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Associations between adverse childhood experiences and vascular indicators of atherosclerosis measured in childhood and early to mid-adulthood: A systematic review

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ABSTRACT

Objectives: Adverse childhood experiences are associated with impaired vascular function and cardiovascular disease incidence and mortality, but mechanisms remain unclear. This systematic review assessed associations between adverse childhood experiences and vascular indicators of subclinical atherosclerosis, including the effects of mediating or moderating variables.

Methods: Searches were conducted through May 2024. Cross-sectional and longitudinal studies from childhood through adulthood, reporting cumulative measurement of ≥5 adverse childhood experiences exposures, and outcomes including ≥1 vascular indicators of subclinical atherosclerosis were included. The review was reported using Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.

Results: 3338 articles were identified, with 10 meeting the inclusion criteria (total participants = 4784). Five studies were longitudinal, four were cross-sectional, and one used pilot intervention baseline data. All 10 studies used retrospective adverse childhood experiences measurement. The strongest evidence was between adverse childhood experiences and arterial stiffness, with 5/8 studies showing positive associations. Positive associations between adverse childhood experiences and atherosclerotic progression (2/3 studies), and negative associations with endothelial function (2/2 studies) were identified, although quantity of evidence was small. Mediating and moderating variables were heterogeneous among studies, with only 5 measuring the effects of variables in isolation and limiting our ability to make inferences about their effects.

Conclusions: Findings support associations between adverse childhood experiences and subclinical atherosclerotic progression, but evidence lacks quantity and quality. Prospective evidence identifying vascular changes associated with adverse childhood experiences, including analysis of mediating and moderating variables, is required to better understand the mechanisms underpinning associated risk of cardiovascular disease.

1. Introduction

Adverse childhood experiences (ACEs) include exposures to abuse, household challenges and neglect (Felitti et al., 1998). Meta-analyses have shown a pooled prevalence of >23 % of individuals with one ACE in Europe and North America, with 18.7 % having ≥2 ACEs in Europe and 35 % with ≥2 ACEs in North America (Bellis et al., 2019). Further, ACE attributable costs are estimated at around €498 billion in Europe and $748 billion in North America annually (Bellis et al., 2019). ACEs are associated with substantial societal costs (Hughes et al., 2021), and the relationships between ACE exposures and the development of cardiovascular disease contribute markedly towards these impacts. Prospective longitudinal studies have shown that high levels of ACE exposure are associated with ~10–18 more cases of cardiovascular disease per 100,000 individuals in early adulthood compared with low ACE exposure (Bengtsson et al., 2023). Moreover, cardiovascular disease

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is the leading cause of disease burden globally, particularly ischemic heart disease, which alone accounted for an age-standardised rate of 108.8 deaths per 100,000, and global disability-adjusted life years of 2276 per 100,000 (Mensah et al., 2023).

Existing research has identified that the pathways linking ACEs to cardiovascular disease in adulthood are both varied and complex, involving an array of plausible mechanisms (Su et al., 2015). Review and meta-analytical evidence support the associations between ACEs and traditional cardiovascular disease risk factors, such as obesity, insulin resistance and hypertension (Galobardes et al., 2006; Hughes et al., 2017; Tan et al., 2024). These traditional cardiovascular disease risk factors, used in prediction models such as the Framingham Risk Score (Kannel et al., 1961), are thought to contribute to cardiovascular disease development by accelerating the process of atherosclerosis involved in the pathogenesis of cardiovascular disease (Frostegård, 2013). However, such measures have limited utility in children where cardiovascular disease is not yet clinically apparent, but alternatively, subclinical atherosclerosis can be measured using numerous vascular outcomes which are more closely associated with the development of cardiovascular disease (Balagopal et al., 2011; Urbina et al., 2009). This is important, as vascular changes may provide earlier indicators of cardiovascular disease risk, detectable at younger ages in the general population, and have been recommended in an existing scientific statement from the American Heart Association (Urbina et al., 2009).

Observational evidence has illustrated that adverse childhood experiences may be related to vascular outcomes. For example, positive associations have been found with carotid intima-media thickness (Loucks et al., 2014), which measures arterial structure, and when increased, may indicate an increased rate of atherosclerotic progression (Stein et al., 2008). ACEs have also been positively associated with arterial stiffness in adolescents (Kellum et al., 2023), suggesting changes in arterial structure and function indicative of impaired vascular elasticity, and reduced ability to respond to fluctuations in blood volume (Urbina et al., 2009). ACEs have also been associated with impaired microvascular function in young adults (Rodriguez-Miguelez et al., 2022), and cross-sectional evidence suggests that higher arterial stiffness can be related to reduced microvascular function and elevated cardiovascular disease risk (Mitchell et al., 2005). Yet, empirical evidence linking ACEs with vascular measures of subclinical atherosclerosis is lacking. This highlights a clear need for further research to clarify these associations using both longitudinal and cross-sectional designs (Suglia et al., 2018).

Providing a more in-depth insight into the relationships between ACEs and vascular outcomes, a scientific statement from the American Heart Association highlighted the potential influences of key mediators, including health risk behaviours, mental health, or substance use (Suglia et al., 2018). At a biological level, biomarkers related to inflammation and oxidative stress such as Interleukin-6 and C-Reactive Protein have also been linked with ACE exposure, and have been proposed as important indicators of processes involved with atherosclerotic progression and development of cardiovascular disease (Balagopal et al., 2011). Suglia and colleagues also state that relationships between ACEs and cardiovascular disease risk may be further altered through moderators including socioeconomic status (SES), ethnicity/race, sex, and dose or age at exposure to ACEs (Suglia et al., 2018). Investigating these factors is crucial for identifying groups of individuals who may be most vulnerable to suffering negative health consequences (Suglia et al., 2018). However, existing research focused on these potential mediating and moderating factors has tended to concentrate on traditional cardiovascular disease risk factors (Campbell et al., 2016), or an overall cardiovascular disease clustered risk score (Doom et al., 2017), with limited investigation of vascular measures of subclinical atherosclerosis. Moreover, numerous studies included in existing reviews employed retrospective methods for the assessment of ACEs, introducing biases such as through recall and social desirability, and potentially weakened associations between ACEs and outcomes (Appleton et al., 2017; Doom et al., 2020). Consequently, an updated review incorporating more recent prospective longitudinal evidence is needed.

Although evidence on the associations between ACEs and vascular indicators of subclinical atherosclerosis is limited, no systematic synthesis of the available literature exists. This is important, given that vascular changes involved in the atherosclerotic process could be detected earlier than traditional cardiovascular disease risk factors, which could aid in the evaluation of cardiovascular disease risk in ACE-exposed children and adolescents (Balagopal et al., 2011). To address this gap, we conducted a systematic review of the evidence pertaining to the relationships between ACEs and vascular indicators of atherosclerosis, including any potential mediators and moderators of these associations. Our primary aim was to investigate the associations between ACEs and vascular outcomes related to cardiovascular disease risk in childhood, adolescence and adulthood. Secondary aims investigated whether the relationships between ACEs and vascular outcomes are influenced by potential mediating and moderating variables.

2. Methods

The review was pre-registered on PROSPERO (CRD42024547235) and followed the 2020 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) reporting guidelines (Page et al., 2021). A completed PRISMA checklist is provided in the Supplementary Materials (Table S1).

2.1. Search strategy

A systematic literature search was carried out through May 2024 to identify relevant studies from six electronic databases, including EMBASE, Ovid MEDLINE, Scopus, APA PsycINFO, Web of Science, and CINAHL Ultimate. Full search strategies are provided in Supplementary Materials (Table S2).

Database searches included title/abstract search terms using keywords related to cardiovascular disease risk factors, such as hypertension, type 2 diabetes, triglycerides, cholesterol, vascular indicators of atherosclerosis (i.e. pulse wave velocity and carotid intima-media thickness), and childhood adversity. Each related set of terms was added to separate lines and combined using the 'OR' operator. Proximity searching was used to precisely locate articles using terms near to each other, such as ("heart disease" adj5 "risk factor"). Subject headings were identified for each main search term where possible, i.e. "cardiovascular risk/", and "childhood adversity/". Subject headings were exploded to include references indexed to related search terms, whilst the focus function was used to improve search precision if large numbers of irrelevant articles were found. The 'OR' operator was also used to combine searches using subject headings with keywords. Finally, the 'AND' operator was used to combine all completed searches for cardiovascular disease risk factors and ACEs.

All articles were exported into Endnote 21 (Clarivate Analytics, Philadelphia, PA, USA) for automated removal of duplicates. The remaining articles were exported into Rayyan (Ouzzani et al., 2016), where manual removal of any potential remaining duplicate articles took place before screening.

2.2. Inclusion & exclusion criteria

Inclusion and exclusion criteria were formed around the PECO (participants, exposures, comparisons, and outcomes) framework. There was no restriction on participant demographics for inclusion in the review, however non-human and in-utero studies were excluded. Articles must have included cumulative measurement of exposure $\geq$5 ACEs, as described within the ACEs study (Felitti et al., 1998) (Table 1). This was decided as the minimum number to consistently include studies which had measured more than one ACE construct (i.e., not only abuse), without excessively limiting studies by choosing a higher threshold.

Table 1
Categories and definitions of ACEs, based upon the Center for Youth Wellness ACE Questionnaire (Burke Harris and Renschler, 2015) and adapted from the ACE study (Felitti et al., 1998).

Category		Definition
Abuse	*Emotional abuse*	Household member swore at, insulted, humiliated, or put down child in a way that scared child or household member acted in a way that made child afraid that she/he might be physically hurt
	Physical abuse	Someone pushed, grabbed, slapped or threw something at child or child was hit so hard that she/he was injured or had marks
	Sexual abuse	Someone touched child's private parts or asked child to touch that person's private parts in a sexual way that was unwanted, against child's will, or made child feel uncomfortable
Household Challenges	*Parental violence*	Child saw or heard household members hurt or threaten to hurt each other
	Household substance abuse	Household member had a problem with drinking or using drugs
	Household mental illness	Household member was depressed, mentally ill, or attempted suicide
	Parental separation	Child's parents or guardians were separated or divorced
	Parental incarceration	Household member served time in jail or prison
Neglect	*Emotional neglect*	Child often felt unsupported, unloved and/or unprotected
	Physical neglect	More than once, child went without food, clothing, a place to live, or had no one to protect her/him

Exposure measurement included prospective or retrospective measurement. For studies including a clinical population, a comparator/control group was required for inclusion. The inclusion of a control group enabled the isolated effect of ACE exposure upon vascular health outcomes to be measured, without being confounded by potential influences of underlying clinical conditions. For the synthesis of findings across included studies, only data from the control groups were examined in the current review.

Initially, required outcomes for study inclusion were the measurement of $\geq$1 biological cardiovascular disease risk factor in childhood or adulthood, including hypertension, type 2 diabetes, insulin, blood glucose, triglycerides or cholesterol; and vascular measures such as carotid intima-media thickness arterial distensibility or pulse wave velocity. To enable a more focused approach to the review, these broad inclusion criteria were later narrowed down to only include studies with vascular measures of subclinical atherosclerosis, therefore deviating from the initial protocol (Fig. 1).

Included study designs were observational cohort studies; case-control studies from childhood through to adolescence or adulthood; or cross-sectional studies. Finally, studies were excluded if full texts were not available; articles not available in English; or were unsuitable publication types such as review articles, opinion articles or other comments, abstracts, editorials, conference proceedings or PhD theses. Backwards and forwards citation searching was carried out on included studies, by searching reference lists or identifying any relevant more recent works which have since cited the study via library search tools.

2.3. Study selection

Title and abstracts of articles identified through database searches were screened by two individual reviewers (LM, AVAM) who were blinded to each other's decisions. Conflicts were resolved by a third reviewer (AB). All retained articles from title/abstract screening were screened using full text, if available, according to the above criteria, which was carried out independently by the same two reviewers (LM, AVAM).

2.4. Data extraction

The final selection of studies determined to be eligible for inclusion in the review were exported to Endnote for ease of data extraction. Extracted data was carried out by one reviewer (LM), and results were recorded in Microsoft Excel. Extracted data included the following: Aspects related to identifying the source, such as citation and contact details if required for confirmation of study details; study aims, design, and setting; recruitment, inclusion/exclusion criteria and sample size; participant characteristics; analytical and statistical methods; details of ACE exposures and measurement methods; details of vascular outcome and measurement methods; relevant secondary outcomes; main results and key conclusions, and finally relevant comments from authors/reviewers. Any studies with missing data were noted as 'not reported' within the relevant area.

2.5. Risk of bias assessment

Risk of bias assessment was carried out manually by a single reviewer (LM) using the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NIH, 2014). This tool was selected as it is suitable specifically for cross-sectional and cohort study types included within this review, using 14 criteria (Table 2), developed by a team of methodologists from National Heart, Lung, and Blood Institute and Research Triangle Institute International, which were deemed to provide an appropriate assessment of the internal validity.

For each question, a 'yes', 'no', 'cannot determine', 'not reported' or 'not applicable' response was provided. Questions 7 and 13 were not considered for cross-sectional studies, as these criteria do not apply to this study design. It was necessary to decide upon specific conditions when applying risk of bias criteria within the context of the present review, to ensure internal consistency of study ratings. For question 8, only studies which included $\geq$2 levels of exposure (e.g. ACEs as a continuous variable) were sufficient for 'yes'. For question 9, retrospective studies were only considered sufficient to receive 'yes' if the authors reported statistical evidence supporting the validity and reliability of ACE measurement method for a similar recall period. For example, the study may report metrics such as test-retest reliability (e.g. intraclass correlation coefficients [ICC] or Cohen's kappa), internal consistency of retrospective measurement methods (e.g. Cronbach's alpha $\geq$0.70) or convergent validity with external proxies by correlational evidence. Finally, for question 14, key confounding variables included, at a minimum, age and sex (unless only one sex was studied). The exception to this was studies that used *a priori* analysis of variables which were independently associated with the outcome, to decide on included covariates.

An overall rating of 'good', 'fair' or 'poor' was determined for each study using critical appraisal of the risk of bias (NIH, 2014). Criteria which were particularly important when deciding upon overall ratings were 4, 7, 8, 9, and 14 (see Table 2) as these were considered of greatest relevance to our study aims. This process did not only involve considering the number of areas highlighted at risk of bias, but also the severity of this risk, and the importance of the criteria as discussed above.

2.6. Synthesis of results

Due to heterogeneity within the measurement of ACE exposures and differences in effect measures between studies, it was deemed inappropriate to carry out any meta-analyses. Specifically, studies varied in the types of effect measures reported, the covariates included in adjusted models, and whether results were presented as unadjusted or adjusted associations. Additionally, there was considerable heterogeneity in how ACE exposure was assessed, with some studies treating ACEs as a continuous variable, and others using dichotomous (i.e. any ACEs vs. none) or categorical groupings (i.e. low, moderate or high exposure).

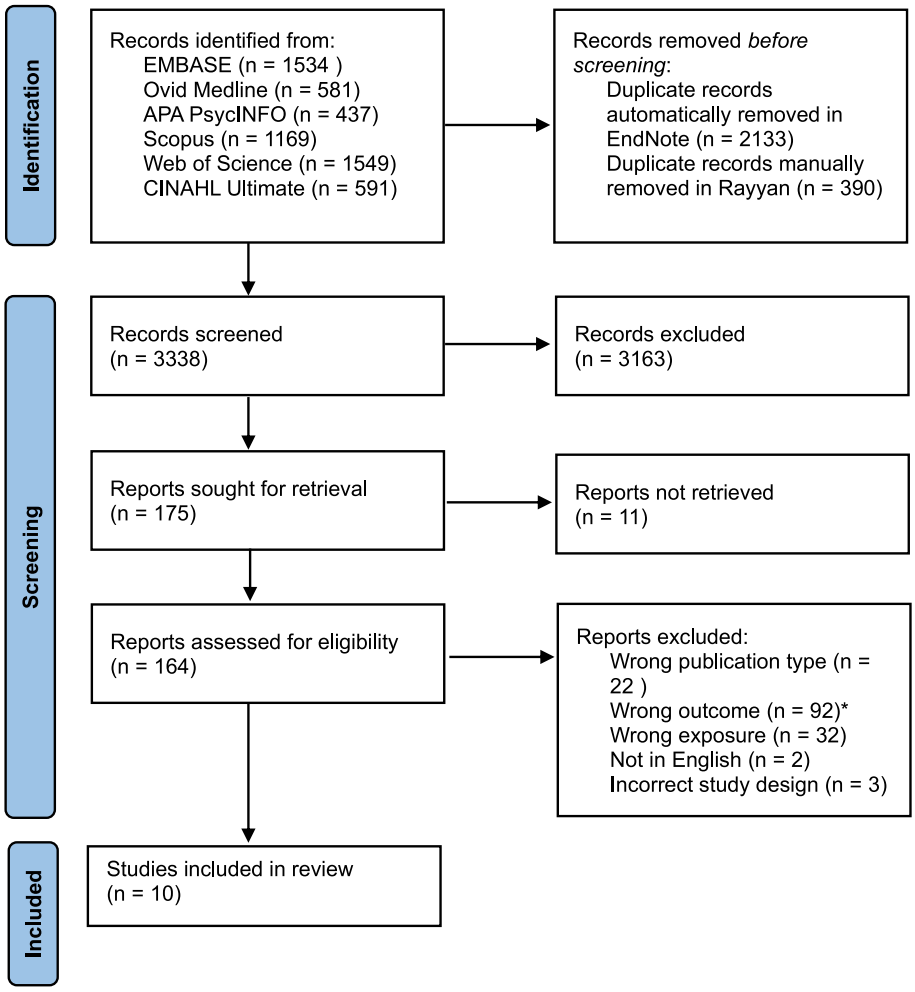

Fig. 1. PRISMA flow diagram demonstrating the study selection process for inclusion in the systematic review. *43 of these studies were excluded latterly following amendments to the focus of the review (see "inclusion & exclusion criteria").

Table 2
List of criteria within the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

#	Criteria
1	Was the research question or objective in this paper clearly stated?
2	Was the study population clearly specified and defined?
3	Was the participation rate of eligible persons at least 50 %?
4	Were all the subjects selected or recruited from the same or similar populations? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5	Was a sample size justification, power description, or variance and effect estimates provided?
6	Were the exposure(s) of interest measured prior to the outcome(s) being measured?
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8	Did the study examine different levels of the exposure as related to the outcome?
9	Were the exposure measures clearly defined, valid, reliable, and implemented consistently across all study participants?
10	Was the exposure(s) assessed more than once over time?
11	Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?
12	Were the outcome assessors blinded to the exposure status of participants?
13	Was loss to follow-up after baseline 20 % or less?
14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

The variations in both statistical approaches and classification of exposures precludes the calculation of valid and interpretable summary estimates from a meta-analysis. However, the SWiM method (Synthesis Without Meta-analysis) (Campbell et al., 2020) checklist was employed to provide a narrative synthesis of results following best practice. Where possible, alternative synthesis methods were carried out using vote counting based on direction of effect. This assists in providing information on the range and distribution of observed effects as well as evidence of an effect within one study and overall (McKenzie and Brennan, 2019). Synthesis of results are discussed according to the type of vascular outcome, assessing differences dependent on the level of ACE exposure (categorical or cumulative). Discussion of studies also includes assessment of the effects of potential mediating and moderating variables.

3. Results

Full results of the search and selection process are illustrated in Fig. 1. The full search produced 5861 studies in total. Following removal of duplicates, 3338 studies remained, and 175 studies were chosen for full-text analysis. 10 studies were identified which aligned with the inclusion criteria.

In terms of location and participant characteristics, six studies took place in the USA (Carson et al., 2022; Jenkins et al., 2021; Kellum et al., 2023; Rodriguez-Miguelez et al., 2022; Su et al., 2014; Thurston et al., 2017), two were based in Canada (Iannarelli et al., 2022; Rafiq et al.,

2020) and a single study was from Turkey (Kani et al., 2023) and the UK (Anderson et al., 2018). Sample sizes for the included studies ranged from 42 (Jenkins et al., 2021) to 3612 (Anderson et al., 2018) (median, $n = 119$). Only one study included an adolescent population (<18 years), four included a young adult population (18–29 years) and five included an older adult population (Table 3). Additionally, four studies only recruited women (Anderson et al., 2018; Carson et al., 2022; Jenkins et al., 2021; Thurston et al., 2017).

We identified various study designs, including five longitudinal studies, four cross-sectional and one pilot intervention trial with baseline data being used within this review (Jenkins et al., 2021) (Table 3). All 10 studies employed retrospective, self-report questionnaire methods to measure ACEs. Questionnaire structure and content varied, with four papers using the ACE Questionnaire, three using the Child Trauma Questionnaire and two using the Childhood Trust Events Survey (Table 3). One study did not clarify a specific questionnaire measure (Anderson et al., 2018). Eight studies assessed arterial stiffness whilst two studies measured endothelial function, three measured indicators of atherosclerosis and one study also provided a measure of vascular resistance, with several studies addressing multiple outcomes (Table 3).

3.1. Bias assessment

Results from the risk of bias assessment are presented in Fig. 2. Out of 10 studies, 9 provided clear descriptions of their aims, objectives and study populations. Participants were selected from similar populations, with clear inclusion criteria applied within seven studies. However, reporting of participation rates was poor, with only three studies providing this statistic within their text (Anderson et al., 2018; Kellum et al., 2023; Su et al., 2014). Similarly, only three studies provided a sample size justification or power calculation (Iannarelli et al., 2022; Kellum et al., 2023; Rodriguez-Miguelez et al., 2022), thus, it is uncertain whether the remaining studies may lack power due to an inadequate sample size.

All five longitudinal studies reported losses of participants at follow-up, with attrition of >20 %, increasing their risk of bias. In terms of exposure measurement, areas that posed the greatest risk of bias resulted from studies employing questionnaires which had been adapted and not validated (Anderson et al., 2018; Rafiq et al., 2020; Su et al., 2014). Furthermore, all studies may suffer from increased bias due to retrospective recall of ACEs. Seven of the included studies provided measures of multiple levels of exposure, however, a particular pitfall was that none provided evidence of having assessed ACEs more than once during their participants' lifetime.

Validity and reliability of outcome measures were generally good, with all nine studies achieving 'yes' for this criterion. One study (Kellum et al., 2023) was considered at risk of bias for this criterion as their measure of blood pressure was only clinic or ambulatory measurement, with clinic measurements being unfamiliarised and at greater risk of being elevated, and additionally potential confounders of ambulatory blood pressure, such as physical activity were not considered. Conversely, only one study (Kani et al., 2023) reported that the outcome assessor was blinded to the status of the participant. Finally, a drawback of several studies was a lack of measurement of key confounding variables, with two not reporting any measurement of these variables whatsoever (Kani et al., 2023; Rodriguez-Miguelez et al., 2022) and one failing to consider the effects of age (Kellum et al., 2023). Overall, three studies were of 'good' overall quality, five were rated as 'fair' and two studies rated as poor.

3.2. Primary outcomes

3.2.1. Arterial stiffness

Arterial stiffness was the most reported vascular outcome, with eight studies including this measurement. Overall, the evidence suggests a positive association between ACE exposure and increases in arterial stiffness, with some inconsistencies.

Five studies measured carotid-femoral pulse wave velocity, one measured radial pulse wave velocity and one identified brachial pulse wave velocity (Table 3), which provides a measure of the velocity that the blood pressure pulse moves along the arteries. Three of these studies also included a measure of augmentation index, which is derived from pulse wave velocity; in both cases, higher values indicate greater arterial stiffness. Two studies included a measurement of arterial distensibility, the reciprocal of stiffness, indicating the ability of the artery to respond to changes in pressure (Table 3). Five out of the seven studies measuring pulse wave velocity demonstrated a higher pulse wave velocity in participants exposed to ACEs compared to unexposed controls, supporting a positive association between ACE exposure and pulse wave velocity. Two studies found no evidence of exposed vs. unexposed group differences (Kani et al., 2023; Kellum et al., 2023).

There were contrasting findings between the three studies assessing augmentation index. Kellum et al. (2023) reported a positive association of ACE exposure with augmentation index, which remained following adjustment for sex and body mass index. Rodriguez-Miguelez et al. (2022) also found higher augmentation index in ACE-exposed individuals in comparison with controls, with a large effect size (Table 4). Conversely, Kani et al. (2023) did not find evidence of associations between augmentation index and ACE exposure. Finally, there were also varied findings when assessing arterial distensibility. Anderson et al. (2018) found negative associations between cumulative adversity score and arterial distensibility. In contrast, Rafiq et al. (2020) found no evidence of relationships between the ACEs group (≥4 ACEs) and arterial distensibility, despite showing positive relationships between ACEs and pulse wave velocity.

3.2.2. Endothelial function

Endothelial function was assessed in only two studies, using flow-mediated dilation. Both studies reported flow-mediated dilation to be lower in ACE-exposed participants in comparison with controls (Jenkins et al., 2021; Rodriguez-Miguelez et al., 2022). Additionally, Rodriguez-Miguelez show large effect sizes for these differences (Rodriguez-Miguelez et al., 2022). Only Jenkins et al. (2021) assessed the impact of covariates, including age, blood pressure, body mass index, and depression/anxiety, finding that these variables did not have any effect on differences in flow-mediated dilation between ACE-exposed vs. unexposed groups (Table 4).

3.2.3. Vascular structure & vascular resistance

Evidence on changes in vascular structure and resistance was limited and showed mixed findings. Whilst some studies reported increases in vascular resistance and carotid intima-media thickness related to higher levels of ACE exposure, some studies demonstrated no associations.

Three studies used measurement of carotid intima-media thickness to indicate changes in vascular structure related to atherosclerotic progression. Two studies identified that individuals exposed to ACEs showed higher carotid intima-media thickness (Rafiq et al., 2020; Thurston et al., 2017), but it should be noted that the level of comparison differed between these studies. Both represented ACE exposure dichotomously, did not carry out linear regression analysis with ACEs as a continuous variable, and did not describe the average ACE exposures in each group. Rafiq and colleagues (2020) compared groups of <4 versus ≥4 ACE exposures, whilst Thurston et al. (2017) examined differences between ACE-exposed (≥1) and control (unexposed) individuals, and mean differences in carotid intima-media thickness between groups corresponded to small effect sizes. Meanwhile, Anderson et al. (2017) found no associations between continuous measures of adversity exposures and carotid intima-media thickness within their sample of middle-aged women. Lastly, one study measured vascular resistance using Total Peripheral Resistance (Su et al., 2014), with the authors finding an increasingly higher total peripheral resistance index in groups exposed to 1 or 2+ ACEs respectively, and this was only

Table 3
Key characteristics of the 10 studies included in the review assessing childhood adversity and vascular health outcomes, grouped by overall quality rating from risk of bias assessment and arranged thereafter by study author.

First Author (Year, Setting)	Design	Sample Characteristics	Mean Age (years), mean (SD)	Sample Size	Adversity Measures (Method)	Primary Outcomes	Secondary Outcomes
'Good' Quality Rating							
Anderson et al. (2018), UK	Longitudinal (retrospective ACE measure)	ALSPAC Prospective Birth Cohort Study; women recruited at pregnancy and followed up in mid-adulthood; 98.2 % white	48.1 (4.4)	3612	Maternal lack of care, maternal overprotection, parental mental illness, household dysfunction, sexual abuse, and non-sexual abuse including physical and emotional abuse or neglect (Questionnaire not identified, retrospective self-report)	Carotid intima-media thickness, arterial distensibility	C-Reactive Protein, smoking status
Carson et al. (2022), USA	Longitudinal (retrospective exposure measure)	Healthy late perimenopausal and postmenopausal non-smoking women; mostly white	ACE + group = 58.1 (4.6) ACE- group = 59.4 (3.8)	162	Sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect (Child Trauma Questionnaire, retrospective self-report)	Carotid-femoral pulse wave velocity	Current alcohol use, leisure time physical activity, depression
Thurston et al. (2017), USA	Cross-sectional	MsHeart Cohort Study; healthy late perimenopausal and postmenopausal non-smoking women aged 40–60 years, 77.91 % white (ACE + group); 65.15 % white (ACE- group); 15.34 % black (ACE + group); 30.30 % black (ACE- group)	ACE + group = 54.3 (3.9) ACE- group = 53.7 (4.1)	295	Sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect (Child Trauma Questionnaire, retrospective self-report)	Carotid intima-media thickness	Sleep time/ efficiency, C-Reactive Protein
'Fair' Quality Rating							
Iannarelli et al. (2022), Canada	Longitudinal (retrospective exposure measure)	Niagara Longitudinal Heart Study; healthy school-based sample followed up into young adulthood; 55.1 % female	22.5 (0.1)	185	Sexual abuse, physical abuse, emotional abuse, neglect, household dysfunction (Childhood Trust Events Survey, retrospective self-report)	Carotid-femoral pulse wave velocity	Physical activity level, smoking status, C-Reactive Protein, telomere length, mitochondrial DNA copy number
Jenkins et al. (2021), USA	Pilot Clinical Trial (Baseline data used within present review)	Healthy females between 18 and 29 years, reporting 0 or $\geq$ 4 ACE; 82 % white (ACE + group); 71 % white (ACE- group)	ACE + group = 20.8 (3.0) ACE- group = 20.6 (3.0)	42	Sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect, household dysfunction (ACE Questionnaire, MACE Questionnaire, retrospective self-report)	Brachial artery flow-mediated dilation	Depression and anxiety, Sirtuin-1
Kani et al. (2023), Turkey	Cross-sectional	Adults between 18 and 65 years including patients recruited from hospital psychiatry outpatient clinic, and a group of healthy controls; 87 % female (patients); 69 % female (controls)	Patient group = 37.9 (10.3) Control group = 37.7 (10.3)	70	Sexual abuse, physical abuse, emotional abuse, physical neglect, emotional neglect (Turkish version of the Childhood Trauma Questionnaire, retrospective self-report)	Brachial pulse wave velocity, augmentation index	Mental health status (depression and anxiety)
Kellum et al. (2023), USA	Cross-sectional, Pilot study for ACEs intervention study	ESTaBLISH Pilot Study; healthy adolescents 11–18 years; 48 % female (ACE- group), 51 % female (ACE- group); 41 % white (ACE + group), 31 % white (ACE- group)	ACE + group = 15 (13–18)[a] ACE- group = 16 (13–18)[a]	76	Sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect, household dysfunction (ACE Questionnaire, retrospective self-report)	Carotid-femoral pulse wave velocity, augmentation index	N/A
Rafiq et al. (2020), Canada	Longitudinal (retrospective exposure measure)	Niagara Longitudinal Heart Study: healthy school-based sample followed up into young adulthood (18+ years); 57.9 % female	21.0 (1.0)	76	Sexual abuse, physical abuse, emotional abuse, neglect, household dysfunction (Childhood Trust Events Survey, retrospective self-report)	Carotid intima-media thickness, arterial distensibility, arterial compliance, carotid-femoral pulse wave velocity	N/A
'Poor' Quality Rating							

(*continued on next page*)

Table 3 (*continued*)

First Author (Year, Setting)	Design	Sample Characteristics	Mean Age (years), mean (SD)	Sample Size	Adversity Measures (Method)	Primary Outcomes	Secondary Outcomes
Rodriguez-Miguelez et al. (2022), USA	Cross-sectional	Healthy adults; 36 % female (ACE group); 57 % female (controls); 9 Caucasian, 13 African American (ACE group); 11 Caucasian, 12 African American (controls).	ACE group = 34.0 (3.0) Controls = 31.0 (5.0)	45	Sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect, household dysfunction (ACE questionnaire, retrospective self-report)	Brachial artery flow-mediated dilation, carotid-femoral pulse wave velocity, peripheral microvascular function	N/A
Su et al. (2014), USA	Longitudinal (retrospective exposure measure)	Overtly healthy adults recruited at 7–16 years from a 1989 cohort study; 52.5 % female; 50.7 % European American; 49.3 % African American	21.3 (2.8)	221	Sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect, household dysfunction (ACE Questionnaire, retrospective self-report)	Radial pulse wave velocity, total peripheral resistance	Endothelin-1

[a] values presented as median (range). SD = standard deviation, ACE = adverse childhood experiences.

Fig. 2. Risk of bias assessment within selected studies. CD = cannot determine; NA = not applicable; NR = not reported.

slightly attenuated when controlling for covariates including age, sex, race, body mass index, and father's education level (Table 4).

3.3. Effects of mediating variables

Formal mediation analysis was rare and was only conducted in two studies which explored physiological biomarkers as potential mediators, with mixed evidence (Iannarelli et al., 2022; Su et al., 2014). An

Table 4
Summary of key findings of included studies, grouped by study design and arranged in order of study author.

First Author (Year, Setting)	ACEs Prevalence	Main Results	Secondary Findings
Longitudinal Studies			
Anderson et al. (2018), UK	Cumulative adversity score = 0.14 (SD = 0.77)	• (−) Psychosocial adversity was negatively associated with arterial distensibility (Mean Difference [95 % CI] = - 0.01 [-0.01, - 0.004]; $p < 0.01$) • (∅) Associations with arterial distensibility remained after adjustment for potential confounders and for adult SEP (Mean Difference [95 % CI] = 0.01 [-0.01, - 0.003]; p < 0.01) • (∅) There was no evidence that adversity was associated with carotid intima-media thickness, C-Reactive Protein or any other factors	• (+) Higher adversity was associated with greater C-Reactive Protein in adults with high adult SEP, but not low SEP (B [95 % CI] = 1.02 [0.98–1.07], $p = 0.04$)
Carson et al. (2022), USA	44 % of sample reported ≥1 ACE	• (+) History of adversity → higher carotid-femoral pulse wave velocity, controlling for time between visits, age, and race/ethnicity (B [SE] = 0.53 [0.22]; $p = 0.02$) • (+) Associations remained after adjusting for education, body mass index and heart rate (B [SE] = 0.50 [0.21]; $p = 0.02$)	• (∅) Menopause status, leisure time physical activity, alcohol consumption and depressive symptoms were not related to carotid-femoral pulse wave velocity and did not alter ACE-carotid-femoral pulse wave velocity associations
Iannarelli et al. (2022), Canada	57.8 % reported 1–3 ACEs 24.9 % reported ≥4 ACEs	• (+) Positive correlation between ACEs and carotid-femoral pulse wave velocity ($r = 0.20$, $p < 0.01$) • (+) Association remained after adjusting for age, sex, smoking status, body mass index, physical activity, heart rate, systolic blood pressure and serum C-Reactive Protein (B [SE] = 0.09 [0.04]; $p = 0.04$)	• (+) Physical activity (B [SE] = −0.13 [0.06]; $p = 0.04$) and regular smoking (B [SE] = 0.53 [0.26]; $p = 0.04$) were also predictors of carotid-femoral pulse wave velocity • (∅) Neither telomere length or mitochondrial DNA copy number mediated associations between ACEs and carotid-femoral pulse wave velocity
Rafiq et al. (2020), Canada	48.7 % reported 1–3 ACEs 44.7 % reported ≥4 ACEs	• (+) Individuals with ≥4 ACEs → accelerated increase in carotid-femoral pulse wave velocity over time compared to those <4 ACEs (Estimate = 0.20, $p = 0.03$) • (+) Individuals with ≥4 ACEs → accelerated increase in carotid intima-media thickness over time compared to those with <4 ACEs (Estimate = 0.074, $p < 0.001$)	• (∅) There was no interaction between ACEs group and time for arterial compliance or distensibility • (∅) Sex did not impact findings for any of the vascular outcomes measured
Su et al. (2014), USA	28.1 % reported 1 ACE 41.6 % reported ≥2 ACEs	• (+) Participants with ≥2 ACEs had higher radial pulse wave velocity (9 %) compared with those who were not exposed • (+) Participants with 1 ACE and ≥2 ACEs showed 3 % and 12 % higher total peripheral resistance index than those with no ACEs ($p < 0.01$) • Associations were attenuated but still significant when controlling for covariates ($p < 0.05$) • (+) Individuals with 1 and ≥2 ACEs had 18 % and 24 % higher plasma endothelin-1 levels ($p < 0.01$)	• (∅) No associations of endothelin-1 with DBP and radial pulse wave velocity, but plasma endothelin-1 levels were associated with total peripheral resistance index (partial R = 0.15, $p = 0.03$) after adjusting for covariates. • (−) The mediation model showed that the associations of ACE scores with total peripheral resistance index were partially mediated by endothelin-1 by 19 % • (∅) There were no interactions between ACE scores, ethnicity or sex
Cross-sectional Studies			
Kani et al. (2023), Turkey	Patients mean CTQ score = 44.5 (SD = 15.6) Healthy participants mean CTQ score = 31.8, (SD = 9.7)	• (∅) Total trauma score was not correlated with brachial pulse wave velocity in the control group ($r = 0.12$) • (∅) Total trauma score was not correlated with augmentation index in the control group ($r = 0.02$)	• (∅) Trait anxiety and depression scores were not correlated with arterial stiffness measures • (−) Duration of remission among depressive attacks had a negative correlation with augmentation index ($r = -0.33$, $p = 0.04$)
Kellum et al. (2023), USA	65 % of sample reported ≥1 ACE	• (+) ACEs were associated with higher levels of augmentation index ($\beta = 0.22$, $p = 0.04$) even after adjustment for sex and body mass index ($\beta = 0.21$, $p < 0.05$) • (+) Modelled continuously, ACEs → higher augmentation index ($\beta = 0.24$, $p = 0.03$) • (∅) There were no differences in carotid-femoral pulse wave velocity between groups	• (−) Found an interaction of body mass index and ACEs with pulse wave velocity ($\beta = -2.92$, $p = 0.01$); the effect of body mass index on pulse wave velocity was less positive in the ACE + group
Rodriguez-Miguelez et al. (2022), USA	Mean (SD) ACE score in patient group = 4.0 (2.0).	• (−) Flow-mediated dilation response was significantly lower in the ACE group compared to the Control group ($p = 0.042$; Cohen's d = 0.70) • (+) Carotid-femoral pulse wave velocity was significantly higher in the ACE group ($p < 0.01$, Cohen's $d = 1.30$) • Augmentation index was significantly higher in the ACE group ($p < 0.001$, Cohen's d = 1.51) with positive correlation ($r_s = 0.55$; $p < 0.01$) • (−) Between ACE + groups, scores were negatively associated with flow-mediated dilation ($r_s = -0.34$; $p = 0.02$) and augmentation index decreased with higher ACE exposure • (+) Between ACE + groups, scores were positively associated with pulse wave velocity ($r_s = 0.53$; $p < 0.01$)	• (−) ACE scores were negatively associated with maximal dilation, a measure of microvascular function ($r_s = -0.37$; $p < 0.01$)
Thurston et al. (2017), USA	45 % of sample reported ≥1 ACE	• (+) Any abuse or neglect was associated with 0.3 mm higher mean carotid intima-media thickness than controls (B [SE] = 0.04 [0.01]; $p < 0.01$)	• (+) Sleep time modified relations between ACEs and carotid intima-media thickness ($p = 0.05$), primarily higher among women sleeping <6 h/night

(*continued on next page*)

Table 4 (*continued*)

First Author (Year, Setting)	ACEs Prevalence	Main Results	Secondary Findings
		• (+) Higher total abuse or neglect score was associated with higher carotid intima-media thickness (B [SE] = 0.110 [0.034] • (+) Associations remained significant after adjusting for demographics and cardiovascular disease risk factors (including C-Reactive Protein)	• (+) Race/ethnicity modified the relationships between abuse/neglect and carotid intima-media thickness ($p < 0.05$) with stronger associations for non-white women (B [SE] = 0.03 [0.01]; $p = 0.04$) • (∅) Depressive symptoms and anxiety did not alter ACE-Carotid intima-media thickness associations
Clinical Trial (Baseline Data)			
Jenkins et al. (2021), USA	Mean (SD) ACE score in ACE + group = 6.0 (1.0)	• (∅) No differences in baseline diameter between groups ($p = 0.40$) • (−) Flow-mediated dilation ($p = 0.002$) and absolute diameter change ($p = 0.004$) was lower in the ACE + group • (∅) Adjusting for age, mean arterial pressure, body mass index, depression and anxiety scores had no effect on differences in flow-mediated dilation between groups ($p = 0.001$)	• (−) Sirtuin-1 acted as an adjuster of the means ($p < 0.05$) and adjusting for Sirtuin-1 contributed to reduced ACE-related difference in flow-mediated dilation. • (+) There were associations between flow-mediated dilation and Sirtuin-1 in the ACE + group but not the ACE-group, such that $r = 0.53$ for ACE + group ($p < 0.01$) and $r = 0.25$ ($p = 0.21$) for ACE-group

ACE = adverse childhood experience, SEP = socioeconomic position, CI = confidence interval, (+) refers to positive associations, (−) refers to negative associations, (∅) refers to null effects.

additional study from Anderson et al. (2018) included adjustment for mediation by body mass index and smoking, but formal mediation statistics were not reported.

Both Iannarelli et al. (2022) and Su et al. (2014) assessed the influences of biomarkers including plasma endothelin-1, telomere length and mitochondrial DNA copy number. Su et al. (2014) found no associations between endothelin-1 and pulse wave velocity, although there were small positive associations between endothelin-1 levels and total peripheral resistance index, and increases in ACE exposure were also related to increased plasma endothelin-1 levels. The authors also identified that endothelin-1 partially mediated the associations between ACE scores and total peripheral resistance by 19 % (Su et al., 2014), providing some evidence that endothelin-1 could play a role in explaining physiological pathways between ACEs and vascular health outcomes. Alternatively, Iannarelli et al. (2022) found no associations between telomere length or mitochondrial DNA copy number with ACEs, and additionally neither telomere length or mitochondrial DNA copy number mediated associations between ACEs and carotid-femoral pulse wave velocity (Table 4). However, it should be noted that both studies measured both the mediating variables and vascular outcomes at a single time point, which limits causal inference due to a lack of temporal ordering among exposure, mediator and outcome.

3.4. Effects of moderating variables

3.4.1. Sex, ethnicity/race and socioeconomic status

Studies examining demographic moderators such as sex, ethnicity/race and SES were few, with varied findings on their effects upon the relationships between ACEs and vascular outcomes.

Four studies measured the influence of sex within their analyses, although only two of these assessed the independent effects of sex as a moderator, with no notable findings (Rafiq et al., 2020; Su et al., 2014). Similarly, four studies included measurement of ethnicity or race but only two carried out independent analyses of the effects of these variables as a moderator (Su et al., 2014; Thurston et al., 2017). Results were contrasting between these two studies, which both assessed different vascular indicators. Su et al. (2014) found no interactions between ACE scores, ethnicity and pulse wave velocity or total peripheral resistance index, whilst Thurston et al. demonstrated that race moderated relationships between ACEs and carotid intima-media thickness, finding stronger positive associations between ACE exposure and carotid intima-media thickness in non-white women (Table 3). However, the latter study assessed an older population of midlife women (Thurston et al., 2017), in contrast to Su et al. (2014) who studied a population of young adults whereby physiological effects may not yet be as pronounced. Anderson et al. (2018) included measurement of socioeconomic position within their analyses, both within childhood and adulthood, but adjustment for both these variables was carried out alongside other covariates. Nonetheless, the inclusion of neither childhood nor adult socioeconomic position contributed to any changes in the negative associations between ACEs and arterial distensibility. In contrast, these authors did show that higher adversity was associated with greater C-Reactive Protein levels amongst individuals in the high adult socioeconomic position group, suggesting that interactions may exist between ACEs, C-Reactive Protein and SES (Table 4).

3.4.2. Effects of ACE exposure timing and dose

A notable limitation of included studies within this review, as highlighted by the risk of bias assessment (Figur 2) is the lack of studies assessing ACEs over more than one point in time during childhood. All 10 studies relied upon a single retrospective measure of ACE exposure, recalling any experiences across the whole of childhood (<18 years) (Table 3). Regarding dose of ACE exposure, there were seven studies which measured multiple levels of exposure (Anderson et al., 2018; Iannarelli et al., 2022; Kani et al., 2023; Rafiq et al., 2020; Rodriguez-Miguelez et al., 2022; Su et al., 2014; Thurston et al., 2017). Overall, this evidence suggests that higher ACE exposures may be associated with greater detrimental changes in vascular outcomes.

For measures of arterial stiffness, a higher dose of ACEs was negatively associated with arterial distensibility (Anderson et al., 2018) and pulse wave velocity (Iannarelli et al., 2022; Rafiq et al., 2020; Rodriguez-Miguelez et al., 2022; Su et al., 2014). Rodriguez-Miguelez and colleagues (2022) found that as ACE dose increased, pulse wave velocity also increased, and this effect was large (Table 4). Additionally, the highest levels of exposure (5–7 and >8 ACEs) showed a greater increase in pulse wave velocity compared to having low levels of exposure (1–4 ACEs) (Rodriguez-Miguelez et al., 2022). Similarly, Rafiq et al. (2020) demonstrated that being exposed to ≥4 ACEs was associated with an accelerated increase in pulse wave velocity in comparison with <4 ACEs. However, Rodriguez-Miguelez et al. (2022) found that the effects of dose on augmentation index were less straightforward. The correlation between the dose of ACEs and augmentation index was positive and reflects a moderate effect size supporting greater augmentation index in ACE-exposed groups in comparison with non-exposed. Yet, mean augmentation index values decreased with categories of higher levels of ACE exposure, indicating that the dose-response relationship may not be linear. Only one study failed to find any meaningful effects of ACE exposure dose upon outcomes of arterial stiffness (Kani et al., 2023).

In terms of carotid intima-media thickness, the effects of dose were mixed. When ACEs were represented continuously, one study showed that increasing ACE dose was positively associated with carotid intima-media thickness (Thurston et al., 2017) whilst conversely, another study

did not find any effect of dose upon carotid intima-media thickness outcomes (Anderson et al., 2018). When comparing categories of groups experiencing <4 and ≥ 4 ACEs, higher exposure appeared to be associated with an accelerated increase in carotid intima-media thickness between time points (Rafiq et al., 2020).

Finally, for measures of endothelial function using flow-mediated dilation, only one study carried out analyses involving multiple levels of ACE exposure. Rafiq et al. (2020) found that there was a negative association between ACE dose and flow-mediated dilation outcomes, with a moderate level of effect (Table 4).

4. Discussion

The present systematic review is, to our knowledge, the first to specifically assess the associations between ACEs and vascular indicators of subclinical atherosclerosis, with consideration of key mediating and moderating variables facing populations exposed to ACEs.

The largest body of evidence assessed arterial stiffness, showing positive associations between ACEs and pulse wave velocity or augmentation index. These findings may indicate that exposure to ACEs puts individuals at risk of higher levels of arterial stiffness in later life. However, evidence for other measures of vascular function was less convincing, predominantly due to a lack of available data. Nonetheless, there was some evidence to suggest that individuals exposed to ACEs may demonstrate lower flow-mediated dilation and higher carotid intima-media thickness, respectively related to endothelial dysfunction and atherosclerotic progression, but additional research is required to corroborate these findings.

It was difficult to determine the effects of mediating variables such as health risk behaviours and biomarkers, due to a lack of studies that specifically examine the independent effect of these variables using formal mediation analysis. The effects of moderators such as demographic factors and ACE exposure timing were also unclear, due to homogenous populations, limited measurement of these variables and only two studies providing insight into independent effects of ethnicity or race (Su et al., 2014; Thurston et al., 2017). Further use of analytical methods which allow the authors to understand how such variables may alter associations between ACEs and measures of subclinical atherosclerosis are needed.

4.1. Biological stress responses, sex and arterial stiffness

The results of this study have a mixed level of agreement with existing literature. The positive associations between ACEs and pulse wave velocity align with our hypotheses, based upon inferences made within the American Heart Association scientific statement (Suglia et al., 2018). Importantly, increased arterial stiffness is believed to be related to cardiovascular disease risk through the development of systolic hypertension and reductions in healthy arterial function (Chirinos et al., 2019). Furthermore, mechanistic evidence has suggested that stress and hormonal responses are likely to play a considerable role in the pathophysiology of arterial stiffening. This is particularly noteworthy in females, who face variations in levels of hormones such as oestrogen between puberty and menopause (Kajantie and Phillips, 2006). It is important to keep this point in mind when making comparisons against other studies.

Building on these theoretical considerations, it is important to examine how sex and age may influence observed associations. For example, Klassen et al. (2016) also assessed the relationships between ACEs and pulse wave velocity but only found positive associations in males, not females. In contrast, a female-only study showed positive associations between ACEs and carotid-femoral pulse wave velocity (Carson et al., 2022). A possible explanation for such differences may be related to participant ages in these samples, and the relationships with hormonal changes around puberty or menopause. Klassen et al. (2016) studied a population of children aged 10–14 years old, whilst only one of the seven studies assessing pulse wave velocity in this review included a paediatric population (Kellum et al., 2023). Indeed, this was one of only two studies which did not identify any notable associations between ACEs and pulse wave velocity. These biological mechanisms may partly explain the divergent findings seen in paediatric versus adult populations.

It is understood that exposure to adversity can provoke a biological stress response, such as stimulation of the hypothalamic-pituitary-adrenal axis and sympathetic nervous system, which has been related to inflammation and changes in vascular structure and function linked to atherosclerosis (Slopen et al., 2012). Additionally, increased levels of oestrogen, observed in females through puberty, attenuates sympathetic and adrenal responsiveness (Kajantie and Phillips, 2006). Kellum et al. (2023) did not directly measure puberty, thus one could hypothesise that more females had undergone puberty than males, since this commonly occurs earlier in females (Malina et al., 2004) – possibly leading to diminished effects upon vascular function in response to stress. Other explanations for these findings could relate to factors affecting the ability to detect significant changes in pulse wave velocity within adolescents. For example, it has been suggested that pulse wave velocity may be a less reproducible and sensitive measure of arterial stiffness in children than other methods such as augmentation index (Lowenthal et al., 2014). This may be relevant since Kellum et al. (2023) did show positive associations between ACEs and augmentation index, but not pulse wave velocity.

Furthermore, age-related changes in vascular measures pose challenges in detecting early effects of ACE exposure. Reference values for arterial stiffness have indicated that both mean values and variance within pulse wave velocity appear to be the smallest amongst the younger adult age groups (<30 years) and increase with age (Reference Values for Arterial Stiffness' Collaboration, 2010). Additionally, pulse wave velocity values among children and adolescents are likely to be lower than the aforementioned reference values among young adults, as shown within both the study from Kellum et al. (2023) and other representative samples of children and adolescents (Santos et al., 2021). Kellum et al. (2023) note that a longer period between ACE exposure and outcome measurement may be required to find important changes in pulse wave velocity, which combined with generally lower variability of pulse wave velocity values amongst this age group, may contribute to reduced ability to detect differences dependent on ACE exposure.

Some interesting findings emerged when considering other arterial stiffness measures, such as augmentation index. Rodriguez-Miguelez et al. (2022) found a negative correlation between ACEs and augmentation index when examining groups with increasing levels of exposure. This is unexpected based on the positive associations between ACEs and pulse wave velocity, and the assumption that augmentation index should also be a valid indicator of arterial stiffness (Stoner et al., 2014). However, the study from Rodriguez-Miguelez et al. (2022) had a notably small sample size (n = 45) in comparison with many other studies in this review, and did not consider any possible covariates such as age or sex in their analyses. In addition, the authors did not clarify the numbers of participants, or demographics, within each sub-group of individuals who were ACE-exposed. Consequently, their statistical approach to comparing these sub-groups is likely to be underpowered and exposed to considerable bias, particularly if there are very few participants or varied demographics among the sub-groups. Other authors have emphasised that augmentation index is influenced by factors such as age, sex and heart rate and that the normalised adjustment of augmentation index by a heart rate of 75 beats per minute may be statistically inappropriate as it assumes that the relationship between augmentation index and heart rate is uniform across different populations (Stoner et al., 2014). It is also known that there may be independent positive associations between ACE exposure and heart rate (Pretty et al., 2013). Since the demographic composition of each ACE subgroup is unknown, one may question whether an inappropriate statistical approach for the normalisation of augmentation index could

contribute to the reversal of associations with ACEs in comparison with measurement using pulse wave velocity.

4.2. Effects of ACE measurement and analysis

This review identified that methods for the assessment of ACEs varied between the included studies. There were similarities in that all studies chose to use retrospective recall of ACEs in adulthood, which aids internal validity for comparison of findings here, although this method has been criticised due to the possibility of recall bias (Appleton et al., 2017). Yet, a more prominent aspect that may exacerbate variations in findings involves the specific ACE constructs measured, and statistical approaches used for analysis. For example, Klassen et al. (2016) were unable to measure outcomes related to maltreatment, such as sexual abuse. Since it has been stated that sexual abuse is reported more often amongst females (Cavanaugh et al., 2015; Suglia et al., 2018), this may have contributed to the lower overall ACE exposures in females within their sample. Moreover, this may explain the weaker associations between ACEs and pulse wave velocity in females than males which contrasts our findings, particularly as sexual abuse has been found to exert independent effects upon multiple outcomes related to cardiovascular disease risk such as coronary heart disease, risk behaviours, and diabetes (Campbell et al., 2016).

Interestingly, only one study found null associations between ACEs and carotid intima-media thickness, however, these authors also provided insight into how vascular outcomes were associated with individual constructs of the ACE score (Anderson et al., 2018). In contrast to existing systematic reviews which have suggested violence and mental illness are the strongest predictors of adverse health outcomes (Hughes et al., 2017), Anderson et al. revealed the strongest associations between carotid intima-media thickness and constructs of maternal lack of care and maternal overprotection (Anderson et al., 2018). Furthermore, their study reported a low prevalence of ACEs overall in comparison with other studies included in this review. One might postulate that this could be reflective of differences in the population being studied, as this was the only UK-based study, sampled from a restricted area with a homogenous, mostly Caucasian population. Accordingly, there may be limited scope for the detection of ACEs, particularly those which contribute more substantially to associations with carotid intima-media thickness.

4.3. Effects of mediating variables

Existing reviews have identified the possible contributions of mediators such as health risk behaviours, biomarkers and mental health status upon the associations between ACEs and cardiovascular disease risk factors (Slopen et al., 2012; Su et al., 2015; Suglia et al., 2018). For example, exposure to adversity appears to increase the incidence of health risk behaviours such as smoking, alcoholism, physical inactivity, obesity and poor sleep (Tan et al., 2024), considered the most important contributors to cardiovascular health by the American Heart Association (Lloyd-Jones et al., 2022). However, specific mediation effects between ACEs and vascular indicators of atherosclerosis were less clear. Not only was there high heterogeneity of methods within these studies, but very few studies reported mediation effects of individual variables, reducing our ability to assess the effects of mediating variables in isolation, or the relative importance of each of these factors. As a result, this review cannot provide firm conclusions for the effects of any variable. For example, both studies assessing the effects of smoking only provided a value for mediation effect when combined with other variables in their model (Anderson et al., 2018; Iannarelli et al., 2022). Consequently, there is a clear need for more advanced models and transparent reporting of results to draw firm conclusions with respect to the independent effects of mediating variables assessed within this review.

Moreover, it is important to consider the reliability of the methods that were used to measure lifestyle mediators such as physical activity, sleep, smoking or alcohol use. All studies included within this review employed self-report questionnaire methods to assess these outcomes, and whilst both studies recording physical activity reported the specific questionnaire they utilised (Carson et al., 2022; Iannarelli et al., 2022), methods to assess other lifestyle mediators in other studies were not specified. Whilst questionnaire methods are practical, being cheaper and easier to administer in a large sample, there are potential threats to the reliability of such measures. Biases commonly associated with self-report measurements in health research, such as social desirability and approval (Adams et al., 2005; Kimberlin and Winterstein, 2008) could result in under-reporting of the prevalence of such factors and therefore alter the strength of the associations found within these studies. Where possible, using objective forms of measurement, such as accelerometer-based methods for physical activity, may provide more reliable measurements and thus improve the validity of results.

Interestingly, whilst this review identified studies which assessed C-Reactive Protein, endothelin-1 and Sirtuin-1 as biomarkers, no studies measured cortisol levels, despite evidence that chronic exposures to stress may be linked to glucocorticoid metabolism (Anderson et al., 2018) and the aetiology of cardiovascular disease, albeit indirectly (Slopen et al., 2012). This variable may still be informative and can be less invasive than many other biomarkers which require blood sampling. Furthermore, Brindle et al. (2022) have demonstrated that ACEs may be related to blunted cortisol levels in younger children, but with no differences in adolescence. This highlights the importance of timing of measurement (Brindle et al., 2022; Oh et al., 2018) and the requirement for further prospective studies with multiple points of outcome measurement to build our understanding of temporal changes in associations with biomarkers.

4.4. Considerations & future research recommendations

There are important considerations of both the included studies and the present systematic review which must be considered. Firstly, the heterogeneity within how ACE exposures were assessed, and varied statistical methods and approaches to adjusting for covariates meant it was not appropriate to carry out meta-analyses; additionally, the small number of studies with comparable outcomes reduces the power of our findings and ability to draw meaningful conclusions. Whilst this review carried out more practical analysis using the SWiM method, there was often a lack of detail in how results were reported within studies as well as a range of statistical methods and reporting of outcomes. As a result, vote counting was relied upon to quantify a direction of effect, without being able to carry out other recommended methods for reporting results (McKenzie and Brennan, 2019). Further studies employing comparable and robust statistical methods, such as regression models including adjustment for covariates, as well as utilising continuous measurement of ACEs to capture a full range of exposures, may allow for valid and meaningful meta-analyses to be conducted in future research.

It should also be acknowledged that we did not include studies which assessed clinical populations without the presence of a control group. Consequently, our findings are not generalisable to individuals with pre-existing clinical conditions, and we cannot determine whether relationships between ACEs and vascular outcomes differ in clinical vs. non-clinical populations. Future comparative studies which include both clinical and non-clinical populations may provide important insight into the effects of underlying health conditions on relationships between ACEs and vascular health.

Multiple questionnaires were used for ACE measurement, and many of these were adapted without determining their validity (Rafiq et al., 2020; Su et al., 2014). Furthermore, there was a reliance upon retrospective measurement of ACEs, in some cases ~40–50 years later, increasing the risk of recall bias (Appleton et al., 2017). Future research should carry out prospective assessment of ACEs within longitudinal study designs, or make use of data emerging from large prospective cohort studies (Lacey et al., 2020). It was also noted that no studies

assessed the timing of ACE exposures, which should be an additional focus for future research by including multiple time points of ACE measurement. This is important since earlier research has identified sensitive periods during childhood where the environment is particularly likely to alter stress response system development (Suglia et al., 2018). Moreover, since there is no consensus on what classifies as an ACE or how to operationalise ACE measurement (Appleton et al., 2017), the authors had to use subjective judgment to decide upon specific types and quantities of ACEs for study inclusion criteria, and relevant data may have been missed by excluding studies which did not measure ≥5 of these ACEs. However, including studies with fewer ACEs may have brought in a body of evidence which purely focused on childhood trauma (i.e., measuring physical, emotional and sexual trauma). This is only a small part of what makes up the wider definition of ACEs according to the original ACE study (Felitti et al., 1998) and consequently, this is unlikely to have considerably affected the validity of this study in relation to our specific research question.

The assessment of moderating variables was missing among most studies, or variables were simply controlled for as confounders without insight into their moderation effect. This was more pronounced for ethnicity/race and SES, which may be attributed to the limited variation in geographical location and populations included in these studies. Researchers should aim to consistently measure possible moderating variables as called for by the American Heart Association (Suglia et al., 2018), within a more diverse range of populations, since childhood and adult SES have been linked to cardiovascular disease risk factors such as atherosclerosis (Galobardes et al., 2006). Additionally, the moderating effects of age, or time between exposure and outcome, were only present within one study (Rafiq et al., 2020). Further studies which formally assess the moderating effects of age would provide important insight into how the relationships between ACEs and vascular health may change over time. It should be ensured that both moderating and mediating variables are not only controlled for as covariates, but their effects upon relationships between ACEs and vascular outcomes should be measured independently through more advanced statistical approaches, such as mediation models and subgroup analyses.

Finally, due to time restraints, data extraction and risk of bias assessment were carried out by a single reviewer, which may increase the risk of bias and errors, however, all other aspects of the review were carried out by more than one reviewer. Nevertheless, this review provides a much-needed insight into the current research within our topic area, with the greatest proportion of limitations stemming from the available evidence itself.

5. Conclusion

This study shows that there is some evidence to support relationships between increased ACE exposure and negative impacts upon vascular measures of subclinical atherosclerosis. However, this evidence is limited in both quantity and quality. Upon highlighting these findings, it is anticipated that researchers will further strive to develop higher-quality prospective studies, including assessment of both potential mediating and moderating variables between exposure and outcomes. This will not only provide evidence which will be crucial to understanding the mechanistic pathways linking ACEs and cardiovascular disease risk, but also to identify specific populations who may be at greatest risk of suffering adverse consequences to vascular health due to ACE exposure. Subsequently, researchers and stakeholders can be better informed for the delivery of successful interventions, to promote improvements in health outcomes within individuals predisposed to ACEs.

CRediT authorship contribution statement

Laura E. Macro: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Ana E. von Ah Morano:** Writing – review & editing, Methodology, Investigation, Data curation. **Sarah L. Halligan:** Writing – review & editing, Supervision, Conceptualization. **Alan R. Barker:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization.

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Rights retention

Ethical approval and consent to participate

As this work is a systematic review of existing published literature, ethical approval was not applicable.

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Glossary

Adverse Childhood Experiences (ACEs) Potentially traumatic events that occur in childhood (0–17 years), such as abuse, household challenges, or neglect

Subclinical Atherosclerosis The early stages of atherosclerosis - a condition characterized by the buildup of fats, cholesterol, and plaque on the artery walls - where there are not yet any noticeable symptoms. Indicators include but are not limited to, measures of pulse wave velocity, carotid intima-media thickness and flow-mediated dilation

Pulse Wave Velocity A measure of the velocity that the blood pressure pulse moves along the arteries, indicative of arterial stiffness with higher values indicating a reduced ability of a vessel to respond to fluctuations in blood volume

Carotid Intima-Media Thickness A measurement to assess the thickness of the inner two layers of the carotid artery wall, the intima and the media, with higher values signifying the possible progression of atherosclerosis

Flow-Mediated Dilation A technique used to assess endothelial function, indicating the ability of the inner lining of blood vessels to regulate the dilation of blood vessels in response to increased blood flow. A higher FMD is indicative of increased endothelial function

Mediating Variable A variable that helps to explain the mechanism or process through which an independent variable influences a dependent variable and lies between the cause and the effect

Moderating Variable A variable that influences the strength or direction of the relationship between an independent variable and a dependent variable

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2025.118515.

Data availability

No data was used for the research described in the article.

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