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Reply to Wolever

Dear Editor,

We appreciate the comments made by Dr. Wolever concerning our systematic review on whole grains and health outcomes. There were indeed substantial heterogeneities in the published literature, with intervention trials of metabolic intermediates displaying far greater heterogeneities than prospective cohorts linking whole grain intake to disease outcomes of interest.

As described in the main text of our paper (RCT section, p. 1308–9), “Characteristics of the whole-grain interventions, control groups, duration, and design varied widely across studies.” “We observed heterogeneity across trials (P < 0.05), which remained significant in subgroups after stratification by duration, study quality and health status.” Even with a small number of 21 trials identified, differences in study outcomes across trials were not likely due to sampling variation.

While analyzing these heterogeneous studies, we compared the difference in postintervention means, not the difference in differences between intervention and control groups mentioned in Wolever’s letter. To provide some consistent comparison across trials, we also used the standardized mean difference as a summary statistic of effect measures. For example, in the study by Tighe et al. (1), the raw mean difference of LDL-cholesterol in the wheat and oat group compared to the controls is $m_1 - m_2 = 3.35 - 3.5 = -0.15$ mmol/L with a pooled standard deviation of 0.1,

$$PSD = \sqrt{\frac{(n_1-1) \times SD_1^2 + (n_2-1) \times SD_2^2}{n_1 + n_2 - 2}}$$

resulting in a standardized mean difference of $-0.15/0.1 = -1.5$ mmol/L. Thus, Wolever’s interpretation of the standardized mean differences as crude mean differences taken directly from the original reports is not correct. In re-checking our database, however, we did correct two conversion errors regarding findings of total cholesterol levels (2) and LDL cholesterol levels (3). The pooled mean difference in levels of total cholesterol remained the same albeit with a wider 95% CI, while the pooled mean difference in LDL cholesterol levels was of $-0.82$ mmol/L. These changes do not affect the interpretation of findings from our meta-analysis (revised Supplemental Fig. 2 C, D).

While we agree that caution must be exercised in integrating findings from a pooled analysis of heterogeneous intervention trials particularly concerning the specific magnitude of effect, we wish to note that different dietary portfolios have been shown to be effective and powerful medicine as pharmaceuticals, such as statins in terms of reducing CVD risk (1,4,5). Perhaps more importantly, the specific heterogeneities identified in previous intervention trials in our meta-analysis should help design future intervention trials that use regimens that are comparable to those observed in prospective cohort studies (6).

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