounding; there was no unmeasured confounding of exposure, mediator and outcome relationships; data about childhood is an antecedent of data regarding adulthood, despite the retrospective data being collected with or after other data (temporality). We used IPW to balance the exposed and unexposed groups, but this assumes that the IPW adequately captured confounding. Our DAG suggested childhood socioeconomic position as a key confounding variable, yet a direct measure was not available in the UK Biobank, and we instead used age on leaving education/educational attainment as a proxy. Due to lack of information available in UK Biobank, we were unable to investigate the effects of childhood experiences other than abuse and neglect, though several other household challenges and traumatic events have also been implicated in poor health outcomes [e.g. 23, 27]. Selection bias in the UK Biobank has been well described [10], and we recognise the potential of bias through selection of ‘healthy volunteers’, though we suspect the direction of this bias, if present, would be an attenuation. Attrition within the recruited sample may be another selection bias, which we attempted to address in our sensitivity analysis using imputed data. It should also be noted that the wording of the second question which we used to identify people with chronic ‘all over’ body pain may have included people with discomfort rather than pain all over the body, though participants must also have indicated chronic pain in the prior question to be counted as a case.

An advantage to the UK Biobank is its size, which enabled us to describe the risk of chronic ‘all over’ body pain by type of maltreatment, by sex, across several ethnic groupings and further to assess the joint effects of exposures in childhood and adulthood. Additionally, we were able to include, and jointly assess, four potential mediators.

A key strength of our analyses was the inclusion of a negative control exposure, childhood sunburn. With no plausible mechanism linking sunburn to adult chronic pain, we would not

expect to see an effect on risk, and we would conclude that any such estimated effect would likely be due to bias. Our analysis found a very small effect of the negative control exposure, suggesting some bias; however, the risk difference was much smaller than that of childhood maltreatment. Our interpretation of this is that only a small proportion of the estimated effect of childhood maltreatment is due to recall bias, assuming that similar recall mechanisms operate for the retrospective reporting of childhood maltreatment and sunburn. Previous authors have identified discrepancies between the conclusions of retrospective and prospective studies and suggested that recall bias explains much of the observed associations [26, 37]. By triangulating with findings using a negative control exposure, our analyses suggest that recall bias is not (wholly) responsible for these discrepancies. Attempting to quantify the impact of recall bias is important in a field where at least some reliance on retrospective assessment is necessary – the often delayed disclosure of adverse childhood experiences makes purely prospective measurement unrealistic [3].

Several other studies have demonstrated a dose-response relationship, summing the number of types of ACEs [7]. We were also able to demonstrate a dose-response relationship with frequency, but even maltreatment occurring ‘sometimes’ conferred risk. We preferred to use frequency as an indicator of severity rather than an accumulation of multiple types of adversity, though further research could investigate if particular patterns of co-occurring maltreatment types, or the experience of ‘polyadversity’, confer extra risk in this context (see for example [22]).

In our mediation analyses, we found that anxiety/depression alone mediated the greatest proportion of the effect. This accords with another analysis in this sample, which found interactions between childhood maltreatment and some anxiety symptoms (rather than diagnosis), impacting on the odds of reporting any chronic pain (not necessarily all over the body) [8]. With some exceptions [39], mediation analyses in other samples have tended not to find such an effect for anxiety or depression [50, 6], though other psychological factors have been implicated, such as PTSD [36, 26, 1], emotion regulation [48] and stress [43]. We note, however, that the data we used for mediation was captured in mid-to-later life and therefore did not capture potential mediators more proximal to exposure.

The results suggest that adult trauma may also have a causal role in the development of chronic ‘all over’ body pain: both independently and by exacerbating the effect of childhood trauma. Stressful adult events have previously been implicated as a risk factor in the development of pain both in this [47] and other populations [13], and they have been investigated as potential mediators leading from childhood experiences [19, 43].

Some of the potentially confounding aspects of studying the impact of traumatic events are absent in animal models of adversity. Nor is it possible to model all aspects of childhood trauma in animals. Studies of maternal neglect during the neonatal period reveal an impact on persistent pain in adulthood [31, 42]. Furthermore, exposure of rodents subjected to early life adversity to stress in adulthood increases the association with persistent hyperalgesia [2]. To our knowledge, though, our study provides the first evidence of a joint interactive effect in humans. Finding an independent effect of adult experiences lends weight to a cumulative model of exposures (in childhood and adulthood), rather than there being a sensitive period in childhood.

There remained a risk of chronic 'all over' body pain in (pseudo)populations who did not report any of the childhood maltreatment in this survey. This risk differed between demographic groups, being higher in women, and amongst Black participants. It is possible that the questions did not capture other forms of childhood adversity that have been proposed as influential [3]. The wider context of structural and societal inequalities and experiences of discrimination could also play a role in these differences [24].

The key implication of these findings is that reducing childhood maltreatment is likely to prevent cases of chronic widespread pain in adulthood. Mental health as a key mediator of the causal pathway suggests that successfully identifying and treating psychological disorders in survivors of maltreatment could help to prevent some cases of chronic pain. Our findings suggest that stressful life events through adulthood may also be important opportunities for intervention. Longitudinal analysis of data across the life course would be necessary to understand more about these potential mediators and interactions.

In conclusion, we need no further evidence that prevention of childhood maltreatment is a worthy goal, but an improved understanding of the mechanisms linking childhood adversity to poor adult health could guide targeted interventions. To that end, causally linking childhood maltreatment to chronic pain in adulthood is an important step from which to channel future efforts in research and practice. Identifying modifiable mediators – such as mental health - could guide preventative efforts.

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Tables & Figures

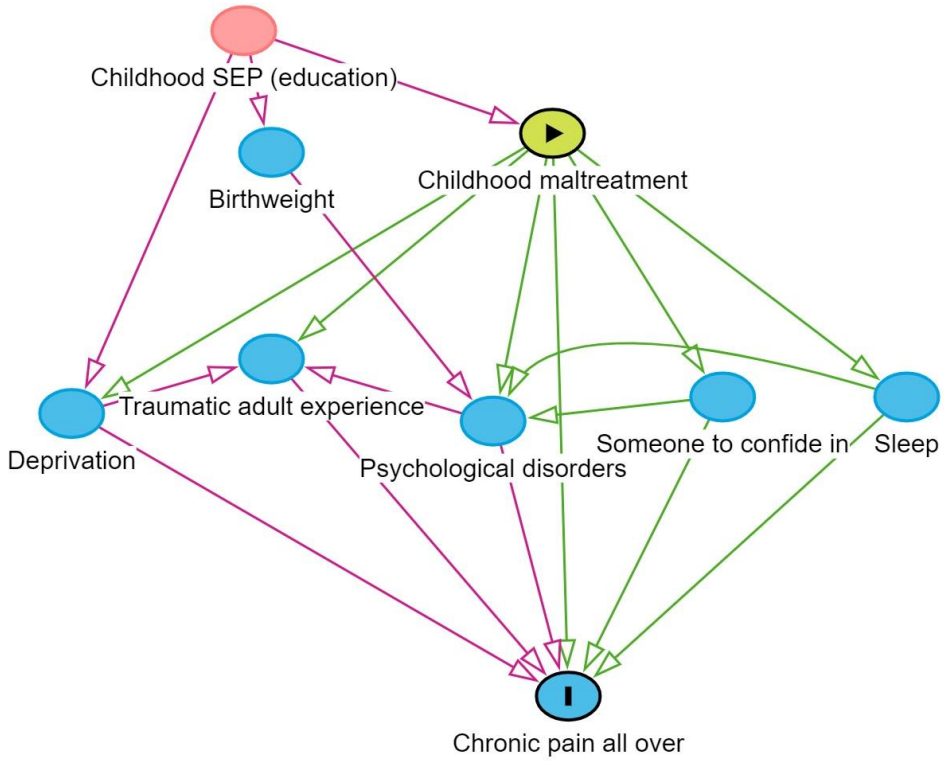

Figure 1: Directed acyclic graph (DAG) showing hypothesised causal pathways from childhood maltreatment to the development of chronic pain all over, showing measured factors in the UK Biobank. Moderators are not depicted in the graph, but include biological sex and ethnicity. Supporting references for each arc are listed in Appendix A. SEP: socioeconomic position.

Table 1: Characteristics of the analytical sample

Characteristic		All participants (n=118,347)	No childhood maltreatment (n=68,933)	Childhood maltreatment (any) (n=49,414)	Childhood maltreatment (rarely/ sometimes) (n=37,264)	Childhood maltreatment (often/very often) (n=12,150)
% Female		57%	57%	57%	56%	62%
Ethnicity	White	97%	98%	96%	97%	94%
	Asian or Asian British	<1%	<1%	1%	<1%	1%
	Black or Black British	<1%	<1%	1%	<1%	2%
	Chinese	<1%	<1%	<1%	<1%	<1%
	Mixed	<1%	<1%	<1%	<1%	1%
	All other ethnic groups	<1%	<1%	<1%	<1%	1%
Age at recruitment (median years, IQR)		57 (50, 62)	57 (51, 62)	56 (49, 61)	56 (49, 61)	56 (49, 61)
Education	Degree/college qualification	47%	48%	46%	55%	45%
	Other adult education	9%	10%	9%	10%	10%
	Left education at 18yr	16%	17%	16%	18%	18%
	Left education at minimum school-leaving age*	14%	13%	16%	16%	25%
	Left education before minimum school-leaving age	1%	1%	1%	1%	3%

Characteristic		All participants (n=118,347)	No childhood maltreatment (n=68,933)	Childhood maltreatment (any) (n=49,414)	Childhood maltreatment (rarely/ sometimes) (n=37,264)	Childhood maltreatment (often/very often) (n=12,150)
IMD	1 (least deprived)	24%	26%	22%	24%	19%
	2	22%	23%	21%	22%	20%
	3	20%	20%	20%	20%	21%
	4	18%	17%	19%	19%	20%
	5 (most deprived)	13%	12%	16%	15%	20%
Stressful life event in prior 2 yr		50%	47%	53%	52%	56%
Chronic pain all over		5%	4%	7%	6%	10%
Sunburn ≥1 occasion in childhood		52%	50%	55%	56%	51%

*in England & Wales the minimum school-leaving age was raised in 1972. Derived data took this into account, based on year of birth. IMD = Index of Multiple Deprivation.

Table 2: Risks and risk differences from the treatment effects models, comparing the effects of exposure to childhood maltreatment on the risk of chronic pain all over

Model	Weights	n	Baseline (unexposed) risk	Exposed risk	Risk difference (treatment effect)
Whole sample (unweighted)	-	118,347	0.042 (0.040, 0.043)	0.068 (0.065, 0.070)	0.026 (0.023, 0.029)
Whole sample (no stratification)	Education Sex Ethnicity	103,725	0.040 (0.038, 0.042)	0.063 (0.060, 0.065)	0.023 (0.020, 0.025)
Men	Education Ethnicity	44,673	0.013 (0.009, 0.016)	0.039 (0.036, 0.042)	0.026 (0.024, 0.028)
Women	Education Ethnicity	58,952	0.050 (0.048, 0.053)	0.081 (0.077, 0.084)	0.030 (0.026, 0.035)
White	Education Sex	100,783	0.039 (0.038, 0.041)	0.062 (0.059, 0.064)	0.023 (0.020, 0.025)
Mixed ethnicity	Education Sex	547	0.046 (0.016, 0.075)	0.090 (0.059, 0.120)	0.044 (0.002, 0.086)
Asian or Asian British	Education Sex	815	0.059 (0.034, 0.083)	0.097 (0.069, 0.124)	0.038 (0.001, 0.075)
Black or Black British	Education Sex	660	0.106 (0.062, 0.150)	0.118 (0.089, 0.148)	0.012 (-0.041, 0.066)
Chinese	Education Sex	244	0.052 (0.007, 0.096)	0.067 (0.028, 0.105)	0.015 (-0.044, 0.074)
Other ethnic groups	Education Sex	576	0.066 (0.034, 0.097)	0.103 (0.071, 0.136)	0.038 (-0.008, 0.083)

*95% confidence intervals are shown in brackets.

Table 3: Differences in risk of chronic pain all over compared by exposure to childhood maltreatment and/or recent stressful life events. Covariates are education, sex and ethnicity (n=103,344)

Exposure group	Risk of chronic pain all over	Risk difference (compared to unexposed)
No ACEs, no stressful life event	0.033 (0.030, 0.035)	-
≥1 ACE, but no stressful life event	0.048 (0.045, 0.051)	0.016 (0.012, 0.019)
No ACEs, but ≥1 stressful life events	0.048 (0.045, 0.050)	0.015 (0.012, 0.018)
≥1 ACE and ≥1 stressful life events	0.075 (0.072, 0.078)	0.042 (0.039, 0.046)

Table 4: Total, indirect and direct effects (relative risks and 95% confidence intervals) of childhood maltreatment on chronic 'all over' body pain. Inverse odds weights incorporate mediators (as specified for each model), sex and ethnicity. IMD: index of multiple deprivation

	Model 1: All 4 mediators	Model 2: Mental health	Model 3: IMD	Model 4: Sleep problems	Model 5: Social support
Indirect effect	1.16 (1.14, 1.18)	1.09 (1.08, 1.11)	1.03 (1.02, 1.03)	1.04 (1.03, 1.05)	1.01 (1.01, 1.02)
Direct effect	1.35 (1.28, 1.43)	1.44 (1.36, 1.52)	1.53 (1.45, 1.62)	1.51 (1.43, 1.60)	1.55 (1.47, 1.64)
Total effect	1.57 (1.49, 1.66)	1.57 (1.49, 1.66)	1.57 (1.49, 1.66)	1.57 (1.49, 1.66)	1.57 (1.49, 1.66)

Table 5: Risks and risk differences, comparing the effects of 5 types of childhood maltreatment on the risk of chronic pain all over

Maltreatment type	Sex	n	Baseline (unexposed) risk	Exposed risk	Risk difference (treatment effect)
Physical abuse	Male	44,897	0.028 (0.027, 0.030)	0.043 (0.039, 0.047)	0.014 (0.010, 0.018)
	Female	59,525	0.058 (0.056, 0.060)	0.089 (0.083, 0.094)	0.031 (0.025, 0.036)
Emotional abuse	Male	44,889	0.029 (0.027, 0.030)	0.051 (0.046, 0.057)	0.023 (0.017, 0.029)
	Female	59, 468	0.056 (0.054, 0.058)	0.098 (0.092, 0.103)	0.042 (0.036, 0.048)
Sexual abuse	Male	44,716	0.031 (0.029, 0.032)	0.041 (0.033, 0.048)	0.010 (0.002, 0.017)
	Female	58,777	0.060 (0.058, 0.062)	0.089 (0.082, 0.096)	0.029 (0.022, 0.036)
Physical neglect	Male	44,759	0.030 (0.029, 0.032)	0.061 (0.050, 0.072)	0.031 (0.020, 0.042)
	Female	59, 253	0.061 (0.059, 0.063)	0.106 (0.096, 0.117)	0.046 (0.034, 0.057)
Emotional neglect	Male	44,815	0.029 (0.027, 0.031)	0.041 (0.037, 0.044)	0.011 (0.007, 0.016)
	Female	59,453	0.055 (0.053, 0.058)	0.090 (0.085, 0.095)	0.034 (0.029, 0.039)

Doubly-robust estimation with inverse probability weights for education and ethnicity. Brackets show 95% confidence intervals.

Table 6: Risks and risk differences from the treatment effects models, comparing the effects of exposure to childhood sunburn (negative control exposure) on the risk of chronic pain all over.

Model	Weights	n	Baseline (unexposed) risk	Exposed risk	Risk difference (treatment effect)
Whole sample	-	125,663	0.063 (0.062, 0.065)	0.057 (0.055, 0.058)	-0.007 (-0.010, -0.004)
Whole sample	Education Sex Ethnicity	110,583	0.054 (0.052, 0.056)	0.061 (0.058, 0.064)	0.007 (0.004, 0.010)
Men	Education Ethnicity	47,076	0.035 (0.033, 0.037)	0.040 (0.037, 0.043)	0.005 (0.001, 0.009)
Women	Education Ethnicity	63,507	0.068 (0.065, 0.071)	0.076 (0.072, 0.080)	0.008 (0.003, 0.013)

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