Differential vulnerability and susceptibility: how to make use of recent development in our understanding of mediation and interaction to tackle health inequalities

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Abstract:

This paper discusses the concepts of vulnerability and susceptibility and their relevance for understanding and tackling health inequalities. Tackling socioeconomic inequalities in health is based on an understanding of how an individual's social position influences disease risk. Conceptually, there are two possible mechanisms (not mutually exclusive): there is either some cause(s) of disease that are unevenly distributed across socioeconomic groups (differential exposure) or the effect of some cause(s) of disease differs across groups (differential effect). Since differential vulnerability and susceptibility are often used to denote the latter we discuss these concepts, their current use and suggest an epidemiologically relevant distinction. The effect of social position can thus be mediated by causes that are unevenly distributed across social groups and/or interact with social position. Recent improvements in the methodology to estimate mediation and interaction have made it possible to calculate measures of relevance for setting targets and priorities in policy for health equity that include both mechanisms i.e. equalize exposure or equalize effects. We finally discuss the importance of differential susceptibility and vulnerability for the choice of preventive strategies including approaches that target high risk individuals, whole populations and vulnerable groups.

Key messages:

- Priority setting for tackling health inequalities could benefit from estimating both differential exposure to- and differential effects of- mediators.

- New methodologies have been developed that make it possible to decompose the effect of social position on health into four components of mediation and interaction.

- Knowledge of differential susceptibility can be used to target susceptible groups, but also to identify exposures where a general reduction of exposure would benefit more susceptible and often less privileged groups.

- Knowledge of differential vulnerability and identification of vulnerable groups and communities is on other hand essential for decisions on allocation of resources that can widen the capabilities for action.

Introduction

Tackling socioeconomic inequalities in health is based on an understanding of how an individual's socio-economic position (SEP) influences risk of disease and consequences of disease. While the latter is strongly influenced by the health care system, the former is generated by exposure to causes of disease. There are here, in theory, two possible mechanisms (not mutually exclusive): there are either some cause(s) of disease that are unevenly distributed across socioeconomic groups (differential exposure), or the effect of some cause(s) differs across groups (differential effect - often called differential vulnerability or susceptibility as discussed below). While the first mechanism has been extensively studied, the second has been subject to much less theoretical analysis and empirical research. Yet it might play an important role and have distinct implications for preventive health policies.

Let us illustrate with an example from alcohol epidemiology: It has been found that mortality rates from alcohol-related conditions in many countries are higher in more disadvantaged groups[1]. That is surprising since high alcohol consumption in many of these countries is more prevalent in more advantaged groups[2]. The question is then whether there exists a differential effect of alcohol in different socioeconomic groups. Recently a Danish cohort study[3] found evidence of such a differential effect. While the rate difference among men for drinking >28 drinks per week compared to 0-14 drinks was 577 cases per 100,000 person-years of alcohol related disease among well-educated, the rate difference among those with short education was 866 per 100,000. This means that the differential effect can be expressed as the difference in effect: 866-577=289 (95% CI = 123-457)[3]. Studies from Finland and England have similar

findings[4,5]. Some studies on the role of differential exposure and differential effect have been carried out on cardiovascular and mental health outcomes[6-12], and in particular in the last few years more papers have been published. But studies on differential effects across socioeconomic groups are still scarce and the applied methodologies very greatly. Assumptions are often made that effects, at least in relative terms, are the same across socioeconomic groups[13] (which means that they might differ in absolute terms).

The potential relevance of differential effect for understanding health inequalities and for making the policies to tackle them was raised several years ago[14,15] and pointed out by WHO in the work on social determinants of health[16]. There exist however in the literature a certain confusion about both conceptual issues and the methods used to estimate these mechanisms. The aim of this paper is therefore to contribute to the discussion of both the theoretical and methodological issues involved, to suggest the use of new methodologies developed on how to estimate mediation and interaction and to discuss the implications for public health policy.

Conceptual issues

Vulnerability and susceptibility

Most of the current studies in social epidemiology that analyze differential effects use the term differential vulnerability. The concept of vulnerability is however also used by many other very different disciplines ranging from bioethics to environmental science, psychology and genetics.

Vulnerability was a key concept in the early version of the international bioethical guidelines for medical research, there used in the sense of lack of individual

autonomy[17]. Henk ten Have has recently proposed a more political analysis and a contextual definition where humans are seen as vulnerable since they are dependent on other people. As we live in a context where resources and power are unequally distributed in society some people become more dependent and vulnerable than others[18]. Researchers within bioethics, environmental sciences and some areas of epidemiology have now adopted a functional definition of vulnerability that covers three dimensions: *exposure* to hazard, *susceptibility* i.e. effect of exposure and *capacity of response* by coping and adaptability[19-21]. This definition has recently been used by the US Environmental Protection Agency in their analysis of health effects of climate change[22]. Here vulnerability not only refers to individuals but also to communities and systems. From an epidemiological perspective this definition is problematic since it tends to conflate exposure and susceptibility. Capacity of response is however important as a separate dimension as it reflects power and resources to change exposures and to cope with, adapt to and recover from their effects. It raises– from an inequality perspective - interesting research questions of what determines people's options and capabilities to respond and act, and therefore has relevance for health promotion[23,24]. To avoid confusion it might therefore be preferable in epidemiology (as we will do in the rest of this paper) to use the term differential *susceptibility* when referring to differential effects. Differential vulnerability should then be used when it is relevant to include all three dimensions: exposure, susceptibility and capacity of response.

In epidemiology the definition of susceptibility is closely linked to Rothman's sufficient-component-cause model[25], where component causes complement each other to generate a sufficient cause. The effect of one cause depends on the exposure to other – interacting - component causes of the same disease. Susceptibility to the health effects

of one specific cause can then be defined as the set of complementing genetic or environmental causes sufficient to make a person contract a disease after being exposed to the specific cause[26]. This definition provides an understanding of susceptibility as conditional causation and causal interaction.

While interaction is a clear empirical criterion for differential susceptibility the estimation of mediation is not only reflecting differential exposure but will also be influenced by differential susceptibility (as it is often estimated by comparing the effects of exposure before and after adjusting for the potential mediator.

Measurement issues:

Interaction and mediation

For priority- and target-setting in policies aiming at tackling health inequalities different estimates are relevant. It is important to be able to estimate how much of the effect of SEP on health would be removed if a mediating exposure is removed - what has been called the "proportion eliminated"[27] - or if the social distribution of the mediator is changed. But it might also be important to estimate how much the inequality would be reduced if an interaction between socio-economic position (SEP) and the mediator is removed, for example by eliminating another interacting mediator. Achieving unbiased estimates of mediated (indirect) effects, direct effects and effects due to interaction between SEP and mediators has however turned out to be difficult. It is only now 40 years after the first efforts in social epidemiology that VanderWeele has presented an elegant solution on how to decompose the health effect of an exposure (e.g. SEP) into

its components created by mediation and interaction. Four different pathways are involved, each representing a mechanistic alternative[27,28].

i) SEP has a direct effect on disease even among those who are not exposed to the mediator ("controlled direct effect");

ii) The effect of SEP on disease is dependent on the exposure to the mediator and vice versa: the effect of the mediator is dependent on SEP i.e. they interact, but SEP does not influence exposure to the mediator ("reference interaction");

iii) The effect of SEP is (as in ii) dependent on exposure to the mediator (and vice versa), but here SEP has an influence on the exposure level of the mediator ("mediated interaction");

iv) The effect of SEP on disease is entirely mediated by differential exposure to the mediator ("pure indirect effect").

The health effect of SEP mediated by what we have called *differential exposure* to a mediating cause is expressed by the sum of component (iii) and (iv), while *differential susceptibility* is expressed by the sum of component (ii) and (iii) – i.e. "portion attributable to interaction"[27]. The *portion eliminated* by removing the mediator is the sum of (ii) + (iii) + (iv).

The statistical analysis of interaction still builds on some critical assumptions such as the functional relationship or dose-response relationship between exposure and disease risk[29]. The importance in mediation analysis of controlling not only for exposure-outcome confounding but also for mediator-outcome confounding has been emphasized earlier[28], but the fact that many mediator-outcome confounders might be influenced by

SEP might be less of a problem since the decomposition includes controlled direct effect and not natural direct and indirect effects[28].

A very simple calculation of the relative importance of differential exposure and differential susceptibility and the decomposition of effects is made in Box 1.

[Box 1]

Interaction analysis demands much statistical power since it depends on the number of double-exposed cases. Interaction analysis is in addition very sensitive to misclassification of exposures, in particular when the misclassification of one exposure is dependent on the other. In social epidemiology it might not be unusual that a mediator is differentially misclassified across SEPs. The interaction effect will then often be underestimated[30].

Empirical examples and mechanisms

Social epidemiology

In social epidemiology the issue of differential susceptibility was raised already in the early 1970s. Dohrenwend found in 1973 that differential exposure to stressful life evets could only partly explain social inequalities in distress[31], and that the correlation between stressor and distress was stronger among lower status groups. Syme and Berkman[32] noted in 1976 that the same social patterning was found for many (albeit not all) diseases with very different etiology and suggested the existence of a *generalized susceptibility* as an explanation. Kessel[33] and later Grzywacz[34] analyzed more systematically both differential exposure and differential susceptibility to stressors. None of these early studies applied an understanding of susceptibility as causal

interaction. That was later done by Hallqvist and colleagues[6], and recent studies have analyzed departure from additivity as criterion for differential susceptibility[11] and some of them have applied additive hazard models for survival analysis[3,8,9]. Many studies still compare relative risks across socioeconomic strata[4,5,10,12,13].

The findings on cardiovascular outcomes are heterogeneous. Some find a clear differential susceptibility to the effect of smoking while findings for hypertension and BMI are mixed. The methodologies applied are, however, still very different, which might explain some of the heterogeneities. None has so far applied VanderWeele's decomposition and as a result, they cannot fully separate the effects of differential exposure and differential susceptibility.

Susceptibility at the molecular level

Individual variation in susceptibility to health effects of many exposures might often be genetically determined. If genotypes associated with diseases are unequally distributed across SEPs they might have relevance for socioeconomically differential susceptibility. The relevance of this for health inequalities is however still unclear[35] and the few population-based studies that exist have not shown any association between, for example, diabetes-related polymorphisms and SEP[36]. But even equally, distributed genes are obviously of relevance if they interact with unequally distributed exposures[37].

The growing insights of epigenetics have, however, shifted the focus from gene sequence to gene expression. Environmental epigenetics has shown that a broad range of physical and social exposures may influence how genes are regulated and modify

their influence on disease etiology[38]. Studies have, for example, shown that early childhood SEP is associated with differential methylation of several gene promotor regions[39,40]. Even during adulthood gene expression can be modified by SES in ways that influence inflammatory reactions of importance for susceptibility to causes of both chronic disorders and infections[41]. So even if disease related genotypes are not unequally distributed across socioeconomic groups then epigenetically modified gene function might be. This leads to the hypotheses that epigenetic changes might mediate the effects on health of SEP. An exposure-generated epigenetic change might also modify the effect of another exposure if its effect depends on the expressed gene[38,42]. The ability of a cell to respond to a specific exposure such as social stress may thus be dependent upon the underlying epigenetic state i.e. whether the cell is methylated in the region of the gene involved in responding to stress[42]. If that response is silenced, then the organism might not react appropriately to stress exposure, and the effect of repeated or long-term exposure might then cause allostatic load[43].

While allostasis and allostatic load might be both a cause and an effect of epigenetic changes it might also be a mechanism in its own right of relevance for differential susceptibility. Allostasis refers to the multiple adaptive responses to stress including neuroendocrine, autonomic, immune and metabolic mediators as well as health behaviors. These responses might initially be adaptive but repeated over a long time they might create allostatic load, that in itself increases the susceptibility to further stressor exposure[37,43]. With allostatic load the normal adaptive responses to stress are worn out or otherwise dysregulated. Increased susceptibility to stress then occurs, not as

a result of interaction between different mediators, but as an interaction between earlier and later exposure to the same or similar stressors.

Vulnerability at the community level

Many exposures such as environmental air pollution and climate change, infectious agents and social contexts are characterized by being non-differential in the sense that everybody in the population is exposed. Their health consequences are however sometimes still very unequally distributed across communities[22,44]. The question of what makes communities vulnerable to environmental exposures has stimulated much research. Models of both Turner[20] in US and Birkmann[21] in Europe apply the concept of vulnerability to the community level, covering the three dimensions: exposure, susceptibility and capability of response, including the options and ability to change exposure or susceptibility in the population. This aspect of capability was in focus in UNDP's annual Human Development Report in 2014 that focused on vulnerability[45]. The dimension of capability is according to these models what primarily makes vulnerability different from susceptibility in its policy relevance. Vulnerability has been operationalized into a mapping technology and applied in epidemiological studies that e.g. aim to understand why water/related and vector-borne diseases such as Dengue fever show a very unequal distribution between similar equally exposed areas[46]. Measures of vulnerability then include different items that represent each of the three dimensions, but interactions between them have not been studied. A similar approach has been suggested in studies of the recent, alarming (and so far poorly understood) case of geographical and social variations in susceptibility to the teratogenic effects of Zika virus. Cases of Congenital Zika Syndrome including microcephaly have accumulated in

poor urban areas of North Eastern Brazil, while cases of Zika virus infections are spread over most of Latin America[47].

Policy implications:

The existence of differential susceptibility and vulnerability influences the choice of preventive strategies to tackle health inequalities. How different preventive programs actually impact on health inequalities depend on at least four aspects[15]: *differential implementation i.e.* how programs are implemented and reach different population groups*; differential effectiveness* in how an intervention influence exposure to risk factors in different population groups all reached by the same intervention; *differential susceptibility,* i.e. how a certain change in exposure levels translate into changing incidence of disease in different groups. There might finally also be *differential capability* of how different actually can change exposures, and cope with them.

A key question in preventive policies is the balance between three options[23,48]: 1) the high-risk strategy of identifying and treating high risk individuals; 2) the population strategy moving the whole distribution of exposure; 3) "vulnerable population approach" targeting population groups with high levels of vulnerability including at least one of the dimensions of exposure, susceptibility and capability[24].

The first option - the high-risk strategy - aims at identifying individuals with a high level of exposure and then treating them. If such identification is based on SCORE-charts[49] or similar instruments estimating total risk of a combination of often clustering and interacting risk factors, it can be argued that this approach takes into account the

existence of differential susceptibility. Recent analysis has shown, however, that combining SCORE estimates with data on educational level significantly improves the discriminatory power[50]. The main questions relating to equity effects in clinical prevention is about differential implementation and differential effectiveness of screening, treatment and follow up. Individual behavioral interventions require mobilization of an individual's resources and will thus often primarily benefit those with more capabilities [23,51].

The second option - the population strategy – is by definition reaching the whole population but the differential effectiveness will depend on what intervention methods are chosen. Broad information campaigns on smoking, physical activity and diet have been shown to be less effective in changing behavior among more disadvantaged groups, contributing to increased health inequalities[23,48]. In contrast, more "structural" universal measures such as increased tobacco tax and environmental legislation may have differential effectiveness in the opposite direction i.e. being more effective with low-income groups[48]. One important conclusion is, however, that when differential susceptibility exists, then also preventive interventions with equal impact on exposure across groups will have a stronger health effect among the more susceptible – which often will be the disadvantaged. That does not change the fact that vulnerable groups might still suffer larger health effects than others from exposure to the same reference dose level, and differential susceptibility might therefore be an argument for having stricter reference dose levels when heterogeneous populations include more vulnerable segments[44]. Schwarz has for example shown that the effect of lead exposure on child development is stronger among children living in poverty[44].

Because some universal population measures due to differential effectiveness may widen inequalities, it has been argued that such measures should be combined with a strategy that targets vulnerable groups[23]. Estimates made by modelling have however shown that programs aiming at empowerig populations in deprived areas may not succeed in reducing health inequalities, when fundamental contextual causes such as neighborhood economical segregation is not addressed[51]. This illustrates the importance of viewing vulnerability as a contextual phenomenon[18]. The net result will clearly depend on what resources are addressed. The theoretical understanding favors a policy that focuses on the capability dimension of vulnerability by increasing contextual and not only individual resources that widen people's range of options and capabilities[46].

Conclusions:

Estimating both differential exposure and differential susceptibility to causes mediating the effect of social position is relevant in health inequality research. Recent methodological developments have made it possible to decompose the effect of social position on health into 4 components of mediation and interaction and to estimate absolute effects based on different study designs. Knowledge of biological mechanisms from epigenetics and stress research indicate that differential susceptibility might be highly relevant in social epidemiology. So too is the concept of differential vulnerability, though the empirical evidence is still sparse and needs to identify for which exposures differential vulnerability is particularly important.

Box 1

Does differential susceptibility matter quantitatively? -A theoretical but realistic example of decomposed effects

Let us assume we have two social groups – rich and poor. The incidence of ischemic heart disease (IHD) is 500 per 100,000 in the rich group and 1000 among the poor i.e. a *total effect* of 500 in VanderWeele's terminology[27]. Assume that this is partly due to differential exposure to smoking- that occurs with a prevalence of 8% and 20% among rich and poor respectively. We also assume that smoking has a relative risk of 3 in its effect on IHD without any confounding in both groups. (A relative risk that is constant across levels of other exposures is a common assumption[13]). This means that the rate difference is higher in the poor group since the overall incidence is higher. With this knowledge about incidence, exposure to mediator and RR for both groups it is possible to calculate the 4 components of mediation and interaction[27]. Lowering exposure to smoking in the poor group to a non-differential 8% in the poor group reduces the incidence among the poor to 828.6 and thereby reduces the absolute inequality between rich and poor by 171.4 i.e. the *total indirect effect*. If we can identify and eliminate the specific causes of the increased susceptibility to smoking among the poor we can remove the differential susceptibility so that the poor group has the same rate difference as the rich group for the effect of smoking. That will reduce the absolute inequality by 113.3 to 386.7 i.e. by 22.7%. This reduction corresponds to the *portion attributable to interaction* i.e. what we have called differential susceptibility. If we equalize both exposure and susceptibility, the incidence among the poor will be reduced to 783.3 and the inequality between rich and poor has then been reduced to 283.3 corresponding to the *controlled direct effect* without any mediator involved. The *reference interaction* corresponds to (828.6 – 500) – (783.3 - 500) = 45.3 and the *mediated interaction* is 113.3 - 45.3 = 68.0 per 100,000 i.e. what is left of the portion attributable to interaction when the reference interaction is removed. The *pure indirect effect* can then be calculated as 171.4 - 68.0 =103.4 i.e. what is left of the total indirect effect when mediated interaction is removed.

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