

ORIGINAL RESEARCH

Adverse Childhood Experiences and the Risk of Coronary Heart Disease in Adulthood: Examining Potential Psychological, Biological, and Behavioral Mediators in the Whitehall II Cohort Study

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BACKGROUND: This study investigated potential psycho-bio-behavioral mediators of the association between adverse childhood experiences (ACEs) and the risk of coronary heart disease (CHD) in adulthood.

METHODS AND RESULTS: Participants were 5610 British civil servants (mean age, 55.5; 28% women) from the Whitehall II cohort study without CHD at baseline in 1997 to 1999 (wave 5) when retrospective data on the number of ACEs were collected via questionnaire (range, 0–8). Potential mediators assessed at wave 5 included depression and anxiety symptoms, health behaviors (smoking, alcohol dependence, sleep, and physical activity), and cardiometabolic dysregulations. New diagnoses of CHD (myocardial infarction, definite angina, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty) were assessed from wave 6 (2001) to wave 11 (2012–2013). Logistic regressions examined associations between ACEs, potential mediators, and CHD during the follow-up period. Natural indirect effects were examined using mediation analysis. A total of 566 (10.1%) participants developed CHD during the follow-up period. ACEs were associated with an increased likelihood of CHD (odds ratio per ACE, 1.09; 95% CI, 1.00–1.19). Controlling for age and sex, mediation analyses revealed an indirect effect of depression symptoms (natural indirect effects, 1.05; 95% CI, 1.03–1.07), anxiety symptoms (natural indirect effects, 1.12; 95% CI, 1.10–1.15), and a greater number of cardiometabolic dysregulations (natural indirect effects, 1.02; 95% CI, 1.01–1.03) in the association between ACEs and incident CHD. Behavioral factors were not statistically significant mediators.

CONCLUSIONS: Depression symptoms, anxiety symptoms, and cardiometabolic dysregulations partially mediated the association between ACEs and CHD. Regular screening and treatment of symptoms of psychological disorders and cardiometabolic dysregulations may help mitigate the long-term health burden of ACEs.

Key Words: adverse childhood experiences ■ coronary heart disease ■ health behaviors ■ mental health ■ metabolic dysregulations

Hear disease is a leading cause of death globally, and prevalence rates are on the rise.¹ In particular, coronary heart disease (CHD) accounts for approximately one-third of deaths among individuals >35 years of age.² A better understanding of the modifiable risk factors for CHD and the mechanisms for these risk factors is needed to improve CHD prevention. Adverse childhood experiences (ACEs) have

been linked to the emergence of CHD.³ ACEs are characterized as potentially traumatic events that occur in childhood and are reported by ≈50% of adults.^{4–6} A broad range of ACE event types have been examined in the research literature, such as parental abuse and neglect, witnessing or experiencing violence in the household, parental substance abuse, household dysfunction, and being separated from parents,⁵ and

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CLINICAL PERSPECTIVE

What Is New?

- Adverse childhood experiences (ACEs) are associated with an increased risk of heart diseases in adulthood, but the mechanisms underlying these associations are unclear.
- This study examined potential psychological (depression and anxiety), behavioral (smoking, alcohol dependence, sleep, and physical activity), and cardiometabolic pathways linking ACEs and coronary heart disease with a prospective cohort study.

What Are the Clinical Implications?

- Our study suggests an important role for mental health and cardiometabolic dysregulations in the association between ACEs and the risk of coronary heart disease in adulthood.
- Understanding the ways in which ACEs might lead to coronary heart disease can ultimately help to mitigate the long-term health burden of ACEs.

Nonstandard Abbreviations and Acronyms

ACE	adverse childhood experience
NIE	natural indirect effect

studies have shown that experiencing these events confers a greater risk of CHD in adulthood. For example, evidence from a recent meta-analysis suggests that experiencing abuse in childhood is associated with an increased risk of adulthood cardiovascular diseases with a moderate effect size ($d=0.42$; 95% CI, 0.39–0.45).⁷ A systematic review also suggested a positive association between broadly defined ACEs and the risk of CHD in adulthood.³

It has been posited that it is not only the experience of an adverse event that increases the risk of poor health outcomes but that the cumulative exposure to such events increases the risk of poor health outcomes in adulthood in a dose-response manner.⁸ A recent meta-analysis demonstrated that cumulative exposure to childhood adversity is modestly associated with cardiometabolic disease, including heart diseases, in adulthood.⁹ The authors found a pooled odds ratio (OR) of 1.46 (95% CI, 1.33, 1.61) for cumulative ACEs and cardiovascular disease clinical outcomes.⁹ However, knowledge gaps remain in understanding the mechanisms linking cumulative exposure to ACEs with CHD in adulthood given the dearth of prospective studies on mediators of these associations.¹⁰ The

American Heart Association recently published a scientific statement highlighting the need for research aimed at identifying the mechanisms for the associations between ACEs and cardiometabolic outcomes, including CHD.¹⁰ Mental health factors linking ACEs and cardiometabolic diseases, with emphasis on depression and anxiety, were proposed as important potential pathways in need of further study. The report highlights, however, that prospective studies explicitly testing the hypothesized mechanisms linking ACEs and cardiometabolic disease using comprehensive mediation models are lacking.¹⁰ The present study aims to address this knowledge gap by testing several potential mediators, including psychological, behavioral, and cardiometabolic variables, to better understand the mechanisms linking ACEs with adulthood CHD in a prospective cohort study.

ACEs have been shown to increase the likelihood of depression,^{11,12} which is a potentially modifiable/treatable risk factor for the development of CHD.^{13,14} ACEs are also associated with increased anxiety.¹² There is also increasing evidence suggesting that anxiety is an independent risk factor for CHD,¹⁵ though findings have been inconsistent.¹⁶ Therefore, it is possible that depression and anxiety mediate the association of ACEs and the incidence of CHD. Health behaviors might also mediate this association. ACEs are also associated with later health-risk behaviors such as smoking, excessive alcohol use, and physical inactivity.^{17,18} Health-risk behaviors, in turn, are associated with CHD.^{19,20} Sleep disturbances and short sleep durations may also play an important role, as ACEs have been shown to also be associated with sleep problems^{21,22} as well as with CHD.^{23–25} Cardiometabolic dysregulations may also mediate the association between ACEs and CHD in adulthood. The biological embedding of childhood adversity model^{26,27} hypothesizes that experiencing adverse events during childhood predisposes individuals to having exaggerated biological responses, which might increase allostatic load and risk of cardiometabolic dysregulations such as fasting glucose, triglyceride, cholesterol, and blood pressure levels. In cohort studies, ACEs have been shown to be associated with cardiometabolic dysregulations,^{28,29} which are important risk factors for CHD.^{30,31}

The present study investigated psychological, behavioral, and biological factors as potential modifiable mediators of the association between ACEs and the incidence of CHD in adulthood in a prospective cohort study of British civil servants, the Whitehall II cohort study. Given that ACEs are associated with the later development of depression and anxiety symptoms, health-risk behaviors, and cardiometabolic dysregulations, and that these factors are associated with the development of CHD, we hypothesized that the association between ACEs and CHD in adulthood would

be accounted for by these indirect pathways. We have previously shown that depression and cardiometabolic dysregulations mediate the association between ACEs and an increased risk of type 2 diabetes mellitus in adulthood in this cohort.³² However, the potential mediating role of depression and anxiety symptoms, health behaviors, and cardiometabolic factors has not been examined for the association between ACEs and CHD.

METHODS

Sample

Data were from the Whitehall Cohort Study II, a prospective study of 10 308 British civil servants, aged between 35 and 55 years when the survey began in 1985. Data collection has occurred every 2 to 3 years since, alternating between clinical examination and questionnaire survey. Participants provided informed consent and institutional review board approval for the study was obtained by the University College London Medical School Committee on the Ethics of Human Research. Detailed study procedures are described elsewhere.^{33,34} Information on the Whitehall II data sharing policies and procedures can be found at <https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-and-public-health/research/whitehall-ii/data-sharing>. For the present study, assessment wave 5 (1997–1999) served as the study baseline given that ACEs were first measured in this wave. ACEs were retrospectively assessed, and current depression and anxiety symptoms, health behaviors, and cardiometabolic dysregulations were assessed at wave 5. Incident CHD was assessed from wave 6 (2001) to wave 11 (2012–2013).

A total of 7870 participants took part in the wave 5 assessment. Of these participants, 540 with prevalent CHD at or before wave 5 were excluded. An additional 1720 participants (23.5% of the wave 5 sample) were excluded because of missing data on the main exposure, outcome, or mediator variables, which includes ACEs, CHD, and the potential mediators of depression and anxiety symptoms, physical activity, alcohol dependence, smoking, sleep duration, and cardiometabolic dysregulations. The final sample size for the present study was therefore $N=5610$ participants. Participants with missing data were compared with those with complete data (ie, those included in the present sample), on age, sex, the prevalence of all mediator variables when data were available, ACEs, and likelihood of CHD during the follow-up period. Overall, participants with missing data were more likely to be female, to smoke, and to be physically inactive, and had higher mean levels of depressive and anxiety symptoms, were

≈1 year older, and reported more ACEs, but did not differ on likelihood of CHD, sleep duration, alcohol dependence, or the mean number of cardiometabolic dysregulations present. Exposure, outcome, and mediator variables are described below.

Measures

ACEs were assessed with the question, “Did any of the following things happen during your childhood (that is, up until you were 16)?” and included unintentional parental unemployment, parental mental illness or parental problematic alcohol consumption, physical abuse by someone close, exposure to frequent parental argument or fights, being hospitalized for ≥ 4 weeks, parental divorce, being in an orphanage, and maternal separation for 1 year or more. Response options were “yes” or “no,” and positive responses were summed to create a continuous ACEs score ranging from 0 to 8.

Depression and anxiety symptoms were assessed using subsets of items from the 30-item General Health Questionnaire,³⁵ which has been validated for the Whitehall II cohort study.³⁶ The General Health Questionnaire assesses general mental health status, with a 5-item subscale assessing anxiety symptoms and 4-item subscale that assesses depressive symptoms, experienced within the past week, on a rating scale from 0 to 3. For the depression subscale, items reflected the cognitive symptoms of depression and included assessments of feelings of worthlessness, hopelessness, that life is not worth living, and of being unable to do anything because of nerves. Scores on the depression subscale can range from 0 to 12 (Cronbach $\alpha=0.87$), with higher scores reflecting greater depressive symptom severity. For the anxiety subscale, items related to the loss of sleep over worry, feeling constantly under strain, getting scared or panicky for no good reason, feeling overwhelmed (“finding everything getting on top of you”), and feelings of nervousness. Scores on the anxiety subscale range from 0 to 15 (Cronbach $\alpha=0.86$), with higher scores reflecting greater anxiety symptom severity.

Behavioral factors were assessed by self-report and included physical activity, smoking, alcohol dependence, and short sleep duration. Physical activity was assessed with a modified Minnesota leisure-time physical activity questionnaire³⁷ and included questions related to the frequency and duration of various physical activities such as cycling, walking, and swimming. Each activity was assigned a metabolic equivalent of task value and categorized as either mild or moderate to vigorous physical activity. This method has been previously described in Whitehall II studies.^{38–40} For the present study, participants were

categorized as either meeting the recommended physical activity guidelines according to the World Health Organization⁴¹ of at least 2.5 hours of moderate to vigorous physical activity per week or not meeting these guidelines. Smoking was assessed by self-report, and participants were categorized as current smokers or nonsmokers. Alcohol dependence was assessed using the CAGE questionnaire,⁴² a four-item instrument designed to screen for alcohol dependence by assessing whether respondents have ever felt they should Cut down on their drinking, felt Annoyed by people criticizing their drinking, felt bad or Guilty about their drinking, and had ever had a drink first thing in the morning (*Eye opener*). This measure has been used in previous Whitehall II studies.⁴³ Participants were categorized as having alcohol dependence if they had ≥ 2 positive responses.⁴⁴ Self-reported sleep duration was assessed with the question, "How many hours of sleep do you have on an average weeknight?" Response options were ≤ 5 , 6, 7, 8, and ≥ 9 hours and, in the present study, short sleep was defined as a self-reported average sleep duration of ≤ 6 hours.⁴⁵

Cardiometabolic dysregulations were assessed by clinical examination and were based on the criteria for the metabolic syndrome⁴⁶ and systemic inflammation. They included high levels of fasting glucose (≥ 5.6 mmol/L), triglycerides (>1.7 mmol/L), and C-reactive protein (≥ 3.0 mg/L), as well as low levels of high-density lipoprotein cholesterol (<1.03 mmol/L in men and <1.30 mmol/L in women), high blood pressure ($>130/85$ mm Hg), and high waist circumference (≥ 102 cm in men and ≥ 88 cm in women). For the present study, the number of cardiometabolic dysregulations present was modeled as a continuous variable. A follow-up exploratory analysis additionally examined cardiometabolic dysregulations (presence versus absence) individually.

Diabetes mellitus status was assessed at wave 5 by self-reported physician diagnosis of diabetes mellitus, antidiabetic medication, and fasting plasma glucose levels ≥ 7.0 mmol/L, or a 2-hour oral glucose tolerance test ≥ 11.1 mmol/L. A participant was considered to have diabetes mellitus at wave 5 if identified by any of these methods. Diabetes mellitus status was included in a sensitivity analysis, described below.

CHD was objectively assessed using clinical assessments and medical records. Clinical assessments were conducted with 12-lead resting ECG recordings assessing myocardial infarction, definite angina, reported coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty and with data linkages with the national Hospital Episode Statistics using *International Classification of Diseases, Ninth Revision (ICD-9)* codes 410–414, *International*

Classification of Diseases, Tenth Revision (ICD-10) codes I20–I25, or procedures K40–K49, K50, K75, and U19.

Statistical Analysis

Descriptive and frequency statistics were examined. The associations between ACEs, potential mediators, and CHD were examined using logistic and linear regressions. ORs or unstandardized regression coefficients with 95% CIs are reported.

Mediation occurs when 1 variable influences variation in an outcome indirectly via ≥ 1 intervening variables.⁴⁷ To examine the extent to which the association between ACEs and CHD was mediated by depression and anxiety symptoms, health behaviors, and cardiometabolic dysregulations, a mediation analysis⁴⁸ was conducted. This approach draws from the causal mediation analysis framework⁴⁹ and is used to decompose the total effect into the direct effect of ACEs on the likelihood of CHD and the indirect effect via depression and anxiety symptoms, health behaviors, and cardiometabolic dysregulations. The Figure represents the conceptual mediation model tested in the present study. The indirect effect represents the extent to which the association between ACEs and CHD is mediated, or accounted for, by the intermediate variables included in the model. This statistical approach is based on a counterfactual conceptual framework.⁵⁰ The direct effect estimates the association between ACEs and CHD that is independent of the mediator. For example, in a model with depression as the potential mediator, the direct effect would be evaluated as the effect of ACEs on CHD with depression set to the level that would have naturally occurred in the absence of any ACEs. The indirect effect estimates the proportion of the total effect that is accounted for, or mediated, by depression. Using a counterfactual framework, the indirect effect estimates the effect of ACEs on CHD that can be explained by the effect of ACEs on depression, that is, if greater depression results in a greater risk of CHD among those with ACEs. This is obtained by comparing the risk of CHD associated with ACEs when setting the level of depression to what it would have been in the presence versus absence of ACEs. The total effect represents the product of the direct and indirect effect ORs. Mediation analyses were adjusted for age and sex.

Analyses were conducted in Stata version 14 using the *paramed* command,⁵¹ which uses the Delta method to calculate standard errors and CIs. ACEs were modeled as a continuous variable, where the baseline level of exposure being compared was 0, with a value of 4 set as the new exposure level in the counterfactual model, given that this value

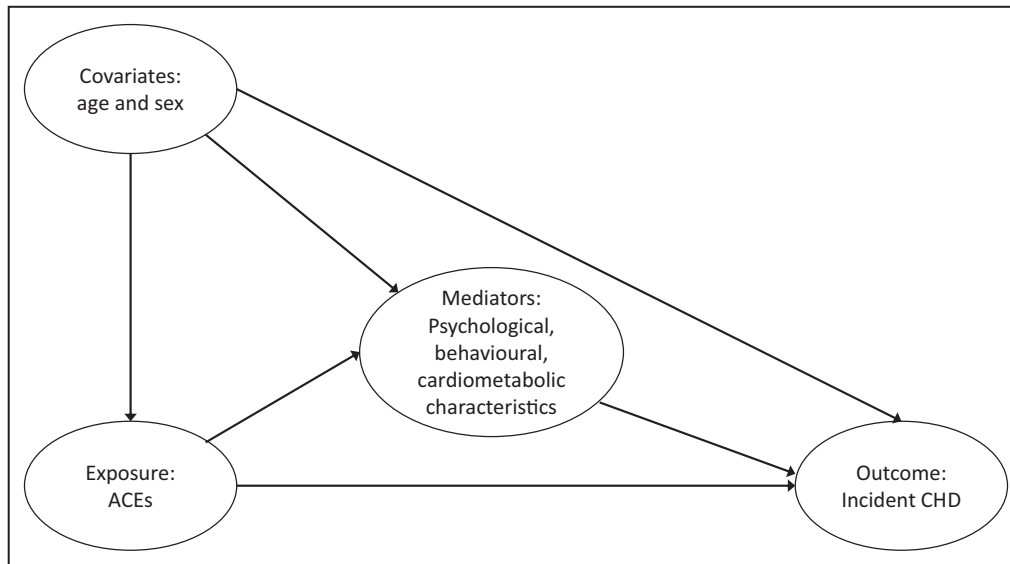


Figure. Conceptual model.

ACEs indicates adverse childhood experiences; and CHD, coronary heart disease.

is often used in the literature to denote high risk.^{5,8} The level of the mediator at which to compute controlled direct effects was set to the sample mean for continuous mediators and was set to 0 for dichotomous mediators. The outcome model was set as a logistic model, with the mediator model set to either linear or logistic model depending on the nature of the mediating variable (ie, continuous or categorical, respectively). This mediation analysis method is advantageous over traditional mediation models, as it allows for exposure-mediator interaction.⁵² Using this framework, 2 regression models were conducted: In the first model, CHD was regressed on the exposure of ACEs, the mediator and the covariates of age and sex, while in the second model, the mediator was regressed on the exposure of ACEs and covariates age and sex. The proportion of the total effect that is mediated by each mediator (% mediation) was calculated using the recommended formula: $NDE \times (NIE - 1) / (NDE \times NIE - 1)$,⁴⁹ where NDE is natural direct effect and NIE is natural indirect effect. The proportion mediated reflects the extent to which the pathway via the mediator explains the association between the exposure and the outcome,⁵³ that is, between ACEs and CHD. Seven mediation models were conducted, with each mediator examined in a separate model.

Four sets of sensitivity analyses were conducted. First, the analyses were performed using a categorical ACE variable by dichotomizing groups into 0 or ≥ 1 ACEs. Second, to account for potential shared variable among all the mediator variables, analyses that entered all potential mediators together in the same model were conducted. Third, to account for potential overlap between CHD and diabetes mellitus, and given

that diabetes mellitus is a risk factor for CHD⁵⁴ and that we have previously shown links between ACEs, depression, and cardiometabolic dysregulations, and the risk of diabetes mellitus,³² analyses were repeated with diabetes mellitus status at wave 5 as an additional covariate. Finally, the main analyses were repeated with highest educational attainment (5 categories: no formal education, lower secondary education, higher secondary education, Bachelor of Arts/Bachelor of Science university degree, and higher degree) as an additional covariate in a subset of participants with complete data on this variable ($n=5318$).

RESULTS

The final sample consisted of 5610 participants (28.3% women) with a mean age of 55.5 (SD=6.0) years at the wave 5 baseline assessment. Sample characteristics are described in Table 1, stratified by those who did and did not develop CHD during the follow-up period. The mean depression score in our sample was 1.01 (SD=1.82), and the mean anxiety score was 3.35 (SD=2.82). The average number of cardiometabolic dysregulations was 1.14 (SD=1.18), with hypertension (36%) and elevated triglycerides (21%) being the most prevalent conditions. With regards to health behaviors, $\approx 10\%$ of the sample were smokers, 41% reported average sleep durations of < 7 hours per night, 24% met the World Health Organization weekly physical activity recommendation, and 11% screened positive for alcohol dependence.

A total of 566 (10.1%) participants had incident CHD. Participants who developed CHD were older ($P < 0.001$), more likely to be men ($P < 0.001$), and tended to have

Table 1. Participant Characteristics at Baseline (Wave 5, 1997–1999; N=5610)

	Participants Who Did Not Develop CHD (n=5044)	Participants Who Developed CHD (n=566)
	N (%) or Mean (SD)	N (%) or Mean (SD)
Age, y	55.2 (5.9)	58.1 (5.9)
Sex, female	1481 (29)	107 (19)
Depression	1.0 (1.8)	1.2 (2.0)
Anxiety	3.3 (2.8)	3.6 (3.0)
Number of cardiometabolic dysregulations	1.1 (1.2)	1.5 (1.3)
Cardiometabolic dysregulation category		
Elevated C-reactive protein	789 (16)	123 (22)
Elevated glucose	648 (13)	103 (18)
Elevated triglycerides	1009 (20)	165 (29)
Hypertension	1747 (35)	256 (45)
High waist circumference	688 (17)	85 (19)
Low HDL cholesterol	669 (15)	108 (21)
Currently smoke	475 (9)	66 (12)
Short sleep	2059 (41)	221 (39)
Physical activity	1225 (24)	144 (25)
Alcohol dependence	539 (11)	58 (10)
Number of ACEs	0.67 (0.9)	0.75 (1.0)
ACE category		
Parental arguments	1011 (21)	92 (17)
Parental divorce	184 (4)	21 (4)
Parental mental illness/alcohol abuse	313 (6)	35 (6)
Parental unemployment	481 (10)	78 (14)
Physical abuse	126 (3)	14 (3)
Long-term hospitalization	608 (12)	83 (15)
Orphanage	58 (1)	9 (2)
Long-term maternal separation	581 (12)	92 (16)

Depression and anxiety symptoms were assessed using General Health Questionnaire subscales, with a depression score range of 0–12 and an anxiety score range of 0–15; cardiometabolic dysregulations were assessed using criteria for the metabolic syndrome; current smoking status was assessed by self-report; short sleep was defined by self-reported average sleep duration of <7 hours; physical activity was assessed using the recommended physical activity guidelines according to World Health Organization of at least 2.5 hours of moderate to vigorous physical activity per week; alcohol dependence was assessed using the CAGE questionnaire. ACE indicates adverse childhood experience; CHD, coronary heart disease; and HDL, high-density lipoprotein.

higher depression ($P=0.001$) and anxiety ($P=0.01$) and more cardiometabolic dysregulations ($P<0.001$) than participants who did not develop CHD during the follow-up period (see Table 1). The mean number of ACE categories experienced was 0.67 (SD=0.95), with 44.0% of the sample having experienced at least 1 type of ACE and 16.1% having experienced ≥ 2 types of ACEs. The ACE category most frequently endorsed was parental arguments, with 20.3% of participants having experienced this ACE.

We found that each single ACE increase was associated with 9% higher odds of CHD (OR, 1.09; 95% CI, 1.00–1.19; $P=0.05$). This association was reduced to an OR of 1.08 (95% CI, 0.98–1.18; $P=0.11$) after adjusting for age and sex.

Table 2 describes the results of linear and logistic regression analyses for the associations between ACEs

and each mediator and for associations between each mediator and incident CHD. Overall, retrospectively reported ACEs were associated with higher levels of depression and anxiety symptoms, alcohol dependence, and smoking. Higher levels of depression and anxiety symptoms, as well as smoking and a greater number of cardiometabolic dysregulations, were associated with incident CHD.

Table 3 describes the results of the causal mediation analysis for all potential mediators examined, controlling for age and sex. Results demonstrated that ACEs were indirectly associated with an increased risk of CHD in adulthood via depressive symptoms and via anxiety symptoms. The NIE of depressive symptoms was 1.05, with $\approx 19.5\%$ of the effect of ACEs on CHD being mediated by depression. The NIE of anxiety symptoms was 1.12, with $\approx 40.9\%$ of the effect of

Table 2. Associations Between ACEs and Each Mediator, and Between Each Mediator and Incident CHD

Mediator Variable	ACEs → Mediator				Mediator → CHD		
	OR	B (SE)	95% CI	P Value	OR	95% CI	P Value
Depression*		0.13 (0.03)	0.08 to 0.18	<0.001	1.12	1.07 to 1.17	<0.001
Anxiety*		0.24 (0.04)	0.17 to 0.32	<0.001	1.10	1.06 to 1.13	<0.001
Physical activity [†]	1.01		0.94 to 1.08	0.815	0.85	0.69 to 1.04	0.114
Alcohol dependence [†]	1.24		1.14 to 1.34	<0.001	1.05	0.79 to 1.41	0.713
Smoking [†]	1.17		1.07 to 1.27	<0.001	1.43	1.08 to 1.89	0.012
Short sleep [†]	1.04		0.98 to 1.10	0.197	1.03	0.86 to 1.24	0.728
Cardiometabolic dysregulations*		0.02 (0.02)	-0.01 to 0.05	0.280	1.26	1.17 to 1.35	<0.001

N=5610. ACEs are modeled as a continuous variable, with higher values representing a greater number of ACE categories endorsed. All models in the table control for age and sex. Depression and anxiety symptoms were assessed using General Health Questionnaire subscales, with a depression score range of 0–12 and an anxiety score range of 0–15; physical activity was assessed using the recommended physical activity guidelines according to World Health Organization of at least 2.5 hours of moderate to vigorous physical activity per week; alcohol dependence was assessed using the CAGE questionnaire; current smoking status was assessed by self-report; short sleep was defined by self-reported average sleep duration of <7 hours; cardiometabolic dysregulations reflect the number of dysregulations present. ACE indicates adverse childhood experience; B, unstandardized beta coefficient; CHD, coronary heart disease; and OR, odds ratio.

*Continuous mediator variable.

[†]Binary mediator variable.

ACEs on CHD being mediated by anxiety. Health behaviors did not significantly mediate the association between ACEs and incident CHD. That is, the NIE of physical activity, smoking, alcohol dependence, and short sleep duration were not statistically significant (Table 3). Although not statistically significant, the effect size for alcohol dependence was moderate, with ≈18.2% of the effect of ACEs on CHD being mediated by alcohol dependence (NIE, 1.05). Finally, ACEs were indirectly associated with an increased risk of CHD in adulthood via cardiometabolic dysregulations. The NIE of cardiometabolic dysregulations was 1.02, with ≈7.45% of the effect of ACEs on CHD being mediated by a greater number of cardiometabolic dysregulations present in adulthood, before the onset of CHD. When each cardiometabolic dysregulation was

examined separately in a follow-up exploratory analysis, C-reactive protein was found to mediate 12% and high waist circumference was found to mediate 6% of the association between ACEs and CHD. Examined separately, the other cardiometabolic dysregulations each accounted for <3% of the association between ACEs and CHD.

Four sensitivity analyses were conducted. First, a set of analyses using a binary ACEs variable (0 versus ≥1) was conducted. Using this definition of ACEs, we found that having ≥1 ACEs compared with having no ACEs was associated with a 14% increase in the odds of adulthood CHD, though the CI was wider and thus this was not statistically significant (OR, 1.14). Results of mediation analyses with ACEs modeled as a binary variable demonstrated that only anxiety significantly

Table 3. Results of Mediation Analysis for the Association Between Adverse Childhood Experiences and Coronary Heart Disease in Adulthood

Mediator	Total Effect OR (95% CI)	NDE OR (95% CI)	NIE OR (95% CI)	% Mediated	P Value for NIE
Depression*	1.33 (1.21–1.45)	1.26 (1.15–1.38)	1.05 (1.03–1.07)	19.5	<0.001
Anxiety*	1.36 (1.24–1.50)	1.21 (1.11–1.33)	1.12 (1.10–1.15)	40.9	<0.001
Physical activity [†]	1.39 (0.97–2.00)	1.39 (0.97–2.00)	1.00 (0.97–1.02)	0.0	0.817
Alcohol dependence [†]	1.36 (0.95–1.94)	1.29 (0.90–1.84)	1.05 (0.95–1.17)	18.2	0.305
Smoking [†]	1.34 (0.93–1.91)	1.33 (0.93–1.91)	1.00 (0.95–1.07)	0.0	0.902
Short sleep [†]	1.35 (0.94–1.93)	1.34 (0.94–1.92)	1.00 (0.98–1.03)	0.0	0.711
Cardiometabolic dysregulations*	1.35 (1.24–1.48)	1.33 (1.21–1.46)	1.02 (1.01–1.03)	7.45	<0.001

N=5610. Analyses control for age and sex. Depression and anxiety symptoms were assessed using General Health Questionnaire subscales, with a depression score range of 0–12 and an anxiety score range of 0–15; physical activity was assessed using the recommended physical activity guidelines according to World Health Organization of at least 2.5 hours of moderate to vigorous physical activity per week; alcohol dependence was assessed using the CAGE questionnaire; current smoking status was assessed by self-report; short sleep was defined by self-reported average sleep duration of <7 hours; cardiometabolic dysregulations reflect the number of dysregulations present. NDE indicates natural direct effect; NIE, natural indirect effect; and OR, odds ratio.

*Continuous mediator variable.

[†]Denotes a binary mediator variable.

Table 4. Sensitivity Analysis: ACEs Modeled as a Binary Variable (0 vs ≥1)

Mediator	Total Effect OR (95% CI)	NDE OR (95% CI)	NIE OR (95% CI)	% Mediated	P Value for NIE
Depression*	1.32 (1.10–1.58)	1.37 (1.14–1.64)	0.97 (0.90–1.04)	12.5	0.325
Anxiety*	1.88 (1.50–2.37)	1.38 (1.14–1.66)	1.37 (1.25–1.50)	57.3	<0.001
Physical activity [†]	1.66 (0.78–3.53)	1.68 (0.79–3.56)	0.99 (0.92–1.07)	2.5	0.810
Alcohol dependence [†]	1.51 (0.71–3.21)	1.49 (0.73–3.03)	1.01 (0.77–1.33)	3.0	0.923
Smoking [†]	1.44 (0.70–2.94)	1.49 (0.72–3.05)	0.97 (0.82–1.14)	10.0	0.686
Short sleep [†]	1.53 (0.73–3.21)	1.50 (0.73–3.07)	1.02 (0.89–1.17)	5.7	0.745
Cardiometabolic dysregulations*	1.55 (1.30–1.86)	1.55 (1.29–1.87)	1.00 (0.99–1.01)	0.0	0.896

N=5610. Analyses control for age and sex. Depression and anxiety symptoms were assessed using General Health Questionnaire subscales, with a depression score range of 0–12 and an anxiety score range of 0–15; physical activity was assessed using the recommended physical activity guidelines according to World Health Organization of at least 2.5 hours of moderate to vigorous physical activity per week; alcohol dependence was assessed using the CAGE questionnaire; current smoking status was assessed by self-report; short sleep was defined by self-reported average sleep duration of <7 hours; cardiometabolic dysregulations reflect the number of dysregulations present. ACEs indicates adverse childhood experiences; NDE, natural direct effect; NIE, natural indirect effect; and OR, odds ratio.

*Continuous mediator variable.

[†]Denotes a binary mediator variable.

mediated the association between ACE category, that is having experienced any ACE, and the risk of CHD (Table 4). Second, to examine potential shared variance among mediators, a series of sensitivity analyses were conducted that included all other mediators as covariates in the model. After all other potential mediators were controlled for, anxiety symptoms and a greater number of cardiometabolic dysregulations remained significant mediators, whereas depression was no longer a significant mediator of the association between ACEs and incident CHD (Table 5). Third, to examine potential overlap with diabetes mellitus, the main analyses were repeated with diabetes mellitus status as an additional covariate. A total of 272 participants had diabetes mellitus (182 participants had missing diabetes mellitus status data). The pattern of results was similar to the results of the main analysis, with depressive symptoms, anxiety symptoms, and cardiometabolic

dysregulations as statistically significant mediators of the association between ACEs and incident CHD. Finally, educational attainment was included as an additional covariate in a subset of participants with complete data on that variable. The interpretation of the main analysis results did not change after adjustment for educational attainment level (NIE of depressive symptoms, 1.06; 95% CI, 1.04–1.08; $P<0.001$; NIE of anxiety symptoms, 1.13; 95% CI, 1.11–1.16; $P<0.001$; NIE of cardiometabolic dysregulations, 1.01; 95% CI, 1.00–1.02; $P=0.03$).

DISCUSSION

The goal of the study was to examine potential psychological, biological, and behavioral pathways linking ACEs with CHD in adulthood in a prospective cohort study of men and women in the United Kingdom. The

Table 5. Sensitivity Analysis: Main Model Controlling for All Other Mediators

Mediator	Total Effect OR (95% CI)	NDE OR (95% CI)	NIE OR (95% CI)	% Mediated	P Value for NIE
Depression*	1.21 (1.10–1.32)	1.20 (1.10–1.32)	1.00 (1.00–1.01)	0.0	0.382
Anxiety*	1.23 (1.12–1.35)	1.19 (1.08–1.30)	1.03 (1.02–1.05)	15.8	<0.001
Physical activity [†]	1.23 (0.85–1.78)	1.24 (0.86–1.80)	0.99 (0.96–1.02)	5.4	0.405
Alcohol dependence [†]	1.17 (0.81–1.68)	1.14 (0.78–1.65)	1.03 (0.96–1.10)	19.6	0.447
Smoking [†]	1.21 (0.84–1.74)	1.21 (0.84–1.75)	1.00 (0.95–1.04)	0.0	0.857
Short sleep [†]	1.19 (0.83–1.72)	1.19 (0.83–1.72)	1.00 (1.00–1.00)	0.0	0.929
Cardiometabolic dysregulations*	1.21 (1.10–1.32)	1.19 (1.09–1.31)	1.01 (1.00–1.02)	5.9	0.003

N=5610. Analyses control for age and sex. Depression and anxiety symptoms were assessed using General Health Questionnaire subscales, with a depression score range of 0–12 and an anxiety score range of 0–15; physical activity was assessed using the recommended physical activity guidelines according to World Health Organization of at least 2.5 hours of moderate to vigorous physical activity per week; alcohol dependence was assessed using the CAGE questionnaire; current smoking status was assessed by self-report; short sleep was defined by self-reported average sleep duration of <7 hours; cardiometabolic dysregulations reflect the number of dysregulations present. NDE indicates natural direct effect; NIE, natural indirect effect; and OR, odds ratio.

*Continuous mediator variable.

[†]Denotes a binary mediator variable.

results provide preliminary evidence of a mediating role of depression and anxiety symptoms and cardiometabolic dysregulations in the association between ACEs and CHD in adulthood. Overall, we found that psychological factors were the strongest mediators of the association between ACEs and incident CHD in adulthood, as they explained the largest proportion of the association. Cardiometabolic dysregulations also explained a significant proportion of the association between ACEs and CHD, which was examined as a summary score of number of dysregulations present including C-reactive protein and components of the metabolic syndrome (high triglycerides, high high-density lipoprotein cholesterol, high glucose, hypertension, and high waist circumference). Of those, high C-reactive protein and high waist circumference were the strongest mediators when examined separately. We hypothesized that health behaviors would partially mediate the association between ACEs and CHD, but no health behaviors were found to statistically mediate this association.

Our findings are consistent with previous studies reporting an association between ACEs and CHD.⁷ Depression and anxiety symptoms follow the theoretical ordering framework necessary for mediation, given that ACEs are linked with the incidence of depression and anxiety,^{11,12} and these, in turn, are risk factors for cardiac conditions such as CHD.¹³ Anxiety symptoms explained the highest proportion of mediation, accounting for $\approx 41\%$ of the association between ACEs and CHD. Although anxiety in adulthood is a well-established consequence of ACEs,¹² the association between anxiety and incidence of CHD has been mixed.^{15,55} High anxiety was also the most consistent mediator demonstrated by sensitivity analyses. Given that depressive symptoms and cardiometabolic dysregulations were significant mediators when ACEs were modeled as a continuous variable, these factors may be more related to the cumulative experience of ACEs, rather than the experience of any one particular ACE.⁸

Our finding that adult health behaviors did not mediate the association between ACEs and adulthood CHD is consistent with results of a recent study demonstrating that health behaviors in adulthood do not mediate the association between a favorable childhood environment and cardiac health in adulthood.⁵⁶ We did, however, find that $\approx 18\%$ of the association was mediated by alcohol dependence, though this was not statistically significant. Interestingly, this proportion was higher than that of cardiometabolic dysregulations, a statistically significant mediator, which may have been attributable to the small number of participants reporting alcohol dependence. This may have also reflected the lack of significant association between alcohol dependence and CHD in our data. A recent review⁵⁷

suggests that ACEs can alter the neural circuitry that underlies cognitive control and emotional reactivity, and such changes are associated with changes in neural responsivity to rewards, poorer emotion regulation, and low self-control, which can increase the likelihood of health-risk behaviors such as alcohol abuse. A continuous assessment of alcohol consumption in future research may yield a more powerful analysis and may shed further light on the nuances of these associations. Future research is needed to examine the potential mediating role of alcohol use frequency and alcohol abuse in the association between ACEs and CHD.

There are also many potential additional intermediate pathways linking ACEs with depression, anxiety, and cardiometabolic dysregulations. For instance, ACEs might cause prolonged stress activation, leading to depression and anxiety and producing an allostatic load, which in turn might increase susceptibility to CHD.^{58,59} It has been posited that stressors such as ACEs that occur during sensitive developmental periods, such as during childhood and adolescence, could induce important biological changes that might exert long-term consequences for health.⁶⁰ Though some of these biological responses to childhood stress may be adaptive in the short term,⁶¹ in keeping with a biological embedding of an ACE conceptual model,^{26,27} the long-term and cumulative impact of several ACEs may lead to chronic dysregulations in allostatic systems such as endocrine, metabolic, immune, and nervous systems, producing a greater physiological “wear and tear,” which in turn can impact mental and physical health.⁶¹ This study further highlights the negative long-term impact of ACEs and a need for increased efforts at reducing exposure to ACEs in pediatric populations and related upstream risk factors.¹⁰ However, evidence also suggests that the effect of early life stress on adulthood health conditions operates via indirect effects through adulthood exposures,⁶² and therefore it is also necessary to identify potential modifiable targets for intervention throughout the life course, following exposure to ACEs. The present study provides preliminary evidence of such potential intervening variables, which should be further examined in subsequent research.

Strengths and Limitations

To our knowledge, this is the first study to directly test multiple potential mediators of the association between ACEs and CHD in adulthood with a prospective cohort study. Strengths of the present study included the use of a well-established large prospective cohort without prevalence of CHD at the time of the assessment of the potential mediating variables. In addition, the present study employed a multidimensional approach to examining potential pathways linking ACEs with CHD

in adulthood by examining the roles of psychological, behavioral, and biological factors.

There are also important limitations. The Whitehall cohort study sample is not a representative population-based sample. It consists of working-age adults at baseline and is predominantly men (~70%) and White race/ethnicity (~90%). This sample therefore limits generalizability to older adults, women, and other races/ethnicities. The lack of ethnic diversity may have also influenced the relative low exposure to some of the ACEs in our sample. Future research with more diverse populations is needed. Socioeconomic status may be an important confounder in the association between ACEs, potential mediators, and CHD. In the present study, we did not account for socioeconomic status because of limits with sample size for complete data. However, including highest educational attainment as an additional covariate in a smaller data set with complete data on education did not alter the pattern of results obtained. In addition, assessments of depression and anxiety symptoms were limited to symptoms experienced over the past week, which may have reflected transient experiences in response to exceptional circumstances rather than underlying mental disorders. The mean depression and anxiety symptom scores were relatively low, which might limit the generalizability of the findings. No detailed assessments of depression and anxiety symptoms and history or detailed assessment of ACEs were available. Assessments of other important and severe ACEs, such as sexual and emotional abuse and witnessing intimate partner violence, were not included in the survey. Similarly, in our mediation analyses, we set the exposure level of the counterfactual to 4, given that this cutoff is often used in the literature. However, we did not assess all ACEs that are often used with this cutoff (eg, sexual abuse was not included). In addition, other potential mediating variables were not included in these models but may represent important pathways linking ACEs with adulthood cardiovascular health, such as cortisol and other stress biomarkers,⁶³ physiological markers of autonomic nervous system functioning such as heart rate variability, or psychological resilience factors, which have recently been reviewed and proposed as potential pathways.⁶⁴ Long sleep duration may also be an important mediator, but we were not able to examine long sleep duration in the present study because of the small proportion of the sample reporting long sleep (≥ 9 hours).

Another study limitation is that the exposure (ACEs) and the mediators were measured at the same time point. Mediation occurs when there is a temporal trajectory linking these variables, and although these variables theoretically follow a temporal trajectory (ie, ACEs, mediators, incidence of CHD), ACEs were retrospectively reported at the same time point as the

assessment of the mediators. VanderWeele⁴⁹ suggests that the most effective way to ensure temporal ordering is to use at least 3 waves of data, with the exposure assessed at wave 1, the mediator at wave 2, and the outcome at wave 3. In the present study, the exposure and mediators were assessed at the same wave. However, there is a strong theoretical temporal trajectory between the ACEs retrospectively assessed and the mediators measured in adulthood. In addition, incidence of CHD was examined after the assessment of the mediators. Nonetheless, we cannot preclude that some of the mediators, particularly depression and anxiety, might have impacted how participants responded to the retrospective ACE assessment questions.

In addition, the measure of depressive symptoms used in the present study assessed only cognitive items related to depression. It is possible that the somatic symptoms of depression, such as sleep and appetite changes, are stronger mediators of the association between ACEs and CHD, but further research is needed. Finally, definitions of ACEs and retrospective measures for the assessment of ACEs vary widely, and research on ACEs could benefit greatly from a unified measure of ACEs. In addition to addressing the present study limitations, future research on the long-term health impact of ACEs could also consider the inclusion of factors occurring outside the home such as experiencing racism or bullying or living in an unsafe neighborhood.⁶⁵ Protective or resilience factors should also be examined in future longitudinal studies on the association between ACEs and CHD.

CONCLUSIONS

In this prospective cohort study of 5610 adults originally recruited as British civil service employees, we found that depression, anxiety, and cardiometabolic dysregulations partially mediated the association between retrospectively reported adverse experiences during childhood and the likelihood of developing CHD in adulthood. Alcohol dependence may be an additional important mediator of this association, though more research is needed. Other health behaviors, including physical activity, smoking, and short sleep duration, did not mediate the association between ACEs and CHD in this study. This study helps to fill a gap in the literature with prospective research testing the potential mental health pathways linking ACEs with cardiometabolic outcomes.¹⁰ These findings suggest that mental health screening and monitoring of cardiometabolic dysregulations could be beneficial for those who have been exposed to ACEs and may potentially help reduce the long-term health burden of ACEs.

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Disclosures

None.

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