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Invited Commentary

Invited Commentary: Considerations about Specificity of Associations, Causal Pathways, and Heterogeneity in Multilevel Thinking

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During the past decade, there has been a dramatic increase in the use of multilevel modeling in epidemiologic analysis. There were 10 times as many papers in *Index Medicus* identified by the terms ''multilevel'' and ''epidemiology'' in 2005 than there were in 1995. In recent years, the *American Journal of Epidemiology* has published papers that use multilevel analyses to consider the associations between group-level characteristics and a range of health indicators (1–7). Accompanying these content-specific contributions have been several discussions of the strengths and limitations of multilevel modeling techniques (8, 9) and the rationale for applying these methods to public health (10, 11).

In this issue of the *Journal*, Wight et al. (12) examine whether neighborhood context influences the cognitive function of older adults. This paper contributes to the literature that considers the role of group-level education as a determinant of individual health (13, 14). The authors show that older adults living in areas characterized by low aggregate education have lower cognitive function than do older adults living in areas characterized by high aggregate education, independent of the participants' own education. In many ways, this analysis is representative of the growing multilevel analysis literature. This study makes use of a large, nationally representative cross-sectional sample in the United States. Participants were geocoded to their census tract of residence, and US Census data were used to characterize census tracts (equated here with ''neighborhoods'') and to test for an association between neighborhood educational level and individual-level cognition. However, this paper is especially successful on several fronts and provides us with an opportunity to reflect on directions that might fruitfully move the field forward. It is the purpose of this commentary to offer thoughts about 1) specificity of association, 2) multilevel causal pathways, and 3) heterogeneity of associations, motivated by the work of Wight et al. and building on the extant literature on multilevel epidemiologic analyses.

SPECIFICITY OF ASSOCIATIONS

One key challenge facing studies of the macrolevel context and health is the relative paucity of theoretical development compared with the rapid progress of methodological development (9, 15, 16). This limitation places epidemiology in sharp contrast with other disciplines, such as sociology, where substantial theoretical work has developed strong frameworks that provide the basis for posing and testing hypotheses on the relations between macrolevel exposures and individual outcomes (17–19).

The principal danger of having underdeveloped theoretical frameworks is that multilevel analyses run the risk of becoming another form of ''black box epidemiology'' (20), where the associations between ''exposures'' and ''outcomes'' are explored, and statistically significant associations are reported, without a theoretical basis for *why* such associations should exist and *why* specific factors would cause particular diseases. Although atheoretical epidemiologic explorations can reveal associations that then generate mechanistic hypotheses that can guide future research (21), they risk unearthing statistically significant relations that represent only the play of chance.

Multilevel analysis in all aspects of health would do well to focus on evaluating specific theoretically driven hypotheses, transcending black box approaches in order to fruitfully identify macrolevel domains that may influence particular health outcomes. Where no such theoretical or mechanistic work has been conducted for a particular macrolevel determinant, it would be productive for the field if we focused our energy on developing it. Wight et al. (12) present an analysis predicated on a *specific* neighborhood

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characteristic (aggregate area-level education) with the theoretical potential to predict a *specific* outcome (cognitive function). The authors build their hypothesis on two observations: that educational attainment at the individual level predicts a range of other factors that may be salutary, or deleterious, for health; and that high levels of education are cognitively protective for individuals (22–25). Therefore, the authors admirably bring together the evidence from previous work, present plausible theoretical reasons as to why the macrolevel determinant of interest may matter for this particular outcome, and use multilevel analysis to assess their hypothesis.

Wight et al. (12) also show results from an analysis in which they calculated a composite measure of neighborhood ''disadvantage'' and were able to replicate the central neighborhood main effects that are the focus of this paper. The authors note that they prefer treating neighborhood education as the exposure because the analysis illustrates a specific impact of educational disadvantage. We suggest that the choice of neighborhood educational attainment as the central independent variable in this analysis is not only preferable but also the only meaningful choice based on the articulated mechanistic pathways, and it is a core strength of this analysis. However, this discussion also highlights the challenges of discerning the association of one potential macrolevel exposure with an outcome when it is highly collinear with other macrolevel exposures. There may be causal relations among macrolevel characteristics that need to be better understood before we can untangle their separate and combined influences on health.

THINKING ABOUT CAUSAL PATHWAYS

Multilevel analyses can move further from atheoretical approaches by explicitly discussing the pathways that may link macrolevel exposures with individual outcomes and, more ambitiously, through attempts at testing these various pathways. The paper by Wight et al. (12) is perhaps more successful than most papers on the first of these counts but, as is often the case in multilevel analyses, is limited on the second. Wight et al. suggest three plausible mechanisms for explaining the observed association between low neighborhood educational attainment and poor individual cognitive function. These mechanisms include potential decreased individual activity due to neighborhood stressors, more limited availability of cognitively stimulating material resources such as libraries, and a greater social tolerance for illness. However, similar to many multilevel analyses, this paper does not explore *which* of the potential mechanisms might actually explain the observed main-effects association.

In many ways, this shortcoming lays bare an essential tension in epidemiologic analysis more broadly, and one that is particularly germane to multilevel analyses. The predominant regression modeling techniques are designed to control for potential confounding. Regression approaches are not designed to consider mediation and are even more ill-suited to differentiating between confounding and mediation. This issue clearly is relevant to all epidemiologic analysis. However, it is particularly challenging in the multilevel context, where exposures may be quite distal from the outcomes. The pressure to demonstrate multilevel associations in models with extensive covariate control is substantial and, to some extent, understandable. The relative newness of examining distal exposures places an extra onus on investigators to demonstrate that their work is not simply a reflection of unmeasured confounding. Therefore, it is commonplace in papers that present multilevel analyses to adjust for the individual-level variables that may either confound, but could also plausibly mediate, the observed association between the macrolevel determinant and individual health. Insofar as macrolevel factors influence individual-level risk factors as well as individual-level outcomes, adjusting for individual-level factors will ultimately render all multilevel associations statistically insignificant (15, 26, 27).

The decision about which variables to include in multilevel models then is a particular challenge faced by analyses interested in explicating the pathways that link macrolevel exposures with individual outcomes. The analysis by Wight et al. (12) is commendable for its judicious use of individual-level controls to reassure us that the findings are not simply a reflection of confounding by well-recognized risks for poor cognitive function without overadjustment for covariates that likely mediate the association of interest. However, in the interest of testing hypothesized pathways between macrolevel exposures and individual outcomes, methodological development that provides tools to isolate the role of specific mediators of multilevel associations would go a long way toward furthering the contribution of multilevel analyses.

One additional note about this issue is in order. Suppose that this analysis had included adjustment for limited physical activity, a variable that can plausibly be considered a confounder of the relation of interest but could also plausibly be considered a mediator (as suggested by the authors (12)). Suppose further that the final model then did not show a statistically significant association between neighborhood education and individual cognitive function. To what extent would such a model suggest that neighborhood educational attainment is not an ''important'' contextual determinant of health? This question gets at the heart of causal determination and the extent to which, in epidemiology, we are interested in causes distal from the individual. If a compositional characteristic of a neighborhood—the general level of education—causes less individual activity, and if that lower level of individual activity causes residents in that neighborhood to have lower cognitive function, are we interested only in limited physical activity as a cause, or are we also interested in what might be considered ''causes of causes'' (28)? Ultimately, this is not an empiric question as much as a reflection of the values of the epidemiologic research community that influence our analyses and the relevance of our work to the broader public health community. To some extent, it is self-evident that features of social context influence health. We epidemiologists must then choose whether we want to contribute to the body of empiric evidence that demonstrates what aspects of social context may matter for what. We suggest that epidemiology, as the science of public health, might do well to consider causes at multiple levels regardless of their proximity to disease outcomes, providing a broader understanding of the processes that produce health and disease

in populations and a wider array of potential points of intervention in the disease process.

HETEROGENEITY OF ASSOCIATION

Much of our energy in epidemiologic analysis is focused on optimizing our explanatory models, explaining to the extent possible the risk of individual disease as a function of individual ''independent'' covariates (exposures), and treating residual variation as random error. However, as we broaden the epidemiologic lens of inquiry to include determinants at different levels of aggregation, we are beginning to understand that much of the residual variability from individual-level models is not random variability but rather a reflection of a web of interrelations among covariates at multiple levels of influence (10, 29, 30). Multilevel modeling expands on the individual-level regression approach by including explanatory variables at different levels of aggregation and provides one opportunity to better explore a more comprehensive range of factors that might explain variability in individual health and disease.

Fundamentally, however, multilevel approaches remain concerned with the same goal of optimizing model-based explanation of the likelihood of individual disease. Regression model-based approaches explicitly endeavor to explain dependent variables (health outcomes) as a function of a fixed set of variables in the hope of providing generalizable explanations. Relations between covariates at multiple levels of aggregation in nature are unlikely to be unidirectional or simple. Several authors have called for the broader use of more flexible analytic tools that can take into account mediation, multidirectional causation, and nonlinear relations in epidemiologic research (31–35). Unfortunately, at this time, most of these methods remain largely inaccessible because of both limitations of most readily available data and challenges in implementing more sophisticated analytic strategies.

Wight et al. (12) demonstrate an interaction between neighborhood education and individual education in explaining individual cognitive function. They surmise that this modification of the neighborhood education–individual cognition effect by individual education might reflect the greater import of social context for those who are already vulnerable, in this case, persons with low levels of education. The authors suggest that this might guide context-specific health interventions informed by this work. While this approach is indeed instructive, this demonstration of heterogeneity of association by Wight et al. only scratches the surface of the potential dynamic processes that shape individual cognition in older adults. Insights from some epidemiologic disciplines such as infectious disease epidemiology (36–39) and, to some extent, the emerging epidemiologic study of frailty among the elderly (40) might lend themselves to broader adoption of epidemiologic methods that account for the complexity of nature across multiple levels.

CONCLUSION

Broad acceptance of multilevel techniques in the epidemiologic literature presents epidemiologists with a way to consider exposures that extend beyond typical individual exposures or risk behaviors and that may encompass more distal variables that are causes of these more proximal causes of disease. However, introduction of these methods has also brought challenges for epidemiology. Methodologically, multilevel analytic techniques force us to consider the analytic difficulties of differentiating between confounders and mediators and of assessing indirect, reciprocal relations as part of a more comprehensive causal framework. Conceptually, these techniques force us to rethink, yet again, what we might mean by ''cause'' and to reconsider the uneasy alliance between the most widely used sufficient-cause frameworks in epidemiology that focus on proximate exposures (41) and the notion of causes of causes. Through clear exploration of specific associations, and potential heterogeneity within these associations, papers such as the one in this issue of the *Journal* by Wight et al. (12) are a small step in the right direction. Future epidemiologic theoretical and methodological work will be needed to take bigger steps to satisfactorily address the challenges faced in multilevel analyses.

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