JACC
JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
JULY 2, 2019
VOLUME 73
NUMBER 25

■ www.onlinejacc.org
ELSEVIER
ISSN 0735-1097

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 25, 2019

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Mechanistic Understanding of Socioeconomic Disparities in Cardiovascular Disease*

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Demographers have noted socioeconomic disparities in morbidity and mortality for more than a century. But, it was not until Marmot's pioneering studies of British civil servants began to appear in the 1980s (1,2) that socioeconomic status (SES) started to receive serious attention as a cardiovascular risk factor. In the ensuing years, we have learned a great deal about the scope and scale of these disparities (3,4). The gap is large, and it is growing. In a recent meta-analysis of 22 million adults, low education was associated with a 42% to 66% increased risk of cardiovascular disease (CVD) (5,6). We have also learned a great deal about the relative importance of various mechanisms thought to underlie these disparities. Genetic variations and lifestyle differences both play a role, and so does access to health care. Yet, none of these factors can fully explain the gaps (7). These observations, coupled with animal studies indicating that there is a robust, lasting physiological response to subordination, have led researchers with a focus on health disparities to hypothesize that stressors associated with low SES may contribute directly to CVD pathogenesis (8,9). Consistent with that view, research has found higher levels of multiple CVD biomarkers in low-SES populations, including endothelial dysfunction, inflammation, and platelet activation (9). But, convincing evidence for this hypothesis is lacking.

Against that backdrop, this issue of the *Journal* features a fascinating and important report from Tawakol et al. (10), examining a putative stress-associated neurobiological pathway connecting low SES with CVD risk. The paper leverages a statistical technique called mediation path analysis to integrate data on neighborhood conditions, whole-body ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging, and CVD outcomes. In doing so, it offers the most detailed mechanistic account to date of how low SES, a stress exposure, "gets inside of the body" to accelerate CVD progression. Briefly, the results suggest that adverse neighborhood SES factors, such as low median income and high crime rate, induce persistent activation of the amygdala, a brain region that is centrally involved in judging the degree of threat posed by external stimuli. In turn, higher amygdala activation is associated with greater metabolic activity in the bone marrow.

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Based on previous evidence, the authors suggest that this connection is mediated by the sympathetic nervous system, which, under conditions of threat, causes hematopoietic stem and progenitor cells to egress from bone marrow (11–13). This stress-related mobilization of progenitor cells is selective, and it is dominated by immature myeloid cells with a strong pro-inflammatory skew (14). Once in circulation, these cells migrate to sites of trauma and infection, including atherosclerotic lesions. This chain of events helps to explain the findings in the study by Tawakol et al. (10) that individuals with higher ^{18}F-fluorodeoxyglucose bone marrow uptake show greater metabolic activity in the aortic wall, and over the

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2019.04.043

ensuing 5 years, increased risk of CVD events, defined as cardiac death, myocardial infarction, unstable angina, stroke, peripheral artery disease with revascularization, or heart failure.

The pathogenic sequence depicted in this scenario will sound familiar to many readers. This conceptual model maps closely onto the contemporary understanding of atherosclerosis as a chronic inflammatory disease of the vessel wall, maintained by leukocytes initially recruited there to remove debris, repair damage, and clear pathogens. By situating the findings in this pathogenic framework, the study illustrates how neighborhood socioeconomic factors intersect with biological processes at the forefront of cardiovascular research and practice. In a similar way, the study gives researchers with a focus on health disparities a mechanistic roadmap to begin following that is drawn from basic science insights, yet feasible to navigate in human subjects.

Like all highly innovative studies, this one raises numerous questions. As such, the findings of the study should be considered promising rather than definitive. For instance, it is uncertain what "stress" exposure at the individual level is being captured by median household income. In the United States, neighborhoods are often comprised of households with similar levels of income, wealth, and education. However, there is socioeconomic heterogeneity between individuals, particularly in neighborhoods with high minority predominance (15). These observations create some ambiguity about the meaning of the paper's findings, because its statistical models do not contain markers of individual SES. Thus, one possible explanation of the study's findings is that neighborhoods are simply acting as a proxy for households. In that case, the chain of events depicted would be understood as an individualized response to stressors and exposures associated with low individual-level SES. However, the findings could also reflect exposures at the level of the neighborhood, which are not mediated through socioeconomic conditions of its constituent households. Indeed, lower-income neighborhoods can lack fresh food, health care, and safe space for exercise. They also have relatively high amounts of violent crime, as well as traffic-related and industry-related air pollution (16). These features would presumably elevate the CVD risk of residents, irrespective of their individual SES. A blended scenario is also plausible, where both neighborhood and individual SES factors initiate the cascade described by Tawakol et al. (10). Clarifying the relative importance of individual versus neighborhood conditions in the cascade is an important task for future research, because each scenario offers a distinct set of opportunities for research, practice, and policy.

The results from Tawakol et al. (10) highlight the importance of the amygdala in connecting SES with CVD. In subsequent research, it will be important to ask which other brain regions are involved, and whether additional insights might be gleaned from a network-based approach. Of special interest here is the cortico-basal ganglia circuit, which supports reward-related brain functions and is implicated in CVD risk behaviors like smoking, consumption of calorically dense foods, and obesity (17). Low SES is associated with structural and functional alterations of this circuitry (18,19), so like the amygdala, it is likely to play a role in the origin of CVD disparities. Also of interest is the prefrontal executive control system, which can exert top-down influences on threat and reward circuitries, and facilitates impulse control, as well as regulation of thoughts, feelings, and physiology during stress (20). Again, SES affects the structure and function of these prefrontal regions, as well as the architecture of white matter pathways connecting them with other brain regions (19,21,22). A recent study of children in Chicago illustrated how considering these networks has the potential to enhance understanding of neighborhood risks like those studied here (23). Similar to previous work, it found that youth in high-violence neighborhoods had more cardiovascular risk, as reflected in adiposity metrics, insulin resistance, and metabolic syndrome. But, these risks were only present among youth with lower functional connectivity of the brain's central executive network, which supports emotion regulation, suppression of unwanted thoughts, and self-control. For youth who displayed higher connectivity in this network, there was no association between neighborhood violence and cardiovascular risk, suggesting that this might be a neural marker of (or contributor to) resilience.

Finally, in considering ways to ameliorate CVD disparities, Tawakol et al. (10) suggest using medications to interrupt the cascade their study identifies. We agree that it is difficult to substantially alter SES, and that downstream processes offer promising targets for intervention. In that regard, there is mounting evidence to suggest we can mitigate some of the pathological processes that Tawakol et al. (10) identify by improving the social conditions of low-SES youth, even without bolstering income or education. For instance, 1 randomized trial of low-SES adolescents found that volunteering reduced

obesity, cholesterol, and inflammation (24). Also notable are long-term follow-ups of individuals who, as children, participated in randomized trials aimed at optimizing early caregiving and strengthening family relationships. As adults, these individuals showed larger amygdala volumes, lower inflammatory biomarkers, and fewer metabolic syndrome signs relative to nonparticipating control subjects (25–27). These findings are preliminary, and larger-scale trials are needed to clarify the efficacy and durability of these interventions. Still, they illustrate the potential for mitigating disparities by targeting processes downstream of SES.

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KEY WORDS cardiovascular disease, neurobiology, positron emission tomography, socioeconomic disparities, stress