Nontraditional Risk Factors as Mediators of Racial Differences in Diabetes Risk

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Diabetes continues to be a growing problem for the old and young, affecting 25.8 million people in the United States; 7 million of whom remain undiagnosed.¹ In 2010, nearly 2 million adults (20 years and older) were newly diagnosed with diabetes.¹ This phenomenon has been attributed to multiple factors, including genetics, environment, and modifiable risk factors such as obesity, unhealthy diets, and sedentary lifestyles. Compared to whites, African Americans have a 77 % higher risk of diagnosed diabetes, and once diagnosed, are more likely to have poorer outcomes and increased morbidity and mortality.¹ Evidence indicates that diabetes can be prevented with the adoption of healthier behaviors (i.e., weight loss, dietary changes, increased physical activity).² Despite this awareness, ethnic disparities in diabetes risk persist.¹ Therefore, substantial interest exists to explain these persistent differences and to design interventions that are effective in bridging the racial divide in risk of diabetes.

In this issue of the Journal, Chatterjee and colleagues³ present evidence that nontraditional risk factors contribute substantially to the excess risk of diabetes incidence in African American adults compared to white adults. In an analysis of 11,162 African American and white participants without diabetes from the Atherosclerosis Risk in Communities (ARIC) Study, they demonstrated that nontraditional factors, particularly forced vital capacity (FVC) and serum potassium (K⁺), serve as potentially significant mediators of excess risk for diabetes in African Americans compared to whites, accounting for an additional 26 % of excess risk above and beyond traditional risk factors. This study is noteworthy because it provides additional evidence on the need to account for nontraditional risk factors in risk engines for diabetes. The analysis is strengthened by a relatively large sample size, sensitivity analyses to test the robustness of the results, and adjustment for multiple potential confounders, including traditional demographic and lifestyle risk factors, biomarkers, and nontraditional risk factors.

While the findings are thought-provoking, limitations of the study should be taken into consideration in interpreting the results. First, not all relevant confounders were accounted for. For example, the study did not control for psychological variables such as depression and anxiety. So it is possible that other nontraditional factors may have been more significant. Second, because of the limitation of the African American sample to Jackson, Mississippi and Forsyth County, North Carolina, selection bias remains a concern, even though the authors performed sensitivity analyses. Third, generalizability to the US population of African Americans and whites is limited since participants were selected from only four US communities. Fourth, only two of four possible criteria to diagnose incident diabetes were used (fasting glucose and random glucose). Hemoglobin A1c levels and oral glucose tolerance test were not used to identify incident diabetes, which may have biased the sample. Finally, although the risk factors were assumed to be mediators, they could also be moderators. Without explicit mediator–moderator analyses and testing for direct and indirect effects, it is difficult to accurately determine if the risk factors identified are full mediators, partial mediators or moderators of the relationship between race and risk of diabetes.

This study highlights the need for better understanding of the mechanism through which nontraditional risk factors impact the risk of diabetes. Previous studies have documented an association between lung function and adverse metabolic profiles, but the findings have been inconsistent.^{4,5} Clinical metrics such as forced expiratory volume in 1 s (FEV₁) and the ratio of FEV₁ to FVC, as well as obstructive versus restrictive disease, have been postulated as predictors of incident diabetes, but the results have been inconclusive. Questions remain about whether an indirect pathway exists that results in increased insulin resistance (i.e., decreased lung volumes resulting in less physical activity, therefore leading to obesity and insulin resistance). Furthermore, the impact of inflammatory markers such as C-reactive protein (CRP) and interleukin (IL)-6 in the pathophysiology of both lung and metabolic disorders must be considered.

In addition, the risk imparted by traditional and nontraditional risk factors may be influenced by mental

health. Psychological factors such as depression, anxiety, and stress have been shown to increase the risk of diabetes,^{6,7} and in the US almost 30 % of adults with diabetes have depression.⁸ Also, research has shown that depression is associated with immune and inflammatory markers such as CRP and IL-6.⁹ The negative impact of depression and other psychological factors on diabetes processes of care and outcomes has been extensively reported.¹⁰ Therefore, consideration should be given to the mechanisms through which psychological factors increase the risk of diabetes.

In conclusion, we agree with Chatterjee and colleagues³ that further studies are needed to examine the importance of nontraditional risk factors of diabetes and identify causal pathways for intervention. However, we should not allow the attention on nontraditional risk factors to detract from addressing the well-known impact of traditional risk factors on the risk of diabetes, especially in ethnic minorities. Even in the current study, 41 % of excess risk of diabetes in African Americans was explained by traditional risk factors. Aggressive efforts to address these well-established risk factors are needed, while we await confirmatory studies on the nontraditional risk factors.

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