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 Boyko et al.

We thank Boyko et al. (1) for their interest in our work (2). However, they seemed to have misunderstood our case definition. As a priori, our definition of diabetes was clinical diabetes with a special focus on those who were treated with hypoglycemic drugs or insulin. According to this standardized definition in our cohort, all the "prevalent" cases were indeed excluded from our original sampling space at baseline. Although these clinical diabetes cases may only represent one specific phenotype (treated and more severe cases) whose etiology may be different from that of other diabetes phenotypes (including those based on one measure of fasting glucose), our standardized strategy consistently applied in a well-defined prospective setting should be better than the less stringent criteria of post hoc measurement of fasting glucose alone to define diabetes. Further, the exclusion based solely on the single determination of fasting glucose violates the predetermined risk-set sampling and matching design, especially when we were also studying fasting glucose, homeostasis model assessment (HOMA), other biomarkers, and their candidate genetic variants as major exposures of interest in the Women's Health Initiative Observational Study (WHI-OS) (2,3). Thus, we have clearly stated that any analysis after excluding individuals with high fasting glucose levels (≥126 mg/dl) should be considered a post hoc analysis because the threshold of 126 mg/dl in fasting glucose (at least two time measures within 24 h) was not even introduced by the American Diabetes Association as one of the three criteria for diabetes diagnosis until 1997, which was long after the baseline WHI-OS samples had been collected. Nevertheless, the consistency between the results from our secondary analyses and our primary results indicates the robustness of our findings on prospective associations between HOMA indexes, endothelial biomarkers, and diabetes risk.

We agree with Boyko et al. that the observed multiplicative interactions of HOMA-IR and HOMA-B may implicate an important synergy of insulin resistance and β-cell function for the development of type 2 diabetes. However, we wish to reiterate the importance of separating the biological concept of interaction from statistical multiplicative interaction (4). Also, "additive" or "multiplicative" are two exchangeable terms for statistical interactions depending on the scale for the effect measures. For example, multiplicative interaction of the risk ratio corresponds to departure from the additivity on the log-risk scale for the outcome (4). We do not believe that sole reliance on the statistical testing for multiplicative interactions could provide insight in assessing potential biological interactions, since the ultimate resolution of the biological interrelationships between insulin resistance and pancreatic β-cell function will have to come from well-designed physiologic experiments.

Finally, the specific associations of diabetes risk with fasting glucose, insulin, HOMA-IR, or HOMA-B were tested independently and separately in all our models because of their high correlations with one another. Our correlational analysis of all covariates in the models does not indicate any problem of collinearity in our model. As we pointed out, the apparently wide CI observed in the Asian/Pacific Islander subgroup simply reflected the lack of statistical power due to the few cases available in that subgroup.

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