The contribution of time-varying measures of health behaviors to socioeconomic inequalities in mortality: How to understand the underlying mechanisms?

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ABSTRACT

A higher prevalence of unhealthy behaviors in lower socioeconomic groups contributes to socioeconomic inequalities in mortality. Recent cohort studies suggest that the contribution of health behaviors to socioeconomic inequalities in mortality is larger when measured repeatedly over time ("time-varying") instead of once only ("time-fixed"). Explanations for a larger contribution of health behaviors however, are hardly discussed in the current literature, and appear to be more complex than a widening of inequalities in health behaviors over time alone. We describe the use of time-varying health behaviors to examine socioeconomic inequalities in mortality, systematically list underlying mechanisms that may cause differences between time-varying and time-fixed models, and show that these mechanisms may be specific for each health behavior. The use of time-varying health behaviors advances our understanding of the explanation of socioeconomic inequalities in mortality, but underlying mechanisms must be carefully examined.

INTRODUCTION

Studies investigating explanations for socioeconomic inequalities in mortality have usually added material, behavioral and psychosocial factors to a model linking socioeconomic position to mortality during follow-up. They suggest that maximally half of these inequalities are due to health behaviors.[1-7] This contribution of health behaviors to socioeconomic inequalities in mortality is determined by the percentage reduction in the estimated association between socioeconomic position and mortality after inclusion of the mediating health behaviors in the model. Generally, the behavioral factors included in such mediation analyses are measured once (often at baseline) and therefore treated as 'time-fixed' mediators. In these cases, the underlying assumption is that health behaviors are fairly stable over time, and that the initial baseline measurement is a good indicator for life-long exposure. Since this is often not the case, some recent papers have started to include behavioral factors measured repeatedly during follow up. In these models, health behaviors were treated as so-called 'time-varying' mediators.[8-14] An initial study suggested that the contribution of health behaviors is greater when measured multiple times,[8] which is in line with findings in some but not all studies published ever since.[9-14] The main explanation given to a more prominent role of health behaviors is that repeated measures are able to account for an increasing socioeconomic gradient in unhealthy behavior over time. However, an increasing socioeconomic gradient is not the only possible explanation for differences in results between time-fixed and time-varying models. For example, the role of physical activity in the explanation of socioeconomic inequalities in mortality has been shown to increase when multiple measurements of physical activity are used, even in the presence of a declining socioeconomic gradient in physical activity.[8] Also, while inequalities in smoking increased over time, some studies have found no difference in the contribution of smoking between time-fixed and time-varying models.[8, 11] We argue that several mechanisms may cause differences in results between time-fixed and time-varying models, and that the extent to which they do so may vary by mediator. In this paper we briefly introduce the concept of time-varying covariates, systematically describe potential mechanisms that may lead to different results between time-fixed and time-varying models, and recommend how to report results of studies using time-varying models in order to advance our understanding of socioeconomic inequalities in mortality.

TIME-DEPENDENT MODELS

Socioeconomic inequalities in mortality are usually explored with a Cox proportional hazards regression where all covariates are only measured once, often at baseline:

$$h(t|SES, M, C) = h_0(t)\, exp(\beta_1 SES + \beta' M + \beta'' C) \quad (1)$$

In this model, h_0 is the baseline hazard, *SES* the indicator for socioeconomic position, *M* a vector of potential mediators, *C* a vector of potential confounders, and the β's a vector of regression coefficients. The hazard ratio of the mediators $exp(\beta' M)$ is independent from time *t*. This implies that the health behaviors are assumed to be fixed over the entire follow-up period, e.g. a smoker at baseline will be treated as a smoker during follow-up, even if the person quit soon after the baseline measurement. This may cause misclassification of the exposure. A solution to reduce this misclassification is to measure smoking several times over the follow-up period, and take behavior changes into account.

The role of repeatedly measured health behaviors can be explored with an expansion of the Cox proportional hazards regression in which time-dependent covariates are allowed in the model:

$$h(t|SES, M(t), C(t)) = h_0(t)\, exp(\beta_1 SES + \beta' M(t) + \beta'' C\,(t)) \quad (2)$$

In this model, the hazard at time *t* depends on the value of the mediators *M* and confounders *C* at time *t*. While *SES* is still measured at baseline only, repeatedly measured mediators and confounders are entered into the model as time-dependent covariates.

In studies that used this model to explain socioeconomic inequalities in mortality, the mediating health behaviors were measured as categorical variables (i.e. non-smoker, former smoker and current smoker). According to the technique, subjects are then re-classified as exposed or non-exposed at every assessment.[8-13] Since people changed their behaviors over time (some quit smoking, others became inactive), accounting for these changes should reduce misclassification and provide a more accurate measure of the exposure. Further, the quality of measurement could be increased by using time-varying behaviors, especially for behaviors that are difficult to measure (e.g. physical activity).

It is important to realize that exposure to a risk factor in time-varying models as described here is not equivalent to cumulative exposure in accumulation models.[15-17] For instance, a subject who quit smoking at the last assessment, is grouped together with all former smokers at that point in time regardless of when the other subjects quit. Thus, accumulation of unhealthy behavior at more than one point in time is not modelled, exposure is only re-classified at every assessment. Formally, the statistical methods do allow the modelling of time-varying mediators as more complex functions over time,

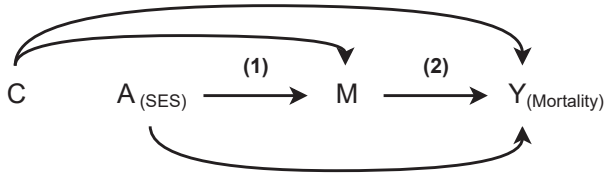
but these methods are often not employed since they also increase the potential for erroneous inference.[18] Preferably, the modelling of the mediators should be consistent with the hypothesis. So, when the causal process of health behaviors is hypothesized as a cumulative effect (e.g. supposed in some life-course models), one should try to model the mediators accordingly.

CAUSAL PATHWAYS OF THE MEDIATION ANALYSIS

Differences in the estimated contribution of health behaviors measured once only or measured multiple times can be caused by changes in one or both of the causal pathways of the mediation analysis (figure 1): (1) the association between socioeconomic position and health behaviors has changed over time, and/or (2) the association between health behaviors and mortality has changed when behaviors are measured repeatedly over time instead of once only.

Although socially patterned changes in health behaviors may have instigated this line of research and dominate the explanation, our main message is that the second pathway may be just as important in understanding differences in results between models with time-fixed and time-varying risk factors.

Figure 1. Mediation diagram with mediators M measured only once, exposure A (assumed to be effectively randomized), outcome Y, and confounders C.



(1) Association between socioeconomic position and risk factor
(2) Association between risk factor and mortality

Changing socioeconomic gradients in risk factors

The first pathway of interest ((1) in figure 1) is a change in the association between socioeconomic position and mediators (i.e. changes in the socioeconomic gradient of the health behaviors). A larger gradient in health behaviors will, ceteris paribus, lead to a larger contribution of the behaviors to health inequalities. Evidence of widening inequalities in health behaviors (and other cardiovascular disease risk factors)[19-23] makes this a likely and dominant explanation. Changing gradients can be related to progress in a behavioral epidemic over time, to a differential impact of policies and interventions between higher and lower socioeconomic groups or to different life-course

progressions between socioeconomic groups. First, trends in behaviors have been shown to be socially patterned.[24-26] For instance, smoking was first adopted by more advantaged groups, but the social distribution of smoking has reversed over time and smoking is now more prevalent among disadvantaged groups. Second, it has also been shown that policies and interventions targeted at promoting healthy behavior are often more effective among higher socioeconomic groups, resulting in a widening of health behavior inequalities.[27-30] Third, disparities in health behaviors may widen with increasing age. For instance, due to an accumulation of socioeconomic disadvantage over time it may be more difficult for lower socioeconomic groups to quit smoking in a later stage in life than it is for higher socioeconomic groups.

Some studies however, have reported a larger contribution of behaviors to inequalities in mortality even when the socioeconomic gradient in health behaviors reduced, for instance with regard to physical activity.[8] Clearly, the second pathway cannot be neglected.

Changing associations between risk factors and mortality

The second pathway of interest ((2) in figure 1) is a change in the estimated association between mediating risk factors and mortality. We list four mechanisms that may be responsible for changes in the estimates. The first and second are related to actual changes in the association between health behavior and mortality, the third and fourth are related to the methodological properties of the time-varying models.

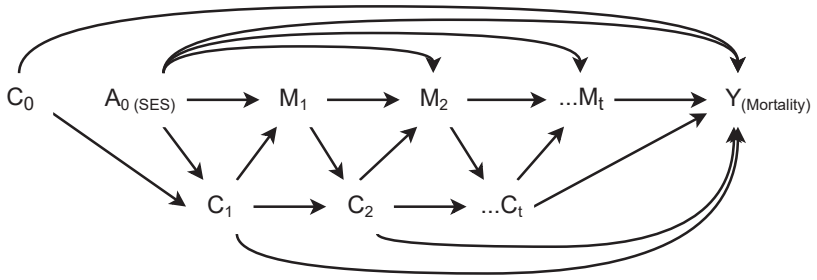
Firstly, taking changes in health behaviors into account reduces exposure misclassification and provides a better estimate of the association between health behaviors and mortality. Reducing misclassification leads, in most cases, to an increase in the observed association.[31]

Secondly, mortality risks of health behaviors may change over time. For example, better treatment of lifestyle related chronic diseases (e.g. the treatment of obese patients) [32, 33] or an improvement in the early detection of diseases caused by unhealthy behavior (e.g. lung cancer screening) will, ceteris paribus, decrease the association between behaviors and mortality. Those who become exposed in times of better treatment or more effective screening will thus have a lower mortality risk than those exposed at baseline, resulting in a decreased association in time-varying models. The impact of this mechanism will be even greater when such changes in relative risks differ between socioeconomic groups. This may be especially relevant with regard to health-related innovations, which are often adopted earlier by higher socioeconomic groups. [27, 34, 35] Mortality risks may also increase in time-varying models. For instance, the health benefit of light or moderate physical activity in leisure time may increase after retirement,[36-38] since work related physical activity no longer protects older adults from a sedentary lifestyle.

Thirdly, the time lapse that is needed for changes in behavior to have an effect on mortality may affect the differences in the estimates.[9, 18]. This concerns the time it takes for a risk exposure to increase a subject's mortality risk as well as the time it takes to lower a subject's mortality risk after changing from being exposed to being non-exposed. Importantly, these time periods differ by health behavior and require insights into the etiology of the risk factor. For changes that require a long time to affect mortality risks, and which are not captured in time-varying models, there is a large potential for exposure misclassification. For instance, a person who quit during follow-up after 20 years of smoking will be re-classified as a former smoker at the first follow-up measurement, but will remain at an increased risk of dying for many years.[39] If the person dies soon after the follow-up measurement, the event will be attributed to the 'former smoker' level of the exposure. While death may have been caused by smoking, it is not attributed to smoking in the model, resulting in an underestimation of the effect of smoking.

Fourthly, if changes in the mediators are associated with confounders, bias will be introduced in the time-varying models (figure 2).[10, 18] For example, the role of repeatedly measured physical activity can be confounded by the subject's health status. If poor health results in less physical activity among initially active persons, and if poor health results in shorter survival, the association between physical activity and mortality will be larger in the time-varying models, due to confounding. It may also be that perceived or diagnosed poor health triggers favorable behavioral changes, such as quitting smoking or increasing physical activity. Again, for the purpose of understanding inequalities in mortality this is even more relevant because the first example may occur more often among persons in lower socioeconomic groups and the second example more often among higher socioeconomic groups. Potential time-varying confounding can be checked when data is available (i.e. examine the association between confounders and subsequent health behavior). Controlling for time-varying confounding however, is not possible with conventional regression methods and requires the use of more sophisticated methods, such as marginal structural models or g-estimation.[10, 40, 41]

Figure 2. Mediation diagram with time-varying mediators M, exposure A (assumed to be effectively randomized), outcome Y, and time-varying confounders C.



CONCLUSION AND IMPLICATIONS

Some recent studies have analyzed health behaviors as time-varying mediators and estimated they contribute up to 75% to socioeconomic inequalities in mortality depending on the context.[8-13] Moreover, these studies suggest a tendency that the contribution of health behaviors is larger when longitudinal data of health behaviors are used.[8, 11, 13] We have argued that several mechanisms may be responsible for differences between time-fixed and time-varying models and that the extent to which they do so may vary by health behavior. Interpreting these results requires examination of possible changes in both pathways of the mediation analysis and cannot solely be attributed to socially patterned behavioral changes. Clearly, the same applies to studies on other groups of mediators, such as material and psychosocial factors.

The mechanisms listed here are relevant for the general adult populations and some may gain in importance if populations are getting older (e.g. time-varying confounding by health status). The choice for either a time-fixed or time-varying model depends on the context of the study. In some studies, the time-fixed approach would be preferable (e.g. because time lapse and confounding may seriously impact upon the results); in others the time-varying approach may be preferred (e.g. when inequalities in the risk factors widen over time and it is reasonable to assume time lapse and confounding are not an issue). To aid the interpretation, we recommend future studies in this field to explicitly discuss possible explanations for changes over time in both the socioeconomic gradient in risk factors and the association between risk factors and mortality. Since mechanisms may differ between risk factors, these results should also be provided for separate risk factors.

In sum, the use of time-varying mediators advances understanding of the explanation of socioeconomic inequalities in mortality, but underlying mechanisms must be carefully examined.

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