

# Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials<sup>1,2</sup>

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## ABSTRACT

**Background:** Soluble fibers, including those from psyllium husk, have been shown to augment the cholesterol-lowering effects of a low-fat diet in persons with hypercholesterolemia. As evidence of this, the US Food and Drug Administration recently authorized the use of health claims on food products containing soluble fiber from psyllium that state that they are associated with a decreased risk of coronary heart disease.

**Objective:** This meta-analysis was conducted to more precisely define the hypolipidemic effects and safety of psyllium when used adjunctive to a low-fat diet in men and women with hypercholesterolemia.

**Design:** The 8 studies in the meta-analysis included a total of 384 and 272 subjects receiving psyllium or cellulose placebo, respectively. All studies evaluated the hypocholesterolemic effects of 10.2 g psyllium/d adjunctive to a low-fat diet for  $\geq 8$  wk in individuals with mild-to-moderate hypercholesterolemia after a low-fat diet lead-in phase lasting  $\geq 8$  wk. The safety and adverse events associated with psyllium consumption were summarized from pooled data of 19 clinical studies ranging from 6 wk to 6 mo in duration.

**Results:** Consumption of 10.2 g psyllium/d lowered serum total cholesterol by 4% ( $P < 0.0001$ ), LDL cholesterol by 7% ( $P < 0.0001$ ), and the ratio of apolipoprotein (apo) B to apo A-I by 6% ( $P < 0.05$ ) relative to placebo in subjects already consuming a low-fat diet, with no effect on serum HDL or triacylglycerol concentrations.

**Conclusions:** Psyllium supplementation significantly lowered serum total and LDL-cholesterol concentrations in subjects consuming a low-fat diet. Psyllium is well tolerated and safe when used adjunctive to a low-fat diet in individuals with mild-to-moderate hypercholesterolemia. *Am J Clin Nutr* 2000;71:472–9.

**KEY WORDS** Psyllium, cholesterol, LDL cholesterol, meta-analysis, hypercholesterolemia, fiber, lipoprotein, apolipoprotein, analysis of covariance, Delta method

## INTRODUCTION

According to the guidelines of the National Cholesterol Education Program (NCEP),  $\approx 30\%$  of Americans have undesirably high serum cholesterol concentrations (1, 2). Although a low-fat diet is

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the primary intervention for these individuals, diet alone may not produce a sufficient response in the estimated 7% of Americans with overt coronary heart disease or severe hyperlipidemia (3–5).

Soluble fiber has been shown to augment the cholesterol-lowering effects of low-fat diets in individuals with mild-to-moderate hypercholesterolemia (6–11). Psyllium is a source of natural and concentrated soluble fiber derived from the husks of blonde psyllium seed. Psyllium is well accepted as a safe and effective bulk laxative and is an adjunct to dietary intervention for individuals who do not adequately respond to a low-fat, low-cholesterol diet (12). When consumed as part of a low-fat diet, previous studies indicated that psyllium decreases serum total cholesterol concentrations an additional 3–6% and serum LDL-cholesterol concentrations an additional 5–9% relative to placebo, with no effect on serum HDL-cholesterol or triacylglycerol concentrations and inconclusive effects on serum apolipoprotein (apo) B concentrations (12–17). Psyllium has also been reported to reduce serum total cholesterol concentrations 5–15% and serum LDL-cholesterol concentrations 8–20% in hypercholesterolemic men consuming a typical, high-fat American diet (18, 19).

To more precisely determine psyllium's effects on serum lipids, we performed a meta-analysis of 8 clinical studies that evaluated the effects of psyllium in hypercholesterolemic subjects. Meta-analysis is a statistical technique in which results of separate studies are combined to increase statistical power, clarify results, and more accurately estimate the size of treatment effects, if any (20–22). We also reviewed safety data from 19 clinical trials in which psyllium was used. The purpose of this study was to determine the size and consistency of psyllium's hypolipidemic effects and the safety of psyllium when used adjunctive to an American Heart Association (AHA) Step I diet in men and women with primary hypercholesterolemia.

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## METHODS

### Study identification and selection

The meta-analysis included 19 studies sponsored by The Procter & Gamble Co clinical program (Cincinnati) that met the following criteria: 1) psyllium was used adjunctive to an AHA Step I diet (1, 23) with a pretreatment dietary lead-in period  $\geq 8$  wk, 2) subjects consumed 10.2 g psyllium/d for  $\geq 8$  wk, and 3) a placebo control group was included. Studies of psyllium cereals were excluded from the meta-analysis. On the basis of the above criteria, 5 published (12–16) and 3 psyllium studies, which included  $\geq 8$  wk of psyllium therapy and which were conducted between 1989 and 1994, were included in the meta-analysis. Four studies had 8 wk as an endpoint, whereas 4 studies lasted  $> 8$  wk (12–26 wk) but also had an 8-wk evaluation point.

The pooled data from these 8 studies represent the combined results of 656 evaluable adult subjects with mild-to-moderate hypercholesterolemia aged 24–83 y (384 in the psyllium group and 272 in the placebo group). All studies investigated the hypocholesterolemic effects of 10.2 g psyllium/d given in either 2 or 3 doses daily (5.1 g twice daily or 3.4 g three times daily, with all doses mixed in 240 mL water). In all studies, psyllium was provided as Metamucil in either a sugar-free formulation or one sweetened with sugar (The Procter & Gamble Co) and placebo was provided as microcrystalline cellulose. Informed, written consent was obtained and protocols were approved by the appropriate institutional committee for each study.

### Meta-analysis

Overall reductions in total and LDL-cholesterol concentrations were the outcomes of primary interest in the meta-analysis. Nine lipid profile measures were analyzed: serum total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerol, the ratio of LDL to HDL cholesterol, ratio of total to HDL cholesterol, apo A-I, apo B, and the ratio of apo B to apo A-I. The potential for treatment effects in subpopulations was also considered.

The 9 lipid measures were analyzed 3 ways: 1) the actual change in values from baseline to 8 wk, 2) the percentage change from baseline to 8 wk, and 3) the mean percentage change with psyllium at 8 wk compared with that with placebo. Baseline values were used as the model covariate in the first and third types of analyses. Patient evaluability was determined exactly as it was in each individual study. Baseline values were calculated as defined in each individual study. For each lipid measure, 8-wk final values were calculated by using the mean of individual time point data collected during weeks 6–8 of the treatment phase.

For change from baseline to 8 wk, differences between 8-wk final values and baseline values were calculated for each lipid measure. The change scores were analyzed by using an analysis of covariance (ANCOVA) procedure that examined baseline, study, treatment, and interaction effects. For each study, adjusted least-squares treatment means were estimated from this full model at the mean baseline value. Overall treatment means across studies were then calculated as unweighted averages of individual study-adjusted treatment means. These unweighted averages correspond to least-squares treatment means of the baseline values. Two-sided *t* tests were conducted at the 0.05 level of significance to test for overall treatment differences by using a pooled estimate of the variance. Within treatments, comparisons were done by using two-sided *t* tests on changes from baseline.

Similar analyses were conducted to determine the percentage change from baseline to 8 wk. Adjusted least-squares treatment means were calculated for each study and for the unweighted average of all studies. In contrast with actual change scores, the percentage change scores were analyzed by using an analysis of variance (ANOVA) procedure that examined study, treatment, and study-by-treatment interactions.

In the meta-analysis, studies were treated as fixed. An additional analysis (not reported in this article) was done by using random-effects models. Because both results were similar, we report only those results based on fixed-effects models.

The percentage change with psyllium compared with placebo at 8 wk was calculated as the ratio (multiplied by 100) of the 8-wk final mean scores obtained from an ANCOVA model. Two-sided *z* tests were conducted at the 0.05 level of significance to test for the overall significance of the treatment effect by using an estimate of the large sample variance obtained by the Delta method (24). The ANCOVA model of change from baseline was also used to address the effect of the baseline covariate on treatment.

Subgroup analyses were performed by using baseline triacylglycerol concentration status [ $< 2.26$  mmol/L (200 mg/dL) or  $> 2.26$  mmol/L], sex, age group (18–39 y, 40–49 y, 50–59 y, and  $> 60$  y), treatment regimen (2 or 3 times daily), psyllium texture type (original or smooth), and psyllium sanitization method (high-heat extrusion or steam sanitization). Data were available in most of the 8 studies for the first 3 subgroup analyses (triacylglycerol concentrations, sex, and age). For these subgroups, three-way ANOVA procedures were used on the change from baseline scores, examining subgroup, study, treatment, subgroup-by-treatment interaction, subgroup-by-study interaction, study-by-treatment interaction, and subgroup-by-study-by-treatment interaction effects. Overall treatment means across studies were calculated as unweighted averages of individual study-adjusted treatment means for each subgroup. Two-sided *t* tests were then conducted at the 0.05 level of significance to test for overall treatment differences by using a pooled estimate of the variance.

For baseline triacylglycerol concentrations, data from 2 studies (15, 16) were excluded from analysis because both studies had only patients with serum triacylglycerol concentrations  $< 2.26$  mmol/L. With these studies included, the three-way interaction model would have resulted in nonestimable treatment means across studies. For age group analysis, one unpublished study (Bell LP, 1994) and one published study (16) were excluded from the analysis because these studies did not have at least one subject in each age group.

For the last 3 subgroup analyses (treatment regimen, particle size, and sanitation method), data were available at only one level for each subgroup in all 8 studies. For these subgroups, ANOVA procedures were used on the change from baseline scores, examining subgroup, study within subgroup treatment, and subgroup-by-treatment interaction effects. Two-sided *t* tests were conducted by subgroup at the 0.05 level of significance to test for treatment differences by using a pooled estimate of the variance.

### Safety analysis

The safety of psyllium was also assessed by pooling data from all 19 clinical studies. These 19 studies include the 9 published (12–19, 25) and 10 unpublished psyllium studies funded by The Procter & Gamble Co since 1987. These combined safety data represent 966 subjects receiving psyllium and 662 subjects receiving placebo from 19 clinical studies, regardless of whether the subjects completed the

study. Treatment duration was from 6 wk to 6 mo. Most subjects received 10.2 g psyllium/d, although amounts varied from 5.1–20.4 g/d across studies. The 8 studies included in the meta-analysis are included in the safety analyses. The meta-analysis included an unpublished study in an elderly ( $\geq 65$  y) population ( $n = 50$  and  $51$  in the psyllium and placebo groups, respectively). In addition to the 8 meta-analysis studies, the safety analysis also included 2 psyllium studies for individuals with type 2 diabetes (25; second study was unpublished and by Proctor & Gamble), 2 uncontrolled or semicontrolled open-label psyllium studies (unpublished, by Proctor & Gamble), 2 studies of psyllium plus a high-fat diet (13, 18), 1 psyllium study for obese individuals (unpublished, by Proctor & Gamble), 1 study of psyllium coadministered with cholestyramine, 1 study using a high dose ( $\leq 20.4$  g/d) of psyllium (17), 1 study of psyllium sanitized by a high-heat extrusion method (unpublished, by Proctor & Gamble), and 1 psyllium study that was terminated with no subjects completing the study.

Serum clinical laboratory and hematology data and vital signs were collected pre- and poststudy in 8 studies included in the safety analysis. A subset of patients in either a 4- or 6-mo trial were assessed pre- and posttreatment for potential effects of psyllium or placebo on vitamin and mineral status. Serum analyses included magnesium, iron, ferritin, hemoglobin, zinc, calcium, total-iron-binding capacity, prothrombin and partial prothrombin times (as indirect measures of vitamin K status), vitamin A, vitamin D,  $\beta$ -carotene, and vitamin E ( $\alpha$ - $\beta$ -, and  $\gamma$ -tocopherols). A urinalysis in a subset population was conducted to assist in the interpretation of mineral status and included measurement of the following: calcium, magnesium, hydroxyproline, creatinine, and creatinine clearance.

## RESULTS

### Study characteristics

The characteristics of the 8 studies included in the meta-analysis are listed in **Table 1**. Seven studies used a parallel design, whereas one study was the first period of a crossover study. Pooled demographic characteristics and prediet lipid values of subjects in the psyllium and placebo groups from these 8

studies are given in **Table 2**. The psyllium and placebo groups in the meta-analysis study population were well-matched with respect to sex, race, age, and serum lipid profiles at entry.

### Serum lipid changes

Baseline serum lipid values and changes in serum lipids for subjects consuming psyllium or placebo for 8 wk are summarized in **Table 3**. Treatment groups were adequately balanced at baseline with respect to all lipid variables. Subjects in the psyllium group had a significant decrease from baseline in serum total cholesterol, LDL-cholesterol, the ratio of LDL to HDL cholesterol, the ratio of total to HDL cholesterol, and the ratio of apo B to apo A-I, and a significant increase from baseline in serum triacylglycerol and apo A-I concentrations ( $P < 0.05$ ). The 95% CIs for within-treatment change in the psyllium group showed a decrease of  $0.21$ – $0.33$  mmol/L ( $8.12$ – $12.93$  mg/dL) for serum total cholesterol concentrations and a decrease of  $0.24$ – $0.36$  mmol/L ( $9.32$ – $13.73$  mg/dL) for serum LDL-cholesterol concentrations. Psyllium was associated with significant reductions in serum total and LDL-cholesterol concentrations and in the ratios of LDL to HDL cholesterol, total to HDL cholesterol, and apo B to apo A-I compared with placebo. As shown in Table 3, the net difference (psyllium minus placebo) in serum total cholesterol concentrations was  $-0.238$  mmol/L ( $9.20$  mg/dL), or a  $-3.87\%$  change compared with placebo. The net difference in serum LDL-cholesterol concentrations was  $-0.281 \pm 0.042$  mmol/L ( $10.87$  mg/dL), or a  $-6.68\%$  change compared with placebo. The net difference in the ratio of LDL to HDL cholesterol was  $-0.23 \pm 0.05$ , or a  $-6.58\%$  change compared with placebo, whereas the net difference in the ratio of total to HDL cholesterol was  $-0.19 \pm 0.06$ , or a  $-3.68\%$  change compared with placebo. The net difference of  $-0.05 \pm 0.03$  in the ratio of serum apo B to apo A-I was nearly significant, whereas the change of  $-5.63\%$  compared with placebo for this lipid variable was significant.

Psyllium intake did not significantly affect serum HDL-cholesterol concentrations. Although triacylglycerol concentrations increased significantly compared with baseline within the psyllium group, no significant differences were found in changes in serum triacylglycerol concentrations between the psyllium and placebo groups.

**TABLE 1**

Design characteristics of studies included in the meta-analysis of the hypolipidemic effects of psyllium

Study and year	Duration of low-fat	Duration of	Study design <sup>1</sup>	Psyllium dose	Treatment regimen
	dietary lead-in	treatment			
	wk	wk		g/d	
Published studies					
Bell et al (15), 1989 ( $n = 38$ M, 37 F)	12	8	DB, P, R	10.2	3.4 g three times/d
Levin et al (14), 1990 ( $n = 47$ M, 11 F)	8	16	DB, P, R	10.2	5.1 g twice/d
Anderson et al (12), 1991 ( $n = 27$ M, 25 F) <sup>2</sup>	8	8	IB, P, R	10.2	3.4 g three times/d
Sprecher et al (13), 1993 ( $n = 39$ M, 42 F) <sup>3</sup>	8	8	DB, P, R	10.2	5.1 g twice/d
Weingand et al (16), 1997 ( $n = 16$ M, 7 F)	12	8	DB, CO, R	10.2	5.1 g twice/d
Unpublished studies					
Crouch, 1994 ( $n = 68$ M, 57 F)	8	8	DB, P, R	10.2	3.4 g three times/d
Anderson, 1994 ( $n = 88$ M, 75 F)	8	26	DB, P, R	10.2	5.1 g twice/d
Bell, 1994 ( $n = 25$ M, 54 F)	12	12	DB, P, R	10.2	5.1 g twice/d

<sup>1</sup>DB, double-blind; P, parallel; R, randomized; IB, investigator blind; CO, crossover.

<sup>2</sup>Subjects consuming FiberCon (Whitehall-Robins Healthcare, Madison, NJ) or Citrucel (Lakeside Pharmaceuticals, Cincinnati) were excluded from the meta-analysis.

<sup>3</sup>Subjects consuming the high-fat diet were excluded from the meta-analysis.

**TABLE 2**

Pooled demographic and prediet lipid characteristics of subjects included in the meta-analysis

Variable	Psyllium group (n = 384)	Placebo group (n = 272)
Sex		
Females	172 (44.8) <sup>1</sup>	137 (50.4)
Males	212 (55.2)	135 (49.6)
Age (y)	55.2 ± 12.2 (24–82) <sup>2</sup>	54.4 ± 12.6 (27–83)
Serum cholesterol (mmol/L) <sup>3</sup>	6.31 ± 0.72 (4.27–9.26)	6.44 ± 0.78 (4.61–9.44)
Serum LDL cholesterol (mmol/L) <sup>3</sup>	4.33 ± 0.63 (2.53–7.15)	4.40 ± 0.68 (2.04–7.11)

<sup>1</sup>n; percentage in parentheses.

<sup>2</sup> $\bar{x} \pm SEM$ ; range in parentheses.

<sup>3</sup>To convert values to mg/dL, divide by 0.02586.

The percentage change in serum total and LDL-cholesterol concentrations compared with placebo at 8 wk in subjects consuming psyllium for each of the 8 studies included in the meta-analysis is shown in **Figures 1** and **2**. The change was significant in all but 2 studies for both total and LDL-cholesterol concentrations.

**Effect of baseline triacylglycerol values**

Baseline triacylglycerol concentration was investigated as a separate covariate for the meta-analysis, with 2 groups of subjects: those with baseline triacylglycerol values  $\geq 2.26$  mmol/L (n = 342 in the psyllium group and 240 in the placebo group) and those with baseline triacylglycerol values <2.26 mmol/L (n = 42 in the psyllium group and 32 in the placebo group).

A significant triacylglycerol group-by study-by-treatment effect was found for the analysis of serum LDL-cholesterol values. Full elucidation of the nature of this 3-way interaction required an evaluation of each individual study. For all but 2 of the 14 baseline triacylglycerol group combinations for which data were available, observed treatment differences indicated at least a directionally greater reduction in LDL-cholesterol concentrations for subjects consuming psyllium than for those consuming placebo. Furthermore, in both cases, the means were based on only 2 placebo subjects within the subset baseline triacylglycerol group. Therefore, despite the triacylglycerol response, LDL cholesterol decreased as was expected. For generality, when data were pooled across studies, treatment differ-

ences were consistent between baseline triacylglycerol groups. Therefore, the analysis across studies does not support the differences seen in the 2 outlier studies. For both the low and high baseline triacylglycerol groups, psyllium significantly reduced total and LDL-cholesterol concentrations over 8 wk of treatment compared with placebo and baseline values.

**Effect of sex**

A significant sex-by-study-by-treatment effect was also found for serum LDL-cholesterol concentrations. However, for all but 1 of the 16 study-sex combinations, observed treatment differences indicated at least a directionally greater reduction in LDL cholesterol for psyllium than for placebo. When the data were pooled across studies, treatment differences were consistent between sexes; reductions in serum LDL-cholesterol concentrations for psyllium compared with placebo were 0.269 mmol/L (10.4 mg/dL) for women and 0.243 mmol/L (9.4 mg/dL) for men. For both men and women, psyllium significantly reduced serum total and LDL-cholesterol concentrations over 8 wk of treatment compared with placebo and baseline values.

**Effect of age**

Significant age group-by-study-by-treatment interactions were found for serum ratios of LDL to HDL cholesterol and total to HDL cholesterol. In general, the older the age group, the greater the decreases in the ratios of LDL to HDL cholesterol and in total

**TABLE 3**

Baseline serum lipid concentrations and posttreatment changes in subjects consuming psyllium or placebo for 8 wk<sup>1</sup>

Serum variable	Psyllium group (n = 384)		Placebo group (n = 272)		Net difference (psyllium – placebo)
	Baseline	Change	Baseline	Change	
Total cholesterol (mmol/L) <sup>2</sup>	6.144 ± 0.710	-0.272 ± 0.032 <sup>3</sup>	6.230 ± 0.742	-0.034 ± 0.033	-0.238 ± 0.046 <sup>4</sup> (-3.87 ± 0.74) <sup>4,5</sup>
LDL cholesterol (mmol/L) <sup>2</sup>	4.189 ± 0.591	-0.298 ± 0.029 <sup>3</sup>	4.269 ± 0.611	-0.017 ± 0.030	-0.281 ± 0.042 <sup>4</sup> (-6.68 ± 0.96) <sup>4</sup>
HDL cholesterol (mmol/L) <sup>2</sup>	1.273 ± 0.310	-0.013 ± 0.009	1.270 ± 0.322	0.000 ± 0.010	-0.013 ± 0.013 (-1.04 ± 1.04)
Triacylglycerol (mmol/L) <sup>6</sup>	1.491 ± 0.641	0.064 ± 0.029 <sup>3</sup>	1.514 ± 0.678	0.008 ± 0.029	0.055 ± 0.041 (3.67 ± 2.78)
LDL:HDL cholesterol	3.49 ± 0.97	-0.21 ± 0.04 <sup>3</sup>	3.60 ± 0.95	0.02 ± 0.04	-0.23 ± 0.05 <sup>4</sup> (-6.58 ± 1.47) <sup>4</sup>
Total:HDL cholesterol	5.10 ± 1.25	-0.17 ± 0.04 <sup>3</sup>	5.20 ± 1.24	0.02 ± 0.05	-0.19 ± 0.06 <sup>7</sup> (-3.68 ± 1.22) <sup>8</sup>
Apo A-I (g/L)	1.50 ± 0.334	0.0873 ± 0.020	1.48 ± 0.440	0.0397 ± 0.0241	0.0475 ± 0.0314 (3.18 ± 2.14)
Apo B (g/L)	1.31 ± 0.274	0.0172 ± 0.0214	1.33 ± 0.478	0.0058 ± 0.0238	0.0114 ± 0.0320 (-0.89 ± 2.50)
Apo B:apo A-I	0.91 ± 0.26	-0.06 ± 0.01 <sup>3</sup>	0.92 ± 0.29	-0.01 ± 0.02	-0.05 ± 0.03 <sup>9</sup> (-5.63 ± 2.87) <sup>10</sup>

<sup>1</sup> $\bar{x} \pm SEM$ . Apo, apolipoprotein.

<sup>2</sup>To convert values to mg/dL, divide by 0.02586.

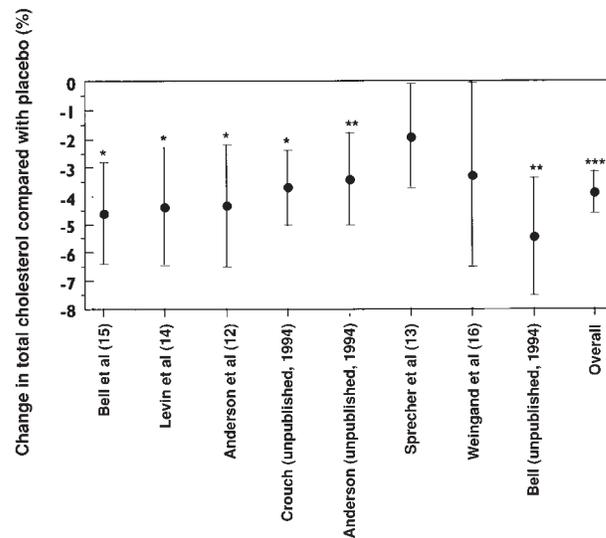
<sup>3</sup>Significantly different from zero within treatment group, P < 0.05.

<sup>4,7,8,10</sup>Significantly different from zero: <sup>4</sup>P < 0.0001, <sup>7</sup>P = 0.0032, <sup>8</sup>P = 0.0025, <sup>10</sup>P = 0.0496.

<sup>5</sup>Percentage change compared with placebo in parentheses; calculated as the ratio (multiplied by 100) of the week 8 adjusted means for subjects consuming psyllium relative to placebo. Results are based on an analysis of covariance model in which the baseline score was used as the covariate.

<sup>6</sup>To convert values to mg/dL, divide by 0.01129.

<sup>9</sup>Different from zero, P = 0.0600.



**FIGURE 1.** Mean ( $\pm$ SE) percentage change from placebo in serum total cholesterol concentrations at 8 wk in subjects consuming psyllium. \*, \*\*, \*\*\*Significantly different from placebo: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.0001$ .

to HDL cholesterol with psyllium treatment. Interpretation of these results, however, is limited because of the small sample sizes in the age group–study–treatment combination.

#### Effect of treatment regimen and formulation changes

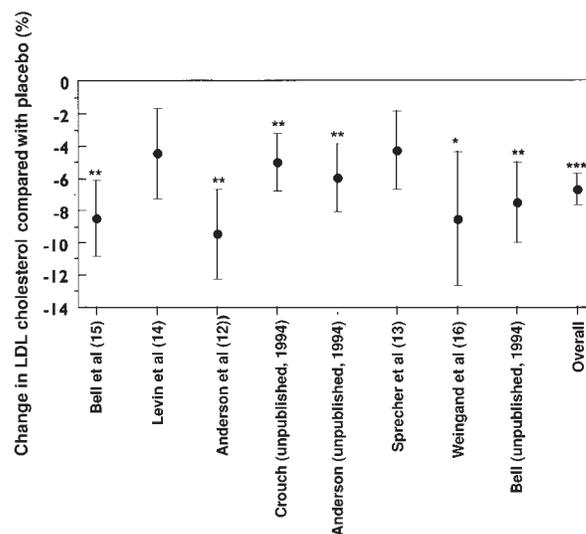
Treatment differences were consistent between treatment regimens, indicating that, adjunctive to diet, 5.1 g psyllium 2 times daily or 3.4 g psyllium 3 times daily was equally effective. Likewise, there were no significant treatment differences when formulation methods (texture or sanitization) were analyzed, indicating that these changes did not affect treatment outcomes.

#### Safety analyses

Across all 19 clinical studies assessed, the overall dropout rate due to adverse events was 3.2% for subjects treated with

psyllium ( $n = 966$ ), which was comparable with the 2.6% rate for subjects treated with placebo ( $n = 662$ ; chi-square test,  $P = 0.45$ ). Completion rates were high, ranging from 76% to 100%. Treatment periods for most studies were  $\geq 8$  wk, following an 8-wk dietary lead-in period.

The incidence of adverse events was also similar between psyllium and placebo groups. An integrated summary of adverse events data available in 11 of these studies (Table 4) is representative of the most commonly reported symptoms. Symptoms involving the digestive system (eg, flatulence, abdominal pain, diarrhea, constipation, dyspepsia, or nausea) and symptoms typical of upper respiratory tract infections were the most commonly reported symptoms for both the psyllium and placebo groups. In a subpopulation of elderly subjects ( $\geq 65$  y of age) receiving psyllium or placebo for 8 wk, psyllium was well toler-



**FIGURE 2.** Mean ( $\pm$ SE) percentage change from placebo in serum LDL-cholesterol concentrations at 8 wk in subjects consuming psyllium. \*, \*\*, \*\*\*Significantly different from placebo: \* $P < 0.05$ , \*\* $P < 0.01$ , \*\*\* $P < 0.0001$ .

ated and adverse events were comparable with those for the total psyllium-exposed population.

Across all 19 studies, a total of only 20 patients experienced serious adverse events ( $n = 14$  in the psyllium group, 4 in the placebo group, and 2 receiving another fiber supplement, calcium polycarbophil). In 18 of the 20 subjects with serious adverse events, the event was judged by the investigator to have no relation to psyllium treatment. In the remaining 2 subjects (1 subject receiving psyllium with hernia surgery and 1 subject receiving calcium polycarbophil with a potential ovarian aneurysm), the relation of the event to psyllium treatment was judged to be unknown.

There were no serious or unexpected psyllium-related adverse events and no deaths reported in the 966 psyllium-exposed subjects across the 19 studies (ranging from 6 wk to 6 mo in duration, with exposures of 5.1–20.4 g psyllium/d). Clinical laboratory and hematology data were available for 8 studies. The percentages of individuals with values outside the normal range were comparable between the psyllium and placebo groups, suggesting that psyllium does not adversely affect these measures. Serum and urine vitamin and mineral analyses were conducted in a subset of subjects who consumed psyllium or placebo for either 4 or 6 mo. Psyllium treatment had no clinically significant effects on vitamin and mineral status in either of these studies. Likewise, there were no adverse effects on clinical vital signs in subjects receiving either psyllium or placebo.

## DISCUSSION

This meta-analysis of 8 clinical studies was conducted to determine the size and consistency of psyllium's hypolipidemic effects in hypocholesterolemic individuals already consuming a low-fat diet. Results confirm that psyllium significantly lowers serum total and LDL-cholesterol concentrations and ratios of serum LDL to HDL cholesterol and of total to HDL cholesterol beyond reductions achieved with diet only. In this meta-analysis, psyllium lowered serum total cholesterol concentrations an additional 4% and serum LDL-cholesterol concentrations an additional 7% relative to placebo in subjects consuming an AHA Step I diet. Psyllium also significantly lowered serum ratios of apo B to apo A-I an additional 6% relative to placebo. Psyllium did not significantly affect serum HDL-cholesterol or triacylglycerol concentrations.

Individual studies of the hypocholesterolemic effects of psyllium report similar reductions in serum total and LDL-cholesterol concentrations, ranging from 3–6% for serum total cholesterol concentrations to 5–9% for serum LDL-cholesterol concentrations over 8–12 wk (12–17). Reductions of  $\leq 15\%$  for serum total cholesterol concentrations and of  $\leq 20\%$  for serum LDL-cholesterol concentrations have been reported for hypercholesterolemic subjects eating a typical, high-fat American diet (18, 19).

Two individual studies included in this meta-analysis reported significant changes in serum apo concentrations. Bell et al (15) noted a 6.8% decrease in apo B concentrations relative to placebo in subjects consuming psyllium. Sprecher et al (13) noted a 6.4% increase from baseline in serum apo A-I concentrations in subjects consuming psyllium. The significant 6% decrease relative to placebo in serum ratios of apo B to apo A-I of subjects consuming psyllium in this meta-analysis is consistent with changes seen in individual studies. Apo B promotes atherogenesis, whereas apo A-I—the protective factor in HDL cholesterol—reduces atherogenesis (27).

**TABLE 4**

Percentage of subjects reporting adverse events in the psyllium and placebo groups<sup>1</sup>

Symptom <sup>2</sup>	Psyllium group ( $n = 807$ )	Placebo group ( $n = 476$ )
Digestive	24.1	20.6
Flatulence	9.0	5.0
Abdominal pain	6.6	5.0
Diarrhea	5.9	4.0
Constipation	3.1	4.4
Dyspepsia	3.1	2.3
Nausea	2.2	1.9
Respiratory	16.8	14.1
Rhinitis	9.3	7.8
Infection	5.2	5.9
Pharyngitis	3.3	3.6
Cough increase	3.0	2.5
Sinusitis	2.1	0.8
Body as a whole	16.5	13.9
Headache	6.3	5.3
Back pain	2.4	2.9
Urogenital	5.5	2.3
Musculoskeletal	5.0	4.4
Nervous	4.0	3.2
Skin	4.0	4.0
Special senses	2.9	1.9
Cardiovascular	2.4	1.5
Metabolic and nutritional	1.0	0.4
Endocrine	0.4	0.2
Hemic and lymphatic	0.2	0.8

<sup>1</sup>Data from an integrated safety database of 11 clinical studies, including 5 published studies (9–12, 15) and 6 unpublished studies.

<sup>2</sup>COSTART body systems and terms were used in the pooled safety analysis (26). COSTART terms with a frequency  $\geq 2\%$  are included in the table.

The hypocholesterolemic effects of psyllium-enriched ready-to-eat cereals have also been reported (28, 29). Olson et al (30) conducted a meta-analysis of 8 published studies and 4 unpublished studies of the hypocholesterolemic effects of psyllium-enriched cereals for hypercholesterolemic individuals already consuming a low-fat diet. Their results compare closely with our results. In the meta-analysis of cereal studies, subjects received 3–12 g psyllium/d, with subjects receiving 10–12 g psyllium/d in most studies. Also, serum total cholesterol concentrations were reduced an additional 5% and serum LDL-cholesterol concentrations an additional 9% relative to placebo, in addition to reductions achieved with diet. Serum HDL-cholesterol concentrations did not change significantly, serum apo concentrations were not reported, and no effects of age, sex, or menopausal status were found.

A recent study of the long-term effects (24 wk) of consuming 3.4, 6.8, or 10.2 g psyllium daily from psyllium-containing foods was also reported (31). Psyllium was provided in 5 different ready-to-eat breakfast cereals, bread, pasta, and snack bars. After 8 wk of an AHA Step I diet lead-in phase, serum LDL-cholesterol concentrations were reduced a significant 5.3% compared with control concentrations with 24 wk of treatment with 10.2 g psyllium/d.

In our study, subgroup analyses performed for baseline triacylglycerol concentration, sex, age, dosing regimen, and formulation showed that although there were a few isolated interactions for

individual studies, treatment differences were fairly consistent for each subgroup when data were pooled across studies.

A study by Neal and Balm (17) also noted no significant differences in the serum lipid responses of men and women to psyllium treatment, although men had significant reductions in serum total and LDL-cholesterol concentrations during the diet-only lead-in phase of this study, whereas women did not. Subjects with higher initial serum triacylglycerol values also had greater reductions in serum total cholesterol concentrations during the dietary lead-in phase of the study. In a recent study of the consumption of psyllium-containing foods (31), a trend was observed toward a greater LDL-cholesterol response in men than in women, with some groups consuming amounts of psyllium daily that were lower than the standard for this meta-analysis (10.2 g). More research is needed to clarify the effects of psyllium on serum lipids in population subgroups.

The mechanisms by which psyllium lowers serum total and LDL-cholesterol concentrations remain unclear, and there may be several different ones. The preponderance of data suggest that psyllium and other soluble fibers increase bile acid excretion in animals and humans, diverting hepatic cholesterol for bile acid production (19, 32). Fiber may also affect absorption of cholesterol and fat (33). Short-chain fatty acid byproducts of fiber fermentation may also inhibit hepatic cholesterol synthesis (34, 35).

Pooled safety data from 19 clinical trials in this analysis indicate that psyllium is well tolerated and is not causally associated with serious adverse events (12–19, 25). No medically significant adverse effects on clinical laboratory data, vital signs, or in serum vitamin or mineral status were seen. Psyllium intake of  $\leq 20.4$  g/d was well tolerated. The exposed population included subset groups of the elderly ( $>65$  y), subjects with type 2 diabetes, and obese subjects. Although rare, other investigators have reported allergic reactions to psyllium in individuals with prior psyllium exposure from manufacturing or bulk dispensing (36). Psyllium has been marketed as an over-the-counter bulk fiber laxative for  $>60$  y in the United States and for several decades in Europe and Canada and has an excellent safety record. The safety of psyllium has been documented by other scientific groups, including the US Food and Drug Administration (37), the Select Committee on Generally Recognized Safe Substances (38), and the Expert Panel from the Life Sciences Research Office (39) of the Federation of American Societies for Experimental Biology.

In the United States,  $\approx 32\%$  of adult men and 27% of adult women have undesirably high serum cholesterol concentrations (2). The NCEP recommends stepwise reductions in dietary fat, saturated fat, and cholesterol as the primary therapy for hypercholesterolemia, reserving drug therapy for individuals with severe hypercholesterolemia or for those who do not adequately respond to diet. This meta-analysis shows that incorporating 10.2 g psyllium fiber/d into the diet of individuals already consuming a low-fat diet further reduces serum total and LDL-cholesterol concentrations without affecting HDL-cholesterol concentrations. Psyllium is safe, well accepted, and provides a useful adjunct to a low-fat diet for individuals with mild-to-moderate hypercholesterolemia. 

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