Psyllium-Enriched Cereals Lower Blood Total Cholesterol and LDL Cholesterol, but Not HDL Cholesterol, in Hypercholesterolemic Adults: Results of a Meta-Analysis[1]

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ABSTRACT We conducted a meta-analysis to determine the effect of consumption of psyllium-enriched cereal products on blood total cholesterol (TC), LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) levels and to estimate the magnitude of the effect among 404 adults with mild to moderate hypercholesterolemia (TC of 5.17–7.8 mmol/L) who consumed a low fat diet. Studies of psyllium cereals were identified by a computerized search of MEDLINE and Current Contents and by contacting United States–based food companies involved in psyllium research. Published and unpublished studies were reviewed by one author and considered eligible for inclusion in the meta-analysis if they were conducted in humans, were randomized, controlled experiments, and included a control group that ate cereal providing ≤3 g soluble fiber/d. Eight published and four unpublished studies, conducted in four countries, met the criteria. Analysis of a linear model was performed, controlling for sex and age. Female subjects were divided into two groups to provide a rough estimate of the effect of menopausal status (premenopausal = <50 y, postmenopausal = ≥50 y) on blood lipids. The meta-analysis showed that subjects who consumed a psyllium cereal had lower TC and LDL-C concentrations [differences of 0.31 mmol/L (5%) and 0.35 mmol/L (9%), respectively] than subjects who ate a control cereal; HDL-C concentrations were unaffected in subjects eating psyllium cereal. There was no effect of sex, age or menopausal status on blood lipids. Results indicate that consuming a psyllium-enriched cereal as part of a low fat diet improves the blood lipid profile of hypercholesterolemic adults over that which can be achieved with a low fat diet alone. J. Nutr. 127: 1973–1980, 1997

KEY WORDS: • *psyllium* • *ready-to-eat cereal* • *blood lipids* • *humans* • *meta-analysis*

Diets high in water-soluble fibers such as pectins, gums, mucilages and some hemicelluloses lower blood total cholesterol (TC)[8] by 2–26% and LDL cholesterol (LDL-C) by 3–29% in hyper- and normocholesterolemic adults. High intakes of some soluble fibers (e.g., ≥100 g/d dried beans or oat bran) lower TC and LDL-C levels significantly, even when subjects consume diets providing fat at 37% of total energy. High density lipoprotein cholesterol (HDL-C) concentrations are reported to decrease by 3–20%, increase by 3–35% or remain unchanged by high intakes of soluble fiber (Glore et al. 1994).

Psyllium, which is derived from the seed husk of *Plantago ovata*, is a gel-forming mucilage (Sandhu et al. 1981) that lowers blood lipid concentrations. As early as 1965, Garvin et al. (1965) showed that psyllium administered as a hydrophilic mucilloid (i.e., the commercial bulk-forming laxative, Meta-

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[8] Abbreviations used: CHD, coronary heart disease; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; TC, total cholesterol.

0022-3166/97 $3.00 © 1997 American Society for Nutritional Sciences.
Manuscript received 3 February 1997. Initial review completed 15 April 1997. Revision accepted 20 May 1997.

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mucil; Procter and Gamble, Cincinnati, OH) reduced serum TC by 9% in five subjects who incorporated 9.6 g psyllium/d into their usual diets for 5 wk. More recent studies (Anderson et al. 1988, Bell et al. 1989, Everson et al. 1992, Neal and Balm 1990) have shown reductions in TC of 5–17% and in LDL-C of 8–20% in adults with mild to moderate hypercholesterolemia given 3.4–10.2 g of psyllium hydrophilic mucilloid two to three times daily for 6–12 wk. The HDL-C increased, decreased or remained unchanged in these studies.

The observation that consumption of psyllium as a bulk-forming laxative sometimes reduced HDL-C as well as TC and LDL-C concentrations led to investigations of the blood lipid effects of psyllium consumed in food form. Ready-to-eat cereals were an appropriate vehicle for psyllium administration, because they are widely consumed by the general public (Haines et al. 1996). Several studies of the effects of psyllium-enriched cereals on blood lipids have been undertaken, mainly among hypercholesterolemic men and women who consumed a low fat diet throughout the intervention. In these studies, TC and LDL-C levels were reduced to varying extents, whereas HDL-C levels were either unchanged or reduced slightly with psyllium cereal consumption.

We were interested in determining the effect of psyllium cereals on blood lipids and the size and consistency of the treatment effect, if any, using meta-analysis. Meta-analysis is a statistical method for evaluating a body of separate but similar experiments (Gibaldi 1993). A meta-analysis is usually undertaken to increase the statistical power for primary outcome measures, clarify results when uncertainties in outcome measures exist, evaluate study validity, improve estimates of the size of an effect or generate hypotheses for future research (Irwig et al. 1994, Sacks et al. 1987). This article describes a meta-analysis of studies of psyllium cereals and was undertaken to measure the consistency and size of the effect of psyllium cereals on blood TC, LDL-C and HDL-C levels in adults.

METHODS

Study identification. The agriculture and life sciences literature in English and foreign languages was searched to identify human studies that examined the effects of ready-to-eat cereals containing psyllium on blood lipids. Using the key words "psyllium," "cereal" and "blood lipids," a search of MEDLINE (1966 to February 1996) and Current Contents (1993 to 1996) was conducted. Studies published in English and foreign languages were sought, because there is evidence that including studies published in languages other than English improves the precision and validity of meta-analyses (Moher et al. 1996). No studies of psyllium-enriched cereals published in languages other than English were found. Studies in animals or human studies in which psyllium was consumed in a form other than cereal (e.g., bulk laxative, crackers) were not considered for inclusion in the meta-analysis.

Other food companies known to be involved in psyllium research were contacted as to unpublished human studies involving psyllium cereals. Unpublished studies were considered for inclusion to minimize the possibility of publication bias, because published trials are more likely to be positive than unpublished trials (Ellenberg 1988). Including unpublished trials that met the selection criteria increased the likelihood of obtaining a reliable estimate of the effects of psyllium cereals on blood lipids. Only the Kellogg Company had unpublished studies of psyllium cereals and blood lipids in humans.

Study selection. Ten published articles and five unpublished manuscripts were reviewed for eligibility by one author (BHO), who was aware of the study designs or methodologies. To be included in the meta-analysis, all studies had to meet the following criteria: *1*) studies were conducted in human adults; *2*) studies were randomized, controlled experiments that used either a crossover design or a design with parallel arms for treatment and control conditions to determine the effects of psyllium cereals on blood lipids and *3*) studies included a control group that ate cereal providing ≤3 g soluble fiber/d. Of the 15 studies identified, three (Davidson et al. 1996, Dennison and Levine 1993, Williams et al. 1995) were excluded because they involved children or adolescents, and one (Wolever et al. 1994a) was excluded because subjects in the study were already represented in another published study by this research group (Wolever et al. 1994b). Thus, 11 studies—seven published studies (Anderson et al. 1992, Bell et al. 1990, Jenkins et al. 1997, Roberts et al. 1994, Stoy et al. 1993, Summerbell et al. 1994, Wolever et al. 1994b) and four unpublished studies (Jenkins, D.J.A., et al., Study A; Rippe, J. M., et al., Study B; Rippe, J. M., et al., Study C; Stoy, D. B., et al., Study D)—were eligible for the meta-analysis. The research protocols for all studies had been approved by the appropriate institutional committees.

Analysis of study methodologies and data. The study design and raw data of the 11 eligible studies were obtained from senior investigators and reviewed prior to the meta-analysis. Because one research report (Roberts et al. 1994) involved data collected from subjects at two centers (University of Sydney and University of Newcastle, Australia), and there was an effect of center on the outcome variables, the data from the original trial were split into two groups and treated as two separate studies. This increased to 12 the total number of studies analyzed.

Five studies used designs with parallel arms for treatment and control conditions. Seven studies used crossover designs with either two or three treatment periods. Because the length of the washout period between treatment periods was not uniform among the crossover studies, data from the first period only of all crossover studies were used in the meta-analysis to eliminate questions about carryover effects between treatment periods. One ramification of limiting the analyses of crossover studies to data from the first period is that the results of the meta-analysis are more conservative than those reported in the research reports for the individual studies.

In all studies, blood samples were collected for lipid analysis in serum or plasma. The raw data were inspected for missing values, outliers and other anomalies. Some blood lipid values included in the original research studies were excluded from the meta-analysis. The blood lipid values for two subjects in one study (Summerbell et al. 1994) were dropped, because one subject had a serum TC concentration that significantly exceeded the screening criterion and one had abnormal triglyceride levels throughout the study, which yielded questionable LDL-C levels. The data for some subjects in one study (Wolever et al. 1994b) were excluded because they had participated in another study sponsored by the research group and received an intervening treatment that may have influenced blood lipid concentrations. Data from another study (Rippe, J. M., et al., Study C) were excluded, because the actual intake of psyllium cereal in one group was lower than that specified by the study protocol, resulting in a soluble fiber intake similar to that of the control group; values for the remaining subjects were pooled for the meta-analysis. In the studies of Jenkins et al. (1997), data were included for those subjects in Study 1 who had completed the study at the time the meta-analysis was conducted; data for the remaining subjects in Study 1 and for all subjects in Study 2 were not available for inclusion in the meta-analysis.

Statistical methods for the meta-analysis. The meta-analysis had two objectives: *1*) to determine the effect of treatment (consumption of a psyllium-enriched cereal) vs. control (consumption of a cereal low in soluble fiber and not containing psyllium) on blood TC, LDL-C and HDL-C concentrations; and *2*) to estimate the size of the effect, if any. The a priori null hypotheses were that there were no differences in TC, LDL-C and HDL-C concentrations between treatment and control conditions. The measure used to quantify the blood lipid effects of psyllium was the difference (DIFFERENCE) between the baseline and end-of-study lipid levels [(end-of-study lipid concentrations) minus (baseline lipid concentrations)]. A comparison of treatment and control conditions was also made regarding the subjects' change in LDL-C category as defined by the National Cholesterol Education Program (NCEP) (Expert Panel 1993).

Analysis of a linear model was performed using PROC GLM of the SAS software program (SAS/STAT versions 6.09 and 6.11, SAS Institute, Cary, NC) to estimate differences between baseline and end-of-study concentrations for TC, HDL-C and LDL-C, controlling

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TABLE 1

Study characteristics of published trials of effects of psyllium-enriched cereals on blood cholesterol in hypercholesterolemic adults

Source, year	Country	Study design	Screening TC[1] level	Background diet	Length of test diet	Dose of psyllium	Type of control cereal
			mmol/L		*d*	*g/d*	
Anderson et al., 1992	U.S.	Parallel arms with 1-wk baseline	5.17–7.76[2]	Step 1[3]	42	12.0	Wheat bran flake cereal
Bell et al., 1990	U.S.	Parallel arms with 6-wk dietary lead-in	5.35–7.01[2]	Step 1	42	3.0	Cornflakes
Jenkins et al., 1997	Canada	Crossover, no baseline	>6.72[2]	Step 2[4]	30	9.4	Extruded wheat bran cereal
Roberts et al., 1994[5]	Australia (Sydney)	Crossover, with 1-mo+ dietary lead-in[6]	6.00–7.75[7]	Low fat[8]	42	10.2	Wheat/wheat bran flake cereal
Roberts et al., 1994	Australia (Newcastle)	Crossover, with 1-mo+ dietary lead-in	6.00–7.75[7]	Low fat	42	10.2	Wheat/wheat bran flake cereal
Stoy et al., 1993	U.S.	Crossover with 4-wk dietary lead-in	>6.22[7]	Step 1	56	11.6	Wheat bran flake cereal
Summerbell et al., 1994	U.K.	Parallel arms with 3-wk dietary lead-in	5.2–7.8[2]	Low fat[9]	42	9.6	Bran flake
Wolever et al., 1994b	Canada	Crossover with 1-mo dietary lead-in	>6.21[2]	Step 2	14	6.7	Wheat bran flake cereal

[1] TC = total cholesterol.
[2] Measured in serum.
[3] Step 1 diet provided ≤30% of energy as fat, 8–10% of energy as saturated fat and <300 mg cholesterol.
[4] Step 2 diet provided ≤30% of energy as fat, <7% of energy as saturated fat and <200 mg cholesterol.
[5] The Roberts et al. study was analyzed as two separate trials because there was a significant effect of trial location on blood lipid levels.
[6] Most subjects were already following a low fat diet on entry into the study; those with fat intakes >30% of energy received dietary counseling over a period of 1 mo.
[7] Measured in plasma.
[8] Low fat diet provided <30% of energy as fat.
[9] Low fat diet provided 30% of energy as fat, with no more than 15% of energy as saturated fat.

for sex and age, two factors known or suspected to be associated with blood lipid concentrations. Least squares means provided the estimates of the size of the effect of psyllium cereal on blood lipid concentrations. A P value of 0.05 or less was considered significant.

Factors in the full model included treatment, study, age category, sex, the interaction of treatment with each of the others, and the three-way interaction of treatment, sex and age categories. Any or all nonsignificant interactions were eliminated in a reduced model. The variable "study" was included as a factor in the analysis because the studies differed in psyllium dosage, methodology and subject population. For the age analysis, four age categories grouped by 10-y intervals were created: ≤39, 40–49, 50–59 and ≥60 y.

A separate analysis was conducted using only female subjects, who were divided into two age groups (<50 y, ≥50 y) to provide a rough estimate of the effect of menopausal status on the blood lipid variables. The <50 y category served as a proxy for premenopausal status, and the ≥50 y category served as a proxy for postmenopausal status. The effect of hormone replacement therapy on blood lipid variables could not be determined because these data were not available for the female subjects.

To test the appropriateness of using only the first period of all crossover studies in the primary meta-analysis, a secondary meta-analysis was conducted using only the crossover studies. A crossover linear model with "study" as an additional term in the model was performed. Results showed an effect (P = 0.0001) due to psyllium for TC and LDL-C that was consistent with the findings of the primary meta-analysis in which only the first arm of the seven crossover studies was used. However, in the secondary meta-analysis, HDL-C decreased by 0.02 mmol/L (P = 0.06) during the control period, a change that was not significant at the a priori P value of 0.05 or less. Because the HDL-C difference was small and not likely to be of biological importance, and because there was no significant effect of period in this analysis, we concluded that it was appropriate to use only the first arm of the seven crossover studies in the primary meta-analysis. Only the results from the primary meta-analysis are described in this article.

RESULTS

Study characteristics. Study characteristics of the published trials included in the meta-analysis are shown in **Table 1;** those for the four unpublished studies are given in **Table 2.** The studies were undertaken in four countries: Australia, Canada, the United Kingdom and the United States. The study designs were either a crossover design or one with parallel arms for treatment and control conditions. Subjects with mild to moderate hypercholesterolemia (TC of 5.17–7.8 mmol/L) were typically recruited through community cholesterol screenings, radio announcements or physician referrals. Three studies had no dietary lead-in period, whereas others had a 3- to 6-wk dietary lead-in period, during which time subjects were instructed to adhere to a low fat diet.

Most subjects consumed either a low fat diet (total fat ≤30% of energy) or the NCEP Step 1 diet during the experimental period. The NCEP Step 1 diet specifies a total fat intake ≤30% of energy, a saturated fat intake of 8–10% of energy and a cholesterol intake <300 mg/d. The NCEP Step 2 diet is typically prescribed if patients are already following a Step 1 diet at the time their hypercholesterolemia is detected or if the Step 1 diet fails to achieve the goals of diet therapy. The Step 2 diet specifies a total fat intake ≤30% of energy, a saturated fat intake <7% of energy and less than 200 mg of cholesterol per day (Expert Panel 1993). In general, subjects consumed the background diet, with or without psyllium cereal, for a period of 14–56 d (mean 42 d). The amount of

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TABLE 2

Study characteristics of unpublished trials of effects of psyllium-enriched cereals on blood cholesterol in hypercholesterolemic adults

Source, year[1]	Country	Study design	Screening TC[2] level	Background diet	Length of test diet	Dose of psyllium	Type of control cereal
			mmol/L		*d*	*g/d*	
Study A,[3] 1993	Canada	Crossover, no baseline	>6.2[4]	Step 2[5]	30	7.6	Extruded wheat bran cereal
Study B,[6] 1989	U.S.	Parallel arms with 4-wk dietary lead-in	5.17–6.21[7]	Step 1[8]	56	9.5	Oat loop cereal
Study C,[9] 1990	U.S.	Parallel arms with 6-wk dietary lead-in	6.21–7.76[4]	Step 1	56	11.2	Wheat bran flake cereal
Study D,[10] 1989	U.S.	Crossover with 4-wk dietary lead-in	>6.22[7]	Step 1	56	11.6	Wheat bran cereal

[1] Year of publication of research report or year the trial was conducted.
[2] TC = total cholesterol.
[3] Jenkins, D.J.A., Wolever, T.M.S., Mueller, S., McMillan, K., & Fulgoni, V., III, ''Psyllium fiber timing study,'' St. Michael's Hospital, University of Toronto, Toronto, ON.
[4] Measured in serum.
[5] Step 2 diet provided ≤30% of energy as fat, <7% of energy as saturated fat and <200 mg cholesterol.
[6] Rippe, J. M., Bell, K., Fortlage, L., Morris, D. H., Puleo, E., Ward, A. & Stuart, M., ''Effects of a cereal containing psyllium on blood cholesterol levels in men,'' Department of Medicine, University of Massachusetts Medical Center, Worcester, MA.
[7] Measured in plasma.
[8] Step 1 diet provided ≤30% of energy as fat, 8–10% of energy as saturated fat and <300 mg cholesterol.
[9] Rippe, J. M., Morris, D. H., Ward, A., Rider, L. G., Cuneo, P., Teuwen, L. & Puleo, E., ''Effect of a psyllium-supplemented cereal on blood cholesterol levels in hypercholesterolemic men,'' Department of Medicine, University of Massachusetts Medical Center, Worcester, MA.
[10] Stoy, D. B., LaRosa, J. C., Brewer, B. K., Saldanha, L. & Meusing, R. A., ''Lipid lowering effects of ready-to-eat cereal containing psyllium: a randomized cross-over trial,'' The George Washington University Medical Center, Washington, DC.

soluble fiber in the psyllium cereals ranged from 3.0 to 12.0 g/d. One study used cornflakes as the control cereal, one used an oat loop cereal, and the remaining 10 studies used a wheat bran cereal as the control cereal.

Data from 404 hypercholesterolemic subjects, 68 women and 336 men, were included in the meta-analysis. Subjects ranged in age from 27 to 72 y (**Table 3**). Female subjects were enrolled in five of the smaller studies (Anderson et al. 1992; Jenkins, D.J.A., et al., Study A; Jenkins et al. 1997; Summerbell et al. 1994; Wolever et al. 1994b) and were generally underrepresented in these studies. Most female subjects were 50–59 y and older; male subjects were variably distributed across all age categories.

Baseline blood lipid values. Average baseline concentrations of TC, LDL-C and HDL-C by study and treatment groups are shown in **Table 4.** There were no significant differences in baseline blood lipid concentrations between the control and psyllium groups.

TABLE 3

Distribution of subjects by treatment, sex and age category in studies of the effects of psyllium-enriched or control cereals on blood cholesterol in hypercholesterolemic adults

	Females		Males	
Age category	Control	Psyllium	Control	Psyllium
y	*n*			
≤39	1	3	34	38
40–49	6	2	54	49
50–59	16	14	37	52
≥60	11	15	36	36

Effect of treatment. The observed significance levels for the DIFFERENCE measurement are shown in **Table 5.** Treatment with psyllium cereal significantly lowered TC and LDL-C but had no effect on HDL-C.

Consistency of effect of treatment. There was no significant interaction between the variables ''treatment'' and ''study'' for TC, LDL-C or HDL-C. Lack of a significant interaction indicates that treatment with psyllium cereal had the same effect on subjects' blood lipid concentrations, regardless of the study in which they were enrolled.

Estimates of the size of the effect. **Table 6** shows the estimates for the size of the effect of treatment with psyllium cereal on TC, LDL-C and HDL-C. The table shows the 95% confidence intervals (CI) for the true values of the average difference between the baseline and end-of-study lipid levels. A CI that does not contain 0.0 represents a decrease in blood lipids. The table shows that two differences do not contain 0.0, indicating a reduction in TC and LDL-C among subjects consuming psyllium cereal. The overall average difference figures, shown at the bottom of Table 6, were obtained by pooling all data across all studies using the main effects linear model. The data indicate that subjects who ate a psyllium cereal had lower TC and LDL-C concentrations (differences of 0.31 and 0.35 mmol/L, respectively) than subjects who ate the control cereal. The HDL-C levels were unchanged in subjects eating psyllium cereal.

Sex effects. Sex did not influence the effect of psyllium cereal treatment or control on blood lipid concentrations (data not shown). When the data for women were divided by age (<50 y vs. ≥50 y) as a proxy for assessing the effect of menopausal status on blood lipids, treatment with psyllium cereal significantly reduced TC and LDL-C, regardless of menopausal status (**Table 7**). Neither treatment with psyllium cereal nor menopausal status affected HDL-C.

Age effects. There was no effect of age category on any of the lipid concentrations. No trend was exhibited between

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TABLE 4

Baseline cholesterol concentrations by study and treatment groups and for all studies combined in hypercholesterolemic adults consuming psyllium-enriched or control cereals[1]

	TC		LDL-C		HDL-C	
Study	Control	Psyllium	Control	Psyllium	Control	Psyllium
			mmol/L			
Published trials						
Anderson et al. (1992)[2]	6.73	6.67	4.80	4.62	1.19	1.20
Bell et al. (1990)[2]	5.50	5.54	3.68	3.81	1.18	1.21
Jenkins et al. (1997)[2]	7.07	7.25	4.91	5.15	1.41	1.57
Roberts et al. (1994; Sydney)[3]	6.83	6.69	4.72	4.60	1.27	1.24
Roberts et al. (1994; Newcastle)[3]	6.41	6.64	4.38	4.55	1.12	1.19
Stoy et al. (1993)[3]	5.99	6.04	3.98	4.20	1.22	1.09
Summerbell et al. (1994)[2]	6.07	6.14	4.02	4.15	1.37	1.44
Wolever et al. (1994b)[2]	6.56	6.37	4.51	4.36	1.03	1.25
Unpublished trials						
Jenkins et al. (1993)[2]	7.04	7.26	4.80	5.07	1.41	1.48
Rippe et al. (1989)[3]	4.98	5.26	3.22	3.42	1.13	1.23
Rippe et al. (1990)[2]	5.64	5.41	3.68	3.71	1.09	1.12
Stoy et al. (1989)[3]	5.85	6.19	3.91	4.19	1.36	1.19
Overall mean	6.16	6.39	4.14	4.33	1.33	1.36
Pooled SEM	0.10	0.09	0.10	0.09	0.05	0.04

[1] Abbreviations used: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; SEM, standard error of the mean.
[2] Measured in serum.
[3] Measured in plasma.

increasing age and the effect of treatment with psyllium cereal. Using age as a covariate in the model likewise showed no effect on any lipid concentrations.

Change in LDL cholesterol categories. The LDL-C intervention categories prescribed by the NCEP Expert Panel (1993) and the numbers and percentages of subjects in each category at baseline and end of study are shown in **Table 8.** The distribution of subjects across LDL-C categories was the same for psyllium cereal and control groups at baseline ($P = 0.55$). However, there was a difference in the distribution between the two groups at end of study ($P = 0.02$). For the control group, there was no change from baseline to end of study ($P = 0.29$) in the distribution of subjects across the four LDL-C categories. Among subjects who ate psyllium cereal, a significant change ($P = 0.001$) occurred between baseline and end-of-study LDL-C concentrations, with a trend toward lower values. Among subjects who ate psyllium cereal, the proportion of subjects classified into the lower two LDL-C categories increased at the end of study, whereas the number of subjects in the higher LDL-C categories decreased.

TABLE 5

Analysis of the difference between baseline and end-of-study cholesterol concentrations in studies of the effects of psyllium-enriched or control cereals on blood cholesterol in hypercholesterolemic adults[1]

	Observed significance level for DIFFERENCE[2]		
Variable	TC	LDL-C	HDL-C
Study	0.0001	0.0001	0.0002
Treatment	0.0002	0.0001	0.34
Age category	0.68	0.13	0.94
Sex	0.24	0.25	0.93

[1] Abbreviations used: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.
[2] DIFFERENCE = [(End-of-study) minus (baseline)] blood cholesterol concentrations (mmol/L).

DISCUSSION

In this meta-analysis of 12 studies, subjects who consumed a psyllium-enriched cereal had lower TC and LDL-C concentrations [differences of 0.31 mmol/L (5%) and 0.35 mmol/L (9%), respectively] than subjects who ate a control cereal. High density lipoprotein cholesterol concentrations were not different in subjects consuming either psyllium or control cereals and were not different between the two groups. Among subjects who ate psyllium cereal, the distribution of LDL-C levels, as outlined in the NCEP's lipid classification scheme (Expert Panel 1993), changed toward more favorable values by the end of the treatment period, with a larger number of subjects having LDL-C concentrations in the desirable and borderline categories and fewer subjects having levels in the high-risk categories. The number of subjects in the high-risk category was nearly halved in the group that ate psyllium cereal, indicating that a significant proportion of the high-risk group responded positively to this type of diet therapy and had substantial improvement in blood lipid profiles. The effect of psyllium cereal on blood lipids was not affected by sex, age or a proxy estimate of menopausal status. The subjects in these studies were adults with mild to moderate hypercholesterolemia who consumed a low fat diet.

We believe these results represent a conservative estimate of the consistency and size of the effect of psyllium cereal consumption on blood lipid concentrations for two reasons. First, data from the first period only of eligible crossover studies

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TABLE 6

Estimates of the size of the effect of psyllium-enriched and control cereals on blood cholesterol in hypercholesterolemic adults[1]

Variable	DIFFERENCE[2]		
	TC	LDL-C	HDL-C
	mmol/L		
Control			
Average difference	0.01	0.03	0.01
95% CI	(−0.10, 0.11)	(−0.07, 0.13)	(−0.04, 0.02)
Psyllium			
Average difference	−0.30	−0.32	0.01
95% CI	(−0.40, −0.20)	(−0.42, −0.22)	(−0.04, 0.03)
Overall			
Average difference	−0.31	−0.35	0.00
95% CI	(−0.37, −0.25)	(−0.40, −0.29)	(−0.04, 0.03)

[1] Abbreviations used: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; CI, confidence interval.
[2] DIFFERENCE = [(End-of-study) minus (baseline)] blood cholesterol concentrations (mmol/L).

were used in the meta-analysis. This decision resulted in instances in which the significant results achieved in an individual crossover study did not carry over to the meta-analysis, thereby reducing the power of specific studies and yielding more conservative results. Secondly, a variable "study" was included in the meta-analysis to minimize differences in study population, psyllium dose and methodology. There was no significant interaction between the variables "study" and "treatment" for any of the lipid values.

Both published and unpublished studies were included in the meta-analysis. It is generally recognized that restricting the meta-analysis to published studies introduces a bias, because published studies are more likely to report positive research outcomes than unpublished ones (Dickersin and Berlin 1992).

TABLE 7

Analysis of data for hypercholesterolemic women categorized by age as a proxy for menopausal status in studies of the effects of psyllium-enriched and control cereals on blood cholesterol[1,2]

Variable	Observed significance level for DIFFERENCE[3]		
	TC	LDL-C	HDL-C
Study (S)	0.02	0.21	0.03
Treatment (T)	0.006	0.004	0.12
Pre/post[4] (P)	0.44	0.33	0.93
S × T[5]	0.94	0.76	0.55
T × P[6]	0.48	0.43	0.47

[1] Proxy estimate of menopausal status by age: premenopausal = <50 y, postmenopausal = ≥50 y.
[2] Abbreviations used: TC, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.
[3] DIFFERENCE = [(End-of-study) minus (baseline)] blood cholesterol concentrations (mmol/L).
[4] Pre/post = Surrogate variable representing menopausal status.
[5] S × T = Study × treatment interaction.
[6] T × P = Treatment × (pre/post) interaction.

TABLE 8

Change in distribution of subjects across LDL cholesterol (LDL-C) categories from baseline to end of study in studies of the effects of psyllium-enriched and control cereals on blood cholesterol in hypercholesterolemic adults

Intervention group	LDL-C category	Study period	
		Baseline	End of study
	mmol/L[1]	*n (%)*	
Control	≤3.4	33 (17)	40 (20)
	>3.4 but ≤4.1	69 (35)	60 (31)
	>4.1 but ≤4.9	54 (28)	63 (33)
	>4.9	39 (20)	32 (16)
Psyllium cereal	≤3.4	37 (18)	58 (28)
	>3.4 but ≤4.1	49 (23)	74 (36)
	>4.1 but ≤4.9	89 (43)	56 (27)
	>4.9	33 (16)	20 (9)

[1] Blood LDL-C concentration.

Even so, including unpublished studies in the meta-analysis has been criticized on the grounds that they may be unreliable or less rigorous in their design or implementation, factors that possibly contributed to their being rejected for publication (Sacks et al. 1987). Several methods have been proposed to address this problem, including keeping the quality reviewer unaware of such particulars as the researchers, study location and journal of publication. These methods are not foolproof, however. Quality reviewers who are not given information about the study particulars, for example, can identify study researchers through their familiarity with the literature (Haselkorn et al. 1994). In this meta-analysis, the issue of publication bias was addressed by having one author (BHO) systematically apply the same criteria to published and unpublished studies to determine their eligibility for inclusion. One of the major design criteria stipulated that eligible studies must be randomized, controlled experiments using either a crossover design or a design with parallel arms for treatment and control conditions. This decision ensured that studies selected for the meta-analysis were conducted in a consistent, rigorous and valid manner.

The results of the meta-analysis indicate significant reductions in TC and LDL-C, with no change in HDL-C, among adults with mild to moderate hypercholesterolemia who consumed a psyllium-enriched cereal as part of a low fat diet. Soluble fibers other than psyllium, such as legumes, oats and oat bran, pectin, apples and some vegetable fibers, also reduce TC and LDL-C significantly without altering HDL-C, although the effect has not been consistent; in some instances, HDL-C fell 20% following soluble fiber supplementation (Glore et al. 1994).

Incorporating a psyllium-containing bulk laxative into a low fat diet has yielded reductions in TC of about 5% and in LDL-C of about 5–8%, with no change in HDL-C, among adults with mild to moderate hypercholesterolemia (Bell et al. 1989, Neal and Balm 1990). Adding a psyllium-containing bulk laxative to mixed diets providing 30–40% of total energy as fat, a level typical of the North American diet and higher than the fat intakes reported in the studies analyzed in the meta-analysis, has yielded variable results. Reductions in TC and LDL-C concentrations ranged from about 6% (Everson et al. 1992) to 15–20% (Abraham and Mehta 1988, Anderson et al. 1988). These data suggest that adding psyllium in the

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form of a bulk laxative to typical mixed diets high in fat may result in substantial reductions in TC and LDL-C. These health gains, however, are roughly equivalent to those which can be expected by adhering to a low fat diet that includes a psyllium-enriched cereal or a psyllium-containing bulk laxative.

An important finding of the meta-analysis is that HDL-C levels were not affected by incorporating psyllium-enriched cereals into a low fat diet. Levels of HDL-C are inversely related to the development of coronary heart disease (CHD). Because low HDL-C levels (<0.9 mmol/L) are now recognized as a major risk factor for CHD, interventions that protect or elevate HDL-C are desirable (Expert Panel 1993). The results of the meta-analysis provide support for diet therapies that focus on low fat eating patterns and include psyllium cereals.

The NCEP recommends pursuing diet therapy over drug therapy among individuals with low to moderate CHD risk. Drug therapy should be reserved for high-risk individuals (Expert Panel 1993), a group that may constitute about 7% of U.S. adults (Gaziano et al. 1996). Compared with interventions that focus on diet and physical activity, drug therapy is relatively expensive. A cost analysis of therapy with three alternative agents—cholestyramine resin, colestipol and oat bran—found that the cost per year of life saved among adults with high blood TC (>6.85 mmol/L) was highest for cholestyramine resin packets ($117,400), intermediate for colestipol ($70,900) and lowest for oat bran ($17,800); the yearly cost per person was estimated at $1442 for cholestyramine resin, $879 for colestipol and $248 for oat bran. Most of the cost associated with oat bran use was due to the cost of medical supervision by physicians and dietitians and not due to the cost of oat bran itself (Kinosian and Eisenberg 1988). Treatment for hypercholesterolemia by a dietitian has been estimated at $163 compared with $1450 for drug therapy (McGehee et al. 1995).

The emerging view is that diet therapy alone is not sufficient for patients with overt CHD or for those with severe hyperlipidemia (Caggiula et al. 1996, Kannel 1996). Our findings suggest that some high-risk individuals may respond, even in short-term periods lasting 8 wk, to low fat dietary interventions that include psyllium cereals. Long-term consumption of psyllium cereals for 24–26 wk by adults with hypercholesterolemia has also resulted in reductions in TC and LDL-C of 3–6.7%, with no effect on HDL-C (Anderson, J. W., Davidson, M. H., Blonde, L., Brown, W. V., Howard, W. J., Ginsberg, H., Allgood, L. D. & Weingand, K. W., Veterans Administration Medical Center, Lexington, KY, unpublished data; Davidson, M. H., Maki, K. C., Kong, J. C., Dugan, L. D., Torri, S. A., Hall, H. A., Drennan, K. B., Anderson, S., Fulgoni, V., Saldanha, L. & Olson, B., Chicago Center for Clinical Research, Chicago, IL, unpublished data).

For the ~30% of U.S. adults with mild to moderate hypercholesterolemia and for whom nonpharmacologic interventions to lower cholesterol are appropriate and efficacious (Gaziano et al. 1996, Shaffer and Wexler 1995), our findings support incorporating a psyllium cereal into low fat eating patterns to lower TC and LDL-C. In this meta-analysis, the reduction in TC associated with eating psyllium cereal was attributed to the decrease in LDL-C. Similar results have been shown among studies of hypercholesterolemic adults consuming a low fat diet with added psyllium hydrophilic mucilloid. Because both approaches seem to produce equivalent benefits, the issue for consumers is partly one of taste and preference. Although bulk-forming laxatives containing psyllium are generally well-tolerated, some subjects have reported gastrointestinal discomfort and nausea on first consuming such products (Borgia et al. 1983, Neal and Balm 1990). Adding a psyllium-enriched cereal to a low fat diet may be a more palatable choice than bulk laxatives for some consumers. Having both options available provides alternatives to improve compliance with fiber intake recommendations.

From the standpoint of general eating patterns, adding cereal to the diet provides many benefits. The intake of selected vitamins and minerals increases (Morgan et al. 1986) and the overall intake of fat and cholesterol decreases when cereals are consumed as part of breakfast (Stanton and Keast 1989). In addition, total dietary fiber intake, especially the intake of cereal fiber, is inversely associated with risk of myocardial infarction in men (Rimm et al. 1996), and high dietary fiber intakes are associated with lower risk of CHD (He et al. 1995, Khaw and Barrett-Connor 1987, Kushi et al. 1985). Moreover, adding soluble fiber to diets already low in saturated fat and cholesterol helps lower blood cholesterol concentrations (Jenkins et al. 1993). Finally, with cereal consumption the emphasis remains on foods as sources of nutrients and fiber, which reinforces the basic principles of the 1995 Dietary Guidelines for Americans (Kennedy et al. 1996).

For more than a decade, the dietary recommendations of government agencies (Expert Panel 1993, National Institutes of Health Consensus Development Panel 1985, U.S. Department of Agriculture 1992, U.S. Surgeon General 1988) and nonprofit health organizations (Grundy et al. 1985) have called for a dietary pattern that is low in fat, saturated fat and cholesterol and high in dietary fiber, which can be achieved by eating plenty of grain products, fruits and vegetables. Even so, the average fiber intake of the U.S. population is low, with children and adults consuming less than half of the recommended 20 to 35 g/d (Albertson and Tobelmann 1995, Nicklas et al. 1995). Incorporating a psyllium-enriched cereal into the diet is a relatively simple and inexpensive means of increasing dietary fiber intake, reducing blood cholesterol concentrations and approaching an overall eating pattern that more closely resembles current dietary guidelines.

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