Health Inequalities Research

NEW METHODS, BETTER INSIGHTS?

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FOREWORD

Dear reader,

Health, be it physical, mental or social, is undoubtedly one of the most precious cornerstones in people's lives. It enables us to thrive, lead meaningful, fulfilling lives and fully participate in our communities. Most recently, this has become more apparent with the COVID-19 pandemic: although the disease has reached all parts of society, the most vulnerable groups have been affected more severely to pose a greater risk to their physical, mental, social and economic well-being. With this, the health gap between different socio-economic groups has grown larger, exacerbating the inequalities long known to researchers.

Such health disparities often have their root causes in a variety of factors ranging from education, employment status to level of income. Analysing and understanding the role of social determinants can aid in advancing the research and ultimately informing public policy on possible strategies to mitigate health inequalities.

In an effort to explore this pivotal topic through the lens of different disciplines, the European Federation of Academies of Sciences and Humanities (ALLEA) and the Federation of European Academies of Medicine (FEAM) initiated a joint project on health inequalities in Europe aimed at reviewing existing research findings. They established a scientific committee chaired by the Royal Netherlands Academy of Arts and Sciences (KNAW), which led the project from the outset to the publication of this final report. In between, several expert workshops were held to share, examine and review the latest scientific insights into socio-economic differences in health. This report is the outcome of those deliberations followed by a peer-review process.

We are delighted to share this report including its annexes with you. It has been elaborated by the ALLEA–FEAM–KNAW scientific committee, chaired by Johan Mackenbach. We thank the committee for the substantial efforts that went into facilitating this project, which could not be more timely and relevant.

We wish you a pleasant reading.

Antonio Loprieno
President of ALLEA

George Griffin
Immediate Past President of FEAM

SUMMARY

People who are worse off in socio-economic terms on average die younger, and within their shorter lives often have more health problems. These "health inequalities" are a persistent challenge for public policy in all European countries and have been studied extensively by researchers from various disciplines.

While these research efforts have importantly increased our understanding of health inequalities, and have supported the development of policies and interventions that may help to reduce health inequalities, three fundamental questions remain topics for scientific debate: (1) to what extent are health inequalities *caused* by differences in education, occupational class or income? (2) what is the relative importance of specific factors involved in the relationship between education, occupational class or income and health? (3) what is the effectiveness of interventions and policies to reduce health inequalities?

Recently, new quantitive research methods have been developed, such as "counterfactual" approaches to causal inference, applications of genetics, advanced methods of mediation and moderation analysis, and "quasi-experimental" methods to study "natural experiments" with interventions and policies. These methods promise to shed new light on these questions, and this report reviews their strengths and limitations as well as the first substantive results that studies applying these methods have produced.

We conclude that these new methods can indeed contribute to a better understanding of health inequalities, and thus help to develop effective policies and interventions. Moreover, these new methods have pointed to several limitations of the conventional methods, which need to be taken into account when interpreting the results of previous research. However, the newer methods also have limitations, and, if properly executed, conventional studies retain their value. For robust conclusions, it will often be necessary to "triangulate" the results of studies using different approaches, taking into account the particular strengths and weaknesses of each approach.

In substantive terms, application of these new methods has led to some new insights in the causal role of education and income on health, in the possible role of genetics in generating health inequalities, and in the effects of interventions and policies on health inequalities. However, it is too early to say whether new methods of mediation and moderation analysis will change current views on the relative contributions of specific factors involved in health inequalities.

We therefore recommend expanding the use of these new methods, and making the investments in data infrastructure that are required for their application, such as birth cohort and other life-course studies which are necessary for mediation and moderation analyses, and data linkage facilities which are necessary to study natural experiments. This is the responsibility not only of national research funding bodies but also of the European Commission's research funding mechanisms which should foster international cooperation and between-country comparisons.

In the meantime, there is sufficient robust "explanatory" evidence to underpin interventions and policies to tackle health inequalities. Large-scale implementation should, however, be accompanied by rigorous evaluation efforts, for which a stronger commitment to evaluation among both policy-makers and researchers is necessary.

1. INTRODUCTION

People who are worse off in socio-economic terms on average die younger, and within their shorter lives often have more health problems. In many European countries, differences in average life expectancy at birth between people with a lower and a higher level of education, occupation or income amount to between 5 and more than 10 years, and differences in healthy life expectancy often amount to even more than 15 years. These "health inequalities" have become a major concern for health policy-makers and have, over the past four decades, been studied extensively by researchers from various disciplines.

These research efforts have substantially increased our understanding of health inequalities. Originally starting with descriptive research, the field has moved into an increasingly sophisticated explanatory mode, and has more recently made progress in developing and evaluating policies and interventions that may help to reduce health inequalities. However, at least three fundamental questions remain topics for scientific debate:

(1) to what extent are health inequalities *caused* by differences in education, occupational class or income ("causation")?;

(2) what is the relative importance of specific factors involved in the relationship between education, occupational class or income and health ("mediation and moderation")?;

(3) what is the effectiveness of interventions and policies to reduce health inequalities ("effectiveness")?

Crucially, not only are the answers to these three questions being debated, but also how these questions should be answered: what are the best methods to study health inequalities? Recently, several new quantitative research methods have been introduced that promise to shed more light on each of these questions. Examples include the use of "counterfactual" methods for establishing causality, the use of new "mediation" techniques to study the role of specific factors in generating health inequalities, and the use of "natural (or quasi-) experiments" for evaluating policies and interventions. Application of these newer methods has produced valuable insights, but the results sometimes seem to be in conflict with the conclusions of studies using more conventional methods. As a result, it is not always clear how the results of studies using different methods should be weighed, and there is no consensus yet among scientists from different disciplines on the relative merits of these new approaches.

The European Federation of Academies of Sciences and Humanities (ALLEA) and the Federation of European Academies of Medicine (FEAM) have therefore initiated a project to bring together experts from various scientific disciplines to assess the theoretical and methodological issues involved, and to develop recommendations for future cross-disciplinary research, with the ultimate aim of helping to narrow the enormous health gap between socio-economic groups in all European countries. The report is therefore aimed at scientists involved in health inequalities research and at national and European policy-makers interested in using research results for reducing health inequalities.

This report presents the general conclusions of this project in a concise and accessible format. After a description of the approach of the project (section 2), the main conclusions will be presented in three sections, corresponding to the three issues mentioned above: causation (section 3), mediation and moderation (section 4), and effectiveness of policies and interventions (section 5). The report ends with general recommendations (section 6). The scientific underpinnings for the conclusions summarized in this report can be found in a series of more detailed background documents that also contain extensive references to the scientific literature: three discussion papers (Annexes 2, 4 and 6) and three workshop reports (Annexes 3, 5 and 7).

2. APPROACH

To implement the project, ALLEA and FEAM established a committee on health inequalities by asking their member academies to nominate leading scientists from various disciplinary backgrounds and countries (Annex 1). The Royal Netherlands Academy of Arts and Sciences (Koninklijke Nederlandse Akademie van Wetenschappen, KNAW) took the lead in performing the work by providing the chair and secretary to the committee for desk-research, organizing meetings and drafting discussion papers.

The project was done in two phases. In the first phase, the committee reviewed the scientific literature to chart the main areas of scientific agreement and disagreement in the first two topics, "causation" and "mediation/moderation". The results from this review were presented in a discussion paper, "*Health inequalities: an interdisciplinary exploration of socioeconomic position, health and causality*", which served as input for an international symposium on 24 May 2018 in Amsterdam, The Netherlands, bringing together key opinion leaders from various scientific backgrounds. The symposium showed that further discussion was necessary, and that it would be desirable to add a third topic: effectiveness of interventions and policies.

In the second phase, the remaining areas of debate with regard to "causation" and "mediation/moderation" were topics for in-depth discussion in two workshops, organized in collaboration by, respectively, the German National Academy of Sciences Leopoldina (see Annex 3 for the workshop report) and the French National Academy of Medicine (see Annex 5 for the workshop report). As input to these workshops, the chair and secretary of the commission prepared new versions of the discussion paper(s) on "causation" and "mediation/moderation", which were then revised in light of the discussions (see Annexes 2 and 4 for the final versions).

A third workshop on "effectiveness of interventions and policies" was organized in collaboration with the Italian Academy of Medicine (see Annex 7 for the workshop report). The input for this workshop consisted of a discussion paper on interventions and policies, prepared by Professor Clare Bambra (Newcastle University, UK) and Dr Peter Craig (University of Glasgow, UK) (Annex 6).

On the basis of all these documents, internal deliberations and an external review (see Annex 8), the committee wrote this final report. The committee expresses its gratitude to the national academies that have supported this initiative, to the large number of experts participating in the workshops, and to the external reviewers for their constructive comments.

This report has several limitations that need to be mentioned to prevent misunderstandings about what this report is (and is not) about. First, the committee has focused on several new quantitative research methods, and has not dealt with qualitative approaches, such as anthropological or biographical studies of the causal pathways between low socio-economic position and ill-health. As mentioned above, the reason for the particular focus of this report is that there is much discussion about the merits of some of the newer quantitative methods. This should not, however, be taken as an indication that the committee disregards qualitative research methods; on the contrary, the committee fully recognizes their value, but simply did not have the resources also to cover this vast field.

Secondly, the review of empirical evidence was 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 ones, in which absolute poverty is far more common. Within the European setting, this may apply to countries in Eastern Europe, where the role of material disadvantage in generating health inequalities may be more pervasive than in Western Europe. Unfortunately, the committee did not have the resources to review empirical evidence at a more global scale, but is confident that most of its conclusions about the value of new quantitative research methods apply beyond the context of high-income countries.

Thirdly, this report focuses on socio-economic health inequalities, defined as systematic differences in the occurrence of health problems (disease, disability, death, etc.) within countries between people with a lower and a higher socio-economic position, as indicated by their level of education, occupational class, income or similar characteristics. So, although we will use the shorthand term "health inequalities" throughout this report, it does not deal with other social determinants of health, such as ethnicity and migrant status. It also does not deal with between-country differences. There are, again, good reasons for this focus: socio-economic health inequalities are large within all European countries, and they are very pervasive, in the sense that inequalities in health between other social groupings (men–women, urban–rural, migrant–non-migrant, etc.) tend to be partly determined by differences in socio-economic conditions. Nevertheless, the committee emphasizes that other types of health inequality are also very important, and deserve to be studied (and addressed by public policy) in their own right.

3. CAUSAL ROLE OF EDUCATION, OCCUPATIONAL CLASS AND INCOME IN GENERATING HEALTH INEQUALITIES[1]

3.1 Introduction

The relationship between indicators of socio-economic position such as education, occupational class and income on the one hand, and various health indicators on the other, is one of the most widely reproduced findings in population health research. Although education, occupational class and income are not equivalent concepts, they all predict health outcomes in a robust way. There is no doubt that, even in high-income countries, people with a lower socio-economic position on average live substantially shorter lives, and have substantially higher rates of morbidity than people with a higher socio-economic position. When confronted with these findings, most people agree that this state of affairs is undesirable. However, to what extent these relationships always represent causal effects of socio-economic conditions on health outcomes is another matter.

This is because some of the associations could also be due to "selection" (i.e. health status affecting socio-economic position, instead of the other way around) or to "confounding" (i.e. "third" factors which are related to both socio-economic position and health, but which do not lie on a causal pathway linking socio-economic position to health, such as cognitive ability). Social–epidemiological studies have tried to eliminate these alternative explanations, for example by using longitudinal designs (to make sure that a lower socio-economic position precedes ill-health instead of the other way around) and by using multivariate analysis techniques (to statistically control for third factors). However, as in other areas of epidemiological research, there has always remained some doubt on how successful these strategies are.

Disentangling these different explanations for the relationship between socio-economic position and health is important, not only for scientific reasons but also because it matters for policy. If socio-economic 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, or efforts to reduce income inequalities, or other redistributive social and economic

1 For more details, and a full account of the argumentation behind this section including references, see Annexes 2 and 3.

policies. On the other hand, to the extent that health-related selection plays an important role, social security policies that protect people with health problems against loss of income may be considered.

Recently, two developments in health inequalities research have shed some new light on the issue of "causation": counterfactual approaches and genetic studies.

3.2 New insights from the "counterfactual" approach to causal inference

It is well known that the – theoretically – best way to study causation is by conducting experiments, in which the investigators actively manipulate exposure to the putative causal factor, and decide who will be exposed and who will not, preferably using some randomization procedure. Such planned experiments are often impractical when one wants to study the effect of education, occupation or income on health, and other approaches are therefore necessary.

As mentioned above, the conventional approach in social epidemiology has been to rely on carefully conducted observational studies, but over the past decades new methods have been introduced which have blurred the boundaries between experimental and observational studies. In addition to planned experiments, "natural" experiments have come to be seen as important opportunities for assessing the effects of socio-economic (or any other) factors on health. Also, new analytical techniques have been developed that mimic experimental conditions, but actually use observational data.

These methods usually apply the "counterfactual" (or "potential outcomes") approach, which tries to bring methodological rigour to causal inference. Some of these methods exploit occasions when people's exposure to socio-economic conditions changes in a quasi-random way, independent from the researchers' actions ("natural experiments"). Examples include a change in compulsory schooling age, which can be used to study the effect of education on health in later life, and lotteries, which can be used to study the effect of a change in income on health. Other methods use advanced statistical techniques, such as "instrumental variables" or "regression discontinuity", to identify subsets of data within which exposure varies in a quasi-random way, to isolate the effect of socio-economic conditions in observational data.

Now that these counterfactual techniques have been applied for some time, it is possible to take stock of new insights about a causal effect of socio-economic indicators, particularly education and income, on health. (They have not often been used to study the health effects of occupational class yet.) An important caveat is that practical application of this new approach has been limited to a narrower range of questions than many health inequalities researchers would like to answer. This is because this approach requires the investigators to identify a well-defined and measurable difference

in exposure; for example one extra year of education at the age of 16, or giving people a certain amount of money such as one would win in a lottery.

Proponents of this approach argue that studying these well-defined exposures is particularly relevant, because the results of a study can readily be translated into recommendations for policy. Others, however, argue that such studies capture only a limited part of the effect of socio-economic conditions on health. Because health inequalities are generated in a lifelong process of cumulative exposure to favourable or unfavourable living conditions, they warn against generalizing from such "well-defined" effects to explain health inequalities in the real world.

Despite this caveat, some substantive conclusions can be drawn from the application of counterfactual techniques to health inequalities. Many of these new studies have found that more years of schooling lead to a reduction in mortality in mid-life and beyond, albeit with large variations in effect size. This is to be expected, because the beneficial effects of schooling depend on context, the quality of education, the educational curricula, behavioural responses and many other factors. Nevertheless, these studies show that at least part of the association between education and health is due to a causal effect of education on health.

For income the picture is more nuanced. Counterfactual studies on the effect of income on physical health in adulthood have led to inconsistent results. On the basis of these studies it cannot be concluded that income causally affects physical health in adulthood in high-income countries. However, it is important to note that these studies have generally captured modest and temporary changes in income only, and have not captured the effects of a lifelong low or high income.

Furthermore, it should be emphasized that the evidence for a causal effect of parental income on children's health is relatively strong. In this case, results of studies using a counterfactual approach clearly corroborate findings from more "conventional" longitudinal studies among children, which are considered to be less sensitive to selection bias than studies among adults. It can therefore be concluded that at least part of the association between parental income and children's health is due to a causal effect of income on health.

3.3 New insights from genetic studies

The second new development in quantitative health inequalities research that promises to shed new light on "causation" is the application of genetics. People's genetic make-up is a potential "confounder" of the relationship between socio-economic indicators and health: if genetic factors predisposing to ill-health were more prevalent in lower socio-economic groups, this should be considered as a confounding factor because a person's genotype temporally precedes his or her socio-economic position. With

the advent of genetic techniques, such as whole-genome sequencing, it has become possible to investigate a confounding role of genetics directly.

Before going into the results, however, it should be noted that this is a highly contentious area. Some health inequalities researchers think it is not helpful to study the role of genetics in generating health inequalities, because it detracts from addressing remediable environmental conditions, or even believe that it is dangerous because of potential eugenic implications. Others, however, think that identifying the role of genetic factors involved in health inequalities can improve our understanding of the complex mechanisms underlying health inequalities, and may even strengthen the case for compensatory policies aiming to improve health outcomes in disadvantaged groups.

It is also important to keep in mind that, whatever the role of genetic factors in health inequalities is, it is likely to be very complex. It is clear that in matters of health both "genes" and the "environment" are likely to play a role, in various combinations and interactions. Also, finding a role for genetic factors does not necessarily imply biological determinism: genes may operate through environmental channels, such as children's experiences in the school system or differences in behaviour, and these can be intervened on through social policies. Furthermore, the early environment may increase or decrease the expression of specific genes through epigenetic mechanisms.

Most of the evidence collected so far on the role of genetics in social inequalities deals with the way genetic determinants of cognitive ability influence educational outcomes. (There is emerging, and somewhat similar, evidence for income.) Although educational achievement is partly dependent on the parents' socio-economic position, educational achievement is also dependent on an individual's own cognitive ability, which is strongly genetically determined. It has recently been estimated that "polygenic risk scores" could explain more than 10% of all inter-individual differences in educational achievement, through differences in cognitive ability, but also through personality traits such as self-control and risk aversion.

In combination with the fact that some of the genes that are associated with educational achievement also are associated with smoking, obesity, depression and various chronic health conditions, this implies that genetic factors may well confound the relationship between education and health. Although it is not yet clear what the extent of this confounding bias might be, these findings imply that one cannot safely assume that the associations between socio-economic indicators and health, even if found in longitudinal studies, wholly rest on causal effects of socio-economic conditions on health. To clarify this, further research into the role of genetics, including gene–environment interactions, will be necessary.

4. RELATIVE IMPORTANCE OF SPECIFIC FACTORS INVOLVED IN THE RELATIONSHIP BETWEEN EDUCATION, OCCUPATIONAL CLASS OR INCOME AND HEALTH[2]

4.1 Introduction

Socio-economic health inequalities have a complex explanation, not only in terms of "what causes what", but also in terms of how the underlying causal pathways actually work: what are the specific factors involved in this relationship? There are many candidates, which range from psychosocial stress in the workplace to lack of access to medical treatment, and from adverse childhood experiences to smoking. A thorough understanding of these factors is not only scientifically interesting, but also highly policy-relevant, because it allows one to identify potential targets for interventions and policies that may help to reduce health inequalities. Over the past four decades, many studies have sought to identify the specific factors involved, and then to quantify their relative importance using a statistical technique called "mediation analysis". (This is almost always done in the context of observational studies, although experimental study-designs could or should perhaps be considered as well.)

"Mediators" are defined as factors that represent an intermediate step in the effect of one variable, in this case education, occupational class or income, on another variable, in this case health. All the specific factors mentioned above (as well as scores of other factors) are known to be more prevalent in lower socio-economic groups, and are known to be detrimental to health. So they are likely to be involved in the relationship. But how important are they, and are some more important than others? Mediation analysis can tell us which part (say, percentage) of health inequalities is accounted for by each factor, and thus allows us not only to identify potential targets for interventions but also to prioritize those targets to maximize the impact of policies aimed at reducing health inequalities.

2 For more details, and a full account of the argumentation behind this section including references, see Annexes 3 and 4.

Recently, however, the conventional method of mediation analysis has come under critique, and alternative methods have been proposed. It has also become clear that a simple scheme of "mediation" is unlikely to account for all of the contributions of specific factors to health inequalities. This is because third variables may not only act as mediators but also as "moderators" of the relationship between socio-economic indicators and health.

4.2 New insights from mediation analysis

Mediation analysis is usually applied within the framework of large-scale epidemiological studies with information on people's socio-economic conditions, other health determinants and health outcomes. Because such studies have become much more common, and data for mediation analysis thus become more widely available, there is now a wealth of information on the relative contribution of a range of different factors to health inequalities from a range of high-income countries.

Study results suggest that five groups of specific health determinants play an important role in the explanation of health inequalities: early childhood environment, material living conditions, social and psychological factors, health-related behaviours and access to good-quality health care. Where comparative evidence is available, it shows that the relative contribution of these determinants differs between countries, thereby illustrating the more general phenomenon that the nature of health inequalities is rather strongly context-dependent. Nevertheless, quantitative estimates from mediation analyses suggest that the contribution of some of these factors, particularly material living conditions, social and psychological factors, and health-related behaviours, is often substantial (e.g. 10–40% each of inequalities in mortality in some countries).

However, in recent years new methodological developments have cast some doubt on these results. The results just mentioned were obtained with a relatively simple form of mediation analysis (i.e. the "difference method" developed by Baron and Kenny), which has come under critique. One criticism is that the results are biased when there is uncontrolled confounding, which is difficult to eliminate in the three-way relationship between socio-economic indicators, specific health determinants and health outcomes. Another criticism is that the results are biased when the effect of health determinants differs between socio-economic groups ("effect heterogeneity"), which may well be the case (as will be argued in more detail in the section on "moderation" below).

New methods of mediation analysis have therefore been designed that can circumvent these problems. These methods (like the new methods for assessing causality discussed in the previous section) apply a "counterfactual" approach, and therefore also have a more straightforward connection to policy, because they directly estimate the effect on health inequalities of "counterfactually" removing a mediator.

Applications to health inequalities data are still rare, and it is therefore not yet clear to what extent the new methods lead to substantially different results. Some head-to-head comparisons of the "conventional" and the "counterfactual" approaches have found different results, but others have not. More importantly, it has become clear that, if applied correctly, the results of the conventional approach are likely to be no less valid than those of the new approach. But this is an important "if": "correct application" means adequate control for confounding and (having checked for) absence of effect heterogeneity.

Systematic reviews of the available evidence as gathered with the "conventional" approach should therefore check whether the "difference method" has been applied correctly. This has not been common practice, so there is a clear need for re-assessment of the evidence base. At the same time, new evidence should be collected with the "counterfactual" approach wherever possible. In the meantime, the results obtained with the conventional method may still be used to guide policy as long as the results are not used as if they are numerically precise.

4.3 New insights from moderation analysis

As mentioned above, a simple model of "mediation" cannot take into account all possible ways in which specific factors and their interactions contribute to health inequalities. To take an earlier example: if the low educated are not only exposed to more stressful situations in the workplace (this would be "mediation") but are also less able to cope with the stress, leading to more health problems (this would be "moderation"), simple mediation analysis will not fully show the contribution of this factor to health inequalities. Moderation captures the intuition that health inequalities may partly be explained by the fact that people in lower socio-economic groups are more "susceptible" (in a biological sense) or "vulnerable" (in a psychological or social sense) to the negative health effects of various health determinants.

Although there is a long history of theorizing about moderation, and although it seems rather plausible, empirical evidence has remained scarce. A major barrier has been that, to establish moderation, very large datasets are required not only to reliably estimate the "main effects" of socio-economic position and health determinants, but also their "interaction effects" (i.e. the extent to which the effect of the health determinant differs between socio-economic groups or vice versa). Furthermore, most of the available evidence has been generated with a "conventional" method of moderation analysis, which is an extension of the "conventional" method of mediation analysis, and unable to clearly separate mediation from moderation.

Fortunately, new methods of moderation analysis have been developed, as an extension of the new methods of mediation analysis mentioned above, and first applications have produced promising results. These confirm the intuition that health inequalities can

to some extent be explained by the fact that people in lower socio-economic groups are more "susceptible" or "vulnerable" to certain health risks, in the sense that the effects of some health determinants, such as smoking, excessive alcohol consumption or psychosocial stressors in the work environment, are stronger in lower than in higher socio-economic groups.

More research is needed before more definitive conclusions can be drawn, and before findings on moderation can be translated into specific recommendations for policy; however, further research on the role of moderation, building on the theoretical frameworks that have been developed, can potentially fill a large gap in our understanding of health inequalities.

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 susceptibility or vulnerability to health determinants) points to the importance of strengthening the resilience of individuals and taking protective or compensatory measures. Also, substantial moderation effects suggest that "universal" policies (i.e. social or health policies targeting the whole population instead of disadvantaged people only) may have larger effects in lower socio-economic groups, thereby helping to reduce health inequalities. Findings on mediation and moderation therefore complement each other, thus extending the possibilities for health inequality interventions.

5. EFFECTIVENESS OF INTERVENTIONS AND POLICIES TO REDUCE HEALTH INEQUALITIES[3]

5.1 Introduction

Since the 1980s, when health inequalities were "rediscovered" as a public health problem in many high-income countries, research has improved our understanding to a stage that allows us to identify entry-points for interventions and policies. Around the year 2000, several European countries had reached this stage, and because some of their efforts have been accompanied by scientific evaluation studies it is possible to take stock of what works in practice and what does not.

Evaluating policies and interventions for their impact on health inequalities has proved to be very challenging, among other things because planned experiments are often difficult to conduct. However, as for the other two questions discussed in this report, new quantitative research methods have been introduced which promise to be important additions to the existing "tool-box" of health inequalities researchers. These methods originate in the same "counterfactual" philosophy for establishing causality as mentioned previously, and make use of "natural experiments" (changes in interventions or policies that occur in a "natural", i.e. non-manipulated, setting) or sophisticated statistical techniques to identify quasi-random variation within observational data. Together, these "quasi-experimental" methods can substantially increase the range of interventions and policies that can properly be evaluated.

5.2 New insights from systematic reviews of "what works"

On the basis of the current understanding of how health inequalities arise, there is a very broad spectrum of (specific) interventions and (broader) policies that could be considered. One important distinction is by their main entry-point, for example education or income, or hazardous working conditions, excessive alcohol consumption, access to cancer screening, etc.

Another important distinction is between interventions and policies that focus on improving the situation of the most disadvantaged groups, versus those that focus on reducing the "steepness" of the whole health gradient from lower to higher socio-

3 For more details, and a full account of the argumentation behind this section including references, see Annexes 5 and 6.

economic groups (or on something in-between). Still another distinction is between interventions and policies that target individuals and their behaviour, and those that try to change the macro-context in which individuals live (again, with several other possibilities in-between).

These distinctions are important, because there is much more evidence for how effective the "simpler" options are (i.e. addressing specific mediating factors, focusing on disadvantaged groups, targeting individuals and their behaviour) than for the more complex ones. This is partly because the "simpler" options are easier to implement, and partly because they are easier to study using conventional methods such as randomized controlled trials and other well-established research designs. However, this is unfortunate because the more complex options (i.e. addressing inequalities in education and income, flattening the whole gradient, changing the macro-context) are potentially much more effective. This "inverse evidence law" should be kept in mind when assessing the available evidence.

A way of summarizing the available evidence on the effectiveness of interventions and policies to reduce health inequalities is by conducting "umbrella reviews", i.e. structured overviews of systematic reviews of empirical evaluation studies. Over the past decade, 12 such umbrella reviews have been published, each based on substantial numbers of systematic reviews which in their turn were based on hundreds of separate effectiveness studies. Although this suggests that evidence is abundantly available, in reality the evidence base is still rather thin.

The overall conclusion from these umbrella reviews is that there is evidence – albeit limited in size and quality – that some interventions and policies are effective in reducing health inequalities. These include several interventions and policies targeting health-related behaviours (e.g. raising tobacco taxes, taxing unhealthy foods and drinks), some other public health interventions (e.g. water fluoridation, population-based cancer screening) and some workplace and housing interventions (e.g. increasing job control, increasing housing warmth). At the macro-level, only increasing unemployment insurance generosity was found to be effective in reducing health inequalities.

For many other interventions and policies that were evaluated in the umbrella reviews, no evidence for effectiveness was found. In addition to highlighting that there is very little evidence on more "complex" options, the authors of these umbrella reviews point out that the quality of the evidence in individual studies is often rather weak owing to methodological issues, such as focusing on short-term outcomes, the possibility of bias due to low response rates and high attrition, and study populations that are too small. All in all, the results of these evaluations seem quite mixed, and raise the question of how to proceed with implementing policies and interventions aimed at reducing health inequalities.

Many of those working in the field of health inequalities feel that, because health inequalities are such a major public health problem, it is unethical to delay large-scale interventions and policies until their effectiveness has been proved beyond reasonable doubt. They argue that the more robust and extensive descriptive and explanatory evidence on health inequalities, such as described in Annexes 2 and 4, combined with the more limited evidence on effectiveness of interventions and policies, is sufficient to justify large-scale implementation of plausible countermeasures. However, others correctly argue that interventions and policies may have unintended negative side-effects, and have opportunity costs in the sense that they may stand in the way of other – perhaps more effective – interventions and policies. The committee therefore recommends that, if policy-makers decide on large-scale implementation of non-proven interventions and policies, these are accompanied by adequate evaluation efforts.

5.3 New methodological developments (again)

How can gaps in the evidence base on what works and what does not be filled more rapidly? One of the reasons why planned experiments (e.g. randomized controlled trials) are often unfeasible is that they depend on the willingness of policy-makers to implement policy changes as experiments. While this is understandable, this willingness is also subject to change, as the recent popularity of randomized experiments in economic and social policy in the USA and the UK shows. This suggests that health inequalities researchers could also more often create and use opportunities for experiments in their field. It may also be possible to add evaluations of health impact more often onto planned experiments in other fields.

In addition to this, a recent development that can help to generate more evidence on interventions and policies is the use of "quasi-experimental" methods. These provide an alternative when a planned experiment is ruled out for political, ethical or practical reasons, or simply when a policy has already been implemented in the past without concurrent evaluation efforts. Quasi-experimental methods therefore considerably widen the range of opportunities for rigorous evaluation.

These quasi-experimental methods are part of the same evolving "tool-box" as those that have been used to strengthen causal inference. Examples are "interrupted time-series analysis" and "difference-in-difference" methods (which are often used for evaluating natural experiments), and "propensity scores", "instrumental variables" and "regression discontinuity" (which are often used to identify quasi-random variation within observational data). Each of these has their own indications and specific strengths and weaknesses.

They are particularly useful for evaluating the health impacts of policies which are primarily implemented for other reasons (as in the case of most social and economic

policies), and/or when health impacts take a long time to accrue (so that planned experiments would require withholding the intervention from the control group for too long). They can also be used to measure the health effect of withdrawing a seemingly beneficial policy—a situation in which a randomized experiment is even more unlikely to be possible than when a potentially beneficial policy is introduced.

A key strength of these approaches is that, by definition, they evaluate interventions and policies as they are implemented (or withdrawn) in practice, rather than in an artificial research setting, so that there is more reason to believe that the results are generalizable to other real-life settings. However, there are some downsides as well. One is that, compared with planned experiments, there is more uncertainty about whether the intervention or policy was indeed the main cause of the measured effects on health. Opportunities for evaluating natural experiments also often depend heavily on the availability, quality and relevance of routinely collected data, which often depends on an adequate data linkage infrastructure. Fortunately, many countries are making good progress in improving their data infrastructure.

Several promising examples are now available of studies that have used these methods for evaluating the impact of interventions and policies on health inequalities. These methods can also be used to evaluate the impact of bundles of policies, as illustrated by some recent studies that have evaluated the long-term impact of the English national strategy to reduce health inequalities (1997–2010) by using interrupted time-series and difference-in-difference analyses.

6. CONCLUSIONS AND RECOMMENDATIONS

This report has reviewed several new quantitative research methods that have recently been introduced to the field of health inequalities, and that may shed more light on three fundamental issues: (1) to what extent are health inequalities caused by differences in education, occupational class or income? (2) what is the relative importance of specific factors involved in the relationship between education, occupational class or income and health? (3) what is the effectiveness of interventions and policies to reduce health inequalities?

The general conclusion is that these new approaches hold considerable promise, and are a valuable addition to the health inequalities researchers' tool-box. This applies to all the approaches reviewed: the "counterfactual" approach to causal inference; new statistical methods for mediation and moderation analysis; inclusion of genetics in explanatory research; and evaluation of policies and interventions with quasi-experimental methods. Results obtained with these methods have already added some important new insights, or at least hint at the possibility of answering important questions in the future.

However, although these new approaches bring more scientific rigour to health inequalities research, the results that have been obtained so far with these new approaches should not be overrated. For example, in the case of the "counterfactual" approach to causal inference there seems to be a paradox, in the sense that the stricter one is on establishing causality and the closer one gets to identifying a causal effect, the farther one may get from actually understanding how socio-economic position – as a lifelong experience of living in socio-economic (dis)advantage – affects health. More generally, there often seems to be a trade-off between precise answers to limited questions and less precise answers to broader questions.

This and other limitations of the new methods discussed in this report imply that conventional methods have by no means lost their relevance. On the contrary, straightforward descriptive studies (e.g. for monitoring purposes), conventional mediation analyses and planned experiments retain their value. All of these deserve further support by research funding agencies. The same applies to qualitative studies, which fall outside the scope of this report, such as anthropological studies to explain health inequalities from people's lived experiences, and case studies of comprehensive, multi-faceted regional or national programmes to reduce health inequalities. For robust

conclusions, it will often be necessary to "triangulate" the results of studies using different approaches, taking into account the particular strengths and weaknesses of each approach, against the background of well-established theoretical knowledge.

In view of the magnitude of health inequalities, also compared with other population health problems, this area deserves substantial research funding. With its expanding evidence base and the incorporation of new methodological developments, health inequalities research can play an important role in helping European countries cope with this societal challenge. There is also a need for investments in data infrastructure, for example in birth cohort and other life-course studies which are necessary for mediation and moderation analyses, and data linkage facilities which are necessary to study natural experiments. Because study results are often context-dependent, it is important that all countries collect their own evidence. Adequate research funding is not only the responsibility of national research funding bodies, but also of the European Commission which can play an important role in fostering international cooperation and between-country comparisons.

While continued research is necessary, and while this will benefit from the expanded methodological tool-box, there is already considerable evidence (summarized above) to support action against health inequalities. In practice, policy-making is very rarely based on "perfect" evidence, and the methodological issues highlighted in this report should thus not be used 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 is effective, is a very potent source of knowledge on understanding health inequalities, and can be used to improve those very policies.

ANNEX 1.

ALLEA AND FEAM COMMITTEE ON HEALTH INEQUALITIES

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ANNEX 2.

DISCUSSION PAPER. IS THERE A CAUSAL EFFECT OF SOCIO-ECONOMIC POSITION ON HEALTH?

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A2.1 Introduction

A2.1.1 Why is this an important question?

Starting with the publication of the Black report (1), which brought health inequalities back into the focus of public health research, the question whether "causation" (i.e. socio-economic position influences health) or "selection" (i.e. health influences socio-economic position) was the more important mechanism involved in generating health inequalities has been central to debates about the explanation of socio-economic inequalities in health (2, 3).[5] In support of these debates, many studies have been conducted to disentangle the two directions of effect, and most of these have found both "causation" and "selection" to play a role (4).

There are several reasons why this issue occupies such a central place. The first is that if socio-economic 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 (5). By contrast, if there is no causal relationship between socio-economic position and health,

5 For economists/econometrists, "health-related selection" falls under the heading of "simultaneity": owing to a loop of causality between socioeconomic position and health, the presumed dependent variable actually affects the independent variable, potentially leading to "simultaneity bias".

such redistributive policies are unlikely to be effective as far as health outcomes are concerned.

A second reason is that "selection" is often – mistakenly – considered to be less of a problem for public policy than "causation". Health inequalities due to "causation" mechanisms are often perceived to be more unfair, particularly by those who feel that the underlying socio-economic inequalities are already unfair in themselves (6). 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 (7)(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 socio-economic position on health can thus be seen as 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 socio-economic 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 socio-economic position, because of the substantial differences in remaining life expectancy at age 65 (8). For this discussion it does not really matter whether the differences are due to "causation" or "selection", because in either case people in lower socio-economic groups have fewer remaining life-years at 65.

Furthermore, it is a mistake to think that "selection" mechanisms have less relevance for policy than "causation" mechanisms: if "selection" mechanisms aggravate the problems of people with a low socio-economic position, we may want to find ways to counter these mechanisms, for example by removing barriers to work for people with chronic diseases (9). Measures to reduce the impact of health problems on people's income and other socio-economic conditions are at the heart of European welfare policies. The equivalence goes even further: both "selection" and "causation" mechanisms imply causal relationships, and the only difference is that in the case of "selection" mechanisms the causal arrow goes from health to socio-economic position, instead of the other way around. We will therefore 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 are likely to interact over the life-course, as we will describe more extensively in section A2.1.3.

Nevertheless, and despite all these nuances, it is important to know whether, or to what extent, the strong and persistent associations between socio-economic position and health that have so abundantly been documented are due to an effect of socio-economic position on health, or to other mechanisms. But before we can address this question properly, we should first clarify what we mean by "socio-economic position"—a term that we have so far used in a somewhat loose fashion.

A2.1.2 Socio-economic position versus specific socio-economic determinants

Terms such as "social class", "socio-economic status" and 'socio-economic position' are often used interchangeably, and derive from the idea that societies are "stratified", in the sense that a "higher" relative position in society gives a greater level of control over important resources such as money, power or prestige, which then generates "social inequality" (10).

While this idea is generally accepted in the social sciences, there is also a consensus that a person's relative position in this hierarchy can only be measured on the basis of specific characteristics, such as level of education, type of occupation, household income, wealth, etc., or a combination of two or more such characteristics (11). Still, in many studies of health inequalities these more specific characteristics are considered to be "indicators" of socio-economic position, and not to be "the real thing".

This pragmatic approach becomes somewhat problematic, however, when we want to assess causality more rigorously. As will be seen below, scientific methods that allow a rigorous assessment of causality require precise measurement of the putative cause. In the case of socio-economic position this implies that we must study the effect of a specific aspect of socio-economic position, such as education or income, and even more specifically the effect of a particular measure of educational achievement (e.g. one extra year in school) or a particular measure of income (e.g. a couple of hundred Euros extra in household equivalent income).

Some scientists in the field of health inequalities see only benefits in doing such highly specific studies, not only because these studies allow us to assess causality, but also because the exposures studied (e.g. one extra year in school, or a couple of hundred Euros extra in monthly income) come close to what one can actually intervene on. In their view, the question of whether an unmeasurable construct such as "socio-economic position" is causally related to health is unanswerable (12).

Other scientists object that studies focusing on the causal effect of specific socio-economic conditions lose sight of the cumulative effect of (dis)advantage in many spheres of life. The fact that it is impossible to study the health effects of "socio-economic position" as rigorously as it is to study the health effects of one extra year

in school or a couple of hundred Euros extra does not imply that such broader effects do not exist (105).

Ultimately, this disagreement comes down to whether or not one believes that the full effect of social inequality on people's lives can be adequately captured by one or a few specific, measurable characteristics. We do not take sides in this debate, but note that the field of health inequalities is, to some extent, split between these two visions, and that this debate cannot be resolved on the basis of empirical evidence. For proponents of the "specific" approach there is little value in studying the effects of something as unobservable as "socio-economic position", whereas for proponents of the "inclusive" approach there is little relevance in studying the observable but highly specific aspects only. In the final reflections at the end of this paper we will come back to this issue, and discuss whether the two positions can somehow be reconciled.

A2.1.3 A third mechanism: confounding

In addition to "causation" and "selection" there is another possible explanation for the association between socio-economic position and health: "confounding" by third factors which are related to both socio-economic position and health, but are not on the causal pathway linking socio-economic position to health or vice versa[6] (13) (pp. 129–134).

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 socio-economic position, they are "mediators" and not "confounders". (On mediation, see Annex 4.)

Confounding can certainly occur, because social mobility, and thus a person's socio-economic 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 socio-economic position, and thus cannot mediate the effect of socio-economic position on health) and cognitive ability, coping styles, control beliefs and personality traits (14, 15).

For example, childhood obesity can affect social mobility later in life owing to discrimination during recruitment for jobs or promotion, and can 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

6 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".

being the *cause* of diabetes (16, 17). Another example is excessive alcohol consumption, which may stand in the way of upward occupational mobility and may even lead to loss of income (18), 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 the use of health services (19).

To the extent that these factors are not determined by the person's current socio-economic position, the resulting association between current socio-economic 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 socio-economic status. Cognitive ability and personality are largely formed before adulthood, and some health-related behaviours (e.g. smoking) are also already adopted during adolescence.

A higher prevalence in lower socio-economic groups of genetic factors that predispose to ill-health should also be seen as an instance of "confounding". This is explained conceptually in Box A2.1. Empirical evidence for the role of genetics in generating health inequalities will be discussed in section A2.1.3.

Box A2.1 Genetic factors as possible "confounders"

A higher prevalence in lower socio-economic 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 socio-economic position. But how would a higher prevalence of such genetic factors in lower socio-economic groups arise? To answer this question we need to consider social mobility, as we did in the case of other confounders.

An association between socio-economic 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) (20).

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 socio-economic 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 socio-economic 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) (21).

In the case of health inequalities, "gene–environment correlation" would exist if certain genotypes are more frequent in lower or higher socio-economic 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 socio-economic status. This does not give rise to confounding, but is closer to mediation, and will therefore be further discussed in Annex 4.

Finally, 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, for example owing 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 (22, 23). However, epigenetic mechanisms would again be an instance of mediation, not of confounding.

Although it is important (and technically possible) to correct for confounding when studying the effect of socio-economic position on health, the underlying phenomena (e.g. the concentration of certain personal attributes in lower socio-economic 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 programmes in terms of tailoring them to specific groups or targeting these groups (24).

According to some, this also applies to genetic factors that contribute to persistent disadvantage. However, studies of the role of genetics in explaining social disadvantage are surrounded by dispute, fuelled by fears that research findings may be misused to justify existing inequalities (25). Proponents of these studies argue, however, that it is not only scientifically important to know whether genetic factors play a role, but also potentially policy relevant (26). To achieve full equality of opportunity, so their reasoning goes, it is important that society compensates for the negative consequences of innate disadvantage, as has also been argued by ethicists (27, 28). This would then also apply – at least in theory – to health inequalities that are determined by differences in genetic factors (29).

A2.1.4 The importance of a life-course perspective

In sections A2.1.1 and A2.1.3 we introduced three types of explanation for the association between socio-economic position and health: "causation", "reverse causation" and "confounding". These explanations all imply a focus on measuring the effect of people's socio-economic position at one point in their adult lives on health outcomes later 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 socio-economic positions during their life-course. For example, an individual may start out from a situation that is largely determined by their parents' socio-economic position and their school environments, and may then, depending 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 socio-economic position, and a determinant of their current and future socio-economic position. Moreover, both health and socio-economic position may be determined by personal attributes that may themselves be consequences of socio-economic 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 socio-

economic 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 socio-economic position (30).

A life-course perspective has proved 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 socio-economic 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 socio-economic position some years later, and so on (33). Accumulation of risk, which is often seen as a simple addition of risks, can in fact be 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 socio-economic circumstances, and in its turn influences both adult socio-economic 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 socio-economic position and health.

A2.2 Methodological requirements

A2.2.1 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 socio-economic position does not have to be a sufficient nor a necessary cause of ill-health, but it must induce a greater likelihood of ill-health to qualify for a causal role.

Establishing that low socio-economic status causes ill-health of course requires more than demonstrating an association—as noted above, associations between low socio-economic status and ill-health may also be due to "reverse causation" (alias "selection" mechanisms) or "confounding by third variables" (37). At the very least, the temporal relationship should be such that low socio-economic 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 making sure that the study is limited 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, and empirical evidence fulfilling them is rare.

In the empirical sciences, the most reliable evidence of causation can be obtained in an experimental setting. Such a research design is, however, mostly unfeasible or unethical in the area of socio-economic inequalities in health. Although there are a few examples of experiments in which people have been randomized into more or less education, or more or less income (106), in this field one has to rely almost completely on clever observation, and try to come as close as possible to the clean contrast of a controlled experiment.

In a purely observational study design, such a clean contrast is difficult to obtain owing to the multiple links between socio-economic position, health and third variables over a person's lifetime. One would not only have to use a prospective design ensuring that low socio-economic status precedes ill-health, but also control for a range of third factors that precede low socio-economic position. This requires very extensive data collection, and after all the data on measurable confounders have been collected, one would still be left with the possibility of unmeasured confounders that have simply been overlooked or that are currently unknown.

A2.2.2 Quasi-experimental study designs

This is why "quasi-experimental" study designs have increasingly become popular. This is part of a wider movement in the empirical sciences which advocates the "counterfactual" approach to causal inference, and uses the "potential outcomes" framework for assessing causality. This approach requires the investigator to identify occasions when people's exposure to socio-economic conditions changed in a quasi-

random way, for example because the company where they worked went bankrupt and all employees, regardless of their personal circumstances or characteristics, lost their main source of income, or because the government decided to increase the statutory school leaving age for all children born after a particular date (38).

As these examples show, practical application of this approach is dependent on whether or not such occasions can be found (or mimicked statistically). This approach requires the investigators to identify a difference in exposure that can be regarded as a well-defined intervention, which is often challenging (39). It is important to recognize that such occasions may not be representative of the full range of socio-economic exposures that we may have reason to include in our studies. Application of this approach is limited to instances in which putative causes are manipulable, which means that quasi-experimental studies of the studies of the effect of socio-economic position on health usually focus on discrete and specific aspects, such as those mentioned above (40).

This implies that practical application of the "counterfactual" or "potential outcomes" approach, in the form of quasi-experimental study designs, is limited to a narrower range of questions than some health inequalities researchers would like (41, 42), and that results may need to be triangulated with results obtained with other approaches to come to broader conclusions (39).

Some of the quasi-experimental study designs that have been proposed as promising approaches for isolating the causal effects of socio-economic position on health (43, 44) are listed in Box A2.2.

Box A2.2 Quasi-experimental study designs

In quasi-experimental studies the investigators exploit a "natural experiment" that has created quasi-random variation in exposure to education, occupation, income, wealth or other socio-economic conditions. This allows the researchers to mimic a truly randomized experiment, and to avoid some of the problems mentioned in section A2.2, particularly confounding by both observed and unobserved third variables (45).

Within this family of study designs, two groups can be distinguished:

- studies in which this quasi-randomness is created statistically, for example. "propensity score matching", "differences-in-differences", "instrumental variables", "regression discontinuity";

- studies in which random allocation has occurred in reality, but not in the context of a randomized experiment, for example a lottery or gradual but random roll-out of an intervention programme.

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 (46). 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, socio-economic 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. However, 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 perhaps unlikely (47). Another example is random roll-out of an intervention programme which sometimes occurs spontaneously, as in the roll-out of a higher age of compulsory education across Swedish municipalities in the 1930s (48).

One other quasi-experimental design that has sometimes been used to study the causal effect of education or other socio-economic factors on health is "Mendelian randomization". This approach uses the genetic determinants (e.g. a polygenic risk score) of a particular "phenotype" (e.g. education) to study the causal effects of that phenotype on health (e.g. mortality), usually in an "instrumental variables" analytical framework. The idea behind this is that whether people have certain genes or not is the outcome of a "natural experiment" occurring at conception, when each child inherits half of each of their parents' genomes, and that whether a child inherits a particular gene from its father or mother is the outcome of a random process (49).

Note: this is partly based on references (37, 45).

A2.2.3 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 – as mentioned above – 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 worthwhile to briefly illustrate its approach to causality. A large part of the research of this subdiscipline is based on prospective cohort studies, and the classic epidemiological approach to assessing causality which was codified in a set of nine criteria for assessing causality proposed by Bradford Hill (50). 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 it has been recognized that these criteria do not guarantee valid conclusions on causality (13)(pp. 26–30), they are still frequently used, for example in the evaluation of carcinogenic risks to humans (51).

The association between low socio-economic position and ill-health as found in prospective cohort studies fulfils many of these criteria: it is a strong association; it has consistently been observed; it is observed longitudinally, namely in studies in which exposure to low socio-economic position precedes the occurrence of ill-health; the association has the form of a gradient with worse health at each step down the socio-economic ladder; it plausibly fits what we know about the socio-economic 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 socio-economic position.

As previously mentioned, economists have over the past decade shown the keenest interest in identifying causal effects of socio-economic position on health, and vice versa. Their interest in the effect of health on income and other socio-economic 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 socio-economic position on health. Studies

by economists using some of the quasi-experimental approaches mentioned in Box A2.2 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 sections.

A2.3 Inventory of empirical evidence

A2.3.1 Evidence of a causal effect of education on health

There are many longitudinal studies that show 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 (52). 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 (11). 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 (4). 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 there may well be a causal effect of education on health (37, 54, 55).

An important candidate for a usually unobserved confounding factor can be found in an individual's genotype. Although variations in educational achievement are partly dependent on parents' socio-economic 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 studies of twins, which generally find substantial heritability (of the order of at least 50% for cognitive ability measured in adulthood) (57, 58). Genome-wide association studies 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 studies of twins) 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, with polygenic risk scores now explaining more than 10% of all inter-individual differences in educational achievement (57, 63). Genome-wide association studies 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 include genetically determined aspects of personality such as the "big five" personality traits, self-control, risk aversion, time preferences, etc. (65).

It is important to note that these results do not imply that educational achievement (or cognitive ability and personality traits) are wholly or even largely biologically determined (66). First, the effect of children's genes on their functioning goes partly via environmental channels, such as their experiences in the school system, and these can be intervened on through social policies. Secondly, the effect of children's genes as measured in most studies includes the effect of their parents' genes on how they grow up. This indirect effect, which has been called "genetic nurture", may occur through various pathways, for example an effect of parental cognitive ability on the child's early learning environment. Its potential importance is illustrated by the fact that even parental genes that are not transmitted to the child influence that child's educational achievement (67).

Nevertheless, the correlation between educational achievement and certain genotypes does suggest that genetic factors could confound the relationship between education and health. If these genetic factors influence health through other pathways than through educational achievement, for example by independently determining cognitive ability, self-control or other determinants of health in later life, they may well act as confounders to some extent. That this may actually be the case is illustrated by the fact that there is considerable overlap in the genetic correlates of education on the one hand, and smoking, obesity, depression and various chronic conditions on the other (68). It is, however, not yet clear what the extent of this confounding bias might be.

In the presence of these and other risks of confounding, which are difficult to control 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 USA that have assessed the long-term health effects of early childhood (or preschool) 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 several quasi-experimental studies. The most common approach has been to study the impact of compulsory schooling laws (37, 54, 55, 69). 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.

The evidence from these studies is not entirely consistent, which is perhaps to be expected, in view of the fact that whether or not staying longer in school reduces mortality will depend on context, quality of education, behavioural responses and many other factors. Nevertheless, many 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, 70). Other conclusions were that extra education improves intelligence (71) and reduces the risk of taking up smoking (54, 55), and that better-educated parents also have healthier children (54). On the other hand, extra education seemed to have little effect on the prevalence of chronic illness in adult life (72).

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, for example, 16 can be generalized to the whole range of variation in length of education currently seen), these findings do suggest that there is likely to be a causal effect of education on mortality.

This is also suggested by the results of a few "Mendelian randomization" studies (see Box A2.2). It has recently been shown that genetic variants associated with educational attainment lower the likelihood of being a smoker (73) and lower the risk of coronary heart disease (74), thereby providing evidence for a causal effect of education on these health outcomes.

Interpretation of these results is, however, still challenging. "Mendelian randomization" studies only produce valid outcomes if the genetic determinants do not affect the health outcome via other mechanisms than the exposure of interest, in this case educational achievement (75), of which it is difficult to be certain. Also, "Mendelian randomization" assumes that children's genotypes are randomly assigned, but this is only true conditional on their parents' genotype, and the latter therefore needs to be controlled for (76).

A2.3.2 Evidence of a causal effect of occupational class on health

As 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 (77–79). The main issue is whether this is due to a causal effect of occupational class on health or to "reverse causation" or confounding. There seem 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) (80).

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 USA have found that the association between occupational class and health disappears after controlling for level of education (81, 82), but studies from several European countries have shown an independent effect of occupational class (11, 83, 84).

Because education is a determinant of occupational class, some of the findings reviewed in the previous section must also apply to inequalities in health by occupational class: some of the observed association between occupational class and health is probably due to confounding by the same unobserved factors as mentioned in section A2.3.1, 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 (85), 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 (86). 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)(pp. 44–47), an analysis of the British 1958 birth cohort study found a reduction of only a few percentage points (87)(pp. 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 (88).

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 downwards 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 upwards 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 (89, 90).

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 with 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 (91, 92).

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 (79, 93, 94).

A2.3.3 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, 95). 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 (96). 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 (11, 83, 97, 98).

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 (99).

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 (100). 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 (11).

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 (101). With regard to these genetic determinants, it is important to note that similar caveats (e.g. on biological determinism) apply as in the case of the genetic determinants of education (see section 2.3.1).

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 several 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, several comprehensive reviews of this type of study has been done (99, 102, 103), and we summarize their main findings below.

Overall, 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 lifetime 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, 99, 102, 103).

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 seemed to be context-dependent, i.e. dependent upon employment and social policies (99)[7]. 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. Ill-health can thus have a very long reach from childhood to constrained economic opportunities in adulthood (99).

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 with no effect, 2 with a negative effect (i.e. more money, worse health) and 6 with a positive effect (i.e. more money, better health). On the basis of 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" (99).

A second recent review summarizing the results of 9 studies of income effects on health in adulthood (6 of which were also included in the first review) found 4 with no effect, 2 with a negative effect and 3 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

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

can lead to less healthy behaviours such as increased drinking and smoking. The authors conclude that for physical health in adulthood "the evidence is mixed" (102).

Some of the reviewed studies focused on so-called windfall gains in income, for example 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 (99). The weakness of this strategy is, of course, that this variation in "income" does not necessarily correspond to that of normal monthly or annual 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 sizeable prizes and paid them out over longer periods of time, but this study also found largely null effects on physical health in adulthood (104). Similar limitations apply to other quasi-experimental "identification strategies" (Box A2.2). 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 (99).

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, 99, 103). This conclusion is further supported by the fact that there is also good evidence for income effects on intermediate outcomes (i.e. mediators), such as parenting, the physical home environment, maternal depression, smoking during pregnancy, and children's cognitive ability, school achievement and behaviour (103). Long-term increases in the incomes of lower socio-economic groups may in this way have health benefits that accumulate over generations (37).

A2.4 Final comments

It may be useful to reiterate that, whether or not there is a causal effect on health of socio-economic position, or one of its components or indicators, is an important question, not only scientifically but also for policy-making. Whether or not health inequalities are perceived to be unfair may partly depend on how they are generated, and the same applies to what we can do about them.

Over the past two decades, new scientific methods have been developed which allow a more rigorous assessment of causality, and these quasi-experimental methods have increasingly been applied to the study of health inequalities. In view of the limited number of applications, however, and the lack of consistency in the results, only the following tentative conclusions can be drawn.

First, we need many more studies of health inequalities applying quasi-experimental methods. Despite their limitations, these methods can provide many new insights, which will also be highly policy-relevant, particularly when triangulated against results obtained with other approaches. Only after many more quasi-experimental studies have been done will it be possible to identify the conditions under which specific socio-economic factors have, or do not have, a causal effect on health.

Secondly, the evidence from quasi-experimental studies does not contradict the idea that socio-economic position, conceptualized in broader terms such as a person's educational achievement or level of income, or even more generally as that person's relative position in society, has a causal effect on health. The limitations of quasi-experimental studies imply that they do not shed light on the health effects of lifelong exposure to socio-economic (dis)advantage. Furthermore, there is a sufficient number of studies with "positive" results to warrant the conclusion that education and income may, in certain forms and/or under certain conditions, causally affect health.

Thirdly, there is uncertainty about the evidence so far to support claims that health inequalities are largely due to a causal effect of socio-economic position, or its specific components or indicators, on health. Differences of opinion around the evidential threshold required to determine causality also exist within the field. There are new and emerging data (e.g. on genetics) that require further interrogation. Health inequalities may or may not be causally linked to socio-economic status but, in view of the lack of consistent evidence from the more rigorous studies, we can only conclude that it is not yet possible to form a definitive opinion. This implies that caution is required when making policy recommendations for reducing health inequalities.

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ANNEX 3.

WORKSHOP REPORT. CAUSALITY AND SOCIO-ECONOMIC INEQUALITIES IN HEALTH

This workshop was held on 2 December 2020. It was supported by the German National Academy of Sciences Leopoldina, ALLEA, FEAM and KNAW. Virtual platform. Report by Jean Philippe de Jong.

A3.1 ATTENDANTS

Ingelise Andersen, Hans-Peter Blossfeld, Axel Börsch-Supan (chair), Hans Bosma, Rosa Castro (FEAM observer), Giuseppe Costa, George Davey Smith (speaker), Eddy van Doorslaer, Maria Glymour (speaker), George Griffin, Karthrin Happe (speaker), Rasmus Hoffmann, Tanja Houweling, Domantas Jasilionis, Jean Philippe de Jong (writer of the report), Carlijn Kamphuis, Hans van Kippersluis, Philipp Koellinger (speaker), Anton Lager, Eero Lahelma, Alastair Leyland, Johan Mackenbach (co-chair), Umida Masharipova (ALLEA observer), Pekka Martikainen, Maria Melchior, Guillem Lopez Casasnovas, Vincent Lorant, Olle Lundberg, Christiaan Monden (speaker), Anne-Marie Nybo Andersen, Owen O'Donnell (speaker), Joost Oude Groeniger, Anna Pearce, Johannes Siegrist, Vera Skalicka, Alfred Spira, David Taylor-Robinson, Denny Vågerö, Nicole Valentine, Margaret Whitehead, Bogdan Wojtyniak

A3.2 PROGRAMME (CET)

Chair: Professor Axel Börsch-Supan, German National Academy of Sciences Leopoldina

14:00–14:05	Opening address (Prof Regina Riphahn, German National Academy of Sciences Leopoldina)
14:05–14:20	Causality and socio-economic inequalities in health: what are the issues? (Professor Johan Mackenbach, Erasmus MC, Rotterdam, The Netherlands)

14:20–14:35	Health inequalities and the potential outcomes approach: opportunities and pitfalls
	(Professor Maria Glymour, University of California, Berkeley, USA)
14:35–14:50	Q&A
14:50–15:05	Causality and health inequalities: an economist's view
	(Professor Owen O'Donnell, Erasmus University, Rotterdam, The Netherlands)
15:05–15:20	Q&A
15:20–15:25	Minibreak
15:25–15:40	Social inequalities and causation: a sociologist's view
	(Professor Christiaan Monden, Oxford University, UK)
15:40–15:55	Q&A
15:55–16:25	Moderated discussion
16:25–16:40	Break
16:40–16:55	Genetics and social inequalities
	(Professor Philipp Koellinger, Vrije Universiteit Amsterdam, The Netherlands)
16:55–17:10	Q&A
17:10– 17:25	Genetics and health inequalities
	(Professor George Davey Smith, University of Bristol, UK)
17:25–17:40	Q&A
17:40–17:45	Minibreak
17:45–18:15	Moderated discussion
18:15–18:30	Summary and conclusions
	(Professor Axel Börsch-Supan, Münich Center for the Economics of Aging, Germany)

A3.3 AIM

- Evaluate scientific evidence on causal relationships between socio-economic position and health, focusing on methodological issues.
- Identify areas of agreement and disagreement between scientific experts, and agree on priorities for further substantive and methodological research.
- Clarify to what extent the available evidence permits reliable recommendations for policy-makers on how to reduce health inequalities.

A3.4 WAY-OF-WORKING

- The ALLEA and FEAM Committee on Health Inequalities prepared a short document with several questions for discussion, referring to the longer document "*Health inequalities: an interdisciplinary exploration of socioeconomic position, health and causality*" that the Committee had produced in the first phase of this project. Both documents were circulated among speakers and participants in advance of the workshop.
- This draft report has been circulated among the attendants of the workshop, asking for feedback and additional inputs.

A3.5 INTRODUCTION

Regina Riphahn welcomed participants and speakers. The German National Academy of Sciences Leopoldina has been active on the topic of health inequalities because it is an important issue to address, both in Germany and abroad. It therefore wholeheartedly supports the ALLEA/FEAM project on methodological issues about the study of socio-economic health inequalities. The current workshop is the second in a series of three. The workshop was originally planned in Berlin in March but had to be postponed owing to the COVID-19 pandemic.

Johan Mackenbach introduced the ALLEA/FEAM/KNAW health inequalities project and the place of this workshop in it. The association between socio-economic position and health is presumed to be due to a combination of "causation", "selection" and "confounding". Traditionally, "causation" has been considered the most important of the three, with profound implications for policies to reduce health inequalities. However, the results of recent "counterfactual" (or "potential outcomes") approaches to causal inference, relying on "quasi-experimental" study designs, cast doubt on the causal effects of income, education, wealth, etc. on health. In addition, recent genetic research suggests that genetic factors may confound the association between socio-economic position and health. It is unclear how this new evidence should be interpreted and weighed, with different disciplines taking different views. The aims of this workshop are to evaluate this new scientific evidence, identify areas of agreement

and disagreement, agree on priorities for further research and clarify its impact on policy-making.

A3.6 CAUSATION

Maria Glymour presented her views on the opportunities and pitfalls of the potential outcomes approach. There is a broad set of statistical tools labelled "causal inference tools" which can be used for studying social and other determinants of health in cases where an interventional approach is impossible. For every causal question, we observe an actual outcome, but not the "counterfactual" of what might have occurred. We therefore have to work backwards from observed patterns of statistical association to understand the causal processes. "Counterfactual" thinking helps us to be clear about the causal contrast we wish to estimate. There are three ways to do so: (1) correct for all factors that could impact the causal relationship between a cause and its effect; (2) measure all pathways from a cause to its effect directly; (3) use an instrument (natural/ quasi-experiment) that impacts the cause directly and study the corresponding effect. The second approach is impractical because this requires too many data sources. The first approach, favoured by epidemiologists, is often too optimistic about measuring all factors. The third (quasi-experimental) approach, favoured by economists, is often too optimistic about identifying an instrument that is relevant for the question and population of interest[8]. The reason for this is that this approach requires a "well-defined intervention", comparable to treatments in a randomized controlled trial. They must be manipulable under the stable unit treatment value assumption[9], which rules out many real-world causal factors/interventions. There are also some technical pitfalls, including overdetermined outcomes and reliance on local average treatment effects. So, the preferred approach to causal inference should depend on the available data, the question of interest, details of the setting and the limitations of previous work in the area. In addition, causal effect estimation is typically conducted within the scope of one study, and inferences need to be interpreted with respect to that study's strengths, limitations and underlying assumptions. So, causal inferences can be strengthened by leveraging multiple approaches that require different assumptions or that have different strengths and limitations, i.e. "triangulation". The question is not whether low socio-economic position causes worse health outcomes (this is an obvious "yes"), but how much, which outcomes, which specific dimensions of socio-economic position for whom and in what circumstances.

In the **questions and answers**, a participant stated that in designing a study one needed to start from theory, for example how do things develop over the life-course? A randomized controlled trial design cannot capture this. Professor Glymour responded

8 Matthay EC, et al. Alternative causal inference methods in population health research: evaluating tradeoffs and triangulating evidence. *SSM Population Health* 2020; 10: 100526.

9 Schwartz S. Is the "well-defined intervention assumption" politically conservative? *Social Science & Medicine* 2016; 166: 254–257.

that, in principle, randomized controlled trials can be used for any intervention, although for practical interventions generalizability becomes a problem.

Professor Mackenbach asked what Maria Glymour's interpretation was of the mixed results of application of counterfactual (quasi-experimental) approaches to the effects of income or education on health.

Professor Glymour responded that one needed to carefully interpret the results: why are they different in different studies? This should be done on a case-by-case basis.

Owen O'Donnell started his presentation by stating that there are a lot of similarities between the causal inference approached taken in economics and epidemiology, and that differences should not be over-emphasized.

Results of quasi-experimental studies show much variation. This is probably the result of using different constructs (complex, interlinking and dynamic causal chains of causation and selection, behavioural responses), contexts (location, timing, population groups, social and economic (/personal) background) and methods (defining the measures, availability of data). Results of quasi-experimental studies should therefore be very carefully interpreted and not over-generalized. Without additional knowledge of the underlying mechanisms quasi-experimental studies give a limited understanding of causes. Moreover, the external validity and usefulness for policy can be limited. Nevertheless, quasi-experimental studies have given some new insights into selection and causation, and into the link between education or income and health. A study on polio suggests that the effect of health problems in childhood on socio-economic position in adulthood is more mixed than was previously thought[10]. The effect of education reforms on later life mortality or chronic conditions is less consistent than the ALLEA and FEAM committee claims in its report[11]. Quasi-experimental studies have delivered mixed evidence on the effect of wealth shocks on adult health[12]. US studies that show a mortality spike on "pay day"[13] are consistent with liquidity impacting on health. There is also evidence of a positive effect of cash transfers paid at low incomes on maternal health[14]. Professor O'Donnell highlighted the difficulties of identifying a causal effect of

10 Gensowski M, et al. Childhood health shocks, comparative advantage, and long-term outcomes: evidence from the last Danish polio epidemic. *Journal of Health Economics* 2019; 66: 27–36.

11 Galama T, et al. *Oxford Research Encyclopedia of Economics and Finance*. Oxford University Press, 2018. Janke K, et al. The causal effect of education on chronic health conditions in the UK. *Journal of Health Economics* 2020; 70: 102252.

12 Cesarini D, et al. Wealth, health and child development: evidence from administrative data on Swedish lottery players. *Quarterly Journal of Economics* 2016; 131: 687–738. Schwandt H. Wealth shocks and health outcomes: evidence from stock market fluctuations. *American Economic Journal: Applied Economics* 2018; 10: 349–377.

13 Evans WN, Moore TJ. Liquidity, economic activity, and mortality. *Review of Economics and Statistics* 2012; 94: 400–418.

14 Evans WN, Garthwaite CL. Giving mom a break: the impact of higher EITC payments on maternal health. *American Economic Journal: Economic Policy* 2014; 6: 258–290.

socio-economic position: socio-economic position is insufficiently precise to conceive its causal effect; if socio-economic position is considered a composite with multiple routes, then a consistent causal interpretation becomes problematic; socio-economic position implies that position or status relative to others matters, which is not easily examined with causal inference. However, by sidestepping these difficulties, there is a risk of missing the effect of relative deprivation in several socio-economic dimensions that *multiplicatively* impact on health.

Establishing causality matters for (1) policy motivation—perceived unfairness of socio-economic health inequality may depend on what causes it; and (2) policy design—to reduce socio-economic health inequality one needs to know what causes it.

In the **questions and answers**, Professor Mackenbach asked whether, in Professor O'Donnell's view, the current evidence of an effect of income on health justifies income redistribution policies as a means to tackling health inequalities. Professor O'Donnell responded that for most cases the evidence is not sufficient. The current evidence is local, contextual. However for some cases, such as US welfare policy, there seems to be sufficient evidence. Börsch-Supan asked whether people with lower income should be able to retire earlier? Professor O'Donnell responded that there are a lot of estimates of the effect of retirement on health, but the results are extremely mixed. George Davey Smith stated that one needs to have very extensive knowledge of the data and methods to be able to interpret studies correctly.

Christiaan Monden started his appraisal of quasi-experimental approaches by stating that socio-economic position is conceptually very imprecise and makes it difficult to think about causality: for example, for education and income there are very different underlying mechanisms. Moreover, there are spillover effects of education, for example on other relatives. The results of quasi-experimental studies largely confirm earlier data but give little additional understanding. In most cases we win in confidence at the costs of being able to generalize to other settings. A more fruitful approach may be to study the generative processes. For example, quasi-experimental studies favour short-term effects, but underlying mechanisms concern the long-term effects of long-term experience. Results and thus their interpretation depend heavily on "location": in place, time and policy context. The "quasi-experimental" tool is a welcome addition, but is not the only tool. Different tools simply answer different types of question. Recommendations for research are to treat education and income as separate concepts, improve and enrich measurements, work interdisciplinarily (e.g. workshops, systematic reviews) and provide broader training in methods. Causality matters for policy: sometimes more, sometime less, it really depends on what we want to achieve/change.

In the **questions and answers**, a participant stated that education is a multi-dimensional matter, so the real question is what is behind it exactly. The context

matters greatly, so a holistic perspective is needed to understand what is going on. Another participant stated that education, occupational position and income are in practice strongly intercorrelated, so there may still be value in studying socio-economic position, even social class. Professor Mackenbach asked whether generative processes are interesting at all if there is no causal effect? Monden responded that when we have descriptive data then we can either focus on specific causes with quasi-experimental methods (although in practice there is often a lack of appropriate natural experiments), or we could study generational processes, such as behavioural mechanisms (which may often be more practical and more useful). Professor Börsch-Supan stated that the causal chains are what matters. The outcome is clear, but the interesting things happen before that. Professor Glymour responded that the distal causes are still of importance, because they are sometimes more amenable to policy intervention. One should be pragmatic: do what works, done does not always have to know the whole mechanism.

In the **moderated discussion** after the presentations Johan Mackenbach presented the following statements, to see what participants thought:

The "counterfactual approach" helps to better understand how health inequalities arise, if only by eliminating some of the "simpler" causal relationships.

Professor Börsch-Supan: what do you mean by "counterfactual approach"? Is it the broader philosophy or is it the quasi-experimental method which creates an artificial counterfactual?

Professor Mackenbach: this statement refers to the quasi-experimental method.

Professor O"Donnell: quasi-experimental studies do not help with the why, the how.

Professor Glymour: they can help to some extent to understand the why/how because they can point to a potential pathway. We need multi-disciplinary reviews of the evidence.

A participant: quasi-experimental designs should be used together with other methods.

- *The "negative" results of studies using the "counterfactual approach" do not exclude a causal effect of education or income on health.*

Professor Glymour: there is a big difference between education of individuals and the community getting better education.

A participant: quasi-experimental data show that there is no positive effect of short-term financial fluctuations on health.

Professor Glymour: except negative effects in poor groups: the pay-day effect.

Professor Börsch-Supan: this shows one has to understand the causal chain.

A participant: there are important conditions/contextual factors that need to be taken into account in quasi-experimental studies.

Another participant: for example, winning the lottery actually has a negative effect on (wage) income. So, to make generalizations, one would need a lot of quasi-experimental studies to cover an area.

- *Scientific evidence for a causal effect of education or income on health is insufficient to recommend educational reform or income redistribution.*

Professor Börsch-Supan: this statement is too general. The evidence and the policy recommendation have to be very closely linked.

A participant: for people with very little income, an increase and decrease has substantial effects on health; the evidence is strong there and the relevance for policy is clear.

Another participant: the quasi-experimental evidence does show an effect of income on child health.

A3.7 GENETICS

Philipp Koellinger presented the current state of research on the role genetic factors play in generating social inequalities (education, income). Progress has been made, thanks to large, genotyped datasets, new methods and collaborations. Genetic studies show that socio-economic status and health are both partly heritable (just as all other behavioural traits). However, heritability estimates are specific for a specific population at a particular point in time. These estimates also require us to assume that genetic and environmental factors can be neatly separated. However, in practice the interplay of environments and genetic factors leads to inequalities. So, genes influence health outcomes partly through environmental channels that can be intervened upon, including education. Genetic factors do not imply determinism and do not put an upper bound of the potential of policies. Nevertheless, the evidence that a person's genotype is associated with his or her education and income is now overwhelming. For example, a recent study shows that polygenic scores explain 11–13% of the variance in educational attainment[15]. Gene–environment correlations are pervasive and strong, but gene–environment interactions do not seem to be pervasive, systematic or universal; for example, a recent study showed similar effects, regardless of parental socio-economic status, of a polygenic score on a child's educational achievement[16]. The

15 Lee JJ, et al. Gene discovery and polygenic prediction from a genome-wide association study of ducational attainment in 1.1 million individuals. *Nature Genetics* 2018; 50: 1112–1121.

16 Belsky DW, et al. Genetic analysis of social-class mobility in five longitudinal studies. *Proceedings of the National Academy of Sciences of the United States of America* 2018; 115: E7275–E7284.

effect of parental genes on children's social achievement is complex, consisting of a direct effect (biological transmission of genes to younger generations) and a "genetic nurturing pathway" (parental genes, even if they are not passed on, will still influence the environment for the offspring)[17]. Studies show important genetic correlations between education or income and a range of health outcomes[18], suggesting that the genetic architectures of socio-economic status and health partly overlap, and that genetic factors may confound the relationship between socio-economic status and health. Genetic data also offer new opportunities to study causality in socio-economic status–health relationships, but genes often violate the assumptions of instrumental variable regression (e.g. as a result of pleiotropy), and past and current attempts to estimate causal effects of socio-economic status are not convincing.

In the **questions and answers**, a participant asked whether the missing heritability between polygenetic studies and studies of twins is the result of gene–environment interactions and epigenetics.

Professor Koellinger: gene–environment interactions cannot explain the difference because all standard methods that estimate heritability rely on a linear model (just as the polygenic scores do). Epigenetics can also not explain it because it is not part either of heritability estimates or polygenic scores, either.

A participant: polygenetic factors seem to explain a part of the variation in cognitive ability, but could they also explain variation in addictive health behaviours such as smoking and heavy drinking?

Professor Koellinger: yes, and we are starting to look at that.

Another participant asked whether or not genetic correlation between education or income and health necessarily means confounding.

Professor Koellinger: no, a genetic correlation can arise from various causal constellations between genes, socio-economic status and health. So, in the same way that correlation does not imply causation, genetic correlation does not imply genetic confounding.

Another participant: most sociologists will not accept that genetic factors have a causal effect on socio-economic status.

Professor Koellinger: within-family studies that use random differences in polygenic score values between siblings clearly show that there is a causal effect of genes on

17 Kong A, et al. The nature of nurture: effects of parental genotypes. *Science* 2018; 359: 424–428.

18 Harden KP, Koellinger PD. Using genetics for social science. *Nature Human Behaviour* 2020; 4: 567–576.
Kweon H, et al. Genetic fortune: winning or losing education, income, and health. Tinbergen Institute Discussion Paper, November 2020. https://bit.ly/32VPC3u.

socio-economic status. But these effects often work through environmental/behavioural pathways which can be tackled by policy.

George Davey Smith started his presentation by recalling his own first steps in the field of health inequalities research, which followed from the observation that a large proportion of socio-economic health inequalities cannot be explained by well-known biological or behavioural pathways, which then lead to the hypothesis that fibrinogen was the missing factor. Unfortunately, this proved to be wrong. The problem is that there are myriad intermediate biological factors that can be studied, and that observational studies can produce biased results. To deal with these problems a study design called Mendelian randomization has been developed. This is a quasi-experimental method that exploits variation in a gene with a known biological pathway to study the effect of a particular exposure on a health outcome. This design helps to control for confounding and reverse causation. The strength of this approach is that it uses genes as unbiased causal "anchors". However, this comes at the cost of providing only very simple models of causal pathways which cannot capture the complex and dynamic paths linking socio-economic position and health outcomes. In addition, more distal factors are likely to be highly context-dependent[19].

In the **questions and answers**, Professor Glymour stated that one needs to be sceptical of, and careful with, new evidence on genetics. Professor Koellinger said that the interpretation of the results can be problematic. However, the evidence about genetic influences seems to be robust. It is important to consider that genetic differences have an influence within a particular environment. Professor Mackenbach asked whether, in Professor Koellinger's view, Mendelian randomization is useful for studying the causal effect of education or income on health. Professor Koellinger responded that one first has to make a plausible case for the mechanism; that is, for how a gene can influence an outcome. So, in case of a single gene that influences smoking behaviour, the answer would be yes. For a gene for educational success, the answer may be no.

In the **moderated discussion** after the presentations Johan Mackenbach presented the following statements, to see what participants thought.

- *Genetic factors are likely to seriously confound the relationship between education/income and health.*

Professor Koellinger: the genetic correlations do not necessarily imply confounding.

A participant: it is too early to tell.

19 After the meeting, George Davey Smith provided references to two papers on the use of Mendelian randomization to study the effect of education on health:
Munafò M, et al. Can genetics reveal the causes and consequences of educational attainment. *Journal of the Royal Statistical Society* 2020; 183: 681–688.
Sanderson E, et al. Mendelian randomisation analysis of the effect of educational attainment and cognitive ability on smoking behaviour. *Nature Communications* 2019; 10: 2949.

Another participant: this kind of study can be technically sound, but they have not contributed to understanding socio-economic health inequalities or had any policy implications.

Professor Mackenbach: if genetic factors play a role they can help to develop policy.

Professor Davey Smith: to call genes confounders you would have to demonstrate both a causal effect on education and a causal effect on health which does not go through education, and that has not been done.

Professor Koellinger: agreed.

Professor Börsch-Supan: a correlation in itself can already lead to confounding, causality does not have to be demonstrated for that.

- *Policies to tackle health inequalities should include measures to compensate for genetic disadvantage.*

Professor Mackenbach: social scientists who study genetics sometimes motivate their research by pointing to the possibility of compensatory policies to reduce genetic disadvantage, for example by offering extra support to children with genetically determined cognitive disadvantage.

A participant: this is impractical, there are so many factors: so many genes and so many health outcomes.

Another participant: I am uncomfortable by many of these questions and methods with regard to personal rights.

Another participant: it is not necessary to look at genetic disadvantage, we can also just focus on the phenotype.

Professor O'Donnell: actually we do this now already: we help people with genetic diseases.

Another participant: no, we make policies for disadvantages in terms of actual problems, not genetics, for example children with reading problems whatever their causes.

Another participant: all the statements are too strong because we know there are so many uncertainties and a lack of systematic evidence for countries experiencing different levels of mortality and mortality inequality.

Another participant: for cystic fibrosis, we know for example that socio-economic status is the most important factor for health outcomes. Talking about genetic disadvantage is not helpful, and miles away from the practical problems we are dealing with in public health.

A3.8 SUMMARY AND CONCLUSIONS

In the summary and conclusions at the end of the workshop, **Axel Börsch-Supan** made the following observations.

Causality

1. We actually did not talk about this, but could you make policies without knowing that causation is present? No, it is always implied.
2. Is there a good alternative to this "artificial" counterfactual approach? Unfortunately most often not, but we have to keep in mind that there are many ways to create the counterfactual: what assumptions do you make and what can you achieve with these?
3. There is rarely a direct link between cause and effect. More often, there is a causal chain between a deep cause and a final effect and this chain will often develop during the life-course. So, one has to look at the deep factors that can have effects decades later.

Genetics

1. What do we consider to be a genetic disadvantage? This question distracts from the deeper question about what genetics can teach us about pathways of causality.
2. One can use genetics as an indicator of confounding factors. Then one needs to dig deeper to find out what they are.
3. Polygenic scores can be used as instrumental variables. However, while they are nicely exogenous, they tend to be weak instruments, since they typically have only very weak associations with the endogenous variable to be replaced.

ANNEX 4.

DISCUSSION PAPER. WHICH FACTORS MEDIATE OR MODERATE THE EFFECT OF SOCIO-ECONOMIC POSITION ON HEALTH?

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A4.1 Introduction

A4.1.1 Why is this an important question?

Understanding how health inequalities arise is important from both a scientific and a policy perspective. A scientific approach to the explanation of health inequalities cannot stop at the demonstration of an effect of socio-economic position on health (see Annex 2): it 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 socio-economic position has an effect on health (1).

Understanding the causal pathways is also important from a policy perspective. Broadly speaking, one can distinguish two strategies for reducing health inequalities (2). The first and most radical option is equalizing the distribution of socio-economic factors, for example by reducing inequalities in educational attainment or income. To the extent that there is a causal effect of socio-economic factors on health, this can be expected also to 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 questionable

whether variations in levels of education or occupational class can ever be completely eliminated, given the fact that people will always differ in their cognitive abilities and other talents, and that modern economies require a certain division of labour.

It is important, therefore, also to consider a second, more pragmatic strategy for reducing health inequalities, which is to reduce the exposure to specific health determinants among lower socio-economic groups (3). For example, to the extent that socio-economic inequalities in mortality are determined by differences in specific working conditions, smoking behaviour 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 socio-economic groups can be expected also to reduce health inequalities.

This implies that identification of the factors involved in generating the effect of socio-economic 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 socio-economic groups are *caused by* people's socio-economic 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 socio-economic groups are coincidental, reducing them will help to reduce health inequalities (4). For example, as long as we know for sure that smoking causes lung cancer, we can reasonably assume that reducing smoking among those with lower levels of education 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 less educated are actually caused by their lower level of education, it may be more difficult to lower their rates of smoking than if this were not the case, and this should then be taken into account in developing an effective intervention programme. Also, whether or not there is a causal relationship between socio-economic 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 socio-economic groups are caused by their lower socio-economic position, the resulting health inequalities are more likely to be considered unfair, because they clearly are not freely chosen (5).

A4.1.2 Mediation and mediators

The causal pathways leading to health inequalities can be studied in various ways, using both qualitative and quantitative approaches. For example, anthropological studies can generate insights into these causal pathways by documenting individual biographies and the social and psychological mechanisms producing advantage and disadvantage over people's lifetimes. While such studies may lead to in-depth knowledge, they will not tell us what the relative importance at the population level is of all the factors contributing to health inequalities.

For this we need quantitative studies, and the most commonly used analytical technique for studying the relative importance of various factors in generating health inequalities is "mediation analysis". This technique allows us to quantify the contribution of one or more so-called "mediators" to the effect of socio-economic position on a health outcome. It is a very useful technique, but it rests on a some important assumptions which become clear when we look at the formal definition of a "mediator".

"Mediators" are defined as third factors that represent an intermediate step in the causal pathway between two variables, in this case socio-economic position and health (6). Other terms used to denote "mediators" are "intermediate variables", "mediating variables" and "intervening variables" (7). As in the case of confounders, mediators are involved in the relationship between socio-economic position and health; however, in contrast to confounders which *may not* lie on the causal pathway between socio-economic position and health, mediators *must* lie on this causal pathway (8)(p. 186).

This means that, strictly speaking, a third variable can be considered a mediator of the effect of socio-economic position on health if, and only if, (1) a person's socio-economic position causally influences his or her exposure to the third variable, and (2) exposure to the third variable causally influences his or her health outcome. In other words, assessment of mediation requires evaluation of two causal relationships (9).

For example, we may want to know to what extent socio-economic 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 socio-economic 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.

It is important to note that the analytical technique of mediation analysis does not test for causality, but simply assumes that the factors whose quantitative contribution is

assessed are involved in such a cascade of causal effects from socio-economic position to mediators to health outcome. So, whether a factor studied in a mediation analysis indeed qualifies as a "mediator" *sensu stricto* always requires careful evaluation, taking into account the possibility of reverse causation, uncontrolled confounding, etc.

As 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 socio-economic 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 socio-demographic characteristics or personal attributes such as cognitive ability – it would still be policy-relevant to know that these differences explain some of the higher mortality rates of lower socio-economic groups. However, in such a situation it would be better to avoid using the stricter term "mediator", and use a more neutral term such as "contributory factor" instead.

A4.1.3 Moderation and 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 socio-economic groups. This is the type of explanation of health inequalities we know most about.

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 socio-economic position and health, and socio-economic 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 (6, 9). In theory, the same factor may be both a mediator and a moderator, but it is also possible for a factor to be only a mediator, or only a moderator, of the relationship between socio-economic position and health.

For example, suppose that people with low levels of education are more sensitive to the negative health effects of smoking than people with high levels of education, for example because they consume fewer fruits and vegetables which increases the risk of lung cancer from inhaling tobacco smoke, or because they consult a doctor at 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 those with low levels of education than among those with high levels, which would indicate that socio-economic status is a "moderator" of the

effect of smoking on lung cancer[20]. So, in this example smoking would contribute to the explanation of health inequalities, *even if* the prevalence of smoking is the same among those with low and high levels of education.

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" or "effect modification". In quantitative analyses, "moderation" shows up as "statistical interaction".

A4.2 Mediation

A4.2.1 Methodological requirements

As mentioned above, determining mediation requires an assessment of two causal relationships: one between socio-economic position and the mediator, and one between the mediator and the health outcome. As in the case of assessing a causal relationship between socio-economic position and health (see Annex 2), this implies we need to consider the possibility of reverse causation and confounding.

Reverse causation would bias the results of mediation analysis if there were a "reverse" effect of the mediator on socio-economic position, and/or if there were 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 (10). Reverse causation would then be a serious possibility, both in the relationship between low income and obesity (obesity may lead to low income, for example 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, for example 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 socio-economic 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 those with low levels of education. 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 those with low levels of education and that predispose to obesity (11), or that there may be

20 It would also lead to a larger difference in mortality between those with low and high levels of education among smokers than among non-smokers, indicating that smoking is a "moderator" of the effect of socio-economic position on lung cancer mortality. These are two sides of the same coin.

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 section A4.1.1, 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 socio-economic 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.

In principle, because of the necessity to establish causal relationships, one would prefer to investigate mediation using an experimental approach, for example 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.

The simplest approach to quantifying the contribution of mediating factors to socio-economic inequalities in health is to take one or more health determinants whose effects on health we know, calculate differences in exposure to these health determinants between socio-economic groups, and then to estimate the contribution of these inequalities in exposure to inequalities in health between socio-economic groups.

For example, if we know that smoking doubles the risk of mortality, and if we see that smoking is twice as prevalent among those with low levels of education than those with high levels, we can estimate the contribution of smoking to inequalities in mortality using the method of population-attributable fractions (12). 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. 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 (13–16).

However, this method has serious shortcomings, because it relies on estimates of the health effects of determinants taken from the literature which may not apply to the population at hand, and because it does not adequately take into account the multivariate nature of the explanation of health inequalities, in which many factors are involved at the same time. For example, in addition to smoking, other factors such as obesity and stressful working conditions may also play a role, and their contribution to inequalities in mortality may overlap with that of smoking (12).

A more accurate assessment of the contribution of each factor requires a multivariate analysis in which any overlap with other 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 socio-economic 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. For example, when designing a strategy to reduce health inequalities it may 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).

A4.2.2 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 and Kenny approach which was developed in the 1980s (6, 17). In this approach, one studies whether the relationship between socio-economic 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 socio-economic 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" (6, 17).

In other words, mediation analysis then decomposes the "total effect" of socio-economic 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 (6, 17).

For example, suppose the mortality rate among people with low levels of education is 20 per 1000, and that the mortality rate among people with high levels of 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 those with low levels of education, 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 those with low and high levels of education, 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 × (10 – 7)/10 =) 30% of the effect of low education on mortality. Equivalently, if the rate ratio of mortality comparing those with low and high levels of education, 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 × (2.0 – 1.7)/(2.0 – 1.0) =) 30% of the effect of low education on mortality[21].

This approach can be extended into a multivariate analysis, in which the contribution of more than one "mediator" to socio-economic inequalities in health is assessed simultaneously, and in which the contribution of all mediators together is decomposed into separate parts for each of them (18, 19). In health economics, a different but conceptually similar approach to mediation analysis is sometimes used. This approach is based on the so-called Blinder- Oaxaca decomposition method which was originally developed in labour economics in the 1970s (20, 21)[22].

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 (22–24).

21 The same analysis can also be performed without the explicit aim of assessing mediation *sensu stricto*. When we relax the assumption of a causal effect of socio-economic position on smoking, but maintain the assumption of a causal effect of smoking on mortality, we need only to 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 those with low levels of education.

22 A modification of this method, proposed by Wagstaff et al.(62), 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.

Recently, however, the "difference method" has been criticized for several methodological shortcomings (9, 17, 25). (Because the Oaxaca–Blinder decomposition method and structural equation modelling are based on the same assumptions as the regression-based difference method, the same limitations apply to these techniques (9).[23]) Some of these criticisms overlap with the points mentioned above: for example, the "difference method" assumes that there is no uncontrolled confounding in the relationships between socio-economic position, mediator and health outcome.

Although problems of confounding could, in principle, be handled by better control for confounding variables in the analysis, this does not apply to some other problems in the conventional approach which have come to light, particularly the risk of bias due to interaction between socio-economic position and the mediator (9, 17, 25). For example, when one is interested in the contribution of smoking to inequalities in mortality, the "difference method" of mediation analysis will only give correct estimates if the effect of smoking on mortality does not differ between socio-economic groups. As we will see below, such "moderation" or "effect modification" is a real possibility (and should not be seen as a statistical–technical problem only, but as a phenomenon with explanatory potential and substantive relevance).

Now that these problems have come to be understood, new methods of mediation analysis have been designed that no longer assume "homogeneity" of the effect of the mediator across socio-economic strata. These methods (like the new methods for assessing causality discussed in Annex 2) apply a "counterfactual" approach, and are therefore not only more flexible in allowing interaction between socio-economic position and mediator but also have a more straightforward connection to policy because they directly estimate the effect on health inequalities of "counterfactually" removing a mediator (9, 17).

Health inequalities researchers are increasingly aware of the problems with the older techniques, and have started to apply the new techniques to their research questions (26–28). Applications to real-life data aiming to explain socio-economic inequalities in health are still rare, partly because of the necessity to adapt these new techniques to situations with typical health outcomes and more than one mediator (29, 30). However, these challenges are gradually being overcome, and the number of applications to studies of health inequalities is now growing steadily (see, for example, (31–33)).

Because of the small number of applications, it is not yet clear to what extent the new methods lead to different results. Some head-to-head comparisons of the "conventional" and the "counterfactual" approaches have found substantially different results (28), but others have not (31). Referring back to the main problems of the "conventional" approach highlighted above, it is probably safe to conclude that, *if applied correctly*,

23 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.

its results are likely to be no less valid than those of the "counterfactual" approach. Correct application here implies adequate control for confounding and (having checked for) the absence of interaction between socio-economic position and the mediator(s).

Systematic reviews of the available evidence as gathered with the "conventional" approach should check whether the "difference method" has been applied correctly, and new evidence should be collected with the "counterfactual" approach wherever possible, if only because it asks researchers to check more explicitly the assumptions underlying their estimates.

A4.2.3 Notes on the evidence

The methodological issues mentioned above imply that the available evidence on what mediates the relation between socio-economic position and health needs to be taken with a grain of salt. Most studies done so far take the observed association between socio-economic position and the health outcome as if this represents a causal effect of socio-economic position on health, and apply conventional analysis methods (i.e. the "difference method") ignoring the potential sources of bias mentioned above. Nevertheless, a few preliminary conclusions do emerge, particularly if we refrain from claiming mediation *sensu stricto* and from giving precise quantitative estimates.

The available evidence – almost all of it gathered with the "conventional" approach – suggests that five groups of specific health determinants play a role in explaining 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 probably differs between countries, and has probably also changed over time, and that general statements about their relative contribution cannot therefore be made. Note that early childhood environment can, strictly speaking, not be considered a "mediator" between adult socio-economic position and health.

A4.2.3.1 Early childhood environment

Systematic reviews show that growing up in disadvantaged socio-economic circumstances is associated with many negative effects on children's health and development, including their general health and illness, developmental outcomes, asthma, dental caries and mental health problems (34). This is commonly thought to reflect a causal effect of growing up in socio-economic 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 (35), although it is also possible that there are common underlying factors in the association between parents' socio-economic disadvantage and children's health and development, such as genetic factors shared by parents and their children (36).

Such health inequalities initiated in childhood also partly explain the social gradient in health observed throughout the remaining life-course (34). Adults with lower education, occupational class and income have often grown up in less advantaged socio-economic circumstances whose health effects may carry through into adulthood (37, 38). Systematic reviews indeed show that growing up in less advantaged socio-economic circumstances has many long-term negative health effects, independent of the influence of adult socio-economic 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 (39, 40).

A4.2.3.2 Material living conditions

Material living conditions probably play an important role in generating health inequalities. As discussed in Annex 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 lifetime income, particularly at the lower ends of the income distribution.

Studies show that poverty is associated with a range of adverse health outcomes (41, 42), and a few mediation analyses that link indicators of socio-economic position to health outcomes through indicators of poverty suggest that poverty does indeed contribute to the explanation of health inequalities (19, 43, 44). Although most 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 may also reduce 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)(45–47).

A second group of material living conditions that probably 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) (48). It is unclear, however, to what 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 (49).

A4.2.3.3 Social and psychological factors

Psychosocial factors beyond the workplace may also be important contributing factors (50, 51). People with a low socio-economic position on average are exposed to more psychosocial stressors, in the form of negative life events (e.g. loss of loved 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 (52). 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 (53), as well as less effective coping styles (e.g. a more external "locus of control") (54).

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 (55–58). 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, for example, 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 susceptibility to a range of diseases (59–61).

To the extent that there is an independent health effect of psychosocial factors, the combination of a higher exposure to psychosocial stressors and less capacity to remove or buffer these exposures in lower socio-economic groups may explain part of socio-economic 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 socio-economic inequalities in cardiovascular health, including in mediation analyses (48). 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 (19, 63).

A4.2.3.4 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 socio-economic groups in many high-income countries (64–68). This is also the group of factors for which most formal mediation analyses have been done, 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. Systematic reviews and other overviews have shown the prevalence of smoking to differ strongly between socio-economic groups in many high-income countries (64, 69), particularly among men, and several mediation analyses have found that smoking alone accounts for a substantial part of socio-economic inequalities in mortality (18, 70). 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 (14, 71).

Excessive alcohol consumption is bad for health too, and harmful drinking (including "binge drinking") is probably more common in lower socio-economic groups but difficult to capture in survey data (65, 72). 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 (73, 74). Mediation analyses confirm that excessive alcohol consumption does contribute to the explanation of health inequalities in some countries but less so in others (18, 70, 75).

Overview studies show that spending little leisure time on physical activity tends to be more common in the lower socio-economic groups (76, 77). The same is true for overweight and obesity, but the magnitude (and sometimes even the direction) of these inequalities differs strongly between countries (68, 78). As a result, the contribution of inequalities in obesity to inequalities in health is also likely to differ strongly between countries (15). Mediation analyses confirm that inequalities in physical activity and obesity do play a role in generating health inequalities in some countries (18, 70, 75, 79).

A4.2.3.5 Health care

A final group of factors that could explain health inequalities is health care: if people with a lower socio-economic position receive less, or lower quality, health care than people with a higher socio-economic position, this could exacerbate the inequalities in health generated by all the other factors mentioned above. 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 socio-economic groups, as shown by many comparative studies (80-84, 86).

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. That this is indeed the case is suggested by studies showing that interventions for which inequalities have been found include interventions of proven effectiveness, for example in the field of cardiology (87–90), and that for diseases such as cancer 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 (91–96).

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 (97). It is interesting to note that, in contrast to the four groups of factors mentioned above, the role of health care does not easily lend itself to formal mediation analyses, perhaps because it is very difficult to accurately measure the effect of health care in observational studies (in which it is exceedingly difficult to control for the fact that people using health care by definition are in worse health ("confounding by indication")).

A4.3 Moderation

A4.3.1 Methodological requirements

Assessing "moderation" is at least as challenging as assessing "mediation". A convincing demonstration that a lower socio-economic position strengthens (or weakens) the health effects of a particular factor needs to overcome several methodological hurdles. As in the case of mediation, one will first need to seek reassurance that two causal relationships are involved. In this case the requirements are that there is a causal relationship between this factor and health, and that there is a causal relationship between socio-economic position and the effect of this factor on health[24]. As in the case of mediation, reverse causality and confounding must be excluded as alternative explanations.

24 Note that in this section we have conceptualized "moderation" as differences between socio-economic groups in the effect of a particular factor on health. As explained previously, "moderation" can equivalently be conceptualized as differences between those exposed and those not exposed to a particular factor in the effect of socio-economic position on health. In this alternative conceptualization, the requirements are that there is a causal effect of socio-economic position on health, and that there is a causal relationship between the putative moderator and the effect of socio-economic position on health. Because it is usually easier to think of specific factors having different effects in lower than in higher socio-economic groups, we have not chosen this factor alternative conceptualization for our exposé.

This is far from easy in observational studies, which are the usual source of information on both mediation and moderation. For example, to show that the effect of smoking on health differs between socio-economic groups, one will first need to ensure that one is measuring a pure causal effect of smoking on health (without reverse causality of health problems on smoking behaviour, and net of confounding by other determinants of health which are more frequent among smokers than non-smokers). In addition, one will also need to ensure that a stronger effect of smoking on health in lower socio-economic groups is due to these people's lower socio-economic position (and not to a reverse effect of smoking-related health problems on their socio-economic position, or to confounding by other factors associated with smoking, such as dietary behaviours or psychosocial stress).

While fulfilling these basic requirements may already be difficult, there are additional challenges that further complicate the assessment of moderation. The first is that one will need to ensure that apparent differences between socio-economic groups in the effect of a particular factor on health are not due to differences in measurement or to measurement error. For example, smoking, measured as being a regular cigarette smoker at a particular point in time, may seem to have a stronger effect on health in subsequent years in lower socio-economic groups, simply because people in lower socio-economic groups started smoking at a younger age, and have therefore accumulated more "pack-years" when their smoking behaviour was assessed, and not because inhaling cigarette smoke has an inherently stronger effect on health among people in lower socio-economic groups.

A second challenge is that assessment of moderation requires large study samples. To reliably measure differences between socio-economic groups in the effect of a particular factor on health, one needs substantially larger numbers of study participants than one would need for the measurement of the "main effects" of that factor (or of socio-economic position). Even large epidemiological cohorts of several thousand participants will often be "underpowered" to assess moderation as a mechanism underlying socio-economic inequalities in health. The solution may be to use registries covering complete national or regional populations, but these usually have more limited data per participant.

Finally, to assess moderation, one needs an *a priori* decision for relative or absolute effect measures (98). The main effect of any factor on health can be expressed in either relative terms (e.g. as a Rate Ratio, in which the morbidity or mortality rate among the exposed is divided by the morbidity or mortality rate among the non-exposed) or in absolute terms (e.g. as a Rate Difference, in which the morbidity or mortality rate among the non-exposed is subtracted from the morbidity or mortality rate among the exposed). The same applies to moderated effects, which can also be expressed in

relative terms (e.g. by variations between subgroups in the Rate Ratio) or in absolute terms (e.g. by variations between subgroups in the Rate Difference)[25].

While both can go together, this is not a necessity, and absence of moderation on a relative scale can go together with presence of moderation on an absolute scale, and vice versa (99). For example, even if the relative effect of smoking on mortality is the same in lower and in higher socio-economic groups, the absolute effect will be larger in lower than in higher socio-economic groups, because, owing to other factors, the mortality rate among non-smokers is greater in lower socio-economic groups than in higher ones.

It can be argued that, for public health purposes (e.g. for the development of policies to reduce health inequalities), equalizing absolute effect sizes between socio-economic groups is more important than equalizing relative effect sizes, and that finding presence or absence of moderation on an absolute scale is more relevant than finding moderation on a relative scale (100). However, and as the example of smoking illustrates, differences in absolute effect sizes can have a trivial explanation, and it can therefore also be argued that for scientific explanation (e.g. for the discovery of biological mechanisms underlying health inequalities) finding differences in relative effect sizes is more informative.

A.4.3.2 Moderation analysis

The conventional approach to moderation analysis is an extension of the conventional approach to mediation analysis. As explained above, conventional mediation analysis decomposes the "total effect" of socio-economic position on a 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)). This is usually done by fitting a multivariate regression model in which the health outcome is modelled as a function of both socio-economic position and one or more variables representing the putative mediators.

This approach can be extended to encompass the possibility of moderation (or effect modification) by incorporating one or more interaction terms between socio-economic position and the variable(s) representing the mediator(s). The value and statistical significance of these interaction terms will then indicate whether the effect of the mediators differs between socio-economic groups (or, equivalently, whether the effect of socio-economic position on health differs between those who are and those who are not exposed to the mediator).

However, although the explicit consideration of interaction between socio-economic

25 In more technical terms, variations between subgroups in relative effect sizes are often called "deviations from multiplicativity", whereas variations between subgroups in absolute effect sizes are often called "deviations from additivity".

position and mediator(s) removes some of the problems inherent to conventional mediation analysis (see section A4.2.2), several other problems remain. Fortunately, recent advances in mediation analysis have also led to new, and potentially better, methods for analysing moderation (9, 101).

This new approach, which is based on similar "counterfactual" estimation methods as briefly explained above, allows a decomposition of the total effect of (in this case) socio-economic position on health in four components. Each of these mutually exclusive components represents a different pathway: (1) socio-economic position has a direct effect on health even among those who are not exposed to the mediator; (2) the effect of socio-economic position on health is dependent on exposure to the mediator (and vice versa), but socio-economic position does not influence exposure to the mediator; (3) the effect of socio-economic position on health is dependent on exposure to the mediator (and vice versa), and in addition socio-economic position has an influence on exposure to the mediator; (4) the effect of socio-economic position on health is due to differences between socio-economic groups in exposure to the mediator (100, 101)[26].

These four components correspond to the portion of the effect that is due, respectively, to (1) neither mediation nor moderation, (2) moderation but not mediation, (3) both mediation and moderation, and (4) mediation but not moderation. In the example of socio-economic position, smoking and health, these components would correspond to (1) the direct effect of socio-economic position on health, not via smoking; (2) the effect of socio-economic position on health due to just the differences in effect of smoking between socio-economic groups; (3) the effect of socio-economic position on health due to the combination of differences in effect of smoking ánd differences in smoking behaviour between socio-economic groups; (4) the effect of socio-economic position on health due to just the differences in smoking behaviour between socio-economic groups.

A4.3.3 A note on the evidence

In the health inequalities literature, there is a long tradition of theorizing about "moderation" under somewhat different labels, i.e. "differential susceptibility" or "differential vulnerability". These terms translate the widespread intuition that health inequalities may be partly explained by the fact that people in lower socio-economic groups are more "susceptible" (in a biological sense) or "vulnerable" (in a psychological or social sense) to the negative health effects of various determinants[27] (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).

26 These effects have been called, respectively, the "controlled direct effect", "reference interaction", "mediated interaction" and "pure indirect effect" (101).

27 Recently, Diderichsen et al. (100) have proposed a somewhat different distinction between "differential susceptibility" and "differential vulnerability". We will refrain from expanding on these semantic distinctions.

However, although the existence of "differential susceptibility" is plausible, empirical evidence has remained scarce. One of the main reasons why empirical evidence on this phenomenon is limited – already alluded to above – is that establishing moderation, for example by performing interaction analyses, requires large sample sizes to generate sufficient statistical power to reliably estimate not only the main effects of socio-economic position and health determinants but also their interaction effects[28]. Furthermore, practically all the available evidence has been generated with "conventional" methods for moderation analysis, which are unable to clearly separate the contributions of mediation and moderation (for which, as mentioned above, a four-way, not a three-way, decomposition is required).

Nevertheless, the available evidence suggests that some of the health-related behaviours that act as mediators in the relationship between socio-economic position and health do indeed have stronger effects in lower than in higher socio-economic groups. For example, applying some of the new "counterfactual" methods, Danish studies have found a stronger effect among those with low levels of education than high levels (as measured on an absolute scale) of smoking on mortality (104), of smoking on lung cancer (105), and of obesity on mortality (104) and diabetes (Mathiesen). Using conventional methods, a Scottish study has found a stronger effect among lower than higher socio-economic groups (as measured on a relative scale) of excessive alcohol consumption on mortality (106). There is also some evidence that psychosocial stressors, particularly in the work environment, have stronger health effects (as measured on a relative scale) in lower socio-economic groups (48, 107–110).

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 A4.1)(111–113). However, here again the evidence is still very limited.

28 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.

Box A4.1 Genetic factors as possible "moderators"

People in lower socio-economic 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 socio-economic disadvantage (or to the positive health effects of socio-economic advantage).

This awareness has been raised by the results of behavioural genetics studies of "gene–environment interaction", with socio-economic position acting as an "environmental" factor (114). The general idea is that, even if genetic risk factors are equally distributed across socio-economic groups, differences in susceptibility to these genetic risks as a result of groups' different environments could lead to health 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 socio-economic 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) (115).

Similar interactions between socio-economically defined environments and genetic risk factors can be imagined, with some genotypes increasing or decreasing the susceptibility to a disadvantaged environment (116). A possible example is that in studies of twins the heritability of mental ability has been found to be larger in higher than in lower socio-economic groups, probably because the effect of the environment overwhelms the effect of genetic determinants in lower socio-economic groups (117).

Although the evidence base is still very thin, differential susceptibility/vulnerability is a potentially important mechanism for explaining health inequalities and therefore 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. Also, substantial moderation effects (in the sense that certain determinants of ill-health have stronger health effects in lower socio-economic groups) suggest that universal measures may have larger effects in lower socio-economic groups. Findings on mediation and moderation complement each other, thus extending the possibilities for health inequality interventions.

A4.4 References

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ANNEX 5.

WORKSHOP REPORT. MEDIATION AND MODERATION IN HEALTH INEQUALITIES RESEARCH

This workshop was held on 23 January 2020. It was supported by the Académie Nationale de Médecine (France), ALLEA and FEAM. Paris. Report by Johan Mackenbach.

A5.1 ATTENDANTS

Hans Bosma, Graham Caie (speaker), Rosa Castro (FEAM observer), Giuseppe Costa, Cyrille Delpierre, Siegfried Geyer, Peter Goldblatt, George Griffin (speaker), Naja Hulvej Rod (speaker), Domantas Jasilionis, Jay Kaufman (speaker), Anton Lager, Frank van Lenthe, Alastair Leyland (speaker), Guillem Lopez Casasnovas, John Lynch, Johan Mackenbach (co-chair and writer of report), Umida Masharipova (ALLEA observer), Maria Melchior (speaker), Anne-Marie Nybo Andersen, Anna Pearce, Mikael Rostila (speaker), Johannes Siegrist (speaker), Vera Skalicka, Alfred Spira (chair), Marc Suhrcke, David Taylor-Robinson, Margaret Whitehead

A5.2 PROGRAMME (CET)

Chair: Professor Alfred Spira, Académie Nationale de Médecine

09.00–09.10	Introduction to the ALLEA/FEAM Health Inequalities project Professor Graham Caie (ALLEA) and Professor George Griffin (FEAM)
09:10–09:30	Mediation, moderation and health inequalities: what are the issues? Professor Johan Mackenbach (Erasmus MC, Rotterdam, The Netherlands)
09:40–10:25	Balancing the promises and limitations of mediation analysis in health inequalities research

	Professor Jay Kaufman (McGill University, Montreal, Canada)
10:25–10:40	Mediation analysis in health inequalities research: reflections Dr Maria Melchior (Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France)
10:40–11:10	General discussion (mediation)
11.10– 11.25	Coffee break
11:25–12:10	Challenges and opportunities of moderation analysis in health inequalities research Professor Naja Hulvej Rod (University of Copenhagen, Denmark)
12:10–12:25	Moderation analysis in health inequalities research: reflections Professor Alastair Leyland (University of Glasgow, UK)
12:25–12:45	General discussion (moderation)
12:45–13:45	Lunch break
13:45–14:05	Mediation: what do we know and what do we not know? Professor Mikael Rostila (Stockholm University, Sweden)
14:05–14:25	Moderation: what do we know and what do we not know? Professor Johannes Siegrist (University of Düsseldorf, Germany)
15:25–15:40	Tea break
15:40–15:45	General discussion
15:45–16:00	Summary and conclusions (Professor Johan Mackenbach, Erasmus MC, Rotterdam, The Netherlands)

A5.3 AIM

- Evaluate existing evidence on the role of mediators and moderators in explaining socio-economic inequalities in health, focusing on methodological issues.
- Identify areas of agreement and disagreement between scientific experts, and agree on priorities for further substantive and methodological research.
- Clarify to what extent the available evidence permits reliable recommendations for policy-makers on how to reduce health inequalities.

A5.4 WAY-OF-WORKING

- The ALLEA and FEAM Committee on Health Inequalities prepared a short document with several questions for discussion, referring to the longer document "*Health inequalities: an interdisciplinary exploration of socioeconomic position, health and causality*" that the Committee had produced in the first phase of this project. Both documents were circulated among speakers and participants in advance of the workshop.

- This draft report has been circulated among the attendants of the workshop, asking for feedback and additional inputs.

A5.5 MEDIATION

The workshop started with a presentation by **Jay Kaufman** of methodological issues in the assessment of mediation (and moderation) in health inequalities research. Jay summarized the main problems with the conventional approach ("Baron and Kenny"), which assumes homogeneity of the effect of the exposure across levels of the mediator. He then described the emergence and development of the new "counterfactual" approach (by, among others, Pearl, Robins, VanderWeele, and Tchetgen Tchetgen), which relaxes this assumption. Although there is still some discussion about the appropriateness of these new methods, there is now a reasonable degree of consensus that this new approach is better suited than the conventional approach to answer substantive questions about the role of mediators (and moderators) in explaining health inequalities. It is more flexible in allowing interaction between exposure and mediator, and has a more direct connection to policy interventions. However, many caveats still apply regardless of the method chosen, related to the possible role of measurement error, confounding, statistical power, generalizability, etc. Jay expressed confidence that, as long as the Baron and Kenny approach has been applied carefully (e.g. after checking for the homogeneity assumption), one should not expect too many discrepancies with the results of the newer approaches.

Maria Melchior then commented on Jay Kaufman's presentation by giving a few examples of mediation analyses from her own work, using both the conventional approach and the newer counterfactual approaches. Among other things she highlighted the availability of statistical programs (e.g. as developed by Theis Lange) which now allow the application of the counterfactual approach to multiple mediators and survival as an outcome (instead of binary outcomes). However, some difficulties remain: for example, these programs cannot routinely handle imputed data.

Later in the day, **Mikael Rostila** gave his views about gaps in the knowledge base on mediation, and about priorities for further research. He emphasized the necessity of looking beyond the methodological concerns highlighted by other speakers, and to

address the need for a good theoretical understanding, for valid and accurate data, and for limiting non-response and attrition. However, he was in agreement with other speakers about the need for upscaling efforts on mediation, which would then also provide more opportunities for comparative work, for example between historical periods and national contexts.

The general discussion highlighted several important points, as follows.

(1) There was a commonly shared impression that results from the conventional approach and the counterfactual approach are unlikely to differ much. This feeling was partly based on comparisons that several participants had made between the two approaches. Perhaps a more important difference is that the new approach asks researchers to more explicitly check the assumptions. In an analogy used by Jay Kaufman, one can think of the conventional approach as a Peugeot, and of the counterfactual approach as a Ferrari: although a Ferrari might be considered a better car, the quality of the driver is even more important. Under most driving conditions and with a capable driver, having the "better" car offers no distinct advantage.

(2) Another important side-effect of the emergence of the counterfactual approach is that the focus of mediation analysis should not primarily or exclusively be to "explain away" health inequalities, but to focus on finding actionable entry-points, in order to assist the development of effective policies to reduce health inequalities. This new approach requires researchers to adopt an "interventionist" perspective, which is often very useful.

(3) Several participants emphasized the need for good-quality data. Measurement error can easily lead to biased results, for example when a mediator is measured with low precision the "controlled indirect effect" will be underestimated, and the "direct effect" (of socio-economic position on health) will be overestimated. It is therefore important that recommendations for more mediation analyses are accompanied by recommendations for increased investments in good-quality data collections, for example cohort studies with validated, longitudinal measures of socio-economic position, potential mediators and health outcomes.

A5.6 MODERATION

Naja Hulvej Rod presented her views about the unreliability of the conventional approach to moderation analysis, which is to look for statistically significant deviations from multiplicativity of effects by adding an interaction term of socio-economic position and a specific determinant. She argued that, for public health purposes, deviation from additivity is more important, and that assessment of such deviation requires substantially larger study samples than those needed to assess a main effect. In countries such as Denmark, larger study-populations can be found by using linked

register data. She then gave a few examples of moderation analyses with linked register data, in which she and her co-workers applied the counterfactual approach as explained by Jay Kaufman (using VanderWeele's three-way decomposition as implemented in a statistical program developed by Theis Lange). In these examples (on education, smoking and lung cancer; and on education, obesity and diabetes) there was clear evidence for moderation, in the sense that the effect of smoking and obesity was found to be stronger in people with less education. She pointed out an important limitation of these studies, which is that they used single measurements of socio-economic position and the mediators at a random point in people's lives, and then presented the results of an analysis of the cumulative effects of various forms of childhood adversity on premature mortality.

In his commentary, **Alastair Leyland** agreed that moderation by socio-economic position of the effect of specific determinants of health is likely to be an important mechanism in the explanation of health inequalities, and that register data will often be needed to get sufficient statistical power. He illustrated this with an empirical example of the larger effect of excessive alcohol consumption on alcohol harms (hospital admission or death attributable to alcohol) in lower socio-economic groups.

Later in the day, **Johannes Siegrist** gave a series of other empirical examples of moderation, found with conventional approaches, for example larger effects of work-stress on health in lower socio-economic groups, and larger effects of "mastery" on depression in lower socio-economic groups. He argued that we need far more moderation analyses to provide input into policy, for example for targeting vulnerable groups in a strategy of proportionate universalism. He also listed several priorities for further research, including large-scale application of the new methods in existing datasets.

In the general discussion, the following points came up.

(1) The evidence base on moderation is growing slowly, and there are good reasons to expect moderation to be present everywhere: through a range of possible mechanisms, socio-economic position is likely to enhance the health effects of many specific health determinants. This creates a huge task for further research. To guide our search for the role of moderation in explaining health inequalities, it would help to have a better theoretical underpinning of where to expect such effects.

(2) It is difficult to judge whether moderation effects are large enough to matter for policy-making. Some of the examples seen during the workshop suggest that they are, but we need more evidence to draw definitive conclusions. It is also not always certain that the interaction effects found are really moderation effects: larger effects in lower socio-economic groups may also be due to subtle differences in exposure to the determinant not captured by its measurement, or to confounding by other factors not taken into account in the analysis.

(3) Another unresolved issue relates to the choice between additive and multiplicative effects. Participants agreed that deviations from additivity are the most important for policy-making, because these more directly point to where most cases of disease can be prevented. However, it was argued that deviations from multiplicativity remain important as well, particularly for mechanistic studies of biological and other mechanisms. A deviation from additivity does not necessarily point to a stronger acting mechanism of the determinant in lower socio-economic groups, but may simply be because baseline risks are higher in lower socio-economic groups.

(4) Some doubts were expressed about the desirability of using the results of moderation analyses for targeting health and social policies. For example, a higher sensitivity of lower socio-economic groups to the effect of smoking should not detract from the necessity to take universal countermeasures (e.g. by limiting access to tobacco for everyone). Nevertheless, it is important to know that determinants have differential effects by socio-economic position, because this suggests that policies targeting these determinants will also have differential effects.

A5.7 CONCLUSIONS

In an interactive session at the end of the workshop, **Johan Mackenbach** made an attempt to answer the questions circulated before the workshop:

Mediation

1. To what extent is the existing knowledge base on the factors mediating the relationship between socio-economic position and health likely to be incorrect?

There is no need to over-emphasize the methodological criticisms of the conventional approach to assess mediation. The Baron and Kenny approach, if applied appropriately, is likely to have produced results that are reasonably robust. However, the existing evidence base needs to be checked for this "if", including an evaluation of whether homogeneity of the effect of the mediator across socio-economic groups has been checked in the analysis, and whether confounding has adequately been controlled.

2. Which of the recently proposed alternative methods of mediation analysis should be used? Are these methods ready for routine application?

The counterfactual approaches developed by VanderWeele and others are superior to the conventional method, and should be used to assess mediation in the study of health inequalities. Recent advances in creating statistical programs that implement these methods for a wider range of situations now allow large-scale application.

3. What recommendations for further research follow from questions 1 and 2? For example, should we recommend large-scale application of new methods in existing datasets?

We do recommend large-scale application of the new methods in existing datasets. We recommend that the European Commission supports dedicated efforts to rapidly expand the knowledge base on mediation by using existing cohort studies and other datasets containing the necessary information on socio-economic position, potential mediators and health outcomes. At the same time, we also urge the collection of better-quality data for use in future analyses.

4. What are the implications for policy advice? How likely is it that new methods of mediation analysis will lead to a change in priority setting for policies to reduce health inequalities?

The emergence of new methods for mediation analysis does not necessitate an overhaul of previous policy advice, which, although it was based on conventional methods, is still likely to be valid in general terms. Fortunately, policy-makers usually do not require very precise estimates of the role of specific mediators before contemplating action.

Moderation

1. How likely is it that moderation plays a major role in the explanation of health inequalities? Which moderation effects at the individual or group levels are likely to be important?

The available evidence clearly suggests the existence of major moderation effects, but how widely this applies across the board of all specific health determinants, and whether these are "true" moderation effects, can only be assessed after the evidence base has been expanded substantially. There is currently no clear theoretical guidance of where moderation effects are most likely.

2. What analytical methods should be used to study the role of moderation? Are these methods ready for routine application?

The counterfactual approaches developed by VanderWeele and others (particularly the four-way decomposition) are appropriate for studying moderation in the area of health inequalities, and they are ready for large-scale application.

3. What recommendations for further research follow from questions 1 and 2? For example, should we recommend large-scale application of moderation analysis in existing datasets?

We do recommend large-scale application of the new methods in existing datasets of sufficient size. We recommend that the European Commission supports dedicated efforts to rapidly expand the knowledge base on moderation by using existing datasets. At the same time, efforts at expanding the evidence base will benefit greatly from the development of a better theoretical understanding of what moderation effects to expect.

4. What are the implications for policy advice? For example, will moderation analyses lead to better targeting of interventions to reduce health inequalities?

In some cases, results of moderation analyses can be used for targeting of interventions to reduce health inequalities (in the form of "proportionate universalism"). One should be aware of the risk that targeting may introduce forms of discrimination that are not socially acceptable. In other cases, results of moderation analyses will help to underpin universal policies by showing that they are likely to have a stronger effect in lower socio-economic groups.

ANNEX 6.

DISCUSSION PAPER. POLICIES AND INTERVENTIONS TO REDUCE HEALTH INEQUALITIES: INSIGHTS FROM PRACTICE AND METHODOLOGICAL ISSUES

Clare Bambra [1] and Peter Craig [2]

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A6.1 Introduction

Reducing health inequalities is the "holy grail" of public health (1) However, our understanding of what works to reduce health inequalities is limited, the evidence base about effective policies and interventions is small, and there are methodological limitations. This discussion paper engages with this theoretical, empirical and methodological uncertainty to provide an overview of the state of the art in terms of how we can act to reduce health inequalities. In the first section (theory), it outlines theoretical insights from the policy and intervention literature to explore how health inequalities *could* be reduced. In the second section (practice), evidence from case studies of real-world evaluations of policies and interventions to reduce health inequalities are summarized, to ascertain which policies and interventions actually work in practice. We find a growing (albeit methodologically limited) evidence base and identify several interventions with *some* evidence of being effective in reducing health inequalities. The third section (methods) reflects on how we can improve our understanding of what works—both in *theory and practice*, through methodological development and the potential of quasi-experimental designs to advance the field. The discussion paper then draws the insights from theory, practice and methods together—reflecting on the implications for our understanding of the future action required to reduce health inequalities.

A6.2 Insights from Theory

There is a small policy literature outlining how health inequalities *could* be reduced from a theoretical perspective. It highlights the different *approaches* taken to conceptualizing how to reduce health inequalities and the different *levels* of action at which interventions could be implemented (2, 3). This section outlines these intervention *approaches* and *levels* of intervention delivery.

A6.2.1 Approaches to Reducing health inequalities

Approaches to intervening to reduce health inequalities fall into four broad but interlinked categories: (1) by focusing on improving the position of the most disadvantaged groups; (2) by reducing the gap between the best and worst off; (3) by reducing the entire social gradient in health (2); and (4) by providing universal interventions "*but with a scale and intensity that is proportionate to the level of disadvantage*" (4).

The "disadvantaged groups" approach focuses on improving the health of the most disadvantaged groups by concentrating on absolute levels of health by improving social conditions, reducing risk factors and increasing life opportunities (2). This approach has the advantage of directing attention to those of highest need but it also equates the language of inequality to the language of disadvantage, the consequence of which is a shift in the focus of health inequalities interventions from the whole population to a smaller proportion of people—potentially stigmatizing people in these groups or neighbourhoods (2).

The "reducing the gap" approach is driven by the realization that improvements in health have been paralleled by a widening of inequalities between the best off and worst off in the population. Interventions under this category therefore necessitate "raising the health of the poorest, fastest" (2)(p. 8). It thereby enables (scarce) resources to be targeted. However, as with the "disadvantaged groups" approach, this strategy also only targets a small section of the population and tends to engender a focus on lifestyle factors as the cause of inequalities - ignoring wider societal influences (2).

The "reducing the social gradient" approach aims to reduce the entire social gradient in health (2). As such, it "*locates the causes of health inequality, not in the disadvantaged circumstances and health-damaging behaviours of the poorest groups, but in the systematic differences in life chances, living standards and lifestyles associated with people's unequal position in the socio-economic hierarchy*" (2)(p. 10). The benefits of this type of approach are to refocus attention to the largest proportion of the population sitting between the two extremes of the hierarchy, thereby achieving maximum health gains for the majority.

The "proportionate universalism" approach combines aspects of the "disadvantaged groups", "gaps" and "gradient" approaches with the intention of improving the health

of all, but the health of the poorest most (4). It proposes the use of interventions which are universally targeted "*but with a scale and intensity that is proportionate to the level of disadvantage*" (4)(p. 15). This approach has the benefit of ensuring that those most in need gain additional support, while those occupying other parts of the social gradient also receive interventions.

A6.2.2 Levels of action to reduce health inequalities

There are four different *levels* of action at which interventions to reduce health inequalities could be implemented (3): (1) strengthening individuals (person-based strategies to improve the health of disadvantaged individuals); (2) strengthening communities (improving the health of disadvantaged communities and local areas by building social cohesion and mutual support); (3) improving living and working conditions (reducing exposure to health-damaging material and psychosocial environments across the whole population); (4) promoting healthy macro-policy (improving the macro-economic, cultural and environmental contexts that influence the standard of living achieved by the whole population).

A6.3 Evidence from Practice

A6.3.1 Evidence reviews of policies and interventions to reduce health inequalities

From the theoretical literature we get a sense of what could/should work to reduce health inequalities. This section presents evidence from real evaluations of policies and interventions to reduce inequalities to ascertain what works in practice—not just in theory. Because of time constraints, it draws exclusively on umbrella reviews: that is, overviews of systematic reviews which build on the strengths of individual reviews and add scale by integrating the findings of multiple reviews together (5). We identified 11 umbrella reviews of relevance to this discussion paper, all published within the past 12 years. In terms of the theoretical framework elaborated above, these umbrella reviews cover several types of policy approach, levels of intervention and draw on different theories of the causes of health inequalities. The umbrella reviews identify the effects on health inequalities of certain macro-economic policies (6), social protection policies (7), housing policies (8), changes to the work environment (9), transport policies (10), public health regulations (11), gambling (12), physical activity (13), health-care interventions (14) and changes to the organization and financing of the health-care system (15), and the social determinants of health (16).

All umbrella reviews included an assessment of the quality of the underlying systematic reviews, with more recent umbrella reviews applying the Assessment of Multiple Systematic Reviews (AMSTAR) approach. One of the criteria in this approach, and in its less formalized predecessors, is that the systematic reviews had assessed

the methodological quality of primary studies. Primary studies were predominantly observational (with few examples of quasi-experimental or experimental studies—a limitation explored further in section 6.4), and a common conclusion of the umbrella reviews is that both the primary studies and the systematic reviews were often of only moderate quality. Another common finding is the dominance of USA-based studies in the evidence base, which potentially limits the transferability of findings into European health and social welfare contexts.

A6.3.1.1 Macro-economic policies

In their umbrella review of macro-economic factors and health inequalities, Naik et al. (6) looked at a wide range of economic circumstances and policies, including market regulation; institutions; supply of money; finance and loans; the balance between the public, private and third sectors; labour; production and consumption; and approaches to the economy. The review found a large (n = 62) but low-quality systematic review-level evidence base. They found evidence for health inequalities reducing the effect of unemployment insurance generosity, raising tobacco taxes, regulating tobacco advertising, taxing unhealthy food and drink, and subsidizing healthy food. The evidence for some other policies was considered inconclusive (e.g. welfare interventions).

A6.3.1.2 Social protection

For their umbrella review of social protection policies, Hillier-Brown et al. (7) found six systematic reviews (reporting 50 unique primary studies) which looked at the health impacts of these policies. Some of these reviews examined income maintenance and poverty relief policies, finding some, low-quality, evidence that increased unemployment benefit generosity may improve mental health. Others looked at active labour-market policies (such as welfare-to-work programmes), finding some, low-quality, evidence that return to work initiatives may lead to short-term health improvements, but that, in the longer term, these can lead to declines in mental health. The more rigorously conducted reviews found no significant health effects of any of social protection policies under investigation.

A6.3.1.3 Housing

Gibson et al. (8) included five systematic reviews (reporting 130 primary studies) in their umbrella review of housing interventions. These looked at the effect of neighbourhood mobility programmes moving disadvantaged people from areas of high poverty to areas of low poverty (finding that this probably improves their health), urban regeneration programmes (finding both positive and negative effects on residents' health) and interventions aimed at internal housing conditions (finding compelling evidence that warmth and energy efficiency interventions have positive health effects among vulnerable individuals).

A6.3.1.4 Work

Bambra et al. (9) conducted an umbrella review of changes to the psychosocial work environment. They found five systematic reviews examining effects on health inequalities (reporting over 75 primary studies). These looked at the effect of increasing employee control (finding weak evidence that this may reduce inequalities in mental health between lower- and higher-grade employees) and at the effect of organizational changes such as alternative shift schedules (finding positive health effects but no evidence for differential effects by socio-economic status).

A6.3.1.5 Transport

Cairns et al. (10) summarized systematic reviews of the effects of reducing traffic speeds (to 20 miles per hour (mph); equivalent to about 32 kilometres per hour) on health and health inequalities among adults and children. Five medium- to high-quality systematic reviews were included covering 10 unique primary studies. Overall, there was convincing evidence that these measures are effective in reducing accidents and injuries, and there was also evidence that such interventions are potentially cost effective. However, there was no evidence of the effects on health inequalities in these outcomes, but Cairns et al. speculated that targeting such interventions in deprived areas may be beneficial.

A6.3.1.6 Public health regulation

The umbrella review by Thomson et al. (11) covers a wide range of public health policies. It includes 29 systematic reviews (reporting 150 unique primary studies), which unsurprisingly had mixed results across the public health domain. Some policies were shown to reduce health inequalities (e.g. food subsidy programmes, control on advertising and promotion of tobacco, water fluoridation, population-based cancer screening for female cancers, well-conducted immunization programmes). For many other policies no effects on health inequalities were found, whereas a few policies seemed to increase inequalities (e.g. folic acid mass-media campaign, 20 mph and low emission zones in cities).

A6.3.1.7 Gambling

In their umbrella review, McMahon et al. (12) examined the effects of prevention and harm reduction interventions on gambling behaviours, gambling-related harm and inequalities in both. Ten (low-quality) systematic reviews were identified reporting 55 unique relevant primary studies. Much of the review evidence base related to voluntary systems and educational messages, and only a minority of studies reported positive outcomes. No review reported on the differential effects of intervention strategies across socio-demographic groups.

A6.3.1.8 Physical activity

Craike et al. (13) conducted an umbrella review of interventions to improve physical activity among socio-economically disadvantaged groups. They included 17 reviews– of mixed quality. They concluded that targeted physical activity interventions can be successful at improving physical activity among children from socio-economically disadvantaged groups, with evidence for other age groups weak or inconclusive. Group-based and school-based interventions and policies were effective, and interventions that were more intensive tended to be more effective.

A6.3.1.9 Health-care interventions

Another umbrella review by Thomson et al. (17) examined the effectiveness of community pharmacy-delivered public health services also examined impacts on inequalities in health. They found 15 systematic reviews reporting 157 unique primary studies. There were several community pharmacy initiatives with positive intervention effects on health outcomes and included smoking cessation, weight management programmes, syringe exchange programmes and inoculation services. However, there was little evidence of the impact on health inequalities.

A6.3.1.10 Health-care system

Bambra et al. (15) did an umbrella review of the effects on equality of health-care access and/or health status of health-care system organizational and financial reforms. They identified nine systematic reviews (reporting on 29 unique primary studies) of generally poor quality, which looked at changes in financing (e.g. private insurance and out-of-pocket payments) and changes in organization (e.g. introduction of "managed care" and integration of health and social services). This umbrella review found that introduction of market elements in health care tended to increase inequalities in health-care access, but that evidence for most other changes was inconclusive.

A6.3.1.11 Social determinants of health

Bambra et al. (16) conducted a wide-ranging review of interventions based on the social determinants of health (the conditions in which people work and live, or the "causes of the causes" (4)). They included 30 systematic reviews covering housing and living environment (nine); work environment (seven); transport (five); access to health services (four); unemployment and welfare (three); agriculture and food (one); and water and sanitation (one). All reviews were high or medium quality. They concluded that there is a lack of evidence about the health impacts of interventions aimed at the wider social determinants of health, particularly in relation to health inequalities. Changes to housing conditions were associated with small positive effects on physical and mental health. Workplace interventions seemed to have differing effects on different levels of employees. Several transport interventions seemed to

deliver reductions in crash injuries. Evidence for the health effects of interventions aimed at unemployment and welfare, and health service access, was either absent or inconclusive.

A6.3.2 Summary: what works in reducing health inequalities?

In this section we have synthesized the results of 11 umbrella reviews conducted over the past decade. Together, these umbrella reviews summarize the results of several hundred systematic reviews—in turn reflecting countless primary evaluation studies. There is some – albeit limited in size and quality – evidence of which policies and interventions may be effective in reducing health inequalities. These include the following:

- increased unemployment insurance generosity (6, 7);
- raising tobacco taxes (6);
- regulating tobacco advertising (6);
- taxing unhealthy food and drink (6);
- subsidizing healthy food (6, 7);
- controls on advertising and promotion of tobacco (7);
- water fluoridation (7);
- population-based cancer screening (7);
- immunization programmes (7);
- physical activity interventions (13);
- neighbourhood mobility programmes (8);
- increasing housing warmth and energy efficiency (8, 16);
- increasing job control (9, 16).

This is an improvement in terms of the size of the evidence base. Eleven years ago, Bambra et al. (16) conducted an umbrella review which concluded that there was a lack of evidence about the health impacts of interventions aimed at reducing health inequalities through action on the social determinants of health. However, although there is now a sizeable list of interventions that have *some* evidence of being effective in reducing health inequalities, it must be noted that the evidence base is subject to significant limitations.

Firstly, there are methodological concerns. The evidence base for health inequalities policy is still small, with the conclusions drawn by systematic reviews and umbrella reviews of what is or is not effective, potentially based on the findings of only one or two primary studies. The umbrella reviews all commented on concerns with the methodological quality of the underpinning systematic review and primary study evaluations. Most primary studies included in the underpinning systematic reviews reported short-term, rather than longer-term, outcomes, and common methodological limitations included high probabilities of selection bias, low response rates and high attrition. They were also dominated by many small, underpowered studies, which

often led to the conclusion that the intervention was ineffective. So there is a need to improve the quality of evaluations; this is turn might enable us to identify effective interventions. Quasi-experimental designs were lacking in the primary studies in the included reviews (probably because they had only recently started to be conducted in public health (18)). We address the methodological limitations of the current evidence base on health inequalities – and the potential of quasi-experimental designs – in section 6.4 "Methodological issues".

Secondly, the umbrella reviews examined here only provided partial coverage of the potential policies and interventions that could be implemented. Most umbrella reviews focused on the social determinants of health, particularly in the domains of "living and working conditions" and "macro-political economy". The most notable gaps in the umbrella review evidence base related to community- and individual-level interventions. It is possible – indeed likely given the growing size of the health inequalities evidence base – that systematic reviews have been conducted of evidence in these other domains (e.g. the systematic review by Milton et al. (19) which examined the health effects of interventions to increase community control), but that they have not yet been incorporated into an umbrella review. Another key absence from umbrella review level of evidence concerns the impact of interventions to reduce inequalities in health care, where again there were individual systematic reviews (see, for example, 20), but no umbrella overview available. This is a limitation of the use of umbrella reviews in this discussion paper.

Thirdly, from a theory perspective, the evidence base is limited because a lot of the primary studies and systematic reviews included in the umbrella reviews tended to conceptualize health inequalities through a "targeted" approach (evaluating interventions targeted at the most disadvantaged, particularly behavioural ones). This means that conclusions cannot be drawn about the impact on the social gradient or on inequalities between different socio-economic groups. Further, from a more political economy, life-course or materialist theoretical perspective, it could also be asserted that the "right type" of interventions are not actually being implemented and evaluated. Indeed, the evaluations summarized in the reviews tended to examine specific, small-scale, single interventions (e.g. changes in housing quality) or single policy areas (e.g. work environment). In section 6.3.4, we examine a more multi-faceted, large-scale, longer-term policy approach: the English Health Inequalities Strategy.

A6.3.3 Case study: the English health inequalities strategy

The examples presented in the previous section are drawn from evidence reviews of the health equity effects of specific interventions (e.g. changes in housing quality) or

single policy areas (e.g. work environment). They therefore tend to use just one of the approaches (e.g. targeted) or levels (e.g. living and working conditions) of intervention to reduce health inequalities. They also combine evaluations of large- and small-scale interventions together. So, in this section, a case study of policy action taken at scale is also outlined – the English health inequalities strategy (2000–2010) – the most comprehensive national strategy ever implemented (21). This policy case study also highlights how different levels and approaches can be taken to delivery. It was also evaluated using quasi-experimental designs so it provides an example of the benefits of this approach to evaluation (discussed further in section 6.4).

In 1997, a Labour government was elected in the UK on a manifesto that included a commitment to reducing health inequalities. This led to the implementation between 2000 and 2010 of a wide-ranging and multi-faceted health inequalities reduction strategy for England in which policy-makers systematically and explicitly attempted to reduce inequalities in health (21). The strategy focused specifically on supporting families, engaging communities in tackling deprivation, improving prevention, increasing access to health care and tackling the underlying social determinants of health (21). For example, the strategy included large increases in levels of public spending on a range of social programmes, the introduction of the national minimum wage, area-based interventions such as the Health Action Zones and a substantial increase in expenditure on the health-care system, particularly in areas of higher deprivation (5). Furthermore, the government made tackling health, social and educational inequalities a public service priority by setting public service agreement targets.

The key targets of the Labour government's health inequalities strategy were to (1) reduce the relative gap in life expectancy at birth between the most deprived local authorities and the English average by 10% by 2010, and (2) reduce relative inequalities in infant mortality rates between manual socio-economic groups and the English average by 10%. There has been some debate about the success or failure of the English Health Inequalities Strategy (21, 22). However, studies have found that social inequalities in the key social determinants of health – including unemployment, child poverty, housing quality, access to health care and educational attainment – decreased during the strategy period (23–25), and recent quasi-experimental analyses have shown that these were accompanied by reductions in health inequalities (26–29).

Barr et al. (28) used a quasi-experimental approach (interrupted time-series, see section 6.4 for more about this method) and found that inequalities in life expectancy declined during the period of the English health inequalities strategy, reversing a previously increasing trend. Before the strategy, the gap in life expectancy between the most deprived local authorities in England and the rest of the country increased at a rate of 0.57 months each year for men and 0.30 months each year for women.

During the strategy period this trend reversed, and the gap in life expectancy for men declined by 0.91 months each year and for women by 0.50 months each year. Barr et al. (28) also found that since the end of the strategy period the inequality gap had increased again at a rate of 0.68 months each year for men and 0.31 months each year for women. At the end of the strategy period, the gap in male life expectancy was 1.2 years smaller and the gap in female life expectancy was 0.6 years smaller than it would have been if the trends in inequalities before the strategy had continued.

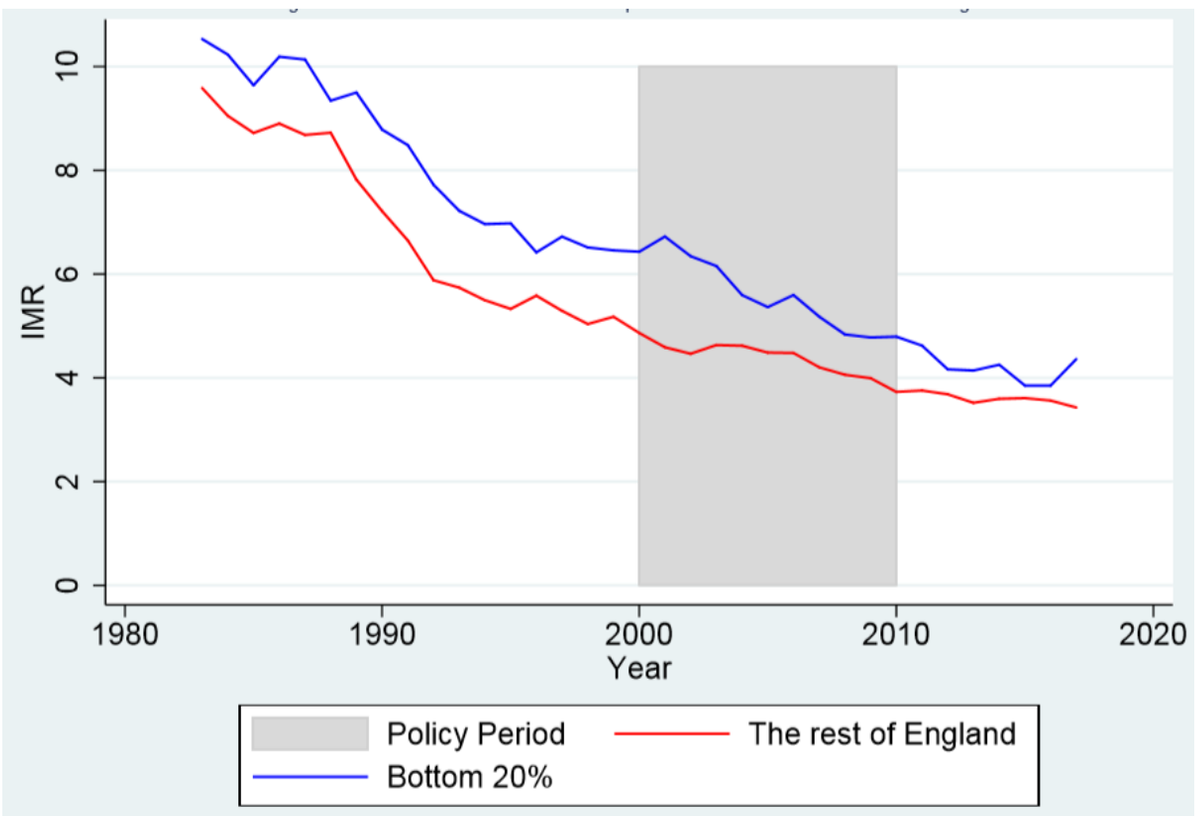

Figure A6.1 Trends in infant mortality rate (IMR) in the 20% most deprived local authorities and rest of England, 1980–2017. From Robinson et al. (29).

Further, Robinson et al. (29) also used a quasi-experimental approach (interrupted time-series, see section 6.4 for more about this method) to investigate whether the English health inequalities strategy was associated with a decrease in inequalities in infant mortality rate. They found that before the Labour government's health inequalities strategy (that is, from 1983 to 1998), the gap in the infant mortality between the most deprived local authorities and the rest of England increased at a rate of 3 infant deaths per 100,000 births per year. During the strategy period (2000–2010), the gap narrowed by 12 infant deaths per 100,000 births per year and after the strategy period ended (2011–2017) the gap began increasing again at a rate of 4 deaths per 100,000 births per year (Figure A6.1).

Another area of strategy success was around reducing inequalities in mortality amenable to health care, which is defined as mortality from causes for which there is evidence that the inequalities can be prevented given timely, appropriate access to high-quality care (30). NHS funding was increased from 2001 when the "health inequalities weighting" was added to the way in which NHS funds were geographically distributed to target funding to areas of higher deprivation. Analysis, using a fixed-effects approach to account for differences between areas other than their level of funding, has shown that this policy of increasing the proportion of resources allocated to deprived areas compared with more affluent areas was associated with a reduction in absolute health inequalities from causes amenable to health care (27). Increases in NHS resources to deprived areas accounted for a reduction in the gap between deprived and affluent areas in male "mortality amenable to health care" of 35 deaths per 100,000 and female mortality of 16 deaths per 100,000. Each additional £10 million of resources allocated to deprived areas was associated with a reduction in 4 male deaths per 100,000 and 2 female deaths per 100,000 (27).

So, the English strategy reduced health inequalities in terms of life expectancy, infant mortality rates and mortality amenable to health care. However, it has to be acknowledged that the decreases were on the modest side. Arguably, the English health inequalities strategy may have been even more effective in reducing health inequalities if there had not been a gradual "lifestyle drift" in governance, whereby policy went from thinking about the social determinants of health alongside behaviour change to focusing almost exclusively on individual behaviour change (31). The strategy may also have been even more effective if it had been sustained over a longer period. The English strategy has also been evaluated using quasi-experimental studies; the benefits and limitations of different methods of evaluating interventions will be discussed in section 6.4.

A6.4 Methodological issues

The previous section revealed that there is only a small and methodologically limited evidence base on what works to reduce health inequalities. This section follows on by addressing two questions: why is it difficult to assess the effects of policies and interventions on health inequalities, and how can these difficulties be addressed? The difficulties are of two kinds. There are the methodological challenges of identifying effects that are often small at the individual level, slow to emerge and influenced by many factors other than the intervention of interest. And there are the political, ethical and practical difficulties of conducting research on large-scale interventions in which governments, corporations and other powerful organizations have large stakes. The effects of a policy on health inequalities may be a by-product of actions oriented towards other goals. Research to identify such effects may be unwelcome to stakeholders, and

experimentation may be unethical if it involves withholding direct benefits in order to explore the side-effects of a policy.

This first section reviews alternative research designs for evaluating the effects of interventions on health inequalities, identifying three groups of designs, and it summarizes their potential uses, strengths and weaknesses and provides a case study of each. The second section considers the methodological challenges in expanding the evidence base. It provides further examples of how each research design has been used, summarizes common problems and then suggests some ways in which better use can be made of the methodological "tool-kit" available to researchers working on the effects of interventions on health inequalities.

A6.4.1 Methodological issues I: opportunities, strengths and limitations of design options

The research designs that can be used to evaluate the effect of policies and interventions on health inequalities fall into three broad groups: planned experiments (e.g. randomized trials), natural (or quasi-) experiments, and modelling or simulation studies. The strengths and weaknesses of the different approaches are to some extent complementary: planned experiments are, by definition, prospective, but natural experiments can be (and often are) conducted retrospectively. Modelling studies allow extrapolation beyond directly observed effects, on the basis of known relationships between exposures and outcomes, but may rely heavily on untested assumptions, for example about the causal relationships underpinning observed associations. However, it does not follow that, when a trial is impractical, a good natural experimental or model-based option will always be available.

Evaluating the impact of policies and interventions on health inequalities is more challenging than determining whether they improve health because it entails the assessment of how effects vary between more or less disadvantaged groups. Studies can measure the impact of polices on health inequalities directly, for example by comparing effects on more or less disadvantaged groups through stratified analyses or the use of (exposure by group) interaction terms (32). This corresponds to the second ("reducing the gap") approach to reducing inequalities as described earlier in section 6.2. and to the example in Box A6.2. An alternative is to use a measure of inequality as the outcome measure, corresponding to third approach ("reducing the social gradient"). Studies can also identify effects indirectly, for example by estimating the impact of policies that are targeted at disadvantaged groups, corresponding to the first approach ("improving the position of the most disadvantaged"). Or they can take a hybrid approach, first identifying effects on a disadvantaged group and then modelling the effects on wider health inequalities.

A6.4.1.1 Opportunities, strengths and limitations of experimental study designs

Opportunities for this kind of study depend on willingness of policy-makers to implement policy changes as experiments. Classic examples include the Negative Income Tax experiments in the USA in the 1970s and the Seguro Popular trial in Mexico from 2005 to 2006 (Box A6.1). Policy-makers' willingness to use randomized trials to evaluate policies has waxed and waned, but the approach has been strongly advocated in recent years, with many successful examples in the field of development economics in particular (Banerjee and Duflo, 2015). This success has influenced domestic policy-makers' thinking too. The Behavioural Insights Team in the UK Cabinet Office has effectively promoted the use of trials, and has provided a model for similar developments in other countries (33). A notable outcome is the UK Government's decision to include provision to vary policy implementation experimentally in its 2012 welfare reform legislation (34).

Box A6.1 The Seguro Popular trial: does extending health insurance to a previously uninsured population reduce health inequalities?

Researchers from the USA and Mexico conducted a large-scale cluster randomized trial of a programme designed to increase enrolment in health insurance and to provide improved access to medical treatment and preventive care (35). Randomization was feasible because implementation of the programme took place in a phased way (rather than being introduced at the same time throughout the country). The researchers were able to divide communities that were waiting to receive health insurance into matched pairs and to randomly assign one community to receive the intervention at least a year earlier than it otherwise would have done. The intervention consisted of encouragement to enrol in the Seguro Popular health insurance system, plus improvements in health services in the "treated" communities. Expenditure and self-assessed health data, along with data on household assets, were collected by a baseline survey done pre-implementation and a follow-up survey 10 months later. Not every household in the intervention clusters enrolled in Seguro Popular, but some households in the control clusters did, so the researchers estimated both intention-to-treat and complier average causal effects. Intention-to treat estimates capture the effect of assignment, regardless of compliance, whereas the complier average causal effects estimates capture the effect of the programme on compliers. The study found a 23% reduction in the proportion of households undergoing catastrophic health expenditures in the intervention clusters and a 55% reduction among compliers, with larger effects on low-asset than on high-asset households. It also found substantial reductions in overall health expenditures in the intervention clusters, again higher among low-asset households and among compliers, but no differences in use of health services or in any of nine self-assessed health measures. The researchers suggested that this may have reflected delays in fully implementing the service improvements.

Strengths of the experimental approach include straightforward causal inference, if the trial is well-designed and implemented. Randomization, coupled with other safeguards, provides an effective measure against the bias associated with selective exposure to the intervention that plagues observational study designs, including natural experiments.

Limitations include limited external validity, except for large-scale pragmatic trials. The advantages of unbiased effect estimates are substantially reduced if the estimates refer to a restricted population or setting, so that additional assumptions are needed to apply the results to the populations that decision-makers are actually interested in (36). The Seguro Popular trial took place in 7 of Mexico's 32 states, selected from 13 that agreed to modify the roll-out of the intervention according to the trial protocol, so the effect estimates are not straightforwardly transferable to the whole of the country. Internal validity may be compromised by contamination, confounding of intervention effects by trial procedures (e.g. measures to maintain retention in the trial may improve compliance beyond the levels that would be see in routine practice) or poor design/conduct (37). Blinding is rarely possible in policy experiments, so self-assessed outcomes measures may not be reliable—in the Seguro Popular trial a difference-in-difference estimator was used to take account of possible placebo effects after positive (intervention-favouring) effects were observed in the health measurements taken at baseline.

A6.4.1.2 Opportunities, strengths and limitations of natural or quasi-experimental study designs

Natural or quasi-experimental study designs widen the range of opportunities for rigorous evaluation. Natural experimental studies are a subset of observational studies that use the process by which exposure to an intervention is determined to identify treatment effects. Understanding how this assignment process works is therefore key to the design of a good natural experimental study. Because such processes rarely give rise to exposed and unexposed groups that are perfectly balanced on all of the characteristics that may affect outcomes, natural experiments also rely on statistical models that take into account both the allocation process and any observed differences between the groups in characteristics that may affect outcomes. Although often used interchangeably with natural experiment, the term "quasi-experiment" is also used to refer to true experiments (involving manipulation of exposure by the researcher) but which are non-randomized (38). To avoid confusion, the preferred term in the remainder of this discussion paper is "natural experiment".

Natural experimental designs may provide an alternative when a planned experiment is ruled out for political, ethical or practical reasons, or simply where a policy has been implemented piecemeal. Until recently, natural experiments were regarded primarily as

a historical curiosity. That view no longer prevails, and natural experimental approaches are now widely, but not universally, accepted as central to efforts to improve the evidence base for large-scale public health interventions.

Opportunities for natural experimental studies depend heavily on the availability, quality and relevance of routinely collected data (see Box A6.2); good data linkage infrastructure and streamlined information governance processes are critical, especially where exposure and outcome data come from separate sources.

Natural experimental approaches are particularly useful for evaluating (1) health impacts of policies implemented for other reasons (e.g. to improve work incentives), where equipoise is unlikely even if there is uncertainty about health benefits or harms, and (2) impacts that take a long time to accrue, so that it may not be possible to withhold the intervention from a control group in an experimental study for long enough to identify effects. They can also be used to identify the effect of a policy from changes that occur when the policy is withdrawn—a situation in which a randomized experiment is unlikely to be possible (39). A key strength of natural experiments is that, by definition, they evaluate policies as they are implemented (or withdrawn), rather than in a restricted research setting, so external validity of a well-designed natural experimental study should be high.

Box A6.2 Do 20 mph zones reduce inequalities in road traffic casualties?

Twenty mile per hour zones are used in many British cities to reduce traffic speeds and make roads safer. They are defined as area-wide traffic calming measures including speed limit signs and physical measures such as speed humps. Road traffic casualties are socially patterned and there is a strong relationship between traffic speed and casualty rates. Effective traffic calming measures should therefore reduce overall casualty rates and may, depending on how the schemes are implemented, reduce inequalities. Researchers from the London School of Hygiene and Tropical Medicine used information routinely collected by the police on road casualties, combined with information on 20 mph zones collated by the London Road Safety Unit, to classify casualties over a 20-year period occurring on road segments inside or outside a 20 mph zone (40). They were also able to use information from the UK 10-year census to classify road segments according to a deprivation score for the small area in which the road was located (41). To identify the effects of the 20mph zones, the researchers conducted a controlled interrupted time-series analysis, comparing changes in casualty counts on road segments in 20 mph zones with trends on other roads. They found a 40% reduction in casualties associated with introduction of the zones, which was robust to sensitivity analyses and a test of regression to the mean. The rate of decline was similar in the least and most deprived quintiles, but the fall in the number of casualties was greater in the most deprived areas. Reduction in the burden of road traffic casualties was therefore greater in poorer areas, where the zones were disproportionately located. The researchers noted that the widespread implementation of 20mph zones in London over the period covered by the study left little scope for further reductions in inequalities from this kind of intervention.

Natural experimental methods work best when exposure to the intervention is clearly defined, in terms of timing and population affected, and the effects are large and/or rapid; they work less well when process determining exposure is hard to model, effects are small or gradual. As noted above, an important advantage of natural experimental approaches is that they can be applied retrospectively. A corollary is that they often rely on routinely collected data, from censuses, long-running surveys, vital events registration or monitoring done in the course of programme implementation. Investment in infrastructure for linking exposure and outcomes data at an individual level is opening up new opportunities both for trials and for natural experiments. To enable researchers to make the most of these opportunities, information governance processes need to be rigorous, but also efficient and proportionate to the real risk of disclosure. For their part, researchers need to be alert to the opportunities provided by the withdrawal or scaling back of existing interventions, the fine details of assignment rules, or by imperfections in programme delivery, as well as by the implementation of large-scale policies or programmes.

A6.4.1.3 Opportunities, strengths and limitations of modelling approaches

Identifying the effect of a policy or intervention on health inequalities is more challenging than simply identifying the average effect because it involves estimating differential effects. Larger overall samples will be needed to identify effects on subgroups, and differences in outcomes between subgroups are likely to be smaller than the difference between outcomes in an exposed and an unexposed population. Modelling approaches can be used to extend understanding of impacts of policies on inequalities beyond directly observed effects, by using data from multiple sources as inputs to a simulation model (Box A6.3). Such approaches can be particularly useful for gaining insights into potential outcomes of policies that have not yet been implemented, longer-term outcomes of a recently implemented policy or the equilibrium effects of an intervention that has only been tested on a small scale.

Box A6.3 The Sheffield Alcohol Policy Model: understanding the effects of alcohol tax and pricing policies on health inequalities

The Sheffield Alcohol Research Group developed a simulation model for appraising the effects on health and health inequalities of alcohol tax and pricing policies, such as setting a minimum price per unit of alcohol purchased, introducing a sales tax or increasing rates of existing alcohol duties (42). The model included an economic component linking changes in price with consumption, and an epidemiological component linking changes in consumption with morbidity and mortality. The economic component used data on alcohol purchases – price paid and volume purchased for 10 kinds of drink – by households with different levels of income from a UK household survey, along with estimates of the effects of tax and pricing policies on purchase prices to generate new price distributions for each drink category and population subgroup. These data were combined with estimates of alcohol consumption preferences for population subgroups defined by age, gender, consumption and income, and published estimates of price elasticities (how much consumption changes in relation to a price change), to model the effects of a range of alcohol tax and pricing policies on alcohol consumption of each population subgroup. To model the effects of the policies on alcohol-related harm, risk functions were calculated for 43 alcohol-related diseases and injuries, and used to estimate the changes in alcohol-related mortality risk that would be expected given the effect of the policies on alcohol consumption. Effects were calculated for cohorts defined by age, gender, consumption and socio-economic position. Extensive sensitivity analyses were undertaken using repeated samples from the survey datasets, information on the uncertainties in the risk functions and alternative estimates of the price elasticities. All of the policies were estimated to reduce health inequalities because consumption and harm were concentrated in lower socio-economic groups, but the minimum price per unit of alcohol purchased and sales taxes had a stronger effect because they targeted the cheaper drinks that were disproportionately purchased by poorer drinkers. The sensitivity analyses suggested that the central estimates were, if anything, conservative. The model has proved highly influential in UK policy-making, with country-specific estimates commissioned by the Scottish, Welsh and Northern Ireland governments (43–45).

A6.4.2 Methodological issues II: expanding the evidence base

As the examples show, all three approaches have been used successfully to expand the evidence base. The designs used in those examples are only a fraction of the range of options available. Others are considered below.

A6.4.2.1 Policy trials

Seguro Popular is an unusual (and impressive) policy experiment, in that it sought to evaluate the impact of the policy as a whole, rather than of some variant of the design or delivery of the policy. Many policy trials have more limited ambitions. So far, the only use made by the UK government of its powers to randomly assign welfare benefit recipients to alternative policy conditions is in a trial of "in work progression", involving

differing levels of support with job-seeking (46). To evaluate whether the new benefits introduced under the 2012 Welfare Reform Act are succeeding in their overall aim of encouraging recipients to increase their labour supply, the government's analysts are using natural experimental methods (47). It is no coincidence that the recent enthusiasm for policy experiments is closely aligned with the growing popularity of interventions that are underpinned by behavioural economics (33). Such interventions seek to change behaviour by providing small incentives or by changing the way choices are presented to people, rather than by mandating or banning certain forms of behaviour. Although policy trials are by no means limited to evaluating behavioural "nudges" (there have been many trials of conditional cash transfer programmes in low- and middle-income countries (48)), policy-makers in high-income countries have shown relatively little appetite for treating large-scale reforms as experiments.

A6.4.2.2 Natural experiments

Basu and colleagues make a useful distinction between different kinds of natural experiment in terms of the processes by which the policy or intervention divides a population into exposed and unexposed groups (49). Sometimes the challenge is to distinguish the effect of the policy from time trends in the outcome of interest or from pre-existing differences between exposed and unexposed populations. In other cases the key problem is the lack of a well-matched comparator for the exposed population. The third group of cases is where an eligibility rule within a policy, such as a means test for an income-related benefit, distinguishes exposed from unexposed individuals. Often these assignment processes fail to create perfectly balanced or "exchangeable" groups, so natural experimental studies usually rely on a model of the assignment process coupled with tests of assumptions and additional statistical adjustment for residual confounding.

Different approaches are available for each of these situations. Wickham and colleagues used difference-in-difference methods to identify the effect of a new system of benefits and tax credits on the mental health of unemployed claimants in the UK (50). The new system, known as "Universal Credit", was introduced in a phased way, with benefit offices switching from the "legacy benefits" to Universal Credit over a period of 5 years. The researchers were able to use data from a large-scale longitudinal population survey to compare changes in health among people after Universal Credit was implemented in their area with changes among people who remained under the legacy system. This difference-in-difference approach, like the closely related fixed-effects approach used by Barr et al. (27), controls for differences in fixed characteristics of the populations subject to the two systems, so compensates for some of the potential biases associated with the non-random implementation process. The study found a substantial increase in psychological distress among unemployed people once they were subject to Universal Credit. As unemployed people tend to have relatively poor health and low incomes, such an effect implies an increase in health inequalities.

In the second kind of case, a propensity score can be used to improve the comparability of exposed and unexposed groups. A propensity score is the conditional probability of exposure to the intervention given several covariates. Melhuish and colleagues used propensity scores to match areas with or without Sure Start Local Programmes (SSLPs), an area-based intervention to improve the health and well-being of young children targeted at those growing up in relatively deprived households (51). Although propensity score-based methods will produce results similar to those obtained using standard regression adjustment with the same covariates, they have several practical advantages, such as ease of testing for covariate balance. In the SSLP evaluation the researchers identified improvements on several measures of child health and development in the SSLP areas, suggesting that the intervention should reduce health inequalities. A limitation of the study was that the most highly deprived areas had to be excluded from the analysis as there were no such areas that were not exposed to SSLPs.

Methods available in the third kind of situation include the use of instrumental variables and regression discontinuity designs. Although instrumental variable methods have some theoretical strengths and have been widely used in genetic, and increasingly in social, epidemiology, they have not been extensively used for the evaluation of public health interventions, possibly because of the difficulty of finding variables that meet the demanding conditions required of a good instrument (52). Regression discontinuity methods have (so far) been found to be more widely applicable, possibly because they rely on a method of identification that exploits eligibility conditions widely used in the targeting of social interventions (53). The regression discontinuity design uses a cutoff in a continuous variable, such as income or age, that determines whether or not individuals (or clusters of individuals) receive the intervention. The key assumption is that units either side of the cutoff will be similar in terms of other characteristics that may influence outcomes, especially if there is a degree of random error in the assignment variable. Ludwig and Miller used this approach to estimate the impact of the US Head start programme on child health (54). Assistance with enrolment in the programme was assigned to counties on the basis of a poverty score. Comparisons of counties within a narrow band of poverty rates either side of the cutoff identified substantial reductions in mortality for causes amenable to Headstart programmes (such as vaccination) but not from other causes of death. A limitation of this approach is that effects are estimated for a subset of the population, which reduces statistical power and requires the use of additional assumptions if the findings are to be interpreted more broadly.

A6.4.2.3 Modelling approaches

In the example of the Sheffield Alcohol Policy Model (Box A6.3), the researchers were able to draw on well-established relationships between alcohol price, consumption and harm, so it is not surprising that some of their predictions are turning out to

be accurate. For such models to provide reliable predictions, all of the links in the chain need to be strong. Researchers from the Scottish Public Health Observatory (55) applied estimates of the effects on income of a range of tax and benefit policies from an established microsimulation model, EUROMOD, to Scottish households in the Family Resources Survey. They then estimated the effects of the income changes on mortality, from the cross-sectional relationship between mortality and deprivation in Scotland, and used these estimates to work out the effect on years of life lost of each policy, using another established modelling tool, Triple I (56) and how the effect varied across quintiles of the Scottish Index of Multiple Deprivation. The results therefore depended on the assumption that the effect on mortality of increasing a household's income was equivalent to the observed mortality difference between households with the baseline level of income and the level attained under the policy—equivalent to assuming that mortality risk was related only to current income. The researchers noted this dependency and conceded that the effects of the policies would be smaller if the relationship between income and mortality was weaker than assumed (and performed sensitivity analyses to test the importance of the assumption). Nevertheless, this example emphasizes the uncertainties involved in modelled estimates, even when established tools and datasets are used.

A6.4.3 What are the most common methodological limitations and weaknesses in the evidence base?

The weaknesses of the evidence base are likely to reflect the limitations of the available study designs. The main limitations of policy trials are that they often focus on small variations in policy delivery, rather than on the overall impacts of the policy. Because they are conducted prospectively and involve withholding the experimental treatment from a substantial proportion of participants, they are not well suited to capturing long-term outcomes, or to identifying impacts on outcomes that are essentially by-products of a policy rather than its principal aim. Natural experiments markedly widen the range of interventions that can be rigorously evaluated, although estimation is often complicated, not least by the extensive testing that is often needed to demonstrate that underpinning assumptions are reasonable and that biases associated with selective exposure to the intervention, etc. have been satisfactorily dealt with. Modelling approaches further widen the range of impacts that can be explored and are particularly valuable for the appraisal of policy options before implementation. Reliability is a key question, given the dependency on the quality of the underlying evidence, although sensitivity analysis can go a long way towards testing reliance on critical assumptions.

A6.4.4 What are promising new approaches for evaluating the effect of policies and interventions on health inequalities?

There is much still to be gained from wider and better application of established methods, both policy trials and natural experimental approaches, as well as from the newer ones

such as synthetic controls. Methodology of trials is extremely well-developed and there is a wide range of designs to draw on. The practical logistics of organizing policy trials are so daunting that methodological innovation is unlikely to be a priority, and may even be a distraction. Large, simple trials are better suited to providing the clear answers that decision-makers are likely to find useful than are complex or innovative designs. A criticism of the income maintenance experiments done in the USA in the 1970s is that the complex allocation methods made the results hard to interpret (57, 58). Nevertheless, if policy-makers are serious about wanting evidence-informed policies, they should be more willing to undertake trials where there is substantial uncertainty about whether the policy is a good use of resources, and researchers should be ready to make the case for trials where a natural experimental approach is unlikely to provide the answers. Even so, policy trials are unlikely to be politically or practically feasible in many cases, and natural experiments are likely to remain the best available option for evaluating the effects of policies and interventions on health inequalities.

Natural experimental studies should follow well-established good practice in clinical trials, such as the involvement of stakeholders including decision-makers, patients and the public in defining research questions, etc. Previous publication or registration of study protocols is also useful – and increasingly a requirement of journal publication – so that it is clear which questions were theoretically motivated, rather than driven by the data. The importance of understanding process and context is underplayed in the natural experiments literature, which tends to focus on methods of identifying effects. Good natural experimental studies require a clear understanding of how the intervention works, in particular of the processes that determine exposure. An explicit logic model or programme theory, best developed in conjunction with stakeholders, is a useful way of capturing this. Coupled with a process evaluation (59) such a theory can support an understanding of how policies achieve their effects, how context-dependent the observed effects are and therefore how transferable the effect estimates are to other contexts, as well as informing the modelling approach taken. Whatever method is chosen for identifying the effects of the intervention, careful testing of assumptions and, where possible, the comparison of results from alternative methods helps to build confidence in conclusions.

As noted above, natural experimental approaches are increasingly accepted as central to efforts to improve the evidence base for large-scale public health interventions. Leading national and international public health agencies have invested in initiatives to promote the use of natural experiments (60, 61). The success of modelling approaches, exemplified by the Sheffield Alcohol Policy Model, should be a spur towards the greater use of these kinds of method too.

This section has set out the case for seeing trials, natural experimental and simulation modelling methods as belonging to a common tool-kit of approaches available to researchers, rather than as occupying separate levels of an evidence hierarchy that

is stratified only by risk of bias. Exactly the same reasoning applies to the different natural experimental approaches described. There is no single approach that is best in all circumstances. Instead, there is a range of methods that provide researchers with the tools to tackle a wide array of evaluation problems. Choice of methods should depend on the specific details of the problem, rather than on more general assumptions about the superiority of some methods over others (36, 52).

A6.5 Conclusion

This discussion paper has examined the effectiveness of policies and interventions in reducing health inequalities. In doing so, it has set out the key theoretical and methodological issues in the field and provided an overview of the latest evidence of what policies and interventions are effective in reducing health inequalities—including a case study of the multi-intervention English health inequalities strategy. It has identified several specific interventions that have *some* umbrella review-level evidence of being effective in reducing health inequalities–in terms of addressing the social determinants of health: social protection (increased unemployment insurance generosity); housing (neighbourhood mobility programmes; increasing housing warmth and energy efficiency); work environment (increasing job control); and more traditional public health policies (raising tobacco taxes; regulating tobacco advertising; taxing unhealthy food and drink; subsidizing healthy food; controls on advertising and promotion of tobacco; water fluoridation; population-based cancer screening; immunization programmes; physical activity interventions). Quasi-experimental studies (see, for example, 27) have also found that the multi-faceted English health inequalities strategy was effective in reducing inequalities in mortality amenable to health care.

We have also identified clear gaps in the existing health inequalities evidence base (at least in terms of umbrella reviews), where there is a lack of evaluations of community- and individual-level interventions, particularly in terms of interventions to reduce inequalities in health-care access. Future research should address these. However, although we have identified a sizeable list of interventions that have *some* evidence of being effective in reducing health inequalities, it must be noted that the evidence base upon which these conclusions are drawn is subject to significant methodological limitations. In particular, most evaluations report only short-term effects on health inequalities and common methodological limitations across the evidence base include selection bias, low response rates and high attrition. The health inequalities evaluation literature that we have examined is also dominated by many small, underpowered observational studies, which often lead to the conclusion that the intervention was ineffective.

So, there is a need to improve the quality of evaluations; this is turn might enable us to identify more interventions that are effective in reducing health inequalities in the

future. In this discussion paper we have outlined the methodological approaches that could enable this improvement in evaluation techniques, including planned policy trials, natural (or quasi-) experiments, and modelling or simulation studies. We have tried to show how these approaches complement one another, providing researchers with a versatile tool-kit of evaluation methods. Nevertheless, opportunities for high-quality trials or natural experimental studies of the effects of policies and other interventions on health inequalities are likely to remain scarce (62), for example because policies and interventions that may reduce health inequalities often have other primary goals, such as education or labour-market participation, or because their effects on health are small at an individual level, or they take a long time to accumulate, requiring very large-scale, long-term measurement to yield convincing results. The key to improving the quality of evaluations and therefore the value of evidence for decision-makers is to be alert to the opportunities that arise to use each approach to best effect, rather than to seek methodological innovation for its own sake.

A6.6 Acknowledgements

We thank Johan Mackenbach for comments and support–particularly with the evidence from practice section. Clare Bambra is funded by a grant awarded by the Norwegian Research Council (CHAIN: Centre for Global Health Inequalities Research, project number 288638). Peter Craig is supported by the UK Medical Research Council and the Scottish Government Chief Scientist Office (MC_UU_12017/13 and SHSU13).

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ANNEX 7.

WORKSHOP REPORT. EVALUATING POLICIES AND INTERVENTIONS TO REDUCE HEALTH INEQUALITIES

This workshop was held on 2 March 2021. It was supported by Academia Nazionale di Medicina (Italy), ALLEA, FEAM and KNAW. Virtual platform. Report by Jean Philippe de Jong.

A7.1 ATTENDANTS

Ingelise Andersen, Clare Bambra (speaker), Marielle Beenackers, Helen Burke, Rosa Castro, Giuseppe Costa (chair), Caroline Costongs, Peter Craig (speaker), Goran Dahlgren, Finn Diderichsen, John Frank, George Griffin, Johanna Hanefeld, Domantas Jasiolonis, Jean Philippe de Jong, Michelle Kelly-Irving, Ilko Keskimak, Marlou de Kroon, Johan Mackenbach (speaker), Eero Lahelma (speaker), Daniel La Parra Casado, Frank van Lenthe, Guillem Lopez Casasnovas, Rikke Lund, Olle Lundberg (speaker), Julia Lynch, Michael Marmot (speaker), Michele Marra, Umida Masharipova, Maria Melchior, Tom van Ourti, Anna Pearce, Mark Petticrew, Christina Plantz, Maarten Prak, Vania Putatti, Bucciardini Raffaella, Chiara Saraceno (speaker), Yvette Shajanian-Zarneh, Johannes Siegrist, Alfred Spira, Ingrid Stegeman, David Taylor-Robinson, Rotko Tuulia, Ellen Uiters, Denny Vågerö, Paolo Vineis, Margaret Whitehead (chair)

A7.2 FINAL PROGRAMME

Chairs: Professor Margaret Whitehead (University Liverpool, UK) and Professor Giuseppe Costa (University of Turin/ACCMED, Italy)

14:00–14:05	Opening address, Professor Giuseppe Costa (ACCMED)
14:05–14:15	Policies and interventions to reduce health inequalities: what are the issues? Professor Johan Mackenbach (Erasmus MC, Rotterdam, The Netherlands)
14:15–14:30	Methods to evaluate the impact of policies and interventions on health inequalities, Dr Peter Craig (University of Glasgow, UK)

14:30–14:45	Existing evidence on the impact of policies and interventions on health inequalities, Professor Clare Bambra (Newcastle University, UK)
14:45–15:05	Q&A
15:05–15:15	Reflection, Professor Eero Lahelma (University of Helsinki, Finland)
15:15–15:25	Reflection, Professor Olle Lundberg (Stockholm University, Sweden)
15:25–16:00	Moderated discussion (Giuseppe Costa)
16:00–16:15	Break
16:15–16:30	Keynote: Policies and interventions to reduce health inequalities: what do we know? Professor Michael Marmot (University College London)
16:30–16:45	Q&A
16:45–17:00	What do international policy-makers need to know? Dr Chris Brown (WHO Europe)
17:00–17:15	What do national policy-makers need to know? Professor Chiara Saraceno (University of Turin, Italy)
17:15–17:35	Q&A
17:35–18:10	Moderated discussion (Giuseppe Costa)
18:10–18:30	Summary and conclusions, Professor Margaret Whitehead

A7.3 AIM

- Assess available empirical and analytical methods to evaluate the impact of policies and interventions on socio-economic inequalities in health.
- Identify areas of agreement and disagreement between scientific experts, and agree on priorities for further substantive and methodological research.
- Clarify to what extent the available evidence permits reliable recommendations for policy-makers on how to reduce health inequalities.

A7.4 WAY-OF-WORKING

- The ALLEA and FEAM committee on health inequalities circulated two documents to speakers and participants in advance of the workshop: (1) a "*Brief for policies*

workshop" which listed the questions that the committee would like to see addressed in the discussion during the workshop; (2) at the request of the ALLEA and FEAM committee, Peter Craig and Clare Bambra have written the discussion paper. "*Policies and interventions to reduce health inequalities: Insights from Theory, Evidence from Practice AND Methodological Issues*" (Annex 6). Speakers were asked to respond to the document, and discussions were guided by the areas of agreement/disagreement identified in the documents.

- The draft of the workshop has been circulated among the participants of the workshop, asking for feedback and additional inputs.

A7.5 OPENING ADDRESS, PROFESSOR GIUSEPPE COSTA (ACCMED)

Giuseppe Costa welcomed participants and speakers on behalf of the Italian Academy of Medicine. The workshop was originally planned to take place in Genoa in April 2020 but had to be postponed owing to the COVID-19 pandemic. The Italian Academy is now, together with KNAW, hosting this virtual workshop for the ALLEA and FEAM committee on Health Inequalities. The Italian Academy of Medicine also has a leading role in the Joint Action Health Equity Europe, funded by the European Union's Health Programme. The COVID pandemic affects health inequalities and poses a challenge to counteract the pandemic's negative impact on health inequalities. The outcomes from this workshop could form input for this Joint Action.

The ALLEA and FEAM committee on health inequalities has organized several workshops on scientific issues with regard to health inequalities. The main question for today is how scientific evidence can be translated into policies and interventions. Do we have enough evidence to make policy recommendations and what further evidence is needed?

A7.6 POLICIES AND INTERVENTIONS TO REDUCE HEALTH INEQUALITIES: WHAT ARE THE ISSUES? PROFESSOR JOHAN MACKENBACH (ERASMUS MC, ROTTERDAM)

Johan Mackenbach introduced the ALLEA/FEAM/KNAW health inequalities project and the place of this workshop in it. There are three big scientific question with respect to health inequalities that the committee wants to address in the project: (1) is there a causal effect of socio-economic position on health?; (2) what mediates the effect of socio-economic position on health; and (3) what is the effect of policies and interventions on inequalities in health? The first two questions have already been addressed in previous workshops, the third is the topic for today. The results of all three workshops will form the basis of a final report to be presented at a conference in Amsterdam in the second half of 2021.

The issue of the effectiveness of policies and interventions for reducing health inequalities consists of three sub-questions.

1. "What we should know". From a scientific perspective, what types of evidence are needed before policies and interventions can confidently be recommended (e.g. theoretical versus empirical, observational versus experimental, effectiveness versus cost-effectiveness, single studies versus systematic reviews)? How do these scientific requirements relate to the needs of policy-makers? How to deal with lack of scientific evidence in the real world?
2. "What we do know". What is the state of the current scientific evidence base, in terms of types of scientific evidence, and how well does it cover all relevant factors? In which areas of intervention and policy is the evidence base sufficient to recommend/adopt large-scale implementation? What are the main gaps in knowledge on effectiveness of policies and interventions, and what should be priorities for further research?
3. "How we can get to know". What is the best way to collect further evidence on the effectiveness of policies and interventions to reduce health inequalities? Can "quasi-experimental" approaches be useful in closing the main gaps in knowledge on the effectiveness of interventions and policies to reduce health inequalities? In which areas are they most likely to be useful? What are their main limitations? In view of the gaps in knowledge, what would be a good strategy to increase the "learning speed"? Is there a role for national and European academies of science?

This workshop has three aims.

1. Have an in-depth discussion on the three main questions, and identify areas of agreement and disagreement.
2. Clarify to what extent the available evidence allows reliable recommendations for policy-makers on how to reduce health inequalities.
3. Identify priorities for further substantive and methodological research, and develop ideas on how "learning speed" can be enhanced.

A7.7 METHODS TO EVALUATE THE IMPACT OF POLICIES AND INTERVENTIONS ON HEALTH INEQUALITIES, DR PETER CRAIG (UNIVERSITY OF GLASGOW)

Peter Craig addressed the topic of methods to evaluate the impact of policies and interventions on health inequalities. There are two types of difficulty in assessing the effects of policies and interventions on health inequalities: methodological and practical. Examples of methodological difficulties are that interventions that have important effects at a population level may have very small effects at the level of the

individual, which makes them difficult to measure. Practical difficulties include the fact that there often exist other justifications for policies (e.g. social security) than health – let alone health inequalities – so other stakeholders also play a role which can lead to an unwillingness to experiment with these policies in order to understand their effects on health.

In clinical medicine, methods for the collection of scientific evidence have been conceptualized as a hierarchical pyramid, with expert opinion at the base and systematic reviews of randomized controlled trials at the top. For public health policy, including policies on health inequalities, it can be more useful to consider methods for evidence collection as a tool-box and not as hierarchy.

There are three (partial) solutions to the difficulty of evaluating the impacts of policies on health inequalities: (1) planned experiments; (2) natural experiments; and (3) modelling studies.

The idea of the "experimental government" is increasingly popular: governments should not only try something new, but also study whether it worked. The ideal is to conduct planned experiments. Randomized controlled trials can be applied to individuals or to larger aggregates of people, and can in principle lead to causal conclusions that an intervention indeed has the desired effect. However, even if practically and ethically feasible (which they are often not), these types of study are often limited to "tweaks" rather than fundamental questions about the impact of a policy. Moreover, they can only provide limited insight into outcomes that would occur if the intervention were implemented at a larger scale and over a longer period.

An alternative is to conduct natural experiments. The assignment ("exposure") here is determined by the way the policy or programme is implemented, rather than by the researcher. However, this is rarely at random. Usually there is selection on the basis of income, age or some other characteristic. Understanding and taking account of this selection process is key to designing a good natural experimental study. There is no single, universally applicable solution to the problem of selection, but a range of partial solutions that each work well in some circumstances but not in others. Advantages of natural experiments are that they are useful when planned experiments are impractical (e.g. national legislation), unethical (e.g. to assess the health impacts of interventions that have other clear benefits) or politically unacceptable (e.g. when there is previous commitment to implementing a policy). Further advantages are that they can be conducted retrospectively, have high external validity and avoid threats to internal validity specific to trials, such as confounding of the intervention and trial procedures. On the other hand, the analysis of natural experiments can be complicated—it is often hard to rule out the possibility that observed "effects" are the result of differences other than exposure to the policy. The conduct of natural experiments could be improved by incorporating best practices from clinical trials, for example previous registration of

protocols, involvement of patients/public and other stakeholders, and the use of mixed – including qualitative – methods and process evaluation.

A third possibility to evaluate the impacts of policies is modelling studies. These can be used to extend the understanding of impacts of policies on inequalities beyond directly observed effects, by using data from multiple sources as inputs to a simulation model. They can be an option when randomized trials and natural experiments would be impractical, in the case of *ex ante* appraisal of policies and for exploring longer-term impacts. Modelling studies should be seen as an extension, rather than an alternative, to other methods. They may rely on a long chain of assumptions, although dependencies can be tested in sensitivity analysis.

In conclusion, in health inequalities research, we should not try to reinvent a hierarchy of study designs akin to clinical trials, but think in terms of strengths and weaknesses of specific designs and the set-up of specific studies in specific circumstances.

A7.8 EXISTING EVIDENCE ON THE IMPACT OF POLICIES AND INTERVENTIONS ON HEALTH INEQUALITIES, PROFESSOR CLARE BAMBRA (NEWCASTLE UNIVERSITY)

Clare Bambra presented her analysis of existing scientific evidence on the impact of policies and interventions on health inequalities. She started out by giving an overview of the theories behind the study of health inequalities and correspondingly how policies could intervene. Theories that link social inequality to health inequality focus on different aspects: cultural-behavioural, materialist, psychosocial, political economy, life-course. Studies suggest a total contribution of between 40% and 70% of all these factors to inequalities in health. When thinking about policies and interventions they can be distinguished along two axes. (1) The focus of the approach to reducing health inequalities: the most disadvantaged, the gap between top and bottom, a social gradient, or proportionate universalism. (2) The level of action: strengthening individuals, strengthening communities, improving living and working conditions, promoting healthy macro-policy.

The methods chosen to analyse existing scientific evidence on the impact of policies and interventions, the results of which are presented in Annex 6, had to be pragmatic because of time and resource constraints. A simple search of the Web of Science from 2008 onwards was performed to uncover umbrella reviews (i.e. overviews of systematic reviews). Eleven relevant umbrella reviews were found, all of which included an assessment of the quality of the underlying systematic reviews (using the assessment of multiple systematic reviews approach) and the reviews all assessed the quality of included primary studies. Together, these umbrella reviews reflect the results of several hundred systematic reviews, in turn reflecting countless primary evaluation studies. The umbrella reviews covered the following areas: macro-economic policies,

social protection policies, housing policies, work environment, transport policies, public health regulations, gambling, physical activity, health care interventions, health care system, and the social determinants of health.

The following are policies with some evidence of effectiveness in terms of reducing health inequalities:

- increased unemployment insurance generosity (Naik et al., 2019; Hillier-Brown et al., 2019);
- raising tobacco taxes (Naik et al., 2019);
- regulating tobacco advertising (Naik et al., 2019);
- taxing unhealthy food and drink (Naik et al., 2019);
- subsidizing healthy food (Naik et al., 2019; Thomson et al., 2018);
- controls on advertising and promotion of tobacco (Thomson et al., 2018);
- water fluoridation (Thomson et al., 2018);
- population-based cancer screening (Thomson et al., 2018);
- immunization programmes (Thomson et al., 2018);
- physical activity interventions (Craike et al., 2018);
- neighbourhood mobility programmes (Gibson et al., 2011);
- increasing housing warmth and energy efficiency (Bambra et al., 2010; Gibson et al., 2011);
- increasing job control (Bambra et al., 2009; Bambra et al., 2010).

Reflections on the evidence from umbrella reviews are as follows:

- They cover a small but growing evidence base.
- Primary studies include observational, quasi-experimental and experimental studies.
- A common conclusion of the umbrella reviews is that both the primary studies and the systematic reviews were often of only mediocre quality. Common methodological limitations included high probability of selection bias, low response rates and high attrition. There are many small, underpowered studies, which often lead to the conclusion that the intervention was ineffective.
- Dominance of USA-based evaluation studies in the evidence base, which potentially limits the transferability of findings into European health and social welfare contexts.
- The umbrella reviews only provide partial coverage of the potential policies and interventions that could be implemented. The most notable gaps in the umbrella review evidence base relate to community level interventions and health care. However, the “inverse evidence law” suggests that there are many primary studies of these types of small-scale intervention.
- Reviews tended to examine specific, small-scale, single interventions (e.g.

changes in housing quality) or single policy areas (e.g. work environment), not holistic changes).

In addition to umbrella reviews, policy case studies can provide valuable information on the effectiveness of interventions and policies. One example is the national programme for reducing health inequalities in England (1997–2010). It was a large-scale, national and holistic effort to decrease health inequalities in England. Recent studies have shown that it led to a reduction of the gap in health (which had been increasing before) between the most deprived local authorities and the national average during the period 2001–2011. Another case study is the unification of East Germany and West Germany starting in 1989. The unification was associated with a closing of the gap in health between East Germany and West Germany. This was not a direct policy goal but a by-product of decreasing socio-economic differences.

The following conclusions can be drawn:

- Theory provides insights in how health inequalities might be reduced. Reviews and policy case studies can show how they have been reduced.
- Umbrella reviews provide some evidence of effective interventions, but this evidence base is still small and incomplete. There is likely to be much more evidence elsewhere, in particular also about policies that were not directly aimed at reducing health inequalities, but where it was a by-product of striving for other policy goals.
- Case studies of macro-changes provide an alternative approach.
- More evaluations are needed using the natural experiment methods, especially of larger, more wide-reaching interventions.

A7.9 QUESTIONS AND ANSWERS

Professor Costa: How much of the poverty in evidence is related to a lack of commitment to produce good evidence and how much to technical problems? For example, the USA has developed more of a culture to evaluate new policies than Europe.

Professor Bambra: The lack of commitment is the more important problem.

Professor Mackenbach: Finding good opportunities for natural experiments is difficult. Not many policies are clearly directed at reducing health inequalities and for the ones that are, there is often a lack of data. Are natural experiments currently underutilized?

Professor Craig: Yes. We have to look closely at policies to identify the opportunities to study natural experiments. For example, the withdrawal of policies and flaws in the implementation of policies (partial implementation) can also be studied.

Participant: We should look at the methods in terms of a tool-box instead of a hierarchy. How can we promote this idea and move away from a sole focus on trials?

Professor Craig: The UK 2012 Welfare Reform Act is an unusual example of the opportunity for planned experiments. The opportunity to experiment was actually part of the policy itself. But we should use the whole range of approaches, and not just focus on trials.

Participant: In the discipline of political science in the USA, there has been a strong shift towards valuing evidence mainly from (quasi-)experiments. However, with natural experiments it is often very hard to define what the intervention exactly is. The rising value of evidence from experiments in political science has led both to a devaluing of other forms of evidence and to a loss of expertise in generating and evaluating data from other methods and study designs, for example in case studies, in-depth interviews and process-tracing studies. This should be avoided in health equity research.

Professor Marmot: Policy-makers often ask (and researchers are inclined to do so as well) to single out the "most important" intervention. However, single interventions are very uncommon in real life. Many things happen together in practice, and in practice combinations of interventions work better than single ones.

Professor Bambra: An alternative to experiments is to look at changes in health inequalities over a period and then study what happened before/in that period. One of the problems at gathering evidence is that policy-makers need quick gains, and want to show that their policies work.

Professor Craig: There is a trade-off between precise answers to limited questions and less precise answers to broader questions.

Participant: For the effectiveness of interventions, does that concern absolute or relative inequalities? I would suggest focusing more on absolute inequalities. It could also be easier to obtain the right type and level of evidence in that way.

Participant: There is not a single policy with a single outcome. We should take a complex systems perspectives: look at the whole system, how it works and what its unintended effects are.

Professor Craig: It has been challenging to be clear about what types of question a complex systems approach would work best.

A7.10 REFLECTION, PROFESSOR EERO LAHELMA (UNIVERSITY OF HELSINKI)

Eero Lahelma reflected on what we can conclude from studies on policies and interventions. Over 40 years, tens of thousands of studies have been conducted on

health inequalities (Bouchard et al. 2015). There has been a shift from descriptive to causal studies. These studies have found three key areas of determinants of health inequalities: (1) material and psychosocial living/working conditions: poverty, housing, unemployment, physical demands, control; (2) health behaviours/lifestyles: tobacco, alcohol, diet, exercise, obesity; (3) health care (Mackenbach 2019, Bambra & Craig 2021). For the first two areas there is more evidence than for the third.

Most studies concern the influence of socio-economic position on health; fewer deal with the influence of health on socio-economic position. Most studies are observational and apply modelling. Causal studies suggest where policies and interventions are effective and feasible: for example working conditions and health behaviours explain 64% of inequalities in self-rated health in European data (Schram et al. 2021); smoking and drinking explain 30–55% of inequalities in life expectancy within the Nordic countries (Östergren et al. 2019).

On the basis of research, three key areas for reducing health inequalities have emerged: (1) material factors; (2) behavioural factors; (3) health care and social care/security. Evaluations of policies/interventions for reducing health inequalities show "some albeit limited evidence" (Bambra and Craig 2021).

To collect more evidence on policies and interventions, we need a broad range of studies (observational/modelling causal factors, policy evaluations, natural experiments). Each type of study can be improved: more powerful designs; more powerful analyses (e.g. by using intersectionality: socio-economic position + age, gender, ethnicity); better, larger, longitudinal data; more reliable measurements, novel methods. Evidence also needs to be summarized in systematic reviews, meta analyses and umbrella reviews (Bambra and Craig 2021).

Practical conclusions are that three key areas should be prioritized for policy-making: (1) improving (physical) working conditions; (2) combating smoking and drinking; (3) providing equal access to needs-based health care. The main conclusion is that on the basis of currently available evidence conclusions can – and should – be drawn, and communicated to policy-makers. An important question is whether to focus on absolute or relative health inequalities because this is also relevant for designing interventions.

A7.11 REFLECTION, PROFESSOR OLLE LUNDBERG (STOCKHOLM UNIVERSITY)

Olle Lundberg reflected on the impact of policies and interventions on health inequalities. Current theories focus on important "exposures" that people in lower strata are more exposed to. That is a simplification of the underlying processes. We thereby tend to miss that inequalities are formed in dynamic and probabilistic processes (with large variations within strata) that involve the interplay of a range of conditions over the life-course and that are also shaped by the individual's actions and reactions.

The role of agency is often neglected. People's conditions and opportunities differ systematically across social strata. How people act and react in relation to specific situations *also* differs, both between and within strata. Together with the probabilistic nature of the links between "exposures" and "outcomes", this leads to large variations, also within strata.

More attention should be paid to the relationship between the individual and groups. Inequalities between groups (group averages) is our way of identifying how unequal probabilities play out, because probabilities are not observable on the individual level. Still, we often discuss inequalities as if those averages apply uniformly to the whole group although this is not the case. For example, life expectancy is much lower in low socio-economic status groups, but the typical age of death is more similar between strata. And smoking is much more common in low socio-economic status groups, but in Sweden most people of low socio-economic status do not smoke.

Implications for research are the following: (1) more focus on the interplay between conditions, opportunities and people's actions would improve our understanding of health inequalities and present new insights for policy recommendation; (2) with this approach we get a stronger focus on specific subgroups within strata and the quality and content of services of importance; (3) avoid policy advice for whole groups that only apply to a smaller part of the group.

Lessons for researchers with respect to policy-making are the following: (1) policy is usually not constructed from principles, but often starts with a reform that has political support; (2) to inform policy and practice across the broad range of social determinants, start to ask what problems policy-makers struggle with; (3) descriptive and causal science will not in itself provide policy recommendations: designing policies can be done in many ways. So there is a need to fill the gap between mechanisms and evaluations.

A7.12 MODERATED DISCUSSION

Professor Costa started the moderated discussion by presenting a short summary of what previous speakers had said about "what we know" and "how can we get to know". The available evidence is limited to the positive impact of some structural factors (living and working conditions) and macro-policies, with clear indications for the "inverse evidence law". Moreover, most of the evidence is on interventions and policies targeting the disadvantaged, while the other approaches (gap, gradient, proportionate universalism) have been less investigated. This lack of evidence is probably due to a lack of commitment to evaluation. Nevertheless, a set of interventions has been demonstrated effective, such as social protection, housing, work environment and traditional public health interventions; the common denominator of these interventions is that they regulate changes in the living condition/environment without conditioning on the collaboration of the individual.

Participant: There has been a development in parts of the UK putting in place infrastructure (see, for example, https://www.health.org.uk/funding-and-partnerships/programmes/from-data-to-decisions-embedding-a-real-world-intervention-) for evaluation of local area policies and interventions, whereby policies can be rolled out in an experimental/stepped-wedge manner to allow more causal evaluation of system changes that are happening anyway.

Participant: Granting agencies are not flexible enough in how they allocate funding; they require detailed specifications beforehand. This is a problem for natural experiments because implementation of policies is often unpredictable in terms of timelines and practicalities which would not fit the granting agency's requirements.

Participant: Differences in health inequalities as a function of age should be studied and heeded in policies: elderly people have their own specific mechanisms for health inequalities.

Participant: We should include policy-makers as stakeholders. How can we use case studies to help convince policy-makers?

Professor Craig: The use of health impact assessments is well-established in Scotland. However, one can also do these assessments in a very trivial way, which would not help the understanding of the impact of policies. To address Professor Franks' point, one way that funders could help would be to sort out problems with data linkage and sharing. This is often is seen as a infrastructural problem, but it is actually more a political one related to the willingness of agencies to share data.

Professor Mackenbach: Do we actually agree that there is evidence on effectiveness of policies and interventions in several areas? For what topics do we want to see more evidence? We should set priorities.

Professor Whitehead: There is still an "inverse evidence law" with regard to public health policies and interventions, in that the value and quality of available evidence is inversely related to the potential impact/importance of the intervention for whole populations (Nutbeam, 2001). We see this, for example, in the systematic review literature, where there are many good-quality trials of relatively small-scale interventions based on health education/promotion aimed at changing personal behaviour, but fewer investigations of the health impact of wider, more structural policies that have much greater potential to have an effect at the population level (Ogilvie et al., 2005). Systematic reviews find even fewer evaluations that examine differential effectiveness across different social groups in the population to inform attempts to tackle inequalities in health. Two discussion points come from this state of affairs: (1) although Clare Bambra's umbrella review found few *umbrella reviews* of community- and individual-level interventions, that does not mean that this is a significant gap in

the evidence base that needs to be filled. As she clarified in the discussion, there are already plenty of primary studies and systematic reviews on individual-level health promotion interventions. (2) One of the reasons for the relative dearth of evaluations of the wider policies with potentially greater population impact may be methodological. Over-reliance on the hierarchy of evidence may inhibit the use of the most appropriate mix of methods for the population-wide policies of interest. I agree with Julia Lynch's previous point about the value of recently neglected methods, including case studies.

Participant: Some policies are mainly politically driven. For example, while interventional evidence on preventing or mitigating adverse childhood experiences is scant, there has been a big policy push for interventions.

Professor Lundberg: We should focus more on how interventions affect individuals, focus more on how people react to policy. Withdrawal of policies is also interesting, but it is important to keep in mind that the effect of the introduction and withdrawal of interventions need not be symmetrical. For example, the withdrawal of alcohol policies would lead to more addiction, which would lead to higher alcohol consumption after the policies were reinstated compared with their initial period of working.

Participant: We lack evidence on the impact of (bundles of) macro-level policies, which is generally best assessed using comparative case study research. Comparative case study research should be promoted as a way of generating the evidence base surrounding these types of policy.

A7.13 KEYNOTE: POLICIES AND INTERVENTIONS TO REDUCE HEALTH INEQUALITIES: WHAT DO WE KNOW? PROFESSOR MICHAEL MARMOT (UNIVERSITY COLLEGE LONDON)

Michael Marmot presented his ideas on what evidence is needed for policy-making. Looking at other areas of policy-making than health inequalities, we see similar debates on what constitutes enough evidence to justify policies. For example, there has been a debate on whether overseas development assistance actually helps to reduce poverty. Economists have looked at the evidence and drawn sharply different conclusions. Easterly said the evidence shows clearly that aid does not help. Collier looks at the evidence and concludes that aid is a kind of resource curse and does harm. Sacks looks at the evidence and concludes that aid helps people out of the poverty trap. Not only does it work, says Sacks, but we know how many dollars per person we need to spend. Banerjee and Duflo (in *Poor Economics*) say the question is too general. Specific aid policies have been shown to work. It depends on the specific policies and the circumstances. We should look closer at when and how things work. Two lessons come from this example. First, no one method gives the "correct" answer. Secondly, individual investigators bring their own prejudices and judgements to bear on the evidence.

To take a simpler example: does capital punishment deter homicide? Reviews of the evidence come to sharply different conclusions. In general, those reviews performed by economists concluded that capital punishment does work as a deterrent. Those reviews performed by criminologists conclude it does not. One cannot escape the conclusion that previous views shape judgements on the evidence. Economists tend to subscribe to incentives and disincentives as informing rational choices. Criminologists are closer to social determinants. But surely there is an evidence base? The issue is that capital punishment and homicide are endogenous. Other things being equal, comparing US states, the more homicide there is, the more capital punishment. The controversy centres on the choice of instrumental variable. Here previous views have a huge role to play.

Even on apparently very simple questions the evidence can be debated: for example, whether the Astra Zeneca vaccine protects against COVID-19 among the elderly. The only way to answer the question is a randomized controlled trial. In Britain we have concluded that the evidence supports giving it to older people. However, Germany and the EU conclude that the evidence does not support this. But incoming observational epidemiological data suggest it does protect older people. So we should also look at other types of data, laboratory research and epidemiology. But keep in mind: there will always be insufficient evidence. Judgements in the light of all the evidence from different sources come into play.

So, we should conclude that although evidence is fundamental, the interpretations of the evidence are also fundamental and they are strongly influenced by ideology, sociology and psychology. Coming back to health inequalities, here is a telling example: do national strategies work to reduce health inequalities? Mackenbach wrote a paper saying it did not work in the UK. Knowing our previous histories, it is far more likely that Mackenbach would have written such a paper than that I, Marmot, would have written it. Our previous views of the evidence on social determinants and health equity influenced the likelihood that each of us would have drawn the conclusions we did. For one thing, I was influenced by the Swedish view that there are two ways to judge whether the national policies worked: did the health of the poor improve; and did inequalities diminish? The health of the worst off did improve during this period. Subsequently, Bambra and Craig concluded the national strategy did work. It is important to take heed of the judgements we bring to the table. At what parts of the evidence are you looking? The message from these examples is that it would be quite wrong to suggest that there are certain gaps in knowledge that a limited suite of well-designed studies would fill. The world of health inequalities is more complex than that, and so is the scientific enterprise of reaching judgements.

In the World Health Organization Social Determinants of Health Commission report, we wrote that if we would have limited ourselves only to what is considered high-quality evidence it would have been a very slim report indeed. Yes, there are many gaps, so

we need better evidence. But we should also give recommendations to policy-makers. There are many areas where we can conclude there is enough evidence now.

We may need a chain of reasoning to draw conclusions rather than a specific study. For example, there is a social gradient in adverse childhood experiences: more deprivation, more adverse childhood experiences; and in good early child development: less deprivation better early child development. These, in turn, will influence what happens in school, which will influence the kind of job a person gets, how much money they have, where they live, social relations and health. There is evidence to support every step in this chain of reasoning. There may not be one mega-study that shows that poverty in childhood, via early child development and adverse childhood experiences, influences inequalities in mortality at age 60. That should not be seen as a gap in knowledge.

We should also look at the changing overall distribution of income due to tax and benefit policies. Whereas most groups have experienced a growth in income during the past 10 years, the poorest people have benefited the least, and the poorest groups with children even experienced a substantial decline in income as a result of fiscal policies (IFS Deaton Review, 2020). We can and should construct a causal story here: how income affects housing and other intermediate factors leading to lesser health. Should this count as "evidence" or not?

We have just published a report on how the COVID-19 pandemic has widened health inequalities and what we can do to counteract that (Build Back Fairer, the COVID-19 Marmot Review). In the pre-pandemic UK, life expectancy was stalling, inequalities were increasing and life expectancy for the poorest people was even falling. The UK slow-down in life expectancy is nearly the highest of all rich countries and during the pandemic we had the highest excess mortality. Could there be a link between the two? I suggest the link is poor governance and political culture, increasing social and economic inequalities, reduction in spending on public services and the UK being generally unhealthy coming into the pandemic? How could you measure these factors, single them out? And if we cannot isolate them, does that mean the explanation is invalid? We can and should make a coherent story. Evidence is essential, but so, too, are the vital elements of judgement.

A7.14 QUESTIONS AND ANSWERS

Professor Marmot: Vaccination seems to be a straightforward intervention, but social groups such as black people are more hesitant. And now it becomes complicated: why is that; is it just their economic position or are there other factors at play such as a history of racism? In general, for minorities the evidence is incomplete: social and economic deprivation contributes to the health pattern of minorities, but does not explain all of it. Structural racism is probably part of the causal chain.

Participant: Policy-makers want clear examples of policies that are proved effective, in the not too long term, and clearly measurable. The question for researchers is, how can we make a "business case" of the evidence towards an intervention, to cross the bridge from evidence to policy?

Professor Marmot: How could "green" (environmental) policies help to improve health? If one does not take into account health inequalities while developing green policies, one could actually be widening them. One should develop the measures in such a way that they actually help to reduce health inequalities.

Participant: Scottish politicians have not been supporting free early childhood education for all because they believe people of "high quality" will make their children succeed and people of "low quality" will not. Thus a moral set of views makes them not hear the evidence.

Professor Marmot: You could make a moral counterargument: you are blaming children for their choice of parents. It is how you use the evidence in the debate.

Participant: My conclusion is that we should be pragmatic in developing interventions on the basis of evidence and not wait too long for even better evidence.

Professor Marmot: I learned as a physician "*primum non nocere*": first, we should do no harm. That is the first principle when the evidence is incomplete. But incomplete evidence cannot be a reason for inaction. We need to use best judgements on the available evidence, and consider the harm of inaction. There will be good reasons to reduce child poverty regardless of strength of the evidence base on reducing health inequalities, in 50 years time.

Professor Lundberg: Research is more than just methods, it is also interpretation and judgement. But researchers should also be careful not to voice their own personal belief as evidence. Be clear about where there is evidence and where not, and where you have other (moral) arguments.

Professor Marmot: First, you should tell the truth to each other as scientists. We make progress by arguing. Second, use the evidence we have. Third, engage other people on what kind of society we want: let's have that discussion.

Participant: What the researchers find interesting and feasible to study guides what is researched. You therefore miss the most difficult and complex questions and mechanisms. For example: what is the health impact of a hospital? Within natural experiments, researchers are often in the position to influence the policies themselves by their research. And not acting is also acting.

Professor Marmot: We should think carefully about absolute and relative risks and how they should play a role in policies. For example, relative inequality in infant mortality in the UK is now a factor three, but the absolute level is very low now. In the past, the relative difference was actually lower but the absolute difference much higher. So, from a policy point, although the relative risk has been rising, the fall in absolute risk is much more important here.

WHAT DO INTERNATIONAL POLICY-MAKERS NEED TO KNOW? DR CHRIS BROWN (WHO EUROPE)

Chris Brown was unable to attend.

A7.15 WHAT DO NATIONAL POLICY-MAKERS NEED TO KNOW? PROFESSOR CHIARA SARACENO (UNIVERSITY OF TURIN)

Chiara Saraceno presented her views on what we should know to be able to inform policy-making and how we can get there. Before being able to analyse the impact of a given policy, or of a set of policies, one should know how the policy is implemented, and whether or not it is beneficial in practice and for whom. Thus we need more research on actual access to interventions and on the different reasons why access might be constrained for some social group (and for different age groups). Data on the organization and implementation of the health service in the field, social class and regional differences in access to its various levels should be collected systematically, because even where there is a national system there may be local differences in availability and social class differences in actual access. For example: despite a national policy for children under 3 to visit a paediatrician annually, the poor groups visit them less because paediatricians have such a high work load that they cannot see all children and thus are not actively inviting them to come.

We know that there is an intergenerational transmission of inequality also in health. But we need extensive research and data on the mechanisms and drivers of this transmission to understand what works and what does not at the policy level.

It is not enough to know the drivers of health inequality and the impact on them of social policies; we also need to investigate the reverse: how policies may reduce the impact of bad health on income inequalities and educational achievements.

In addition to the systematic collection of data on the organization of, implementation of, and access to health services, ongoing policies not directly related to health might be used as an opportunity for natural experiments. For instance:

- There are data on the impact on (inequalities of) cognitive development of attending early childhood education and care. It might be useful to develop similar/parallel studies on the impact on inequality on children’s health (1) of attending early childhood education and care; (2) of their parents being exposed

to parental education programmes; (3) of having regular health checks; and (d) of having access to school meals.

- The impact on the health of disadvantaged persons belonging to various age groups and household composition receiving minimum income benefits might be studied either longitudinally or in comparison with similar individuals not receiving it for some reason, taking into consideration not only the financial benefit in itself, but the specific characteristics of its conditionality and the other forms of support that integrate it.
- In many countries all women aged 50–69 are invited to a regular annual screening for breast cancer, free of charge. It is an opportunity to study (1) whether there are socio-economic and regional differences in taking up this opportunity and why; and (2) if these differences have an impact on whether or not a cancer is detected at an early stage.

The following conclusions can be drawn:

- There are interaction effects, not always clear causal links between drivers and outcomes. This may undermine any attempt at pinpointing any specific, singular policy as efficacious in reducing health inequalities.
- Before/instead of trying to change the behaviour of the disadvantaged, policies should focus on treating them equitably: in the provision of health services, but also in the provision of opportunities and resources to choose the life they consider good for themselves.
- Thus it is important to focus research/have data on the actual working of general/universal policies for different social groups and particularly for the more disadvantaged ones.

A7.16 MODERATED DISCUSSION

Professor Costa started the discussion by giving a few reflections on "what we should know". In the Berlin workshop we concluded that there is only limited evidence of a direct causal role of income, education and occupational class in health inequalities. These limitations have never prevented policy-makers from combating poverty, creating employment or improving educational opportunities. This is because these policies are not decided for their marginal impact on health. It is only in some cases that the marginal impact on health (or health inequalities) will make a difference. One recent example is the closure of an iron factory in southern Italy, where saving 15,000 jobs could be in conflict with the severe pollution caused in surrounding deprived neighbourhoods.

Professor Saraceno: Policy-makers are not primarily interested in sound scientific evidence to develop and evaluate their policies. They are more interested in moral arguments.

Professor Mackenbach: It is, of course, comforting that we can make recommendations for policies even without a lot of evidence. But how could we prioritize further research? And how could we increase the "learning speed" here?

Participant: One important topic is the COVID-19 pandemic. What are the health consequences related to mass unemployment for example?

Participant: How can we convince other "investors" in health such as development banks, not only government policy-makers? And policy-makers need an actual plan for making a policy, not only scientific information about what is wrong and why. We should also be proactively looking towards big societal changes, such as the green and digital transitions: how will this affect health inequalities? We should be more future-oriented as researchers. And how could we tackle policies and developments that are currently harming health equality?

Participant: We should also think about the consequences of demographic and compositional changes, including ageing and increasing education both for national health trends and for health inequalities. For example, the recent massive compositional changes concern a massive expansion of higher education, in some countries already exceeding 50% in youngest cohorts. Is it realistic to assume a further expansion of higher education? If the answer is "yes", then to what extent? It is important that, despite the increasing size of the highest education group (presumably making this group less and less selective), longevity and health advantages of highly educated people have remained substantial or even increased further. The ongoing compositional changes bring new questions and methodological challenges related to quantitative measurement and qualitative interpretation of changes in group-specific health inequalities. Understanding and considering dimensions of compositional changes at the population level is the first necessary step before going on to more complex causal analyses at the individual level.

Participant: Children should at a very young age be better educated about healthy behaviour.

Professor Marmot: On the other hand, differences in the level of education as a whole are a more important factor than health education itself.

Professor Bambra: There has been a lag between development of policies and the data resulting from the UK health inequalities approach. You could also use intermediate outcomes/proxies (e.g. reductions in child poverty) to get evidence on health (e.g. infant mortality rate) and inform policy sooner.

Participant: The current funding opportunities are much better suited for studies aimed more directly at health inequalities, so the more downstream interventions, as opposed to the more macro-level factors. With regard to healthy schools: we have

been able to change the curriculum and lunch at schools, but it has cost so much time to set this up and study it. You could also analyse the factors within the approach itself and tweak them, so not set up a whole new prospective study.

A7.17 SUMMARY AND CONCLUSIONS, PROFESSOR MARGARET WHITEHEAD

Margaret Whitehead gave her summary of the workshop and presented preliminary conclusions.

What do we know already about effective actions to reduce health inequalities?

- There are insights from theory and practice in many sectors about how health inequalities could be reduced.
- From the umbrella review, legal and fiscal measures to improve living and working conditions and create enabling environments have a positive impact on health.
- Health is rarely a primary aim of policies outside the health sector, but these are still important for our aim.
- Some of the individual-level interventions (i.e. person-based health promotion on knowledge and skills) are effective for improving average health, but very few reduce inequalities.
- There is an "inverse evidence law": there are many studies for downstream small-scale interventions, but fewer on macro-policies with the greatest potential impact for population health.
- "*There may not be one mega-study that shows that poverty in childhood, via early child development and ACES, influences inequalities in mortality at age 60. That should not be seen as a gap in knowledge*" (Marmot). We already have compelling evidence from a broad spectrum of sources of the impact of child poverty on health.

Areas of debate include the following.

- How are inequalities formed in dynamic processes and interplay of conditions?
- What is the role of agency in the sociological sense, that is, people's actions and reactions to the conditions they find themselves in, including policies?
- What are the implications for policy recommendations of large variations within strata as well as between strata?
- How can funding bodies be influenced to structure research grant opportunities to better suit the type of studies needed to address health inequalities?
- Which is more important for policy-making: measures of relative or absolute inequalities?

What is needed for policy-making?

- We always need to make policy on the evidence we currently have, so make the best of it.
- Or, in the words of Michael Marmot: "*there are many areas where we can conclude there is enough evidence now*" Make recommendations on best judgement.
- Do not stop at the question of "what works?" but go on to look at "*when* and *how* things work" in detail: what are the "active ingredients" or effective components of a policy in specific contexts?
- Policy-makers are asking for help in how to implement more equitable policies: for example, how to put proportionate universalism into practice; how to implement "building back fairer" in the aftermath of the COVID pandemic.
- Develop an early warning system on adverse impacts of policies.
- Policy is rarely constructed from principles, but often starts with a reform that has political support: evaluation needs to adapt to the real world.
- Timeliness: policy-makers need answers now, not in several years.

What are the knowledge gaps?

- From the umbrella review, reviews tended to examine specific, small-scale, single interventions (e.g. changes in housing quality) or single policy areas (e.g. work environment), not holistic changes.
- Many evaluations of interventions and policies still do not assess differential effectiveness (what are the effects on different groups?).
- In political science, there has been a shift towards quasi-experiments and a corresponding devaluing of (and loss of expertise in) other evaluative methods and study designs, for example case studies, qualitative interviews and process-tracing studies. Health equity research needs to re-discover, and re-value, these neglected methods.
- There is a need for more comparative case studies, for example studies of macro-level bundles of policies.

How should we best study policies and interventions?

- The various methods are best seen as a tool-kit rather that an evidence hierarchy.
- Chose the most appropriate methods to answer the specific policy question.
- There is a trade-off between precise answers to limited questions and less precise answers to broader questions.
- We need a broad range of studies: policy case studies, qualitative insights, observational/modelling causal factors, natural policy experiments, evidence synthesis—all are needed and can be improved/combined.
- Judgements in the light of all the evidence from different sources come into play in drawing conclusions about effectiveness.

- It would be quite wrong to suggest that there are certain gaps in knowledge that a limited suite of well-designed studies would fill. The world of health inequalities is more complex than that. And so is the scientific enterprise of reaching judgements.
- Finally, a confidence-boost from Mark Petticrew: public health too often allows itself to be hamstrung by demands for perfect evidence, and this plays into the hands of the enemies of public health. Public health needs to be more confident (as other disciplines are not often bedevilled by a lack of a confidence).

What are priorities for future research?

- Start by asking policy-makers what problems they struggle with.
- Then involve other people in a discussion on what kind of society we want, as part of public and policy engagement in health inequalities research.
- Conduct policy implementation research.
- Evaluate both positive and adverse health effects of population-wide policies by socio-economic status and ethnicity.
- Specific priorities mentioned: combat inequalities in working conditions, unemployment, smoking and drinking, and children’s life chances/poverty

ANNEX 8.

EXTERNAL REVIEW

ALLEA and FEAM organized a peer-review procedure to receive feedback on the draft report, and to ensure the quality of the final report. ALLEA and FEAM asked their Member Academies to nominate peer reviewers and the committee was asked to provide suggestions as well. Peer reviewers should be independent from the committee and its members and have expertise in the following areas:

- Background in a relevant scientific discipline (e.g. epidemiology, sociology, economics).
- Experience with conducting research into health inequalities.
- Active interest in applying 'counterfactual' approaches to causal analysis.

The peer reviewers were selected by the Boards of ALLEA and FEAM to ensure an appropriate number of reviewers and a balance in expertise and geographical coverage.

Reviewers were requested to review the draft report on the following criteria: factal errors, omissions, consistency and overall quality.

The report has been reviewed by the following persons:

- Professor Mihajlo Jakovljević, University of Kragujevac, Serbia

- Dr Mall Leinsalu, Institute for Health Development, Tallinn, Estonia

- Professor Alastair Leyland, University of Glasgow, UK

- Professor Jaap Seidell, Free University, Amsterdam, The Netherlands

- Dr Karri Silventoinen, Univeristy of Helsinki, Finland

The reviewers' comments were consequently used by the committee to improve the report. The committee presented the final report together with the reviewers' comments and a response to those comments to the ALLEA and FEAM boards for approval.

About ALLEA, the European Federation of Academies of Sciences and Humanities

ALLEA is the European Federation of Academies of Sciences and Humanities, representing more than 50 academies from over 40 countries in Europe. Since its foundation in 1994, ALLEA speaks out on behalf of its members on the European and international stages, promotes science as a global public good, and facilitates scientific collaboration across borders and disciplines. Jointly with its Member Academies, ALLEA works towards improving the conditions for research, providing the best independent and interdisciplinary science advice, and strengthening the role of science in society. In doing so, it channels the intellectual excellence and experience of European academies for the benefit of the research community, decision-makers and the public.

About FEAM, the Federation of European Academies of Medicine

FEAM is the European umbrella group of national Academies of Medicine, Pharmacy and Veterinary Science, or national Academies via their medical division. It brings together under one umbrella 23 National Academies representing thousands among the best scientists in Europe. FEAM's mission is to promote cooperation between National Academies of Medicine and Medical Sections of Academies of Sciences in Europe; to provide a platform to formulate their collective voice on matters concerning human and animal medicine, biomedical research, education, and health with a European dimension; and to extend to the European authorities the advisory role that they exercise in their own countries on these matters.

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