Socioeconomic inequalities in cardiovascular disease: a causal perspective

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Abstract

Socioeconomic inequalities in cardiovascular disease (CVD) persist in high-income countries despite marked overall declines in CVD-related morbidity and mortality. After decades of research, the field has struggled to unequivocally answer a crucial question: is this association causal? We review relevant evidence from various study designs and disciplinary perspectives. Traditional observational, family-based and Mendelian randomization studies support the widely accepted view that low socioeconomic position (SEP) causally influences CVD. However, results from quasi-experimental and experimental studies are both limited and equivocal. While more experimental and quasi-experimental studies are needed to aid causal understanding and inform policy, high-quality descriptive studies are also required to document inequalities, investigate their contextual dependence and consider SEP throughout life; no simple hierarchy of evidence exists for an exposure as complex as SEP. The COVID-19 pandemic illustrates the context-dependent nature of CVD inequalities, with new causal pathways linking SEP and CVD potentially having been generated. The linked goals of understanding the causal nature of SEP

and CVD associations, their contextual dependence and their remediation by policy interventions necessitates a detailed understanding of society, its change over time and the phenotypes of CVD. Interdisciplinary research is therefore key to advancing both causal understanding and policy translation.

[H1] Introduction

Low socioeconomic position (SEP), defined below, has a well-replicated association with increased risk of cardiovascular disease (CVD)[1]. The strength of this association is broadly similar to that of other major biomedical and behavioural risk factors[1] (Fig. 1). The salience of this form of health inequality or disparity has increased over the past 3–4 decades due to widening income gaps[2] and indications that favourable trends in CVD are reversing in some high-income countries[3]. The consequences of the coronavirus disease 2019 (COVID-19) pandemic, recent cost-of-living challenges and climate change add to concerns that these inequalities might widen in the future[2].

Many reviews have been published on the topic of social inequalities and CVD[4-15], but the question of whether and when the association between SEP and CVD is causal remains unresolved. This knowledge gap hinders the development of evidence-based policy to address these health inequalities. In this Review, we highlight the importance of a causal perspective and suggest future lines of research. We summarize evidence from divergent study designs and describe how each can add to causal understanding; we demonstrate the potential for a more fined-grained assessment of CVD phenotypes, including the assessment of early or subclinical disease, to aid causal understanding; and we consider how causal processes might change as a result of the COVID-19 pandemic.

[H1] Causality in the context of SEP and CVD

[H2] Defining SEP

SEP is multidimensional and captures the relative position of an individual in society according to one or more socioeconomic measures[16,17]. These measures can be either individual-level (typically education, income, occupational social class or wealth) or area-based (neighbourhood deprivation or regional development). The nature of many societies is such that parental SEP influences offspring SEP (intergenerational stability or mobility) and that education in turn typically benefits job opportunities, income and wealth accrual (intragenerational). Therefore, different SEP indicators to varying degrees correlate over the life course and are partly interdependent (Fig. 2). Area-based SEP can influence CVD either through influencing individual or family-level SEP or by influencing CVD independently. However, the relative importance of each specific indicator in social stratification and CVD risk can differ by context. For instance, in societies in which health care is entirely privately funded, the role of parental or own income on CVD might be particularly important independently of other dimensions. If early life influences are important for the development of CVD in adulthood, then childhood SEP might influence adult CVD independently of adult SEP. There is, therefore, merit in investigating when in life SEP influences CVD, as well as which specific dimension is particularly important. Social scientists continue to investigate social stratification amidst the changing nature of society, which means that novel indicators of SEP (for example, new forms of social class amidst changes in the labour market[18]) can become available to investigate in terms of their effect on CVD, whereas others might cease to have relevance over time.

[H2] Defining causation

The concept of causation is complex and has a long history[19-22]. In this Review, we distinguish between observing a correlation between SEP and CVD and identifying a causal link between the two; the latter implies that intervening on SEP would reduce rates of CVD, for example through policies that increase education or income levels. Broader societal change might also influence SEP and thereby influence rates of CVD, such as recessions or changes in education provision. Similarly, intervening on factors that lie on the causal pathway between SEP and CVD (such as weight loss or smoking cessation interventions) would also be expected to reduce rates of CVD. By reducing CVD in the most disadvantaged groups, each approach would be anticipated to reduce inequalities in CVD — that is, the absolute or relative difference in CVD between SEP groups.

Readers might be familiar with the 1965 Bradford Hill 'criteria' for understanding whether associations are causal (strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence and analogy)[23]. Although not originally intended as strict criteria, some of the components (such as the plausibility of causal links between SEP and CVD, and consistency across epidemiological and experimental evidence) are useful to consider, others are absent (such as the independence from associations with confounding factors) and others are not particularly pertinent (for example, consistency of association is unlikely if SEP effects are context specific, and specificity of effects is unlikely because SEP can causally affect many diverse aspects of health other than CVD).

[H2] The importance of demonstrating causality

Evidence-based policy requires robust evidence. This premise is true whether the exposure is behavioural, biological or social. Although a common view is that low SEP causes poor cardiovascular health[24], this conclusion is almost wholly based on correlation, that is, associations found in traditional observational studies (cross-sectional or longitudinal studies).

Any correlation between an exposure and an outcome can arise from causal or non-causal processes (Fig. 3). SEP and CVD might both be determined by shared causes of both factors ('confounders') leading to a non-causal association between them (Fig. 3a). No consensus exists on what these factors are, but they could be psychological factors (such as conscientiousness[25-27] or cognitive capability[28-31]), shared genetic[32] or developmental[33,34] factors, or the influence of other non-CVD conditions that predispose an individual to CVD and impair SEP development (such as developmental disorders)[35,36]. Different indicators of SEP can also confound the effects of others (for example, early life education could confound the effects of adult income on CVD) — a causal approach can help to identify which aspects of SEP should be targeted to reduce the risk of CVD. Additionally, CVD might impair employment, earnings or wealth accrual, which would be a form of reverse causation[35,36] (Fig. 3b).

Each scenario can have different implications for policies to reduce inequality in CVD. For instance, if associations are explained by preceding health conditions, then targeting these conditions would be expected to reduce future differences in CVD between SEP groups. In this sense, an improved understanding of causal processes can aid evidence-based policy[37,38] rather than, as has been argued[39], distracting from it. The benefits of carefully considering causality in epidemiological analyses are increasingly being recognized[40], and several frameworks and tools have become available that can help to clarify causal assumptions (such as the creation of causal diagrams[41,42] or sensitivity analyses to inform the possibility of bias[43,44]).

The credibility of hypothesized causation is improved when multiple modes of evidence with different biases agree, sometimes termed triangulation[45,46]. Associations might be consistently found in observational studies but not be replicated in randomized controlled trials (RCTs) due to bias in observational studies; the inefficacy of vitamins for the prevention of CVD is a well-known example[47,48]. However, no simple hierarchy of evidence exists. Although (well-executed and analysed) RCTs generate plausible effect estimates, their results might not be generalizable beyond the sample population, the period of observation or the intervention studied[49]. This limitation is particularly important when investigating the effects of policy experiments to change SEP — for example, by expanding welfare programmes. These interventions might be short-lived, relatively small and targeted at a selected subsection of the population (such as adults without children on particularly low incomes[50]). The observational literature suggests that any influence of SEP on CVD is likely to accumulate over the life course[6], and lifelong interventions are typically not feasible. Furthermore, RCTs might not be feasible or ethical for other reasons, particularly when studying an exposure as important and complex as SEP.

Consequently, we consider evidence from various study designs: traditional observational studies (such as cohort or cross-sectional studies), family-based studies, Mendelian randomization studies, and quasi-experimental and experimental approaches. Each design has strengths and weaknesses, which — in the context of links between SEP and CVD — is evident in how each type of study captures SEP (at what ages and for how long) (Fig. 2), the sources of bias addressed and the different inferential challenges that apply (Table 1).

We primarily examine links between SEP and CVD outcomes (morbidity or mortality) or, when these are not available in a subcategory of evidence, well-established causal risk factors

(plasma cholesterol level, hypertension, diabetes mellitus, obesity or smoking). We focus on efforts to identify the causal effect of SEP on CVD from various study designs, drawing on the extensive literature that examines the links between SEP and health (more broadly conceived) across the health and social sciences (reviewed previously[36,38,51-61]). Finally, given the considerable breadth of evidence available across health and social science disciplines, our approach is narrative rather than systematic and limited in focus to ensure tractability. We focus on the evidence of average effects rather than on mediating pathways (Box 1) and do not cover related topics in the health inequalities literature, such as the influence of ethnicity and/or discrimination, migration, unemployment or social capital on CVD. We also focus on high-income countries; future work is required to review the evidence in lower-income countries, particularly because social gradients in the risk of CVD are increasingly being observed in these countries[62,63].

[H2] Defining CVD

CVD encompasses a wide range of conditions affecting the heart and blood vessels (Fig. 4). Sequelae of CVD, such as heart failure and other conditions resulting from ischaemic, hypertensive or rheumatic heart disease, together with the consequences of stroke, are major causes of global disability, hospitalization and economic burden[64,65].

The occurrence of CVD and patterning of subtypes varies by geography, socioeconomic conditions, cultural context and time. Less traditional, but increasingly important, consequences of CVD, such as renal disease and vascular cognitive impairment and dementia, have rarely been included in studies of the causal links between SEP and CVD.

Atherosclerosis is a contributory cause of the majority of CVD. Atherosclerosis begins in early life[66] and is causally linked to multiple risk factors. The association between individual-level risk factors (such as age, sex, smoking, blood pressure, plasma lipid levels, diet and physical activity) and CVD subtypes varies[67]. Relationships between measures of SEP and subtypes of CVD also vary[15,68]. However, most studies on the associations between SEP and CVD focus on ischaemic heart disease or use composite outcomes for CVD that are dominated by ischaemic heart disease and stroke because these conditions account for the majority of the global burden of CVD-related morbidity and mortality[64]. This focus might obscure differential associations between SEP and particular subtypes of CVD (even under the questionable assumption that ischaemic heart disease and stroke are homogeneous)[15,68,69]. For example, differences in the first manifestation of CVD according to sex is at least in part explained by differential burdens of CVD subtype, and patterns of stroke in relation to risk factors differ considerably between regions of the world where haemorrhagic stroke predominates and those where ischaemic stroke predominates[70,71].

Detailed phenotyping of subclinical CVD might provide more insights into associations with SEP and facilitate its use in RCTs because it avoids the need for the long-term follow-up that is required for accrual of CVD morbidity or mortality data. Phenotyping of subclinical CVD had been used successfully in several longitudinal studies commencing in childhood[72-76]. The use of biomarkers of early disease should also reduce the risk of reverse causality, decrease the effect of competing risks between CVD subtypes or other causes of death, and reduce the bias associated with access to health care, which influences the likelihood of both diagnosis and being prescribed medication[77]. However, biomarkers of adult subclinical disease might not always be transportable to young people. For example, the utility of carotid intima–media thickness as an

indicator of atherosclerosis in adolescence has been questioned[78], and other methods, such as coronary artery calcium scoring, might have limited value in people aged <30 years[79]. The use of dynamic assessments, for example stress tests such as myocardial perfusion imaging and cardiopulmonary exercise testing accompanied by detailed imaging or the use of wearable devices that monitor responses to activities of daily living, might improve the detection of early disease in young people, but require careful validation.

[H1] Evidence linking SEP and CVD

[H2] Observational studies

Associations between SEP and CVD are context-specific; their presence and magnitude differ markedly over time[15,57,80] and according to place[57,80,81], possibly due to differences in how SEP relates to risk factors for CVD[82,83]. SEP-related differences in CVD in high-income countries were increasingly documented after the emergence of CVD as a dominant cause of morbidity and mortality in the twentieth century; mortality peaked in most high income countries in the 1950–1960s, before declining[15,84]. However, in England and Wales in the 1930s, mortality from coronary heart disease was reportedly threefold higher in professional workers than in unskilled workers[85] (see also[86]), whereas studies in later years repeatedly found that the rates of coronary heart disease were higher in lower SEP groups[1,8-15,87]. By 1978, CHD mortality from coronary heart disease was 3–6 times higher in UK civil servants with the lowest SEP than in those with the highest SEP[88]. A similar pattern was observed over a 200-year period in Sweden, with greater risks of CVD in those of low SEP evident only from the 1970s[82,89]. A change in the socioeconomic patterning of behaviours, particularly smoking, alcohol consumption, diet and exercise, are possible explanations for these findings[82,89]. Despite recent overall declines in CVD

mortality, the relative inequality in CVD mortality between SEP groups has either been stable or has widened in Europe over the period 1990 to 2014[90], and data from the USA indicate that SEP-related differences in CVD widened between 1999 to 2016–2018[3,91,92].

Comparisons of links between SEP and CVD over time are often used to motivate and inform policy. They can additionally be used to study the 'social history' of disease and thereby aid causal understanding[93]. The evolution of social inequalities following societal, scientific and technological developments can shed light on the factors that drive causal links between SEP and CVD; for example, the unequal availability of new medical technologies can lead to an initial strengthening of the causal link between SEP and CVD, which weakens as availability of the technology increases across the population. However, this approach has not been widely applied to research on CVD.

Links between SEP and CVD can also vary over the life course. Low SEP in childhood and adulthood are typically associated with CVD independently of each other and to varying degrees[83,94,95], potentially implying either a single cumulative process or multiple distinct processes operating in both early and adult life. Inequalities in CVD are also found across multiple different dimensions of SEP (such as education, occupational social class and income)[11]. It is currently unclear which (if any) is the crucial driver and, therefore, we do not know which dimension would be the most effective target for intervention. If different dimensions of SEP act together on CVD, then addressing any single dimension might be insufficient to fully reduce inequalities in CVD. In addition to family-level or individual-level indicators, measures of regional deprivation are also associated with CVD in high-income countries[11]. SEP has been implicated as a contributor to the so-called 'stroke belt', the high incidence of stroke in southeastern USA[96,97].

Traditional observational studies are the most widely available form of evidence showing links between SEP and CVD (Table 1). These studies benefit from considerable flexibility in the types of questions that can be addressed (such as investigating SEP throughout life and in different time periods or countries, or investigating the pathways that might link SEP and CVD). Although the volume of evidence is high, common biases might have been recapitulated across different studies[98]. Causal inference is generally not possible if unmeasured confounding or reverse causation has occurred. Accounting for these factors comprehensively is often challenging — for example, confounding factors are often either not measured at all, are not distinguished from mediating factors (those on the causal pathway from SEP to CVD) or are measured with a high degree of error. Evidence from the broader health[99] and social science[100] literature has repeatedly shown that findings from observational studies can be substantially biased by these processes, undermining the possibility of drawing reliable conclusions from this form of evidence alone.

Using longitudinal within-person 'fixed effects' analysis to account for confounding factors that do not change over time (for example, place of birth) is one method often used to address causal questions in the social sciences[101]. This approach analyses how observable changes in SEP within individuals are related to changes in health outcomes. Most studies use social science-oriented surveys, which often capture mental health or self-reported health outcomes. We found few papers that used this approach specifically to examine CVD; some[102,103] but not all[104] reported that SEP (income or area-level SEP) was associated with CVD. Of note, this method does not account for reverse causality or for confounding factors that vary over time (such as health shocks that influence both SEP and CVD), nor can it analyse the influence of SEP indicators that do not change across time (such as SEP at birth).

[H2] Family-based studies

Family-based study designs exploit the environmental and genetic factors that are shared by members of a family to reduce confounding. Given that family members typically share some genetic and environmental exposures (such as childhood SEP or parenting practices), family members who differ with regard to other exposures (such as education or adult income) can be used to estimate associations between adult SEP and CVD independently of confounding factors shared within families.

Studies which have compared siblings with different educational or income levels have reported associations between lower SEP and composite mortality from CVD[105,106], all-cause mortality[105,107] or risk factors for CVD[108]. Similarly, some twin-based studies have provided evidence that associations between lower education level and CVD might be causal[109,110], although one twin study did not find evidence of a strong relationship with educational attainment[111]. Family-based studies have typically found weaker associations between SEP and CVD than those reported in conventional observational studies (one-third in one study[108]), suggesting that the latter estimates might be confounded (for example, by unmeasured early-life factors).

Although family-based studies provide some evidence for causal links between SEP (education) and CVD (Table 1), they are not immune to bias[112]. Comparisons between family members are still subject to bias due to unobserved confounding that affects individual siblings rather than entire families (see the confounding factors listed in Fig. 3) — indeed, sibling-based studies can increase bias from these factors[113]. These studies are also vulnerable to ‘carryover effects’, such as when a sibling with a higher level of education influences another sibling with a

lower level of education to have improved health, thereby attenuating any differences that would otherwise have been present.

Another type of family-based design is adoption-based studies, which include twins or non-identical siblings who are raised apart. These designs can account for individual-specific factors, such as genetics, which could confound the association between family SEP and adult CVD. However, because SEP is not randomly assigned to the household, household-level and family-level confounders remain. Although adoption-based studies and studies of twins raised apart are understandably rare and typically have small sizes, they have been used to study the aetiology of non-CVD health outcomes[114,115]. We were unable to find studies of this kind that examined the causal nature of links between SEP and CVD, but we did find two studies of adoptees that reported an association between low SEP in early life and higher body mass index in adulthood[116,117].

[H2] Mendelian randomization studies

The logic underpinning Mendelian randomization studies has been described previously[118]. Briefly, Mendelian randomization exploits the random allocation of genes during gamete formation and conception to avoid the confounding and reverse causation that can bias most traditional observational studies. Genetic polymorphism acts as an instrumental variable, allowing the causal relationship between an exposure and a health outcome to be estimated, akin to an RCT. Using this method, genetically linked increases in level of education were found to be associated with a reduced risk of coronary heart disease[119]. The effect sizes were large: an additional 3.6 years of education was associated with a one-third reduction in the risk of coronary heart disease[119]. Subsequent studies have reported similar findings[120-125].

Mendelian randomization has proved understandably popular in many contexts, but has limitations, particularly when used for exposures such as SEP that are multidimensional and far-distanced from the information encoded by DNA[126,127]. Two important limitations are that genes often affect multiple bodily processes and so polymorphisms associated with SEP might influence CVD independently of SEP[32,126] (horizontal pleiotropy[128]) and that population stratification (differences in allele frequencies due to ancestral differences) and assortative mating (mating choice based on phenotypic or genetic traits)[129] can introduce confounding into genomic data by social or environmental processes. Some forms of horizontal pleiotropy can be accounted for by using multivariable Mendelian randomization (which estimates direct effects independently of other traits, such as cognition)[30], and the population stratification and/or assortative mating can be accounted for by conducting Mendelian randomization within families[122]. Multivariable Mendelian randomization studies have found associations between education level and CVD that are independent of cognitive ability[30]. A study that used within-family Mendelian randomization also found evidence for causal links between education level and CVD[122]. However, even in the absence of these problems, the effect of a polymorphism usually acts across the whole of life (in utero onwards), so inferring the influence of SEP timing on CVD is challenging. Taken together, although few Mendelian randomization studies in this context exist, they support the evidence that SEP (education in particular) is causally linked with CVD (Table 1).

[H2] Quasi-experimental studies

Quasi-experimental studies use events in which SEP differences are plausibly randomly allocated in order to estimate causal links between SEP and CVD. For example, past policies that

have allocated people to an intervention (such as longer education) or a control group (no change in education) based on arbitrary thresholds (year of birth). These studies have examined links between education and CVD[53-56] and income and CVD[36,38,59,130-132].

A number of studies have focused on education, comparing the risk of CVD in those born before or after compulsory increases in education. Previous reviews of this evidence have reported heterogeneous findings[53-56] (Table 1). When associations are present, effect sizes are often small to modest. For example, a recent meta-analysis reported that a 1-year increase in duration of education was associated with a 5% reduction in all-cause mortality, a 1% reduction in the likelihood of smoking and the risk of hypertension, but a 20% reduction in the risk of obesity[54]. Results of the individual studies varied considerably and, for some outcomes (such as hypertension), the direction of the association differed[54]. This observation might capture differences in the context in which changes in education occur. For example, in a French sample, increases to compulsory education led to worse CVD outcomes in disadvantaged subgroups[133], potentially explained by the observation that the increased time in education did not improve qualifications obtained and therefore did not benefit future socioeconomic opportunities. This finding contrasts with evidence from other settings, such as the USA[134].

A small number of studies have used changes to compulsory schooling or other sources of quasi-experimental variation (such as geographical differences) to examine how parental education links to offspring health. These are typically published in the economics literature. Some have reported that higher parental education is associated with lower levels of risk factors for CVD (such as hypertension[135] or smoking[136]). Several studies have reported positive effects of higher parental education on other non-CVD health outcomes, such as self-reported health[135,137,138], although null findings have also been reported[139].

Studies have also examined links between unexpected (plausibly randomly allocated) income losses or gains and health outcomes. The overarching pattern of these results is that mixed findings have been reported (that is, null findings alongside evidence of some beneficial or even detrimental effects)[36,38,59,130]. This situation seems to be the case for the minority of studies that examined CVD outcomes directly[131,132]. For example, a follow-up of over 400,000 lottery players in Sweden found no significant difference in CVD outcomes between those with higher versus lower subsequent income, in contrast to results from a conventional observational analysis[132]. However, the study did report favourable changes in the risk of obesity in the children of the study participants. Other quasi-experimental studies that focused specifically on children's health have mostly reported beneficial effects of parental income on child health (for example, on birth weight or general assessments of health), although CVD outcomes are not typically measured[140].

The mixed findings in this literature might reflect the challenges of comparing the processes involved in leading to correlations between SEP and CVD. A causal effect of SEP might take many years to influence CVD, whereas most quasi-experimental studies are short-term. Furthermore, the benefits of income on CVD might differ when allocated randomly compared with when part of a traditional career path. The latter might have additional non-financial benefits, such as social networks and behavioural patterns, which might improve CVD outcomes independently of income itself.

[H2] RCTs and experimental studies

Despite practical and ethical barriers to this form of research, CVD responses to SEP interventions, for example, education interventions in early life and welfare-to-work programmes

in adulthood, have been studied and reviewed[51]. Most studies focus exclusively on non-CVD outcomes that might readily change in the short term, such as mental health, self-rated health or substance use; a minority of studies examine all-cause death or risk factors for CVD such as diabetes, obesity and hypertension. Most studies have been underpowered, with mixed effects in those that were sufficiently powered. For example, a highly cited trial provided intensive early-life education interventions in a small sample of families (n = 109) who were then followed up into their mid-30s[141]. The findings (analysed by sex) showed some evidence of benefit; however, effect sizes were not consistent across sex or risk factors for CVD (obesity, blood pressure and plasma cholesterol level)[141]. When effects were found, they were sometimes unusually large (for example, a 17.5-mmHg difference in systolic blood pressure in men — more than double the typical response to antihypertensive monotherapy[142]). By contrast, another similar study of a pre-school programme found no significant overall improvement in physical health despite improvements in educational attainment and behavioural risk factors after 37 years of follow-up[143].

Another RCT, the Moving to Opportunity study, examined the outcomes of 4,498 families living in high-poverty areas; some of which were randomly assigned to move to more advantaged areas, whereas other families (controls) were not. Follow-up revealed some evidence of benefit in reducing the prevalence of extreme obesity and diabetes[144], but null findings for other relevant outcomes such as blood pressure[145]. This study highlights the challenges of generalizing from RCTs: researchers and policymakers might wish to know the effect of reducing neighbourhood deprivation on the subsequent risk of CVD at the population level, but randomization of neighbourhood deprivation is practically and ethically challenging, as well as politically inexpedient. Studies such as these provide evidence on a subtly different effect: that of

moving neighbourhoods, which could capture both the effect of reduced deprivation and other factors such as the social challenges resulting from abruptly moving to a different neighbourhood.

Overall, interpreting and extrapolating the findings from RCTs is challenging, given the lack of well-powered evidence, the likelihood of publication bias, the marked differences between the types of interventions investigated and the mixed findings obtained (Table 1). Interventions in RCTs are also generally smaller and provided for a shorter duration than other SEP 'exposures' in which we might be interested (such as differences in household earnings spanning years or even decades). This limitation is not to argue that future interventions are not worthwhile or that RCTs should not be undertaken; instead, we recommend the inclusion of CVD-related outcomes in well-powered future trials to provide more evidence. This approach could be complemented by the use of linked health records to enable long-term follow-up and to analyse the effects on CVD outcomes in trials that were initially focused on other social or health outcomes.

[H1] Effects of COVID-19 on SEP and CVD

A notable finding reviewed above is the context-specific nature of links between SEP and CVD. The direction and strength of the association seems to depend on time and place. This observation indicates that causal processes are context specific and are subject both to broader patterns of societal change and to policy intervention. As we continue to make sense of historical evidence on links between SEP and CVD in the pre-COVID-19 pandemic era, the vast disruptions caused by COVID-19 prompt reconsideration of the causal processes in this new context.

Various causal processes could have been affected by COVID-19, either associated with the infection itself or associated with societal measures to control the pandemic (Fig. 5). First, infection was more likely to occur, and was more likely to be severe, in those of lower SEP[146,147]. A similar SEP gradient has been observed in historical influenza pandemics from 1918–1920 through to 2009[148]. Although vaccination reduces susceptibility to infection, uptake has been poorer in those of low SEP, further exacerbating the risk of disease[149]. COVID-19 increases the risk of subsequent CVD; both arterial and venous events are markedly elevated in the immediate aftermath of infection, and the incidence remains elevated up to 1 year after infection[150]. The same was also found in historic pandemics: the 1918–1920 influenza pandemic was associated with an immediate excess mortality from 'organic heart disease', accounting for up to ~50% of excess deaths in the later epidemic[151]. Recent influenza outbreaks (2006–2012) have been associated with a more modest 2–7% increased risk of CVD[151,152]. Taken together, this evidence suggests that a new causal pathway linking SEP and CVD (mediated by COVID-19) might have strengthened the association between SEP and CVD.

Similarly, broader societal responses to the pandemic might have introduced new links between SEP and CVD, including modification of existing causal links between SEP and CVD (red arrow in Fig. 5). Specifically, COVID-19 might increase the risk of CVD to a greater extent in those of low SEP due to both increased COVID-19 severity and a higher prevalence of pre-existing comorbidities[153].

Second, the societal responses to the pandemic (such as the effects of lockdown) seem to have particularly affected those of lower SEP, especially in terms of job losses and adverse educational effects. Mental and physical health were also likely to be affected by lockdown, either directly or via the socioeconomic effects or health-care disruptions. These health

consequences could worsen the SEP of some individuals, leading to new indirect pathways linking SEP and CVD, including associations due to confounding factors.

Third, a ‘reverse causation’ pathway might have emerged or been strengthened: CVD might have increased the risk of COVID-19, because of either heightened exposure due to hospital admission or increased susceptibility as a consequence of comorbidities. These processes might have worsened the SEP of affected persons, with acute illness or persistent symptoms altering labour force or educational engagement.

The opportunity to test these processes is aided by the substantial volume of data collected during and after the pandemic. Never has such detailed information been available across the course of a global pandemic. The continued follow-up of observational studies will enable tests of the long-term changes in association, while new forms of large-scale administrative data might provide sufficient power for quasi-experimental approaches.

[H1] Conclusions

Findings from traditional observational, family-based and Mendelian randomization studies suggest that causal links exist between SEP and CVD. These findings support the generally well-accepted view among epidemiologists, the broader public health community and clinicians. However, mixed and often null results exist from quasi-experimental and experimental studies, supporting the scepticism towards causal claims that is typically shown by economists and quantitative social scientists, despite fewer studies using these designs. Further research using quasi-experimental and experimental studies is necessary to improve our understanding and inform translation, given their clear link with future interventions[154].

All study designs have limitations — particularly when examining an exposure as complex as SEP — so evidence from various divergent study designs must be considered (as process known as triangulation). Few studies have sought to use multiple approaches together in the same population[155]. High-quality descriptive evidence is likely to remain valuable, given the practical and inferential limits of alternative approaches. Links between SEP and CVD are likely to be context-specific, so documenting links between SEP and CVD in different contexts (time and place) remains important, as does explaining when and why these differences emerge.

The linked goals of understanding the causal links between SEP and CVD, their contextual dependence and their remediation by policy interventions transcends traditional disciplinary boundaries, necessitating a detailed understanding of the nature of society, its change over time and of different phenotypes of CVD. Close collaboration between health and social scientists is required to better inform the aetiology of disease and public health translation.

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Acknowledgements

The authors thank the following individuals for helpful comments on an earlier version of this manuscript: George Davey Smith (University of Bristol, UK), Alice Goisis (University College London, UK) and Emilie Courtin (London School of Economics, UK).

Author contributions

The authors contributed substantially to all aspects of the article.

Competing interests

The authors declare no competing interests.

Peer review information

Nature Reviews Cardiology thanks the anonymous reviewer(s) for their contribution to the peer review of this work.

Key points

- Socioeconomic disparities in cardiovascular disease (CVD) remain an important public health challenge; however, the causal nature of this association remains elusive.
- Understanding causality is crucial for robust evidence and informed policy.
- Evidence from traditional observational, family-based and Mendelian randomization studies supports the generally well-accepted view that low socioeconomic position (SEP) causally influences CVD.
- Results from quasi-experimental and experimental studies are mixed and often null, with fewer available studies; more evidence is required to improve causal understanding and inform policy.
- No simple hierarchy of evidence exists for an exposure as complex as SEP; each study design has value and a need remains both for more evidence across each study design and for studies that triangulate across multiple designs.
- High-quality descriptive studies remain valuable to document associations and examine their contextual dependence; for example, the COVID-19 pandemic might have altered causal processes linking SEP and CVD.

Table 1 | SEP inequalities in CVD in high-income countries: findings across different domains of evidence

Evidence domain	Evidence of causal effect of SEP on CVD?	Volume of evidence in support of causal effect	SEP captured	Key inferential and translational concerns
Observational studies[a]	Yes	High	Multiple dimensions across the life course (parental, own SEP)	Confounding, reverse causation, other biases (such as selection and attrition)
Family-based (sibling or twin comparison) studies	Yes	Low	Typically, own SEP in adulthood (not parental); existing studies largely use education attainment	External validity (twin-based studies in particular), bias specific to within-family designs
Mendelian randomization studies	Yes	Low	Total (lifetime) exposure to genetic liability to social disadvantage (SEP); existing studies use education attainment	Pleiotropy (genes influencing CVD through pathways other than SEP), confounding by environmental factors which correlate with genes, for example, due to population stratification or assortative mating
Quasi-experimental studies	Mixed	Low	Change in a dimension of SEP (typically narrow component of total SEP gradient)	Generalizability and transportability to the wider population or other samples
Randomized controlled trials and experimental studies	Mixed	Very low	Typically, short-term change in SEP	Generalizability and transportability to the wider population or other samples

Evidence is largely limited to high-income countries. Not all inferential concerns are listed (for example, randomized controlled trials might be subject to bias when randomization fails or when assumptions of no interference are invalid. The volume of evidence was categorized based on the numbers of studies specifically examining cardiovascular disease (CVD) outcomes using different underpinning data sets, and the extent to which different dimensions of socioeconomic position (SEP) had been examined. [a]Refers to traditional epidemiological observational studies (such as cross-sectional or longitudinal studies).

Fig. 1 | Hazard ratios associated with various risk factors for CVD death. Unadjusted (part **a**) and mutually adjusted (part **b**) hazard ratios associated with various risk factors for death from cardiovascular disease (CVD). Individuals in a low compared with a high socioeconomic position (occupation) had a 1.52-fold (52%) higher risk of CVD death before adjustment, and 1.29-fold (29%) higher risk of CVD death after adjustment for all other risk factors. These estimates are from a large (n = 1.7 million) observational study[1]. This highly cited study provided precise estimates of association and valuable descriptive evidence; however, as with all observational studies, these estimates are potentially biased by unobserved confounding and reverse causation. Confounders adjusted for were age, sex, ethnicity and marital status.

Fig. 2 | SEP across the life course. a, Different study designs typically capture socioeconomic position (SEP) at different points of the life course. Traditional observational studies (such as cohort studies) capture multiple dimensions across the life course, whereas other study designs typically test the effects of a narrower set of dimensions (for example, education in family-based and Mendelian randomization studies) or a short-term change in SEP at particular points in life (quasi-experimental and experimental studies) on the risk of cardiovascular disease. Mendelian randomization studies have examined genetic liability to education, but the effect of genetic polymorphisms usually acts across the whole of life (in utero onwards), so inferring the influence of SEP timing on the risk of cardiovascular disease is challenging. **b**, Various dimensions of SEP occur at different stages from childhood to older ages. Panel b adapted from REF.[16,17].

Fig. 3 | Associations between socioeconomic position and cardiovascular disease can be generated by causal links or by confounding or reverse causation. a, Confounding factors

(that is, shared causes of both) could lead to a spurious non-casual association between socioeconomic position and cardiovascular disease. **b**, Reverse causation could lead to a situation in which cardiovascular disease (including its preclinical manifestations) impairs future socioeconomic position. Note that other processes (such as collider bias), not shown here, could also occur leading to spurious associations between socioeconomic position and cardiovascular disease or a biased estimate of this association.

Fig. 4 | Cardiovascular disease outcomes. An illustration of the diversity of cardiovascular diseases, including some often-overlooked consequences, such as cognitive impairment, dementia and renal disease. The wide range of conditions might be affected by socioeconomic position to varying degrees, but studies typically report effects on composite cardiovascular disease outcomes.

Fig. 5 | Links between the COVID-19 pandemic, SEP and CVD. Both contracting coronavirus disease 2019 (COVID-19) (part **a**) and the societal responses to COVID-19 (part **b**) could alter the causal processes linking socioeconomic position (SEP) and cardiovascular disease (CVD).

Box 1 | Challenges to understanding the pathways linking SEP and CVD

Identifying factors (mediators) that lie on the causal pathway between socioeconomic position (SEP) and cardiovascular disease (CVD) can help to build causal understanding and provide insights to aid intervention. Among individuals exposed to lower SEP, intervening on the mediating factors could help to lower their risk of CVD. Therefore, the discovery of mediating factors provides an opportunity to intervene to reduce CVD inequalities in addition to targeting SEP itself (such as through education or income-support programmes). These mediators might be behavioural (such as diet, smoking and physical activity), psychological (such as stress) or biological (such as atherosclerotic plaque formation, endothelial function, autonomic function or inflammation) in nature. However, well-founded concerns exist in the social determinants of health literature that targeting mediating factors (such as interventions to change individual behaviour) is considerably more politically expedient than intervening on SEP itself. Accordingly, the former tends to take prominence (so-called lifestyle drift[156]). Additionally, interventions targeted at individual behaviour change might inadvertently widen inequalities, because they can disproportionately benefit those with the most resources (high SEP groups)[157,158].

Mediation analysis presents its own challenges for obtaining unbiased estimates, even in RCTs. Adding a third variable (the mediator) to a model adds a surprising number of additional complications. If the exposure–outcome association is already biased, the estimates of mediated and unmediated effects will be biased too. Even when the exposure–outcome association is causal, adding mediators into analyses can generate problems. A prosaic reason is measurement: poorly measured mediators will lead to the underestimation of mediated effects and the overestimation of unmediated effects. For example, diet and physical activity are likely partly to

mediate the link between SEP and CVD but are notoriously difficult to measure accurately. Another reason is that identifying the specific effect of different mediating factors is difficult due to their interrelatedness and the possibility of exposure–mediator or mediator–outcome confounders. Ideally, separate unconfounded sources of variation for both SEP and mediators could be used to clarify pathways to CVD[159,160]. However, identifying these sources is challenging, necessitating a reliance on observational methods and their associated complications. The problems of mediation analysis and their possible solutions have been discussed previously in more detail[161].

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