RESPONSE TO COMMENT ON SKUDDER-HILL ET AL.

Fat Distribution Within the Pancreas According to Diabetes Status and Insulin Traits. Diabetes 2022;71:1182–1192

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We thank Drs. Yang and Chen (1) for their interest in our recent article (2). The diagnostic criteria for diabetes used in our study followed the most up-to-date American Diabetes Association (ADA) guidelines, which state that fasting plasma glucose (FPG), HbA_{1c}, and the oral glucose tolerance test are "equally appropriate" for diagnosis (3). The ADA guidelines currently do not require the combination of FPG and HbA_{1c} for the diagnosis of diabetes. This statement from Yang and Chen is somewhat misleading, as they reference a (possibly not peer-reviewed) commentary that only suggested the use of the combination of FPG and HbA_{1c}; however, this was not a clinical guideline and was not from the ADA. Even if this combined approach is proven to be more accurate in the future, our approach is still preferable now because it is in accordance with the current standards of medical care in diabetes (including those used internationally) and therefore has greater generalizability. Studies on the effects of FPG and HbA_{1c} discordance on diabetes diagnosis are still relatively few, and it is not yet accepted that this has a substantial impact on the diagnosis of diabetes clinically. As Yang and Chen noted, the ADA guidelines do offer the oral glucose tolerance test as an alternative option for diagnosis (3); however, this would have been impractical and redundant in our large population-based study.

We appreciate that pancreas volume may influence intrapancreatic fat deposition (IPFD). Two 2018 systematic reviews by the Clinical and Epidemiological Investigations in Metabolism, Nutrition, and Pancreatic Diseases (COSMOS) group investigated key factors that affect pancreas volume variability, including age, sex, and BMI (4,5). Notably, all of these covariates were adjusted for in our study. Further, in a 2022 study of healthy individuals, although total IPFD was significantly inversely associated with pancreas volume in the most adjusted analysis, total IPFD did not have significant associations with the three regional diameters in both adjusted and unadjusted analyses (6). It is therefore unlikely that pancreas volume substantially affected the associations investigated in our study, and we perceive the statement by Yang and Chen regarding "flawed data" to be excessive.

The shortcomings of HOMA of insulin resistance (HOMA-IR) were acknowledged as a limitation in our article. The gold standard measure of insulin resistance, the hyperglycemic-euglycemic clamp, was not feasible in our large study. Despite HOMA-IR not being a perfect measure, it is widely used and therefore generalizable. We maintain that its use in our study offers valuable insight into pathophysiological mechanisms related to insulin resistance. Further, if there was bias related to use of HOMA-IR, this would have been nondifferential, as HOMA-IR was consistently used in analyses of all three regions of the pancreas. With results from our study supporting insulin resistance initially occurring in the tail (and body) of the pancreas, there is now opportunity for further studies to confirm this using the gold standard measure.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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