



K O N I N K L I J K E N E D E R L A N D S E
A K A D E M I E V A N W E T E N S C H A P P E N

DISCUSSION PAPER

HEALTH INEQUALITIES an Interdisciplinary Exploration of Socioeconomic Position, Health and Causality



Amsterdam, November 2018

FEAM/ALLEA Committee on Health Inequalities

Reporters: Johan Mackenbach and Jean Philippe de Jong (KNAW)

CONTENTS

Preface	3
1 Introduction	4
1.1 The impact of health inequalities	4
1.2 Scientific uncertainties concerning health inequalities	4
1.3 The role of academies of science	5
1.4 Scope of this discussion paper	6
1.5 Outline of this discussion paper	7
2 Is there a causal effect of socioeconomic position on health?	8
2.1 Conceptual introduction	8
2.1.1 Why is this an important question?	8
2.1.2 Possibility of confounding by third factors	9
2.1.3 The importance of a life-course perspective	10
2.2 Methodological requirements	11
2.2.1 Why is it difficult to establish causality?	11
2.2.2 Practical approaches to assessing a causal relationship	13
2.2.3 Differences between (sub)disciplines	14
2.3 Inventory of empirical evidence	15
2.3.1 Evidence of a causal effect of education on health	15
2.3.2 Evidence of a causal effect of occupational class on health	16
2.3.3 Evidence of a causal effect of income on health	17
3 What mediates the effect of socioeconomic position on health?	20
3.1 Conceptual introduction	20
3.1.1 Why is this an important question?	20
3.1.2 Definition of a mediator	21
3.1.3 Mediators versus moderators	21
3.1.4 Possibility of reverse causation and confounding	23
3.2 Methodological requirements	23
3.2.1 How can mediation be demonstrated?	23
3.2.2 Mediation analysis	24
3.3 Overview of empirical evidence	27
3.3.1 Early childhood environment	28
3.3.2 Material living conditions	28
3.3.3 Social and psychological factors	29
3.3.4 Health-related behaviours	30
3.3.5 Health care	31
4 Conclusions and recommendations	32
4.1 Is there a causal effect of socioeconomic position on health?	32
4.2 What mediates the effect of socioeconomic position on health?	33
4.3 Recommendations	34
Annex 1: FEAM/ALLEA Committee on Health Inequalities	36
Annex 2: FEAM/ALLEA symposium programme	37
References	39

PREFACE

At the start of the 21st century, all European societies are faced with substantial inequalities in health between socioeconomic groups. Despite decades of research into health inequalities there is still no consensus amongst scientists on some of the underlying questions: to what extent are health inequalities caused by socioeconomic factors – or the other way around – and what underlying mechanisms are most important: genetics, behaviour, living conditions, or health care? This makes it difficult to mitigate these health inequalities. One important factor underlying the lack of consensus is the fact that researchers from various disciplines, be they epidemiologists, sociologists, geneticists or economists, use very different methods.

The Royal Netherlands Academy of Arts and Sciences (KNAW) is committed to help policy makers in making optimal use of the scientific evidence base. The KNAW therefore chairs and supports the ALLEA-FEAM Scientific Committee on Health Inequalities in writing a discussion paper on the various methods for studying health inequalities. This discussion paper served as input for an ALLEA/FEAM/KNAW symposium, held in May 2018 in Amsterdam, that served as a platform for interdisciplinary discussion. The KNAW strives to further stimulate this interdisciplinary collaboration on a European level and to help reach consensus on how health inequalities arise and what can be done to address them.

Wim van Saarloos

President of the Royal Netherlands Academy of Arts and Sciences

1 INTRODUCTION

1.1 The impact of health inequalities

At the start of the 21st century, all countries are faced with substantial differences in health between socioeconomic groups within and between their populations. People with a lower level of education, a lower occupational class, or a lower level of income die on average at a younger age, suffer more often from (chronic) physical and mental disease and disabilities and experience a higher prevalence of many different health problems. This leads to disparities between socioeconomic groups of more than 10 years in life expectancy at birth, and up to 20 years in healthy life expectancy (the number of years that a person can expect to live in good health) (1, 2). For the countries of the European Union it has been estimated that there are more than 700,000 excess deaths per year, and 33 million extra cases of ill health, as compared to the hypothetical situation in which everyone would have a high socioeconomic position (3).

These health differences have been recognized as a major challenge for public policy, for three main reasons. First, the higher morbidity and mortality rates among individuals with a lower socioeconomic position are an obstacle for health progress at the national level. Or, seen from a more positive angle: higher morbidity and mortality rates among individuals with a lower socioeconomic position indicate that part of their health burden could in principle be prevented or ameliorated by public health and health care interventions, and that these individuals thus constitute a high-risk group that could be targeted by public policy in order to improve health on a national level.

Second, the excess health problems experienced by individuals with a lower socioeconomic position lead to a significant loss in social and economic welfare, both on the level of the individual and the level of the population. People who suffer from health problems more often have difficulties working and more often have to rely on social security, thus threatening economic performance. Health losses among lower socioeconomic groups account for 20% of the total costs of healthcare and 15% of the total costs of social security benefits in the EU as a whole (3).

The third reason why health differences are considered a major challenge for public policy is that they can be considered a form of social injustice, which is why they are often referred to as 'health inequities' (4). People with a lower socio-economic position, who already have to face many social and economic challenges, also more frequently experience health related problems, which can deteriorate their socioeconomic position even further. This means that groups with a low socio-economic position can become trapped in a vicious cycle.

In response to the challenge of health inequalities, many countries have made reduction of health inequalities a priority in their health and social policies, even setting quantitative targets for reducing these inequalities. For example, a target to reduce health inequalities by 25% was introduced by the World Health Organization in 1985, and renewed in 1998. Several European countries, such as England, Finland and Lithuania, have adopted national targets for the reduction of socio-economic inequalities in mortality (5). Despite these commitments, health inequalities have persisted, and have even widened on some measures over the past decades (6).

1.2 Scientific uncertainties concerning health inequalities

Effective policy-making requires a proper understanding of what drives these health inequalities, and research over the past 30 years in Europe and beyond has produced important insights into the factors and mechanisms underlying them. Reviews of available evidence, with the explicit aim to support policy-making, have been published, e.g. by the WHO Commission on Social Determinants (1) and the European Review on Health Inequalities (2), and some countries have already taken action based on this evidence.

However, new methodological insights have come to the fore in recent years, and empirical evidence based on these new methodological approaches is starting to emerge which questions previous findings. The emerging uncertainty concerns two crucial questions:

- 1 Is there a causal effect of socioeconomic position on health?
- 2 What mediates the effect of socioeconomic position on health?

There is currently no scientific consensus on the answers to these questions, nor on how to answer these questions. However, the answers are relevant from both a scientific and a policy point of view. For example, it has been argued that a reduction of income inequality is an important means to mitigate health inequalities. However, whether or not this would indeed be an effective policy to reduce health inequalities depends largely on whether or not income exerts a causal influence on health - an issue on which studies with different research methodologies provide different answers as we will show in this discussion paper. Other examples where scientists disagree with respect to the causal status of factors are smoking (according to some scientists, smoking explains up to half of all inequalities in mortality, whereas others argue that studies demonstrating such large effects do not adequately take into account other factors) and access to health care (according to some scientists, inequalities in access to health care magnify existing health inequalities, whereas others argue that "it is a mistake to see lack of aspirin as the cause of fever": a lack of health care can never be the actual *cause* of health problems in the population).

The lack of scientific consensus on causal mechanisms underlying health inequalities is partly due to a lack of consensus on research methodologies. 'Classical' experimental methods, which are useful in clinical settings, can only be applied rarely in this area, for obvious ethical and practical reasons. This means that explanatory research has to rely almost exclusively on observational methods. However, there are many different methodologies available to study observational data, and there is limited consensus between disciplines on the relative merits of different methods. For example, as we will discuss later, the cohort study - a popular study design used by epidemiologists working in this area - has been criticized for its inability to identify *causal* effects of socioeconomic position on health outcomes. Also, conventional statistical approaches used to assess the contribution of specific risk factors to health inequalities have been criticized for their susceptibility to various sources of bias. On the other hand, newer approaches to assess causality, advocated by economists, such as instrumental variables and regression discontinuity designs, have been criticized too: for not leading to generalizable results and inability to fully capture the effects of social inequality.

There is thus a clear need to critically review the available evidence on the explanation of health inequalities and to strive for interdisciplinary consensus on the methodological challenges faced by this type of research, based on a common theoretical framework for the understanding of health inequalities.

1.3 The role of academies of science

Resolving the uncertainties mentioned above is highly relevant for all countries in Europe and beyond, and thus requires input from Europe's best scientists. FEAM (Federation of European Academies of Medicine) and ALLEA (All European Academies - European Federation of Academies of Sciences and Humanities), which together span a broad spectrum of relevant disciplines (including epidemiologists, public health researchers, medical sociologists, health psychologists, health economists and political scientists), have therefore decided to take up the challenge of reviewing existing scientific literature on mechanisms underlying health inequalities and the methodological issues involved. In order to build a basis for interdisciplinary consensus on causes and remedies of health inequalities FEAM and ALLEA have appointed a multidisciplinary committee (Annex 1). The committee is supported by the Royal Netherlands Academy of Arts and Sciences.

The committee has envisaged a project in two steps. In step one the committee reviews the scientific literature in order to chart the main areas of scientific consensus and disagreement. The results from this review are presented in this discussion paper, which served as input for an international symposium on 24 May 2018 in Amsterdam, bringing together key opinion leaders from various scientific backgrounds. The programme of this symposium can be found in Annex 2. The symposium aims to kick-start the much-needed interdisciplinary discussion about these issues, which will be further elaborated on in the second step of the project.

In next step of the project, input and support from all member academies of FEAM and ALLEA should be sought in order to strive for interdisciplinary consensus and to draft a report on mechanisms underlying health inequalities and proper methodologies to study them. In addition, the report should review existing policy recommendations in the light of these new insights. The report should be aimed at researchers studying health inequalities and at national and European policy-makers interested in reducing health inequalities.

1.4 Scope of this discussion paper

This discussion paper is solely intended as input for interdisciplinary discussion, and does not in any way reflect the final opinions of the authors, the committee overseeing the preparation of the paper, or the academies under whose umbrella it has been prepared. A previous version of this paper has been discussed at an international symposium, held on 24 May 2018 in Amsterdam. A report of this symposium is available [at the ALLEA website](#).¹ The current discussion paper has been slightly modified to remove obvious errors or omissions, and to take away some misunderstandings which came to light during the symposium. We hope that this discussion paper, together with the report of the symposium, will serve as a useful starting-point for phase 2 of this project, in which we intend to hold more in-depth discussions on the issues raised in this paper.

Our objective is to improve the scientific understanding of health inequalities, in order to strengthen policy making aimed at reducing health inequalities. In the mean-time, we would like to stress that policy-making can never be based on 'perfect' evidence, and that the methodological issues highlighted in this discussion paper should thus not be seen as an 'excuse for inaction'. Indeed, much of the current evidence is solid enough to serve as entry-points for actions aimed at reducing health inequalities. Moreover, implementing policies based on the available evidence, and then evaluating what works and what not, is a very potent source of knowledge on understanding health inequalities, and can be used to improve those very policies.

This discussion paper has several limitations. First, we have focused on quantitative research methods and have largely ignored qualitative approaches to identify the causal pathways between low socioeconomic status and ill-health, such as anthropological or biographical studies of people living in poverty. These studies are also potentially very relevant, not only for elaborating the causal pathways (7) and identifying targets for intervention, but also by providing insights in the lived experiences of people in disadvantaged circumstances. These insights are also necessary for building community-based strategies for tackling health inequalities in which they have an active role (8). However, the committee did not have the resources to properly evaluate qualitative research methodologies.

Second, our review of the empirical evidence is limited to countries with relatively high incomes. It is likely that the role of various mechanisms and factors differs between high income countries and low and middle-income countries, in which absolute poverty is far more common. Within the European setting, this may apply particularly to countries in Eastern Europe, where the role of material disadvantage in generating health inequalities may be more pervasive than in Western Europe.

Third, in reviewing mechanisms that link socioeconomic position to health we have paid relatively little attention to biological mechanisms. This is not because they are unimportant, but because there is less disagreement on the methodology for studying these final steps in the causal pathways between socioeconomic position and health.

Finally, this discussion paper focuses on 'health inequalities', defined as systematic differences in the occurrence of health problems between people with a lower and a higher socioeconomic position as indicated by their level of education, occupational class, income or similar characteristics. So, this discussion paper does not deal with other social determinants of health, such as ethnicity and migrant status, or aggregate socioeconomic factors such as neighbourhood deprivation or national income.

¹ https://www.allea.org/wp-content/uploads/2018/11/Health_Inequalities_Symposium_Report.pdf

1.5 Outline of this discussion paper

This discussion paper aims to summarize recent methodological insights into how best to approach the two crucial questions highlighted above, and then to review the existing evidence in the light of these new methodological insights.²

Chapter 2 focuses on the first question: is there a causal effect of socioeconomic position on health? We take stock both of recent insights into the validity of available research methodologies and of the available empirical evidence.

Chapter 3 focuses on the second question: What mediates the effect of socioeconomic position on health? Here again, we take stock both of recent insights into the validity of available research methodologies and of the available empirical evidence.

Chapter 4 summarises preliminary conclusions, mainly in the form of questions to be addressed in the next step of this project, and makes recommendations for how this next step can be conducted.

² This report draws heavily on a draft book-in-preparation (Mackenbach JP. Health inequalities; persistence and change in modern welfare states. Oxford University Press, 2019) and on a published book chapter (ref. 9. Mackenbach JP. Socioeconomic inequalities in health in high-income countries: the facts and the options. In: Detels R, Gulliford M, Karim QA, Tan CC, editors. Oxford Textbook of Global Public Health. 1. Oxford etc.: Oxford University Press; 2014.)

2 IS THERE A CAUSAL EFFECT OF SOCIOECONOMIC POSITION ON HEALTH?

2.1 Conceptual introduction

2.1.1 Why is this an important question?

Starting with the publication of the Black report (10), which brought health inequalities back into the focus of public health research, the question whether ‘causation’ (i.e., socioeconomic position influences health) or ‘selection’ (i.e., health influences socioeconomic position) was the more important mechanism involved in generating health inequalities, has been central to debates about the explanation of socioeconomic inequalities in health (11, 12).³ In support of these debates, many studies have been conducted to disentangle the two directions of effect, and most of these studies have found both ‘causation’ and ‘selection’ to play a role (13).

There are several reasons why this issue occupies such a central place. The first is that if socioeconomic position causally determines health, this opens up a whole array of potential countermeasures against health inequalities, such as increasing the educational achievement of those at the bottom of the social hierarchy, efforts to reduce income inequalities, and other ‘egalitarian’ social and economic policies (1). By contrast, if there is no causal relationship between socioeconomic position and health, such redistributive policies are unlikely to be effective as far as health outcomes are concerned.

A second reason is that ‘selection’ is often considered to be less of a problem for public policy than ‘causation’, because health inequalities due to ‘causation’ mechanisms are perceived to be more unfair, particularly by those who feel that the underlying socioeconomic inequalities are already unfair in themselves (4). The fault lines in this debate are therefore to some extent ideological, with ‘causation’ explanations being more popular among those leaning towards the political left, and ‘selection’ explanations more popular among those with a more conservative or economically liberal outlook (14)(p. 109). Unfortunately, the polarization of this debate has not always been conducive to reaching nuanced conclusions.

Although whether or not health inequalities are due to a causal effect of socioeconomic position on health is thus an important question, it is not equally relevant in all contexts. If what matters is the total burden of problems among people with a lower socioeconomic position, it may not be relevant that some of these problems arise from ‘selection’ instead of ‘causation’. For example, some countries are discussing whether they should differentiate their statutory pension age by socioeconomic position, because of the substantial differences in remaining life expectancy at age 65 (15). For this discussion it does not really matter whether the differences are due to ‘causation’ or ‘selection’, because in either case people in lower socioeconomic groups have fewer remaining life-years at 65.

Furthermore, ‘selection’ mechanisms have their own relevance for policy: if these mechanisms aggravate the problems of people with a low socioeconomic position, we may want to find ways to counter these mechanisms, for example by removing barriers to work for people with chronic diseases (16). To avoid the impression that explanations in terms of health-related selection are not causal mechanisms, we will often use the term ‘reverse causation’ to denote them.

Finally, since the Black report introduced the distinction between ‘causation’ and ‘selection’, it has become clear that these are not two mutually exclusive mechanisms, but that both mechanisms are likely to interact over the life-course, as we will describe more extensively in par. 2.1.3.

³ For economists/econometricists, ‘health-related selection’ falls under the heading of ‘simultaneity’: due to a loop of causality between socioeconomic position and health, the presumed dependent variable actually affects the independent variable, potentially leading to ‘simultaneity bias’.

2.1.2 Possibility of confounding by third factors

In addition to 'causation' and 'selection' there is another possible explanation for the association between socioeconomic position and health: 'confounding' by third factors which are related to both socioeconomic position and health, but are not on the causal pathway linking socioeconomic position to health or vice versa⁴ (17)(p. 129-134).

Please note, however, that not all other factors involved in generating health inequalities can be seen as confounders: to the extent that health-related behaviour (such as smoking or diet) or the living environment (such as housing and working conditions) are determined by a person's socioeconomic position, they are 'mediators' and not 'confounders'. (On mediation, see chapter 3.)

Confounding can certainly occur, because social mobility, and thus a person's socioeconomic position, may be dependent on individual characteristics that are *also* determinants of good or bad health. Examples of possible confounders are health-related behaviours (if they are formed before a person attains his or her socioeconomic position, and thus cannot mediate the effect of socioeconomic position on health) and cognitive ability, coping styles, control beliefs, and personality traits (18, 19).

For example, childhood obesity can affect social mobility later in life due to discrimination during recruitment for jobs or promotion, and can also lead to diabetes and health problems in later life. This may then contribute to a higher prevalence of both obesity and diabetes in lower occupational classes, without lower occupational class being the *cause* of diabetes (20, 21). Another example is excessive alcohol consumption, which may stand in the way of upward occupational mobility and may even lead to loss of income (22), while also leading to health problems in later life, thus producing a non-causal association between low occupational class and low income on the one hand, and health problems at the other hand.

Potentially equally important as confounders are personal attributes such as cognitive ability, coping styles, control beliefs, personality, and bodily and mental fitness. These personal attributes influence educational and occupational achievement, and at the same time partly determine later health, either directly or indirectly through health-related behaviours such as consumption and exercise patterns and use of health services (23).

To the extent that these factors are not determined by the person's current socioeconomic position, the resulting association between current socioeconomic position and health can be seen to be 'confounded' by such third factors. This may indeed be the case, because many of the personal attributes just mentioned were already formed before the person arrived at his or her current socioeconomic status. Cognitive ability and personality are largely formed before adulthood, and some health-related behaviours (e.g., smoking) are also already adopted during adolescence.

Although it is important to correct for confounding when studying the effect of socioeconomic position on health, the underlying phenomena (e.g., the concentration of certain personal attributes in lower socioeconomic groups) may be important in themselves, and relevant to policy making. For example, knowledge about differences in cognitive ability may be relevant for the design of intervention programs in terms of tailoring them to specific groups or targeting these groups (24). Furthermore, from an ethical perspective it has been argued that a genetically determined disadvantage should be compensated by society in order to achieve true equality of opportunity (25).

A higher prevalence in lower socioeconomic groups of genetic factors that predispose to ill-health should also be seen as an instance of 'confounding' (Box 2.1).

⁴ Epidemiologists label such situations 'confounding', whereas economists call the bias resulting from not controlling for such confounders 'omitted variable bias'. 'Simultaneity bias' and 'omitted variable bias' are the two important causes of what economists/econometricians call 'endogeneity', a technical term referring to the problem that the independent variable is correlated with the error term in a regression analysis. Social epidemiologists, in recognition of the mechanism through which these personal attributes get sorted across socioeconomic groups, sometimes use the term 'indirect selection'.

Box 2.1 Genetic factors as possible ‘confounders’

A higher prevalence in lower socioeconomic groups of genetic factors that predispose to ill-health should also be seen as an instance of ‘confounding’, because a person’s genotype temporally precedes his or her socioeconomic position. But how would a higher prevalence of such genetic factors in lower socioeconomic groups arise? Here again we need to consider social mobility and selection mechanisms (26).

An association between socioeconomic status and a certain genotype is most likely to arise when that genotype affects social mobility, through an effect on the likelihood of getting a disease that affects social mobility (e.g., mental health problems that stand in the way of educational achievement or upward occupational mobility), through an effect on health-related behaviour that affects social mobility (e.g., predisposition to alcohol addiction), or through an effect on personal attributes that affect social mobility (e.g., cognitive ability or personality traits) (26).

Such selection effects may occur in each new generation, but may also lead to intergenerational transmission of disadvantage. Genetic factors predisposing to ill-health that have contributed to the low socioeconomic position of parents may be transmitted to their children, and could make it even more difficult for these children, on top of their disadvantaged social conditions, to reach a higher socioeconomic position than their parents.

In genetics, the relative contributions of ‘genes’ and the ‘environment’ in generating differences in ‘phenotype’ have been a long-standing issue for discussion. It is becoming increasingly clear that often both play a role, in various combinations and interactions. Two forms of ‘gene-environment interplay’ can be distinguished: ‘gene-environment correlation’ (i.e., genetic factors occur more frequently in some environments than in others) and ‘gene-environment interaction’ (i.e., genes determine the effects of the environment, or the environment influences gene expression) (27).

In the case of health inequalities, ‘gene-environment correlation’ would exist if certain genotypes are more frequent in lower or higher socioeconomic groups. As mentioned above, this may give rise to confounding if these genotypes also predispose to good or bad health. ‘Gene-environment interaction’ would exist if people with certain genotypes are more sensitive than others to the health effects of low or high socioeconomic status. This does not give rise to confounding, but is closer to mediation, and will therefore be further discussed in chapter 3.

A discussion of the role of genetics in explaining health inequalities also needs to consider ‘epigenetics’, i.e. heritable changes in gene function that do not involve changes in the DNA sequence, e.g. due to methylation of DNA. Such changes may be the result of various exposures, such as smoking, nutrition, psychosocial stress and environmental toxicants, and may play a role in the generation of health inequalities and their intergenerational transmission (28, 29). Epigenetic mechanisms would again be an instance of mediation, not of confounding.

2.1.3 The importance of a life-course perspective

In par. 2.1.1 and 2.1.2 we introduced three types of explanation for the association between socioeconomic position and health: ‘causation’, ‘reverse causation’ and ‘confounding’. These explanations all imply a focus on measuring the effect of people’s socioeconomic position at one point in their adult lives on health outcomes later on in life. Such a focus on discrete episodes in life allows us to make clear distinctions between various factors and their effects.

However, reality is more complex. Individuals go through several transitions between socioeconomic positions during their life-course. For example, an individual may start out from a situation that is largely determined by their parents’ socioeconomic position and their school environments, and may then, dependent on their own educational achievement, enter the labour market and move through various occupations and varying levels of income during their adult life until they reach retirement. During each of these life stages health problems may be both a consequence of their previous and current socioeconomic position, and a determinant of their current and future socioeconomic position. Moreover, both health and

socioeconomic position may be determined by personal attributes that may themselves be consequences of socioeconomic conditions in previous stages of life.

It has therefore been argued that for a proper understanding of health inequalities a life-course perspective is necessary. Such a life-course perspective sees the higher rates of illness and premature death among adults and elderly persons in lower socioeconomic groups as a cumulative result of socially patterned exposures acting at different stages of the life-course, and at the same time as possible determinants of changes in socioeconomic position (30). A life-course perspective has proven to be very useful for integrating different pieces of evidence.

The simplest conceptual model for life-course influences is that of ‘accumulation of risk’. Different forms of material and immaterial disadvantage tend to cluster in the same persons, with one disadvantage increasing the likelihood of another one at a later point in time, and health disadvantage arising as a result of cumulative social disadvantage (31, 32). Such accumulation models can incorporate both ‘selection’ and ‘causation’ mechanisms, because a low socioeconomic position in one stage of the life-course may translate into a health disadvantage in the next, which may then lead to a still lower socioeconomic position some years later, and so on (33). Accumulation of risk, which is often seen as a simple addition of risks, can in fact, due to interactions between risk factors, result in a multiplication of risks, leading to considerable increases in risk.

Life-course models may also incorporate ‘critical periods’: time windows of exposure that are particularly important for health at later ages. One possible example of a ‘critical period’ is intra-uterine life, as elaborated in the ‘foetal origins of adult disease’ hypothesis (34). Another is childhood: the child’s physical, cognitive and emotional development is strongly influenced by socioeconomic circumstances, and in its turn influences both adult socioeconomic position and adult health in many ways (“the long arm of childhood”) (35).

Circumstances in early life also set up a pattern of social learning, which may, for example, generate a sense of powerlessness, which may be reinforced by other individuals in the social network who have been similarly disadvantaged and socially excluded, sometimes over generations (36). Such intergenerational transmission of personal, social and health disadvantage may thus contribute to the persistence of health inequalities over time.

While application of a life-course perspective does not take away the need for an accurate measurement of the discrete steps involved in generating health inequalities, it does caution against broad conclusions based on studies narrowly focused on single steps in the causal pathways between socioeconomic position and health.

2.2 Methodological requirements

2.2.1 Why is it difficult to establish causality?

There are many definitions of ‘causality’. Here we will build on the common sense notion that ‘causality’ is “what links one state or process [e.g., low socioeconomic position] with another state or process [e.g., ill-health], where the first is partly responsible for the second, and the second is partly dependent on the first. In general, a process has many causes, which are said to be causal factors for it, and all lie in its past” (<https://en.wikipedia.org/wiki/Causality>). This means that a low socioeconomic position does not have to be a sufficient nor a necessary cause of ill-health, but may increase the likelihood of ill-health.

Establishing that low socioeconomic status causes ill-health of course requires more than demonstrating an association – as noted above, associations between low socioeconomic status and ill-health may also be due to ‘reverse causation’ or ‘confounding by third variables’ (37). At the very least, the temporal relationship should be such that low socioeconomic status precedes ill-health instead of vice versa, and confounding by other factors should be eliminated either in the design of the study (e.g., by limiting the study to people who are identical in terms of these other factors) or in the analysis (e.g., by controlling for these other factors in a multivariate analysis). Although these requirements are widely recognized, in practice they are difficult to fulfil.

In the empirical sciences, the most reliable evidence of causation can be obtained in an experimental setting. Such a research design is mostly unfeasible or unethical in the area of socioeconomic inequalities in health. We can perhaps randomize people into small parts of the relevant exposure (say, a few months more or less of schooling, or a couple of thousands Euros more or less of yearly income), but not into life-long exposure to primary or tertiary education, a manual or upper non-manual occupational class, or a household income in the lowest or highest quintile of the income distribution.

In this field, one therefore has to rely almost completely on clever observation, and try to come as close as possible to the clean contrast of a controlled experiment. Such a clean contrast is, however, difficult to obtain due to the multiple links between socioeconomic position, health and third variables over a person's lifetime. In a purely observational study of whether low socioeconomic position causes ill-health one would not only have to use a prospective design ensuring that low socioeconomic status precedes ill-health, but also to control for a range of third factors that precede low socioeconomic position.

Consider the example of two groups of 35-year old, and perfectly healthy persons. The first group has only primary education, and has a routine manual job and an income in the lowest quintile. The second group has university education, a professional occupation and an income in the highest quintile. When we follow these two groups over time, we will most likely find a higher incidence of ill-health and premature deaths in the first than in the second group. We have ruled out the possibility of health-related selection because both groups were perfectly healthy at the start of follow-up. But how do we rule out the possibility of confounding by third factors?

One option is to restrict the comparison to 35-year old and perfectly healthy people who are identical in terms of all the personal attributes that predispose to good or bad health, and that were formed before the individuals had attained their adult socioeconomic position. Such attributes would include cognitive ability, personality traits, some health-related behaviours, genetics, etc. Another option is to accept a certain degree of heterogeneity of the two groups, and to statistically control for all these potential confounders in the analysis.

The first problem with both of these options is that they require very extensive data collection, and after all the data on measurable confounders have been collected, we would still be left with the possibility of unmeasured confounders that we have simply overlooked or that are currently unknown. One could even argue that it is impossible for two individuals who at 35 years of age have attained such different socioeconomic positions, to be identical with regard to all these personal attributes.

The second problem is that even if it were practically feasible to select on, or control for, all the known and unknown confounders, it would be difficult to avoid over-adjustment. As was explained in par. 2.1.3, over the life-course socioeconomic position and health are likely to be linked in a mutually reinforcing way. In our example, removing the effect of third variables that preceded the attainment of their current socioeconomic position of 35 year olds will also remove some of the effect of socioeconomic conditions in preceding life stages. For example, removing the cognitive ability would also remove some of the effect of growing up in more or less advantaged socioeconomic circumstances, to the extent that these circumstances exert their effect through the cognitive development of children. In other words, the risk is that the closer we get to identifying a true causal effect, the farther we get from a good understanding of how socioeconomic position affects health.

This dilemma may be difficult to solve, and can ultimately be traced back to fundamental differences in conceptions of causality. The 'counterfactual' approach to causal inference that is increasingly popular in many empirical disciplines, including epidemiology and economics, uses the 'potential outcomes' framework for assessing causality, and this requires that putative causes can be manipulated in experiments, at least in theory (38). In the case of smoking, it is not difficult to imagine the 'counterfactual' of an otherwise identical person who has never smoked, but in the case of social exposures like low socioeconomic position (or gender, or race), this is much more difficult. Adherents of the 'counterfactual' approach have therefore argued that assigning causal status to – in their eyes – vague and non-

manipulable concepts like socioeconomic position (or gender, or race) is problematic, and that only more specifically defined and manipulable exposures qualify as possible causes of health problems (39).

However, other epistemological positions have been defended as well. Several authors have argued for a more pluralistic approach to causality which recognizes the evident existence of causes of ill-health that cannot be manipulated, such as earthquakes, non-white race, or low socioeconomic position. Although the effects of these exposures cannot be studied according to the rigorous framework prescribed by the 'counterfactual' approach to causal inference, their role as possible causes of ill-health is too important to be ignored (40, 41). Paradoxically, in this alternative view it is precisely because low socioeconomic position often implies life-long exposures which are inextricably linked to social processes – and thus cannot be construed as a counterfactual cause – that it has such pervasive and persistent health effects.

In this discussion paper we do not take sides in this debate, but will highlight some of the more specific disagreements that follow from the split between the two perspectives on causality.

2.2.2 Practical approaches to assessing a causal relationship

Box 2.2 describes analytical approaches that can be used in a non-experimental setting to isolate causal effects of socioeconomic position on health.

Box 2.2. Study designs for assessing causality in the relationship from socioeconomic position to health

The following is a list of possible study designs for studying the association between socioeconomic position and health.

Purely observational studies

(i.e., the investigators exploit naturally occurring variations in exposure):

- *cross-sectional and case control studies, e.g. in which current health is related to current or previous socioeconomic position, with regression adjustment for observed confounders*
- *longitudinal studies, e.g. cohort or panel studies relating socioeconomic position to health at a later point in time, with regression adjustment for observed confounders, or fixed effects adjustment for observed and unobserved confounders*
- *twin studies, relating socioeconomic position to health of twins who are discordant on socioeconomic position, thereby controlling for genetic factors*

Quasi-experimental studies

(i.e., investigators exploit 'natural experiments' that have created quasi-random variations in exposure):

- *cross-sectional or longitudinal studies with statistical creation of quasi-randomness in the allocation of socioeconomic resources, e.g. by propensity score matching, differences-in-differences, instrumental variables, regression discontinuity*
- *cross-sectional or longitudinal studies exploiting naturally occurring randomness in the allocation of socioeconomic resources, e.g. lotteries, random roll-out of intervention programs*

Purely observational studies potentially suffer from many of the problems mentioned in par. 2.2.2, although (partial) solutions are available. For example, fixed effects adjustment (e.g., analyses which link changes in socioeconomic position to changes in health within the same individual) can be used to remove bias by both observed and unobserved confounders. Also, studying twins who have ended up in different socioeconomic positions guarantees extensive control for genetic factors.

Quasi-experimental approaches, which try to mimic randomized experiments by cleverly exploiting 'natural experiments', avoid some of the problems mentioned in the par. 2.2.2, particularly confounding by both observed and unobserved third variables (42).

For example, in a regression discontinuity analysis one can exploit income thresholds in the allocation of financial benefits to compare health outcomes among people falling just below or above the threshold and therefore getting or just not getting the benefit. Because people just below and just above the threshold

are likely to be otherwise similar, this may produce an unbiased estimate of the effect of the financial benefit (43). However, getting close to a clean contrast comes at a price: the external validity (or generalizability) of the results of regression discontinuity studies for the wider problem of income-related inequalities in health is dependent on whether the health effect of the small difference in financial benefits around the threshold correctly represents the health effects of income along the whole income ladder.

Sometimes, socioeconomic resources are allocated at random in real life. The prime example is lotteries which at first sight offer an excellent opportunity to evaluate the causal effects of money on health – but whether the health impact of an incidental amount of money obtained in a lottery adequately represents the health effects of years of living on a higher income is rather unlikely (44). Another example is the roll-out of certain intervention programs which sometimes occurs more or less at random, as in the roll-out of a higher age of compulsory education across Swedish municipalities in the 1930s (45).

Note: partly based on ref. (37, 42).

Epidemiology – a discipline that for many of its study questions can only use observational study designs – has often relied on a set of nine criteria for assessing causality proposed by Bradford Hill (46). These criteria are used for assessing the likelihood of a causal relationship between an exposure and a health outcome, and include strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy. Although these criteria have been useful in practice, as illustrated by the fact that they are still frequently used, e.g., in the evaluation of carcinogenic risks to humans (47), their epistemological basis has been criticized and they do not guarantee valid conclusions on causality (17)(p.26-30). Nevertheless, if the only option for studying a particular phenomenon (such as the effect of low socioeconomic position on health) is to use a purely observational design, the Bradford-Hill criteria or recently advocated approaches that use triangulation to arrive at ‘inference to the best explanation’ (48) may be the best way to proceed.

Because of the risks of bias in observational studies quasi-experimental study designs, which try to mimic randomized experiments by cleverly exploiting ‘natural experiments’, have been proposed as promising approaches for isolating the causal effects of socioeconomic position on health (Box 2.2)(49, 50). Application of some of these approaches will be illustrated in par. 2.3.

2.2.3 Differences between (sub)disciplines

Different disciplines, such as epidemiology, sociology, demography and economics, put varying degrees of emphasis on isolating causal from non-causal effects. Demography has a strong tradition of descriptive research, with relatively little attention to issues of causality, but the potential to fully encompass the whole phenomenon of health inequalities. At the other end of the scale, modern economics/econometrics tends to focus on rigorously identified causal relationships, but at the risk of losing sight of the complete picture. Epidemiology, including social epidemiology, and sociology are somewhere in-between – having a clear interest in causality but until recently largely relying on observational research methods that may not always have been adequate for isolating causal effects.

Because of the dominant position of social epidemiology in this area, particularly when it comes to the evidence-base for policy, it may be worth-while to briefly illustrate its approach to causality. A large part of this type of research is based on large cohort studies, and the classical epidemiological approach to assessing causality which was codified in the Bradford Hill criteria (see par. 2.2.2). The association between low socioeconomic position and ill-health fulfils many of these criteria: it is a strong association; it has consistently been observed; it is observed longitudinally, i.e. in studies in which exposure to low socioeconomic position precedes the occurrence of ill-health; the association has the form of a gradient with worse health at each step down the socioeconomic ladder; it plausibly fits what we know about the socioeconomic distribution of specific risk factors for ill-health, etc.

However, fulfilling these criteria does not exclude the possibility of confounding by some unobserved third variables, such as personal attributes that predispose to good or bad health, and whose formation has preceded the attainment of an individual’s current socioeconomic position. It is only in birth cohort

studies that such adjustments can properly be made, but it is only recently that participants in these birth cohort studies have reached the age at which the major health problems of Western countries occur. We will briefly review some of this emerging evidence in par. 2.3.2.

As said before, economists have over the past decade shown the keenest interest in identifying causal effects of socioeconomic position on health, and vice versa. Their interest in the effect of health on income and other socioeconomic variables follows naturally from the fact that economic phenomena are their main focus of interest – just as health being the main focus of epidemiologists' interest makes the latter primarily interested in the effect of socioeconomic position on health.

Studies by economists employing some of the quasi-experimental approaches mentioned in box 2.2 have, to some extent, revolutionized the field, and raised important doubts about the validity of the causal claims made by other disciplines, as will be illustrated in the following paragraphs.

2.3 Inventory of empirical evidence

From a sociological point of view, socioeconomic position is a multi-faceted phenomenon, which may not be completely captured by measures of education, occupational class and income. Nevertheless, the best evidence that we have on the causal effects of low socioeconomic position on health comes from studies in which socioeconomic position has been disaggregated in its component parts. In this paragraph we review some of the recent evidence concerning the health effects of education, occupational class and income.

2.3.1 Evidence of a causal effect of education on health

There are many longitudinal studies which show that adults with a lower level of education have a higher likelihood of ill-health or premature death: indeed, these inequalities have been found in all countries in which this information is collected (51). Because most of these health problems arise long after the age at which most people usually complete their education, health-related selection is unlikely to be involved in this association (52). A systematic review of studies that compared the relative importance of causation and health-related selection in the relationship between education and health indeed found causation to be the more important mechanism (13). However, some health-related selection may occur in a previous life-stage, because children with chronic diseases are somewhat less likely to achieve a higher level of education (53).

The main question is whether and, if so, to what extent the association between education and health may be confounded by third variables. The short answer is that even in the best longitudinal studies the association between education and health is likely to be confounded, but that it is currently impossible to assess the degree to which this may be the case. However, several recent reviews of the evidence, including evidence from quasi-experimental studies that are less likely to be confounded, conclude that it is also very likely that there is indeed a causal effect of education on health (37, 54, 55).

An important candidate for a usually unobserved confounding factor is can be found in an individual's genotype. Although variations in educational achievement are partly dependent on parents' socioeconomic position, educational achievement is also strongly dependent on an individual's own cognitive ability during childhood and adolescence. And although children's cognitive ability is partly dependent on the environment in which they grow up, variations in cognitive ability among children are also strongly genetically determined (56).

The important role of genetic determinants for a child's cognitive ability has been convincingly shown in twin studies, which generally find substantial heritability (in the order of at least 50% for cognitive ability measured in adulthood) (57, 58). Genome-Wide Association Studies (GWAS) have started to corroborate these findings by identifying specific genetic variants that are associated with cognitive ability (57, 59), and although there is still a substantial 'heritability gap' (i.e., the combined effects of all genetic variants that have so far been identified cannot fully account for the amount of heritability estimated in twin studies), this gap seems to be slowly filled as the findings of more molecular studies accumulate (60, 61).

It has recently been estimated that genetic differences explain around half of all inter-individual differences in educational attainment (62), with polygenic risk scores now explaining up to 10% of all

inter-individual differences in educational achievement (57, 63). Genome-wide association studies (GWAS) have also identified many genetic variants that influence educational achievement (64). The underlying mechanisms are likely to include more than cognitive ability alone, and may also include genetically determined aspects of personality such as the 'Big Five' personality traits, self-control, risk aversion, time preferences etc. (65). Because cognitive ability, self-control and other genetically determined personal attributes are independent predictors of health in later life, one can reasonably infer that genetic factors could to some extent confound the relationship between education and adult health.

In the presence of these and other risks of confounding, which are difficult to control for in observational studies, experimental and quasi-experimental studies may provide more reliable evidence for a causal effect of education on health. Truly experimental evidence is limited to a few studies from the US that have assessed the long-term health effects of early childhood (or pre-school) education. These showed that children receiving preschool education were more healthy and less likely to be smoking or obese as adults (55).

In the past decade, the effect of school education on health later in life has been assessed in a number of quasi-experimental studies. The most common approach has been to study the impact of compulsory schooling laws (37, 54, 55, 66). During the 20th century, many countries have introduced such laws, increasing the minimum age at which children may leave school. Because the resulting changes in years of schooling can be regarded as 'exogenous' (i.e., independent of personal attributes of the children involved), any improvements in health occurring in cohorts that left school after the change can reasonably be attributed to the extra years of schooling.

Although the evidence is not entirely consistent, most of these studies found that more years of schooling led to a reduction in mortality in mid-life and beyond, albeit with large variations in effect size (55). Other conclusions were that education improves intelligence (67), and reduces the risk of taking up smoking (54, 55), and that better-educated parents also have healthier children (54). Although studies exploiting compulsory schooling laws have important limitations (e.g., it is unclear whether the effect of one year of extra schooling at the age of, e.g., 16 can be generalized to the whole range of variation in length of education currently seen), these findings do suggest that there is indeed a causal effect of education on mortality. This implies that the association between education and mortality as found in observational studies is to some extent causal, and is not only due to confounding by genetic or other usually unobserved factors.

2.3.2 Evidence of a causal effect of occupational class on health

Like in the case of education, there are many studies showing that a 'lower' occupational class is associated with higher rates of morbidity and mortality in all countries that collect the information (68-70). The main issue is whether this is due to a causal effect of occupational class on health, or due to 'reverse causation' or confounding. There appear to be no studies with rigorous identification strategies to isolate a causal effect of occupational class on health (although there is reasonably strong evidence of the effect of specific working conditions on ill-health) (71).

Because educational achievement usually precedes entry to the labour market, and a higher level of education is a requirement for entry into 'higher' occupations, and because education influences health, education is a potential confounder of the association between occupational class and ill-health. Some studies from the US have found that the association between occupational class and health disappears after controlling for level of education (72, 73), but studies from several European countries have shown an independent effect of occupational class (52, 74, 75).

Because education is a determinant of occupational class, some of the findings reviewed in the previous paragraph must also apply to inequalities in health by occupational class: some of the observed association between occupational class and health is likely due to confounding by the same unobserved factors as mentioned in par. 2.3.1, including genetic variations in cognitive ability. Many studies have shown that adjusting for cognitive ability in adulthood substantially reduces the association between adult occupational class and a range of health outcomes (76), but a true test of the independent role of cognitive ability must first control for social conditions during childhood.

British birth cohort studies, some of which now have participants in their 50s and 60s, have begun to shed light on the independent role of cognitive ability in generating occupational class differences in adult health, by taking into account the role of childhood social conditions. However, so far these studies have not distinguished between genetically and environmentally determined variations in cognitive ability, making it unclear to what extent cognitive ability is indeed an independent (confounding) factor. In these studies, measures of cognitive ability in childhood have been found to be strong predictors of a wide range of health and social outcomes later in life, but these measures have also been found to be strongly determined by social exposures early in life (77). However, in-depth analyses of the extent to which inequalities in adult health by occupational class can statistically be 'explained' by differences in childhood cognitive abilities have produced mixed results. For example, while an analysis of the British 1946 birth cohort study found that adjusting for cognitive ability in childhood reduced the association between adult occupational class and lung function by two-fifths (32)(p. 44-47), an analysis of the British 1958 birth cohort study found a reduction of only a few percentage points (78)(p. 174-180).

Other possibilities for 'reverse causation' and confounding need to be considered too. An important difference between education and occupational class is that whereas one's level of education will usually remain constant after the age of, say, 25, one's employment status and occupational class can change in major ways during the life-course. This implies that the scope for 'reverse causation' by health-related conditions is much larger in the case of occupational class than in the case of education. A rigorous analysis of the labour market effects of health-related conditions in a range of high-income countries has indeed shown that having a chronic disease, and being a smoker or obese, have negative effects on employment, wages, sick leave and early retirement (79).

That health-related selection in and out of employment, and during occupational careers does occur is thus undisputed, but there is no consensus on the direction of the effect of health-related occupational mobility on health inequalities. Several studies have found that the health of people who move downward is worse than that of those who remain in their class of origin, and better than that of those in their class of destination, whereas the health of those who move upward is better than that of others in their class of origin, and worse than that of others in their class of destination. It has therefore been claimed that health-related occupational mobility will tend to 'constrain' or 'dilute' health inequalities (80, 81)

While this may seem straightforward, others have argued that the net effect of health-related selection on occupational class inequalities in health also depends on the relative numbers of people moving upwards and downwards from and into each occupational class. Some studies have indeed found 'gradient constraint' when the whole cohort's social gradient in health is compared to that of the socially stable, but also widening health inequalities in the whole cohort. This has been attributed to the fact that the net effect of social mobility on the social gradient at follow-up depends on the relative influence of people who enter or exit each occupational class (82, 83).

However, whatever the direction of the effect is, the contribution of health-related selection to the explanation of occupational class inequalities in health at adult and higher ages is likely to be limited. Most health problems occur in late middle or old age, after people have reached their final occupational class, and any health effects would have to be substantial for a change in occupational class to occur. This reasoning is confirmed by the fact that longitudinal studies in which occupational class has been measured before health problems are present, and in which the incidence of health problems has been measured during long-term follow-up, also show clearly higher risks of developing health problems in the lower occupational classes (70, 84, 85).

2.3.3 Evidence of a causal effect of income on health

Many studies have found a positive association between income and health: people with a higher income tend to experience better health and live longer (37, 54, 86). The relationship is non-linear: at the lower end of the income distribution, the relationship is steeper than at the upper end, suggesting that whatever mechanisms explain these inequalities, their effects are stronger among those with a very low income (87). Studies that have assessed whether the association between income and health still holds after

controlling for education and/or occupational class often (but not always) find that this is indeed the case (52, 74, 88, 89).

As in the case of education and occupational class, the question then is whether this association is due to a higher income leading to better health ('causation'), or to better health leading to a higher income ('reverse causation'). The common view among public health scientists, and the policy reports to which they have contributed, is that 'causation' accounts for a substantial part of this relationship, whereas the dominant view in the economics literature is that 'reverse causation' is far more important (90).

Both directions of causality are certainly plausible. A higher level of income may lead to better health through several mechanisms: for example, it increases access to healthy foods and good housing conditions, it reduces the stress of financial insecurity and boosts self-confidence, and it makes it easier to pay for the costs of health care. But better health may also lead to a higher income, for example by increasing the capacity to work, and by increasing labour productivity and wages (91). In a comparison of health inequalities by education, occupational class and income, health inequalities by income probably have the largest scope for health-related selection (52).

In addition to these two directions of causality, confounding by third variables (such as cognitive ability or personality traits) is also possible. Some studies have indeed shown that differences in cognitive ability and other personal attributes – whose formation plausibly predates the attainment of various income levels in adult life – explain part of the income-related inequalities in health. There is also emerging evidence of genetic determinants of income and material deprivation, again probably acting through cognitive ability and other personal attributes (92).

Because of the possibility of 'reverse causation' and confounding, assessment of a causal effect of income on health requires experimental and quasi-experimental studies, but it is important to recognize from the outset that most of these studies have a number of important limitations. They often study the effect of rather small variations in income, sometimes in settings (such as lotteries or stock market gains) that may not represent the experience of a lower or higher regular income over longer periods of life. It is also more difficult to demonstrate 'causation' (i.e., the effects of a change in income on health, which may take long to materialize) than to demonstrate 'selection' (i.e., the effects of a 'health shock' on income, which can be seen within a couple of years).

Nevertheless, the strongest evidence for a causal effect of income on health comes from experimental and quasi-experimental studies. Recently, a number of comprehensive reviews of this type of studies has been carried out (90, 93, 94), and we summarize their main findings below.

Over-all, the main conclusion of these reviews is that in high-income countries there is clear evidence for a causal effect of major changes in health ('health shocks') on income, but there is no consistent evidence for a causal effect of modest and short-term changes in income on physical health in adulthood. However, all reviews emphasize that the available evidence does not rule out the possibility that there is a causal effect of larger variations in life-time income on physical health in adulthood. Also, they agree that the evidence for a causal effect of parental income on the health of children is more consistent (37, 54, 90, 93, 94). Stewart 2013).

The evidence for 'reverse causation' is generally considered convincing. In a range of studies exploiting 'exogenous' changes in health (i.e., health events that are abrupt and unforeseen), ill-health in adulthood had a modest negative effect on wages among those who work, and a stronger effect on income through decreasing the employment rate and reducing the hours worked among the employed. Some of these effects appeared to be context-dependent, i.e. dependent upon employment and social policies (90)⁵. In addition, ill-health in early life and childhood had substantial effects on lifetime earnings, through decreasing the build-up of cognitive and non-cognitive abilities, constraining the acquisition of education, and by continuing into ill-health in adulthood which then interferes with labour productivity in adulthood.

⁵ There is also strong evidence for an effect of health on wealth, but this is outside the scope of this chapter.

Ill-health can thus have a very long reach from childhood to constrained economic opportunities in adulthood (90).

On the other hand, studies trying to find evidence for a causal effect of income on physical health in adulthood in high income countries using a quasi-experimental set-up have had inconsistent results. One review summarizing the results of 16 studies found 8 studies with no effect, 2 studies with a negative effect (i.e., more money, worse health), and 6 studies with a positive effect (i.e., more money, better health). Based on a further evaluation of the methodological quality of these studies, the authors conclude that “the evidence that income does have a causal impact on health in adulthood is weak” (90).

A second recent review summarizing the results of 9 studies of income effects on health in adulthood (6 of whom were also included in the first review) found 4 studies with no effect, 2 studies with a negative effect, and 3 studies with a positive effect. When looking at other outcomes, the review did find strong evidence that additional financial resources during adulthood make people happier and reduce mental health problems, but also that more money can lead to less healthy behaviours such as drinking and smoking more. The authors conclude that for physical health in adulthood “the evidence is mixed” (93).

Some of the reviewed studies focused on so-called windfall gains in income, e.g. lottery winnings, which closely approximate a true experimental setting. Some European studies found that the recipients of lottery prizes experience positive changes in self-reported health. These positive effects are particularly seen for mental health and less so for physical health, perhaps because winning a lottery also tends to increase smoking and drinking (90). The weakness of this strategy is, of course, that this variation in “income” does not necessarily correspond to that of normal monthly or yearly income. This limitation has to some extent been circumvented in a recent study of a Swedish lottery, not included in the reviews quoted above, that distributed sizable prizes and paid them out over longer periods of time, but this study also found largely null effects on physical health in adulthood (95). Similar limitations apply to other quasi-experimental ‘identification strategies’ (box 2.2). For low- and middle-income countries the evidence for a causal effect of income on health – which partly comes from true experiments – is considered to be more convincing (90).

The reviews also agree that the evidence for a causal effect of parental income on children’s health is considerably stronger than that for adults’ income on their own health. As the likelihood of ‘reverse causation’ is less, because children’s health will not directly impinge on their parents’ income, observational evidence does not have to be discarded altogether, as long as there is sufficient control for confounding by third variables. Although evidence from experimental and quasi-experimental studies is again somewhat mixed, reviews conclude that a causal effect of parental income on children’s health is likely to exist (54, 90, 94). This conclusion is further supported by the fact that there is also good evidence for income effects on intermediate outcomes, such as parenting, the physical home environment, maternal depression, smoking during pregnancy, and children’s cognitive ability, school achievement and behaviour (94). Long-term increases of incomes of lower socioeconomic groups may have health benefits that may even cumulate over generations (37).

3 WHAT MEDIATES THE EFFECT OF SOCIOECONOMIC POSITION ON HEALTH?

3.1 Conceptual introduction

3.1.1 Why is this an important question?

Understanding how health inequalities arise is important both from a scientific and a policy perspective. A scientific approach to the explanation of health inequalities cannot stop at the demonstration of an effect of socioeconomic position on health (see previous chapter), but also requires an understanding of the factors involved in generating this effect. We need to be able to identify plausible causal pathways before we can reasonably conclude that socioeconomic position has an effect on health (46).

Understanding the causal pathways is also important from a policy perspective. Broadly speaking, one can distinguish two strategies for reducing health inequalities (96). The first and most radical option is equalizing the distribution of socioeconomic factors, for example by reducing inequalities in educational attainment or income. To the extent that there is a causal effect of socioeconomic factors on health, this can be expected to also reduce health inequalities.

However, there are obvious limits to such an approach. Apart from the challenge of finding political support for far-reaching income redistribution policies, it is unlikely that variations in levels of education or occupational class can be completely eliminated, given the fact that people will always differ in their cognitive ability and other talents, and that economies will always require a certain division of labour.

It is important, therefore, to also consider a second, more pragmatic strategy for reducing health inequalities, which is to reduce the exposure to specific health determinants among lower socioeconomic groups (97). For example, to the extent that socioeconomic inequalities in mortality are determined by differences in working conditions, smoking or access to health care, reducing or – even better – eliminating these differences by improving working conditions, reducing smoking or improving access to health care for lower socioeconomic groups can be expected to also reduce health inequalities.

This implies that identification of the factors involved in generating the effect of socioeconomic position on health is not only scientifically relevant, but also highly policy-relevant. However, although these aims often coincide, there is a subtle difference between the requirements of scientific explanation and the requirements of policy support.

In the latter case, it may not be necessary to have certainty about whether differences in exposure to specific health determinants between socioeconomic groups are caused by people's socioeconomic position. As long as we do have certainty about the causal effect of the determinants on health, and even if the differences in exposure between socioeconomic groups are coincidental, reducing them will help to reduce health inequalities (98). For example, as long as we know for sure that smoking causes lung cancer, we can reasonably assume that reducing smoking among the lower educated will reduce their higher risks of lung cancer, even if we do not know whether their higher rates of smoking are actually *caused* by their lower level of education.

This is not to say that the presence or absence of such a causal relationship is not important at all – on the contrary. Sticking to the example of smoking, if the higher rates of smoking among the lower educated are actually caused by their lower level of education, it may be more difficult to lower their rates of smoking than if this would not be the case, and this should then be taken into account in developing an effective intervention program. Also, whether or not there is a causal relationship between socioeconomic position and specific health determinants can also influence society's normative assessment of the resulting health inequalities, and hence influence policy: if the higher rates of smoking in lower socioeconomic groups are

somehow caused by their lower socioeconomic position, the resulting health inequalities may be considered unfair, whereas this would less evidently be the case if they are unrelated (4).

3.1.2 Definition of a mediator

The most commonly used analytical technique for studying causal pathways with respect to health inequalities is 'mediation analysis'. This technique allows one to quantify the contribution of one or more so-called 'mediators' to the effect of an independent variable (in this case: socioeconomic position) on a dependent variable (in this case: a health outcome). 'Mediators' are defined as third factors that represent an intermediate step in the causal pathway between independent and dependent variable (99). Other terms used to denote 'mediators' are 'intermediate variables', 'mediating variables', and 'intervening variables' (100). Like in the case of confounders, mediators are involved in the relationship between an independent variable and a health outcome, but in contrast to confounders which *may not* lie on the causal pathway between independent variable and health outcome, mediators *must* lie on this causal pathway (17)(p.186).

This means that, strictly speaking, a third variable can be considered a mediator of the effect of socioeconomic position on health if, and only if, (a) a person's socioeconomic position causally influences his or her exposure to the third variable, and (b) exposure to the third variable causally influences his or her health outcome. In other words, assessment of mediation requires evaluation of two causal relationships (101).

For example, we may want to know to what extent socioeconomic inequalities in mortality are explained by differences in working conditions, smoking, or access to health care. Working conditions, smoking, and access to health care would qualify as potential mediators if we can assume (or demonstrate) that a person's socioeconomic position causally influences his or her exposure to unfavourable working conditions, smoking behaviour, and lack of access to health care, *and* if we can assume (or demonstrate) that exposure to unfavourable working conditions, smoking behaviour, and lack of access to health care causally influences mortality.

As we have noted above, while such strict requirements may be essential for scientific explanation, the first of the two requirements can often be relaxed in a context of policy support. Even if socioeconomic differences in exposure to unfavourable working conditions, smoking behaviour, and lack of access to health care are coincidental – for example, brought about by chance, or by confounding variables such as other sociodemographic characteristics or personal attributes like cognitive ability – it would still be policy-relevant to know that these differences explain some of the higher mortality rates of lower socioeconomic groups. However, in such a situation it would be better to avoid using the stricter term 'mediator', and use a more neutral term like 'contributory factor' instead.

3.1.3 Mediators versus moderators

Central to mediation analysis is the assumption that health inequalities are likely to be explained by differences in exposure to specific health determinants between people in lower and higher socioeconomic groups. This is the type of explanation of health inequalities we know most about, and is therefore the main focus of this chapter.

However, another possible explanation of health inequalities also needs to be considered, although it is more difficult to investigate and therefore less common in the literature. Third variables may not only act as mediators, but also as 'moderators' of the relationship between socioeconomic position and health, and socioeconomic position can act as a 'moderator' of the relationship between other determinants and health. A 'moderator' is defined as a variable that affects the *strength* of the relationship between an independent variable and a health outcome (99, 101).

For example, suppose that people with low education are more sensitive to the negative health effects of smoking than people with high education, e.g., because they consume less fruits and vegetables which increases the lung cancer risk of inhaling tobacco smoke, or because they consult a doctor in a later stage of their smoking-related disease which increases their likelihood of dying. This would lead to a larger difference in lung cancer mortality between smokers and non-smokers among the low than among the

high educated, which would indicate that socioeconomic status is a ‘moderator’ of the effect of smoking on lung cancer⁶. So, in this example smoking would contribute to the explanation of health inequalities, *even if* the prevalence of smoking is the same among low and high educated.

Various technical terms are used to denote this phenomenon of ‘moderation’. Whereas ‘moderation’ is a term commonly used in the social sciences, epidemiologists more commonly use the term ‘effect modification’ or more fully ‘effect measure modification’. ‘Moderation’ is also sometimes called ‘effect heterogeneity’. In quantitative analyses, ‘moderation’ shows up as ‘statistical interaction’ (on a relative or absolute scale) (17)(p.61).

In the health inequalities literature, we encounter the concept of ‘moderation’ in a more specific form as ‘differential susceptibility’ or ‘differential vulnerability’. These terms imply that health inequalities may partly be explained by the fact that people in lower socioeconomic groups are more ‘susceptible’ (in a biological sense) or ‘vulnerable’ (in a psychological or social sense) to the negative health effects of various determinants⁷ (102). This may apply to the negative health effects of smoking as in the example given above, but also to a range of other biological, psychological and social factors (103).

However, although the existence of ‘differential susceptibility’ is certainly plausible, empirical evidence has remained scarce (104-106). One of the main reasons why empirical evidence on this phenomenon is limited is that establishing moderation, for example by carrying out interaction analyses, requires large sample sizes to generate sufficient statistical power to not only reliably estimate the main effects of socioeconomic position and health determinants, but also their interaction effects⁸.

Nevertheless, differential susceptibility remains a potentially important mechanism for explaining health inequalities and deserves more attention, also from a policy point of view. Whereas mediation (i.e., differential exposure to health determinants) suggests that a change in the distribution of health determinants would be an effective measure against health inequalities, moderation (i.e., differential vulnerability to health determinants) points to strengthening the resilience of individuals and taking protective and compensatory measures as more effective interventions. Findings on mediation and moderation complement each other, thus extending the possibilities for health inequality interventions.

More recently, there is increasing awareness of the possible role of genetics in creating ‘differential susceptibility’ to negative environmental influences (and to a mirror image of the same idea: ‘differential plasticity’ in response to positive environmental influences) (Box 3.1)(107-109). However, here again the evidence is still very limited.

Box 3.1. Genetic factors as possible ‘moderators’

People in lower socioeconomic groups may not only be more susceptible to the negative health effects of certain behavioural or environmental factors, but also to the negative health effects of certain genetic risk factors. This is the same as saying that people with certain genetic risk factors may be more susceptible to the negative health effects of socioeconomic disadvantage (or to the positive health effects of socioeconomic advantage).

This awareness has been raised by the results of behavioural genetics studies of ‘gene-environment interaction’, with socioeconomic position acting as an ‘environmental’ factor (60). The general idea is, that even if genetic risk factors are equally distributed across socioeconomic groups, differences in susceptibility to these genetic risks as a result of groups’ different environments could lead to health

⁶ It would also lead to a larger difference in mortality between the low and the high educated among smokers than among non-smokers, indicating that smoking is a ‘moderator’ of the effect of socioeconomic position on lung cancer mortality.

⁷ These ideas are partly inspired by older ideas: social epidemiologists previously coined the concepts of ‘general susceptibility’ and ‘host resistance’, based on the idea that individuals may react differently to the same exposure. The fact that we find so many health problems to be more frequent in lower socioeconomic groups indeed may lead one to think that people in lower socioeconomic groups are somehow more susceptible to disease. In a related sense, demographers use the concept of ‘frailty’ based on the notion that some individuals are more susceptible to the risk of death than others.

⁸ Another reason is that it is also quite challenging to exclude the possibility that what seems to be differential susceptibility is actually differential exposure inadequately measured.

inequalities. In such a case, genetics can contribute to the explanation of health inequalities, even if the prevalence of genetic factors is the same in all socioeconomic groups.

There is indeed some emerging evidence, particularly in the fields of child development and mental health, that such gene-environment interaction may partly explain health inequalities. For example, Caspi et al. found an interaction between stressful life events (such as child maltreatment) and a polymorphism of the serotonin transporter gene on depression among young adults, suggesting that susceptibility to the mental health effects of this gene was moderated by the environment (and vice versa) (110).

Similar interactions between socioeconomically defined environments and genetic risk factors can be imagined, with some genotypes increasing or decreasing the susceptibility to a disadvantaged environment (111). A possible example is that in twin studies the heritability of mental ability has been found to be larger in higher than in lower socioeconomic groups, probably because the effect of the environment overwhelms the effect of genetic determinants in lower socioeconomic groups (112).

3.1.4 Possibility of reverse causation and confounding

As already mentioned, determining mediation requires an assessment of two causal relationships, one between socioeconomic position and the mediator, and one between the mediator and the health outcome. Like in the case of assessing a causal relationship between socioeconomic position and health (see chapter 2), this implies that we need to consider the possibility of reverse causation and confounding.

Reverse causation would bias the results of mediation analysis if there would be a 'reverse' effect of the mediator on socioeconomic position, and/or if there would be an effect of health on the mediator. Suppose that we are studying the higher prevalence of disability among people with a low income, and would like to know to what extent obesity explains the relationship between income and disability (113). Reverse causation would then be a serious possibility, both in the relationship between low income and obesity (obesity may lead to low income, e.g., because obese people have more difficulty finding a job and making promotion), and in the relationship between obesity and disability (disability may lead to obesity, e.g., because disabled people have difficulty performing physical exercise).

Confounding would bias the results of mediation analysis if there are other variables that are associated with socioeconomic position *and* affect the mediator, or if there are other variables that are associated with the mediator *and* affect health. Suppose, again, that we are investigating the role of obesity in explaining the higher prevalence of disability among the low educated. One would then have to take into account that there may be personal characteristics, such as a tendency to prefer short-term gratification over long-term benefits, that are more prevalent among the low educated and that predispose to obesity (114), or that there may be other determinants of health, such as a low consumption of fruits and vegetables, that are more frequent among obese people and increase the risk of disability.

As noted in par. 3.1, if the objectives of the analysis are more limited, as in the case of a study aiming to find entry-points for policy, we can largely ignore the possibility of reverse causation and confounding of the relationship between socioeconomic position and the putative 'mediator', but we would still have to consider the possibility of reverse causation and confounding of the relationship between the putative 'mediator' and the health outcome.

3.2 Methodological requirements

3.2.1 How can mediation be demonstrated?

In principle, because of the necessity to establish causal relationships one would prefer to investigate mediation using an experimental approach, e.g. by intervening on a mediator in a randomized trial and assessing the effect of removal of the mediator on the magnitude of health inequalities. This would potentially remove all biases related to reverse causation and confounding.

However, experimental manipulation of mediators, with the purpose of assessing their contribution to health inequalities, is quite rare. Experimental studies of the effect of lowering exposure to various health

determinants that play a role in generating health inequalities are of course quite common, and sometimes such trials have been used to assess whether the effects of the intervention differ by socioeconomic position (115-117). However, most of these studies use exposure to the determinants in question targeted by the intervention as their end-point, and therefore do not provide insight in the extent to which changes in exposure to these determinants affect the magnitude of health inequalities. Where studies with health outcomes as end-point have been conducted they will be mentioned in par. 3.3.

The simplest approach to assessing mediation, which unfortunately has serious shortcomings, is to identify one or more health determinants that are known to causally affect health, to show that there are substantial inequalities in exposure to these health determinants between socioeconomic groups, and then to claim that these inequalities in exposure must partly explain inequalities in health between socioeconomic groups.

For example, if we know that smoking causes premature mortality, and if we see a much higher prevalence of smoking among the low than the high educated, we may infer that smoking partly explains inequalities in mortality between the low and high educated. Although this seems plausible, such an approach does not tell us how large the contribution of smoking to inequalities in mortality is.

To fill this gap a quantitative technique has been developed: if we know the prevalence rates of smoking in each education group, and if we know the relative risk of smoking on mortality from the literature, we can roughly estimate the contribution of smoking to mortality and mortality inequalities using the method of population-attributable fractions (118). Because data requirements for this approach are modest, it can be applied in many settings, and has produced estimates of the contribution of various risk factors to inequalities in mortality for many countries (119-122).

Apart from the fact that this approach cannot determine whether or not the observed inequalities in exposure are *caused* by socioeconomic position, and therefore has to refrain from claims of mediation *sensu stricto*, the main problem is that this approach cannot deal with the multivariate nature of the explanation of health inequalities, because it does not directly quantify the effect of the specific determinant on the health outcome within the dataset in which health inequalities have been found.

For example, we may be interested to know which part of inequalities in mortality is due to inequalities in working conditions, which part to inequalities in smoking, and which part to inequalities in lack of access to health care. The population-attributable fractions method would quantify these parts without taking into account that unfavourable working conditions, smoking, and lack of access to health care may occur in the same people. It would also assume that the relative risks taken from the literature apply to all populations (118). A more valid assessment of the contribution of each of these three factors requires a multivariate analysis in which any overlap between the three factors is removed and which takes into account the actually observed relationships between the risk factors and the health outcome. This is what formal 'mediation analysis' does, but at the expense of greater data requirements, particularly the need for individual level data on socioeconomic position, mediators and health outcomes, preferably collected in a longitudinal set-up.

Precise quantification of the contribution of putative mediators may not always be required, but is useful when translating the findings of explanatory studies into priorities for policy. When designing a strategy to reduce health inequalities it would make sense to prioritize interventions targeting mediators that make a substantial contribution (say, explain more than 10% of health inequalities), and to ignore mediators that make a minor contribution (say, explain less than 1% of health inequalities).

3.2.2 Mediation analysis

The practice of mediation analysis in social epidemiology (and in other disciplines such as psychology and sociology) has long been based on the so-called Baron & Kenny approach which was developed in the 1980s (99, 123). In this approach one studies whether the relationship between socioeconomic position and health disappears, either completely or partly, upon statistically controlling for the putative mediator(s). Our current knowledge of the quantitative contribution of health determinants to health inequalities largely derives from this approach.

When implemented in a multiple regression format, as is common in social epidemiology, this approach usually takes the form of the so-called 'difference method', in which one estimates the difference between the regression coefficient for the effect of socioeconomic position on a health outcome before and after controlling for the mediator(s). This reduction in the size of the regression coefficient for the 'effect' of the independent variable on the health outcome is called 'attenuation' (99, 123).

In other words, mediation analysis decomposes the 'total effect' of socioeconomic position on the health outcome into an 'indirect effect' (i.e., the part of the total effect that is explained by the mediator(s)) and a 'direct effect' (i.e., the part of the total effect that is not explained by the mediator(s)). The regression coefficient found before controlling for the mediator is thought to represent the total effect, the regression coefficient found after controlling for the mediator the direct effect, and the difference between the two is thought to represent the indirect effect, i.e. the contribution of the mediator (99, 123).

For example, suppose that the mortality rate among people with low education is 20 per 1000, and that the mortality rate among people with high education is 10 per 1000, and let us assume for the moment that all of the difference between the two ($20 - 10 = 10$ per 1000) can be seen as a causal effect of education on mortality. Suppose also that smoking, a well-documented cause of premature mortality, is more prevalent among the low educated, and that this higher prevalence reflects a causal effect of education on smoking. We can then apply mediation analysis to estimate the extent to which the total effect of education on mortality is mediated by smoking.

For example, if the rate difference of mortality between the low and high educated, as estimated from the regression coefficient, goes down from 10 per 1000 to 7 per 1000 upon controlling for smoking, one would conclude that smoking explains $(100 \times (10 - 7) / 10 =)$ 30% of the effect of low education on mortality. Or, if the rate ratio of mortality comparing the low to the high educated, as estimated from the regression coefficient, goes down from 2.0 to 1.7 upon controlling for smoking, one would similarly conclude that smoking accounts for $(100 \times (2.0 - 1.7) / (2.0 - 1.0) =)$ 30% of the effect of low education on mortality⁹.

This approach can be extended into a multivariate analysis, in which the contribution of more than one 'mediator' or 'contributory factor' to socioeconomic inequalities in health is assessed simultaneously, and in which the contribution of all mediators/contributory factors together is decomposed into separate parts for each of them (124, 125). In health economics, a different but conceptually similar approach to mediation analysis is sometimes used. This approach is based on the so-called Oaxaca-Blinder decomposition method which was originally developed in labour economics in the 1970s (126, 127)¹⁰.

In the social sciences, another technique to study mediation is 'structural equation modelling'. This is a family of multiple regression techniques that can be used for various purposes, including mediation analysis. In structural equation modelling, a dependent variable in one regression equation can become an independent variable in another regression equation. Specific techniques that may be useful for mediation analysis include 'path analysis' (in which the putative causal 'paths' between several variables can be modelled in linked regression equations) and 'latent growth modelling' (in which repeated measures of the dependent variable can be modelled as a function of several explanatory variables). The main added value of these techniques is that they allow the estimation of more complex relationships than those between a single independent variable, a single dependent variable, and a set of unrelated mediators (128-130).

Recently, the 'difference method' has been criticized for a number of methodological shortcomings (Box 3.2) (101, 123, 131). As the Oaxaca-Blinder decomposition method and structural equation modelling are

⁹ The same analysis can also be performed without the explicit aim to assess mediation *sensu stricto*. When we relax the assumption of a causal effect of socioeconomic position on smoking, but maintain the assumption of a causal effect of smoking on mortality, we need to only slightly change the interpretation of the findings of the analysis to still obtain a meaningful result. In that case, one can interpret the findings as implying that smoking accounts for 30% of the excess mortality among the low educated.

¹⁰ A modification of this method, proposed by Wagstaff et al., allows the 'decomposition' of health inequalities, as measured by the 'concentration index', into the contribution of differences in the distribution of various explanatory variables and a residual or 'unexplained' portion.

based on the same assumptions as the regression-based difference method, the same limitations apply to these techniques (101).¹¹

Box 3.2. Problems of conventional approaches to mediation analysis

It has been demonstrated that the conventional approaches to mediation analysis (Baron & Kenny, Oaxaca-Blinder decomposition, structural equation modelling) only give unbiased results under conditions which are rarely fulfilled. Two relatively straightforward conditions for unbiased results are that

- *there is no uncontrolled socioeconomic position-outcome confounding, and*
- *there is no uncontrolled mediator-outcome confounding (101, 123, 131).*

The first of these conditions is self-evident and usually receives at least some attention in studies of health inequalities: mediation analyses often control for confounders of the relationship between socioeconomic position and health, e.g., age and other sociodemographic factors such as ethnicity, although usually not for other antecedent conditions of socioeconomic position such as (genetic determinants of) cognitive ability and personality traits.

The second condition is more difficult to satisfy, because it requires measurement of many more factors than the putative mediator(s) and socioeconomic position-outcome confounders alone. Mediation analyses that include only a single mediator are almost certain to produce biased results of the explanation of health inequalities, because most health outcomes have several risk factors and most risk factors are more prevalent in lower socioeconomic groups. For example, one can only arrive at an unbiased estimate of the contribution of smoking to educational inequalities in mortality if other determinants of mortality which may act as confounders of the smoking-mortality relationship are controlled for, such as other health-related behaviours or material living conditions. Even in a multivariate mediation analysis, complete coverage of all exposure-outcome confounders will be exceedingly difficult to obtain.

In addition to these relatively straightforward conditions there are two other conditions which are less self-evident:

- *there is no socioeconomic position-mediator interaction on the outcome (i.e., the effect of the mediator on the health outcome does not differ between socioeconomic groups), and*
- *there is no mediator-outcome confounding affected by socioeconomic position (i.e., confounders of the mediator-outcome relationship may not be on the causal pathway between socioeconomic position and the health outcome) (101, 123, 131). We will explain each of these conditions with an example.*

As mentioned above, inequalities in mortality may be partly due to inequalities in smoking, but in the conventional approach the contribution of smoking to these inequalities can only be estimated correctly if the effect of smoking on mortality does not differ between socioeconomic groups (requirement iii). As we have seen in par. 3.1.3, such 'moderation' or 'effect modification' is a real possibility (although it has not often been empirically demonstrated).

Also, the contribution of smoking will only be estimated correctly if confounders of the smoking-mortality relationship, such as other health-related behaviours, psychosocial factors or material living conditions, do not play a role in the effect of socioeconomic position on health (requirement iv). It is easy to see that this condition is unlikely to be fulfilled. For example, if smokers are more likely to be heavy drinkers, heavy drinking will be a confounder of the smoking-mortality relationship, and therefore needs to be controlled for in the analysis. However, if heavy drinking is itself on the causal pathway between socioeconomic condition and mortality, controlling for heavy drinking will not only remove confounding but will also take away some of this other pathway, and this will then lead to a biased estimate of the mediating role of smoking.

Now that these problems have come to be understood, new methods of mediation analysis have been designed that may remove these sources of bias (101, 123). For example, a variant of the Baron & Kenny

¹¹ Other problems with mediation analysis, not covered in this discussion paper, relate to selection and information bias, including measurement error of exposure, mediator and outcomes, which can also jeopardize the validity of the results.

approach is the 'generalized product method', which additionally controls for an interaction between the independent variable and the mediator. This allows for socioeconomic position-mediator interaction (requirement iii), but not for mediator-outcome confounding affected by socioeconomic position (requirement iv) (132).

Other solutions include the following (101, 132):

- inverse probability-weighted marginal structural models, in which the mediator and exposure are first modelled, generating inverse probability weights from these models, and then a weighted regression model is fitted of the outcome against the exposure, the mediator, and their interaction;
- the structural transformation method (also known as sequential g-estimation), in which the outcome is modelled using an identity link function, and then transformed using the parameter estimates from this model, after which this transformed outcome is regressed against the exposure and exposure-outcome confounders;
- g-estimation of a structural nested model, in which a nested mean model is created, outcomes and mediators are transformed using the outcomes of separately estimated models, and in which parameters are estimated using a modified doubly robust g-estimator;
- targeted minimum loss-based estimation, in which initial outcome predictions are obtained under the desired exposure-mediator combination, and in which the outcome predictions are allowed to fluctuate against an inverse probability weight that serves as an independent variable in the regressions.

Fortunately, now that these problems have come to be understood, new methods of mediation analysis have been designed that may remove these sources of bias (box 3.2) (101, 123). Social epidemiologists are increasingly aware of the problems with the older techniques, and have started to apply the new techniques to their research questions (132-134). However, applications to real-life data aiming to explain socioeconomic inequalities in health are still very rare, partly because of the necessity to adapt these new techniques to situations with typical health outcomes and more than one mediator (135, 136). The first experiences show that they may lead to substantially different results as compared to the conventional 'difference' method (132).

While applications of these newer methods cast doubt on the validity of the results of previous studies using conventional methods, it is too early to say to what extent these previous results are biased. Rules to evaluate the potential degree of bias in studies using conventional methods have been proposed (101), but application requires detailed information which is usually not readily available.

3.3 Overview of empirical evidence

The methodological problems mentioned above imply that the available evidence on what mediates the relation between socioeconomic position and health needs to be re-evaluated. To the extent that results of mediation analyses are available, these potentially suffer from all the problems mentioned above. Almost all the available studies take the observed association between socioeconomic position and the health outcome as if this represents a causal effect of socioeconomic position on health, and apply conventional analysis methods (i.e., the 'difference method') ignoring the potential sources of bias mentioned above.

In reviewing and summarizing the empirical evidence we therefore have to be pragmatic, which in this case means two things:

- 1 adjust the explanatory ambition downwards, i.e., refrain from claiming mediation *sensu stricto* and instead interpret the evidence as indicating the role of differences in exposure to various specific health determinants in generating health inequalities ('contributing factors'), and
- 2 refrain from presenting quantitative estimates of the role of these differences in exposure, and instead present conclusions in more qualitative terms.

The overview that follows is partly based on various other overviews, such as two major policy-oriented reports prepared under the umbrella of the World Health Organization (the final report with its background documents of the Commission on Social Determinants of Health (1), and the European Review of Health Inequalities with its background reports (2)) and some recent European projects which have included attempts to summarize the available evidence (particularly the DRIVERS, EURO-GBD, and

DEMETRIQ projects). In addition, the literature was searched for systematic reviews of socioeconomic inequalities in health determinants and their contribution to health inequalities. These existing overviews were assessed against the background of the methodological considerations mentioned above.

On the basis of the available evidence five groups of specific health determinants can be distinguished that are likely to play an important role in the explanation of health inequalities: early childhood environment, material living conditions, social and psychological factors, health-related behaviours, and health care. It is important to note, however, that the relative contribution of these determinants may differ between countries, and has probably also changed over time.

3.3.1 Early childhood environment

Systematic reviews show that growing up in disadvantaged socioeconomic circumstances is associated with many negative effects on children's health and development, including children's general health and illness, developmental outcomes, asthma, dental caries and mental health problems (137). This is commonly thought to reflect a causal effect of socioeconomic disadvantage on health, because there is less potential for 'reverse causality' in the case of children's health than in the case of adult health outcomes (14), although it is also possible that there are common underlying factors in the association between parents' socioeconomic disadvantage and children's health and development, such as genetic factors shared by parents and their children (65).

Health inequalities initiated in childhood may partly explain the social gradient in health observed throughout the remaining life course (137). Adults with lower education, occupational class and income often have grown up in less advantaged socioeconomic circumstances whose health effects may carry through into adulthood (138, 139). Systematic reviews indeed show that growing up in less advantaged socioeconomic circumstances has many long-term negative health effects, independent from the influence of adult socioeconomic position. These long-term effects include increased all-cause mortality, mortality from various specific causes, having cardiovascular risk factors, impaired cognitive and physical functioning, and lower self-rated health (77, 140).

Some of these long-term effects may be brought about by epigenetic mechanisms (see par. 2.1.4). There is now increasing interest in the possibility that the socioeconomic environment in which children grow up impacts their epigenome with effects on health and development throughout the life-course (141). For example, some studies have found an association between childhood socioeconomic status and DNA methylation of genes that regulate stress reactivity and inflammation, suggesting a specific pathway linking childhood disadvantage to adult ill-health (142, 143).

3.3.2 Material living conditions

Material living conditions probably play an important role in generating health inequalities. As discussed in chapter 2, it is uncertain whether differences in income play a role in generating inequalities in physical health in adulthood in high income countries, but the available evidence does not rule out a causal effect of larger variations in life-time income, particularly at the lower ends of the income distribution. Poverty does plausibly play a role, but probably to a different extent in different European countries, depending on its depth and impact on access to other resources important for health. Poverty may be defined either in relative terms, e.g. as a net household income level below 60% of the median, or in absolute terms, e.g. as a net household income below a threshold deemed to represent the minimum income necessary for a decent life (144).

Studies show that poverty is associated with a range of adverse health outcomes (145, 146), and a few mediation analyses which link indicators of socioeconomic position to health outcomes via indicators of poverty suggest that poverty does indeed contribute to the explanation of health inequalities (125, 147, 148). Although the majority of the available evidence comes from observational studies which potentially suffer from incomplete control for confounding factors, the plausibility of a causal effect of poverty on health is supported by the existence of a range of well-documented pathways through which poverty may affect health. Poverty reduces financial access to activities and products that are important for the maintenance and promotion of health, such as a healthy diet, sports, and social contacts. Poverty also reduces access to health care services, particularly when out-of-pocket payments are required. And it

often leads to psychosocial stress, which has negative biological and mental effects and increases the likelihood of risk-taking behaviours (such as smoking and excessive alcohol consumption) (149-151).

A second group of material living conditions which contribute to the explanation of health inequalities are working and employment conditions. Poor working conditions are more prevalent among employed people with lower levels of occupation: many studies have shown both physical/chemical exposures and psychosocial exposures to be more common in lower occupational groups, and there is also moderate to good evidence that these exposures lead to various forms of ill-health. A recent systematic review of mediation analyses using the 'difference method' confirms a possible role for both the physical/chemical work environment (i.e., higher exposure to physical demands, biomechanical strains and chemical substances in certain lower occupations) and the psychosocial work environment (i.e., higher prevalence of demand-control and effort-reward imbalance in certain lower occupations) (152). It is unclear, however, to which extent the estimates of the contribution of work conditions were controlled for other determinants/confounders. An imbalance between effort and reward at work has also been found to exert a mediating role in the association of occupational class with depressive symptoms (58). In addition to mediation, some support for 'moderation' with regard to dangerous materials and psychosocial working conditions has been observed: some studies found that unfavourable working conditions had stronger negative health effects on workers with lower socioeconomic status (152, 153).

Under the broad heading of working conditions we also need to consider unemployment and precarious employment. These conditions are more common in lower socioeconomic groups (154). The health effects of unemployment have been a long-standing issue for debate, partly because there is a strong selection of unhealthy persons into unemployment.

Selection of unhealthy persons into unemployment is less pronounced during mass unemployment. Several studies have used this insight to look at health consequences during and after episodes of mass unemployment. It appears that deep recessions with mass unemployment cause excess mortality among those who experience unemployment, for instance from suicide, alcohol-related and cardiovascular mortality, in particular if those unemployed were of low education (155-157). Moreover, precarious employment, high job insecurity and wages that are low or considered unfair pay have been reported to be associated with elevated risks of stress-related disorders (154)

A third group of factors are the conditions under which people live, both in the immediate sense of the quality of their housing (as in the case of crowding, dampness, or accident risks) (158) and in the more indirect sense of their neighbourhood conditions (159-161) and environmental exposures such as air pollution and toxic waste dumps (162, 163), all of which tend to be less favourable for lower socioeconomic groups.

3.3.3 Social and psychological factors

Psychosocial factors beyond the work place may also be important contributing factors (164, 165), although there is no scientific consensus about the importance of their role, independent of that of other mediating variables. People with a low socioeconomic position on average are exposed to more psychosocial stressors, in the form of negative life events (e.g., loss of beloved ones or loss of paid work), 'daily hassles' (e.g., in the form of financial difficulties), and a combination of high demands and low control in life as a whole (166). At the same time, they also tend to have less support to deal with psychosocial stressors, such as social networks, social support, and 'social capital' generally (167), as well as less effective coping styles (e.g., a more external 'locus of control') (168)

At least two pathways may be involved. The first is a behavioural pathway: psychosocial stress and other unfavourable psychosocial factors increase the likelihood of unhealthy behaviours, such as smoking, excessive alcohol consumption and lack of physical exercise (169-172). The second is a more direct biological pathway. The experience of stress affects the neural, endocrine and immune systems of the body, and chronic stress may lead to maladaptive responses in the form of, e.g., high blood pressure, a prolonged high level of cortisol, higher blood viscosity, or a suppression of the immune response, which may in their turn increase the susceptibility to a range of diseases (173-175).

Although both pathways have been documented, an important issue remains whether these psychosocial factors have an independent negative effect on health. There is some evidence that higher exposure to psychosocial stressors, in combination with less capacity to remove or buffer these exposures, has negative health effects, but consensus has not yet emerged. A recent 'umbrella review' (i.e., systematic review of literature reviews) of the health effects of psychosocial risk factors in home and community settings found "some evidence of favourable psychosocial environments [being] associated with better health, [and of] unfavourable psychosocial risk factors [being] linked to poorer health, particularly among socially disadvantaged groups. However, the more robust reviews each [also] identified studies with inconclusive findings" (176).

If there is an independent health effect of psychosocial factors – which does seem plausible – then the combination of a higher exposure to psychosocial stressors and less capacity to remove or buffer these exposures in lower socioeconomic groups may explain part of socioeconomic inequalities in health. This has been best documented for psychosocial factors related to work organization, such as job strain, which as mentioned above have been shown to contribute to socioeconomic inequalities in cardiovascular health, including in mediation analyses (152). Mediation analyses focusing on the role of psychosocial stressors outside the work environment are less common, but have also suggested a non-trivial role for psychosocial factors in generating health inequalities (177, 178).

3.3.4 Health-related behaviours

The role of health-related behaviours, such as smoking, excessive alcohol consumption, inadequate diet, lack of physical exercise and obesity, in generating health inequalities has been relatively well documented. These are established causal determinants of morbidity and mortality, and are often more prevalent in the lower socioeconomic groups in many high-income countries (20, 179-182). This is also the group of factors for which most formal mediation analyses have been carried out, which generally show that health-related behaviours make substantial contributions to the explanation of health inequalities. However, the fact that almost all of these mediation analyses followed the conventional 'difference method' calls for caution in the interpretation.

By far the most widely available data on a specific determinant of health inequalities relate to smoking. In many European countries cigarette smoking is the number 1 determinant of health problems. Systematic reviews and other overviews have shown the prevalence of smoking to differ strongly between socioeconomic groups in many high-income countries (179, 183), particularly among men, and several mediation analyses have found that smoking alone accounts for a substantial part of socioeconomic inequalities in mortality (124, 184). There are, however, important differences between European countries in the magnitude of inequalities in smoking, and consequently in the contribution of smoking to inequalities in mortality and other health outcomes (120, 185).

Excessive alcohol consumption is bad for health too, and although harmful drinking (including 'binge drinking') is probably more common in lower socioeconomic groups survey data have produced mixed results, probably due to real variations between countries and sampling and reporting biases in survey data (180, 186). Therefore, many studies use mortality due to alcohol-related causes of death as a proxy indicator of harmful alcohol consumption and the burden of disease related to alcohol. These studies show substantial but variable contributions of alcohol-related mortality to inequalities in all-cause mortality (187, 188). Mediation analyses confirm that excessive alcohol consumption does contribute to the explanation of health inequalities in some countries but less so in others (124, 184, 189).

Men and women in lower socioeconomic groups tend to eat less fresh vegetables and fruits, particularly in the North of Europe. Differences in fresh vegetable and fruit consumption may be smaller in the South of Europe, perhaps because of the larger availability and affordability of vegetables and fruits in Mediterranean countries (181).

Overview studies show that spending little leisure-time on physical activity tends to be more common in the lower socioeconomic groups (190, 191). The same is true for overweight and obesity, but the magnitude (and sometimes even the direction) of these inequalities differs strongly between countries (20, 192). As a result, the contribution of inequalities in obesity to inequalities in health is also likely to

differ strongly between countries (121). Mediation analyses confirm that inequalities in physical activity and obesity do play a role in generating health inequalities in some countries (124, 184, 189, 193).

The systematic nature of these differences in health-related behaviour indicates that these are not simply a matter of free choice, but at least partly determined by constraints imposed by conditions beyond the control of the individual. Some psychosocial factors that could play a role in generating these behaviour patterns were mentioned above (150). Other constraints are neighbourhood conditions: people with a lower socioeconomic position tend to live in less well-to-do neighbourhoods which may have limited opportunities for physical exercise and purchase of healthy foods (194).

3.3.5 Health care

A final group of factors that could explain health inequalities is health care: if people with a lower socioeconomic position receive less, or lower quality, health care than people with a higher socioeconomic position this could exacerbate the inequalities in health generated by all the other factors mentioned above. Less use of effective preventive services by lower socioeconomic groups may contribute to a higher incidence of diseases, and less use of effective treatment services may contribute to a lower recovery rate or higher case fatality rate of diseases. There are good reasons for suspecting that this may play a role, depending on the degree to which countries have, or have not, eliminated socioeconomic inequalities in access and quality of health care.

Although most high-income countries have created health care financing systems that have substantially reduced financial barriers to health care use, these and other barriers have not been completely eliminated and still generate important differences in health care use between socioeconomic groups, as shown by a series of comparative studies (195-197). The most recent of these studies found important differences in health care use between income groups after adjustment for 'need', or health status, in all OECD countries. Although people with a low income are as likely to see a general practitioner as people with a high income, the latter are much more likely so see a specialist and a dentist, and to participate in cancer screening (198). Similar differences in health care use are found between people with a low and high education (199-201).

Whether these inequalities in health care use in fact generate inequalities in health outcomes depends on the effectiveness of the specific interventions that the services deliver, and that are forgone by those who do not use the service. Two separate pieces of evidence suggest that this is indeed the case:

- Specific interventions for which inequalities have been found favouring people with a higher socioeconomic position, are many and include interventions of proven effectiveness (202-205).
- For several diseases, inequalities in case fatality rates have been found that cannot be accounted for by inequalities in stage of disease at presentation, or other non-health care determinants of survival (206-211) – a finding that can only partly be explained by inequalities in stage at diagnosis or other patient or tumour characteristics, suggesting that inequalities in treatment must also play a role (212).

Other suggestive evidence for a role of health care in explaining health inequalities comes from studies of inequalities in mortality from conditions that are amenable to medical intervention, such as cerebrovascular disease, tuberculosis, appendicitis and perinatal mortality, which show that these inequalities are substantial (213).

4 CONCLUSIONS AND RECOMMENDATIONS

4.1 Is there a causal effect of socioeconomic position on health?

The association between socioeconomic position and health is one of the most widely reproduced findings in population health research. There is solid evidence that, even in high income countries, people with a lower socioeconomic position on average live substantially shorter lives, and also have substantially higher rates of morbidity during their shorter lives, than people with a higher socioeconomic position. However, even after decades of research, there still is uncertainty about the extent to which this reflects a causal effect of socioeconomic position on health, ‘reverse causation’ of health on socioeconomic position, or ‘confounding’ (underlying factors that affect both socioeconomic position and health).

Social epidemiologists have generally tended to interpret the association between socioeconomic position and health as being largely due to a causal effect of socioeconomic position on health (1, 214). However, recent research in other disciplines, such as genetics and economics, suggests that this idea needs to be qualified. The new evidence reviewed in this discussion paper suggests that both reverse causation (in the case of the association between income and health) and confounding by unobserved personal attributes (in the case of the association between education, occupational class and income) may play a more important role than previously recognized. The mixed results of (quasi-)experimental studies, particularly with regard to an effect of income on adult health, also cast doubt on the idea that all of the association between socioeconomic position and health reflects a causal effect of socioeconomic position on health.

At the same time, the value of the new evidence should not be overrated. In the case of genetic research, current evidence is insufficient to reach firm conclusions about the role of genetic determinants of cognitive ability and other personal attributes in generating health inequalities. For example, genetic variants that have been identified so far can only very partly account for the influence of heritability as estimated from twin studies. More generally, the role of genetic factors in determining social and health outcomes has to be further elucidated, including in particular the role of environmental factors in gene expression.

Also with respect to new (quasi-)experimental evidence there is reason for pause before final conclusions are drawn. As mentioned above, the paradox here is that the stricter we are on establishing causality and the closer we get to identifying a genuine causal effect, the farther we may get from actually understanding how socioeconomic position affects health. The reason for this is that more rigorous studies inspired by the ‘counterfactual’ approach to causal inference probably do not capture the full experience of living in socioeconomic (dis)advantage. If one accepts the idea – common in sociology – that social inequality consists of much more than differences in a few years of education or differences in few hundred Euros of monthly income, one must conclude that the new methods for identifying causal effects do not fully capture the many cumulative and interacting effects on health of being in a lower socioeconomic position.

On the other hand, adherents to the ‘causal inference’ approach could argue that such a broader and vaguer concept of socioeconomic position does not lend itself to testing of causal relationships, and that studies of more narrowly defined and manipulable exposures are more relevant for policy. Further interdisciplinary discussions are clearly necessary to clarify and hopefully bridge these differences of opinion.

In the mean-time, and based on our review of scientific literature, we offer the following preliminary conclusions on how socioeconomic position relates to health:

- (a) There is probably an independent causal effect of education on health, and the observed association between education and health is probably partly due to such a causal effect.
- (b) It is uncertain whether there is an independent causal effect of occupational class on health.
- (c) It is unlikely that small changes in income have an independent causal effect on adult health in the

short term. However, the available evidence does not exclude the possibility that larger and long-lasting changes in income have effects on adult health in the longer term, particularly at the lower end of the income distribution. It is also likely that parental income has an independent causal effect on the health of children.

- ‘Reverse causation’ (or health-related selection) likely plays an important role in the association between income and health, but much less so in the association between education and health, with the association between occupational class and health probably somewhere in-between.
- ‘Confounding’ by personal attributes such as genetic factors, cognitive ability, and personality traits may play a more important role in the association between education, occupational class and income and health than previously recognized. However, direct evidence for a confounding role of these factors is still scarce and inconclusive. Moreover, with the exception of genetic factors these personal attributes can only be considered confounders if social inequalities are narrowed down to the effects of low education, occupational class and income in adulthood. If one takes a broader point of view on social inequalities, one has to take into account that cognitive ability and personality traits are themselves (partly) the result of inequalities in social conditions during childhood.

4.2 What mediates the effect of socioeconomic position on health?

Based on our review of scientific literature, we also conclude that it is likely that health inequalities can partly be explained by differential exposure to a range of well-known health determinants, including early childhood environment, material living conditions, social and psychological factors, health-related behaviours, and health care. That these factors play a role in generating health inequalities – with variable contributions depending, among other things, on type of health outcome and national context – is sufficiently certain to underpin the development of policies to tackle health inequalities.

However, new methodological insights have emerged which suggest that the available evidence also has several limitations. The first is that conventional mediation analyses do not assess the extent to which these factors truly lie on the causal pathway between socioeconomic position and health. They leave open the possibility of ‘reverse causation’ and ‘confounding’ of the relationship between socioeconomic position and the putative mediator. As we explained in par. 3.1.1, this does not invalidate all policy recommendations based on the results of conventional mediation analyses, but does need to be taken into account when interpreting the results, for example by using the term ‘contributing factor’ instead of ‘mediator’.

A second limitation is that conventional mediation analyses do not provide reliable estimates of the quantitative contributions of putative mediators to health inequalities. It therefore also remains unknown which of the contributing factors should receive the highest priority in policies aiming to reduce health inequalities. The complexity of the many interrelationships between measures of socioeconomic position, contributing factors, and various health outcomes requires more sophisticated analytical approaches than have commonly been applied. There is a need for more comprehensive and more systematic mediation analyses using newly developed methods that are less subject to various forms of bias than conventional mediation analyses. The results of these studies will have to be awaited before we can conclude whether quantitative estimates from conventional mediation analyses are biased or not. Fortunately, these new methods can be used to re-analyse existing data, so that obtaining new data would not always be needed.

A third limitation of the available evidence is that, in addition to differential exposure, differential susceptibility to health determinants may play a role in generating health inequalities. So far, empirical evidence on differential susceptibility is scarce. For example, a potentially important aspect of differential susceptibility is gene-environment interaction, i.e. differences between socioeconomic groups in susceptibility to the health effects of certain genotypes. However, there is a need for more and better powered studies to investigate differential susceptibility, because this may have important implications for policy: interventions aimed at reducing differential exposure may be inadequate for tackling differential vulnerability.

Based on our review of scientific literature as presented in the previous chapters, we offer the following preliminary substantive conclusions.

4.3 Recommendations

- **Have more interdisciplinary dialogue on methodological issues with respect to the study of health inequalities.**

This discussion paper underscores that there is a need for more interdisciplinary dialogue on the methodological issues highlighted in this report. The committee anticipates that reaching consensus on these methodological issues will also require an interdisciplinary dialogue on the theoretical framework(s) used for studying health inequalities, e.g. concerning the nature of social inequality. The need for more interdisciplinary dialogue on methodological issues applies to both of the major questions of this report:

1. Is there a causal effect of socioeconomic position on health? Recent methodological advances offer opportunities for increasing the level of scientific certainty about causal relationships, but tend to focus on narrowly defined variations in socioeconomic position. This may lead to results that are indeed valid within a specific research setting, but at the expense of sacrificing how they can be applied to the real world. This dilemma needs to be solved in order to be able to study the full impact of variations in socioeconomic position on health.
2. What mediates the effect of socioeconomic position on health? How can the three limitations of the available evidence on mediation be overcome? I.e.:
 - i) How can we increase the level of scientific certainty about the causal effect of socioeconomic position on putative mediators?
 - ii) To what extent are the results of conventional mediation analyses biased, and does that necessitate a reconsideration of policy approaches aimed at reducing health inequalities?
 - iii) How can moderation be included more fully in analyses of the explanation of health inequalities?

In addition to these two major questions, there is a third major question which could not be addressed in this discussion paper:

3. How can socioeconomic inequalities in health be reduced? Evaluating policies and interventions that aim to reduce health inequalities poses many methodological challenges, with regard to both research design and data analysis. Exchanging methodological insights from various disciplines is likely to be as useful for this third question as for the first two questions.

The committee therefore recommends the European academies of science to support step two of this project, which aims to address these methodological challenges and work towards more interdisciplinary consensus on these issues.

- **Fill substantive knowledge gaps with respect to the explanation of health inequalities.**

Although research into the explanation of health inequalities has made great advances over the past 30 years, many knowledge gaps remain. This discussion paper does not claim to have provided an exhaustive overview of the available evidence, and thus has also not led to a systematic overview of gaps in knowledge. Nevertheless, it is clear that many knowledge gaps remain.

- There is a need for more studies into the nature of the relationship between socioeconomic position and health: to what extent is this relationship due to causation, 'reverse causation', and confounding? Particular attention is necessary for the possible role of genetics. There is also a need to look beyond conventional indicators of socioeconomic status: as the nature of social stratification is changing, the health problems of 'new' disadvantaged groups (e.g., refugees, homeless people) need to be studied.
- There is also a need for more studies into the specific health determinants contributing to health inequalities. Evidence from conventional mediation analyses is limited in scope, and likely needs to be replaced by results based on new methods of mediation analysis that are less susceptible to bias.

In addition to mediation, moderation is likely to be an important mechanism but is greatly under-researched.

For both study areas, life-course approaches will be necessary to disentangle the complex relationships involved.

- **In the mean-time, move forward policy-making aimed at reducing health inequalities.**

The methodological considerations, and resulting doubts about the accuracy of some of the research findings, highlighted in this discussion paper, should not be seen as an excuse for inaction. Effective policy-making does not require complete certainty, and effective policy-making does also not necessarily require evidence on causality in the relationship between socioeconomic position and putative mediators. For example, specifically tackling those health determinants that are more common in disadvantaged groups, such as problems in early childhood, unfavourable material living conditions, unfavourable social and psychological conditions, health-damaging behaviours and lack of access to good quality health care, will improve the health of these disadvantaged groups and thus lead to a reduction of health inequalities.

Nevertheless, more explicit consideration of the strength of available evidence is necessary in underpinning policy recommendations with respect to health inequalities. This will help to prioritize policies for which the evidence is relatively strong, and also will help to prioritize further research efforts, including policy evaluations. Interventions aiming to reduce health inequalities should be evaluated carefully, not only because this creates a more robust underpinning of policies in this area, but also because both positive and negative results of evaluation studies will contribute to a better understanding of the mechanisms generating health inequalities.

ANNEX 1: FEAM/ALLEA COMMITTEE ON HEALTH INEQUALITIES

Professor Johan Mackenbach, *chair*

- Professor of Public Health, Erasmus Medical Center, Rotterdam, The Netherlands
- Royal Netherlands Academy of Arts and Sciences

Professor Giuseppe Costa

- Professor of Public Health, Dept. Clinical and Biological Sciences, University of Turin, Italy

Professor Johannes Siegrist

- Senior Professor Work Stress Research, Institut für Medizinische Soziologie, Heinrich-Heine-Universität Düsseldorf, Germany

Dr Domantas Jasilionis

- Max Planck Institute for Demographic Research, Rostock, Germany
- Center for Demographic Research, Vytautas Magnus University, Kaunas, Lithuania

Professor Alfred Spira

- Professor of Public Health and Epidemiology, Université Paris Sud, France
- French Academy of Medicine

Professor Denny Vågerö

- CHESS, Centre for Health Equity Studies, Stockholm University/ Karolinska Institutet, Sweden
- Royal Swedish Academy of Sciences

Professor Brian Nolan

- Professor of Social Policy, Institute for New Economic Thinking, Nuffield College, University of Oxford
- Royal Irish Academy

Dr Jean Philippe de Jong, *secretary*

- Royal Netherlands Academy of Arts and Sciences

ANNEX 2: FEAM/ALLEA SYMPOSIUM PROGRAMME



A report of this symposium is available [at the ALLEA website](#).¹²

Health inequalities

An interdisciplinary discussion of socioeconomic position, health and causality

Hosted by KNAW

Date: 24 May 2018, 9.30 a.m. – 5.00 p.m.

Venue: De Nieuwe Liefde, Da Costakade 102, Amsterdam, the Netherlands

Chairs: George Griffin, FEAM (morning); Johan Mackenbach, KNAW (afternoon)

Programme

- 9.00 a.m. *Registration*
- 9.30 a.m. Wim van Saarloos, KNAW; Bernhard Charpentier, FEAM; Graham Caie, ALLEA – *Opening, welcome*
- 10.00 a.m. Johan Mackenbach, Erasmus Medical Center, The Netherlands – *Health Inequalities, an overview of unresolved scientific issues*
- 10.30 a.m. Eric Brunner, University College London, United Kingdom – *Explanations of health inequalities emerging from the Whitehall study*
- 11.30 a.m. Jay Kaufman, McGill University, Canada – *Methodological issues in explaining health inequalities*
- 12.30 p.m. *Lunch*
- 1.30 p.m. Eddy van Doorslaer, Erasmus University Rotterdam, The Netherlands – *Does low income cause ill-health? An economist's perspective*
- 1.55 p.m. Margaret Whitehead, University of Liverpool, United Kingdom – *Does low income cause ill-health? A public health perspective*
- 2.20 p.m. David Hill, University of Edinburgh, United Kingdom – *Does low education cause ill-health? A geneticist's perspective*
- 2.45 p.m. Olle Lundberg, Centre for Health Equity Studies, Sweden – *Does low education cause ill-health? A sociologist's perspective*
- 3.10 p.m. Domantas Jasilionis, Vytautas Magnus University, Lithuania & Max Planck Institute for Demographic Research, Germany – *Health inequalities in Eastern Europe – Do they have the same explanation?*
- 3.35 p.m. *Break*

¹² https://www.allea.org/wp-content/uploads/2018/11/Health_Inequalities_Symposium_Report.pdf

- 3.50 p.m. Giuseppe Costa, University of Turin, Italy – *Policy implications of explanations of health inequalities*
- 4.05 p.m. *Panel discussion*
- 4.50 p.m. Graham Caie, ALLEA – *The role of academies, closing remarks*
- 5.00 p.m. *Drinks*

REFERENCES

1. Commission on Social Determinants of Health. Closing the gap in a generation. *Health equity through the social determinants of health*. Geneva: World Health Organization; 2008.
2. Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P. WHO European review of social determinants of health and the health divide. *The Lancet*. 2012;380(9846):1011-29.
3. Mackenbach JP, Meerding WJ, Kunst AE. Economic costs of health inequalities in the European Union. *Journal of Epidemiology & Community Health*. 2011;65(5):412-9.
4. Whitehead M. The concepts and principles of equity and health. *International journal of health services : planning, administration, evaluation*. 1992;22(3):429-45.
5. Wismar M, McKee M, Ernst K, Srivastava D, Busse R. *Health targets in Europe: learning from experience*. Copenhagen: World Health Organization; 2008.
6. Mackenbach JP, Kulhánová I, Artnik B, Bopp M, Borrell C, Clemens T, et al. Changes in mortality inequalities over two decades: register based study of European countries. *British Medical Journal*. 2016;353:i1732.
7. Maxwell JA. *Using qualitative methods for causal explanation*. *Field methods*. 2004;16(3):243-64.
8. Hedström P, Swedberg R. *Social mechanisms: An analytical approach to social theory*. Cambridge etc.: Cambridge University Press; 1998.
9. Mackenbach JP. *Socioeconomic inequalities in health in high-income countries: the facts and the options*. In: Detels R, Gulliford M, Karim QA, Tan CC, editors. *Oxford Textbook of Global Public Health*. 1. Oxford etc.: Oxford University Press; 2014.
10. *Inequalities in Health: Report of a research working group (the Black report)*. London Department of Health and Social Services; 1980.
11. Macintyre S. The Black Report and beyond: what are the issues? *Soc Sci Med*. 1997;44(6):723-45.
12. Vågerö D, Illsley R. Explaining health inequalities: beyond Black and Barker: a discussion of some issues emerging in the decade following the Black Report. *European Sociological Review*. 1995;11(3):219-41.
13. Kröger H, Pakpahan E, Hoffmann R. What causes health inequality? A systematic review on the relative importance of social causation and health selection. *European Journal of Public Health*. 2015;25(6):951-60.
14. Marmot M. *The health gap: the challenge of an unequal world*: Bloomsbury Publishing; 2015.
15. Majer IM, Nusselder WJ, Mackenbach JP, Kunst AE. Socioeconomic inequalities in life and health expectancies around official retirement age in 10 Western-European countries. *Journal of epidemiology and community health*. 2011;65(11):972-9.
16. Burstrom B, Whitehead M, Lindholm C, Diderichsen F. Inequality in the social consequences of illness: how well do people with long-term illness fare in the British and Swedish labor markets? *International journal of health services : planning, administration, evaluation*. 2000;30(3):435-51.
17. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 2008.
18. Lounsbury JW, Sundstrom E, Loveland JM, et al. Intelligence, "big five" personality traits, and work drive as predictors of course grade. *Person Individ Diff*. 2003;35:1231-9.
19. Judge TA, Higgins CA, Thoreson CJ, et al. The big five personality traits, general mental ability, and career success across the lifespan. *Person Psychol*. 1999;52:621-52.

20. Sobal J, Stunkard AJ. Socioeconomic status and obesity: a review of the literature. *Psychol Bull.* 1989;105(2):260-75.
21. Heraclides A, Brunner E. Social mobility and social accumulation across the life course in relation to adult overweight and obesity: the Whitehall II study. *Journal of Epidemiology & Community Health.* 2010;jech. 2009.087692.
22. Makela P. Alcohol-related mortality as a function of socio-economic status. *Addiction.* 1999;94(6):867-86.
23. Mackenbach JP. New trends in health inequalities research: now it's personal. *Lancet.* 2010;376(9744):854-5.
24. Carey G, Crammond B. A glossary of policy frameworks: the many forms of 'universalism' and policy 'targeting'. *Journal of epidemiology and community health.* 2017;71:303-7.
25. Segall S. *Health, luck, and justice.* Princeton: Princeton University Press; 2009.
26. Mackenbach JP. Genetics and health inequalities: hypotheses and controversies. *Journal of epidemiology and community health.* 2005;59(4):268-73.
27. Shanahan MJ, Boardman JD. *Genetics and behavior in the life course: A promising frontier.* In: Elder GH, Giele JZ, editors. *The craft of life course research.* New York: Guildford Press; 2009. p. 215-35.
28. Thayer ZM, Kuzawa CW. Biological memories of past environments: epigenetic pathways to health disparities. *Epigenetics.* 2011;6(7):798-803.
29. Fiorito G, Polidoro S, Dugué P-A, Kivimaki M, Ponzi E, Matullo G, et al. Social adversity and epigenetic aging: a multi-cohort study on socioeconomic differences in peripheral blood DNA methylation. *Scientific reports.* 2017;7(1):16266.
30. Ben-Shlomo Y, Kuh D. *A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives.* Oxford University Press; 2002.
31. Smith GD, Hart C, Blane D, Gillis C, Hawthorne V. Lifetime socioeconomic position and mortality: prospective observational study. *BMJ.* 1997;314(7080):547-52.
32. Power C, Kuh D. Lifecourse development of unequal health. In: Siegrist J, Marmot MG, editors. *Social inequalities in health New evidence and policy implications.* Oxford: Oxford University Press; 2006. p. 27-53.
33. Mheen Hvd, Stronks K, Mackenbach JP. A lifecourse perspective on socioeconomic inequalities in health: the influence of childhood socioeconomic position and selection processes. *Sociology of Health and Illness.* 1998;20:754-77.
34. Barker DJP, Robinson RJ, editors. *Fetal and infant origins of adult disease.* London: *British Medical Journal*; 1992.
35. Hayward MD, Gorman BK. The long arm of childhood: The influence of early-life social conditions on men's mortality. *Demography.* 2004;41(1):87-107.
36. Keating DP, Hertzman C, editors. *Developmental health and the wealth of nations: Social, biological and educational dynamics.* New York: Guildford; 1999.
37. Kawachi I, Adler NE, Dow WH. Money, schooling, and health: Mechanisms and causal evidence. *Ann N Y Acad Sci.* 2010;1186:56-68.
38. Kaufman JS, Cooper RS. Seeking causal explanations in social epidemiology. *American Journal of Epidemiology.* 1999;150(2):113-20.
39. Oakes JM. Invited commentary: paths and pathologies of social epidemiology. *American Journal of Epidemiology.* 2013;178(6):850-1.
40. Krieger N, Smith GD. Re:"Seeking causal explanations in social epidemiology". *American Journal of Epidemiology.* 2000;151(8):831-2.
41. Krieger N, Davey Smith G. The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. *International Journal of Epidemiology.* 2016;45(6):1787-808.

42. Hu Y, van Lenthe FJ, Hoffmann R, van Hedel K, Mackenbach JP. Assessing the impact of natural policy experiments on socioeconomic inequalities in health: how to apply commonly used quantitative analytical methods? *BMC Med Res Methodol*. 2017;17(1):68.
43. Snyder SE, Evans WN. The effect of income on mortality: evidence from the social security notch. *The Review of Economics and Statistics*. 2006;88(3):482-95.
44. Apouey B, Clark AE. *Winning Big but Feeling No Better? The Effect of Lottery Prizes on Physical and Mental Health*. Bonn: Institute for the Study of Labor (IZA); 2010.
45. Lager AC, Torssander J. Causal effect of education on mortality in a quasi-experiment on 1.2 million Swedes. *Proceedings of the National Academy of Sciences of the United States of America*. 2012;109(22):8461-6.
46. Hill AB. Environment and disease: association or accusation? *Proceedings of the Royal Society of Medicine*. 1965;58:295-300.
47. IARC Monographs on the evaluation of carcinogenic risks to humans - preamble. Lyon: *International Agency for Research on Cancer*; 2006.
48. Lawlor DA, Tilling K, Davey Smith G. Triangulation in aetiological epidemiology. *International Journal of Epidemiology*. 2016;45(6):1866-86.
49. Petticrew M, Cummins S, Ferrell C, Findlay A, Higgins C, Hoy C, et al. Natural experiments: an underused tool for public health? *Public health*. 2005;119(9):751-7.
50. Whitehead M, Petticrew M, Graham H, Macintyre SJ, Bambra C, Egan M. Evidence for public health policy on inequalities: 2: assembling the evidence jigsaw. *Journal of epidemiology & community health*. 2004;58(10):817-21.
51. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. *The New England journal of medicine*. 2008;358(23):2468-81.
52. Galobardes B, Lynch J, Smith GD. Measuring socioeconomic position in health research. *British medical bulletin*. 2007;81-82:21-37.
53. Smith JP. The impact of childhood health on adult labor market outcomes. *The review of economics and statistics*. 2009;91(3):478-89.
54. Cutler DM, Lleras-Muney A, Vogl T. Socioeconomic status and health: dimensions and mechanisms. *National Bureau of Economic Research*; 2008.
55. Galama T, Lleras-Muney A, van Kippersluis H. *The effect of education on health and mortality: a review of experimental and quasi-experimental evidence*. Cambridge, MA: National Bureau of Economic Research; 2018.
56. Plomin R, Deary IJ. Genetics and intelligence differences: five special findings. *Molecular psychiatry*. 2015;20(1):98.
57. Deary IJ, Johnson W, Houlihan LM. Genetic foundations of human intelligence. *Human genetics*. 2009;126(1):215-32.
58. Polderman TJC, Benyamin B, De Leeuw CA, Sullivan PF, Van Bochoven A, Visscher PM, et al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics*. 2015;47(7):702-9.
59. Marioni RE, Davies G, Hayward C, Liewald D, Kerr SM, Campbell A, et al. Molecular genetic contributions to socioeconomic status and intelligence. *Intelligence*. 2014;44:26-32.
60. Conley D, Fletcher J. *The Genome Factor: What the social genomics revolution reveals about ourselves, our history, and the future*: Princeton University Press; 2017.
61. Hill WD, Arslan RC, Xia C, Luciano M, Amador C, Navarro P, et al. Genomic analysis of family data reveals additional genetic effects on intelligence and personality. *Molecular psychiatry*. 2018:1.

62. Hill WD, Arslan RC, Xia C, Luciano M, Amador C, Navarro P, et al. Genomic analysis of family data reveals additional genetic effects on intelligence and personality. *Molecular Psychiatry*. 2018.
63. al. Le. Gene discovery and polygenic prediction from a 1.1-million-person GWAS of educational attainment. *Nature Genetics*. 2018;forthcoming.
64. Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA, et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature*. 2016;533(7604):539–42.
65. Krapohl E, Plomin R. Genetic link between family socioeconomic status and children’s educational achievement estimated from genome-wide SNPs. *Molecular psychiatry*. 2016;21(3):437.
66. Davies NM, Dickson M, Smith GD, van den Berg GJ, Windmeijer F. The causal effects of education on health outcomes in the UK Biobank. *Nature Human Behaviour*. 2018;in press.
67. Lager A, Seblova D, Falkstedt D, Lövdén M. Cognitive and emotional outcomes after prolonged education: a quasi-experiment on 320 182 Swedish boys. *International Journal of Epidemiology*. 2016;46(1):303-11.
68. Kunst AE, Groenhouf F, Mackenbach JP. Occupational class and cause specific mortality in middle aged men in 11 European countries: comparison of population based studies. *British Medical Journal* 1998;316(7145):1636-42.
69. Toch-Marquardt M, Menvielle G, Eikemo TA, Kulhanová I, Kulik MC, Bopp M, et al. Occupational class inequalities in all-cause and cause-specific mortality among middle-aged men in 14 European populations during the early 2000s. *PLoS One*. 2014;9(9):e108072.
70. Marmot MG, Stansfeld S, Patel C, North F, Head J, White I, et al. Health inequalities among British civil servants: the Whitehall II study. *The Lancet*. 1991;337(8754):1387-93.
71. Ravesteijn B, van Kippersluis H, van Doorslaer E. *The contribution of occupation to health inequality*. In: Rosa Dias P, O’Donnell O, editors. Health and inequality ((Research on Economic Inequality, Volume 21). Bingley: Emerald Group Publishing; 2013. p. 311-32.
72. Miech RA, Hauser RM. Socioeconomic status and health at midlife: a comparison of educational attainment with occupation-based indicators. *Annals of epidemiology*. 2001;11(2):75-84.
73. Winkleby MA, Jatulis DE, Frank E, Fortmann SP. Socioeconomic status and health: how education, income, and occupation contribute to risk factors for cardiovascular disease. *American journal of public health*. 1992;82(6):816-20.
74. Geyer S, Hemström Ö, Peter R, Vågerö D. Education, income, and occupational class cannot be used interchangeably in social epidemiology. Empirical evidence against a common practice. *Journal of Epidemiology & Community Health*. 2006;60(9):804-10.
75. Smith GD, Hart C, Hole D, MacKinnon P, Gillis C, Watt G, et al. Education and occupational social class: which is the more important indicator of mortality risk? *Journal of Epidemiology & Community Health*. 1998;52(3):153-60.
76. Batty GD, Der G, Macintyre S, Deary IJ. Does IQ explain socioeconomic inequalities in health? Evidence from a population based cohort study in the west of Scotland. *BMJ*. 2006;332(7541):580-4.
77. Power C, Kuh D, Morton S. From developmental origins of adult disease to life course research on adult disease and aging: insights from birth cohort studies. *Annual review of public health*. 2013;34:7-28.
78. Bartley M. *Health inequality: an introduction to concepts, theories and methods* (2nd edition). Cambridge: Polity Press; 2017.
79. Devaux M, Sassi F. *The labour market impacts of obesity, smoking, alcohol use and related chronic diseases*. Paris: OECD Publishing; 2015. Report No.: 1815-2015.
80. Bartley M, Plewis I. Increasing social mobility: an effective policy to reduce health inequalities. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*. 2007;170(2):469-81.

81. Blane D, Harding S, Rosato M. Does social mobility affect the size of the socioeconomic mortality differential?: evidence from the Office for National Statistics Longitudinal Study. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*. 1999;162(1):59-70.
82. Boyle PJ, Norman P, Popham F. Social mobility: evidence that it can widen health inequalities. *Social Science & Medicine*. 2009;68(10):1835-42.
83. Claussen B, Smits J, Naess O, Smith GD. Intragenerational mobility and mortality in Oslo: social selection versus social causation. *Social Science & Medicine*. 2005;61(12):2513-20.
84. Kunst AE, Leon DA, Groenhof F, Mackenbach JP. Occupational class and cause specific mortality in middle aged men in 11 European countries: comparison of population based studiesCommentary: Unequal inequalities across Europe. *BMJ*. 1998;316(7145):1636-42.
85. Marmot MG, Shipley MJ. Do socioeconomic differences in mortality persist after retirement? 25 year follow up of civil servants from the first Whitehall study. *BMJ*. 1996;313(7066):1177-80.
86. Doorslaer Ev, Koolman X. Explaining the differences in income-related health inequalities across European countries. *Health economics*. 2004;13(7):609-28.
87. Mackenbach JP, Martikainen P, Looman CW, Dalstra JA, Kunst AE, Lahelma E. The shape of the relationship between income and self-assessed health: an international study. *International journal of epidemiology*. 2004;34(2):286-93.
88. Backlund E, Sorlie PD, Johnson NJ. A comparison of the relationships of education and income with mortality: the national longitudinal mortality study. *Social science & medicine*. 1999;49(10):1373-84.
89. Lahelma E, Martikainen P, Laaksonen M, Aittomäki A. Pathways between socioeconomic determinants of health. *Journal of Epidemiology & Community Health*. 2004;58(4):327-32.
90. O'Donnell O, Van Doorslaer E, Van Ourti T. Health and inequality. *Handbook of Income Distribution*. 2: Elsevier; 2015. p. 1419-533.
91. Smith JP. Healthy bodies and thick wallets: the dual relation between health and economic status. *Journal of Economic perspectives*. 1999;13(2):145-66.
92. Hill WD, Hagenaars SP, Marioni RE, Harris SE, Liewald DC, Davies G, et al. Molecular genetic contributions to social deprivation and household income in UK *Biobank*. *Current Biology*. 2016;26(22):3083-9.
93. Cooper K, Stewart K. *Does money in adulthood affect adult outcomes?* York: Joseph Rowntree Foundation; 2015.
94. Cooper K, Stewart K. *Does Money Affect Children's Outcomes?: A Systematic Review*. York: Joseph Rowntree Foundation; 2013.
95. Cesarini D, Lindqvist E, Östling R, Wallace B. Wealth, health, and child development: Evidence from administrative data on Swedish lottery players. *The Quarterly Journal of Economics*. 2016;131(2):687-738.
96. Dahlgren G, Whitehead M. *Policies and strategies to promote social equity in health*. Stockholm: Institute for future studies. 1991.
97. Whitehead M, Dahlgren G. Concepts and principles for tackling social inequities in health: Levelling up Part 1. *World Health Organization: Studies on social and economic determinants of population health*. 2006;2.
98. Mackenbach JP, Bakker MJ. Tackling socioeconomic inequalities in health: analysis of European experiences. *Lancet*. 2003;362(9393):1409-14.
99. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. *Journal of personality and social psychology*. 1986;51(6):1173.
100. MacKinnon DP, Lockwood CM, Hoffman JM, West SG, Sheets V. A comparison of methods to test mediation and other intervening variable effects. *Psychological methods*. 2002;7(1):83.

101. VanderWeele T. *Explanation in causal inference: methods for mediation and interaction*: Oxford University Press; 2015.
102. Diderichsen F, Evans T, Whitehead M. *The social basis of disparities in health*. Challenging inequities in health: From ethics to action. 2001;1:12-23.
103. Diderichsen F. *Policies for health equity: an ethical and epidemiological framework and targets for a new national health policy in Sweden*. HEALTH CARE PRIORITY SETTING. 2003:57.
104. Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. Low-level lead exposure, social class, and infant development. *Neurotoxicology and teratology*. 1988;10(6):497-503.
105. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. *American journal of epidemiology*. 2013;178(6):865-76.
106. Katikireddi SV, Whitley E, Lewsey J, Gray L, Leyland AH. Socioeconomic status as an effect modifier of alcohol consumption and harm: analysis of linked cohort data. *The Lancet Public Health*. 2017;2(6):e267-e76.
107. Belsky J, Pluess M. Beyond diathesis stress: differential susceptibility to environmental influences. *Psychological bulletin*. 2009;135(6):885.
108. Belsky J, Jonassaint C, Pluess M, Stanton M, Brummett B, Williams R. Vulnerability genes or plasticity genes? *Molecular psychiatry*. 2009;14(8):746.
109. Vågerö D, Aronsson V, Modin B. Why is parental lifespan linked to children's chances of reaching a high age? A transgenerational hypothesis. *Social Science and Medicine - Population Health*. 2018;4:45-54.
110. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, et al. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*. 2003;301(5631):386-9.
111. Belsky DW, Moffitt TE, Caspi A. Genetics in population health science: strategies and opportunities. *American journal of public health*. 2013;103(S1):S73-S83.
112. Turkheimer E, Haley A, Waldron M, d'Onofrio B, Gottesman II. Socioeconomic status modifies heritability of IQ in young children. *Psychological science*. 2003;14(6):623-8.
113. Ferraro KF, Kelley-Moore JA. Cumulative disadvantage and health: long-term consequences of obesity? *American sociological review*. 2003;68(5):707.
114. Gerlach G, Herpertz S, Loeber S. Personality traits and obesity: a systematic review. *Obesity reviews*. 2015;16(1):32-63.
115. Main C, Thomas S, Ogilvie D, Stirk L, Petticrew M, Whitehead M, et al. Population tobacco control interventions and their effects on social inequalities in smoking: placing an equity lens on existing systematic reviews. *BMC public health*. 2008;8:178.
116. Bambra C, Gibson M, Sowden A, Wright K, Whitehead M, Petticrew M. Tackling the wider social determinants of health and health inequalities: evidence from systematic reviews. *Journal of epidemiology and community health*. 2010;64(4):284-91.
117. Thomas S, Fayter D, Misso K, Ogilvie D, Petticrew M, Sowden A, et al. Population tobacco control interventions and their effects on social inequalities in smoking: systematic review. *Tobacco control*. 2008;17(4):230-7.
118. Hoffmann R, Eikemo TA, Kulhánová I, Dahl E, Deboosere P, Dzúrová D, et al. The potential impact of a social redistribution of specific risk factors on socioeconomic inequalities in mortality: illustration of a method based on population attributable fractions. *Journal of epidemiology and community health*. 2012;jech-2011-200886.
119. Eikemo TA, Hoffmann R, Kulik MC, Kulhánová I, Toch-Marquardt M, Menvielle G, et al. How can inequalities in mortality be reduced? A quantitative analysis of 6 risk factors in 21 European populations. *PLoS One*. 2014;9(11):e110952.

120. Kulik MC, Hoffmann R, Judge K, Looman C, Menvielle G, Kulhánová I, et al. Smoking and the potential for reduction of inequalities in mortality in Europe. *European journal of epidemiology*. 2013;28(12):959-71.
121. Hoffmann R, Eikemo TA, Kulhánová I, Kulik MC, Looman C, Menvielle G, et al. Obesity and the potential reduction of social inequalities in mortality: evidence from 21 European populations. *The European Journal of Public Health*. 2015;25(5):849-56.
122. Kulhánová I, Menvielle G, Hoffmann R, Eikemo TA, Kulik MC, Toch-Marquardt M, et al. The role of three lifestyle risk factors in reducing educational differences in ischaemic heart disease mortality in Europe. *The European Journal of Public Health*. 2016;27(2):203-10.
123. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *International journal of epidemiology*. 2013;42(5):1511-9.
124. Schrijvers CT, Stronks K, van de Mheen HD, Mackenbach JP. Explaining educational differences in mortality: the role of behavioral and material factors. *American Journal of Public Health*. 1999;89(4):535-40.
125. van Oort FVA, van Lenthe FJ, Mackenbach JP. Material, psychosocial, and behavioural factors in the explanation of educational inequalities in mortality in The Netherlands. *Journal of Epidemiology & Community Health*. 2005;59(3):214-20.
126. Oaxaca R. Male-female wage differentials in urban labor markets. *International economic review*. 1973:693-709.
127. Fortin N, Lemieux T, Firpo S. Decomposition methods in economics. *Handbook of labor economics*. 4: Elsevier; 2011. p. 1-102.
128. Ditlevsen S, Christensen U, Lynch J, Damsgaard MT, Keiding N. The mediation proportion: a structural equation approach for estimating the proportion of exposure effect on outcome explained by an intermediate variable. *Epidemiology*. 2005;16(1):114-20.
129. Little TD, Card NA, Bovaird JA, Preacher KJ, Crandall CS. Structural equation modeling of mediation and moderation with contextual factors. *Modeling contextual effects in longitudinal studies*. 2007;1:207-30.
130. Gunzler D, Chen T, Wu P, Zhang H. Introduction to mediation analysis with structural equation modeling. *Shanghai archives of psychiatry*. 2013;25(6):390.
131. VanderWeele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. *Statistics and its Interface*. 2009;2(4):457-68.
132. Naimi AI, Schnitzer ME, Moodie EE, Bodnar LM. Mediation analysis for health disparities research. *American journal of epidemiology*. 2016;184(4):315-24.
133. Kaufman JS. *Methods in social epidemiology*: John Wiley & Sons; 2017.
134. Oakes JM, Naimi AI. Mediation, interaction, interference for social epidemiology. *International journal of epidemiology*. 2016;45(6):1912-4.
135. VanderWeele TJ. Causal mediation analysis with survival data. *Epidemiology (Cambridge, Mass)*. 2011;22(4):582.
136. VanderWeele T, Vansteelandt S. Mediation analysis with multiple mediators. *Epidemiologic methods*. 2014;2(1):95-115.
137. Pillas D, Marmot M, Naicker K, Goldblatt P, Morrison J, Pikhart H. Social inequalities in early childhood health and development: a European-wide systematic review. *Pediatric research*. 2014;76(5):418.
138. Graham H, Power C. *Childhood disadvantage and adult health: a lifecourse framework*: Health Development Agency London; 2004.
139. Van De Mheen H, Stronks K, Van Den Bos J, Mackenbach JP. The contribution of childhood environment to the explanation of socio-economic inequalities in health in adult life: a retrospective study. *Social Science & Medicine*. 1997;44(1):13-24.

140. Galobardes B, Lynch JW, Davey Smith G. Childhood socioeconomic circumstances and cause-specific mortality in adulthood: systematic review and interpretation. *Epidemiologic reviews*. 2004;26(1):7-21.
141. Landecker H, Panofsky A. From social structure to gene regulation, and back: A critical introduction to environmental epigenetics for sociology. *Annual Review of Sociology*. 2013;39.
142. Stringhini S, Polidoro S, Sacerdote C, Kelly RS, Van Veldhoven K, Agnoli C, et al. Life-course socioeconomic status and DNA methylation of genes regulating inflammation. *International journal of epidemiology*. 2015;44(4):1320-30.
143. Needham BL, Smith JA, Zhao W, Wang X, Mukherjee B, Kardina SLR, et al. Life course socioeconomic status and DNA methylation in genes related to stress reactivity and inflammation: The multi-ethnic study of atherosclerosis. *Epigenetics*. 2015;10(10):958-69.
144. Morris JN, Wilkinson P, Dangour AD, Deeming C, Fletcher A. Defining a minimum income for healthy living (MIHL): older age, England. *Int J Epidemiol*. 2007;36(6):1300-7.
145. Fritzell J, Rehnberg J, Hertzman JB, Blomgren J. Absolute or relative? A comparative analysis of the relationship between poverty and mortality. *International Journal of Public Health*. 2015;60(1):101-10.
146. McDonough P, Berglund P. Histories of poverty and self-rated health trajectories. *Journal of Health and Social Behavior*. 2003:198-214.
147. Aldabe B, Anderson R, Lyly-Yrjänäinen M, Parent-Thirion A, Vermeulen G, Kelleher CC, et al. Contribution of material, occupational, and psychosocial factors in the explanation of social inequalities in health in 28 countries in Europe. *Journal of Epidemiology & Community Health*. 2010;65(12):1123-31.
148. Skalická V, Van Lenthe F, Bamba C, Krokstad S, Mackenbach J. Material, psychosocial, behavioural and biomedical factors in the explanation of relative socio-economic inequalities in mortality: evidence from the HUNT study. *International Journal of Epidemiology*. 2009;38(5):1272-84.
149. Morris JN, Donkin AJM, Wonderling D, Wilkinson P, Dowler EA. A minimum income for healthy living. *Journal of Epidemiology & Community Health*. 2000;54(12):885-9.
150. Lynch JW, Kaplan GA, Salonen JT. Why do poor people behave poorly? Variation in adult health behaviours and psychosocial characteristics by stages of the socioeconomic lifecourse. *Social Science & Medicine*. 1997;44(6):809-19.
151. Marsh A, McKay S. *Poor smokers*. London: Policy Studies Institute; 1994.
152. Hoven H, Siegrist J. Work characteristics, socioeconomic position and health: a systematic review of mediation and moderation effects in prospective studies. *Occup Environ Med*. 2013;70(9):663-9.
153. Dragano N, Wahrendorf M. A Social Inequalities Perspective on Effort-Reward Imbalance at Work. *Work Stress and Health in a Globalized Economy: Springer*; 2016. p. 67-85.
154. Benach J, Vives A, Amable M, Vanroelen C, Tarafa G, Muntaner C. Precarious employment: understanding an emerging social determinant of health. *Annual review of public health*. 2014;35.
155. Vågerö D, Garcy AM. Does unemployment cause long-term mortality? Selection and causation after the 1992–96 deep Swedish recession. *European Journal of Public Health*. 2016;26(5):778-83.
156. Dupre ME, George LK, Liu G, Peterson ED. The cumulative effect of unemployment on risks for acute myocardial infarction. *Archives of internal medicine*. 2012;172(22):1731-7.
157. Milner A, Page A, LaMontagne AD. Long-term unemployment and suicide: a systematic review and meta-analysis. *PloS one*. 2013;8(1):e51333.
158. Dunn JR. Housing and health inequalities: review and prospects for research. *Housing Studies*. 2000;15(3):341-66.
159. Pickett KE, Pearl M. Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. *Journal of Epidemiology & Community Health*. 2001;55(2):111-22.
160. Bernard P, Charafeddine R, Frohlich KL, Daniel M, Kestens Y, Potvin L. Health inequalities and place: a theoretical conception of neighbourhood. *Social Science & Medicine*. 2007;65(9):1839-52.

161. van Lenthe FJ, Brug J, Mackenbach JP. Neighbourhood inequalities in physical inactivity: the role of neighbourhood attractiveness, proximity to local facilities and safety in the Netherlands. *Social Science & Medicine*. 2005;60(4):763-75.
162. Wheeler BW, Ben-Shlomo Y. Environmental equity, air quality, socioeconomic status, and respiratory health: a linkage analysis of routine data from the Health Survey for England. *Journal of Epidemiology & Community Health*. 2005;59(11):948-54.
163. Brulle RJ, Pellow DN. Environmental justice: human health and environmental inequalities. *Annual Review Public Health*. 2006;27:103-24.
164. Brunner E. Biology and health inequality. *PLoS biology*. 2007;5(11):e267.
165. Marmot M, Wilkinson RG. Psychosocial and material pathways in the relation between income and health: a response to Lynch et al. *BMJ: British Medical Journal*. 2001;322(7296):1233.
166. Siegrist J, Marmot M. Health inequalities and the psychosocial environment—two scientific challenges. *Soc Sci Med*. 2004;58(8):1463-73.
167. Stansfeld SA. *Social support and social cohesion*. In: Marmot M, Wilkinson RG, editors. *Social determinants of health*. 2 ed. Oxford: Oxford University Press; 2006. p. 148-71.
168. Kristenson M. *Socio-economic position and health: the role of coping*. In: Siegrist J, Marmot M, editors. *Social inequalities in health New evidence and policy implications*. Oxford: Oxford University Press; 2006. p. 127-51.
169. Droomers M, Schrijvers CT, Mackenbach JP. Why do lower educated people continue smoking? Explanations from the longitudinal GLOBE study. *Health psychology : official journal of the Division of Health Psychology*, American Psychological Association. 2002;21(3):263-72.
170. Droomers M, Schrijvers CT, Mackenbach JP. Educational differences in starting excessive alcohol consumption: explanations from the longitudinal GLOBE study. *Soc Sci Med*. 2004;58(10):2023-33.
171. Droomers M, Schrijvers CT, Stronks K, van de Mheen D, Mackenbach JP. Educational differences in excessive alcohol consumption: the role of psychosocial and material stressors. *Preventive medicine*. 1999;29(1):1-10.
172. Droomers M, Schrijvers CT, van de Mheen H, Mackenbach JP. Educational differences in leisure-time physical inactivity: a descriptive and explanatory study. *Soc Sci Med*. 1998;47(11):1665-76.
173. Steptoe A. *Psychobiological processes linking socio-economic position to health*. In: Siegrist J, Marmot M, editors. *Social inequalities in health New evidence and policy implications*. Oxford: Oxford University Press; 2006. p. 101-26.
174. Brunner E. Stress and the biology of inequality. *BMJ*. 1997;314(7092):1472-6.
175. Brunner E, Marmot M. *Social organization, stress, and health*. In: Marmot M, Wilkinson RG, editors. *Social determinants of health*. 2 ed. Oxford: Oxford University Press; 2006. p. 6-30.
176. Egan M, Tannahill C, Petticrew M, Thomas S. Psychosocial risk factors in home and community settings and their associations with population health and health inequalities: a systematic meta-review. *BMC public health*. 2008;8(1):239.
177. van Oort FV, van Lenthe FJ, Mackenbach JP. Material, psychosocial, and behavioural factors in the explanation of educational inequalities in mortality in The Netherlands. *Journal of epidemiology and community health*. 2005;59(3):214-20.
178. Matthews KA, Gallo LC, Taylor SE. Are psychosocial factors mediators of socioeconomic status and health connections? *Annals of the New York academy of sciences*. 2010;1186(1):146-73.
179. Hiscock R, Bauld L, Amos A, Fidler JA, Munafò M. Socioeconomic status and smoking: a review. *Annals of the New York Academy of Sciences*. 2012;1248(1):107-23.
180. Bloomfield K, Grittner U, Kramer S, Gmel G. Social inequalities in alcohol consumption and alcohol-related problems in the study countries of the EU concerted action 'Gender, Culture and Alcohol Problems: a Multi-national Study'. *Alcohol and alcoholism*. 2006;41(suppl_1):i26-i36.

181. De Irala-Estevez J, Groth M, Johansson L, Oltersdorf U, Prättälä R, Martínez-González MA. A systematic review of socio-economic differences in food habits in Europe: consumption of fruit and vegetables. *European journal of clinical nutrition*. 2000;54(9):706.
182. Sanchez-Villegas A, Martinez JA, Prättälä R, Toledo E, Roos G, Martinez-Gonzalez MA. A systematic review of socioeconomic differences in food habits in Europe: consumption of cheese and milk. *European journal of clinical nutrition*. 2003;57(8):917.
183. Giskes K, Kunst AE, Benach J, Borrell C, Costa G, Dahl E, et al. Trends in smoking behaviour between 1985 and 2000 in nine European countries by education. *Journal of Epidemiology & Community Health*. 2005;59(5):395-401.
184. Stringhini S, Sabia S, Shipley M, Brunner E, Nabi H, Kivimäki M, et al. Association of socioeconomic position with health behaviors and mortality. *Jama*. 2010;303(12):1159-66.
185. Gregoraci G, Van Lenthe FJ, Artnik B, Bopp M, Deboosere P, Kovács K, et al. Contribution of smoking to socioeconomic inequalities in mortality: a study of 14 European countries, 1990–2004. *Tobacco control*. 2016;tobaccocontrol-2015-052766.
186. Devaux M, Sassi F. *Alcohol consumption and harmful drinking: trends and social disparities across OECD countries*. Paris; 2015. Report No.: 1815-2015.
187. Probst C, Roerecke M, Behrendt S, Rehm J. Socioeconomic differences in alcohol-attributable mortality compared with all-cause mortality: a systematic review and meta-analysis. *International journal of epidemiology*. 2014;43(4):1314-27.
188. Mackenbach JP, Kulhánová I, Bopp M, Borrell C, Deboosere P, Kovács K, et al. Inequalities in alcohol-related mortality in 17 European countries: a retrospective analysis of mortality registers. *PLoS medicine*. 2015;12(12):e1001909.
189. Stringhini S, Dugravot A, Shipley M, Goldberg M, Zins M, Kivimäki M, et al. Health behaviours, socioeconomic status, and mortality: further analyses of the British Whitehall II and the French GAZEL prospective cohorts. *PLoS medicine*. 2011;8(2):e1000419.
190. Beenackers MA, Kamphuis CBM, Giskes K, Brug J, Kunst AE, Burdorf A, et al. Socioeconomic inequalities in occupational, leisure-time, and transport related physical activity among European adults: a systematic review. *International journal of behavioral nutrition and physical activity*. 2012;9(1):116.
191. Demarest S, Van Oyen H, Roskam A-J, Cox B, Regidor E, Mackenbach JP, et al. Educational inequalities in leisure-time physical activity in 15 European countries. *The European Journal of Public Health*. 2013;24(2):199-204.
192. Roskam A-JR, Kunst AE, Van Oyen H, Demarest S, Klumbiene J, Regidor E, et al. Comparative appraisal of educational inequalities in overweight and obesity among adults in 19 European countries. *International journal of epidemiology*. 2009;39(2):392-404.
193. Hart CL, Gruer L, Watt GCM. Cause specific mortality, social position, and obesity among women who had never smoked: 28 year cohort study. *BMJ*. 2011;342:d3785.
194. Popkin BM, Duffey K, Gordon-Larsen P. Environmental influences on food choice, physical activity and energy balance. *Physiology & behavior*. 2005;86(5):603-13.
195. Doorslaer Ev, Wagstaff A, Rutten F. *Equity in the finance and delivery of health care: an international perspective*. Oxford etc.: Oxford University Press; 1992.
196. Van Doorslaer E, Wagstaff A, Van der Burg H, Christiansen T, De Graeve D, Duchesne I, et al. Equity in the delivery of health care in Europe and the US. *Journal of health economics*. 2000;19(5):553-83.
197. Van Doorslaer E, Masseria C, Koolman X, Group OHER. Inequalities in access to medical care by income in developed countries. *Canadian medical association journal*. 2006;174(2):177-83.
198. Devaux M, De Looper M. *Income-related inequalities in health service utilisation in 19 OECD countries, 2008-2009*. Paris: OECD Publishing; 2012. Report No.: 1815-2015.

199. Stirbu I, Kunst AE, Mielck A, Mackenbach JP. Inequalities in utilisation of general practitioner and specialist services in 9 European countries. *BMC health services research*. 2011;11(1):288.
200. Carrieri V, Wübker A. *Assessing inequalities in preventive care use in Europe. Health policy*. 2013;113(3):247-57.
201. Palència L, Espelt A, Rodríguez-Sanz M, Puigpinós R, Pons-Vigués M, Pasarín MI, et al. Socio-economic inequalities in breast and cervical cancer screening practices in Europe: influence of the type of screening program. *International Journal of Epidemiology*. 2010;39(3):757-65.
202. Lumme S, Manderbacka K, Keskimäki I. Trends of relative and absolute socioeconomic equity in access to coronary revascularisations in 1995–2010 in Finland: a register study. *International Journal for Equity in Health*. 2017;16(1):37.
203. Manderbacka K, Arffman M, Leyland A, McCallum A, Keskimäki I. Change and persistence in healthcare inequities: Access to elective surgery in Finland in 1992—2003. *Scandinavian Journal of Public Health*. 2009;37(2):131-8.
204. Manderbacka K, Keskimäki I, Reunanen A, Klaukka T. Equity in the use of antithrombotic drugs, beta-blockers and statins among Finnish coronary patients. *International Journal for Equity in Health*. 2008;7(1):16.
205. Ricci-Cabello I, Ruiz-Pérez I, Labry-Lima D, Olry A, Márquez-Calderón S. Do social inequalities exist in terms of the prevention, diagnosis, treatment, control and monitoring of diabetes? *A systematic review. Health & Social Care in the Community*. 2010;18(6):572-87.
206. Stirbu I, Looman C, Nijhof GJ, Reulings PG, Mackenbach JP. Income inequalities in case death of ischaemic heart disease in the Netherlands: a national record-linked study. *Journal of epidemiology and community health*. 2012;66(12):1159-66.
207. Davies CA, Leyland AH. Trends and inequalities in short-term acute myocardial infarction case fatality in Scotland, 1988-2004. *Population Health Metrics*. 2010;8(1):33.
208. Kirchberger I, Meisinger C, Golüke H, Heier M, Kuch B, Peters A, et al. Long-term survival among older patients with myocardial infarction differs by educational level: results from the MONICA/KORA myocardial infarction registry. *International Journal for Equity in Health*. 2014;13(1):19.
209. Dalton SO, Schüz J, Engholm G, Johansen C, Kjær SK, Steding-Jessen M, et al. Social inequality in incidence of and survival from cancer in a population-based study in Denmark, 1994–2003: summary of findings. *European Journal of Cancer*. 2008;44(14):2074-85.
210. Aarts MJ, Lemmens VEPP, Louwman MWJ, Kunst AE, Coebergh JWW. Socioeconomic status and changing inequalities in colorectal cancer? A review of the associations with risk, treatment and outcome. *European Journal of Cancer*. 2010;46(15):2681-95.
211. Rachet B, Ellis L, Maringe C, Chu T, Nur U, Quaresma M, et al. Socioeconomic inequalities in cancer survival in England after the NHS cancer plan. *British Journal of Cancer*. 2010;103(4):446-53.
212. Woods LM, Rachet B, Coleman MP. Origins of socio-economic inequalities in cancer survival: a review. *Annals of Oncology*. 2005;17(1):5-19.
213. Stirbu I, Kunst AE, Bopp M, Leinsalu M, Regidor E, Esnaola S, et al. Educational inequalities in avoidable mortality in Europe. *Journal of Epidemiology & Community Health*. 2010;64(10):913-20.
214. *Independent Inquiry into Inequalities in Health (the Acheson report)*. London: Department of Health; 1998.