COMMENTS AND RESPONSES

Insulin Sensitivity and Insulin Secretion Determined by Homeostasis Model Assessment and Risk of Diabetes in a Multiethnic Cohort of Women: the Women's Health Initiative Observational Study

Response to Song et al.

We read with interest the article (1) on the risk of incident diabetes in the Women's Health Initiative Observational Study (WHI-OS) in relation to homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) and β-cell function (HOMA-B). In this letter, we raise a number of issues that we believe require further clarification.

The aim of Song et al.'s study was "to prospectively examine the relations of HOMA . . . with diabetes risk" (1). Why, then, are 766 women with a fasting glucose at baseline ≥126 mg/dl included in the analysis? Although these women were excluded from other analyses, it is unclear why they were included in the first place, given the stated aim to prospectively estimate risk.

We disagree with the conclusion that the effects of high HOMA-IR and low HOMA-B (see Table 4 of Ref. 1) on diabetes risk are additive. We believe that the combined effects (odds ratio 36.9) exceed what would be expected from a combination of the individual effects (HOMA-IR 9.97 and HOMA-B 1.72) under not only an additive ($9.97 + 1.72 - 1 = 10.69$) but also a multiplicative ($1.72 \times 9.97 = 17.15$) model. Our reanalysis of the crude data presented in Table 4 for the multiplicative interaction of HOMA-IR by HOMA-B using logistic regression resulted in a significant *P* value of 0.009 for the interaction term coefficient ($\beta = 0.726$) by the likelihood ratio test, indicating that the null hypothesis of no interaction is rejected. This result suggests the presence of biologic synergy between high insulin resistance and low insulin secretion in the development of type 2 diabetes, but unfortunately this is not discussed in the article. We acknowledge that our reanalysis is limited, as we could not exclude women with glucose ≥126 mg/dl at baseline and lacked information on matching factors and covariates. Further analysis of interaction by the authors would be welcome.

The authors propose that low statistical power due to exclusion of 762 women with fasting glucose ≥126 mg/dl at baseline explains widening of CIs. In one comparison among Asian/Pacific Islander women, the width of the CIs for the odds ratio for fasting glucose and diabetes risk ranges from 0.19 to 111,426. We do not believe that low power alone could explain this extreme widening and would be concerned about other known causes of variance inflation, such as multicollinearity.

We also find the models presented in Table 2 to be ambiguous regarding which covariates were included. We cannot determine whether multivariable models 1 and 2 in Table 2 include fasting glucose, insulin, HOMA-IR, and HOMA-B in the same model, or whether multivariable models 1 and 2 each display four separate models (one each for glucose, insulin, or HOMA-IR or -B). We note that if the former is true, then the authors would have included two variables in the same regression model that they report are correlated to $r = 0.99$ (HOMA-IR and fasting insulin), which would raise concerns about multicollinearity. We look forward to further publications on diabetes and related conditions from this large cohort.

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