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Invited Commentary

Invited Commentary: Does the Childhood Environment Influence the Association Between Every *X* and Every *Y* in Adulthood?

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The conditions under which children are raised have a long-term impact on health throughout the life course. Because childhood conditions can have such a strong influence on adult risk factors for disease, failure to account for their influences could distort observed associations between adult risk factors and subsequent health outcomes. In other words, childhood conditions could confound the association between every *X* and *Y* when *X* is measured in adulthood. Comparisons of health outcomes between exposed and unexposed siblings have the potential to eliminate confounding effects due to vulnerability factors shared between siblings (i.e., 50% of their genes and aspects of the childhood environment that affect siblings equally). In a large, population-based study of siblings in Denmark, Søndergaard et al. (*Am J Epidemiol*. 2012;176(8):675–683) found that individuals with higher educational qualifications lived longer than did their siblings with lower educational qualifications. Their results provide evidence for the returns to health resulting from investment in expanded educational opportunities. However, even sibling designs are not conclusive regarding causality; they remain subject to the unmeasured confounding influences of factors that vary within families. Nonetheless, sibling-based approaches should be used more often in studies of adult risk factors to address the long-term influences of the childhood environment on health.

causal inference; education; health; mortality; siblings; social epidemiology

In 1996, Hertzman and Weins commented that "rapidly accumulating evidence is revealing an impact of childhood experiences on subsequent health, well-being, and competence which is more diverse, profound, and long-lasting than was ever understood in the past" (1, p. 1083). In the ensuing years, even more evidence has accumulated that demonstrated the long-term reach of the early childhood environment (2–4). The conditions under which children are raised shape their opportunities for cognitive development, academic achievement, socioemotional development, and health risk behaviors (5–8). Early life conditions also matter for adult physical and mental health (9–13).

In part, these associations exist because childhood encompasses developmentally sensitive periods for the acquisition of cognitive, physiologic, and social functioning that bound an individual's capacity for long-term health (3, 14). These associations also exist because early childhood conditions provide opportunities for—and constraints on—adult socioeconomic conditions, a key determinant of which is educational attainment. For example, Power and Matthews, using data from the 1958 British Birth Cohort, demonstrated that social class at birth strongly predicted adulthood economic conditions (e.g., income, housing type, unemployment, and job insecurity), health-related behaviors (e.g., smoking and diet), social integration (e.g., marital status and social support), and of particular interest here, educational attainment (15).

In social epidemiology, low educational attainment has been one of the most-studied adulthood risk factors for poor health, and the pattern of evidence establishing the health consequences of a low educational level has been generally consistent with a causal association. Education has been shown in a large number of observational studies to be inversely associated with mortality and major health outcomes, such as coronary heart disease and type 2 diabetes mellitus (16–18). Education occurs long before the

onset of most major causes of death in developed nations, such as coronary heart disease and cancer. There is typically a dose-response relation between educational level and health (19), and the biologic and behavioral underpinnings of premature death (such as smoking, blood pressure, obesity, and type 2 diabetes mellitus) are also associated with educational level (17, 20–22). However, the extent to which health outcomes such as death change in response to changes in educational level remains unclear (23–25). In addition, the possibility that these associations are confounded by factors known to predict both educational level and health remains difficult to overcome. For example, a recent study in which propensity score matching was used to account for potential confounding due to 21 early life risk factors (e.g., intelligence, socioeconomic circumstances, parental mental illness, chronic health conditions, and birth weight) demonstrated that the associations between educational level and the risk of coronary heart disease were reduced by half after accounting for factors that could act as prior common causes of both lower educational level and poor health (26).

Thus, any study that aims to determine the impact on health of risk and protective factors measured in adulthood should therefore be concerned that the suspected factors were caused by childhood conditions that exert independent influences on adult health. In other words, as our title suggests, childhood conditions could influence the association between every *X* and *Y*, where *X* is an adulthood risk or protective factor. Absent the ability to randomly assign the *X*'s of major interest, quasi-experimental designs, such as within-sibling comparisons, offer the hope of minimizing the confounding influences of the early life determinants of adult health in studies of adult risk and protective factors. From a life-course perspective, this work is critical because it aims to identify modifiable intervention points once trajectories of risk have already been set in motion and to determine whether modifying risk factors in adulthood can offset the harm posed by early childhood adversity.

The study by Søndergaard et al. on educational differences in mortality leverages data from a population-based sample of siblings in Denmark that is large enough to provide a highly informative test of the education and health hypothesis (27). Their study demonstrates a significant health advantage to increased schooling in terms of overall life expectancy.

The design assumptions of using within-sibling comparisons to infer the causal effects of risk factors (i.e., the effects of risk factors independent of familial vulnerability) are described in detail by Søndergaard et al. (27) and have been commented on at length elsewhere (28–32). Briefly, within-sibling comparisons eliminate confounding due to factors shared by siblings (including, on average, 50% of their genetic vulnerability, as well as aspects of the childhood environment that affect all siblings equally) and do not eliminate confounding due to factors that are not shared by siblings (including, on average, 50% of their genetic vulnerability, as well as aspects of the childhood environment that are unique to each sibling). We refer to this as the "shared vulnerability" assumption.

WHEN SIBLING COMPARISONS PRODUCE EVIDENCE THAT SUGGESTS A CAUSAL EFFECT

An observation of a statistically significant association between a hypothesized risk or protective factor that varies within siblings and a subsequent health outcome is consistent with a causal association. The study by Søndergaard et al. demonstrates just that: Individuals with higher educational qualifications lived longer than did their siblings who had lower educational qualifications (27). The major caveat with respect to the inferences that can be drawn relates to the potential confounding influences of vulnerability factors unshared between siblings. The fundamental problem is how to assess the validity of the shared vulnerability assumption. Note that not all differences between siblings matter—just those that relate to both educational attainment and subsequent health.

The issue of birth order provides a useful illustration of the problem. Of course, birth order varies between siblings in the same family. Birth order has repeatedly been found to be inversely correlated with cognitive ability, which is a predictor of educational attainment (33). Setting aside the question of whether birth order itself is a causal variable or whether it is a marker of sibling differences in factors such as parental investment (34, 35), to the extent it predicts later health outcomes (36) it is a potential confounder in within-sibling comparisons. Fortunately, information on birth order is usually available in studies of siblings and was controlled for in the analyses here (without much effect).

Beyond birth order, what other factors lead siblings in the same family to achieve varying educational qualifications? Trying to understanding the origins of sibling differences has been a longstanding concern in the fields of sociology and child development (37–41) and a more recent concern in the field of epidemiology (42). Certainly, the availability of material resources influences the ability of parents to invest in their children's education; yet, family resources may also predict the degree of sibling resemblance in educational attainment. For example, Conley et al. demonstrated that siblings raised in families with fewer resources had more similar achievement and behavioral outcomes than did siblings raised in families with more resources (43). Strictly speaking, this may not represent a violation of the shared vulnerability assumption, as long as the influences of the family's economic circumstances on offspring educational attainment and later health outcomes affect all siblings equally.

More problematic is the issue of parenting differences between siblings. Brody et al. reported that parents' differential treatment of their offspring led to sibling differences in negative emotionality (38), an independent risk factor for subsequent heart disease (44). Differential parenting has also been shown to predict sibling differences in psychiatric symptoms (45), also a predictor of later health and mortality (46). Complicating the problem even further is the impact that siblings have on each other during childhood and adolescence. For example, Rende et al. showed that sibling relationships act as "contagion" effects for smoking and drinking behaviors (47). To the extent that these effects are present, they could distort the results of within-sibling comparisons.

The studies highlighted above raise the concern that comparisons of mortality rates between siblings with differing educational qualifications cannot be attributed to the causal effects of schooling (48). Importantly, Søndergaard et al. controlled for a range of potential confounders that are sibling-specific (childhood physical and psychiatric problems) and that have been linked with both shortened educational careers and mortality (46, 49). They also conducted a sensitivity analysis limited to twins in their sample to partly address sibling differences in genetics. However, without further stratifying on zygosity, residual confounding due to genes remains a concern (50).

A final point is that the shared vulnerability assumption must hold across all of the educational levels being compared. The degree of discordancy in educational attainment within families in the study by Søndergaard et al. is reported in Table 3 of their article. On the basis of their ordering of educational categories (from lowest to highest: primary school, high school, vocational education, short- and middle-length higher education, and advanced higher education), we observed that in the majority of discordant sibling pairs analyzed (86.4%), the educational qualifications differed by 2 levels. Although we have not found evidence directly addressing this point, it seems plausible that the presence of confounding factors could differ between families in which siblings achieved adjacent (or nearly adjacent) education qualifications and families in which siblings attained markedly different educational qualifications (e.g., the 13,523 pairs in the sample in which one sibling completed primary school and the other an advanced degree). Additional work is needed to empirically evaluate this concern.

Finally, Søndergaard et al. conducted separate analyses for males and females; our understanding of their methodology is that opposite-sex sibling pairs were excluded from all of their within-sibling analyses. It would be useful to for readers to know the sample sizes and degree of intersibling discordance in educational attainment among families with same-sex siblings only (i.e., the basis for the sibling analyses reported in their Tables 4 and 5).

WHEN SIBLING COMPARISONS FAIL TO PRODUCE EVIDENCE OF A CAUSAL EFFECT

Though not the case in the analysis by Søndergaard et al., many prior applications of the within-sibling methodology failed to detect a significant association between *X* and *Y*. Low statistical power is usually the first concern, as studies with low power are not highly informative regarding the absence of a causal effect (20, 31). Few of these null studies have gone to the trouble of formally estimating their statistical power, although the null studies that have are more convincing (51). This is simple enough to do for simple designs using standard methods (52), but we would welcome further methodological work to address sample size requirements in designs with varying numbers of siblings per family and incorporating different types of outcomes (e.g., binary, Poisson, and time-to-event).

Well-powered studies of siblings indicating no statistical association between exposure and disease offer compelling evidence that no causal effect exists. For example, in the case of maternal smoking during pregnancy, studies using sibling-based designs found virtually no differences in cognitive, behavioral, and academic outcomes between exposed and unexposed siblings (53–56). Yet, even well-powered sibling comparisons showing no significant effects may be subject to the same problems of unmeasured confounding noted above. However, this would require an unmeasured confounding factor that varies within families to somehow mask a true causal effect. We have yet to see this occur in practice.

CONCLUSIONS REGARDING THE PUTATIVE CAUSAL EFFECTS OF EDUCATION ON HEALTH AND THE ROLE OF SIBLING STUDIES

The results of the study by Søndergaard et al. suggest that there are long-term returns to health of investments made in expanding educational opportunities. If this is true, expanded educational opportunities could partly mitigate the adverse impact on health of the early childhood environment reviewed above, thereby reducing disparities in health within generations and minimizing the reproduction of disparities across generations (57–59).

Family-based approaches to investigating education differences in health have yet to reach their full potential, though, because many of the influences identified have little if any correspondence to a realistic public health or public policy intervention (other than the general proposition of maximizing education for all). For example, the strongest effects observed in the study by Søndergaard et al. correspond to contrasts between individuals with a vocational education and their siblings with an advanced degree (e.g., an adjusted hazard ratio for mortality among males in the youngest cohort of 0.36). What is the real-world intervention of which this hazard ratio quantifies the impact? We think future studies of this topic should be structured so as to more directly estimate the impact of real-world interventions. For example, what are the long-term health benefits associated with providing 2 years of college education (an associate's degree in the United States) to individuals who would otherwise terminate their schooling with a high-school degree (60)?

In conclusion, well-designed sibling studies offer substantial gains over standard observational designs in the ability discern hypothesized causal effects, and therefore they should be applied more broadly to study more *X*'s and *Y*'s. That said, advances are needed to more accurately determine the sample size requirements of sibling-based comparisons and also to empirically evaluate the shared vulnerability assumption.

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