**Response by Tabák et al to Letters Regarding Article, "Risk of Macrovascular and Microvascular Disease in Diabetes Diagnosed Using Oral Glucose Tolerance Test With and Without Confirmation by Hemoglobin A1c: The Whitehall II Cohort Study"**

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**In Response:**

We thank Schmidt and colleagues for their thoughtful comments on our article.[1] In agreement with other studies,[2] our data from the Whitehall study show a similarly higher risk of cardiovascular disease associated with incident diabetes at baseline on the basis of a single measurement of hemoglobin A1c (HbA1c; relative risk, 1.66 [95% CI, 1.09–2.52]) and oral glucose tolerance test (OGTT, 1.41 [95% CI, 1.04–1.90]). Thus, we agree with the commentators that there is no inherent rank order between different glycemic measures in predicting cardiovascular risk.

Rather than comparing glycemic measures in cardiovascular disease prediction, the aim of our article was to describe potential consequences of changing a glucose/OGTT-based diagnostic approach of diabetes to an HbA1c-based approach. We found that people whose OGTT-based diagnosis did not meet HbA1c criteria for diabetes during follow-up had a long-term cardiovascular disease risk similar to that of the background population. This finding is clinically important because it suggests that the current change from the OGTT-based to HbA1c-based diagnostic approach is not harming people, but rather appears beneficial. Unfortunately, the overlap of HbA1c measurements and OGTTs in our study is limited, and thus, we cannot answer the interesting question by Schmidt and colleagues about the risk associated with HbA1c-diagnosed diabetes with or without OGTT confirmation.

We agree with Schmidt et al that an unconfirmed diabetic glucose value may signal random (or nonrandom) variation and is not sufficient for a diabetes diagnosis. However, there is sufficient evidence to show that the short-term repeatability of HbA1c values is substantially better than that of fasting or postload glucose.[3] We confirmed this in an additional analysis of a subgroup of Whitehall participants with blood samples used to estimate methodological variability (the same sample was split and analyzed twice) and biological variability (the test was repeated in the same individual within 1 month). We found that for HbA1c, the correlation between the 2 values was similar in split samples and repeat samples (*r*, 0.99 [95% CI, 0.98–0.995] versus *r*, 0.97 [95% CI, 0.95–0.98]), but for fasting glucose (*r*, 0.98 [95% CI, 0.96–0.99] versus *r*, 0.76 [95% CI, 0.64–0.84]) and for postload glucose (*r*, 0.99 [95% CI, 0.98–0.99] versus *r*, 0.68 [95% CI, 0.57–0.78]), there was a substantially stronger correlation for the split samples than for repeat samples (unpublished data). In light of these observations, the observed "regression to the mean over 3.4 years" in ELSA-Brasil (Brazilian Longitudinal Study of Adult Health) may reflect both biological variability in glycemic measures and the natural history of type 2 diabetes that includes frequent (up to 30%) natural remissions in people with newly diagnosed diabetes and an ≈5% remission in those with a mean diabetes duration of 5 years.[4,5]

Deng et al highlight that the association between vascular diseases and glycemia is not limited to levels higher than the diabetes diagnostic values, although independent associations are clearer above an HbA1c of 6.5%. However, there is only limited evidence suggesting that interventions to prevent or screen diabetes in high-risk individuals would reduce the risk of macrovascular disease in high-income countries with universal health care.[6] Furthermore, to the best of our knowledge, it is not known what cutoff level of glycemia is associated with any "legacy effect."

We agree with Deng et al that HbA1c has certain limitations as a diagnostic measure. However, compared with HbA1c, the other measures, such as the OGTT and continuous glucose monitoring–based time in range, are either much more variable and complicated, or costly and labor-intensive. Given this, their use is unlikely to be adopted for screening purposes.

Deng et al correctly pointed out that estimated glomerular filtration rate is not an ideal proxy for diabetic kidney disease (ie, diabetic nephropathy). Unfortunately, urinary albumin, which is a better marker of diabetic nephropathy, was not measured in the Whitehall study. However, most chronic kidney disease cases (individuals with low estimated glomerular filtration rate) are a result of diabetes and hypertension in high-income countries.[7] To minimize other causes of chronic kidney disease, we performed a sensitivity analysis after the exclusion of persons with systemic autoimmune diseases and anemia, and the results remained unchanged.

Considering all these points, our general conclusion is robustly supported by our findings. Even so, because the findings are from a single study, confirmation in other prospective cohort studies with diabetes diagnoses based on different glycemic measures and long follow-up would be valuable.

**Article Information**

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**References**

1. Tabak AG, Brunner EJ, Lindbohm JV, Singh-Manoux A, Shipley MJ, Sattar N, Kivimaki M. Risk of macrovascular and microvascular disease in diabetes diagnosed using oral glucose tolerance test with and without confirmation by hemoglobin A1c: the Whitehall II cohort study. Circulation. 2022;146:995–1005. doi: 10.1161/CIRCULATIONAHA.122.059430

2. Di Angelantonio E, Gao P, Khan H, Butterworth AS, Wormser D, Kaptoge S, Kondapally Seshasai SR, Thompson A, Sarwar N, Willeit P, et al; Emerging Risk Factors Collaboration. Glycated hemoglobin measurement and prediction of cardiovascular disease. JAMA. 2014;311:1225–1233. doi: 10.1001/jama.2014.1873

3. Selvin E, Crainiceanu CM, Brancati FL, Coresh J. Short-term variability in measures of glycemia and implications for the classification of diabetes. Arch Intern Med. 2007;167:1545–1551. doi: 10.1001/archinte.167.14.1545

4. Dambha-Miller H, Day A, Kinmonth AL, Griffin SJ. Primary care experience and remission of type 2 diabetes: a population-based prospective cohort study. Fam Pract. 2021;38:141–146. doi: 10.1093/fampra/cmaa086

5. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, Pownall HJ, Johnson KC, Safford MM, Kitabchi AE, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA. 2012;308:2489–2496. doi: 10.1001/jama.2012.67929

6. Kivimaki M, Tabak AG. Does addressing prediabetes help to improve population health? Lancet Diabetes Endocrinol. 2018;6:354–356. doi: 10.1016/S2213-8587(18)30030-5

7. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2020;395:709–733. doi: 10.1016/S0140-6736(20)30045-3