



Should Viscous Fiber Supplements Be Considered in Diabetes Control? Results From a Systematic Review and Meta-analysis of Randomized Controlled Trials

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OBJECTIVE

Evidence from randomized controlled trials (RCTs) suggests that viscous dietary fiber may offer beneficial effects on glycemic control and, thus, an improved cardiovascular disease risk profile. Our purpose was to conduct a systematic review and meta-analysis of RCTs to synthesize the therapeutic effect of viscous fiber supplementation on glycemic control in type 2 diabetes.

RESEARCH DESIGN AND METHODS

MEDLINE, Embase, and Cochrane Central Register of Controlled Trials were searched through 15 June 2018. We included RCTs ≥ 3 weeks in duration that assessed the effects of viscous fiber on markers of glycemic control in type 2 diabetes. Two independent reviewers extracted data. Data were pooled using the generic inverse variance method and expressed as mean differences (MD) with 95% CIs. Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was used to evaluate the overall certainty of the evidence.

RESULTS

We identified 28 eligible trial comparisons ($n = 1,394$). Viscous fiber at a median dose of ~ 13.1 g/day significantly reduced HbA_{1c} (MD -0.58% [95% CI $-0.88, -0.28$]; $P = 0.0002$), fasting blood glucose (MD -0.82 mmol/L [95% CI $-1.32, -0.31$]; $P = 0.001$), and HOMA-insulin resistance (IR) (MD -1.89 [95% CI $-3.45, -0.33$]; $P = 0.02$) compared with control and in addition to standard of care. The certainty of evidence was graded moderate for HbA_{1c}, fasting glucose, fasting insulin, and HOMA-IR and low for fructosamine.

CONCLUSIONS

Viscous fiber supplements improve conventional markers of glycemic control beyond usual care and should be considered in the management of type 2 diabetes.

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Despite advancements in preventive medicine and pharmacotherapy, diabetes remains an overwhelming health problem. Diet and lifestyle are among the main pillars in the management of type 2 diabetes, with fiber consistently considered a significant component of dietary interventions steering glycemic control (1). However, a 2014 position statement from the American Diabetes Association (ADA) deemphasized the impact of fiber in diets, reporting its potential for gluco-regulation as marginal, with modest improvements of 0.2–0.3% in HbA_{1c} requiring “unrealistic” quantities of >50 g/day (2,3).

In contrast, there is a plethora of clinical evidence on using soluble viscous dietary fiber supplements in the regulation of hyperglycemia and reduction of conventional cardiovascular disease risk factors (4–7). This has been reflected in the 2018 ADA *Standards of Medical Care in Diabetes*, which recommends an increase in viscous fiber intake from sources such as oats, legumes, and citrus (8). Nonetheless, the commonly shared view is that it is difficult to achieve a high dietary fiber intake within the context of a conventional Western diet without the use of fortified foods or addition of fiber isolates (9,10). In response, many isolated fiber supplements have been developed and extensively studied over the past three decades with the intention of offering convenience of use and facilitating clinical study of the potency of a concentrated source, with a favorable record on glycemic benefits (11).

Although the mechanisms of action have yet to be elucidated, it is hypothesized that fiber isolates, such as guar gum, β -glucan, or psyllium, have the ability to increase viscosity in the human gut and reduce the rate of nutrient absorption, and thus demonstrate greater potential to flatten the postprandial glycemic and insulinemic responses compared with nonviscous fibers (4,12,13). It is less certain, however, whether and to what extent the postprandial effects are reliably reflected in long-term improvements, such as reduction in HbA_{1c}. Therefore, the magnitude of benefit from viscous fiber intake in diabetes management remains ambiguous and warrants comprehensive and robust assessment. Hence, the objective of this study was to evaluate, through a systematic review and meta-analysis of

randomized controlled trials (RCTs), the effect of viscous dietary fiber supplementation on glycemic parameters in individuals with type 2 diabetes receiving usual care.

RESEARCH DESIGN AND METHODS

Protocol and Registration

This study followed the guideline of the Cochrane Handbook for Systematic Reviews of Interventions (14) and results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15). The protocol is available at ClinicalTrials.gov (NCT02629263).

Data Sources and Searches

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched using the strategy presented in Supplementary Table 1 to identify RCTs that investigated the effect of viscous fiber on glycemic outcomes in individuals with type 2 diabetes. The search was performed through 15 June 2018. A manual search of the references of included trials supplemented the electronic search. No language restrictions were applied.

Study Selection

Included RCTs were those conducted in individuals with type 2 diabetes with ≥ 3 weeks duration (16) that investigated the effect of viscous fiber supplementation (β -glucan, guar gum, konjac, psyllium, pectin, xanthan gum, locust bean gum, alginate, agar) compared with an appropriate control (i.e., fiber-free supplement or one containing insoluble fiber, background diet, placebo) on at least one of these glycemic measures: HbA_{1c}, fasting glucose, fasting insulin, HOMA-insulin resistance (IR), and fructosamine. For multiarm trials, we included the groups that allowed us to isolate the effect of viscous fiber supplements from control treatments. Trials that precluded the isolation of the effect of the viscous fiber because it was incorporated into a fiber mixture or included as part of a complex dietary pattern, or because of lack of comparison with a calorie-matched control, were excluded. Glycemic outcomes criteria were determined in accordance with the ADA and Diabetes Canada Clinical Practice Guidelines (17,18).

Data Extraction and Quality Assessment

Using a standardized proforma, two independent reviewers (R.K. and N.M.) assessed articles and extracted relevant data from each report, including fiber type, study design (crossover or parallel), participant characteristics, comparator, dose, duration, background diet, compliance measures, statistical analysis, country of conducted research, and funding sources. Disagreement between reviewers was resolved by consensus or when necessary by a third reviewer. If β -glucan was not reported, viscous fiber from oat β -glucan was conservatively estimated at 5% (19). The mean and SD were extracted for HbA_{1c}, fasting glucose, fasting insulin, fructosamine, and HOMA-IR at change from baseline for both control and intervention groups. When SD values were not reported, they were calculated from available data (95% CIs or SEM) using standard formulae (14). Authors were contacted for additional information where necessary (20,21).

The Cochrane risk-of-bias tool was used to assess the study risk of bias (14). Domains of bias assessment include sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. The study was considered low risk of bias when proper methods were taken to reduce bias, high risk of bias when improper study methods likely affected the true outcome, and unclear risk of bias when insufficient information was provided to permit judgment of bias level.

Data Synthesis and Analysis

Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for primary data analyses and Stata version 14 (StataCorp, College Station, TX) for subgroup, dose-response, and publication bias analyses. The difference between change-from-baseline values for intervention and control arms was derived from each trial for the end points of HbA_{1c}, fasting glucose, fasting insulin, fructosamine, and HOMA-IR. When change from baseline was not reported, the mean and SD for baseline and end values were used to calculate change from baseline for both control and intervention groups. When HOMA-IR was not reported, it was calculated using the equation (HOMA-IR = fasting

insulin (microU/L) \times fasting glucose (mmol/L)/22.5) (22). A previously published formula was used to derive SD for calculated values of HOMA-IR (23). If change-from-baseline values were not available, end-of-treatment values were used. For multiarm trials, a weighted average was used to create a single pairwise comparison and to reduce the unit-of-analysis error. A correlation coefficient of 0.50 was assumed for SD of crossover trials. Sensitivity analysis was conducted with the use of different correlation coefficient values (0.25 and 0.75) to test for the robustness of the effect size. Pooled analyses were conducted using the generic inverse variance method with random-effects models. When data from <5 trials were available, fixed-effects models were used. Data were expressed as mean difference (MD) with 95% CI and significance was considered as $P < 0.05$. Interstudy heterogeneity was assessed using the Cochran Q statistic and quantified using the I^2 statistic, with $I^2 \geq 50\%$ indicating substantial heterogeneity and $P < 0.10$ significance (14). If >10 studies were included for an outcome, sources of heterogeneity were explored with a priori subgroup analyses for baseline values of HbA_{1c}, fasting glucose, and HOMA-IR, as well as for dose, design, duration, fiber type, and food matrix (i.e., powder, capsule, food source) with $P < 0.05$ significance. A post hoc analysis was also conducted for baseline BMI. To determine whether any single study exerted particular influence on the overall results, an additional sensitivity analysis was performed by removing each study individually from the meta-analysis and recalculating the effect size of the remaining studies. Dose-response analysis was performed using meta-regressions to generate linear and nonlinear dose estimates using the MKSPLINE procedure, with $P < 0.05$ significance. Visual inspection of funnel plots was used to assess publication bias and formally tested using Egger and Begg tests, where $P < 0.05$ was considered evidence for small-study effects. If funnel plot asymmetry was suspected, the Duval and Tweedie "trim and fill" method was performed to impute missing study data and correct for asymmetry.

Grading of the Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (24) was used

to assess the overall certainty of the evidence. Quality can be graded as very low, low, moderate, or high. Evidence obtained from RCTs receives an initial grade of high. Scores can be downgraded based on study limitations (assessed by the Cochrane risk-of-bias tool), inconsistency (substantial unexplained heterogeneity, $I^2 > 50\%$, $P < 0.10$), indirectness (presence of factors that limit the generalizability of the findings), imprecision (CI for the effect estimates that are wide or cross a minimally important difference for benefit or harm), and publication bias (significant evidence of small-study effects).

RESULTS

Search Results

Figure 1 shows the flow of the literature. Our initial search yielded 2,716 publications, of which 66 articles were reviewed in full and 27 (28 trial comparisons) were included in the final analysis ($n = 1,394$) (20,21,25–49). Twenty trial comparisons reported on HbA_{1c} ($n = 1,148$) (21,25,27,29–35,37–42,44, 47–49), 28 on fasting glucose ($n = 1,394$) (20,21,25–48), 9 on fasting insulin ($n = 228$) (21,25,26,29,35,38,41,46,48), and 2 on fructosamine ($n = 23$) (42,46), and 11 trial comparisons reported on HOMA-IR directly or reported enough

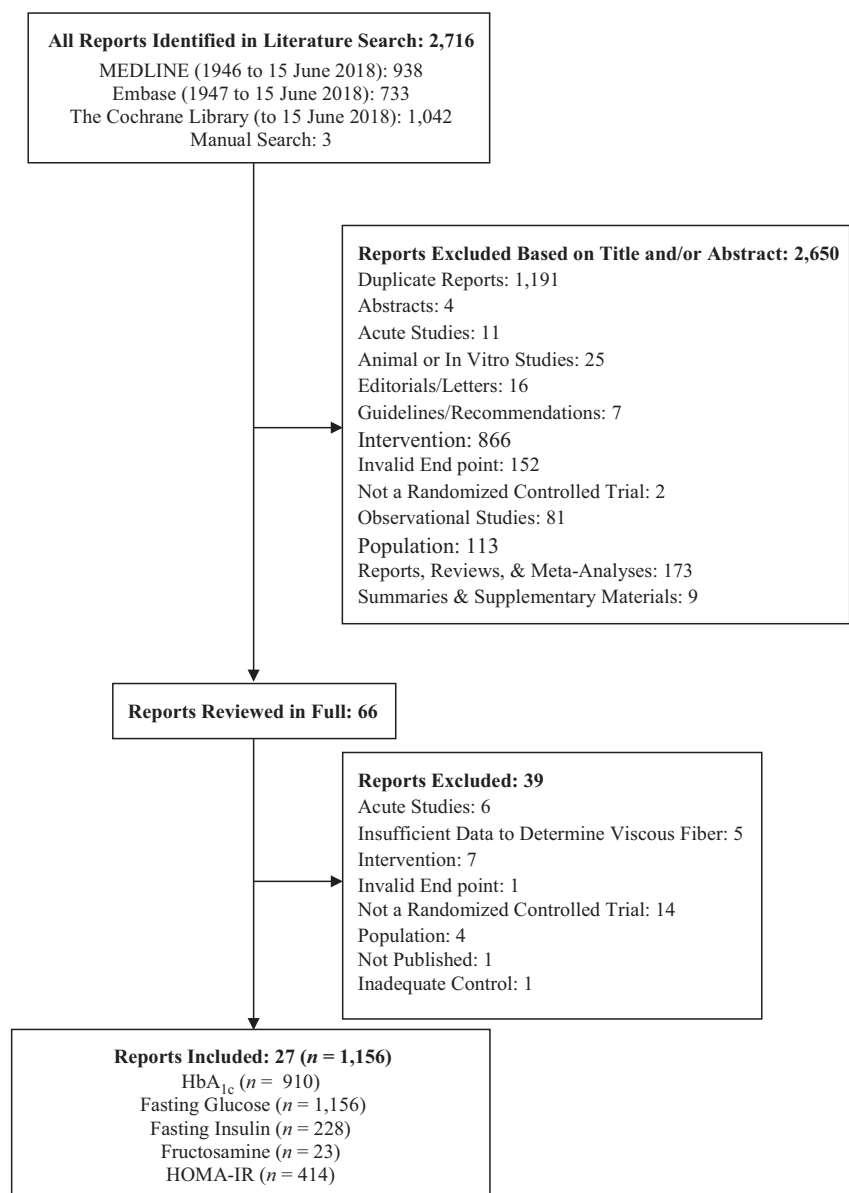


Figure 1—Flow of the literature.

information for calculation ($n = 652$) (21,25,26,29,35,37–39,41,46,48).

Trial Characteristics

Table 1 shows the characteristics of included studies. The majority of trials were conducted in an outpatient setting, with 15 (54%) in Europe, 5 (18%) in Asia, 2 (7%) in North America, 4 (14%) in the Middle East, and 2 (7%) in South America. Of the included trials, 15 (54%) were crossover design and 13 (46%) parallel design. The median age of participants was 60 years (range 48–67), with a median BMI of 27 kg/m² (range 26–32). The median dose of viscous fiber supplementation for all included trials was 13.1 g/day (range 2.55–21.0) and median duration was 8 weeks (range 3–52). The Cochrane risk-of-bias tool (Supplementary Fig. 1) showed that 25 trials (90%) had unclear risk of bias and three trials (10%) had low risk of bias for sequence generation. All trials (100%) had unclear risk of bias for allocation concealment. Seventeen trials (61%) had low risk of bias, 8 trials (29%) unclear risk, and 3 trials (10%) high risk of bias for blinding. Sixteen trials (57%) had low risk of bias, 8 trials (29%) unclear risk, and 4 (14%) high risk of bias for incomplete outcome data.

The majority of trials (96%) had low risk but one (4%) had high risk of bias for selective outcome reporting. Funding sources included agency for 6 trials (21%), industry for 5 (18%), agency-industry for 5 (18%), and were not reported for 12 (43%).

Effect on HbA_{1c}

Figure 2 shows the effect of viscous fiber supplementation on HbA_{1c} in individuals with diabetes. A median dose of 10.9 g/day for a median duration of 8 weeks resulted in a significant reduction in HbA_{1c} (MD -0.58% [95% CI $-0.88, -0.28$]; $P = 0.0002$) compared with control, with evidence of substantial interstudy heterogeneity ($I^2 = 91\%$, $P < 0.00001$). Systematic removal of individual studies did not alter the results or explain heterogeneity. The use of different levels of correlation coefficients (0.25 and 0.75) for crossover studies did not influence the HbA_{1c} effect or heterogeneity in the overall pooled results.

Supplementary Table 2 and Supplementary Fig. 2 show the results of continuous and categorical a priori and post hoc subgroup analyses for HbA_{1c}.

Continuous meta-regression analyses did not reveal an effect of dose, duration, baseline fasting glucose, or baseline BMI. Categorical meta-regression analyses, however, revealed a greater reduction in trials with higher baseline HbA_{1c} values (between-subgroup difference -0.70% [$-1.36, -0.03$]; $P = 0.04$), with residual $I^2 = 84\%$.

Effect on Fasting Glucose

Figure 3A shows the effect of viscous fiber supplementation on fasting glucose in individuals with diabetes. Compared with control, a median dose of 13.1 g/day for a median duration of 8 weeks resulted in a significant reduction in fasting glucose (MD -0.82 mmol/L [95% CI $-1.32, -0.31$]; $P = 0.001$) with evidence of substantial heterogeneity ($I^2 = 92\%$, $P < 0.00001$). Systematic removal of individual studies did not alter results or explain heterogeneity. The use of different levels of correlation coefficients (0.25 and 0.75) for crossover studies did not influence the fasting glucose effect or heterogeneity in the overall pooled results.

Continuous and categorical a priori and post hoc subgroup analyses did not reveal any significant subgroup effects and failed to explain heterogeneity (Supplementary Table 2 and Supplementary Fig. 3).

Effect on Fasting Insulin

Figure 3B shows the effect of viscous fiber supplementation on fasting insulin in individuals with diabetes. With a median dose of 15.0 g/day and median duration of 8 weeks, no significant effect on fasting insulin was observed (MD -17.56 pmol/L [95% CI $-37.54, 2.42$]; $P = 0.08$) compared with control, with substantial interstudy heterogeneity ($I^2 = 90\%$, $P < 0.00001$). Removal of Abutair et al. (25) during our sensitivity analyses reduced overall heterogeneity ($I^2 = 43\%$, $P = 0.09$) and modified the effect size (MD -9.18 pmol/L [$-18.97, 0.60$]; $P = 0.07$). The use of different levels of correlation coefficients (0.25 and 0.75) for crossover studies did not influence the fasting insulin effect or heterogeneity in the overall pooled results.

Continuous and categorical a priori and post hoc subgroup analyses were not performed for fasting insulin as <10 trial comparisons were available for analyses.

Effect on HOMA-IR

Figure 3C shows the effect of viscous fiber supplementation on HOMA-IR in individuals with diabetes. A median dose of 10.5 g/day for a median duration of 6 weeks significantly reduced HOMA-IR (MD -1.89 [95% CI $-3.45, -0.33$]; $P = 0.02$) compared with control, with substantial evidence of interstudy heterogeneity ($I^2 = 94\%$, $P < 0.00001$). Removal of Abutair et al. (25) during sensitivity analyses reduced overall heterogeneity ($I^2 = 63\%$, $P = 0.004$) and modified the effect on HOMA-IR (MD -1.07 [$-1.88, -0.26$]; $P = 0.01$). The use of different levels of correlation coefficients (0.25 and 0.75) for the crossover studies did not influence the HOMA-IR effect or heterogeneity in the overall pooled results.

Supplementary Table 2 and Supplementary Fig. 4 show the findings of a priori and post hoc subgroup analyses for HOMA-IR. Continuous meta-regression analysis revealed that the effect of viscous fiber on HOMA-IR is modified by baseline values (MD -0.42 [$-0.67, -0.16$]; $P < 0.01$), with residual $I^2 = 72\%$. Categorical meta-regression analysis was consistent with these findings, revealing a greater reduction in trials with higher baseline HOMA-IR values (between-subgroup difference -3.49 [$-5.85, -1.14$]; $P < 0.01$), with a residual $I^2 = 67\%$. Additional subgroup analyses were not significant.

Effect on Fructosamine

Figure 3D shows the effect of viscous fiber supplementation on fructosamine in individuals with type 2 diabetes. Only two trials reported on this outcome measure, with a median dose of 13.2 g/day and median duration of 7.5 weeks. Compared with control, no significant effect was observed for fructosamine (MD -0.12 mmol/L [95% CI $-0.39, 0.14$]; $P = 0.37$) and no evidence of interstudy heterogeneity was present ($I^2 = 0\%$, $P = 0.60$). Systematic removal of individual studies and the use of different levels of correlation coefficients (0.25 and 0.75) for crossover studies did not influence the fructosamine effect or heterogeneity.

Continuous and categorical a priori and post hoc subgroup analyses were not performed as <10 trial comparisons were available for analyses.

Table 1—Characteristics of included trial comparisons

Study	Participants* M:F	Age* y	BMI* Kg/m ²	Baseline HbA1c* % (mmol/mol)		Baseline FG* mmol/L	Design	Duration wk	Viscous Fiber	Control	Dose** g/d	Food Matrix	Diet	Funding	Country
				C: 8.5 (69) T: 8.5 (69)	C: 8.7 T: 9.0										
Abutair, 2016	36 18M:18F	47.5†	31.7	C: 8.5 (69) T: 8.5 (69)	C: 8.7 T: 9.0	C: 8.7 T: 9.0	P n/r	8	psyllium	no psyllium	10.5	powder	usual	n/r	Palestine
Abutair, 2018	36 18M:18F	47.5	n/r	n/r	8.9	8.9	P n/r	8	psyllium	no psyllium	10.5	powder	usual	n/r	Palestine
Aro, 1981	9 5M:4F	53	n/r	n/r	C: 11.5 T: 10.6	C: 11.5 T: 10.6	C DB	12	guar gum	wheat flour	21	granules	usual	A-I	Finland
Baker, 1988	30 n/r	C: 64.3 T: 59.1	n/r	C: 11.9 (107) T: 12.0 (108)	C: 11.7 T: 12.1	C: 11.7 T: 12.1	P SB	9	guar gum	n/r	15	tablets	usual	n/r	United Kingdom
Chen, 2003	22 10M:12F	64	25.5	n/r	9.1	9.1	C DB	4	konjac	cornstarch	3.6	capsules	NCEP	A-I	Taiwan
Chuang, 1992	13 n/r	54.9	25.8	7.9 (63)	10.6	10.6	C DB	8	guar gum	n/r	15	powder	liquid meals	A	Taiwan
Cugnet-Anceau, 2010	53 n/r	C: 61.8 T: 61.9	C: 29.0 T: 30.5	C: 7.5 (58) T: 7.3 (56)	C: 8.4 T: 8.8	C: 8.4 T: 8.8	P DB	8	β-glucan	soup	3.5	enriched soups	usual	A	Sweden
Dall'Alba, 2013	44 27M:17F	C: 63.6 T: 60.5	C: 29.3 T: 30.2	C: 7.0 (53) T: 6.9 (52)	C: 7.9 T: 7.4	C: 7.9 T: 7.4	P OL	6	guar gum	n/r	10	powder	usual	A-I	Brazil
Feinglos, 2013	33 n/r	C: 56.5 TA: 61.8 TB: 64.8	n/r	C: 7.6 (60) TA: 7.4 (57) TB: 7.9 (63)	C: 11.8 TA: 11.2 TB: 10.3	C: 11.8 TA: 11.2 TB: 10.3	P DB	12	psyllium	fiber-free placebo	10.2	n/r	restricted	n/r	United States
Fuessli, 1987	18 12M:6F	61.3	30.1	C: 9.3 (78) T: 9.7 (83)	9.1	9.1	C DB	4	guar gum	wheat bran	15	granules	usual	A	United Kingdom
Holman, 1987	29 24M:5F	54.2	26.5	n/r	n/r	n/r	C n/r	8	guar gum	n/r	15	tablets	n/r	I	United Kingdom
Lajjam, 1990	39 11M:28F	51.5	31.2	11.4 (101)	12.5	12.5	C DB	4	guar gum	beef gelatin	15	granules	usual	n/r	Saudi Arabia
Lalor, 1990	19 8M:11F	56.5	31.5	n/r	10.9	10.9	C DB	12	guar gum	n/r	15	granules	usual	A-I	United Kingdom
Li, 2016	228 n/r	59	27	C: 8.1 (65) TA: 8.4 (68) TB: 8.3 (67)	C: 9.5 TA: 9.9 TB: 9.7	C: 9.5 TA: 9.9 TB: 9.7	P n/r	52	β-glucan	no β-glucan	3.98	oat	low-fat high-fiber	I	China
Liatis, 2009	41 n/r	C: 66.5 T: 60.2	C: 27.0 T: 29.6	C: 6.9 (52) T: 7.3 (56)	C: 7.7 T: 8.8	C: 7.7 T: 8.8	P DB	3	β-glucan	no β-glucan	3	bread	usual	n/r	Greece

Continued on p. 760

Table 1—Continued

Study	Participants* M:F	Age* y	BMI* kg/m ²	Baseline		Design	Duration wk	Viscous Fiber	Control	Dose** g/d	Food Matrix	Diet	Funding	Country
				HbA1c* % (mmol/mol)	Baseline FG* mmol/L									
Ma, 2013	186 n/r	57.5†	C: 26.6 TA: 26.6 TB: 26.7	C: 9.7 (83) TA: 9.9 (85) TB: 9.8 (84)	C: 9.5 TA: 10.1 TB: 10.1	P SB	4	β-glucan β-glucan	no β-glucan	2.55	oat	SDI	I	China
McGeoch, 2013	27 18M:9F	60.9	31.5	6.8 (51)	n/r	C NB	8	β-glucan	no β-glucan	4	oat-based products	usual	A	United Kingdom
Niemi, 1988	18	63	27	C: 11.4 (101)	C: 12.5	C	12	guar gum	micro-crystalline cellulose	15	n/r	usual	A-I	Finland
Peterson, 1987	n/r	60	27.3	T: 12.1 (109)	T: 11.7	DB	6	guar gum	no guar gum	16.6	granules	usual	A	United Kingdom
Rodriguez-Moran, 1998	123	C: 56.5	C: 28.6	n/r	C: 7.8	P	6	psyllium	micro-crystalline cellulose	15	powder	low-fat	n/r	Mexico
Sels, 1993	55M:68F 6M:6F	T: 57.0	T: 29.1	11.3 (100)	T: 10.7	DB	12	guar gum	HF control bread	11.2	bread	usual	n/r	Netherlands
Uusitupa, 1990	9 4M:5F	47.8	n/r	n/r	10.6	C DB	4	guar gum	wheat flour	15	granules	usual	n/r	Finland
Uusitupa, 1989	39 13M:26F	C: 60.9 T: 60.1	n/r	C: 9.4 (79) T: 8.9 (74)	C: 12.8 T: 12.2	P DB	12	guar gum	wheat flour	15	granules	usual	A	Finland
Uusitupa, 1984	17 n/r	62	n/r	n/r	9.7	C DB	18	guar gum	wheat flour	21	granules	usual	n/r	Finland
Vuksan, 1999	11 5M:6F	M: 62 F: 59	n/r	M: 7.4 (57) F: 8.3 (67)	C: 9.3 T: 9.6	C DB	3	konjac	wheat bran	15.1	biscuit	NCEP	I	Canada
Wolffenbut, 1992	12 6M:6F	62	25.8	11.3 (100)	9.8	C n/r	12	guar gum	control bread	11.2	powder	usual	n/r	Netherlands
Ziai, 2005	36 n/r	C: 53.6 T: 51.9	C: 27.5 T: 26.6	C: 9.1 (76) T: 10.5 (91)	C: 9.9 T: 11.6	P DB	8	psyllium	micro-crystalline cellulose	10.2	powder	usual	n/r	Iran

A, agency; A-I, agency-industry; C, control; Cr, crossover; DB, double blind; F, female; FG, fasting glucose; I, industry; M, male; NB, not blinded; NCEP, National Cholesterol Education Program; n/r, not reported; OL, open label; P, parallel; SB, single blind; SDI, Structured Dietary Intervention; T, treatment; TA, treatment A; TB, treatment B. *Mean values presented. †Dose of viscous fiber.

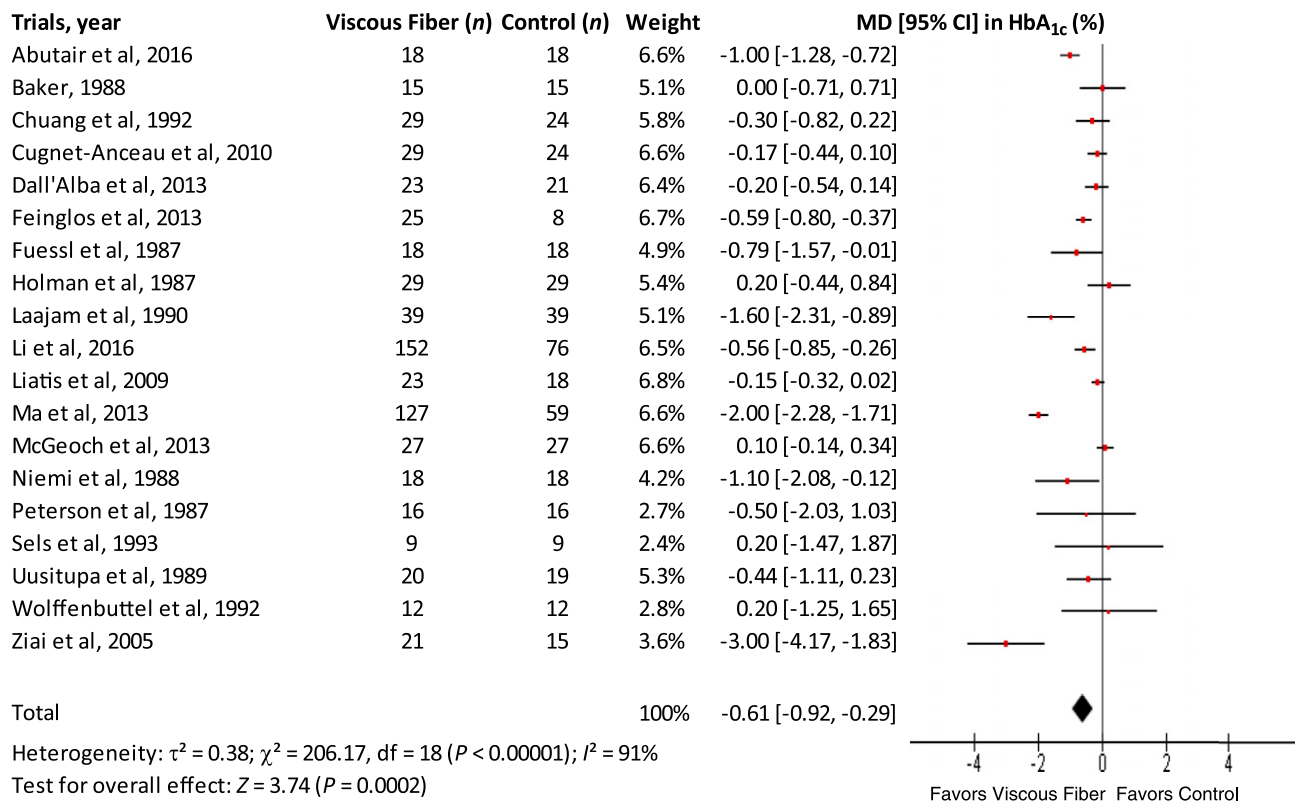


Figure 2—The effect of viscous fiber supplementation in individuals with type 2 diabetes on primary outcome HbA_{1c}. Diamond represents the pooled effect estimate for overall analysis. Data are represented as MD with 95% CI, using the generic inverse variance random-effects model. Interstudy heterogeneity quantified by I^2 with significance $P < 0.10$.

Dose-Response Analyses

There was no significant evidence of a dose-response effect (Supplementary Figs. 5 and 6). Visual inspection of data suggests doses >10 g/day may be more effective in HOMA-IR improvement, but the difference in slopes for <10 vs. >10 g/day was not significant ($P = 0.06$). Because of insufficient data, dose-response analyses could not be conducted for fructosamine and only linear analysis was performed for fasting insulin.

Publication Bias

Supplementary Fig. 7 shows the funnel plots for HbA_{1c}, fasting glucose, and HOMA-IR. Visual inspection of funnel plots suggests no asymmetry in HbA_{1c} and fasting glucose and mild asymmetry in HOMA-IR. Formal testing with the Egger and Begg tests was not significant for evidence of small-study effects. Trim and fill analyses were conducted for HOMA-IR, identifying four additional studies imputed to adjust for funnel plot asymmetry (Supplementary Fig. 8). Inclusion of imputed studies resulted

in an adjusted MD of -2.67 (95% CI $-4.17, -1.18$), $P < 0.01$, suggesting evidence of small-study effects. Publication bias was not assessed for fasting insulin and fructosamine as there were <10 trial comparisons available.

Grading of the Evidence

Supplementary Table 3 shows the summary of the GRADE assessment for each outcome. The effect estimates for HbA_{1c}, fasting glucose, fasting insulin, and HOMA-IR were graded as moderate quality based on downgrades of serious inconsistency for HbA_{1c}, fasting glucose, and HOMA-IR and serious imprecision for fasting insulin. Evidence for fructosamine was graded low quality owing to downgrades for very serious imprecision.

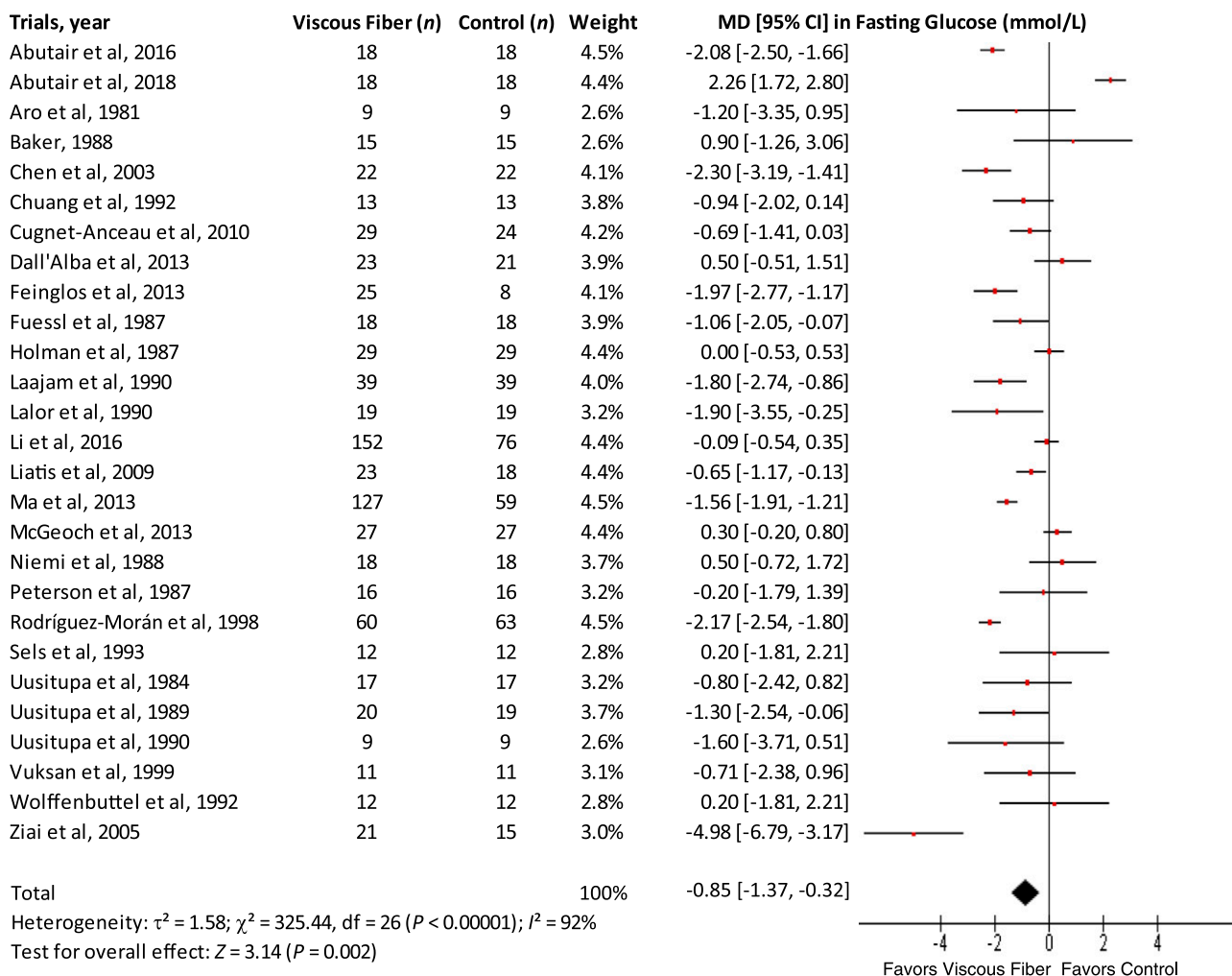
CONCLUSIONS

This systematic review and meta-analysis quantified the effect of viscous fiber supplementation on indices of glycemic control in 28 RCT comparisons involving individuals with type 2 diabetes. Pooled analyses demonstrate an

absolute reduction of 0.58% in HbA_{1c}, 0.82 mmol/L in fasting blood glucose, and 1.89 in HOMA-IR following a median dose of ~ 13.1 g/day for a median duration of ~ 8 weeks. No significant effects were revealed for fasting insulin and fructosamine. Subgroup analyses revealed those with higher baseline HbA_{1c} and HOMA-IR values appear to show greater reductions. There did not appear to be any subgroup effects of dose, design, duration, baseline BMI, fiber type, or the form of intervention.

Results from our analyses suggest that viscous fiber may be clinically meaningful in the management of type 2 diabetes, with reductions in HbA_{1c} exceeding the U.S. Food and Drug Administration threshold of $\geq 0.3\%$ established for new antihyperglycemic drug development (50). Our findings build on those of an earlier systematic review and meta-analysis by Silva et al. (51), who reported a decrease of 0.52% in HbA_{1c} and 0.55 mmol/L in fasting blood glucose in type 2 diabetes patients following a high intake of various types of dietary fiber, including soluble and insoluble

A



B

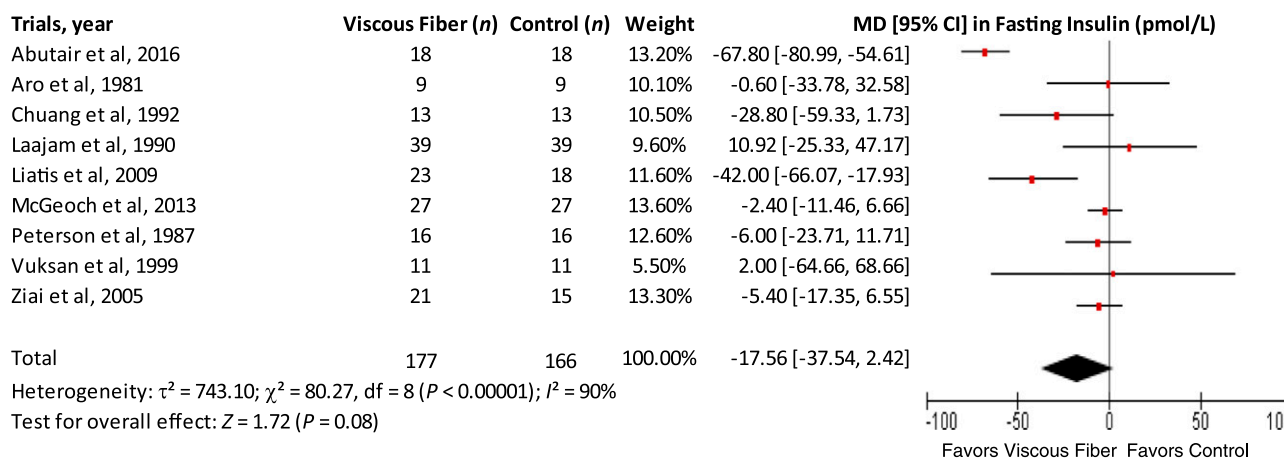
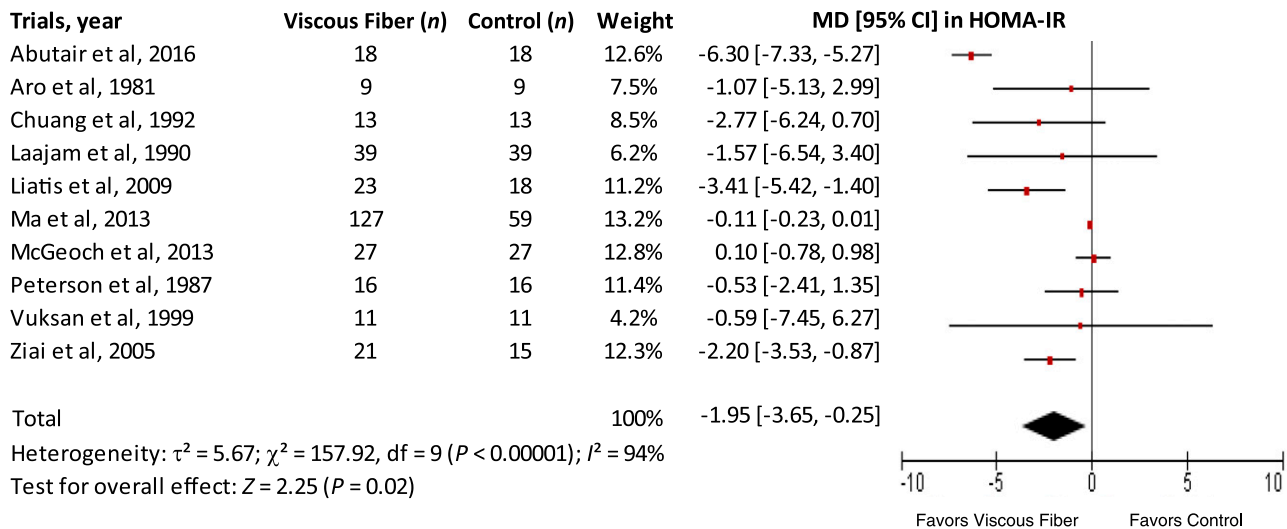


Figure 3—The effect of viscous fiber supplementation in individuals with type 2 diabetes on secondary outcomes: fasting glucose (A), fasting insulin (B), HOMA-IR (C), and fructosamine (D). Diamond represents the pooled effect estimate for overall analysis. Data are represented as MD with 95% CI, using the generic inverse variance random-effects and fixed-effects models. Interstudy heterogeneity is quantified by I^2 with significance $P < 0.10$.

C



D

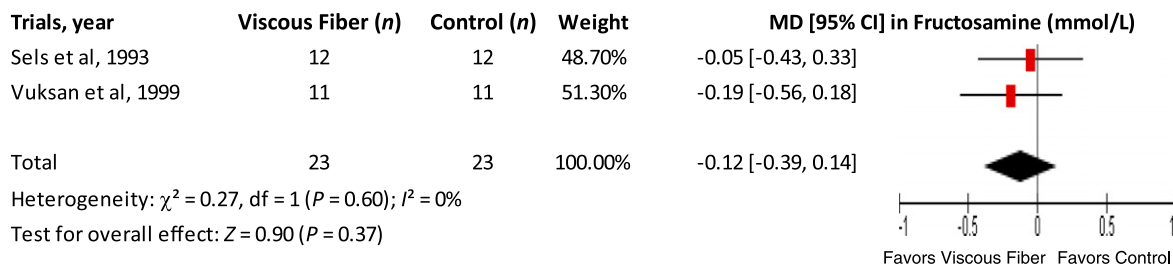


Figure 3—Continued.

sources, from 12 RCTs. Although the two reviews cannot be directly compared given the variation in study inclusion criteria, it is interesting that there was a similar reduction in HbA_{1c}, suggesting that the benefits observed by Silva et al. (51) may be mostly attributed to viscous fiber. Despite this similarity, grouping viscous soluble and insoluble fiber does not provide a reliable estimate of metabolic benefit as it is analogous to grouping therapeutic entities with different physiochemical and, hence, physiological characteristics. While insoluble fiber seems to have specific application, likely in the area of colonic health and stool bulking, viscous fibers appear to have pleiotropic effects metabolically, as they improve glycemic control, lipid levels, blood pressure, and possibly weight, in addition to potential prebiotic activity (52). Conversely, the strong and consistent paradoxical association of non-viscous cereal fiber and whole-grain consumption to reduced type 2 diabetes incidence from prospective cohort data

remains of important clinical interest (53). Although residual confounding might preclude a potential case for causality, the recently hypothesized link of modulating gut microbiota by extended cereal fiber intake deserves further investigation (54). The protective role of cereal fiber against type 2 diabetes should therefore not be overlooked and fits within a broader public health case for increasing overall dietary fiber intake.

The variable efficacy of fiber on glycemic control was first highlighted in a seminal study in which Jenkins et al. (55) compared the response to an oral glucose tolerance test supplemented with five fiber types varying in level of viscosity. A positive correlation was found between the viscosity of the fiber type and reduction in peak postprandial blood glucose and insulin concentrations (55). This benefit was abolished when fiber was hydrolyzed to its nonviscous form (55). Thus, through its effect in changing the rate of nutrient delivery and endocrine response, viscous fiber intake

resulted in flattening of the glycemic response and reduced insulin requirements, ultimately leading to a reduction in HbA_{1c}, as observed in the present analysis. More recently, Chandalia et al. (56) demonstrated that an effective level of intake can be achieved by consuming fiber-rich foods. In that study, they found that doubling fiber intake above the level recommended by ADA at the time achieved a powerful reduction in 24-h blood glucose and hyperinsulinemia (56). The authors concluded that these effects seem to be predominantly a result of increasing the viscous fiber foods from the typically recommended 8 g/day in the control arm to 25 g/day in the test arm, a difference that approximates the median effective dose of 13.1 g/day seen in the current study. Further supporting the case for viscosity, a study comparing several types of viscous fiber supplements revealed that the most viscous fiber, konjac glucomannan, resulted in the greatest reduction of postprandial blood glucose

(57). These acute benefits were translated to long-term metabolic improvements in individuals with type 2 diabetes and metabolic syndrome (46,58), as well as lipid lowering in healthy individuals, compared with lower viscosity fibers including insoluble fiber or wheat bran control (52). Similarly, a 6-month intervention study in participants with metabolic syndrome showed no glycemic benefits on the American Heart Association Step II diet, but the addition of 7 g/day of psyllium fiber led to a sustained improvement in glycemic and insulinemic response, including a significant reduction of 0.6% in HbA_{1c} (59).

Despite a relatively small quantity of viscous fiber being required to obtain clinically meaningful benefits in diabetes, the main challenge remains how to incorporate it into foods while preserving sensory characteristics. From a palatability standpoint, semimoist foods including crisp breads, crackers, muffins, and biscuits are suggested to be the most suitable vehicles for optimal fiber delivery (60).

Even though the prevalent notion is to favor food rather than supplement use as a primary source of fiber, the use of the latter would allow one to achieve the goal of an individualized eating plan even in the absence of major dietary restrictions, such as in the context of lack of willingness or ability of an individual to change (8). Notably, with the exception of one study where treatment was through diet only, studies included in our analysis utilized fiber supplements as the intervention, with antihyperglycemic oral medication and insulin having not been altered throughout the study period. This suggests that the effect of viscous fiber, primarily through supplements, seen within the pooled analysis is beyond that of standard pharmaceutical therapy.

The current study has several strengths. Importantly, to our knowledge this is one of the largest and most comprehensive systematic reviews and meta-analyses of RCTs on dietary fiber, in particular investigating the isolated effect of viscous fiber sources in diabetes. No prior study had differentiated dietary fiber on the basis of viscosity but rather had done so on the basis of the gravimetrics. Furthermore, the majority of trials in this study reported glycemic control end points as the primary

outcome and the study included trials spanning multiple countries, thereby allowing for generalizability of findings and reducing potential confounders associated with a single geographic location. Finally, the overall quality and strength of evidence was assessed using the GRADE approach.

Limitations of this analysis should also be recognized when interpreting the findings. First, we downgraded the certainty of the evidence for serious inconsistency in the estimates across trials for some of the assessed outcomes. This was due to evidence of heterogeneity that could not be explained by sensitivity and subgroup analyses. Further, the certainty of the evidence was downgraded for serious and very serious imprecision. Although the 95% CI of the pooled effect estimate for some of our outcomes did not overlap with our minimally important difference for harm (i.e., did not contain evidence for harm), the upper bound of the 95% CI included 0. The number of participants for the fructosamine outcome was also less than the optimal information size criterion, which resulted in an additional downgrade for imprecision owing to insufficient power. Due to the small number of observations for some outcomes, meta-regression analyses could not be conducted, limiting our exploration of these outcomes. Additionally, of the included trials, only 11 had a duration of 12 weeks or longer and 13 trials were less than 8 weeks in length. Given the conventional estimate that HbA_{1c} reflects blood glucose levels in the preceding three months, inclusion of shorter trials potentially underestimated the effect size, as they may not have been of sufficient duration. The certainty of evidence was not downgraded for indirectness as subgroup analyses revealed no effect modulation by duration. It was also not downgraded for risk of bias as plausible selection bias was unlikely to seriously alter the results. Finally, there was evidence of publication bias. Although visual inspection of the funnel plots suggested asymmetry for HOMA-IR and trim and fill analyses suggested small-study effects, we elected not to downgrade for publication bias, as Egger and Begg tests were not significant and the adjusted pooled effect estimate after trim and fill analyses did not change direction or significance.

Balancing the strengths and limitations, we graded the overall certainty of available evidence as moderate for HbA_{1c}, fasting glucose, fasting insulin, and HOMA-IR and low for fructosamine.

Conclusion

This study illustrated that viscous fiber supplementation improved conventional markers of glycemic control beyond usual care in individuals with type 2 diabetes. Future dietary guidelines should be revisited in light of these findings, although taking into consideration the limitations raised by GRADE. Additional high-quality RCTs are required to further explore the effect by fiber type and to optimize the incorporation of highly viscous supplements into the daily diet.

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scientific advisor for the Food, Nutrition, and Safety Program and the Technical Committee on Carbohydrates of the International Life Science Institute North America. He is a member of the International Carbohydrate Quality Consortium, Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and director of the Toronto 3D Knowledge Synthesis and Clinical Trials Foundation. His wife is an employee of Unilever Canada. A.L.J. is part owner and Vice President at Glycemic Index Laboratories, Inc. (GI Labs), a contract research organization. L.D. has previously received honoraria for speaking and consultancy and grants for attending scientific conferences from Abbott, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Merck Sharp & Dohme, Novo Nordisk, Novartis, Sanofi, Servier, and Takeda. V.V. holds a research grant from the Canadian Diabetes Association for study of dietary intervention including viscous soluble fiber and holds the Canadian (2,410,556) and American (7,326,404) patents on the medical use of viscous fiber blend for reducing blood glucose for treatment of diabetes, increasing insulin sensitivity, and reducing systolic blood pressure and blood lipids.

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Author Contributions. E.J., A.Z., A.K., H.V.T.H., and V.V. designed the research. R.K. and N.M. conducted the research. R.K., A.K., J.L.S., S.B.M., and D.L. performed or assisted in performing the statistical analysis of the data. E.J., R.K., A.Z., A.K., A.L.J., and L.D. wrote the manuscript draft. E.J., J.L.S., and V.V. had primary responsibility for the final content. All authors contributed to the critical revision of the manuscript for important intellectual content and approved the final manuscript.

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