Life course socioeconomic influences on risk of cardiovascular disease in low- and middle-income countries

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Declaration

I, Poppy Mallinson, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Poppy Mallinson, November 2020

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Abstract

Background: Cardiovascular disease is the leading cause of premature death in most low- and middle-income countries. Studies suggest that socioeconomic factors acting at various points in an individual's life course can strongly influence their later risk of cardiovascular disease. However, evidence is mostly from high-income countries, and may not generalise to low- and middle-income countries where the material conditions associated with low socioeconomic position, and the socioeconomic patterning of risk factors, are distinct. Given the limited data on cardiovascular disease from low- and middle-income countries, there remain substantial gaps in our knowledge around the association between socioeconomic factors across the life course and risk of cardiovascular disease. This thesis aims to identify and fill several evidence gaps in this area by reviewing the existing evidence and analysing secondary data from two populous middle-income countries.

Objectives (corresponding to specific evidence gaps identified for low- and middle-income countries):

1. To examine the association between socioeconomic position in adulthood and cardiovascular mortality (method: analysis of the states of Brazil using national mortality and census data)
2. To summarise the existing evidence on socioeconomic position in childhood and risk of cardiovascular disease in adulthood (method: systematic literature review)
3. To evaluate the association between socioeconomic position in childhood and risk of cardiovascular disease in adulthood (method: analysis of pooled cohorts from India)
4. To evaluate the association between parents' socioeconomic position in childhood and risk of cardiovascular disease in their adult offspring (method: analysis of an intergenerational cohort in rural India)

Findings: Evidence from the states of Brazil suggests that lower socioeconomic groups are at a higher risk of cardiovascular mortality regardless of the stage of area-level economic development. Through a systematic review, I identified limited evidence on the association between childhood socioeconomic position and cardiovascular disease, while studies of cardiovascular risk factors showed little consistent evidence for an association. In India, I found some evidence to support an association between childhood poverty and increased blood pressure (but not other cardiovascular risk factors); however, there was no evidence of an intergenerational effect of parents' poverty in childhood on cardiovascular risk factors or subclinical atherosclerosis in their adult offspring.

Conclusion: Limited evidence indicates that lower socioeconomic groups face a higher risk of mortality from cardiovascular disease across low- and middle-income countries. Childhood and intergenerational poverty appear to play a limited role in explaining this excess risk. Further evidence, especially from low- and lower middle-income countries, and with prospective measures of life course socioeconomic position and cardiovascular disease incidence and mortality, are needed to confirm these findings and elucidate possible mechanisms. In the meantime, policies to prevent cardiovascular disease in low- and middle-income countries should be oriented towards reducing the risk in lower socioeconomic groups, for example by reducing tobacco use, improving air quality, and promoting equitable access to cardiovascular disease treatments.

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Abbreviations

I have tried to keep use of abbreviations to a minimum throughout this thesis. All abbreviations are defined when they first appear in a chapter, and also below for reference.

APCAPS is Andhra Pradesh Children and Parents' Study

CI is Confidence Interval

CIMT is Carotid Intima-Media Thickness

CVD is Cardiovascular Disease

ECG is Electrocardiogram

GDP is Gross Domestic Product

HDI is Human Development Index

HDL is High-Density Lipoprotein

HIC is High-Income Country

HOMA is Homeostasis Model Assessment

ICD is International Classification of Diseases

IHD is Ischaemic Heart Disease

IMS is Indian Migration Study

IQR is Interquartile Range

LDL is Low-Density Lipoprotein

LMIC is Low- and Middle-Income Country

PURE is Prospective Urban Rural Epidemiology study

PRISMA is Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SD is Standard Deviation

SEP is Socioeconomic Position

SLI is Standard of Living Index

STROBE is Strengthening the Reporting of Observational Studies in Epidemiology

UK is United Kingdom

US is United States

WHO is World Health Organisation

Chapter 1: Introduction

1.1 Background

1.1.1 Cardiovascular disease in low- and middle-income countries

1.1.1.1 Definitions

The term “cardiovascular disease” is used in this thesis to refer to disorders of the heart and blood vessels linked to atherosclerosis and/or hypertension. Atherosclerosis and hypertension are involved in the pathophysiology of the vast majority of disorders of the cardiovascular system in adults, the main exceptions being rare genetic or infectious causes which are not considered further in this thesis. Atherosclerosis is the process whereby fatty and damaged tissue builds up in the walls of the arteries, which can eventually result in impaired flow of blood to vital organs. Hypertension is a state of chronic increased pressure in the arteries, which can weaken the artery walls and also contributes to atherosclerosis. Atherosclerosis and hypertension often occur together, and share a number of common environmental and behavioural determinants. The grouping of various cardiovascular diseases into one broad category therefore makes sense from a public health and epidemiological perspective. The main clinical subtypes of cardiovascular disease are heart disease and stroke, which together cause over 90% of cardiovascular deaths. Heart disease is usually the result of atherosclerosis in the arteries supplying the heart (ischaemic or coronary heart disease), although can be caused by chronic hypertension (hypertensive heart disease). Stroke can be the result of atherosclerosis in the arteries supplying the brain (ischaemic stroke), or due to a bleed in the brain often associated with hypertension (haemorrhagic stroke).

1.1.1.2 Epidemiology

Data on the epidemiology of cardiovascular disease in low- and middle-income countries is less comprehensive than in high-income countries. The absence of high-quality mortality registration systems, or other representative sources of prospective data, prevent accurate estimation of the burden of cardiovascular disease incidence and mortality in most low- and middle-income countries[1,2]. The Global Burden of Disease study has attempted to bridge some of these data gaps by using models to predict the distribution of causes of death and disease in every country[3]. However, the accuracy of these estimates varies substantially between different countries and health conditions, being inevitably limited by the availability of primary data sources. The study’s use of complex modelling techniques to combine data from multiple sources often makes it difficult to assess the data sources, and therefore the likely accuracy, underlying a given estimate[4]. Another source of information on global cardiovascular disease incidence and mortality is the Prospective Urban Rural Epidemiology (PURE) study, which is following over 150,000 adults from 21 low-, middle- and high-income countries[5]. Although this study enables standardised comparisons of countries at different income levels, participants in each country were purposively sampled from specific urban and rural communities (generally chosen based on convenience for the study operating site), so are not representative of their respective countries. In addition, 80% of the participants from low-income countries are from India (which is considered a low-income country in PURE analyses, although it has been classified as middle-income since 2007), suggesting that PURE estimates may not generalise to all low-income countries. Other sources of mortality information in countries lacking vital registration systems include Sample Registration Systems[6] and Health and Demographic Surveillance Sites[7]. These collect information on vital events across a random sample of the population, or in a specific geographic site, respectively. They tend to use verbal autopsies to ascertain causes of death, which have demonstrated reasonable validity for deaths occurring before the age of 70 years[8], but nevertheless are likely to be subject to more error than the medical certification of deaths in higher income countries. However, few countries have high-quality Sample Registration Systems (India being a notable example), while Health and Demographic Surveillance Sites, although more numerous, generally only cover a small geographical area. Bearing these data limitations in mind, in this section I describe some key features of the epidemiology of cardiovascular disease and its risk factors in low- and middle-income countries.

The Global Burden of Disease study estimated that a quarter of all premature deaths in low- and middle-income countries were due to cardiovascular disease in 2019 (10% in low-income countries, 23% in lower middle-income countries, and 29% in upper middle-income countries), making this the leading cause of premature death globally[9]. Data from other sources are broadly concordant with these estimates. For example, verbal autopsy data from Health and Demographic Surveillance Sites in urban areas of Burkina Faso and Kenya found that 12% and 15% of all deaths were due to cardiovascular disease, respectively, representing the single largest cause group[10,11]. In the nationally representative Sample Registration System of India, cardiovascular disease caused 19% of premature deaths[6], compared with 30% of all deaths in a similar study from Malaysia[12]. In Colombia and Brazil, national mortality statistics report that 22% and 27% of premature deaths are due to cardiovascular disease[13,14].

Risk of cardiovascular disease increases dramatically with age, leading to higher crude cardiovascular mortality rates in countries with older populations (i.e. higher income countries). However, limited data suggest that, after accounting for population age-structures, cardiovascular mortality tends to be higher in lower income countries (Figure 1.1, panels A, B and C). The Global Burden of Disease study estimated an age-standardised cardiovascular mortality rate of ~300/100,000 in low-income and lower middle-income countries, ~260/100,000 in upper middle-income countries, and ~130/100,000 in high-income countries in 2019, with a similar trend observed in the PURE study[15]. Studies from individual countries with nationally representative mortality data show a broadly consistent pattern, although interestingly both India and Malaysia reported lower cardiovascular mortality than was estimated by the Global of Burden of Disease study[12,16]. For example, age-standardised cardiovascular mortality was ~230/100,000 in India in 2015[16], ~200/100,000 in Malaysia in 2013[12], ~210/100,000 in Brazil in 2011[17], ~140/100,000 in the UK in 2011, and ~90/100,000 in Japan in 2011[9].

Data on the incidence of cardiovascular disease in the general population are particularly limited in low- and middle-income countries. The PURE and the Global Burden of Disease studies both suggest a higher age-standardised incidence of cardiovascular disease in lower income countries, similar to the pattern for mortality[9,15]. In PURE, the incidence of major cardiovascular disease (defined as hospitalisation for myocardial infarction (an acute form of ischaemic heart disease), stroke, or heart failure, or fatal cardiovascular disease) was 643/100,000 in low-income countries, 538/100,000 in middle-income countries, and 399/100,000 in high-income countries. Further standardised data on cardiovascular disease incidence from low- and middle-income countries would be valuable to confirm and understand the reasons behind the higher incidence of cardiovascular disease in low- and middle-income countries.

Heart disease and stroke, respectively, account for over 55% and 35% of cardiovascular deaths in low- and middle-income countries, according to the Global Burden of Disease study (Figure 1.1, panel D)[18]. The relative burden of these conditions varies between world regions, with stroke deaths being more common than heart disease deaths in East Asia[19] and Southeast Asia[20], but heart disease being more common than stroke (nearly two heart disease deaths to every stroke death) in South Asia[6] and in most high-income countries[21]. The reasons for these differences are unclear, but may relate to relative importance of hypertension in the pathophysiology of cardiovascular disease in lower income countries, as evidenced by the higher mortality from hypertensive heart disease and haemorrhagic stroke[18]. However, the reliability of data on stroke subtypes from most low- and middle-income countries is highly questionable, as these conditions cannot be distinguished through verbal autopsy, suggesting further data are needed to confirm this hypothesis.

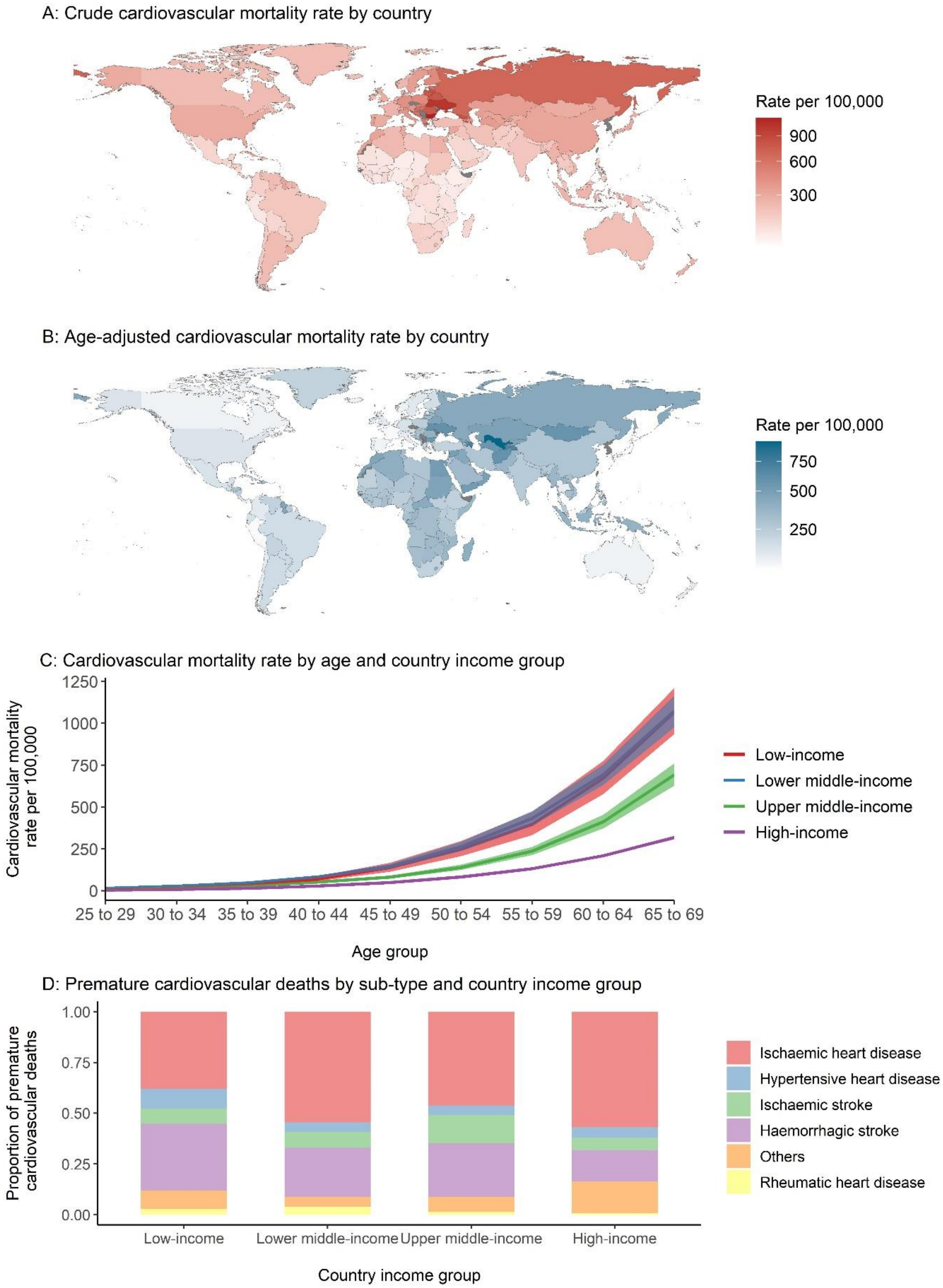

Figure 1. 1 Graphs describing the epidemiology of cardiovascular disease in low- and middle-income countries, 2019.
Figures were drawn by me using data from the Global Burden of Disease Study (2019), available at http://ghdx.healthdata.org/gbd-results-tool.

Early prospective studies from the United States proposed number of risk factors which are strongly predictive of cardiovascular disease, namely blood pressure, serum lipids, diabetes, and tobacco use[22]. Now well-established, these are known as the "conventional" or "traditional" cardiovascular risk factors. Obesity is sometimes included among these conventional risk factors, although its independent contribution to cardiovascular disease (beyond the other risk factors) is less clear. Data from prospective studies in low- and middle-income countries have generally reported similar or stronger associations between cardiovascular mortality and hypertension[23–25], diabetes[26,27], lipid levels[5], obesity[28–30] and tobacco use[31,32] compared with high-income countries. Our knowledge of the global distribution of these risk factors is more comprehensive than for cardiovascular disease incidence and mortality, because of the widespread use of nationally representative health monitoring surveys[33,34]. In a large meta-analysis, the prevalence of hypertension was ~30% across low- and middle-income countries, and was similar in high-income Asia-Pacific countries, but was lower in high-income western countries (~20%)[35]. On the other hand, meta-analyses have reported a higher prevalence of lipid abnormalities and obesity in higher income countries[36,37]. Trends for diabetes are less clear, with one global meta-analysis finding little difference in the prevalence between regions, except for a lower prevalence in Sub-Saharan Africa[38], while a multi-country survey found a higher prevalence of diagnosed diabetes in higher income countries[39]. The prevalence of tobacco use is highly variable between countries, but on average tends to be higher among men in low- and middle-income countries, and higher among women in high-income countries[40].

Cardiovascular disease and its risk factors are linked to a number of behavioural, environmental and psychosocial determinants. Behavioural determinants include physical inactivity and an unhealthy diet. Physical inactivity may be linked to cardiovascular disease through its influence on obesity and the other conventional risk factors, as well as through a direct effect on atherosclerosis via inflammatory pathways. However the relative importance of these pathways, and of various forms of physical activity (e.g. moderate, vigorous, weight-bearing), remain unclear[41]. In addition to the role of excess energy intake in obesity, specific components of diet have been linked to cardiovascular risk, including high dietary intake of saturated fats, trans fats, and sodium, and low dietary intake of fruit and vegetables and whole grains[42]. However, the precise causal elements of diet in cardiovascular disease have been difficult to tease out and remain subject to debate[43,44]. Environmental determinants of cardiovascular risk include ambient air pollution (for example emitted by motor vehicles and industrial facilities)[45], but also indoor air pollution (resulting from biomass fuel use in the home), which is particularly prevalent in many low- and middle-income countries[46]. More speculative determinants include psychosocial factors such as stress and depression[47]. Although depression and (to a lesser extent) stress are associated with cardiovascular disease in meta-analyses from high-income countries[48,49], and in the few studies from low- and middle-income countries[50], the causal nature and mechanisms of these associations remain unclear.

Although cardiovascular disease mostly affects older adults, autopsy studies demonstrate that the process of atherosclerosis can begin from young adulthood or even adolescence[51]. This led to the recognition that risk factors across the life course, not just in adulthood, contribute to the development of cardiovascular disease[52]. Raised levels of cardiovascular risk factors have been observed from childhood onwards, although less commonly in low- and middle-income countries compared with high-income countries. In a global meta-analysis, the prevalence of obesity (defined as >2 standard deviations above the median weight-for-height) in children aged 0-5 years was 12% in high-income countries compared with 6% in low- and middle-income countries[53]. Global differences in childhood blood pressure are less pronounced, with one meta-analysis reporting a 3.5% prevalence of raised blood pressure (defined as >95th percentile for height and age of systolic or diastolic blood pressure) in children and adolescents in high-income countries, compared with a 4.4% prevalence in low- and middle-income countries[54]. In prospective studies from high-income countries, childhood obesity and (to a lesser extent) blood pressure are predictive of adult levels of these risk factors[55,56], subclinical atherosclerosis[57,58], impaired cardiac function[59], and cardiovascular disease[60,61]. The few prospective studies from low- and middle-income countries have examined childhood obesity. In two birth cohorts from India, childhood body mass index was directly associated with adult adiposity, but not consistently associated other cardiovascular risk factors[62–64]. However, in these studies, and in a pooled study of birth cohorts from five middle-income countries, relative weight gain during childhood was associated with increased risk of diabetes[65]. The inconsistent association between body mass index in childhood and cardiovascular risk in adulthood may reflect the low prevalence of childhood obesity in many low- and middle-income countries such as India until recently[66]. Further prospective evidence is needed to establish the role cardiovascular risk factors in early life for cardiovascular disease in these countries.

1.1.1.3 Prevention

In spite of the gradual declines in age-specific cardiovascular mortality occurring globally, the burden of cardiovascular disease is projected to increase as populations age in low- and middle-income countries[67]. This high and rising burden is associated with substantial social and economic costs. The World Health Organisation estimated the economic cost of cardiovascular disease in low- and middle-income countries to be over $250 billion per year, or roughly 2% of GDP, in 2010[68]. Because of the severe and often chronic nature of cardiovascular disease, it is associated with high out-of-pocket costs for households, which can in turn lead to impoverishment and further health problems[69].

In response to the threat to global health and social development posed by cardiovascular disease, the World Health Organisation's Global Action Plan for the Prevention and Control of Non-Communicable Diseases 2013-2020 set the ambitious target of a 25% reduction in premature mortality from cardiovascular disease, cancer, diabetes or chronic respiratory diseases by 2025[70]. This commitment to tackling cardiovascular disease was reaffirmed in the 2015 Sustainable Development Goals (Goal 3.4), which aimed to reduce premature mortality due to non-communicable diseases by one third by 2030[71]. However, by 2019 there had been no reduction in premature mortality due to these non-communicable diseases[72], suggesting that additional solutions will be required to meet global targets.

Advances in the medical treatment and management of cardiovascular disease and its risk factors have played an important role in reducing premature death due to the condition in high-income countries[73]. However, such interventions can be expensive and resource intensive. Achieving widescale access to them in countries with weak health systems will be a challenge[74]. On the other hand, modelling studies have demonstrated that primary prevention of cardiovascular risk factors may be cheaper and more cost-effective than medical treatment and management[75]. Prevention of cardiovascular disease through action on its behavioural, environmental and psychosocial determinants could also align closely with other health and development agendas[76]. However, interventions aimed at modifying individuals' health behaviours (especially diet and activity) have only been modestly effective, possibly because such an approach fails to address the underlying social and cultural contexts within which health behaviours are embedded[77]. Some researchers have called for a broader approach that seeks to identify and tackle the determinants of cardiovascular risk behaviours – the so-called "causes of causes" of cardiovascular disease[78,79]. These broader social, economic and political determinants might provide important opportunities for intervention to prevent the rise of cardiovascular disease and its risk factors in low- and middle-income countries.

1.1.2 Socioeconomic position and cardiovascular disease

1.1.2.1 Definitions

The term "socioeconomic position" is used throughout this thesis to refer to the broad construct underlying commonly measured socioeconomic indicators such as occupation, education, income and wealth. This term is preferred to others (such as socioeconomic status and social class) because it is considered to incorporate both material resources and prestige-related aspects of social stratification[80]. Material resources influence the environmental conditions to which people are exposed[81], as well as constraining the availability of goods and services (including education, skills and healthcare), and influencing social prestige. Social prestige influences social norms, thereby determining behaviour and environment, as well as possibly constraining access to services, and providing structures for discrimination and psychosocial adversity[82]. Further discussion around the measurement of socioeconomic position, in particular in relation to research in low- and middle-income countries, is provided in section 1.1.2.5.

1.1.2.2 Socioeconomic position in adulthood

For more than a century, researchers in the UK and US noted an increased risk of cardiovascular mortality among adults of a lower occupational grade[83,84]. A large body of evidence now confirms the existence of inequalities in cardiovascular mortality, incidence and risk factors by a range of socioeconomic indicators in high-income countries[85–88]. Landmark reports such as the Black Report commissioned by the UK government in 1980[89], and the World Health Organisation's Commission on the Social Determinants of Health published in 2008[90], have called for policy action to tackle the inequitable burden of cardiovascular disease on disadvantaged socioeconomic groups. These signalled a shift in emphasis from describing the social distribution of diseases such as cardiovascular disease, to viewing socioeconomic factors as modifiable determinants of disease, and thus seeking to elucidate their aetiological mechanisms and develop interventions[91,92].

Several social theories have been advanced to explain how socioeconomic position influences risk of cardiovascular disease[93]. Perhaps most widely applied is the "social production of disease" theory, which proposes that the political and economic systems in which we operate create and maintain the social patterning of resources, behaviours, environments and healthcare access to generate health outcomes. In high-income countries, for example, unequal access to knowledge and resources results in the social patterning of healthy diets, physical activity, clean air, and timely and effective health care, which all contribute to inequalities in cardiovascular disease[78,94]. Ecosocial theory expands on these ideas to introduce the notion that social hierarchies can be biologically embedded, for example through chronic stress and inflammation, to generate inequalities in health outcomes[95]. Psychosocial theory emphasises the role of an individual's capacity to cope with stressors, and the role of supportive social environments for protecting against these stressors, in generating health outcomes[96]. These theories are not mutually exclusive, and the mechanisms they posit may act in conjunction or on different aspects of cardiovascular disease aetiology. Importantly, in highlighting that the association between socioeconomic position and cardiovascular disease is a product of the broader structural and political context, these theories emphasise the context-dependent nature of socioeconomic influences on health across places and times, and provide a theoretical basis to better understand these differences.

The most comprehensive analysis to date in high-income countries, using pooled data from 46 prospective studies, indicated that adults with a lower occupational socioeconomic position had a 50% increased risk of cardiovascular mortality[86]. The magnitude of this association was similar to that of several conventional cardiovascular risk factors. Systematic reviews have reported similar associations for cardiovascular disease incidence[87,97]. However, evidence on the association between adult socioeconomic position and cardiovascular disease incidence and mortality from low- and middle-income countries is more limited. Of the few prospective studies of cardiovascular disease mortality, several[14,98–100], but not all[101,102], demonstrated an inverse association with socioeconomic position, similar to high-income countries. However, these studies mostly assessed a limited geographical area, and all but one of them were from middle-income countries. To my knowledge, PURE is the only prospective study to have examined the association between adult socioeconomic position and cardiovascular incidence and mortality across multiple low-, middle- and high-income countries, and it found an inverse association all countries, which was strongest in the low-income countries[103]. Findings from a number of case-control and cross-sectional studies have reported inconsistent associations[39,104–107].

There is a larger body of evidence on the association between adult socioeconomic position and cardiovascular risk factors in low- and middle-income countries. In many low- and lower middle-income countries, studies have reported a direct association (i.e. higher risk in higher socioeconomic groups) between adult socioeconomic position and obesity[108], diabetes[39], blood pressure[109] and physical inactivity[110], in contrast to the inverse associations in high-income countries. On the other hand, studies from upper middle-income countries have generally reported non-linear or inverse associations[109,111–113], especially among women, more similar to high-income countries. Some researchers have attributed this difference in association between countries at different levels of economic development to a 'social cross-over' in the patterning of cardiovascular risk factors, from high to low socioeconomic groups, that occurs with economic development[114,115]. Specifically, it has been suggested that declines in subsistence agriculture and manual labour, and the increasing availability of cheap, energy-dense foods, lead to increased cardiovascular risk among lower socioeconomic groups as countries develop economically. At the same time, changing cultural norms, such as a preference for slim body types and leisure-time physical activity, may lead to decreased cardiovascular risk among higher socioeconomic groups. However not all cardiovascular risk factors conform to this theory, for example tobacco use is more prevalent among men from lower socioeconomic groups in most low- and middle-income countries, similar to high-income countries, while the association among women is less consistent[116].

Given the substantial body of evidence on socioeconomic position and risk of cardiovascular disease, but differing levels of evidence, and potential differences in associations, between different countries and different types of outcome (cardiovascular incidence, mortality, or risk factors), an overview of systematic reviews on this topic is presented in the next section (1.2).

1.1.2.3 Early life socioeconomic position

Early ecological studies in Norway and the UK highlighted the strong correlation between infant mortality in an area, and mortality from ischaemic heart disease several decades later[117,118]. This led a number of individual-level studies to investigate the hypothesis that poverty in infancy and childhood increases risk of later cardiovascular disease[119]. This evidence (mostly from high-income countries) provides strong support for an inverse association between childhood socioeconomic position and cardiovascular disease, which in most[120–126], but not all[127], studies was robust to adjustment for socioeconomic position in adulthood.

A number of mechanisms linked to poor childhood living conditions, such as in utero and childhood undernutrition and impaired growth, childhood exposure to indoor air pollution, and childhood stress and psychosocial adversity, have been proposed to explain this association[128–132]. The most well-developed of these theories suggests an effect of impaired foetal and childhood growth on later cardiovascular risk[133]. This hypothesis has been very influential, and formed the basis of a research field known as the Developmental Origins of Health and Disease (or DOHaD)[134]. The central proposition is that vulnerability to cardiovascular disease is affected (possibly irreversibly) by certain exposures in early life. Experimental studies in animals have implicated a number of specific pathways, such as dietary restriction in utero leading to stunted growth and endothelial dysfunction[135], insulin resistance[136], and impaired nephrogenesis and hypertension[137]. Despite strong support for an association of impaired foetal and childhood growth with cardiovascular disease in observational studies from high-income countries[138,139], interventions studies targeting intrauterine or early childhood nutrition have had limited effect on cardiovascular risk factors in adulthood[140,141], so the public health relevance of these pathways remains unclear.

Another set of explanations for the association between childhood socioeconomic position and cardiovascular disease relate to the early life establishment (and maintenance) of cardiovascular risk factors[95]. In high-income countries, obesity, blood pressure and (to a lesser extent) lipid levels are inversely associated with socioeconomic position from childhood onwards[142,143], especially in more recent cohorts[144]. Childhood levels of these risk factors are predictive of their levels in adulthood[56,145,146], especially among lower socioeconomic groups[147]. This tracking of cardiovascular risk factors and their inequalities may be linked to the early life establishment and tracking of inequalities in risk behaviours[148–150]. However, several studies have found that the association between childhood socioeconomic position and adult cardiovascular risk was only partially attenuated by adjustment for later risk behaviours, suggesting that other mechanisms may also be operating[151,152]. Prospective studies of cardiovascular risk factors from childhood are limited in low- and middle-income countries, but cross-sectional studies of the association between socioeconomic position and cardiovascular risk factors in children suggest that the associations mirror that of adult socioeconomic position and cardiovascular risk in these countries. In systematic reviews from India and Sub-Saharan Africa, socioeconomic position was directly associated with obesity in school-aged children[66,153], although the association with blood pressure was less consistent[154–156].

Finally, it is possible that socioeconomic position in childhood only affects cardiovascular risk through its influence on socioeconomic position in adulthood. This would imply that there is no independent effect of childhood socioeconomic position, and that the association observed in many high-income studies instead reflects inadequate adjustment for adult socioeconomic position. However, the consistency of the independent inverse association of childhood socioeconomic position with cardiovascular disease across a number of studies[121,125], and the fact that this association is not observed for several other socially patterned health outcomes[120,157], suggest that this may not be the only explanation.

Some potential implications of the mechanisms described above for low- and middle-income countries are worth highlighting. If mechanisms related to early life undernutrition and impaired growth were important, one would expect socioeconomic position to be strongly and inversely associated with risk of cardiovascular disease in low- and middle-income countries where severe childhood poverty remains prevalent. However, if the social patterning of childhood risk behaviours (such as physical inactivity or a high fat diet) was a more important mechanism, there might be no association, or even a direct association, in low- and lower-middle income countries, where childhood obesity remains less prevalent and limited to higher socioeconomic groups[158]. If the main effect of childhood socioeconomic position was via adult socioeconomic position, then the association in low- and middle-income countries would mirror the association of adult socioeconomic position with cardiovascular risk in that setting. However, few studies have examined the association of childhood socioeconomic position with risk of cardiovascular disease, and its potential mechanisms, in low- and middle-income countries; these are reviewed fully in the next section (1.2) and in chapter 3.

1.1.2.4 Life course approaches

Research into childhood determinants of cardiovascular disease assumes a life course perspective, because it considers cardiovascular disease as a consequence of experiences that occur across life, rather than contemporaneous with the occurrence of disease[52]. Expanding on this, researchers have asked what combinations of socioeconomic exposures at multiple times across life best explain risk of cardiovascular disease. A number of life course models have been proposed, which are general in nature but have been extensively applied to the case of socioeconomic position and cardiovascular disease[125]. Most commonly, researchers have supposed that socioeconomic position at a particular stage of life, such as in childhood or adulthood, has a lasting effect on risk of cardiovascular disease, either exclusively (the *critical period model)* or in addition to effects at other life stages (the *sensitive period model)*. It has also been suggested that insults related to adverse socioeconomic conditions accumulate in an additive fashion across someone's lifetime (the *accumulation model)*, which can be thought of as a special case of the sensitive period model. Finally, some researchers have proposed a role of different trajectories of socioeconomic position across the life course, such as persistently low, persistently high, increasing or decreasing socioeconomic position, in determining cardiovascular risk (the *trajectory model* or *social mobility model*). A review of evidence from high-income countries concluded that most studies support the accumulation model, with some finding support for a critical period in childhood or adulthood[125]. Few studies supported a trajectory model. Recent studies applying more rigorous methods for comparing life course models have reported similar findings[159–161].

Very few studies have compared different life course models of the association between socioeconomic position and cardiovascular disease in low- and middle-income countries. One study of older adults from southern China reported that the association between life course socioeconomic position and metabolic syndrome was best explained by a late adult critical period model in men (direct association), and a childhood and early adult sensitive period model in women (inverse associations)[162]. However, some potential issues with interpreting the results of life course models in low- and middle-income countries are worth highlighting. In these countries, theory suggests that the association of cardiovascular risk with socioeconomic position in childhood may not go in the same direction as the association with socioeconomic position in adulthood. These associations depend on the underlying mechanisms linking socioeconomic position with cardiovascular risk, which can be distinct between childhood and adulthood, across places and times. For example, according to some theories, risk of diabetes may be inversely associated with childhood socioeconomic position (via undernutrition and poor foetal growth), but at the same time be directly associated with adult socioeconomic position (via physical inactivity and obesity). It is not clear how the accumulation model should be interpreted in such a situation[163]. A necessary first step towards applying and comparing multiple life course models in low- and middle-income countries is to better characterise the associations of socioeconomic position at each stage of the life course with risk of cardiovascular disease.

A further insight highlighted by the life course approach has been the potential influence of socioeconomic exposures even before an individual's conception on their later risk of cardiovascular disease[164,165]. These so-called intergenerational (or transgenerational) effects of socioeconomic position have been relatively little studied, possibly due to a lack of intergenerational data or plausible mechanisms. Evidence from animal experiments, however, now demonstrates plausible epigenetic pathways that might link pre-conception exposure to undernutrition, obesity and stress with later cardiovascular risk[164,166]. Maternal childhood undernutrition leading to poor growth and consequently poor growth of her offspring is another proposed mechanism[167]. Limited studies from high-income countries suggest that parents' socioeconomic position in childhood is inversely associated with obesity in their adult offspring[168,169]. Parents' height, a marker of their childhood nutrition, is also inversely associated with some offspring cardiovascular risk factors[170]. However other studies, including one from multiple middle-income countries, did not find evidence of an association between maternal height and risk of cardiovascular disease in the offspring[171–173]. In some low- and middle-income countries, most notably in South Asia, there is widespread transmission of poverty, undernutrition and stunting across generations[174,175]. This might plausibly be contributing to the population-level burden of cardiovascular disease in such settings, although evidence is currently limited.

Figure 1.2 provides a conceptual diagram of some of the key potential pathways linking life course socioeconomic position with cardiovascular disease and its risk factors in low- and middle-income countries.

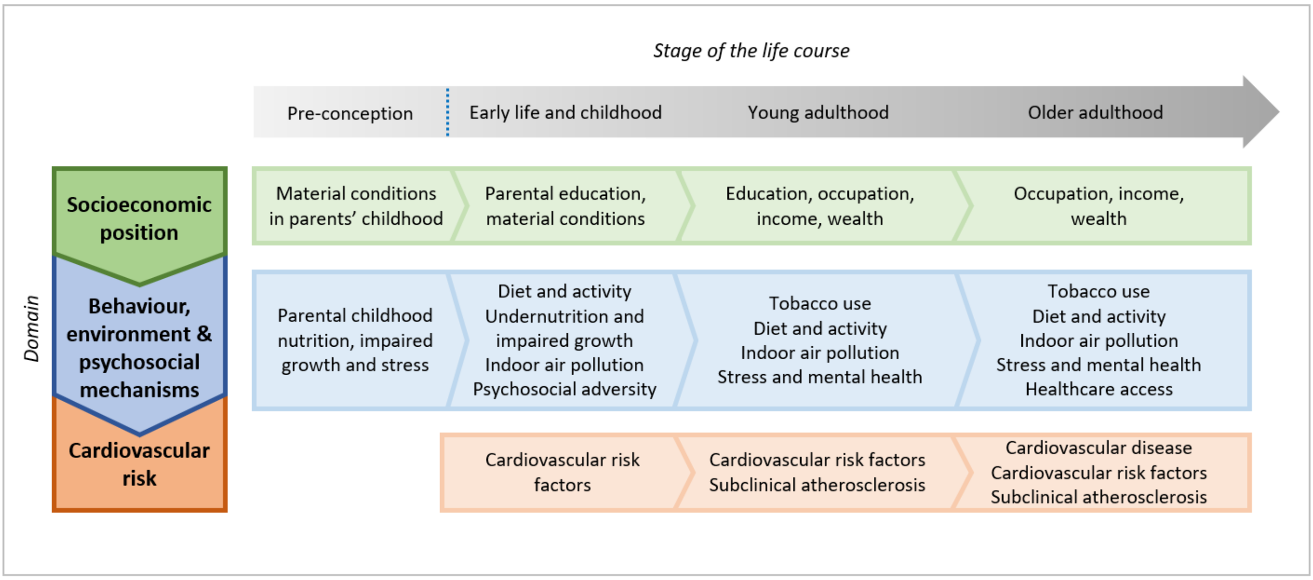

Figure 1. 2 Conceptual diagram linking socioeconomic position at multiple stages of life to cardiovascular risk factors and disease in low- and middle-income countries.

1.1.2.5 Indicators of socioeconomic position

A number of different indicators have been used in epidemiological studies to capture both material resources and prestige-related aspects of socioeconomic position. Some common indicators thought to capture the material aspects of socioeconomic position include income, expenditure, wealth, housing quality and possessions. Indicators more closely aligned to social prestige-related aspects of socioeconomic position include educational attainment, occupational social class, and perceived social class[176,177]. However, resources and prestige are closely inter-related, so in practice all of these indicators are likely to capture some aspects of both material resources and social prestige, to varying extents depending on the context. Another important class of socioeconomic indicators are those measured at the area- or neighbourhood-level, which emphasise the influence of socially-patterned environmental characteristics on health[178]. These have been most commonly applied in settings characterised by residential segregation, such as the US, and demonstrate small but consistent inverse associations with risk of cardiovascular disease, even after individual-level socioeconomic indicators are taken into account[179]. Theoretical and empirical development in this field has been more limited in low- and middle-income countries[180], although a few studies support a similar role for neighbourhood-level socioeconomic influences on cardiovascular risk factors[181].

A similar set of indicators, but at a family or household level, have been used to classify socioeconomic position in childhood. Some studies have considered an individual's education as an indicator of their early life socioeconomic position[182], although education is more commonly considered as an indicator of socioeconomic position in young adulthood, because of its strong influence on adult occupational status, earning potential and social prestige[176].

Some specific considerations for measuring socioeconomic position in low- and middle-income countries should be noted. In settings characterised by an informal economy, subsistence agriculture or trading of goods instead of money, income and expenditure may be poor measures of an individual's material resources[183]. In such cases, indicators of housing quality and household possessions (also called assets) may be more appropriate, and also have the benefit of being easier to recall accurately[184]. Education is widely used in low- and middle-income countries, although can be highly influenced by cohort effects (older adults tend to have less formal education than their descendants of similar relative social position)[183]. Setting-specific knowledge must be applied to ensure that meaningful variation in social stratification is being captured by a given indicator.

The choice of indicator of socioeconomic position will depend on the setting and specific aims of the study. Some researchers have argued for the use of composite indicators (for example combined using a principle component analysis), although these may be of more value when adjusting for confounding by socioeconomic position[82] or using socioeconomic position to predict health outcomes[185]. When trying to elucidate pathways linking socioeconomic position and health, single indicators, chosen based on the specific pathways of interest, may be more informative. For example, when investigating the association of childhood socioeconomic position with cardiovascular risk, if undernutrition is a key hypothesised pathway, material resource-based indicators (e.g. household income or assets in childhood) might be most appropriate. In one study from Brazil, income was directly associated with obesity, while education was inversely associated[186]. This demonstrates that different indicators may represent different pathways (and variably between settings), highlighting the importance of the choice of socioeconomic indicator.

Box 1 Key messages from the background (section 1.1)

Cardiovascular disease in low- and middle-income countries

- Cardiovascular disease is the leading cause of premature death in most low- and middle-income countries. Age-specific cardiovascular mortality is higher in low- and middle-income countries compared with high-income countries.
- The vast majority of cardiovascular disease globally is the result of atherosclerosis and/or hypertension. Heart disease and stroke make up over 90% of cardiovascular deaths.
- The causes of cardiovascular disease and its conventional risk factors (blood pressure, diabetes, lipid levels, obesity and tobacco use) are multifactorial, and may include behavioural (e.g. diet high in saturated fat and low in fruit and vegetables, physical inactivity), environmental (e.g. ambient and indoor air pollution) and psychosocial (e.g. depression, stress) factors.
- Although cardiovascular disease mostly affects older adults, cardiovascular risk factors and subclinical vascular damage can accrue from young adulthood or even earlier, suggesting that prevention of cardiovascular disease may need to start in early life.
- Based on current trends, substantial additional measures will be needed to prevent cardiovascular disease in low- and middle-income countries in order to meet global targets for the reduction of non-communicable diseases by 2030.

Socioeconomic position and cardiovascular disease

- Socioeconomic disadvantage in adulthood is an important determinant of cardiovascular disease and its risk factors in high-income countries.
- In low- and middle-income countries, limited evidence suggests that cardiovascular disease incidence and mortality may be highest among lower socioeconomic groups. On the other hand, levels of most cardiovascular risk factors are higher among high socioeconomic groups, especially in low- and lower middle-income countries, attributed to their increased risk behaviours (e.g. physical inactivity, diets high in saturated fat,).
- Socioeconomic disadvantage at other stages of the life course, in particular in childhood, is also associated with risk of cardiovascular disease in high-income countries. Proposed mechanisms include impaired foetal and childhood growth, and the establishment of harmful risk behaviours and obesity from childhood.
- The potential contribution of socioeconomic disadvantage in childhood to the cardiovascular disease epidemic in low- and middle-income countries is unclear.
- Some researchers have proposed that intergenerational socioeconomic disadvantage may contribute to risk of cardiovascular disease, but evidence is limited.

1.2 Systematic overview of evidence gaps

1.2.1 Introduction

A large number of systematic reviews have been published on the association between socioeconomic position and cardiovascular disease or its risk factors. The majority focussed on adult socioeconomic position, although a few examined the role of socioeconomic position at other stages of the life course. Studies identified by the reviews were heavily skewed towards high-income countries, except for a few reviews which explicitly focussed on low- and middle-income countries.

I conducted a systematic overview on the topic of socioeconomic position and risk of cardiovascular disease, with the following aims:

a) To describe and appraise the current evidence on the association between life course socioeconomic position and cardiovascular disease in low- and middle-income countries.
b) To situate the evidence on this topic from low- and middle-income countries in the context of the evidence from high-income countries.
c) To identify key evidence gaps to be addressed in this thesis.

1.2.2 Methods

This overview is reported in line with published reporting guidelines for overviews[187]. All systematic reviews on the association between socioeconomic position (at any life stage) and cardiovascular disease (clinical or subclinical) or the conventional cardiovascular risk factors (blood pressure, lipid profile, diabetes and obesity), in any country globally, were eligible for inclusion. Articles had to be published in English, but there were no restrictions on publication date or the types of study included in the reviews.

The search was updated to 7th September 2020. I searched three major biomedical databases (MEDLINE, Embase and Global Health, all via Ovid), as well as the Cochrane Database of Systematic Reviews, and the PROSPERO registry of systematic review protocols. The search terms used are given in Table 1.1.

Characteristics of eligible reviews were extracted into a pre-made data extraction form, organised according to the types of outcome included. For each review, the number of included studies from high-income countries and low- and middle-income countries were also extracted.

Findings were summarised using a narrative approach. Risk of bias in the reviews is discussed but was not formally assessed.

Table 1. 1 Search terms used for database search in the overview of systematic reviews

#	Domain	Terms
1	Outcome (cardiovascular disease and its risk factors)	"Cardiovascular or cardio-vascular or cardiometabolic or cardio-metabolic or myocardial infarction or heart disease or stroke or cerebrovascular or hypertension or blood pressure or diabetes or obesity or overweight or adiposity or lipids or cholesterol or atherosclerosis or atherosclerotic or mortality or non-communicable or chronic disease or chronic diseases"
2	Exposure (socioeconomic position)	"Social or socio-economic or socioeconomic or economic or socio-demographic or sociodemographic or education or educational or occupation or income or poverty or deprivation or affluence or wealth"
3	Type of study (review)	"Review"
4	Final search	1 and 2 and 3 (searched in the titles of the articles only)

1.2.3 Results

The search returned 1740 abstracts (924 after de-duplication). 82 full-text articles were assessed for eligibility, of which 59 were eventually included in the overview. Table 1.2 summarises the included reviews, by outcome and exposure type.

Table 1. 2 Summary of included systematic reviews of the association between socioeconomic position and risk of cardiovascular disease

Outcome	Adult socioeconomic position			Life course socioeconomic position		
	# of reviews	# of HIC studies	# of LMIC studies	# of reviews	# of HIC studies	# of LMIC studies
Cardiovascular mortality	5	~40	~10	2	~20	0
Cardiovascular disease	7	~100	~15	2	~50	0
Cardiovascular disease and risk factors	13	~150	~70	4	~80	5
Cardiovascular risk factors	2	~100	~70	2	~40	2
Hypertension	2	~100	~40	0	-	-
Diabetes	7	~100	~30	0	-	-
Obesity	8	>200	~100	3	~50	4
Survival/outcomes of cardiovascular disease	2	11	6	0	-	-
Total # of reviews	46			13		
HIC is high-income countries; LMIC is low- and middle-income countries. Review articles do not appear more than once in the table, but individual study counts may include overlaps between reviews.						

The majority (46/59) of the systematic reviews identified examined the association of socioeconomic position in adulthood (not at other stages of the life course) with risk of cardiovascular disease. Of these, 25 included studies from any geographic region, 2 were restricted to high-income countries, 7 were restricted to low- and middle-income countries, and 12 focussed on a specific region or country (10 of which included at least one low- or middle-income country). Several of these reviews were recent and conducted comprehensive searches using a large number of databases[87,109,188–190]. The reviews indicate that there is a large body of evidence on the association between adult socioeconomic position and cardiovascular disease and its risk factors from high-income countries, and a large-to-moderate body of evidence for cardiovascular disease risk factors from low- and middle-income countries. There is a limited amount of evidence on prospective cardiovascular disease mortality, incidence or survival from low- and middle-income countries; fewer than 20 studies were identified across all reviews, most of which were from a single country (China).

There were 13 systematic reviews which examined socioeconomic position in childhood and risk of cardiovascular disease. Most of these did not specify any geographic restriction to their search, except 2 reviews restricted to high-income countries, and 1 review restricted to low- and middle-income countries. The review of studies from low- and middle-income countries, published in 2013, examined the association between any early life factors and a range of health outcomes in older adults, but searched only 1 database, and used generic search terms such as "older adult health", which may have been inadequate to identify all studies on this topic[191]. The reviews without geographic restrictions identified very few studies from low- and middle-income countries (between 0 and 2 studies each), and no studies on prospective cardiovascular disease incidence, mortality or survival. However, these reviews were all conducted more than 10 years ago (prior to 2010)[119,125,192,193], apart from one review of obesity from 2017[194] and one review of metabolic syndrome from 2020[195]. Findings from the included reviews are summarised in table 1.3.

Table 1. 3 Summary of findings from included systematic reviews of the association between socioeconomic position and risk of cardiovascular disease

Setting	Exposure	Association with risk of cardiovascular disease
High-income countries	Socioeconomic position in adulthood	- A large number of systematic reviews on cardiovascular incidence and mortality, subclinical atherosclerosis, hypertension, dyslipidaemia, diabetes and obesity (n=31) report a consistent inverse association with adult socioeconomic position.
	Socioeconomic position	- A few systematic reviews on cardiovascular disease incidence and mortality (n=5) report moderate to strong

	across life course	evidence of an inverse association with childhood socioeconomic position - A few reviews on obesity, diabetes and metabolic syndrome (n=5) report a consistent inverse association with childhood socioeconomic position among women but no association among men. - There were no reviews on intergenerational socioeconomic position and risk of cardiovascular disease.
Low- and middle-income countries	Socioeconomic position in adulthood	- Global reviews on cardiovascular disease incidence or mortality (n=15) found few studies from low- and middle-income countries; these tended to be from upper middle-income countries and report some evidence of an inverse association with adult socioeconomic position. Findings were less consistent for prevalent disease. - Global reviews on obesity, diabetes and other cardiovascular risk factors (n=28) contain a number of studies from low- and middle-income countries, generally reporting an inverse or non-linear (highest risk in intermediate socioeconomic groups) association in upper middle-income countries and null or direct association in low- and lower middle-income countries. However, associations were less consistent for hypertension than for obesity and diabetes. Associations were more likely to be inverse for education than income. For obesity and diabetes, the association was more likely to be direct amongst men, and inverse amongst women.
	Socioeconomic position across life course	- Global reviews on childhood socioeconomic position and cardiovascular mortality or incidence (n=5) found no studies from low- and middle-income countries, although were 10+ years old. - Global reviews on obesity, diabetes and metabolic syndrome (n=6) contained very few studies from low- and middle-income countries; these reported weak evidence of an inverse association, mostly restricted to women. Studies only came from a few upper middle-income countries (Brazil, Mexico, China). - There were no reviews on intergenerational socioeconomic position and risk of cardiovascular disease.

1.2.4 Summary and evidence gaps

There is a large body of epidemiological evidence on the association between life course socioeconomic position and risk of cardiovascular disease, although this is highly skewed towards high-income countries. In high-income countries globally, there is strong evidence of an inverse association of cardiovascular disease and its risk factors with socioeconomic position in childhood and adulthood. In low- and middle-income countries, the association of adult socioeconomic position with cardiovascular risk factors (especially obesity) seems to vary between countries and by gender, being direct in some low- and lower middle-income countries, and inverse in some upper middle-income countries (particularly among women). Evidence from low- and middle-income countries on cardiovascular disease incidence or mortality is limited, despite recent high-quality reviews on this topic. There is also limited evidence on the association between childhood socioeconomic position and risk of cardiovascular disease, although this has not been reviewed in over ten years.

This overview highlights a number of key evidence gaps in low- and middle-income countries which will be addressed in this thesis.

Evidence gap 1: The association between socioeconomic position in adulthood and cardiovascular disease incidence and mortality.
Evidence gap 2: The association between socioeconomic position in childhood and cardiovascular disease and its risk factors.
Evidence gap 3: The association between intergenerational socioeconomic position and cardiovascular disease and its risk factors.

Other evidence gaps which were noted, but which are not the focus on this thesis, include:

- The association between socioeconomic position (adult or childhood) and survival or outcomes after cardiovascular disease in low- and middle-income countries.
- The association between neighbourhood socioeconomic position (adult or childhood) and cardiovascular disease and its risk factors in low- and middle-income countries.
- The association between perceived socioeconomic position and cardiovascular disease and its risk factors in low- and middle-income countries.
- The association between intergenerational socioeconomic position and cardiovascular disease and its risk factors in high-income countries.
- The evidence for different life course models of socioeconomic position and cardiovascular disease and its risk factors (all countries).

1.3 Aim, objectives and hypotheses

1.3.1 Thesis aim

Evidence from high-income countries supports a consistent association between socioeconomic disadvantage in childhood and adulthood and risk of cardiovascular disease. However, research on this topic from low- and middle-income countries remains relatively limited, despite the higher rates poverty and cardiovascular mortality in many low- and middle-income countries. The extent to which associations observed in high-income countries can be generalised to low- and middle-income countries is unclear. Through an overview of systematic reviews on this topic, I identified several evidence gaps around life course socioeconomic position and cardiovascular disease in low- and middle-income countries. Specifically, there is evidence that the social patterning of certain cardiovascular risk factors differs in some low- and middle-income countries compared with high-income countries, but it is not clear whether these differences extend to cardiovascular disease incidence and mortality. The roles of childhood and intergenerational poverty for the development of cardiovascular disease in low- and middle-income countries are also unclear. This thesis aims to address these evidence gaps by reviewing existing evidence and analysing secondary data from two populous middle-income countries.

1.3.2 Specific objectives and hypotheses

The specific objectives and hypotheses of this thesis, corresponding to the evidence gaps identified in the previous section (1.2.4), are described below and depicted in Figure 1.3.

<u>Objective 1</u>: To examine the association between socioeconomic position in adulthood and cardiovascular mortality in lower and upper middle-income countries.

Approach	Cross-sectional analysis of national census and mortality data from Brazil.
Justification	Given the lack of representative data on cardiovascular mortality across low- and middle-income countries, I used the states of Brazil, a large transitioning middle-income country, as a proxy to investigate the association between education and cardiovascular mortality in lower and upper-middle income countries, and whether this association might vary systematically by a country's level of economic development.
Hypothesis	A direct association in the less economically developed states, and an inverse association in the more economically developed states, consistent with the theory that the association between socioeconomic position and cardiovascular disease exhibits a "social cross-over" (from direct to inverse) with economic development.

Objective 2: To summarise existing evidence on the association between childhood socioeconomic position and risk of cardiovascular disease in adulthood from low- and middle-income countries.

Approach	Systematic literature review.
Justification	Previous reviews on this topic were conducted over ten years ago, and identified no studies from low- and middle-income countries. Emerging data from these countries has not been summarised.
Hypothesis	An inverse association between childhood socioeconomic position and risk of cardiovascular disease, after adjusting for adult socioeconomic position, consistent with data from high-income countries, and supportive of mechanisms linked to poverty and undernutrition.

Objective 3: To evaluate the association between childhood socioeconomic position and risk of cardiovascular disease in adulthood in a lower middle-income country?

Approach	Cross-sectional analysis of data from pooled cohorts in India.
Justification	South Asia has high rates of cardiovascular mortality and childhood poverty. Although prospective data on cardiovascular disease incidence or mortality are lacking, examining cardiovascular risk factors in this large sample will help to establish the potential contribution of childhood socioeconomic position to cardiovascular disease in this region.
Hypothesis	An inverse association between childhood socioeconomic position and risk of cardiovascular disease, after adjusting for socioeconomic position in adulthood.

Objective 4: To evaluate the association between parents' socioeconomic position in childhood and the risk of cardiovascular disease in their adult offspring.

Approach	Cross-sectional analysis of an intergenerational cohort in rural India.
Justification	Socioeconomic determinants of cardiovascular disease may extend beyond an individual's life course to conditions experienced by previous generations, although epidemiological data are lacking globally.
Hypothesis	An inverse association between childhood socioeconomic position of the parents and risk of cardiovascular disease in their offspring, after adjusting for socioeconomic position of the offspring.

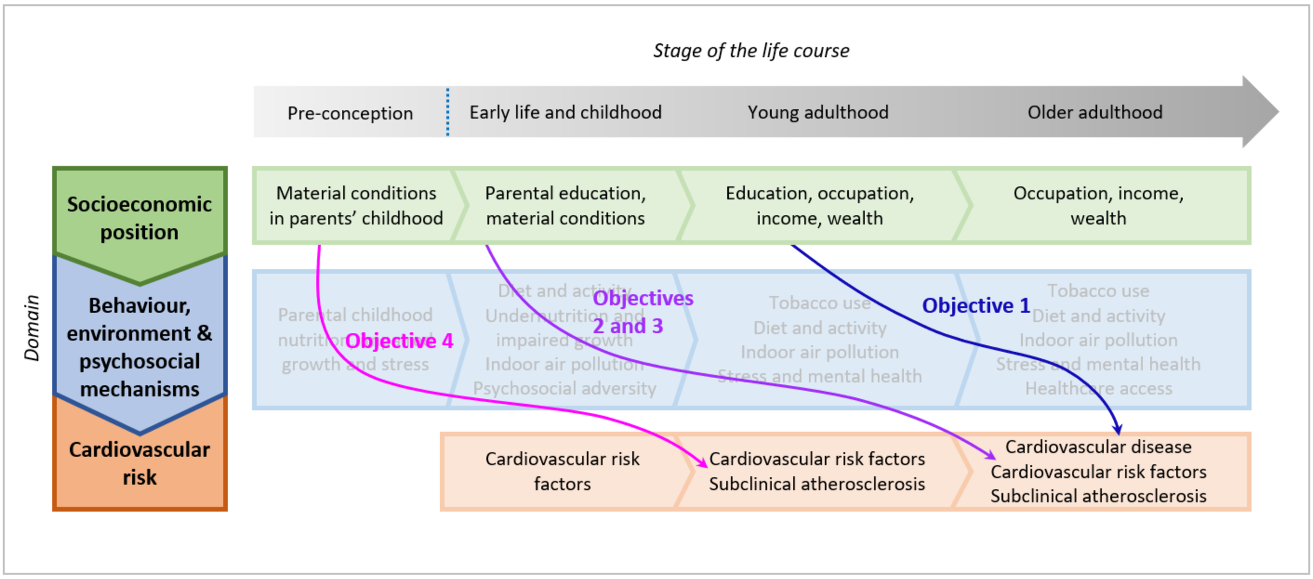

Figure 1. 3 Objectives of this thesis in relation to the conceptual diagram linking socioeconomic position at multiple stages of life to cardiovascular risk factors and disease in low- and middle-income countries.

1.4 Thesis structure

This thesis is comprised of six chapters. Having provided a general introduction to the topic of social determinants of cardiovascular disease and an overview of evidence gaps in this field in chapter 1, chapters 2-5 aim to address these evidence gaps using a mixture of systematic review and secondary data analysis. Chapter 6 provides a summary and discussion of the findings of the thesis and presents implications for future practice and research.

The four main analysis chapters (chapters 2-5) are presented in research paper style, one paper per chapter. One has been published in a peer-reviewed journal (chapter 4), one is awaiting editorial decision following re-submission with revisions (chapter 2), and two have recently been submitted (chapters 3 and 5). Preparing these analyses for publication required substantially reducing the word counts, so some additional relevant details are provided in the appendices to this thesis. A small degree of repetition between the research papers (covering key aspects such as description of the data) was unavoidable given the style of the thesis. Changes required by the article submission process may have introduced some small inconsistencies in formatting or language between the chapters. I have tried to highlight these in the introduction to each chapter.

Finally, it is worth mentioning that the path to putting together this thesis has not been a linear one. My funding was initially obtained to examine life course socioeconomic determinants of cardiovascular mortality in Brazil using national linked data. I conducted an analysis of publicly available national data from Brazil (chapter 2) and the systematic review (chapter 3), but the linked national datasets, due to be released in 2016, were still not available two years into my PhD. This forced me to adapt my research plan, instead analysing data from two large surveys in India (chapters 4 and 5) to address the original thesis questions.

Chapter 2: Socioeconomic position in adulthood and cardiovascular mortality in the states of Brazil

2.1 Introduction to chapter

This chapter aims address the first evidence gap and objective of the thesis, namely the association between adult socioeconomic position and cardiovascular mortality in low- and middle-income countries. To do this I used Brazil, a populous middle-income with states at varying levels of economic development (similar to lower middle- and upper middle-income countries), as a proxy to investigate whether association between education and cardiovascular mortality systematically varies by level of economic development. This work has been submitted for publication in a peer-reviewed journal (BMJ Heart), where it is awaiting editorial decision following re-submission with minor revisions. Further detail on the analysis methods, additional description of the study population, and results of sensitivity analyses are provided in Appendix 1 at the end of the thesis.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	1400500	**Title**	Ms
First Name(s)	Poppy Alice Carson		
Surname/Family Name	Mallinson		
Thesis Title	Life course socioeconomic influences on risk of cardiovascular disease in low- and middle-income countries		
Primary Supervisor	Sanjay Kinra		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION C – Prepared for publication, but not yet published</u>

Where is the work intended to be published?	BMJ Heart
Please list the paper's authors in the intended authorship order:	Poppy Mallinson, Shammi Luhar, Elizabeth Williamson, Mauricio Barreto, Sanjay Kinra
Stage of publication	Undergoing revision.

<u>SECTION D – Multi-authored work</u>

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualised the study, extracted the data, analysed the data, wrote the first draft of the manuscript, revised the manuscript according to comments from co-authors.

<u>SECTION E</u>

Student Signature	[redacted]
Date	20/11/2020

Supervisor Signature	[redacted]
Date	23/11/2020

Socioeconomic position and cardiovascular mortality in 63 million adults from Brazil

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2.2 Abstract

Background: It has been suggested that cardiovascular disease exhibits a 'social cross-over', from greater risk in higher socioeconomic groups to lower socioeconomic groups, on economic development, but robust evidence is lacking. We used standardised data to compare the social inequalities in cardiovascular mortality across states at varying levels of economic development in Brazil.

Methods: We used national census and mortality data from 2010. We used age-adjusted multilevel Poisson regression to estimate the association between educational status and cardiovascular mortality by state-level economic development (assessed by quintiles of Human Development Index).

Results: In 2010, there were 185,383 cardiovascular deaths among 62.5 million adults whose data were analysed. The age-adjusted cardiovascular mortality rate ratio for women with <8 years of education (compared to 8+ years) was 3.75 (95% confidence interval (CI) 3.29, 4.28) in the least developed one-fifth of states, and 2.84 (95% CI 2.75, 2.92) in the most developed one-fifth of states (p-value for linear trend=0.002). Among men, corresponding rate ratios were 2.53 (95% CI 2.32, 2.77) and 2.26 (95% CI 2.20, 2.31), respectively (p-value=0.258). Associations were similar across subtypes of cardiovascular disease (ischaemic heart disease and stroke) and robust to the size of geographical unit used for analysis.

Conclusions: Our results do not support a 'social cross-over' in cardiovascular mortality on economic development. Our analyses, based on a large standardised dataset from a country that is currently experiencing economic transition, provide strong evidence that low socioeconomic groups experience the highest risk of cardiovascular disease, irrespective of the stage of national economic development.

2.3 Introduction

Some researchers have suggested that cardiovascular disease exhibits a social cross-over, from greater risk in higher socioeconomic groups to lower socioeconomic groups, on economic development[188,196–198]. However, further scrutiny of data from the United States and United Kingdom (on which this suggestion was based) using standardised measures found little evidence of a positive association between socioeconomic position and cardiovascular mortality[85,115]. Since then, several comparisons of countries at different levels of economic development have reported inconsistent findings, which may be attributable to systematic differences in data sources and quality between countries at different levels of economic development[97,103,105,199]. Linked temporal data on socioeconomic position and cause-specific mortality are lacking for most low- and middle-income countries. Therefore, we used an innovative approach to test this hypothesis. Many highly-populated low- and middle-income countries that are currently experiencing economic transition exhibit considerable sub-national variation in levels of economic development, which could be utilised as counterfactuals to address this hypothesis using cross-sectional data.

Brazil is middle-income country of 200 million people. The level of economic development of its 26 states ranges from that of lower middle-income to upper middle-income countries. Cardiovascular disease is the leading cause of death in Brazil, with trends comparable to other low- and middle-income countries[17]. Brazil has standardised national data and universal healthcare, providing a unique opportunity to simultaneously examine the association between socioeconomic position and cardiovascular mortality across different levels of economic development, while minimising potential bias from other factors which vary between countries. We used national census and mortality data to assess the association between education (a widely used indicator of status and wealth) and cardiovascular mortality in states of Brazil at different levels of economic development. We hypothesised that the association between socioeconomic position and cardiovascular mortality would be positive in less developed states and inverse in more developed states, consistent with a change in the association on economic development.

2.4 Methods

This study is reported in accordance with the STROBE guidelines (see appendix Table S1.1 for completed checklist). We conducted a cross-sectional study using routinely collected mortality and census data, which are available online on Brazilian government websites[200,201]. Data on age, sex, education and municipality of residence were available from both data sources.

Deaths are notifiable in Brazil, with coverage of mortality registration estimated to be over 95% in 2010[202]. For both data sources, we used data from 2010, as this was the most recent year for which accurate census data were available[203].

We identified cardiovascular deaths using ICD-10 codes I00-99. We also examined cardiovascular disease subtypes ischaemic heart disease (IHD) and stroke (using ICD-10 codes I20-25 and I60-69 respectively), as some studies have suggested that the social-crossover between socioeconomic position and cardiovascular mortality is driven largely by IHD[204]. We examined overall, as well as premature, cardiovascular mortality (defined as deaths under the age of 70 years), as recommended in the World Health Organisation's Non-Communicable Disease Global Monitoring Framework.

Socioeconomic position was defined by number of completed years of education. Education captures multiple dimensions of socioeconomic position relevant to cardiovascular disease, including relative social status, earning potential and health-related knowledge[176]. Education in Brazil follows the same grading system across all states as it is delivered federally. In 2010, the education categories on death certificates were: 0, 1-3, 4-7, 8-11 and 12 or more years of education completed; and on census were: none, creche/pre-school, elementary school, high school (and subcategories of these), graduate, masters, and doctorate. To minimise potential misclassification of education between the two data sources, we categorised education into two broad groups (<8 vs 8+ years of education completed, corresponding to did not vs did complete elementary school).

We classified state-level economic development using Human Development Index (HDI), a composite measure combining education, health and economic productivity, as is thought to capture economic development better than solely income-based measures such as Gross Domestic Product (which can be highly influenced by industrial production).

Statistical analyses

We collapsed both datasets on common variables (sex – male/female, age – 5-year groups, education – <8/8+ years, municipality – categorical), to allow data linkage. The resulting aggregated dataset contained, for every unique combination of variables, data on the person-years at risk in 2010 (approximated by mid-year population size) and the number of cardiovascular disease deaths in 2010.

We restricted the study population to adults aged over 20 years, as cardiovascular disease rarely affects children and adolescents. As the quality of mortality reporting varies across Brazil[202], we derived an indicator for high coverage of mortality registration for each municipality by comparing the number of deaths reported in the 2010 census[205] to the number of deaths in the mortality registry over the same period. We included municipalities for which agreement between deaths in the mortality registry and census was of a comparable level to states known to have near-complete mortality registration (ratio of registry to census deaths of ≥1.08). To assess the sensitivity of results to this choice of indicator, we also repeated the analyses using data from all municipalities. Three states (Roraima, Acre and Amapá) were too small to be analysed individually, so we merged with their most similar neighbour, resulting in 23 geographical units (hereafter referred to as states). To assess the sensitivity of results to this choice of geographical unit, we also repeated the analyses stratifying by the five regions of Brazil (North, North-east, Centre-west, South, South-east).

We modelled cardiovascular mortality count using age-adjusted multilevel Poisson regressions to compare mortality between people with <8 vs 8+ years of education. To capture the non-linear relationship between age and mortality, in addition to age we adjusted for age-squared and age-cubed, both of which significantly improved the model fit. Person-years at risk was included as an offset term. We included state-level and municipality-level random intercepts to account for geographical clustering of cardiovascular mortality, and additionally allowed the association with education to vary randomly across states. To assess for systematic variation in the association between education and cardiovascular mortality by state-level HDI we included an interaction term between these variables, with HDI considered as a categorical (splitting the 23 states into quintiles according to their HDI), and then a continuous measure.

We used multiple imputation with chained equations to minimise the potential for bias due to missing data on education (~20%) and ill-defined causes of death (~8% of deaths, considering ICD-10 garbage codes R00-R99 to be “missing”) in the mortality registry (see Methods S1.1 in the appendix).

Ethical approval was not obtained as this study used only de-identified secondary data available in the public domain.

2.5 Results

In 2010, there were 185,383 reported cardiovascular deaths among 62,568,055 adults included in the study (49% of all Brazilian adults). Our primary analyses were restricted to municipalities with high mortality registration (2004 out of 5565 municipalities). The excluded population were more likely to live in the less economically developed regions of Brazil, and were less likely to be educated. Cardiovascular mortality was lower among the excluded population, as expected due to the lower mortality registration in excluded municipalities. Sizes of the included and excluded population, and differences between them, are given in the appendix (Table S1.2 and Table S1.3).

The crude cardiovascular mortality rate in Brazil was 296 per 100,000. After adjusting for age, cardiovascular mortality was over twice as high in men with <8 years education compared to 8+ years education, and nearly three times higher in women with <8 years education compared to 8+ years education (Table 2.1).

HDI of the states ranged from 0.63 to 0.78. We observed an inverse association between education and cardiovascular mortality in states of Brazil across all levels of economic development, but with considerable subnational variation (Figure 2.1). Among women, higher state-level HDI was associated with a lower rate ratio for education (P-value for log-linear trend=0.002), whereas this trend was less pronounced among men (P=0.258) (Table 2.2). For example, the age-adjusted cardiovascular mortality rate ratio for women with <8 years of education (compared to 8+ years) was 3.75 (95%CI: 3.29, 4.28) in the least developed quintile of states and 2.84 (2.75, 2.92) in the most developed quintile. The age-adjusted cardiovascular mortality rate ratio for men with <8 years of education (compared to 8+ years) was 2.53 (2.32, 2.77) in the least developed quintile and 2.26 (2.20, 2.31) in the most developed quintile (Table 2.2). For IHD and stroke mortality we observed an inverse association with educational status in all states, and among women, higher state-level HDI was associated with lower rate ratios (although confidence intervals were consistent with no linear trend by HDI). Restricting the analyses to 'premature' cardiovascular deaths (age <70 years) did not substantively alter the results.

As a sensitivity analysis, we repeated the analyses using all municipalities (n=5565, population=127,826,740), and found similar results (appendix Table S1.4). Our results were also robust to use of region (n=5) instead of state as the geographical unit of analysis (appendix Table S1.5). Age-standardised cardiovascular mortality rates (appendix Table S1.6) and corresponding rate differences (appendix Table S1.7 and Figure S1.1) demonstrated a similar pattern of strong inverse inequalities in all states, although the trends by state-level HDI were less distinct, and among men were non-linear (for example the highest absolute inequalities among men were seen in the most developed quintile of states, driven by the high mortality rates in these areas).

Table 2. 1 Description of the included sample and age-adjusted associations between education and cardiovascular mortality in Brazil, 2010

	n (N=62,568,055)	Number of deaths in 2010[a]			Crude mortality rate per 100,000			Age-adjusted rate ratio for <8 vs 8+ years education (95% CI)		
		CVD	IHD	Stroke	CVD	IHD	Stroke	CVD	IHD	Stroke
Women										
All	32,899,916	89,392	23,692	25,526	271.7	72.0	77.6			
8+ years education	20,615,737	14,443	4,564	3,906	70.1	22.1	18.9	1	1	1
<8 years education	12,284,179	74,949	19,128	21,619	610.1	155.7	176.0	2.93 (2.85, 3.01)	2.54 (2.45, 2.64)	3.02 (2.88, 3.17)
Men										
All	29,668,139	95,991	31,876	25,322	323.5	107.4	85.4			
8+ years education	17,999,163	21,921	9,058	4,894	121.8	50.3	27.2	1	1	1
<8 years education	11,668,976	74,070	22,818	20,427	634.8	195.5	175.1	2.21 (2.17, 2.25)	1.78 (1.72, 1.84)	2.63 (2.53, 2.73)

CVD=Cardiovascular disease, IHD=Ischaemic heart disease, CI=Confidence interval
[a] Death numbers are averaged across the 5 imputed datasets.

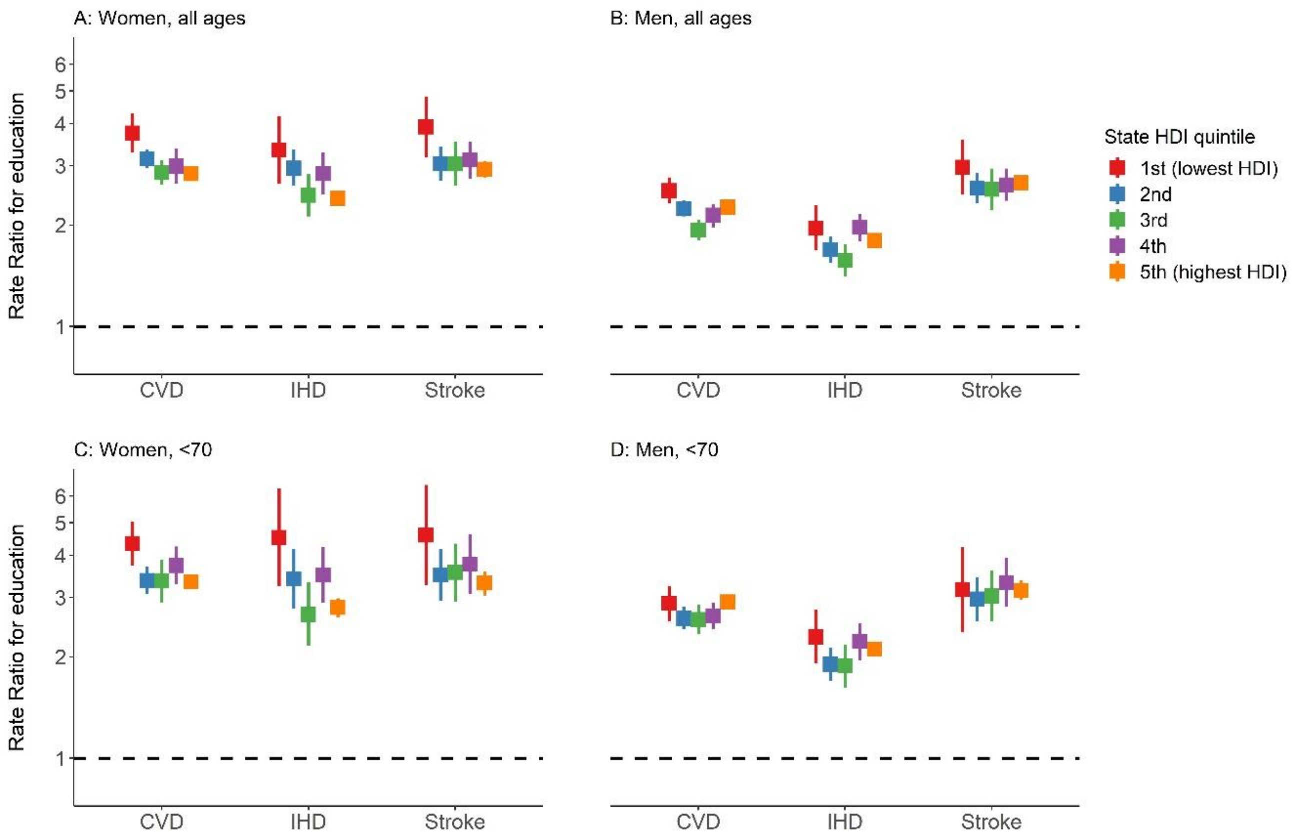

Figure 2. 1 Rate ratios for the association between education (<8 vs 8+ years) and cardiovascular mortality by quintile of state Human Development Index in Brazil, 2010.

HDI=Human Development Index, CVD=Cardiovascular disease, IHD=Ischaemic heart disease.

Table 2. 2 Associations between education and cardiovascular mortality stratified by quintile of state-level Human Development Index in Brazil, 2010

	Age-adjusted rate ratio for having <8 vs 8+ years education (95% CI) by quintile of state HDI					*P*- trend by quintile	Change in log rate ratio per 0.1 unit change in state HDI (95% CI)	*P*- linear trend
	1 (lowest)	2	3	4	5 (highest)			
Women, all ages								
CVD	3.75 (3.29, 4.28)	3.15 (2.96, 3.35)	2.86 (2.63, 3.12)	2.99 (2.65, 3.37)	2.84 (2.75, 2.92)	0.005	-0.18 (-0.28, -0.07)	0.002
IHD	3.34 (2.65, 4.21)	2.95 (2.61, 3.34)	2.45 (2.12, 2.83)	2.84 (2.47, 3.28)	2.40 (2.29, 2.51)	0.188	-0.12 (-0.29, 0.05)	0.182
Stroke	3.91 (3.17, 4.81)	3.04 (2.71, 3.42)	3.04 (2.61, 3.54)	3.12 (2.75, 3.54)	2.93 (2.77, 3.10)	0.177	-0.13 (-0.32, 0.05)	0.164
Men, all ages								
CVD	2.53 (2.32, 2.77)	2.24 (2.12, 3.37)	1.93 (1.80, 2.07)	2.14 (1.97, 2.31)	2.26 (2.20, 2.31)	0.568	-0.06 (-0.15, 0.04)	0.258
IHD	1.96 (1.68, 2.29)	1.69 (1.54, 1.85)	1.57 (1.41, 1.75)	1.97 (1.79, 2.16)	1.80 (1.73, 1.87)	0.184	0.07 (-0.08, 0.23)	0.334
Stroke	2.97 (2.46, 3.59)	2.57 (2.32, 2.85)	2.55 (2.21, 2.94)	2.63 (2.36, 2.94)	2.67 (2.54, 2.80)	0.765	-0.03 (-0.21, 0.14)	0.713
Women, <70								
CVD	4.34 (3.74, 5.03)	3.37 (3.07, 3.70)	3.36 (2.90, 3.89)	3.73 (3.28, 4.25)	3.34 (3.19, 3.50)	0.042	-0.14 (-0.26, -0.01)	0.032
IHD	4.52 (3.24, 6.31)	3.41 (2.78, 4.18)	2.67 (2.16, 3.32)	3.50 (2.89, 4.24)	2.80 (2.62, 2.98)	0.119	-0.16 (-0.37, 0.05)	0.143
Stroke	4.59 (3.26, 6.47)	3.50 (2.93, 4.18)	3.56 (2.92, 4.33)	3.77 (3.07, 4.63)	3.31 (3.04, 3.59)	0.293	-0.13 (-0.33, 0.08)	0.222
Men, <70								
CVD	2.88 (2.55, 3.24)	2.60 (2.41, 2.82)	2.58 (2.33, 2.86)	2.64 (2.42, 2.89)	2.91 (2.83, 2.99)	0.651	0.04 (-0.08, 0.15)	0.545
IHD	2.29 (1.91, 2.76)	1.90 (1.70, 2.13)	1.88 (1.62, 2.17)	2.22 (1.95, 2.52)	2.11 (2.01, 2.21)	0.316	0.07 (-0.10, 0.24)	0.414
Stroke	3.16 (2.37, 4.22)	2.97 (2.55, 3.45)	3.03 (2.55, 3.61)	3.32 (2.81, 3.93)	3.15 (2.95, 3.37)	0.584	0.06 (-0.14, 0.25)	0.552

CI=confidence interval, HDI=Human Development Index, CVD=Cardiovascular disease, IHD=Ischaemic heart disease

2.6 Discussion

Summary of main findings

We found that lower educational status was associated with higher cardiovascular mortality in both more and less economically developed states of Brazil. Among women, these social inequalities in cardiovascular mortality were larger in the less economically developed states. Associations were robust to use of different geographical units of analysis and different inclusion criteria for data quality. Thus, we find no evidence to support a 'social cross-over' in cardiovascular mortality, from greater risk in higher socioeconomic groups to greater risk in lower socioeconomic groups, on economic development in a large middle-income country.

Relation to literature

The phenomenon of a 'social cross-over' in cardiovascular disease on economic development is frequently cited in the global health literature[188,196–198]. Historical data from the UK demonstrated a change in the association between occupational social class and non-valvular heart disease mortality from positive to inverse between 1951 and 1971[115]. However subsequent re-analysis of this data suggested the apparent 'cross-over' may have been an artefact of bias in mortality coding practices (deaths among low socioeconomic groups were less likely to be attributed to IHD)[85]. A review of studies from the United Kingdom and United States between 1930 and 1960 which measured IHD objectively found a null or inverse association in 11 out of 12 studies[85]. An ecological study from Hong Kong reported a change in the association between neighbourhood median income and cardiovascular mortality from positive to inverse between 1976 and 1995, but this 'cross-over', is unlikely to be attributable to economic development as Hong Kong was relatively economically advanced throughout this period[206]. Long term data from a demographic surveillance site in Bangladesh reported that household wealth was positively associated with IHD mortality in 1983, and not associated in 2005, although the tenfold increase in IHD mortality between surveys (presumably due to the high proportion of unassigned deaths in earlier surveys) suggests that this data could not be reliably compared over time[101].

By comparing areas at varying levels of economic development at one point in time to investigate a 'social cross-over' in cardiovascular mortality on economic development, we avoided potential biases related to systematic changes in cardiovascular mortality coding practices and data quality over time. A few other studies have compared social inequalities in cardiovascular disease across countries at different levels of economic development, and generally found an inverse association in high- as well as low/middle-income countries[97,103,105,199]. However all of these studies except one[103] combined low- and middle-income countries into a single category, and did not examine variation in the association by stage of economic development, which could have provided more relevant evidence for the 'social cross-over' hypothesis given that the inverse association in high-income countries is well-established[204]. A recent prospective study of 20 low-, middle- and high-income countries found that inverse associations between socioeconomic position and incident cardiovascular disease were stronger in low-income countries than middle-income countries, consistent with our findings and inconsistent with the 'social cross-over' hypothesis[103].

Mechanisms

Explanations for a 'social cross-over' in cardiovascular disease generally refer to changes in the socioeconomic patterning of cardiovascular risk behaviours. An important factor in high-income countries may have been the shift in smoking from high to low socioeconomic groups around mid-20th century[115,204], although there is no evidence to support a similar shift in low- and middle-income countries[116]. More relevant to low- and middle-income countries may be the replacement of occupational physical activity among low socioeconomic groups in pre-industrialised economies, by leisure-based physical activity among high socioeconomic groups in industrialised economies and the increasing availability of low-quality, calorie dense diets[115]. Accordingly, many middle-income countries are experiencing dramatic increases in obesity prevalence, especially among low-socioeconomic groups[114]. While it seems plausible that a 'social cross-over' in diet, activity and obesity might explain a similar 'cross-over' in cardiovascular mortality, data from low- and middle-income countries do not support this. For example in India, socioeconomic position is associated positively with overweight/obesity[207] but inversely with cardiovascular mortality[103]; if a 'social cross-over' in cardiovascular mortality had already occurred in India, it would have preceded a 'social cross-over' in obesity, and thus could not have been caused by it. However it is possible that the earlier 'social cross-over' in obesity among women compared with men, observed in many countries including Brazil, has contributed to the gender differences in inequalities in cardiovascular mortality that we observed[114,208].

The lack of plausible mechanisms to account for a 'social cross-over' in cardiovascular mortality is consistent with our findings from Brazil of greater cardiovascular mortality in low socioeconomic groups, irrespective of state-level economic development. Reasons for greater cardiovascular mortality in low socioeconomic groups in low- and middle-income countries may be similar to those in high-income countries, for example reduced access to health services[103], exposure to harmful environmental conditions (e.g. air pollution and occupational hazards), increased smoking rates[116], and diets low in fruits and vegetables[103]. Novel and unestablished risk factors, such as early life undernutrition, frequent infections and psychosocial adversity, could play an important role in low- and middle-income countries, warranting further research in these settings.

Strengths and limitations

We used an innovative study design to circumvent the lack of high-quality temporal data on social inequalities in cardiovascular mortality from low- and middle-income countries. The large population sizes (ranging from 1.5 to 45 million) and diversity in economic development (encompassing levels of HDI comparable to lower middle-income (e.g. Bangladesh and Honduras) and upper middle-income (e.g. Mexico and Albania) countries) in Brazilian states allowed us to use them as counterfactuals to investigate the change in social inequalities on economic development, while controlling for bias from other factors that vary between countries or within countries over time (e.g. data quality and health-system factors). Furthermore, our use of national routine data allowed us to precisely estimate inequalities across a large number of geographical units.

However, the study also has some limitations. We used a single transitioning country to test a generalisable hypothesis, but each country is likely to have its own setting-specific factors that modify trends in social inequalities in cardiovascular disease. For example, in Brazil, there was an expansion of primary care services and other progressive social reforms from the mid-1990s onwards, which may have resulted in an underestimation of the inverse associations noted in even the least developed states[210]. Furthermore, the Brazilian states included in our analyses were comparable to lower- and upper-middle income countries, but the results may not be generalisable to countries outside this range of economic development. Supportive data from countries at extremely low levels of economic development are needed.

The coverage and quality of mortality reporting was variable across states, which could have introduced some potential for bias. Firstly, there was more under-registration of deaths in the lower HDI states[211]. To minimise the potential bias arising from this, we restricted our analyses to municipalities with high mortality registration using a robust indicator based on an independent data source[205]. The socio-demographic characteristics of the included and excluded populations were similar, and the results hardly changed when we included the whole population in sensitivity analyses (appendix Table S1.3 and Table S1.4). Secondly, a greater proportion of causes of deaths were ill-defined in the lower HDI states. Although we used multiple imputation to account for this, multiple imputation assumes that the data were missing-at-random, which may not have been the case. In Brazil, ill-defined causes of death are more common in populations with reduced access to medical facilities (e.g. rural populations), while cardiovascular diseases are over-represented among the ill-defined causes of death[211,212]. However, we expect that any residual bias due to mortality under-reporting or ill-defined causes of death would under-estimate the inequalities in cardiovascular mortality in lower HDI states, suggesting that, if anything, our conclusions are likely to be conservative.

It is possible that there was some misclassification of educational status in the census or, more likely, on the death certificates (which are usually completed by the attending physician). This could potentially introduce numerator-denominator bias, a bias which arises when covariates used to link numerators to denominators are misclassified. The extent or direction of numerator-denominator bias is difficult to predict; however, the social inequalities for IHD mortality in our study were comparable to those for prevalent disease reported in another nationally representative survey, providing face-validity to our results[39]. Our use of a binary categorisation for education will have helped to reduce misclassification and achieve a more valid match between education categories on the death certificate and census. Furthermore, education has been shown to be less prone to numerator-denominator bias compared to other socioeconomic indicators such as occupation and income, and does not change with age among older adults, making it particularly suitable for adult mortality studies[176,213].

Another potential limitation is that we used HDI to classify the level of development of the states, which incorporates life expectancy and thus may be influenced by the outcome of cardiovascular mortality. Lower HDI states will tend to have higher mortality rates (including cardiovascular), leading to smaller relative inequalities in mortality in these states[17]. Similar to the other potential biases discussed above, this may have led to an under-estimation of social inequalities in cardiovascular mortality in lower HDI states, suggesting our conclusions could be conservative.

Implications

The belief in a 'social cross-over' in cardiovascular mortality on economic development is not supported by evidence from low- and middle-income countries. We urge caution when referring to this phenomenon, as doing so risks propagating a misrepresentation of social inequalities in cardiovascular disease in low- and middle-income countries. Our findings highlight a need for high-quality prospective data from low- and middle-income countries to describe and elucidate mechanisms of social inequalities in cardiovascular disease. Policies for the control of cardiovascular disease and its risk factors in low- and middle-income countries must be inclusive of low socioeconomic groups.

Conclusions

Our results do not support the 'social cross-over' in cardiovascular disease, from greater risk in high socioeconomic groups to greater risk in low socioeconomic groups, on economic development. Our analyses, using a large standardised dataset encompassing a range of levels of economic development, suggest that low socioeconomic groups experience the highest risk of cardiovascular disease, irrespective of the stage of economic development.

Chapter 3: Systematic review of socioeconomic position in childhood and risk of cardiovascular disease in low- and middle-income countries

3.1 Introduction to chapter

This chapter aims to address the second evidence gap and objective of the thesis, namely the association between childhood socioeconomic position and risk of cardiovascular disease in adulthood in low- and middle-income countries. The published literature on this topic has not been summarised since 2003, when no studies from low- and middle-income countries were identified. I therefore conducted a systematic review of evidence on the association between childhood socioeconomic position and cardiovascular disease and its risk factors in low- and middle-income countries. This work has been submitted for publication in a peer-reviewed journal (European Journal of Preventive Cardiology), and is awaiting a decision. Additional tables containing the full search strategy, and a detailed description of the results of included studies, are provided in Appendix 2 of the thesis.

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SECTION A – Student Details

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Thesis Title	Life course socioeconomic influences on risk of cardiovascular disease in low- and middle-income countries		
Primary Supervisor	Sanjay Kinra		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	European Journal of Preventive Cardiology
Please list the paper's authors in the intended authorship order:	Poppy Mallinson, Judith Lieber, Sanjay Kinra
Stage of publication	Submitted.

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualised the study, wrote the protocol, performed the database search, extracted the data, analysed the data, wrote the first draft of the manuscript, revised the manuscript according to comments from co-authors.

SECTION E

Student Signature	[redacted]
Date	20/11/2020

Supervisor Signature	[redacted]
Date	23/11/2020

<u>Socioeconomic position in childhood and risk of cardiovascular disease: A systematic review of evidence from low- and middle-income countries</u>

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3.2 Abstract

Background: Socioeconomic disadvantage in childhood is an established determinant of cardiovascular disease in high-income countries. The association between childhood socioeconomic position and risk of cardiovascular disease in low- and middle-income countries, where childhood poverty remains prevalent, is poorly understood.

Methods: We systematically searched the MEDLINE, Embase and Global Health databases (updated to 19th September 2020) for articles on the association between socioeconomic position in childhood and risk of cardiovascular disease in adulthood in low- and middle-income countries. Outcomes included cardiovascular mortality and disease (overall or subtypes), sub-clinical markers of cardiovascular disease (e.g. carotid intima-media thickness) and major cardiovascular risk factors (e.g. hypertension, dyslipidaemia, diabetes). Where available, we extracted associations before and after adjustment for socioeconomic position in adulthood. We synthesised results qualitatively by outcome, and appraised their risk of bias using a modified version of the Newcastle-Ottawa Scale. The study protocol is registered on PROSPERO (CRD42018086984).

Results: Our search returned 3568 unique abstracts, from which we identified 29 eligible articles from 14 middle-income countries, and none from low-income countries. The eligible articles analysed 20 unique datasets, representing over 150,000 participants. The most commonly reported outcomes were cardiovascular risk factors (hypertension, diabetes and lipid profile). Only a few studies reported prevalent measures of cardiovascular disease, and no studies reported cardiovascular disease incidence or mortality. Of the 46 reported associations between childhood socioeconomic position and risk of cardiovascular disease, 8 were inverse, 0 were direct, and 38 showed no clear evidence of an association. All articles were judged to have high (16/29) or medium (13/29) risk of bias.

Conclusions: Current evidence from middle-income countries provides little support for an association between childhood socioeconomic position and risk of cardiovascular disease, whilst evidence from low-income countries is lacking. It would be premature to consider socioeconomic position in childhood as a target for cardiovascular prevention in these settings.

3.3 Introduction

Cardiovascular disease is the leading cause of premature death in most low- and middle-income countries[9]. The burden of cardiovascular disease is rising as populations age, placing increasing pressure on healthcare systems and indicating an urgent need for preventive strategies[67]. Socioeconomic disadvantage in childhood is independently associated with risk of cardiovascular disease in high-income countries[119,124,125,214]. It follows that socioeconomic disadvantage in childhood could be a substantial contributor to cardiovascular disease burden in low- and middle-income countries, where over 20% of children live in extreme poverty[196,215]. If true, strategies to tackle childhood poverty might play an important role in controlling the cardiovascular disease epidemic in low- and middle-income countries.

Previous systematic reviews on the association between childhood socioeconomic position and cardiovascular disease were conducted in 2003 and 2004, and identified studies from high-income countries only[119,125]. It is not clear whether findings from high-income countries can be generalised to low- and middle-income countries, given the distinct range of socioeconomic conditions experienced across these settings[216]. We systematically reviewed the literature on the association between childhood socioeconomic position and risk of cardiovascular disease in low- and middle-income countries. We hypothesised that as in high-income countries, socioeconomic position in childhood would be inversely associated with risk of cardiovascular disease in low- and middle-income countries.

3.4 Methods

We conducted a systematic review of the association between socioeconomic position in childhood and risk of cardiovascular disease in adulthood in low- and middle-income countries. This review is reported according to the PRISMA checklist (see appendix Table S2.1). The protocol is registered on PROSPERO (number CRD42018086984).

Exposure

The exposure of interest was socioeconomic position measured or reported in childhood (age <18 years). To operationalise childhood socioeconomic position, we considered a range of commonly used indicators of relative social status and material conditions, such as parental education, parental occupation during childhood and household income or assets during childhood[82]. We did not consider individuals' own education as an indicator of their socioeconomic position in childhood as it is typically used as an indicator of adult socioeconomic position, and has been reviewed previously[87,217]. We were primarily interested in the association of childhood socioeconomic position independent of adult socioeconomic position, as adult socioeconomic position is a known determinant of cardiovascular risk and tracks strongly from early life. For this, we considered associations either adjusted for adult socioeconomic position or stratified by adult socioeconomic position (sometimes presented as social trajectory or social mobility analyses).

Outcome

The primary outcomes of interest were incidence and mortality of cardiovascular disease, coronary heart disease or stroke, subclinical measures of cardiovascular disease (carotid intima-media thickness, carotid plaque, arterial stiffness), major cardiovascular risk factors (blood pressure or hypertension, lipid profile or dyslipidaemia, fasting glucose, insulin or diabetes) and composite variables derived from these (cardiovascular risk score or metabolic syndrome). To be eligible, studies had to report outcomes measured in adulthood (age ≥18 years). We included incident or prevalent outcomes. We also included self-reported disease and risk factors, but considered these to be secondary to objectively measured outcomes, because underdiagnosis of cardiovascular conditions is common in many low- and middle-income countries[218]. We did not include obesity as an outcome in the review, as it is less proximally related to cardiovascular disease than the above risk factors, and has been reviewed recently[194].

Inclusion/exclusion criteria

Peer-reviewed journal articles published in English, Spanish, French or Portuguese were eligible for inclusion (non-English language articles had to have a title and abstract in English as the search was not translated). We restricted our search to studies published since 2003, when a previous review conducted on this topic identified no studies from low- and middle-income countries[125]. Studies had to be conducted in low- and middle-income countries, which for practicality was defined according to the World Bank's country classification in the year that the study was published[219]. Studies reporting only pooled data from both low- or middle- and high-income countries were not eligible. We excluded studies which focussed on congenital or childhood cardiovascular diseases, and rheumatic heart disease, as the aetiology and epidemiology of these are distinct from most cardiovascular disease in adults. Studies using proportional mortality as an outcome, or measuring the outcome on an ecological level, were also excluded; all other study designs (prospective, case-control, cross-sectional) were eligible.

Search strategy

We searched three major biomedical databases (MEDLINE, Embase and Global Health, all through Ovid). An overview of the search strategy is given in Table 3.1 (full search terms in appendix Table S2.2). Titles and abstracts were screened for relevance by the main reviewer, with a 20% subsample independently screened by a second reviewer. Reference lists of eligible articles and relevant reviews identified by the main search were hand searched for additional articles. Discrepancies were resolved in discussion with a third reviewer as necessary.

Table 3. 1 Overview of search strategy for the systematic review

No.	Domain	**Example search terms used** (exhaustive synonyms for each term were included; see appendix Table S2.2 for full search strategy)
1	Exposure (socioeconomic position before age 18 years)	• Early, in utero, perinatal, childhood, adolescent, life course, intergenerational AND socioeconomic, social class, poverty, disadvantage, living conditions, household assets • Parental education, parental occupation, parental socioeconomic position, parental social class, parental income, parental assets • Early experiences, childhood conditions, childhood circumstances • Social mobility
2	Outcome (cardiovascular disease and its risk factors)	• Cardiovascular, cardiometabolic, heart disease, stroke • Atherosclerosis, carotid-intima media thickness, arterial stiffness • Blood pressure, hypertension, diabetes, fasting glucose, lipids, cholesterol, metabolic syndrome
3	Setting (low- and middle-income countries)	• Low- and middle-income countries, LMICs, developing countries, transitional countries, global south • Africa, Asia, Latin America, South America, Central America, Middle east, Eastern Mediterranean, Eastern Europe, Pacific, Micronesia • List of all countries that have been classified as low- or middle-income by the World Bank since 2003
4	Final search	1 AND 2 AND 3

Data extraction

Data from eligible articles were extracted into a pre-made data extraction form and double checked for accuracy by a second reviewer. Where possible, we extracted the associations between childhood socioeconomic position and risk of cardiovascular disease adjusted for i) age and sex, and ii) age, sex and at least one indicator of socioeconomic position in adulthood. When the association adjusted for adult socioeconomic position was not reported, but authors reported the association stratified by adult socioeconomic position (for example in a social trajectory analysis), we extracted these estimates, as they allow similar inferences to be made. Due to the diversity in exposures and outcomes across eligible studies, we anticipated that only a qualitative synthesis of evidence would be possible. We pre-decided to group study results by outcome. For each class of outcome, we used a vote-counting approach to summarise directions of associations after adjusting for adult socioeconomic position (i.e. direct, inverse, or null if not significant at the 95% level). If there were multiple associations reported using the same dataset for the same class of outcome (e.g. in the case of multiple eligible exposure variables, or slightly different outcome definitions), we counted the association as direct/inverse if more than half of the reported associations were inverse/direct. We extracted the associations stratified by sex where available.

Quality assessment

Risk of bias within studies was assessed independently by two reviewers, with discrepancies resolved in discussion with a third reviewer. We rated included articles based on an adapted version of the Newcastle-Ottawa Scale for assessing quality of observational studies[220]. We interpreted study results alongside their risk of bias, giving more weight to studies of higher quality in the discussion. Risk of bias across studies (i.e. publication bias) was not formally assessed because of heterogeneity in study exposures and outcome, but the potential impact of publication bias on our conclusions is addressed in the discussion.

3.5 Results

The search was executed on 19/09/2020 and returned 5891 articles (3568 after de-duplication). Screening of titles and abstracts returned 56 articles for full-text screen, of which 26 were eligible for inclusion. We found a further 3 articles through hand searches of the reference lists of relevant articles, giving a total of 29 articles included in the review. Figure 3.1 shows the flow chart of article selection.

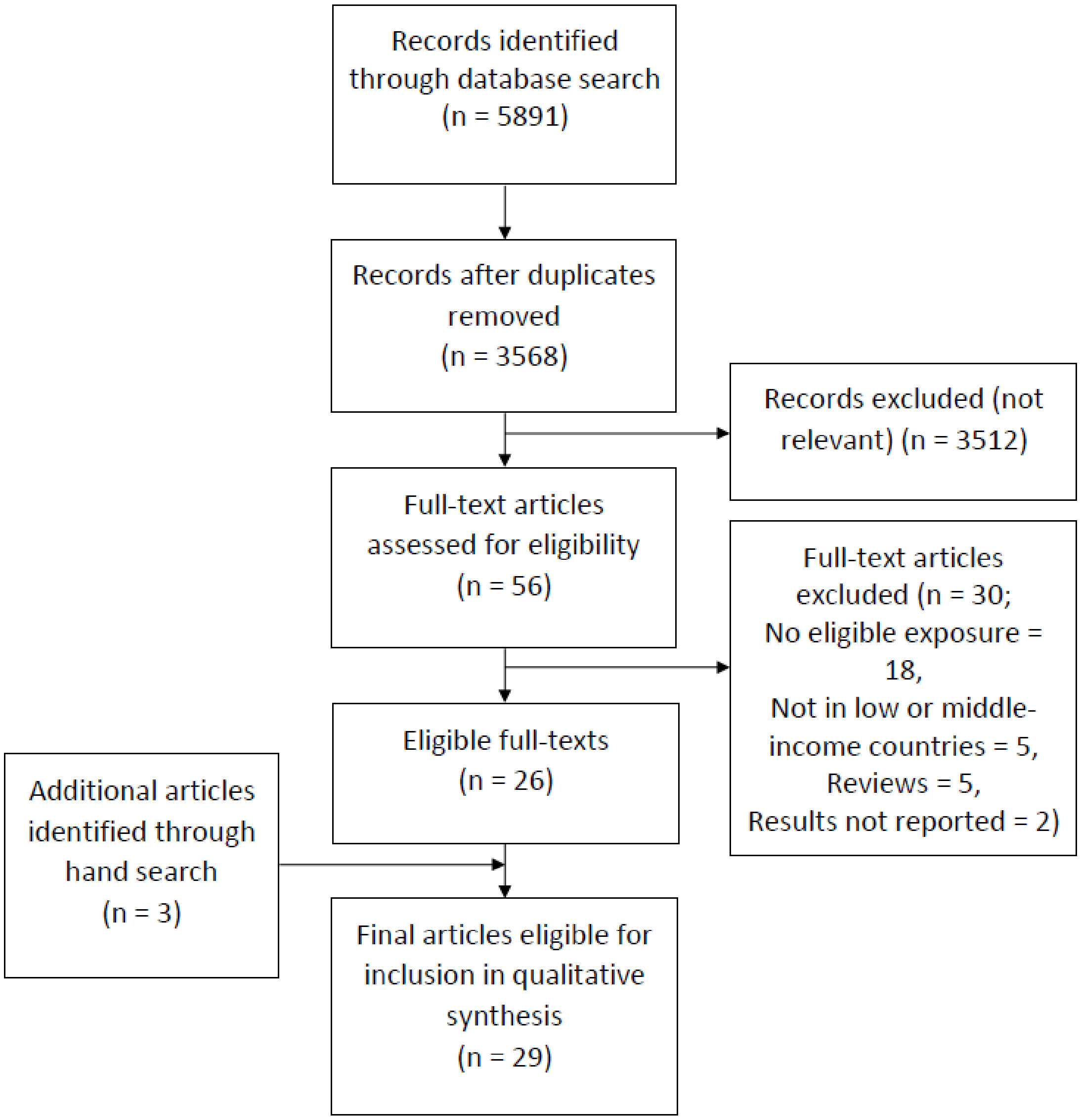

Figure 3. 1 Flowchart of articles included in the systematic review.

Overview of studies

Characteristics and key findings of eligible articles are given in Table 3.2 (full extracted results in appendix Table S2.3). The 29 eligible articles analysed data from 20 unique datasets or studies. Nine of these studies were from the Americas (4 from Brazil, 2 from Mexico, 1 from Colombia, 1 from Jamaica, 1 from multiple Latin American cities), 6 were from Asia (3 from India, 2 from China, 1 from Indonesia), 3 were from Africa (1 from South Africa, 1 from Ghana, 1 from Botswana), 1 was from Russia, and 1 included data from multiple world regions. All of the included studies were from middle-income countries (7 lower middle-income and the rest upper middle-income); we found no studies from low-income countries. Six of the studies collected prospective measures of childhood socioeconomic position, while the rest relied on retrospectively recalled measures of childhood socioeconomic position. Across all included studies there were over 150,000 unique participants. Two of the studies had under 1000 participants, 9 had between 1000 and 5000 participants, and 9 had over 5000 participants.

The most commonly measured indicator of childhood socioeconomic position was parental education (9/20 studies). Other indicators used were: parental occupation (3 studies); household conditions, assets or income in infancy (3 studies) or childhood (7 studies); subjectively assessed socioeconomic position in childhood (i.e. high/medium/low, 3 studies); and a composite of multiple measures (1 study). Only 4 of the included studies reported cardiovascular disease as an outcome, 3 of which used self-reported diagnosis or symptoms of heart disease, and 1 of which measured prevalent coronary heart disease using ECG. Three articles, all based on the same study from Brazil (ELSA-Brasil), reported on subclinical measures of cardiovascular disease (carotid intima-media thickness and carotid-femoral pulse wave velocity). Fourteen studies reported on hypertension or blood pressure as an outcome (2 of which relied on self-reported diagnosis of hypertension), and 11 studies reported on diabetes or impaired fasting glucose as an outcome (5 of which relied on self-reported diagnosis of diabetes). Other outcomes included lipid levels (5 studies), metabolic syndrome (2 studies) and cardiovascular risk score (1 study). In total, studies reported 46 associations between socioeconomic position in childhood and these different outcomes. Of these, 39 associations were adjusted for at least one marker of socioeconomic position in adulthood, of which 6 were also adjusted for at least one marker of adult health (most commonly overweight or obesity). Two out of 46 associations were only presented stratified, not adjusted for, adult socioeconomic position (i.e. social trajectory analyses). Findings of the included studies, organised by outcome, are summarised below and in Table 3.3.

Table 3. 2 Description and key findings of articles included in the systematic review (n=29)

Author/ year	**Dataset/ study, country**	**Study design**	**Recruitment year(s)**	**N**	**Participant ages**	**Exposure(s)**	**Outcome(s)**	**Key findings**
Keetile, 2020[221]	Non-communicable disease survey in Botswana	Cross-sectional	2016	1178 (50% men)	15-80 (mode age group 25-34)	Composite SEP index, retrospectively reported	Hypertension, self-reported Diabetes, self-reported	Childhood SEP index was directly associated with self-reported hypertension in crude models, and inversely associated in models adjusted for adult SEP. No associations between childhood SEP and diabetes.
Camelo, 2015[222]	ELSA-Brasil	Cross-sectional	2008-10 (baseline)	8806 (46% men)	35-74 (mean age 50)	Parental education, retrospectively reported	Carotid intima-media thickness	Maternal education was inversely associated with CIMT in women but not men, although this association was not robust to adjustment for adult SEP.
Guimaraes, 2016[223]	ELSA-Brasil	Cross-sectional	2008-10 (baseline)	7343 (47% men)	35-74 (mean age 50)	Parental occupation and own occupation, retrospectively reported (trajectory analysis)	Carotid intima-media thickness	Stable low SEP trajectory had the highest CIMT, then downwards trajectory. Upwards trajectory was not different from stable high.
Coelho, 2019[224]	ELSA-Brasil	Cross-sectional	2008-10 (baseline)	13365 (46% men)	35-74 (mean age 51)	Parental education, retrospectively reported	Carotid-femoral pulse wave velocity	Maternal education was inversely associated with pulse wave velocity. After adjustment for adult SEP as well as some behavioural and biological risk factors, the association remained among black and brown participants only.
Camelo, 2016[225]	ELSA-Brasil	Cross-sectional	2008-10 (baseline)	13629 (45% male)	35-74 (mean age 51)	Parental education and own education; parental occupation and own occupation, retrospectively reported (trajectory analysis)	Diabetes, undiagnosed	Stable low SEP trajectory had highest diabetes, then downwards SEP trajectory. Upwards SEP trajectory was not different from stable high.
De Sousa Andrade, 2017[226]	ELSA-Brasil	Cross-sectional	2008-10 (baseline)	13544 (46% men)	35-74 (mean age 51)	Parental education, retrospectively reported	cardiovascular risk score	Maternal education was inversely associated with cardiovascular risk score, which was robust to adjustment for adult SEP.
Lopez, 2017[227]	ELSA-Brasil	Cross-sectional	2008-10 (baseline)	13571 (46% men)	35-74 (mean age 51)	Parental education, retrospectively reported	Blood pressure	Maternal education was inversely associated with systolic blood pressure, which was robust to adjustment for adult SEP and behavioural risk factors.
Nishida, 2020[228]	EpiFloripa Cohort Study, Brazil	Cross-sectional	2012 (second wave)	926 (44% men)	20-65 (mode age group 20-29)	Parental education, retrospectively reported	Hypertension	Parental education was not associated with hypertension (before or after adjustment for adult SEP).

Horta, 2008[229]	Pelotas 1982 birth cohort, Brazil	Prospective	1982, followed-up 2004-5	4291 (51% men)	22-23	Parental education Household income at birth	Blood pressure	Maternal education and household income at birth were not associated with blood pressure in crude models, except for a direct association between maternal education and diastolic blood pressure in women only (results adjusted for adult SEP were not presented).
Figueiredo, 2007[230]	Ribeirao Preto birth cohort, Brazil	Prospective	1978-79, followed up 2002-4	2063 (50% men)	23-25	Household income at birth	Total cholesterol LDL cholesterol HDL cholesterol Triglycerides	Household income at birth was directly associated with HDL cholesterol, and among men only, directly associated with LDL and total cholesterol, all of which were robust to adjustment for adult SEP. No associations were seen with triglycerides.
Elwell-Sutton, 2011[162]	Guangzhou Biobank Cohort Study, China	Cross-sectional	2005-8 (phases 2 and 3)	20,086 (27% men)	50+ (mean age 61)	Household assets in childhood, retrospectively reported	Metabolic syndrome	Childhood assets were inversely associated with metabolic syndrome in women but not men, but this association was not robust to adjustment for adult SEP.
Schooling, 2008[231]	Guangzhou Biobank Cohort Study, China	Cross-sectional	2005-6 (phase 1)	9746 (28% men)	50+ (mean age 60)	Household assets in childhood, retrospectively reported	Metabolic syndrome Blood pressure Fasting glucose Triglycerides HDL	Childhood assets were inversely associated with metabolic syndrome in women but not men, which was robust to adjustment for adult SEP and behavioural factors. Childhood assets were inversely associated with SBP (both sexes) and fasting glucose (women only), and directly associated with DBP and triglycerides (both males only), none of which were robust to adjustment for adult SEP and behavioural risk factors. Childhood assets were inversely associated with HDL in males only, which was robust to adjustment for adult SEP.
Fan, 2010[232]	Peking Union Hospital births, China	Prospective	1921-54, followed up 2002-4	2033 (50% men)	50-84 (mean age 60)	Parental education, retrospectively reported Parental occupation, retrospectively reported	Coronary heart disease, prevalent	Parental occupation and education were not associated with prevalent coronary heart disease (measured by ECG), although associations were only presented adjusted for adult behavioural and biological risk factors.
McEniry, 2019[233]	SABE Colombia	Cross-sectional	2014-15	14657 (46% men)	60+ (mode age group 60-64)	Subjective SEP in childhood, retrospectively reported	Coronary heart disease, self-reported	Subjective SEP in childhood was not associated with reported diagnosis of heart disease (before or after adjustment for adult SEP).

Addo, 2009[234]	Survey of civil servants in Ghana	Cross-sectional	2006	1015 (60% men)	Mean age 44	Household assets in childhood, retrospectively reported	Hypertension	Childhood assets were not associated with hypertension (before or after adjustment for adult SEP).
Mallinson, 2020[235]	APCAPS and Indian Migration Study, India	Cross-sectional	2010-12/ 2005-07	14011 (56% men)	Mean age 38	Household assets in childhood, retrospectively reported	Blood pressure Total cholesterol LDL cholesterol Triglycerides Fasting glucose Insulin HOMA	Childhood assets were not associated with blood pressure in crude models, although were inversely associated after adjustment for adult SEP. Childhood assets were directly associated with total cholesterol, LDL cholesterol, triglycerides, fasting glucose, insulin and HOMA in crude models, but these associations were not robust to adjustment for adult SEP.
Sovio, 2013[236]	Indian Migration Study, India	Cross-sectional	2005-07	7067 (58% men)	15-76 (mean age 41)	Household assets in childhood, retrospectively reported	Blood pressure HOMA	Childhood assets were not associated with SBP or HOMA score, except for a direct association with HOMA score in males, which was robust to adjustment for adult SEP.
Samuel, 2012[237]	Vellore birth cohort, India	Prospective	1969-73, followed up 1998-2002	2218 (52% men)	26-32 (mean age 28)	Parental education	High TC:HDL ratio High triglycerides Hypertension Diabetes/IGT/IFG	Paternal education was not associated with high total:HDL cholesterol, high triglycerides, hypertension or diabetes/IFG/IGT after adjustment for adult SEP and physical activity (crude models not shown).
Peele, 2019[238]	Indonesian Family Life Survey	Cross-sectional	2014-15	6530 (47% men)	50+ (mean age 60)	Household conditions in childhood, retrospectively reported	Hypertension, self-reported Diabetes, self-reported	Childhood assets were not associated with self-reported hypertension in crude models, but inversely associated after adjustment for adult SEP. Childhood assets were not associated with self-reported diabetes.
Ferguson, 2010[239]	Jamaica 1986 birth cohort	Prospective	1986, followed up 2005-7	839 (45% men)	18-20	Parental education	Metabolic syndrome High blood pressure Low HDL High Triglycerides IFG	Parental education was not associated with metabolic syndrome, high blood pressure, impaired fasting glucose, low HDL or high triglycerides in crude models (adjusted models not presented).
Ferguson, 2015[240]	Jamaica 1986 birth cohort	Prospective	1986, followed up 2005-7	794 (46% men)	18-20	Parental occupation	Blood pressure	Maternal occupation was not associated with blood pressure in crude models, but after adjustment for height, BMI and birthweight, there was an inverse association with SBP among males.
Carrillo-Vega, 2019[241]	Mexican Health and Aging Study	Prospective	2012 and 2015	8848 (44% men)	50+ (mean age 64)	Household conditions in childhood, retrospectively reported	Diabetes incidence and prevalence, self-reported	Possession of shoes in childhood, but not child hunger, was inversely associated with incidence of self-reported diabetes between the two survey waves, but not with prevalent

								diabetes, in models adjusted for adult SEP, health behaviours and comorbidities (crude models not shown).
Kohler, 2005[242]	Mexican Health and Aging Study	Cross-sectional	2001	6423 (49% men)	50+ (mean age 61)	Parental education, retrospectively reported Household conditions in childhood, retrospectively reported	Diabetes, self-reported	Maternal, but not paternal, education was inversely associated with self-reported diabetes, robust to adjustment for adult SEP and overweight. Inconsistent associations were seen for household conditions and hunger in childhood.
Beltran-Sanchez, 2011[243]	Mexican Family Life Survey	Cross-sectional	2002	14280 (~50% men)	20+ (mode age group 20-39)	Household assets in childhood, retrospectively reported	Hypertension	Household possession of a toilet in childhood was inversely associated with hypertension in females but not males, which was robust to adjustment for adult SEP and overweight.
Palloni, 2006[244]	SABE (Chile, Brazil, Cuba, Mexico, Uruguay)	Cross-sectional	2000	4540	60-74 (mean age not stated)	Subjective SEP in childhood, retrospectively reported	Coronary heart disease, self-reported Diabetes, self-reported	Subjective SEP in childhood was not associated with self-reported heart disease or diabetes in models adjusted for adult SEP, obesity and height (crude models not shown).
Ogunsina, 2018[245]	WHO-SAGE (China, Mexico, India, South Africa, Russia)	Cross-sectional	2007-10	38297 (42% men)	18+ (mode age group 40-64)	Parental education and own education, retrospectively reported (trajectory analysis)	Hypertension, measured and self-reported Diabetes, self-reported	Stable high SEP trajectory was associated with higher prevalence of self-reported, but not measured, hypertension, among men only. Stable high or downwards SEP trajectories were associated with higher self-reported diabetes, among men only.
Vagero, 2005[246]	Household survey in Russia	Cross-sectional	1998	1972	18-70 (mean age not stated)	Subjective SEP in childhood, retrospectively reported	Coronary heart disease, self-reported symptoms	Subjective SEP in childhood was inversely associated with self-reported heart disease symptoms in models adjusted for adult SEP (crude models not shown).
Kagura, 2016[247]	Birth to Twenty Cohort, South Africa	Prospective	1990, followed up 2008	838 (48% men)	18	Household assets at birth	Blood pressure Hypertension	Household asset score in infancy was not associated with blood pressure or hypertension in models adjusted for SEP trajectory (crude models not shown).
Naidoo, 2019[248]	Birth to Twenty Cohort, South Africa	Prospective	1990, followed up 2013	1540 (49% men)	23	Parental education	Elevated blood pressure	Maternal education was not associated with elevated blood pressure (before or after adjustment for adult SEP).
SEP is socioeconomic position; LDL is low-density lipoprotein; HDL is high-density lipoprotein; TC is total cholesterol; HOMA is homeostasis model assessment; IGT is impaired glucose tolerance; IFG is impaired fasting glucose.								

Cardiovascular disease and subclinical markers

Four studies reported on cardiovascular disease outcomes. In a cohort of births from one hospital in China between 1921 and 1954 (N=2033, <20% follow-up rate), paternal education and occupation at birth were not associated with prevalent coronary heart disease diagnosed by ECG and Rose/WHO angina questionnaire[232]. However, the authors only presented the association adjusted for adult cardiovascular risk factors (including hypertension, diabetes, dyslipidaemia), which may have attenuated the association. In two large cross-sectional surveys in Latin America (one in Colombia[233], one in multiple capital cities in the region[244]), self-reported subjective socioeconomic position in childhood was not associated with self-reported diagnosis of coronary heart disease. On the other hand, in a household survey in a town in southern Russia, self-reported childhood poverty was associated with increased risk of self-reported coronary heart disease symptoms, which was robust to adjustment for the participants' education[246]. Subclinical measures of cardiovascular disease were only reported in one cross-sectional study of Brazilian civil servants (ELSA-Brasil, N=~13,000). One analysis found an inverse association between maternal education and carotid intima-media thickness (CIMT) in women only[222], although this disappeared after adjustment for socioeconomic position in adulthood. An analysis of the association of occupational social class trajectory between parents and participants with CIMT in the same dataset reported consistent findings[223]. Another analysis of the same dataset reported a crude inverse association between maternal education and carotid-femoral pulse wave velocity, a measure of arterial stiffness, although after adjustment for adult socioeconomic position, the association only remained for black and brown participants[224].

Hypertension and blood pressure

In 5/6 studies which reported on the association between childhood socioeconomic position and adult hypertension or elevated blood pressure (3 prospective[237,239,240,247,248], 2 cross-sectional[228,234]), no strong evidence of an association was reported. In 1 cross-sectional study in Mexico, an inverse association was observed in females but not males, which was robust to adjustment for adult socioeconomic position[243]. Five other studies reported on the association between childhood socioeconomic position and blood pressure (assessed as a continuous outcome). There was little evidence of an association in 1 prospective study[229], while in 2 cross-sectional studies[231,236], the crude associations disappeared after adjustment for adult socioeconomic position. In a cross-sectional study of Brazilian civil servants (ELSA-Brasil), there was an inverse association between maternal education and systolic blood pressure, which was robust to adjustment for the participants' education and wealth status[227]. In a cross-sectional analysis of two pooled studies from India, household assets in childhood were inversely associated with systolic and diastolic blood pressure after adjusting for adult socioeconomic position[235]. Two cross-sectional surveys from Botswana[221] and Indonesia[238] examined the association of childhood socioeconomic position with self-reported diagnosis of hypertension, both reporting that an inverse association emerged after adjustment for socioeconomic position in adulthood. An analysis of the WHO-SAGE cross-sectional study (conducted in China, Mexico, India, South Africa and Russia, N=38,297) reported the association of cardiovascular risk factors with participants' socioeconomic trajectories between childhood and adulthood[245]. The authors found that the prevalence of measured hypertension did not vary between socioeconomic trajectory groups, suggesting no association of childhood socioeconomic position with measured hypertension. However, among males only, the prevalence of diagnosed hypertension was highest in the persistent high socioeconomic group and slightly raised in the declining socioeconomic group, suggesting a direct association between childhood socioeconomic position and diagnosed hypertension.

Diabetes and impaired fasting glucose

Two prospective studies examined impaired fasting glucose or diabetes as an outcome, neither finding any association with parental education[237,239]. Three cross-sectional studies examined fasting glucose, insulin or HOMA score (a measure of insulin resistance based on fasting glucose and insulin) as continuous outcomes. In a study of internal migrants in India there was a direct association between household assets in childhood and HOMA score among males only, which was robust to adjustment for household assets in adulthood[236]. However in a larger pooled dataset from India (which included these participants as well as participants from the APCAPS study), the direct associations with fasting glucose, insulin and HOMA score were not robust to adjustment for adult socioeconomic position[235]. In a study of older adults from southern China, there was an inverse association between household assets in childhood and fasting glucose in females only, which was not robust to adjustment for adult socioeconomic position[231]. Three out of four cross-sectional studies which examined the association of childhood socioeconomic position with self-reported diabetes found no clear evidence of an association[221,238,244]. In one nationally representative survey in Mexico, there was some evidence of an inverse association between maternal, but not paternal, education and self-reported diabetes, although the associations of childhood assets with self-reported diabetes were highly inconsistent[241,242].

Two studies examined the association between diabetes and participants' socioeconomic trajectory between childhood and adulthood. In the ELSA-Brasil study, diabetes risk was highest in the persistent low and declining socioeconomic groups[225], suggesting that socioeconomic position in adulthood, but not childhood, was inversely associated with diabetes. In the WHO-SAGE study, among men only, prevalence of self-reported diabetes was highest in the declining and persistent high socioeconomic groups, suggesting that childhood socioeconomic position is directly associated with risk of diabetes, independent of adult socioeconomic position[245].

Other outcomes

Five studies (3 prospective and 2 cross-sectional) reported on the association between childhood socioeconomic position and lipid profile in adulthood. Total and low-density lipoprotein (LDL) cholesterol were examined in 2 studies. In a pooled dataset from India (N=14011), household assets in childhood were directly associated with total and LDL cholesterol, but these associations were not robust to adjustment for adult socioeconomic position[235]. In a birth cohort from Brazil (N=2063), household income at birth was directly associated with total and LDL cholesterol among males only, which was robust to adjustment for adult socioeconomic position[230]. High-density lipoprotein (HDL) cholesterol was directly associated with childhood socioeconomic position in the same study, although was inversely associated in a cross-sectional study from China[231], and not associated in two other studies in India and Jamaica[237,239]. There was no evidence for an association between childhood socioeconomic position and triglycerides in any of the 5 studies. Two studies looked at metabolic syndrome (defined by International Diabetes Federation criteria). In a cross-sectional study of older adults in southern China (N=9746), metabolic syndrome was inversely associated with childhood assets in women only, which was robust to adjustment for adult socioeconomic position[162,231]. In a birth cohort from Jamaica (N=839), there was no evidence that metabolic syndrome was associated with maternal education[239]. One cross-sectional study of Brazilian civil servants (ELSA-Brasil, N=13544) found a strong inverse association between maternal education and Framingham Risk Score (a composite of blood pressure, total and HDL cholesterol, diabetes and smoking), which was robust to adjustment for adult socioeconomic position[226].

Table 3. 3 Summary of the directions of associations between childhood socioeconomic position and risk of cardiovascular disease in low- and middle-income countries.

	Direction of association with childhood socioeconomic position		
Outcome	**Inverse**	**Null**	**Direct**
Prevalent coronary heart disease		China (Peking hospital)	
Self-reported coronary heart disease	Russia	Colombia Multiple cities (SABE)	
Subclinical measures of cardiovascular disease	Brazil (ELSA-Brasil)	Brazil (ELSA-Brasil)	
Hypertension and blood pressure	Mexico F (MxFLS) Brazil (ELSA-Brasil) India (APCAPS/IMS)	Mexico M (MxFLS) Brazil (EpiFloripa) Brazil (Pelotas) Jamaica Ghana South Africa China (GBCS) India (Vellore) India (IMS) Multi-country (SAGE)	
Self-reported hypertension	Botswana Indonesia	Multi-country F (SAGE)	Multi-country M (SAGE)
Diabetes and fasting glucose		India F (IMS) India (APCAPS/IMS) India (Vellore) Jamaica China (GBCS) Brazil (ELSA-Brasil)	India M (IMS)
Self-reported diabetes		Mexico (MHAS) Multiple cities (SABE) Botswana Indonesia Multi-country F (SAGE)	Multi-country M (SAGE)
Total or low-density lipoprotein cholesterol		Brazil F (RPBC) India (APCAPS/IMS)	Brazil M (RPBC)
Lower high-density lipoprotein cholesterol	Brazil (RPBC)	China F (GBCS) Jamaica India (Vellore)	China M (GBCS)
Triglycerides		Brazil (RPBC) Jamaica China (GBCS) India (Vellore) India (APCAPS/IMS)	
Metabolic syndrome	China F (GBCS)	China M (GBCS) Jamaica	
Cardiovascular risk score	Brazil (ELSA-Brasil)		
Total both sexes (N=39)	**8**	**31**	**0**
Total males (N=7)	**0**	**2**	**5**
Total females (N=7)	**2**	**5**	**0**

MxFLS is Mexican Family Life Survey; GBCS is Guangzhou Biobank Cohort Study; IMS is Indian Migration Study; MHAS is Mexican Health and Aging Study; RPBC is Ribeirao Preto Birth Cohort.

Risk of bias within and between studies

Risk of bias ratings for each article are shown in Figure 3.2. None of the articles included in the review were judged to be of low risk of bias. Thirteen out of 29 were judged to be at medium risk of bias, while the remaining 16 articles had high risk of bias. The articles with medium risk of bias were generally birth cohort studies with prospectively measured information on childhood socioeconomic position and objective outcome measures, or nationally representative surveys with objective outcome measures. The articles with high risk of bias were generally cross-sectional with self-reported exposures and outcomes, or focussed on specific population subgroups (such as occupational cohorts) that might not generalise to the rest of the population. It was not possible to quantitatively assess risk of bias between studies (i.e. publication bias) in a funnel plot because exposures, analysis approaches and outcomes were highly variable between studies.

Author, year	Risk of bias					
	A	B	C	D	E	F
Keetile, 2020	2	2	0	0	1	5
Camelo, 2015	1	2	2	2	1	8
Camelo, 2016	1	2	2	2	1	8
Coelho, 2019	1	2	2	2	2	9
De Sousa Andrade, 2017	1	2	2	2	1	8
Guimaraes, 2016	1	2	2	2	1	8
Lopez, 2017	1	2	2	2	2	9
Nishida, 2020	1	2	2	1	1	7
Horta 2008	1	0	1	1	2	5
Figueiredo, 2007	1	0	2	1	1	5
Elwell-Sutton, 2011	1	2	0	2	1	6
Schooling, 2008	1	2	0	2	1	6
Fan, 2010	1	0	2	1	2	6
McEniry, 2019	2	2	1	0	2	7
Addo, 2009	1	2	1	2	1	7
Mallinson, 2020	1	2	1	1	1	6
Sovio, 2013	1	2	2	1	1	7
Samuel, 2012	1	0	1	1	1	4
Peele, 2019	2	2	1	0	2	7
Ferguson, 2010	1	2	2	0	2	7
Ferguson, 2015	1	0	2	0	2	5
Carrillo-Vega, 2019	2	2	1	0	2	7
Kohler, 2005	2	2	1	0	2	7
Beltran-Sanchez, 2011	1	2	1	0	2	6
Palloni, 2006	2	2	2	0	2	8
Ogunsina, 2018	1	2	1	0	1	5
Vagero, 2005	2	2	2	1	1	8
Kagura, 2016	1	0	2	1	1	5
Naidoo, 2019	1	0	2	1	1	5

Legend

A: Assessment of outcomes
- 0: Incident cardiovascular disease or risk factors
- 1: Prevalent cardiovascular disease or risk factors
- 2: Self-reported cardiovascular disease or risk factors

B: Assessment of exposures
- 0: Prospective individual-level measure
- 1: Prospective ecological measure
- 2: Retrospective measure

C: Non-response and loss-to-follow-up
- 0: <10%
- 1: 10-50%
- 2: >50%

D: Representativeness
- 0: representative population sample
- 1: population-based single site sample
- 2: specific group sample (e.g. occupational cohort)

E: Comparability of exposed and unexposed
- 0: robust comparison (e.g. trial or natural experiment)
- 1: appropriate confounders adjusted for
- 2: inadequate adjustment for confounders

F: Total
- 0-3: low risk of bias
- 4-6: medium risk of bias
- 7-10: high risk of bias

Figure 3. 2 Risk of bias of articles included in the systematic review (n=29)

3.6 Discussion

Most of the studies we identified examined the association between socioeconomic position in childhood and risk factors for cardiovascular disease such as hypertension and diabetes; very few studies examined cardiovascular disease as an outcome. All of the studies we identified were from middle-income countries. Overall, the literature we identified provided limited evidence for an association between childhood socioeconomic position and cardiovascular risk factors, especially after adjustment for socioeconomic position in adulthood.

Our findings contradict previous reviews of the evidence from high-income countries, which have consistently noted inverse associations between childhood socioeconomic position and risk of cardiovascular disease[119,125]. This is surprising because it has been suggested that conditions associated with material deprivation (such as undernutrition and infections) may mediate the association, which would suggest a stronger inverse association in lower income countries[198]. However, previous reviews focussed largely on cardiovascular disease incidence and mortality, for which evidence is lacking from low- and middle-income countries. The few studies on prevalent coronary heart disease that we identified had major methodological limitations, making it difficult to interpret their findings (for example, adjustment for potential mediators of the association, and use of self-reported disease outcomes). The interpretation of studies of prevalent outcomes is also complicated by the high case fatality rate of cardiovascular disease in many lower income settings[15]. Recently, a multi-country prospective study from 15 low- and middle-income countries found that adult socioeconomic position was inversely association with cardiovascular incidence and mortality, even though it was directly associated with most major cardiovascular risk factors[103]. This implies that our conclusions about cardiovascular risk factors in the current review cannot necessarily be extrapolated to cardiovascular disease incidence and mortality, and that evidence on these outcomes is urgently needed.

Although we observed no strong evidence of association between childhood socioeconomic position and risk of cardiovascular disease, some general patterns across studies were noted. Firstly, studies from countries with higher levels of economic development (i.e. Brazil, Russia, China and Mexico) were more likely to report independent inverse associations between childhood socioeconomic position and cardiovascular risk factors, similar to studies from high-income countries. This suggests that the association between childhood socioeconomic position and cardiovascular risk factors may vary by a country's stage of economic development, as has been observed for adult socioeconomic position[249]. This gives some insight into the mechanisms, as it implies that the association between childhood socioeconomic position and cardiovascular risk may be driven by setting-specific factors (such as the social patterning of childhood physical activity and diet), rather than conditions associated with absolute poverty (such as undernutrition and infections). However further high-quality studies, especially from low- and lower middle-income countries, are needed to confirm this speculation. Secondly, a greater proportion of studies reported an inverse association between childhood socioeconomic position and blood pressure than for other cardiovascular risk factors. These included several large studies from Brazil, India and Indonesia, which did not find evidence that childhood socioeconomic position was associated with diabetes or lipid levels[227,235,238]. This is consistent with some early studies from high-income countries that found blood pressure, but not lipid levels, to be inversely associated with childhood socioeconomic position[250,251], raising the possibility that different mechanisms may be operating for blood pressure compared with other cardiovascular risk factors. Further high-quality studies of blood pressure in low- and middle-income countries are needed to investigate this. Thirdly, several studies reported differences in the association between childhood socioeconomic position and cardiovascular risk factors between men and women. Studies from Mexico and China found evidence that childhood socioeconomic position was inversely associated with hypertension[243] and metabolic syndrome[231], respectively, in women only, while in China, India and Brazil, childhood socioeconomic position was directly associated with metabolic syndrome[231], insulin resistance[236] and LDL cholesterol[230], respectively, among men only. These observations are consistent with the sex-differences in association between adult socioeconomic position and cardiovascular risk factors seen in several middle-income countries[112,252]. Researchers have speculated that these sex-differences might arise upon economic development due to occupational factors (e.g. men more likely to remain engaged in occupational physical activity), as well as differing cultural pressures for men and women, although how this might translate to childhood socioeconomic position is unclear[253].

Limitations

A primary limitation of the conclusions drawn from our review is that many of the studies had a high risk of bias. Several studies included only self-reported outcomes, which may be particularly unreliable in low- and middle-income countries where many cardiovascular conditions are undiagnosed. Potential bias in self-reported outcomes was demonstrated in the WHO-SAGE study from 5 middle-income countries, which reported an association between the stable high socioeconomic trajectory and self-reported hypertension, but no association with measured hypertension[245]. To try to limit bias due to self-reported outcomes in our review, we presented these findings separately from objectively measured outcomes, and gave them less weight when interpreting the overall evidence. Another common limitation of the studies was that many used recalled childhood exposures, which may be prone to measurement error and thus have attenuated the associations. However, studies have previously found that people are able to recall their childhood socioeconomic conditions with reasonable accuracy[254], and in the current review, findings did not generally differ between prospective and cross-sectional studies. A further limitation of the evidence we identified is that the prospective studies, which in theory provide the highest quality of evidence, had a number of issues in common. Firstly, 5/6 prospective studies examined adults at age <30 years, when levels of cardiovascular risk factors are generally low. This may have made it difficult for studies to detect associations. Secondly, most of these studies only managed to follow up a low proportion of the original participants into adulthood (<30%), resulting in highly selected samples of participants which limits generalisability.

We also acknowledge some limitations in our review methodology. Firstly, we were not able to formally assess risk of bias across studies (publication bias), because of heterogeneity in exposure and outcome measures and categorisations. Observational studies are at a high risk of selective publication of "positive" results, because they often collect data on many possible exposures and outcomes without pre-specifying the analyses. In this review, however, even a moderate to high amount of publication bias would not substantially alter our main conclusions. Secondly, as we were unable to quantitatively pool study estimates, we could not formally investigate sources of heterogeneity between studies. For example, previous reviews have found that associations vary between different indicators of socioeconomic position, which might have shed light on the mechanisms linking childhood socioeconomic position with risk of cardiovascular disease[82]. The vote-counting approach we used to summarise study results did not take account of study size or strength of association, and did not distinguish between different indicators of socioeconomic position, so must be interpreted with caution. Thirdly, although we systematically searched the major biomedical databases, we did not search grey literature or articles in most non-English languages. This could have led to some relevant studies being omitted from our review. However, we felt it was unlikely that eligible analyses based on large-scale population-based studies would be absent from the databases and reference lists we searched.

Conclusions

Evidence identified in this review demonstrates limited support for an association between childhood socioeconomic position and risk factors for cardiovascular disease in middle-income countries. This suggests it would be premature to advocate for policies targeting childhood poverty for the prevention of cardiovascular disease in these settings. Until more evidence is available, interventions focussing on established risk factors in adulthood (e.g. tobacco prevention, promotion of physical activity, and reduction of sodium content of foods) should be prioritised[255]. Evidence on cardiovascular disease incidence and mortality was completing lacking, suggesting further prospective studies are needed. There is also a need for studies from low-income countries, as evidence from middle-income countries may not generalise to these settings.

Chapter 4: Socioeconomic position in childhood and risk of cardiovascular disease in pooled cohorts from India

4.1 Introduction to chapter

This chapter aims to address the second evidence gap and third objective of the thesis, namely the association between childhood socioeconomic position and risk of cardiovascular disease in adulthood in a lower middle-income country. Previous studies have mostly been from upper middle-income countries, or have lacked statistical power to detect an association between childhood socioeconomic position and cardiovascular risk independent of adult socioeconomic position. I combined data from two large population-based studies in India, the Andhra Pradesh Children and Parents' Study (APCAPS) and the Indian Migration Study (IMS) to examine the association of an index of household assets in childhood with a range of cardiovascular risk factors in 14,000 adults. This work has been published in a peer-reviewed journal (the Journal of Epidemiology and Community Health). The final submitted version of the manuscript (rather than published version) is included here, to avoid duplication of the reference lists. It should be noted that the term socioeconomic conditions, rather than socioeconomic position, is used throughout this chapter, in order to refer specifically to material aspects related to socioeconomic position, the primary aspects of interest for this analysis. Some additional analysis results which are mentioned in the chapter text are provided in Appendix 3 of the thesis.

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<u>SECTION A – Student Details</u>

Student ID Number	1400500	**Title**	Ms
First Name(s)	Poppy Alice Carson		
Surname/Family Name	Mallinson		
Thesis Title	Life course socioeconomic influences on risk of cardiovascular disease in low- and middle-income countries		
Primary Supervisor	Sanjay Kinra		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

Where was the work published?	Journal of Epidemiology and Community Health		
When was the work published?	June 2020 (E-pub ahead of print)		
If the work was published prior to registration for your research degree, give a brief rationale for its inclusion	N/A		
Have you retained the copyright for the work?*	**No**	Was the work subject to academic peer review?	**Yes**

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<u>SECTION D – Multi-authored work</u>

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualised the study, analysed the data, wrote the first draft of the manuscript, revised the manuscript according to comments from co-authors.

<u>SECTION E</u>

Student Signature	[signature]
Date	20/11/2020

Supervisor Signature	[signature]
Date	23/11/2020

Childhood socioeconomic conditions and risk of cardiovascular disease: results from a pooled sample of 14,011 adults from India

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4.2 Abstract

Background: South Asians are at an increased risk of premature cardiovascular disease, but the reasons for this are unclear. Poor socioeconomic conditions in childhood are associated with an increased risk of cardiovascular disease in many high-income countries and may be particularly relevant to South Asia, where socioeconomic deprivation is more prevalent and severe. However, evidence from South Asia is limited.

Methods: We pooled data from two large population-based studies in India to provide a geographically representative and adequately powered sample of Indian adults. We used multilevel linear regression models to assess associations between standard of living index in childhood (measured by recalled household assets at age 10-12 years) and major cardiovascular risk factors including adiposity, blood pressure, and fasting blood lipids, glucose and insulin.

Results: Data on 14,011 adults (median age 39 years, 56% male) were analysed. Standard of living index in childhood was inversely associated with systolic and diastolic blood pressure, independent of socioeconomic conditions in adulthood, with beta coefficients (95% confidence intervals) of -0.70mmHg (-1.17 to -0.23) and -0.56mmHg (-0.91 to -0.22) respectively per standard deviation increase in standard of living index in childhood. There was no strong evidence for an association between standard of living index in childhood and other risk factors of cardiovascular disease.

Conclusions: Poor socioeconomic conditions in childhood may contribute to the increased risk of premature cardiovascular disease among South Asians by raising their blood pressure. Elucidating the mechanisms, and improving socioeconomic conditions for children in South Asia, could provide major reductions in the burden of cardiovascular disease.

4.3 Introduction

Over a fifth of deaths from cardiovascular disease globally occur in South Asia[9]. Among South Asians, cardiovascular mortality is higher and occurs at younger ages than in other populations[103,256]. Differences in behavioural risk factors in adulthood have failed to account for this observation[257]. This has led some researchers to hypothesise a role for factors operating earlier in life[258].

Evidence from high-income countries suggests that poor socioeconomic conditions in childhood are associated with an increased risk of cardiovascular disease[119,125]. Countries in South Asia are experiencing rapid economic development; until recently poor socioeconomic conditions characterised by severe material deprivation were widespread, especially in rural areas[215]. This suggests that the association of childhood socioeconomic conditions with cardiovascular disease could be particularly strong in South Asia, and account for the excess premature cardiovascular disease. Yet, the few studies from South Asia have failed to identify an association[236,237]. Confirming this association and its pathways could inform the development of appropriate interventions for cardiovascular disease prevention in South Asia.

We examined the association of socioeconomic conditions in childhood with a range of cardiovascular disease risk factors to investigate the potential pathways for an association. We pooled data from two population-based studies to provide a large sample representing different regions and varying levels of urbanisation in India.

4.4 Methods

This study is reported in accordance with the STROBE guidelines (see appendix Table S3.1 for completed checklist). We used data from two population-based studies: the Andhra Pradesh Children and Parents' Study (APCAPS) and Indian Migration Study (IMS). Both studies were conducted by the same investigator teams using similar protocols, facilitating pooled analyses. APCAPS is a family-based cohort in 29 rural and peri-urban villages near Hyderabad in South India[259]. It began as the long-term follow up of offspring from a pregnancy nutrition trial conducted in 1987-1990, and was later expanded to cover family members of traced trial participants. In the present study we used data from the third wave survey conducted in 2010-12, in which 6944 of 10,213 (68%) invited family members attended the clinical examination. The IMS was conducted in 2005-07 to investigate the effects of rural to urban migration on risk of cardiovascular disease[260]. Factory workers and their spouses were recruited from four factory sites in urban centres (Lucknow, Nagpur, Hyderabad and Bangalore), and asked to invite their rural-dwelling siblings to the study. In total 7067 of 15,118 (47%) invited participants attended clinical examinations.

Clinical assessment

Social and demographic information was collected using standard questions. These included a subset of questions from the standard of living index, which is an asset-based scale developed to measure household wealth in India[261]. We only asked about items deemed most relevant for the study settings (11/29 questions on recalled household assets in childhood (age 10-12 years) and 14/29 questions on current household assets). These items were: housing material, toilet facilities, lighting source, drinking water source, and household possession of agricultural land, television, radio, clock, bicycle, motorcycle, and refrigerator (plus household possession of a car, telephone and tractor for current assets). We derived the index by applying the recommended weights to the available household asset questions, then summing across all items to give a total score for each individual[261]. A higher score indicates greater material affluence. Household-level measures of socioeconomic conditions are particularly appropriate for use in India, where joint family structures render individual-level measures (such as occupation and education) less informative. We assessed socioeconomic conditions in adulthood by standard of living index (as above) and by occupational status (categorised as unemployed/unskilled manual labour, skilled manual labour, non-manual/professional, or student/housewife/retired), in order to capture multiple dimensions that might be relevant to risk of cardiovascular disease[183].

Anthropometric measurements (height, weight and waist circumference) were taken twice using standard equipment. Systolic and diastolic blood pressure were measured at the right upper arm in the sitting position using a validated oscillometric device (Omron M5-I model). Participants were asked to rest for five minutes before multiple readings were taken (three readings in APCAPS and two readings in IMS, each one minute apart).

Venous blood samples were drawn after a minimum of eight hours fasting and centrifuged immediately. Assays for fasting glucose were conducted locally on the same day as sampling using an enzymatic method. For all other assays, samples were transported in batches to our central laboratories for analysis. Total and high-density lipoprotein (HDL) cholesterol and triglycerides were estimated using enzymatic colorimetric methods, and fasting insulin by radioimmunoassay. Quality of assays was assured by internal duplicates and regular external standards.

In both studies, we re-surveyed a random 5% sub-sample of participants before the end of data collection to assess the reliability of the responses.

Data analysis

We analysed data on the following cardiovascular risk factors: body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, and fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, glucose, insulin, and insulin resistance. We also examined the association of childhood socioeconomic conditions with height because it is thought to be closely associated with childhood socioeconomic conditions[262]. Before analysis we checked distributions of outcomes variables and excluded extreme outliers. The mean of the first two blood pressure readings was used for consistency across studies. The mean of the two readings was used for all anthropometric measures. Body mass index was calculated as weight in kilograms/(height in metres)^2. LDL cholesterol was estimated using the Friedewald-Fredrickson formula (Total cholesterol – HDL cholesterol – (triglycerides/5))[263]. Homeostasis model assessment (HOMA) insulin resistance score was estimated as fasting insulin*fasting glucose/22.5[264]. We applied a log transformation to the values of skewed variables (triglycerides, fasting glucose, insulin and HOMA score) to improve the normality of residuals.

To estimate the effect of standard of living index in childhood on cardiovascular risk factors in adulthood we used multilevel linear regression models. We included a random intercept term at the family level to account for the potential correlation of cardiovascular risk factors between members of the same household and between sibling pairs. After first checking for evidence of non-linearity in its association with cardiovascular risk factors, we used standard of living index in childhood as a linear exposure. Age and sex are strongly associated with cardiovascular risk factors, so we included both as covariates in all models. We included linear, quadratic and cubic terms for age to account for its non-linear association with cardiovascular risk factors. We included a dummy variable for study (i.e. APCAPS or IMS) to account for any systematic differences in measurement between the studies. Our primary models were further adjusted for place of residence (i.e. urban or rural) and socioeconomic conditions (measured by standard of living index and occupation) in adulthood. Socioeconomic conditions in adulthood are highly correlated with socioeconomic conditions in childhood, and are directly associated with increased cardiovascular risk in India[103,207,237]. Therefore, socioeconomic conditions in adulthood could mask an inverse association between socioeconomic conditions in childhood and risk of cardiovascular disease unless appropriately accounted for. We included a quadratic term for standard of living index in adulthood because there was some evidence of non-linearity in its association with cardiovascular disease risk factors. We checked for evidence of interactions between age and the other covariates (sex, study, place of residence and socioeconomic conditions in adulthood), and included any substantial interactions in our final models to improve the precision of the estimates of interest. We repeated the analyses stratified by socioeconomic conditions in adulthood (above or below median standard of living index) and by sex, as previous studies have suggested that these factors may modify the association between childhood socioeconomic conditions and cardiovascular risk factors[117,194,124]. We also repeated the analyses stratified by study (i.e. APCAPS or IMS) to investigate whether the associations of interest varied between the study populations.

To mitigate potential error in the recall of household assets in childhood, we fitted measurement error models using repeat data on a 5% sub-sample. We used the regression calibration method, which is an appropriate and efficient method when measurement error can be assumed to be non-differential with respect to the outcome[265]. This assumption was reasonable in this case since levels of cardiovascular risk factors are generally not known to the participants and would therefore be unlikely to influence their recall of household assets in childhood. We regressed the repeat measure of the exposure on the original exposure (in the sub-sample), adjusting for covariates that may have influenced the reporting (i.e. age, sex, adult socioeconomic conditions). We used this model to predict a measurement error-adjusted exposure for all participants, and used these predictions as the exposure variable in the main analyses. We estimated standard-errors using an adjusted delta method to account for the extra uncertainly from using predicted values as the exposure[265].

We restricted all analyses to participants with complete exposure and outcome data, as a small number (<5%) were missing data for most outcomes, and participants with missing data were similar to those without. All analyses were performed on Stata 16.

Ethical approval and role of the study sponsor

Ethical approval for the APCAPS and IMS studies were obtained from appropriate local review boards as well as the London School of Hygiene and Tropical Medicine. All participants provided written informed consent (or witnessed thumbprint if illiterate). The study sponsor had no role the design, analysis, interpretation, write-up of this manuscript, or decision to submit for publication.

4.5 Results

We analysed data on 14,011 participants (6944 from APCAPS, 7067 from IMS, figure 4.1). The mean age of participants was 37.5 years and 56% were male (table 4.1). Complete data were available for 93% to 99% of the participants, depending on the outcome. More outcome data were missing for APCAPS than IMS participants, although the sociodemographic characteristics of participants with complete and incomplete outcome data were otherwise similar (see appendix Table S3.2).

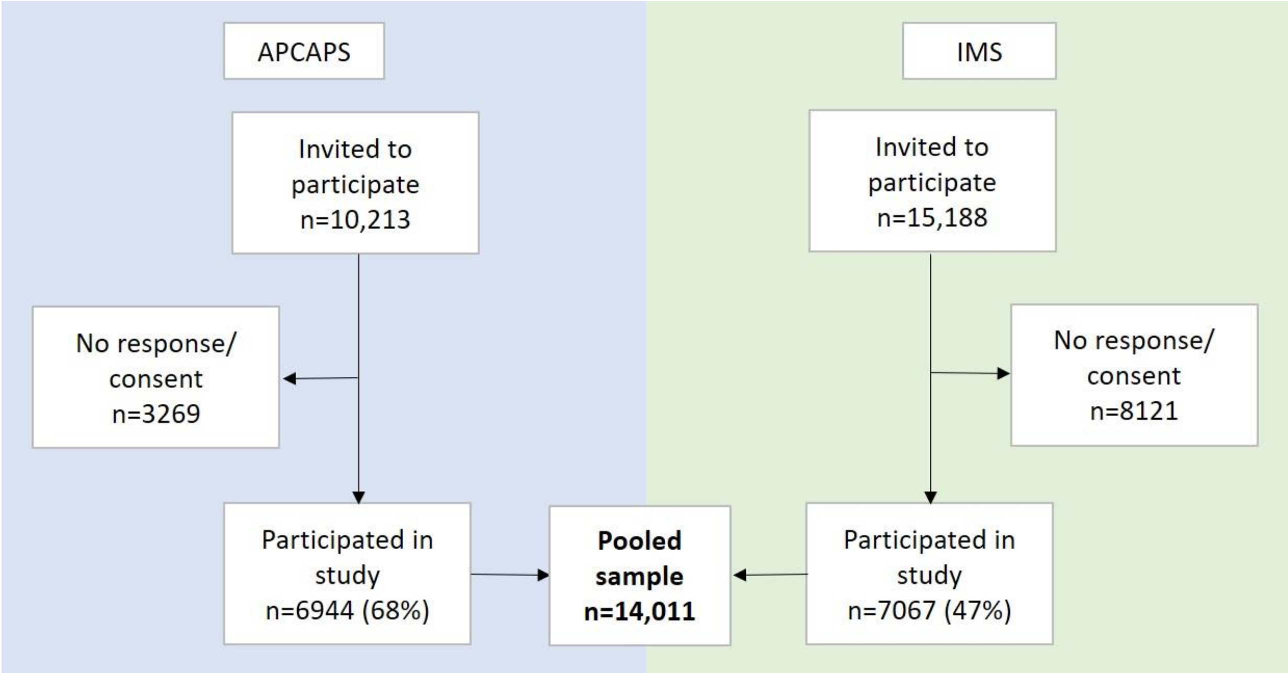

Figure 4. 1 Flowchart of included study participants from the Indian Migration Study (IMS, 2005-7) and Andhra Pradesh Children and Parents' Study (APCAPS, 2010-12)

Table 4. 1 Description of study participants in pooled sample of IMS (2005-7) and APCAPS (2010-12)

Characteristic		% complete	N (%) / mean (SD)		
			APCAPS (N=6944)	IMS (N=7067)	Pooled sample (N=14,011)
Sociodemographic					
Age		>99%	34.2 (14.4)	40.8 (10.4)	37.5 (12.9)
Sex	Male	>99%	3646 (52.6%)	4123 (58.3%)	7769 (55.5%)
	Female		3283 (47.4%)	2944 (41.7%)	6226 (44.5%)
Childhood standard of living index		>99%	8.8 (4.8)	10.5 (5.1)	9.6 (5.0)
Adult standard of living index		>99%	18.6 (5.1)	23.3 (6.7)	21.0 (6.4)
Adult occupation	Unskilled labour or unemployed	>99%	2918 (42.1%)	314 (4.4%)	3232 (23.1%)
	Student, retired or housewife		2202 (31.8%)	2612 (37.0%)	4814 (34.4%)
	Semi-skilled labour		732 (10.6%)	918 (13.0%)	1650 (11.8%)
	Skilled labour		709 (10.2%)	1548 (21.9%)	2257 (16.1%)
	Professional		365 (5.3%)	1675 (23.7%)	2040 (14.6%)
Adult residence	Rural	>99%	6944 (100%)	2668 (37.8%)	9612 (68.6%)
	Urban		0 (0%)	4399 (67.6%)	4399 (32.7%)
Cardiovascular risk factors					
Systolic blood pressure, mmHg		>99%	118.5 (15.3)	122.1 (17.0)	120.3 (16.3)
Diastolic blood pressure, mmHg		>99%	77.5 (12.7)	77.9 (11.0)	77.7 (11.9)
Total cholesterol, mmol/L		97%	4.2 (1.0)	4.7 (1.1)	4.5 (1.1)
LDL cholesterol, mmol/L		93%	2.8 (0.9)	3.3 (1.1)	3.1 (1.0)
Triglycerides, mmol/L (median, IQR)		95%	1.1 (0.8, 1.6)	1.3 (1.0, 1.8)	1.2 (0.9, 1.7)
Fasting glucose, mmol/L (median, IQR)		95%	5.0 (4.7, 5.4)	5.1 (4.6, 5.5)	5.1 (4.7, 5.5)
Insulin, mU/L (median, IQR)		95%	5.2 (3.1, 8.2)	6.0 (3.4, 9.6)	5.6 (3.2, 9.0)
HOMA score (median, IQR)		94%	1.2 (0.7, 1.9)	1.3 (0.8, 2.3)	1.3 (0.7, 2.1)
Body mass index, kg/m^2		>99%	20.6 (3.9)	23.8 (4.5)	22.2 (4.5)
Waist circumference, cm		>99%	71.5 (10.7)	82.3 (11.7)	77.0 (12.5)
Height, cm		>99%	158.1 (9.5)	160.3 (8.8)	159.3 (9.3)

APCAPS=Andhra Pradesh Children and Parents' Study, IMS=Indian Migration Study, SD=standard deviation, IQR=interquartile range, LDL=low-density lipoprotein, HOMA=homeostasis model assessment

In age- and sex-adjusted analyses, standard of living index in childhood was directly associated with body mass index, waist circumference, total cholesterol, LDL cholesterol, triglycerides, glucose, insulin, and HOMA score; but was not associated with blood pressure (table 4.2). After adjustment for socioeconomic conditions in adulthood, standard of living index in childhood was inversely associated with systolic and diastolic blood pressure, with beta coefficients (95% confidence intervals) of -0.70mmHg (-1.17 to -0.23) and -0.56mmHg (-0.91 to -0.22), respectively, per standard deviation increase in childhood standard of living index. For all other cardiovascular risk factors there was no strong evidence of an association with standard of living index in childhood. The direct association of height with standard of living index in childhood was only partially attenuated by adjustment for socioeconomic conditions in adulthood, with adjusted beta coefficient (95% confidence interval) of 5.1mm (3.2 to 7.1) per standard deviation increase in childhood standard of living index.

We found no strong evidence of effect modification by standard of living index in adulthood, sex or study for most of the cardiovascular risk factors (appendix Table S3.3, Table S3.4 and Table S3.5). An exception was for markers of adiposity: the direct association between standard of living index in childhood and waist circumference and body mass index was stronger among participants below the median standard of living index in adulthood than those above (p-interaction <0.001 and 0.01, respectively). Waist circumference was directly associated with standard of living index in childhood among males but inversely associated among females (p-interaction <0.001), while a reverse pattern was observed for body mass index (p-interaction=0.001). There was evidence of a direct association of childhood standard of living index with waist circumference and body mass index in IMS, but an inverse association in APCAPS (both p-interaction<0.001).

In analyses without accounting for measurement error in childhood standard of living index, results were similar but effect estimates were slightly attenuated (appendix Table S3.6).

Table 4. 2 Association between standard of living index (SLI) in childhood and cardiovascular risk factors in pooled sample of IMS (2005-7) and APCAPS (2010-12)

	Model 1: Age- and sex-adjusted					Model 2: model 1 + adult socioeconomic conditions*				
Cardiovascular risk factor	N	β-coefficient for 1 SD change in childhood SLI	Lower confidence limit	Upper confidence limit	p-value	N	β-coefficient for 1 SD change in childhood SLI	Lower confidence limit	Upper confidence limit	p-value
Systolic blood pressure, mmHg	13931	-0.139	-0.562	0.284	0.520	13931	-0.698	-1.165	-0.232	0.003
Diastolic blood pressure, mmHg	13950	0.040	-0.275	0.355	0.805	13950	-0.564	-0.912	-0.216	0.001
Total cholesterol, mmol/L	13592	0.072	0.041	0.102	<0.001	13592	0.006	-0.026	0.039	0.712
LDL cholesterol, mmol/L	12974	0.055	0.027	0.083	<0.001	12974	-0.010	-0.040	0.020	0.525
Log triglycerides, mmol/L	13144	0.018	0.005	0.032	0.009	13144	-0.009	-0.024	0.005	0.212
Log fasting glucose, mmol/L	13224	0.015	0.009	0.020	<0.001	13224	0.004	-0.002	0.009	0.174
Log insulin, mU/L	13231	0.094	0.068	0.120	<0.001	13231	0.021	-0.006	0.048	0.134
Log HOMA score	13184	0.109	0.082	0.137	<0.001	13184	0.025	-0.004	0.054	0.089
Body mass index, kg/m^2	13942	0.812	0.688	0.936	<0.001	13942	0.083	-0.032	0.198	0.158
Waist circumference, mm	13918	18.965	15.861	22.068	<0.001	13918	-0.707	-3.629	2.216	0.636
Height, mm	13942	9.076	7.168	10.984	<0.001	13942	5.135	3.185	7.085	<0.001

APCAPS=Andhra Pradesh Children and Parents' Study, IMS=Indian Migration Study, SD=standard deviation, SLI=standard of living index, LDL=low-density lipoprotein, HOMA=homeostasis model assessment

*Adult standard of living index (linear and quadratic term), adult occupation (categorical) and adult urban or rural residence (binary)

4.6 Discussion

Main findings

In a large and geographically representative sample from India, we found that standard of living index in childhood was inversely associated with systolic and diastolic blood pressure in adulthood. There were no clear associations between standard of living index in childhood and other cardiovascular risk factors, including adiposity, total and LDL cholesterol, triglycerides, glucose, insulin, and insulin resistance.

Relation to literature

A large body of evidence from high-income countries supports an inverse association between socioeconomic conditions in childhood and adiposity, blood pressure, cholesterol and insulin resistance, independent of socioeconomic conditions in adulthood[124,125,194,251,266–268]. Our findings, of an inverse association between childhood socioeconomic conditions and blood pressure, but not with the other risk factors, suggest that different mechanisms are operating for different risk factors, and that these are likely to be setting-specific. The lack of association we detected for the other risk factors, which are strongly linked to excess adiposity, may be due to relatively lower levels of adiposity in this study population. However hardly any studies have been conducted in South Asia. A study of a birth cohort from Vellore in South India reported no evidence of association between parental education (an indicator of childhood socioeconomic conditions) and overweight, hypertension, high triglycerides, or diabetes at age 26-32 years[237]. However, the confidence intervals were wide and could have been consistent with either an inverse or direct association. An earlier analysis of the Indian Migration Study data alone (N=4120 males and N=2940 females) failed to detect an independent association of childhood standard of living index with systolic blood pressure, but this may have been due to inadequate adjustment for adult socioeconomic conditions or lower statistical power (<30% power to detect the effect size found in our study as opposed to >99% power in our combined dataset)[236]. In our analyses, the inverse association of blood pressure with socioeconomic conditions in childhood was masked until we adjusted for socioeconomic conditions in adulthood, demonstrating the importance of adequate adjustment and large sample size to disentangle the effects of childhood from adult socioeconomic conditions. In contrast, for the other risk factors, a crude direct association was attenuated to the null after adjustment for adult socioeconomic conditions. This is consistent with the strong direct association between adult socioeconomic conditions and adiposity (compared to the weaker associations with blood pressure) observed in many studies in India[269], including the APCAPS and IMS studies (see appendix Table S3.7).

Mechanisms

In this population, blood pressure was the only major cardiovascular risk factor associated with socioeconomic conditions in childhood. Exposure to undernutrition during foetal development and early infancy has been linked to increased blood pressure in adulthood, for which a range of biological mechanisms have been proposed[270]. However, evidence for this is inconclusive. In high-income countries, the link between early life undernutrition and blood pressure has been largely inferred from studies of low birthweight, despite maternal undernutrition being rare and thus a less important cause of low birthweight. Subsequent observational studies and a community trial in South Asia have failed to confirm the association with blood pressure[62,63,271,272]. Dehydration in infancy and early childhood caused by frequent diarrhoeal disease has been hypothesised to increase blood pressure in adulthood, although epidemiological evidence has been inconsistent[273,274]. Emerging evidence suggests that frequent infection with malaria during childhood may also increase adult blood pressure, although confirmatory studies are needed[275]. Other setting-specific environmental factors linked to poor socioeconomic conditions, such as household use of biomass fuel, may play a role[276]. However evidence on the long-term effects of this and other putative local risk factors is lacking. Poor socioeconomic conditions in childhood have also been linked to increased levels of risk behaviours (e.g. smoking and alcohol consumption) and psychosocial adversity (e.g. stress and depression) in adulthood, which are associated with increased blood pressure[196]. However, the majority of evidence comes from high-income countries; further research is needed to understand the relevance of these mechanisms in South Asia.

Strengths and limitations

Our study is one of few studies from South Asia to have examined the association between childhood socioeconomic conditions and cardiovascular risk factors. Our study had sufficient sample size to disentangle the effects of socioeconomic conditions in childhood from adulthood, and precision was further improved by the use of regression calibration to reduce potential bias due to error in the recall of childhood assets used to derive the standard of living index. The study population represented different regions of India and varying levels of urbanisation making our results broadly generalisable to India. However, some limitations must be acknowledged. We cannot exclude the possibility of residual confounding by adult socioeconomic conditions, which may have masked associations between childhood socioeconomic conditions and other cardiovascular risk factors; however, this is unlikely to be the case given our use of multiple indicators for adult socioeconomic conditions and sufficient sample size. There is also a possibility of residual bias due to differential recall of household assets in childhood. However, most participants were unaware of their cardiovascular risk factor levels, suggesting differential recall according to outcome status was unlikely. Furthermore, we noted a high degree of concordance in childhood standard of living index between siblings in the Indian Migration Study (ρ=0.82) suggesting participants were able to recall accurately. Previous studies have also noted accurate recall of childhood socioeconomic circumstances, and found this not to vary according to the educational status of the participants[277,278]. Finally, we cannot exclude risk of selection bias because not all those invited chose to participate in the studies. However analysis of baseline demographic characteristics of people who did and did not participate suggested few systematic differences[259,260].

Implications

Our findings suggest that poor socioeconomic conditions in childhood could be contributing to the high cardiovascular disease burden in South Asia through their association with blood pressure. To put the effect sizes we observed into context, a study from the United States estimated that a 1mmHg reduction in systolic or diastolic blood pressure across adults aged 45-64 could prevent approximately 30 events of coronary heart disease, stroke and heart failure per 100,000 person-years[279]. If applied to the population of South Asia[219], this would equate to prevention of 185,000 premature cardiovascular events per year. Although there is a need for formal modelling of these estimates for South Asia, clearly the potential impact is appreciable. If these associations are proven to be causal, reductions in child poverty could have a meaningful impact on population blood pressure levels and associated cardiovascular events, and could reduce social inequalities in cardiovascular disease. Further research should aim to confirm these findings in other South Asian settings and to elucidate the specific mechanisms underpinning the association, in order to inform setting-specific interventions for the primordial prevention of cardiovascular disease.

Conclusion

We found that socioeconomic conditions in childhood, independent of socioeconomic conditions in adulthood, are inversely associated with blood pressure, but not associated with other cardiovascular risk factors. Improvements in childhood socioeconomic conditions could have beneficial effects on adult blood pressure levels in South Asia. Further research is needed to understand the underlying mechanisms.

Chapter 5: Intergenerational socioeconomic position and risk of cardiovascular disease in rural India

5.1 Introduction to chapter

This chapter aims to address the third evidence gap and fourth objective of the thesis, namely the intergenerational influence of socioeconomic position on risk of cardiovascular disease in adulthood. It has been suggested that socioeconomic influences on cardiovascular disease may extend beyond an individual's life course, to conditions experienced by previous generations, although epidemiological data are lacking globally. This chapter presents some of the first evidence on the association of parents' socioeconomic position in childhood with cardiovascular risk factors and markers of subclinical atherosclerosis in their adult offspring. I used data from the intergenerational APCAPS study in Telangana, South India, which collected information on parents and their adult offspring including recalled household assets in childhood. This study setting is particularly appropriate to address this question because severe poverty and undernutrition (a key proposed mechanisms of the association) have been prevalent until recently. This work has been submitted for publication in a peer-reviewed journal (European Journal of Preventive Cardiology), and is currently awaiting a decision. As in the previous chapter, I use the term "socioeconomic conditions" in this chapter to refer specifically to material aspects related to socioeconomic position, the primary aspects of interest for this analysis. Additional description of the study population and analysis results are provided in Appendix 4 of the thesis.

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If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conceptualised the study, analysed the data, wrote the first draft of the manuscript, revised the manuscript according to comments from co-authors.

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Association between parents' socioeconomic conditions and nutritional status during childhood and the risk of cardiovascular disease in their adult offspring: An intergenerational study in south India

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5.2 Abstract

Aims: Some researchers have suggested that parents' exposure to poor socioeconomic conditions during childhood can increase their offspring's risk of cardiovascular disease, primarily through poor maternal nutrition and growth. However epidemiological data on this association are limited. In an intergenerational cohort from rural India, we examined the association of parental childhood socioeconomic conditions and stature with offspring's cardiovascular risk, hypothesising an inverse association between the two.

Methods: We analysed data on 3175 adult offspring (aged 18-35 years, 58% male) and their parents from the third wave of the Andhra Pradesh Children and Parents' Study (2010-12). We used multilevel linear regression to estimate the association of parents' Standard of Living Index (SLI, an asset-based measure of socioeconomic conditions) in childhood, height and leg length with subclinical atherosclerosis and cardiovascular risk factors in their offspring.

Results: In multivariable models adjusted for the offspring's socioeconomic conditions in childhood and adulthood, associations (beta coefficients and 95%CIs) of mother's and father's childhood SLI (per SD) were: -0.00mm (-0.01, 0.01) and 0.01mm (-0.00, 0.02) for carotid intima media thickness, -0.17mmHg (-0.61, 0.27) and -0.30mmHg (-0.78, 1.20) for systolic blood pressure, -0.43mg/dL (-2.00, 1.15) and -1.07mg/dL (-2.79, 0.65) for total cholesterol, and -0.00mU/L (-0.04, 0.03) and 0.01mU/L (-0.03, 0.04) for log fasting insulin. Results were of similar magnitude for parental height and leg length.

Conclusion: Our findings do not support an inverse association between parental childhood socioeconomic conditions or stature and offspring's risk of cardiovascular disease. Intergenerational socioeconomic influences on cardiovascular risk may be of limited public health significance for this setting.

5.3 Introduction

There is an excess burden of premature cardiovascular mortality in South Asia, but the reasons for this are unclear[280]. Socioeconomic conditions across the life course are an established determinant of an individual's risk of cardiovascular disease[52,125]. However, some recent evidence suggests that socioeconomic conditions experienced by an individual's parents before their conception may also determine their risk of cardiovascular disease, independent of the individual's own socioeconomic conditions[281,282]. Several mechanisms have been proposed to explain the intergenerational effects of adverse socioeconomic conditions. The most notable of these is the influence of maternal childhood undernutrition on her own growth and consequently the growth of her offspring, which has been linked to future risk of cardiovascular disease[283,284]. This mechanism could be important in South Asia where intergenerational poverty and undernutrition have been prevalent until recently[285]. If true, this could suggest the need to consider childhood socioeconomic and/or nutritional interventions to control the cardiovascular disease epidemic in this region.

Despite the potential importance of the hypothesis, limited evidence supports the cardiovascular effects of intergenerational poverty or undernutrition. In studies from Sweden and the United States, socioeconomic position of the grandparents (as a marker of parental childhood socioeconomic conditions) was inversely associated with individual's body mass index, although other cardiovascular risk factors were not examined[168,169]. Evidence on the role of parents' nutritional status in childhood for their offspring's cardiovascular risk comes mostly from animal experiments[286–288]. In the few epidemiological studies that have examined the association of parents' stature (as a marker of their childhood nutrition) with cardiovascular disease and its risk factors in their offspring, findings have been inconsistent[170–173].

The Andhra Pradesh Children and Parents' Study (APCAPS) is an intergenerational cohort set in a rural area of south India where poverty and undernutrition have been prevalent until recently[259]. In the third wave of data collection, detailed information was collected on parents' and offspring's life course socioeconomic conditions and stature, along with a range of measures of cardiovascular risk including subclinical atherosclerosis, arterial stiffness and conventional cardiovascular risk factors. Our objective was to examine the association of parents' socioeconomic conditions in childhood and stature with risk of cardiovascular disease in their offspring. We hypothesised an inverse association between parental childhood socioeconomic conditions and stature and their offspring's risk of cardiovascular disease.

5.4 Methods

This study is reported in accordance with the STROBE guidelines (see appendix Table S4.1 for completed checklist). The Andhra Pradesh Children and Parents' Study (APCAPS) is set in 29 rural villages and towns ~50km from the city of Hyderabad[259]. APCAPS began as the long-term follow up of offspring from a pregnancy nutrition trial conducted in 1987-1990, and was later expanded to cover family members of traced trial participants. In the present study we used cross-sectional data from the third wave of data collection conducted in 2010-12, in which 6944 of 10,213 (68%) invited family members attended a clinical examination. Adult offspring (aged 18 to 35 years) with at least one parent who was also examined were included in the analysis.

Clinical assessment

We collected social and demographic information using standard questions. These included a subset of questions from the Standard of Living Index (SLI), which is an asset-based scale developed to measure household wealth in India[261]. To assess socioeconomic conditions during childhood, we asked participants to recall their household's assets at age 10-12 years. We only asked about items deemed most relevant for the study setting (19 of out 29 original questions). These items were: housing material, toilet facilities, lighting source, drinking water source, fuel source, whether they had a separate kitchen, and household possession of agricultural land, television, radio, clock, bicycle, motorcycle, car, telephone, refrigerator, water pump, cart, thresher and tractor. We derived the index by applying the recommended weights to the available household asset questions, then summing across all items to give a total score for each individual[261]. A higher score indicates greater material affluence. Household-level measures of socioeconomic conditions are particularly appropriate for use in India, where joint family structures render individual-level measures (such as occupation and education) less informative. We assessed socioeconomic conditions in adulthood by current SLI (as above), as well as by occupational status (categorised as low – unemployed/unskilled manual labour; medium – skilled manual labour; high – non-manual/professional; or other – student/housewife/retired), in order to capture multiple dimensions that might be relevant to the risk of cardiovascular disease[183].

Anthropometric measurements (height, weight and waist circumference) were taken twice using standard equipment. The mean of the two readings was used for analyses. We examined both height and leg length as markers of parent's nutritional status in childhood; height as it is more commonly used in the literature, and leg length as it is the component of height thought to more specifically reflect childhood nutrition and growth[289,290]. To estimate leg length, we also measured sitting height on a stool of known height. Leg length was calculated as (standing height – (sitting height – stool height)). Body mass index was calculated as (weight in kilograms ÷ (height in metres)^2).

Systolic and diastolic blood pressure were measured at the right upper arm in the sitting position using a validated oscillometric device (Omron M5-I model). Participants were asked to rest for five minutes before three readings were taken, each one minute apart. The mean of the final two blood pressure readings was used for analyses, as the first reading is often inflated.

Venous blood samples were drawn after a minimum of eight hours fasting and centrifuged immediately. Assays for fasting glucose were conducted locally on the same day as sampling using an enzymatic method. For all other assays, samples were transported in batches to our central laboratories for analysis. Total and high-density lipoprotein (HDL) cholesterol and triglycerides were estimated using enzymatic colorimetric methods, and fasting insulin by radioimmunoassay. High-sensitivity C-reactive protein (hs-CRP) was measured using a particle-enhanced immunoturbidimetry method. Quality of assays was assured by internal duplicates and regular external standards.

A sub-sample of participants agreed to attend an additional clinic in Hyderabad for examination of subclinical measures of cardiovascular disease. Here we measured intima media thickness of the right common carotid artery, a marker of subclinical atherosclerosis, using B-mode ultrasonography (Ethiroli Tiny-16a, Surabi Biomedical Instrumentation, Coimbatore, India). A semi-automated software (AtheroEdge) was used to derive the mean of the measurements. We measured pulse wave velocity and augmentation index, markers of arterial stiffness, in the supine position using a Vicorder device (Skidmore Medical Limited, Bristol, UK). Body composition was measured by whole-body Dual X-ray Absorption (DXA) scan (Hologic models Discovery A or 4500W), and standard Hologic software was used to derive abdominal fat mass.

Data analysis

The following cardiovascular risk factors were considered in the analysis: body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, and fasting total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glucose, insulin and C-reactive protein, and in a subsample, carotid intima media thickness, pulse wave velocity, augmentation index and abdominal fat mass. Before analysis we checked distributions of outcome variables and excluded extreme outliers. Skewed variables (HDL cholesterol, triglycerides, glucose, insulin, C-reactive protein and abdominal fat mass) were log transformed to improve the normality of residuals.

To estimate the association of parental SLI in childhood, height and leg length with offspring's cardiovascular risk factors we used multilevel linear regression. We included a random intercept term at the family level to account for the potential correlation of cardiovascular risk factors between siblings. After first checking for evidence of non-linearity in their association with offspring's cardiovascular risk factors, we used parental SLI in childhood, height and leg length as linear exposures. We fitted separate models for maternal and paternal exposures because a number of participants did not have data on both parents. Age and sex are strongly associated with cardiovascular risk factors, so we included both as covariates in all models. We included linear and quadratic terms for age to account for its non-linear association with cardiovascular risk factors. Because socioeconomic conditions track strongly across generations, and adult and (to a lesser extent) childhood socioeconomic conditions are well-established determinants of cardiovascular disease risk, we present all models unadjusted and adjusted for indicators of offspring's childhood and adult socioeconomic conditions. We conducted additional analyses stratified by sex of the offspring, as experimental studies in rodents indicate that associations between parental early life nutrition and offspring's cardiovascular disease risk may be sex-specific[287,288]. We restricted all analyses to participants with complete outcome and exposure data, as data were missing for a relatively small number of participants. Power calculations indicated that with data on over 1000 offspring for all outcomes, we would have more than 80% power to detect even small effect sizes of <0.1SD per SD change in exposure. We performed all analyses on Stata version 16.

To mitigate risk of type 1 error (i.e. false positives) due to performing multiple statistical tests, we also report which p-values are significant at a false discovery rate of 5% using the Benjamini-Hochberg method[291]. For this we considered all models with the same exposure as part of the same family of tests (i.e. 14 tests per family).

Ethical approval and role of the study sponsor

Ethical approval for APCAPS was obtained from local review boards (National Institute of Nutrition of India and Public Health Foundation of India), as well as the London School of Hygiene and Tropical Medicine. All participants provided written informed consent (or witnessed thumbprint if illiterate). The study sponsor had no role in the design, analysis, interpretation, write-up of this manuscript, or decision to submit for publication.

5.5 Results

We analysed data on 3175 young adult offspring from 1434 families. The mean age of the offspring was 24 years (SD 4), and 58% were males (Table 5.1). Data on the mother was available for 3016 offspring (95%), and data on the father was available for 2457 offspring (77%). Since most offspring (86%) had at least one sibling also in the study, the number of unique parents contributing data to the analysis was 2489 (1368 mothers and 1121 fathers). The mean age of mothers and fathers respectively was 47 years (SD 6) and 54 years (SD 7). Completeness of outcome data varied from 95% to 99%. Offspring with complete data on maternal exposures had similar socio-demographic profile to offspring with incomplete maternal data (appendix Table S4.2). For paternal exposures, offspring with complete data were more likely to be male, younger and have higher SLI. A subsample of 1519 (48%) offspring attended the additional clinic for subclinical cardiovascular measurements. Compared to the overall sample, attendees were disproportionately male and likely to work in unskilled professions or be unemployed (to be expected since the clinic visit took most of a day). Among those who attended, outcome data were 88% to 99% complete.

Socioeconomic conditions were poorer in the parents' childhood than for the offspring, as expected. Mean SLI score was 8/67 (SD 4) in parents' childhood, 16/67 (SD 8) in offspring's childhood, and 30/67 (SD 9) for offspring currently. Parents had shorter height and leg length than their offspring (difference of 3.5cm (SD 6) and 1.0cm (SD 4), respectively, for both sexes). Among the offspring, prevalence of overweight and obesity (BMI≥23kg/m^2) was 23%, while 37% had hypertension or pre-hypertension (blood pressure ≥120/80mmHg), and 4% had impaired fasting glucose (≥6.1mmol/L).

Table 5. 1 Description of the study sample, Andhra Pradesh Children and Parents' Study (APCAPS), 2010-2012.

Offspring characteristic (N=3175)		% complete	N (%) / mean (SD) / median (IQR)
Socio-demographic			
Age (years)		>99%	24.4 (3.8)
Sex	Male	>99%	1842 (58%)
	Female		1326 (42%)
Childhood SLI (out of 67)		>99%	15.9 (7.7)
Height (cm) (males/females)		>99%	167 (6.3) / 153 (5.7)
Leg length (cm) (males/females)		>99%	80.9 (4.1) / 74.7 (3.7)
Adult SLI (out of 67)		>99%	30.0 (8.5)
Adult occupation	Unskilled labour or unemployed	>99%	803 (25%)
	Student, retired or housewife		1233 (39%)
	Semi-skilled labour		331 (10%)
	Skilled labour		522 (16%)
	Professional		278 (9%)
Mother's	Age (years)	95%	46.9 (6.0)
	Childhood SLI (out of 67)	95%	8.9 (4.4)
	Height (cm)	95%	151 (5.4)
	Leg length (cm)	95%	73.8 (3.6)
Father's	Age (years)	77%	54.2 (6.7)
	Childhood SLI (out of 67)	77%	7.7 (3.9)
	Height (cm)	77%	162 (6.3)
	Leg length (cm)	77%	80.0 (4.1)
Cardiovascular risk factors			
Systolic blood pressure, mmHg		>99%	115 (11.1)
Diastolic blood pressure, mmHg		>99%	75 (10.7)
Total cholesterol, mg/dL		97%	157 (36)
HDL cholesterol, mg/dL		96%	41 (34, 49)
Triglycerides, mg/dL		96%	94 (70, 135)
Fasting glucose, mmol/dL		96%	5.0 (4.6, 5.3)
Fasting insulin, mU/L		95%	6.0 (3.9, 9.2)
C-reactive protein, mg/L		96%	0.77 (0.35, 2.05)
Body mass index, kg/m^2		>99%	20.6 (3.6)
Waist circumference, mm		>99%	70.7 (9.8)
Carotid intima-media thickness, mm		46% (97%*)	0.65 (0.17)
Pulse wave velocity, m/s		45% (94%*)	6.1 (0.8)
Augmentation index, %		42% (88%*)	15.6 (7.9)
Abdominal fat mass, kg		47% (99%*)	1.0 (0.6, 1.6)

SLI is Standard of Living Index; HDL is high-density lipoprotein
*% of those who attended the additional clinic for subclinical cardiovascular measures.

In age- and sex-adjusted models, maternal childhood SLI was positively associated with offspring's body mass index and waist circumference, but not with other risk factors, while paternal childhood SLI was not associated with any of the offspring's cardiovascular risk factors (Figure 5.1 and appendix Table S4.3 and Table S4.4). Maternal and paternal height were positively associated with offspring's fasting insulin and waist circumference, with paternal height additionally associated with offspring's total cholesterol (Figure 5.2 and appendix Table S4.5 and Table S4.6). Maternal leg length was positively associated with offspring's waist circumference only, while paternal leg length was not associated with any of the offspring's cardiovascular risk factors (Figure 5.3 and appendix Table S4.7 and Table S4.8). In the final models also adjusting for offspring's childhood and adult socioeconomic conditions, only maternal and paternal height remained positively associated with offspring's waist circumference. No other associations remained for any parental exposures.

We found no evidence that associations varied by sex of the offspring for most outcomes, except for paternal childhood SLI with offspring's systolic and diastolic blood pressure: in female offspring, there was an inverse association (beta -0.75mmHg (-1.39, -0.11), p=0.021; and beta -1.03mmHg (-1.67, -0.40), p=0.001, per SD increase in parental childhood SLI, respectively), but in males there was no association (beta 0.14mmHg (-0.43, 0.71), p=0.6; and beta 0.24mmHg (-0.33, 0.81), p=0.4).

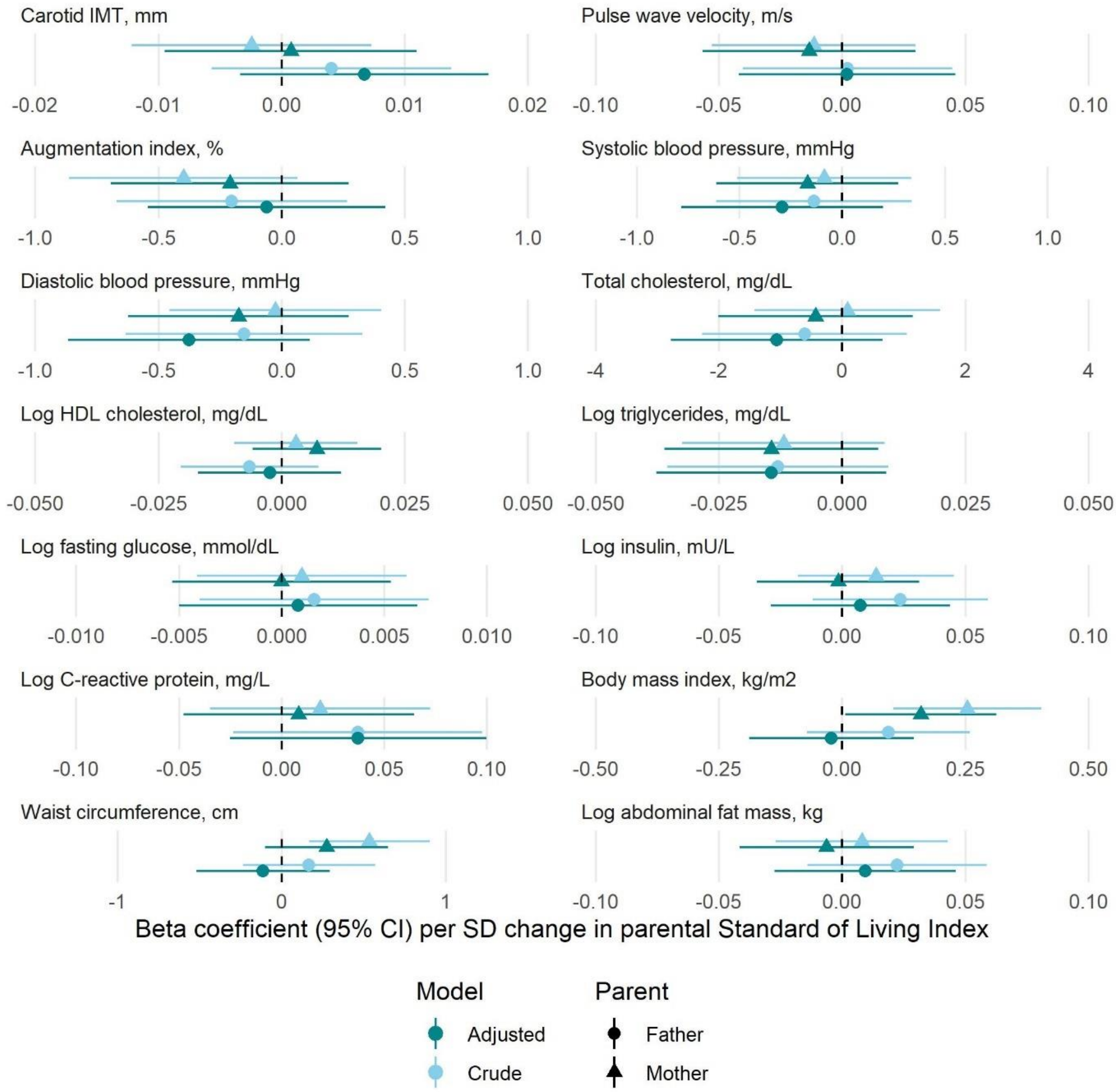

Figure 5. 1 Linear regression beta coefficients for the association between parental childhood Standard of Living Index (SLI) and cardiovascular risk of the offspring in the Andhra Pradesh Children and Parents' Study (APCAPS), 2010-2012.

IMT is intima media thickness; HDL is high-density lipoprotein. Crude models are adjusted for offspring's age and sex; adjusted models are additionally adjusted for offspring's childhood SLI (linear), adult SLI (linear) and adult occupation (categorical). No adjusted associations were significant after accounting for multiple testing (using Benjamini Hochberg method with 5% false discovery rate).

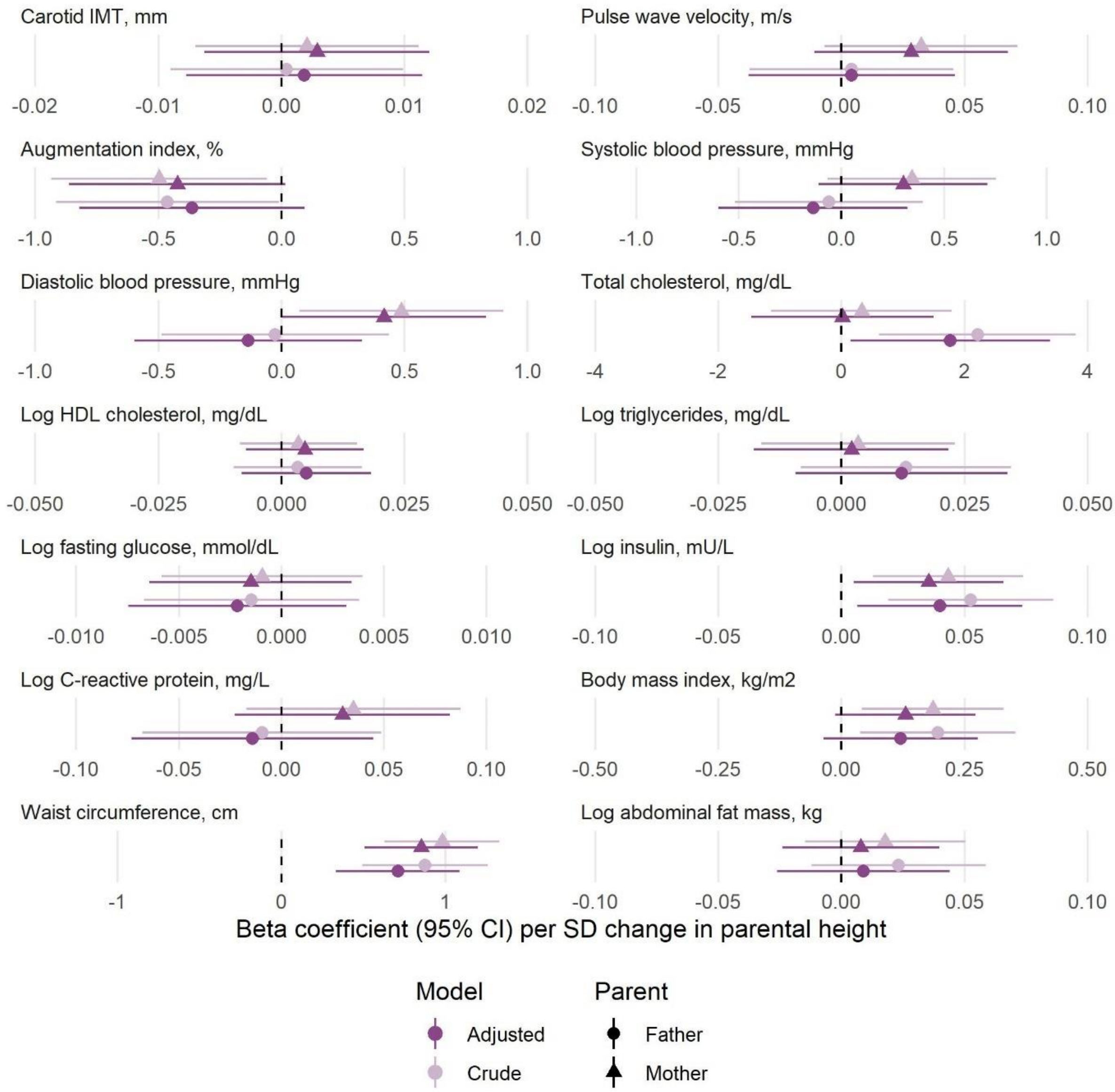

Figure 5. 2 Linear regression beta coefficients for the association between parental height and cardiovascular risk of the offspring in the Andhra Pradesh Children and Parents' Study (APCAPS), 2010-2012.

IMT is intima media thickness; HDL is high-density lipoprotein. Crude models are adjusted for offspring's age and sex; adjusted models are additionally adjusted for offspring's childhood SLI (linear), adult SLI (linear) and adult occupation (categorical). After adjustment, only the associations of mother's and father's height with offspring's waist circumference were significant after accounting for multiple testing (using Benjamini Hochberg method with 5% false discovery rate).

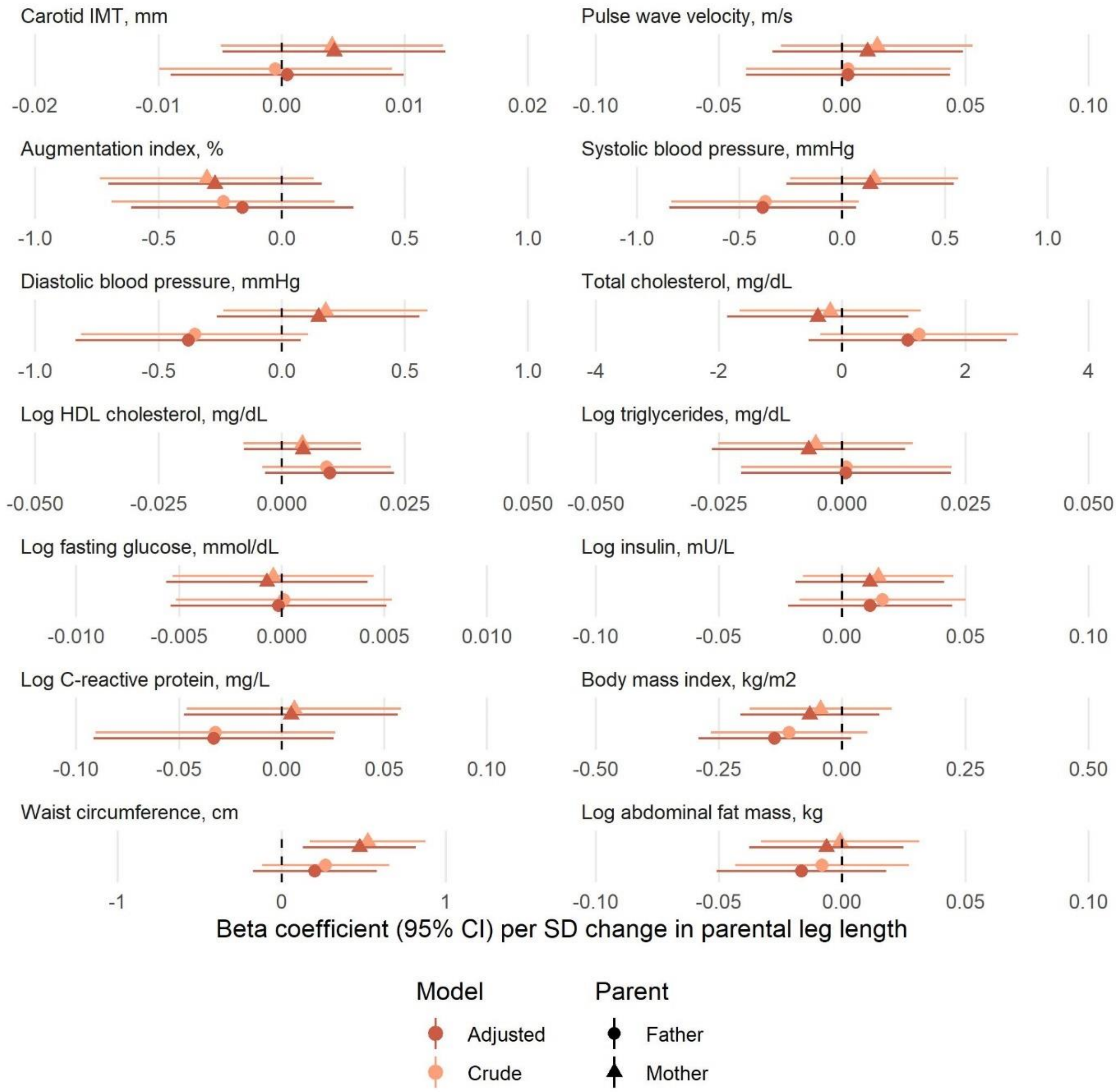

Figure 5. 3 Linear regression beta coefficients for the association between parental leg length and cardiovascular risk of the offspring in the Andhra Pradesh Children and Parents' Study (APCAPS), 2010-2012.

IMT is intima media thickness; HDL is high-density lipoprotein. Crude models are adjusted for offspring's age and sex; adjusted models are additionally adjusted for offspring's childhood SLI (linear), adult SLI (linear) and adult occupation (categorical). No adjusted associations were significant after accounting for multiple testing (using Benjamini Hochberg method with 5% false discovery rate).

5.6 Discussion

Main findings

In this rural Indian setting, we found no clear evidence that parents' socioeconomic conditions in childhood or stature were associated with subclinical atherosclerosis or cardiovascular risk factors in their offspring.

Relation to literature

As far as we are aware, few studies globally, and none from South Asia, have examined the association between parents' socioeconomic conditions in childhood and risk of cardiovascular disease in their offspring. In particular, there is a lack of evidence for offspring outcomes other than obesity. In a cohort of young adults from a town in Sweden (N=~5000, 100% male), income of their grandparents (who were born between 1915-29) was inversely associated with participants' body mass index, even after adjusting for their parents' income[168]. In a nationally representative cohort from the United States (N=4648, response rate ~50%), educational level of the grandparents (born in ~1900-1940) was inversely associated with obesity in white but not black offspring, which persisted after adjustment for parents' and offspring's education[169]. One possible reason for the discrepancy between findings from these studies and our own study is residual confounding by the offspring's socioeconomic conditions in adulthood. The inverse associations observed in previous studies may reflect the well-established inverse association between socioeconomic conditions in adulthood and obesity in high-income countries, rather than an independent association with parental childhood conditions[292]. Conversely, it is possible that a true inverse association between parental childhood socioeconomic conditions and offspring obesity was masked in our analysis because of the positive association between adult socioeconomic conditions and obesity observed in many studies in India[207], including APCAPS (see appendix Table S4.9).

Similarly, few studies have examined the association between parental stature (a marker of nutritional status and growth in childhood) and offspring's risk of cardiovascular disease. These studies examined parental height only; to our knowledge no previous studies have examined the association between parental leg length and offspring cardiovascular risk. In a family-based cohort from two towns in Scotland conducted in 1993-4 (N=2306), maternal, but not paternal, height was inversely associated with prevalent coronary heart disease (diagnosed by electrocardiogram) in the offspring, which persisted after adjustment for parental socioeconomic conditions[170]. However, in the same study, maternal height was positively associated with offspring's waist circumference, and not associated with other risk factors such as body mass index, blood pressure and blood glucose. It is interesting that we also found offspring's waist circumference, but not other measures of adiposity, to be positively associated with parental height, although this may simply reflect the fact that an individual's waist circumference (unlike the other measures of adiposity) is correlated with their height. In analyses of a cohort of individuals born in a hospital in Finland between 1924-1933 (N=3302 men and 3447 women), maternal height was not associated with the offspring's coronary heart disease mortality or hospitalisation[171,172]. An analysis of birth cohort studies from four middle-income countries (Brazil, South Africa, Philippines and Guatemala, N=~10,000) found no evidence of association of maternal height with body mass index, blood pressure or plasma glucose in offspring aged ~20-30 years, before or after adjusting for the offspring's socioeconomic conditions in childhood[173]. Although no data from low-income countries were included, it is notable that similar null findings were observed across cohorts ranging from urban and upper middle-income (Brazil) to rural and lower middle-income (Guatemala).

Our finding of an inverse association between paternal socioeconomic conditions in childhood and the blood pressure of female but not male offspring is intriguing, but is not supported by previous studies[170,173]. As this finding may have arisen due to chance, confirmation in further studies is warranted.

Strengths and limitations

Our study is among few to have examined intergenerational socioeconomic influences on cardiovascular health. We used data from a large population-based study in a rural area of India, where undernutrition, a key proposed mechanism of this association, has been prevalent until recently. We assessed cardiovascular risk in the offspring using a comprehensive range cardiovascular risk factors and markers of subclinical disease.

Some limitations must be acknowledged. Firstly, we relied on parents' recall of their childhood socioeconomic conditions, which may be prone to measurement error and thus have caused associations to be attenuated towards the null. However, in a repeat questionnaire administered to a 5% sub-sample, reliability of these responses was found to be high (over 80% correlation between the two measures), suggesting that measurement error may not have been a substantial problem. Secondly, we cannot exclude residual confounding by offspring socioeconomic factors. Although we adjusted for multiple indicators of offspring's socioeconomic conditions, this construct is inherently difficult to capture in epidemiological studies. At the same time, there is a risk that including offspring's socioeconomic conditions in our models could have introduced collider stratification bias if there were unmeasured causes of both offspring socioeconomic conditions and the exposure or outcome. However, as both of these potential biases would tend to bias associations away from the null, it is unlikely that they caused substantial bias to our main conclusions (of no association). Thirdly, although minimal data were missing for most exposures and outcomes (less than 5%), data on paternal exposures were missing for 23% of participants, which could have introduced bias in the analyses of paternal exposures. We opted not to use multiple imputation because we included several socio-demographic variables that might predict missingness in our final models (such as age, sex and occupation), and assumed that beyond these, missingness would not depend strongly on the outcome (as participants were largely unaware of their outcome status); in such a situation multiple imputation offers little additional benefit[293]. Fourthly, although our study setting is in many ways typical of rural areas within India and South Asia, caution should be exercised when generalising these findings to urban areas or other countries.

Implications

We had hypothesised that poor parental socioeconomic conditions in childhood, and associated undernutrition and stunted growth, leads to raised cardiovascular risk in the offspring. Given the high levels of poverty and stunting in South Asia, we thought this might contribute substantially to the excess premature cardiovascular mortality in South Asia. Contrary to these hypotheses, our findings suggest that intergenerational influences of poverty and undernutrition may be less important for cardiovascular disease risk than has been proposed based on findings from animal experiments and limited epidemiological data from high-income countries[281,282]. Socioeconomic factors acting within an individual's lifetime may be more fruitful targets for interventions to reduce cardiovascular mortality and its inequalities in South Asia. Further studies with prospective measures of parental childhood conditions and longer-term follow-up are needed to confirm this.

Conclusion

We did not find clear evidence for an association between parental socioeconomic conditions in childhood and offspring's risk of cardiovascular disease in a rural Indian population. Socioeconomic factors operating before conception may be of limited public health relevance for controlling the cardiovascular disease epidemic in South Asia. Interventions targeting socioeconomic factors operating within an individuals' lifetime should be prioritised.

Chapter 6: Discussion

The preceding chapters of this thesis have aimed to identify and address some of the key evidence gaps surrounding life course socioeconomic influences on risk of cardiovascular disease in low- and middle-income countries. In this concluding chapter, I provide a summary of what was already known and what this thesis adds for each evidence gap. I then provide a cross-cutting discussion of the strengths and limitations of this thesis, and outline some key implications and areas for further research in this field.

6.1 Summary of thesis findings

Evidence gap 1: The association between socioeconomic position in adulthood and cardiovascular disease incidence and mortality in low- and middle-income countries.

What was already known: In high-income countries, socioeconomic position is strongly and inversely associated with cardiovascular disease incidence and mortality. There is a widespread belief among researchers in this field that this inverse association only emerges after economic development, and that in countries at earlier stages of economic development, socioeconomic position is directly associated with cardiovascular disease (that is, higher cardiovascular disease in higher socioeconomic groups)[188,196–198]. This notion has been reinforced by observations of a direct association between socioeconomic position and cardiovascular risk factors such as obesity in many low- and lower middle-income countries[294]. However, early studies from the UK and US apparently documenting a change in direction of the association during the early 20th century have since been called into question[85,115]. The limited data from low- and middle-income countries provide no support for a direct association between socioeconomic position and cardiovascular disease incidence and mortality. Systematic reviews from 2017[87] and 2018[188] found 5 studies from low- and middle-income countries, of which 4 reported no clear evidence of an association[101,102,295,296], and one reported evidence of an inverse association of education, but not income, with cardiovascular mortality[100]. I am aware of 4 other studies of socioeconomic position and cardiovascular disease incidence or mortality in low- and middle-income countries, all of which reported an inverse association[14,98,103,297]. Given this limited evidence base, it is still unclear whether the association between socioeconomic position and cardiovascular disease changes from direct to inverse upon economic development, and therefore whether there may be a direct association in low- and middle-income countries.

What this thesis adds: I used a case study of Brazil, a populous middle-income country with 26 states at varying levels of economic development (similar to lower middle- and upper-middle income countries), to demonstrate a strong inverse association between education and cardiovascular mortality regardless of state-level economic development (chapter 2). Among women, there was some evidence that the association was more inverse in less economically developed states. The inverse associations were probably even larger than estimated in the less developed states, because these states tended to have lower quality mortality reporting. These findings provide some of the first evidence that the association between socioeconomic position and cardiovascular mortality does not change from direct to inverse upon economic development, instead suggesting that the association is inverse regardless of a country's level of economic development.

Interpretation of all available evidence: Available evidence offers no support for the notion that there is a direct association between socioeconomic position and cardiovascular mortality in countries at early stages of economic development. The continued reference to this notion in the literature risks detracting from problematic inequalities in cardiovascular disease mortality in low- and middle-income countries. However, low-income countries remain hardly represented in the literature, so additional data are needed to confirm if the inverse association extends to these countries. It also remains unclear whether the inverse association of socioeconomic position with cardiovascular mortality in middle-income countries extends to cardiovascular disease incidence. Similar data from Brazil but on cardiovascular disease incidence would be valuable to investigate this question.

<u>Evidence gap 2</u>: The association between socioeconomic position in childhood and cardiovascular disease and its risk factors in low- and middle-income countries.

What was already known: There is limited evidence on the association between socioeconomic position in childhood and risk of cardiovascular disease in low- and middle-income countries. The existence of a consistent inverse association in high-income countries[119], and the proposed role of early undernutrition in explaining this association[298], suggest that childhood socioeconomic position may be of particular relevance for cardiovascular disease in low- and middle-income countries where severe poverty remains prevalent. In a cohort of civil servants from Brazil, maternal education was inversely associated with cardiovascular risk score[226], diabetes[225], hypertension[227] and markers of subclinical atherosclerosis[222,224], although the latter was not robust to adjustment for adult socioeconomic position. However, other studies in Brazil observed inconsistent associations between childhood socioeconomic position and cardiovascular risk factors[229,230]. In a study of internal migrants from India, an index of recalled household assets in childhood was not associated with blood pressure, although was directly associated with insulin resistance amongst men[236]. Birth cohorts from India, Jamaica and South Africa found no clear evidence of association between maternal education and cardiovascular risk factors[237,239,248]. However, these studies were mostly small and examined outcomes in young adults (age 20-30 years), which may explain why they did not detect an association. These inconsistencies across studies suggested value in systematically reviewing the state of the evidence from low- and middle-income countries.

What this thesis adds: I systematically reviewed existing evidence on the association between childhood socioeconomic position and risk of cardiovascular disease in low- and middle-income countries, and conducted a new analysis of childhood socioeconomic position and cardiovascular risk factors in a pooled dataset from India. The systematic review (chapter 3) identified 28 articles addressing this research question from low- and middle-income countries (29 including my analysis from chapter 4 of this thesis). These studies came from a limited range of countries, and many studies had a high risk of bias, highlighting the need for further rigorous studies from a range of countries. The studies presented mixed findings, with the majority (35/42 associations) reporting no clear evidence of an association. There were no studies from low-income countries and few from lower middle-income countries (4/28). Several of the studies from lower middle-income countries were limited by study power, which may have contributed to the lack of observed associations[234,236–238]. Chapter 4 aimed to address this gap through an analysis based on pooled data from the APCAPS and IMS studies in India, a populous lower middle-income country. This study benefitted from a large sample covering multiple regions of India, a comprehensive questionnaire recalling household assets in childhood, and repeat questionnaires administered to a sub-sample. Measurement error models were used to mitigate potential attenuation of associations due to poor recall, which previous studies had not attempted to do. Household assets in childhood were directly associated with adiposity, fasting glucose and insulin, LDL cholesterol and triglycerides in adulthood, although these associations were attenuated to the null after adjustment for socioeconomic position in adulthood. After adjustment, household assets in childhood became inversely associated with diastolic and systolic blood pressure, although the size of this effect was modest.

Interpretation of all available evidence: These findings from India and other low- and middle-income countries suggest that obesity, lipid levels and diabetes are not independently associated with childhood socioeconomic position, contradicting the evidence from high-income countries[194]. This may shed some light on the mechanisms of the association observed in high-income countries. For example, it suggests that the association in high-income countries may be explained by higher adiposity and behavioural risk factors in lower socioeconomic groups from childhood onwards[299] (which remain less prevalent in low- and middle-income countries[300]), rather than factors linked to extreme poverty. For blood pressure, there was evidence of an inverse association with childhood socioeconomic position in a few studies, although still the majority found no clear evidence of an association. The small but statistically significant inverse association observed between household assets in childhood and blood pressure in India (chapter 4) is somewhat consistent with the rest of the literature, given that this study was substantially larger than most previous studies. Two other large studies from Brazil and Mexico also reported an inverse association between childhood socioeconomic position and blood pressure[227,243]. An inverse association between childhood socioeconomic position and blood pressure, but not other cardiovascular risk factors, is indirectly supported by the relatively high prevalence of hypertension, despite low obesity, in many low- and middle-income countries[5]. This tendency for high blood pressure is evident from young adulthood, possibly suggesting a role for early life factors[35]. Further data are needed to establish the public health relevance of this association for controlling cardiovascular disease in low- and middle-income countries. In particular, there is a need for evidence on the association between childhood socioeconomic position and cardiovascular disease incidence and mortality in these countries.

<u>Evidence gap 3</u>: The association between intergenerational socioeconomic position and cardiovascular disease and its risk factors in low- and middle-income countries.

What was already known: Researchers have proposed a number of mechanisms that might link socioeconomic position in an individual's childhood with cardiovascular risk in their offspring, such as maternal undernutrition, poor growth, and stress[164,165,167]. These so-called intergenerational effects could potentially make an important contribution to cardiovascular disease risk in low- and middle-income countries where poverty and stunting have persisted across generations[175]. However epidemiological studies addressing this hypothesis are limited and inconsistent. In studies from the US and Sweden, socioeconomic position of the grandparents (a proxy for the parents' socioeconomic position in childhood) was inversely associated with obesity[168,169], although other cardiovascular risk factors were not examined. Maternal, but not paternal, height was inversely associated with offspring's coronary heart disease (measured by ECG) in a study from Scotland, although the authors also found a direct association with waist circumference, and no association with cardiovascular risk factors such as blood pressure and glucose[170]. In a pooled analysis of four birth cohorts from middle-income countries, maternal height was not associated with offspring's body mass index, blood pressure or blood glucose in young adulthood[173].

What this thesis adds: Chapter 5 presents a study of the association between parents' socioeconomic position in childhood and cardiovascular risk in their adult offspring; the first study to my knowledge to examine intergenerational socioeconomic influences on a range of cardiovascular risk factors including subclinical atherosclerosis. This analysis found no strong evidence that parents' socioeconomic position in childhood, height or leg length were associated with cardiovascular risk in their adult offspring, after adjusting for their offspring's own socioeconomic position in childhood and adulthood. However, it is possible that a small sample size (especially for subclinical atherosclerosis), error in recalling childhood socioeconomic position, and limited exposure variation in this study setting, may have contributed to this null finding.

Interpretation of all available evidence: Evidence from this analysis in rural India and one other analysis of birth cohorts from four middle-income countries suggests that intergenerational poverty and undernutrition may not be important contributors to risk of cardiovascular disease in these settings. However, given this limited evidence-base, there is a need for further studies before an association can be ruled out. Studies representing more varied populations and with prospectively measured information on parents' socioeconomic position in childhood would be valuable.

6.2 Strengths and limitations

6.2.1 Issues around generalisability

The aim of this thesis was to improve understanding of the life course socioeconomic determinants of cardiovascular disease in low- and middle-income countries. This group of over 130 less economically developed countries (as classified by the World Bank) represents a diverse range of cultures, economies and geographies. This thesis primarily used data from Brazil, an upper middle-income country, and India, a lower middle-income country. These countries provide important case studies from two major world regions (Latin America and South Asia), which together comprise 40% of the global population of low- and middle-income countries. Brazil is the largest country in Latin America, in terms of landmass and population. Due to its colonial history, the people of Brazil are racially/ethnically diverse (mostly of European-, African- and Indigenous Brazilian-descent). India is the world's largest lower middle-income country. Its population, of 1.2 billion, is projected to overtake that of China by 2027. Both Brazil and India are both federal countries marked by substantial geographic, cultural and socioeconomic diversity. Brazil is classified as an upper middle-income country by the World Bank, but the Human Development Index of its 26 states range from 0.68 in Alagoas (similar to India and Morocco) to 0.83 in Sao Paulo (similar to Portugal and Russia). India is classified as a lower middle-income country, but the Human Development Index of its 28 states range from 0.58 in Bihar (similar to Pakistan and Angola) to 0.78 in Kerala (similar to Mexico and Thailand). However, the prevalence and socioeconomic patterning of various behavioural and (to a lesser extent) environmental and psychosocial determinants of cardiovascular disease has been observed to vary across settings, suggesting a need to interrogate the validity of generalising the findings of this thesis to other countries and regions.

Studies demonstrate substantial heterogeneity in the association between adult socioeconomic position and cardiovascular risk factors across different low- and middle-income countries. In particular, obesity, diabetes and lipid levels tend to be directly associated with adult socioeconomic position in low- and lower middle-income countries, while the association is null or inverse in upper middle-income countries, especially among women[114,294]. This has been attributed to broad social changes that tend occur upon economic development, such as the shift away from subsistence agriculture, an increase in high fat diets and mechanised transport, and changing cultural preferences around body types and lifestyle choices[198]. However, this is not a universal pattern, and substantial variation in these factors can exist even between countries at a similar level of economic development. For example, in some lower middle-income countries in Latin America, such as Bolivia and Nicaragua, there is little association between wealth and overweight, whilst in some upper middle-income countries in Sub-Saharan Africa, such as Namibia and Gabon, there is a strong direct association[294], which may be related to differing cultural preferences around body type between these regions[301].

The more limited data on cardiovascular disease incidence and mortality from low- and middle-income countries suggest a different pattern of associations with adult socioeconomic position compared with that observed for cardiovascular risk factors. Analysis of the states of Brazil (chapter 2), and the multi-country PURE study, suggested that the association between adult socioeconomic position and cardiovascular disease mortality is inverse irrespective of the level of economic development, and may be even more inverse in lower income countries[103]. This could be due to greater inequalities in access to healthcare in lower income countries, reflected by the higher case-fatality rates in lower socioeconomic groups[103]. However, there is hardly any evidence on the association between adult socioeconomic position and cardiovascular incidence and mortality from low-income countries and certain world regions such as Sub-Saharan Africa, making it difficult to know if associations can be generalised to those settings. The PURE study included data from Zimbabwe and South Africa, finding that in both, cardiovascular disease incidence was higher in people with lower education, although these were not statistically robust due to small sample sizes[103]. In a case-control study of myocardial infarction (INTERHEART-Africa, of which 80% of participants were from South Africa), income and education were directly associated with myocardial infarction among black participants, but not associated among other participants[302].

The extent to which the association between childhood socioeconomic position and risk of cardiovascular disease can be generalised between low- and middle-income countries may depend on the mechanisms underlying this association. The systematic review (chapter 3) identified no studies from low-income countries and only four from lower middle-income countries, prohibiting comparisons between country-income groups. However, the lack of strong associations across included middle-income countries, in contrast to the inverse associations in high-income countries, suggests there is unlikely to be an inverse association in low-income countries. Additional data from these countries would be valuable to confirm this.

Overall, it may sometimes be necessary to generalise the association of socioeconomic position with risk of cardiovascular disease between countries, for example where data are lacking. Low- and middle-income countries share some relevant characteristics, as distinct from high-income countries, which may make such generalisations valid. However, substantial variation still exists within each country-income group. Generalisations should be applied with due caution and do not obviate the need for evidence from a wider range of countries. Of note, patterns across countries may differ when considering cardiovascular risk factors vs cardiovascular incidence or mortality, and for socioeconomic position at different stages of life. Thus, the findings from this thesis provide insight into socioeconomic influences on cardiovascular disease in Latin America and South Asia, and to a lesser extent, other middle-income countries. Caution should be used when extending these findings to other world regions and to low-income countries.

6.2.2 Issues around causality

The analyses conducted in this thesis, and most of the literature cited, are based on observational data. The extent to which these associations represent causal relationships merits scrutiny. Alternative explanations which might account for the association between socioeconomic position and cardiovascular disease include confounding, selection bias and reverse causality[303].

Confounding occurs when a common determinant of the exposure and outcome induces an association between them. The most commonly considered confounders of the association between adult socioeconomic position and cardiovascular disease are an individual's age and sex (as, for example, older adults and women tend to have lower education and income). These individual-level demographic factors are relatively straightforward to account for in statistical analyses. Other potential confounders of the association between adult socioeconomic position and cardiovascular risk include health and socioeconomic factors in childhood. Not accounting for these could result in overestimating the association between adult socioeconomic position and cardiovascular risk. Although it was not possible to account for these factors in the analysis of education and cardiovascular mortality in states of Brazil (chapter 2), a number of studies which used more robust studies designs have reported similar findings, suggesting that confounding may play a limited role in explaining the association. For example, in Sweden and Norway, an inverse association has been observed between education and cardiovascular risk within pairs of siblings, even though they are matched on early life socioeconomic position[304,305]. A quasi-experimental evaluation of changes to the school leaving age in the UK supported an inverse association between years of education and diagnosis of hypertension, diabetes, stroke and heart disease[306]. In Mexico, longer receipt of a cash transfer programme (3 to 5 years) was inversely associated with risk of hypertension among women[307], while in Sweden, refugees quasi-randomly allocated to live in more deprived neighbourhoods showed an increased incidence of diabetes compared to those allocated to affluent neighbourhoods[308].

In studies of the association between childhood socioeconomic position and risk of cardiovascular disease, a greater concern is the potential for bias introduced when trying to estimate the association independent of adult socioeconomic position[125]. There are a number of potential issues with this approach, which could have biased the associations in this thesis and also in the literature more broadly. Firstly, as childhood and adult socioeconomic position are often highly correlated, statistical power to isolate their independent effects may be limited. This could result in incorrectly concluding that there is no independent association of childhood socioeconomic position with cardiovascular risk. However, this has not prevented an inverse association from being observed in high-income countries, and if anything may be less of a problem in low- and middle-income countries where socioeconomic conditions are changing more rapidly for individuals. Secondly, incorrectly accounting for adult socioeconomic position (for example due to measurement error or model misspecification) could bias the direction of association of childhood socioeconomic position towards that of adult socioeconomic position. In high-income countries, this would be expected to induce an inverse association between childhood socioeconomic position and cardiovascular risk. In low- and middle-income countries, this might induce a direct association with certain risk factors (such as obesity), because of their direct association with adult socioeconomic position. The assumption of sufficient adjustment for adult socioeconomic position cannot be tested. However, in India (chapter 4), the crude direct associations between childhood socioeconomic position and obesity, lipid levels and insulin were all attenuated to the null after adjustment for adult socioeconomic position, suggesting that adult socioeconomic position may have been sufficiently accounted for. One way to explore this further might be to triangulate findings with evidence obtained from alternative study designs, such as migration studies or adoption studies[309,310]. A third problem is that adjusting for adult socioeconomic position, a mediating variable, can introduce collider stratification bias if there are unmeasured common causes of childhood and adult socioeconomic position, or of adult socioeconomic position and cardiovascular risk[311,312]. For example, an individual's intrinsic motivation may be causally related to increased adult socioeconomic position, and to reduced cardiovascular risk (through improved health behaviours), but not causally related to their socioeconomic position in childhood (making it a common cause of mediator and outcome)[313]. Controlling for adult socioeconomic position amounts to comparing individuals with different childhood socioeconomic position, but the same adult socioeconomic position. Among individuals with low adult socioeconomic position, those with high childhood socioeconomic position would tend to have lower intrinsic motivation, and therefore increased cardiovascular risk (and the converse among individuals with high adult socioeconomic position). Thus, a direct association could be induced between childhood socioeconomic position and cardiovascular risk. It cannot be excluded that in this thesis (chapters 4 and 5, and in the studies included in the systematic review), some true inverse associations were attenuated due to this type of bias. However, it is unclear why evidence from high-income countries would not also have been attenuated in a similar way. Furthermore, some researchers have questioned the likely extent of such a bias in practice[314]. In future, studies could benefit from measuring and accounting for common causes of the mediator and outcome (such as intrinsic motivation), as well as sensitivity analyses to explore what degree of bias would be required to influence the conclusions[315]. Fourthly, it has been shown that the conventional approach to estimating the unmediated effect of an exposure (i.e. by adjusting for the mediator) can give biased answers in the presence of an interaction between exposure and mediator, or if the mediators or outcomes are not continuous[316]. This could have been an issue for studies included in the systematic review, most of which used binary outcomes and/or mediators to examine the association of childhood socioeconomic position with risk of cardiovascular disease. However, studies from Sweden and Finland comparing traditional methods with more robust weighting-based approaches to estimating unmediated effects reported similar results with both approaches, suggesting that findings may not have been substantially biased in practice[121,317]. In our analyses in India (chapters 4 and 5), inclusion of adult occupation as a categorical mediator had no appreciable effect on the estimates. Nevertheless, the literature from low- and middle-income countries would benefit from further use of weighting-based approaches when outcomes or mediators are binary, and from robust investigation of the interaction between childhood and adult socioeconomic position on risk of cardiovascular disease.

Another source of potential bias in the association between socioeconomic position and cardiovascular disease is selection bias resulting from differential mortality experiences in different socioeconomic groups[318]. Lower socioeconomic groups tend to experience higher mortality (beyond their excess mortality due to cardiovascular disease), which could induce an association between socioeconomic position and risk of cardiovascular disease if those who survived differed from those who died with respect to their underlying risk of cardiovascular disease. For example, it is often suggested that in high-mortality populations, individuals who survive to older ages must be more resilient to disease than the average member of a low-mortality population. This issue may be particularly relevant for studies of childhood socioeconomic position in countries with high infant and child mortality rates, such as low- and middle-income income countries. This could result in an artefactually lower cardiovascular mortality rate in low socioeconomic groups, that does not represent a causal protective association. If true, the inverse associations observed in Brazil (chapter 2) and India (chapter 4) may be underestimated. To my knowledge, the likely extent of this bias has not been formally examined in low- and middle-income countries. However, in studies from high-income countries, a strong inverse association between childhood socioeconomic position and cardiovascular risk has been noted even among cohorts born in the early 20th century, when infant mortality was relatively high[250]. This suggests that bias due to mortality selection is unlikely to explain the difference in association between middle- and high-income countries.

Finally, reverse causality (also known as health selection in this context) has been proposed to account for the inverse association between socioeconomic position and cardiovascular disease[319]. This is based on the observation that poor cardiovascular health can influence an individual's income, occupation and social prestige[69,320]. However, while this might be important source of bias for cross-sectional studies of income and occupation in adulthood, the analyses in this thesis used education and childhood socioeconomic position as exposures, which are unlikely to be influenced by reverse causality in this way[321].

6.2.3 Issues around measurement of socioeconomic position

The numerous ways in which socioeconomic position is defined and measured poses an inherent problem for reaching general conclusions in social epidemiology. Not only are specific indicators imperfect at capturing the underlying construct of socioeconomic position, but the underlying construct of socioeconomic position is itself ill-defined. Furthermore, specific indicators of socioeconomic position are often measured with error as they rely on participant's self-report and recall. This measurement error could result in an attenuation of true associations. In this thesis, various approaches were used to limit the potential for bias due to measurement error in socioeconomic indicators. For the analysis in Brazil (chapter 2), a binary indicator for education was used to reduce the chance of misclassification, and multiple imputation with a range of predictors was used to deal with missing education data. As the quality of vital registration is generally poorer in the less developed states of Brazil, residual bias due to measurement error in education would, if anything, lend further strength to the study conclusions. In India (chapter 4), socioeconomic position was measured using a validated index comprised of indicators of housing quality and ownership of household assets[261]. Measurement error models (based on repeat questionnaires in a 5% sub-sample) were used to account for potential misclassification in recalled childhood assets. Despite this, some attenuation due to measurement error cannot be excluded, especially in the analysis of intergenerational socioeconomic position (chapter 5), where the sample size was insufficient to apply stable measurement error models. Many of the studies included in the systematic review used retrospectively recalled measures of socioeconomic position, which may partly explain the high proportion of null findings. A particular problem for life course studies is that socioeconomic position in childhood is generally recalled with more error than socioeconomic position in adulthood, which could systematically underestimate the relative importance of childhood socioeconomic position[192]. However, the few studies included in the review which measured childhood socioeconomic position prospectively also found no evidence of association with cardiovascular disease, suggesting that this may not have substantially biased the conclusions of the review.

A further limitation may be the appropriateness of drawing conclusions about socioeconomic position across studies which use different socioeconomic indicators. However, using a standardised socioeconomic indicator does not necessarily resolve this problem either, because the same indicator might be distributed differently or take on different meanings in different settings. For example, the number of years of education required to achieve a basic standard of literacy varies substantially between countries[322]. Likewise, completion of secondary education might represent relative affluence in one country, whilst being a minimal standard of education in another. The association of certain material assets (such as a bicycle) with socioeconomic position could vary between countries or even within a country (such as in rural compared with urban areas)[183]. Instead, selection of socioeconomic indicators based on the specific research question and setting being examined is likely to facilitate a more nuanced and theory-based understanding of the socioeconomic influences on cardiovascular disease. In the analysis of education and cardiovascular mortality in Brazil (chapter 2), education was selected as an indicator of adult socioeconomic position because it has shown the strongest association with cardiovascular mortality in various upper middle-income and high-income countries[87], and was considered to be the most reliable indicator available on the death certificates. In India (chapters 4 and 5), an index of household assets was used in order to best capture material aspects related to childhood socioeconomic position, a key hypothesised pathway of its association with cardiovascular risk. Household-level (as opposed to individual-level) and asset-based (as opposed to income-based) measures are also more appropriate for capturing material conditions in settings characterised by joint household structures and an informal labour market[183]. In future, comparison of these with other socioeconomic indicators may shed further light on the mechanisms operating.

6.3 Implications

Cardiovascular disease is the leading cause of premature death in most low- and middle-income countries. Concerted action to control the rising burden of cardiovascular disease will be needed to meet the Sustainable Development Goal target of a one-third reduction in non-communicable disease mortality by 2030. In addressing the first evidence gap, this thesis found evidence that lower socioeconomic groups may experience higher cardiovascular mortality regardless of a country's level of economic development, highlighting that solutions to control cardiovascular disease must be inclusive of lower socioeconomic groups. In some countries, this inverse association of adult socioeconomic position with cardiovascular mortality is despite the direct association of adult socioeconomic position with cardiovascular risk factors such as obesity. The most appropriate targets for intervention may be risk factors which are higher in low socioeconomic groups, such as tobacco use, low fruit and vegetable intake and indoor air pollution[110]. Existing cross-sectional surveys could be used to identify the risk factors most strongly associated with low socioeconomic position in a given setting[34]. Limited access to healthcare services is also likely to be an important contributor to the high cardiovascular mortality in low socioeconomic groups[103]. Brazil provides an example of a country where the strengthening of primary care services has been associated with appreciable reductions in cardiovascular mortality and inequalities[210,323]. In India, the recent introduction of state health insurance for poor households to cover major hospital expenditures may enable access to secondary and tertiary care for people who were previously unable to afford it[324].

Monitoring the effect of such policies on social inequalities in cardiovascular disease will be important for supporting their implementation in other settings. Poverty reduction and social development programmes being implemented in many low- and middle-income countries are likely to impact positively on the burden and social inequalities of cardiovascular disease, but may also be associated with rising levels of risk behaviours and obesity, which could offset some of these gains. Careful consideration of how development policies can be coupled with promotion of healthier behaviours will be needed to avoid the rise in obesity among lower socioeconomic groups seen in high-income countries. Finally, there may be other mechanisms contributing to the high cardiovascular mortality in low socioeconomic groups which have not yet been identified. Indoor air pollution is an example of a factor which was only recently recognised as a major contributor to cardiovascular disease burden in low- and middle-income countries[5]. Further exploratory research into the causes of cardiovascular disease in low- and middle-income countries, with a focus on factors associated with poverty, might improve understanding of the aetiology of cardiovascular disease globally.

A further implication is the need for better monitoring of social inequalities in cardiovascular disease incidence and mortality, rather than just risk factors, in low- and middle-income countries. The current focus on monitoring cardiovascular risk factors, enabled by the widespread use of cross-sectional surveys (such as Demographic and Health Surveys and WHO-STEPS), has highlighted that some cardiovascular risk factors are higher among high socioeconomic groups, which may be detracting attention from the excess cardiovascular mortality among low socioeconomic groups. Effective monitoring of inequalities in cardiovascular disease mortality could involve use of national census and mortality data, as has been done in several Latin American countries[14]. However, high-quality vital statistics are not available in many low- and middle-income countries. A more feasible option may be vital registration on a random sample of the population, as has been done in India[6]. It is important that countries collect appropriate socioeconomic indicators at baseline when implementing these systems. Nationally representative cohort studies have provided some of the most powerful resources for monitoring social inequalities in cardiovascular risk factors, incidence and mortality in high-income countries. However, without linkage to other data sources to ascertain health outcomes (which may not be possible in many low- and middle-income countries), these require substantial long-term investment. Increased opportunities for telephone and web-based follow-up, as well as growing networks of community health workers, may enhance the feasibility health and vital event surveillance at scale in low- and middle-income countries.

In addressing the second evidence gap, this thesis found evidence that childhood socioeconomic position may not be a major determinant of cardiovascular risk in low- and middle-income countries, contrary to findings from high-income countries. Although poverty in childhood was associated with higher blood pressure in some studies, the overall evidence was inconsistent, suggesting that more evidence is required before childhood poverty is targeted as a strategy to control blood pressure in low- and middle-income countries. These findings also have some implications for the interpretation of the association between childhood socioeconomic position and cardiovascular risk in high-income countries. The absence of a clear association in middle-income countries suggests that factors universally related to low socioeconomic position, such as low intake of fruits and vegetables and psychosocial stress in childhood, may be less likely to explain the association in high-income countries. Instead, factors which are linked to low socioeconomic position in high-income countries only, such as obesity, high intake of saturated fats and physical inactivity in childhood, may be more important mechanisms of this association. Rigorous cross-cohort comparisons which include data from a range of country-income levels would be valuable to confirm this suggestion. The third evidence gap related to the association of intergenerational poverty with risk of cardiovascular disease. This thesis did not find evidence to support an association of parents' socioeconomic position in childhood with cardiovascular risk in their offspring, even in a setting with high levels of intergenerational poverty and stunting. However, it would be premature to derive policy implications from the limited evidence-base on this topic. Larger studies from more varied populations are needed to further understand the intergenerational influence of poverty on risk of cardiovascular disease.

6.4 Further research

This thesis has highlighted the limited evidence on socioeconomic position across the life course and risk of cardiovascular disease in most low- and middle-income countries. For adult socioeconomic position, studies that examine cardiovascular disease incidence and mortality are needed, especially from low-income countries. For childhood socioeconomic position, the systematic review demonstrated a need for studies with prospective measures of childhood conditions, which follow up participants into middle and older adulthood, and which examine cardiovascular disease incidence and mortality. Studies of intergenerational socioeconomic influences on cardiovascular disease are lacking globally. Prospective studies with a range of measures of socioeconomic position across the life course (including in the previous generation) and highly characterised data on cardiovascular disease, as well as relevant behavioural, environmental and psychosocial factors, will help to clarify these associations and elucidate their mechanisms. Studies from a broader range of country-income levels and regions will help to understand cultural and historical influences on the association between socioeconomic position and risk of cardiovascular disease, and allow us to move towards more nuanced generalisation of these findings. However, these approaches will take time and substantial resources to implement. Until such data are available, some more feasible avenues for research might include:

a) Pooling of cohorts across multiple low- and middle-income countries to enhance generalisability and power. Especially in middle-income countries, there are an increasing number of prospective studies which measure cardiovascular disease incidence or mortality[325,326]. Some regional initiatives to pool cohorts have been successful, for example the Asia Pacific Cohort Studies Collaboration, although this has limited data from low- and middle countries (out of 24 cohorts, 1 was from Thailand, 10 were from China, and the rest from high-income countries)[327,328]. The Consortium of Health Orientated Research in Transitioning Societies (COHORTS) group has brought together birth cohorts from 5 middle-income countries (South Africa, India, Philippines, Brazil and Guatemala) to improve understanding of how early growth and social environment influence adult health; however the relatively young age of most participants (20-30 years) has prohibited examination of cardiovascular incidence or mortality[329]. The INDEPTH network brings together 48 Health and Demographic Surveillance Sites from 19 low- and middle-income countries, to harmonise and improve collection of data on health events and cause of death by verbal autopsy[7]. Ensuring the collection of appropriate socioeconomic indicators, and integrating sub-studies to improve the quality of cardiovascular measures within these existing collaborations, could represent easy wins. In regions where the data are available, for example in Latin America, pooled analyses of national mortality and census data along with national cross-sectional surveys could provide substantial insights.

b) Linkage of data sources to obtain prospective measures of socioeconomic position at multiple time-points during the life course. Recalled measures of socioeconomic position pose a challenge for life course research, although prospective data are often not available in existing studies. Linkage to other data sources may provide a near-term solution. For example, in Brazil, data linkage between government vital statistics, health and social registries has enabled life course variables to be extracted (e.g. parental occupation and education history, birth conditions and previous health issues[330]). In countries without such rich government databases, extraction of area-level indicators of deprivation may still feasible, which could be linked to the residential address history of individuals and their parents. This approach has been applied in the UK for example[331,332], although I am not aware of its use in low- and middle-income countries. Having access to socioeconomic information at multiple time-points across the life course (rather than just childhood and adulthood) will allow more advanced life course modelling approaches to be applied[159,333].

c) Long-term follow-up of trials and quasi-experimental designs to improve causal inference around socioeconomic position and its mechanisms. The majority of evidence from alternative study designs comes from high-income countries. There may be ample opportunities for experimental and quasi-experimental study designs in low- and middle-income countries, where socioeconomic conditions and policy landscapes are changing rapidly. In Brazil, researchers have examined the effect of the roll-out of primary care and cash transfer interventions on various health outcomes[323,334,335]. In India, a sibling-paired design was used to examine the effect of rural to urban migration on cardiovascular risk factors[260]. Numerous social development programmes implemented in low- and middle-income countries during the Millennium Development Goal-era, including some trials, have the potential to be evaluated to understand their long-term impact on risk of cardiovascular disease.

d) Integration of qualitative and quantitative findings to develop a more theory-based understanding of the social determinants of cardiovascular disease in low- and middle-income countries. Social theories around socioeconomic position and health were mostly developed in relation to high-income countries. The proposed mechanisms of this association also tend to reflect the experiences of high-income countries. Context-specific understanding of the experiences of different socioeconomic groups with respect to determinants of cardiovascular disease may help identify new hypotheses around the causes of inequalities, and ultimately interventions. For example, a qualitative study in informal settlements in urban Kenya demonstrated participants' concerns around of the role of psychosocial factors and poor healthcare access, instead of behavioural factors, for their cardiovascular risk[336]. Studies from South Africa emphasised the importance of the unaffordability of nutritious foods[301] and challenges in navigating both the allopathic and traditional healthcare systems[337]. At the APCAPS study site in rural India, environmental issues were perceived as paramount for chronic disease risk, with participants also commenting on the negative impacts of increased social inequality and discrimination[338]. A valuable starting point could be to synthesise existing qualitative evidence around socioeconomic influences on cardiovascular risk in low- and middle-income countries. This will help to bridge the gap between the broad insights and generalisations offered by national and multi-country studies, and the highly contextualised local application of these issues. It may also help to identify the most appropriate socioeconomic indicators for monitoring inequalities in cardiovascular disease in a given setting.

6.5 Concluding remarks

Understanding the association of socioeconomic position with cardiovascular risk is vital to inform equitable strategies to control cardiovascular disease. This thesis aimed to address several evidence gaps related to life course socioeconomic influences on the risk of cardiovascular disease in low- and middle-income countries, which are systematically under-represented in existing evidence. A case study of the states of Brazil demonstrated that lower socioeconomic groups may be at higher risk of cardiovascular mortality regardless of a country's level of economic development, arguing against the widely held view that an inverse association between socioeconomic position and cardiovascular disease only emerges after economic development. A systematic review of published evidence and a new analysis of pooled cohorts from India found little evidence to support a role of childhood poverty in the development of cardiovascular risk, although there was some suggestion of an association with blood pressure which warrants confirmation in other datasets. In an intergenerational study from rural India, there was little evidence to support a role for intergenerational poverty and poor growth in cardiovascular risk. However, given the few studies in this area, further evidence is needed to confirm this finding.

To move towards a fuller understanding of how socioeconomic position across the life course influences risk of cardiovascular disease in low- and middle-income countries, we need studies with multiple prospective measures of socioeconomic indicators and potential mechanisms, linked to information on cardiovascular disease incidence and mortality. Importing assumptions about these relationships from high-income countries may not be appropriate for many low- and middle-income countries. Novel or under-appreciated risk factors for cardiovascular disease may come to light through rigorous research in a wider range of countries than are currently represented in the literature. In the meantime, policies to prevent cardiovascular disease in low- and middle-income countries should be oriented towards reducing the risk in disadvantaged socioeconomic groups, for example through reducing tobacco use, improving air quality, and promoting equitable access to cardiovascular disease treatments.

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