RESPONSE TO COMMENT ON HUH ET AL.

Remnant Cholesterol Is an Independent Predictor of Type 2 Diabetes: A Nationwide Population-Based Cohort Study. Diabetes Care 2023;46:305–312

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We express our gratitude to Canyelles et al. (1) and Hegele (2) for their interest in our recent publication in *Diabetes Care* (3).

In this cohort study, LDL cholesterol (LDL-C) levels were measured using the Friedewald formula for samples with triglyceride (TG) levels <4.5 mmol/L, while samples with TG levels ≥4.5 mmol/L had directly measured LDL-C values. Since individuals with TG levels ≥3.4 mmol/L were excluded from our study (3), LDL-C levels were measured using the Friedewald formula. We acknowledge the comments made by Canyelles et al. (1) and Hegele (2) that remnant cholesterol (remnant-C) can be derived as fasting TG divided by 2.2 (in mmol/L) when LDL-C is calculated using the Friedewald formula. However, the Friedewald equation has been fully validated for its accuracy in estimating LDL-C levels, and current guidelines recommend its use for reasonable estimation of β quantification–derived LDL-C in most cases when TG concentration is <4.5 mmol/L (4). Moreover, the Copenhagen General Population Study found a linear association between directly measured remnant-C and calculated remnant-C (5). The European Atherosclerosis Society recommends the use of estimated remnant-C, calculated by multiplying plasma TG by the ratio of cholesterol to TG in very-low-density lipoprotein (VLDL), along with direct assay (6). Therefore, recent epidemiologic studies have utilized calculated remnant-C using the Friedewald LDL-C, like our study (7). While direct measurement of LDL-C and remnant-C is more accurate, our findings emphasize the practicality of these simple and cost-effective calculated values derived from the conventional lipid profile in clinical settings. Additionally, methods that estimate LDL-C levels using an adjusting factor for the TG-to-VLDL cholesterol ratio (e.g., Martin-Hopkins) can also be used to calculate remnant-C. Interestingly, we observed that calculated remnant-C was still associated with incident diabetes even when we applied Martin-Hopkins to estimate LDL-C levels.

Although remnant-C and TG differ conceptually, they are inevitably similar considering their metabolism because hypertriglyceridemia results in increased production of TG-rich lipoproteins and decreased clearance of such lipoproteins, leading to an increase in the cholesterol component in TG-rich lipoproteins. In fact, numerous epidemiological studies have reported a linear relationship between remnant-C and TG.

Regarding the use of remnant-C to predict incident diabetes versus the use of TG levels, we were unable to include TG levels in the fully adjusted model due to multicollinearity issues between remnant-C and TG. Instead, we analyzed the risk for type 2 diabetes (T2D) based on quartiles of remnant-C, stratified by the presence or absence of hypertriglyceridemia. This analysis revealed that the highest quartile of remnant-C was significantly associated with an increased risk of incident T2D regardless of TG level (Supplementary Table 2 [3]). Considering that remnant-C is distinct from TG, our study aimed to investigate whether remnant-C is associated with a higher risk of T2D, and we clarified the relationship between remnant-C and T2D.

Finally, we agree on the need for further studies, such as Mendelian randomization studies, to elucidate mechanisms that underlie the association between remnant-C and T2D. Given the distinct nature of remnant-C compared with that of TG, Mendelian randomization studies focused on remnant-C can provide valuable insights into the role of remnant-C in the development of diabetes.

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

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