Whole-grain intake and risk of type 2 diabetes Reply

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In a randomized controlled trial (5) in 316 overweight and obese participants with a WG intake of 30 g/d, both WG interventions of 60 and 120 g/d significantly increased alkylresorcinol concentrations compared with the control group, whereas no differences in alkylresorcinol concentrations were observed between the 2 intervention groups. These observations suggest a possible threshold effect of WG intake on alkylresorcinol concentrations and health outcomes. Although Biskup et al. reported no altered risk of T2D for the highest compared with the lowest WG intake (Supplemental Table 3 in their article), their data indeed showed a somewhat U-shaped association between WG intake and the risk of T2D, with a 31% (RR: 0.69; 95% CI: 0.47, 1.00) lower risk for all participants and a 75% (RR: 0.25; 95% CI: 0.07, 0.93) lower risk for Swedish women in the third quintile of WG intake. Given these observations, it would be interesting to test whether the nonlinear trend in the population is significant.

Biskup et al. (1) indeed showed a positive association of plasma alkylresorcinols with the risk of T2D among Swedish subjects (RR per 25 nmol/L: 1.21; 95% CI: 1.08, 1.35), specifically among Swedish men (RR per 25 nmol/L: 1.31; 95% CI: 1.14, 1.51) (their Table 2), with a similar trend in the analyses with dietary WG intake. These findings are highly unexpected. Of note, participants with preclinical disorders may change their diet habits (probably increasing WG intake), which may reverse the association between WG intake, corresponding biomarkers, and the risk of T2D. Therefore, sensitivity analyses that exclude cases diagnosed during the first several years of follow-up are also needed to further elucidate these problems.

None of the authors had a conflict of interest.

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Reply to J-B Qin et al.

Dear Editor:

We thank Qin et al. for their interest in our recent publication about the association between plasma alkylresorcinols, biomarkers of whole-grain (WG) wheat and rye intake, and the risk of type 2 diabetes (T2D) in Scandinavian men and women (1). It is worth underlining that in our nested case-control study we report ORs, not RRs. We showed no overall association between alkylresorcinol concentrations in plasma and the odds of developing T2D. Recent meta-analyses have suggested a plateau effect of WG intake on T2D risk, with the greatest risk reductions observed at a lower range of WG (2, 3). In our article, we suggested that this may be the reason why we did not observe any overall significant association for total WG wheat and rye intake estimated by food-frequency questionnaire and reflected by using the biomarker, because the WG intake is high in the current population. Qin et al. raised the possibility that if we have a nonlinear relation between WG intake and plasma alkylresorcinol concentration that this may explain the lack of an association. They also wished to know if we observed any deviation from linearity with regard to alkylresorcinol concentrations and the odds of developing T2D.

From extensive investigations on the relation between WG intake and plasma alkylresorcinol concentrations in different populations under controlled intervention conditions, we are confident that plasma alkylresorcinol concentrations respond linearly to WG intakes within the range consumed in the present population (4, 5). The most likely reason why no significant differences between plasma alkylresorcinol concentrations were observed at a group level when comparing 30 and 60 g but not when comparing 60 and 120 g WG consumption/d among the 316 overweight and obese participants in the WholeHeart intervention (6) is probably the large interpersonal variability in plasma alkylresorcinol concentrations, possible poor compliance, and/or low alkylresorcinol content in consumed foods and not the lack of a linear dose-response relation.

With regard to the potential deviation from linearity between alkylresorcinol concentrations and the odds of developing T2D pointed out by Qin et al., we used sex- and country-specific quartiles for wheat and rye intake derived from a food-frequency questionnaire for the Swedish women and recalculated the ORs. We did not observe any significant deviation from linearity, which was also supported by splines with 3, 4, and 9 kn based on wheat and rye intakes for this subpopulation.

Qin et al. also highlighted the unexpected finding of a positive association between WG intake assessed by the biomarker and the odds of developing T2D among Swedes, particularly among Swedish men. They suggest the possibility that changes (probably an increase in WG intake) may have occurred among participants with preclinical disorders and that this may have reversed the association between WG intake, corresponding biomarkers, and the odds of T2D. We acknowledge that this could be a possible explanation and we therefore conducted further sensitivity analysis in which we excluded participants diagnosed at $\leq$2 y after baseline. However, the estimates hardly changed and reverse causation is therefore unlikely to be the reason for the unexpected finding.

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The role of nutritional biomarkers in prediction and understanding the etiology of type 2 diabetes

Dear Editor:

I read with interest the recent article by Biskup et al. (1) that described epidemiologic evidence for the role of whole-grain and rye biomarkers in type 2 diabetes. They measured the concentrations of alkylresorcinols in plasma as exposure biomarkers to investigate the risk of development of type 2 diabetes in 2 prospective cohorts. I agree with the notion that such data may provide valuable insights into our understanding of type 2 diabetes or for exploring novel predictors for the disease prevention. However, epidemiologic observations are limited by residual confounding and reverse causality (2). One traditional approach is to examine biomarkers in randomized clinical trials to evaluate the nature of relations found in observational studies. Currently, it is not cost-effective or feasible to implement randomized trials of interventions specific to each biomarker. Because natural randomization occurs at the time of conception (based on Mendel's laws), which happens before the onset of disease and is free of confounding, the analysis of integrated epidemiologic-genetic data is considered very similar to that in clinical trials. This approach is called "Mendelian randomization" (2, 3). Complementary evidence from Mendelian randomization, for which confounding or reverse causality is less likely, needs to examine the nature of the relation between nutritional biomarkers and type 2 diabetes, to match another piece of the puzzle.

To date, a large number of common genetic markers, with the use of genomewide association studies (GWASs), have been identified for type 2 diabetes and diabetes-related traits. To further translate the associated genetic loci into biochemical variation in intermediate phenotypes and the pathophysiology of diabetes, future work should pursue searching for the second source of information that is obtained from large-scale collaborations and GWAS consortia for biomarkers (3–6). In the context of Mendelian randomization, a given biomarker is causally related to type 2 diabetes if the biomarker-associated genetic markers are also associated with type 2 diabetes only through a given phenotype (a certain biomarker) (3).

Another area of research for biomarker-diabetes associations is to explore whether the addition of these biomarkers to clinical information can potentially improve risk prediction. In this context, the performance of prediction models and the utility of biomarkers should be evaluated by using classical prediction measures—including calibration by goodness-of-fit statistics, discrimination on the basis of the c statistic (a rank classifier), and reclassification (7–10). Here, the predictive utility of such nutritional biomarkers for type 2 diabetes remains unknown (1). In the future, researchers should leverage available data by integrating GWAS summary data in Mendelian randomization studies for possible biomarkers (e.g., nutritional biomarkers and metabolomics) and by broadly investigating biomarkers for predictive utility across cohort consortia in clinically relevant settings.

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