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Childhood Risk Factors and Adulthood Cardiovascular Disease: A Systematic Review

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Abstract

Objective—To conduct a comprehensive review of the literature on childhood risk factors and their associations with adulthood subclinical and clinical cardiovascular disease (CVD).

Study design—A systematic search was performed using the MEDLINE, EMBASE, PsycINFO, CINAHL, and Web of Science databases to identify English-language articles published through June 2018. Articles were included if they were longitudinal studies in community-based populations, the primary exposure occurred during childhood, and the primary outcome was either a measure of subclinical CVD or a clinical CVD event occurring in adulthood. Two independent reviewers screened determined whether eligibility criteria were met.

Results—There were 210 articles that met the predefined criteria. The greatest number of publications examined associations of clinical risk factors, including childhood adiposity, blood pressure, and cholesterol, with the development of adult CVD. Few studies examined childhood lifestyle factors including diet quality, physical activity, and tobacco exposure. Domains of risk

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beyond “traditional” cardiovascular risk factors, such as childhood psychosocial adversity, seemed to have strong published associations with the development of CVD.

Conclusions—Although the evidence was fairly consistent in direction and magnitude for exposures such as childhood adiposity, hypertension, and hyperlipidemia, significant gaps remain in the understanding of how childhood health and behaviors translate to the risk of adulthood CVD, particularly in lesser studied exposures like glycemic indicators, physical activity, diet quality, very early life course exposure, and population subgroups.

Cardiovascular disease (CVD) is the leading cause of death in the US: more than 1 million adults experience coronary events and more than 800 000 adults experience strokes each year.[1] Although childhood clinical CVD is rare, CVD events that occur in adulthood, including myocardial infarction and stroke, are the products of the lifelong atherosclerotic process that begins in youth.[2] Thus, the prevention and management of childhood risk factors and preservation of cardiovascular health across the lifespan are pediatric care priorities.[3]

Recognizing the early origins of CVD risk, research studies have begun to address the complex processes of risk development across the life course.[4,5] Identifying childhood risk factors that are most strongly linked to the development of adult CVD can provide scientific evidence for childhood intervention, whereas identifying risk factors for which long-term data are sparse may guide future investigation.

Our objectives were to provide a comprehensive review of the existing literature on associations of childhood risk factors with adulthood subclinical and clinical CVD and identify evidence of emerging disparities in CVD risk as individuals age from childhood into adulthood, including age, sex, and race/ethnicity. The literature search and review was based on known adult risk factors for CVD, potential risk factors as stated in pediatric guidelines, and developmental factors arising at birth that may significantly impact the risk of adult CVD.[3,6]

Methods

A literature search was conducted using the MEDLINE, EMBASE, PsycINFO, CINAHL, and Web of Science databases to identify English-language articles published through June 2018. A research librarian assisted in planning the search and created correct search strings for the electronic databases. A full list of the search terms appears in Table I (available at www.jpeds.com). We did not search for unpublished articles nor did we review reference lists of included articles to identify additional studies. After deduplication, the search returned 8652 titles and abstracts.

Articles were included if they met the following a priori criteria: (1) longitudinal study design; (2) exposure occurred/characteristic emerged during childhood (infancy through age 20 years); (3) outcome ascertained in adulthood (ages ≥20 years); (4) the primary outcome was either a measure of subclinical CVD or a clinical CVD event; and (5) the study population was community based, not a clinically defined population (eg, patients with congenital heart disease). Descriptions of the included clinical and subclinical CVD

outcomes and their common measurement methods are outlined in Table II. Articles that included multiple subtypes of CVD (eg, coronary heart disease [CHD] and stroke) in the outcome without estimating the association for each subtype of CVD separately were classified as having a CVD mixed definition outcome and were included in this review. Studies that only included as the main outcome CVD risk factors, such as hypertension or diabetes, were not included in this review.

Titles and abstracts were reviewed to assess for the defined eligibility criteria. After review, full-text was retrieved for 884 articles. Two independent reviewers screened all full-text articles to ensure all eligibility criteria were met. Inter-rater agreement of this screening was high (Cohen K = 0.89). A third reviewer resolved discrepancies for the 34 articles that were left unresolved by the initial review. Ultimately, 210 articles were included in the review (Figure 1; available at www.jpeds.com).

Results

A listing of all articles included in this review is available in Table III (available at www.jpeds.com). This table includes the basic study characteristics of study cohort, sample size, exposure, outcome, and main finding; a listing of any subgroup analyses by age, sex, and race/ethnicity that were reported in the article; and 3 study quality indicators, namely, self-reported or objective exposure and outcome measurements, and type of outcome analysis. Figure 2 is the corresponding heat map by childhood risk factor and adulthood outcome, color coded by number of publications.

Adiposity

We identified 61 studies that examined the association between childhood adiposity and adulthood subclinical and clinical CVD. Almost all studies used body mass index (BMI) as the adiposity measure, but there was heterogeneity in whether BMI was analyzed continuously, categorically using percentile cut-points, or categorically using numeric cut-points.[6]

Subclinical CVD Outcomes.—Four articles found no significant association between childhood adiposity and adulthood arterial stiffness,[7–10] but 2 other studies found associations between adiposity and increased arterial stiffness.[11,12] One study found an association between adiposity at age 4 years and adulthood stiffness; however, this association was not found when examining adiposity at age 2 years.[13]

In 19 articles, childhood adiposity was associated with greater adult carotid intima-media thickness (cIMT).[7–10,14–28] Sex differences in the association were examined in 11 of these articles, 7 articles found no difference between men and women, 3 articles found the association held among women only, and 1 article found the association held among men only.[7–10,16,18,21,22,26–28] When examining the association by exposure age, there was a stronger association in adolescence (age ≥12 years) compared with earlier childhood.[16,24] One article had a null finding, where overweight in early childhood (ages 2–11 years) was not associated with cIMT in older adulthood.[29]

The association between greater childhood adiposity and adverse adulthood left ventricular (LV) structure and function was significant across 11 articles.[15,30–39] One study examined the association of BMI in adolescence and presence of adult coronary artery calcification, finding a positive association.[40]

Clinical CVD Outcomes.—Eleven articles examined associations between childhood adiposity and adult CHD finding higher risk of CHD with each SD increase in BMI (hazard ratio range per SD, 1.05–1.22).[41–51] One article examined the associations by age group and found more robust associations at age 13 years as compared with age 7 years between childhood adiposity and a higher risk of adult CHD.[46] Seven articles examined the associations between childhood adiposity and adulthood stroke; the hazard ratio range of higher risk of stroke with each SD increase in BMI was 1.15–1.29. Two articles found significant associations of increased adiposity with risk of adulthood heart failure.[42,44,50,52–57] Last, there were 10 articles that used mixed-type definitions of CVD (eg, includes both CHD and stroke combined as a single outcome); the hazard ratio range of higher risk of CVD with each SD increase in BMI was 1.09–1.21 and the hazard ratio range of higher risk of CVD with childhood obesity was 2.3–3.9.[58–67] One article stratified by childhood age group, finding stronger associations with CVD among children aged 8–14 years as compared with 2–8 years.[62]

Birthweight

Low birthweight is also a contributor to the pathogenesis of CVD. We found 28 articles examining associations of birthweight with adulthood subclinical and clinical CVD, all adjusted for gestational age. Three articles specifically examined subclinical CVD: 1 article found low birthweight (<2500 g) to be associated with greater arterial stiffness, and the other 2 found no association between low birthweight and either arterial stiffness or LV mass.[13,32,68] The associations between lower birthweight and higher risk of clinical CVD were consistent across 25 studies and multiple CVD outcomes, including CHD, stroke, and CVD mortality; the hazard ratio range of higher risk of CVD with each SD decrease in birthweight was 1.11–1.43 and the hazard ratio range of higher risk of CVD with low birthweight was 2.2–3.6.[43,45,49,69–90]

Change in Adiposity Across Childhood

We identified 19 articles examining how change in adiposity across childhood may affect risk of adulthood CVD. Four studies examined the velocity of weight gain during early childhood, finding that lower levels of weight gain through age 2 years were associated with higher risk of CVD.[79,83,91,92] However, after infancy, faster childhood weight gain was associated with a greater risk of CVD.[45,52,53,63,79,93] Further, individuals who had low birthweight and then gained weight rapidly in childhood were at the greatest risk for adult CVD.[45,79,93,94]

Blood Pressure

We identified 29 articles examining childhood blood pressure (BP) and adult CVD outcomes, and these articles used a mix of continuous BP measurement and dichotomous elevated/not elevated BP classification. To determine elevated BP, studies applied the

pediatric hypertension guidelines in effect at the time of analysis; thus, there is heterogeneity across publication date in how elevated BP is defined.

Subclinical CVD Outcomes.—Ten articles examined childhood BP and the association with adulthood arterial stiffness. Nine of these studies found that elevated BP was associated with greater arterial stiffness.[7,8,11,12,95–100]

The association between childhood BP and adult cIMT was measured in 11 articles. In 9 articles, there was an association between elevated BP and thicker cIMT.[7,8,16,19–21,96,97,101–103] Five of these studies stratified the results by sex, but only 1 study found sex-specific differences with the association, present only among women.[7] One study stratified by exposure age, and the association between BP and cIMT was only significant among adolescents aged 12–18 years.[16] The association between childhood BP and adult coronary artery calcification was examined in 2 articles; both showed an association between elevated BP and the presence of coronary artery calcification.[40,104]

Eight articles examined associations between childhood BP and adulthood LV structure and function. Three articles found positive associations between BP and LV mass,[35,102,105] but a fourth article found no association.[30] The remaining 4 articles examined adulthood LV hypertrophy as the outcome; pediatric hypertension was associated with a higher risk of LV hypertrophy.[36,39,96,97]

Clinical CVD Outcomes.—Five articles examined childhood BP and adulthood CVD events.[41,106–109] Elevated BP was associated with greater risk of CVD; the hazard ratio range of higher risk of CVD with each SD increase in BP was 1.05–1.18 and in the 1 study that examined higher risk of CVD with a dichotomous hypertension cut-off, the hazard ratio was 1.51. One study stratified risk of CVD by childhood BMI, finding significant associations between hypertension and CVD across BMI strata that were strongest among obese children.[106]

Lipids

We identified 16 articles using a heterogeneous mix of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and/or triglycerides as the exposure of interest, with several articles comparing the performance of these lipid measures.

Subclinical CVD Outcomes.—Ten articles established consistent findings between pediatric hyperlipidemia and adult cIMT, but there were differences by type of lipids. LDL-C was measured in 8 articles, and higher LDL-C was consistently associated with thicker cIMT.[16,19,20,27,110-113] There was consistently no association between triglyceride levels and cIMT across 7 studies.[16,19–22,111,113] The findings on HDL-C were mixed: 3 studies found lower HDL-C associated with thicker cIMT, whereas 4 studies did not find any significant associations.[16,19,20,22,111–113] One article examined total cholesterol, finding a positive association with thicker cIMT.[21] In 2 articles that examined pediatric lipid levels and coronary artery calcification, the presence of coronary artery calcification was association with higher LDL-C in 1 article and lower HDL-C in the other article.[40,104] One

article examined childhood triglyceride levels and LV mass; the association between higher triglycerides and greater LV mass was significant.[105]

Two studies of childhood lipid levels and adult cIMT stratified their findings by age group, and in both, the associations held for adolescents but were not significant in early childhood.[16,21] In another study, stratified by race and sex, the significant association between higher childhood LDL-C cholesterol and thicker adult cIMT was present for White men, White women, and Black women, but not for Black men.[111] Several studies tested for sex differences in the association between pediatric lipid levels and adult cIMT, but none were found.[16,21,22,27]

Clinical CVD Outcomes.—Three articles examined childhood triglyceride levels and adulthood CVD, all showing significant associations between higher triglyceride levels and a higher incidence of CVD (hazard ratio range, 5.4–6.1).[66,114,115] We found no articles examining other childhood lipid measures and adult CVD outcomes in the general population.

Glycemic Indicators

We found scant research connecting childhood glycemic indicators to adulthood CVD. One study examined fasting glucose and found associations with greater cIMT, but did not find any associations between fasting glucose and adult arterial stiffness.[116] In another study, type 2 diabetes in adolescence was associated with a higher risk of stroke.[55]

Tobacco Exposure

Assessment of tobacco exposure includes both self-smoking in adolescence, that is, personal use of tobacco cigarettes, and secondary exposure to smoking in home- and community-based environments throughout childhood and adolescence.[3] We identified 4 articles examining childhood self-smoking. Cigarette smoking was associated with thicker adulthood cIMT as well as CVD incidence.[16,117,118] Another study, conducted only among current and former smokers, found a higher risk of developing CVD among those who initiated smoking before age 17 years as compared with those who started at age 17 years or after.[119] Additionally, 3 articles examined exposure to parental smoking, finding significant associations with thicker adulthood cIMT and carotid atherosclerotic plaque.[120–122] There was evidence of a dose response; the risk of thicker cIMT was higher if both parents reported smoking, and the risk of carotid plaque was lower if there was evidence of good “smoking hygiene” as demonstrated by reported parental smoking without concomitant detectable levels of serum cotinine in the child.[120,122]

Physical Activity

We identified 6 articles addressing childhood physical activity and risk of adulthood subclinical and clinical CVD. All but one of the studies relied on self-reported physical activity, and all studies used a continuous measure of physical activity.

Associations between childhood physical activity and adult arterial stiffness were mixed. In 1 study, greater childhood physical activity was associated with lower adulthood stiffness

among men only,[123] in 2 studies only vigorous physical activity was associated with lower stiffness (among both men and women), and in a fourth study both moderate and vigorous physical activity were associated with lower stiffness.[124–126] In 2 studies, both moderate and vigorous physical activity during childhood were associated with lower adult cIMT.[22,126] Finally, 1 study on adulthood atrial fibrillation among men did not find an association between physical activity at age 15 years and later incidence of atrial fibrillation.[127]

Diet

Nine articles evaluated various aspects of diet quality; 3 articles focused on overall diet quality and 6 articles focused on specific food groups, such as fruits and vegetables.

Subclinical CVD Outcomes.—Four studies focused on childhood diet and its potential impact on adult arterial stiffness. In 1 study, greater intake of fruits and vegetables was associated with less arterial stiffness, and in another study, greater intake of dietary fiber was associated with less arterial stiffness.[128,129] Two studies examined the Mediterranean diet score finding an association with greater adherence to the Mediterranean diet and less arterial stiffness in 1 study and no association with arterial stiffness in the other study, respectively.[130,131]

Another 3 studies examined the association between childhood diet and adulthood cIMT as the outcome of interest. Greater fruit consumption was associated with thinner cIMT, as was consumption of omega-3 fatty acids.[22,132] In contrast, greater consumption of saturated, monounsaturated, and polyunsaturated fat was associated with thicker adulthood cIMT.[132] The third study found that adherence to a traditional Finnish diet was associated with a thicker cIMT among men only, most likely attributable to high consumption of fat and sodium.[133]

Clinical CVD Outcomes.—Two studies examined the association between childhood diet and adulthood CVD events. One study found an association between dairy/calcium consumption and lower risk of stroke, but found no association with CHD.[134] The other study found that greater vegetable consumption was associated with lower risk of stroke, but greater fish consumption was associated with higher risk of stroke; importantly, this finding may be confounded by the dietary patterns of children during the Great Depression.[135]

Breastfeeding

Six articles examined associations between breastfeeding in infancy and adulthood CVD outcomes. Two studies examined breastfed infants and adult cIMT in those offspring; in 1 study, there was no association in younger adults (mean age of 31 years) and the other study found that breastfeeding in infancy was associated with thinner cIMT in older adults (mean age of 71 years).[136,137] One article examining exposure to breastfeeding and adult arterial stiffness and 1 article examining breastfeeding and endothelial function showed no association.[13,136] In 3 articles examining breastfeeding and adult CVD events, 1 study found no association with either CHD or stroke, 1 study found no association with CVD mortality, and the third study found a protective association between breastfeeding and CHD.[138–140]

Psychosocial Risk Factors

Socioeconomic Status.—We identified 13 articles examining childhood socioeconomic status (SES) with adult subclinical and clinical CVD. Most articles used the father's occupation category as the socioeconomic measure, but childhood household income or parental educational attainment were also used to classify exposure. Two studies that examined SES and adult cIMT showed no association, as did the 1 study that examined SES and endothelial function.[141,142] The 1 study examining SES and adult LV structure and function found an association between lower childhood SES and larger adulthood LV mass.[143] In the 9 studies examining SES and clinical CVD outcomes, lower childhood SES was associated with higher incidence of clinical CVD (relative risk range, 1.3–1.8), including CHD, stroke, and CVD mortality.[81,144–152] These associations were robust to multivariable adjustment of childhood and adulthood CVD risk factors, such as adiposity, hyperlipidemia, hypertension, smoking, and family history of CVD.

Psychosocial Adversity.—There were 18 articles examining childhood psychosocial adversity and adulthood CVD outcomes. There was little standardization across articles in the definition of adverse experiences; some studies measured a single adversity, such as exposure to famine or early life parental death, and other studies used scales with multiple adversities, such as an adverse childhood experiences scale or a life events scale. Almost all exposures were assessed retrospectively in adulthood.

Subclinical CVD Outcomes.—Associations between childhood psychosocial adversity and adulthood subclinical CVD were inconsistent or showed no association. There were 4 studies examining psychosocial adversity and cIMT; 2 studies found no association with cIMT, a third study found an association with cIMT for childhood sexual abuse only, and a fourth study found an association with cIMT among White individuals but not Black individuals.[153–156] Three studies examined childhood psychosocial adversity and adulthood arterial stiffness; 2 studies found no association with arterial stiffness, but the third study found increased childhood exposure to racism was associated with greater arterial stiffness.[153,154,157] There was no association observed in the 1 study that assessed the impact of childhood psychosocial adversity and adult LV mass.[154] In the 1 study that examined coronary artery calcification, there was a significant association between greater childhood psychosocial adversity and adulthood presence of coronary artery calcification.[158]

Clinical CVD Outcomes.—There were 11 studies examining childhood psychosocial adversity and adulthood clinical CVD, finding significant positive associations with CHD, stroke, heart failure, and CVD mortality.[159–169] The magnitude of the association varied by type of adversity exposure. The hazard ratio range of higher incidence of CVD associated with greater psychosocial adversity was 1.3–3.6, and each additional adversity conferred a 30%–70% higher risk of CVD.[164] These associations were robust to adjustment for CVD risk factors as well as childhood SES.

Risk Factor Clustering

Metabolic Syndrome.—The metabolic syndrome (MetS) is defined as having at least 3 of the following risk factors: elevated BMI, elevated triglyceride levels, elevated BP,

elevated fasting blood glucose, and lower HDL-C. We found 9 studies examined childhood MetS and adulthood CVD risk. Five studies reported that MetS was associated with greater cIMT.[25,170–173] In 1 study, MetS was associated with greater arterial stiffness.[174] In 3 studies, MetS was associated with greater CVD incidence.[175–177] In the 1 study that examined the associations with adult cIMT by childhood age group, the association was only significant for adolescents aged 11–18 years.[171]

Other Risk Factor Combinations.—Seven additional studies examined traditional CVD risk factors, including lipids, BMI, BP, diabetes, smoking, diet, and physical activity in different childhood exposure combinations and examined their additive associations with adulthood subclinical CVD; all reported positive associations. Six studies found the number of CVD risk factors was associated with greater cIMT, 2 studies found the number of risk factors was associated with increased arterial stiffness, and 1 study demonstrated associations with presence of coronary artery calcification.[12,16,21,22,110,178,179] Two studies that examined associations by age group found that the number of childhood risk factors and adulthood cIMT were only significant for ages 9–18 years.[16,21]

Other Risk Factors

The 36 remaining articles examined a heterogeneous mix of childhood exposures and the association with adulthood subclinical and clinical CVD. These articles fell into 2 broad categories: maternal and perinatal exposures, an emerging area of interest for cardiometabolic health, and other childhood characteristics and experiences.[180–216] A full list of the articles is available in Table IV (available at www.jpeds.com).

Discussion

In this review of 210 articles examining childhood exposures and the development of subclinical and clinical CVD among adults, robust evidence linked increased pediatric adiposity with subclinical and clinical CVD; robust evidence linked pediatric hypertension, hyperlipidemia, and risk factor clustering with subclinical CVD, but limited evidence to date linked these factors with adult clinical CVD. Robust evidence linked low birthweight, worse SES, and psychosocial adversity with clinical CVD, but limited evidence was available for subclinical CVD. Breastfeeding, poor glycemic control, tobacco exposure, less physical activity, and worse diet quality during childhood all had limited numbers of studies across heterogeneous populations, and more research is necessary to determine whether those factors are consistently associated with subclinical and clinical CVD among adults. One promising new study to address some of the existing gaps in the research is the International Childhood Cardiovascular Cohort Consortium Outcomes Study (i3C Outcomes), in which detailed biological, physical, and socioeconomic measures collected in childhood are being harmonized across 7 existing longitudinal cohorts, and connected with self-reported incident CVD endpoints, medical records to adjudicate these endpoints, and national death records to explore CVD-related mortality.[217] We found no consistent evidence for major sex differences in risk of subclinical or clinical CVD for childhood risk factors. Most studies that examined sex differences found similar associations for men and women with null interaction terms. In contrast, few studies examined potential differences by race and/or

ethnicity; most cohorts had samples that were homogenous in race/ethnicity, and therefore did not permit analyses of this nature. Furthermore, the majority of cohorts were based in the US or Europe, with majority White populations. Few studies in this review were from cohorts based in Africa, Latin America, or Asia. New recruitment of diverse cohorts is needed to adequately understand any complex racial/ethnic differences in the associations between childhood risk factors and adulthood CVD, and special consideration should be given to global cohorts that have been underrepresented in previous research.

The majority of systematic reviews and meta-analyses linking childhood exposures and adult outcomes have focused on the development of risk factors in adulthood, such as hypertension or dyslipidemia. However, several have examined subsets of this comprehensive review. A systematic review published in 2014 relating either early life BP, BMI, and/or glycemic control to future cardiac structure and/or function found all 3 risk factors to be associated with worse future diastolic function.[218] The age of exposure criteria differed, in that articles with young adults over age 20 years were included, but nevertheless, conclusions were similar to those we observed for childhood BMI and BP and LV structure and function. In another systematic review of childhood socioeconomic circumstances and CVD risk in adulthood published in 2006, the authors concluded that childhood SES was a robust predictor of adulthood CVD risk, as we have concluded in this review.[219]

There are multiple life course models (Figure 3) that may reflect contributory pathways from childhood exposure to adulthood CVD. Articles that have more robust associations with CVD as the exposure is measured in adolescence as compared with early childhood or in adulthood as compared with childhood may support a chain-of-risk life course model. This finding demonstrates that childhood risk factors may increase the likelihood of having adulthood risk factors, but the adulthood risk factor status primarily affects the outcome, which represents an encouraging pediatric model because childhood risk status may be modifiable, with favorable long-term consequences.[5]

Articles that find the highest risk of adulthood CVD among those with persistent exposures in childhood and adulthood may represent an accumulation-of-risk model, whereby exposures at each point in the life course further increase likelihood of CVD development. Furthermore, in a sensitive period model, exposure at a certain point in the life course confers increased risk that is less harmful at a different time point. Both the accumulation-of-risk and sensitive periods models highlight the necessity of prevention in early childhood and the prenatal period, to decrease the likelihood of having the exposure and thus developing CVD in adulthood. Several complexities of longitudinal research emerged in this literature review.[4] A prospective cohort with decades of follow-up requires a substantial investment of resources; consequently, a limited number of unique cohorts exist. There were multiple articles using the same cohort data, perhaps oversaturating findings that are specific to the sample population. Childhood exposures were frequently assessed retrospectively, leading to broad measures that are subject to recall bias. Other cohorts used medical and other administrative records to collect childhood exposures and/or adult CVD events. The increased use of electronic medical records may be a novel method to facilitate research on childhood exposures, but some risk factors are not routinely collected in clinical encounters, such as lifestyle behaviors.

Although many of the cohorts followed participants for decades, often the adulthood exposure assessments were conducted around ages 30–40 years. Although population-level subclinical atherosclerotic differences may be present by those ages, CVD events are rare. The studies that did use a prospective cohort design were, therefore, mostly examining "premature" CVD. It is likely that findings would shift with additional years of data collection and thus continued resources to encourage follow-up of these cohorts is necessary to capture the natural history of CVD. Further, few articles directly accounted for differential loss to follow-up in which healthier individuals are more likely to continue participating in the study and less likely to have a severe competing risk (such as non-CVD-related death), resulting in survivor bias toward the null.

Incomplete adjustment for confounding was major source of threat to internal validity. Retrospective studies often had only a few questions about childhood, limiting the adjustment for contextual factors that could influence the outcome and the exposure. For example, studies on birthweight and adulthood CVD often lacked data on maternal health, which could include family history of CVD risk. Prospective studies tended to have a greater range of childhood risk factors measured, but often lacked behavioral and lifestyle factors that could inform clinical risk factors in childhood, continuing into adulthood. External validity to contemporary prevention settings was limited by exposures that have had significant secular change over the course of follow-up. For example, dietary patterns and tobacco exposure—particularly secondhand tobacco exposure in children—have shifted over time. Findings must, therefore, be placed into context before applying them to preventive strategies.

Last, there are limitations in how the literature review was conducted and the results reported. This review was intended to broadly cover childhood exposure to known CVD risk factors and the relationship to adulthood subclinical and clinical CVD. We created search terms based on the extant knowledge of major CVD risk factors, and studies focused on emerging areas of research, such as the prenatal environment or neurodevelopment health, may not be not be fully captured in our systematic search. Further, with the known publication bias in the biomedical literature whereby articles with statistically significant findings are more likely to be submitted and accepted, analyses with null findings are likely underrepresented within our study and may bias our results toward significant findings. Given the breadth of the topic, we were unable to give detailed assessment of the quality of each of the included studies, and there may be differences in methodology, for example, sample size, sampling frame, adjustment for potential confounders, potential for measurement error, that impact the relative strength of the evidence. If the findings of a study were counter to the other included studies for a similar exposure and outcome, we did attempt to provide additional details to understand the divergent findings. Finally, the heterogeneous nature of the exposure measurements, outcome ascertainment, duration of follow-up, and background environment of the studies, as well as the potential for oversaturation from specific study cohorts precluded reliable quantification of associations through meta-analysis.

In conclusion, an examination of childhood risk factors and their associations with adulthood subclinical and clinical CVD reveals a large and varied body of evidence in which

some areas of consistency can be discerned. As robust evidence emerges demonstrating that risk of CVD-related morbidity and mortality have origins in childhood, pediatric clinicians can continue to be encouraged to address major risk factors in their practice, understanding that they may alter life-long health trajectories and improve outcomes across decades for their patients. Likewise, the public health implications of intervening on childhood risks factors such as obesity or pediatric hypertension can amount huge improvements in the population-level incidence of CVD, as well as improvements in the long-term sequalae of chronic disease: years of potential life lost, disability adjusted life years, and overall spending on healthcare.

Nevertheless, major gaps remain in the research and in understanding how childhood health behaviors translate to risk of CVD later in life. This review is intended to update the current data to guide future research not only towards to addressing gaps, but also toward developing novel risk factor trajectories, cardiovascular health growth curves, and a priori exploration of maternal and intergenerational risk transmission. It may also point the way to future interventional studies designed to decrease the long-term incidence of subclinical and clinical CVD.

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Data Statement

Data sharing statement available at www.jpeds.com.

Glossary

BP	Blood pressure
BMI	Body mass index
CVD	Cardiovascular disease
cIMT	Carotid intima-media thickness
CHD	Coronary heart disease
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LV	Left ventricular
MetS	Metabolic syndrome
SES	Socioeconomic status

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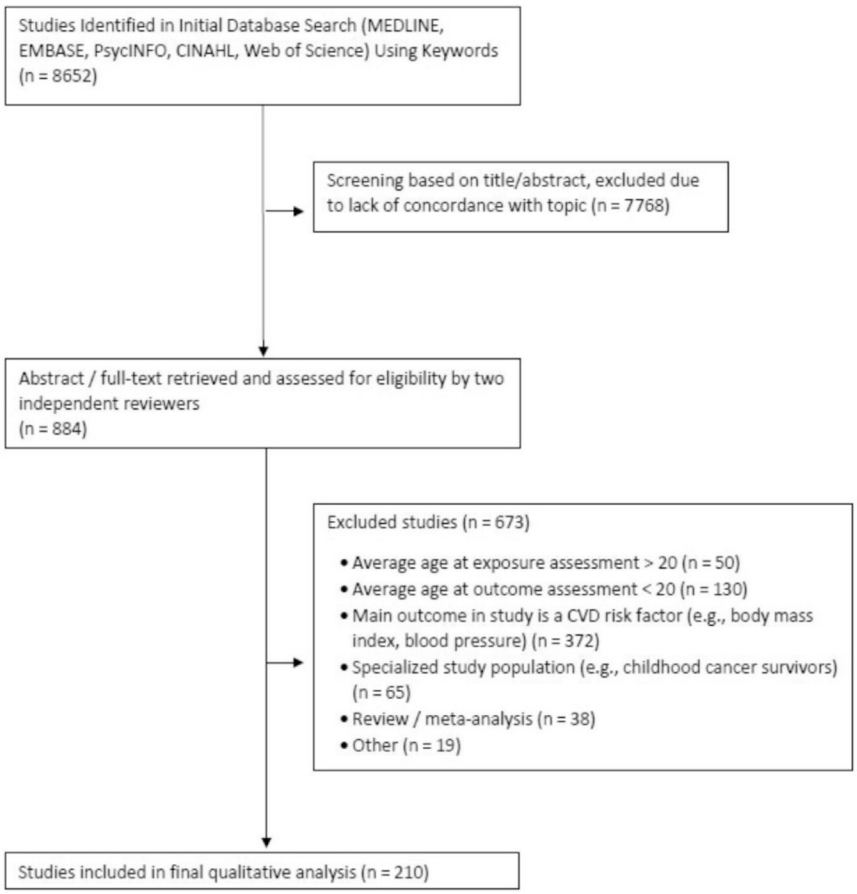

Figure 1.

The CONSORT diagram illustrates the review search and extraction process, from the initial database search to the studies included in the final qualitative analysis.

Childhood Risk Factor	# of papers	Subclinical CVD				Clinical CVD			
		Arterial Stiffness	cIMT	CAC	LV structure and function	CHD	Stroke	Heart failure	CVD Mixed Definition
Increased Adiposity	61	3 papers: higher risk 5 papers: null	19 papers: higher risk 1 papers: null	1 paper: higher risk	11 papers: higher risk	9 papers: higher risk 2 papers: null	6 papers: higher risk 1 papers: null	2 papers: higher risk	10 papers: higher risk
Low Birthweight	28	1 paper: higher risk 1 paper: null	no papers	no papers	1 paper: null	13 papers: higher risk	3 papers: higher risk 1 paper: null	no papers	8 papers: higher risk
Pediatric Hypertension	29	9 papers: higher risk 1 paper: null	10 papers: higher risk 1 paper: null	2 papers: higher risk	7 papers: higher risk 1 paper: null	2 papers: higher risk	no papers	no papers	3 papers: higher risk
Pediatric Hyperlipidemia	16	no papers	10 papers: higher risk	2 papers: higher risk	1 paper: higher risk	1 paper: higher risk	no papers	no papers	3 papers: higher risk
High Glycemic Indicators	2	1 paper: null	1 paper: higher risk	no papers	no papers	no papers	1 paper: higher risk	no papers	no papers
Tobacco Exposure	7	no papers	3 papers: higher risk	1 paper: higher risk	no papers	1 paper: higher risk	1 paper: higher risk	no papers	3 papers: higher risk
Physical Activity	6	4 papers: lower risk	2 papers: lower risk	no papers	no papers	no papers	no papers	no papers	1 paper: null
Dietary Quality	9	3 papers: lower risk 1 paper: null	3 papers: lower risk	no papers	no papers	1 paper: null	2 papers: lower risk	no papers	no papers
Breastfeeding	6	1 paper: null	1 paper: lower risk 1 paper: null	no papers	no papers	1 paper: lower risk 1 paper: null	1 paper: null	no papers	1 paper: null
Low Socioeconomic Status	13	no papers	2 papers: null	no papers	1 paper: higher risk	2 papers: higher risk	2 papers: higher risk	no papers	7 papers: higher risk
Psychosocial Adversity	18	1 paper: higher risk 2 papers: null	4 papers: higher risk	1 paper: higher risk	no papers	3 papers: higher risk	1 paper: higher risk	1 paper: higher risk	5 papers: higher risk 1 paper: null
Metabolic Syndrome	9	1 paper: higher risk	5 papers: higher risk	no papers	no papers	no papers	no papers	no papers	3 papers: higher risk
Other Risk Factor Clustering	7	2 papers: higher risk	6 papers: higher risk	1 paper: higher risk	no papers	no papers	no papers	no papers	no papers

Figure 2.

Heat map of identified articles examining childhood exposures and adulthood CVD. Each box lists the number of articles corresponding the exposure and CVD outcome pair. Yellow indicates that only null associations have been observed between the exposure and outcome. Colors deepen from light orange to red with an increasing number of articles indicating the exposure may be associated with higher CVD outcome risk. Colors deepen from light green to dark green with an increasing number of articles indicating the exposure may be associated with lower CVD outcome risk. Gray indicates that no articles examining the

exposure and outcome pair were identified in this review. Articles that included multiple subtypes of CVD (eg, CHD and stroke) in the outcome without estimating the association for each subtype of CVD separately were classified as “CVD Mixed Definition”.

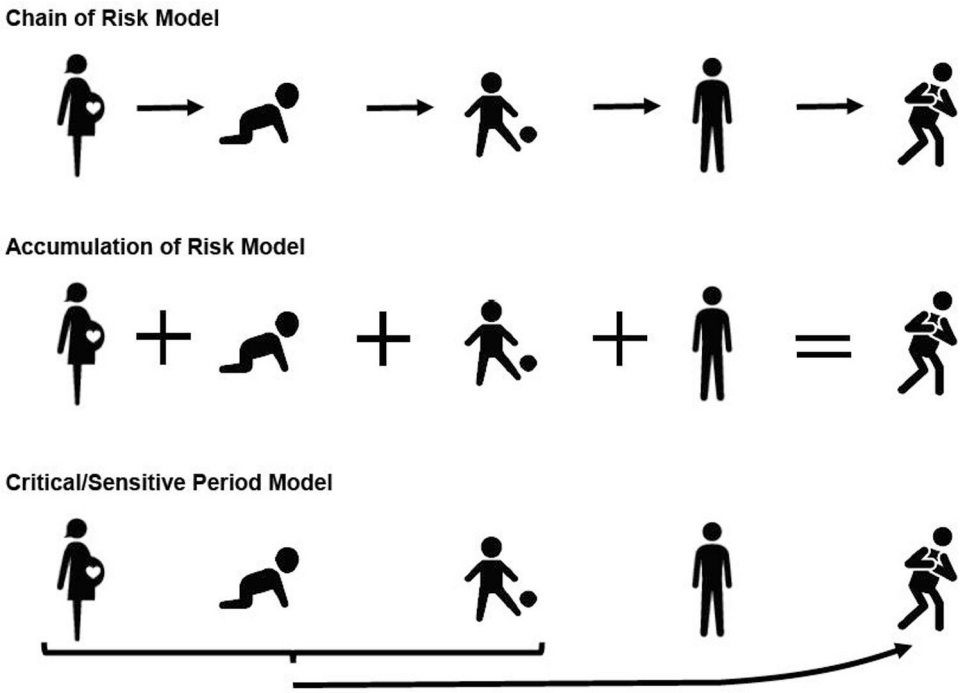

Figure 3.

Life course models for CVD development. The 3 hypothesized life course models for the development of CVD: chain of risk, where childhood risk is entirely mediated through adulthood risk; accumulation of risk, where risk factors present at each life stage further increase adulthood risk; and the critical/sensitive period, where exposure at a certain point in the life course confers more risk as compared with other life course stages.

Table I.

Review search terms

Concepts	Terms
Population at the time of exposure	fetal environment, birth, childhood through age 20 years Terms: child*, adolescen*, infan*, puberty, youth
Childhood exposure	Terms: metabolic syndrome, MetS, blood pressure, BP, hypertens*, cholesterol, lipid, hypercholesterolemia, dyslipidemia, hyperlipidemia, triglycerides, statin, glucose, glycemic, diabet*, insulin, adiposity, obes*, weight, waist circumference, BMI, body mass index, body composition, body size, diet*, nutri*, food*, intake, beverage*, physical activit*, exercise, fitness, sedentary, acceleromet*, smok*, cigar*, tobacco, secondhand, cotinine, preterm, birthweight, gestation*, breastfeed*, advers*, adverse childhood experiences, emotional distress, socioeconomic*, parental death, in utero
Population at the time of outcome	adulthood age 20 years and older Terms: adult*, middle age, older age

Table II.

Description of adulthood clinical and subclinical CVD outcomes included in the literature review

Characteristics	Description	Common clinical presentation
Types of clinical CVD		
CHD also known as ischemic heart disease, coronary artery disease	Reduced blood flow to the heart due to narrowing or obstruction of the coronary arteries (atherothrombosis)	Myocardial infarction, angina, sudden cardiac death
Stroke	Reduced blood flow to the brain due to a blockage or rupture of the arteries supplying the brain	Ischemic stroke, hemorrhagic stroke, transient ischemic attack
Heart failure	Inability of the heart to supply body's circulatory needs, commonly due to heart muscle pump dysfunction or inadequate relaxation	Congestive heart failure - syndrome manifested by shortness of breath, decreased exertional tolerance, and/or peripheral edema
Measurement methods		
Arterial stiffness	Reduced elasticity of the large arteries	Pulse wave velocity - speed that systolic BP wave travels through the vascular system body. Distensibility and compliance - measures of volume and pressure in an artery during heart muscle contraction
Arterial wall thickness	Thickening of the large arterial walls, tracks the presence and progression of atherosclerosis	cIMT, the thickness of innermost 2 layers of the wall of the artery, where atherosclerosis develops
Arterial calcification	Build-up of calcium in the large arteries, marker of atherosclerosis	Coronary artery calcium scan determines the area and density of calcium deposits, which correlates with overall coronary plaque burden
Endothelial dysfunction	Ability of the small arteries to dilate and constrict properly	Flow mediated dilation - measures the ability of the artery to dilate as blood flow increases after ischemia
LV structure and function	Enlarged mass and thickness of the walls of the left ventricle (hypertrophy) and reduced volume of blood pumped from the left ventricle (ejection fraction) are subclinical signs of heart failure	Echocardiography - produces images of the left ventricle to measure: LV mass, LV hypertrophy, Relative wall thickness, LV ejection fraction

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Table III.

Listing of all articles described and cited in the main text

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Ceponiene et al[7]	2015	Kaunas Cardiovascular Risk Cohort study	380	BP, adiposity	Objective	cIMT arterial stiffness	Objective	Continuous outcome	Higher BP and BMI associated with thicker cIMT in women only higher BP and BMI null association with PWV, both sexes		X	
Yan et al[8]	2017	Beijing Blood Pressure Cohort	1252	BP adiposity	Objective	cIMT arterial stiffness	Objective	Categorical outcome	Higher SBP and BMI associated with thicker cIMT, both sexes higher SBP associated with greater PWV, both sexes BMI null association with PWV, both sexes		X	
Ferreiraet al[9]	2004	Amsterdam Growth and Health Longitudinal Study	159	Adiposity	Objective	cIMT arterial stiffness	Objective	Categorical outcome	Higher BMI associated with thicker cIMT BMI null association with PWV no differences by sex		X	
Huynh et al[10]	2013	Childhood Determinants of Adult Health (CDAH)	2328	Adiposity	Objective	cIMT arterial stiffness	Objective	Continuous outcome	Higher BMI associated with thicker cIMT BMI null association with PWV no differences by sex		X	
Ferreira et al[11]	2012	Amsterdam Growth and Health Longitudinal Study	373	BP adiposity	Objective	Arterial stiffness	Objective	Continuous outcome	Highest tertile arterial stiffness had greater mean SBP, and greater mean BMI			
Juonala et al[12]	2005	The Cardiovascular Risk in Young Finns Study	2255	BP adiposity multiple risk factors	Objective	Arterial stiffness	Objective	Continuous outcome	Higher SBP and skinfold thickness associated with reduced arterial compliance greater number of risk factors associated with reduced arterial compliance			
Vianna et al[13]	2014	Pelotas (Brazil) Birth Cohort Study	3701	Breastfeeding, birthweight, adiposity	Self-reported	Arterial stiffness	Objective	Continuous outcome	Null association between breastfeeding or birthweight and PWV higher relative			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
									weight gain associated with greater arterial stiffness			
Su et al[14]	2014	YOung TAiwanese Cohort (YOTA) Study	789	Adiposity	Objective	cIMT	Objective	Categorical outcome	Childhood overweight and obesity associated with high cIMT			
Hao et al[15]	2018	Georgia Stress and Heart study	626	Adiposity	Objective LV	cIMT structure and function	Objective	Continuous outcome	Higher BMI groups associated with thicker cIMT and greater LV mass index			
Raitakari et al[16]	2003	The Cardiovascular Risk in Young Finns Study	2229	Lipids BP adiposity tobacco exposure multiple risk factors	Objective	cIMT	Objective	Continuous outcome	Greater LDL-C, SBP, BMI, smoking, and number of risk factors present was associated with thicker cIMT in men and women, when stratified by age groups 39 years and 12–18 years, only significant in 1218 years	X	X	
Oren et al[17]	2003	Atherosclerosis Risk in Young Adults (ARYA)	750	Adiposity	Objective	cIMT	Objective	Continuous outcome	A 1-SD increase in BMI associated with thicker cIMT			
Juonala et al[18]	2011	Combined cohort of Bogalusa Heart Study, Muscatine Heart Study, Childhood Determinants of Adult Health, and Cardiovascular Risk in Young Finns Study	6328	Adiposity	Objective	cIMT	Objective	Event rate	Overweight/obese associated with thicker cIMT as compared with normal weight no differences by sex		X	
Li et al[19]	2003	Bogalusa Heart Study	486	Adiposity BP lipids	Objective	cIMT	Objective	Categorical outcome	Higher LDL-C and BMI associated with high cIMT; null association for SBP, HDL-C, triglycerides			
Koskinen et al[20]	2018	combined cohort of Bogalusa Heart Study, the Insulin Study, Childhood Determinants of Adult Health, and Cardiovascular	2893	Adiposity BP lipids	Objective	cIMT	Objective	Event rate	Prehypertension, hypertension, overweight, obesity, borderline high LDL-cholesterol , high LDL-cholesterol and borderline low HDL-			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
		Risk in Young Finns Study							cholesterol associated with thicker cIMT; triglycerides not associated with cIMT			
Juonala et al[21]	2010	Combined cohort of Bogalusa Heart Study, Muscatine Heart Study, Childhood Determinants of Adult Health, and Cardiovascular Risk in Young Finns Study	4380	Adiposity BP lipids multiple risk factors	Objective	cIMT	Objective	Categorical outcome	Higher BMI, SBP associated with thicker cIMT; higher total cholesterol and number of risk factors only associated with thicker cIMT in exposure age 9–18; no association for triglycerides no sex differences	X	X	
Juonala et al[22]	2010	Cardiovascular Risk in Young Finns Study	1809	Adiposity lipids physical activity diet multiple risk factors	Objective	cIMT	Objective	Continuous outcome	Low HDL-C, obesity, low physical activity, infrequent fruit consumption, and number of risk factors associated with thicker cIMT; no association for LDL-C or triglycerides no sex differences		X	
Juonala et al[23]	2006	Cardiovascular Risk in Young Finns Study	2260	Adiposity	Objective	cIMT	Objective	Continuous outcome	Overweight/obese associated with thicker cIMT as compared with normal weight			
Freedman et al[24]	2004	Bogalusa Heart Study	513	Adiposity	Objective	cIMT	Objective	Continuous outcome	Higher BMI associated with thicker cIMT, more strongly associated among women than men, and among White subjects than Blacks, and among ages 15–18 years at exposure as compared with younger ages	X	X	X
Koskinen et al[25]	2014	Cardiovascular Risk in Young Finns Study	1617	Adiposity MetS	Objective	cIMT	Objective	Event rate	Overweight/obese and MetS associated with thicker cIMT			
Menezes et al[26]	2016	Bogalusa Heart Study	3264	Adiposity	Objective	cIMT	Objective	Continuous outcome	Higher BMI associated with thicker cIMT no sex differences			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Davis et al[27]	2001	Muscatine Heart Study	725	Adiposity Lipids	Objective	cIMT	Objective	Categorical outcome	Higher BMI associated with thicker cIMT in women only higher LDL associated with thicker cIMT in both men and women		X	
Johnson et al[28]	2014	MRC National Survey of Health and Development Study	1273	Adiposity	Objective	cIMT	Objective	Categorical outcome	Higher BMI associated with thicker cIMT in males only, and only at exposure ages 4 and 20	X	X	
Charakida et al[29]	2014	MRC National Survey of Health and Development Study	1273	Adiposity	Objective	cIMT	Objective	Continuous outcome	Overweight/obese not associated with thicker cIMT			
Sabo et al[30]	2014	Fels Longitudinal Study	697	Adiposity BP	Objective	LV structure and function	Objective	Continuous outcome	Higher BMI associated with greater LV mass in both men and women, but not associated with wall thickness BP not associated with LV mass or thickness		X	
Yang et al[31]	2017	Childhood Determinants of Adult Health	8498	Adiposity	Objective	LV structure and function	Objective	Continuous outcome	Higher BMI associated with worse cardias function			
Hardy et al[32]	2016	MRC National Survey of Health and Development Study	1617	Birth weight adiposity	Objective	LV structure and function	Objective	Continuous outcome	Birthweight not associated with LV mass no sex differences higher BMI associated with higher LV mass		X	
Li et al[33]	2004	Bogalusa Heart Study	467	Adiposity	Objective	LV structure and function	Objective	Continuous outcome	Higher BMI associated with greater LV mass, stronger association in Blacks as compared with Whites			X
Tapp et al[34]	2014	Childhood Determinants of Adult Health	181	Adiposity	Objective	LV structure and function	Objective	Continuous outcome	Higher BMI associated with greater LV mass no sex differences		X	
Lai et al[35]	2014	Bogalusa Heart Study	1061	Adiposity BP	Objective	LV structure and function	Objective	Continuous outcome	Higher SBP and BMI associated with greater LV mass			
Yan et al[36]	2017	Beijing Blood Pressure Cohort	1256	Adiposity BP	Objective	LV structure and function	Objective	Categorical outcome	Higher SBP and BMI associated with LV hypertrophy			

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References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Zhang et al[37]	2017	Bogalusa Heart Study	710	Adiposity	Objective	LV structure and function	Objective	Categorical outcome	Higher BMI associated with greater LV mass			
Sivanandam et al[38]	2006	Fifth- to eighth-grade students in the Minneapolis and St. Paul, Minnesota, public schools with top 15% BP	132	Adiposity	Objective	LV structure and function	Objective	Continuous outcome	Higher BMI associated with greater LV mass			
Toprak et al[39]	2008	Bogalusa Heart Study	824	Adiposity BP	Objective	LV structure and function	Objective	Categorical outcome	Higher BMI and DBP associated with LV hypertrophy, association stronger in Blacks as compared with Whites			X
Mahoney et al[40]	1996	Muscatine Heart Study	384	Adiposity BP lipids	Objective	Coronary artery calcification	Objective	Categorical outcome	Higher BMI and SBP, and lower HDL-C associated with presence of coronary artery calcification no sex differences		X	
Berenson et al[41]	2016	Bogalusa Heart Study	5991	Adiposity BP	Objective	Clinical CVD: CHD	Objective	Categorical outcome	Higher BMI and BP associated with greater CHD death			
Lawlor et al[42]	2006	Combined cohort of the Boyd- Orr, Christ's Hospital, Glasgow Alumni studies	14 561	Adiposity	Objective	Clinical CVD: CHD clinical CVD: stroke	Objective	Time to event	Higher BMI associated with greater rate of CHD death no association with rate of stroke death no sex differences		X	
Andersen et al[43]	2010	Danish and Finnish individuals born 1924–1976	216 771	Birth weight adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Low birthweight and higher BMI associated with higher risk of CHD			
Falkstedt et al[44]	2007	Swedish military conscription between 1949 and 1951	49 321	Adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Higher BMI associated with greater risk of CHD and stroke study sample includes men only		X	
Eriksson et al[45]	1999	Men who were born at the Helsinki University Central	3641	Birth weight adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Lower birthweight, higher BMI, and faster change in BMI across childhood associated with greater risk of		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
		Hospital, 1924–1933							CHD death study sample includes men only			
Baker et al[46]	2007	Copenhagen schoolchildren born from 1930 to 1976	289 044	Adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Higher BMI associated with greater CHD risk; stronger associations for women vs men and those who had high BMI at age 13 vs age 7 years	X	X	
Crump et al[47]	2017	Swedish military conscripts, 1969–1997	1 547 407	Adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Overweight or obese associated with increased risk of CHD study sample includes men only		X	
Must et al[48]	2012	Third Harvard Growth Study	1877	Adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Overweight associated with increased risk of CHD, among men only		X	
Osler et al[49]	2009	Men born in Copenhagen, Denmark in 1953	9143	Birth weight adiposity	Objective	Clinical CVD: CHD	Objective	Time to event	Low birthweight and higher BMI associated with higher risk of CHD study sample includes men only		X	
Lawlor et al[50]	2005	Aberdeen Children of the 1950's Study	11 106	Adiposity	Objective	Clinical CVD: CHD clinical CVD: stroke	Objective	Time to event	Higher BMI not associated with CHD obesity associated with increased risk of stroke no sex differences		X	
Park et al[51]	2013	Three British birth cohorts, born in 1946,1958 and 1970	11 447	Adiposity	Objective	Clinical CVD: CHD	Self-reported	Categorical outcome	Overweight not associated with risk of CHD			
Gjaerde et al[52]	2017	Copenhagen schoolchildren born from 1930–1987	307 677	Adiposity	Objective	Clinical CVD: stroke	Objective	Time to event	Higher BMI and faster weight gain during childhood associated with risk of stroke no sex differences		X	
Ohlsson et al[53]	2017	Men born in Gothenburg, Sweden from 1945–1961	37 669	Adiposity	Objective	Clinical CVD: stroke	Objective	Time to event	Faster weight gain in childhood associated with increased risk of stroke study sample includes men only		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Crump et al[54]	2016	Swedish military conscripts, 1969–1997	1 547 294	Adiposity	Objective	Clinical CVD: stroke	Objective	Time to event	Overweight or obese associated with increased risk of stroke study sample contains men only		X	
Hogstrom et al[55]	2015	Swedish military conscription between 1969–1986	811 579	Adiposity diabetes	Objective	Clinical CVD: stroke	Objective	Time to event	Higher BMI and type 2 diabetes associated with increased risk of stroke study sample contains men only		X	
Crump et al[56]	2017	Military conscripts in Sweden during 1969–1997	1 330 610	Adiposity	Objective	Clinical CVD: heart failure	Objective	Time to event	Higher BMI associated with higher risk of heart failure study sample contains men only		X	
Rosengren et al[57]	2017	Military conscripts in Sweden during 1968–2005	1 610 437	Adiposity	Objective	Clinical CVD: heart failure	Objective	Time to event	Higher BMI associated with higher risk of heart failure study sample contains men only		X	
Twig et al[58]	2017	military conscripts in ISRAEL during 1967–2010	2 294 139	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Higher BMI associated with higher risk of CVD no sex differences		X	
Bjorge et al[59]	2008	National tuberculosis screening in Norway, 1963–1975	226 678	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Obesity associated with greater risk of CVD death no sex differences		X	
Twig et al[60]	2016	Military conscripts in Israel during 1967–2010	2 298 130	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Higher BMI associated with higher risk of CVD death			
Batty G et al[61]	2016	1947 Scottish Mental Survey	3839	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Higher weight at age 11 years was associated greater CVD mortality			
Gunnell et al[62]	1998	Boyd Orr cohort	2399	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Obesity associated with greater risk of CVD death stronger association in exposure age >8 years than younger than 8 years	X		
Imai et al[63]	2014	Icelanders born between 1921 and 1935 and living in Reykjavik	1924	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Faster BMI velocity associated with greater risk of CVD mortality no sex differences		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Zheng et al[64]	2017	Combined cohort of the Nurses' Health Study and the Health Professionals Follow-up Study	122 498	Adiposity	Self-reported	Clinical CVD: mixed definition	Self-reported	Time to event	Those who had higher BMI in childhood had greater risk of CVD, stronger associations for women as compared with men		X	
Must et al[65]	1992	Third Harvard Growth Study	508	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Higher BMI associated with greater CVD mortality risk, among men only		X	
Morrison et al[66]	2012	Princeton Lipid Research Clinics Follow-Up Study	770	Adiposity	Objective	Clinical CVD: mixed definition	Self-reported	Categorical outcome	High BMI associated with higher CVD risk			
Furer et al[67]	2018	Military conscripts in Israel during 1967–2010	2 294 139	Adiposity	Objective	Clinical CVD: mixed definition	Objective	Time to event	Higher BMI associated with higher CVD mortality no sex differences		X	
Bhuiyan et al[68]	2010	Bogalusa Heart Study	538	Birth weight	Objective	Arterial stiffness	Objective	Continuous outcome	Low birthweight associated with reduced arterial compliance		X	X
Rich-Edwards et al[69]	1997	Nurses' Health Study	70 297	Birth weight	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Low birth weight associated with increased risk of nonfatal CVD study sample included women only		X	
Lawani et al[70]	2014	Atherosclerosis Risk in Communities	10 132	Birth weight	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Low birth weight associated with higher risk of atrial fibrillation			
Larsson et al[71]	2015	Swedish Inpatient Register cohort	53 005	Birth weight	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Both low birth weight and high birth weight associated with increased risk of atrial fibrillation, among men only		X	
Baker J et al[72]	2008	Danish schoolchildren born from 1936–1979	216 464	Birth weight	Objective	Clinical CVD: mixed definition	Objective	Time to event	Both low and high birth weight associated with increased CVD mortality no sex differences		X	
Lawlor et al[73]	2004	British women's heart and health study	1394	Birth weight	Self-reported	Clinical CVD: CHD	Self-reported	Categorical outcome	Low birth weight was associated with greater		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
									CHD risk study sample included women only			
Lawlor et al[74]	2005	Aberdeen Children of the 1950's Study	10 803	Birth weight	Objective	Clinical CVD: CHD	Objective	Time to event	Low birth weight was associated with greater CHD risk			
Oberg et al[75]	2011	Population-based cohort of like-sexed twinswith known zygosity born in Sweden from 1926 to 1958	23 689	Birth weight	Objective	Clinical CVD: mixed definition	Objective	Categorical outcome	Birth weight was found to be inversely associated with risk of CVD within dizygotic but not monozygotic twin pairs			
Syddall et al[76]	2005	Hertfordshire Cohort Study	37 615	Birth weight	Objective	Clinical CVD: mixed definition	Objective	Time to event	Each SD lower birth weight associated with increased risk of CVD mortality no sex differences		X	
Frankel et al[77]	1996	Caerphilly Heart Disease Study	1258	Birth weight	Self-reported	Clinical CVD: CHD	Self-reported	Categorical outcome	Low birth weight associated with higher risk of CHD when adult BMI is also elevated study sample includes men only		X	
Rajaleid et al[78]	2008	Uppsala Birth Cohort	11 822	Birth weight	Objective	Clinical CVD: CHD	Objective	Time to event	Low birth weight associated with higher risk of CHD mortality, only present in higher social class men		X	
Eriksson et al[79]	2001	Helsinki Birth Cohort	4630	Birth weight	Objective	Clinical CVD: CHD	Objective	Time to event	Lower birthweight associated with higher risk of CHD study sample includes men only		X	
Osmond et al[80]	1993	Hertfordshire Cohort Study	4630	Birth weight	Objective	Clinical CVD: mixed definition	Self-reported	Categorical outcome	Low birthweight associated with higher risk of CVD no sex differences		X	
Johnson et al[81]	2011	Panel Study of Income Dynamics	4387	Birth weight SES	Objective	Clinical CVD: mixed definition	Self-reported	Categorical outcome	Low birth weight and childhood poverty associated with higher risk of CVD			
Forsen et al[82]	1999	Women born in Helsinki University Central	3447	Birth weight	Objective	Clinical CVD: mixed definition	Objective	Time to event	Both low birth weight associated with increased risk of CHD		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
		Hospital during 1924–33							study sample includes only women			
Osmond et al[83]	2007	Helsinki Birth Cohort	12 439	Birth weight adiposity	Objective	Clinical CVD: stroke	Objective	Time to event	Low birth weight and slow growth in first 2 years after birth associated with increased risk of stroke no sex differences		X	
Koupilova et al[84]	1999	Uppsala Birth Cohort	1334	Birth weight	Objective	Clinical CVD: mixed definition	Objective	Time to event	Low birth weight associated with higher CVD mortality study sample includes only men		X	
Rich-Edwards et al[85]	2005	Nurses' Health Study	66 111	Birth weight	Self-reported	Clinical CVD: CHD clinical CVD: stroke	Objective	Time to event	Low birth weight associated with higher risk of CHD, but no association with stroke study sample includes onlywomen		X	
Arnold et al[86]	2016	Prospective cohort in a remote Indigenous Australian community	852	Birth weight	Objective	Clinical CVD: mixed definition	Objective	Time to event	Low birth weight associated with higher risk of CVD, stronger association for women as compared with men		X	
Zoller et al[87]	2015	National cohort study of individuals who were live- born in Sweden in 1973 through 1992	1 984 858	Birth weight	Objective	Clinical CVD: CHD	Objective	Time to event	Low birth weight associated with higher risk of CHD			
Leon et al[88]	1998	Uppsala Birth Cohort	14 611	Birth weight	Objective	Clinical CVD: CHD	Objective	Time to event	Low birth weight associated with higher risk of CHD, among men only		X	
Smith et al[89]	2016	The Women's Health Initiative	63 815	Birth weight	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Low birth weight was associated with increased risk of CVD, associations less strong for Hispanic and African American women study sample includes onlywomen		X	X

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Hypponen et al[90]	2001	Uppsala Birth Cohort	14 611	Birth weight	Objective	Clinical CVD: stroke	Objective	Time to event	Low birth weight was associated with increased risk of stroke			
Forsen et al[91]	2004	Helsinki Birth Cohort	2345	Weight gain	Objective	Clinical CVD: CHD	Objective	Time to event	Lower weight gain in infancy associated with increased risk of CHD study sample included men only		X	
Forsen et al[92]	2004	Helsinki Birth Cohort	4130	Weight gain	Objective	Clinical CVD: CHD	Objective	Time to event	Lower weight gain in infancy associated with increased risk of CHD study sample included women only		X	
Leunissen et al[93]	2012	PROgramming factors for GRowth And Metabolism (PROGRAM) study	323	Weight gain	Self-reported	cIMT	Objective	Continuous outcome	Faster weight gain in childhood associated with thicker cIMT			
Terzis et al[94]	2012	Cohort from Athens, Greece recruited in 1983	106	Weight gain	Self-reported	cIMT	Objective	Continuous outcome	Faster weight gain in childhood associated with thicker cIMT			
Chu et al[95]	2017	Hanzhong adolescent hypertension cohort	4623	BP	Objective	Arterial stiffness	Objective	Continuous outcome	Higher SBP associated with greater arterial stiffness			
Xi et al[96]	2017	Bogalusa Heart Study	1225	BP	Objective	cIMT arterial stiffness LV structure and function	Objective	Time to event	Pediatric hypertension associated with high cIMT, greater arterial stiffness, and LV hypertrophy			
Liang et al[97]	2014	Beijing Blood Pressure Cohort	1259	BP	Objective	cIMT arterial stiffness LV structure and function	Objective	Categorical outcome	Pediatric hypertension associated with high cIMT, greater arterial stiffness, and LV hypertrophy			
Li et al[98]	2004	Bogalusa Heart Study	835	BP	Objective	Arterial stiffness	Objective	Categorical outcome	Higher SBP associated with greater arterial stiffness			
Aatola et al[99]	2017	Cardiovascular Risk in Young Finns Study	1540	BP	Objective	arterial stiffness	Objective	Event rate	High BP not associated with arterial stiffness, unless adult BP levels		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
									were also high; no sex differences			
Aatola et al[100]	2013	Cardiovascular Risk in Young Finns Study	1241	BP	Objective	Arterial stiffness	Objective	Categorical outcome	High BP associated with greater arterial stiffness			
Vos et al[101]	2003	Atherosclerosis Risk in Young Adults (ARYA)	750	BP	Objective	cIMT	Objective	Continuous outcome	Higher BP associated with thicker cIMT			
Hao et al[102]	2017	Georgia Stress and Heart study	551	BP	Objective	cIMT LV structure and function	Objective	Continuous outcome	Higher BP associated with thicker cIMT and greater LV mass no sex differences	X		
Juhola et al[103]	2013	International Childhood Cardiovascular Cohort Consortium	4210	BP	Objective	cIMT	Objective	Event rate	High BP associated with thicker cIMT			
Hartiala et al[104]	2012	Young Finns	589	BP lipids	Objective	Higher SBP and LDL- C associated with coronary artery calcification	Objective	Categorical outcome	Higher SBP associated with presence of coronary artery calcification			
Magnussen et al[105]	2014	prospective cohort of 181 individuals	181	BP lipids	Objective	LV structure and function	Objective	Continuous outcome	Higher triglycerides and higher DBP associated with greater LV mass			
Sundstrom et al[106]	2011	Swedish military conscription between 1969–1995	1207329	BP	Objective	Clinical CVD: mixed definition	Objective	Time to event	BP associated with increased CVD study sample includes men only	X		
Silventoinen et al[107]	2008	Swedish military conscription between 1969 and 1994	1 145 758	BP	Objective	clinical CVD: mixed definition	Objective	Time to event	BP associated with increased CVD across levels of BMI, strongest in obese study sample includes men only	X		
Leiba et al[108]	2016	Israeli military conscription between 1967–2010	2 298 130	BP	Objective	Clinical CVD: mixed definition	Objective	Time to event	Pediatric hypertension associated with increased risk of CVD mortality			
Erlingsdottir et al[109]	2010	Children admitted to Landspitali University	126	BP	Objective	Clinical CVD: CHD	Self-reported	Categorical outcome	Pediatric hypertension associated with increased risk of CHD			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
		Hospital in Iceland for elective surgical procedures between 19501967										
Juonala et al[110]	2008	Cardiovascular Risk in Young Finns Study	2265	lipids Multiple risk factors	Objective	cIMT)	Objective	Continuous outcome	Type IIb dyslipidemia associated with thicker cIMT higher number of risk factors associated with thicker cIMT			
Li et al[111]	2007	Bogalusa Heart Study	868	Lipids	Objective	cIMT	Objective	Continuous outcome	Differences by race and sex in the association of lipids and thicker cIMT: White men, LDL-C and triglycerides significant; White women, LDL-C significant ; Black women, LDL-C significant; Black men, no significant association for any lipid levels	X	X	
Magnussen et al[112]	2009	Combined cohort of Bogalusa Heart Study, Childhood Determinants of Adult Health, and Cardiovascular Risk in Young Finns Study	1711	Lipids	Objective	cIMT	Objective	Categorical outcome	Dyslipidemia associated with thicker cIMT			
Frontini et al[113]	2008	Bogalusa Heart Study	437	lipids	Objective	cIMT	Objective	Categorical outcome	Higher LDL-C associated with high cIMT; no association for HDL-C and triglycerides			
Morrison et al[114]	2012	Princeton Lipid Research Clinics Follow-Up Study	909	Lipids	Objective	clinical CVD: mixed definition	Self-reported	Categorical outcome	High triglycerides associated with increased risk of CVD			
Morrison et al[115]	2009	Princeton Lipid Research Clinics Follow-Up Study	808	Lipids	Objective	Clinical CVD: mixed definition	Self-reported	Time to event	High triglycerides associated with increased risk of CVD			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Yajnik et al[116]	2015	Pune Children's Study	357	Glycemic indicators	Objective	cIMT	Objective	Continuous outcome	Higher fasting glucose associated with thicker cIMT			
McCarron et al[117]	2001	Glasgow Alumni study	8354	Tobacco exposure	Objective	Clinical CVD: mixed definition	Objective	Time to event	All categories of smoking exposure associated with higher risk CVD, with significant linear trend for amount of smoking study sample included men only		X	
Whitley et al[118]	2012	Harvard Alumni Health Study	28 236	Tobacco exposure	Objective	Clinical CVD: mixed definition	Objective	Time to event	Smoking associated with higher risk of CVD mortality study sample included men only		X	
Choi et al[119]	2017	National Health Interview Survey linked to the National Death Index	90 278	Tobacco exposure	Self-reported	Clinical CVD: mixed definition	Objective	Categorical outcome	Current and former smokers who started smoking at or before age 16 had higher risk of CVD	X		
Geerts et al[120]	2008	Atherosclerosis Risk in Young Adults (ARYA)	732	Tobacco exposure	Self-reported	cIMT	Objective	Continuous outcome	In utero parental smoking exposure associated with thicker cIMT			
Gall et al[121]	2014	Cardiovascular Risk in Young Finns Study	1375	Tobacco exposure	Self-reported	cIMT	Objective	Continuous outcome	Greater exposure to parental smoking was associated with thicker cIMT			
West et al[122]	2015	Cardiovascular Risk in Young Finns Study	2448	Tobacco exposure	Self-reported	coronary artery calcification	Objective	Event rate	Greater exposure to parental smoking was associated with higher risk of presence of coronary artery calcification			
Palve et al[123]	2014	Cardiovascular Risk in Young Finns Study	2416	Physical activity	Objective	Arterial stiffness	Objective	Continuous outcome	Greater physical activity associated with lower arterial stiffness, among men only		X	
van de Laar et al[124]	2011	Amsterdam Growth and Health Longitudinal Study	373	Physical activity	Objective	Arterial stiffness	Objective	Continuous outcome	Vigorous activity associated with lower arterial stiffness, no associations for light/ moderate activity			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
van de Laar et al[125]	2010	Amsterdam Growth and Health Longitudinal Study	373	Physical activity	Objective	Arterial stiffness	Objective	Continuous outcome	Vigorous activity associated with lower arterial stiffness			
Ried-Larsen et al[126]	2015	European Youth Heart Study, Danish participants only	277	Physical activity	Objective	Arterial stiffness	Objective	Continuous outcome	Higher physical activity levels associated with lower arterial stiffness			
Drca et al[127]	2014	Population-based cohort of Swedish men	44 410	Physical activity	Objective	clinical CVD: mixed definition	Objective	Time to event	No association between physical activity and atrial fibrillation study sample included men only		X	
Aatola et al[128]	2010	Cardiovascular Risk in Young Finns Study	1622	Diet	Objective	Arterial stiffness	Objective	Continuous outcome	Higher fruit and vegetable intake associated with lower arterial stiffness			
van de Laar et al[129]	2012	Amsterdam Growth and Health Longitudinal Study	373	Diet	Self-reported	Arterial stiffness	Objective	Continuous outcome	Lower intake of fiber associated with lower arterial stiffness			
van de Laar et al[130]	2013	Amsterdam Growth and Health Longitudinal Study	373	Diet	Self-reported	Arterial stiffness	Objective	Continuous outcome	Greater adherence to the Mediterranean diet pattern associated with lower arterial stiffness			
McCourt et al[131]	2014	Northern Ireland Young Hearts Project	487	Diet	Self-reported	Arterial stiffness	Objective	Continuous outcome	No association between adherence to Mediterranean diet pattern and arterial stiffness			
Kaikkonen et al[132]	2013	Cardiovascular Risk in Young Finns Study	823	Diet	Self-reported	cIMT	Objective	Continuous outcome	Saturated, monounsaturated, and polyunsaturated fat consumption associated with thicker cIMT, but omega-3 fatty acid consumption associated with less thick cIMT, among women only	X		

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Mikkila et al[133]	2009	Cardiovascular Risk in Young Finns Study	785	Diet	Self-reported	cIMT	Objective	Continuous outcome	Traditional Finnish dietary pattern (characterized by intake of rye, potatoes, butter, milk, sausages, and coffee) was associated with thicker cIMT, among men only	X		
van der Pols et al[134]	2009	Boyd Orr cohort	4374	Diet	Self-reported	clinical CVD: mixed definition	Objective	Time to event	Diet high in calcium associated with lower risk of stroke mortality, no association with CHD mortality			
Ness et al[135]	2005	Boyd Orr cohort	1234	Diet	Self-reported	clinical CVD: stroke	Objective	Time to event	Higher intake of vegetables and lower intake of fish associated with lower risk of stroke death			
Jarvisalo et al[136]	2009	Cardiovascular Risk in Young Finns Study	3596	Breastfeeding	Self-reported	Endothelial function cIMT	Objective	Continuous outcome	Breastfeeding in infancy associated with higher endothelial function, among men only breastfeeding in infancy not associated with cIMT	X		
Martin et al[137]	2005	Boyd Orr cohort	362	Breastfeeding	Self-reported	cIMT	Objective	Continuous outcome	Breastfeeding in infancy associated with less thick cIMT			
Rich-Edwards et al[138]	2004	Nurses' Health Study	87252	Breastfeeding	Self-reported	Clinical CVD: CHD clinical CVD: stroke	Objective	Time to event	Breastfeeding in infancy not associated with CHD or stroke			
Martin et al[139]	2004	Boyd Orr cohort	3555	Breastfeeding	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Breastfeeding in infancy not associated with CVD mortality			
Fall et al[140]	1992	Hertfordshire Cohort Study	5718	Breastfeeding	Self-reported	Clinical CVD: CHD	Objective	Event rate	Breastfeeding in infancy associated with CHD, but only among those who had weaned before 1 year study sample included men only	X		

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Kivimaki et al[141]	2005	Cardiovascular Risk in Young Finns Study	2290	SES	Self-reported	cIMT	Objective	Continuous outcome	No association between SES and cIMT			
Kivimaki et al[142]	2006	Cardiovascular Risk in Young Finns Study	1922	SES	Self-reported	cIMT endothelial function	Objective	Continuous outcome	No association between SES and cIMT No association between SES and flow-mediated dilation No sex differences		X	
Laitinen et al[143]	2017	Cardiovascular Risk in Young Finns Study	1871	SES	Self-reported	LV structure and function	Objective	Continuous outcome	Low family SES was associated with higher LV mass			
Smith et al[144]	1998	cohort of men aged 35–64 who were recruited from workplaces in the west of Scotland between 1970 and 1973	5766	SES	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Father's occupation status associated with risk of CHD and stroke mortality			
Kittleson et al[145]	2006	John Hopkins Precursors Study	1131	SES	Self-reported	Clinical CVD: CHD	Objective	Time to event	Low parental SES associated with increased incidence of CHD			
Lynch et al[146]	1994	Kuopio Ischaemic Heart Disease Risk Factor Study	2636	SES	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Low parental SES associated with increased incidence of CVD only if adult SES also low Study sample included men only		X	
Gliksman et al[147]	1995	Nurses' Health Study	117 006	SES	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Low childhood SES associated with higher risk of CVD Study sample included women only		X	
Heshmati et al[148]	2017	Uppsala Birth Cohort	10 593	SES	Self-reported	Clinical CVD: stroke	Objective	Time to event	Social mobility was associated with risk of stroke, among women only		X	
Lawlor et al[149]	2006	Aberdeen Children of the 1950's Study	12 150	SES	Self-reported	clinical CVD: mixed definition	Objective	Time to event	Father's occupation status associated with risk of CHD and stroke mortality			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
Melchior et al[150]	2006	GAZEL Cohort Study	20 570	SES	Self-reported	clinical CVD: mixed definition	Objective	Time to event	Low SES only associated with higher risk of CVD if adult SES was also low			
Kamphuis et al[151]	2012	GLOBE study	11 701	SES	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Lowest group of childhood SES associated with higher risk of CVD mortality			
Osler et al[152]	2003	Project Metropoli	11 376	SES	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Low SES in early life was associated with higher CVD mortality risk			
Anderson et al[153]	2018	Avon Longitudinal Study of Parents and Children	4957	Psychosocial adversity	Self-reported	cIMT arterial stiffness	Objective	Continuous	Cumulative psychosocial adversity in childhood not associated with cIMT or arterial stiffness; Study sample included women only		X	
Rotar et al[154]	2015	survivors of the Leningrad siege with age-sex matched individuals	356	psychosocial adversity	Self-reported	LV structure and function	Objective	Continuous outcome	Exposure to famine not associated with LV mass			
Thurston et al[155]	2014	Study ofWomen's Health Across the Nation	1369	Psychosocial adversity	Self-reported	cIMT	Objective	Continuous outcome	A history of childhood sexual abuse, but not childhood physical abuse was associated with thicker cIMT Study sample included women only		X	
Loucks et al[156]	2014	Coronary Artery Risk Development in Young Adults (CARDIA) Study	2659	Psychosocial adversity	Self-reported	cIMT	Objective	Continuous outcome	Adverse childhood family psychosocial environment associated with thicker cIMT in White men and women, but not in Black men or White		X	X
Cruickshank et al[157]	2016	The Determinants of Adolescent, Now Young Adult, Social Wellbeing, and Health	666	Psychosocial adversity	Self-reported	Arterial stiffness	Objective	Continuous outcome	Greater perceived racism associated with greater arterial stiffness			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
		Longitudinal Study										
Juonala et al[158]	2016	Cardiovascular Risk in Young Finns Study	311	Psychosocial adversity	Self-reported	Coronary artery calcification	Objective	Categorical outcome	Favorable childhood psychosocial environment associated with lower likelihood of the presence of coronary artery calcification			
Head et al[159]	2008	individuals born in Guernsey Island 1923–1937, later occupied by Germans during WWII	873	Psychosocial adversity	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Exposure to war-related occupation associated with higher risk of CVD			
Korkeila et al[160]	2010	Health and Social Support Study	23 916	Psychosocial adversity	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Greater number of adversities associated with greater risk of CVD, among women only		X	
Halonen et al[161]	2015	Finnish Public Sector Study	37 699	Psychosocial adversity	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Higher childhood adversity only associated with greater CVD risk if adult neighborhood disadvantage was also low			
Morton et al[162]	2014	National Survey of Midlife Development in the United States	3032	Psychosocial adversity	Self-reported	Clinical CVD: CHD	Self-reported	Categorical outcome	Higher levels of childhood misfortune associated with greater risk of CHD			
Woo et al[163]	2010	elderly individuals in Hong Kong attending health check	3732	Psychosocial adversity	Self-reported	Clinical CVD: CHD	Self-reported	Categorical outcome	Exposure to famine associated with greater risk of CHD			
Dong et al[164]	2004	Kaiser Permanente's Health Appraisal Center	17 337	Psychosocial adversity	Self-reported	Clinical CVD: CHD	Self-reported	Categorical outcome	Number of childhood adverse childhood experiences associated with greater risk of CHD			
Hollingshaus et al[165]	2015	Utah Population Database	663 729	Psychosocial adversity	Self-reported	Clinical CVD: mixed definition	Objective	Time to event	Early-life parental death was associated with a higher risk of		X	

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
									CVD mortality No sex differences			
Robertson et al[166]	2017	Swedish military conscription between 1968–2005	1 784 450	Psychosocial adversity	Self-reported	Clinical CVD: heart failure	Objective	Time to event	Low stress resilience associated with higher risk of heart failure Study sample included men only		X	
Garad et al[167]	2017	National Population Health Survey	4048	Psychosocial adversity	Self-reported	clinical CVD: mixed definition	Self-reported	Categorical outcome	Greater number of adversities associated with greater risk of CVD, among women only		X	
Bergh et al[168]	2014	Swedish military conscription	237 879	Psychosocial adversity	Self-reported	Clinical CVD: stroke	Objective	Time to event	Lower stress resiliency group associated with greater risk of stroke Study sample included men only		X	
Shi et al[169]	2018	China Health and Retirement Longitudinal Study	5772	Psychosocial adversity	Self-reported	Clinical CVD: mixed definition	Self-reported	Categorical outcome	Exposure to famine in childhood associated with lower risk of CVD			
Magnussen et al[170]	2012	Combined cohort of Bogalusa Heart Study and Cardiovascular Risk in Young Finns Study	1757	MetS	Objective	cIMT	Objective	Event rate	Persistent MetS associated with greater risk of high cIMT			
Koskinen et al[171]	2017	Combined cohort of Bogalusa Heart Study, Cardiovascular Risk in Young Finns Study, Minnesota Insulin Study, and Princeton Lipid Research Clinics Follow-Up Study	5803	MetS	Objective	cIMT	Objective	Categorical outcome	MetS associated with greater risk of high cIMT, among exposure age groups 1118 years only No sex differences	X	X	
Magnussen et al[172]	2016	Cardiovascular Risk in Young Finns Study	1453	MetS	Objective	cIMT	Objective	Categorical outcome	MetS associated with greater risk of high cIMT			
Magnussen et al[173]	2010	Combined cohort of Bogalusa Heart Study and	1781	MetS	Objective	cIMT	Objective	Event rate	MetS associated with greater risk of high cIMT, but BMI only			

References	Year	Study cohort	Sample size	Exposure(s) measured in childhood	Type of exposure measurement (objective vs self-reported)	Outcome(s) measured in adulthood	Type of outcome measurement (objective vs self-reported)	Type of outcome analysis	Main finding(s)	Population subgroup analyses		
										Age group	Sex	Race/ ethnicity
		Cardiovascular Risk in Young Finns Study							has the same predictive capacity			
Koivistoinen et al[174]	2011	Cardiovascular Risk in Young Finns Study	945	MetS	Objective	Arterial stiffness	Objective	Continuous outcome	MetS associated with greater arterial stiffness			
DeBoer et al[175]	2016	Princeton Lipid Research Clinics Follow-Up Study	711	MetS	Objective	Clinical CVD: mixed definition	Self-reported	Categorical outcome	MetS associated with greater risk of CVD			
Morrison et al[176]	2007	Princeton Lipid Research Clinics Follow-Up Study	771	MetS	Objective	Clinical CVD: mixed definition	Self-reported	Categorical outcome	MetS associated with greater risk of CVD			
DeBoer et al[177]	2015	Princeton Lipid Research Clinics Follow-Up Study	341	MetS	Objective	Clinical CVD: mixed definition	Self-reported	Categorical outcome	MetS associated with greater risk of CVD			
Laitinen et al[178]	2012	Cardiovascular Risk in Young Finns Study	856	Number of risk factors	Objective	cIMT	Objective	Categorical outcome	Greater number risk factors associated with greater risk for high cIMT			
Laitinen et al[179]	2015	Cardiovascular Risk in Young Finns Study	370	Number of risk factors	Objective	Coronary artery calcification	Objective	Event rate	Lower number of risk factors associated with decreased risk of presence of coronary artery calcification No sex differences		X	

DBP, diastolic BP; *SBP*, systolic BP; *PWV*, pulse wave velocity.

Table IV.

Additional articles identified, not described in main text

References	Year	Study population	Exposure	Outcome	Main findings
Tatsukawa et al[180]	2008	1559 Japanese men and women atomic bomb survivors	Amount of radiation exposure in utero	CVD: mixed definition	Greater dose of radiation associated with greater risk of CVD
Roseboom et al[181]	2000	736 men and women born during Dutch famine in 1943–1947	Exposure to famine in utero	CVD: CHD	Exposure to famine in early gestation associated with higher risk of CHD
Ekamper et al[182]	2015	41 096 male military conscripts born in the Netherlands between 1944 and 1947	Exposure to famine in utero	CVD: mixed definition	No increase in CVD mortality associated with prenatal famine exposure
Painter et al[183]	2007	Dutch Famine Birth Cohort, 2414 men and women born in Amsterdam in 1943–1947	Exposure to famine in utero	Arterial stiffness	Exposure to famine in utero was not associated with arterial stiffness in adulthood
van Abeelen et al[184]	2012	Dutch Famine Birth Cohort, 2414 men and women born in Amsterdam in 1943–1947	Exposure to famine in utero	CVD: mixed definition	Women exposed to famine in early gestation had a high risk of CVD mortality, no association among men
Rerkasem et al[185]	2012	565 twenty-year-olds whose mothers, while pregnant, participated in a nutritional study during 1989–1990 in Chiang Mai, Thailand	Maternal protein intake during pregnancy	cIMT	Lower maternal protein intake during pregnancy was associated with thicker cIMT in adulthood
Eriksson et al[183]	2014	Helsinki Birth Cohort, 13 345 men and women born in Helsinki, Finland during 1934–1944	Maternal BMI during pregnancy	CVD: mixed definition	Higher maternal BMI associated with increased risk of CVD in adulthood
Kajantie et al[187]	2009	Helsinki Birth Cohort, 6410 men and women born in Helsinki, Finland during 1934–1944	Exposure to preeclampsia or gestational hypertension in utero	CVD: stroke only	Exposure to preeclampsia or gestational hypertension in utero associated with increased risk of stroke in adulthood
Bjarnegard et al[188]	2013	37 young adults born at term with IUGR and controls in Malmo, Sweden	IUGR	LV structure and function	IUGR associated with small LV diameter
Skilton et al[189]	2011	Cardiovascular Risk in Young Finns Study	Impaired fetal growth	cIMT and endothelial function	Impaired fetal growth was associated with impaired endothelial function and thicker cIMT in adulthood
Fan et al[190]	2010	2033 men and women born in Beijing, China between 1921 and 1954	Fetal growth retardation	CVD: CHD only	Fetal growth retardation associated with increased risk of CHD in adulthood
Ueda et al[191]	2014	1 306 943 infants born in Sweden between 1983 and 1995	Preterm birth	CVD: mixed definition	No association between preterm birth and CVD, except among for those born very preterm - higher incidence of stroke
Kajantie et al[192]	2015	Helsinki Birth Cohort, 19 015 men and women born in Helsinki, Finland during 1934–1944	Preterm birth	CVD: CHD and stroke	No increased risk of CHD or stroke in people born preterm, except for women born early preterm (<34 weeks)
Lewandowski et al[193]	2013	234 men and women 20 to 39 years of age who underwent cardiovascular magnetic resonance in Oxford, UK	Preterm birth	LV structure and function	Preterm birth associated with increased LV mass in adulthood
Risnes et al[194]	2009	31 307 Norwegian men and women born between 1934 and 1959	Placenta-to-birth-weight ratio	CVD: mixed definition	Higher placenta-to-birth-weight ratio associated with increased risk of CVD mortality

References	Year	Study population	Exposure	Outcome	Main findings
Barker et al[196]	2010	Helsinki Birth Cohort, 13 345 men and women born in Helsinki, Finland during 1934–1944	Placental surface area	CVD: heart failure	Small placental surface area (<225 cm^2) was associated with increased risk of heart failure in adulthood
Risnes et al[195]	2009	46 311 births in Trondheim, Norway, from 1920 to 1959	Head circumference at birth	CVD: CHD/MI	Small head size at birth associated with increased risk of CHD death
Gunnell et al[198]	1998	Boyd-Orr Cohort, 2547 children living in England and Scotland in 1937–1939	Age and sex specific z scores for height, leg length, and trunk length	CHD	Shorter leg length associated with higher risk of CHD in both men and women, only for 8 and under
Silventoinen et al[199]	2012	232 063 children born in 19301976 who attended school in Copenhagen, Denmark	Growth in height from 7 to 13 years of age	CVD: CHD/MI	Height was inversely related to risk of CHD, but rapid growth in height was also associated with increased CHD risk
Whitley et al[200]	2012	Boyd-Orr Cohort, 1043 children living in England and Scotland in 1937–1939	Childhood stature: height, shoulder breadth, leg, trunk and foot length	CVD: mixed definition	Childhood stature associated with CVD morbidity and mortality in adulthood
Batty et al[201]	2007	Hertfordshire Cohort, 4351 children in UK	Diarrhea in early childhood (age 05 years)	CHD	No evidence that diarrhea in early life associated with increased risk of CHD in older adults
Mueller et al[202]	2012	Singapore Chinese Health Study, 34 022 women	Age at menarche	CVD: mixed definition	Higher age at menarche associated with lower risk of CHD among nonsmokers, but no association for smokers or stroke
Canoy et al[203]	2015	Million Women Study, 1 217 840 women based in UK	Age at menarche	CVD: mixed definition	U-shaped association, early and late ages at menarche associated with increased CVD risk
Wang et al[204]	2016	CHARLS: 2013 China Health and Retirement Longitudinal Study -nationally representative of Chinese residents aged ≥45, 10 000 men and women	Self-reported health in childhood (retrospective assessment)	CHD	Poor childhood health associated with higher risk of CHD
Juonala et al[205]	2006	Cardiovascular Risk in Young Finns Study, 1617 children	C-reactive protein levels	cIMT	Childhood C-reactive protein did not predict adult cIMT
Du et al[206]	2018	Bogalusa Heart Study, 1052 men and women	Serum adiponectin levels and BMI	cIMT	Association between higher BMI and thicker cIMT only present in those with childhood adiponectin levels below the median
Saarikoski et al[207]	2017	Cardiovascular Risk in Young Finns Study	Serum adiponectin levels	cIMT	Lower adiponectin levels associated thicker cIMT in adulthood
Batty et al[208]	2005	6910 men born in 1953 in Copenhagen, Denmark	Childhood intelligence test scores, as measured by the Swedish Harnqvist intelligence test	CVD: mixed definition	Low intelligence associated with increased risk of CHD by not stroke
Keltikangas-Jarvinen et al[209]	2006	Cardiovascular Risk in Young Finns Study, 708 children	Hyperactivity in childhood	cIMT	Hyperactivity predicted cIMT
Dedman et al[210]	2001	Boyd-Orr Cohort, 4301 children living in England and Scotland in 1937–1939	Housing conditions included crowding, water supply, toilet facilities, adequacy of ventilation, and cleanliness	CHD	Poorer housing conditions in childhood were associated with increased CHD mortality, independent from SES

References	Year	Study population	Exposure	Outcome	Main findings
Howard et al[211]	2013	Reasons for Geographic and Racial Differences in Stroke study, 24 544 stroke-free men and women enrolled 2003–2007	Residence in stroke belt during childhood	CVD: stroke only	Residence in the stroke belt important during adolescence, effect stronger in Blacks vs Whites
Aberg et al[212]	2015	1 166 035 Swedish male military conscripts registered in 1968–2005	Aerobic fitness and muscle strength	CVD: stroke only	Low fitness and low muscle strength associated with increased risk of stroke
Ferreira et al[213]	2002	Amsterdam Growth and Health Longitudinal Study, 154 men and women in the extended cardiorespiratory follow-up	Aerobic fitness	cIMT and arterial stiffness	Increased aerobic fitness associated with thinner cIMT and less arterial stiffness
Ferreira et al[214]	2003	Amsterdam Growth and Health Longitudinal Study, 154 men and women in the extended cardiorespiratory follow-up	Changes in VO_{2max} from adolescence to age 36	cIMT and arterial stiffness	Increases in VO2max from adolescence to age 36 were associated with less arterial stiffness, but no association with cIMT
Lindgren et al[215]	2017	1 226 623 Swedish male military conscripts registered in 1969–2005	Cardiorespiratory fitness	Heart failure	Greater fitness associated with lower risk of hospitalization for heart failure
Hogstrom et al[216]	2014	743 498 Swedish male military conscripts registered in 1969–1984	Aerobic fitness	CVD: CHD/MI	Low aerobic fitness associated with increased risk of myocardial infarction

IUGR, intrauterine growth restriction; *MI,* myocardial infarction.