Invited Commentary

Invited Commentary: The Life Course Epidemiology of Depression

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Received for publication May 7, 2007; accepted for publication June 12, 2007.

Lifetime trajectories of risk for major depression appear to be established early in childhood. Within the broader frameworks of life course epidemiology and developmental psychopathology, Pesonen et al. (Am J Epidemiol 2007;166:1126–1133) provide new evidence that traumatic experiences in childhood increase the risk of depressive symptoms in adulthood. They reported on a follow-up study of 1,658 members of the Helsinki Birth Cohort, born in 1934–1944 (Finland), 410 of whom were evacuated to foster care during World War II. More than six decades later, the adults who were evacuated as children had significantly higher depressive symptom scores than the adults who were not evacuated. Their study highlights important challenges to determining whether or not specific childhood experiences have a causal effect on adult depression. This commentary reviews three challenges to causal inference in life course research: unmeasured confounding, sampling bias, and model specification. Despite the strengths of birth cohort studies for investigating developmental trajectories and for establishing the temporality of exposures, such studies often do not overcome threats to causal inference that are common to observational research in general. The study by Personen et al. provides further motivation for research that can address commonly recognized sources of bias and identify intervening pathways linking early life exposures with adult health outcomes.

causal inference; depression; psychopathology

The notion that childhood experiences are related to mental health throughout the life span has been a longstanding concern in psychiatric epidemiology. Although this concern dates back at least to Freud (1), investigations into the childhood origins of psychiatric disorders, and similarly the long-term psychiatric consequences of childhood adversity, are now intellectually and methodologically situated within the emerging field of “life course epidemiology” (2, 3). Ben-Shlomo and Kuh defined life course epidemiology as “the study of long-term effects on chronic disease risk of physical and social exposures during gestation, childhood, adolescence, young adulthood and later adult life” (4, p. 285). The impact of childhood adversity on psychiatric functioning is also a fundamental concern of the relatively new discipline of “developmental psychopathology” (5), which combines theories and methods of developmental psychology and clinical psychiatry to understand the conditions under (and pathways by) which normal development diverges toward pathologic endpoints. Both fields, life course epidemiology and developmental psychopathology, share the fundamental principles that health at any given point in time is substantially influenced by prior circumstances, and that disease processes unfold through a combination of risks operating at multiple levels—ranging from genetic inheritance and psychological vulnerability to social conditions.

The types of adversity in childhood that have been associated with elevations in risk for depression include socioeconomic disadvantage (6, 7), parental divorce (8), sexual abuse (9), and physical abuse (10). Pesonen et al. (11) now report the results of a study of depressive symptoms in 1,658 adult members of the Helsinki Birth Cohort, 410 of whom were evacuated from their hometowns as children during World War II. More than six decades later, the adults

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evacuated as children had significantly higher depressive symptom scores than the adults who were not evacuated. This finding is alarming given that children comprise approximately half of all refugees globally (12). Within the contexts of life course epidemiology and developmental psychopathology, this study by Pesonen et al. raises two broad categories of questions regarding the long-term mental health consequences of war-time evacuation: 1) Is the association causal? 2) If so, what are the mechanisms linking the evacuation experience with depressive symptoms 60 years later? With respect to question 1, Pesonen et al. suggest that, by virtue of being a “natural experiment,” their study design eliminates many sources of potential confounding and, therefore, provides strong evidence of a causal link. With respect to question 2, the authors posit mechanisms related to heightened stress reactivity and to disrupted attachments.

CAUSAL INERENCE IN LIFE COURSE EPIEDIOLOGY

Evaluating the long-term consequences of severe exposures in humans such as parental separation almost always requires researchers to draw inferences from observational data. Occasionally, conditions arise out of “nature” that approximate a randomized experiment and thereby eliminate the problem of confounding, because the “exposure” is uncorrelated with any potential confounding factors (13). For example, Costello et al. (14) investigated the relation between income supplementation that occurred as the result of the opening of a casino and subsequent reductions in certain types of child psychopathology. This was considered a natural experiment, because the opening of the casino (i.e., the intervention) was uncorrelated with individual or familial characteristics that could have confounded the association between income and psychopathology. Can the evacuation of children from Finland during World War II also be considered a “natural experiment” of the impact of the evacuation on adult depressive symptoms? It can, to the extent that evacuations were uncorrelated with factors that might reasonably be considered potential confounders.

Pesonen et al. described both childhood evacuations that were identified through the Finnish National Archives registry, which were presumably the result of mandatory evacuation orders, and evacuations arranged “through the personal contacts of the families” (11, p. 1128). It is difficult to know whether and to what extent parent or child factors influenced the likelihood of either category of evacuation. One possible confounding factor might have been parental socioeconomic status, which was controlled for in their analyses. A potentially important unmeasured confounder is parental depression, which is an established risk for offspring depression (15, 16) and might well have influenced the likelihood of evacuation.

In addition to the problem of unmeasured confounding, it is important to consider the possibility of at least one source of sampling bias. A requirement for inclusion in the Helsinki Birth Cohort study was residence in Finland in 1971 (17). Historical accounts of the evacuation of children from Finland indicate that a sizable proportion of children, estimated to be upwards of 10,000 of the 70,000 evacuees (18), were permanently adopted by their foster families abroad and never returned home to Finland. The absence of these children from the sampling frame distorts the estimate of the true causal effect of the evacuation to an unknown (and perhaps unknowable) degree. The lack of information on the entire cohort at baseline (i.e., at birth) makes it difficult to quantify the effects of sampling biases, such as the one just described, and to incorporate statistical adjustments for such biases as has been done in other established cohort studies (19).

A final issue regarding causal inference is one of model specification, a subject of considerable interest for research on the developmental pathways to adult illness within the framework of life course epidemiology (20). Despite epide-miologic dogma not to control for variables on the causal pathway between exposure and disease, researchers continue to do so. Pesonen et al. controlled for adult socioeconomic status, as indicated by participants’ own educational attainment, in their models of the association between evacuation during childhood and adult depressive symptoms. Although a justification for this approach was not provided, one would assume that the investigators intended to estimate the effect of evacuation on adult depressive symptoms that was not due to disrupted socioeconomic trajectories. Pesonen et al. do not report the magnitude of the association between evacuation and subsequent educational attainment, but there is evidence from a prior follow-up study of children evacuated from Finland during World War II that the evacuation experience had a significantly adverse impact on educational attainment (21). It is unclear why this specific pathway should be of less substantive interest than all other pathways. Obtaining an unbiased estimate of the causal direct effect of evacuation on adult depression (i.e., that which is not mediated through adult education) is substantially more challenging, because all common causes of both education and depression need to be controlled for. Otherwise, as Hernández et al. remind us, the model produces a “non-null noncausal association” between exposure and disease (22, p. 181). As a result, whatever ability this study design had to minimize confounding by virtue of being a “natural experiment” was potentially lost if there were unmeasured common causes of education and depression (e.g., childhood illness) (23, 24).

Despite these limitations, the observation of elevated depressive symptoms among adults who experienced evacuation during World War II is similar to the finding of Foster et al. (25) in their report of children evacuated in Britain but, as noted by Pesonen et al., appears to differ from the results of other British studies (26, 27). Two reports of a follow-up investigation of 568 children evacuated from Kuopio County in Finland are more directly comparable with the study of Pesonen et al. (21, 28). These investigations failed to find significant differences in the mental health status of adults evacuated as children and a comparison group of adults of the same age from Kuopio County who were not evacuated. However, a protective effect of the evacuation was observed with respect to physical health, as the evacuated children had a significantly lower rate of cardiovascular disease as adults than those in the comparison group.
A COUNTERFACTUAL PERSPECTIVE

The “counterfactual contrast” (29) of the study by Pesonen et al. is defined by the difference between the depressive symptoms of adults who were evacuated and of the same adults had they remained in Finland during the war. This difference corresponds to the causal effect of evacuating children versus not evacuating children (and thereby subjecting them to the dangers of the Russian-Finnish wars such as air raids and bombardments) (30). This effect is of potential interest for the purposes of evaluating the Finnish policy of evacuation and of identifying a group of adults at risk for clinically significant depression. On the basis of the study by Pesonen et al. and the other studies of evacuated war children cited above, there is evidence for a protective effect of the policy on children’s physical health, but there is also evidence for both null and adverse effects on children’s long-term mental health. Importantly, none of the studies was able to evaluate differences in mortality risk between children who were evacuated and those who remained in Finland during the war (i.e., the number of lives saved by the evacuation).

Pesonen et al. argue that their study is better able to isolate the effects of parental separation from other types of adversity than were prior investigations. While stressors such as parental separation do often occur in the context of multiple adversities (31, 32), the counterfactual analysis above makes it clear that the effects of separation were not distinguishable from other types of adversity that children were exposed to as a result of the evacuation. As described in the two studies from Kuopio (21, 28) and by a detailed first-person account of the evacuation (33), evacuated children faced numerous difficulties in addition to parental separation: a protracted and sometimes dangerous journey to a foreign place, repeated evacuations and returns, being unable to communicate with a foster family, economic hardship, and various forms of maltreatment. It is therefore not possible to conclude that any single aspect of the evacuation, whether parental separation or some other accompanying exposure, gave rise to the increase in depressive symptoms observed in adulthood. Furthermore, as children in the comparison group (i.e., those who were not evacuated) were also likely exposed to substantial adversity during the period of World War II, isolating the specific effects of any single type of traumatic experience seems incredibly difficult.

IDENTIFYING PATHWAYS BETWEEN EARLY LIFE EXPOSURES AND ADULT OUTCOMES

Pesonen et al. posit two explanations for the association between the evacuation of Finnish children and adult depressive symptoms. First, they speculate that the evacuation experience permanently heightened stress-reactivity responsiveness (34). Second, they hypothesize that the separation from parents associated with the evacuation disrupted parental attachments (35). Both of these pathways have been implicated in the etiology of depression. A developmental psychopathology perspective on depression would argue for considering a broader range of mechanisms operating across multiple domains (e.g., cognitive, biologic, socioemotional, and representational) (36), with specific attention paid to the timing of exposures within developmentally sensitive periods. Such an approach would seem particularly appealing given the observation in the study by Pesonen et al. that both the timing and duration of the evacuation influenced the level of depressive symptoms in adulthood.

Studies of the long-term effects of early life exposures on adult outcomes are extremely valuable for determining when trajectories of disease risk begin and for generating hypotheses about intervening pathways. They are also subject to many of the same criticisms leveled against “risk-factor” (i.e., “black box”) (37) epidemiology. Identifying the “causal chains” (38) linking childhood exposures to depression and other mental health outcomes across the life span and across generations is therefore a necessary future direction for the field of life course epidemiology, which will benefit from further integration with the theories and methods of developmental psychopathology. Prospective cohort studies (39) will be critical for this endeavor, as they enable researchers to directly observe perturbations in developmental trajectories (40) and to implement causal modeling strategies that can minimize unmeasured sources of confounding (41). Embedding controlled intervention studies within the context of this work will further enhance our understanding of modifiable disease trajectories (42).

ACKNOWLEDGMENTS

The author appreciates the helpful comments of Medelena Glymour and Kerith Conron.
Conflict of interest: none declared.

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