THE EFFECT OF VISCOUS AND NON-VISCOUS FIBRE SUPPLEMENTATION ON GLYCEMIC CONTROL IN INDIVIDUALS WITH DIABETES MELLITUS

by

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ABSTRACT

This thesis project includes two systematic reviews and meta-analyses (SRMA) of randomized controlled trials (RCTs) to assess the effect of viscous and non-viscous dietary fibre supplementation on glycemic control in individuals with diabetes mellitus. In study one, including 31 trials (n=1428), diets supplemented with viscous fibre isolates significantly lowered HbA1c, fasting glucose and HOMA-IR. In the second study, which included 13 trials (n=545), diets supplemented with non-viscous fibre significantly lowered HbA1c, fasting glucose and fasting insulin. Although both SRMA revealed significant improvements in glycemic control, the effect of viscous fibre supplementation appears to be stronger and with higher quality evidence as assessed by the GRADE tool. Overall, the results suggest that supplementing diet with fibre leads to modest improvement in conventional markers of glycemic control in diabetes mellitus, especially in T2DM. More research is needed to address the limitations of our analyses raised by GRADE.

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LIST OF ABBREVIATIONS

SRMA: systematic review and meta-analysis

RCTs: Randomized Controlled Trials

HbA1c: Glycated hemoglobin

HOMA-IR: Homeostatic Model Assessment- Insulin Resistance

GRADE: Grading of Recommendations Assessment, Development and Evaluation

T1DM: Type 1 Diabetes Mellitus

T2DM: Type 2 Diabetes Mellitus

ADA: American Diabetes Association

DC: Diabetes Canada

GDM: Gestational Diabetes Mellitus

MODY: Maturity-Onset Diabetes of the Young

IDDM: Insulin Dependent Diabetes Mellitus

β- cells: beta cells

NIDDM: non-insulin dependent diabetes mellitus

ID: International Dollar

WC: waist circumference

IFG: impaired fasting glucose

IGT: impaired glucose tolerance

2-h PG: 2 hour plasma glucose

OGTT: oral glucose tolerance test

HDL: high-density lipoproteins

TG: triglycerides

FPG: fasting plasma glucose

GAD: anti-glutamic acid decarboxylase

ICA: islet cell antibodies

GIT: gastrointestinal tract

MRFIT: Multiple Risk Factor Intervention Trial

CVD: Cardio-Vascular Disease

DCCT: Diabetes Control and Complications Trial

UKPDS: UK Prospective Diabetes Study

ACCORD: Control Cardiovascular Risk in Diabetes

ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation

VADT: Veterans Affairs Diabetes Trial

CSII: continuous subcutaneous insulin infusion

AMP: adenosine monophosphate

LGI: low glycemic index

LC: very-low-carbohydrate, high–unsaturated fat, low–saturated fat

HC: high-carbohydrate, low-fat

LCD: low-carbohydrate diet

CRD: calorie-restricted diet

BMI: body mass index

ILI: Intensive Lifestyle Intervention

LOADD: Lifestyle Over and Above Drugs in Diabetes

BP: blood pressure

CRP: C-reactive protein

MLP: Mediterranean Lifestyle Program

LCMD: low-calorie Mediterranean diet

DP: degree of polymerization

OGTT: oral glucose tolerance test

FOS: fructo-oligosaccharide

RS: resistant starch

HAMRS2: high-amylose maize (HAMRS2)

VFS: Viscous Fibre Supplementation

NVFS: Non-Viscous Fibre Supplementation

ITF: inulin-type fructans

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CHAPTER I- INTRODUCTION

Despite significant advancements in pharmacotherapy, diabetes mellitus remains a global health challenge with approximately 425 million adults living with diabetes in 2017 and approximately 212 million (1 in 2) remain undiagnosed (1). Diabetes is a major risk factor for cardiovascular disease, presenting as ischaemic heart disease, stroke, and peripheral vascular disease and with an estimated two-thirds of people with the disease being of working age and living in urban areas, it is suggested that obesity and inactive lifestyle may be to blame (1). The significant increase in diabetes incidence places a heavy burden on health and economic systems with approximately $727 billion of global health expenditure is spent on the disease annually (1). While there is no evidence to support the prevention of Type 1 diabetes melliuts (T1DM), Type 2 diabetes mellitus (T2DM) can be delayed or managed by lifestyle modifications including healthy diet, physical activity and pharmacotherapy agents (2-5). Diet modification has been shown to be a convenient and effective approach to improve glycemic control (6-8), which plays a key role in delaying the macro and micro-vascular diabetes-related complications (9, 10).

Increased fibre consumption has been associated with improved diabetes management (11, 12), and consuming 25-50 g/d of dietary fibre has been recommended by the American Diabetes Association (ADA) and Diabetes Canada (DC) (13, 14). In reality, it is considerably challenging to meet these daily fibre recommendations due to the quantity required and often unpalatability of fiber-rich food sources (15). Therefore, fibre supplements are attracting considerable interest as an adjunctive therapy for diabetes due to the potential favorable effects on glycemic control outcomes; however, in the most recent dietary recommendation the ADA and DC have not made specific recommendations for fibre supplements. Many studies have been conducted to investigate the effect of fibre supplements on glycemic control, but debate continues about the best fibre type and the quantity required for the management of diabetes (16). While

some studies show viscous fibre supplements to be more effective in diabetes management, others are less convincing or favor non-viscous fibres sources (17, 18).

Therefore, the objective of this thesis project was to evaluate the effect of viscous and non-viscous dietary fibre supplementation on glycemic parameters in individuals with T1DM and T2DM, using two systematic review and meta-analyses of randomized controlled trials (RCTs).

CHAPTER II- LITERATURE REVIEW

2.1 DIABETES MELLITUS

2.1.1 INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia due to insufficient insulin secretion, insulin action or both (14, 19). Diabetes classifications include type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes (GDM) which occurs in the second or third trimester of pregnancy. The remainder of this review will focus on the two main classifications: T1DM and T2DM (20).

T1DM, formerly referred to as insulin dependent diabetes mellitus (IDDM), is primarily caused by the absence of insulin due to destruction of the pancreatic β- cells (19, 20). Only about 5-10% of those who have diabetes are diagnosed with T1DM (20). Although genetic and environmental factors are believed to be involved in its development, the main cause is still idiopathic (14, 20). T2DM, formerly called non-insulin dependent-diabetes mellitus (NIDDM), is caused by genetic susceptibility and lifestyle factor; and it is characterized by insulin resistance accompanied by reduced insulin secretion (19, 20). Furthermore obesity and other environmental factors play a key role in insulin resistance (IR) (21). Both types of diabetes are increasing globally (14).

According to the International Diabetes Federation (IDF), approximately 425 million individuals were living with diabetes in 2017 and this number is expected to increase up to 629 million by 2045 (1). Diabetes has become a major health burden of the 21st century, contributing to approximately 79,535 deaths in the United States in 2015 (22) and causing substantial economic loss to not only the individuals with the condition and their families but also to government and health care systems. In 2012, the total estimated cost of diagnosed diabetes was approximately $245 billion including direct costs for hospital inpatient

care, prescription medications and indirect costs including increased absenteeism, decreased productivity and inability to work due to disease-related disability or mortality (23).

Several risk factors are associated with the development of T2DM including: obesity and in particularly abdominal obesity (waist circumferences ≥ 102 cm for males and ≥ 88 cm for females), physical inactivity, family history, ethnicity (e.g. Aboriginal, Hispanic, Asian, South Asian, or African descent), age (≥ 40 years), history of pre-diabetes (IFG; fasting glucose values between 6.1-6.9 mmol/L, IGT; 2h-PG in 75g OGTT values between 7.8-11.1 mmol/L, or HbA1c values between 6.0-6.4 mmol/L) or gestational diabetes (GDM), or the presence of vascular disease risk factors including: hypertension, reduced HDL cholesterol (< 1.0 mmol/L in males and < 1.3 mmol/L in females), and high TG (≥ 1.7 mmol/L) (14).

Several diagnostic tests are identified by DC including, FPG ≥ 7.0 mmol/L, HbA1c ≥ 6.5% (in adults), 2h-PG in a 75 g OGTT ≥ 11.1 mmol/L, or random PG ≥ 11.1 mmol/L (14). In order to distinguish between T1DM and T2DM, assessment of physical signs of insulin resistance (IR), and autoimmune markers such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell antibody (ICA) antibodies may be considered (14).

2.1.2 PATHOPHYSIOLOGY OF DIABETES MELLITUS

Defects in insulin secretion or utilization, present in both T1DM and T2DM, result in the inability of body cells to sufficiently use glucose for energy which leads to glucose accumulation in the blood causing hyperglycemia. Several symptoms occur as a result of hyperglycemia including: glucosuria (glucose excreted in the urine), polyuria (increased urination), polydipsia (increased thirst), blurred vision, polyphagia (increased appetite or excessive hunger), slow healing cuts/ bruises, weight loss (in T1DM), tingling, pain, or numbness in the limbs (in T2DM) (14).

T1DM is an auto-immune disease that is mainly caused by the destruction of the pancreatic β- cells leading to an absolute insulin deficiency and can cause diabetes ketoacidosis(14). When cells lack

sufficient amount of glucose, the body begins to burn fat for energy producing ketones which accumulate in the blood increasing its acidity which can lead to diabetic coma or death (24). The specific cause of T1DM is unknown, but genetic and environmental factors are believed to play a role (14).

On the other hand, T2DM is characterized by a combination of insulin resistance and pancreatic β-cell dysfunction. Several organs and tissues are involved in its pathophysiology including the brain, liver, pancreas, kidney, gastrointestinal tract (GIT), skeletal muscle and adipose tissue (25). The exact mechanism of T2DM is not completely understood; however, many theories have emerged in an attempt to understand the underlying pathogenesis including, deficiency in insulin-mediated glucose uptake in the muscle, dysfunction in the pancreatic β-cells, and impairment in the secretion of adipocytes or the insulin action in the liver (26).

2.1.3 DIABETES COMPLICATIONS AND MORTALITY

Diabetes-related chronic hyperglycemia is associated with the progression of both macro-vascular diseases (coronary artery disease, peripheral arterial disease, and stroke) and micro-vascular diseases (neuropathy, nephropathy, and retinopathy) (20). The Multiple Risk Factor Intervention Trial (MRFIT) revealed that individuals with diabetes are at higher risk for developing cardiovascular disease (CVD) (27), which was the leading cause of death in the United States (US) in 2015 (28). A recently published cohort study found that heart failure and peripheral arterial disease were the most common initial indications of cardiovascular disease in T2DM(29). Another cohort study suggested diabetes to be a greater contributing factor in American mortality than it is commonly believed, revealing that diabetes accounts for approximately 12% of deaths in the US, making it the third leading cause of death after heart disease and cancer (30). Risk of death among those with diabetes compared to the general population varies greatly depending on sex, age, glycemic control, and renal complications (31, 32). It has been repeatedly shown that mortality increases significantly with increasing mean HbA1c, especially in older adults and heart

failure patients (33, 34). Both fasting and postprandial glucose contribute to the measurement of HbA1c and correlate with the risk of complications (14).

Several major trials have found that improved glycemic control significantly decreased the progression of micro-vascular complications. The Diabetes Control and Complications Trial (DCCT) showed that intensive therapy effectively postpones and slows the progression/development of retinopathy, nephropathy and neuropathy in individuals with T1DM (9). Specifically, 10% reduction in HbA1c was positively associated with 40-50% decreased risk of retinopathy (9). In terms of T2DM, The UK Prospective Diabetes Study (UKPDS) revealed that intensive blood glucose control using insulin therapy or pharmaceutical drugs, namely sulphonylurea, significantly reduced the risk of micro-vascular diabetic complications (10). Regarding macro-vascular complications, metformin showed a greater risk reduction for any diabetes-related outcome, stroke, all-cause mortality and death in overweight individuals with T2DM, compared to conventional therapy (35). Each 1.0% reduction in mean HbA1c was associated with reduction of 37% in deaths related to diabetes, 14% in myocardial infarction (MI), and 21% in macro-vascular complications (36). A latter meta-analysis including 8 RCTs in T1DM (n=1800) and 6 RCTs (n=4472) in T2DM confirmed the positive association between the improved glycemic control and reduction in the incidence of macro-vascular events in both types of diabetes highlighting the particular importance of these findings in younger individuals with shorter duration of diabetes (37).

2.1.4 PREVENTION AND MANAGEMENT OF DIABETES

To date, there is no evidence to support effective therapies for the prevention of T1DM. Conversely, T2DM can be often prevented or delayed by lifestyle modification including diet modification, regular exercise and weight loss (14). In individuals at higher risk of T2DM, beneficial lifestyle based on weight loss, reduced intake of total and saturated fat and increased intake of dietary fibre, and increased physical activity have resulted in 43% reduction in relative risk (38). Interestingly, a lifestyle-modification program aiming for at least 7.0% weight loss with at least 150 minutes of physical activity per week was more

effective than metformin in delaying the incidence of T2DM (3). Diet modification including dietary patterns such as the Mediterranean diet, Dietary Approaches to Stop Hypertension (DASH), and Alternative Healthy Eating Index (AHEI) are recommended for T2DM prevention and management (39, 40). In contrast, specific dietary patterns such as those high in meat and fat, especially processed red meat (41) appear to increase the risk of diabetes regardless of ethnicity (42).

Achieving optimal glycemic control is considered the gold standard for diabetes management. Several major trials such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) showed the benefits of intensive glycemic control on the development/progression of micro-vascular complications in individuals with long term T2DM. Hence, an HbA1C ≤ 7.0% is the target for most individuals with diabetes to prevent the progression of micro-vascular complications and macro-vascular ones if implemented in early stage (43-46). Accordingly, DC and ADA recommend a general HbA1c target level of ≤ 7.0% with a range of specific targets based on age, diabetes duration, the presence of hyperglycemia, the presence of CVD and life expectancy (14, 20). An HbA1c ≤ 6.5% should be considered in some cases to reduce the risk of some micro-vascular complications such as nephropathy and retinopathy considering the balance against the risk of hypoglycemia (14). A few studies have found that HbA1c ≤ 7.0% is associated with reduction in development of macro-vascular events and death while HbA1c of ≤ 6.5% is associated with lower risk of micro-vascular events (47).

In order to achieve an HbA1c ≤7.0%, individuals with DM should aim for fasting glucose of 4.0-7.0 mmol/L and postprandial glucose of 5.0-10.0 mmol/L which requires a high adherence to a personalized diabetes management plan based on physical activity, pharmacotherapy (anti-hyperglycemic agents or insulin) and nutrition therapy (14).

T1DM could be managed with basal-bolus regimens or continuous subcutaneous insulin infusion (CSII) adjusted according to treatment goals, general health, lifestyle, diet, age, motivation, status of hypoglycemia awareness and ability for self-management. It is crucial to advise all individuals with T1DM about hypoglycemia symptoms, treatment and prevention (15). In terms of T2DM, if lifestyle modification fails to optimally control blood glucose within 2 to 3 months, anti-hyperglycemic agents should be introduced taking into consideration regular adjustment to the regimen to achieve HbA1c within 3 to 6 months (14). Unless contraindicated, metformin is the primary drug of choice with additional anti-hyperglycemic agent considering multiple factors such as contraindication to drug, effect on body weight, glucose lowering effect, and risk of hypoglycemia (14). By activation of adenosine monophosphate (AMP), metformin increases insulin sensitivity in the liver and peripheral tissues which reduces in HbA1c by 1.0%-1.5%. Irrespective of increased risk of vitamin B12 deficiency and gastrointestinal side effects, metformin is the first-line medicine for T2DM management (14). Metformin has been shown to effectively lower blood glucose and improve CVD outcomes in overweight individuals with decreased risk of hypoglycemia and weight gain especially when combined with other anti-hyperglycemic agent (14). To improve glycemic control faster with fewer side effects, It is highly recommended to use a combination of smaller doses of anti-hyperglycemic agents with different mechanisms of action (14). In case of sever hyperglycemia (HbA1c ≥ 8.5%), anti-hyperglycemic agents should be introduced/prescribed accompanying lifestyle modifications taking into account/consideration using combination therapy with two agents, one of which may be insulin (14).

Lifestyle modification including nutritional therapy and physical activity plays a significant role in diabetes management. Moderate to high levels of physical activity can help reduce morbidity and mortality in men and women with diabetes (14). In T2DM, supervised exercise programs have been favorably associated with reduction in the need for anti-hyperglycemic medications, improving glycemic control and

maintenance of weight loss(14). Aerobic exercise (e.g. walking) and resistance exercise (e.g. pushups) are both beneficial for individuals with DM. A minimum of 150 minutes / week of aerobic exercise and at least two sessions of resistance exercise is recommended taking into consideration that advice of physical activity for T1DM should include strategies to decrease the risk of hypoglycemia that may occur after intense exercise (14). Many cohort studies revealed that regular aerobic exercise improved glycemic control, reduced insulin resistance, improved lipid profile, reduced blood pressure and helped in maintenance of weight loss in DM. Resistance training has been shown to improve glycemic control by reducing HbA1c, decreasing insulin resistance, and increasing muscle strength in T2DM (14). In general, the combination of both aerobic and resistance training has shown greater benefit on glycemic control in T2DM (48). Contrary to T2DM, most interventional clinical trials have not revealed beneficial effects of physical activity on glycemic control in T1DM (14).

Nutrition therapy has been identified as a major contributing factor for improved diabetes status as it is associated with 1-2% reduction in HbA1c and decrease in the use of hypoglycemic agents (14). Therefore, it is recommended that individuals with diabetes be supervised by a registered dietitian that will provide dietary advice based on personal preference and treatment goals (14). In Canada specifically, diabetes meal plans should be designed according to Eat Well with Canada's Food Guideline with replacing high glycemic index (HGI) foods with low glycemic index (LGI) options (14). Regularity in timing and spacing of meals, consuming various foods from all food groups and limiting sugars and sodium intake should also be given special consideration (14). It is important to closely monitor the amount of consumed fat particularly the amount of saturated and trans fat that is usually found in processed foods (14). The recommended macronutrient distribution for individuals with diabetes is similar to that of the general population with 45-60% of total energy intake coming from carbohydrate, 15-20% from protein, and 20-35% from fat (14). However, macronutrient ratio-intake must be individualized based on personal preferences and palatability (14). Several studies have shown the effect of macronutrient substitution on

glycemic control in diabetes. A randomized controlled trial (RCT) compared the effect of very-low-carbohydrate, high–unsaturated fat, low–saturated fat (LC) diet with a high-carbohydrate, low-fat (HC) diet on glycemic control and cardiovascular disease (CVD) risk factors in 115 obese T2DM patients over 52 weeks (49). Although both diets have demonstrated improvements in body weight, glycemic control and CVD risk factors, LC diet showed greater improvements in blood glucose stability, lipid profile and reduction in diabetes medication requirements (49). Another study compared the effect of low-carbohydrate diet (LCD) to calorie-restricted diet (CRD) in 66 poorly controlled T2DM patients. After 6 month follow up, the LCD led to a greater reduction in HbA1c and body mass index (BMI) (50). One year later, the beneficial effect of LCD was not maintained in comparison to the CRD. However, a clinically significant improvement from baseline was observed when combining the data suggesting that well-designed nutrition therapy programs are effective in HbA1c reduction for a minimum of one year (51). In support, structured exercise programs for a minimum of 150 minutes per week showed a greater reduction in HbA1c compared to those of 150 minutes or less per week. Interestingly, physical activity advice was associated with improvement in HbA1c only when combined with dietary advice (5). Foods must be wisely chosen using the daily value percentage; when two foods are matching in calorie-intake, the one with less saturated fat, less sodium, and higher fibre content must be prioritized (14). Teaching how to match insulin quality and quantity to carbohydrate and keeping consistency in carbohydrate type and amount is necessary to prevent hypoglycemia in T1DM (14).

It is well documented that approximately 80-90% of individuals with T2DM are overweight or obese; hence, a nutritionally balanced, energy restricted diet is recommended for most individuals with diabetes (14). A reduction of 5 to 10% of the primary body weight was associated with improved glycemic control, insulin sensitivity, lipid profile and blood pressure control (52). Intensive lifestyle intervention (ILI) that is based on behavioral interventions combined with nutritional modifications and increased physical activity has demonstrated benefits for diabetes management (14). The Lifestyle Over and Above Drugs in Diabetes

(LOADD) study assessed the effect of individualized nutritional advice in 93 participants with T2DM, hyperglycemia (HbA1C > 7%) in addition to at least two of overweight or obesity, hypertension, and dyslipidemia(53). After six months of intervention and despite use of any anti-hyperglycemic agent, a greater reduction in HbA1C was observed in the treatment group (53). Of all these diets recommended for individuals with diabetes, the Mediterranean, DASH and diet emphasizing nuts are considered the safest with the Mediterranean being the most beneficial, showing an improvement in HbA1c, blood pressure (BP), C-reactive protein (CRP) and improvement in lipid profile (14). Furthermore, a clinically significant improvement in anthropometric biomarkers was seen in postmenopausal women with T2DM after following a Mediterranean Lifestyle Program (MLP) for 6 months in comparison to usual care (54). Compared with a low-fat diet, low-calorie Mediterranean diet (LCMD) resulted in a greater decline in HbA1c levels, higher percentages of diabetes reverse, and delay in need for diabetes medications in newly diagnosed T2DM patients (55). The effectiveness of Mediterranean diet may attribute to its unique combination of fibre rich foods including vegetables, fruits, legumes, nuts, and whole-grain cereals that have shown promising results in epidemiological and clinical observations (56).

2.2 DIETARY FIBRE

2.2.1 INTRODUCTION

The discovery of dietary fibre dates back to 130 A.D. when Galen wrote about the foods that “excite the bowels to evacuate and those that prevent them,” indicating that brown bread is better than white for these matters (57). Since then, indigestible carbohydrates have been associated with gut health (57). However, the term “dietary fibre” was not introduced until 1953 when Hippsley used it to refer to indigestible carbohydrates and associated components in the diet (58). He perceived that eating high-fibre diets was inversely associated with toxemia development during pregnancy (58). In 1970’s, Trowell and Burkitt noticed the rarity of certain Western diseases in Africa and linked this to the unrefined nature

of the African diet (59). Between 1972 and 1975, Trowell and Burkitt co-workers developed their “dietary fibre hypotheses” that a high fibre diet would lead to reduction in constipation, diabetes, obesity, coronary heart disease and cancer of the large bowel (59-61).

A generally accepted definition of dietary fibre is lacking due to the inability to define it as a single chemical entity or a group of related chemical compounds, having one or more health benefits that might be similar or different between various fibre types, and the controversy regarding the efficacy of fibre within food matrix versus its efficacy when isolated (57). Therefore, many definitions of dietary fibre have been developed based on the physio-chemical properties or the analytical methods. In 2001, the Institute of Medicine defined “Total fibre” as the sum of “dietary fibre” and “functional fibre” where dietary fibre is indigestible carbohydrate and lignin while functional fibres are isolated indigestible carbohydrates physiologically benefit for humans (62). However, according to Health Canada, “dietary fibre consists of:

1) Carbohydrates with a degree of polymerization (DP) ≥ 3 that naturally occur in foods of plant origin and that are resistant to digestion and absorption by the small intestine; and

2) Accepted novel fibres, which are ingredients manufactured to be sources of dietary fibre and consist of carbohydrates with DP ≥ 3 that are resistant to digestion and absorption by the small intestine. They are synthetically produced or are obtained from natural sources which have no history of safe use as dietary fibre or which have been processed so as to modify the properties of the fibre contained therein. Accepted novel fibres have at least one physiological effect demonstrated by generally accepted scientific evidence. This definition includes resistant oligosaccharides, resistant starch and resistant maltodextrins (63).

In the absence of specific values, Health Canada considers the energy value for dietary fibre to be 2 kcal (8 kJ)/g including soluble and insoluble dietary fibre (63). Only products that have energy value of < 2

kcal/g are excepted and it may carry a label to declare its specific value (63). For example, the energy value of the fibre portion of wheat bran is 0.6 kcal (2.5 kJ)/g and the wheat bran itself (containing around 40 % of fibre) has an energy value of 2.4 kcal (10 kJ)/g (63). In the US, 2 kcal (8 kJ)/g is used to calculate energy value for soluble non-digestible carbohydrates with no exceptions (63). However, the Food and Agriculture Organization (FAO) reported that considerations could be made for future changes (63). Dietary fibre is recognized as an "under-consumed nutrient" among American adults, according to the Dietary Guidelines for Americans (2015-2020) (64). To better understand and quantify its effect, several approaches have been used for dietary fibre analysis and measurements including the enzymatic-gravimetric and enzymatic-chemical methods (63). Dietary fibre does not have a glycemic index (GI) value as it does not comprise any available carbohydrate, but added to carbohydrate food may reduce its level. However, the addition of fibre to carbohydrate meals appreciatively affects the GI of food (15).

2.2.2 DIETARY FIBRES: CLASSIFICATIONS AND PROPERTIES

To date, there is no agreement upon the best definition, classification and measurement methodology of fibre in food due to the wide diversity of chemical and physical properties in addition to the distinct physiological effects of fibre from different food sources (57, 65). The most widely accepted classification is based on fibre solubility, which classifies fibre as soluble and insoluble. β-glucan, fiber from barley and oat, and wheat bran obtained from the plant cell wall, are examples on soluble and insoluble fiber forms, respectively (65). While intake of specific soluble forms of fibre has been prominently associated with beneficial metabolic effects, including improvements in fasting and postprandial glycaemia, insulinemia, cholesterol, HbA1c and other CVD risk factors (15), insoluble forms of fibre have been advocated for their benefits for colonic health due to water-holding capacity and their role in increasing fecal bulk and decreasing gastrointestinal the transit time (15).

Fermentability may also contribute to the physiological effect of fibre. Since they cannot be digested by human enzymes, non-starch polysaccharides are fermented in the large intestine producing short chain fatty acids (SCFAs) and gases after resisting digestion in the small intestine (15). In general, soluble fibres are fermented to a greater extent than the insoluble ones (15, 65). Specifically, microbiota use rapidly fermented fibres for short chain fatty acid (SCFS) production while slowly or partially fermented fibres improve bowel health by promoting laxation, decreasing transit time and enhancing stool weight (15, 65). In essence, insoluble fibres such as wheat bran have been recognized for their laxative effect and soluble fibres have been advocated for their metabolic benefits (15, 16).

Despite the prominent agreement on the integral role of dietary fibre for optimal health, the ideal types and proportions remain unclear (15). Furthermore, currently used classifications are based on chemical compositions and analytical methods, not taking into account the physiological effects of the various fibre forms (65). For previous reasons, viscosity has been proposed to be a more appropriate classification for solubility (65).

2.2.3 RHEOLOGICAL PROPERTIES AND IMPORTANCE OF VISCOSITY

Sir Isaac Newton (1642-1727) defined viscosity as the proportional relationship between the flow of a fluid and force directed on that fluid. Newtonian fluids are fluids subjected to Newton's law, and the general equation to calculate its viscosity is shear stress/shear rate (η= shear stress/shear rate) (65). Viscosity is measured using rheometers and/or viscometers (65). While viscometers are used only for measuring viscosity, rheometers can be used to measure different fluid characteristics (65). This physio-chemical property is expressed in millipascal second (mPa.s) or centipoise (cP) where 1000 mPa.s=1 Pascal second (Pa.s) while 100 cP= 1 poise (P), and 1 cP= 1 mPa.s (65). However, many fluid foods and biological fluids, namely Ketchup, custard, starch suspensions, and honey, are non-Newtonian in nature, and are greatly different from Newtonian ones especially due to the dependence of viscosity on shear rate (65).

Non-Newtonian flow includes shear thinning (pseudoplastic flow), where apparent viscosity inversely associates with stress (e.g. ketchup, syrups and whipped cream) and shear thickening (dilatant flow), where apparent viscosity is directly associated with stress (e.g. suspension of corn starch in water) (65). Intestinal content is considered non-Newtonian shear thinning as higher shear rates result in decreased viscosity (65).

It is suggested that the effectiveness of dietary fibre mainly depends on its quantity and viscosity (15, 66, 67). Viscous forms of fibre, including gums, pectins, psyllium and B-glucans, thicken when mixed with fluids forming a gel-like solution and increasing the liquid tendency to resist flow. Increased viscosity of digesta has been appreciatively associated with glycemic response modification, blood lipid attenuation, and improvement in colonic health (65). The degree of thickening depends on the chemical composition and concentration of the fibre (65). Several additional factors may modify the viscosity of fibre in solution including the concentration or dose of fibre, temperature, moisture content, time, shear rate, particle size, food matrix, molecular weight, chemical composition and structure, acid and alkaline conditions (acidification and neutralization) and processing conditions (65). These factors are discussed in more detail below.

Molecular Weight:

There is a positive, non-linear relationship between molecular weight of dietary fibre in solution, at equal concentrations, and viscosity (65). For instance, guar gum of high and medium molecular weight resulted in greater digesta viscosities (68). In previous studies, high and medium molecular weight guar gum flours led to greater viscosities of digesta in comparison to controls. Although the molecular weight was directly associated with viscosity, reported values were not significantly different from controls suggesting that molecular weight may not always significantly alter metabolic responses (68). For instance, seven types of wheat bread (one control bread and six guar gum with various molecular weight) were randomly given

to 17 human participants after an overnight fast, on separate days (69). Although no significant difference was observed in postprandial glucose, overall guar gum significantly reduced postprandial plasma insulin (69). The resultant difference may be attributed to the difference in guar gum molecular weight after hydration within distilled water (69). Inconsistent results were reported on the molecular weight-viscosity relationship in β-glucan. While some oat β-glucan samples showed a direct relationship/association between molecular weight and gelation, others revealed the opposite (66, 70-72).

Temperature:

Despite different temperatures, materials with larger particle size and lower moisture content had greater calculated viscosities (65). Briefly, viscosity is positively associated with particle size, but is inversely associated with moisture content (65). Hence, decreasing particle size and the addition of moisture resulted in a lower viscosity (65).

At a constant temperature, a direct, non-linear relationship exists between polysaccharide concentration and viscosity (65). A semi-purified diet supplemented with 0, 20, or 40 g guar gum/kg increased the digesta viscosity in the gastrointestinal tract (GIT) of growing pigs. This increase was highly dependent on guar gum dose/ concentration in the diet. Although it was reported that increased concentrations led to a greater viscosity, the reduction in postprandial glucose and insulin was similar between different doses of guar gum. In other words, although viscosity depends on dose, the metabolic responses may not alter accordingly (68).

Food Matrix:

Food matrix is another factor that affects viscosity (65). Whole oat flour muffins led to a greater increase in viscosity in rats compared to oatmeal-based muffins. The higher viscosities of oat flour may considerably influence the digesta viscosity. Regand et al. indicated that depolymerization of β-glucan when incorporated in baked goods including bread and pasta resulted in reducing its postprandial glucose-

lowering efficacy in healthy human participants (73). Variations in guar gum forms may explain why some fibre preparations are clinically ineffective. In an in vitro modeling, Elis et al measured the hydration rate of different guar gum samples (four pharmaceutical preparations and two food grades guar flour), and found that three out of the pharmaceutical preparations were lower in viscosity during the first hour of the hydration (74). Also, powdered guar gum preparations seem to be more metabolically effective than granules (75).

Processing Conditions:

Processing conditions and extraction methods may also alter viscosity affecting different physiological responses (65). Oat β-glucan was extracted utilizing different processing methods, mainly based on wet milling, and added to rat diets at a 3.3% β-glucan in comparison to control diet with cellulose (76). The highest viscosity at the lower shear rate was observed in the method with solution containing cold ethanol wet milled bran (220 cP) (76).

Acid and Alkaline Conditions:

The effect of acidification (pH) on viscosity has to be considered because ingested dietary fibre will be exposed to different levels of pH within/throughout the gastrointestinal tract (65). While some observations indicate that decrease in pH may increase the viscosity of solution with polysaccharide, contrasting evidence reported a decrease in viscosity after acidification (77). In general, many factors may have led to this discrepancy in the results. It is possible that there is an optimal pH level where polysaccharides are released and increasing viscosity. Viscosity may be eradicated beyond this level because of breakdown of polysaccharides (65).

Chemical Composition:

Finally, chemical composition of the meal containing the polysaccharide may affect its viscosity (65, 78). The complex and distinct flow profiles of the liquid and semi-solid meals make interpreting rheological data more challenging. In addition to physiological complexity, viscosity is not obtained from a static/ constant motion. Occasionally, a shear stress (force) should be applied to manipulate solutions (65).

Dietary fibre viscosity is a multifactorial phenomenon. Therefore, a single measurement of viscosity at only one shear rate is inaccurate, and can be misleading if used to predict the effect of dietary fibre on physiological/metabolic responses, particularly when concentration and shear rate are unknown (65).

2.2.4 EFFECTS OF VISCOUS FIBRE ON GLYCEMIC RESPONSE

In 1976, Jenkins et al. reported that supplementation of test meals with bread containing 16 g of guar gum and marmalade containing 10 g of pectin significantly attenuated mean postprandial blood glucose (PBG) by 42-60% over 15-90 minutes' period in T2DM patients and 36% from 45 to 180 minutes. A significant reduction in insulin response was also observed in T2DM (79). More relevant evidence emerged in 1978 when the same group demonstrated that supplementing diet with viscous polysaccharides significantly reduced postprandial glucose and insulin responses in healthy subjects after administration of oral glucose tolerance test (OGTT). Guar gum, psyllium, and wheat bran showed high, mild, and little (almost none) improvement in glucose response, respectively. Remarkably, viscosity was positively associated with reduction in postprandial glycaemia (80). Since then, a growing body of literature has investigated the effect of viscous fibre supplementation on postprandial glucose and insulin attenuation in in-vitro modeling and animal and human observations (67, 68, 81-83). Wood et al. showed a positive linear association between increased viscosity and flattening peak postprandial glucose and insulin in healthy participants after consumption of glucose drinks supplemented with β-glucan extract (84). Similar results were reported on postprandial blood-glucose and insulin lowering effects related to the highly

viscous psyllium, guar gum and novel blends including viscous, konjac-fibre blend (VFB) and PolyGlycopleX (PGX) in healthy population (81-83). The findings of studies in diabetes population were consistent with those in healthy subjects (81, 85, 86). Guar gum, Konjac, psyllium and β-glucan have shown significant effects on postprandial glucose and insulin, HbA1c, fasting glucose and insulin, and HOMA-IR (17, 87). Interestingly, for those subjects with T2DM, the observed effect of viscous fibre supplementation (e.g. psyllium) was greater than in healthy and pre-diabetes individuals (17).

In an attempt to understand the specific underlying mechanism of viscous fibre to lower postprandial glucose, several mechanisms have been proposed (65). Compelling evidence supports the "gastric emptying hypothesis" to be one of the mechanisms, which proposes that the ingestion of polysaccharides slows gastric emptying by forming thick gel like solution resulting from their high water holding capacity (65). When these viscous hydrated fibres enter the small intestine, the gel matrix thicken the digesta leading to modulation of the digestive processes by reducing diffusion of nutrients for absorption, and exposure of food to digestive enzymes (65). Viscous polysaccharides decrease transportation of glucose to absorptive surfaces by altering the resistance of digesta to contractile movements in the gastrointestinal tract (65). Finally, at the absorptive surfaces, ingestion of viscous fibres may thicken the unstirred water layer that glucose diffuses through slowly (65). Notably, Shear rate is associated with the degree of mixing of digesta induced/produced by peristalsis in the gastrointestinal tract (65). Dikeman et al. used in vitro gastric and small intestine digestion simulation model to compare the viscosity of different soluble and insoluble dietary fibre solutions including guar gum, psyllium, oat bran, and wood cellulose. Despite concentration, guar gum, psyllium and xanthan gum exhibited the highest viscosities suggesting their efficacy for glucose and lipid lowering benefits (88). By contrast, wood cellulose and wheat bran demonstrated the lowest viscosities indicating their possible benefits for laxation (88). In support of viscosity, hydrolysis of guar gum reduced or abolished the desirable glycemic effect , and the best results were seen when the supplement was incorporated into foods (78).

2.2.5 FIBRE RECOMMENDATIONS FOR INDIVIDUALS WITH DIABETES MELLITUS

Fibre recommendations for individuals with diabetes vary between major governing bodies. A sample of these recommendations is shown in **Table 2.1.**

Table 2.1: Dietary Fibre Recommendations for Individuals with Diabetes

RDI= Recommended Daily Intake; *For general population

AGENCY	**RDI (g/d)**
DIABETES CANADA (DC) (14)	25- 50
AMERICAN DIABETES ASSOCIATION (ADA) (20)	> 25 or 25-33
World Health Organization (WHO)*(89)	25

2.2.6 FIBRE SUPPLEMENTS

As mentioned previously, DC recommends daily total fibre intake for individuals with diabetes of 25 - 50 g (14). However, achieving this high intake is challenging often due to unpalatability, limited food options, and the often large quantity of food required to achieve recommended daily intake (15). To overcome these challenges, different forms of fibre supplements, including powder, tablets and capsules, have been developed to provide the same amount of fibre with a smaller volume and energy consumption (15). These isolates, extracted from various high-fibre sources, include but are not limited to β-glucan derived from Avena sativa and Hordeum vulgare, guar gum from Indian cluster bean, and inulin from chicory (76, 90, 91).

Increased awareness of fibre benefits has led to the development of a market for fibre supplements where fibres are being extracted from several underexploited and novel sources. To quantify fractions and eliminate undesired constitutes, various extraction methods have been applied to isolate fibre from plant sources embracing dry processing, wet processing, chemical, gravimetric, enzymatic, physical, microbial or a combination of these methods (92). Thus far, there is no standardized fibre extraction method, hence every specialist modifies an extraction method to suit their individual needs (92). Several factors largely

affect the composition and characteristics of the yielded product including the extraction method, solvent or solvent to sample ratio, drying method, treatment intensity, temperature, and source of polysaccharide(92). Choosing the extraction method highly depends on the composition of the fibre, its complexity, chemical nature, degree of polymerization, and the presence of oligosaccharides (92). Despite the accelerated development in technology, studying and extracting fibres remains challenging because of the wide variation in fibres from the same source due to agronomy variations, genetics, maturity, and climate conditions (92).

2.2.7 TYPES OF FIBRES

There are several varieties of dietary fibre available on the market. For purposes of this thesis, the following will focus only on those fibres included in this project.

Viscous Fibres:

Guar Gum (galactomannan)

Guar gum or guaran is the common name for galactomannan, extracted from the large endosperm of the leguminous guar or cluster bean (Cyamposis tetragonoloba) which is mainly grown in India and Pakistan with small amounts in Africa, Australia and the United States (90, 93). Chemically, galactomannan is a highly branched polysaccharide that contains galactose and mannose in different ratios determining the final product (galactose to mannose ratio is approximately 1:1, 1:2, 1:3, 1:4, and 1:5 for fenugreek, guar gum, tara, locust bean gum and cassia gum, respectively) (94, 95). Among the various ratios, guar gum is the most commonly utilized due to its stability and low price (95). Its rheological properties even at low concentrations and without heating make it highly beneficial in diverse food applications (90, 94). Unlike synthetic food additives, guar gum is safe, economical, biodegradable, and easily available in nature (94). In the food industry, guar gum is used as a thickener, stabilizer, binder and emulsifier in processed foods under the food additive code (E412) (90, 94). It is also used as an edible coating for cake and cheese to

minimize weight loss, oxidation (colour changes) and gas transfer rate and is used for citrus fruits to improve texture and quality (94). Interestingly, the application of guar gum to coat tomato and cucumber has delayed ripening and increased shelf life, respectively (94). Although it is not digested by the human small intestine, it is readily fermented by the gut microbiota (93). Guar gum powder and capsules have been utilized for various therapeutic potential such as the treatment and/or management of body weight, constipation, irritable bowel syndrome (IBS), hypertension, hypercholesterolemia and diabetes. Partially hydrolyzed guar gum was developed to increase palatability and overcome abdominal discomfort (90). It is believed that guar rheological properties significantly contribute to its physiological benefits. Guar gum molecular weight is 220-250 (KDa), and its viscosity is 3000-6000 cps (94).

Oat β-Glucan

β-glucan, primarily derived from oat (*Avena Sativa L.*) and barley (*Hordeum vulgare*), is considered to be the responsible component for the glucose and cholesterol lowering properties in humans. (76). Oat β-glucan is located in the cell wall of the endosperm of oat, and is composed of a linear polymer of D-glucose linked by β-(1→4) and β-(1→3) glucosidic bonds (76, 96). Vast majority of the glucose units are arranged in blocks of β-(1→3)-connected cellotriosyl and cellotetraosyl units, with the rest being the longer cellulosic segments (76). The ratio of trisaccharides to tetrasaccharides in oat and barley is (2:1) and (3:1), respectively (97). This difference in variations results in variations in physical characteristics (76). Interestingly, a small variation in the ratios of trisaccharides to tetrasaccharides exists between β-glucan samples, and it may attribute to growing conditions, differences between species, and methods of analysis and extraction (76). The molecular weight for a properly purified with the minimum depolymerization ranges from 2×10^6 to 3×10^6 (76). However, several factors including extraction and purification methods and food preparations results in differences in reported values (76). For example, molecular weight was decreased and β-glucan was degraded in bread and pasta (98). The content of β-glucan in oat ranges from

1.8 to 5.5% of the total dry weight of groats, but the most frequently reported content is 4.5 to 5.5% (76). It appears that health potential including glucose lowering effects of oats are related to β-glucan with higher viscosities (67).

Konjac (glucomannan)

Glucomannan is a viscous dietary fibre derived from various *Amorphophallus* genus, and is used as an emulsifier and thickener in different food applications (99). Konjac glucomannan (KGM), the most commonly produced crop, is extracted from tubers of *Amorphophallus konjac* c. Koch (100). It has been extensively used for food and medicinal purposes in Asian countries such as Japan and China (101). Over the last few years, KGM gained increasing attention in the US and European countries due to its distinct rheological properties that can be applied in the food industry (100). The high content of viscous glucomannan is believed to be the responsible component for potential health effects including weight loss and glucose management (99). Chemically, KGM consists of β-1,4 linkages of D-mannopyranose and D-glucopyranose sugars in a 1.6:1 ratio (99, 100). The soluble properties attribute to the side chains made up of 5 to 10% acetyl groups appearing every 10 to 19 units of the glucomannan (100). KGM has a molecular weight of between 200,000 to 2,000,000 Da. (99), and it was reported that a 1.0% konjac glucomannan solution generated a viscosity of 20,000-40,000 $mPa.s^{-1}$ at 30 °C (99). Therefore, KGM viscosity is considered to be ~5 times higher than that of guar gum and β-glucan (99).

Psyllium

Psyllium, extracted from dehydrated seeds of *Plantago psyllium*, produces a clear colorless mucilage that is used for commercial purposes (102). Psyllium isolates have repeatedly shown therapeutic effects on irritable bowel syndrome (103), metabolic syndrome (104), constipation (105) and diabetes management (17, 102). Chemically, psyllium is composed of 22.6% arabinose, 74.6% xylose with traces of other sugars (102). It has a backbone chain of β-(1→4)-bonded D-xylopyranosyl residues with some side chains

xylopyranosyl and trisaccharide branches (102). Extensive extraction of ispaghula husk fibre yielded psyllium of average molecular weight of 7×10^6 Da, and accompanying gel of molecular weight ranging from 10-20 $\times 10^6$ Da (106). Average viscosity of 1 % solution containing psyllium was 14 300 centipoise at room temperature (21 °C) (66).

Non-Viscous Fibres:

Inulin and Fructo-oligosaccharides (FOS)

Inulin type fructans includes inulin, oligofructose, and fructo-oligosaccharides (FOS) (107). Inulin, an active prebiotic, composed of fructose units and β-configuration of anomeric carbon bonded by β(1-2) linkages (107). Although inulin is indigestible in the human small intestine due to its unique chemical composition, it can be fermented in the large intestine (91). Naturally, inulin is present in various foods including chicory, onion, banana, leek, and garlic roots, and is widely used in food industry to improve/enhance texture and flavour/taste (91). It has been incorporated into processed food products to replace fat and sugar, increase crispiness, and as a prebiotic to enhance nutritional value (91). Recent observations revealed differences in the composition and function in the gut microbiota between healthy indiviudals and those with diabetes. It is believed that inulin and its derivatives promote health improvements by modulating the gut microbiota and inducing the growth of beneficial Bifidobacteria and Lactobacillius spices (108). A recent meta-analysis synthesized evidence the effect of inulin-type fructans on biomarkers of cardio-metabolic risk factors (TC, TG, LDL, HDL, fasting glucose, and fasting insulin) in four subgroups (healthy population, dyslipidemia, overweight and obese, and DM subjects). Inulin alone improved lipid profile by lowering TC and LDL with no effect on other outcomes (109). Inulin solutions are of relative low viscosity, for example, for 5% inulin solution, 1.65 mPa.s at 10 °C, and for 30% solution 100 mPa.s (91).

Resistant Starch

Resistant starch (RS) is a non-viscous fibre that is mainly classified to four subtypes based on the botanical source and processing: RS1, starch granules usually entrapped in non-digestible plants such as whole grains; RS2, native granules starch naturally found in high-amylose maize (HAMRS2) and raw potato; RS3, retrograded starch that occurred in cooked then cooled foods such as pudding and RS4, chemically modified starches by esterification and cross linkages (110). RS is considered a prebiotic; it is fermented by the microbiota producing short chain fatty acids (SCFAs) and reducing pH in the large intestine (111). Promising results have emerged from animal and human trials regarding the glycemic effect of HAMRS2. Diets involving HAMRS2 improved insulin sensitivity in diabetic mice with no effect on normal counterparts (112). In a randomized glycemic load controlled trial, 48 g HAMRS2 was administered to 20 healthy subjects. Although no change was observed in postprandial glucose, insulin response was significantly lowered (113). In a population at increased risk of T2DM, consumption of bagel containing 25 g/d for 56 days significantly reduced fasting, 2-h and 3-h postprandial insulin and fasting insulin resistance compared to control (114). In the diabetes population, findings are inconsistent, but fasting glucose may be more affected by HAMRS2 than HbA1c (115-117).

Wheat Bran

Wheat bran, a concentrated source of non-viscous fibre, is the second commonly consumed crop after rice (118). The wheat grain consists of the germ (embryo), the endosperm, aleurone layer containing the endosperm and the pericarp (118). The bran fraction, forms 14-16% of the grain, is composed of the precarp, testa, and hyaline and aleurone layers (118). Approximately 50% of the whole grain is non-starch polysaccharide (NSP) presented as arabioxylan (70%), cellulose (24%) and β-glucan (6%) (118). The high content of insoluble fibre has been associated with protection benefits against T2DM, CVD and certain types of cancer(119, 120). Large, coarse particles of wheat bran have been claimed for its laxative effects

as bran increase fecal mass and large intestinal transit time through mechanical effects inducing secretion. Interestingly, finely grinded particles lack this effect (16).

Rice Bran

Rice bran is a non-viscous fibre constitutes about 10% of the rough rice weight, and is derived from the brown outer layer of rice kernel (121). It mainly consists of pericarp, aleurone, subaleurone, and germ, and it is rich of nutrients including protein, fat, dietary fibre in addition to an appreciable amount of vitamins, minerals and antioxidants. In terms of appearance, rice bran has a light colour, sweet taste with nutty flavor and moderate amount of oil (122). This novel ingredient is undervalued in developing countries as 5-8% of it is fed to animals or discarded as waste (121). Percentage and composition of rice bran varies widely according to rice variety, treatment before processing and milling conditions (123). Different desirable effects have been associated with rice bran including antibiotic, anti-allergic, anti-cholesterol and anti-diabetic effects (124). Clinical studies investigating the effect of rice bran on glucose biomarkers revealed some possible therapeutic potential (18).

CHAPTER III – PROJECT OVERVIEW

RATIONALE

High fibre diets are strongly associated with improvement in glycemic control in diabetes mellitus as they have demonstrated reduction in HbA1c, postprandial and fasting glycemia, insulinemia and CVD risk factors (6, 11, 12). Therefore, Diabetes Canada (DC) recommends a higher intake of fibre (25 to 50 g/day) for those with diabetes compared to general population(14). Achieving this amount of fibre intake can be challenging due to palatability, limited food choices and possible gastrointestinal discomfort. Currently, there are no recommendations on the use of fibre supplements for glycemic control management in diabetes mellitus. Although the guidelines briefly mention the difference between soluble and insoluble fibres, it still remains unclear which type and proportion is more beneficial for individuals with diabetes. Despite the growing body of literature that has proposed viscosity to be the main contributing factor in the favorable effect of soluble fibre, the sole mechanism is not fully understood (65, 66, 125).

Many acute and long-term studies have investigated the effect of fibre supplementation on glycemic control in diabetes using different types, forms, duration and doses of fibre supplements (18, 86, 126). Current findings of published RCTs are inconsistent; while some show significant promising results, others show no effect (127, 128). Therefore, in order to gain a better understanding of the relationship between fibre supplementation and glycemic control in diabetes, we have conducted two systematic reviews and meta-analysis to assess the evidence from RCTs on the effect of viscous and non-viscous fibre supplementations on conventional markers of glycemic control (HbA1c,fructosamine, fasting glucose, fasting insulin and HOMA-IR) in individuals with diabetes.

OBJECTIVE

The overall objective is to investigate the effect of fibre supplementation on glycemic control outcomes in individuals with diabetes mellitus, with focus on fibre viscosity.

Specific objectives are:

1) To assess the effect of viscous fibre supplementation on HbA1c, fasting glucose, fasting insulin, HOMA-IR and fructosamine in individuals with Type 1 and Type 2 diabetes in a systematic review and meta-analysis of RCTs.
2) To assess the effect of non-viscous fibre supplementation on HbA1c, fasting glucose, fasting insulin, HOMA-IR and fructosamine in individuals with type 1 and type 2 diabetes in a systematic review and meta-analysis of RCTs.

CHAPTER IV- EFFECT OF VISCOUS FIBRE SUPPLEMENTATION ON GLYCEMIC CONTROL IN INDIVIDUALS WITH DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Background: The prevalence of diabetes mellitus is a major global health concern. With nutrition at the core of its management, rigorous dietary guidelines are needed. Although current recommendations for individuals with diabetes include increasing total dietary fibre for glycemic control, the available evidence on the benefits of viscous fibre supplementation is still inconsistent.

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to investigate the effect of viscous fibre supplementation on glycemic control outcomes in individuals with diabetes.

Methods: MEDLINE, EMBASE, and the Cochrane Library for Registered Controlled Trials were searched (through May 1, 2017). We included RCTs with a duration ≥ 3 weeks that assessed the effect of viscous fibre supplementation, compared to adequate control, on HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine in individuals with type-1 or type-2 diabetes. Data were pooled using the generic

inverse variance method with random effects models and expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was assessed using Cochran Q-statistic and quantified using I^2. The quality of the evidence was assessed using GRADE.

Results: 31 studies (n=1428) met eligibility criteria (70 T1DM; 1358 T2DM). Pooled analyses found a median dose of [13.6 g/day] viscous fibre supplementation for a median duration of eight weeks significantly reduced HbA1c (MD= -0.50% [95% CI: -0.77 to -0.23], P= 0.0003), fasting glucose (MD= -0.93 mmol/L [95% CI: -1.33 to -0.52], P < 0.0001), and HOMA-IR (MD= -1.89 [95% CI: -3.45 to -0.33], P= 0.02), along with substantial unexplained inter-study heterogeneity. Stratified analyses suggest significant effects are limited to individuals with T2DM.

Conclusion: Addition of viscous fibre supplements to standard of care significantly improved glycemic outcomes in individuals with T2DM. Hence, inclusion of viscous fibre isolates as an adjunct therapy is highly recommended for glycemic control in T2DM.

Trial registration number: NCT02629263

Introduction

Regardless of remarkable advancements in health care and pharmacotherapy, diabetes mellitus remains an overwhelming global health problem with approximately 400 million individuals living with diabetes worldwide (1). Dietary fibre has been shown to significantly decrease fasting and postprandial plasma glucose, HbA1c, and insulin resistance (6, 11, 12, 15, 79, 80). The ADA and DC recommend an increased consumption of dietary fibre in individuals with diabetes (> 25 g/d) (14, 20). Therefore, high fibre diets such as the Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets are recommended for individuals with diabetes (7, 8). It is difficult however, to achieve the recommended daily fibre intake

within a typical Western diet due to the low fibre content in some food sources and the unpalatability of others. To overcome this challenge, fibre supplements have been developed to provide a more convenient and concentrated source of fibre with the same health benefits (15, 16, 62, 129) .

Solubility was originally proposed to be the main factor behind the glucose and insulin lowering properties of fibre (130, 131). However, in mid-1970's, Jenkins et al (80) shed light on the importance of fibre viscosity, showing a positive correlation between fibre viscosity and glucose and insulin attenuation in response to an oral glucose challenge (79, 80). Since then, a developing body of literature suggests that the efficacy of dietary fibre on glycemic control may depend primarily on its physicochemical properties or its ability to increase viscosity of digetsa in the gastrointestinal tract (16, 65). The exact mechanism underlying the desirable effect of fibre viscosity on postprandial glucose and insulin response is still controversial. Although some studies suggest that the delayed gastric emptying results from viscosity, other studies have proposed that an inhibitory response in absorption due to the increased viscosity in the small intestine is the sole mechanism (65).

In 2013, a SRMA investigated the effects of total dietary fibre intake, including high fibre diets and fibre supplementation, on some markers of glycemic control in diabetes, and found a significant reduction in HbA1c and fasting glucose in individuals with T2DM who consumed high fibre diet compared to placebo, fibre free or low fibre matched diets (132). To date, the efficacy of incorporating viscous dietary fibre supplementation on the glycemic profile of individuals living with T2DM has not been established. Hence, the objective of this study was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) on the effect of viscous fibre supplementations on HbA1c, fasting glucose, fasting insulin, fructosamine, and insulin resistance via Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in individuals with diabetes.

METHODS

Protocol and registration

The Cochrane Handbook for Systematic Reviews of Interventions was used to plan and conduct this meta-analysis (133). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used to report results (134). The review protocol is available online at ClinicalTrials.gov (registration number: NCT02629263).

Search strategy and data sources

MEDLINE, EMBASE, and the Cochrane Library for Registered Controlled Trials were searched through May 1, 2017, to identify RCTs on the effect of viscous fibre supplementations on glycemic control endpoints (HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine) in individuals with T1DM and T2DM (135, 136). The search strategy is presented in the **Supplementary Table 4.1.** A manual search of the references of included trials was done to supplement the electronic search. No language restrictions were applied.

Study eligibility

According to our inclusion and exclusion criteria presented in Supplementary Table 4.2., we included RCTs ≥ 3 weeks that investigated the effect of viscous fibre supplementation (β-glucan, guar gum, konjac, psyllium, pectin, xanthan gum, locust bean gum, alginate, agar) compared to placebo of free-fibre diet adequate control, on at least one of the glycemic measures: HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine. Trials that incorporated viscous fibre supplementation as a part of a fibre mixture or dietary pattern, and were not compared to a calorie matched control group were excluded to isolate the effect of the viscous fibre supplement. For multi-arm trials, we included the groups that allowed us to calculate the isolated effect of viscous fibre supplements. The most recent publication was used when

multi publications were found, and the one with extra relevant data was used for comparison. Glycemic control endpoints were determined according to American Diabetes Association and Diabetes Canada Clinical Practice Guidelines (14, 20).

Data extraction and quality assessment

Using a standardized pro-forma, two independent reviewers (RK & NM) reviewed articles that met eligibility criteria in full and extracted relevant data on study characteristics and endpoints. Study characteristics included: viscous fibre type, study design (cross-over or parallel), participant characteristics, comparator, viscous fibre dose, duration, background diet, compliance measures, statistical analysis, and funding sources. Disagreement between reviewers was resolved by a third impartial reviewer (HVTH). If the β-glucan content was not reported, oat viscous fibre from β-glucan was estimated at 5% [25]. The mean and standard deviation (SD) values were extracted for HbA1c, 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% CI or SEM) using standard formulae. When change from baseline values were not reported, the mean and SD values for baseline and end values were used to calculate change from baseline values for both control and intervention groups.

The Cochrane Risk of Bias Tool was used to assess the study risk of bias (133). Domains of bias assessed include: sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, and selective outcome reporting. The study was considered ‘unclear risk of bias’ when insufficient information was provided to permit judgment, ‘low risk of bias’ when the flaw of the study was most likely to not affect the true outcome and ‘high risk of bias’ when the study flaw was most likely to affect the true outcome. Authors were contacted for additional information where necessary. All disagreements on Risk of Bias Tool were resolved by consensus.

Data management 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 (V.14, College Station, USA) for subgroup analyses. The difference between the change from baseline values for the intervention and control arms was derived from each trial for the end points of HbA1c, fasting glucose, fasting insulin, fructosamine, and HOMA-IR. When HOMA-IR was not reported, it was calculated using the equation (HOMA-IR= fasting insulin (microU/L) x fasting glucose (mmol/L)/22.5) (137). A previously developed formula was used to calculate SD for calculated values of HOMA-IR (138). If change from baseline values were not available, end-of-treatment values were used. For multi-arm trials, a weighted average was used to create a single pair-wise comparison and to reduce the unit-of-analysis error. A correlation coefficient of 0.5 was assumed for SD of cross-over trials. The generic inverse variance method with random effects models was used to conduct pooled analyses. Data were expressed as MD with 95% CI and significance was considered at $P < 0.05$. Inter-study heterogeneity was assessed using the Cochrane Q-statistic and quantified using I^2 with $P < 0.10$ significance. I^2 values ≥ 50 % indicates 'substantial' level of heterogeneity (133). Sensitivity analyses were performed to determine whether any single study exerted particular influence on the overall results by removing each individual study from the analysis and re-calculating the effect size of the remaining studies. Sources of heterogeneity were explored with *a priori* subgroup analyses (continuous and categorical) for baseline values of HbA1c, fasting glucose and HOMA-IR within the intervention arm, dose, design, follow-up, fibre type and food matrix and significance level set at $P < 0.05$. Visual inspection of funnel plots was used to assess publication bias and formally tested in STATA using Egger and Begg tests, where $P < 0.10$ was considered evidence for small study effects. Trim and Fill tests were applied when asymmetry in funnel plots was present.

Grading of Recommendations Assessment, Development and Evaluation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (139, 140) was used to assess the overall certainty of evidence. In this approach, the quality of total evidence can be graded as 'very low', 'low', 'moderate', or 'high'. Evidence obtained from randomized trials receives an initial grade of 'high'. Scores for randomized trials can be downgraded for study limitations (i.e. weight of studies showed high risk of bias assessed by The Cochrane Collaboration Tool for Assessing Risk of Bias), inconsistency of results due to a substantial ($I^2 > 50\%$, $P < 0.10$) unexplained heterogeneity, indirectness of evidence resulting from the presence of factors that limit the generalizability of the findings, imprecision recognized by the wide confidence interval (CI) around the estimate of the effect, and judged depends on the minimally important differences (MID), and publication bias (evidence of small-study effects).

RESULTS

Search results

The initial search yielded 2426 publications, of which 59 articles were reviewed in full and 31 (n= 1428) were included in the final analysis (Figure 4.1.). In total, 24 trials reported data on HbA1c (n= 1212), 30 on fasting glucose (n= 1419), 9 on fasting insulin (n= 184), 3 on fructosamine (n= 39), and 6 trials reported data on HOMA-IR. However, 6 other trials reported enough information to calculate HOMA-IR (n= 880).

Trial characteristics

A summary of the characteristics of the included studies is available in **Table 4.1**. Majority of trials were conducted in out-patient settings: with 19 in Europe (7 Finland; 5 UK; 3 Netherlands; 1 England; 1 Greece; 1 Norway; 1 Sweden), 5 in Asia (2 Taiwan; 3 China), 3 in North America (1 USA; 1 Canada; 1 Mexico), 3 in Middle East (1 Saudi Arabia; 1 Palestine; 1 Iran), and 1 in South America (Brazil). All trials were randomized,

with 18 trials (58%) using a cross-over design and 13 trials (42%) using a parallel design. Participants were generally middle aged (median age= 60 (range: 27-64) years) with the majority being men. Participants were slightly overweight (median BMI= 27 (range: 23-31) kg/m^2), despite only 3 trials recruiting on the basis of overweight/obese. Twenty-seven trials (87%) were conducted in individuals with T2DM and 4 trials (13%) in individuals with T1DM. The dose of viscous fibre supplementation ranged from 2.5 to 29 g/d with a median dose of 13.6 g/d. Treatment duration ranged from 3 - 52 weeks with the median length being 8 weeks for trials reporting HbA1c, fasting glucose and fasting insulin, 12 weeks for trials reporting fructosamine, and 6 weeks for trials reporting HOMA-IR.

The Cochrane Risk of Bias Tool **(Supplementary Table 4.3.)** demonstrated that 28 trials (90%) had unclear risk of bias and three trials had a low risk of bias for sequence generation. All 31 trials trials had unclear risk of bias for allocation concealment. Eighteen studies (58%), 10 studies (32%) and 3 studies (10%) had low, unclear and high risk of bias for blinding, respectively. A total of 20 trials (66%) had a low risk of bias, 7 trials (22%) had unclear risk if bias and 4 (12%) had a high risk of bias for incomplete outcome data. The majority of trials (94%) had a low risk of bias for selective outcome reporting. Funding sources included agency (29%), industry (16%), agency-industry (16%) or were not reported (39%).

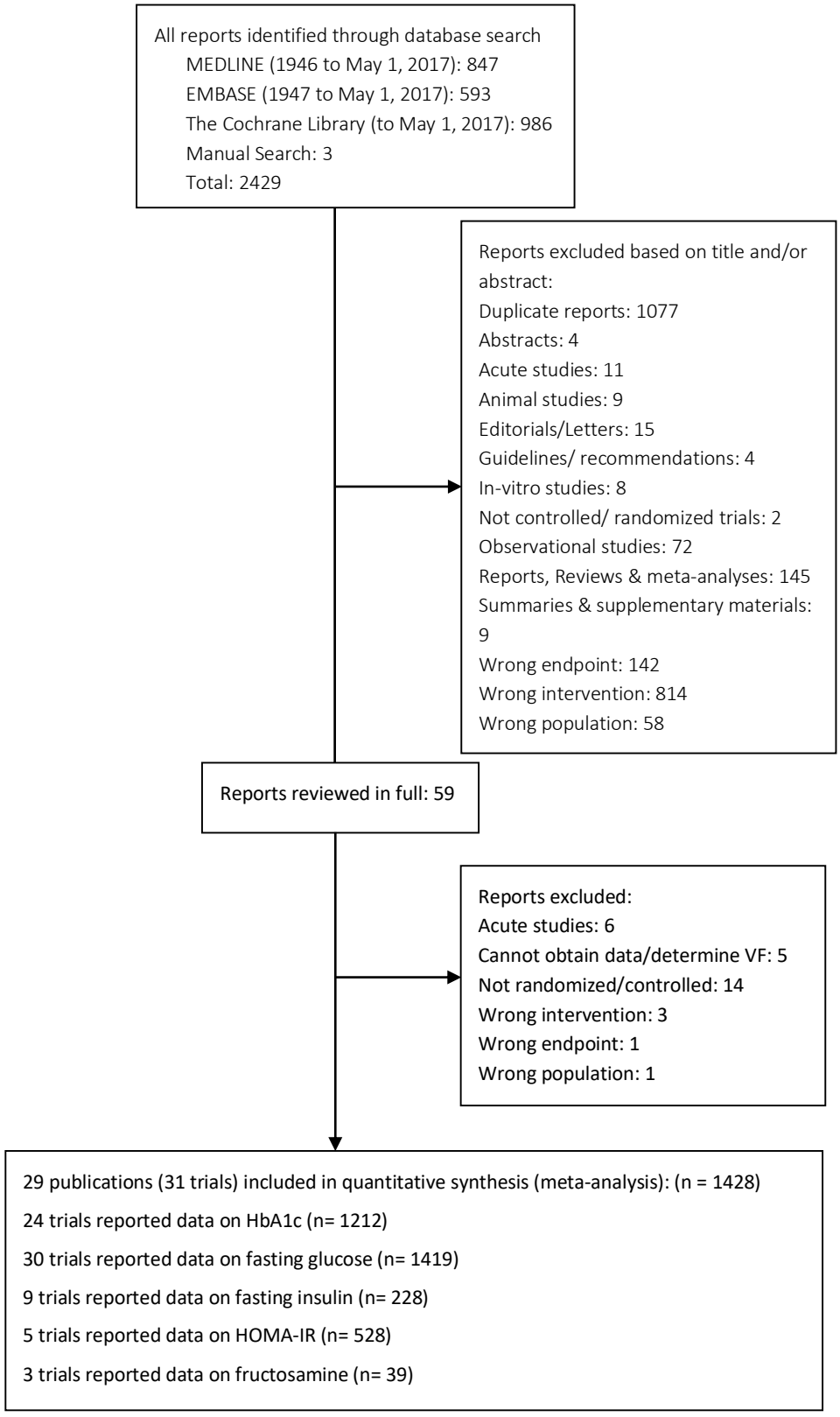


Figure 4.1. Flow of literature

Table 4.1. Characteristics of included studies

Reference	Participants §	Age (y)	Body weight or BMI (Kg/m^2)	Baseline HbA1c (%)	Baseline FG (mmol/L)	Design (wks)	VFS	Comparator	Dose† (g/d)	Food matrix	Background diet	Funding source	Setting
Abutair et al, 2016 (126)	36	> 35	31.7	C: 8.5 T: 8.5	C: 8.7 T: 9.0	P, 8, N/R	Psyllium	No psyllium	10.5	Powder	Usual	N/R	Palestine
Aro et al, 1981 (141)	9 (5M:4F)	53	N/R	N/R	C: 11.5 T: 10.6	C, 12,DB	Guar gum	Wheat flour	21	Granules	Usual	A-I	Finland
Baker et al, 1988 (142)	30	C: 64.3 T: 59.1	N/R	C: 11.9 T: 12	C: 11.7 T: 12.1	P, 9, SB	Guar gum	N/R	15	Tablets	Usual	N/R	England
Chen et al, 2003 (143)	22 (10M:12F)	64	25.5	N/R	9.1	C, 4, DB	Konjac	Corn starch	3.6	Capsules	NCEP	A-I	Taiwan
Chuang et al, 1992 (144)	13	54.9	25.8	7.9	10.6	C, 8, DB	Guar gum	N/R	15	Powder	Liquid form meals	A	Taiwan
Cugnet-Anceau et al, 2010 (145)	53	C: 61.8 T: 61.9	C: 29.02 T: 30.48	C: 7.47 T: 7.31	C: 8.36 T: 8.84	P, 8, DB	β-glucan	Control soup	3.5	Enriched Soups	Usual	A	Sweden
Dall'Alba et al, 2013 (146)	44 (27M:17F)	C: 63.6 T: 60.5	C: 29.3 T: 30.2	C: 7 T: 6.9	C: 7.9 T: 7.4	P, 6, OL	Guar gum	N/R	10	Powder	Usual	A-I	Brazil
Ebeling et al, 1988 (147)	9 (7M:2F)	27	N/R	9.5	N/R	C, 4, DB	Guar gum	N/R	20	Granules	Usual	A	Finland
Feinglos et al, 2013 (148)	33*	C: 56.5 T-A: 61.8 T-B: 64.8	C: 87.09 T-A: 81.51 T-B: 83.82‖	C: 7.6 T-A: 7.4 T-B: 7.9	C: 11.76 T-A: 11.19 T-B: 10.33	P, 12, DB	Psyllium	Free-fibre placebo	6.8 13.6	N/R	Restricted	N/R	USA
Fuessl et al, 1987 (149)	18 (12M:6F)	61.3	30.1	C: 9.27 T: 9.67	9.12	C, 4, DB	Guar gum	Wheat bran	15	Granules	Usual	A	UK

Holman et al, 1987 (150)	29 (24M:5F)	54.2	26.5	N/R	N/R	C, 8, N/R	Guar gum	N/R	15	Tablets	N/R	I	UK
Laajam et al, 1990 (151)	39 (11M:28F)	51.5	31.2	11.4	12.5	C, 4, DB	Guar gum	Beef Gelatin	15	Granules	Usual	N/R	KSA
Lalor et al, 1990 (86)	19 (8M:11F)	40-73	31.5	N/R	10.9	C, 12, DB	Guar gum	N/R	15	Granules	Usual	A-I	UK
Li et al (A), 2016 (152)	238 (116M:85)	59	27	C: 8.10 T-A: 8.37 T-B: 8.28	C: 9.52 T-A: 9.87 T-B: 9.70	P, 4, N/R	β-glucan	No β-glucan	2.65	Oat	Low Fat High Fibre Healthy Diet	I	China
Li et al (B), 2016 (152)	228	59	27	C: 8.10 T-A: 8.37 T-B: 8.28	C: 9.52 T-A: 9.87 T-B: 9.70	P, 52, N/R	β-glucan	No β-glucan	5.3	Oat	Low Fat High Fibre Healthy Diet	I	China
Liatis et al, 2009 (153)	41	C: 66.50 T: 60.22	C: 27.01 T: 29.61	C: 6.91 T: 7.29	C: 7.73 T: 8.81	P, 3, DB	β-glucan	No β-glucan	3	Bread	Usual	N/R	Greece
Ma et al, 2013 (127)	186	50-65	C: 26.57 T-A: 26.64 T-B: 26.74	C: 9.70 T-A: 9.90 T-B: 9.84	C: 9.51 T-A: 10.11 T-B: 10.07	P, 4, SB	β-glucan	No β-glucan	2.5 5	Oat	SDI	I	China
McGeoch et al, 2013 (128)	27 (18M:9F)	60.9	31.5	6.8	N/R	C, 8, NB	β-glucan	No β -glucan	4	Oat-Based Products	Usual	A	UK
Niemi et al, 1988 (154)	18	63	27	C: 11.4 T: 12.1	C: 12.5 T: 11.7	C, 12, DB	Guar gum	Cellulose	15	N/R	Usual	A-I	Finland
Peterson et al, 1987 (155)	16 (10M:6F)	60	27.3	C: 11.3 T: 11.2	C: 9.7 T: 9.5	C, 6, N/R	Guar gum	No guar gum	16.6	Granules	Usual	A	UK
Rodriguez-Moran et al, 1998 (156)	123 (55M:68F)	C: 56.5 T: 57.0	C: 28.6 T: 29.1	N/R	C: 7.77 T: 10.66	P, 6, DB	Psyllium	Cellulose	15	Powder	Low Fat	N/R	Mexico

Sels et al (A), 1993 (157)	16 (10M:6F)*	44.5	24.2	12	9.9	C, 12, N/R	Guar gum	HF control bread	11.2	Bread	Usual	N/R	Netherlands
Sels et al (B), 1993 (157)	12 (6M:6F)*	62	25.8	11.3	9.8	C, 12, N/R	Guar gum	HF control bread	11.2	Bread	Usual	N/R	Netherlands
Uusitupa et al, 1990 (158)	9 (4M:5F)	47.8	N/R	N/R	10.6	C, 4, DB	Guar gum	Wheat flour	15	Granules	Usual	N/R	Finland
Uusitupa et al, 1989(159)	39 (13M:26F)	C: 60.93 T: 60.1	N/R	C: 9.41 T: 8.88	C: 12.80 T: 12.23	P, 12, DB	Guar gum	Wheat flour	15	Granules	Usual	A	Finland
Uusitupa et al, 1984 (160)	17	62	N/R	N/R	9.7	C, 18, DB	Guar gum	Wheat flour	21	Granules	Usual	N/R	Finland
Vaaler et al, 1986 (161)	28 (15M:13F)	27	23.3	10.5	11.4	C, 12, N/R	Guar gum	Wheat bran	29	Bread	Usual	A	Norway
Vuksan et al, 1999 (162)	11 (5M:6F)	M: 62 F: 59	N/R	M: 7.4 F: 8.3	C: 9.29 T: 9.63	C, 3, DB	Konjac	Wheat bran	15.1	Biscuit	NCEP	I	Canada
Vuorinen-Markkola et al, 1992 (163)	17 (12M:5F)	C: 37 T: 39	C: 25.1 T: 24.7	C: 7.9 T: 8.3	C: 7.7 T: 8.7	P, 6, DB	Guar gum	Wheat flour	20	Granules	Usual	A	Finland
Wolffenbutt et al, 1992 (164)	12 (6M:6F)	62	25.8	11.3	9.8	C, 12 , N/R	Guar gum	Control bread	11.2	Powder	Usual	N/R	Netherlands
Ziai et al, 2005 (165)	36	C: 53.6 T: 51.9	C: 27.5 T: 26.6	C: 9.1 T: 10.5	C: 9.94 T: 11.56	P, 8, DB	Psyllium	Cellulose	10.2	Powder	Usual	N/R	Iran

M, male; F, female; VFS, viscous fiber supplement; C, cross-over; P, parallel; SB, single blind; DB, double blind, OL, open label; NB, not blinded; A, agency; I, industry; A-I, agency-industry; N/R, not reported; OP, outpatients; C: control; T: treatment; NCEP, National Cholesterol Education Program; SDI, Structured Dietary Intervention

All values are expressed as mean

§ The number of participants listed for each trial is the number of participants that completed the trial, and therefore the number used in our analyses and the number used for the reported baseline data (age and BMI), unless otherwise indicated with (*)

† Dose of viscous fibre supplement

¶ Agency funding is that from government, university or not-for-profit health agency sources.

‡ Age was reported in range

‖Body weight

Effect on HbA1c

Figure 4.2. demonstrates the effect of viscous fibre supplementation on HbA1c in people with diabetes. Overall, a significant reduction in HbA1c was observed with a median dose of 11.2 g/d [range: 2.5-29 g/d] for a median duration of 8 weeks [range: 3-52 wks] (MD= -0.50% [95% CI: -0.77, -0.23], P= 0.0003). There was evidence of a significant interaction by diabetes type (P=0.03) with the reduction in HbA1c seen only in T2DM (MD= -0.58% [95% CI:-0.88, -0.28]; P<0.0002). Substantial evidence of inter-study heterogeneity was present in the overall analysis (I^2= 89%, P < 0.00001). The systematic removal of individual studies did not alter the results or explain heterogeneity. **Supplementary Table 4.4. (A) & Figure 4.1. (A)** show the results of continuous and categorical subgroup analyses for the effect of viscous fibre supplementations on HbA1c. Meta-regression analyses did not reveal any statistically significant subgroup effects, and could not further explain inter-study heterogeneity. There was no linear (P=0.22) or non-linear (P=0.68) dose response association of viscous fibre supplementation dose with HbA1c reduction **(Supplementary Figures 4.2. A1 & A2).**

Effect on fasting glucose

Figure 4.3. demonstrates the pooled effect of viscous fibre supplementation on fasting glucose in individuals with diabetes. Diets supplemented with a median dose of 12.4 g/d [range: 2.5-29 g/d] of viscous fibre supplementations for a median duration of 8 weeks [range: 3-52 wks] significantly reduced fasting glucose compared to control diets (MD= -0.93 mmol/L [95% CI: -1.33, -0.52], P < 0.0001) with evidence of substantial heterogeneity (I^2= 86%, P < 0.00001). Although there was no evidence of a significant interaction by diabetes status, a significant reduction was only seen in individuals with T2DM. The systematic removal of individual studies did not alter the results. **Supplementary Table 4.4 (B) & Figure 4.1. (B)** show the results of continuous and categorical subgroup analyses for the effect of viscous fibre supplementation on fasting glucose. Continuous meta-regression analyses did not reveal association

between dose, treatment duration or baseline fasting glucose. Categorical meta-regression revealed that the fasting glucose lowering effect of viscous fibre supplementation was modified by guar gum, β-glucan, psyllium, and konjac fibre types (between guar gum and β-glucan group (MD= -1.331 mmol/L [95% CI: -0.100, 0.337], P= 0.006), (between guar gum and psyllium group (MD= -1.519 mmol/L [95% CI: -2.362, -0.675], P= 0.006), (between guar gum and Konjac group (MD= -1.191 mmol/L [95% CI: -2.574, 0.192], P= 0.006), (between β-glucan and psyllium group MD=1.187 [95% CI: 0.350, 2.025], P= 0.006), (between β-glucan and Konjac group (MD= 0.860 mmol/L [95% CI: -0.519, 2.239], P= 0.006), and (between psyllium and Konjac group (MD=-0.327 [95% CI: -1.800, 1.145], P= 0.006). Studies that used guar gum showed a MD of -0.560 mmol/L [95 % CI: -1.037, -0.081], while studies that used β-glucan demonstrated a MD of-0.890 [95% CI: -1.357, -0.423], studies that used psyllium showed a MD of -2.078 mmol/L [95% CI: -2.773, -1.382], and studies that used Konjac demonstrated a MD of -1.750 mmol/L [95% CI: -3.048, -0.453]. Meta regression analyses could not further explain inter-study heterogeneity. There was no linear (P=0.58) or non-linear (P=0.28) dose response association of viscous fibre supplementation dose with FG improvement **(Supplementary Figures 4.2. B1 & B2).**

Effect on fasting insulin

Figure 4.4. shows the pooled effect of viscous fibre supplementation with a median dose of 15 g/d [range: 3-21 g/d] over a duration of 8 weeks [range: 3-12 wks] on fasting insulin in individuals with diabetes. As none of the included T1DM trials reported on fasting insulin, the analysis only includes those with T2DM. Overall, viscous fibre supplementation had no significant reduction on fasting insulin (MD= -17.56 pmol/L [95% CI: -37.54 to 2.42], P= 0.08) with substantial evidence of inter-study heterogeneity (I^2= 90%, P < 0.00001). The removal of Abutair et al, 2016 (126) during our sensitivity analyses decreased the heterogeneity (I^2= 43%, P= 0.09), and decreased the effect size (MD= -9.18 pmol/L [95% CI: -18.97, 0.60], P= 0.07). The use of different levels of correlations coefficients (0.25, 0.75) for crossover studies did not

influence the effect or heterogeneity in the overall pooled results. Continuous and categorical subgroup analyses were not performed for fasting insulin as < 10 trial comparisons were available for analyses.

Effect on HOMA-IR

Figure 4.5. demonstrates the pooled effect of viscous fibre supplementation on HOMA-IR in individuals with DM. As none of the included T1DM trials reported on HOMA-IR, the analysis only includes those with T2DM. Diet supplemented with a median dose of 10.2 g/d [range: 3-21 g/d] viscous fibre over a median duration of 6 weeks [range: 3-52 wks] significantly lowered HOMA-IR in people with DM (MD= -1.89 [95% CI: -3.45 to -0.33], P= 0.02). Substantial evidence of inter-study heterogeneity was observed (I^2= 94%, P < 0.00001). The removal of Abutair et al, 2016(126) trial decreased the overall heterogeneity (I^2= 63%, P= 0.004) and altered results to detect a significant decrease in HOMA-IR (MD= -1.07 [95% CI: -1.88, -0.26], P= 0.010). The use of different levels of correlations coefficients (0.25, 0.75) for crossover studies did not influence the effect or heterogeneity in the overall pooled results. **Supplementary Table 4.4. (C) & Figure 4.1. (C)** shows the results of continuous and categorical subgroup analyses for the effect of viscous fibre supplementations on HOMA-IR. Continuous subgroup analyses revealed that the effect of viscous fibre supplementation on HOMA-IR was modified by baseline values (MD= -0.415 [95% CI: -0.669, -0.161], P= 0.004). Categorical subgroup analyses showed that the effect of viscous fibre supplementation on HOMA-IR was modified by baseline values (MD= -3.138 [95% CI: -5.142, -1.134], P=0.006]). Studies in participants with HOMA-IR $\geq$ 5.44 showed a MD of -3.770 [-5.390, -2.147], P= 0.000, and studies in participants with < 5.44 showed a MD of -0.633 [95% CI: -1.808, 0.543], P= 0.258. Meta regression analyses could not further explain inter-study heterogeneity. There was no linear (P=0.64) dose response association of viscous fibre supplementation (VFS) dose with HOMA-IR improvement. However, there was a suggestion of non-linear association of viscous fibre supplementation (VFS) dose with improvement in HOMA-IR (P=0.07). Visual data suggests that doses of >10 g/d of viscous fibre supplementation (VFS) may be more effective in

HOMA-IR improvement compared to lower dose though the p-value did not reach significance (P value for difference in slops: <10 vs >10: 0.06) **(Supplementary Figures 4.2. C1, C2 & C3).**

Effect on fructosamine

Figure 4.6. shows the effect of a median dose of 11.2 g/d [range: 11.2-15.1 g/d] of viscous fibre supplementation over a median duration of 12 weeks [range: 3-12 wks] on fructosamine in individuals with diabetes. Only three included trials reported on this outcome, including two trials with T2DM and one with T1DM. Overall, viscous fibre supplementation had no significant reduction on fructosamine (MD= -0.12 mmol/L [95% CI: -0.33, 0.08], P= 0.24) with no evidence of inter-study heterogeneity (I^2= 0, P= 0.87). There was no evidence of interaction by diabetes status. The use of different levels of correlations coefficients (0.25, 0.75) for crossover studies did not influence the effect or heterogeneity in the overall pooled results. Continuous and categorical subgroup analyses were not performed on fructosamine data due to the small number of trials.

Publication bias

Figure 4.7. shows funnel plots for HbA1c, fasting glucose, and HOMA-IR. Visual inspection of funnel plots suggested no asymmetry in HbA1c and fasting glucose and major asymmetry in HOMA-IR. Formal testing using Egger and Begg tests were not significant. Duval and Tweedie Trim and Fill analysis **(Figure 4.8.)** identified four missed studies and the imputation of these studies resulted in a significant pooled effect of MD= -2.62 [95% CI: -4.17, -1.18], P= 0.000). Publication bias was not analyzed for fasting insulin and fructosamine as there were < 10 trial comparisons available.

Grading the evidence

A summary of the GRADE assessments for each endpoint is shown in **Table 4.2.** The evidence for HbA1c, fasting insulin and HOMA-IR was rated moderate quality based on a downgrade for inconsistency for

HbA1c and HOMA-IR and imprecision or fasting insulin. Evidence was rated high for fasting glucose, and was rated low for fructosamine based double down grade for very serious imprecision.

Discussion

To our knowledge, this is the first systematic review and meta-analysis of RCTs to assess the effect of viscous fibre supplementation on HbA1c, fasting glucose, fasting insulin, and HOMA-IR in individuals with diabetes. We included 31 RCTs (n=1428) evaluating the effect of viscous fibre supplementation (guar gum, β- glucan, psyllium or Konjac) on these glycemic outcomes in middle-aged adults. Pooled analyses showed a significant reduction in HbA1c (−0.50%), fasting glucose (−0.93 mmol/L), and HOMA-IR (-1.89) at a median dose of 13.6 g/d (ranged 2.5 - 29 g/d) over a median duration of 8 weeks. Although significant benefits for fasting insulin and fructosamine were not observed, the effect did favour viscous fibre supplementation. Stratified analyses suggest that significant effects on HbA1c, fasting glucose and HOMA-IR are limited to individuals with T2DM.

There is a growing body of literature assessing the efficacy of viscous fibre supplementation to improve glycemic control long term. Previous observational studies evaluating dietary components including increased total dietary fibre intake are consistent with our findings (17, 166). Moreover, a recent systematic review and meta-analysis of 13 RCTs in T2DM (132), illustrated a decrease in HbA1c by 0.52% (95% CI: −0.92% to −0.13%), and in fasting glucose by 9.97 mg/dL (95% CI: -18.16 to -1.78) following high fiber intake, through diet or supplements, relative to a conventional dietary pattern or placebo. Both soluble and insoluble fibres were included, and solubility was the main proposed factor attributed to improvement in glycemic control. The present meta-analysis observed only viscous fibre supplementation to isolate the effect of viscous fibre from total dietary fibre, and found a slightly stronger reduction in HbA1c (MD= -0.58% [95% CI: -0.88 to -0.28], P= 0.0002) and fasting glucose (MD= -0.95 mmol/L [95% CI: -1.37 to -0.53]) when confined to individuals with T2DM. An achieved reduction of ≥ 0.3% represents a clinically meaningful change in HbA1c(167). These findings are comparable to the effect of Acarbose (-

0.6%) with less expected serious side effects for the viscous fibre supplementation (14, 168, 169). This may suggest that viscous fibre supplementation could play an important role in diabetes management, decreasing the demand on chemical anti-hyperglycemic agents and to avoid or delay its side effects.

The ability of fibre supplementation to improve glycemic control may relate to its physiochemical and rheological properties. Solubility has been proposed to be the main attributing factor in the glucose lowering effect of fibre (143). However, there is a growing body of evidence supporting viscosity to be the main attributing factor in glycemic control. It is proposed that the ability of fibre to form viscous solution in the gastrointestinal tract slows the gastric emptying and delays the absorption of glucose in the small intestine (15, 65, 125). This alters the rate of starch degradation and digestion which improves the regulation of postprandial glucose resulting in improvement in HbA1c level over the long term (170). Vuksan et al along with Brenelli et al and Gibb et al reported consistent results supporting the role of viscosity in the glycemic control improvements (17, 77, 162). Vuksan et al reported improvement in glycemic control in individuals with T2DM after three week supplementation with konjac-glucomannan, relative to wheat bran (162). Panahi et al further showed more promising results supporting the importance of viscosity in improving glycemia when they found a stronger reduction in postprandial glucose on β-glucan from oat with higher level of viscosity in comparison to the same viscous fibre from a lower viscosity source (67). The pooled analyses reported by Gibb et al showed that a median of 10.2 g/d over 8 weeks significantly improved fasting blood glucose concentration (237.0 mg/dL; P , 0.001) and HbA1c [20.97% (210.6 mmol/mol), P = 0.048] in patients with T2DM (17). Evidence in this area has sparked the development of a number of functional fibre preparations containing highly viscous polysaccharides including PolyGlycopleX (PGX) and Viscous Fibre Blind (VFB), both of which have been shown to promote significant reductions in postprandial glucose (81, 82).

There are several strengths to this study. It is the first meta-analysis to investigate the isolated effect of supplementation of dietary fibre in both T1DM and T2DM, and one of the first to differentiate dietary

fibre on the basis of viscosity rather than solubility. The majority of the trials reported glycemic control endpoints as their primary outcome and had a follow-up period of ≥ 8 weeks which is sufficient to influence the glycemic profile. This marker is reflective of glycemic control in the preceding three months. However, clinical studies suggest that 75% of HbA1c is formed in the current month of the test and the month before (171). The present meta-analysis included RCTs from several countries which may increase generalizability of results. We also assessed the certainty of evidence using GRADE.

Conversely, there are limitations in the present meta-analysis that should be considered when interpreting the results. There was evidence of substantial inter- study heterogeneity in the overall primary analyses for HbA1c, fasting glucose, fasting insulin and HOMA-IR, which was not entirely explained by any of our subgroup analyses. Only fibre type, in the categorical subgroup analyses modified the effect on fasting glucose. Psyllium, Konjac, β-glucan and guar gum showed significant lowering effects on fasting glucose (MD= -2.078 [95% CI: -2.773, -1.382]), (MD= -1.750 [96% CI: -3.048, -0.453]), (MD= -0.890 [95% CI: -1.357, -0.423]), and (MD= -0.560 [95% CI: -1.037, -0.081]), respectively. Some of the included studies were of low quality due to the large number of withdraws (> 10%), selective reporting outcome, small number of included studies and participants and/or relatively short follow-up duration. These results are consistent with findings from other studies suggesting that fibre supplements with greater viscosity may lead to greater improvements in glycemic control (79, 125). Furthermore, some subgroup analyses were underpowered and it was not possible to assess the effect of other factors that may influence glycemic control (i.e. diet composition and physical activity) due to unavailability of data. Overall certainty of evidence for this study was “moderate”, according to GRADE assessment tool. In terms of our ability to assess insulin resistance, only 6 trials reported results for HOMA-IR ± SD or SEM, and 6 trials reported enough information to calculate HOMA-IR. The specific equation that was developed to impute SEM for change between groups for HOMA-IR may be met with inherent limitations for underestimation and uncertainty in the precision of the estimated effect size.

In conclusion, the present systematic review and meta-analysis of RCTs shows that a daily median intake of 13.6 g of viscous fibre supplements over a median duration of 8 weeks significantly reduced HbA1c, fasting glucose and HOMA-IR in individuals with diabetes. The significant results were limited to individuals with T2DM with a reduction in HbA1c by -0.58% [95% CI: -0.88, -0.28], in fasting glucose by -0.95 mmol/L [-1.37, -0.53], and in HOMA-IR by -1.89 [95% CI: -3.45, -0.33]. Although significant benefits were not seen for fasting insulin and fructosamine, the direction of effect favored viscous fibre supplements. To address the current limitations of our analyses, there is a need for longer, higher quality trials using viscous fibre supplements to improve the glycemic control with a specific focus on glycemic endpoints as a primary outcome. Such trials in future meta-analyses may help guide the development of nutrition recommendations and health claims. Especially if these new studies incorporate measures of viscosity when giving fiber supplements to confirm the correlations seen previously and utilize the information in future meta-analyses. Overall, our data supports the inclusion of viscous fibre supplements as part of a healthy diet for the management of glycemia in individuals with T2DM. It is one of few studies that reported promising HbA1c and glucose lowering results that are comparable to anti-hyperglycemic agents with an addition of small dose of viscous fibre supplements to daily meals.

Subgroup and Study, Year (Reference)	VFS (N)	Control (N)	Weight %	Mean Difference (95% CI) in HbA1c, %
T2DM				
Fuessl et al, 1987 (149)	18	18	3.8	-0.79 [-1.57, -0.01]
Holman et al, 1987 (150)	29	29	4.2	0.20 [-0.44, 0.84]
Peterson et al, 1987 (155)	16	16	2.0	-0.50 [-2.03, 1.03]
Baker et al, 1988 (142)	15	15	4.0	0.00 [-0.71, 0.71]
Niemi et al, 1988 (154)	18	18	3.2	-1.10 [-2.08, -0.12]
Uusitupa et al, 1989 (159)	20	19	4.1	-0.44 [-1.11, 0.23]
Laajam et al, 1990 (151)	39	39	4.0	-1.60 [-2.31, -0.89]
Chuang et al, 1990 (144)	29	24	4.6	-0.30 [-0.82, 0.22]
Wolffenbuttel et al, 1990 (164)	12	12	2.1	0.20 [-1.25, 1.65]
Sels et al (B), 1993 (157)	9	9	1.8	0.20 [-1.47, 1.87]
Ziai et al, 2005 (165)	21	15	2.7	-3.00 [-4.17, -1.83]
Liatis et al, 2009 (153)	23	18	5.5	-0.15 [-0.32, 0.02]
Cugent-Anceau et al, 2010 (145)	29	24	5.3	-0.17 [-0.44, 0.10]
Feinglos et al, 2013 (148)	25	8	5.4	-0.59 [-0.80, -0.37]
Dall'Alba et al, 2013 (146)	23	21	5.1	-0.20 [-0.54, 0.144]
Ma et al, 2013 (127)	127	59	5.3	-2.00 [-2.28, -1.71]
McGeaoch et al, 2013 (128)	27	27	5.3	0.10 [-0.14, 0.34]
Li et al (A), 2016 (152)	159	79	5.2	-0.13 [-0.42, 0.17]
Li et al (B), 2016 (152)	152	76	5.2	-0.56 [-0.85, -0.26]
Abutair et al, 2016 (126)	18	18	5.3	-1.00 [-1.28, -0.72]
Subtotal (95% CI)			**84.4**	**-0.58 [-0.88, -0.28]**
Heterogeneity: Tau^2= 0.36, Chi^2= 212.00, df= 19 (P < 0.00001); I^2= 91%				
Test for overall effect: Z = 3.77 (P = 0.0002)				
T1DM				
Vaaler et al, 1986 (161)	28	28	4.4	-0.20 [-0.89, 0.49]
Ebeling et al, 1988 (147)	9	9	3.2	0.20 [-0.39, 0.79]
Vuorinen-Markkola et al, 1992 (163)	9	8	4.1	-0.10 [-0.85, 0.65]
Sels et al (A), 1993 (157)	13	13	3.9	-0.30 [-1.29, 0.69]
Subtotal (95% CI)			**15.6**	**-0.04 [-0.40, 0.32]**
Heterogeneity: Tau2= 0.00, Chi^2= 1.14, df= 3 (P= 0.77); I^2= 0%				
Test for overall effect: Z = 0.23 (P = 0.82)				
Total (95% CI)			**100.0**	**-0.50 [-0.77, -0.23]**
Heterogeneity: Tau^2= 0.34, Chi^2= 218.50, df= 23 (P < 0.00001); I^2= 89%				
Test for overall effect: Z = 3.61 (P = 0.0003)				
Test for subgroup differences: Chi^2= 5.02, df= 1 (P= 0.03); I^2= 80.1%				

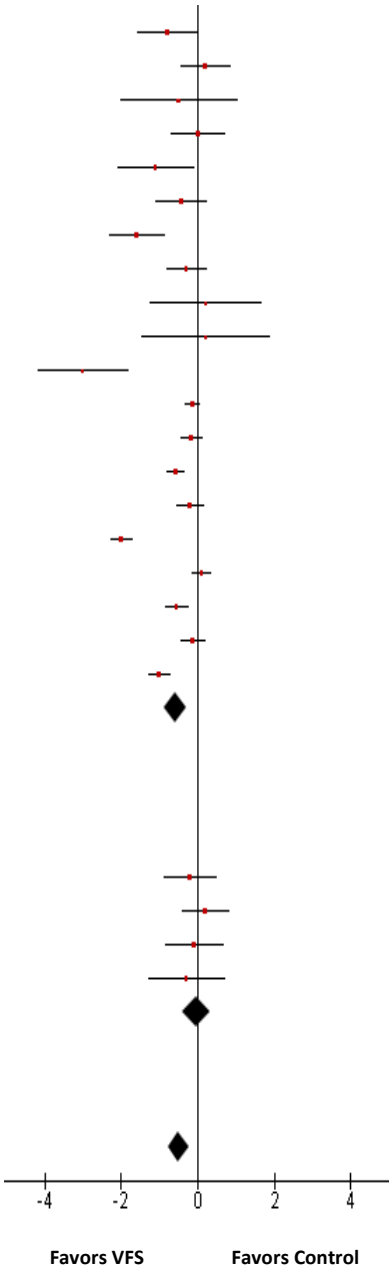


Figure 4.2. shows the effect of viscous fiber supplements on glycated hemoglobin (HbA1c). Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance P < 0.10. N = number of participants in each intervention group. VFS, viscous fibre supplementation; T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus

Subgroup and Study, Year (Reference)	VFS (N)	Control (N)	Weight %	Mean Difference (95% CI) in FBG, mmol/L
T2DM				
Aro et al, 1981 (141)	9	9	2.0	-1.20 [-3.35, 0.95]
Uusitupa et al, 1984 (160)	17	17	2.7	-0.80 [-2.42, 0.82]
Peterson et al, 1987 (155)	16	16	2.8	-0.20 [-1.79, 1.39]
Fuessl et al, 1987 (149)	18	18	3.7	-1.06 [-2.05, -0.07]
Holman et al, 1987 (150)	29	29	4.4	0.00 [-0.53, 0.53]
Niemi et al, 1988 (154)	18	18	3.3	0.50 [-0.72, 1.72]
Baker et al, 1988 (142)	15	15	2.0	0.90 [-1.26, 3.06]
Uusitupa et al, 1989 (159)	20	19	3.3	-1.30 [-2.54, -0.06]
Uusitupa et al, 1990 (158)	9	9	2.1	-1.60 [-3.71, 0.51]
Laajam et al, 1990 (151)	39	39	3.8	-1.80 [-2.74, -0.86]
Lalor et al, 1990 (86)	19	19	2.7	-1.90 [-3.55, -0.25]
Wolffenbuttel et al, 1990 (164)	12	12	2.2	0.20 [-1.81, 2.21]
Chuang et al, 1990 (144)	13	13	3.6	-0.94 [-2.02, 0.14]
Sels et al (B), 1993 (157)	12	12	2.2	0.20 [-1.81, 2.21]
Rodriguez-Moran, 1998 (156)	60	63	4.6	-2.17 [-2.54, 1.80]
Vuksan et al, 1999 (162)	11	11	2.6	-0.71 [-2.38, 0.96]
Chen et al, 2003 (143)	22	22	3.9	-2.30 [-3.19, -1.41]
Ziai et al, 2005 (165)	21	15	2.5	-4.98 [-6.79, -3.17]
Liatis et al, 2009 (153)	23	18	4.5	-0.65 [-1.17, -0.13]
Cugent-Anceau et al, 2010 (145)	29	24	4.2	-0.69 [-1.41, 0.03]
McGeaoch et al, 2013 (128)	27	27	4.5	0.30 [-0.20, 0.80]
Ma et al, 2013 (127)	127	59	4.6	-1.56 [-1.91, -1.21]
Dall'Alba et al, 2013 (146)	23	21	3.7	0.50 [-0.51, 1.51]
Feinglos et al, 2013 (148)	25	8	4.0	-1.97 [-2.77, -1.17]
Li et al (A), 2016 (152)	159	79	4.5	-0.19 [-0.68, 0.29]
Li et al (B), 2016 (152)	152	76	4.5	-0.09 [-0.54, 0.35]
Abutair at al, 2016 (126)	18	18	4.6	-2.08 [-2.50, -1.66
Subtotal (95% CI)			**93.6**	**-0.95 [-1.37, -0.53]**
Heterogeneity: Tau^2= 0.90, Chi^2= 198.93, df= 26 (P < 0.00001); I^2= 87%				
Test for overall effect: Z = 4.45 (P < 0.00001)				
T1DM				
Vaaler et al, 1986 (161)	28	28	3.2	0.30 [-1.03, 1.63]
Vuorinen-Markkola et al, 1992 (163)	9	8	1.4	-2.00 [-4.94, 0.94]
Sels et al (A), 1993 (157)	16	16	1.8	-0.90 [-3.25, 1.45]
Subtotal (95% CI)			**6.4**	**-0.35 [-1.57, 0.87]**
Heterogeneity: Tau^2= 0.18, Chi^2= 2.31, df= 2 (P= 0.32); I^2= 13%				
Test for overall effect: Z = 0.56 (P = 0.57)				
Total (95% CI)			**100.0**	**-0.93 [-1.33, -0.52]**
Heterogeneity: Tau^2= 0.89, Chi^2= 203.24, df= 29 (P < 0.00001); I^2= 86%				
Test for overall effect: Z = 4.49 (P < 0.0001)				
Test for subgroup differences: Chi^2= 0.84, df= 1 (P= 0.36); I^2= 0%				

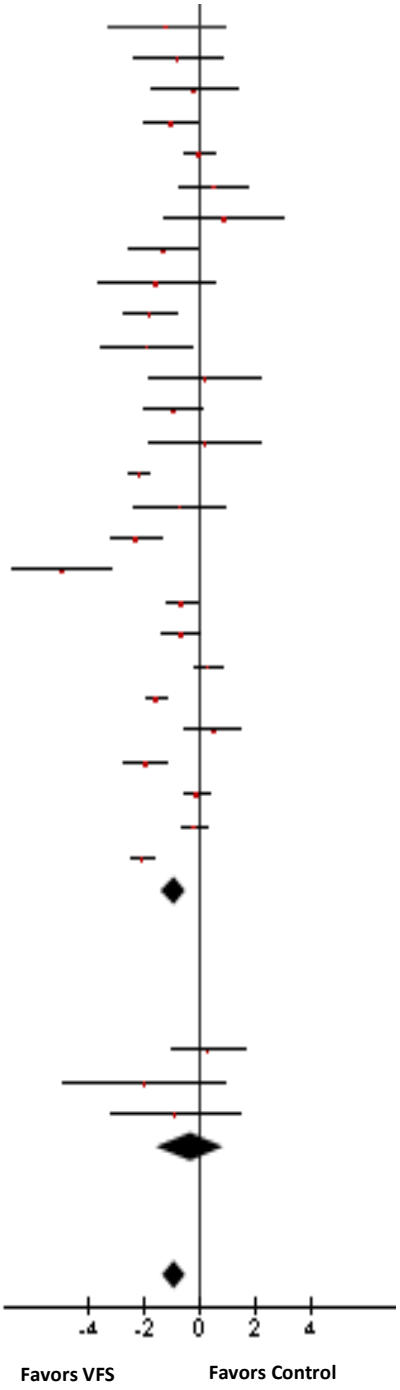


Figure 4.3. demonstrates the effect of viscous fibre supplementation on fasting glucose level in individuals with diabetes mellitus. Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance P < 0.10. N = number of participants in each intervention group. VFS, viscous fibre supplementation; T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus

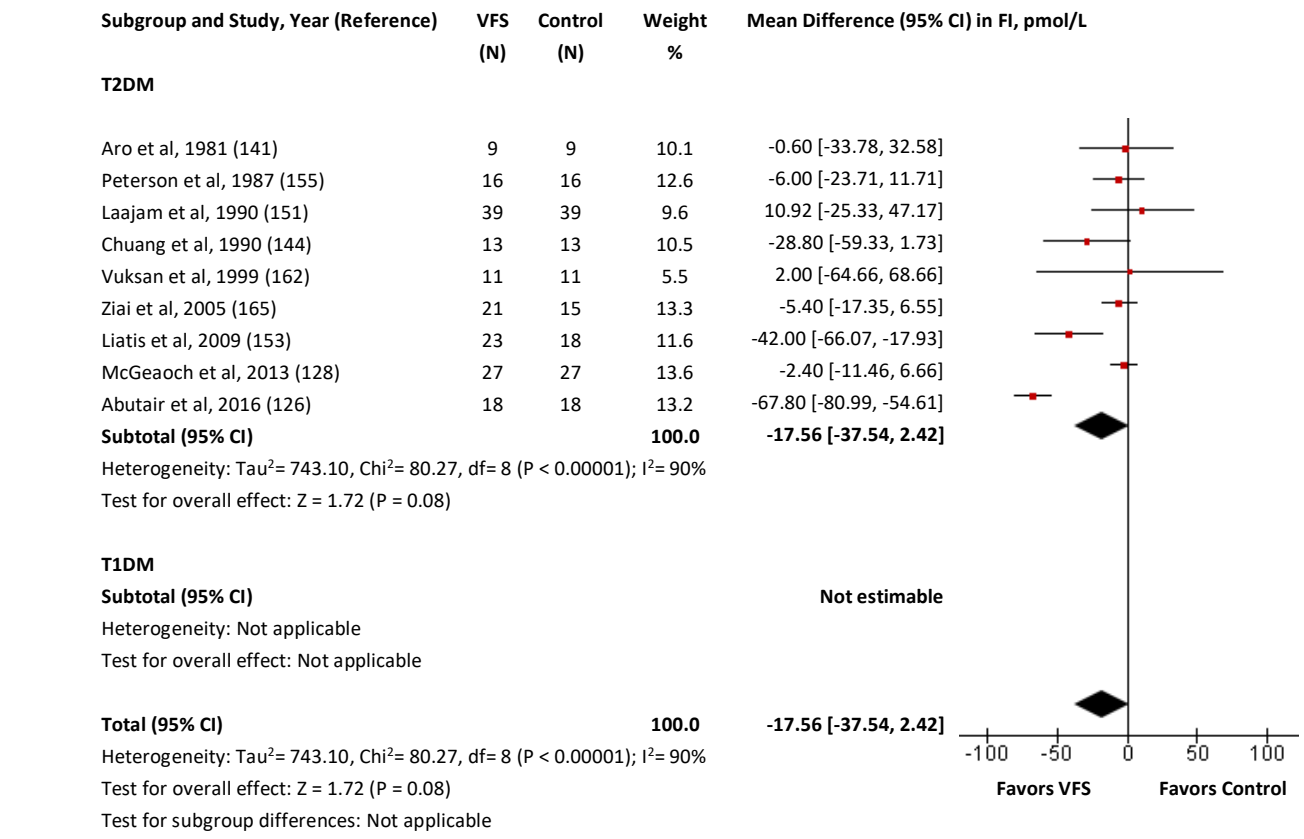


Figure 4.4. shows the impact of viscous fiber supplementation on fasting insulin in individuals with diabetes mellitus. Diamond represents the pooled effect estimate for overall analysis. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group. VFS, viscous fibre supplementation; T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus

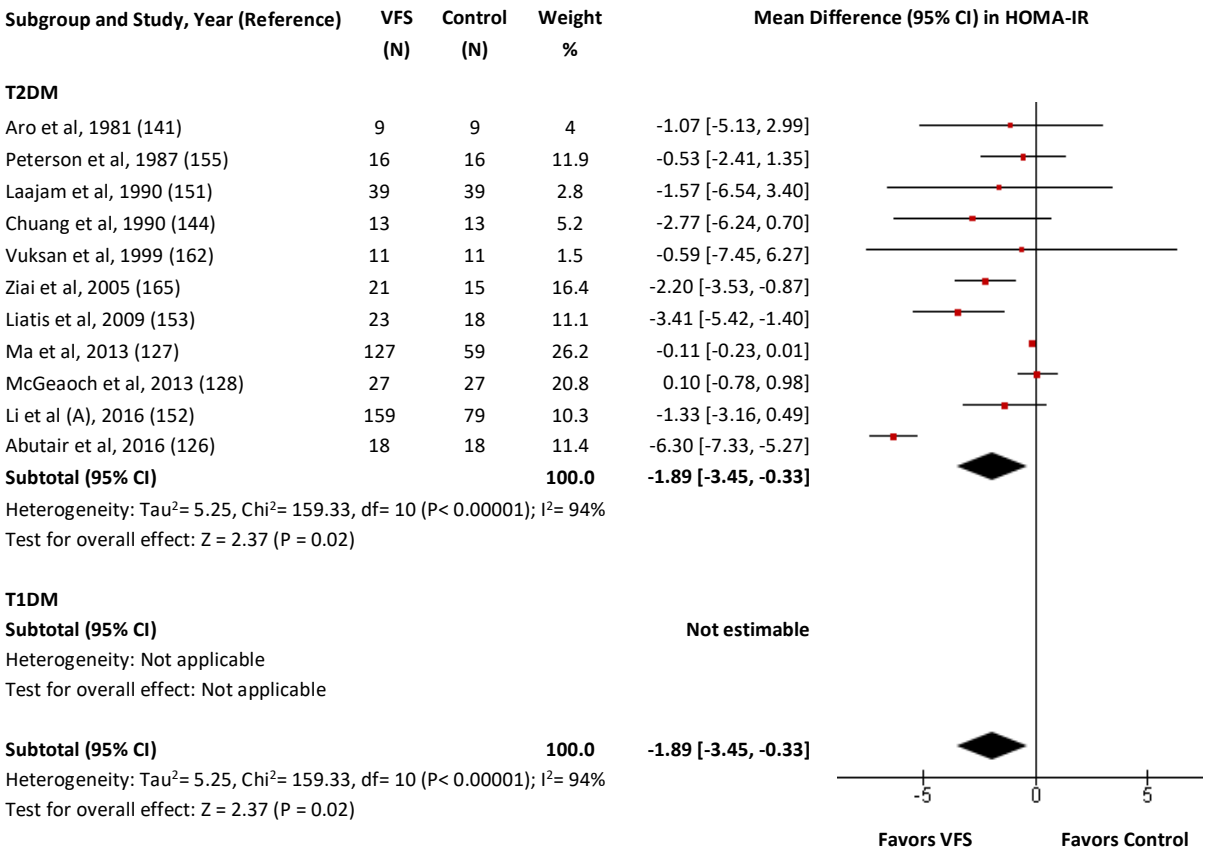


Figure 4.5. demonstrates the effect of viscous fiber supplementation on Homeostasis Model of Insulin Resistance (HOMA-IR) in individuals with diabetes mellitus. Diamond represents the pooled effect estimate for overall analysis. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group. VFS, viscous fibre supplementation; T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus

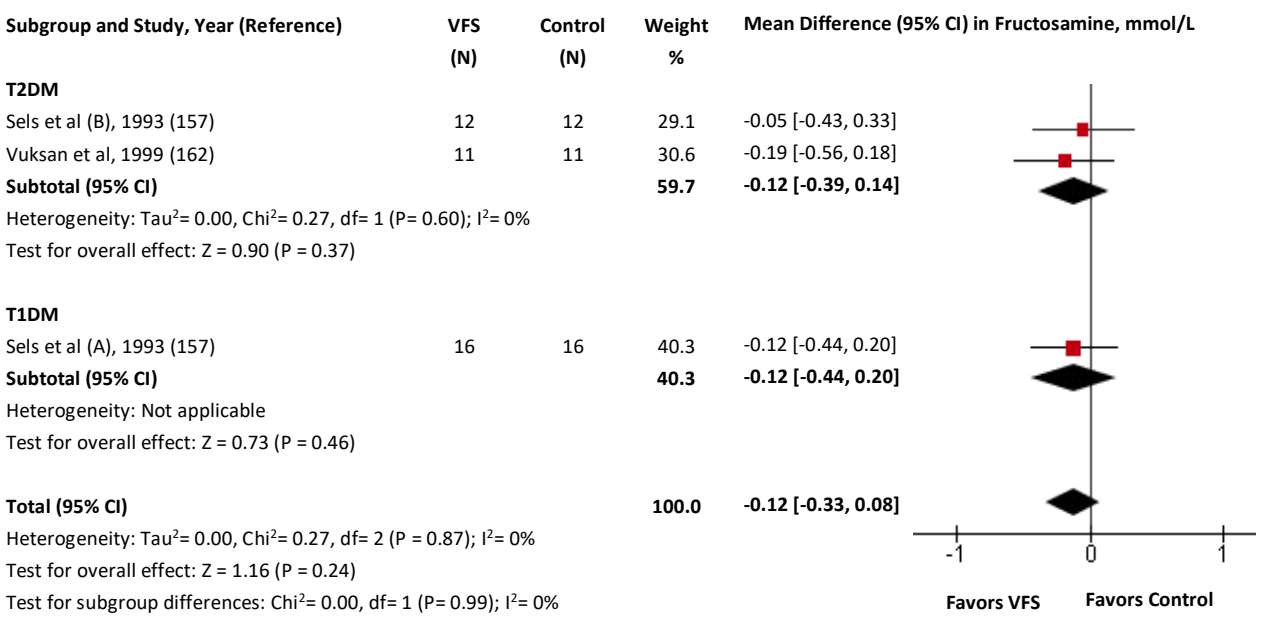


Figure 4.6. shows the effect of viscous fibre supplements on fructosamine in individuals with diabetes mellitus. Diamond represents the pooled effect estimate for overall analysis. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group. VFS, viscous fibre supplementation; T2DM, Type 2 diabetes mellitus; T1DM, Type 1 diabetes mellitus

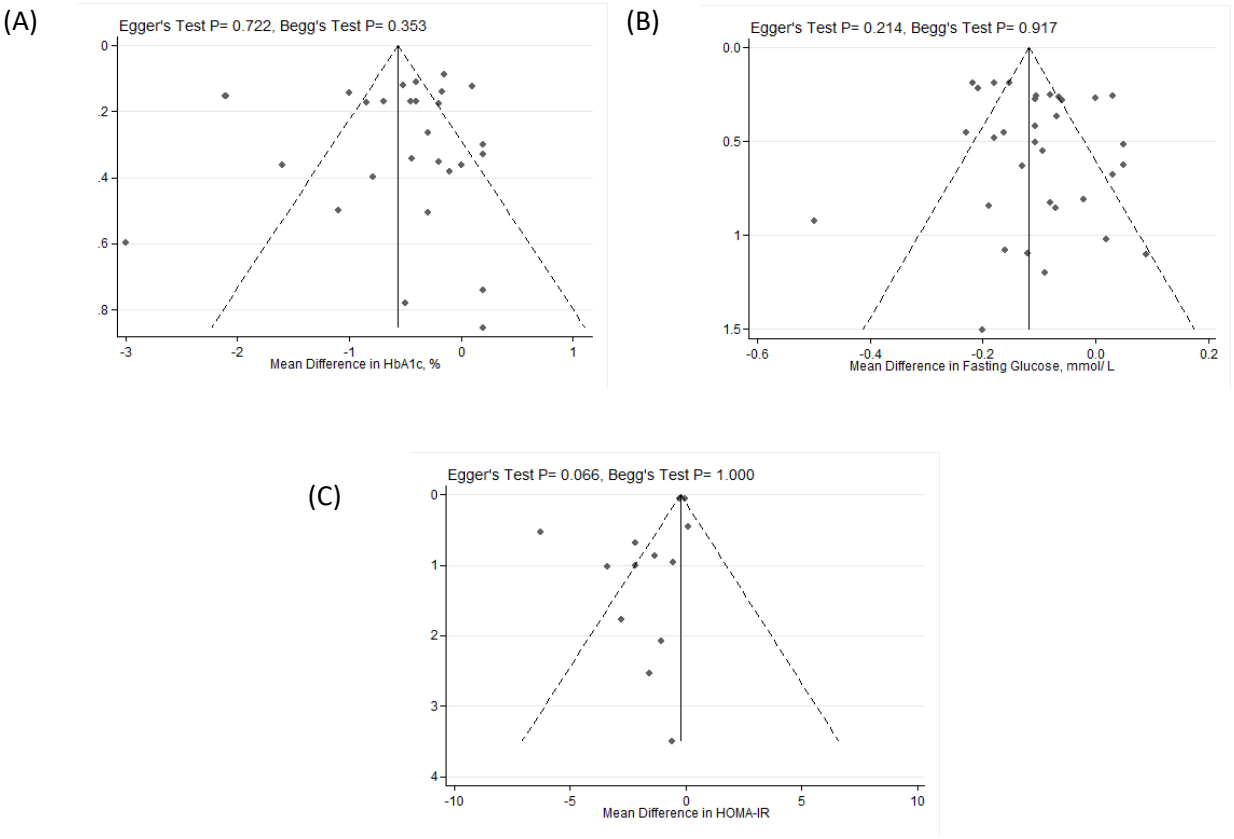


Figure 4.7. Publication bias funnel plots assessing publication bias and effect of small and/or imprecise study effects for (a) HbA1c, (b) fasting glucose, and (c) HOMA-IR. The horizontal line represents the pooled effect estimate expressed as the mean difference for each analysis. Diagonal lines represent the pseudo-95% CI. P-values are derived from quantitative assessment of publication bias by Egger and Begg tests.

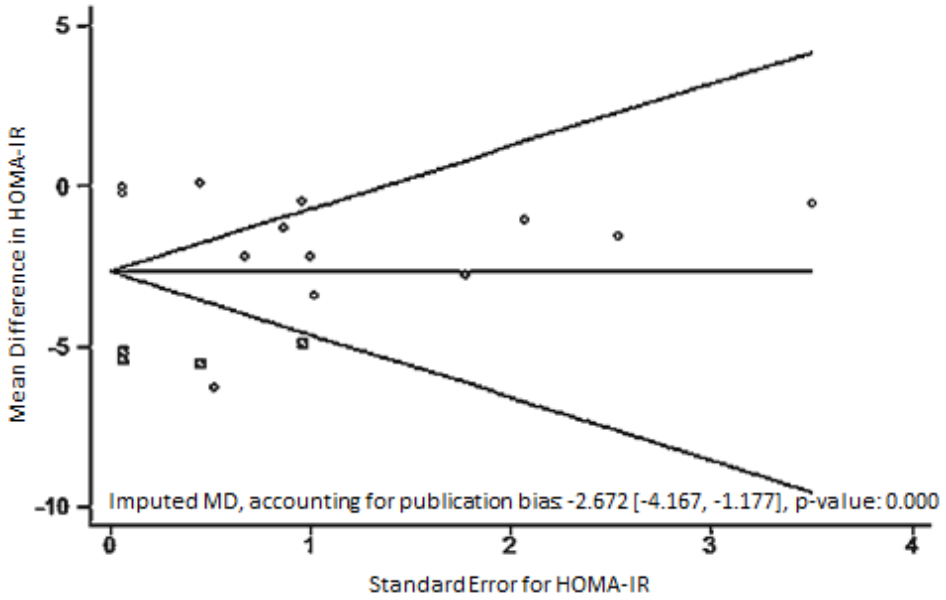


Figure 4.8. Trim and Fill funnel plot evaluating publication bias and effect of small study effects in randomized controlled trials investigating the effect of viscous fibre supplementation on HOMA-IR. The horizontal line represents the pooled effect estimate expressed as MD, the diagonal lines represent the pseudo-95 % CIs of the MD, the clear circles represent effect estimates for each included studies, and black squares represent imputed "missed" studies. Imputed MD, accounting for publication bias and p-values are provided where $p < 0.10$ is considered evidence of small-study effects.

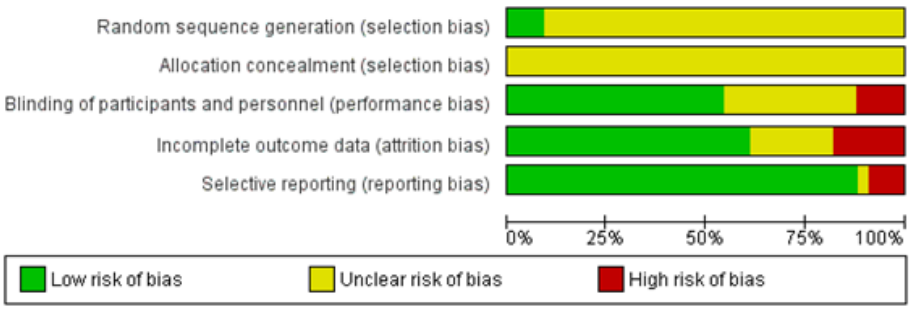


Figure 4.9. Risk of bias

Studies were rated “Low Risk of Bias” if the study design is unlikely to have little influence over the true outcome; “High Risk of Bias” if the design is likely to have an influential effect on the true outcome; “Unclear Risk of Bias” if insufficient information was given to assess risk.

Table 4.2. GRADE Assessment

Quality assessment							No of patients		Effect	Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VFS	P	Absolute (95% CI)	
HbA1c										
24	randomized trials	not serious	serious [a]	not serious	not serious	none [b]	852	591	MD= - 0.5 (-0.77, -0.23)	⊕⊕⊕◯ MODERATE
Fasting Glucose										
30	randomized trials	not serious	not serious [c]	not serious	not serious	none [d]	996	738	MD= -0.93 (-1.33 to -0.52)	⊕⊕⊕⊕ HIGH
Fasting Insulin										
9	randomized trials	not serious	not serious [e]	not serious	serious [f]	none [g]	177	166	MD= -17.56 (-37.54, 2.42)	⊕⊕⊕◯ MODERATE
Fructosamine										
3	randomized trials	not serious	not serious	not serious	very serious [h]	none [g]	39	39	MD= -0.12 (-0.33, 0.08)	⊕⊕◯◯ LOW
HOMA-IR										
11	randomized trials	not serious	serious [i]	not serious	not serious	none [j]	463	304	MD= -1.89 (-3.45, -0.33)	⊕⊕⊕◯ MODERATE

CI: Confidence interval; **MD:** Mean difference, **VFS:** Viscous Fibre Supplementation; **P:** Placebo

Explanations

a. Downgrade for serious inconsistency, as there was evidence of unexplained substantial inter-study heterogeneity (I2= 89%, P < 0.00001). Sensitivity analyses could not explain the heterogeneity.

b. Although visual inspection of funnel plots suggested major asymmetry in HbA1c, Begg's and Egger's tests were not significant for this analysis.

c. Downgrade for serious inconsistency, as there was evidence of substantial inter-study heterogeneity (I2= 89%, P < 0.00001). Subgroup analysis on fibre type partially explained the heterogeneity (P= 0.006).

d. Although visual inspection of funnel plots suggested minor asymmetry in fasting glucose, Begg's and Egger's tests were not significant for this analysis.

e. There was evidence of substantial inter-study heterogeneity (I2= 90%, P < 0.00001). The removal of Abutair et al., 2016 () during sensitivity analyses partially explained the heterogeneity (I2= 43%, P= 0.09).

f. The total number of patients exceeds the OIS criterion, and the pooled estimate of effect includes the clinical decision threshold for meaningful benefit which is equal to 5 pmol/L, but the 95% CI includes 0.

g. No downgrade for publication bias, as publication bias could not be assessed due to lack of power for assessing funnel plot asymmetry and small study effects (<10RCTs included in our meta-analysis)

h. Downgrade for serious imprecision due to the small study effects (<10 RCTs reported results on fructosamine including 39 individuals with diabetes mellitus). 95% CI includes 0, the total number of patients < the OIS criterion, and the pooled estimate of effect excludes the minimally important difference of 10% (MID=0.3) that was calculated using rule of thumb = 0.5 * SD of pooled effect estimate.

i. There was evidence of unexplained substantial inter-study heterogeneity (I2= 94%, P<0.00001). The systematic removal of studies during sensitivity analyses did not explained the heterogeneity.

j. Visual inspection of funnel plots suggested major asymmetry in HOMA-IR, Egger's test was significant for this analysis (P=0.066).

SUPPLEMENTARY MATERIALS

MEDLINE					
Searches	**Results**	**Searches**	**Results**	**Searches**	**Results**
1. exp Dietary Fiber/	16472	31. Locust bean gum.mp.	521	61. Type 1 Diabetes.tw.	32106
2. Dietary fiber*.tw.	5666	32. Carob*.mp.	374	62. T1DM.tw.	3258
3. Dietary fibre*.tw.	2597	33. Galactomannan*.mp.	1897	63. (Juvenile adj2 Diabetes).tw.	1797
4. Amorphophallus/	135	34. Supercol.mp.	2	64. Autoimmune Diabetes.tw.	2882
5. Amorphophallus.mp.	177	35. E410.mp.	7	65. Diabetes Mellitus, Type 2/	108946
6. Konjac*.mp.	399	36. Xanthan.mp.	1372	66. Diabetes type 2.tw.	986
7. Konjak*.mp.	30	37. Alginates/	9286	67. Non insulin dependent diabetes mellitus.tw.	6902
8. Konnyaku*.mp.	18	38. Algin*.mp.	16682	68. NIDDM.tw.	6969
9. Glucomannan*.mp.	739	39. Brown alga*.tw.	1873	69. Type II diabetes.tw.	7089
10. Psyllium/	608	40. Phaeophyta/	1689	70. Type 2 Diabetes.tw.	95204
11. Psyllium*.mp.	843	41. Phaeophy*.tw.	521	71. T2DM.tw.	12716
12. Ispaghula*.mp.	165	42. Kelp/	171	72. Hemoglobin A, Glycosylated/	29248
13. Plantago/	723	43. Kelp.mp.	753	73. Hemoglobin A1c.mp.	13448
14. plantago*.mp.	1289	44. Carrageenan/	7046	74. HbA1c.tw.	24239
15. Metamucil.mp.	53	45. Carrageen*.mp.	11395	75. (blood adj3 glucose).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	181569
16. Cyamopsis/	69	46. Chondrus/	61	76. Blood Glucose/	148572
17. Cyamopsis.mp.	144	47. Chondrus.mp.	189	77. Glyc?emi*.tw.	46158
18. Guar*.mp.	48009	48. Irish moss*.mp.	15	78. Hyperglyc?emi*.tw.	51426
19. Avena/	1921	49. Eucheuma.tw.	62	79. Hypoglyc?emi*.tw.	48962
20. Oat.tw.	2757	50. Agar/	9259	80. Fructosamine/	1491
21. Oats.tw.	6910	51. Agar*.mp.	105924	81. Fructosamine*.tw.	2155
22. Avena*.tw.	2133	52. Kanten.mp.	13	82. Fasting insulin.tw.	6889
23. Hordeum/	8288	53. Sepharose/	6712	83. exp Insulin Resistance/	68905
24. Hordeum.mp.	10212	54. Sepharose.mp.	30024	84. HOMA-IR.tw.	8333
25. Barley.mp.	15089	55. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54	271972	85. 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84	439724
26. beta-Glucans/	3310	56. Diabetes Mellitus, Type 1/	69448	86. 55 and 85	4831
27. Beta glucan*.mp.	6903	57. Diabetes type 1.tw.	657	87. exp Animals/ not Humans/	4390058
28. b-glucan*.mp.	19	58. Insulin dependent diabetes mellitus.tw.	15696	88. 86 not 87	3744
29. Pectins/	4672	59. IDDM.tw.	6871	89. randomized controlled trial.pt. or randomized.mp. or placebo.mp.	784859
30. Pectin*.mp.	11536	60. Type I diabetes.tw.	4835	90. 88 and 89	847

EMBASE					
Searches	**Results**	**Searches**	**Results**	**Searches**	**Results**
1. exp dietary fiber/	17830	31. Locust bean gum.mp.	495	61. Type I diabetes.tw.	6474
2. Dietary fiber*.tw.	6768	32. Carob*.mp.	525	62. Type 1 Diabetes.tw.	46015
3. Dietary fibre*.tw.	3310	33. Galactomannan*.mp.	3233	63. T1DM.tw.	6096
4. Amorphophallus/	174	34. Supercol.mp.	5	64. (Juvenile adj2 Diabetes).tw.	2433
5. Amorphophallus.mp.	271	35. E410.mp.	17	65. Autoimmune Diabetes.tw.	3490
6. Konjac*.mp.	515	36. xanthan/	2058	66. diabetes type 2.tw.	1730
7. Konjak*.mp.	32	37. Xanthan.mp.	2395	67. Non insulin dependent diabetes mellitus.tw.	7622
8. Konnyaku*.mp.	25	38. alginic acid/	17112	68. NIDDM.tw.	7863
9. Glucomannan*.mp.	826	39. Algin*.mp.	24055	69. Type II diabetes.tw.	10332
10. exp ispagula/	2596	40. brown alga/	1644	70. Type 2 Diabetes.tw.	135663
11. Psyllium*.mp.	973	41. Brown alga*.tw.	2086	71. T2DM.tw.	22266
12. Ispaghula*.mp.	205	42. Phaeophyta.mp.	155	72. hemoglobin A1c/	71641
13. Plantago/	902	43. kelp/	251	73. Hemoglobin A1c.mp.	75720
14. plantago*.mp.	2044	44. Kelp.mp.	736	74. HbA1c.tw.	49492
15. metamucil.mp.	417	45. carrageenan/	11897	75. (blood adj3 glucose).mp.	253961
16. Cyamopsis/	18	46. Carrageen*.mp.	15845	76. glucose blood level/	219288
17. Cyamopsis.mp.	160	47. Chondrus/	157	77. Glyc?emi*.tw.	68800
18. Guar*.mp.	62555	48. Chondrus.mp.	275	78. Hyperglyc?emi*.tw.	74382
19. Avena/	140	49. Irish moss*.mp.	15	79. Hypoglyc?emi*.tw.	74527
20. Avena*.tw.	2154	50. Eucheuma.tw.	72	80. fructosamine/	2535
21. Oat.tw.	8230	51. agar/	25903	81. Fructosamine*.tw.	2645
22. Oats.tw.	2584	52. Agar*.mp.	123727	82. Fasting insulin.tw.	9706
23. Hordeum/	1277	53. Kanten.mp.	13	83. insulin resistance/	101899
24. Hordeum.mp.	4461	54. sepharose/	6046	84. HOMA-IR.tw.	14301
25. Barley.mp.	15733	55. Sepharose.mp.	27715	85. 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84	901075
26. beta glucan/	4151	56. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55	323743	86. 56 and 85	8642
27. Beta glucan*.mp.	8116	57. diabetes mellitus/	488866	87. exp Animals/ not Humans/	10805224
28. b-glucan*.mp.	150	58. diabetes type 1.tw.	1105	88. 86 not 87	4344
29. pectin/	7267	59. Insulin dependent diabetes mellitus.tw.	17319	89. random:.tw. or placebo:.mp. or double-blind:.tw.	1422737
30. Pectin*.mp.	13555	60. IDDM.tw.	7653	90. 88 and 89	593

COCHRANE					
Searches	**Results**	**Searches**	**Results**	**Searches**	**Results**
1. exp Dietary Fiber/	1656	27. Locust bean gum. ti,ab,hw.	19	53. (Juvenile adj2 Diabetes). ti,ab,hw.	84
2. Dietary fiber*.ti,ab,hw.	2136	28. Carob*.ti,ab,hw.	21	54. Autoimmune diabetes. ti,ab,hw.	48
3. Dietary fibre*.ti,ab,hw.	382	29. Galactomannan*.ti,ab,hw.	50	55. Diabetes Mellitus, Type 2/	10118
4. Amorphophallus/	3	30. Xanthan. ti,ab,hw.	42	56. Diabetes type 2. ti,ab,hw.	129
5. Amorphophallus. ti,ab,hw.	7	31. Alginates/	213	57. Non Insulin dependent diabetes. ti,ab,hw.	8615
6. Konjac*.ti,ab,hw.	28	32. Algin*.ti,ab,hw.	536	58. NIDDM. ti,ab,hw.	974
7. Glucomannan*.ti,ab,hw.	62	33. Brown alga*.ti,ab,hw.	11	59. Type II diabetes. ti,ab,hw.	721
8. Psyllium/	127	34. Phaeophyta/	6	60. Type 2 diabetes. ti,ab,hw.	14113
9. Psyllium. ti,ab,hw.	218	35. Phaeophyta*.ti,ab,hw.	6	61. T2DM. ti,ab,hw.	2564
10. Ispaghula*.ti,ab,hw.	56	36. Kelp/	1	62. Adult-onset diabetes. ti,ab,hw.	22
11. Plantago/	30	37. Kelp.ti,ab,hw.	5	63. Hemoglobin A, Glycosylated/	4405
12. Plantago*.ti,ab,hw.	67	38. Carrageenan/	30	64. HbA1c. ti,ab,hw.	5939
13. Metamucil. ti,ab,hw.	7	39. Carrageen*.ti,ab,hw.	67	65. Hemoglobin A1c. ti,ab,hw.	6308
14. Guar*.ti,ab,hw.	1720	40. Agar/	18	66. (Blood adj3 glucose). ti,ab,hw.	23025
15. Cyamopsis/	1	41. Agar*.ti,ab,hw.	685	67. Blood Glucose/	13126
16. cyamopsis. ti,ab,hw.	2	42. Kanten. ti,ab,hw.	1	68. Glyc?emi*.ti,ab,hw.	10160
17. Avena. ti,ab,hw.	164	43. Sepharose/	6	69. Hyperglyc?emi*.ti,ab,hw.	4951
18. Oat. ti,ab,hw.	550	44. Sepharose. ti,ab,hw.	26	70. Hypoglyc?emi*.ti,ab,hw.	10891
19. Oats. ti,ab,hw.	141	45. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44	6354	71. Fructosamine/	145
20. Hordeum/	64	46. Diabetes Mellitus, Type 1/	3387	72. Fructosamine*.ti,ab,hw.	389
21. Hordeum. ti,ab,hw.	73	47. diabetes type 1. ti,ab,hw.	47	73. Fasting insulin. ti,ab,hw.	1165
22. Barley. ti,ab,hw.	163	48. Insulin dependent diabetes. Ti,ab,hw.	10793	74. Insulin Resistance/	3025
23. beta-Glucans/	124	49. IDDM. ti,ab,hw.	532	75. HOMA_IR. ti,ab,hw.	29
24. Beta glucan*.ti,ab,hw.	279	50. Type I diabetes. ti,ab,hw.	251	76. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75	41932
25. Pectins/	102	51. Type 1 diabetes. ti,ab,hw.	2849	77. 45 and 76	986
26. Pectin*.ti,ab,hw.	226	52. T1DM. ti,ab,hw.	350		

Supplementary Table 4.1. Search Strategy. For all databases, searches were performed through February 26, 2016 and updated May 1, 2017.

No.	Inclusion Criteria
1	Randomized
2	Controlled
3	≥ 3 weeks
4	Viscos Fibre Supplementation (guar gum, β-glucan, psyllium, Konjac, pectin, xanthan gum, locust bean gum, alginate, or agar)
5	Glycemic control endpoints (HbA1c, fasting glucose, fasting insulin, fructosamine, HOMA-IR)
6	T1DM or T2DM

Supplementary Table 4.2. Eligibility Criteria

Reference	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting
Abutair et al, 2016	Unclear	Unclear	Unclear	Low	Low
Aro et al, 1981	Unclear	Unclear	Low	High	Low
Chen et al, 2003	Unclear	Unclear	Low	Low	Low
Chuang et al, 1992	Unclear	Unclear	Low	Unclear	Low
Cugnet-Anceau et al, 2010	Unclear	Unclear	Low	High	Low
Dall'Alba et al, 2013	Unclear	Unclear	High	Low	Low
Ebeling et al, 1988	Unclear	Unclear	Low	Low	Low
Fuessl et al, 1987	Unclear	Unclear	Low	Low	Low
Holman et al, 1987	Unclear	Unclear	Unclear	Low	Low
Lalor et al, 1990	Unclear	Unclear	Low	Unclear	Low
Li et al (A), 2016	Unclear	Unclear	Unclear	Low	Low
Li et al (B), 2016	Unclear	Unclear	Unclear	Low	High
Liatis et al, 2009	Low	Unclear	Low	Unclear	Low
Ma et al, 2013	Low	Unclear	Unclear	Low	Low
McGeoch et al, 2013	Unclear	Unclear	High	Low	Low
Peterson et al, 1987	Low	Unclear	Unclear	High	Low
Rodriguez-Moran et al, 1998	Unclear	Unclear	Low	Low	Low
Uusitupa et al, 1990	Unclear	Unclear	Low	Low	High
Uusitupa et al, 1989	Unclear	Unclear	Low	Low	Low
Uusitupa et al, 1984	Unclear	Unclear	Low	Low	Low
Vaaler et al, 1986	Unclear	Unclear	Unclear	Low	Low
Vuksan et al, 1999	Unclear	Unclear	Low	Low	Low
Vuorinen-Markkola et al, 1992	Unclear	Unclear	Low	Low	Low
Wolffenbuttel et al, 1992	Unclear	Unclear	High	Low	Low
Ziai et al, 2005	Unclear	Unclear	Low	High	Low
Baker et al, 1988	Unclear	Unclear	Unclear	Unclear	Low
Laajam et al, 1990	Unclear	Unclear	Low	Unclear	Low
Niemi et al, 1988	Unclear	Unclear	Low	Unclear	Low
Sels et al (A), 1993	Unclear	Unclear	Unclear	Low	Low
Sels et al (B), 1993	Unclear	Unclear	Unclear	Low	Low
Feinglos et al, 2013	Unclear	Unclear	Low	Unclear	Low

Supplementary Table 4.3. Cochrane risk of bias tool.

A. HbA1c

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P*-value
Viscous Fiber Dose (g/d)	28	1212	0.027 [-0.017, 0.071]	92.06	0.216
Duration (wk)	28	1212	-0.000 [-0.024, 0.023]	92.12	0.969
Baseline HbA1c (%)	27	1183	-0.139 [-0.310, 0.032]	86.62	0.107

B. Fasting Glucose

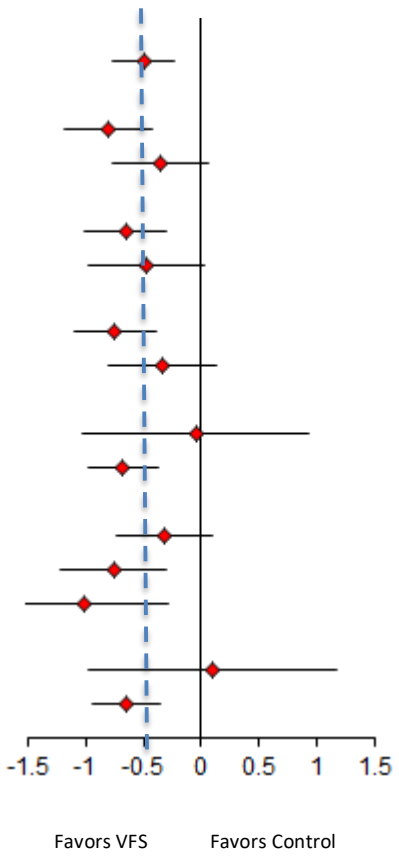
Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P*-value
Viscous Fiber Dose (g/d)	34	1419	0.015 [-0.041, 0.072]	82.39	0.583
Duration (wk)	34	1419	0.006 [-0.022, 0.035]	82.15	0.648
Baseline Fasting Glucose (mmol/L)	33	1390	-0.223 [-0.516, 0.069]	76.49	0.129

C. HOMA-IR

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P*-value
Viscous Fiber Dose (g/d)	13	652	-0.052 [-0.289, 0.184]	90.55	0.636
Duration (wk)	13	652	-0.016 [-0.122, 0.090]	92.77	0.742
Baseline HOMA-IR	12	643	-0.415 [-0.669, -0.161]	71.90	0.004

Supplementary Table 4.4. Continuous *a priori* subgroup analyses. β is the slope derived from meta-regression analyses and represents the treatment effect of viscous fiber for each subgroup for A. HbA1c, B. Fasting Glucose and C. HOMA-IR. The residual I^2 value indicates heterogeneity unexplained by the subgroup and is reported as a percent value, where $I^2 \geq 50\%$ indicated "substantial" heterogeneity. P-value significance for heterogeneity was set as $P < 0.10$. N = number of participants in each treatment group.

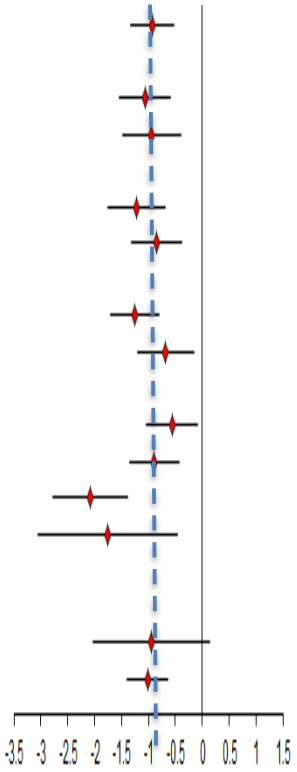
Subgroup	Level	No. of Trials	N	Within Subgroup	Mean Difference [95% CI] in HbA1c (%)		Between Subgroups	Residual I^2 (%)	P-Value
Total		28	1212	-0.50 [-0.77, -0.23]					
Dose	< 11.2	13	870	-0.803 [-1.187, -0.419]			0.447 [-0.116, 1.009]	92.01	0.115
(g/d)	≥ 11.2	15	342	-0.356 [-0.767, 0.054]					
Duration	< 12	18	832	-0.654 [-1.013, -0.295]			0.178 [-0.445, 0.801]	92.13	0.563
(wk)	≥ 12	10	380	-0.476 [-0.985, 0.033]					
Study Design	Parallel	16	981	-0.746 [-1.101, -0.390]			0.414 [-0.175, 1.003]	91.37	0.16
	Crossover	12	231	-0.332 [-0.801, 0.138]					
Baseline HbA1c	≤ 7	2	71	-0.047 [-1.027, 0.932]			-0.632 [-1.658, 0.394]	91.35	0.216
(%)	> 7	26	1141	-0.680 [-0.984, -0.375]					
Fiber Type	Guar Gum	15	334	-0.327 [-0.743, 0.089]		1 vs 2	-0.427 [-1.047, 0.193]		
	B-glucan	9	773	-0.754 [-1.214, -0.294]		1 vs 3	-0.685 [-1.521, 0.151]	92.17	0.181
	Psyllium	4	105	-1.012 [-1.738, -0.287]		2 vs 3	0.258 [-0.601, 1.117]		
Matrix	Capsule/ Tablet	2	59	0.102 [-0.976, 1.180]			-0.749 [-1.867, 0.369]	91.95	0.18
	Other	26	1153	-0.647 [-0.942, -0.352]					



Supplementary Figure 4.1. (A) A *priori* subgroup analyses using dichotomous predictors to assess the effect of viscous fibre supplementation on HbA1c.

*Studies that included multiple comparisons were separated for subgroup analysis. Point estimates for each subgroup level (diamonds) represent the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup. Subgroup effects were assessed by meta-regression analyses where $p < 0.05$ is significant. VFS, viscous fibre supplementation

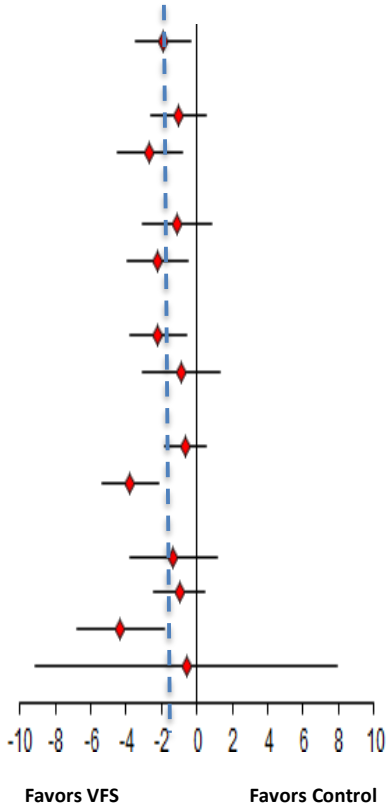
Subgroup	Level	No. of Trials	N	Within Subgroup	Between Subgroups	Residual I^2 (%)	P-Value
Total		34	1419	-0.93 [-1.33, -0.52]			
Dose (g/d)	< 12.4	17	968	-1.064 [-1.542, -0.586]	0.125 [-0.600, 0.850]	82.52	0.728
	≥ 12.4	17	451	-0.939 [-1.484, -0.394]			
Duration (wk)	< 8	17	764	-1.222 [-1.751, -0.693]	0.379 [-0.330, 1.087]	80.22	0.284
	≥ 8	17	655	-0.843 [-1.315, -0.371]			
Study Design	Parallel	17	1104	-1.253 [-1.701, -0.804]	0.573 [-0.120, 1.266]	77.5	0.102
	Crossover	17	315	-0.680 [-1.208, -0.152]			
Fiber Type	Guar Gum	18	385	-0.560 [-1.037, -0.081]	1 vs 2 -0.331 [-0.1000, 0.337]		
	B-glucan	9	773	-0.890 [-1.357, -0.423]	1 vs 3 -1.519 [-2.362, -0.675]		
	Psyllium	5	228	-2.078 [-2.773, -1.382]	1 vs 4 -1.191 [-2.574, 0.192]	71.85	0.006
	Konjac	2	33	-1.750 [-3.048, -0.453]	2 vs 3 1.187 [0.350, 2.025]		
					2 vs 4 0.860 [-0.519, 2.239]		
					3 vs 4 -0.327 [-1.800, 1.145]		
Matrix	Capsule/ Tablet	4	100	-0.942 [-2.027, 0.143]	-0.076 [-1.227, 1.074]	81.88	0.894
	Other	30	1319	-1.018 [-1.400, -0.636]			



Supplementary Figure 4.1. (B) A *priori* subgroup analyses using dichotomous predictors to assess the effect of viscous fibre supplementation on fasting glucose.

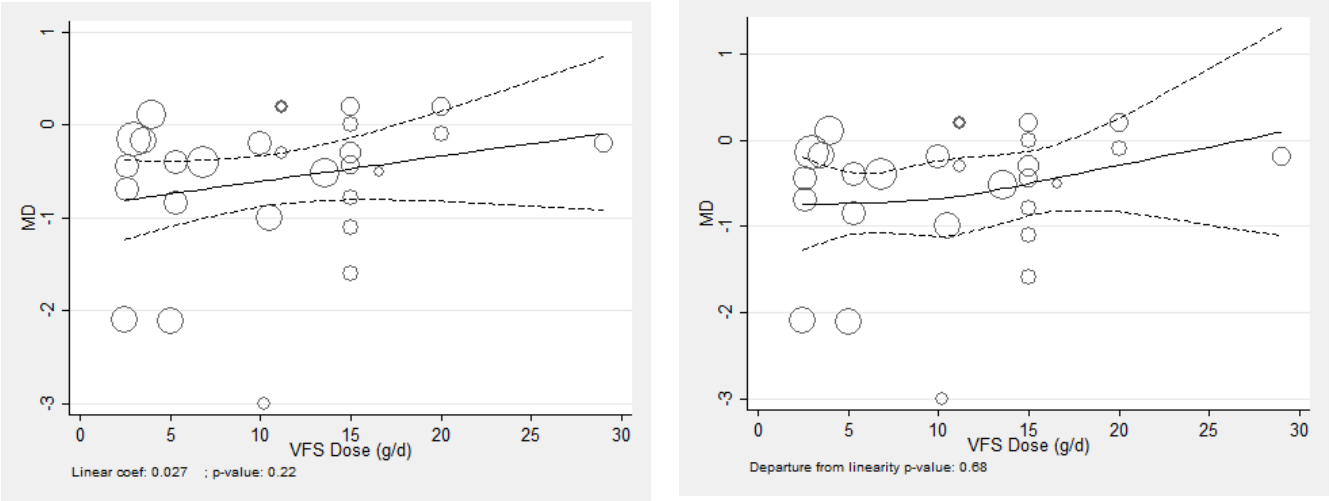
*Studies that included multiple comparisons were separated for subgroup analysis. Point estimates for each subgroup level (diamonds) represent the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup. Subgroup effects were assessed by meta-regression analyses where $p < 0.05$ is significant. VFS, viscous fibre supplementation

Subgroup	Level	No. of Trials	N	Within Subgroup	Between Subgroups	Residual I^2 (%)	P-Value
Total		13	652	-1.89 [3.45, -0.33]			
Dose (g/d)	< 10.2	6	492	-1.042 [-2.653, 0.568]	-1.627 [-4.090, 0.836]	83.18	0.174
	≥ 10.2	7	160	-2.670 [-4.533, -0.806]			
Duration (wk)	< 6	6	396	-1.137 [-3.120, 0.846]	-1.084 [-3.735, 1.566]	89.81	0.387
	≥ 6	7	256	-2.221 [-3.980, -0.463]			
Study Design	Parallel	7	263	-2.193 [-3.808, -0.577]	1.304 [-1.448, 4.056]	93.44	0.319
	Crossover	6	389	-0.890 [-3.117, 1.340]			
Baseline HOMA-IR	< 5.44	6	384	-0.633 [-1.808, 0.543]	-3.138 [-5.142, -1.134]	73.72	0.006
	≥ 5.44	6	259	-3.770 [-5.390, -2.147]			
Fiber Type	Guar Gum	4	77	-1.323 [-3.832, 1.186]	1 vs 2 0.327 [-2.567, 3.220]	80.48	0.134
	B-glucan	6	492	-0.996 [-2.436, 0.444]	1 vs 3 -3.006 [-6.523, 0.510]		
	Psyllium	2	72	-4.329 [-6.793, -1.865]	1 vs 4 0.733 [-8.172, 9.637]		
	Konjac	1	11	-0.590 [-9.134, 7.954]	2 vs 3 3.333 [0.480, 6.187]		
					2 vs 4 -0.406 [-9.070, 8.259]		
					3 vs 4 -3.739 [-12.631, 5.153]		

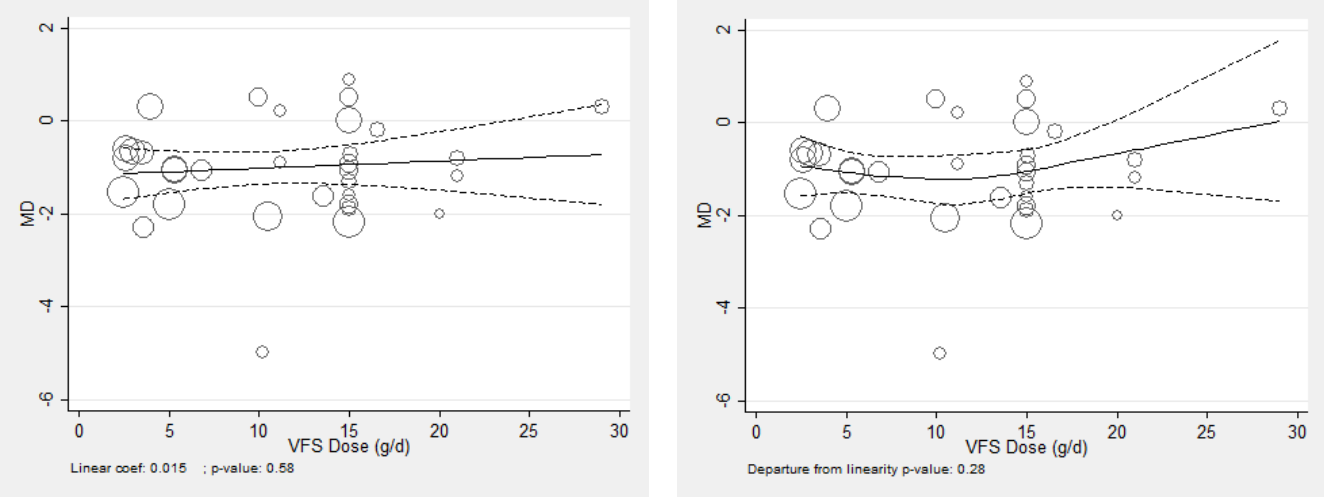


Supplementary Figure 4.1. (C) A *priori* subgroup analyses using dichotomous predictors to assess the effect of viscous fibre supplementation on HOMA-IR.

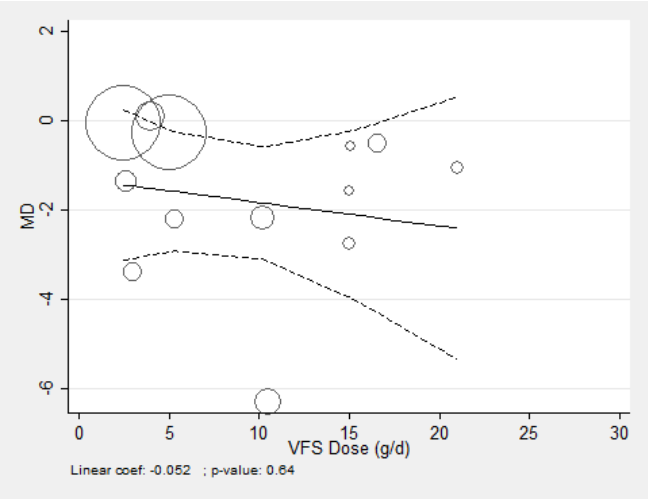
*Studies that included multiple comparisons were separated for subgroup analysis. Point estimates for each subgroup level (diamonds) represent the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup. Subgroup effects were assessed by meta-regression analyses where $p < 0.05$ is significant. VFS, viscous fibre supplementation

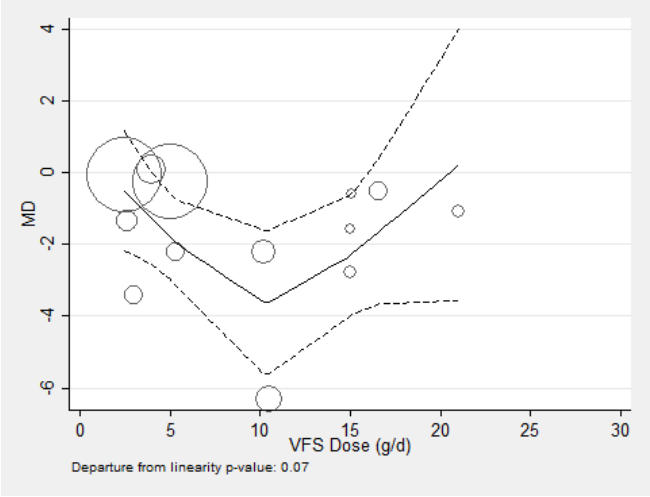


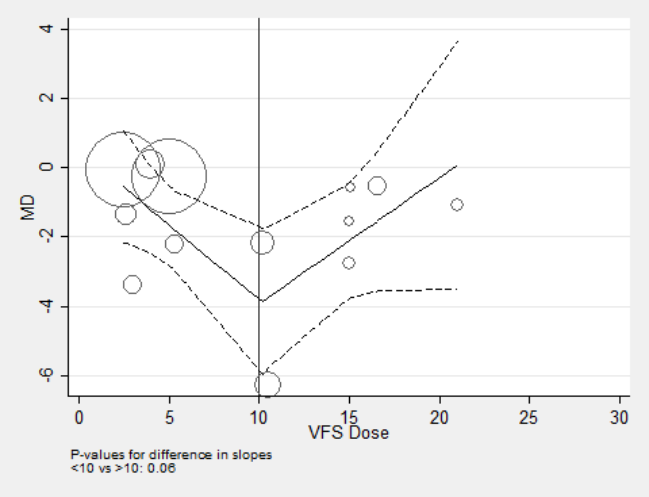
Supplementary figure 4.2 (A1 & A2). Linear and non-linear VFS dose-response analyses on HbA1c



Supplementary figure 4.2 (B1 & B2). Linear and non-linear VFS dose-response analyses on fasting glucose







Supplementary figure 4.2 (C1, C2 & C3). Linear, non-linear, and binary VFS dose-response analyses on HOMA-IR

CHAPTER V- EFFECT OF NON-VISCOUS FIBRE SUPPLEMENTATION ON GLYCEMIC CONTROL IN INDIVIDUALS WITH DIABETES MELLITUS: A SYSTEMATIC REVIEW AND META ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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Abstract

Background: The prevalence of diabetes mellitus (DM) is a major global health concern. With nutrition at the core of its management, rigorous dietary guidelines are needed. Although current recommendations for individuals with DM include increasing total dietary fibre for glycemic control, the available evidence on the benefits of non-viscous fibre supplementation (NVFS) is still inconsistent.

Objective: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted to investigate the effect of non-viscous fibre supplementation from soluble and insoluble sources on glycemic control outcomes in individuals with DM.

Methods: MEDLINE, EMBASE, and the Cochrane Library for Registered Controlled Trials were searched (through Dec.4, 2017). We included RCTs with a duration ≥ 3 weeks that assessed the effect of non-viscous fibre supplementation (inulin, fructo-oligosaccharides (FOS), wheat bran, wheat rice, cellulose, or

resistant starch (RS)) compared to adequate control (not active and does not contain VFS- high vs. low wheat ran diet were accepted), on HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine in individuals with type-1 or type-2 DM. Data were pooled using the generic inverse variance method with random effects models and expressed as mean differences (MD) with 95% confidence intervals (CI). Heterogeneity was assessed using Cochran Q-statistic and quantified using I^2. The quality of the evidence was assessed using GRADE.

Results: 13 studies (n=545 with T2DM) met eligibility criteria (12 HbA1c (n=531); 13 fasting glucose (n=545); 6 fasting insulin (n= 188); 1 fructosamine (n=10); and 6 HOMA-IR (n=188)). Pooled analyses found a median dose of [10 g/day] non-viscous fibre supplementation for a median duration of eight weeks significantly reduced HbA1c (MD= -0.25% [95% CI: -0.48, -0.03], P= 0.03), fasting glucose (MD= -0.54 mmol/L [95% CI: -0.79, -0.30], P < 0.0001), and fasting insulin (MD= -13.98 pmol/L [95% Cl: -24.91, -3.05], P=0.01), along with substantial unexplained inter-study heterogeneity. The quality of reported evidence is low/very low; therefore, results need to be interpreted with caution. Studies with higher quality are needed/ required.

Conclusion: Non-viscous fibre supplementation significantly improved glycemic outcomes in individuals with T2DM. Hence, incorporation of non-viscous fibre supplementation in diet for T2DM patients might be recommended. Inclusion of low quality studies appears to have an impact on the overall effect; therefore, results should be interpreted with caution.

Trial registration number: NCT03259724

Introduction

Diabetes mellitus is exponentially increasing worldwide (1, 172). Increased consumption of dietary fibre has been repeatedly emphasized as an integral component of lifestyle modification for individuals with

diabetes (11, 12). Despite the general consensus upon the importance of fibre in glucose modification, the specific mechanism and type of fibre is not yet clear. Along with some other research groups, we believe that efficacy of fibre fundamentally depends on quantity and viscosity (65, 80). Interestingly, viscosity may transcend/surpass quantity in relation to fibre efficacy in gram per gram studies (66). Conversely, other researchers believe that the effect of non-viscous fibre forms, mostly insoluble, at metabolic level is greater (116). From a historical perspective, wheat bran was considered an important fibre source for modifying glucose tolerance due to earlier evidence from Great Britain showing that overall mortality rate decreased during the Second World War when the wheat extraction rate was increased (173). Weicket et al. indicated a significant improvement in body glucose disposal followed by an 8% improvement in insulin sensitivity in healthy subjects (174). In support, the consumption of whole-grain and bran was inversely associated with all-cause and CVD-specific mortality in females with T2DM (175). The literature has discrepant data on the effect of non-viscous fibre supplementation (NVFS) on glycemic control in diabetes. Therefore, the objective of this systematic review and meta-analysis of RCTs is to assess the evidence on the effect of non-viscous fibre supplementation (NVFS) on HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine in diabetes.

METHODS

Protocol and registration

The Cochrane Handbook for Systematic Reviews of Interventions was used to plan and conduct this study (133). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) was used to report results (134). The review protocol is available online at ClinicalTrials.gov (registration number: NCT03259724).

Search strategy and data sources

MEDLINE, EMBASE, and the Cochrane Library for Registered Controlled Trials were searched through Dec.4, 2017, to identify RCTs that investigate the effect of non-viscous fibre supplementations on glycemic control endpoints (HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine) in individuals with T1DM and T2DM (135, 136). The search strategy is presented in the **Supplementary Table 5.1.** A manual search of the references of included trials was done to supplement the electronic search. No language restrictions were applied.

Study eligibility

According to our inclusion and exclusion criteria presented in **Supplementary Table 5.2.,** we included RCTs ≥ 3 weeks that investigated the effect of non-viscous fibre supplementation (cellulose, wheat bran, rice bran, corn bran, resistant starch, fructo-oligosaccharide (FOS), inulin, wheat dextrin, and cereal fibre) compared to adequate placebo, fibre-free diet, fibre with decreased content of fibre , on at least one of the glycemic measures: HbA1c, fasting glucose, fasting insulin, HOMA-IR, and fructosamine. The most recent publication was used when multi publications were found, and the

one with extra relevant data was used for comparison. Glycemic control endpoints were determined according to Diabetes Canada Clinical Practice Guidelines (14).

Data extraction and quality assessment

Using a standardized pro-forma, two independent reviewers (RK & NM) reviewed articles that met eligibility criteria in full and extracted relevant data on study characteristics and endpoints. Study characteristics included: non-viscous fibre type, study design (cross-over or parallel), participant characteristics, comparator, non-viscous fibre dose, duration, background diet, compliance measures, statistical analysis, and funding sources. Disagreement between reviewers was resolved by a third impartial reviewer (AK). The mean and standard deviation (SD) values were extracted for HbA1c, 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% CI or SEM) using standard formulae(133). When change from baseline values were not reported, the mean and SD values for baseline and end values were used to calculate change from baseline values for both control and intervention groups. In one case (115), mean and SD were imputed from median (25^{th}, 75^{th} percentiles) using Hozo's formula SD = range/4 (176). Authors were contacted for additional information where necessary.

The Cochrane Risk of Bias Tool was used to assess the study risk of bias (133). Domains of bias assessed include: sequence generation, allocation concealment, blinding of participants, personnel, and outcome assessors, incomplete outcome data, and selective outcome reporting. The study was considered 'unclear risk of bias' when insufficient information was provided to permit judgment, 'low risk of bias' when the flaw of the study was most likely to not affect the true outcome and 'high risk

of bias' when the study flaw was most likely to affect the true outcome. All disagreements on Risk of Bias Tool were resolved by consensus.

Data management 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 (V.14, College Station, USA) for subgroup analyses. The difference between the change from baseline values for the intervention and control arms was derived from each trial for the end points of HbA1c, fasting glucose, fasting insulin, fructosamine, and HOMA-IR. When HOMA-IR was not reported, it was calculated using the equation (HOMA-IR= fasting insulin (microU/L) x fasting glucose (mmol/L)/22.5) (137). A previously developed formula was used to calculate SD for calculated values of HOMA-IR (138). For multi-arm trials, a weighted average was used to create a single pair-wise comparison and to reduce the unit-of-analysis error. A correlation coefficient of 0.5 was assumed for SD of cross-over trials. Sensitivity analysis was conducted using 0.25 and 0.75 correlation coefficient values to test for the robustness of the effect size. The generic inverse variance method with random effects models was used to conduct pooled analyses. Data were expressed as MD with 95% CI and significance was considered at $P < 0.05$. Inter-study heterogeneity was assessed using the Cochrane Q-statistic and quantified using I^2 statistic with $P < 0.10$ significance, with an I^2 value ≥ 50 % indicating 'substantial' level of heterogeneity (133). Additional sensitivity analyses were performed to determine whether any single study exerted particular influence on the overall results by removing each individual study from the analysis and re-calculating the effect size of the remaining studies. When more than 10 trials were available for an outcome, sources of heterogeneity were explored with *a priori* subgroup analyses (continuous and categorical) for baseline values of HbA1c and fasting glucose within the intervention arm, dose, design, follow-up, fibre type and significance level set at $P < 0.05$. Visual inspection of funnel plots was

used to assess publication bias and formally tested in STATA using Egger and Begg tests, where $P < 0.10$ was considered evidence for small study effects. If suspected, Duvel and Tweedie Trim and Fill tests were applied to impute missing study data and correct for asymmetry.

Grading of Recommendations Assessment, Development and Evaluation

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (139, 140) was used to assess the overall certainty of evidence. In this approach, the quality of total evidence can be graded as 'very low', 'low', 'moderate', or 'high'. Evidence obtained from randomized trials receives an initial grade of 'high'. Scores for randomized trials can be downgraded for study limitations (i.e. weight of studies showed high risk of bias assessed by The Cochrane Collaboration Tool for Assessing Risk of Bias), inconsistency of results due to a substantial ($I^2 > 50\%$, $P < 0.10$) unexplained heterogeneity, indirectness of evidence resulting from the presence of factors that limit the generalizability of the findings, imprecision recognized by the wide confidence interval (CI) around the estimate of the effect, and judged depends on the minimally important differences (MID), and publication bias (evidence of small-study effects).

RESULTS

Search results

Figure 5.1. shows the flow of literature. The initial search yielded 879 publications, of which 20 articles were reviewed in full and 13 (n= 545) were included in the final analysis. In total, 12 trials reported data on HbA1c (n=531), 13 on fasting glucose (n=545), 6 on fasting insulin (n= 188), 1 on fructosamine (n= 10), and 4 trials reported data on HOMA-IR. However, 2 other trials reported sufficient data to calculate HOMA-IR (n=188). Of the 20 selected articles, 4 trials were excluded as they reported duplicate results, but were published in different journals (177-180).

Trial characteristics

Table 5.2. shows the characteristics of the included studies. The majority of trials were conducted in out-patient settings with 5 in the Middle East (Iran), 3 in Europe (1 France; 1 UK; 1 Sweden), 1 in Asia (Taiwan), 4 in North America (1 USA; 2 Canada; 1 Mexico). All trials were randomized, with 8 trials (62%) using a parallel design and 5 trials (38%) using a cross-over design. Participants were generally middle aged (median age= 55 years (range: 48-65)) with the majority being women. Participants were generally overweight or obese (median BMI= 30 (range: 25-35) kg/m^2), despite only five trials recruiting on the basis of overweight/obesity (115-117, 181-183). All trials were conducted in individuals with T2DM and none in T1DM. The dose of non-viscous fibre supplementation ranged from 5.1 to 40 g/d with a median dose of 10 g/d. Treatment duration ranged from 4 - 13 weeks with the median length being 8 weeks for trials reporting HbA1c, 3 - 13 weeks with the median length of 8 weeks for trials reporting fasting glucose and 4 to 12 weeks with median length of 8 weeks for trials reporting fasting insulin and HOMA-IR.

The Cochrane Risk of Bias Tool **(Supplementary Table 5.3.)** demonstrated that 7 trials (54%) had unclear risk of bias and 6 trials had a low risk of bias for sequence generation. Ten trials (77%) had unclear risk and 3 (23%) trials had low risk of bias for allocation concealment. Ten studies (77%), 2 studies (32%) and 1 studies (7%) had low, unclear and high risk of bias for blinding, respectively. A total of 7 trials (54%) had a low risk of bias, 4 trials (31%) had high risk of bias and 2 (15%) had an unclear risk of bias for incomplete outcome data. The majority of trials (85%) had a low risk of bias for selective outcome reporting. Funding sources included agency (69%), industry (8%), agency-industry (8%) or were not reported (15%).

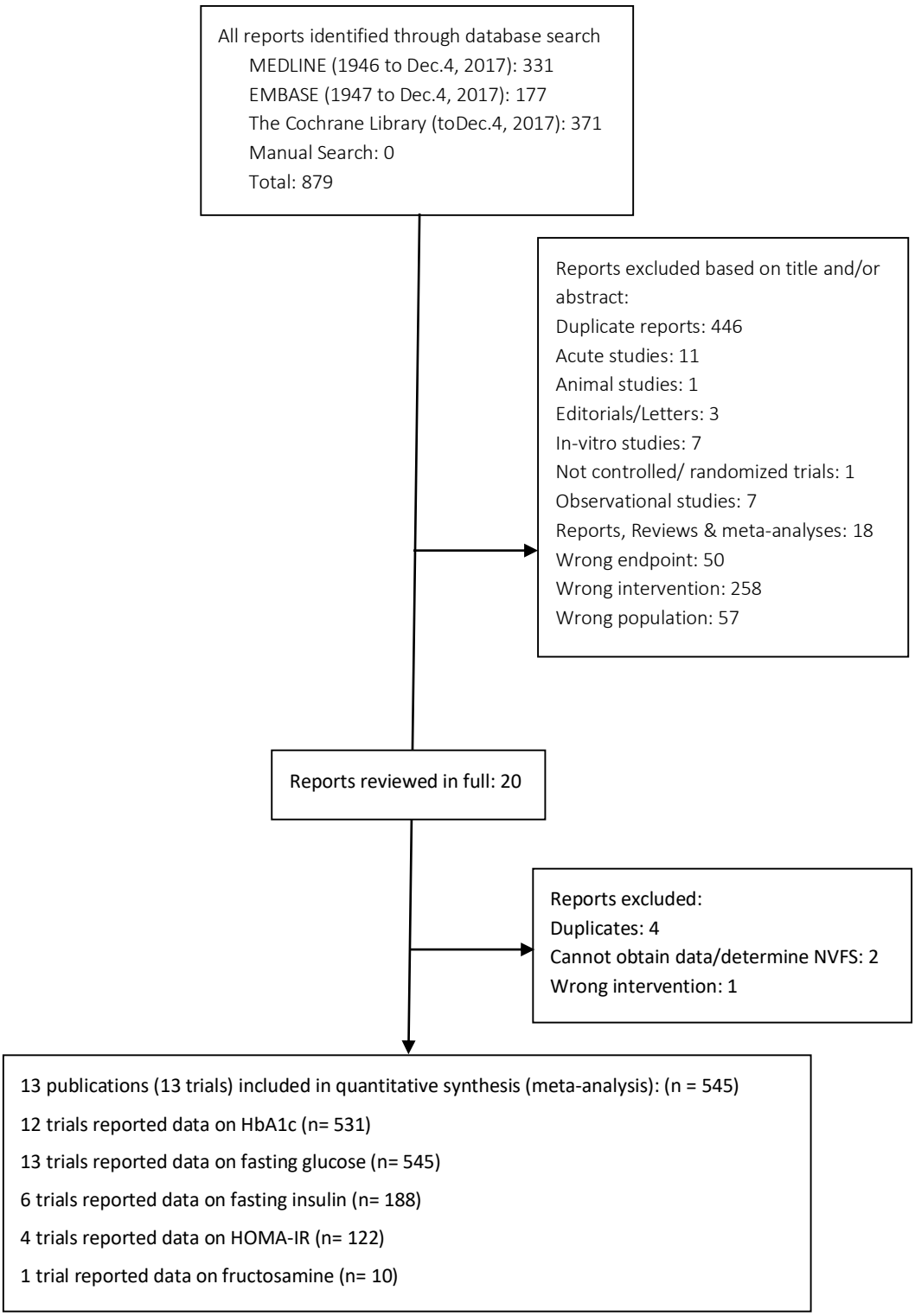


Figure 5.1. Flow of literature

Table 5.1. Characteristics of included studies

Reference	Participants §	Age (y)	BMI	Baseline HbA1c (%)	Baseline FPG	Design	NVFS	Dose (g/d)	Comparator	Background diet	Food matrix	Funding source¶	Country
Ble-Castillo et al, 2010	28 (4M:24F)	51.7	34.9	6.4	8.1	C-SB	RS2	8.16	Soy milk	NR	Powder	Agency	Mexico
Bodinham et al, 2014	17 (12M:5F)	55.0	30.6	-	-	C-SB	RS2	40	Amioca	NR	Powder	Agency	UK
Bonsu et al, 20120	26 (14M:12F)	65.0	30.4	7.2	7.6	P-DB	Inulin	10	Xylitol	NR	Powder	NR	Canada
Cheng et al, 2010	28 (13M:15F)	58.5‡	25.3	7.9	9.9	P-DB	RBF	5.1	MRF	Habitual	Powder	Agency	Taiwan
Dehghan et al, 2014 (1)	49 (0M:49F)	48.3	30.8	8.9	8.76	P-TB	Inulin	10	Maltodextrin	Habitual	Powder	Agency	Iran
Dehghan et al, 2014 (2)	52 (0M:52F)	48.6	30.9	8.2	8.76	P-TB	Inulin	10	Maltodextrin	Habitual	Powder	Agency	Iran
Farhangi et al, 2016	49 (0M:49F)	48.6	30.2	8.22	8.87	P-DB	Inulin	10	Maltodextrin	NR	Powder	Agency	Iran
Gargari et al, 2015	60 (0M:60F)	49.6	31.2	8.2	8.76	P-TB	RS2	10	Maltodextrin	Habitual	Powder	Agency	Iran
Grotz et al, 2003	133	57.6	-	-	-	P-DB	Cellulose	NR	Sucralose	SD	Powder	Industry	US
Jenkins et al, 2002‖	23 (16M:7F)	63.0	26.7	7.3	7.4	C-NA	WB	19	Low WB diet	NCEP	Cereal	Both	Canada
Karimi et al, 2016	56 (0M:56F)	49.1	31.3	8.1	9.05	P-TB	RS2	10	Maltodextrin	NR	Powder	NR	Iran
Karlstrom, et al, 1984	14 (7M:7F)	63‡	24.8	-	11.2	C-NA	WB	42.4	Low WB diet	DD	Cereal	Agency	Sweden
Luo et al, 2000	10 (6M:4F)	57	28	-	8.9	C-DB	FOS	20	Sucrose	Habitual	Powder	Agency	France

M, male; F, female; NVFS, non-viscous fiber supplement; C, cross-over; P, parallel; SB, single blind; DB, double blind, NA: not available; N/R, not reported; C: control; T: treatment; NCEP, National Cholesterol Education Program (before test phase)

All values are expressed as mean

§ The number of participants listed for each trial is the number of participants that completed the trial, and therefore the number used in our analyses and the number used for the reported baseline data (age and BMI), unless otherwise indicated with (*)

† Dose of non-viscous fibre supplement

¶ Agency funding is that from government, university or not-for-profit health agency sources.

‡ Age was reported in range

RS2: Resistant starch 2; RBF: Rice bran flour; MRF: Milled rice flour; §Participants=those who completed the study; WB: Wheat Bran; ‡Average age was calculated; NS: not specified

*SD: participants were on a specific diet: 14% protein, 30-36% fat, and 48-55% carbohydrate, DD: diabetic diet

Effect on HbA1c

Figure 5.2. demonstrates the effect of non-viscous fibre supplementation on HbA1c in individuals with T2DM. Overall, a significant reduction in HbA1c was observed with a median dose of 10 g/d [range: 5.1-40 g/d] and a median duration of 8 weeks [range: 4-13 wks] (MD= -0.25% [95% CI: -0.48, -0.20], P= 0.03). Substantial evidence of inter-study heterogeneity was present in the overall analysis (I^2= 52%, P= 0.02). The systematic removal of Bonsu et al, 2012 (184); Dehghan et al, 2014 (183); Farhangi et al, 2016 (181); Grotz et al, 2003(185) significantly decreased heterogeneity (I^2= 49%, P=0.03); (I^2= 45%, P=0.05); (I^2= 41%, P=0.07); (I^2= 46%, P=0.05), and modified effect size (MD=-0.30% [95%CI: -0.52, -0.07], P=0.009); (MD=-0.20% [95%CI: -0.43, 0.03], P=0.09); (MD=-0.20% [95%CI: -0.42, 0.03], P=0.08); (MD=-0.31% [95%CI: -0.54, -0.08], P=0.008), respectively. Sensitivity analyses using correlation coefficient of 0.25 and 0.75 was performed. While the former significantly decreased heterogeneity (I^2=0.49, P=0.03), the latter altered results from significant to non-significant (MD= -0.23 [95%CI: -0.45 to -0.00], P=0.05). **Supplementary Table 5.4 (A) & Table 5.5 (A)** show the results of continuous and categorical subgroup analyses for the effect of non-viscous fibre supplementations on HbA1c. Continuous meta-regression analyses did not reveal association between dose, and/or treatment duration and modification in HbA1c. Categorical subgroup analyses showed that the effect of non-viscous fibre supplementation on HbA1c was modified by duration (MD=0.58 [95%CI: 0.09, 1.02], P=0.023). Meta-regression analyses could not further explain inter-study heterogeneity.

Effect on fasting glucose

Figure 5.3. demonstrates the pooled effect of a median dose of 10 g/d [range: 5.1-40 g/d] non-viscous fibre supplementation over a median duration of 8 weeks [range: 3-13 wks] on fasting glucose in

individuals with T2DM. Diets supplemented with non-viscous fibre supplementations significantly reduced fasting glucose compared to control diets (MD= -0.54 mmol/L [95% CI: -0.79, -0.30], P < 0.0001) with significant evidence of substantial heterogeneity (I^2= 89%, P < 0.00001). Removal of Grots et al, 2003 (185) during our sensitivity analysis decreased heterogeneity (I^2= 24%, P=0.21) and increased overall estimated effect size (MD=-0.65 [95% CI: -0.85, -0.44], P<0.00001). Use of a correlation coefficient of 0.25 did not alter results however, using correlation coefficient of 0.75 increased heterogeneity (I^2=55%, P=0.008). **Supplementary Table 5.4 (B) & Table 5.5 (B)** show the results of continuous and categorical subgroup analyses for the effect of non-viscous fibre supplementation on fasting glucose. Continuous meta-regression revealed an association between dose (MD= 0.02 mmol/L [95%CI: 0.00, 0.04], P=0.019), duration (MD= 0.13 [95%CI: 0.06, 0.20], P= 0.003) and effect of NVFS on blood glucose. The effect of the treatment was not modified by subgroup analysis investigating the effect of design, dose, treatment duration and fibre type.

Effect on fasting insulin

Figrue 5.4. shows the pooled effect of a median dose of 10 g/d [range: 5.1-40 g/d] of non-viscous fibre supplementation over a median duration of 8 weeks [range: 2-12 wks] on fasting insulin in individuals with T2DM. Overall, non-viscous fibre supplementation significantly reduced fasting insulin (MD= -13.98 pmol/L [95% CI: -24.91, -3.05], P=0.01) with substantial evidence of inter-study heterogeneity (I^2= 71%, P=0.002). The systematic removal of Dehghan et al, 2014 (1) decreased inter-study heterogeneity (I^2=30%, P=0.22) and modified the overall estimated effect (MD= -10.54 [-19.40, -1.67], P=0.02). Sensitivity analysis using correlation coefficient of 0.25 and 0.75 did not alter results. Continuous and categorical subgroup analyses were not performed as < 10 trial comparisons were available for analyses.

Effect on HOMA-IR

Figure 5.5. demonstrates the pooled effect of a median dose of 10 g/d [range: 5.1-40 g/d] of non-viscous fibre supplementation over a median duration of 8 weeks [range: 2-12 wks] on HOMA-IR in individuals with T2DM. There was no significant difference between diet supplemented with non-viscous fibre and control observed (MD= -0.61 [95% CI: -2.43 to 1.22], P=0.52). Substantial evidence of inter-study heterogeneity was observed (I^2= 93%, P < 0.00001). The removal of Ble-Castillo et al, 2010 (115) lowered inter-study heterogeneity (I^2=38%, P=0.17), increased overall magnitude size, and altered results from non-significant to significant (MD= -1.67 [95% CI: -2.49 to -0.86], P<0.0001). Sensitivity analyses using correlation coefficient of 0.25 and 0.75 did not alter results. Continuous and categorical subgroup analyses were not performed as < 10 trial comparisons were available for analyses.

Effect on fructosamine

Only one included study assessed the effect of NVFS short chain fructo-oligosaccharides on fructosamine in T2DM (186). Overall, viscous fibre supplementation had no significant reduction on fructosamine (MD= -0.12 mmol/L [95% CI: -0.33, 0.08], P= 0.24) with no evidence of inter-study heterogeneity (I^2= 0, P= 0.87). Sensitivity analyses and subgroup analyses were not performed as < 10 trial comparisons were available for analyses.

Publication bias

Figure 5.6. shows the funnel plots for HbA1c and fasting glucose. Formal testing using Egger and Begg tests were not significant, but visual inspection of funnel plots suggested asymmetry in both outcomes. Therefore, Duval and Tweedie Trim and Fill analysis was performed **(Figure 5.7.).** The analysis identified two missed studies and the imputation of these studies resulted in a significant pooled effect of MD= -0.32 [95% CI: -0.54, -0.10], P= 0.005) for HbA1c. No missed studies were

identified for fasting glucose. Publication bias was not analyzed for fasting insulin, HOMA-IR and fructosamine as there were < 10 trial comparisons available.

Grading the evidence

Table 5.2. shows a summary of the GRADE assessments for each endpoint. The evidence for HbA1c and fasting glucose was rated low quality based on a downgrade for inconsistency, and it was rated very low for fasting insulin, HOMA-IR and fructosamine based on downgrade for inconsistency and imprecision.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis assessing the effect of non-viscous fibre supplementation on glycemic control outcomes in diabetes. We included 13 RCTs assessing the effect of non-viscous fibre supplementation (inulin (includes FOS), resistant starch, rice bran, or wheat bran (includes cellulose and cereal fibre) on HbA1c, fasting glucose, fasting insulin, fructosamine, and HOMA-IR in middle-aged adults with T2DM. Pooled analyses revealed a significant reduction in HbA1c (-0.25 %), fasting glucose (-0.54 mmol/L), and fasting insulin (-13.98 pmol/L) at a median dose of 10 g/d (ranged 5.1- 40 g/d) over a median duration of 8 weeks with no effects on fructosamine and HOMA-IR.

These results support previous findings from observational studies on the therapeutic potential of soluble non-viscous and insoluble fibres. For instance, it was found that whole-grain and bran intakes were associated with lowered all-cause and CVD-specific mortality in women with T2DM (175). Furthermore, a meta-analysis performed in 2016, investigated the effect of inulin-type fructans (ITF)

on lipid and glycemic profile in adults (109). Twenty RCTs with 607 adults with different health status were included. It was found that ITF may have benefits for LDL-cholesterol in the general population (109). However, improvement in HDL-cholesterol and glycemic control, fasting insulin in particular ($P < 0.0001$), was limited to those with diabetes (109). Our findings are aligned with previous studies undertaken using resistant starch and rice bran (187, 188), with a small but significant reduction being observed in HbA1c, fasting glucose and fasting insulin. Different mechanisms have been proposed to explain the glucose-lowering effect of non-viscous fibres in diabetes. Most recently, investigators shed light on the prebiotic effect of most non-viscous fibre supplementation and suggest this to be a contributing factor in associated metabolic effects (107). Soluble fibres (e.g. inulin) are fermented to a larger extent compared to the insoluble forms (15). Specific fibres, namely inulin, FOS, and resistant starch are fermented by the colonic microbiota in the large intestine producing by-products including short chain fatty acids (SCFAs) that may contribute to glucose reduction (107, 109). Recently, investigators have reported a significant difference in the microbiota between healthy subjects and individuals with diabetes, which may explain the benefits of inulin and FOS as prebiotics in DM management (108). Interestingly, studies utilizing wheat bran showed no effect on glucose biomarkers (185, 189, 190), which highlights a critical question on the previously reported association between wheat bran (cereal bran) and improved glycemic control in T2DM shown in observational studies.

Strengths of this meta-analysis include assessing quality using GRADE and including studies from different countries. However, the present study has several limitations which include having a relatively small number of RCTs with small number of participants. The Cochrane risk of bias tool indicates high risk of bias in incomplete outcome data for some studies due to the larger number of withdraws (> 70%). Risk of bias of random sequence generation and allocation concealment was unclear for the majority of included RCTs (> 50% and > 75%, respectively) due to missing/insufficient

data. It is noteworthy that the significant results from inulin (FOS) and resistant starch studies, published by the same research group, skewed the overall observed effect (116, 117, 181-183). Regardless of the low risk of bias in blinding and selective reporting for these studies, duplicate reports were published in different journals (177-180, 182, 183). A 2016 meta-analysis, assessing the effect of inulin-type fructans (ITF) on lipid and glucose biomarkers, excluded one of the previously mentioned trials due to duplicate publications (179). In support, Mcrorie et al, highlighted several concerns regarding included studies undertaken by the same research group (Dehghan et al) due to the extremely high reduction in LDL cholesterol that exceeds the effects of a high-dose of the highly effective statin drug (191). In addition, a response from the author regarding two of the search yielded articles (179, 182) confirmed publishing the same results in two different journals. Remarkably, removal of these trials altered the overall result for HbA1c and fasting glucose from significant to non-sgnificant (P=0.24, P=0.32, respectively). According to GRADE, evidence of this study is rated as 'low quality' for HbA1c and fasting glucose and 'very low quality' for fasting insulin, HOMA-IR, and fructosamine. Only one study investigated the effect of non-viscous fibre supplementation (FOS) on fructosamine (186); therefore, we were unable to conduct a *priori* subgroup analyses, dose response, GRADE or assess publication bias. In addition, insufficient data was provided to assess the effect of these fibre supplementations in the presence of different background diet. The effect of non-viscous fibre supplementation was modified by duration (≥ 12 wks) which may indicate the need to longer RCTs investigating the effect of these fibres on HbA1c in diabetes patients. Balancing these strengths and limitations; we graded the overall quality of evidence for this analysis as low for HbA1c and fasting glucose, very low for fasting insulin, fructosamine, and HOMA-IR based on downgrades for inconsistency and publication bias for HbA1c and fasting glucose and downgrades for inconsistency and imprecision for fasting insulin, fructosamine, and HOMa-IR.

In summary, the results of this systematic review and meta-analysis provide an estimate for the beneficial effect of non-viscous fibre supplementation in individuals with diabetes. Future research should focus on higher quality studies assessing the effect of non-viscous fibre supplementation, including inulin and resistant starch on glycemic outcomes. Taking into account the limitations raised by GRADE, more high quality RCTs are required to strengthen the evidence.

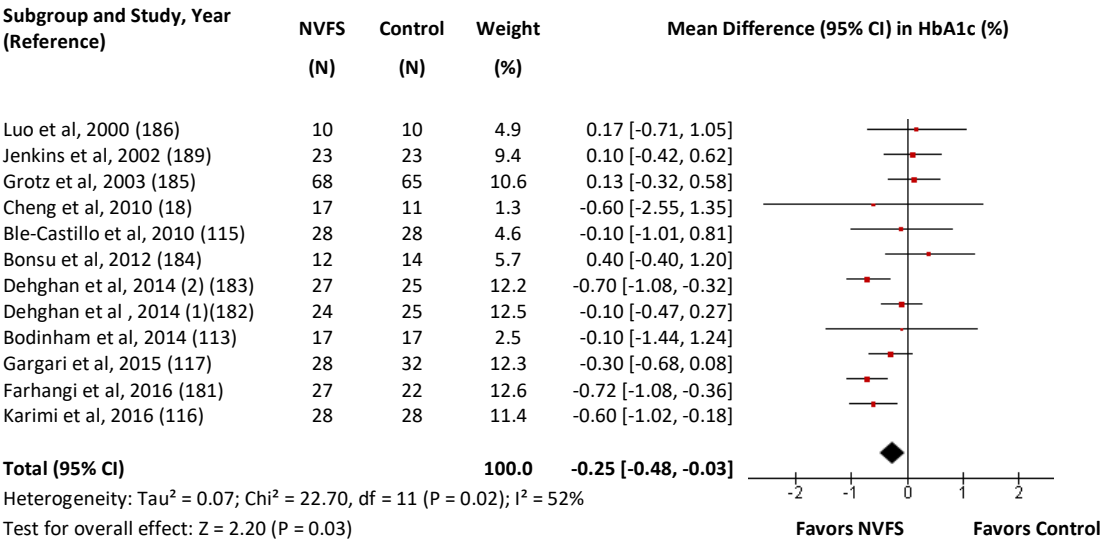


Figure 5.2. shows the effect of non-viscous fiber supplements on glycated hemoglobin (HbA1c). Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance P < 0.10. N = number of participants in each intervention group. NVFS, non-viscous fiber supplement.

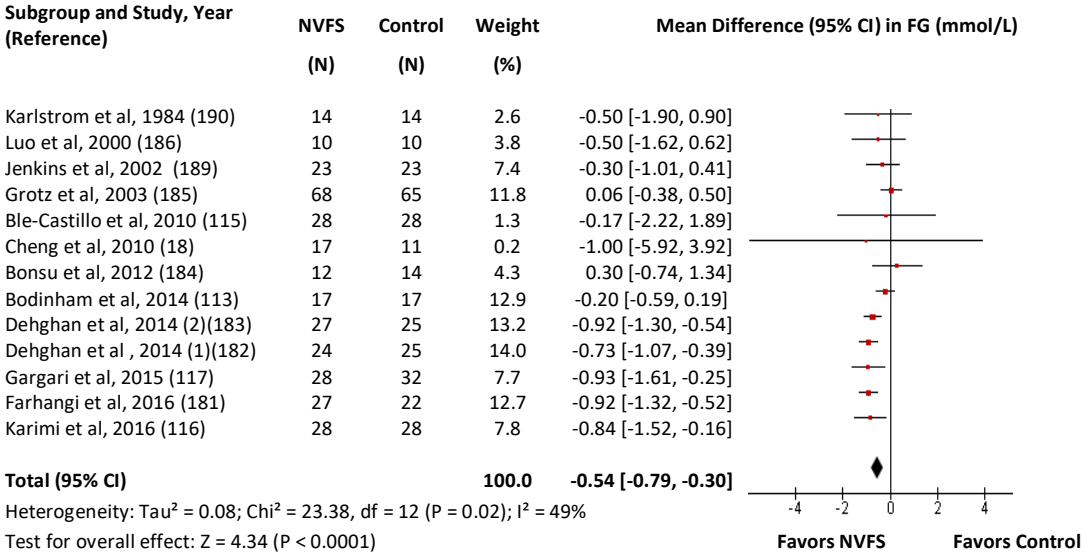


Figure 5.3. shows the effect of non-viscous fiber supplements on fasting glucose. Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance P < 0.10. N = number of participants in each intervention group. NVFS, non-viscous fiber supplement.

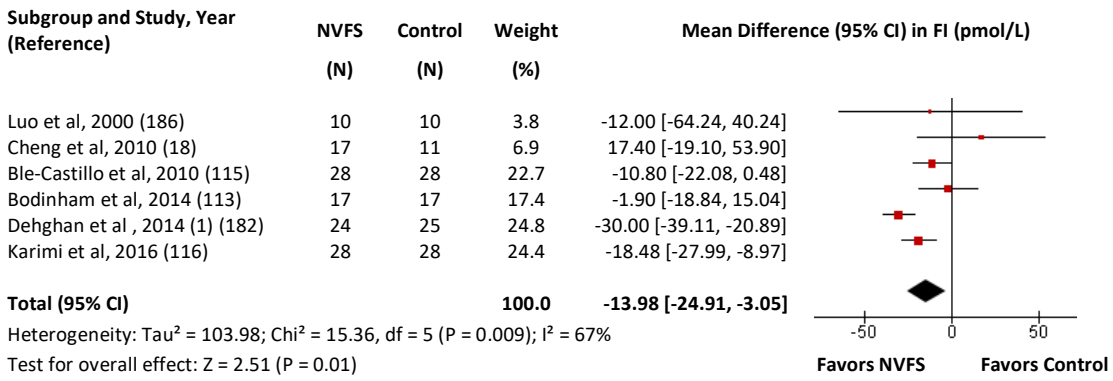


Figure 5.4. shows the effect of nonviscous fiber supplements on fasting insulin. Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group. NVFS, non-viscous fiber supplement.

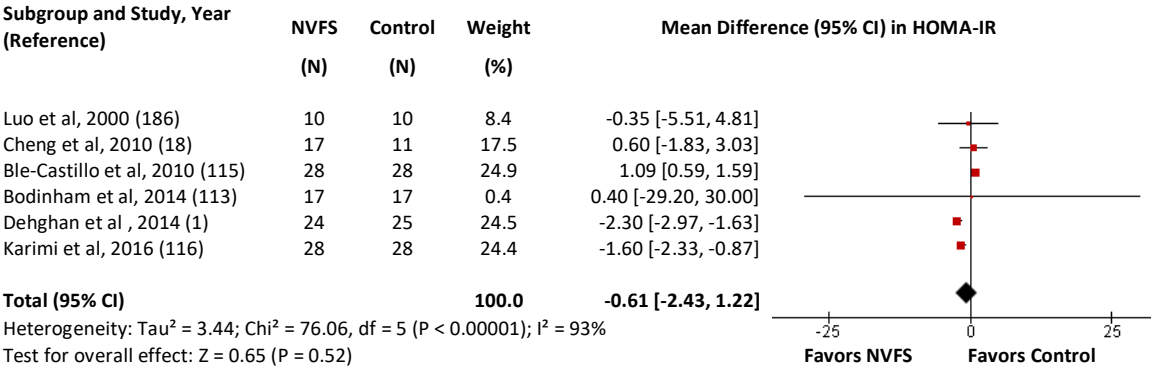
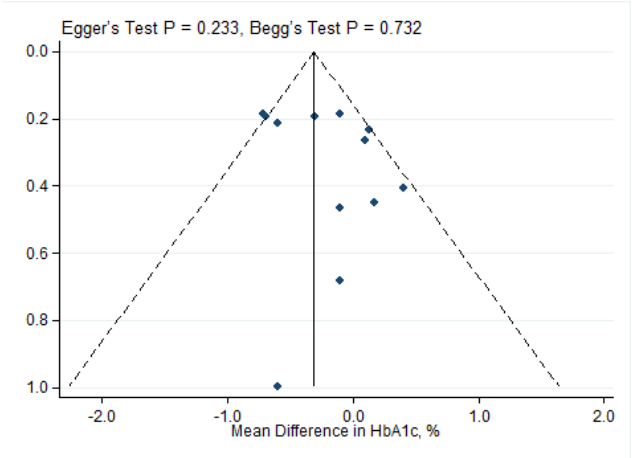


Figure 5.5. shows the effect of non-viscous fiber supplements on HOMA-IR. Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group. NVFS, non-viscous fiber supplement.

(A)



(B)

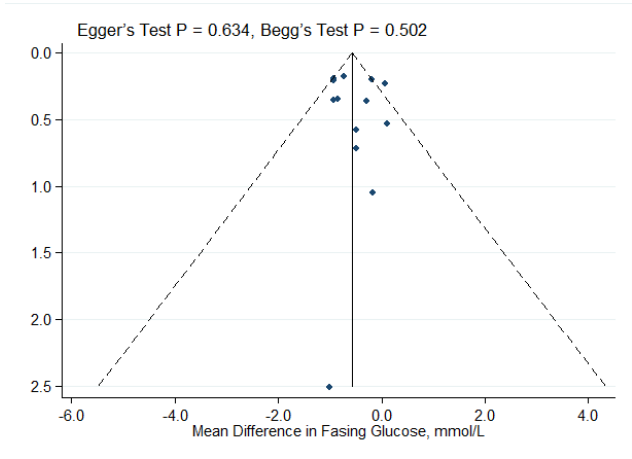
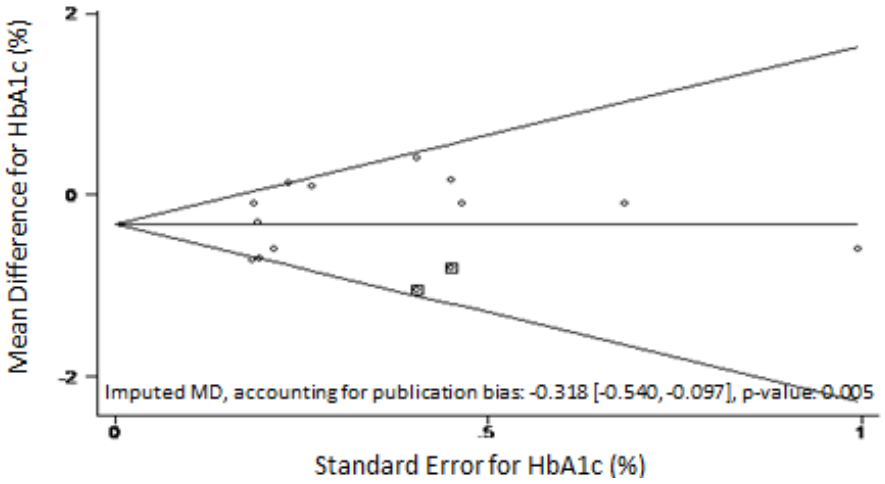


Figure 5.6. Publication bias funnel plots assessing publication bias and effect of small and/or imprecise study effects for (a) HbA1c and (b) fasting glucose. The horizontal line represents the pooled effect estimate expressed as the mean difference for each analysis. Diagonal lines represent the pseudo-95% CI. P-values are derived from quantitative assessment of publication bias by Egger's and Begg's tests.

(A)



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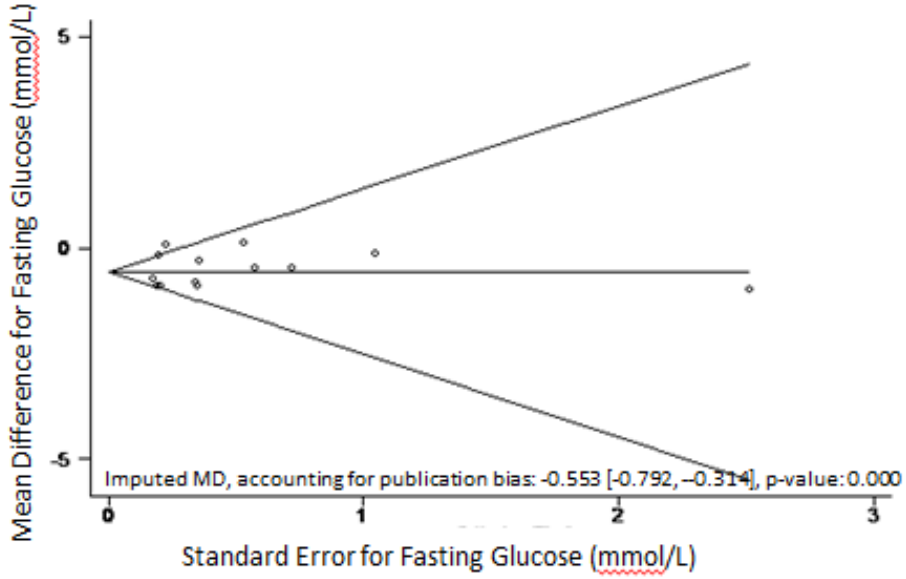

Figure 5.7. Trim and Fill funnel plots evaluating publication bias and effect of small study effects in randomized controlled trials investigating the effect non-viscous fibre supplementation on: (A) HbA1c and (B) fasting glucose. The horizontal line represents the pooled effect estimate expressed as MD, the diagonal lines represent the pseudo-95 % CIs of the MD, the clear circles represent effect estimates for each included studies, and black squares represent imputed "missed" studies. Imputed MD, accounting for publication bias and p-values are provided where $p < 0.10$ is considered evidence of small-study effects.

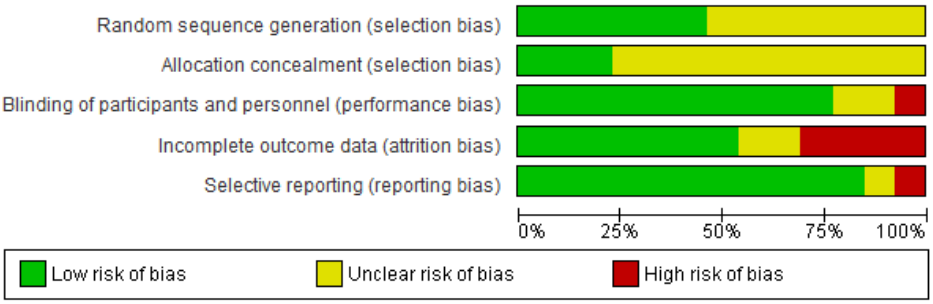

Figure 5.8. Risk of bias

Studies were rated “Low Risk of Bias” if the study design is unlikely to have little influence over the true outcome; “High Risk of Bias” if the design is likely to have an influential effect on the true outcome; “Unclear Risk of Bias” if insufficient information was given to assess risk.

Table 5.2. GRADE Assessment

Quality assessment							No of patients		Effect	Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NVFS	P	Absolute (95% CI)	
HbA1c										
12	randomized trials	not serious [a]	serious [b]	not serious	not serious [c]	publication bias strongly suspected [d]	309	300	MD= -0.25% (-0.48 to,- 0.03)	⊕⊕◯◯ LOW
Fasting glucose										
13	randomized trials	not serious [a]	serious [e]	not serious	not serious [f]	publication bias strongly suspected [g]	323	314	MD= -0.54 mmol/L (-0.79, -0.3)	⊕⊕◯◯ LOW
Fasting insulin										
6	randomized trials	not serious [a]	serious [h]	not serious	very serious [i]	none	124	119	MD= -13.98 pmol/L (-24.91, -3.05)	⊕◯◯◯ VERY LOW
HOMA-IR										
6	randomized trials	not serious [a]	serious [j]	not serious	very serious [k]	none	124	119	MD= -0.61 (-2.43, 1.22)	⊕◯◯◯ VERY LOW
Fructosamine										
1	randomized trials	not serious [a]	not serious	not serious	very serious [l]	none	10	10	MD= 2 mmol/L (-38.5, 42.5)	⊕◯◯◯ VERY LOW

CI: Confidence interval; MD: Mean difference; **NVFS:** Non-Viscous Fibre Supplementation; **P:** Placebo

Explanations

a. Although risk of bias figure shows low risk of bias for the majority of assessed areas, a significant number of trials (>30%) were rated high for incomplete outcome data as >10% of the participants had withdrawn from the study. Approximately, 10% of the assessed trials have high performance and reporting bias. Furthermore, most of the included trials lack sufficient data to adequately assess randomization and allocation concealment. Ble-Castillo et al, 2010 reported non-significant results on LDL-c without reporting specific values.

b. A high level of heterogeneity was observed via visual inspection and I-squared test ≥ 50% (P=0.02). Subgroup analysis looking at the effect of duration may partially explain the inconsistency (MD=0.58 [95%CI: 0.09, 1.02], P=0.023). Systematic removal of Bonsu et al, 2012; Dehghan et al, 2014; Farhangi et al, 2016; and Grotz et al, 2003 significantly decreased heterogeneity to (49%, P=0.03), (45%, P=0.05), (41%, P=0.07,) and (46%, P=0.05), respectively. Interestingly, heterogeneity was abolished when Dehghan et al lab group studies were removed (I-squared=0%, P= 0.97).

c.95% CI of the pooled estimate effect crosses the clinical decision threshold for minimally important difference (MID) which is equal to (0.3%) that is proposed by U.S. Food and Drug Administration for the development of new drugs for diabetes. Confidence intervals are wide for Cheng et al, 2010; Bodinham et al, 2014; Ble-Castillo et al, 2010; Luo et al, 2000; Bonsu et al, 2012.

d. Visual inspection of funnel plot demonstrates asymmetry suggesting a high risk of publication bias despite the non-significance in Begg's and Egger's tests. P=0.732 and 0.233, respectively. Trim and Fill test was significant ($p < 0.10$)

e. A high level of heterogeneity was observed via visual inspection. However, I-squared test ≤50% (P=0.02). Subgroup analysis looking at the effect of design, dose, treatment duration and fibre type failed to explain heterogeneity. Systematic removal of Grotz et al, 2003 decreased heterogeneity (I-squared= 24%, P=0.21) and increased overall estimated effect size (MD=-0.65 [95% CI: -0.85, -0.44], P<0.00001).

f. 95% CI of the pooled estimate effect crosses the clinical decision threshold for minimally important difference (MID) which is equal to (0.5 mmol/L). Confidence intervals are wide for Cheng et al, 2010; Karlstrom et al, 2016; Ble-Castillo et al, 2010; Luo et al, 2000; Bomsu et al, 2012.

g. Visual inspection of funnel plot demonstrates asymmetry suggesting a high risk of publication bias despite the non-significance in Begg's and Egger's tests. P=0.502 and 0.634, respectively.

h. Downgrade for inconsistency due to substantial heterogeneity (I-squared=63%, P=0.02). Subgroup analyses were not performed on fasting insulin data due to the small number of trials.

i. Small number of studies with wide confidence intervals. In addition, confidence interval of the overall effect crosses threshold of minimally important difference (MID) which is equal to (5 pmol/L) for fasting insulin.

j. Downgrade for inconsistency due to substantial heterogeneity (I-squared=0.94%, P<0.00001). Subgroup analyses were not performed on HOMA-IR data due to the small number of trials.

k. Downgrade for imprecision due to the small number of included studies. The confidence interval crosses the threshold of the minimally important difference (MID) which is equal to 1 for HOMA-IR.

l. Only one study (n=10) was included.

SUPPLEMENTARY MATERIALS

MEDLINE					
Searches	**Results**	**Searches**	**Results**	**Searches**	**Results**
Non-viscous.tw,kf.	74	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	98867	HbA1c.tw,kf.	27358
Nonviscous.tw,kf.	100	Exp Diabetes Mellitus/	406473	(blood adj3 glucose).tw,kf.	71843
Low viscosity.tw,kf.	2440	Exp Diabetes Mellitus, Type 1/	76039	exp Blood Glucose/	161057
Insoluble Fiber.tw,kf.	315	Diabetes mellitus type 1.tw,kf.	1120	Glyc?emi*.tw,kf.	50964
Insoluble Fibre.tw,kf.	131	Insulin dependent diabetes mellitus.tw,kf.	17023	Hyperglyc?emi*.tw,kf.	57165
Exp Cellulose/	44495	IDDM.tw,kf.	7273	Hypoglyc?emi*.tw,kf.	53761
Cellulose.tw,kf.	52933	Type I Diabetes.tw,kf.	5167	exp Fructosamine/	1578
Wheat Bran.tw,kf.	2546	Type 1 Diabetes.tw,kf.	36332	Fructosamine*.tw,kf.	2313
Rice Bran.tw,kf.	1503	T1DM.tw,kf.	3660	Fasting insulin.tw,kf.	7512
Fructose Oligosaccharide*.tw,kf.	15	(Juvenile adj2 Diabetes).tw,kf.	2227	exp Insulin Resistance/	76309
Fructooligosaccharide*.mp.	998	Autoimmune Diabetes.tw,kf.	3193	Insulin resistance.tw,kf.	73528
Resistant Starch.tw,kf.	1307	Exp Diabetes Mellitus, Type 2/	120990	HOMA-IR.tw,kf.	9483
Corn Bran.tw,kf.	174	Diabetes type 2.tw,kf.	1178	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52	655339
Wheat Dextrin.tw,kf.	23	Non insulin dependent diabetes mellitus.tw,kf.	7471	21 and 53	2098
Benefiber.tw,kf.	7	NIDDM.tw,kf.	7344	exp Animals/ not Humans/	4743197
Benefibre.tw,kf.	0	Type II diabetes.tw,kf.	7774	54 not 55	1439
Exp fructans/	7953	Type 2 Diabetes.tw,kf.	108038	randomized controlled trial.pt. or randomized.mp. or placebo.mp.	859363
Inulin.tw,kf.	8395	T2DM.tw,kf.	14801	56 and 57	331
Cereal Fiber.tw,kf.	198	exp Hemoglobin A, Glycosylated/	32335		
Cereal Fibre.tw,kf.	103	Hemoglobin A1c.tw,kf.	8681		

EMBASE					
Searches	**Results**	**Searches**	**Results**	**Searches**	**Results**
Non-viscous.tw.	98	diabetes mellitus/	516175	(blood adj3 glucose).mp.	272437
Nonviscous.tw.	90	Diabetes type 1.tw.	1197	glucose blood level/	234650
Low viscosity.tw.	2756	Insulin dependent diabetes.tw.	23158	Glyc?emi*.tw.	75214
Insoluble Fiber.tw.	365	IDDM.tw.	7707	Hyperglyc?emi*.tw.	79858
Insoluble Fibre.tw.	160	type 1 diabetes.tw.	50455	Hypoglyc?emi*.tw.	79081
Cellulose.tw.	61522	type I diabetes.tw.	6691	fructosamine/	2701
Wheat Bran.tw.	2930	T1DM.tw.	6953	Fructosamine.tw.	2763
Rice Bran.tw.	1809	(Juvenile adj2 Diabetes).tw.	2460	Fasting insulin.tw.	10402
Fructose Oligosaccharide*.tw.	21	Autoimmune diabetes.tw.	3724	insulin resistance/	108621
Fructooligosaccharide*.tw.	1074	Diabetes type 2.tw.	1883	HOMA-IR.tw.	15973
Resistant Starch.tw.	1508	Non insulin dependent diabetes.tw.	9685	19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46	968615
Corn Bran.tw.	175	NIDDM.tw.	7912	18 and 47	2051
Wheat Dextrin.tw.	31	Type 2 diabetes.tw.	150785	exp Animals/ not Humans/	11025565
Benefiber.tw.	33	Type II diabetes.tw.	11041	48 not 49	884
Benefibre.tw.	0	T2DM.tw.	26006	random:.tw. or placebo:.mp. or double-blind:.tw.	1529106
Fructan*.tw.	1251	hemoglobin A1c/	80904	50 and 51	177
Inulin.tw.	10640	Hemoglobin A1c.mp.	85260		
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17	82401	HbA1c.tw.	55623		

COCHRANE					
Searches	**Results**	**Searches**	**Results**	**Searches**	**Results**
Non-viscous.ti,ab,hw.	16	cereal fibre.ti,ab,hw.	28	adult-onset diabetes.ti,ab,hw.	22
Nonviscous.ti,ab,hw.	8	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19	2665	Hemoglobin A, Glycosylated/	4606
Low viscosity.ti,ab,hw.	110	Diabetes Mellitus, Type 1/	3465	HbA1c.ti,ab,hw.	6570
Insoluble fiber.ti,ab,hw.	38	diabetes type 1.ti,ab,hw.	51	Hemoglobin A1c.ti,ab,hw.	7061
Insoluble fibre.ti,ab,hw.	17	insulin dependent diabetes.ti,ab,hw.	11927	(blood adj3 glucose).ti,ab,hw.	24503
Cellulose/	418	IDDM.ti,ab,hw.	537	Blood Glucose/	13593
cellulose.ti,ab,hw.	1190	type I diabetes.ti,ab,hw.	255	glyc?emi*.ti,ab,hw.	10962
wheat bran.ti,ab,hw.	222	type 1 diabetes.ti,ab,hw.	3079	hyperglyc?emi*.ti,ab,hw.	5410
rice bran.ti,ab,hw.	67	T1DM.ti,ab,hw.	392	hypoglyc?emi*.ti,ab,hw.	11541
fructose oligosaccharide*.ti,ab,hw.	123	(Juvenile adj2 Diabetes).ti,ab,hw.	86	Fructosamine/	148
fructooligosaccharide*.ti,ab,hw.	121	autoimmune diabetes.ti,ab,hw.	54	fructosamine*.ti,ab,hw.	403
resistant starch.ti,ab,hw.	184	Diabetes Mellitus, Type 2/	10577	fasting insulin.ti,ab,hw.	1225
corn bran.ti,ab,hw.	11	diabetes type 2.ti,ab,hw.	144	Insulin Resistance/	3207
wheat dextrin.ti,ab,hw.	6	non insulin dependent diabetes.ti,ab,hw.	9573	HOMA-IR.ti,ab,hw.	1584
fructan*.ti,ab,hw.	60	NIDDM.ti,ab,hw.	988	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50	45448
Inulin/	188	type II diabetes.ti,ab,hw.	765	20 and 51	371
inulin.ti,ab,hw.	633	type 2 diabetes.ti,ab,hw.	15426		
cereal fiber.ti,ab,hw.	37	T2DM.ti,ab,hw.	2862		

Supplementary Table 5.1. Search Strategy

No.	Inclusion Criteria
1	Randomized
2	Controlled
3	≥ 3 weeks
4	Non-viscous fibre supplementation (cellulose, wheat bran, rice bran, corn bran, resistant starch, fructo-oligosaccharide (FOS), inulin, wheat dextrin, and cereal fibre)
	Adequate comparator (placebo, fibre free diet or decreased fibre diet (for wheat bran))
5	Glycemic control endpoints (HbA1c, fasting glucose, fasting insulin, fructosamine, HOMA-IR)
6	T1DM or T2DM

Supplementary Table 5.2. Eligibility Criteria

Reference	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting
Ble-Castillo et al., 2010	Unclear	Unclear	High	Low	High
Bodinham et al., 2014	Unclear	Unclear	Unclear	Low	Low
Bonsu et al., 2012	Low	Unclear	Low	High	Low
Cheng et al., 2010	Unclear	Unclear	Low	Low	Low
Dehghan et al., 2014 (1)	Low	Low	Low	Low	Low
Dehghan et al., 2014 (2)	Low	Low	Low	Low	Low
Farhangi et al., 2016	Low	Unclear	Low	Unclear	Low
Gargari et al, 2015	Low	Low	Low	Unclear	Low
Grotz et al., 2003	Unclear	Unclear	Low	Low	Unclear
Jenkins et al., 2002	Unclear	Unclear	Low	High	Low
Karimi et al., 2016	Low	Unclear	Low	High	Low
Karlstrom et al., 1984	Unclear	Unclear	Unclear	Low	Low
Luo et al., 2000	Unclear	Unclear	Low	High	Low

Supplementary Table 5.3. Cochrane risk of bias tool

A. HbA1c

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P*-value
Non-Viscous Fiber Dose (g/d)	11	398	0.024 [-0.021, 0.070]	41.96	0.256
Duration (wk)	12	531	-0.062 [-0.035, 0.159]	41.82	0.187

B. Fasting Glucose

Subgroups	No. of Trials	N	β [95% CI]	Residual I^2 (%)	*P*-value
Non-Viscous Fiber Dose (g/d)	12	412	0.020 [0.004, 0.036]	0.00	0.019
Duration (wk)	13	545	0.130 [0.056, 0.203]	0.00	0.003

Supplementary Table 5.4. Continuous *a priori* subgroup analyses. β is the slope derived from meta-regression analyses and represents the treatment effect of viscous fiber for each subgroup for A. HbA1c and B. Fasting Glucose. The residual I^2 value indicates heterogeneity unexplained by the subgroup and is reported as a percent value, where $I^2 \geq 50\%$ indicated "substantial" heterogeneity. P-value significance for heterogeneity was set as $P < 0.10$. N = number of participants in each treatment group.

Subgroup	Level	No. of Trials	N	Within Subgroup	Between Subgroups		Residual I^2 (%)	P-Value
Total		12	531	-0.25 [-0.48, -0.03]				0.03
Dose	< 10	2	45	-0.21 [-1.30, 0.88]		-0.096 [-1.22, 1.03]	51.24	0.852
(g/d)	≥ 10	9	509	-0.30 [-0.60, -0.01]				
Duration	< 8	2	38	-0.43 [-0.67, -0.19]		0.56 [0.07, 1.02]	16.69	0.023
(wk)	≥ 8	10	493	0.13 [-0.27, 0.52]				
Study Design	Parallel	8	453	-0.34 [-0.62, -0.06]		0.390 [-1.01, 0.23]	45.84	0.190
	Crossover	4	78	0.05 [-0.50, 0.60]				
Fiber Type	Inulin	5	322	-0.34 [-0.71, 0.04]	1 vs 2	0.23 [-2.18, 2.65]	47.52	0.460
	Resistant starch	4	101	-0.37 [-0.83, 0.10]	1 vs 3	-0.48 [-1.23, 0.26]		
	Rice bran	1	17	-0.6 [-2.97, 1.77]	2 vs 3	-0.72 [-3.16, 1.73]		
	Wheat bran	2	91	0.12 [-0.46, 0.96]	2 vs 4			

Supplementary Table 5.5. (A) A *priori* subgroup analyses using dichotomous predictors to assess the effect of non-viscous fibre supplementation on HbA1c.

*Studies that included multiple comparisons were separated for subgroup analysis. Point estimates for each subgroup level (diamonds) represent the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup. Subgroup effects were assessed by meta-regression analyses where $p < 0.05$ is significant.

Subgroup	Level	No. of Trials	N	Within Subgroup	Between Subgroups		Residual I^2 (%)	P-Value
Total		13	545	-0.54 [-0.79, -0.30]				<0.0001
Dose	< 10	2	45	-0.29 [-2.49, 1.91]		-0.36 [-2.57, 1.85]	23.11	0.726
(g/d)	≥ 10	10	523	-0.65 [-0.91, -0.39]				
Duration	< 8	3	52	-0.44 [-1.44, 0.56]		-0.12 [-1.16, 0.93]	50.40	0.810
(wk)	≥ 8	10	493	-0.56 [-0.86, -0.26]				
Study Design	Parallel	8	453	-0.65 [-0.97, -0.34]		-0.36 [-0.96, 0.23]		0.206
	Crossover	5	92	-0.29 [-0.80, 0.21]				
Fiber Type	Inulin	5	322	-0.79 [-1.06, -0.52]	1 vs 2	0.51 [-5.19, 6.21]		
	Resistant starch	4	101	-0.49 [-0.87, -0.11]	1 vs 3	-0.41 [-0.10, 0.18]	9.24	0.078
	Rice bran	1	17	-1.0 [-6.69, 4.69]	2 vs 3	-0.92 [-6.62, 4.79]		
	Wheat bran	3	105	-0.08 [-0.54, 0.37]				

Supplementary Table 5.5. (B) A *priori* subgroup analyses using dichotomous predictors to assess the effect of non-viscous fibre supplementation on fasting glucose.

*Studies that included multiple comparisons were separated for subgroup analysis. Point estimates for each subgroup level (diamonds) represent the pooled effect estimates. The dashed line represents the pooled effect estimate for the overall (total) analysis. The residual I^2 value indicates the inter-study heterogeneity unexplained by the subgroup. Subgroup effects were assessed by meta-regression analyses where $p < 0.05$ is significant.

CHAPTER VI- OVERALL DISCUSSION AND CONCLUSION

Despite the presence of extensive evidence on the physiological and metabolic effects of total dietary fibre, data on fibre supplementations are lacking. Although a strong relationship between viscosity and therapeutic potentials has been reported in the literature, data on the specific underlying mechanism and also preferred fibre type remain inconsistent. Jenkins et al. (80, 125) showed a positive correlation between viscosity and glycemic control resulting from ingestion of highly viscous polysaccharides following OGTT and long term administration. In support, previous in-vitro modeling and animal studies have indicated similar findings. However, observational cohort studies have repeatedly shown non-viscous, mainly insoluble cereal fiber, to have a greater effect against obesity, diabetes, CVD, and certain types of cancer. Therefore, in an attempt to contribute to resolution of this dilemma, we conducted two systematic reviews and meta-analyses exploring the effect of viscous and non-viscous fibre supplementations on glycemic outcomes (HbA1c, fasting glucose, fasting insulin, fructosamine, and HOMA-IR) in a diabetes population. In total, we included 44 RCTs (n=1973) assessing the effect of fibre supplementation on at least one of the glycemic outcomes (HbA1c, fasting glucose, fasting insulin, fructosamine, and/or HOMA-IR) in subjects with T1DM or T2DM. Although both forms of fibre supplementations showed statistically significant reductions in HbA1c and fasting glucose, the effect of viscous fibre was approximately double that shown by the non-viscous fibres forms. Regardless of hypoglycemic medication, only viscous fibre supplementations resulted in a clinically meaningful improvement (> 0.3% HbA1c; >1.0 mmol/L) in glycemic control(167). Despite the substantial heterogeneity in both studies, the quality of evidence yielded from viscous fibre supplementations were stronger; HbA1c and fasting glucose were rated ‘moderate quality’ and ‘high quality’,

respectively. A greater number of studies with a larger sample size and high quality RCTs according to Cochrane Risk of Bias Tool were reported investigating viscous fibre supplementations. Non-viscous fibre supplementation resulted in a lower effect in HbA1c and fasting glucose with smaller number of studies and lower quality of evidence, as both HbA1c and fasting glucose were rated 'low'. Collectively, these points provide further support for the hypothesis that efficacy of fibre primarily depends on viscosity.

There was concern; however, about observed glycemic benefits of non-viscous fiber. Based on our subgroup analysis when 5 studies from a single research group in Iran were removed, the overall effect becomes non-significant for any of the glycemic parameters. The reason for removal of their data was based on the fact that they published the same study twice, and because their work has been criticised in literature for possible research bias.

In order to examine the anti-hyperglycemic effect of all included fibre supplementations types on glycemic biomarkers in diabetes, we combined yielded results from both meta-analyses **(Figure 6.1. & 6.2.)**. This combination of findings provides some support for the conceptual premise that fibre supplementations, viscous forms in particular, should be recommended as an adjunctive therapy for diabetes patients. It may offer an affordable solution to contribute to the delay of macro and micro-vascular complications through regulation of important glycemic biomarkers. Governments should encourage the incorporation of fibre supplementation in staple food products, especially those produced and marketed for individuals with diabetes. Health agencies should consider reviewing the guidelines in terms of fibre consumption and address the question of what specific types and quantity of fibre supplementation should be recommended in management of diabetes. The pharmacological effects of fibre supplementations including glucose-lowering potentials must be considered for future research. More RCTs with higher quality are encouraged to address the limitations raised by GRADE in

our meta-analyses. Factors contributing to the viscosity of fibre must be taken into consideration during future trials, and data on the type of fibre used, degree of viscosity and molecular weight, method of fibre extraction, and whether it was incorporated into food or should be taken as a supplement should be provided.

In conclusion, fibre supplementations should be recommended as adjunctive therapy for glycemic management in diabetes. Both types of fibre significantly lowered HbA1c and fasting glucose; however, viscous fibres demonstrated greater reduction in conventional glycemic parameters.

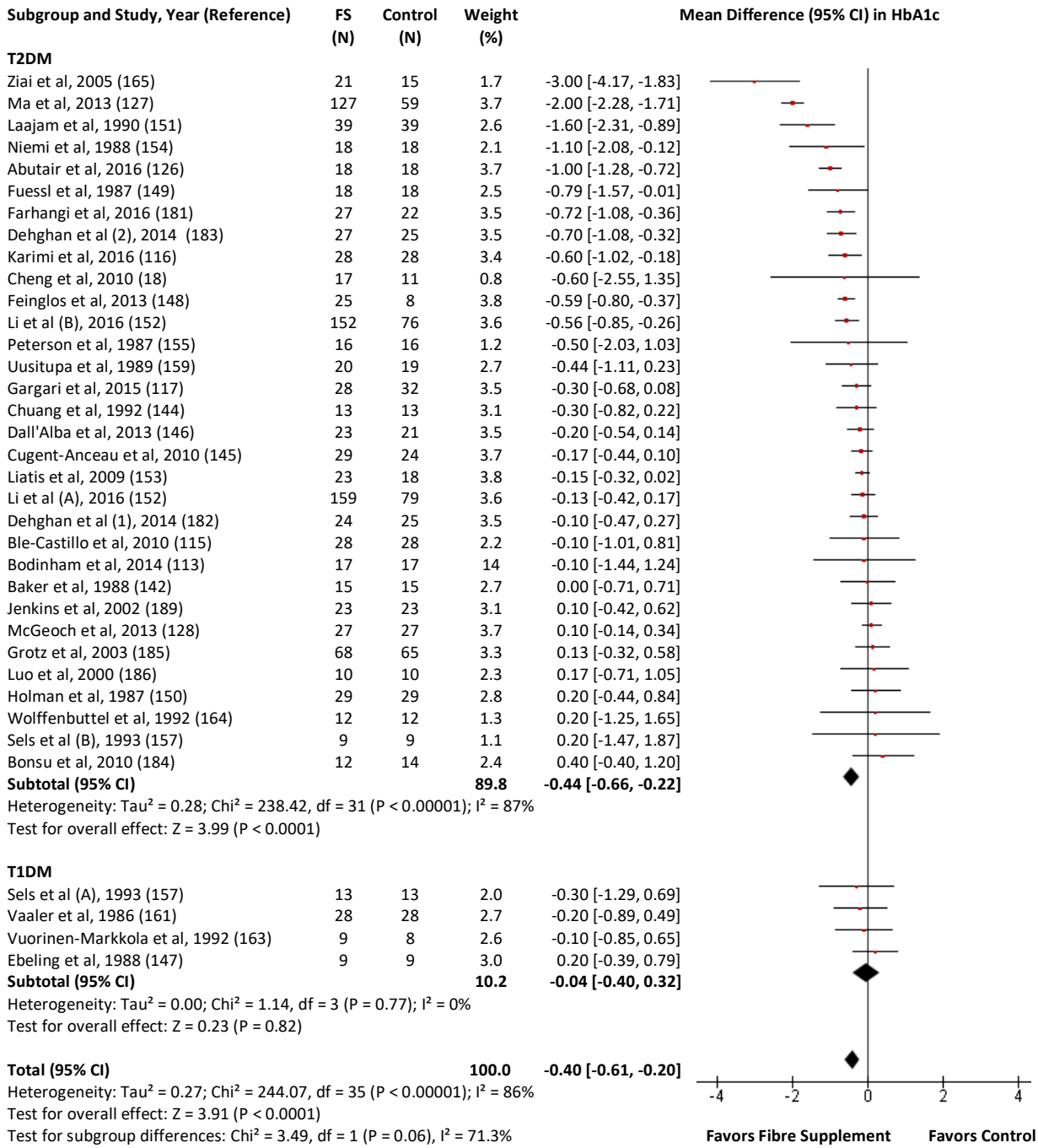

Figure 6.1. shows the effect of fiber supplementation on glycated hemoglobin (HbA1c). Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group.

Subgroup and Study, Year (Reference)	FS (N)	Control (N)	Weight (%)	Mean Difference (95% CI) in FG
T2DM				
Ziai et al, 2005 (165)	21	15	1.4	-4.98 [-6.79, -3.17]
Chen et al, 2003 (143)	22	22	2.6	-2.30 [-3.19, -1.41]
Rodriguez-Moran et al, 1998 (156)	60	63	3.4	-2.17 [-2.54, -1.80]
Abutair et al, 2016 (126)	18	18	3.3	-2.08 [-2.50, -1.66]
Feinglos et al, 2013 (148)	25	8	2.8	-1.97 [-2.77, -1.17]
Lalor et al, 1990 (86)	19	19	1.6	-1.90 [-3.55, -0.25]
Laajam et al, 1990 (151)	39	39	2.6	-1.80 [-2.74, -0.86]
Uusitupa et al, 1990 (158)	20	19	1.2	-1.60 [-3.71, 0.51]
Ma et al, 2013 (127)	127	59	3.4	-1.56 [-1.91, -1.21]
Uusitupa et al, 1989 (159)	20	19	2.1	-1.30 [-2.54, -0.06]
Aro et, 1981 (141)	9	9	1.2	-1.20 [-3.35, 0.95]
Fuessl et al, 1987 (149)	18	18	2.5	-1.06 [-2.05, -0.07]
Cheng et al, 2010 (18)	17	11	0.3	-1.00 [-5.92, 3.92]
Chuang et al, 1992 (144)	13	13	2.3	-0.94 [-2.02, 0.14]
Gargari et al, 2015 (117)	28	32	3.0	-0.93 [-1.61, -0.25]
Dehghan et al (2), 2014 (183)	27	25	3.4	-0.92 [-1.30, -0.54]
Farhangi et al, 2016 (181)	27	22	3.3	-0.92 [-1.32, -0.52]
Karimi et al, 2016 (116)	28	28	3.0	-0.84 [-1.52, -0.16]
Dehghan et al (1), 2014 (182)	24	25	3.4	-0.73 [-1.07, -0.39]
Vuksan et al, 1999 (162)	11	11	1.6	-0.71 [-2.38, 0.96]
Cugent-Anceau et al, 2010 (145)	29	24	2.9	-0.69 [-1.41, 0.03]
Liatis et al, 2009 (153)	23	18	3.2	-0.65 [-1.17, -0.13]
Karlstrom et al, 1984 (190)	28	28	1.9	-0.50 [-1.90, 0.90]
Luo et al, 2000 (186)	10	10	2.3	-0.50 [-1.62, 0.62]
Bonsu et al, 2010 (184)	12	14	2.4	-0.30 [-1.34, 0.74]
Jenkins et al, 2002 (189)	23	23	2.9	-0.30 [-1.01, 0.41]
Bodinham et al, 2014 (113)	17	17	3.4	-0.20 [-0.59, 0.19]
Peterson et al, 1987 (155)	16	16	1.7	-0.20 [-1.79, 1.39]
Li et al (A), 2016 (152)	159	79	3.2	-0.19 [-0.68, 0.29]
Ble-Castillo et al, 2010 (115)	28	28	1.2	-0.17 [-2.22, 1.89]
Li et al (B), 2016 (152)	152	76	3.3	-0.09 [-0.54, 0.35]
Holman et al, 1987 (150)	29	29	3.2	0.00 [-0.53, 0.53]
Grotz et al, 2003 (185)	68	65	3.3	0.06 [-0.38, 0.50]
Wolffenbuttel et al, 1992 (164)	12	12	1.3	0.20 [-1.81, 2.21]
Sels et al (B), 1993 (157)	12	12	1.3	0.20 [-1.81, 2.21]
McGeoch et al, 2013 (128)	27	27	3.2	0.30 [-0.20, 0.80]
Dall'Alba et al, 2013 (146)	23	21	2.4	0.50 [-0.51, 1.51]
Niemi et al, 1988 (154)	18	18	2.1	0.50 [-0.72, 1.72]
Uusitupa et al, 1984 (160)	20	19	1.6	0.80 [-0.82, 2.42]
Baker et al, 1988 (142)	15	15	1.2	0.90 [-1.26, 3.06]
Subtotal (95% CI)			**96.3**	**-0.79 [-1.07, -0.50]**
Heterogeneity: $Tau^2 = 0.58$; $Chi^2 = 242.60$, df = 39 ($P < 0.00001$); $I^2 = 84\%$				
Test for overall effect: $Z = 5.36$ ($P < 0.00001$)				
T1DM				
Vuorinen-Markkola et al, 1992 (163)	9	8	0.	-2.00 [-4.94, 0.94]
Sels et al (A), 1993 (157)	16	16	1.0	-0.90 [-3.25, 1.45]
Vaaler et al, 1986 (161)	28	28	2.0	0.30 [-1.03, 1.63]
Subtotal (95% CI)			**3.7**	**-0.35 [-1.57, 0.87]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 2.31$, df = 2 ($P = 0.32$); $I^2 = 13\%$				
Test for overall effect: $Z = 0.56$ ($P = 0.57$)				
Total (95% CI)			100.0	-0.77 [-1.06, -0.49]
Heterogeneity: $Tau^2 = 0.57$; $Chi^2 = 246.01$, df = 42 ($P < 0.00001$); $I^2 = 83\%$				
Test for overall effect: $Z = 5.40$ ($P < 0.00001$)				
Test for subgroup differences: $Chi^2 = 0.46$, df = 1 ($P = 0.50$), $I^2 = 0\%$				

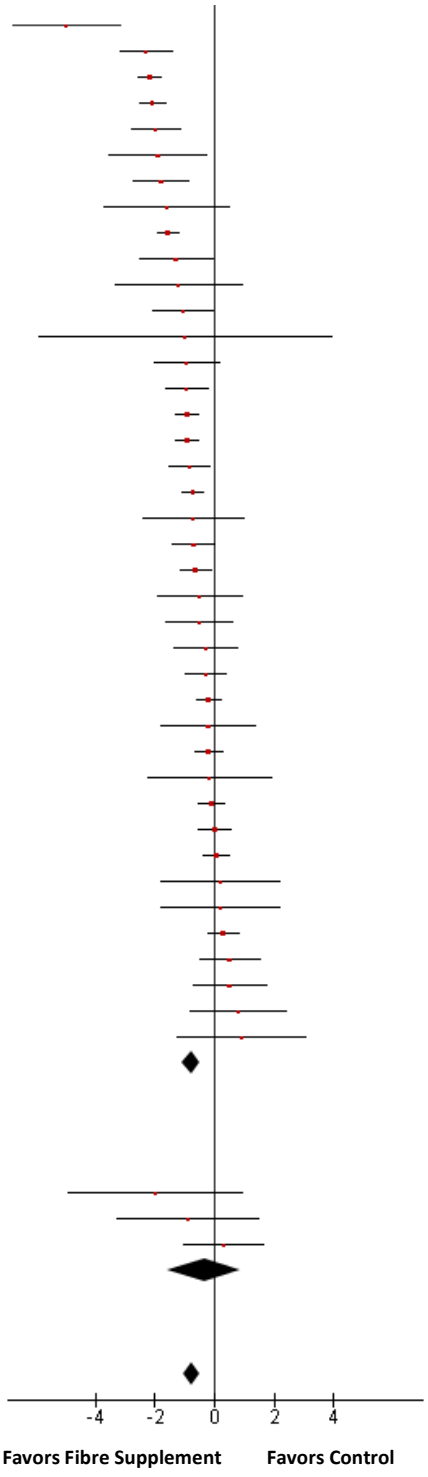

Figure 6.2. shows the effect of fiber supplementation on fasting glucose (FG). Diamonds represent the pooled effect estimates for overall and stratified analyses. Data are represented as MD with 95% CI, using the generic inverse variance random-effects models. Inter-study heterogeneity quantified by I^2 with significance $P < 0.10$. N = number of participants in each intervention group.

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