Cholesterol-lowering effects of dietary fiber: a meta-analysis[1,2]

Lisa Brown, Bernard Rosner, Walter W Willett, and Frank M Sacks

See corresponding editorial on page 1.

ABSTRACT

Background: The effects of dietary soluble fibers on blood cholesterol are uncertain.

Objective: This meta-analysis of 67 controlled trials was performed to quantify the cholesterol-lowering effect of major dietary fibers.

Design: Least-squares regression analyses were used to test the effect on blood lipids of pectin, oat bran, guar gum, and psyllium. Independent variables were type and amount of soluble fiber, initial cholesterol concentration, and other important study characteristics.

Results: Soluble fiber, 2–10 g/d, was associated with small but significant decreases in total cholesterol [-0.045 mmol $\cdot L^{-1} \cdot$ g soluble fiber^{-1} (95% CI: -0.054, -0.035)] and LDL cholesterol [-0.057 mmol $\cdot L^{-1} \cdot g^{-1}$ (95% CI: -0.070, -0.044)]. The effects on plasma lipids of soluble fiber from oat, psyllium, or pectin were not significantly different. We were unable to compare effects of guar because of the limited number of studies using 2–10 g/d. Triacylglycerols and HDL cholesterol were not significantly influenced by soluble fiber. Lipid changes were independent of study design, treatment length, and background dietary fat content.

Conclusions: Various soluble fibers reduce total and LDL cholesterol by similar amounts. The effect is small within the practical range of intake. For example, 3 g soluble fiber from oats (3 servings of oatmeal, 28 g each) can decrease total and LDL cholesterol by ≈0.13 mmol/L. Increasing soluble fiber can make only a small contribution to dietary therapy to lower cholesterol. *Am J Clin Nutr* 1999;69:30–42.

KEY WORDS Meta-analysis, humans, controlled trials, total cholesterol, low-density-lipoprotein cholesterol, LDL cholesterol, high-density-lipoprotein cholesterol, HDL cholesterol, triacylglycerols, dose response, fiber

INTRODUCTION

Coronary artery disease is the major cause of death in the United States and in most Western countries (1), and blood cholesterol is a major risk factor (2). Dietary and pharmacologic reductions in total and LDL cholesterol decrease the risk of coronary events (3–6), and dietary intervention is the first-line approach (7). Increasing dietary fiber has been recommended as a safe and practical approach for cholesterol reduction (8).

Dietary fiber is a collective term for a variety of plant substances that are resistant to digestion by human gastrointestinal enzymes (9). Dietary fibers can be classified in 2 major groups depending on their solubility in water. In humans, the structural or matrix fibers (lignins, cellulose, and some hemicelluloses) are insoluble, whereas the natural gel-forming fibers (pectins, gums, mucilages, and the remainder of the hemicelluloses) are soluble. Studies have focused on soluble fibers such as oats, psyllium, pectin, and guar gum, and qualitative reviews suggested that these fibers lower total and LDL cholesterol (10, 11). Water-insoluble wheat fiber and cellulose have no effect unless they displace foods supplying saturated fats and cholesterol (12).

There is debate as to the degree of cholesterol reduction caused by soluble fibers. The range of effects on total cholesterol varies from -18% to 0% in trials of oat products, from -17% to 3% for psyllium, from -16% to -5% for pectin, and from -17% to 4% for guar gum (12). Reasons for such large variations include small sample sizes, different dosages of fiber, different background diets, concurrent changes in body weight, varying dietary control, and different types of subjects. It is also possible that certain fibers lower cholesterol more effectively than others. For example, Bell et al (13) examined the hypocholesterolemic effects of psyllium-and pectin-enriched cereals in a randomized, controlled study. They found that the psyllium-enriched cereal lowered cholesterol more effectively than the pectin-enriched cereal. Also, trials of oat products suggested that hypercholesterolemic patients are more responsive than normolipidemic persons (14, 15).

Concurrent changes in fat and cholesterol caused by inadequate dietary control can confound the relation between increased fiber intake and blood cholesterol concentrations. For this reason, quantitating the direct effect of fiber on cholesterol lowering, in addition to that attributed to displacement of saturated and *trans*-unsaturated fat in the diet, is difficult.

[1] From the Departments of Nutrition, Epidemiology, and Biostatistics, Harvard School of Public Health, Boston, and The Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, Boston.

[2] Address reprint requests to L Brown, Harvard School of Public Health, Department of Nutrition, 677 Huntington Avenue, Boston, MA 02115.

Received July 30, 1998.

Accepted for publication July 31, 1998.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

In this meta-analysis of controlled trials, we evaluated the cholesterol-lowering effects of several water-soluble fibers. We studied the influence on blood lipid changes of fiber type, dosage, initial cholesterol concentration, concurrent changes in dietary fat and cholesterol, and other aspects of the study designs.

MATERIALS AND METHODS

Trials of the effects of dietary fiber on blood cholesterol concentrations in adults were identified by a computerized literature search (MEDLINE; National Library of Medicine, Bethesda, MD) of articles published from 1966 to June 1996 and examination of cited reference sources. Only published trials reported in English were considered; however, we included one unpublished trial by Beling et al (1991; provided by Quaker Oats, Chicago), which has been previously referenced in the literature (15). Studies were selected for analysis if they met the following criteria: *1*) they were controlled (insoluble fiber or low-fiber diet used for comparison with a high-fiber diet or a placebo used for comparison with a pure fiber supplement) and had either a randomized crossover or a parallel design; *2*) they provided lipid changes in the fiber and control groups to permit calculation of the treatment effect; *3*) they had an intervention period ≥14 d (16–18); *4*) they used soluble fiber from a single source to permit analysis of differences between fiber types; *5*) the amount of soluble fiber used was indicated or could be estimated from the published literature (19–21); *6*) they had a minimum lead-in period of 14 d for studies administering the fiber with a low-fat, low-cholesterol diet to eliminate possible effects on plasma lipids due to overall dietary changes (16–18); and *7*) dietary changes for both the fiber and control groups were made under isoenergetic conditions. This analysis was limited to primary sources of fiber for which there were >5 trials per type: oat products, psyllium, pectin, and guar gum.

The net changes in total cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerols are presented in units of $mmol \cdot L^{-1} \cdot g$ soluble $fiber^{-1}$. For studies with parallel group designs, lipid effects were calculated by subtracting the mean change in the control (low fiber) group from that in the treatment (high fiber) group. In crossover studies, the estimate represents the difference in posttreatment lipid concentrations for the high-fiber and low-fiber periods. The net change was divided by the daily dose of soluble fiber.

Individual studies were weighted by the inverse of the variance of the fiber effect. For each trial, we estimated the SE of the treatment effect for the lipid outcome measures by using the SDs of paired differences (follow-up minus initial) for the treatment and control groups. If the SDs were not provided, we used the SE values derived from the exact *t* ratios, *P* values, or 95% CIs (22). The within-study SE was divided by the average daily dose for each study to estimate the SE of the treatment effect per gram fiber.

We were unable to calculate the correct within-study SEs for more than two-thirds of the trials on the basis of the published data (few reported exact probability values or CIs for the group differences described above). As an alternative, we estimated the SE by using previously published methods and data from the Lipid Research Clinics (23–28; **Appendix A**).

We computed summary estimates (effect sizes) of the net lipid changes by combining the mean effect sizes reported by individual studies weighted by the inverse of the individual and between-study variance according to a random effects model (29). Summary estimates were computed for each type of soluble fiber separately and for all fibers combined. All effect sizes are presented with 95% CIs based on the estimated variances (Appendix A). We assessed the homogeneity of effect sizes by the *Q* test (29), where $Q > \chi^2_{k-1,\,0.95}$ indicated that the individual estimates for *k* studies were not estimators of one underlying effect.

For meta-analyses of each fiber type, we selected one set of lipid results per study to avoid undue weighting of a study. For instance, for the trial by Kestin et al (30), comparing oat bran, wheat bran, and rice bran, we selected the effect size comparing oat bran and wheat bran because wheat was the most often used control fiber in the studies included in the meta-analysis. When more than one dose was studied (31–33), the mean lipid change across all doses was used to provide an average effect size. However, each dose was represented separately in the dose-response analysis.

Weighted least-squares regression analyses were performed by using the general linear models procedure of the SAS program (34) to test for differences in lipid changes (without dividing by the dose of soluble fiber). In addition to the amount of soluble fiber, the following independent variables were included in the model: initial cholesterol concentration; type of dietary fiber; study design (parallel or crossover); health status of study population (healthy, hyperlipidemic, or diabetic); mean age; background diet (low-fat, low-cholesterol diet compared with usual diet); dietary changes (change in the high-fiber period minus change in the low-fiber period) in total fat, saturated fat, and dietary cholesterol; type of control (low-fiber control product compared with diet only); and treatment length. All models were weighted by using the inverse of the variance of each effect estimate. Models of dose response (dose of specific fiber and dose response stratified by initial cholesterol concentration) were examined by forcing the intercept through zero. Further modeling was done to determine the effects of variability of these covariates among studies as predictors of changes in blood lipids after the amount of soluble fiber and initial lipid concentrations were controlled for. We did not assume a zero-intercept model to examine the influence of these other covariates. A two-sided significance level of 0.05 was used.

We calculated predicted changes in blood cholesterol from changes in dietary fatty acids and cholesterol by using the equations of Keys et al (18) and Mensink and Katan (35) when sufficient dietary data were included in the published reports. This calculation was used to determine whether lipid changes could be attributed to dietary changes other than the inclusion of soluble fiber in the diet. An adjusted effect size for soluble fibers was computed for each trial by subtracting the expected lipid changes from the observed lipid changes (the combined effect of fat and fiber). A new summary effect size was then calculated by using the adjusted values for each trial.

RESULTS

Characteristics of the studies

We reviewed 162 clinical studies reporting the effects of oat products, psyllium, pectin, or guar fiber on blood cholesterol. A description of the individual trials considered for this meta-analysis may be requested by contacting the corresponding author. Ninety-two studies were excluded: 81 were not sufficiently controlled, 8 had insufficient information, and 3 had a treatment

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

period <14 d. Seventy published reports were identified for a quantitative analysis. Three of these studies were included only in the dose-response analysis because they did not use a true low-fiber control but rather compared a high with a lower dose of the same intervention fiber (36–38). The 67 trials included in the analysis are summarized in **Table 1** and included 25 trials of oat products (30–33, 39–59), 17 of psyllium (13, 60–74), 7 of pectin (13, 75–80), and 18 of guar gum (81–98). Not all trials of different fiber sources provided total cholesterol, LDL-cholesterol, HDL-cholesterol, and triacylglycerol concentrations.

The meta-analyses included 2990 subjects (1733 men, 1011 women, 246 sex not specified) whose average age was 50 y. The average dose of 9.5 g soluble fiber was administered over a mean treatment period of 49 d. Fifty-seven of 67 (85%) studies included in the meta-analyses used a control fiber that was low in soluble fiber, such as wheat bran, cellulose-based placebo, or corn flakes. The remaining 10 trials (15%) compared the fiber intervention with a diet that excluded the fiber intervention (diet only).

In 38 studies the background diets were the subjects' usual diets, which were most often similar to conventional Western diets in fat and cholesterol contents; in 29 studies the background diets were low in fat and cholesterol (<30% of energy from fat and <300 mg cholesterol/d). During the high-fiber intervention, subjects consumed an average of 188 kJ more energy than during the control period. Dietary fat and cholesterol were slightly reduced during the high-fiber intervention: −2.8 g total fat, −0.34 g saturated fat, and −2.5 g cholesterol. Both groups receiving the high- and low-soluble-fiber interventions lost weight, 0.19 and 0.64 kg, respectively.

Effect of soluble fiber

In the full dose range, soluble fiber significantly reduced both total and LDL cholesterol: −0.028 (95% CI: −0.035, −0.022) $mmol \cdot L^{-1} \cdot g$ soluble $fiber^{-1}$ [−1.10 (−1.34, −0.87) mg/dL] and −0.029 (−0.035, −0.023) $mmol \cdot L^{-1} \cdot g$ soluble $fiber^{-1}$ [−1.13 (−1.37, −0.89) mg/dL], respectively (**Table 2**). High-fiber diets also significantly reduced HDL cholesterol, but by a much smaller amount: −0.002 (−0.004, −0.0003) $mmol \cdot L^{-1} \cdot g$ soluble $fiber^{-1}$ [−0.07 (−0.13, −0.01) mg/dL]. Soluble fiber intake did not significantly affect triacylglycerol concentrations: 0.001 (−0.004, 0.006) $mmol \cdot L^{-1} \cdot g$ soluble $fiber^{-1}$ [0.07 (−0.35, 0.50) mg/dL]. The tests for heterogeneity were highly significant (all $P < 0.001$), indicating that the lipid changes may have been better characterized by separate estimates for studies similar in design or subject characteristics such as type of soluble fiber.

Dose response

The net change in total and LDL cholesterol is plotted against the mean daily dose of soluble fiber in **Figure 1**. The plot suggests a nonlinear dose response. To test for nonlinearity, an exponential term for dose (natural log of the amount of soluble fiber) was used in the weighted least-squares regression models. We found significant nonlinearity with doses >10 g/d for total cholesterol and with doses >8 g/d for LDL cholesterol.

The meta-analyses in Table 2 were repeated for the practical dose range (≤10 g/d) and we found that the overall effects of fiber were greater compared with the results for the total dose range: 1 g soluble fiber/d produced a change in total and LDL cholesterol of −0.045 and −0.057 mmol/L (−1.73 and −2.21 mg/dL). There was no significant dose-response relation between soluble fiber and changes in HDL-cholesterol or triacylglycerol concentrations.

Effect of initial lipid concentration

On the basis of weighted least-squares regression analyses, the initial total cholesterol concentration was not a significant predictor of lipid changes after adjustment for dose when entered into the models as either a continuous variable ($P = 0.18$) or a categorical (> compared with <6.20 mmol/L) variable ($P = 0.91$). There was a greater decrease in LDL cholesterol in studies in which subjects had an average initial LDL-cholesterol concentration >4.3 mmol/L [−0.034 mmol/L (−1.33 mg/dL), $P = 0.02$] compared with an average initial LDL-cholesterol concentration <4.3 mmol/L [−0.015 mmol/L (−0.58 mg/dL), $P = 0.26$]. However, this difference was only marginally significant ($P = 0.05$). Net lipid changes were not significantly related to initial concentrations for either HDL ($P = 0.38$) or triacylglycerols ($P = 0.53$) after adjustment for dose.

Type of soluble fiber

Soluble fiber from oat products, psyllium, pectin, and guar gum each significantly lowered total cholesterol (**Figure 2**, Table 2). One gram of soluble fiber from oats, psyllium, pectin, or guar gum produced changes in total cholesterol of −0.037, −0.028, −0.070, and −0.026 mmol/L (−1.42, −1.10, −2.69, and −1.13 mg/dL), respectively, and in LDL cholesterol of −0.032, −0.029, −0.055, and −0.033 mmol/L (−1.23, −1.11, −1.96, and −1.20 mg/dL), respectively. These values were slightly higher when the meta-analysis was repeated for the practical dose range. Psyllium and guar gum lowered HDL cholesterol significantly but minimally (Table 2). None of the soluble fibers affected triacylglycerols. Type of soluble fiber was not a significant predictor of lipid changes after the initial lipid concentration was controlled for by linear regression. We were unable to compare effects of guar with those of the other fibers because of the limited number of studies using 2–10 g/d.

Effect of other variables

After dose of soluble fiber and initial lipid concentrations were controlled for, none of the following factors was a significant predictor of changes in blood lipids: type of study design, type of control, treatment length, background diet, type of subject, weight change, or changes in dietary intake of fat and cholesterol.

Dietary changes

For 22 of the 67 studies (33%), sufficient dietary data were provided to calculate predicted changes in total cholesterol by using equations from Keys et al (18) or Mensink and Katan (35). There were 13 oat, 6 psyllium, and 3 pectin studies with doses of soluble fiber ranging between 2.2 and 15 g. Most of the studies reported reductions in total cholesterol that were greater than predicted from changes in fatty acid or cholesterol intake. The effect of fiber before adjusting for expected change in total cholesterol was −0.039 (−0.042, −0.037) mmol/L [−1.51 (−1.58, −1.43) mg/dL] compared with −0.033 (−0.035, −0.032) mmol/L [−1.30 (−1.37, −1.23) mg/dL] after adjustment for expected change as estimated by the Keys equation. Expected change as estimated by the Mensink and Katan equation was −0.036 (−0.038, −0.034) mmol/L [−1.40 (−1.48, −1.32) mg/dL]. Thus, because the adjusted estimates were similar to the

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

TABLE 1
Summary of trials included in the meta-analysis[1]

Fiber source	No. of trials	No. of subjects	Average dose of soluble fiber	Average length of treatment	Type of control (no. of trials)	Subject type (no. of trials)	Mean age	Background diet (no. of trials)	Mean initial lipid concentration[2]
			g	*d*			*y*		*mmol/L*
Oat products	25: 13P, 12X	1600: 817M, 598F[3] Parallel: 703T, 552C Crossover: 345T, 345C	5.0 (1.5–13.0)[4]	39 (14–84)	18 Low-fiber control, 7 diet only	10 Healthy, 13 hyperlipidemic, 1 DM+hyperlipidemic, 1 other	48 (26–61)	12 LFLC, 13 usual	TC: 6.31 ± 0.84 LDL: 4.40 ± 0.69 HDL: 1.28 ± 0.15 TG: 1.82 ± 1.98
Psyllium	17: 11P, 6X	757: 515M, 242F Parallel: 279T, 276C Crossover: 202T, 202C	9.1 (4.7–16.2)	53 (14–112)	16 Low-fiber control, 1 diet only	5 Healthy, 12 hyperlipidemic	51 (44–59)	13 LFLC, 4 usual	TC: 6.41 ± 0.68 LDL: 4.37 ± 0.70 HDL: 1.23 ± 0.32 TG: 1.79 ± 0.72
Pectin	7: 3P, 4X	277: 216M, 61F Parallel: 95T, 94C Crossover: 88T, 88C	4.7 (2.2–9.0)	34 (28–42)	5 Low-fiber control, 2 diet only	4 Healthy, 1 hyperlipidemic, 1 DM, 1 other	50 (31–65)	1 LFLC, 6 usual	TC: 5.62 ± 0.73 LDL: 4.01 ± 0.59 HDL: 1.48 ± 0.36 TG: 1.45 ± 0.44
Guar gum	18: 5P, 13X	356: 185M, 110F Parallel: 69T, 59C Crossover: 228T, 228C	17.5 (6.6–30.0)	66 (28–168)	18 Low-fiber control	2 Healthy 4 hyperlipidemic, 8 DM, 4 DM+hyperlipidemic	52 (27–63)	3 LFLC, 15 usual	TC: 6.49 ± 0.88 LDL: 4.12 ± 0.80 HDL: 1.27 ± 0.21 TG: 1.76 ± 0.64
Total[5]	67: 32P, 35X	2990: 1733M, 1011F[3] Parallel: 1146T, 981C Crossover: 863T, 863C	9.5 (1.5–30.0)	49 (14–168)	57 Low-fiber control, 10 diet only	21 Healthy, 30 hyperlipidemic, 9 DM, 5 DM+hyperlipidemic, 2 other	50 (26–65)	29 LFLC, 38 usual	TC: 6.23 ± 0.88 LDL: 4.25 ± 0.72 HDL: 1.27 ± 0.21 TG: 1.76 ± 0.64

[1] P, parallel; X, crossover; T, treated; C, control; hyperlipidemic, initial cholesterol >6.2 mmol/L (>240 mg/dL); DM, diabetes mellitus; LFLC, low-fat, low-cholesterol diet (typically 30% of energy from fat; ≤10% each from saturated, polyunsaturated, and monounsaturated fats; and <300 mg choleserol); TC, total cholesterol; TG, triacylglycerol.

[2] To convert values for cholesterol to mg/dL, divide by 0.02586; to convert values for TG to mg/dL, divide by 0.01129. Not all studies of different fiber sources provided total, LDL-, and HDL-cholesterol and triacylglycerol concentrations.

[3] The number of male and female subjects does not equal the total number of subjects because some studies did not specify the sex of the subjects.

[4] Range in parentheses.

[5] Meta-analysis included 67 trials; however, studies did not necessarily report measurements of all 4 lipid changes (total cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol).

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

TABLE 2
Net change in blood lipids in subjects consuming diets high in soluble fiber compared with low-fiber diets[1]

Lipid measured and fiber source	Full dose range (2–30 g/d)				Practical dose range (2–10 g/d)[2]			
	No. of studies	No. of subjects	Net change per gram soluble fiber[3]	Heterogeneity (Q)	No. of studies	No. of subjects	Net change per gram soluble fiber[3]	Heterogeneity (Q)
			$mmol \cdot L^{-1} \cdot g^{-1}$				$mmol \cdot L^{-1} \cdot g^{-1}$	
Total cholesterol								
Oat products	25	1600 P: 703T, 552C X: 345T, 345C	−0.037 (−0.051, −0.022)[4]	62.6[5]	22	1512 P: 680T, 527C X: 305T, 305C	−0.040 (−0.054, −0.026)	43.4[6]
Psyllium	17	757 P: 279T, 276C X: 202T, 202C	−0.028 (−0.037, −0.020)	27.5[7]	12	535 P: 231T, 226C X: 78T, 78C	−0.037 (−0.049, −0.025)	15.1
Pectin	7	277 P: 95T, 94C X: 88T, 88C	−0.070 (−0.117, −0.022)	32.6[5]	7	277 P: 95T, 94C X: 88T, 88C	−0.070 (−0.117, −0.022)	32.6[5]
Guar gum	17	341 P: 69T, 59C X: 213T, 213C	−0.026 (−0.038, −0.015)	180.5[5]	2[8]	40 P: 20T, 20C X: 0T, 0C	—	—
All fibers[9]	66	2975 P: 1146T, 981C X: 848T, 848C	−0.028 (−0.035, −0.022)	260.4[5]	43	2364 P: 1026T, 867C X: 471T, 471C	−0.045 (−0.054, −0.035)	91.4[5]
LDL cholesterol								
Oat products	22	1439 P: 641T, 493C X: 305T, 305C	−0.032 (−0.047, −0.017)	79.7[10]	13	867 P: 347T, 259C X: 261T, 261C	−0.037 (−0.040, −0.034)	75.8[10]
Psyllium	17	757 P: 279T, 276C X: 202T, 202C	−0.029 (−0.045, −0.025)	123.2[5]	4	151 P: 43T, 48C X: 60T, 60C	−0.067 (−0.146, −0.014)	29.5[5]
Pectin	4	117 P: 20T, 19C X: 78T, 78C	−0.055 (−0.087, −0.022)	7.3[7]	4	117 P: 20T, 19C X: 78T, 78C	−0.055 (−0.087, −0.022)	7.3[7]
Guar gum	12	218 P: 49T, 40C X: 129T, 129C	−0.033 (−0.048, −0.017)	76.6[5]	1[8]	16 P: 8T, 8C X: 0T, 0C	—	—
All fibers[9]	55	2531 P: 989T, 828C X: 714T, 714C	−0.029 (−0.035, −0.023)	193.6[5]	22	1151 P: 418T, 334C X: 399T, 399C	−0.057 (−0.070, −0.044)	35.6[11]
HDL cholesterol								
Oat products	24	1542 P: 674T, 523C X: 345T, 345C	−0.002 (−0.007, 0.003)	70.0[5]	18	998 P: 400T, 305C X: 293T, 293C	−0.001 (−0.007, 0.008)	43.4[5]
Psyllium	17	757 P: 279T, 276C X: 202T, 202C	−0.002 (−0.004, −0.0003)	15.8	12	535 P: 231T, 226C X: 78T, 78C	−0.004 (−0.008, −0.001)	10.0
Pectin	7	277 P: 95T, 94C X: 88T, 88C	−0.004 (−0.028, 0.020)	84.7[5]	7	277 P: 95T, 94C X: 88T, 88C	−0.004 (−0.028, 0.020)	84.7[5]
Guar gum	15	302 P: 69T, 59C X: 174T, 174C	−0.003 (−0.005, −0.002)	11.3	2[8]	40 P: 20T, 20C X: 0T, 0C	—	—
All fibers[9]	63	2878 P: 1117T, 952C X: 809T, 809C	−0.002 (−0.004, −0.0003)	167.3[5]	39	1850 P: 746T, 645C X: 459T, 459C	−0.003 (−0.006, 0.001)	134.8[5]
Triacylglycerol								
Oat products	20	1374 P: 656T, 508C X: 210T, 210C	0.008 (−0.005, 0.022)	24.1	16	882 P: 382T, 290C X: 210T, 210C	0.006 (−0.006, 0.018)	17.5
Psyllium	16	720 P: 260T, 258C X: 202T, 202C	0.003 (−0.007, 0.013)	17.6	11	498 P: 212T, 208C X: 78T, 78C	0.003 (−0.013, 0.020)	13.8
Pectin	6	247 P: 81T, 78C X: 88T, 88C	−0.021 (−0.066, 0.025)	17.6[5]	6	247 P: 81T, 78C X: 88T, 88C	−0.021 (−0.066, 0.025)	17.6[5]

Continued on next page

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

TABLE 2 (*Continued*)

Lipid measured and fiber source	Full dose range (2–30 g/d)				Practical dose range (2–10 g/d)[2]			
	No. of studies	No. of subjects	Net change per gram soluble fiber[3]	Heterogeneity (Q)	No. of studies	No. of subjects	Net change per gram soluble fiber[3]	Heterogeneity (Q)
			$mmol \cdot L^{-1} \cdot g^{-1}$				$mmol \cdot L^{-1} \cdot g^{-1}$	
Guar gum	17	338 P: 69T, 59C X: 128T, 128C	−0.001 (−0.009, 0.006)	48.9[5]	2[8]	40 P: 20T, 20C X: 0T, 0C	—	—
All fibers[9]	59	2679 P: 1066T, 903C X: 710T, 710C	0.001 (−0.004, 0.006)	181.7[5]	35	1667 P: 695T, 596C X: 376T, 376C	0.003 (−0.015, 0.021)	85.31[5]

[1] P, parallel study; X, crossover study; T, treated; C, control. Average daily dose of soluble fiber: oat products, 5.0 g; psyllium, 9.1 g; pectin, 4.7 g: guar gum, 17.5 g; all fibers combined, 9.5 g.

[2] Linear regression analyses were restricted to studies that used a dose ≤10 g/d for total cholesterol, HDL cholesterol, and triacylglycerol because of nonlinearity of the dose response. Analysis of LDL changes was restricted to studies that used a dose ≤8 g/d.

[3] Net change expressed as the value during the high-fiber diet minus that during the control (low fiber) period. To convert values for cholesterol to mg/dL, divide by 0.02586; to convert values for triacylglycerol to mg/dL, divide by 0.01129.

[4] 95% CI in parentheses.

[5] $P < 0.001$.

[6] $P < 0.002$.

[7] $P < 0.05$.

[8] We were unable to analyze guar studies separately because of the limited number of studies within the restricted dose range.

[9] Meta-analysis included 67 trials; however, studies did not necessarily report measurements of all 4 lipid changes (total cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol).

[10] $P < 0.005$.

[11] $P < 0.03$.

unadjusted estimates, the observed lipid changes cannot be attributed primarily to the substitution of dietary fats and cholesterol for dietary fiber within this subset of trials.

DISCUSSION

This analysis of 67 controlled clinical trials indicated that diets high in soluble fiber decrease total and LDL cholesterol. These findings are generally consistent with individual published reports because high intakes of soluble fiber were associated with significant decreases in total and LDL cholesterol in 60–70% of the trials. Dietary fiber had a small HDL-lowering effect at the borderline of statistical significance and did not affect triacylglycerol concentrations.

There was substantial heterogeneity among individual studies, suggesting that effects of fiber are not uniform. Differences in the dose of soluble fiber accounted for some of the variability in study results. Type of fiber apparently did not account for a significant amount of variability; however, it is possible that small differences between fibers of −0.02 to −0.03 $mmol \cdot L^{-1} \cdot g$ soluble $fiber^{-1}$ may not be detectable.

We found significant nonlinearity at higher doses, which may have been due to diminished adherence or a biological maximum being reached at higher doses (32). By analyzing lipid changes within the restricted dose range (≤10 g), we could assess lipid effects within more practical ranges of soluble fiber intake and within the range in which the dose response appeared linear.

Our primary dose-response analyses were conducted by assuming a zero intercept. Analyses allowing a nonzero intercept produced a slightly smaller effect of fiber because the intercepts were negative. This suggests that cholesterol would decrease in the treatment group even if there was no added fiber in the high-fiber group. This could result from nonlinearity of the relation between fiber intake and change in lipids or residual confounding by other important factors, such as body weight or dietary fat changes, for which we were unable to adequately control. For example, although we found that the changes in blood cholesterol could not be attributed to the substitution of fiber for dietary fats and cholesterol in most of the studies with available data, most of the published reports did not provide sufficient dietary data. This lack of sufficient data limits our ability to conclusively rule out this possibility. We also cannot rule out chance as an explanation because the intercepts were not significantly different from zero.

The mechanism by which fiber lowers blood cholesterol remains undefined. Evidence suggests that some soluble fibers bind bile acids or cholesterol during the intraluminal formation of micelles (99). The resulting reduction in the cholesterol content of liver cells leads to an up-regulation of the LDL receptors and thus increased clearance of LDL cholesterol. However, increased bile acid excretion may not be sufficient to account for the observed cholesterol reduction (100). Other suggested mechanisms include inhibition of hepatic fatty acid synthesis by products of fermentation (production of short-chain fatty acids such as acetate, butyrate, propionate) (101); changes in intestinal motility (102); fibers with high viscosity causing slowed absorption of macronutrients, leading to increased insulin sensitivity (103); and increased satiety, leading to lower overall energy intake (104).

Our data do not support previous findings that patients with hypercholesterolemia are more responsive to dietary fiber than are healthy individuals (14, 15). Subgroup analyses of initial cholesterol concentrations showed that persons with moderate or severe hypercholesterolemia (concentrations >6.20 mmol/L, or >240 mg/dL) showed only slightly larger decreases in total cholesterol than did those with lower cholesterol concentrations. We did, however, find that initial LDL cholesterol was a moderately

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

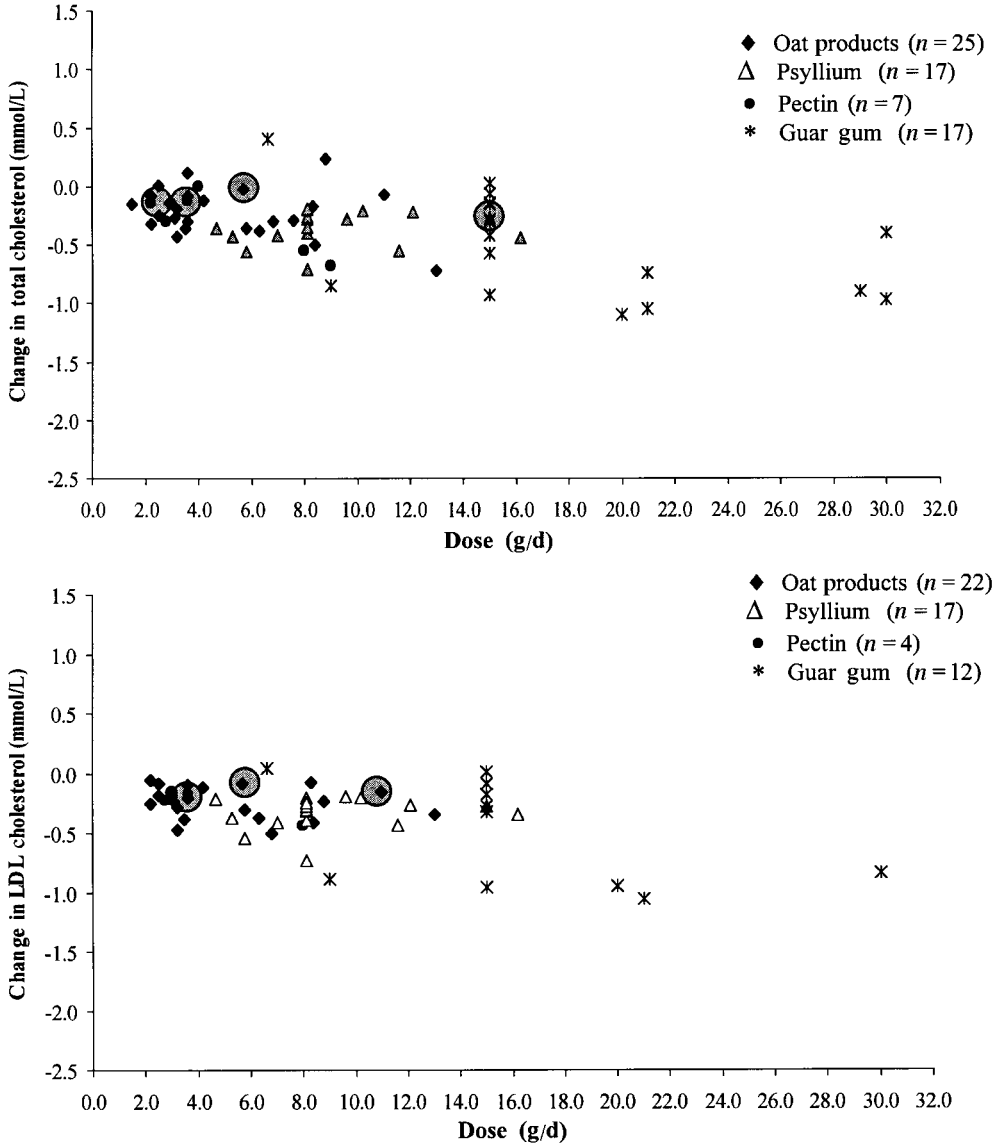

FIGURE 1. Relation between dose of soluble fiber and mean lipid changes. For each study, the net change in total cholesterol and LDL cholesterol (expressed as the change during the high-soluble-fiber period minus the change during the low-soluble-fiber period) is plotted against the mean daily dose of soluble fiber. All models were weighted by using the inverse of the variance of each effect size and forcing the intercept through zero. Plots show an inverse association between dose of soluble fiber and mean changes in total and LDL cholesterol ($P < 0.001$). Individual studies with low variance in the meta-analysis are denoted with circles around the point estimates.

significant predictor of LDL-cholesterol changes, but the difference in responsiveness was small: 0.02 mmol/L (0.75 mg/dL) per gram of soluble fiber ($P = 0.05$).

Most of the available epidemiologic studies suggest that dietary fiber is inversely related to coronary artery disease (5, 105–109). Earlier studies suggested that the effects of fiber may be larger than those shown in this meta-analysis. However, methodologic problems including small sample sizes, incomplete dietary measures, and inadequate control of important confounders made it difficult to determine the effects of dietary fiber independently of other dietary components and, more specifically, the contribution of soluble compared with insoluble fiber. The modest reductions in cholesterol expected from intakes of soluble fiber within practical ranges may exert only a small effect on the risk of heart disease. For example, daily intake of 3 g soluble fiber from either 3 apples or 3 bowls (28-g servings) of oatmeal can decrease total cholesterol by ≈0.129 mmol/L (5 mg/dL), a ≈2% reduction. On the basis of estimates from clinical studies of cholesterol treatment (110), this could lower the incidence of coronary artery disease by ≈4%. These findings are consistent with an earlier summary of the cholesterol-lowering effects of oat products (15).

Publication bias toward studies that showed positive results is always a potential issue in meta-analyses and could be operating in this study. If this were true, then the small effect estimates associated with intake of dietary soluble fiber would be further attenuated, further highlighting the need for conservative public health claims. The major benefit from eating fiber-rich foods

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

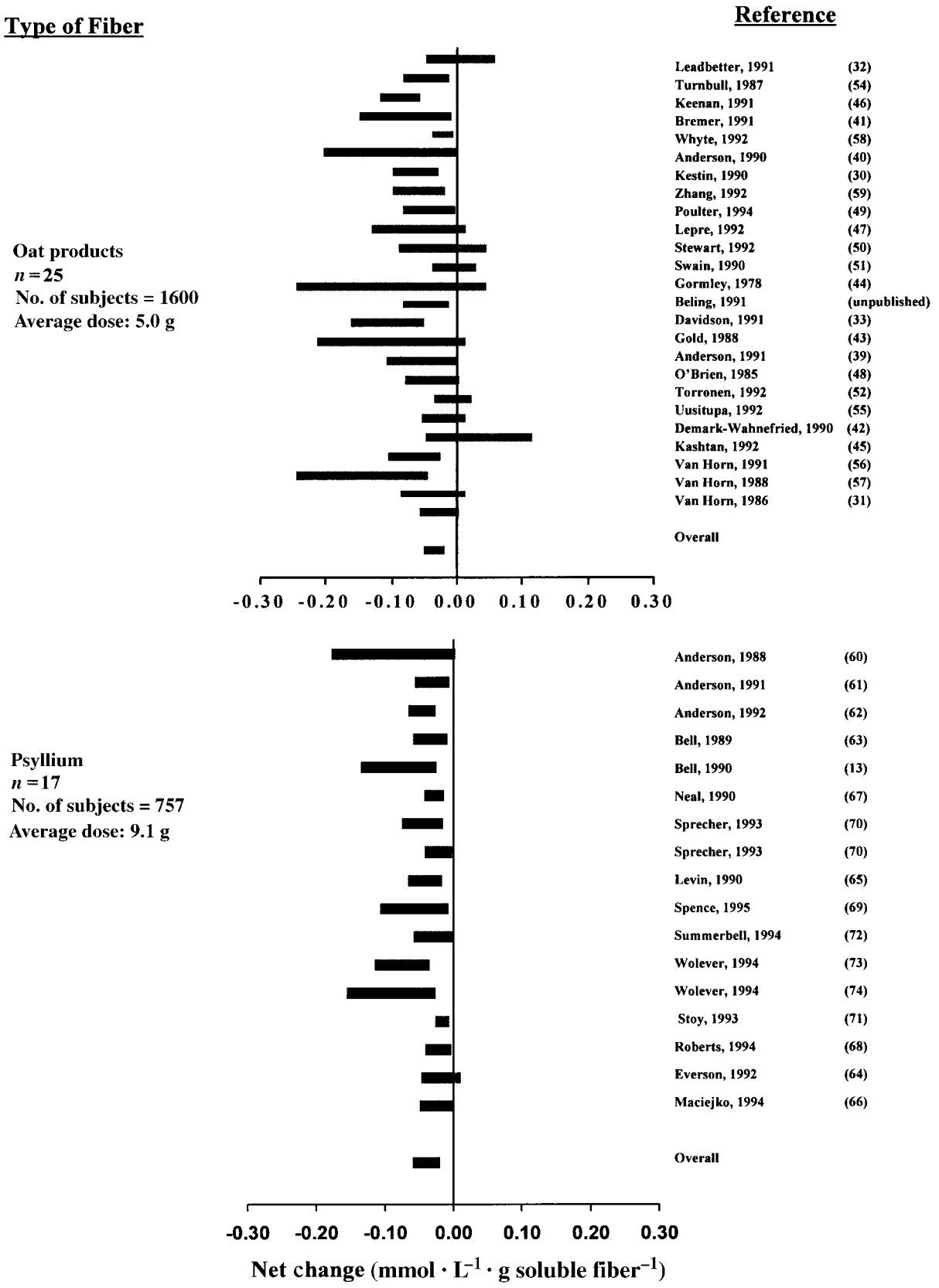

FIGURE 2. Net change in total cholesterol. The net effect of consumption of different dietary fibers on total cholesterol concentrations for oat products, psyllium, pectin, and guar gum. Note that one guar study (85) did not include measures for total cholesterol. The bars represent the width of the 95% CIs for each study. The overall effect estimates and 95% CI are provided for each fiber.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

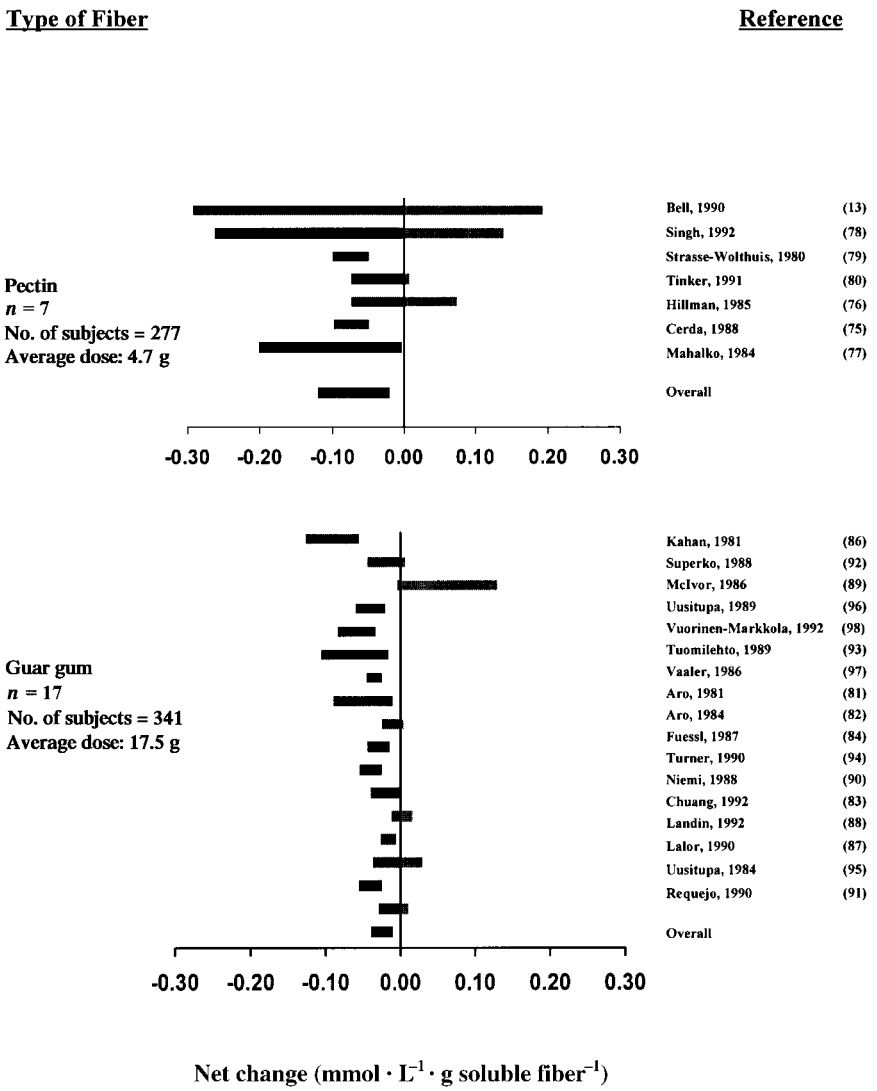

FIGURE 2. *Continued.*

may be a change in dietary pattern, resulting in a diet that is lower in saturated and *trans*-unsaturated fats and cholesterol and higher in protective nutrients such as unsaturated fatty acids, minerals, folate, and antioxidant vitamins.

We are indebted to Peter Goldman, Endel J Orav, Ingrid J Anderson, and Joseph McDevitt for their contributions to the early development of this research and their continued support.

REFERENCES

1. National Center for Health Statistics and the American Heart Association. Facts about cardiovascular disease. Circulation 1992;85: A103 (abstr).
2. Kannel WB, Castelli WD, Gordon T, McNamara PM. Serum cholesterol, lipoproteins, and risk of coronary artery disease. The Framingham Study. Ann Intern Med 1971;74:1–12.
3. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335:1001–9.
4. Byington RP, Jukema JW, Salonen JT, et al. Reduction in cardiovascular events during pravastatin therapy: pooled analysis of clinical events of the Pravastatin Atherosclerosis Intervention Program. Circulation 1995;92:2419–25.
5. Kushi LH, Lew RA, Stare FJ, et al. Diet and 20-year mortality from coronary heart disease: the Ireland-Boston Diet-Heart Study. N Engl J Med 1985;312:811–8.
6. Burr ML, Fehily AM, Gilbert JF. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction. Lancet 1989;2: 757–61.
7. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA 1993;269:3015–23.
8. Trowell HC, Burkitt DP, eds. Western diseases: their emergence and prevention. Cambridge, MA: Harvard University Press, 1981.
9. Eastwood MA, Passmore R. Dietary fibre. Lancet 1983;2:202–6.
10. Truswell AS. Dietary fibre and plasma lipids. Eur J Clin Nutr 1995;49(suppl):S105–9.
11. Glore SR, Van Treeck D, Knehans AW, Guild M. Soluble fiber and serum lipids: a literature review. J Am Diet Assoc 1994;94:425–36.
12. Kris-Etherton PM, Krummel D, Russell ME, et al. The effect of diet on plasma lipids, lipoproteins, and coronary heart disease. J Am Diet Assoc 1988;88:1373–400.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

13. Bell LP, Hectorn KJ, Reynolds H, Hunninghake DB. Cholesterol-lowering effects of soluble-fiber cereals as part of a prudent diet for patients with mild to moderate hypercholesterolemia. Am J Clin Nutr 1990;52:1020–6.
14. Anderson JW. Dietary fibre, complex carbohydrate, and coronary artery disease. Can J Cardiol 1995;11(suppl G):55G–62G.
15. Ripsin CM, Keenan JM, Jacobs DR, et al. Oat products and lipid lowering: a meta-analysis. JAMA 1992;267:3317–25.
16. Keys, Anderson JT, Grande F. Prediction of serum cholesterol responses of man to changes in fats in the diet. Lancet 1957;2:959–66.
17. Brussaard JH, Katan MB, Groot PHE, Havekes LM, Hautvast JGAJ. Serum lipoproteins of healthy persons fed a low-fat diet or a polyunsaturated fat diet for three months. A comparison of two cholesterol-lowering diets. Atherosclerosis 1982;42:205–19.
18. Keys A, Anderson JT, Grande F. Serum cholesterol response to changes in the diet, I-IV. Metabolism 1965;14:747–87.
19. US Department of Agriculture. USDA handbook 8 series: composition of foods. Washington, DC: US Department of Agriculture, 1976–1992. (Agriculture handbooks no. 8-1–8-21.)
20. Nutrition Coordinating Center. Minnesota nutrient data system (NDS) software. Minneapolis: University of Minnesota.
21. Anderson JW. Plant fiber in foods. 2nd ed. Lexington, KY: HCF Nutrition Research Foundation Inc, 1990.
22. D'Agostino RB, Weintraub M. Meta-analysis: a method for synthesizing research. Clin Pharmacol Ther 1995;58:605–16.
23. US Department of Health and Human Services, Public Health Service. The Lipid Research Clinics population studies data book. Vol 1. The prevalence study. Bethesda, MD: National Institutes of Health, 1980. (NIH publication no. 80-1527.)
24. Jacobs DR, Barrett-Connor EB. Retest reliability of plasma cholesterol and triglyceride. Am J Epidemiol 1982;116:878–85.
25. Rosner B, Polk BF. Predictive values of routine blood pressure measurements in screening for hypertension. Am J Epidemiol 1983;117:429–42.
26. Davis CE, Rifkind BM, Brenner H, Gordon DJ. A single cholesterol measurement underestimates the risk of coronary heart disease. An empirical example from the Lipid Research Clinics Mortality Follow Up Study. JAMA 1990;264:3044–6.
27. Cook NR, Rosner BA. Sample size estimation for clinical trials with longitudinal measures: applications to studies of blood pressure. J Epidemiol Biostat 1997;2:65–74.
28. Friedlander Y, Kark JD, Stein Y. Variability of plasma lipids and lipoproteins: the Jerusalem Lipid Research Clinic Study. Clin Chem 1985; 31:1121–6.
29. Laird N, Mosteller F. Some statistical methods for combining experimental results. Int J Technol Assess Health Care 1990;6: 5–30.
30. Kestin M, Moss R, Clifton PM, Nestel PJ. Comparative effects of three cereal brans on plasma lipids, blood pressure, and glucose metabolism in mildly hypercholesterolemic men. Am J Clin Nutr 1990;52:661–6.
31. Van Horn LV, Liu K, Parker D, et al. Serum lipid response to oat product intake with a fat-modified diet. J Am Diet Assoc 1986;86:759–64.
32. Leadbetter J, Ball MJ, Mann JI. Effects of increasing quantities of oat bran in hypercholesterolemic people. Am J Clin Nutr 1991;54:841–5.
33. Davidson MH, Dugan LD, Burns JH, Bova J, Story K, Drennan KB. The hypocholesterolemic effects of β-glucan in oatmeal and oat bran: a dose-controlled study. JAMA 1991;265:1833–9.
34. SAS Institute Inc. SAS/STAT user's guide, version 6, 4th ed. Vol 2. Cary, NC: SAS Institute Inc, 1989.
35. Mensink RP, Katan MB. Effect of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials. Arterioscler Thromb 1992;12:911–9.
36. Mackay S, Ball MJ. Do beans and oat bran add to the effectiveness of a low-fat diet? Eur J Clin Nutr 1992;46:641–8.
37. Fagerberg S-E. The effects of a bulk laxative (Metamucil®) on fasting blood glucose, serum lipids, and other variables in constipated patients with non-insulin dependent adult diabetes. Curr Ther Res 1982;31:166–72.
38. Judd PA, Truswell AS. Comparison of the effects of high- and low-methoxyl pectins on blood and faecal lipids in man. Br J Nutr 1982;48:451–8.
39. Anderson JW, Gilinsky NH, Deakins DA, et al. Lipid responses of hypercholesterolemic men to oat-bran and wheat-bran intake. Am J Clin Nutr 1991;54:678–83.
40. Anderson JW, Spencer DB, Hamilton CC, et al. Oat-bran cereal lowers serum total and LDL cholesterol in hypercholesterolemic men. Am J Clin Nutr 1990;52:495–9.
41. Bremer JM, Scott RS, Lintott CJ. Oat bran and cholesterol reduction: evidence against specific effect. Aust N Z J Med 1991;21: 422–6.
42. Demark-Wahnefried W, Bowering J, Cohen PS. Reduced serum cholesterol with dietary change using fat-modified and oat bran supplemented diets. J Am Diet Assoc 1990;90:223–9.
43. Gold KV, Davidson DM. Oat bran as a cholesterol-reducing dietary adjunct in a young, healthy population. West J Med 1988; 148:299–302.
44. Gormley TR, Kevany J, O'Donnell B, McFarlane R. Investigation of the potential of porridge as a hypocholesterolaemic agent. Int J Food Sci Technol 1978;2:85–91.
45. Kashtan H, Stern HS, Jenkins DJA, et al. Wheat-bran and oat-bran supplements' effects on blood lipids and lipoproteins. Am J Clin Nutr 1992;55:976–80.
46. Keenan JM, Wenz JB, Myers S, Ripsin C, Huang Z. Randomized, controlled, crossover trial of oat bran in hypercholesterolemic subjects. J Fam Pract 1991;33:600–8.
47. Lepre F, Crane S. Effect of oatbran on mild hyperlipidaemia. Med J Aust 1992;157:305–8.
48. O'Brien LT, Barnard RJ, Hall JA, Pritikin N. Effects of a high-complex-carbohydrate low-cholesterol diet plus bran supplement on serum lipids. J Appl Nutr 1985;37:26–34.
49. Poulter N, Chang CL, Cuff A, Poulter C, Sever P, Thom S. Lipid profiles after the daily consumption of an oat-based cereal: a controlled crossover trial. Am J Clin Nutr 1994;59:66–9.
50. Stewart FM, Neutze JM, Newsome-White R. The addition of oat-bran to a low fat diet has no effect on lipid values in hypercholesterolaemic subjects. N Z Med J 1992;105:398–400.
51. Swain JF, Rouse IL, Curley CB, Sacks FM. Comparison of the effects of oat bran and low-fiber wheat on serum lipoprotein levels and blood pressure. N Engl J Med 1990;322:147–52.
52. Törrönen R, Kansanen L, Uusitupa M, et al. Effects of an oat bran concentrate on serum lipids in free-living men with mild to moderate hypercholesterolemia. Eur J Clin Nutr 1992;46:621–7.
53. Turnbull WH, Leeds AR. The effect of rolled oats and a reduced/modified fat diet on apolipoprotein AI and B. J Clin Nutr Gastroenterol 1989;1:15–9.
54. Turnbull WH, Leeds AR. Reduction of total and LDL-cholesterol in plasma by rolled oats. J Clin Nutr Gastroenterol 1987;2:177–81.
55. Uusitupa MIJ, Ruuskanen E, Mäkinen E, et al. A controlled study on the effect of beta-glucan-rich oat bran on serum lipids in hypercholesterolemic subjects: relation to apolipoprotein E phenotype. J Am Coll Nutr 1992;11:651–9.
56. Van Horn L, Moag-Stahlberg A, Liu K, et al. Effects on serum lipids of adding instant oats to usual American diets. Am J Public Health 1991;81:183–8.
57. Van Horn L, Emidy LA, Liu K, et al. Serum lipid response to a fat-modified, oatmeal-enhanced diet. Prev Med 1988;17:377–86.
58. Whyte JL, McArthur R, Topping D, Nestel P. Oat bran lowers plasma cholesterol levels in mildly hypercholesterolemic men. J Am Diet Assoc 1992;92:446–9.
59. Zhang JX, Hallmans G, Andersson H, et al. Effect of oat bran on plasma cholesterol and bile acid excretion in nine subjects with ileostomies. Am J Clin Nutr 1992;56:99–105.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

60. Anderson JW, Zettwoch N, Feldman T, Tietyen-Clark J, Oeltgen P, Bishop CW. Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. Arch Intern Med 1988;148:292–6.
61. Anderson JW, Floore TL, Geil PB, O'Neal DS, Balm TK. Hypocholesterolemic effects of different bulk-forming hydrophilic fibers as adjuncts to dietary therapy in mild to moderate hypercholesterolemia. Arch Intern Med 1991;151:1597–602.
62. Anderson JW, Riddell-Mason S, Gustafson NJ, Smith SF, Mackey M. Cholesterol-lowering effects of psyllium-enriched cereal as an adjunct to a prudent diet in the treatment of mild to moderate hypercholesterolemia. Am J Clin Nutr 1992;56:93–8.
63. Bell LP, Hectorne K, Reynolds H, Balm TK, Hunninghake DB. Cholesterol-lowering effects of psyllium hydrophilic mucilloid: adjunct therapy to a prudent diet for patients with mild to moderate hypercholesterolemia. JAMA 1989;261:3419–23.
64. Everson GT, Daggy BP, McKinley C, Story JA. Effects of psyllium hydrophilic mucilloid on LDL-cholesterol and bile acid synthesis in hypercholesterolemic men. J Lipid Res 1992;33:1183–92.
65. Levin EG, Miller VT, Muesing RA, Stoy DB, Balm TK, LaRosa JC. Comparison of psyllium hydrophilic mucilloid and cellulose as adjuncts to a prudent diet in the treatment of mild to moderate hypercholesterolemia. Arch Intern Med 1990;150:1822–7.
66. Maciejko JJ, Brazg R, Shah A, Patil S, Rubenfire M. Psyllium for the reduction of cholestyramine-associated gastrointestinal symptoms in the treatment of primary hypercholesterolemia. Arch Fam Med 1994;3:955–60.
67. Neal GW, Balm TK. Synergistic effects of psyllium in the dietary treatment of hypercholesterolemia. South Med J 1990;83:1131–7.
68. Roberts DCK, Truswell SA, Bencke A, Dewar HM, Farmakalidis E. The cholesterol-lowering effect of a breakfast cereal containing psyllium fibre. Med J Aust 1994;161:660–4.
69. Spence JD, Huff MW, Heidenheim P, et al. Combination therapy with colestipol and psyllium mucilloid in patients with hyperlipidemia. Ann Intern Med 1995;123:493–9.
70. Sprecher DL, Harris BV, Goldberg AC, et al. Efficacy of psyllium in reducing serum cholesterol levels in hypercholesterolemic patients on high- or low-fat diets. Ann Intern Med 1993; 119:545–54.
71. Stoy DB, LaRosa JC, Brewer BK, Mackey M, Meusing RA. Cholesterol-lowering effects of ready-to-eat cereal containing psyllium. J Am Diet Assoc 1993;93:910–2.
72. Summerbell CD, Manley P, Barnes D, Leeds A. The effects of psyllium on blood lipids in hypercholesterolaemic subjects. J Hum Nutr Diet 1994;7:147–51.
73. Wolever TMS, Jenkins DJA, Mueller S, et al. Psyllium reduces blood lipids in men and women with hyperlipidemia. Am J Med Sci 1994;307:269–73.
74. Wolever TMS, Jenkins DJA, Mueller S, et al. Method of administration influences the serum cholesterol-lowering effect of psyllium. Am J Clin Nutr 1994;59:1055–9.
75. Cerda JJ, Robbins FL, Burgin CW, Baumgartner TG, Rice RW. The effects of grapefruit pectin on patients at risk for coronary heart disease without altering diet or lifestyle. Clin Cardiol 1988;11: 589–94.
76. Hillman LC, Peters SG, Fisher CA, Pomare EW. The effects of the fiber components pectin, cellulose and lignin on serum cholesterol levels. Am J Clin Nutr 1985;42:207–13.
77. Mahalko JR, Sandstead HH, Johnson LK, et al. Effect of consuming fiber from corn bran, soy hulls, or apple powder on glucose tolerance and plasma lipids in type II diabetes. Am J Clin Nutr 1984;39:25–34.
78. Singh RB, Rastogi SS, Singh R, Ghosh S, Niaz MA. Effects of guava intake on serum total and high-density lipoprotein cholesterol levels and on systemic blood pressure. Am J Cardiol 1992; 70:1287–91.
79. Stasse-Wolthuis M, Albers HFF, van Jeveren JGC, et al. Influence of dietary fiber from vegetables and fruits, bran or citrus pectin on serum lipids, fecal lipids, and colonic function. Am J Clin Nutr 1980;33:1745–56.
80. Tinker LF, Schneeman BO, Davis PA, Gallaher DD, Waggoner CR. Consumption of prunes as a source of dietary fiber in men with mild hypercholesterolemia. Am J Clin Nutr 1991;53:1259–65.
81. Aro A, Uusitupa M, Voutilainen E, Hersio K, Korhonen T, Siitonen O. Improved diabetic control and hypocholesterolaemic effect induced by long-term dietary supplementation with guar gum in type 2 (insulin-dependent) diabetes. Diabetologia 1981;21:29–33.
82. Aro A, Uusitupa M, Voutilainen E, Korhonen T. Effects of guar gum in male subjects with hypercholesterolemia. Am J Clin Nutr 1984;39:911–6.
83. Chuang L, Jou T, Yang W, et al. Therapeutic effect of guar gum in patients with non-insulin-dependent diabetes mellitus. J Formos Med Assoc 1992;91:15–9.
84. Fuessl HS, Williams G, Adrian TE, Bloom SR. Guar sprinkled on food: effect on glycaemic control, plasma lipids and gut hormones in non-insulin dependent diabetic patients. Diabet Med 1987;4: 463–8.
85. Holman RR, Steemson J, Darling P, Turner RC. No glycemic benefit from guar administration in NIDDM. Diabetes Care 1987;10: 68–71.
86. Khan AR, Khan GY, Mitchel A, Qadeer MA. Effect of guar gum on blood lipids. Am J Clin Nutr 1981;34:2446–9.
87. Lalor BC, Bhantnagar D, Winocour PH, et al. Placebo-controlled trial of the effects of guar gum and metformin on fasting blood glucose and serum lipids in obese, type 2 diabetic patients. Diabet Med 1990;7:242–5.
88. Landin K, Holm G, Tengborn L, Smith U. Guar gum improves insulin sensitivity, blood lipids, blood pressure, and fibrinolysis in healthy men. Am J Clin Nutr 1992;56:1061–5.
89. McIvor ME, Cummings CC, Van Duyn MA, et al. Long-term effects of guar gum on blood lipids. Atherosclerosis 1986;60:7–13.
90. Niemi MK, Keinanen-Kiukaanniemi SM, Salmela PI. Long-term effects of guar gum and microcrystalline cellulose on glycaemic control and serum lipids in type 2 diabetes. Eur J Clin Pharmacol 1988;34:427–9.
91. Requejo F, Uttenthal LO, Bloom SR. Effects of α-glucosidase inhibition and viscous fibre on diabetic control and postprandial gut hormone responses. Diabet Med 1990;7:515–20.
92. Superko HR, Haskell WL, Sawrey-Kubicek L, Farquhar JW. Effects of solid and liquid guar gum on plasma cholesterol and triglyceride concentrations in moderate hypercholesterolemia. Am J Cardiol 1988;62:51–5.
93. Tuomilehto J, Silvasti M, Manninen V, Uusitupa M, Aro A. Guar gum and gemfibrozil—an effective combination in the treatment of hypercholesterolemia. Atherosclerosis 1989;76:71–7.
94. Turner PR, Tuomilehto J, Happonen P, La Ville AE, Shaikh M, Lewis B. Metabolic studies on the hypolipidaemic effect of guar gum. Atherosclerosis 1990;81:145–50.
95. Uusitupa M, Tuomilehto J, Karttunen P, Wolf E. Long term effects of guar gum on metabolic control, serum cholesterol and blood pressure levels in type 2 (non-insulin-dependent) diabetic patients with high blood pressure. Ann Clin Res 1984;16(suppl):126–31.
96. Uusitupa M, Siitonen O, Savolainen K, Silvasti M, Penttila I, Parviainen M. Metabolic and nutritional effects of long-term use of guar gum in the treatment of noninsulin-dependent diabetes of poor metabolic control. Am J Clin Nutr 1989;49:345–51.
97. Vaaler S, Hanssen KF, Dahl-Jørgensen K, et al. Diabetic control is improved by guar gum and wheat bran supplementation. Diabet Med 1986;3:230–3.
98. Vuorinen-Markkola H, Sinisalo M, Koivisto VA. Guar gum in insulin-dependent diabetes: effects on glycemic control and serum lipoproteins. Am J Clin Nutr 1992;56:1056–60.
99. Anderson JW, Tietyen-Clark JT. Dietary fiber: hyperlipidemia, hypertension and coronary artery disease. Am J Gastroenterol 1986;81:907–19.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

100. Federation of American Societies for Experimental Biology. Physiological effects and health consequences of dietary fiber. Washington, DC: US Department of Health and Human Services, 1987.
101. Nishina PM, Freedland RA. The effects of dietary fiber feeding on cholesterol metabolism in rats. J Nutr 1990;120:800–5.
102. Schneeman BO, Gallaher D. Effects of dietary fiber on digestive enzyme activity and bile acids in the small intestine. Proc Soc Exp Biol Med 1985;180:409–14.
103. Schneeman BO. Dietary fiber and gastrointestinal function. Nutr Rev 1987;45:129–32.
104. Blundell JE, Burley VJ. Satiation, satiety, and the action of fibre on food intake. Int J Obes 1987;11(suppl):9–25.
105. Kromhout D, Bosschieter EB, de Lezenne Coulander C. Dietary fiber and 10-year mortality from coronary heart disease, cancer and all causes: the Zutphen Study. Lancet 1982;2:518–21.
106. Morris JN, Marr JW, Clayton DG. Diet and heart: a postscript. Br Med J 1977;2:1307–14.
107. Khaw KT, Barrett-Connor E. Dietary fiber and reduced ischemic heart disease mortality rates in men and women: a 12-year prospective study. Am J Epidemiol 1987;126:1093–102.
108. Humble CG, Malarcher AM, Tyroler HA. Dietary fiber and coronary heart disease in middle-aged hypercholesterolemic men. Am J Prev Med 1993;9:197–202.
109. Rimm EB, Ascherio A, Giovannucci E, Spiegelman D, Stampfer MJ, Willett WW. Vegetable, fruit, and cereal fiber intake and risk of coronary heart disease among men. JAMA 1996:275:447–51.
110. Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in the incidence of coronary heart disease. JAMA 1984;251:351–64.

APPENDIX A

1. TREATMENT EFFECT CALCULATION

$$\text{Parallel studies: } \Delta_p = [X_{tf} - X_{tb}] - [X_{cf} - X_{cb}] \qquad (A1)$$

$$\left(\begin{array}{c}\text{Mean lipid change}\\ \text{in the treatment group}\end{array}\right) - \left(\begin{array}{c}\text{Mean lipid change}\\ \text{in the control group}\end{array}\right)$$

where X_{tf} is the lipid value at the end of follow-up in the treatment group, X_{tb} is the lipid value before intervention in the treatment group, X_{cf} is the lipid value at the end of follow-up in the control group, and X_{cb} is the lipid value before intervention in the control group.

$$\text{Crossover studies: } \Delta_x = [X_t - X_c] \qquad (A2)$$

$$\left(\begin{array}{c}\text{Response average}\\ \text{after treatment phase}\end{array}\right) - \left(\begin{array}{c}\text{Response average}\\ \text{after control phase}\end{array}\right)$$

where X_t is the lipid value at the end of follow-up and X_c is the lipid value before intervention. The treatment effect was divided by the average daily amount (dose in grams) of soluble fiber. A negative effect size indicates a reduction during the intervention phase.

2. CALCULATION OF WITHIN-STUDY VARIANCE

The primary endpoint is the change in total cholesterol, LDL cholesterol, HDL cholesterol, and triacylglycerol from the end of the dietary run-in period (if applicable) or the concentration before the intervention was initiated (total cholesterol 1) to the end of the intervention period (total cholesterol 2).

To derive a model for the variance of total cholesterol change, we first assumed the following variance component model of Rosner and Polk (1), which includes day-to-day variability and subject-to-subject variability. (Within-day variability is also included but it does not apply in our model because lipids were measured once per visit.)

$$\text{Total cholesterol} = \alpha + \gamma + \beta \qquad (A3)$$

where α is a fixed constant describing the true mean total cholesterol concentration in the population, $\gamma \sim N(0, \sigma^2_p)$ is the true individual deviation about this population mean at the time of the measurements, and $\beta \sim N(0, \sigma^2_d)$ reflects the day-to-day variation.

If we assume that both total cholesterol 1 and total cholesterol 2 are computed as the mean of k measurements, then the variance of each of these measures is given by

$$V(x) = \sigma^2 = \sigma^2_p + \sigma^2_d/k \qquad (A4)$$

The variance of the difference, Δ = total cholesterol 2 – total cholesterol 1, may then be expressed as

$$\text{Var}(\Delta) = 2\sigma^2(1 - r) \qquad (A5)$$

where r is the observed tracking correlation between the cholesterol measures at baseline and follow-up. This quantifies the association between initial and subsequent cholesterol concentrations.

Calculation of variance components

Total cholesterol

By using estimates from the Lipid Research Clinics (2–4) and the above formula, we obtained the following estimates for the variance components, assuming that $k = 2$ (baseline and follow-up).

Day-to-day variation: $\sigma^2_d = 15.7^2 = 246.5$

Between-person variation:
$\sigma^2_p = \sigma^2_{p\ \text{observed}} - \sigma^2_d = 35^2 - 15.7^2 = 978.5$

LDL cholesterol, HDL cholesterol, and triacylglycerol (mg/dL)

	Day-to-day variation: σ^2_d (2,4)	Between-person variation: $\sigma^2_{p\ \text{observed}} - \sigma^2_d = \sigma^2_p$
LDL cholesterol	$15.5^2 = 240.3$	$33^2 - 15.5^2 = 848.8$
HDL cholesterol	$6.4^2 = 41.0$	$11.25^2 - 6.4^2 = 85.6$
Triacylglycerol	$51.0^2 = 2601.0$	$121.0^2 - 51.0^2 = 12040.0$

Calculation of within-study variance

Total cholesterol

The observed tracking correlation between the initial and follow-up total cholesterol equaled 0.815 (4). This value was corrected for within-person variation by using the following formula (5) and the variance components as calculated above. This model assumes that the variance components remain constant over time. The true mean for an individual is allowed to vary over time with a correlation P_{ts} for measurements at time t and s.

$$P_{ts} = P'_{ts} \times \frac{\sqrt{(\sigma p^2 + \sigma w t^2)(\sigma p^2 + \sigma w s^2)}}{\sigma_p{}^2} \qquad (A6)$$

where P_{ts} is the true tracking correlation between cholesterol measures at times t and s where $s > t$, P'_{ts} is the observed tracking correlation between mean cholesterol measures between

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016

times t and s (0.815), σ_p^2 is the between-person variance as calculated on the previous page (978.5), σ_{wt}^2 is the within-person variance at time t (baseline), and σ_{ws}^2 is the within-person variance at time s (follow-up).

Thus,

$$P_{ts} = 0.815 \times \frac{\sqrt{(978.5 + 246/1)\,(978.5 + 246/1)}}{978.5}$$

$P_{ts} = 1$ if the true tracking correlation is 1; eg, if for a short-term period, the only source of variation is within-person variability.

Thus, we estimated that the SD of the change in total cholesterol would be 15.7 mg/dL for one measure taken at baseline and one at the end of treatment as calculated below.

$$\text{Var}\,(\Delta) = 2[\sigma_p^2\,(1 - r) + (\sigma_w^2/2)] \qquad (A7)$$

Thus, Var $(\Delta) = 2[978.5\,(0) + (246/2)] = 246$. SD $= \sqrt{246} = 15.7$ mg/dL (0.41 mmol/L).

LDL cholesterol, HDL cholesterol, and triacylglycerol (mg/dL)

	Observed tracking correlation (4,6)	After correction for within-person variation (P_{ts})	$1 - P_{ts}$	Estimated pre − post SD
LDL cholesterol	0.77	0.99	0.012	16.5
HDL cholesterol	0.67	0.99	0.01	6.5
Triacylglycerol	0.75	0.91	0.09	69.1

3. CALCULATION OF *Q*

Q is used to assess homogeneity of study estimates of effect (7).

$$Q = \Sigma w_i\,(y_i - y_w)^2 \qquad (A8)$$

$$y_w = \Sigma\, w_i\, y_i / \Sigma w_i \qquad (A9)$$

4. CALCULATION OF BETWEEN-STUDY VARIANCE

$$\sigma^2 = [Q - (k - 1)]/\Sigma w_i - (\Sigma w^2{}_i/\Sigma w_i) \qquad (A10)$$

where y_i is the outcome measure for the ith study, σ^2 is between-study variance, $s^2{}_i$ is within-study variance (SE/daily dose of soluble fiber in grams), $w_i = 1/(s^2{}_i)$ for ith study (1/SE), y_w is the weighted mean, and k is the number of studies. $Q > \chi^2_{k-1,\,0.95}$ indicates that individual estimates for k studies are not estimated by one underlying effect.

5. CALCULATION OF SUMMARY ESTIMATE OF EFFECT AND 95% CIs (EFFECT SIZE PER GRAM SOLUBLE FIBER)

Summary estimate: random effects model

The weighted estimate of the overall mean y_w is

$$\bar{y}_w = \frac{\sum_{i=1}^{k} w_{ia} y_i}{\sum_{i=1}^{k} w_{ia}} \qquad (A11)$$

95% CI

$$\bar{y}_w \pm 1.96\,\sqrt{\text{var}\,(y_w)} \qquad (A12)$$

where $w_{ia} = 1/(s^2{}_i + \sigma^2)(d^2)$, d^2 is the daily amount of soluble fiber in grams squared, and var $\bar{y}_w = 1/\Sigma w_{ia}$.

REFERENCES

1. Rosner B, Polk BF. Predictive values of routine blood pressure measurements in screening for hypertension. Am J Epidemiol 1983;117:429–42.
2. US Department of Health and Human Services, Public Health Service. The Lipid Research Clinics population studies data book. Vol 1. The prevalence study. Bethesda, MD: National Institutes of Health, 1980. (NIH publication no. 80-1527.)
3. Jacobs DR, Barrett-Connor EB. Retest reliability of plasma cholesterol and triglyceride. Am J Epidemiol 1982;116:878–85.
4. Davis CE, Rifkind BM, Brenner H, Gordon DJ. A single cholesterol measurement underestimates the risk of coronary heart disease. An empirical example from the Lipid Research Clinics Mortality Follow Up Study. JAMA 1990;264:3044–6.
5. Cook NR, Rosner BA. Sample size estimation for clinical trials with longitudinal measures: applications to studies of blood pressure. J Epidemiol Biostat 1997;2:65–74.
6. Friedlander Y, Kark JD, Stein Y. Variability of plasma lipids and lipoproteins: the Jerusalem Lipid Research Clinic Study. Clin Chem 1985;31: 1121–6.
7. Laird N, Mosteller F. Some statistical methods for combining experimental results. Int J Technol Assess Health Care 1990;6:5–30.

The American Journal of Clinical Nutrition

Downloaded from ajcn.nutrition.org by guest on May 27, 2016