Psyllium fiber improves glycemic control proportional to loss of glycemic control: a meta-analysis of data in euglycemic subjects, patients at risk of type 2 diabetes mellitus, and patients being treated for type 2 diabetes mellitus[1]

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ABSTRACT

Background: A number of health benefits are associated with intake of soluble, viscous, gel-forming fibers, including reduced serum cholesterol and the attenuation of postprandial glucose excursions.

Objective: We assess the effects of psyllium, which is a soluble, gel-forming, nonfermented fiber supplement, on glycemic control in patients who were being treated for type 2 diabetes mellitus (T2DM) and in patients who were at risk of developing T2DM.

Design: A comprehensive search was performed of available published literature (Scopus scientific database) and clinical records stored by Procter & Gamble with the use of key search terms to identify clinical studies that assessed the glycemic effects of psyllium in nondiabetic, pre-T2DM, and T2DM patients.

Results: We identified 35 randomized, controlled, clinical studies that spanned 3 decades and 3 continents. These data were assessed in 8 meta-analyses. In patients with T2DM, multiweek studies (psyllium dosed before meals) showed significant improvement in both the fasting blood glucose (FBG) concentration (-37.0 mg/dL; $P < 0.001$) and glycated hemoglobin (HbA1c) [-0.97% (-10.6 mmol/mol); $P = 0.048$]. Glycemic effects were proportional to baseline FBG; no significant glucose lowering was observed in euglycemic subjects, a modest improvement was observed in subjects with pre-T2DM, and the greatest improvement was observed in subjects who were being treated for T2DM.

Conclusions: These data indicate that psyllium would be an effective addition to a lifestyle-intervention program. The degree of psyllium's glycemic benefit was commensurate with the loss of glycemic control. Because the greatest effect was seen in patients who were being treated for T2DM, additional studies are needed to determine how best to incorporate psyllium into existing prevention and treatment algorithms with concomitant hypoglycemic medications. *Am J Clin Nutr* 2015;102:1604–14.

INTRODUCTION

In 2002, the Institute of Medicine published a definition of total fiber that distinguished between dietary fiber (nondigestible carbohydrates and lignin that are intrinsic and intact in plants) and functional fiber (isolated, nondigestible carbohydrates that have been shown to have beneficial physiologic effects in humans) (1). The health benefits of dietary fiber have been typically assessed in epidemiologic and observational studies, which have established an association between the consumption of fiber-rich whole foods and observed health effects but have lacked the controlled setting necessary to establish causation (1, 2). This lack of control has left unclear how much of an observed health effect can be directly attributed to the increase in fiber consumption compared with how much might be independent of fiber, such as a reduction in calories, the elimination of less healthy dietary components, and an increase in the health-promoting constituents of fruit, vegetables, and whole grains (2).

In contrast with dietary fiber, the Institute of Medicine definition requires that the isolated nondigestible carbohydrates that are present in fiber supplements must show clinical evidence of a health benefit to be considered a "functional fiber" (2). The term "fiber supplement" implies that regular (e.g., daily) consumption will provide health benefits that may be missing from a low-fiber diet. Unfortunately, for most fiber supplements, this implication has not been supported by well-controlled clinical studies (2–4). Therefore, it is reasonable to require evidence of a clinically meaningful health benefit before selecting or recommending a fiber supplement to patients being treated for type 2 diabetes mellitus (T2DM)[5] and to patients at risk of developing T2DM.

More than 3 decades ago, a study established that gel-forming fibers were therapeutically useful in reducing postprandial blood
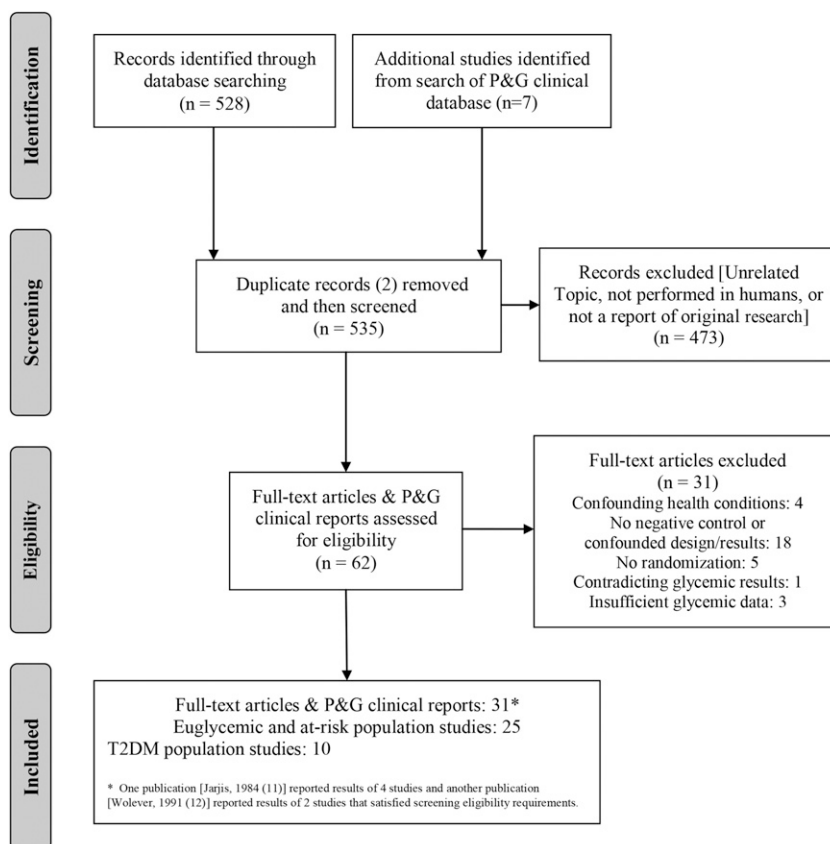
FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the identification, screening, eligibility, and inclusion process. Of the 535 records initially identified, 35 studies met the inclusion and exclusion criteria and were used in the meta-analyses. P&G, Procter & Gamble; T2DM, type 2 diabetes mellitus.

glucose, which is a phenomenon that was highly correlated with the viscosity of the gel-forming fiber ($r = 0.926$; $P < 0.01$) (5). In this 1978 study, raw guar gum (highly viscous and gel forming) showed a marked reduction in peak postprandial glucose (5). When the guar gum was hydrolyzed (e.g., partially hydrolyzed guar gum), viscosity was attenuated and the viscosity and gel-dependent effects on postprandial glucose were lost. The introduction of a gel-forming fiber significantly increases the viscosity of chyme in the upper intestine, which reduces the contact with digestive enzymes and delays absorption, thereby causing an increased fraction of nutrients to be delivered to distal regions of the small bowel (2, 4, 6, 7). This effect is comparable to the effects of intestinal α-glucosidase inhibitors that reduce the digestion and absorption of carbohydrates and, thus, delay and blunt the delivery of glucose to the circulation. Moreover, the delivery of increased amounts of carbohydrate to the ileum has been associated with an increased release of the glucoregulatory factor glucagon-like peptide 1 (GLP-1), which may also contribute to better glycemic control in response to a gel-forming fiber (8, 9). Insoluble fibers (e.g., wheat bran) and soluble nonviscous fibers (e.g., inulin and wheat dextrin) do not exhibit these viscous and gel-dependent effects (2, 4). It was hypothesized that psyllium would have little to no effect on fasting blood glucose (FBG) in euglycemic subjects, that a beneficial effect existed in subjects with prediabetes, and that this effect would be amplified with a progressive loss of glycemic control. The objective of this analysis was to assess the

effects of psyllium, which is a soluble, viscous, gel-forming nonfermented fiber supplement, on glycemic control across a range of glycemia from euglycemia to T2DM with the use of published and unpublished data in meta-analyses.

METHODS

A comprehensive literature review was conducted in April 2014 with the use of the Scopus scientific database. Key search words were as follows: psyllium, plantago, psyllium husk, psyllium-husk, ispaghula, mucilage, Lunelax, Metamucil, and glucose. In addition, the reference section of each identified publication was manually searched for publications that were not identified by the Scopus search. A total of 528 citations were identified. Publications were excluded from consideration for the following pre-established exclusion criteria: not a clinical study that measured a glycemic endpoint or that tested psyllium husk; study participants had potentially confounding health conditions (e.g., type 1 diabetes, gastrectomy, or Parkinson disease); no appropriate negative control (e.g., placebo, meal without added fiber, or glucose load without added fiber); not randomized; glycemic results for psyllium unclear because of a combination of results with another treatment; a parallel design study with a statistically significant ($P < 0.05$) imbalance in glycemic endpoints at baseline; and duplicate publication of data. This screening process left a total of 21 publications (25 studies) that were relevant for additional consideration (10–30). **Figure 1**

TABLE 1
Endpoints, populations, and meta-analyses performed[1]

Glycemic endpoint	Healthy and at-risk subject studies/subjects, n (meta-analysis type)	T2DM patient studies/subjects, n (meta-analysis type)
Fasting glucose	14/1267 (A)	4/245 (A)
	11/1075 (I)	
HbA1c	2/111 (none)	3/120 (A)
Peak postprandial glucose	11/153 (A)	7/108 (A)
Peak postprandial insulin	11/64 (A)	3/44 (A)

[1]A, aggregate data meta-analysis; HbA1c, glycated hemoglobin; I, individual subject data meta-analysis; T2DM, type 2 diabetes mellitus.

diagrams the identification, screening, eligibility, and inclusion processes.

A comprehensive search was also made of Procter & Gamble (P&G) records to identify other relevant clinical trials of psyllium that included measurements of glycemic endpoints. Four company-sponsored studies were published and had already been identified by the literature search (15, 17, 20, 21). Three company-sponsored studies were previously published (31–33) but were not identified in the literature search apparently because glucose results were not reported in the publications (31, 33) or were reported only as a routine clinical measurement (32). A total of 7 unpublished P&G-sponsored clinical trials [P&G 1 (1989), P&G 2 (1990), P&G 3 (1991), P&G 4 (1991), P&G 5 (1994), P&G 6 (2009), and P&G 7 (2011)] that were relevant to these analyses were also identified. Overall, a review of the internal P&G clinical trial database resulted in the identification of 10 additional studies that were not already found by the Scopus search.

In sum, 35 randomized, controlled, clinical trials were identified as appropriate and served as the basis for 8 meta-analyses. Of these meta-analyses, 7 meta-analyses were aggregate data meta-analyses (e.g., analyses of reported means and SEs), and one meta-analysis was an individual subject data meta-analysis (i.e., an analysis with the use of the separate data from individuals in the studies). Four of the 7 aggregate data meta-analyses were in T2DM populations and targeted the following endpoints: FBG, glycated hemoglobin (HbA1c), peak postprandial glucose, and

peak postprandial insulin. The remaining 3 aggregate data meta-analyses included studies in healthy normal and at-risk populations and considered the following glycemic endpoints: FBG, peak postprandial glucose, and peak postprandial insulin. The process of extracting data from publications and P&G study reports was performed independently by 2 individuals and compared to ensure accuracy and completeness. A detailed summary of the study designs and populations is available in **Tables 1–6**.

The objective of the 7 aggregate data meta-analyses was to estimate the overall effect of psyllium compared with a control for each of the glycemic endpoints considered. Because of the heterogeneity of study designs (e.g., psyllium-quantity consumed and diet), random-effects models were fitted in each meta-analysis with the use of the Comprehensive Meta-Analysis application (version 2.2.064; Biostat Inc.). The treatment effect analyzed in 6 of the 7 cases was the mean treatment difference (psyllium compared with control). The exception was the meta-analysis of the peak postprandial insulin concentration in T2DM populations whereby the standardized mean, which was a unitless measure, was analyzed because of an apparent error in the reported units for one study (11). Meta-analyses of postprandial data included only studies or data from a single-meal exposure to psyllium. In cases where peak mean $\pm$ SE postprandial concentrations were not explicitly reported, the maximum mean $\pm$ SE concentrations were extracted from the summarized time-series data. In cases where the correlation between baseline and postbaseline data was

TABLE 2
Psyllium-husk studies in a type 2 diabetes mellitus population: short-term duration[1]

Study	Study design	n (F, %)	Study country	Treatment duration	Dose, meal/day, g	Psyllium dose form	Mean baseline glucose, mg/dL	PP glucose	PP insulin
Sartor et al., 1981 (10)	R, CX, NC, IN, SN	12 (33)	Sweden	1 meal	6.6/6.6	Lunelax powder	~160	X	—
Jarjis et al., 1984 (11)	R, CX, NC, IY, SY	14 (14)	England	1 meal	7/7	Fybogel	Not reported	X	X
Pastors et al., 1991 (15)	R, CX, PC, IY, SY	18 (67)	United States	1 d	6.8/13.6	Mm	121–221	X	X
Wolever et al., 1991 (12)	R, CX, NC, IN, SN	6 (33)	Canada	1 meal	20/20	P-E BF	Not reported	X	—
Frati-Munari et al., 1998 (13)	R, CX, NC, IY, SY	12 (75)	Mexico	1 meal	15/15	Psyllium mucilage	121	X	X
Dastjerdi et al., 2007 (14)	R, DB, PG, NC, IN, SN	12 (67)	Iran	1 meal	5/5	Psyllium granules	134	X	—

[1]CX, crossover; DB, double blind; IN, institutional review board approval not indicated; IY, institutional review board approval; Mm, Metamucil (Procter & Gamble Co.); NC, negative controlled (meal alone without added psyllium or glucose alone without added psyllium); PC, placebo controlled; PG, parallel group; PP, postprandial; P-E BF, psyllium-enriched bran flakes; R, randomized; SN, subject consent not indicated; SY, subject consent obtained.

TABLE 3
Psyllium-husk studies in a type 2 diabetes mellitus population: long-term duration[1]

Study	Study design	n (F, %)	Study country	Treatment duration	Dose, meal/day, g	Psyllium dose form	Mean baseline glucose, mg/dL	Fasting glucose	HbA1c
Rodríguez-Morán et al., 1998 (16)	R, DB, PG, PC, IY, SY	125 (~55)	Mexico	6 wk	5/15	Mm	176	X	—
Anderson et al., 1999 (17)	R, DB, PG, PC, IY, SY	34 (0)	United States	8 wk	5.1/10.2	Mm	187	X	X
Ziai et al., 2005 (18)	R, DB, PG, PC, IY, SY	49 (not reported)	Iran	8 wk	5.1/10.2	Po Forsk	195	X	X
Feinglos et al., 2013 (19)	R, DB, PG, PC, IY, SY	37 (32)	United States	12 wk	3.4/6.8; 6.8/13.6	Mm	200	X	X

[1]DB, double blind; HbA1c, glycated hemoglobin; IY, institutional review board approval; Mm, Metamucil (Procter & Gamble Co.); PC, placebo controlled; PG, parallel group; Po Forsk, Plantago ovata Forsk; R, randomized; SY, subject consent obtained.

needed to complete calculations, the Comprehensive Meta Analysis default correlation of 0.5 was used. The meta-analysis of FBG in healthy and at-risk individuals involved 11 P&G-sponsored studies, 10 of which followed parallel group designs and one that followed a crossover design. To facilitate the most-consistent analysis approach, treatment means and SEs for the studies with parallel group designs were obtained through an ANCOVA of the individual subject data. All analyses were based on intent-to-treat populations with the use of the last measured fasting glucose value during treatment.

The purpose of the individual subject data meta-analysis was to assess whether a baseline FBG-by-treatment interaction exists in healthy and at-risk individuals (i.e., whether the glycemic effect of psyllium varies by the concentration of baseline FBG). It was hypothesized that psyllium has little to no effect on FBG in euglycemic subjects but that a beneficial effect exists in subjects with prediabetes and that this effect is amplified with a progressive loss of glycemic control. The subject-level data from 11 P&G-sponsored clinical studies ($n = 1075$) were included in this meta-analysis; in the studies, 71.3% of subjects had euglycemia and 27.2% of subjects had prediabetes (Table 6). All 11 studies dosed psyllium at 10.2 g/d for a period of 2–52 wk. In the case of the single crossover study, to be consistent with the other 10 studies, only data from the first treatment period were included in the analysis because this portion of the study could be treated as a parallel group design. The individual subject data meta-analysis model was fitted to the data with the use of the Mixed Procedure of SAS software (version 9.4; SAS Institute Inc.).

TABLE 4
Psyllium-husk studies in a general population: short-term duration[1]

Study	Study design	n (F, %)	Study country	Treatment duration	Dose, meal/day, g	Psyllium dose form	Mean baseline glucose, mg/dL	PP glucose	PP insulin
Jarjis et al., 1984 (11) (3 studies, 1 publication)	R, CX, NC, IY, SY	9 (unknown)	England	1 meal	3.5/3.5	Fybogel	—	X	X
	R, CX, NC, IY, SY	13 (unknown)	England	1 meal	7/7	Fybogel	—	X	X
	R, CX, NC, IY, SY	8 (25)	England	1 meal	7/7	Mm	—	X	—
Frati-Munari et al., 1989 (25)	R, CX, NC, IN, SN	8 (0)	Mexico	1 meal	10, 20, 30	Psyllium mucilage	81	X	—
Wolever et al., 1991 (12)	R, CX, NC, IN, SN	10 (60)	Canada	1 meal	20	P-E BF, PS BF	~78	X	—
Cherbut et al., 1994 (26)	R, CX, NC, IY, SY	6 (0)	France	1 meal	15	Ispaghula husk	—	X	X
Rigaud et al., 1998 (27)	R, DB, CX, PC, IY, SY	14 (50)	France	1 meal	7.4	Psyllium	85	X	X[2]
Sierra et al., 2001 (28)	R, CX, NC, IY, SY	10 (100)	Spain	1 meal	10.5	Plantaben	88	X	X
Frost et al., 2003 (29)	R, SB, CX, NC, IY, SY	10 (60)	England	1 meal	1.7	Psyllium in pasta	90	X	X
P&G 6, 2009	R, CX, NC, IY, SY	49 (0)	United States	1 meal	3.4; 6.8	Mm	88	X	—
Karhunen et al., 2010 (30)	R, SB, CX, NC, IY, SY	16 (81)	Finland	1 meal	23	Psyllium	92	X	X

[1]CX, crossover; DB, double blind; IN, institutional review board approval not indicated; IY, institutional review board approval; Mm, Metamucil (Procter & Gamble Co.); NC, negative controlled (meal alone without added psyllium or glucose alone without added psyllium); PC, placebo controlled; PP, postprandial; PS BF, bran flakes with psyllium sprinkled on top; P&G, Procter & Gamble–sponsored clinical trial; P-E BF, psyllium-enriched bran flakes; R, randomized; SB, single blind; SN, subject consent not indicated; SY, subject consent obtained.
[2]Psyllium reduced the postprandial 300-min integrated insulin response relative to placebo ($P < 0.05$), but the peak postprandial insulin concentration could not be estimated from the reported results.

TABLE 5
Psyllium-husk studies in a general population: long-term duration[1]

Study	Study design	n (F, %)	Study country	Treatment duration	Dose, meal/day, g	Psyllium dose form	Mean baseline glucose, mg/dL	Fasting glucose	HbA1c
Anderson et al., 1988 (20)	R, DB, PG, PC, IY, SY	26 (0)	United States	8 wk	3.4/10.2	Mm	100	X	—
Bell et al., 1989 (21)	R, DB, PG, PC, IY, SY	75 (49)	United States	8 wk	3.4/10.2	Mm	94	X	—
P&G 1, 1989	R, DB, PG, PC, IY, SY	79 (68)	United States	12 wk	5.1/10.2	Mm	102	X	—
Levin et al., 1990 (32)	R, DB, PG, PC, IY, SY	58 (19)	United States	16 wk	5.1/10.2	Mm	96	X	—
P&G 2, 1990	R, DB PG, PC, IY, SY	65 (83)	United States	8 wk	3.4/10.2	Mm	84	X	—
P&G 3, 1991	R, DB, PG, PC, IY, SY	255 (43)	United States	8 wk	1.7/5.1; 3.4/10.2; 6.8/20.4	Mm	92	X	—
P&G 4, 1991	R, DB, PG, PC, IY, SY	112 (50)	United States	12 wk	5.1/10.2	Mm	94	X	—
Sprecher et al., 1993 (33)	R, DB, PG, PC, IY, SY	118 (42)	United States	8 wk	5.1/10.2	Mm	99	X	—
P&G 5, 1994	R, DB PG, PC, IY, SY	117 (85)	United States	2 wk	5.1/10.2	Mm	86	X	—
Anderson et al., 2000 (31)	R, DB, PG, PC, IY, SY	163 (46)	United States	26 wk	5.1/10.2	Mm	94	X	—
Cicero et al., 2010 (22)	R, SB, PG, NC, IY, SY	93 (52)	Italy	6 mo	3.5/7	Psyllium powder	110	X	X
P&G 7, 2011	R, DB, CX, PC, IY, SY	18 (72)	United States	8 wk	5.1/10.2	Mm	108	X	X
de Bock et al., 2012 (24)	R, SB, CX, PC, IY, SY	45 (0)	New Zealand	6 wk	Flexible/6	Encapsulated psyllium	Not reported[2]	X	—
Lu et al., 2012 (23)	R, DB, PG, PC, IY, SY	54 (61)	Taiwan	8 wk	6/12	Plantago psyllium	90.4	X	—

[1]CX, crossover; DB, double blind; IY, institutional review board approval; Mm, Metamucil (Procter & Gamble Co.); NC, negative controlled (meal alone without added psyllium); PC, placebo controlled; PG, parallel group; P&G, Procter & Gamble–sponsored clinical trial; R, randomized; SB, single blind; SY, subject consent obtained.

[2]Mean baseline fasting glucose was not reported, but the authors reported that subjects were healthy with no impaired glucose tolerance.

Study and treatment were included as fixed and random effects, respectively, thereby allowing for different treatment-effect sizes by study. Baseline FBG and separate interactions with study and treatment were also modeled to permit the relation between baseline and end-of-treatment FBG to differ by study and treatment. The model also permitted the residual variance to vary by study (see Equation 9 in reference 34).

RESULTS

Patients with T2DM: aggregate data meta-analyses

The basic design elements of the 6 single-meal postprandial studies and 4 multiweek studies in patients with T2DM are summarized in Tables 2 and 5. In these studies, some patients were treated for diabetes with a diet alone, whereas other patients were receiving prescription medications. Forest plots shown in **Figures 2** and **3** summarize the individual study results for FBG and HbA1c, respectively, as well as the meta-analysis mean summary effects and study relative weights. Of the 4 multiweek studies that evaluated FBG in patients with T2DM, all but one study (17) showed a significant improvement with the use of psyllium dosed before meals. Similarly, 2 of 3 studies that evaluated HbA1c [except the study by Anderson et al. (17)] showed significant improvement with the use of psyllium husk. The mean summary effect for the fasting glucose concentration was a decrease of 37.0 mg/dL in T2DM subjects (compared with the control: $P < 0.001$). The mean summary effect for HbA1c was −0.97% (−10.6 mmol/mol), which was also significant compared with the control ($P = 0.048$).

Forest plots for postprandial glucose and insulin in the T2DM populations are provided in **Figures 4** and **5**, respectively. Peak postprandial glucose was significantly decreased with the consumption of psyllium husk in 4 of 6 individual studies, and the magnitude of change was generally similar across studies. Significant differences in postprandial insulin were not observed. The effect of psyllium on the peak postprandial glucose concentration was a mean decrease of 29.0 mg/dL ($P < 0.001$), and the reduction in the peak insulin concentration was a reduction in the standardized mean of 0.19 ($P = 0.23$).

TABLE 6
Demographic characteristics and baseline glycemic variables in 11 P&G studies in euglycemic and at-risk subjects[1]

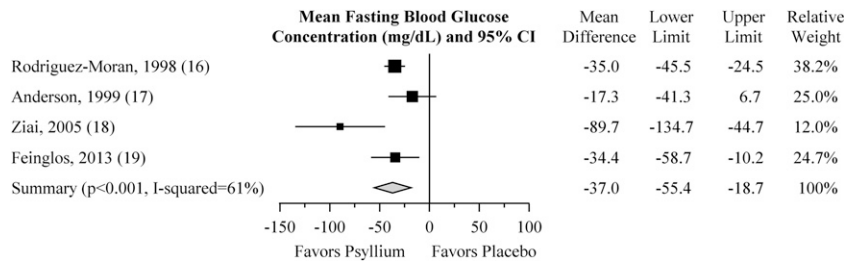|	Placebo (n = 467)	Psyllium husk (n = 608)
Sex, M, n (%)	209 (44.8)	300 (49.3)
Race, n (%)		
Caucasian	212 (45.4)	225 (37.0)
Other	15 (3.2)	13 (2.1)
Unknown	240 (51.4)	370 (60.9)
Age, y	52.5 ± 13.5[2]	52.1 ±13.3
Weight, lb	161.6 ± 29.9	166.2 ± 31.1
Baseline fasting glucose, mg/dL	94.1 ± 12.3	94.4 ± 11.8
Glycemic category, n (%)		
Euglycemia (<100 mg/dL)	334 (71.5)	433 (71.2)
Prediabetes (≥100 to <126 mg/dL)	125 (26.8)	167 (27.5)
Diabetes (≥126 mg/dL)	8 (1.7)	8 (1.3)

[1]P&G, Procter & Gamble.
[2]Mean ± SD (all such values).

	Mean Fasting Blood Glucose Concentration (mg/dL) and 95% CI	Mean Difference	Lower Limit	Upper Limit	Relative Weight
Rodriguez-Moran, 1998 (16)		-35.0	-45.5	-24.5	38.2%
Anderson, 1999 (17)		-17.3	-41.3	6.7	25.0%
Ziai, 2005 (18)		-89.7	-134.7	-44.7	12.0%
Feinglos, 2013 (19)		-34.4	-58.7	-10.2	24.7%
Summary (p<0.001, I-squared=61%)		-37.0	-55.4	-18.7	100%

-150 -100 -50 0 50 100

Favors Psyllium   Favors Placebo

FIGURE 2 Forest plot shows mean differences between psyllium and a negative control in individuals with type 2 diabetes mellitus with respect to fasting glucose. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. A significant ($P \leq 0.048$) improvement in fasting glucose (-37.0 mg/dL) was shown for psyllium compared with placebo.

Healthy and pre-T2DM subjects: aggregate data meta-analyses

Basic design elements of studies that measured fasting glucose, postprandial glucose, and postprandial insulin in the nondiabetic population are summarized in Tables 4 and 5. Many of the multiweek studies were designed to determine the effects of psyllium supplementation in populations with other conditions (e.g., hyperlipidemia) but were otherwise healthy with FBG concentrations determined as a secondary endpoint or as part of a routine clinical laboratory assessment. Subjects in these studies received psyllium supplementation before meals for a period of 2–26 wk.

Forest plots for the 14 studies that measured FBG in nondiabetic subjects are depicted in **Figure 6**. All but 2 trials [22, P&G 4 (1991)] of the individual multiweek studies failed to show a significant difference. However, the overall effect of the studies taken together was a reduction of the mean FBG concentration of 1.60 mg/dL, which showed a trend that approached significance ($P = 0.075$). The mean baseline FBG concentration for the 12 studies that had no significant difference was entirely within the euglycemic range (9 studies) within 2 mg/dL of the euglycemic range (2 studies) or not reported (Table 3). In contrast, the mean baseline FBG concentration for subjects with prediabetes [108 mg/dL; P&G 7 (2011)] and Metabolic Syndrome (110 mg/dL; 22) was roughly in the middle of the prediabetic range (100–125 mg/dL). The P&G study [P&G 7 (2011)] was a randomized, controlled, crossover study that was designed to evaluate the effects of 8 wk of treatment with 2 types of dietary fiber [psyllium and microcrystalline cellulose (placebo)] on glycemic benefits in subjects with pre-T2DM. This small study ($n = 18$) showed a directional improvement in glycemic measures for psyllium (compared with the placebo) that was consistent with the results of the Diabetes Prevention

Program (35). The Cicero study (22) was a randomized, controlled, parallel-group study that compared the American Heart Association Step II diet plus 3.5 g psyllium twice a day with the American Heart Association Step II diet alone. The 6-mo results in subjects with metabolic syndrome showed significant benefits with psyllium husk compared with a control for FBG, fasting insulin, and HbA1c (22).

Eleven studies evaluated postprandial glycemic results in nondiabetic subjects, all of which were done after subjects consumed a single meal; design elements of these studies are summarized in Table 4. All 11 studies reported postprandial glucose results, and 6 studies reported postprandial insulin results. Individual study results are provided in **Figures 7** and **8**. All 11 clinical studies in the nondiabetic population showed a significant or directional reduction in postprandial peak blood glucose concentrations as did the 6 studies that assessed postprandial insulin concentrations. The meta-analysis provided estimates of the overall mean reduction in peak postprandial glucose for psyllium compared with the control (-12.4 mg/dL; $P < 0.001$) and insulin (-126.8 pmol/L; $P = 0.007$), all of which were significant.

Glycemic effect as a function of baseline FBG: individual subject data meta-analysis

The meta-analysis model baseline FBG-by-treatment interaction term was significant ($P = 0.004$), indicating that the effect of psyllium compared with that of the control depended on the concentration of baseline FBG. The specific nature of this relation is summarized in **Figure 9**, which shows that, in euglycemic subjects, psyllium had no significant treatment effect. In subjects with prediabetes, psyllium had a modest glycemic benefit that grew as baseline FBG increased. At the low
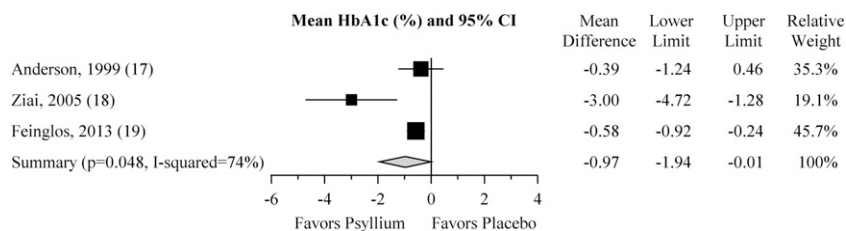
	Mean HbA1c (%) and 95% CI	Mean Difference	Lower Limit	Upper Limit	Relative Weight
Anderson, 1999 (17)		-0.39	-1.24	0.46	35.3%
Ziai, 2005 (18)		-3.00	-4.72	-1.28	19.1%
Feinglos, 2013 (19)		-0.58	-0.92	-0.24	45.7%
Summary (p=0.048, I-squared=74%)		-0.97	-1.94	-0.01	100%

-6 -4 -2 0 2 4

Favors Psyllium   Favors Placebo

FIGURE 3 Forest plot shows mean differences between psyllium and a negative control in individuals with type 2 diabetes mellitus with respect to HbA1c. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. A significant ($P \leq 0.048$) improvement in HbA1c (-0.97%) was shown for psyllium compared with placebo. HbA1c, glycated hemoglobin.
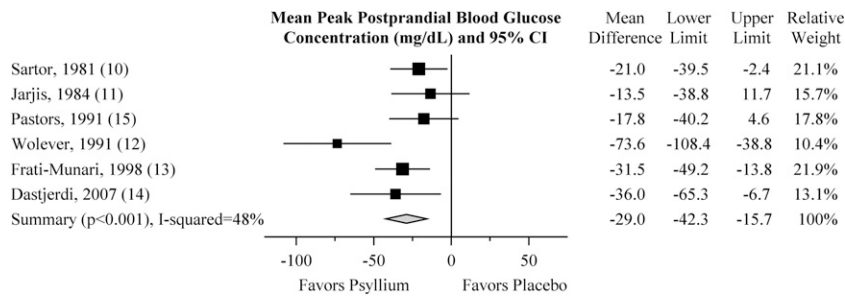
	Mean Peak Postprandial Blood Glucose Concentration (mg/dL) and 95% CI	Mean Difference	Lower Limit	Upper Limit	Relative Weight
Sartor, 1981 (10)		−21.0	−39.5	−2.4	21.1%
Jarjis, 1984 (11)		−13.5	−38.8	11.7	15.7%
Pastors, 1991 (15)		−17.8	−40.2	4.6	17.8%
Wolever, 1991 (12)		−73.6	−108.4	−38.8	10.4%
Frati-Munari, 1998 (13)		−31.5	−49.2	−13.8	21.9%
Dastjerdi, 2007 (14)		−36.0	−65.3	−6.7	13.1%
Summary (p<0.001), I-squared=48%		−29.0	−42.3	−15.7	100%

FIGURE 4 Forest plot shows mean differences between psyllium and a negative control [e.g., placebo (15), meal alone (10, 12–14), or glucose alone (11)] in individuals with type 2 diabetes mellitus with respect to peak postmeal blood glucose. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. A significant (*P* < 0.001) improvement in mean peak postmeal blood glucose (−29.0 mg/dL) was shown for psyllium compared with control. No significant difference in mean standardized peak postmeal insulin was observed.

threshold of prediabetes (baseline FBG concentration: 100 mg/dL), the mean treatment effect was −1.4 mg/dL, and this effect increased to −4.7 mg/dL at the threshold of T2DM (baseline FBG concentration: 125 mg/dL). The treatment differences shown in Figure 9 were significant and ranged from baseline FBG concentrations from 105 to 125 mg/dL.

DISCUSSION

Diabetes is an increasingly common condition and places an enormous burden on public health that has been projected to continue far into the future. These meta-analyses strengthen the existing clinical evidence, which was previously shown in numerous disparate studies (10–33), that psyllium dosed before meals as a dietary supplement provides an effective modality for lowering elevated FBG concentrations. This effect is both significant and clinically meaningful, with an ∼1% (10.6-mmol/mol) lowering of HbA1c, which is comparable to the effect of many drugs that are used to treat diabetes. Moreover, the effect seems to be dependent on blood glucose concentrations, which were minimal in persons with euglycemia and most pronounced in patients who were being treated for T2DM.

In these meta-analyses, we included 35 clinical studies that assessed the effects of psyllium on glycemic control over 3 decades (1981–2011) and across 3 continents (North America, Europe, and Asia). Although many of these studies have been published, a strength of our analysis was the availability of a substantial amount of previously unpublished information. The results of the different studies were generally consistent and mutually supportive. In patients who were being treated for

T2DM, the meta-analysis of chronic psyllium use showed an improvement in both FBG (−37.0 mg/dL, *P* < 0.001) and HbA1c [−0.97% (−10.6 mmol/mol); *P* = 0.048]. Similarly, the meta-analysis of postprandial studies in patients with T2DM showed a significant reduction in peak postprandial blood glucose (−29.0 mg/dL). In contrast, the meta-analyses of nondiabetic groups showed no significant effect on FBG concentrations in multiweek studies but did show a significant effect on postprandial glucose (−12.4 mg/dL; *P* < 0.001) and insulin (−126.8 pmol/L; *P* < 0.007). A more-detailed meta-analysis of these data that explored the effect of psyllium as a function of individual subjects' baseline glycemic status revealed a more-complete picture. In euglycemic subjects, psyllium had no significant treatment effect, but in subjects with prediabetes, psyllium had a modest glycemic benefit that amplified as baseline FBG increased with a maximum mean benefit of −4.7 mg/dL. Although this improvement in FBG may seem relatively small, it is consistent with the glycemic benefit observed with long-term metformin therapy in the Diabetes Prevention Program (35), where a similarly modest improvement in FBG (−4.6mg/dL) in persons at high risk of developing T2DM led to a significant reduction (31%) in the incidence of T2DM.

The benefits of increased dietary fiber intake to mitigate metabolic disease have been broadly shown over the past 40 y (1–7, 10–33, 36, 37). Conclusions from a large body of evidence have shown that diets with a higher fiber content from whole foods are associated with reduced rates of cardiac disease and stroke as well as lower concentrations of plasma lipids and glucose (1–7, 36–38). In contrast with studies of dietary fiber from whole foods, an examination of the effects of isolated fiber
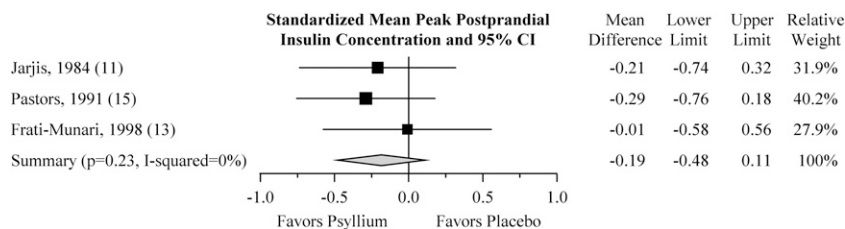

	Standardized Mean Peak Postprandial Insulin Concentration and 95% CI	Mean Difference	Lower Limit	Upper Limit	Relative Weight
Jarjis, 1984 (11)		−0.21	−0.74	0.32	31.9%
Pastors, 1991 (15)		−0.29	−0.76	0.18	40.2%
Frati-Munari, 1998 (13)		−0.01	−0.58	0.56	27.9%
Summary (p=0.23, I-squared=0%)		−0.19	−0.48	0.11	100%

FIGURE 5 Forest plot shows mean differences between psyllium and a negative control [e.g., placebo (15), meal alone (13), or glucose alone (11)] in individuals with type 2 diabetes mellitus with respect to standardized peak postmeal blood insulin. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. A significant (*P* < 0.001) improvement in mean peak postmeal blood glucose (−29.0 mg/dL) was shown for psyllium compared with control. No significant difference in mean standardized peak postmeal insulin was observed.
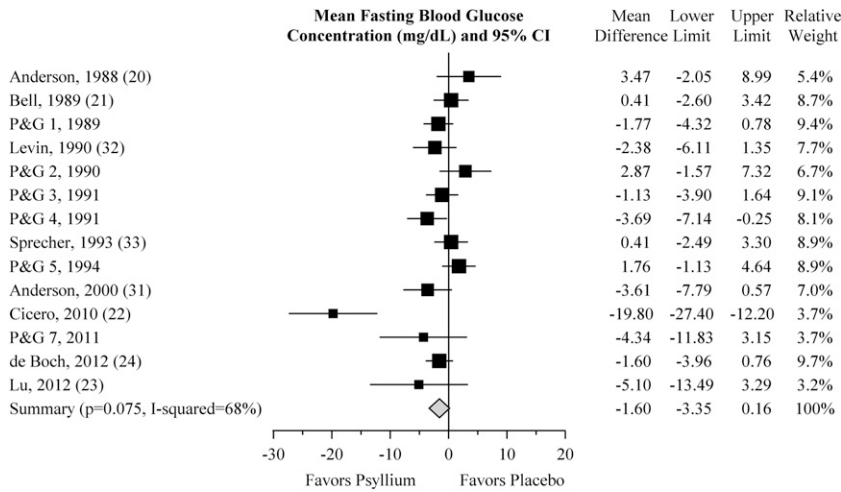
FIGURE 6 Forest plot shows mean differences between psyllium and a negative control [e.g., placebo (20, 21, 23, 24, 31–33, P&G 1–5 and 7)] in euglycemic individuals with respect to fasting blood glucose. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. No significant difference in mean fasting blood glucose was shown. P&G, Procter & Gamble.

sources present in fiber supplements did not provide a mechanistic insight with viscous, gel-forming fibers such as psyllium, guar gum, and β-glucan having been shown to reduce the absorption of bile (cholesterol) and delay the absorption of glucose from the gut (2, 4, 6, 7). These effects are proportional to the degree of viscosity for gel-forming fibers (2, 4, 5, 39, 40), suggesting a significant component of mechanical interference with normal absorptive function of the small intestine.

A clinical study showed that the viscosity of a gel-forming fiber is actually a better predictor of cholesterol-lowering efficacy than is the quantity of fiber consumed (40). Focused studies of specific fibers with attributable actions on physiology have raised the potential for the use of these agents as nutriceuticals. Moreover, because the years of recommendations to increase the proportion of high fiber foods such as fruit, vegetables, and whole-grain cereals have had only a limited impact on the dietary practices of the American populace (38), supplements would seem to provide the most-efficacious application of the health benefits of ingested fiber. However, not all fiber supplements provide these measurable health benefits. Gel-dependent effects in the small bowel (e.g., cholesterol lowering and improved

glycemic control) and in the large bowel (e.g., relief from constipation and diarrhea) are not provided by nongelling, nonviscous, fermentable, soluble supplements (e.g., wheat dextrin and inulin) (2, 4).

Interference with carbohydrate digestion and absorption is an established mechanism for the treatment of T2DM. The effectiveness of α-glucosidase inhibitors has been shown in a range of diabetic populations, and these drugs are now a well-accepted option to treat patients. Beyond effects to delay the breakdown and uptake of complex carbohydrates, α-glucosidase inhibitors increase the release of GLP-1 (8, 9, 41–43), which is a glucoregulatory hormone that is synthesized in greatest amounts in the ileum and colon. There has been speculation that some of the benefits from α-glucosidase inhibitors are mediated by GLP-1. Although this mechanism has not been explored for viscous, gel-forming fibers, the similar effect of these compounds to increase the passage of carbohydrate to the distal gut raises the possibility that changes in gastrointestinal hormone secretion contribute to their actions. Note that, on the basis of 5 clinical studies, psyllium is not fermented like guar gum and β-glucan are, and thus, psyllium does not provide
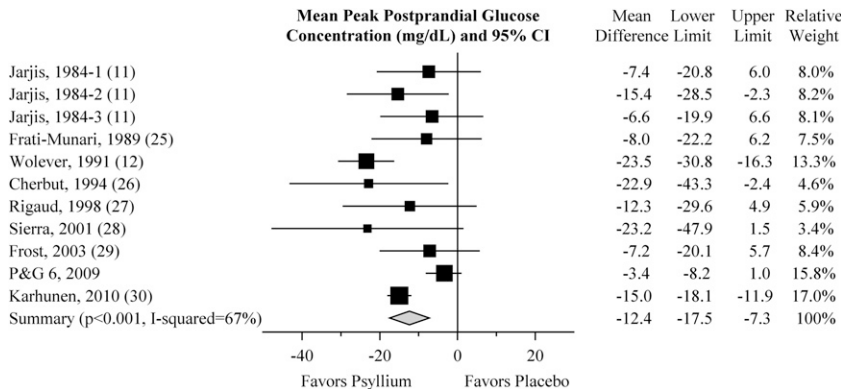

FIGURE 7 Forest plot shows mean differences between psyllium and a negative control [e.g., meal alone (12, 29, 30, P&G 6) or glucose alone (11, 25–28)] in euglycemic individuals with respect to peak postmeal blood glucose. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. A significant ($P \leq 0.007$) improvement in peak postmeal blood glucose (-12.4 mg/dL) was shown for psyllium compared with control. P&G, Procter & Gamble.
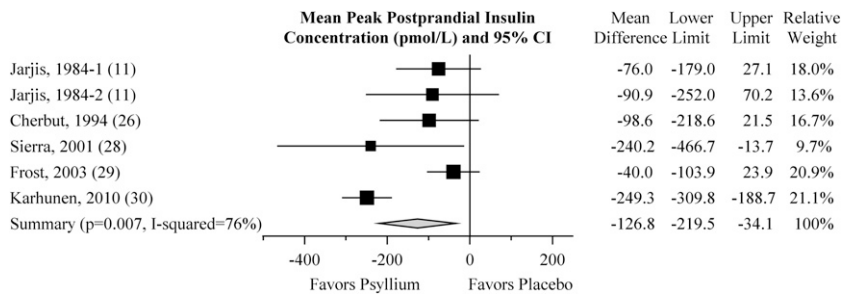
FIGURE 8 Forest plot shows mean differences between psyllium and a negative control [e.g., meal alone (29, 30) or glucose alone (11, 26, 28)] in euglycemic individuals with respect to peak postmeal blood insulin. A random-effects aggregate data meta-analysis was performed to calculate weighted mean differences and 95% CIs. The diamond symbol indicates the overall average effect size and 95% CI. A significant ($P \leq 0.007$) improvement in peak postmeal blood insulin (-126.8 pmol/L) was shown for psyllium compared with control.

a source of nutrients for colonic bacteria (44). Although this consequence minimizes any effect on the microbiome, psyllium is not associated with the increased production of bowel gas that is a frequent side effect of fermentable fiber and α-glucosidase inhibitors.

On the basis of the experience in clinical trials (2, 4, 10–33), there is no attributable risk of clinically significant hypoglycemia that is due to psyllium. However, to our knowledge, there have not been formal studies of the use of psyllium with glucose lowering drugs to examine this possibility. A possible interaction should be evaluated and would need to be monitored in specific patients with the use of the combination of psyllium and drugs that can cause hypoglycemia. Although additional studies are needed to determine how best to incorporate psyllium into clinical practice, because of the broad use of psyllium for numerous health benefits (e.g., cholesterol lowering, satiety, and treatment of constipation, diarrhea, and irritable bowel syndrome) (3, 4, 7, 45–47), the glycemic data presented in the current article show that psyllium would be an effective addition to a lifestyle-intervention program.

The findings reported in the current article were subject to the typical limitations of meta-analyses. A consideration of data in bulk limits a more detailed examination of the results, and the variation in the quality of trials, as well as of their specific subject cohorts and protocols, can obscure important information. In

particular, because we used data from studies across a range of populations, who were studied at widely differing times, there is a real possibility of an important variability within our data set. In contrast, the generally congruent results across these studies and the large and significant outcomes in most of the meta-analyses support our major findings. For the postprandial analyses, the goal was to analyze mean peak glucose and insulin values, but a limitation of these meta-analyses was that these data were not explicitly provided in all of the published studies. In cases where the explicit data were not available, the maximum mean concentrations were extracted from the available mean-time series plots.

In conclusion, on the basis of 8 meta-analyses, psyllium dosed before meals significantly lowered elevated FBG concentrations and HbA1c. This effect was consistent across a variety of populations and a range of study designs. Moreover, both the aggregate and individual data meta-analyses indicate that the effect of psyllium to reduce fasting and postprandial blood glucose is commensurate to the loss of glycemic control with the greatest improvement shown in subjects who were being treated for T2DM. Although additional studies are needed to determine how best to incorporate psyllium into clinical practice, particularly in regards to concomitant hypoglycemic medications, these data show that psyllium would be an effective addition to a lifestyle-intervention program.
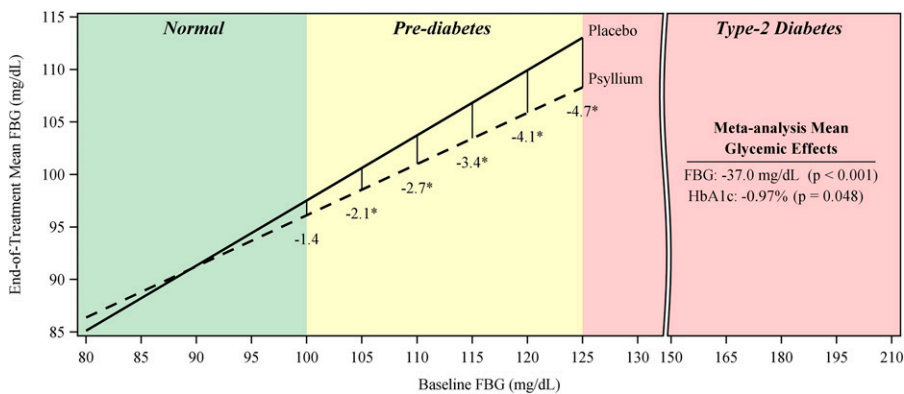

FIGURE 9 End-of-treatment mean fasting glucose compared with baseline fasting glucose is plotted for euglycemic subjects and individuals with pre–type 2 diabetes mellitus ($n = 1075$). An individual subject meta-analysis model was fitted to the data to arrive at the model means and treatment differences shown in the figure. The mean $\pm$ SE treatment difference was shown to increase in magnitude from -1.4 ± 0.63 to -4.7 ± 1.49 as baseline fasting glucose increased from 100 to 125 mg/dL, indicating that the magnitude of benefit from psyllium increased with subjects' loss of glycemic control. *Significant treatment difference, $P < 0.05$. FBG, fasting blood glucose; HbA1c, glycated hemoglobin.

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