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, Deng and their colleagues for thoughtful comments on our paper.[1] In agreement with other studies,[2, 3] our data from the Whitehall study show a similarly increased risk of cardiovascular disease for a single baseline measurement of HbA1c (RR: 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 glycaemic measures in predicting cardiovascular risk.

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

We agree with Schmidt et al that an unconfirmed diabetic glucose value may signal random (or non-random) variation and is not sufficient for diabetes diagnosis. However, we think that there is sufficient evidence to suggest that the short-term repeatability of HbA1c values is much better than that of fasting or postload glucose.[4] 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 analysed twice) and biological variability (the test was repeated in the same individual within one moth). We found that for HbA1c the correlation between the two values was similar in split samples and repeat samples (r=0.99, 95%CI: 0.98-0.995 vs r=0.97, 95%CI: 0.95-0.98) (unpublished data), but for fasting glucose (r=0.98, 95%CI: 0.96-0.99 vs r=0.76 95%CI: 0.64-0.84) and for postload glucose (r=0.99, 95%CI: 0.98-0.99 vs. 0.68, 95%CI: 0.57-0.78) there was a significantly stronger correlation for the split samples than for repeat samples. In light of these observations, the observed 'regression to the mean over 3.4 years' in ELSA-Brasil may reflect both biological variability in glycaemic 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 approximately 5% remission in those with a mean diabetes duration of 5 years.[5, 6]

Deng et al highlight that the association between vascular diseases and glycaemia is not limited to levels above the diabetes diagnostic values. While this is true, 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.[7] Furthermore, to the best of our knowledge, it s not known what is the cut-off level of glycaemia associated with the 'legacy effect'.

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

Deng et al correctly pointed out that estimated glomerular filtration rate (eGFR) is not an ideal proxy for diabetic kidney disease (i.e., 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 eGFR) are due to diabetes mellitus and hypertension in high-income countries.[8] To minimise other causes of chronic kidney disease, we performed a sensitivity analysis after the exclusion of persons with systemic autoimmune diseases and anaemia and the results remained unchanged.

Considering all the above points, we think that our general conclusion is supported by our findings. As the findings are from a single study, they need further confirmation in other prospective cohort studies with diabetes diagnosis based on different glycaemic measures and sufficiently long follow-up.

Disclosures

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