Commentary: Selected samples and nebulous measures: some methodological difficulties in life-course epidemiology

M Maria Glymour

Accepted 17 April 2007

Introduction

Ramsay et al.’s article contributes to a growing body of research on early life characteristics that predict health in adulthood. This research demonstrates that adults who lived in deprived socio-economic circumstances as children are more likely to suffer from cardiovascular disease than adults who had privileged childhoods; an association that holds even among people with comparable indicators of adult socio-economic position (SEP). These articles provide a welcome impetus to consider how adult health is shaped by early life experiences, but they face a number of methodological problems that compromise causal inference regarding the effects of childhood social conditions on adult health. In this commentary, I wish to focus on just two of these problems: loss to follow-up and inadequate measurement.

Throughout, I assume that the primary causal question of interest is how adult health would differ if we intervened to change childhood SEP, and a secondary causal question is how...
adult health would differ if we intervened to change not only childhood SEP but also adult SEP or adult behavioural risk factors. My goal in highlighting these difficulties is to prompt life-course researchers to present evidence addressing these possible biases, and improve our ability to interpret the now well-established association between early childhood circumstances and adult health.

Methodology
What counts as loss to follow-up in a life-course study?
Suppose Ramsay et al. had conducted a randomized trial to estimate the effect of childhood conditions on adult health. In the hypothetical trial, children would be randomly assigned to deprived circumstances or advantaged circumstances, and each child followed into adulthood to establish his or her risk of coronary heart disease (CHD). As with any randomized trial, the researchers would report the loss to follow-up, i.e. the percentage of people who were randomized to each exposure condition but were not included in the outcomes data. With a randomized trial, it is simple to see why this is important: if the treatment affects loss to follow-up, this can create a spurious association between the exposure group and the outcome of interest. This sort of selection process is equally relevant in observational studies and in trials. Loss to follow-up between the time of exposure and the outcome assessment can bias the association of the exposure and the outcome if there are unmeasured common causes of loss to follow-up and the outcome. It is especially relevant in life-course epidemiology because the exposure and outcomes are frequently separated by decades.

How can we calculate the loss to follow-up rates for a retrospectively reported exposure such as childhood social conditions? In our hypothetical trial, who exactly comprises the study sample of interest? The British Regional Heart Study (BRHS) includes, roughly, men born 1920–40, who resided in one of 24 enrolment towns in the years 1978–80; the Ramsay analysis restricts to adult BRHS participants who reported childhood social circumstances in a 1992 interview. To simplify, ignore the possibility of migration and assume the study sample comprises children residing in one of those 24 towns, born in the period 1920–40 and randomized to exposure at age 10 (the oldest age participants were instructed to consider in their reports of childhood social conditions). To estimate loss to follow-up, we need to know what percentage of children in these towns died between ages 10 and 52–73 (the age range of the sample in 1992, when follow-up for CHD began). This information is rarely reported in studies of childhood social circumstances and adult health, but we can estimate it using national mortality data.

In the US, 45% of males born in 1920 who survived to age 10 died by age 72; British survival rates were worse. Later cohorts experienced correspondingly less selection before study enrolment, but even for later cohorts, the selection fraction was not trivial. Loss to follow-up does not necessarily induce bias, and any bias that does occur may lead to an underestimate of the effect of early life conditions on old age outcomes. Unfortunately, overestimation of effects is also plausible. For example, overestimation could occur if childhood deprivation reduces survival (say with a relative risk of 0.8); an unobserved factor ‘U’ impairs both survival (say with a relative risk of 0.7) and adult health; and U and childhood deprivation interact to influence survival such that their joint effect is less (closer to the null) than multiplicative (i.e. the relative risk of survival for those with U and exposed to childhood deprivation is >0.56 compared with individuals with neither U nor childhood deprivation). In this case, the survivors in the no childhood deprivation group will tend to have been selectively culled of anybody with the harmful factor U, relative to the survivors in the childhood deprivation group. Thus, childhood deprivation will come to be spuriously associated with the unobserved risk factor U, and this will lead to an overestimation of any harmful effect of childhood deprivation on adult health. This would be a problem even had we originally randomized childhood deprivation as in the hypothetical trial, and poses a similar threat in the context of an observational study.

With loss to follow-up approaching 50% in some groups, and compelling evidence that the exposure of interest affects this loss to follow-up, it is worth some attention. At a minimum, an estimate of loss to follow-up rates within exposure groups should be reported in studies in which the exposure and the outcome are separated by long periods of time. Even if this is estimated from external data sources, it may be helpful in sensitivity analyses. More ambitiously, the next generation of life-course research might attempt to directly assess how childhood social conditions and biological vulnerabilities interact to influence survival.

Ramsay et al. take a useful step to address this source of bias by examining how the associations between early childhood social class and adult CHD differ between early-century, highly selected birth cohorts and later, less selected birth cohorts. They report the associations are present in both groups, which is an encouraging suggestion that selection is not biasing the results.

What are we measuring and how well are we measuring it?
As Ramsay et al. note, ambiguity about what we are measuring with retrospective childhood SEP measures is a major limitation in this type of research. SEP measures at different points in the life-course are highly correlated. Nothing in results such as those presented by Ramsay demonstrates that childhood SEP matters more or less than, say, prenatal SEP or SEP at age 20.

This difficulty is substantially driven by data limitations—most life-course research is still dependent on retrospective reports, and generally, only limited survey time is devoted to assessing early life conditions. This problem could obviously be addressed by devoting more time to comprehensive assessments, but other options include focusing on birth cohorts for whom SEP at multiple time points has been collected, or linking subject data to external data sources. Analyses linking individual records to external data sources suggest this is a promising approach, but it is a challenge to identify data sources with longitudinal records of SEP as it changes across the life-course. When we move to treating SEP as a time-varying exposure, we will also have to consider better analytic strategies for such time-varying data, hopefully acknowledging the likely reciprocal relationships between SEP and health across the life-course.

A related problem arises in efforts to identify the direct effect of childhood conditions not mediated by adult SEP. Adjustment for a single indicator of adult social class is highly unlikely to adequately block effects of adult SEP. Different dimensions of SEP, e.g. education, income, wealth or occupational class, are
often correlated at only 0.2–0.4, and each of these dimensions may have a unique influence on adult health. If adult health is affected ‘only’ by current SEP, but SEP measures are noisy and measures at different life points are correlated, then earlier SEP indicators will predict even after conditioning on the adult SEP indicators because the childhood measures will proxy for unmeasured aspects of adult SEP. This source of bias may be reduced by more comprehensive adjustment for adult SEP. The relatively modest associations among different dimensions of SEP suggest this type of bias may be a serious problem in many life-course studies (although the problem is by no means unique to life-course epidemiology).

**Conclusion**

There has been substantial discussion of the methodological problems that bedevil life-course epidemiology, including several topics I did not discuss here such as additional difficulties in partitioning direct and indirect effects 9–11 or routine confounding of early life conditions. Progress in some of these areas may be slow. The promising results generated by life-course research to date, despite the methodological limitations, suggest it is worth the investment to overcome these problems. Modelling selection/loss to follow-up processes and improving measurement are both areas in which explicit attention would substantially strengthen our ability to draw causal inferences about the effects of early life SEP on adult health.

**References**


