The adverse health consequences of low socioeconomic position (SEP) are well documented, including several studies that have examined when in the life course socioeconomic differences in health emerge and how inequalities change with age. The findings from these life course studies can shed light on the underlying pathways to disease inequalities and on the degree to which these may differ across health outcomes. Aside from SEP, the physical health consequences of other forms of adversity are less well studied (although a considerable body of evidence exists for mental health [eg]). The study by Su et al in this issue of Circulation therefore makes a valuable contribution to the literature. The authors use data from 394 participants from the Georgia Stress and Heart Study to investigate the cardiovascular consequences of reported adverse child experiences (ACEs), specifically, childhood abuse (emotional, physical, and sexual), childhood neglect (emotional and physical), and growing up with household dysfunction (substance abuse, mental illness, domestic violence, criminal household member, and parental marital discord). The study has repeated measurements of blood pressure obtained in a standardized way. The authors showed that retrospective report of the number of ACEs experienced up to 18 years was not related to mean blood pressure in childhood (<10 years of age) or the change in blood pressure from childhood to early adulthood, but that those who reported a greater number of ACEs had a more rapid age-related increase in systolic and diastolic blood pressure from their mid- to late-20s, such that, by 38 years of age, those who reported 24 ACEs in comparison with those reporting none had 9.3 mm Hg and 7.6 mm Hg higher systolic and diastolic blood pressure, respectively. The authors demonstrated that, in their data, the association between ACEs and blood pressure were similar in males and females and across 2 ethnic groups (blacks and whites), and remained after the adjustment for childhood SEP and health behaviors. Although this study is an important step forward for the understanding of how adversity might influence cardiovascular health, there are several important challenges to this type of research that need to be addressed by future studies.

Defining Adversity

Su et al create a summary score of the number of ACEs, an approach that has become widespread in research into ACEs. The use of a summary variable, such as this, acknowledges that ACEs tend to co-occur and that experiencing multiple forms of adversity has greater adverse health effects than experiencing only 1 ACE. The approach also increases statistical power when, as is the case in this study, some forms of adversity are relatively infrequent. However, a count of the number of ACEs makes the implicit assumption that each form of adversity has the same direction and magnitude of association with the health outcome. The summary score also prevents the examination of interactions between forms of adversity other than assuming an overall additive interaction. Examining each ACE separately, and the interactions between them, as well, would enable more detailed etiologic understanding and provide clearer policy guidance. To do this, a much larger sample size would be needed than in the present study.

A further issue related to the definition of adversity that cannot be addressed by the present study is timing. The health consequences of adversity may differ depending on the stage of childhood in which they are experienced; Su et al had a single retrospective measure of ACE in childhood rather than prospective repeated assessments and so were unable to examine this question. However, it is important for future larger studies to consider the role of timing. This will bring its own challenges, because careful modeling is required to assess the associations between a repeatedly measured exposure and a repeatedly measured outcome.

Establishing Causality

As with all observational studies, correlation cannot be assumed to be causation. Studying the role of adversity in health is challenging, because adverse experiences tend to cluster together with each other and often with low SEP, and so isolating the influence of any 1 factor is difficult. The use of the composite score of ACEs by Su et al, and by others in this field, precludes the examination of whether associations between any given ACE and health outcomes are confounded by other forms of adversity, and hence reduces the strength of causal inference that can be drawn from the results. Su et al attempted to address confounding by SEP in their analysis by multiple regression modeling, but the use of a single measure
of SEP from a single time point is unlikely to completely remove confounding. The use of repeated measures of SEP may help, because repeated-measures data are more likely to capture the true underlying level than any single measurement, but, even then, residual confounding may persist. Other statistical techniques to improve control for confounding\textsuperscript{16} (eg, propensity scores), particularly where both confounders and exposures are repeatedly measured (eg, marginal structural models\textsuperscript{15}), may also be a useful addition to studies of the life course health consequences of ACEs.

These methods, however, still make the unfeasible assumption of no unmeasured confounders. Instrumental-variables analysis\textsuperscript{16,17} has a long history in the social sciences as a tool for dealing with unmeasured confounding. In the study of the health effects of ACEs, it may be possible to identify instrumental variables for some forms of adversity, eg, policy changes in the compulsory school-leaving age could be used as an instrumental variable for parental education, and local labor market shocks could be exploited as an instrumental variable for parental unemployment. Where instrumental-variable methods and other causal analysis techniques are not possible, important strategies for improving inference will include replication in large independent studies, ideally using cross-cohort comparisons in settings with different confounding structures,\textsuperscript{18} and triangulation of research findings from alternative methodological approaches with different underlying assumptions, as well.

Assessment of Mediation Pathways
In the current study, Su et al demonstrated that the associations they observed remained after the adjustment for childhood SEP and self-reported physical activity, smoking, and the use of illicit drugs during childhood. The authors refer to possible mediation by these characteristics in the discussion section of their article, although they do not explicitly mention mediation in their methods or analysis. This may be because the life course period that these characteristics covered overlapped with that of the exposure, and, hence, they could be conceptualized as either potential confounders or mediators. Although the prevention of ACEs is the optimal policy solution, trying to fully understand the ways through which different ACEs might impact future health could be important in deciding how best to minimize any potential future adverse health outcomes of ACEs that are experienced. However, such analyses are plagued with methodological difficulties. Measurement error is known to cause considerable bias in mediation analyses,\textsuperscript{19} and self-reported measures of physical activity such as the one used in this study are likely to experience differential misclassification. Longitudinal data can help to address problems with nondifferential measurement error, but the greater use of objective measures of health behaviors such as accelerometers to assess physical activity and cotinine to assess smoking is the key to addressing differential error. Where there are instrumental variables that are robustly related to exposures and mediators, this may help to improve the strength of inference from mediation studies.\textsuperscript{20}

Loss to Follow-Up
A key challenge of longitudinal studies is loss to follow-up, which is often greatest in the most vulnerable groups and which can result in biased estimates of the association between social exposures and health.\textsuperscript{21} The multilevel modeling approach taken by Su et al minimizes the impact of loss to follow-up in the blood pressure data, because all participants with at least 1 blood pressure measurement can be included in the analysis under a missing at random assumption. Such approaches are to be recommended within life course study designs, although sensitivity analyses around the assumption of missing at random are suggested. However, only participants who completed the ACE questionnaire at the follow-up, when participants were aged 19 to 30 years, were included in this study. The Georgia Stress and Heart study is complex, with participants originally recruited from 65.5% of 13,850 children (n=9072 calculated by us from the statement that 65.5% had complete data in\textsuperscript{22}) on whom complete family history data were obtained in 1989. A random subsample (stratified by ethnicity, sex, and family history of essential hypertension) were selected for further longitudinal assessment, although the exact number selected is difficult to ascertain from the references to previous descriptions of the study provided. Two recent publications using this cohort looking at different associations with blood pressure trajectories included 745 and 663 participants\textsuperscript{22,23} in comparison with the 394 included here. Thus, it appears that there were considerable missing data for the ACE questionnaire and loss to follow-up at the 19- to 30-year follow-up. Information on how those who did not have ACE data in comparison with those who did would help to understand how robust and generalizable the current findings are.

Conclusions and Ways Forward
The study by Su et al highlights important inequalities, with large differences in blood pressure between people who experienced several ACEs and those who did not experience any. The use of longitudinal blood pressure data in this study demonstrates that the associations between ACEs and blood pressure do not emerge until adulthood; this longitudinal approach is a strength, and highlights the value in taking a life course perspective in the study of social influences on health. Such studies present several challenges, and we have outlined our thoughts on how these challenges might be overcome in future studies. Childhood adversity is an extremely important issue that should be a focus of public policy regardless of its causal effects on health. However, understanding the health consequences of adversity can contribute to the evidence base for demonstrating the importance of preventing adversity, and the analysis of mediating pathways can also help us to identify the ways in which we might intervene to prevent the harmful health consequences of adversity.

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None.

References


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