husbandry and commercial meat production practices have evolved, it is likely that older values for the content of both cholecalciferol and 25(OH)D may have changed and are no longer accurate. Indeed, until quite recently, many of the standard food databases listed no vitamin D content at all for most animal products. Interestingly, the University of Minnesota Nutrition Data System for Research (NDSR) listed a cholecalciferol content in eggs as 0.64 μg for one large egg in 2008, and 1.088 μg in 2012. Whether this represents a change in actual content or a change in analytical method is uncertain.

In any event, using published data for cholecalciferol and 25(OH)D content (2,3) and a 4:1 conversion factor for 25(OH)D to cholecalciferol, one can calculate that a 6 oz. serving (170 g) of beef (85% lean) contains over 400 IU vitamin D equivalents. This is of the right order of magnitude to explain the 1600 IU gap Cannell speaks of (4) and is consistent with the finding by Crowe et al. (5) that meat eaters had higher serum 25(OH)D concentrations than meat abstainers. We suspect that we won't know the full contribution of previously unrecognized food sources until such time as we have more comprehensive analyses for both cholecalciferol and 25(OH)D in contemporary foods. One of our purposes was to stimulate such analysis.

Robert P. Heaney*
Creighton University,
Omaha, NE

Literature Cited

1. Heaney RP, Armas LAG, French C. All-source basal vitamin D inputs are greater than previously thought, and cutaneous inputs, smaller. J Nutr. 2013;143:571–5.
2. Ovesen L, Brot C, Jakobsen J. Food contents and biological activity of 25-hydroxyvitamin D: a vitamin D metabolite to be reckoned with? Ann Nutr Metab. 2003;47:107–13.
3. Liu J, Greenfield H, Strobel N, Fraser DR. The influence of latitude on the concentration of vitamin D_3 and 25-hydroxy-vitamin D_3 in Australian red meat. Food Chem. 2013;140:432–5.
4. Cannell JJ. Where is the missing 40 μg/d of vitamin D? J Nutr. 2013; 143:1520.
5. Crowe FL, Steur M, Allen NE, Appleby PN, Travis RC, Key TJ. Plasma concentrations of 25-hydroxyvitamin D in meat eaters, fish eaters, vegetarians and vegans: results from the EPIC-Oxford study. Public Health Nutr. 2011;14:340–6.

[1] Author disclosures: R. P. Heaney, no conflicts of interest.
* To whom correspondence should be addressed: E-mail: rpheaney@creighton.edu.
doi: 10.3945/jn.113.181651.

Do Whole Grain Cereals Really Reduce LDL-Cholesterol by 0.72 mmol/L?[1]

Dear Editor,

Recently, Ye et al. reported the results of a comprehensive meta-analysis of 45 prospective cohort studies and 21 randomized controlled trials (RCTs) on the effect of whole grains on a number of health outcomes (1). Such a comprehensive analysis could provide critically important evidence to establish the role of whole grains in health. However, I am concerned that typographical errors may have occurred in transcribing the data from the original articles to the database used for the meta-analysis. In addition, an important confounder which critically influences the interpretation of the results was not considered.

Ye et al. conclude that the RCTs demonstrate that whole grains significantly reduce fasting-glucose (FG) by 0.93 mmol/L, total-cholesterol (TC) by 0.83 mmol/L and LDL-cholesterol (LDL) by 0.72 mmol/L compared to control (1). I was concerned that the size of these effects seemed too big to be true; e.g., an 0.72 mmol/L reduction in LDL represents a 20–25% change from a starting value of 3.0–3.5 mmol/L, comparable to the effect of starting doses of first-generation statins (2). Closer examination showed that Supplemental Figure 2*C* and 2*D* attributes impossibly large reductions in total- (4.6 mmol/L) and LDL-cholesterol (3.3 mmol/L) to Pins et al. (3) who actually reported that oats reduced LDL by 16.2 mg/dl (0.42 mmol/L) relative to control. Similarly, Ye et al. attribute the following: an LDL increase of ~1.1 mmol/L by whole grains to Brownlee et al. (4) who actually report only a ~1% increase (~0.035 mmol/L); a significant LDL reduction of 1.5 mmol/L by wheat and oats to Tighe et al. (5) who actually report a nonsignificant increase of LDL (relative to control) of only 0.06 mmol/L; and a nonsignificant increase in LDL by whole wheat relative to control of 0.09 mmol/L to Tighe et al. (5), who actually report a significant increase of 0.22 mmol/L. Lack of time prevented my checking all the results reported by Ye et al., but many of the changes reported in Supplemental Figure 2*C* and 2*D* are very large (e.g., 4 of 13 studies with FG reductions > 1.0 mmol/L, 2 of 20 studies with TC reductions > 2.0 mmol/L, 8 of 20 studies with TC reductions between 0.8–2.0mmol/L, and 9 of 19 studies with LDL reductions > 1.0mmol/L) and may represent transcription errors. Also, the significant effect of whole-grains on blood pressure reported by Tighe et al. (5) is not included in the analysis.

Of no less concern is the fact that Ye et al. included in their analysis not only RCTs comparing the effects whole or the same refined grains (e.g., whole wheat/corn versus refined wheat/corn), but also RCTs comparing different types of grains (e.g., whole oats versus refined wheat/corn); however, the confounding effect of these rather different comparisons was not considered. It is well known, for example, that oat fiber lowers cholesterol (6) but wheat fiber does not (7). I believe the most relevant issue to address regarding whole grains is whether the practice of refining grains per se is unhealthy. If this is so (and I may be wrong), then a meta-analysis on the health effects of whole grains should only include studies in which the effects of a whole grain are compared to those of the same refined grain; at least the confounding effect of comparing one type of whole grain versus a different type of refined grain should be considered as a potential source of heterogeneity in the analysis.

Therefore, because of possible data transcription errors and lack of consideration of the potential confounding effects of including comparisons of different types of grains in the analysis, the conclusions of Ye et al. (1) ought to be interpreted with caution.

Thomas M.S. Wolever*
Department of Nutritional Sciences,
Faculty of Medicine,
University of Toronto,
Toronto, Ontario,
Canada

Literature Cited

1. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. J Nutr. 2012;142:1304–13.
2. Jones PH, Davidson MH, Stein EA, Bays HE, McKenney JM, Miller E, Cain VA. Blasetto JW for the STELLAR Study Group. Comparison of the efficacy and safety of Rosuvastatin versus Atorvastatin, Simvastatin, and Pravastatin across doses (STELLAR Trail). Am J Cardiol. 2003; 92:152–60.
3. Pins JJ, Geleva D, Keenan JM, Fraxel C, O'Connor PJ, Cherney LM. Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? J Fam Pract. 2002; 51:353–9.
4. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by increased whole-grain intake: the WHOLEheart study, a randomised, controlled dietary intervention. Br J Nutr. 2010;104:125–34.
5. Tighe P, Duthie G, Vaughan N, Brittenden J, Simpson WG, Duthie S, Mutch W, Wahle K, Horgan G, Thies F. Effect of increased consumption of whole-grain foods on blood pressure and other cardiovascular risk markers in healthy middle-aged persons: a randomized controlled trial. Am J Clin Nutr. 2010;92:733–40.
6. Brown L, Rosner B, Willett WW, Sacks FM. Cholesterol-lowering effects of dietary fiber: a meta-analysis. Am J Clin Nutr. 1999;69:30–42.
7. Jenkins DJ, Kendall CW, Vuksan V, Augustin LS, Mehling C, Parker T, Vidgen E, Lee B, Faulkner D, Seyler H, et al. Effect of wheat bran on serum lipids; influence of particle size and wheat protein. J Am Coll Nutr. 1999;18:159–65.

[1] Author disclosures: T. M. S. Wolever is president and part owner of Glycemic Index Laboratories, Inc. (GI Labs), a contract research organization; president and part owner of Glycaemic Index Testing, Inc., a corporation which provides consulting services to GI Labs; and received, within the last 3 years, consulting fees from McCain Foods Inc., Bunge, Ltd. and Temasek Polytechnic, Singapore.

* To whom correspondence should be addressed: e-mail: thomas.wolever@utoronto.ca.

doi: 10.3945/jn.113.177139.

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,

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

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).

Sara A. Chacko
Division of General Medicine and Primary Care, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

Yilin Chen
University of California, Los Angeles (UCLA), Los Angeles, CA

Simin Liu*
Departments of Epidemiology and Medicine, Brown University, Providence, RI

Literature Cited

1. Ye EQ, Chacko SA, Chou EL, Kugizaki M, Liu S. Greater whole-grain intake is associated with lower risk of type 2 diabetes, cardiovascular disease, and weight gain. J Nutr. 2012;142:1304–13.
2. Pins JJ, Geleva D, Keenan JM, Frazel C, O'Connor PJ, Cherney LM. Do whole-grain oat cereals reduce the need for antihypertensive medications and improve blood pressure control? J Fam Pract. 2002;51:353–9.
3. Brownlee IA, Moore C, Chatfield M, Richardson DP, Ashby P, Kuznesof SA, Jebb SA, Seal CJ. Markers of cardiovascular risk are not changed by