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The Role of Neighborhood Social Characteristics on the Epigenome—Why the Lack of Investigations?

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For centuries, scientists and clinicians alike have wondered how the contexts surrounding children and their families play a role in child health. Spanning multiple disciplines, dozens of empirical studies have investigated the association between features of place (or the macro-level social and physical environments) and numerous child health outcomes. Using a mix of observational, experimental, and quasiexperimental study designs, researchers have begun to unravel the complex ways that neighborhood features can promote or harm child health.[1] Such work is important because it shows that opportunities for child health promotion and disease prevention are shaped by the settings in which children live, learn, and play. That is, such work illuminates the social determinants of child health or "the specific features of and pathways by which societal conditions affect health and that potentially can be altered by informed action."[2(p697)]

For at least 20 years, phrases like *cells to society* and *neurons to neighborhoods* have been part of the scientific lexicon. Use of these phrases is intended to convey a metaphor of layers and the multiple nested factors that shape disease origin and course.[3] Research to bring together multiple levels of analysis is critical because it can inform both etiological understanding and the design of interventions or policy approaches. Yet, few attempts have been made to systematically bridge these levels in empirical analyses. Frequently, researchers focus on variables within a level, without considering ways to link factors between levels.

This bridging of levels is why the study by Reuben and colleagues[4] makes an important contribution to the literature. These authors analyzed data from the Environmental Risk (E-Risk) Longitudinal Twin Study to ascertain whether neighborhood characteristics throughout childhood and adolescence were associated with DNA methylation at age 18 years. They measured multiple aspects of the neighborhood, including deprivation, dilapidation, disconnection, and dangerousness. Reuben and colleagues[4] also characterized the neighborhood and epigenetic associations using 3 distinct approaches. The authors found that children who grew up experiencing neighborhood social disadvantage have epigenetic profiles that are distinct from those of their peers who were raised in more advantaged settings. These findings were detected for inflammation and smoking-related DNA methylation sites as well as probes mapped to genes involved in the metabolism of cigarette smoke and ambient outdoor air pollution. These findings held true even after controlling for family-level socioeconomic status and individual-level tobacco smoking, both of which are known to affect DNA methylation values.[5] The study by Reuben and colleagues[4] provides a useful road map for researchers when operationalizing not just the different aspects of the neighborhood social environment but also the different dimensions of epigenetic processes. This study appears to be the largest and most comprehensive exploration of this topic to date.

The study[4] implicitly prompts readers to ask, why have only a handful of studies evaluated the role of neighborhood social characteristics in the epigenome? According to the authors, only 5 studies have tested for DNA methylation differences among individuals living along neighborhood socioeconomic gradients. The lack of research in this area is curious, especially given that neighborhood-induced epigenetic processes are likely implicated in many adverse health outcomes, spanning from mental health disorders to cancer, obesity, and metabolic diseases, as suggested by the concept of multifinality. Thus, if so much could be learned through research that links neighborhoods to epigenomes, why aren't more investigators conducting it?

Like most things, the answer is multifaceted. Perhaps it reflects the age-old problem of disciplinary silos and the tendency of researchers to not reach across the disciplinary aisle. Perhaps too few incentives exist, such as grant opportunities, or adequate infrastructures (eg, how departments are set up, how conferences are organized, and how different disciplinary groups communicate) that encourage people to work together. In addition, some aspects of nurture-focused research may make the more nature-focused investigator skittish. For example, neighborhood and other aspects of environment are unspecified and unbounded in a way that the genome and, to some degree, the epigenome are not. Such broadness produces challenges in deciding not just what is studied but also when and how such exposures are ascertained.[6] Although studying the epigenome is equally complex, in my experience sometimes the perception is that nonenvironmental-focused and more biologically based work is easier to conduct. Sometimes, nurture-focused researchers talk more about the complexity of their work in ways that sound alarms to researchers outside of the field. For example, in describing the evolution of neighborhood health studies in the Foreword of the second edition of *Neighborhoods and Health*, Ana Diez Roux went so far as to label one of her sections "Oh my God, it's (really) complicated…."[1] The skittishness might also run the other direction, with neighborhood-focused investigators being skeptical about the possibility that genetic research is actually policy relevant. And maybe, as Diez Roux noted, another reason for the lack of research in this area is that the work is hard and complex. To make strong inferences, epigenetic studies require large samples because effect estimates are small, and the number of probes analyzed in an epigenetic study creates a multiple testing problem. Furthermore, neighborhood studies require large samples of people, who are ideally followed up prospectively and are characterized using measures that tap salient and policy-relevant qualities of neighborhoods. These challenges exist when the work is done on its own, let alone when 2 fields are integrated.

Consider these challenges. How can they be overcome, and how can researchers be encouraged to pursue more neighborhood-oriented epigenome studies? Here I think we are on the cusp of exciting days ahead, when we can begin to execute truly multilevel studies. Compared with 2 decades ago, when the field of neighborhood health research was just emerging and studies on environmentally induced epigenetic programming were just finding their footing, considerable advancements in neighborhood theory, measurement, and analyses have been made that should make the examination of place-based effects more viable in all areas of health research, including epigenetics. We now have better sources of data, methods, and ideas that enable us to piece together neighborhood social features with epigenomes. For example, strategies have been outlined to integrate multilevel thinking with multilevel analytical methods.[7] A variety of measurement tools are now widely available that can be used to characterize neighborhood settings (eg, census data, multidimensional geocoded data, and smart phone–based technologies) and that can be incorporated relatively easily into existing epigenetic studies. In addition, genotyping and epigenotyping costs are decreasing, making it more affordable for neighborhood-focused researchers to collect saliva, blood, or other tissues for epigenetic analyses. Innovative analytical approaches and software are also available that allow investigators to model aspects of place in nuanced ways (eg, agent-based models, spatial analyses) and to pair those models with biological data.

I hope that studies like this by Reuben and colleagues[4] will prompt researchers to explore these complex concepts and to bridge social determinants of health with epigenetic processes. I also hope the work of these authors will inspire leaders to build better infrastructure, such as funding opportunities to facilitate interdisciplinary research and strong pipelines to train the next generation of interdisciplinary scientists who can think on multiple levels. In such an environment, we can then usher in a new generation of multilevel studies that work toward the goal of understanding disease origin and course from neurons (or cells) to neighborhoods (and society).

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REFERENCES

1. Duncan DT, Kawachi I. *Neighborhoods and Health*. 2nd edition. Oxford University Press; 2018.

2. Krieger N. A glossary for social epidemiology. *J Epidemiol Community Health*. 2001;55(10):693-700. doi:10.1136/jech.55.10.693

3. Kaplan GA. What's wrong with social epidemiology, and how can we make it better? *Epidemiol Rev*. 2004;26:124-135. doi:10.1093/epirev/mxh010

4. Reuben A, Sugden K, Arseneault L, et al. Association of neighborhood disadvantage in childhood with DNA methylation in young adulthood. *JAMA Network Open*. 2020;3(6):e206095. doi:10.1001/jamanetworkopen.2020.6095

5. Dunn EC, Soare TW, Zhu Y, et al. Sensitive periods for the effect of childhood adversity on DNA methylation: results from a prospective, longitudinal study. *Biol Psychiatry*. 2019;85(10):838-849. doi:10.1016/j.biopsych.2018.12.023

6. Dunn EC, Brown RC, Dai Y, et al. Genetic determinants of depression: recent findings and future directions. *Harv Rev Psychiatry*. 2015;23(1):1-18. doi:10.1097/HRP.0000000000000054

7. Dunn EC, Masyn KE, Yudron M, Jones SM, Subramanian SV. Translating multilevel theory into multilevel research: challenges and opportunities for understanding the social determinants of psychiatric disorders. *Soc Psychiatry Psychiatr Epidemiol*. 2014;49(6):859-872. doi:10.1007/s00127-013-0809-5