Inulin-type fructans supplementation and cardiovascular disease risk factors

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ABSTRACT

Cardiovascular diseases (CVDs) are a leading cause of mortality worldwide, with obesity being a major contributor due to unhealthy dietary habits and sedentary lifestyles. Poor dietary habits increase the risk of obesity, diabetes, hypertension, and other CVDs. However, a new concept called functional food has emerged as a potential solution to this problem. Functional foods are those that provide health benefits beyond basic nutrition and can reduce the risk of diseases. Prebiotics, like inulin-type fructans (ITF), are considered functional foods. These ITFs have been extensively studied and are the only prebiotics that have generated sufficient evidence to enable a comprehensive assessment of their potential as functional food components. They are commonly used in various food products, such as biscuits, bread, cereals, confectionery, drinks, infant feeds, sauces, table spreads, and yogurts, to improve organoleptic quality and a better-balanced nutritional composition. However, the available evidence provides conflicting results regarding the beneficial effects of ITF on health. Given the increased use of ITF in the food industry, we conducted a systematic review and meta-analysis (SRMA) to assess their effects on CVD risk factors.

In this thesis, we first describe the methods used in the SRMA, which were published in a peerreviewed journal. Subsequently, we present the results of the SRMA. The next two chapters discuss the reporting quality of randomized trials and abstracts of randomized controlled trials included in our SRMA. Finally, we summarize the methodological contributions of this thesis. Through our work, we hope to contribute to the growing body of evidence regarding the use of functional foods like ITF as a means of reducing the risk of CVDs and promoting healthier dietary habits.

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DECLARATION OF ACADEMIC ACHIEVEMENT

This is a 'sandwich thesis' comprised of 6 chapters.

Chapter 1 is unpublished. Jhalok Ronjan Talukdar is the sole author.

Chapter 2 is published in *BMJ Open*. RJdS conceived the research question relating to inulintype fructans and cardiometabolic risk factors. JRT, working with co-author DZ, operationalized the approach to the systematic review. JRT conceived the idea of investigating quality of reporting in studies of inulin-type fructans supplementation and the idea of improving subgroup analysis in meta-analysis using the ICEMAN tool. JRT drafted the manuscript. All authors provided critical input and approved the final version.

Chapter 3 is submitted to The American Journal of Clinical Nutrition. RJdS conceived the research question relating to ITF and cardiometabolic risk factors. JRT conducted the systematic review. He was involved in screening titles and abstracts, data extraction, assessment of risk of bias and certainty of the evidence. He prepared the data for meta-analysis and conducted all the analyses presented in the chapter- meta-analysis, subgroup analysis and parallel analysis of crossover trials. He interpreted the data and assessed the quality of the evidence. He wrote the first draft of the manuscript. All authors provided critical input and approved the final version. Chapter 4 is under review in PLOS ONE. JRT conceived the idea. He prepared the data extraction form, extracted data, conducted all the analyses in the study and wrote the first draft. All authors provided critical input and approved the final version.

Chapter 5 is under review in PLOS ONE. JRT conceived the idea. JRT prepared the data extraction form, extracted data, conducted all the analyses in the study and wrote the first draft. All authors provided critical input and approved the final version.

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Chapter 6 is unpublished. Jhalok Ronjan Talukdar is the sole author.

Chapter 1: Introduction

The Global Burden and Risk Factors for Cardiovascular Disease

Cardiovascular diseases (CVDs) are the leading cause of death worldwide (1), contributing to an estimated 20.5 million deaths globally in 2021 (2). CVD also negatively affects quality of life, resulting in 422 million disability-adjusted life years (age-standardized total CVD approximately 4,942 per 100,000 population) in 2021 (2). CVD causes acute coronary syndrome, heart failure and stroke, through the development of atherosclerotic plaque (3-5). The major risk factors for CVD include high blood pressure, high cholesterol, excess body fat, diabetes and unhealthy diet (6).

Modifiable Risk Factors for Cardiovascular Disease

The risk factors that can be changed or controlled through various interventions or lifestyle modification are modifiable risk factors. Several modifiable risk factors have been identified for cardiovascular disease that significantly contribute to the development and progression of the disease. These risk factors include high blood pressure, high cholesterol, excess body fat, diabetes and unhealthy diet (5). High blood pressure puts increased stress on the blood vessels, leading to damage and narrowing of the arteries. This can restrict blood flow to the heart and other organs, increasing the risk of heart disease and stroke (7). High cholesterol particularly LDL cholesterol ("bad" cholesterol), can lead to the formation of plaques in the arteries. These plaques can narrow the arteries and reduce blood flow, potentially causing heart attacks and strokes (8). Excess body fat, especially around the abdomen, can lead to metabolic changes, such as insulin resistance and dyslipidemia, which promote the development of heart disease (9).

Diabetes (both type 1 and type 2) are associated with an elevated risk of CVD. Diabetes can damage blood vessels and nerves, leading to complications such as coronary artery disease, heart failure, and stroke (10, 11).

Diet and Cardiovascular Diseases

An unhealthy diet is characterized by high intake of saturated and trans fats, sodium, and added sugars, and low intake of fruits, vegetables, and whole grains (12). Unhealthy diet can contribute to the development of risk factors for cardiovascular disease such as high blood pressure, high cholesterol, obesity, and diabetes. These risk factors, in turn, increase the likelihood of developing CVD (12-14).

The prevalence of obesity is increasing worldwide, primarily due to the consumption of unhealthy diets and sedentary lifestyles (15). Changes in food supply have drastically altered people's eating habits, with a shift towards fast food outlets and restaurants, resulting in unhealthy diets both at home and outside of home (16). There is a growth in purchase of packaged and ready-to-consume food products. They are usually high in processed food and low in whole foods. Unhealthy diets are high in added sugars, salts, processed food and low in fruits, vegetables, and whole grain. Recently, the intake of ultra-processed foods and sugar-sweetened beverages increased globally. For example, a study reported that among the processed and packaged food supply in US from 2005-2009, over 75% of foods contained some form of added sugar. All these changes in dietary habits and food supply system have dietary implications (16). For example, increased intake of sugar is associated with an increased risk of obesity, overweight, type 2 diabetes and hypertension (16).

The Concept of Functional Food: An Innovative Approach to Improving Diet

The development of functional food as a new concept during the past two decades represents a novel approach to improve diet (17-19). A functional food can be a natural food or food ingredient to which a component has been added or from which a component has been removed or in which one or more components has been modified (17, 20, 21). Functional food is distinguished from food supplements since functional food is part of usual diet instead of provided at a side of the usual diet (21, 22). A food is considered functional if it demonstrates health benefits or reduces the risk of disease beyond simply meeting nutrition requirements (17, 19-21, 23, 24). Functional foods emphasizes the role of certain foods in preventing and reducing the risk of disease (25). Functional foods have long been considered part of a comprehensive dietary approach to the prevention of cardiovascular disease (18, 21).

The Potential of Inulin-type Fructans as Functional Food Components

Prebiotics are considered functional foods because they have been shown to provide health benefits beyond basic nutrition (22, 26). They are non-digestible dietary fibers that are fermented by specific types of colonic bacteria, and they improve host health by selectively promoting the growth and functional activity of one or more bacteria in the colon which are associated with health benefits (27-29).

Inulin-type fructans (ITF) include inulin, fructo-oligosaccharides (FOS), and oligofructose (30). To categorize a compound as a prebiotic, it must meet the following criteria: (i) resistance to stomach acidity and enzymatic breakdown, as well as limited absorption in the gastrointestinal tract, (ii) fermentability by intestinal microbiota, and (iii) selective stimulation of the growth and/or activity of intestinal bacteria, leading to improved host health (31). ITF meet all the criteria of prebiotics. They have been extensively researched, and are the most common

prebiotics in the market (28, 30, 32). ITF is the prebiotic that has been extensively studied, providing substantial evidence for a comprehensive evaluation of its potential as a functional food component (33).

Based on its chemical structure, inulin is categorized as a long-chain ITF (degree of polymerization, 2–60), while oligofructose/FOS are categorized as short-chain ITF (degree of polymerization, 2–8) (34). ITF occur naturally in many plants and vegetables, including chicory, oats, leeks, bananas, garlic, wheat, onions, and artichokes (20, 28, 32, 35, 36). Inulin is primarily extracted from the roots of chicory plants on a large scale (28). Prebiotic effects may occur with daily consumption of ITF at a level of 5 to 8 g. However, these foods contain a low level of prebiotics. As a result, functional food development has focused on extracting the active ITF from these food sources and incorporating them into more commonly consumed products, such as biscuits, bread, cereals, confectionery, drinks, infant feeds, sauces, table spreads, and yogurts (32, 33).

Inulin-type Fructans as a Food Ingredient

Inulin-type fructans are used in food products because they offer improved organoleptic quality and a better-balanced nutritional composition (28). For example, the use of ITF in bakery products and breakfast cereals offers several benefits over other types of fiber. ITF keeps cereals "crunchy" and helps retain moisture in bread and cakes, which keeps these foods fresh for a longer period of time (28). Based on their technological properties and nutritional benefits, ITF can be used to reduce fat and sugar in food products. For example, oligofructose and short-chain oligofructose (scFOS) have greater solubility and a sweetness value 30–35% that of sucrose, making them useful as a sugar replacer. Long-chain ITF have water-binding properties and can form fat-mimicking gels. At concentrations greater than 10 to 20%, they provide reduced-fat

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foods that have similar sensory and textural characteristics to full-fat foods (37). These technological advantages, combined with their nutritional benefits, make ITF valuable components for enhancing human health. Functional ingredients like ITF can easily be added to highly consumed starchy foods like breads and cereals. This makes them a viable option as a preventive measure to reducing the burden of chronic diseases (28).

The Role of Inulin-Type Fructans in Reducing Cardiovascular Disease

The gut microbiota has emerged as an important mediator in cardiovascular health. Inulin-type fructans have shown promising effects on gut microbiota composition and function, with potential cardiovascular benefits (33, 34, 38). ITF work through several mechanisms that contribute to their potential cardiovascular benefits. ITF resist digestion in the upper gastrointestinal tract, remain unabsorbed throughout the gastrointestinal system, and are selectively fermented by specific types of bacteria in the colon (27). This process selectively stimulates the growth and activity of beneficial gut bacteria, such as Bifidobacteria and Lactobacilli. These beneficial bacteria produce short-chain fatty acids as metabolic by-products during the fermentation of inulin-type fructans. Short-chain fatty acids, particularly butyrate, have been associated with cardiovascular health benefits, including reduced inflammation, improved endothelial function, and lower blood pressure (34, 38, 39).

Systematic Reviews of Inulin-type Fructans Supplementation

Previous systematic reviews provided conflicting evidence regarding the beneficial effects of ITF on cardiovascular disease risk factors. Though previous reviews consistently provided beneficial effects of ITF on low-density lipoprotein (40, 41) but the evidence regarding fasting blood glucose and triglycerides were inconsistent (40-43). For example, systematic reviews by Li et al. (2021) (40) and Wang et al. (2019) (43) demonstrated beneficial effects of inulin-type

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fructans supplementation on fasting blood glucose but Liu et al. (2017) (41) did not find significant difference in fasting blood glucose after supplementation of inulin-type fructans. Regarding triglycerides, Li et al. (2021) (40) reported beneficial effects of ITF supplementation but Beserra et al. reported non-significant difference on this outcome (42).

Methodological Limitations in Systematic Reviews of Inulin-type Fructans Supplementation

Several systematic reviews have provided conflicting evidence regarding the beneficial effects of ITF on CVD risk factors (40, 41, 44-46). However, these reviews suffer from many methodological limitations that compromise their trustworthiness. The notable limitations of these reviews include: the authors did not assess the certainty of the evidence using GRADE (The Grading of Recommendations Assessment, Development and Evaluation) or other methods, did not follow recommended guidance for subgroup analysis (especially in hypothesizing the direction of subgroup effects a priori and using a test for interaction), and did not explain how they combined parallel and crossover trials.

Systematic review authors must provide effect estimates and should provide a judgement about the certainty of evidence to judge whether these estimates are likely to be correct (47). Review authors should use a systematic approach to assessing the certainty of evidence based on risk of bias (RoB), indirectness, inconsistency, imprecision, publication bias, dose-response (observational studies) and magnitude of effect (observational studies), preferably with a welldeveloped approach such as GRADE. Other approaches of assessing certainty of evidence include NutriGrade, Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM) and the Oxford Centre for Evidence-Based Medicine Levels of Evidence (48)

Subgroup analysis can help assess whether an intervention works differently in different settings, based on the characteristics of the studied populations (e.g., age, gender, geographic location) or

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the intervention/exposure (e.g., dose, timing of intervention). In subgroup analyses, results are pooled separately by groups of studies that share similar design characteristics (e.g., older vs. younger participants; men vs. women; healthy weight vs. overweight; or high dose vs. low dose interventions) that are thought to modify the outcome of interest (e.g. risk of type 2 diabetes, stroke) (49). The quality of a systematic review and meta-analysis is higher when the authors state the planned subgroup analyses a priori, in a published and/or registered protocol, along with the anticipated direction of effect (e.g., normal weight participants will respond more favorably to the intervention than overweight participants), while the systematic review quality is lower if authors failed to publish a protocol with a specified plan for investigating heterogeneity including subgroups and the anticipated direction of effect. If the authors conduct the subgroup analysis post-hoc then the subgroup findings reported may be less believable because of the perception of "fishing", and/or creating a multiple testing problem (50). Systematic reviews and meta-analysis should report tests of interaction (p-value) for all subgroups (50).

Meta-analyses of crossover trials are challenging if the trials do not conduct them appropriately. Crossover trials can be included in meta-analyses if the trial reports paired analysis or raw data from the crossover trial are available. However, the problem is that the data from crossover trials are often reported as if the trial was a parallel group trial (e.g., report outcome on each treatment instead of paired differences). If a paired analysis of crossover trials is not presented, a metaanalyst can combine crossover trials with parallel trials by ignoring pairing and treating crossover trials as if they were parallel trials. However, ignoring pairing leads to an overestimation of the variance due to the loss of within-subject correlation information. Weighting in meta-analysis is typically based on the inverse of the variance of the treatment effect estimate. As a result, the crossover trials treated as parallel may contribute less weight to

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the overall pooled estimate, reducing its contribution to the final pooled estimate of treatment effect (47). Considering the limitations in current reviews as well as increased use of ITF in the food industry, we sought to address these limitations in our review aimed at assessing the effects of ITF supplementation on CVD risk factors.

Reporting Limitations in Randomized Trials of Inulin-type Fructans Supplementation

Rigorous and transparent reporting of randomized trials (RCTs) is crucial for readers and users to properly assess their validity and reliability. In particular, it is important to report methodological details, such as the specification of primary outcomes, random sequence generation, and blinding (51). This helps readers to assess the validity of RCT results (52), however poor reporting quality might not reflect the actual conduct of a trial (53). Researchers might have conducted the trials properly but failed to report them following available guidelines, or been hampered by journal word limits. Insufficient reporting of RCTs can result in categorizing a study as a high risk of bias, which can ultimately downgrade the CoE of the study. Given the importance of reporting quality of RCTs, we assessed the quality of reporting of RCTs as well as abstracts of RCTs. This will help researchers, journal editors, reviewers, and policy makers to understand the current state of reporting in this field and take initiatives as needed.

Outline of the thesis

The overall theme of this dissertation is to understand the effects of ITF on cardiovascular disease risk factors, and understand how quality of reporting influences the interpretation of findings, and assessment of quality of bodies of evidence in nutrition, using RCTs of ITF as an exemplar. This thesis describes the design, and present the results of a systematic review and meta-analysis that assessed the effects of ITF on CVD risk factors in adults. It also includes an assessment of the reporting quality of abstracts and full reports of RCTs that have investigated

the effects of inulin-type fructans supplementation on cardiovascular disease risk factors. A brief description of these papers is provided below.

Chapter 2: The effect of inulin-type fructans supplementation on cardiovascular disease risk factors: A protocol for a systematic review and meta-analysis of controlled trials (54).

This manuscript outlined the methods for conducting the systematic review assessing the effect of ITF supplementation compared with no supplementation on CVD risk factors in adults. It also briefly outlines the methods for studies assessing the quality of reporting of RCTs and quality of reporting of abstracts of RCTs examining the effects of inulin-type fructans supplementation on cardiovascular risk factors in adults.

Chapter 3: The effects of inulin-type fructans on cardiovascular disease risk factors: A systematic review and meta-analysis of randomized controlled trials. The American Journal of Clinical Nutrition, 2023 (under review).

This paper is the systematic review to assess the effect of ITF supplementation compared with no supplementation on CVD risk factors in adults. The systematic review extends previous reviews of this topic through updated literature search and by addressing several methodological limitations of previous reviews. For example, previous reviews either did not assess certainty of the evidence using GRADE or other methods or did not follow available guidance for subgroup analysis (especially hypothesizing the direction of subgroup effects a priori, using a test for interaction) or did not explain how they combined parallel and cross-over trials together, which were addressed in our systematic review and meta-analysis.

Chapter 4: Assessment of the quality of reporting in abstracts of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey. PLOS ONE, 2022 (under review).

This paper assessed the reporting quality of abstracts of RCTs examining the effects of inulintype fructans supplementation on cardiovascular risk factors, before and after the publication of the Consolidated Standards of Reporting Trials extension for abstracts (CONSORT-A) in 2008. We found an inadequate overall reporting quality of abstracts of RCTs investigating the effects of inulin-type fructans on cardiovascular risk factors.

Chapter 5: Assessment of the quality of reporting of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey. PLOS ONE, 2022 (accepted conditional on minor revision).

This paper assessed the reporting quality of RCTs investigating the effects of inulin-type fructans supplementation on cardiovascular risk factors, before and after the publication of the Consolidated Standards of Reporting Trials (CONSORT) in 2010. We found a poor adherence to CONSORT by RCTs investigating the effects of inulin-type fructans on cardiovascular risk factors.

Chapter 6: Discussion and conclusion

This chapter discusses the methodological contribution of this thesis, which might contribute to the advancement of ITF supplementation studies. Finally, it makes an overall conclusion of this thesis.

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Chapter 2: The effect of inulin-type fructans supplementation on cardiovascular disease risk factors: A protocol for a systematic review and meta-analysis of controlled trials

This paper described the methodology of a systematic review to assess the effects of inulin-type fructans supplementation on cardiovascular disease risk factors (chapter 3). This paper also briefly discussed the methods for conducting studies on reporting quilting of RCTs and abstracts of RCTs (chapter 4 and 5 respectively).

Citation:

Talukdar JR, Cooper M, Lyutvyn L, Zeraatkar D, Ali R, Berbrier R, Janes R, Ha V, Darling R, Sievenpiper JL, Jenkins DJA, Banfield L, Mbuagbaw L, de Souza RJ. The effect of inulin-type fructans supplementation on cardiovascular disease risk factors: A protocol for a systematic review and meta-analysis of controlled trials. BMJ open. 2022;12(7):e058875.

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Protocol

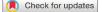
BMJ Open Effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a protocol for a systematic review and meta-analysis of randomised controlled trials

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ABSTRACT

Introduction This review aims to assess the effects of dietary supplementation with inulin-type fructans (ITF) compared with no supplementation on cardiovascular disease risk factors in adults and assess the quality of trial reporting using the Consolidated Standards of Reporting Trials (CONSORT) and CONSORT for abstract (CONSORT-A) checklists.

Methods and analysis We will search randomised controlled trials (RCTs) in MEDLINE, EMBASE, CINAHL, Emcare, AMED and the Cochrane Database of Systematic Reviews from inception to 31 March 2022, without any language restrictions. The RCTs need to administer ITF in adults for at least 2 weeks and assess effects on at least one cardiovascular risk factor. We will exclude RCTs that (1) assessed the postprandial effects of ITE: (2) included pregnant or lactating participants; (3) enrolled participants undergoing treatment that might affect the response to ITF. We will assess the study risk of bias (RoB) using V.2 of the Cochrane RoB tool for RCTs (RoB 2) and the certainty of the evidence using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach. We will pool data using a random-effects model. We will use the χ^2 test to compare compliance of CONSORT and CONSORT-A checklists and Poisson regression to identify factors associated with better reporting.

Ethics and dissemination Ethics approval is not required for secondary analysis of already published data. We will publish the reviews in a peer-review journal. **PROSPERO registration number** CRD42019136745.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death worldwide.¹ In 2019, CVD caused an estimated 17.9 million deaths globally¹ and by 2030, 23.6 million people are expected to die from CVD.² In 2019, it was responsible for 359 million years of life lost (age-standardised rate approximately 4439 per 100 000 population)

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ We will follow Cochrane guidance to conduct this systematic review including screening titles and abstracts, selecting studies and extracting data independently and in duplicate.
- \Rightarrow We will use the Grading of Recommendations, Assessment, Development and Evaluations approach to assess certainty of evidence.
- ⇒ We will follow the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) guidance to conduct subgroup analyses for our systematic review.
- ⇒ Pooled effect estimates are likely to be heterogeneous because of the different types of inulin-type fructans used, and duration of interventions.

and 393 million disability-adjusted life years (age-standardised rate approximately 4864 per 100 000 population).³

CVD can lead to an acute coronary syndrome, heart failure and stroke, mainly through the development of atherosclerotic plaque.^{1 2 4} Plaques are composed of fat, calcium and cholesterol, and they block and/ or narrow arteries, which limits the flow of oxygen-rich blood to the heart and brain.⁵⁶ Furthermore, plaques are recognised by the immune system as a foreign body, which stimulates an inflammatory response.7 8 If these plaques rupture, their contents cause clot formation, which is a precursor to heart attack or ischaemic stroke.78 Some of the wellestablished risk factors for CVD include high blood pressure, high cholesterol, diabetes, and excess body fat.

Dietary fibres are the edible parts of plants that are resistant to digestion and absorption

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in the human small intestine. Dietary patterns high in fibre has been shown to improve several cardiovascular risk factors, and reduce the risk of cardiovascular events.¹⁰⁻¹² Low dietary fibre intake is considered a major contributor to the epidemic of CVD.¹³ The beneficial effects of dietary fibres are partially due to their ability to reduce serum cholesterol through a variety of mechanisms. First, soluble fibre binds cholesterol in the lumen of the small intestine to reduce cholesterol absorption. Second, soluble fibre increases the faecal excretion of bile acids, diverting hepatic cholesterol for bile acid production and lowering circulating plasma LDL cholesterol as it is taken up by the liver from the plasma. Third, fibres that are freely fermentable by the colonic bacteria are converted into short-chain fatty acids such as acetic, propionic and butyric acids. Propionic acid can be absorbed and inhibit the liver's rate-limiting cholesterol synthesis enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase.¹⁴¹⁵ The Canadian Cardiovascular Harmonized National Guidelines Endeavour recommends a dietary pattern that includes ≥30 g of fibre per day to lower the risk of CVD.¹⁶ People with the highest dietary fibre intakes show a 16%-23% lower risk of all-cause mortality than those with the lowest.¹⁷⁻

Inulin-type fructans (ITF) are carbohydrates²⁰ that occur naturally in vegetables and plants including leeks, onions, artichokes, bananas, garlic, wheat and chicory.²⁰⁻²² ITF include fructo-oligosaccharides, oligofructose and inulin, which are soluble dietary fibres known as prebiotics.²³ Prebiotics promote the growth and activity of beneficial gut bacteria²⁴ and confer various health benefits, including improvements in CVD risk factors.²⁵ Several systematic reviews have demonstrated the beneficial effects of ITF on some CVD risk factors in certain subgroups.^{24 26-28}

Our systematic review will advance previous reviews of this topic in the following ways: (1) through an updated literature search; (2) assessing the effect of dietary supplementation with ITF on low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), fasting blood glucose (FBG), body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), waist circumference (WC), waist-to-hip ratio, body weight, apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), glucose haemoglobin A1c (HbA1c), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C) in adults with or without pre-existing cardiometabolic conditions; (3) assessing the quality of evidence using Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach; (4) an assessment of clinically relevant subgroups which may derive particular benefits, such as those with dyslipidaemia, type 2 diabetes and obesity and (5) assessing compliance with the Consolidated Standards of Reporting Trials (CONSORT) statement and the CONSORT extension for abstract (CONSORT-A) in included randomised controlled trials (RCTs).

METHODS

This protocol is reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.²⁹ We established our methods for this systematic review a priori. We will conduct our systematic review using Cochrane methods.³⁰

Criteria for considering studies for this review

Types of studies

We will include only RCTs in our review.

Types of participants

We will include studies of adults (aged 18 years or older) with or without pre-existing CVD, diabetes, hypertension or dyslipidaemia. Studies will be ineligible if they only look at the postprandial effects of ITF or involved participants with conditions or undergoing treatment that seriously alters normal digestion or absorption of nutrients. These include chemotherapy, dialysis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, chronic obstructive pulmonary disease, inflammatory bowel disease, irritable bowel syndrome, chronic pancreatitis, chronic kidney disease and previous gastric bypass surgery. Additionally, we will exclude studies that included pregnant or lactating participants because of the transient effects on cardiometabolic risk factors during these life stages.

Types of interventions

Eligible interventions include the administration of a clearly specified type of ITF for a minimum of 2 weeks. Studies that administered ITF with a co-intervention are eligible if the co-intervention was present in both the treatment and control arms and likely operates through a mechanism independent of the ITF (eg, Roshanravan *et al*⁸¹ compared butyrate versus butyrate+inulin to assess the effect of butyrate and inulin supplementation in patients with diabetes).

Comparator(s)

The comparator(s) will include administration of placebo or control foods for a minimum of 2 weeks.

Types of outcome measures

The main outcomes of our review are LDL-C, TG and FBG. The secondary outcomes of our review are body mass index (BMI), body weight, WC, waist-to-hip ratio, SBP, DBP, HDL-C, VLDL-C, TC, ApoA1, Lipoprotein B (ApoB) and HbA1c.

Search methods for identification of studies

Electronic searches

We developed the search strategies in consultation with a librarian at the McMaster Health Sciences Library (online supplemental file 1). We will search MEDLINE, EMBASE, CINAHL, Emcare, AMED and Cochrane Database of Systematic Reviews databases from inception through 31 March 2022, without any language restrictions.

Searching other resources

We will examine the reference lists of eligible RCTs and relevant reviews to augment our database search.

Data collection and analysis

Selection of studies

A pair of reviewers will screen the titles, abstracts and full-text articles independently and in duplicate. The reviewers will select the full-text articles based on inclusion criteria. They will resolve any disagreement through discussion or consultation with a third reviewer if needed. If there are multiple publications from the same study, then we will consider each study as a unit of interest instead of each report for our review. We will combine information from multiple publications to avoid overlap in participants, prioritising the study with the largest sample size and longest follow-up for each outcome of interest. The reviewers will document the reasons for the exclusion of the studies. We will present the study selection process in a flow diagram.

Data extraction and management

A pair of reviewers will extract information about the study characteristics and results independently and in duplicate. They will resolve any disagreement through discussion or consulting a third reviewer. They will extract information about the study (basic bibliometric information, design, conflicts of interest, funding source, country or countries of conduct), characteristics of participants (baseline information for all relevant outcome measures, baseline comorbidities of the study population, age, BMI, percentage of the population that has comorbidities), intervention (length of intervention, dosage, regimen and any co-interventions) and outcomes reported. The reviewers will extract data presented only in graphs using a Plot Digitizer (http://plotdigitizer.sourceforge.net/).

We will enter data in duplicate into a spreadsheet template (Microsoft Excel, Microsoft) and collect reported outcome measures based on the following hierarchy for parallel RCTs: (1) change in measure from baseline or between-group difference in change from baseline or per cent change in measure from baseline (if baseline score is reported); (2) measure at follow-up or between-group difference in measure at follow-up; (3) regression coefficients. We will extract data based on the following hierarchy for crossover RCTs: (1) between group difference in change from baseline; (2) between-group difference in measure at follow-up; (3) change in measure from baseline; (4) per cent change in measure from baseline when baseline score is reported; (5) regression coefficients for change score; (6) measure at follow-up. We will apply paired analyses to all crossover trials according to the methods of Cochrane Handbook, Elbourne et al or Curtin et al.^{30 32 33} To investigate the effect of imputed correlation coefficients on paired analyses, we will perform sensitivity analyses across a range of possible

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correlation coefficients (0, 0.33, 0.66 and 0.99). To mitigate the unit-of-analysis error from including trials with multiple intervention groups, we will combine groups to create single pairwise comparisons.³⁰

Assessment of risk of bias for included studies

A pair of reviewers will assess the RoB using the Cochrane RoB 2.0 tool³⁴ independently and in duplicate. The reviewers will assess the RoB based on bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported results. The reviewers will resolve any disagreement in the RoB assessment through discussion or consulting a third reviewer, if necessary.

Measures of treatment effect

The data for our meta-analysis will be continuous measures, reported in SI units (eg, mmol/L). We outlined the rules for converting outcome data in online supplemental file 2. We will compute the pooled mean difference if the reported measurement scales are the same (or interconvertible, such as mg/dL to mmol/L), otherwise, the standardised mean difference will be used if the reported measurement scales are different and not interconvertible. Pooled effects along with associated 95% confidence intervals (CIs will be presented. If a study reports multiple arms, then we will only include the relevant arms for our systematic review.

Unit of analysis

We will consider the unit of randomisation of included studies as the unit of analysis. In the case of multi-arm trials, if there is one control arm but more than one relevant intervention arms, we will either combine the two intervention arms to make a single pairwise arm or exclude the intervention arm which is less appropriate for this review as described in Cochrane Handbook.³⁰

Dealing with missing data

We will contact the study authors to obtain any missing outcome data. If study authors are unresponsive, we will conduct a sensitivity analysis to determine the potential impact of missing data relevant to the outcomes of interest. We will use published methods of sensitivity analyses for missing outcome data using extreme but plausible assumptions.^{35,36}

Assessment of heterogeneity

Initially, we will visually inspect the forest plot to assess heterogeneity. Then we will assess the heterogeneity among studies using I^2 statistics and a χ^2 test. We will use the criteria suggested in the Cochrane Handbook to interpret I^2 statistics for heterogeneity. Specifically, 0%-40%: might not be important; 30%-60%: may represent moderate heterogeneity; 50%-90%: may represent substantial heterogeneity; 75%-100%: considerable heterogeneity.³⁰ If there is substantial heterogeneity

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among the studies, we will attempt to explain this through subgroup analysis or meta-regression. 30

Assessment of publication bias

We will visually inspect and conduct statistical tests (eg, Egger's regression), if there are >10 studies to assess the potential for publication bias as per published guidelines.³⁷

Data synthesis

Where two or more studies for a given outcome are eligible, we will conduct a meta-analysis using the 'metafor' package in R. We will use the random-effects model for meta-analysis using the Restricted Maximum Likelihood estimator considering there will be some heterogeneity between studies based on participants and interventions. We will also use a fixed-effects model for meta-analysis if there are fewer than five studies. If we do not have enough data for statistical pooling, then we will conduct a narrative synthesis of the findings.

Subgroup analysis and investigation of heterogeneity

We will follow the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) guidance (ie, hypothesising direction of subgroup effects a priori, prior evidence of subgroup effect, using a test for interaction, testing only a small number of subgroups and avoiding arbitrary cut-off points) to conduct subgroup analyses for our systematic review.³⁸

We will conduct the following six subgroup analyses to understand the effects of sex, baseline disease condition, ITF type, ITF dose, RoB and duration of intervention on health outcomes:

- Sex: a recent meta-analysis suggests that ITF intake leads to better outcomes (eg, reduces fasting blood glucose and HbA1c) for females compared with males.²⁷ We hypothesise the same. We will conduct a subgroup analysis to understand the effects of ITF on females compared with males.
- 2. Baseline disease condition: we hypothesise that participants without pre-existing CVD, diabetes, hypertension or dyslipidaemia in the baseline will exhibit better outcomes. We will conduct a subgroup analysis comparing the studies that include people with these conditions versus without.
- 3. Types of ITF: evidence suggests that inulin may be more efficacious than other ITF.²⁷ We hypothesise the same. We will conduct a subgroup analysis to compare the effects of inulin with other types of ITF.
- 4. Dose of ITF: evidence suggests that 10 g ITF intake per day is an optimal dose.²⁷ We will test this hypothesis by comparing the effects of 10 g ITF intake with other doses of ITF intake. We will also use dose as a continuous variable to explore the effects of lower versus higher intake of ITF. We will also look at the interaction between dose and duration of intervention.
- 5. Risk of bias: studies with high or unclear RoB usually exaggerate effect estimates.³⁹ We hypothesise that

studies with higher or unclear RoB will report larger effect estimates. We will conduct a subgroup analysis to compare the studies with higher or unclear RoB with lower RoB.

6. Duration of intervention: it is recommended to supplement ITF for 6 weeks or longer.²⁷ We will conduct a subgroup analysis to compare the effects of ITF supplemented for \geq 6 weeks vs <6 weeks. We will also use weeks as a continuous outcome to explore the effects of the duration of ITF intake on health outcomes.

Sensitivity analysis

We will repeat the analysis by excluding the high RoB studies to understand their influence on the results. We will perform a sensitivity analysis based on parallel versus crossover study designs. We will also conduct a sensitivity analysis only including food-controlled trials to understand whether the results changed based on control arms. Additionally, if any unanticipated study design or conduct issues are identified during the conduct of the review that we believe would have a potential impact on the results, additional sensitivity analyses will be conducted to quantify their impact on findings. Such ad hoc decisions will be documented appropriately.

Certainty of the evidence

We will use the GRADE approach to assess the certainty of the evidence of each outcome.⁴⁰ The GRADE approach considers five domains, including the RoB, imprecision, inconsistency, indirectness and likelihood of publication bias for each outcome of interest. We will rate each outcome as either high, moderate, low or very low certainty evidence based on these domains.

Summary of findings table

A summary of findings table provides a succinct summary of the key information from systematic reviews needed by decision-makers.⁴¹ We will prepare the GRADE summary of findings tables to report the main comparisons of this review.⁴¹

Substudy

Background

The RCT is considered the gold standard to assessing the effectiveness of health interventions.^{42–44} A wellconducted RCT can transform patient care. However, reporting of the study design, conduct, analysis and interpretation of an RCT must be transparent and sufficiently detailed such that readers and practitioners can appropriately judge the validity and applicability of the trial to particular practice settings.⁴⁵ This is difficult to do when trial reporting is inadequate.⁴⁶ At worst, inadequate reporting can lead to a biased estimate of the treatment effect, leading physicians to avoid truly effective treatments or promote truly ineffective treatments.⁴⁷ The CONSORT statement intends to facilitate improved and transparent reporting of trials by authors.⁴⁸

Just as importantly, abstracts of RCT reports must also adhere to reporting guidelines because clinicians often

make treatment decisions based on the abstracts of research articles^{46,49,50} owing to time limitations, language barriers or paywalls.⁵¹ Ideally, authors should provide sufficient information in an abstract to allow readers to assess the validity of an RCT. The CONSORT-A is intended to guide the authors to provide a minimum list of key details about an RCT.^{46,50}

Objective

The objective of this study is to compare reporting quality of RCTs and abstracts of RCTs that assessed the effects of ITF supplementation on CVD risk factors in adults, published before and after publication of CONSORT and CONSORT-A respectively.

Data extraction and management

The CONSORT statement was developed in 1996⁴⁵ and revised and updated in 2001 and 2010.^{42 52} The CONSORT-A statement was developed in 2008.⁴⁶ The reviewers will collect data following 25- item CONSORT 2010 checklists and 17-item CONSORT-A checklists for RCT publications selected for our systematic review.⁴²⁴⁵⁴⁶⁵² We will simply count (yes/no) to understand whether the RCTs adhered to each item.

Data analysis

We will compare the studies published before and after the publication of CONSORT 2010 and CONSORT-A 2008 statements to assess conformity with CONSORT and CONSORT-A statements. We will use the χ^2 test to assess compliance. We will use Poisson regression to adjust confounders including study publication year (before or after the publication of CONSORT and CONSORTA guidance), journal endorsement (endorsed CONSORT vs non-endorsed), journal impact (high impact vs others), the statistical significance of primary outcome (significant vs non-significant), funding status (industry-funded vs others), sample size (≤100 vs >100), study design (parallel vs crossover), authors' expertise (expertise in research methodology, biostatistics and subject matter vs no such expertise) and interventions (pharmacological vs non-pharmacological).

ETHICS AND DISSEMINATION

Consistent with our institution's policy, ethics approval is not required for secondary analysis of already published data. We will publish the reviews in a peer-review journal. We will also present the results of these reviews in conferences and meetings with other researchers and clinicians.

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Competing interests RJ de Souza has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012-2017 to present and discuss this work. He has presented updates of this work to the WHO in 2022. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has received speaker's fees from the University of Toronto, and McMaster Children's Hospital. He has held grants from the Canadian Institutes of Health Research. Canadian Foundation for Dietetic Research, Population Health Research Institute, and Hamilton Health Sciences Corporation as a principal investigator, and is a co-investigator on several funded team grants from the Canadian Institutes of Health Research. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada), and a co-opted member of the Scientific Advisory Committee on Nutrition (SACN) Subgroup on the Framework for the Evaluation of Evidence (Public Health England). JLS has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of health Research (CIHR), Diabetes Canada, PSI Foundation, Banting and Best Diabetes Centre (BBDC), American Society for Nutrition (ASN), INC International Nut and Dried Fruit Council Foundation, National Dried Fruit Trade Association, National Honey Board (the US Department of Agriculture (USDA) honey 'Checkoff' programme), International Life Sciences Institute (ILSI), Pulse Canada, Quaker Oats Center of Excellence, The United Sovbean Board (the USDA sov 'Checkoff' programme). The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers) and The Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received in-kind food donations to support a randomised controlled trial from the Almond Board of California. California Walnut Commission, Peanut Institute, Barilla, Unilever/Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, WhiteWave Foods/Danone and Nutrartis. He has received travel support, speaker fees and/or honoraria from Diabetes Canada,

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Dairy Farmers of Canada, FoodMinds, International Sweeteners Association, Nestlé, Pulse Canada, Canadian Society for Endocrinology and Metabolism (CSEM), GI Foundation, Abbott, General Mills, Biofortis, ASN, Northern Ontario School of Medicine, INC Nutrition Research & Education Foundation, European Food Safety Authority (EFSA), Comité Européen des Fabricants de Sucre (CEFS), Nutrition Communications, International Food Information Council (IFIC), Calorie Control Council, and Physicians Committee for Responsible Medicine. He has or has had ad hoc consulting arrangements with Perkins Cole, Tate & Lyle, Wirtschaftliche Vereinigung Zucker, Danone and INQUIS Clinical Research. He is a member of the European Fruit Juice Association Scientific Expert Panel and former member of the Soy Nutrition Institute (SNI) Scientific Advisory Committee. 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He has received in-kind supplies for trials as a research support from the Almond Board of California, Walnut Council of California, the Peanut Institute, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from Nutritional Fundamentals for Health (NEH)-Nutramedica, Saint Barnabas Medical Center, The University of Chicago, 2020, China Glycemic Index (GI) International Conference, Atlantic Pain Conference, Academy of Life Long Learning, the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies, the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, Epicure, Danone, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative (THI), Heali Al Corp, Institute of Food Technologists (IFT), Soy Nutrition Institute (SNI), Herbalife Nutrition Institute (HNI), Saskatchewan & Alberta Pulse Growers Associations, Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Quaker Oats, Procter & Gamble, Abbott Laboratories, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. 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(Academic Press/Elsevier 2020 ISBN:978-0-12-810510-8) and his sister. Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. He is also a vegan.

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Chapter 3: The effects of inulin-type fructans on cardiovascular disease risk factors: *systematic review and meta-analysis of randomized controlled trials*

Citation:

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The effects of inulin-type fructans on cardiovascular disease risk factors

A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

OBJECTIVE

To assess the effects of inulin-type fructans supplementation on cardiovascular disease risk factors in adults.

DESIGN

Systematic review and meta-analysis.

DATA SOURCES

MEDLINE, EMBASE, Emcare, AMED, CINAHL, and the Cochrane Library databases were searched from inception through May 15, 2022.

STUDY SELECTION

Eligible randomized controlled trials (RCTs) administered inulin-type fructans or placebo to adults for \geq 2 weeks and reported one or more of: low, very-low, or high-density lipoprotein cholesterol (LDL-C, VLDL-C, HDL-C); total cholesterol; apolipoprotein A1 or B (ApoA1 or ApoB); triglycerides; fasting blood glucose ; body-mass-index (BMI); body weight; waist circumference; waist-to-hip ratio; systolic or diastolic blood pressure (SBP or DBP); or hemoglobin A1c (HbA1c).

MAIN OUTCOMES MEASURES

Primary outcomes: LDL-C, triglycerides and fasting blood glucose; Secondary outcomes: BMI, body weight, waist circumference, waist-to-hip ratio, SBP, DBP, HDL-C, VLDL-C, total cholesterol, ApoA1, ApoB, and HbA1c.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently and in duplicate screened studies, extracted data and assessed risk of bias. We pooled data using random-effects model, and assessed the certainty of the evidence (CoE) using the GRADE approach.

RESULTS

We identified 1,767 studies and included 55 RCTs with 2,518 participants in a meta-analysis. The pooled estimate showed that inulin-type fructans supplementation reduced LDL-C (Mean Difference [MD] -0.14 mmol/l, 95% CI -0.24 to -0.05, 38 RCTs, 1,879 participants, very low CoE), triglycerides (MD -0.06 mmol/l, 95% -0.12 to -0.01, 40 RCTs, 1,732 participants, low CoE), and body weight (MD -0.97 kg, 95% CI -1.28 to -0.66, 36 RCTs, 1,672 participants, low CoE) but little to no effect on other cardiovascular risk factors. Effects were larger when study duration was ≥ 6 weeks and in pre-obese and obese participants.

CONCLUSIONS

Inulin-type fructans may reduce low-density lipoprotein, triglycerides, and body weight. Our findings of low to very low certainty evidence on the effects of inulin-type fructans supplementation suggests further well-designed and executed trials to improve certainty in evidence.

SYSTEMATIC REVIEW REGISTRATION PROSPERO CRD42019136745

WHAT IS ALREADY KNOWN ON THIS TOPIC

Several systematic reviews have demonstrated the beneficial effects of ITF on some CVD risk factors (e.g., low-density lipoprotein, triglycerides) in certain subgroups such as females and patients with comorbidities. However, these studies suffer from many methodological limitations, including: 1) not assessing the certainty of evidence; 2) not following established guidance for the specification, conduct, and reporting of subgroup analyses; and 3) failing to explain statistical approaches for combining parallel and crossover trials.

WHAT THIS STUDY ADDS

Our systematic review assessed the effects of inulin-type fructans supplementation on cardiovascular disease risk factors in adults, incorporating both crossover and parallel trials, conducting prespecified subgroup analyses, and using the GRADE (grading of recommendations assessment, development and evaluation) approach.

Low to very low certainty evidence showed that ITF supplementation had beneficial effects on low-density lipoprotein, triglycerides, and body weight. Subgroup analysis by study duration and BMI suggested that ITF supplementation had a beneficial effect on low-density lipoprotein in longer duration studies (follow-up duration ≥ 6 weeks) and on triglycerides in pre-obese (BMI 25.0 to 29.9 kg/m2) and obese participants (BMI >30 kg/m2), respectively.

These findings have clinical implications for pre-obese and obese people for the management of their cardiovascular health, as well as for policy makers involved in managing cardiovascular diseases for the public.

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Introduction

Inulin-type fructans (ITF) are a group of natural carbohydrates (1) that are found in vegetables and plants including leeks, onions, artichokes, bananas, garlic, wheat and chicory (1-3). ITF include fructo-oligosaccharides (FOS), oligofructose and inulin, all of which are soluble dietary fibers known as prebiotics (4). Prebiotics promote the growth and activity of beneficial gut bacteria (5) and confer various health benefits, including improvements in cardiovascular disease (CVD) risk factors (6). Furthermore, ITF are widely used to replace fat and sugar in foods (7) including bread, cakes and chocolate; but also in less obvious foods such as dairy and meat products (7). In addition to their role as food chemistry adjuvants, as well as flavour enhancers, one must also consider the potential health benefits of enriching foods with ingredients that have similar properties to dietary fiber, which much of the American population fails to consume in sufficient amounts. Some patients, have unwanted side effects from statin therapy and thus prefer dietary modification (8, 9).

Several systematic reviews have demonstrated the beneficial effects of ITF on some CVD risk factors in certain subgroups such as female and patients with comorbidities (5, 10-12). These studies, however, suffer from a number of methodological limitations including 1) not assessing the certainty of evidence; 2) not following established guidance for the specification, conduct, and reporting of subgroup analyses; and 3) a failure to explain statistical approaches for combining parallel and cross-over trials.

Our review comprehensively addresses these issues to provide a systematic assessment of the effects of ITF supplementation compared with no supplementation on CVD risk factors in adults, which can guide clinical decision-making. We perform subgroup analyses to answer questions of "how much" (i.e., dose), "for how long" (i.e., duration), and "for whom" (i.e., by clinically

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relevant subgroups according to health condition). Additionally, we assess the certainty of the evidence for clinical decision making using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach, as recommended by the Cochrane Collaboration (13).

Methods

We conducted the systematic review following the Cochrane Handbook for Systematic Reviews of Interventions (13), and report it following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (14). We prospectively registered (CRD42019136745) and published our protocol (15).

Data sources and Searches

We searched OVID MEDLINE, EMBASE, Emcare, AMED, CINAHL, and the Cochrane Library from inception through May 15, 2022, without language restrictions using a comprehensive search strategy developed with a librarian (LB) (see "Supplementary material"). We supplemented the search by searching the reference lists of included studies.

Outcomes

The primary outcomes for this systematic review are low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and fasting blood glucose (FBG), with LDL-C as the major established modifiable risk factor for CVD and TG and FBG as risk factors of current interest (16-20) that were most likely to also be the primary outcomes of included studies, and would be most strongly influenced by the mechanism of action of ITF. The secondary outcomes of our review are body mass index (BMI), body weight, waist circumference (WC), waist-to-hip ratio, systolic and diastolic blood pressure (SBP and DBP), high-density lipoprotein cholesterol (HDL-C) verylow-density lipoprotein cholesterol (VLDL-C), total cholesterol (TC), apolipoproteins A1 and B (ApoA1 and ApoB), and hemoglobin A1c (HbA1c). These important secondary outcomes are likely also influenced by ITF, but are often secondary outcomes in the studies included in this review.

Study selection

We included randomized control trials (RCTs) investigating the effects of ITF on CVD risk factors in adults (18 years or older) with or without pre-existing CVD, diabetes, hypertension, or dyslipidemia. The ITF and dose must have been specified, administered for \geq 14 days, and a placebo or control carbohydrate comparator arm must have been included. Studies that administered ITF with a co-intervention were eligible if the co-intervention was present in both the control and treatment arms and believed to operate through a mechanism independent of the ITF.

Studies were excluded if they only reported postprandial effects of ITF or involved participants with conditions or undergoing treatment that seriously alters normal digestion or absorption of nutrients. These include chemotherapy, dialysis, liver disease, chronic obstructive pulmonary disease, inflammatory bowel disease, irritable bowel syndrome, chronic pancreatitis, chronic kidney disease, and previous gastric bypass surgery. Additionally, we excluded studies of pregnant or lactating participants because of the transient effects on cardiometabolic risk factors during these life stages.

Pairs of reviewers (LL, MC, AC, FC, HH, SO, LH, JP) screened titles and abstracts independently and in duplicate. The eligibility of full texts was also assessed independently and in duplicate (LL, MC, AC, LH, MM, HH). Eligibility was determined by consensus between reviewers. Conflicts were resolved through discussion with a third reviewer (RJdS).

Data extraction

Study characteristics and data were extracted independently and in duplicate by pairs drawn from seven independent reviewers, after calibration exercises (AC, FC, JP, HH, LH, MC, MM).

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Extracted data included study design, conflicts of interest, funding source, country of conduct, participant characteristics (baseline values of relevant outcome measures, comorbidities, age, ethnicity, BMI, length of intervention, dosage, regimen and co-interventions, and outcomes assessed. Data presented only in figures were extracted using plot digitizer (<u>http://plotdigitizer.sourceforge.net/</u>). Data were entered in duplicate into a spreadsheet template (Microsoft Excel, Microsoft Corp.). The hierarchy of extracted outcome measures for RCTs is reported in Supplementary document S1.

Assessment of risk of bias in included trials

Reviewers assessed the risk of bias (RoB) for included trials independently and in duplicate using version 2 of the Cochrane 'Risk of bias' tool (RoB 2) (13, 21). We assessed RoB based on the randomization process, deviations from intended interventions, missing outcome data, measurements of the outcome(s) and the selection of the reported results. Using the signaling questions, each domain was rated as "low risk", "some concerns", "high risk," or "uncertain". The overall RoB for a particular study was determined by the least favorable assessment (excluding bias due to missing data).

Data synthesis

We summarized participant demographics and outcomes qualitatively. We formatted and converted data according to the rules listed in Supplementary document 2. If two or more eligible studies for a given outcome were included, we conducted a meta-analysis using the 'metafor' package (22) in R version 4.0.3 (23). We used a random-effects model for meta-analysis using the Restricted Maximum Likelihood estimator anticipating some heterogeneity between studies due to variations in participants, interventions, and follow up duration. We used a fixed-effects model for meta-analysis if there were fewer than five studies. The mean difference (MD) and

95% confidence intervals (95% CI) of continuous outcomes measured on the same scale between ITF and control arms at follow up were pooled. A two-sided p-value <0.05 was set as the level of significance for an effect.

Assessment of heterogeneity

Heterogeneity was detected using the chi-square test and quantified using the I² statistic. We considered that an I² value \leq 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and \geq 75% may represent considerable heterogeneity (13). If I² was \geq 50%, we attempted to explain this through *a priori* subgroup analyses and removal of individual trials in the sensitivity analyses (13).

Subgroup Analyses and investigation of heterogeneity

We explored potential reasons for heterogeneity through pre-specified and post-hoc subgroup analyses. We conducted the following *pre-specified* subgroup analyses: sex (female vs male), disease status (diseased vs healthy), ITF type (inulin vs others), ITF dose (<10 g/day vs \ge 10 g/day), risk of bias (low vs high or unclear), duration of intervention (< 6 weeks vs \ge 6 weeks). We conducted three post-hoc subgroup analyses: 1) age (young: <40 years, old: \ge 40 years), 2) BMI (normal: 18.5–24.9, pre-obese: 25.0–29.9, obese: >30), 3) diabetes (present or absent) to improve the clinical application of our findings.

Publication bias

We visually inspected the funnel plots, and conducted statistical tests (e.g., Egger's and Begg's) for primary outcomes when there were more than 10 studies to assess the potential for publication bias (24).

Sensitivity analysis

We performed meta-analyses excluding outliers and influential studies, as well as excluding studies judged to be at high risk of bias, to understand their influence on the results (25). We also analyzed parallel and cross-over trials separately. We then conducted parallel analyses of crossover trials using more conservative correlation coefficients (i.e., 0, 0.33, 0.66 and 0.99). We conducted sensitivity analyses including only food-controlled trials to understand whether the results changed based the nature of control arms.

Certainty (quality) of the body of evidence

We followed the GRADE approach to assess the certainty of the evidence for each outcome (26). GRADE considers five domains: risk of bias, imprecision, inconsistency, indirectness, and likelihood of publication bias. We evaluated the certainty (quality) of the evidence for each outcome as high, moderate, low, or very low based on these domains. We prepared a summary of findings table using GRADEpro (27).

Results

Search Results

From 1,767 identified citations, 151 reports were retrieved for full-text review and 55 included for meta-analyses [Supplementary Figure 1].

Study Characteristics

Of the included studies, 36 were parallel randomized trials and 19 were crossover trials, including 2,518 participants. The median number of participants per study was 40 (range 6 to 199) with a median age of 46 years (range 19 to 67 years). Thirty-nine studies enrolled participants with CVD risk factors (28-63), one with idiopathic reactive hypoglycemia (64), one with \leq 3 bowel movements per week (65) and 14 with otherwise healthy participants (66-78). A total of 30 included studies assessed dietary or supplemental ITF (Inulin, high-performance inulin, FOS, agave fructans) (28, 31-33, 35, 38-43, 45-49, 51-54, 56, 57, 61, 64-74, 76-81), 5 assessed synbiotics (probiotic with inulin and bacteria) (30, 58, 59, 75, 82) and 10 assessed inulin with co-interventions also present in the control arm (29, 34, 36, 37, 44, 50, 55, 60, 62, 63). The median dose of supplemental or dietary ITF was 10 g/day (range 0.75 to 30) and the median follow-up was 8 weeks (range 2 weeks to 2 years) [**Table 1**].

Risk of bias in included trials

Among the included trials, 16 trials (29%) (28, 31, 35, 36, 39, 46, 47, 50, 52-55, 62, 66, 80, 81) were rated at an overall low risk of bias because all domains (excluding bias due to missing data) were rated at low risk of bias (**Supplementary Figure 2**). Twenty-two trials (40%) (33, 37, 38, 40-42, 48, 49, 51, 56-60, 63-65, 67, 75-77, 82) were at an overall high risk of bias because ≥ 1

domain was rated at high risk. The remaining 17 trials (31%) (29, 30, 32, 34, 43-45, 61, 68-74, 78, 79) presented some concerns without any high-risk domains.

Main outcomes

Low-density lipoprotein cholesterol

Compared to the control, ITF supplementation possibly decreases LDL-C (mean difference [MD] -0.14 mmol/l, 95% confidence interval [CI] -0.24 to -0.05 mmol/l, $I^2 = 84.8\%$, P < 0.01 (heterogeneity), 38 RCTs, 1,879 participants, very low certainty of evidence [CoE]) (**Figure 1** and Table 2).

Subgrouping by study duration suggested beneficial effect (p = 0.04) of ITF supplementation on LDL-C in studies for which the follow-up duration ≥ 6 weeks (MD – 0.22 mmol/l, 95% CI -0.35 to -0.08 mmol/l) but no subgroup effects for other subgroups ($p \geq 0.1$) (**Supplementary Figures 3-11**).

A sensitivity analysis excluding the outliers (38, 39, 42, 57, 80) (MD -0.09, 95% CI -0.13 to -0.05 mmol/l, $I^2 = 0.4\%$) and influential RCTs (38, 42) (MD -0.08, 95% CI -0.15 to -0.01 mmol/l, $I^2 = 46\%$) (**supplementary plot 1**) explained or partially explained the heterogeneity and improved the precision of the estimate without changing the conclusion (**Figure 1**). These studies included older (on average ≥ 60 years) (38, 57) or younger (on average 32 years) (80) participants or participants with distinguishable comorbidities (39, 42).

Additional sensitivity analyses including parallel analysis of crossover trials using different correlation coefficients, including only low RoB trials, food-controlled trials and parallel group trials did not appreciably altered the effect estimates. Publication bias was unlikely for this outcome [**Supplementary plot 2**].

Triglycerides

Compared to the control, ITF supplementation may reduce triglycerides (MD -0.06 mmol/l, 95% CI -0.12 to -0.01 mmol/l, $I^2 = 57.5\%$, P < 0.01(heterogeneity), 40 RCTs, 1,732 participants, low CoE) (Figure 2 and Table 2). Subgrouping by BMI suggested beneficial effect (p = 0.01) of ITF supplementation on TG in pre-obese (MD -0.09 mmol/l, 95% CI -0.15 to -0.02 mmol/l), and obese people (MD -0.14 mmol/l, 95% CI -0.21 to -0.06 mmol/l) but no subgroup effects for other subgroups (p \ge 0.1) (Supplementary Figures 12 - 20). The substantial heterogeneity was explained by this subgroup (pre-obese: I² = 0%, obese: I² = 17%, normal: I² = 53.7%). Sensitivity analyses excluding influential (39, 57) (MD -0.08, 95% CI -0.12 to -0.03 mmol/l, I² = 32%) and outliers (39, 45, 51, 57) RCTs (MD -0.05, 95% CI -0.09 to -0.02 mmol/l, I² = 1.2%) (supplementary plot 3) explained the heterogeneity and improved precisions of estimates without changing the conclusion (Figure 2). Including older (age on average \ge 65) (45, 57) or younger (age on average 33) (51) or diverse disease status (39) could be the reasons for high heterogeneity.

Additional sensitivity analyses including parallel analysis of crossover trials using different correlation coefficients, including only low RoB trials, food-controlled trials and parallel group trials did not appreciably alter the effect estimates. There was no evidence of publication bias for this outcome (**Supplementary plot 4**).

Fasting blood glucose

Compared to the control, we are uncertain whether ITF supplementation decreases FBG (MD -0.06 mmol/l, 95% CI -0.16 to 0.05 mmol/l, $I^2 = 72.9\%$, P < 0.01(heterogeneity), 36 RCTs, 1,505 participants, very low CoE) (**Figure 3 and Table 2**). The test for subgroup differences suggested

no statistically significant subgroup effect by any subgroup $(p \ge 0.1)$ (Supplementary figures 21-29).

Removing the influential RCT (46) (MD -0.02 mmol/l, 95% CI -0.12 to 0.08 mmol/l, $I^2 = 62.8\%$) and outliers (40, 42, 46, 57) (MD -0.02 mmol/l, 95% CI -0.07 to 0.04 mmol/l, $I^2 = 0\%$) (**supplementary plot 6**) reduced the heterogeneity without changing the conclusion (**Figure 5**). Including older participants (age on average ≥ 59 years) (46, 57) or diverse disease status (40, 42) could be the reason for high heterogeneity. Additional sensitivity analyses including parallel analysis of crossover trials using different correlation coefficients, including only low RoB trials, food-controlled trials and parallel group trials did not appreciably altered the effect estimates. Publication bias was unlikely for this outcome (**Supplementary plot 3**).

Secondary outcomes

For secondary outcomes, we did not report additional analysis (e.g., subgroup and sensitivity analyses) except effect estimates with 95% CI and GRADE assessment downgrading CoE for unexplained heterogeneity.

Compared to the control, ITF supplementation may decrease body weight (MD - 0.97 kg, 95% CI -1.28 to -0.66 kg, $I^2 = 50.1\%$, P < 0.01(heterogeneity), 36 RCTs, 1,672 participants, low CoE), but little to no effects on BMI (MD -0.14 kg, 95% CI -0.89 to 0.06 kg, $I^2 = 88.5\%$, P < 0.01(heterogeneity), 29 RCTs, 1,330 participants, very low CoE), waist circumference (MD - 1.41 cm, 95% CI -2.82 to 0.00 cm, $I^2 = 78\%$, P < 0.01(heterogeneity), 17 RCTs, 704 participants, very low CoE), waist-to-hip ratio (MD -0.01 ratio, 95% CI -0.02 to 0.00 ratio, $I^2 = 51.3\%$, P = 0.05 (heterogeneity), 10 RCTs, 411 participants, low CoE), SBP (MD 0.09 mmHg, 95% CI -2.23 to 2.42 mmHg, I2 = 90.6\%, P < 0.01(heterogeneity), 15 RCTs, 859 participants, low CoE), DBP (MD -1.28 mmHg, 95% CI -3.18 to 0.62 mmHg, I2 = 88.3\%, P < 0.01(heterogeneity), 14 RCTs,

803 participants, very low CoE), HDL-C (MD 0.03 mmol/l, 95% CI -0.00 to 0.05 mmol/l, I2 = 82%, P < 0.01(heterogeneity), 41 RCTs, 1,786 participants, very low CoE), VLDL-C (MD -0.02 mmol/l, 95% CI -0.08 to 0.11 mmol/l, I2 = 90%, P < 0.57 (heterogeneity), 3 RCTs, 174 participants, low CoE), TC (MD -0.11 mmol/l, 95% CI -0.19 to 0.02 mmol/l, I2 = 85.6%, P < 0.01(heterogeneity), 40 RCTs, 1,875 participants, very low CoE), ApoA1 (MD -0.07 g/l, 95% CI -0.12 to 0.27 g/l, I2 = 92%, P < 0.01(heterogeneity), 6 RCTs, 204 participants, low CoE), ApoB (MD -0.20 g/l, 95% CI -0.38 to 0.79 g/l, I2 = 99%, P < 0.01(heterogeneity), 6 RCTs, 204 participants, low CoE), HbA1c (MD -0.11 %, 95% CI -0.31 to 0.09 %, I2 = 85%, P < 0.01(heterogeneity), 13 RCTs, 514 participants) (Supplementary Figures 30 - and Supplementary Table 1).

Discussion

Summary of main results

We conducted our systematic review to understand the effects of ITF on major cardiovascular risk factors. The meta-analysis including 55 RCTs with 2,518 participants showed that ITF supplementation possibly decreases LDL-C, triglycerides, and body weight. There was little to no effect of ITF supplementation on other cardiovascular risk factors. The results remained mostly unchanged in sensitivity analyses and there was little suggestion of publication bias. Due to low to very low CoE, we had low confidence in the certainty of the effects on LDL-C, triglycerides, and body weight.

Agreements and disagreements with other studies or reviews

The findings of our review are consistent with several other meta-analyses (5, 83-85). A recent meta-analysis by Li et al. (85) including 33 RCTs assed the effects of ITF on body weight, blood glucose, and lipid profile similarly reported a positive effect of ITF on LDL-C (weighted mean difference [WMD] -0.18 mmol/L; 95% CI: -0.32, -0.04), triglycerides (WMD-0.21 mmol/L; 95% CI: -0.37, -0.05) but also on blood glucose (WMD -0.42 mmol/L; 95% CI: -0.71, -0.14) for which we found little to no effect. The transparency of this review may be a cause for concern, as the authors used the Heyland Methodological Quality Score for risk of bias (quality) assessment rather than the Cochrane risk of bias tool that they pre-specified in their protocol, without an accompanying explanation. The authors also did not evaluate the certainty of the evidence. A second review by Faghihimani et al. including 5 RCTs with 233 participants (84) assessed the effects of inulin-type carbohydrates on blood pressure. The review reported non-significant treatment effects on SBP (WMD-5.83 mmHg; 95% CI -12.49 to 0.82 mmHg) and DBP (WMD -2.62 mmHg, 95% CI -6.15 to 0.92 mmHg). Another meta-analysis including 20

RCTs with 607 participants (5) reported a treatment effect of 0.20 mmol/l (95% CI-0.29 to -0.02) decrease in LDL-C; but no change in glucose (MD -0.05; 95% CI -0.18 to 0.08). A meta-analysis of 15 RCTs with 290 participants (83) found that treatment reduced triglycerides by 0.17 mmol/l (95% CI -0.33 to -0.01 mmol/l). Our analytic sets for these outcomes included similar studies as these previous reviews plus subsequently published studies. Our review is the first to assess the overall quality and certainty of the body of evidence using GRADE (86).

A previous meta-analysis by Wang et al. 2019 (11) including 33 RCTs with 1,346 participants assessed the effects of ITF on glycemic control only. The authors reported that ITF reduced fasting blood glucose (WMD - 0.21 mmol/l, 95% CI - 0.33 to - 0.09 mmol/l). However, this review included trials with treatment durations of more than 7 days, whereas we selected trials with treatment durations of at least 14 days (2 weeks). We selected this window to ensure sufficient time for the interventions to work, which for most dietary interventions, can take 2-3 weeks. Though Wang et al. finally selected studies with duration of follow up more than 2 weeks (i.e., 20 days or more) but studies included in our review had longer duration compared to Wang et. al. For example, the length of follow-up in our studies ranges from 14 to 728 days; in Wang et, it was 20 to 252 days. Secondly, although Wang et al. (11) recommend a 10 g intake of inulin-type fructans (ITFs) for at least 6 weeks in participants with comorbidities, and Dou et al. (87) reported an increased number of colonic Bifidobacterium spp. with higher doses (7.5-15)g/day) and prolonged (>4 weeks) ITF intake, the appropriate dosage and duration of ITF supplementation remain unclear (88). By including studies with longer treatment durations and recently published randomized controlled trials (RCTs), our review provided up-to-date evidence on the effects of ITF on fasting blood glucose and its potential long-term effects. Our review also included recent high quality RCTs with low RoB (35, 50, 62, 80, 81). Another important aspect

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is that Wang et al. (11) treated crossover trial as parallels trials. Treating crossover trials as parallel trials fails to appropriately consider the correlation between multiple measures in the same individual over time (i.e., treating all observations as independent) (13). This approach may overestimate the variance of effect sizes by disregarding the valuable information related to subject-specific correlations (13). In meta-analysis, the weighting of studies is commonly determined by the inverse of the variance of the treatment effect estimate. Consequently, when crossover trials are treated as parallel, they may have a lesser impact on the overall pooled estimate, thereby reducing their contribution to the final evaluation of treatment effectiveness (13, 89). Although the authors analyzed subgroups based on the type of study design, they did not utilize the available methods (13, 89, 90) to incorporate crossover and parallel group trials. In contrast, our analysis considered within-subject correlation (91).

In subgroup analysis, the effects of ITF supplementation on triglycerides were more pronounced in participants with comorbidities (e.g., pre-obese and obese). The effect of ITF was more beneficial when the follow-up duration was ≥ 6 weeks for LDL-C. ITF is purported to positively influence gut homeostasis and immunity (92). Thus, the effects of ITF in participants with existing conditions that affect glucose or lipid metabolism including hypertension, obesity and cardiometabolic disease, may be more pronounced (92). The recommended daily intake of fiber intake ranges from 22 to 38 g (93-95), scaled to energy intake. Wang et al. (11) suggest a daily dose of 10 g ITF supplementation for at least 6 weeks for optimal benefit. The longer supplementation periods (e.g., more than 6 weeks) may allow time for sustained, beneficial shifts in the microbiome that improve cardiovascular risk factors. Several trials showed a beneficial effect of long term (3 to 7 months) ITF supplementation in adults (96, 97).

Overall completeness and applicability of evidence

Our review assessed the effects of ITF supplementation compared to no or controlled supplementation on CVD risk factors in adults. We included men and women from high-, lowand middle-income countries aged, on average, from 19 to 67 years and with a range of cardiovascular disease risk factors. The study durations ranged from 2 to 104 weeks (2 years) and the ITF dose ranges from 0.75 g per day (≈1/3 tsp) to 40 g per day (≈15 tsp). The review including 55 RCTs with 2,518 participants showed a positive effect of ITF supplementation on LDL-C, triglycerides, and body weight. We noted that study duration modified the effects of ITF supplementation on triglycerides. The LDL-cholesterol lowering effects were greater among long duration studies. The triglyceride-lowering effects were greater among studies conducted in participants with pre-obesity and obesity. We are uncertain on the quality of the evidence because of low or very low certainty of evidence based on GRADE assessment. The certainty of the evidence was low or very low because of high heterogeneity, imprecision, problems with randomization, missing data, selective reporting, or deviations from the intended intervention.

Strengths and limitations of the review

Our review has potential limitations. First, there was considerable between-studies heterogeneity, which were explored and partially explained through subgroup and sensitivity analyses. Second, we could not access information from two eligible trials and did not receive any data from the original authors. However, we did not identify evidence of publication bias in our analyses. Our review has several strengths. First, we included 55 RCTs and included crossover and parallel trials using appropriate methodological approaches (13, 89, 90). Second, we used a

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comprehensive search strategy to identify the trials. Third, we screened, selected and assessed RoB independently and in duplicate. Lastly, we conducted prespecified subgroup analyses.

Clinical applicability of our findings for physicians

Our review suggested beneficial effects of ITF supplementation on LDL-C, triglycerides, and body weight. Subgrouping by study duration and BMI suggested beneficial effects of ITF supplementation on LDL-C in longer duration study (follow-up duration \geq 6 weeks) and on TG in pre-obese (BMI 25.0 to 29.9 kg/m²) and obese participants (BMI >30 kg/m²) respectively. Subgroup analyses also suggested that age, sex, dose, disease status, type of ITF and RoB do not modify the effects of ITF supplementation compared to control. However, our findings of low to very low certainty evidence on the effects of ITF supplementation suggests that further welldesigned and executed trials are needed to assess the effects of ITF on cardiovascular risk factors with certainty.

Deviations from published protocol

We report two minor deviations from our published pre-specified analysis plan (28). Firstly, we conducted three post-hoc subgroup analyses by age, body weight (BMI) and diabetes status to strengthen the relevance of our findings to a clinical audience. Secondly, our approach to analyzing crossover trials included both analyses in-line with published guidelines, as well as a naïve meta-analysis of crossover trials to enhance comparability with other such studies (13, 90, 91). We report the naïve analysis, supplemented by sensitivity analyses applying paired analyses to crossover trials (13, 90, 91) using correlation coefficients of 0, 0.33, 0.66 and 0.99.

Conclusions

The results of our meta-analysis indicate that inulin-type fructans possibly reduce low-density lipoprotein, triglycerides, and body weight. Inulin-type fructans might be particularly beneficial to patients with obesity, when given for at least 6 weeks. Our findings of low to very low certainty evidence on the effects of ITF supplementation suggests that further well-designed and executed trials that pay careful attention to issues of missing outcome data, deviation from intended interventions, selected reporting, and randomization process are needed to assess the effects of ITF on cardiovascular risk factors with certainty.

Abbreviations:

- ApoA1: Apolipoproteins A1
- ApoB: Apolipoproteins B
- BMI: Body-mass index
- CI: Confidence interval
- Cochrane DSR: Cochrane Database of Systematic Reviews
- CoE: Certainty of evidence
- CVD: Cardiovascular diseases
- DBP: Diastolic blood pressure
- FBG: Fasting blood glucose
- FOS: Fructo-oligosaccharides
- GRADE: Grading of Recommendations, Assessment, Development and Evaluation
- HbA1c: Hemoglobin A1c
- HDL-C: High-density lipoprotein cholesterol
- ITF: Inulin-type fructans
- LDL-C: Low-density lipoprotein cholesterol
- MD: Mean difference
- RCTs: Randomized controlled trials
- SBP: Systolic and diastolic blood pressure
- TC: Total cholesterol
- TG: Triglycerides
- VLDL-C: Very low-density lipoprotein cholesterol
- WC: Waist circumference

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Contributors

RJ de Souza conceived the work. JR Talukdar drafted the manuscript. RJ de Souza and L Mbuagbaw guided JR Talukdar in data analysis and interpretation of the results. D Zeraatkar, M Cooper, L Lyutvyn, R Ali, A Chu, M Xue, F Chowdhury, HE Harnack, L Huan, M Malik J Powless, FV Lavergne contributed to data extraction. L Banfield developed the search strategy consulting with RJ de Souza. RJ de Souza, L Mbuagbaw, M Cooper, D Zeraatkar, L Lyutvyn, R Ali, R Berbrier, S Janes, V Ha, P Darling, A Chu, M Xue, F Chowdhury, HE Harnack, L Huan, M Malik J Powless, FV Lavergne, X Zhang, S Ehrlich, L Banfield, JL Sievenpiper and DJA Jenkins revised the manuscript critically for important intellectual content. RJ de Souza is the guarantor of the manuscript.

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Competing interests

RJ de Souza has served as an external resource person to the World Health Organization's Nutrition Guidelines Advisory Group on trans fats, saturated fats, and polyunsaturated fats. The WHO paid for his travel and accommodation to attend meetings from 2012-2017 to present and discuss this work. He has presented updates of this work to the WHO in 2022. He has also done contract research for the Canadian Institutes of Health Research's Institute of Nutrition, Metabolism, and Diabetes, Health Canada, and the World Health Organization for which he received remuneration. He has received speaker's fees from the University of Toronto, and McMaster Children's Hospital. He has held grants from the Canadian Institutes of Health Research Institute, and Hamilton Health Sciences Corporation as a principal investigator, and is a co-investigator on several funded team grants from the Canadian Institutes of Health Research. He has served as an independent director of the Helderleigh Foundation (Canada). He serves as a member of the Nutrition Science Advisory Committee to Health Canada (Government of Canada), and a co-opted member of the Scientific Advisory Committee on Nutrition (SACN) Subgroup on the Framework for the Evaluation of Evidence (Public Health England).

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Netherlands, Barilla, the Almond Board of California, Agriculture and Agri-food Canada, Pulse Canada, Kellogg's Company, Canada, Quaker Oats, Canada, Procter & Gamble Technical Centre Ltd., Bayer Consumer Care, Springfield, NJ, Pepsi/Quaker, International Nut & Dried Fruit Council (INC), Soy Foods Association of North America, the Coca-Cola Company (investigator initiated, unrestricted grant), Solae, Haine Celestial, the Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Soy Nutrition Institute (SNI), the Canola and Flax Councils of Canada, the Calorie Control Council, the Canadian Institutes of Health Research (CIHR), the Canada Foundation for Innovation (CFI)and the Ontario Research Fund (ORF). He has received in-kind supplies for trials as a research support from the Almond board of California, Walnut Council of California, the Peanut Institute, Barilla, Unilever, Unico, Primo, Loblaw Companies, Quaker (Pepsico), Pristine Gourmet, Bunge Limited, Kellogg Canada, WhiteWave Foods. He has been on the speaker's panel, served on the scientific advisory board and/or received travel support and/or honoraria from Nutritional Fundamentals for Health (NFH)-Nutramedica, Saint Barnabas Medical Center, The University of Chicago, 2020 China Glycemic Index (GI) International Conference, Atlantic Pain Conference, Academy of Life Long Learning, the Almond Board of California, Canadian Agriculture Policy Institute, Loblaw Companies Ltd, the Griffin Hospital (for the development of the NuVal scoring system), the Coca-Cola Company, Epicure, Danone, Diet Quality Photo Navigation (DQPN), Better Therapeutics (FareWell), Verywell, True Health Initiative (THI), Heali AI Corp, Institute of Food Technologists (IFT), Soy Nutrition Institute (SNI), Herbalife Nutrition Institute (HNI), Saskatchewan & Alberta Pulse Growers Associations, Sanitarium Company, Orafti, the International Tree Nut Council Nutrition Research and Education Foundation, the Peanut Institute, Herbalife International, Pacific Health Laboratories, Barilla, Metagenics, Bayer Consumer Care, Unilever Canada and Netherlands, Solae, Kellogg, Ouaker Oats, Procter & Gamble, Abbott Laboratories, Dean Foods, the California Strawberry Commission, Haine Celestial, PepsiCo, the Alpro Foundation, Pioneer Hi-Bred International, DuPont Nutrition and Health, Spherix Consulting and WhiteWave Foods, the Advanced Foods and Material Network, the Canola and Flax Councils of Canada, Agri-Culture and Agri-Food Canada, the Canadian Agri-Food Policy Institute, Pulse Canada, the Soy Foods Association of North America, the Nutrition Foundation of Italy (NFI), Nutra-Source Diagnostics, the McDougall Program, the Toronto Knowledge Translation Group (St. Michael's Hospital), the Canadian College of Naturopathic Medicine, The Hospital for Sick Children, the Canadian Nutrition Society (CNS), the American Society of Nutrition (ASN), Arizona State University, Paolo Sorbini Foundation and the Institute of Nutrition, Metabolism and Diabetes. He received an honorarium from the United States Department of Agriculture to present the 2013 W.O. Atwater Memorial Lecture. He received the 2013 Award for Excellence in Research from the International Nut and Dried Fruit Council. He received funding and travel support from the Canadian Society of Endocrinology and Metabolism to produce mini cases for the Canadian Diabetes Association (CDA). He is a member of the International Carbohydrate Quality Consortium (ICQC). His wife, Alexandra L Jenkins, is a director and partner of INQUIS Clinical

Research for the Food Industry, his 2 daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book that promotes the use of the foods described here, The Portfolio Diet for Cardiovascular Risk Reduction (Academic Press/Elsevier 2020 ISBN:978-0-12-810510-8)and his sister, Caroline Brydson, received funding through a grant from the St. Michael's Hospital Foundation to develop a cookbook for one of his studies. He is also a vegan.

JLS has received research support from the Canadian Foundation for Innovation, Ontario Research Fund, Province of Ontario Ministry of Research and Innovation and Science, Canadian Institutes of health Research (CIHR), Diabetes Canada, American Society for Nutrition (ASN), INC International Nut and Dried Fruit Council Foundation, National Honey Board (the U.S. Department of Agriculture [USDA] honey "Checkoff" program), Institute for the Advancement of Food and Nutrition Sciences (IAFNS; formerly ILSI North America), Pulse Canada, Quaker Oats Center of Excellence, The United Soybean Board (the USDA soy "Checkoff" program), The Tate and Lyle Nutritional Research Fund at the University of Toronto, The Glycemic Control and Cardiovascular Disease in Type 2 Diabetes Fund at the University of Toronto (a fund established by the Alberta Pulse Growers), The Plant Protein Fund at the University of Toronto (a fund which has received contributions from IFF), and The Nutrition Trialists Fund at the University of Toronto (a fund established by an inaugural donation from the Calorie Control Council). He has received food donations to support randomized controlled trials from the Almond Board of California, California Walnut Commission, Peanut Institute, Barilla, Unilever/Upfield, Unico/Primo, Loblaw Companies, Quaker, Kellogg Canada, WhiteWave Foods/Danone, Nutrartis, and Dairy Farmers of Canada. He has received travel support, speaker fees and/or honoraria from ASN, Danone, Dairy Farmers of Canada, FoodMinds LLC, Nestlé, Abbott, General Mills, Comité Européen des Fabricants de Sucre (CEFS), Nutrition Communications, International Food Information Council (IFIC), Calorie Control Council, and International Glutamate Technical Committee. He has or has had ad hoc consulting arrangements with Perkins Coie LLP, Tate & Lyle, Phynova, and Inquis Clinical Research. He is a member of the European Fruit Juice Association Scientific Expert Panel and former member of the Soy Nutrition Institute (SNI) Scientific Advisory Committee. He is on the Clinical Practice Guidelines Expert Committees of Diabetes Canada, European Association for the study of Diabetes (EASD), Canadian Cardiovascular Society (CCS), and Obesity Canada/Canadian Association of Bariatric Physicians and Surgeons. He serves or has served as an unpaid member of the Board of Trustees and an unpaid scientific advisor for the Food, Nutrition, and Safety Program (FNSP) and the Carbohydrates Committee of IAFNS (formerly ILSI North America). He is a member of the International Carbohydrate Quality Consortium (ICQC), Executive Board Member of the Diabetes and Nutrition Study Group (DNSG) of the EASD, and Director of the Toronto 3D Knowledge Synthesis and Clinical Trials foundation. His spouse is an employee of AB InBev.

Patient and public involvement

We did not involve any patients or community people in our systematic review.

Data sharing

The review was conducted using already published data. The detailed risk of bias assessment is available upon reasonable request.

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Figures

Figure 1: Forest plot displaying the effect of inulin-type fructans on low-density lipoprotein

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Vandokkum 1999	24	2.82	0.55	12	2.82	0.51		0.00 [-0.36, 0.36]
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	⊢+	0.02 [-0.47, 0.51
Davidson 1998	21	-0.09	0.05	21	0.45	0.07		-0.54 [-0.58, -0.50]
Causey 2000	12	3.8	0.7	12	3.88	0.83		-0.08 [-0.69, 0.53
Letexier 2003	8	2.9	0.62	8	2.77	0.59	⊢- -	0.13 [-0.46, 0.72
Russo 2010	15	2.82	1.22	15	2.72	0.81	⊢	0.10 [-0.64, 0.84
Clarke 2016	30	2.6	0.55	30	2.5	0.55	. ⊢∎-i	0.10 [-0.18, 0.38
Nishimura 2015	24	0.2	1.61	24	0.03	0.9	<u>⊢_i</u> ∎(0.17 [-0.57, 0.91
Satoh 2013	29	2.94	0.12	27	2.82	0.13		0.12 [0.05, 0.19
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	H	-0.01 [-0.22, 0.20
Rajkumar 2015	15	1.43	0.35	15	1.6	0.23	HERNÍ	-0.17 [-0.38, 0.04
Machado 2019	13	2.66	0.76	13	3.02	0.9	⊢ <u>∎</u> i-i	-0.36 [-1.00, 0.28]
Tovar 2012	30	0.21	0.58	29	0.3	0.58	⊬∎⊣	-0.09 [-0.39, 0.21
Tovar 2012	23	0.11	0.58	28	0.23	0.58	⊦∎	-0.12 [-0.44, 0.20]
Padilla-Camberos 2018	14	3.14	0.75	14	3.14	0.88	⊢ ••	0.00 [-0.61, 0.61
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	⊢∎́-I	-0.10 [-0.53, 0.33
Genta 2009	20	2.52	0.26	15	3.43	0.71	⊢∎⊣	-0.91 [-1.29, -0.53]
Ghavami 2019	23	2.52	1.14	23	2.91	0.84	⊢_■	-0.39 [-0.97, 0.19
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	⊢∎∔	-0.13 [-0.50, 0.24
Dehghan 2016	27	0.96	2.51	22	3.03	1.05 H	;	-2.07 [-3.11, -1.03
Aliasgharzadeh 2015	27	2.44	0.89	25	3.01	1.11	⊢∎⊸i	-0.57 [-1.12, -0.02
Roshanravan 2017	14	2.55	0.86	15	2.12	0.7		0.43 [-0.14, 1.00
Roshanravan 2017	15	1.99	0.96	15	2.51	0.59	⊢ ∎	-0.52 [-1.09, 0.05
Hiel 2020	51	-0.01	0.58	55	-0.09	0.5	H	0.08 [-0.13, 0.29
Shakeri 2014	24	-0.19	0.9	24	-0.31	0.98	┝─┼┉──┤	0.12 [-0.41, 0.65
Bonsu 2012	12	2.4	0.8	14	2.5	0.8	⊢ ∎́	-0.10 [-0.72, 0.52]
Castro-Sanchez 2016	16	3.72	1.17	16	3.16	1.12	<u>⊢_</u>	0.56 [-0.23, 1.35
Williams 2022	20	2.8	0.7	20	3.9	1	⊢ •−-1 :	-1.10 [-1.63, -0.57
Blaedel 2016	20	3.2	0.45	19	3.1	0.57	⊢∎⊣	0.10 [-0.22, 0.42
Buddington 2017	45	2.59	0.89	43	2.83	0.89	⊢∎÷	-0.24 [-0.61, 0.13
Giacco 2004	27	4.58	0.67	27	4.55	0.78	⊢ ≢-1	0.03 [-0.36, 0.42]
Jackson 1999	27	4	0.85	27	4.43	1.08	┝━━━┿┥	-0.43 [-0.95, 0.09
Sorensen 2010	12	2.7	0.7	12	3	0.9	⊢₌∔⊣	-0.30 [-0.95, 0.35
Luo 2000	10	3.85	0.73	10	3.85	0.63	⊢∔⊣	0.00 [-0.60, 0.60]
Wong 2010	23	-0.23	0.12	23	-0.12	0.06		-0.11 [-0.16, -0.06
Alles 1999	20	3.94	0.43	20	3.8	1.04	⊢	0.14 [-0.35, 0.63
Chambers 2019	12	3.3	0.35	12	3.3	0.69	⊢ ∔1	0.00 [-0.44, 0.44
Cronin 2016	99	2.6	1	100	2.9	1	⊢∎-(-0.30 [-0.58, -0.02
Scheid 2014	37	2.93	0.81	35	3.04	0.67	⊢≝⊣	-0.11 [-0.45, 0.23
RE Model for all studies: Effect estimate excluding inf Effect estimate excluding ou		s (Q =	86.64, df	= 36, p < .0	01; $I^2 = 84.8\%$ 1; $I^2 = 46.3\%$ 68; $I^2 = 0.4\%$	$\tau^2 = 0.01$)	ITF Fav	-0.14 [-0.24, -0.05 -0.08 [-0.15, -0.01 -0.09 [-0.13, -0.05 /ours control
						-4 -3	-2 -1 0 1	
						Me	ean Difference	

Note: Total = total number of participants completed the study, ITF = inulin-type fructans, SD = standard deviation, MD = mean

Figure 2: Forest	t plot displaving	the effect of	f inulin-type fi	ructans on	triglycerides
		,e ejjeet oj	$j \cdots j p \cdot j$		

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI
Vandokkum 1999	24	1.3	0.53	12	1.4	0.68	н і н	-0.10 [-0.54, 0.34
Forcheron 2007	9	0.77	0.42	8	0.64	0.31	HH	0.13 [-0.22, 0.48
Davidson 1998	21	-0.04	0.19	21	0.04	0.16		-0.08 [-0.19, 0.03
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.17
Letexier 2003	8	0.77	0.23	8	0.92	0.28	· · ·	-0.15 [-0.40, 0.10
Russo 2010	15	0.85	0.3	15	0.95	0.32	·	-0.10 [-0.32, 0.12
Luo 1996	13	0.83	0.55	12	0.72	0.32		0.11 [-0.22, 0.44
Clarke 2016	30	1.2	0.55	30	1.3	1.64		-0.10 [-0.72, 0.52
Nishimura 2015	24	0.09	0.33	24	0.01	0.39	, , , ≢-	0.08 [-0.24, 0.40
Satoh 2013	24	1.16	0.07	24	1.06	0.39		0.10 [0.06, 0.14
Pedersen 1997	29 64	0.97	0.07	64		0.08	_	-0.01 [-0.15, 0.13
Rajkumar 2015					0.98			
	15	1.16	0.07	15	1.18	0.08		-0.02 [-0.07, 0.03
Machado 2019	13	1.26	0.4	13	1.27	0.65	⊢ , I	-0.01 [-0.42, 0.40
Daud 2014	12	1.58	1.1	10	0.97	0.38	· · ·	0.61 [-0.06, 1.28
Tovar 2012	30	-0.36	0.48	29	-0.29	0.48	는 11 H	-0.07 [-0.31, 0.17
Tovar 2012	23	-0.35	0.48	28	-0.41	0.48	Hier	0.06 [-0.20, 0.32
Padilla-Camberos 2018	14	1.55	0.68	14	3.95	3.08 H	— • — ↓ ;	-2.40 [-4.05, -0.75
Vaghef-Mehrabany 2019	22	-0.09	0.63	23	-0.16	0.57	H a H	0.07 [-0.28, 0.42
Tripkovic 2015	10	2.08	0.86	10	1.79	0.61	⊢÷■−−Ⅰ	0.29 [-0.36, 0.94
Genta 2009	20	2.1	0.97	15	2.19	0.78	⊢⊷	-0.09 [-0.67, 0.49
Ghavami 2019	23	1.9	0.6	23	2.09	0.09	Herji I	-0.19 [-0.44, 0.06
Dewulf 2013	15	-0.09	0.33	15	0.07	0.37	Heiji	-0.16 [-0.41, 0.09
Dehghan 2016	27	1.95	0.71	22	2.49	0.66	H=H	-0.54 [-0.92, -0.16
Aliasgharzadeh 2015	27	2	0.69	25	2.45	0.68	⊢∎-t	-0.45 [-0.82, -0.08
Roshanravan 2017	14	1.84	0.51	15	1.78	0.68	H+H	0.06 [-0.38, 0.50
Roshanravan 2017	15	1.8	0.65	15	1.83	0.71	⊢ .	-0.03 [-0.52, 0.46
Hiel 2020	51	-0.15	1.34	55	-0.1	0.79	⊢	-0.05 [-0.47, 0.37
Shakeri 2014	24	-0.3	0.68	24	-0.36	0.9	⊢ ≢-1	0.06 [-0.39, 0.5
Bonsu 2012	12	1.5	0.6	14	1.8	1.2	⊢	-0.30 [-1.01, 0.4
Gosmez-Reves 2010	20	-0.19	0.03	20	0	0.06		-0.19 [-0.22, -0.16
Castro-Sanchez 2016	16	-0.3	0.61	16	-0.01	0.49		-0.29 [-0.67, 0.09
Williams 2022	20	1.1	0.7	20	1.2	0.4	 ⊦=∔1	-0.10 [-0.45, 0.25
Blaedel 2016	20	1.27	1.03	19	0.96	0.4	⊢=-1	0.31 [-0.16, 0.78
Buddington 2017	20 45	1.27	0.72	43	1.16	0.69		-0.10 [-0.39, 0.19
Jackson 1999	27	1.00	0.72	43 27	1.59	0.58		-0.30 [-0.56, -0.04
Sorensen 2010		1.29						0.00 [-0.46, 0.46
Luo 2000	12		0.4	12	1	0.7	<u>⊢</u> ,	
	10	1.33	0.51	10	1.42	0.38	⊢≢⊣	-0.09 [-0.48, 0.30
Wong 2010	23	1.64	0.14	23	1.73	0.14		-0.09 [-0.17, -0.0]
Alles 1999	20	2.56	0.69	20	2.44	0.79		0.12 [-0.34, 0.58
Chambers 2019	12	1	0.35	12	1.1	0.35		-0.10 [-0.38, 0.18
Scheid 2014	37	1.5	0.78	35	1.48	0.93	⊢ ∎ -1	0.02 [-0.38, 0.42
RE Model for all studies:	(Q	= 177.63, df =	= 40, p < .0 ⁻	1; l ² = 57.59	$(4, \tau^2 = 0.01)$		į	-0.06 [-0.12, -0.0
Effect estimate excluding influe		= 73.06, df =	38, p < .01	; I ⁻ = 32.1%	$\tau^{-} = 0.00)$		ţ	-0.08 [-0.12, -0.0
Effect estimate excluding outlie	ers (Q	= 28.24, df =	36, p = 0.82	z; i⁻ = 1.2%	$\tau = 0.00)$	-		-0.05 [-0.09, -0.02
						Fa	vours ITF : F	avours control
						ГГТ	<u> </u>	
						-4.5	-3 -1.5 0 1	2 3
							Mean Difference	
							iviean Difference	

Note: Total = total number of participants completed the study, ITF = inulin-type fructans, SD = standard deviation, MD = mean

Figure 3: Forest plot displaying the effect of inulin-type fructans on fasting blood glucose

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Forcheron 2007	9	4.03	0.3	8	3.81	0.57	⊦•∎-1	0.22 [-0.22, 0.66]
Letexier 2003	8	4.68	0.4	8	4.62	0.2	Hint I	0.06 [-0.25, 0.37]
Russo 2010	15	4.66	0.29	15	4.97	0.53	HEN	-0.31 [-0.62, -0.00]
Luo 1996	12	4.94	0.35	12	4.86	0.55	H	0.08 [-0.29, 0.45]
Clarke 2016	30	4.9	0.55	30	4.9	0.55	H	0.00 [-0.28, 0.28]
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	,	0.06 [-0.10, 0.22]
Satoh 2013	29	6.95	0.21	27	6.52	0.3		0.43 [0.29, 0.57]
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	Handi	0.07 [-0.18, 0.32]
Machado 2019	13	5.02	0.11	13	5.05	0.11		-0.03 [-0.11, 0.05]
Daud 2014	12	4.62	0.48	10	4.51	0.28	H	0.11 [-0.21, 0.43]
Tovar 2012	30	-0.03	0.51	29	-0.12	0.5	H I H	0.09 [-0.17, 0.35]
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51		0.21 [-0.07, 0.49]
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	 ⊢≢-1	0.04 [-0.37, 0.45]
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87		0.05 [-0.39, 0.49]
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	н е н	-0.11 [-0.40, 0.18]
Genta 2009	20	4.18	0.5	15	4.84	0.66	+≡-1:	-0.66 [-1.06, -0.26]
Ghavami 2019	23	6.63	1.71	23	7.24	1.55		-0.61 [-1.55, 0.33]
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	. — нен	-0.17 [-0.51, 0.17]
Dehghan 2016	27	8.36	1.17	22	9.02	1	,	-0.66 [-1.27, -0.05]
Roshanravan 2017	14	8.83	2.36	15	9.02 8.05	2.33		→ 0.78 [-0.93, 2.49]
Roshanravan 2017	14	8.03	2.30	15	8.05 7.27	2.33		- 0.76 [-0.95, 2.49]
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67		-0.93 [-1.39, -0.47]
Hiel 2020	51	0.23	1.96	25 55	-0.09	0.87		0.41 [-0.19, 1.01]
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.18	2.18		-0.46 [-1.88, 0.96]
Mitchell 2021	13			27	-0.17			0.04 [-1.62, 1.70]
Guess 2015		-0.01	2.6			1.33		-0.56 [-0.69, -0.43]
Bonsu 2012	20	-0.4	0.19	19	0.16	0.23		
Williams 2022	12	7.6	2.6	14	7.4	1.4		0.20 [-1.44, 1.84]
Blaedel 2016	20	5.1	0.5	20	5	0.5	H≣H	0.10 [-0.21, 0.41]
	20	5.6	0.45	19	5.6	0.87	-≢-	0.00 [-0.44, 0.44]
Buddington 2017	45	4.73	0.72	43	4.94	1.15	⊢∎;;;	-0.21 [-0.61, 0.19]
Giacco 2004	27	5.44	1	27	5.38	0.83	⊢ ∎-1	0.06 [-0.43, 0.55]
Jackson 1999	27	4.84	0.51	27	4.99	0.49	H	-0.15 [-0.42, 0.12]
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	⊢ ≡ ;i	-0.30 [-0.74, 0.14]
Luo 2000	10	8.89	1.68	10	8.88	1.61	⊢ ÷ – I	0.01 [-1.43, 1.45]
Alles 1999	20	8.61	0.81	20	8.59	2.66	⊢ <u>+</u> 1	0.02 [-1.20, 1.24]
Chambers 2019	12	5.3	0.69	12	5.3	0.35	⊦≓⊣	0.00 [-0.44, 0.44]
Scheid 2014	37	5.41	1.06	35	5.12	0.59	₩ ₩	0.29 [-0.10, 0.68]
RE Model for all studies:					= 72.9%, τ ² =		•	-0.05 [-0.16, 0.05]
Effect estimate excluding influe					$= 62.8\%, \tau_{2}^{2} = 0$		•	-0.02 [-0.12, 0.08]
Effect estimate excluding outlie	rs	(Q = 42.	89, df = 33,	p = 0.12; I ²	$= 0.0\%, \tau^2 = 0$		ĺ.	-0.02 [-0.07, 0.04]
						Fa	vours ITF ; Fa	vours control
							-2 0 1 2	3
							Mean Differer	

Note: Total = total number of participants completed the study, ITF = inulin-type fructans, SD = standard deviation, MD = mean

Tables

Table 1: Study characteristics

Reference, country	D*	Sex* *	N** *	Age	Baseline com.****	Inulin type	Dosage	Comparator	Outcome
Aliasgharza deh 2015, Iran (1)	Р	100	52	48	Ow/Ob	OFS-enriched inulin supplement	10 g/day (8 weeks)	Maltodextrin	BMI, HDL-C, LDL-C, TC, TG, W
Alles 1999, Netherlands (2)	С	55	40	59	T2DM	FOS supplement in yogurt	15 g/day (20 days)	glucose placebo in yoghurt	FBG, HDL-C, LDL-C, TC, TG, W
Bahmani 2016, Iran (3)	Р	81	50	52	T2DM	Inulin synbiotic bread	8.4 g/day (8 weeks)	probiotic or control bread	BMI, DBP, SBP, W
Blaedel 2016, Denmark (4)	С	-	39	33	Ow/Ob	Inulin supplement	13-15 g/day (3 weeks)	std. isoenergetic diet	FBG, HDL-C, LDL-C TC, TG
Bonsu 2012, Canada (5)	Р	42	26	65	T2DM	Inulin supplement	10 g/day (12 weeks)	xylitol placebo	BMI, FBG, HbA1c, HDL-C, LDL-C, TC, TG, WC, W, WHR
Buddington 2017, USA, Germany (6)	Р	78	88	33	≤3 BM/week	OFS supplement	5/10/15 g/day (4 weeks each/12 weeks total)	Maltodextrin	FBG, HDL-C, LDL-C TC, TG
Castro- Sanchez 2016, Mexico (7)	С	NR	32	-	Dys, Ob	Inulin supplement	9 g/day (8 weeks)	dextrose	BMI, HDL-C, LDL-C TC, TG, WC, W
Causey 2000, USA (8)	С	-	24	27- 49	Dys	Inulin supplement in vanilla icecream	20 g/day (3 weeks)	vanilla ice cream + sucrose +	ApoA, ApoB, HDL-C LDL-C, TC, TG

						+ NCEP step 1 diet		NCEP step 1 diet	
Chambers 2019, UK (9)	С	75	24	60	Ow/Ob	Inulin & esterfied propionate supplement	20 g/day (42 days)	Inulin or cellulose	BMI, FBG, HDL-C, LDL-C, TC, TG, HbA1C
Clarke 2016, Canada (10)	С	57	60	28	Healthy	Inulin/scFOS supplement	15 g/day (28 days)	maltodextrin	BMI, FBG, HDL-C, LDL-C, TC, TG
Cronin 2016, Ireland (11)	Р	100	199	61	PM	scFOS supplement + Ca	3 g/day (24 months)	maltodextrin or calcium	BMI, DBP, LDL-C, SBP, TC, W
Daud 2014, UK (12)	Р	75	21	33	Ow/Ob	OFS supplement + cellulose	30 g/day (6 weeks)	maltodextrin + cellulose	BMI, FBG, HDL-C, TC, TG, W, WHR
Davidson 1998, USA (13)	С	52	22	60	Dys	Inulin supplement in spreads + NCEP 1 diet	18 g/day (6 weeks)	NCEP Step I diet w/o inulin	HDL-C, LDL-C, TC, TG
Dehgahn 2014, Iran (14)	Р	100	42	49	Ow/Ob, T2DM	Inulin supplement	10 g/day (8 weeks)	maltodextrin	BMI, FBG, HbA1C, W
Dehghan 2016, Iran (15)	Р	100	52	48	Ow/Ob, T2DM	OFS-enriched inulin	10 g/day (2 months)	maltodextrin	BMI, DBP, FBG, HbA1c, HDL-C, LDL- C, SBP, TC, TG, WC, W, WHR
Dewulf 2013, Belgium (16)	Р	100	49	47	Ob	Inulin/OFS supplement	16 g/day (3 months)	maltodextrin	BMI, FBG, HbA1c, HDL-C, LDL-C, TC, TG, WHR
Fernandes 2016, Brazil (17)	Р	100	30	31	Healthy	FOS synbiotic	6 g/day (15 days)	maltodextrin or FOS probiotic	BMI, W

Forcheron 2007, France (18)	Р	67	6	32	Healthy	Fructans supplement	10 g/day (6 months)	placebo	FBG, HDL-C, LDL-C, TC, TG, W
Genta 2009, Argentina (19)	Р	100	17	41	Ob, Dys	Dietary FOS in yacon syrup	0.14 or 0.29 g/kg BW/day (120 days)	placebo syrup	BMI, FBG, HDL-C, LDL-C, TC, TG, WC, W
Ghavami 2019, Iran (20)	Р	57	35	42	Ob/Ow, T2DM	Inulin supplement	10 g/day (56 days)	starch powder placebo	BMI, FBG, HbA1c, HDL-C, LDL-C, TC, TG, WC, W, WHR
Giacco 2004, Italy (21)	С	33	46	46	Dys	scFOS supplement (+some maltodextrin + aspartame)	10.6 g/day (2 months)	maltodextrin + aspartame	FBG, HDL-C, LDL-C, TC, TG, VLDL-C
Gosmez- Reyes 2010, Mexico (22)	Р	48	54	65	Dys, HTN, IHD	Inulin/OFS supplement in bread roll	1.15 g/day and 2.2 g/day respectively (12 weeks)	placebo bread roll	BMI, DBP, HDL-C, SBP, TC, TG
Guess 2015, UK (23)	Р	40	40	59	Pre-DM	Inulin supplement	30 g/day (18 weeks)	cellulose	FBG, W
Guess 2016, UK (24)	С	NR	39	62	Pre-DM	Inulin supplement	30 g/day (14 days)	cellulose	W
Hiel 2020, Belgium (25)	Р	67	68	51	Ob/≥1 of pre- DM/DM/d ys/HTN/ele vated LFTs	Inulin supplement	16 g/day (90 days)	maltodextrin	BMI, DBP, FBG, HbA1c, HDL-C, LDL- C, SBP, TC, TG, WC, W, WHR
Holscher 2014, USA (26)	С	50	106	27	Healthy	Inulin supplement in chocolate chews	5.7 and 7.5 g/day (3 weeks)	chocolate chews	W
Jackson 1999, UK (27)	Р	NR	87	52	Healthy	Inulin supplement	10 g/day (8 weeks)	maltodextrin	ApoA, ApoB, FBG, HDL-C, LDL-C, TC, TG

Luo 2000, France Belgium (28)	С	40	54	57	T2DM	scFOS supplement	20 g/day (4 weeks)	sucrose	FBG, HDL-C, LDL-C, TC, TG, ApoA, ApoB, HbA1C
Letexier 2003, France (29)	С	50	20	23- 32	Healthy	Inulin supplement	10 g/day (21 days)	maltodextrin	FBG, HDL-C, LDL-C, TC, TG
Luo 1996, France (30)	С	-	16	24	Healthy	FOS supplement in cookies	20 g/day (4 weeks)	sucrose in cookies	ApoA, ApoB, FBG, HDL-C, TC, TG, WC, W
Machado 2019, Brazil (31)	Р	62	24	31	Ow/Ob	FOS dietary yacon flour drink + energy restricted diet	0.1 g/kg BW/day (6 weeks)	control drink w/o yacon + energy restricted diet	DBP, FBG, HDL-C, LDL-C, SBP, TC, TG, WC, W, WHR
Nishimura 2015, Japan (32)	Р	79	26	54	Healthy	Inulin dietary chicory root tea	0.75 g/day (4 weeks)	barley tea w/ 10% coffee	BMI, DBP, FBG, HbA1c, HDL-C, LDL- C, SBP, TC, TG, W
Padilla- Camberos 2018,Mexic o (33)	Р	43	22	33	Ob	Agave fructans supplement	192 mg/kg BW/ day (x1 week) followed by 96 mg/kg BW/day (11 weeks)	maltodextrin	BMI, FBG, HDL-C, LDL-C, TC, TG, WC, W, WHR
Parnell 2009, Canada (34)	Р	81	48	40	Ow/Ob	OFS supplement	21 g/day (12 weeks)	maltodextrin in drink	BMI, FBG, W
Pedersen 1997, Denmark (35)	С	100	28	20- 36	Healthy	Dietary inulin in low fat spread	360 g/kg @ 40 g/day (4 weeks)	low-fat spread without inulin	BMI, HDL-C, LDL-C, TC, TG

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Pol 2018, Netherlands (36)	Р	69	38	41	Ob/Ow	OFS supplement in a bar	16 g/day (12 weeks)	control granola bar w/o OFS	WC, W
Rajkumar 2015, India (37)	Р	54	128	20- 25	Healthy	FOS synbiotic	10 g/d (6 weeks)	gelatin or probiotic capsules	BMI, FBG, HDL-C, LDL-C, TC, TG
Reimer 2017, Canada (38)	Р	53	55	40	Ob/Ow	OFS +Inulin supplement bar	12 g/day + 4 g/day respectively (12 weeks, 1/2 dose first 2 weeks)	isocaloric control snack bars (control/whey protein/whey protein + inulin)	BMI, WC, W
Roshanravan 2017, Iran (39)	Р	67	30	49	Ob/Ow, T2DM	Inulin supplement + butyrate	10 g/day (45 days)	placebo or (butyrate + inulin)	BMI, DBP, FBG, HDL-C, LDL-C, SBP, TC, TG, WC, W, WHR, HbA1C
Russo 2010, Italy (40)	С	-	43	19	Healthy	Inulin enriched pasta	11 g/day (11% inulin- enriched pasta; 100 g/day) (5 weeks)	Semolina pasta	FBG, HDL-C, LDL-C, TC, TG, HbA1C
Salmean 2019, Kuwait (41)	Р	100	29	23	Ob	Inulin supplement + dietary recommendation s	21 g/day (42 days)	recommendati on w/o inulin	BMI,W
Satoh 2013, Japan (42)	Р	50	30	66	T2DM	FOS/yacon root supplement	8 g/day (5 months)	Aroid control	BMI, DBP, FBG, HDL-C, LDL-C, SBP, TG, W
Scheid 2014, Brazil (43)	Р	NR	12	67	Healthy	FOS/yacon supplement	7.4 g/day (9 weeks)	maltodextrin	FBG, HDL-C, LDL-C, TC, TG, VLDL-C

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Shakeri 2014, Iran (44)	Р	81	56	53	T2DM	Inulin synbiotic bread	8.4 g/d (8 weeks)	Control or probiotic bread	BMI, FBG, HDL-C, LDL-C, TC, TG, VLDL-C, W
Sorensen 2010, Norway (45)	С	50	72	56	IRH	FOS supplement	20 g/day (14 days)	no treatment	FBG, HbA1c, HDL-C, LDL-C, TC, TG
Tajadadi- Ebrahimi 2014, Iran (46)	Р	81	48	52	T2DM	Inulin synbiotic bread	8.4 g/d (8 weeks)	Control or probiotic bread	BMI, FBG, W
Tovar 2012, Mexico (47)	Р	100	24	33	Ob/Ow	Inulin supplement + PMR	10 g/d (90 days)	no treatment or PMR or inulin + PMR	FBG, HDL-C, LDL-C, TC, TG, WC, W
Tripkovic 2015, UK (48)	С	-	54	40	Ob/Ow	Inulin enriched bread rolls	15 g/day (28 days)	wheat grain or wheat fibre bread rolls	BMI, DBP, FBG, HDL-C, SBP, TC, TG, WC, W
Vaghef- Mehrabany 2019, Iran (49)	Р	100	51	39	Ob/MDD	Inulin supplement + weightloss diet	10 g/d (8 weeks)	maltodextrin + weightloss diet	BMÍ, DBP, FBG, HDL-C, LDL-C, SBP, TC, TG, WC, W, WHR
Vandokkum 1999, Netherlands (50)	С	-	20	23	Healthy	FOS or inulin supplement	15 g/d (3 weeks)	basal diet w/o non-digestible oligosaccharid e or galactooligosa ccharide	HDL-C, LDL-C, TC, TG, ApoA, ApoB
Wong 2010, Canada (51)	С	59	45	60	Dys, PM	OFS-enriched inulin supplement + soy protein diet	10 g/d (4 weeks)	maltodextrin + soy protein diet or low dairy fat + OFS supplement	BMI, DBP, HDL-C, LDL-C, SBP, TC, TG, WC, W, ApoA, ApoB

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Crovesy 2021, Brazil (52)	Р	100	36	34	Ob	Synbiotics	5 g/d (8 weeks)	placebo	BMI, WC, W
(32) Mitchell 2021, USA (53)	Р	65	40	54	Ob	Inulin	10 g/day (6 weeks)	placebo	FBG, W
Williams 2022, Australia	Р	78	46	32	Healthy	OFS-enriched inulin	12 g/day (8 weeks)	placebo	BMI, DBP, FBG, HDL-C, LDL-C, SBP, TC, TG, WC, W
(54) Ziaei 2022, Iran (55)	P	100	75	29	Ob, POS	Inulin	10 g/day (12 weeks)	placebo	BMI, DBP, SBP, W

 $D^* = Study design; P = Parallel, C = Crossover, Sex^* = Sex (% of female); N^{***} = Number of participants completed the trial; Baseline com.**** = Baseline comorbidites$

Dys. = dyslipidemia; **FOS** = fructooligosaccharide; **HTN** = hypertension; **IHD** = ischemic heart disease; **IRH** = Idiopathic reactive hypoglycemia; **MDD** = major depressive disorder; **NCEP** = National Cholesterol Education Program; **Ob** = obesity; OFS =Oligofructos **PM** = post-menopausal; **POS** =polycystic ovary syndrome; **Pre-DM** = pre-diabetes mellitus; **scFOS** = short-chain fructooligosaccharide; **T2DM** = type 2 diabetes mellitus; **≤3 BM/week** = ≤3 bowel movements per week; **>1 of pre-DM/DM/dys/HTN/elevated LFTs**= presence of at least one obesity-related metabolic disorder (prediabetes/diabetes, dyslipidemia, hypertension, elevated liver function tests

Outcomes:

BMI = Body mass index; DBP = diastolic blood pressure; FBG = Fasting blood glucose; HDL-C = High-density lipoprotein cholesterol; LDL = Low-density lipoprotein cholesterol; SBP = Systolic blood pressure; TC = Total cholesterol; TG =Triglycerides; WC = Waist circumference; W = Weight; WHR = Waist-to-hip ratio; ApoA = Apolipoprotein A1; ApoB Apolipoprotein B; HbA1C Hemoglobin A1c; VLDL = Very low-density lipoprotein cholesterol

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Outcomes	Risk with inulin-type fructans supplementation	№ of participants (studies)	Certainty of the evidence (GRADE)
Low-density lipoprotein	MD 0.14 mmol/L lower (0.24 lower to 0.05 lower)	1879 (38 RCTs)	⊕○○○ Very low ^{a,b}
Triglycerides	MD 0.06 mmol/L lower (0.12 lower to 0.01 lower)	1732 (40 RCTs)	$ \bigoplus \bigoplus \bigcirc \bigcirc \\ Low^{a,c} $
Fasting blood glucose	MD 0.05 mmol/L lower (0.16 lower to 0.05 higher)	1505 (36 RCTs)	

Inulin-type fructans supplementation compared to placebo for cardiovascular risk factors

Table 2: GRADE assessment - summary of findings table with main outcomes

MD: mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Bias due to the randomization process, missing data, selective reporting and deviation from the intended intervention

b. Considerable heterogeneity (I2 = 84.8%), 22 studies had point estimates <0 and 16 had point estimates ≥ 0 .

c. Moderate heterogeneity (I2 = 57.4%), 26 studies had point estimates <0 and 14 had point estimates ≥ 0 .

d. Considerable heterogeneity (I2 = 72.9%), 13 studies had point estimate <0 and 23 had point estimates ≥ 0 .

e. The clinical decision would be different considering the effect on the lower versus the higher end of confidence e interval PhD Thesis – J. R. Talukdar; McMaster University – Health Research Methodology

Supplementary materials

Search strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

- 1 (fructooligosaccharide* or fructo oligosaccharide*).ti,ab,kf.
- 2 neosugar*.ti,ab,kf.
- 3 Fructans/
- 4 Inulin/
- 5 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kf.
- 6 inulin*.ti,ab,kf.
- 7 asteraceae.ti,ab,kf.
- 8 oligofructose*.ti,ab,kf.
- 9 chicory.ti,ab,kf.
- 10 chicory root.ti,ab,kf.
- 11 Helianthus/
- 12 jerusalem artichoke*.ti,ab,kf.
- 13 or/1-12
- 14 Lipids/
- 15 lipids.ti,ab,kf.
- 16 Lipoproteins/
- 17 Lipoproteins, IDL/
- 18 exp Lipoproteins, LDL/
- 19 exp Lipoproteins, HDL/
- 20 exp Lipoproteins, VLDL/
- 21 lipid.ti,ab,kf.
- 22 lipoprotein*.ti,ab,kf.
- 23 exp Triglycerides/

- 24 triglyceride*.ti,ab,kf.
- 25 triacetin/ or triolein/
- 26 triacylglycerol*.ti,ab,kf.
- 27 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kf.
- 28 cholesterol*.ti,ab,kf.
- 29 apolipoproteins a/ or apolipoprotein a-i/
- 30 apo* a1.ti,ab,kf.
- 31 apo* a i.ti,ab,kf.
- 32 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kf.
- 33 Apolipoproteins B/
- 34 apo* b.ti,ab,kf.
- 35 or/14-34
- 36 exp waist circumference/
- 37 (waist adj3 (circumference* or ratio*)).ti,ab,kf.
- 38 Glucose/
- 39 glucose.ti,ab,kf.
- 40 blood pressure*.ti,ab,kf.
- 41 body mass index/
- 42 (body mass ind* or BMI).ti,ab,kf.
- 43 or/36-42
- 44 random*.ti,ab,kf.
- 45 rct*.ti,ab,kf.
- 46 randomized controlled trial/
- 47 randomized controlled trial.pt.
- 48 random allocation/
- 49 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kf.
- 50 exp clinical trial/
- 51 controlled clinical trial/
- 52 clinical trial*.ti,ab,kf.
- 53 or/44-52
- 54 13 and (35 or 43) and 53

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55 remove duplicates from 54

Database: Embase

Search Strategy:

1 fructose oligosac	charide/
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- 2 (fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*).ti,ab,kw.
- 3 fructan/
- 4 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kw.
- 5 inulin/
- 6 inulin*.ti,ab,kw.
- 7 asteraceae.ti,ab,kw.
- 8 chicory/
- 9 chicory.ti,ab,kw.
- 10 jerusalem artichoke/
- 11 jerusalem artichoke*.ti,ab,kw.
- 12 helianthus.ti,ab,kw.
- 13 or/1-12
- 14 lipid/
- 15 (lipid or lipids).ti,ab,kw.
- 16 lipoprotein/
- 17 intermediate density lipoprotein/
- 18 low density lipoprotein/
- 19 high density lipoprotein/
- 20 very low density lipoprotein/
- 21 lipoprotein*.ti,ab,kw.
- 22 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kw.
- 23 exp triacylglycerol/
- 24 (triglyceride* or triacylglycerol* or triacetin* or triolein*).ti,ab,kw.
- 25 cholesterol/
- 26 cholesterol*.ti,ab,kw.

apolipoprotein/ or apolipoprotein a/ or apolipoprotein a1/ or apolipoprotein b/ or apolipoprotein b100/ or apolipoprotein b48/

- 28 (apo* a1 or apo* a 1 or apo* a i or apo* ai).ti,ab,kw.
- 29 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kw.
- 30 apo* b*.ti,ab,kw.
- 31 (proapoliprotein adj1 b*).ti,ab,kw.
- 32 or/14-31
- 33 waist circumference/
- 34 (waist adj3 (circumference* or ratio*)).ti,ab,kw.
- 35 glucose/
- 36 glucose*.ti,ab,kw.
- 37 blood pressure/
- 38 blood pressure*.ti,ab,kw.
- 39 body mass/
- 40 (body mass ind* or BMI).ti,ab,kw.
- 41 or/33-40
- 42 random*.ti,ab,kw.
- 43 rct*.ti,ab,kw.
- 44 randomized controlled trial/
- 45 exp randomization/
- 46 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kw.
- 47 clinical trial/
- 48 clinical trial*.ti,ab,kw.
- 49 controlled clinical trial/
- 50 or/42-49
- 51 13 and 41 and 50
- 52 remove duplicates from 51

Database: Ovid Emcare

Search Strategy:

1	fructose	oligosacc	haride/
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- 2 (fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*).ti,ab,kw.
- 3 fructan/
- 4 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kw.
- 5 inulin/
- 6 inulin*.ti,ab,kw.
- 7 asteraceae.ti,ab,kw.
- 8 chicory/
- 9 chicory.ti,ab,kw.
- 10 jerusalem artichoke/
- 11 jerusalem artichoke*.ti,ab,kw.
- 12 helianthus.ti,ab,kw.
- 13 or/1-12
- 14 lipid/
- 15 (lipid or lipids).ti,ab,kw.
- 16 lipoprotein/
- 17 intermediate density lipoprotein/
- 18 low density lipoprotein/
- 19 high density lipoprotein/
- 20 very low density lipoprotein/
- 21 lipoprotein*.ti,ab,kw.
- 22 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kw.
- 23 exp triacylglycerol/
- 24 (triglyceride* or triacylglycerol* or triacetin* or triolein*).ti,ab,kw.
- 25 cholesterol/
- 26 cholesterol*.ti,ab,kw.

apolipoprotein/ or apolipoprotein a/ or apolipoprotein a1/ or apolipoprotein b/ or apolipoprotein b100/ or apolipoprotein b48/

- 28 (apo* a1 or apo* a 1 or apo* a i or apo* ai).ti,ab,kw.
- 29 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kw.
- 30 apo* b*.ti,ab,kw.
- 31 (proapoliprotein adj1 b*).ti,ab,kw.
- 32 or/14-31
- 33 waist circumference/
- 34 (waist adj3 (circumference* or ratio*)).ti,ab,kw.
- 35 glucose/
- 36 glucose*.ti,ab,kw.
- 37 blood pressure/
- 38 blood pressure*.ti,ab,kw.
- 39 body mass/
- 40 (body mass ind* or BMI).ti,ab,kw.
- 41 or/33-40
- 42 random*.ti,ab,kw.
- 43 rct*.ti,ab,kw.
- 44 randomized controlled trial/
- 45 exp randomization/
- 46 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kw.
- 47 clinical trial/
- 48 clinical trial*.ti,ab,kw.
- 49 controlled clinical trial/
- 50 or/42-49
- 51 13 and 41 and 50
- 52 remove duplicates from 51

PhD Thesis - J. R. Talukdar; McMaster University - Health Research Methodology

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

1 (fructooligosaccharide* or fructo oligosaccharide* or neosugar* or (fructan* or inutest* or oligofructan* or polyfructosan*) or inulin* or asteraceae or oligofructose* or chicory or chicory root or jerusalem artichoke*).mp. [mp=title, short title, abstract, full text, keywords, caption text]

2 (lipids or lipid or lipoprotein* or triglyceride* or triacylglycerol* or (HDL or LDL or VLDL or IDL or TG or TAG) or cholesterol* or apo* al or apo* a i or (proapoliprotein adj1 (ai or al or a i or a-1)) or apo* b or (waist adj3 (circumference* or ratio*)) or glucose or blood pressure* or (body mass ind* or BMI)).mp. [mp=title, short title, abstract, full text, keywords, caption text]

3 1 and 2

Database: AMED (Allied and Complementary Medicine)

Search Strategy:

1 (fructooligosaccharide* or fructo oligosaccharide* or neosugar* or (fructan* or inutest* or oligofructan* or polyfructosan*) or inulin* or asteraceae or oligofructose* or chicory or chicory root or jerusalem artichoke*).mp.

- 2 Lipids/
- 3 lipoproteins/

4 triglycerides/

5 (lipids or lipid or lipoprotein* or triglyceride* or triacylglycerol* or (HDL or LDL or VLDL or IDL or TG or TAG) or cholesterol* or apo* al or apo* a i or (proapoliprotein adj1 (ai or al or a i or a-1)) or apo* b or (waist adj3 (circumference* or ratio*)) or glucose or blood pressure* or (body mass ind* or BMI)).mp. [mp=abstract, heading words, title]

6 or/2-5

7 1 and 6

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Database: CINAHL

Search Strategy:

S1 fructose oligosaccharide* or fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*

- S2 fructan* or inutest* or oligofructan* or polyfructosan*
- S3 inulin* or asteraceae
- S4 chicory
- S5 jerusalem artichoke*
- S6 helianthus
- S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
- S8 (MH "Lipids")
- S9 lipid or lipids
- S10 MH "Lipoproteins"
- S11 lipoprotein*
- S12 MH "Lipoproteins, LDL+"
- S13 MH "Lipoproteins, HDL+"
- S14 HDL or LDL or VLDL or IDL or TG or TAG
- S15 MH "Triglycerides"
- S16 triacylglycerol* or triacylglyceride*
- S17 MH "Cholesterol"
- S18 cholesterol*
- S19 MH "Apolipoproteins"
- S20 apo* a1 or apo* a 1 or apo* a i or apo* ai
- S21 proapolioprotein N1 (ai or a1 or a i or a 1)
- S22 apo* b*
- S23 proapolioprotein N1 b*
- S24 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
- S25 MH "Waist Circumference"
- S26 waist N3 (circumference* or ratio*)
- S27 MH "Glucose"

- S28 glucose*
- S29 MH "Blood Pressure"
- S30 blood pressure*
- S31 MH "Body Mass Index"
- S32 body mass ind* or BMI
- S33 S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
- S34 S7 AND S24 AND S33
- S35 S7 AND S24 AND S33

Supplementary documents

Document S1: Hierarchy of extracted outcome measure for RCTs

Reported outcome measures were extracted based on the following hierarchy for RCTs: 1) Change in measure from baseline or between group difference of change from baseline or percent change in measure from baseline (if baseline score is reported); 2) Measure at follow-up or between group difference of measure at follow-up; 3) regression coefficients. The following hierarchy for data extraction was used for cross-over RCTs: 1) Between group difference of change from baseline; 2) Between group difference of measure at follow-up; 3) Change in measure from baseline; 4) percent change in measure from baseline when baseline score is reported; 5) Regression coefficients for change score; 6) Measure at follow-up.

Document S2: Rules for formatting and converting data

Data were formatted and converted prior to meta-analysis based on the following rules:

- Fasting blood glucose was converted from mg/dl to mmol/l by dividing by 18 that is mmol/l = mg/dl / 18 (1).
- HDL-C, LDL-C, VLDL-C and TC were converted from mg/dl to mmol/l by multiplying by 0.02586 (1).
- 3. Triglycerides were converted from mg/dl to mmol/l by multiplying by 0.01129 (1).
- 4. ApoA, ApoB was converted from mg/l to g/l by dividing by 1000 (1).
- HbA1C was converted from mmol/mol to % using the following formula: NGSP = (0.09148*IFCC) + 2.152 (2).
- 6. Studies that reported results as medians were converted to means using the following formula obtained from Hozo 2005 et al. $\bar{x} \approx \frac{a+2m+b}{4}$ (3).
- Measures of variability were converted from SE to SD using the following formulas obtained from the Cochrane Handbook (4).
- 8. Ranges were converted to SD using the following formula from Wan 2014 et al. (5).

$$S \approx \frac{b-a}{2\Phi^{-1}\left(\frac{n-0.375}{n+0.25}\right)}.$$

9. Results from Daud 2014 were converted from geometric means using the formula (6)

$$g_l = \exp\left(\bar{z} - t \times \frac{s_z}{\sqrt{n}}\right)$$
 to $g_u = \exp\left(\bar{z} + t \times \frac{s_z}{\sqrt{n}}\right)$

Methodology decisions in data extraction:

- Aliasgharzadeh et al (2015) outcome measures for control including BMI and BW were reported as "unchanged". Authors were contacted and with no response were reported as NA.
- 2. For Aliasgharzadeh et al (2015) outcomes measure of BMI and BW for intervention group were discrepant between outcomes reported in Tables compared to text with no reason given, values in the Tables were extracted and assumed to be more accurate.
- 3. Where discrepancies in units existed as either not reported as in Clarke et al (2016) or discrepancies between results as in Scheid et al (2014), Tovar et al (2012) and Russo et al (2010), the units of measured were deduced based on magnitude in comparison to the results of the other included studies for the outcome measure.
- 4. In studies that had dose escalation Holscher et al (2014), the dose value included in analysis was the ultimate dose.
- For studies that reported FOS dose by weight/day, Padilla-Cambera (2018) and Machado (2019), FOS dosage by g/day was calculated by multiplying by the average participant body weight.
- 6. We preferentially extracted adjusted analyses (paired) for cross-over trials, otherwise we extracted what was available
- 7. Dose of Genta (2009) was extracted as 12.8 g/day as they analyzed 39 people in the study; they removed 16 people who apparently had bad side effects when they tried 0.29 g/kg body weight. We calculated the dose as 0.14 x 91.2 kg (Table 2) to get 12.8 g/d as the administered dose.

Supplementary tables

Table 1: GRADE assessment for additional outcomes

Summary of findings: additional outcomes

Inulin-type fructans supplementation compared to placebo for reduction of cardiovascular disease risk factors

Outcomes	Risk with inulin-type fructans supplementation	№ of participants (studies)	Certainty of the evidence (GRADE)
Body mass	MD 0.41 kg lower (0.89 lower to 0.06 higher)	1330	$\oplus \bigcirc \bigcirc \bigcirc$
index (BMI)		(29 RCTs)	Very low ^{a,b,c}
Weight	MD 0.97 kg lower (1.28 lower to 0.66 lower)	1672 (36 RCTs)	⊕⊕⊖⊖ Low ^{a,m}
Waist circumference	MD 1.41 cm lower (2.83 lower to 0)	704 (17 RCTs)	$\oplus \bigcirc \bigcirc \bigcirc$ Very low ^{c,k,l}
Waist-to-hip ratio	MD 0.01 ratio lower (0.02 lower to 0)	411 (10 RCTs)	$\begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \text{Low}^{k,n} \end{array}$
Systolic blood pressure	MD 0.09 mmHg higher (2.23 lower to 2.42 higher)	859 (15 RCTs)	$ \begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \text{Low}^{c,h} \end{array} $
Diastolic blood	MD 1.28 mmHg lower (3.18 lower to 0.62 higher)	803	⊕○○○
pressure (DBP)		(14 RCTs)	Very low ^{c,d,e}
High-density	MD 0.03 mmol/L higher (0 to 0.05 higher)	1786	⊕○○○
lipoprotein		(41 RCTs)	Very low ^{c,f,g}
Very-low- density lipoprotein	MD 0.02 mmol/L higher (0.08 lower to 0.11 higher)	174 (3 RCTs)	$ \begin{array}{c} \bigoplus \bigoplus \bigcirc \bigcirc \\ \text{Low}^{c,s} \end{array} $
Total	MD 0.11 mmol/L lower (0.19 to 0.02 lower)	1875	$\oplus \bigcirc \bigcirc \bigcirc$
cholesterol		(40 RCTs)	Very low ^{c,f,i,j}
Lipoprotein A1	MD 0.07 g/L higher	204	⊕⊕⊖⊖
	(0.12 lower to 0.27 higher)	(6 RCTs)	Low ^{c,o}
Lipoprotein B	MD 0.2 g/L higher	204	⊕⊕⊖⊖
	(0.38 lower to 0.79 higher)	(6 RCTs)	Low ^{c,p}

Glucose	0.11 % lower (0.31 lower to 0.09 higher)	514	$\oplus \bigcirc \bigcirc \bigcirc$
hemoglobin		(13 RCTs)	Very low ^{c,q,r}
Alc		(15 KC 18)	very low "

MD: mean difference

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Bias due to missing data, selective reporting and deviations from the intended intervention

b. Considerable heterogeneity (I2 = 88.5%)

c. The clinical decision would be different considering the effect on the lower versus higher end of confidence interval

d. Bias due to missing data and some concerns due to missing data, selective reporting and deviations from the intended intervention

e. Considerable heterogeneity (I2 = 88.3%)

f. Bias due to the randomization process, missing data, selective reporting and deviation from the intended intervention

g. Considerable heterogeneity (I2 =82.4 %)

h. Considerable heterogeneity (I2 = 90.6 %)

i. Considerable heterogeneity (I2 = 85.6 %)

j. The Begg's test for publication bias is significant, p=0.03 but Egger's test for publication bias

is not significant, p = 0.35. We did not downgrade for publication bias.

k. Bias due to missing data and selective reporting

1. Considerable heterogeneity (I2 = 78 %)

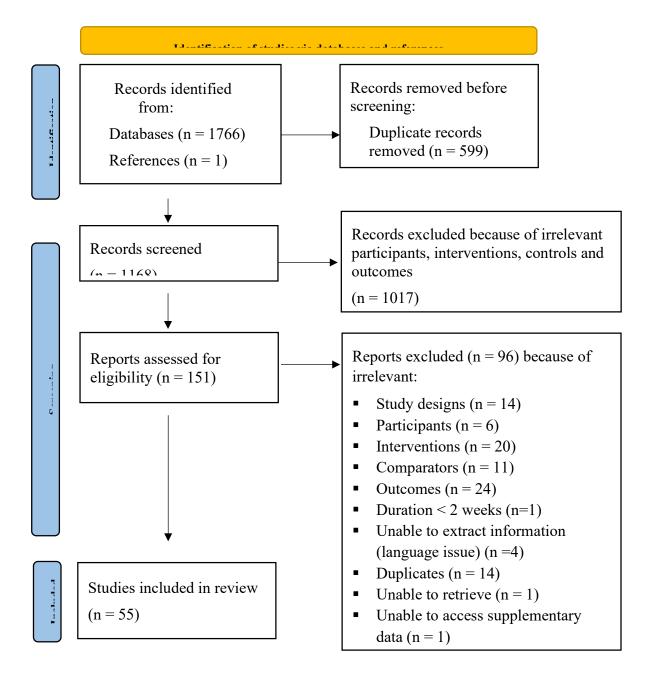
m. Moderate heterogeneity (I2 = 50.1 %)

n. Moderate heterogeneity (I2 = 51.3%)

- o. Considerable heterogeneity (I2 = 91.6%)
- p. Considerable heterogeneity (I2 = 99.4%)
- q. Bias due to the randomization process, deviation from intended interventions and missing data
- r. Considerable heterogeneity (I2 = 85%)
- s. Bias due to selective reporting

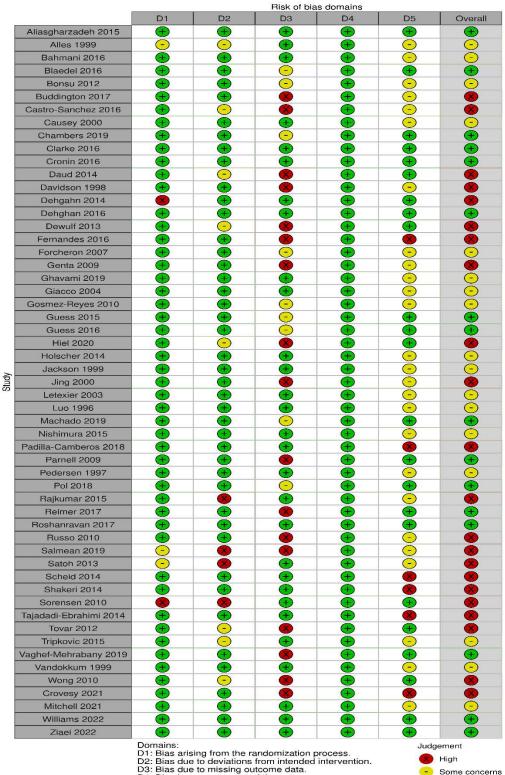
Supplementary figures

Figure 1. PRISMA flow diagram



Flow of studies through the systematic search, assessment of eligibility and inclusion into the review (7)

Figure 2 : Risk of bias in included trails Item-specific risk of bias in included trials (8)



D3: Bias due to deviations nominifiended in D4: Bias in measurement of the outcome. D5: Bias in selection of the reported result.

+ Low

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Risk of bias (continued): summary risk of bias

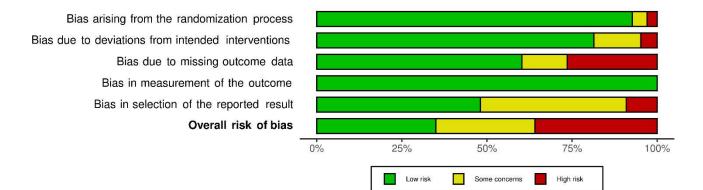


Figure 3: LDL-C - subgroup by sex

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% C
Unknown								
Scheid 2014	07	0.00	0.04	05	0.04	0.07		
Jackson 1999	37 27	2.93 4	0.81 0.85	35 27	3.04 4.43	0.67 1.08	· · · ·	-0.11 [-0.45, 0.2 -0.43 [-0.95, 0.0
Castro-Sanchez 2016								0.56 [-0.23, 1.3
RE Model for Subgroup	16	3.72), df = 2, p =	$1.17 = 0.12 \cdot 1^2 =$	16 51.0% = ²	3.16 = 0.08)	1.12	-	-0.08 [-0.51, 0.3
Both	(02 - 4.20), ui – 2, p –	0.12,1 -	51.970, 1	- 0.08)		Ť	-0.00 [-0.01, 0.0
Williams 2022	20	2.8	0.7	20	3.9	1		1 10 [1 62 0 5
Wong 2010	20	-0.23	0.7	20	-0.12	0.06		-1.10 [-1.63, -0.5 -0.11 [-0.16, -0.0
Sorensen 2010	23 12			23 12	-0.12			-0.30 [-0.95, 0.3
Shakeri 2014		2.7	0.7			0.9		•
	24	-0.19	0.9	24	-0.31	0.98	· · · · · · · · · · · · · · · · · · ·	0.12 [-0.41, 0.6
Satoh 2013	29	2.94	0.12 0.96	27	2.82	0.13	~	0.12 [0.05, 0.1
Roshanravan 2017 Roshanravan 2017	15	1.99		15	2.51	0.59	· · ·	-0.52 [-1.09, 0.0
	14	2.55	0.86	15	2.12	0.7		0.43 [-0.14, 1.0
Rajkumar 2015 Padilla Comboros 2019	15	1.43	0.35	15	1.6	0.23	,=; 	
Padilla-Camberos 2018 Nishimura 2015	14	3.14	0.75	14	3.14	0.88		0.00 [-0.61, 0.6
Machado 2019	24	0.2	1.61	24	0.03	0.9		0.17 [-0.57, 0.9
	13	2.66	0.76	13	3.02	0.9		-0.36 [-1.00, 0.2
_uo 2000	10	3.85	0.73	10	3.85	0.63		0.00 [-0.60, 0.6
Letexier 2003 Hiel 2020	8	2.9	0.62	8	2.77	0.59		0.13 [-0.46, 0.7]
	51	-0.01	0.58	55	-0.09	0.5	,⊫ ⊢≞-1	0.08 [-0.13, 0.2
Giacco 2004	27	4.58	0.67	27	4.55	0.78		0.03 [-0.36, 0.4
Ghavami 2019 Forshoron 2007	23	2.52	1.14	23	2.91	0.84		-0.39 [-0.97, 0.1
Forcheron 2007	9	2.33	0.6	8	2.31	0.42		0.02 [-0.47, 0.5
Davidson 1998 Clarke 2016	21	-0.09	0.05	21	0.45	0.07		-0.54 [-0.58, -0.5
	30	2.6	0.55	30	2.5	0.55		0.10 [-0.18, 0.3
Chambers 2019 Ruddington 2017	12	3.3	0.35	12	3.3	0.69	⊢■┤	0.00 [-0.44, 0.4 -0.24 [-0.61, 0.1
Buddington 2017	45	2.59	0.89	43	2.83	0.89		•
Bonsu 2012 Alles 1999	12	2.4	0.8	14	2.5	0.8		-0.10 [-0.72, 0.5
	20	3.94 .91, df = 22,	0.43	20	3.8	1.04		0.14 [-0.35, 0.6
RE Model for Subgroup	(Q = 421	.91, al = 22,	p < .01; 1	= 89.2%, 1	: = 0.05)		•	-0.11 [-0.24, 0.0
Male								
/andokkum 1999	24	2.82	0.55	12	2.82	0.51		0.00 [-0.36, 0.3
Russo 2010	15	2.82	1.22	15	2.72	0.81		0.10 [-0.64, 0.8
Causey 2000	12	3.8	0.7	12	3.88	0.83		-0.08 [-0.69, 0.5
Blaedel 2016	20	3.2	0.45	19	3.1	0.57	H∎-1	0.10 [-0.22, 0.4
RE Model for Subgroup	(Q = 0.35	5, df = 3, p =	• 0.95; l ² =	0.0%, τ ² =	0.00)		•	0.04 [-0.17, 0.2
Female								
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	⊢⊷⊣	-0.10 [-0.53, 0.3
Tov ar 2012	23	0.11	0.58	28	0.23	0.58	⊢ ∎-1	-0.12 [-0.44, 0.2
Fov ar 2012	30	0.21	0.58	29	0.3	0.58	⊢∎⊣	-0.09 [-0.39, 0.2
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	≑	-0.01 [-0.22, 0.2
Genta 2009	20	2.52	0.26	15	3.43	0.71	┝╼┥┊	-0.91 [-1.29, -0.5
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	┝╼╪┥	-0.13 [-0.50, 0.2
Dehghan 2016	27	0.96	2.51	22	3.03	1.05 H		-2.07 [-3.11, -1.0
Cronin 2016	99	2.6	1	100	2.9	1	⊦∎-i	-0.30 [-0.58, -0.0
Aliasgharzadeh 2015	27	2.44	0.89	25	3.01	1.11	┝━━━┥	-0.57 [-1.12, -0.0
RE Model for Subgroup	$(Q = 32)^{2}$	l6, df = 8, p			= 0.12)		◆	-0.35 [-0.61, -0.0

Test for Subgroup Differences: $Q_M = 4.08$, df = 3, p = 0.25

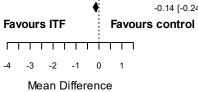


Figure 4: LDL-C - subgroup by disease

_

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]]
With disease								_
Wong 2010	23	-0.23	0.12	23	-0.12	0.06	-0.11 [-0.16, -0.06]	
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	-0.10 [-0.53, 0.33]	
Tovar 2012	23	0.11	0.58	28	0.23	0.58	-0.12 [-0.44, 0.20]	
Tovar 2012	30	0.21	0.58	29	0.3	0.58	-0.09 [-0.39, 0.21]	
Sorensen 2010	12	2.7	0.7	12	3	0.9	-0.30 [-0.95, 0.35]	
Shakeri 2014	24	-0.19	0.9	24	-0.31	0.98	0.12 [-0.41, 0.65]	
Satoh 2013	29	2.94	0.12	27	2.82	0.13	0.12 [0.05, 0.19]	1
Roshanravan 2017	15	1.99	0.96	15	2.51	0.59	-0.52 [-1.09, 0.05]	1
Roshanravan 2017	14	2.55	0.86	15	2.12	0.7	0.43 [-0.14, 1.00]	1
Padilla-Camberos 2018	14	3.14	0.75	14	3.14	0.88	0.00 [-0.61, 0.61]	1
Machado 2019	13	2.66	0.76	13	3.02	0.9	-0.36 [-1.00, 0.28]	1
Luo 2000	10	3.85	0.73	10	3.85	0.63	0.00 [-0.60, 0.60]	1
Hiel 2020	51	-0.01	0.58	55	-0.09	0.5	0.08 [-0.13, 0.29]	i i
Giacco 2004	27	4.58	0.67	27	4.55	0.78	□.03 [-0.36, 0.42]	i i
Ghavami 2019	23	2.52	1.14	23	2.91	0.84	-0.39 [-0.97, 0.19]	i i
Genta 2009	20	2.52	0.26	15	3.43	0.71	-0.91 [-1.29, -0.53]	i i
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	-0.13 [-0.50, 0.24]	i i
Dehghan 2016	27	0.96	2.51	22	3.03	1.05	-2.07 [-3.11, -1.03]	i i
Davidson 1998	21	-0.09	0.05	21	0.45	0.07	•0.54 [-0.58, -0.50]	i i
Chambers 2019	12	3.3	0.35	12	3.3	0.69	□ 0.00 [-0.44, 0.44]	i i
Causey 2000	12	3.8	0.7	12	3.88	0.83	-0.08 [-0.69, 0.53]	i i
Castro-Sanchez 2016	16	3.72	1.17	16	3.16	1.12	0.56 [-0.23, 1.35]	i i
Bonsu 2012	12	2.4	0.8	14	2.5	0.8	-0.10 [-0.72, 0.52]	i i
Blaedel 2016	20	3.2	0.45	19	3.1	0.57	0.10 [-0.22, 0.42]	i i
Alles 1999	20	3.94	0.43	20	3.8	1.04	0.14 [-0.35, 0.63]	i i
Aliasgharzadeh 2015	27	2.44	0.89	25	3.01	1.11	-0.57 [-1.12, -0.02]	i i
RE Model for Subgroup	(Q = 436	.52, df = 25,	p < .01; l	² = 90.3%,	$\tau^2 = 0.07$)		• -0.15 [-0.28, -0.01]	
Without disease								
Williams 2022	20	2.8	0.7	20	3.9	1	-1.10 [-1.63, -0.57]	
Vandokkum 1999	24	2.82	0.55	12	2.82	0.51	□ 0.00 [-0.36, 0.36]	
Scheid 2014	37	2.93	0.81	35	3.04	0.67	-0.11 [-0.45, 0.23]	
Russo 2010	15	2.82	1.22	15	2.72	0.81	0.10 [-0.64, 0.84]	
Rajkumar 2015	15	1.43	0.35	15	1.6	0.23	-0.17 [-0.38, 0.04]	
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	-0.01 [-0.22, 0.20]	
Nishimura 2015	24	0.2	1.61	24	0.03	0.9	0.17 [-0.57, 0.91]	
Letexier 2003	8	2.9	0.62	8	2.77	0.59	0.13 [-0.46, 0.72]	
Jackson 1999	27	4	0.85	27	4.43	1.08	-0.43 [-0.95, 0.09]	
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	0.02 [-0.47, 0.51]	
Cronin 2016	99	2.6	1	100	2.9	1	-0.30 [-0.58, -0.02]	
Clarke 2016	30	2.6	0.55	30	2.5	0.55	0.10 [-0.18, 0.38]	
Buddington 2017	45	2.59	0.89	43	2.83	0.89	-0.24 [-0.61, 0.13]	
RE Model for Subgroup	(Q = 22.2	25, df = 12, p	o = 0.03; l	= 41.1%,	τ ² = 0.02)		• -0.14 [-0.27, -0.00]	i i
								—

RE Model for all studies: (Q = 470.31, df = 38, p < .01; I^2 = 84.8%, τ^2 = 0.05)

Test for Subgroup Differences: $Q_M = 0.00$, df = 1, p = 0.98

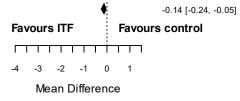


Figure 5: LDL-C - subgroup by dose

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI
Unknown								
Blaedel 2016	20	3.2	0.45	19	3.1	0.57	H a -1	0.10 [-0.22, 0.42
RE Model for Subgroup	(Q = 0.00	0, df = 0, p =	$1.00; I^2 =$	$0.0\%, \tau^2 =$	0.00)		+	0.10 [-0.22, 0.42
Less than 10g								
Shakeri 2014	24	-0.19	0.9	24	-0.31	0.98	┝┿═╾┥	0.12 [-0.41, 0.65
Scheid 2014	37	2.93	0.81	35	3.04	0.67	⊢∎⊣	-0.11 [-0.45, 0.23
Satoh 2013	29	2.94	0.12	27	2.82	0.13		0.12 0.05, 0.19
Padilla-Camberos 2018	14	3.14	0.75	14	3.14	0.88	⊢ ∔ ⊣	0.00 [-0.61, 0.61
Nishimura 2015	24	0.2	1.61	24	0.03	0.9	⊢ i• − - I	0.17 [-0.57, 0.91
Machado 2019	13	2.66	0.76	13	3.02	0.9	┝╾╼┿┥	-0.36 [-1.00, 0.28
Genta 2009	20	2.52	0.26	15	3.43	0.71	┝╼┥	-0.91 [-1.29, -0.53
Cronin 2016	99	2.6	1	100	2.9	1	⊦∎-i	-0.30 [-0.58, -0.02
Castro-Sanchez 2016	16	3.72	1.17	16	3.16	1.12	⊢−−	0.56 [-0.23, 1.35
RE Model for Subgroup	(Q = 39.3	37, df = 8, p					+	-0.12 [-0.39, 0.14
Greater than or equ	al to 10ɑ							
Williams 2022	20	2.8	0.7	20	3.9	1	⊢⊷⊣	-1.10 [-1.63, -0.57
Wong 2010	23	-0.23	0.12	23	-0.12	0.06		-0.11 [-0.16, -0.06
Vandokkum 1999	24	2.82	0.55	12	2.82	0.51	⊢ •−1	0.00 [-0.36, 0.36
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	⊢ ∎-1	-0.10 [-0.53, 0.33
Tovar 2012	23	0.11	0.58	28	0.23	0.58	⊦∎⊣	-0.12 [-0.44, 0.20
Tovar 2012	30	0.21	0.58	29	0.3	0.58	⊢ ∎-1	-0.09 [-0.39, 0.21
Sorensen 2010	12	2.7	0.7	12	3	0.9	┝━━┿┥	-0.30 [-0.95, 0.35
Russo 2010	15	2.82	1.22	15	2.72	0.81	<u>⊢_i</u> ∎	0.10 [-0.64, 0.84
Roshanravan 2017	15	1.99	0.96	15	2.51	0.59	⊢≖⊸i	-0.52 [-1.09, 0.05
Roshanravan 2017	14	2.55	0.86	15	2.12	0.7	<u>⊦</u>	0.43 [-0.14, 1.00
Rajkumar 2015	15	1.43	0.35	15	1.6	0.23	H an i	-0.17 [-0.38, 0.04
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	H#H	-0.01 [-0.22, 0.20
Luo 2000	10	3.85	0.73	10	3.85	0.63	⊢ i − i	0.00 [-0.60, 0.60
Letexier 2003	8	2.9	0.62	8	2.77	0.59	⊢₌−	0.13 [-0.46, 0.72
Jackson 1999	27	4	0.85	27	4.43	1.08	⊢∎⊣	-0.43 [-0.95, 0.09
Hiel 2020	51	-0.01	0.58	55	-0.09	0.5	H	0.08 [-0.13, 0.29
Giacco 2004	27	4.58	0.67	27	4.55	0.78	⊢⊷⊣	0.03 [-0.36, 0.42
Ghavami 2019	23	2.52	1.14	23	2.91	0.84	⊢≖∔∣	-0.39 [-0.97, 0.19
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	⊢ •−1	0.02 [-0.47, 0.51
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	⊢ ∎-1	-0.13 [-0.50, 0.24
Dehghan 2016	27	0.96	2.51	22	3.03	1.05 H		-2.07 [-3.11, -1.03
Davidson 1998	21	-0.09	0.05	21	0.45	0.07		-0.54 [-0.58, -0.50
Clarke 2016	30	2.6	0.55	30	2.5	0.55	H in I	0.10 [-0.18, 0.38
Chambers 2019	12	3.3	0.35	12	3.3	0.69	⊢∔⊣	0.00 [-0.44, 0.44
Causey 2000	12	3.8	0.7	12	3.88	0.83	⊢∔⊣	-0.08 [-0.69, 0.53
Buddington 2017	45	2.59	0.89	43	2.83	0.89	⊢ ∎ +I	-0.24 [-0.61, 0.13
Bonsu 2012	12	2.4	0.8	14	2.5	0.8	⊢	-0.10 [-0.72, 0.52
Alles 1999	20	3.94	0.43	20	3.8	1.04	·	0.14 [-0.35, 0.63
Aliasgharzadeh 2015	20	2.44	0.89	25	3.01	1.11	⊢∎-i .	-0.57 [-1.12, -0.02
		.15, df = 28,	0.00	20	2			-0.16 [-0.26, -0.05

RE Model for all studies: (Q = 470.31, df = 38, p < .01;
$$I^2$$
 = 84.8%, τ^2 = 0

Test for Subgroup Differences:
$$Q_M = 0.80$$
, df = 2, p = 0.67

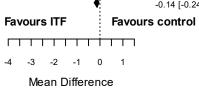


Figure 6: LDL-C - subgroup by ITF type

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% Cl]
Others								
Williams 2022	20	2.8	0.7	20	3.9	1	⊢⊷⊣	-1.10 [-1.63, -0.57]
Wong 2010	23	-0.23	0.12	23	-0.12	0.06		-0.11 [-0.16, -0.06]
Vandokkum 1999	24	2.82	0.55	12	2.82	0.51	⊢∔⊣	0.00 [-0.36, 0.36]
Sorensen 2010	12	2.7	0.7	12	3	0.9	⊢ ∎÷ ł	-0.30 [-0.95, 0.35]
Scheid 2014	37	2.93	0.81	35	3.04	0.67	⊦≖⊣	-0.11 [-0.45, 0.23]
Satoh 2013	29	2.94	0.12	27	2.82	0.13	ju i	0.12 [0.05, 0.19]
Rajkumar 2015	15	1.43	0.35	15	1.6	0.23	H =)	-0.17 [-0.38, 0.04]
Padilla-Camberos 2018	14	3.14	0.75	14	3.14	0.88	⊢ • - 1	0.00 [-0.61, 0.61]
Machado 2019	13	2.66	0.76	13	3.02	0.9	⊢■∔∣	-0.36 [-1.00, 0.28]
Luo 2000	10	3.85	0.73	10	3.85	0.63	⊢ ∔ – I	0.00 [-0.60, 0.60]
Giacco 2004	27	4.58	0.67	27	4.55	0.78	⊢ ••-1	0.03 [-0.36, 0.42]
Genta 2009	20	2.52	0.26	15	3.43	0.71	⊢∎⊣	-0.91 [-1.29, -0.53]
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	i _i	0.02 [-0.47, 0.51]
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	⊢∎⊣	-0.13 [-0.50, 0.24]
Dehghan 2016	27	0.96	2.51	22	3.03	1.05 ⊢	· · ·	-2.07 [-3.11, -1.03]
Cronin 2016	99	2.6	1	100	2.9	1.05		-0.30 [-0.58, -0.02]
Clarke 2016	99 30	2.6	0.55	30	2.9	0.55	- 3 -1	0.10 [-0.18, 0.38]
Buddington 2017	30 45	2.59	0.35	43	2.3	0.89		-0.24 [-0.61, 0.13]
Alles 1999	45 20	3.94	0.89	43 20	3.8	1.04		0.14 [-0.35, 0.63]
Aliasgharzadeh 2015	20	2.44	0.43	20	3.01	1.04	⊢ ∎ i .	-0.57 [-1.12, -0.02]
RE Model for Subgroup		15, df = 19,	o < .01; I ²	= 87.7%, τ ²	$^{2} = 0.08)$	1.11	•	-0.22 [-0.37, -0.06]
Inulin								
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	⊢₊	-0.10 [-0.53, 0.33]
Tovar 2012	23	0.11	0.58	28	0.23	0.58	⊢ ∎i-I	-0.12 [-0.44, 0.20]
Tovar 2012	30	0.21	0.58	29	0.3	0.58	⊢ ∎i i	-0.09 [-0.39, 0.21]
Shakeri 2014	24	-0.19	0.9	24	-0.31	0.98	⊢₌⊣	0.12 [-0.41, 0.65]
Russo 2010	15	2.82	1.22	15	2.72	0.81	⊢ ={	0.10 [-0.64, 0.84]
Roshanrav an 2017	15	1.99	0.96	15	2.51	0.59	⊢■╡	-0.52 [-1.09, 0.05]
Roshanravan 2017	14	2.55	0.86	15	2.12	0.7	<u> -</u>	0.43 [-0.14, 1.00]
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	i÷-	-0.01 [-0.22, 0.20]
Nishimura 2015	24	0.2	1.61	24	0.03	0.9	⊢∔∙−−−−	0.17 [-0.57, 0.91]
Letexier 2003	8	2.9	0.62	8	2.77	0.59	⊢∔≖⊸∤	0.13 [-0.46, 0.72]
Jackson 1999	27	4	0.85	27	4.43	1.08	⊢≖∔	-0.43 [-0.95, 0.09]
Hiel 2020	51	-0.01	0.58	55	-0.09	0.5	, Imil	0.08 [-0.13, 0.29]
Ghavami 2019	23	2.52	1.14	23	2.91	0.84	⊢■┽┥	-0.39 [-0.97, 0.19]
Davidson 1998	21	-0.09	0.05	21	0.45	0.07		-0.54 [-0.58, -0.50]
Chambers 2019	12	3.3	0.35	12	3.3	0.69	⊢ ė ⊣	0.00 [-0.44, 0.44]
Causey 2000	12	3.8	0.00	12	3.88	0.83	┝╼╾┥	-0.08 [-0.69, 0.53]
Castro-Sanchez 2016	16	3.72	1.17	16	3.16	1.12		0.56 [-0.23, 1.35]
Bonsu 2012	10	2.4	0.8	10	2.5	0.8	⊢	-0.10 [-0.72, 0.52]
Blaedel 2016	20	3.2	0.8	14	3.1	0.57		0.10 [-0.22, 0.42]
RE Model for Subgroup		.74, df = 18,	p < .01; l		$t^2 = 0.04)$	0.01	•	-0.08 [-0.22, 0.06]
RE Model for all studies:	(Q = 470	.31, df = 38,	p < .01; I	² = 84.8%, ²	$t^2 = 0.05)$		•	-0.14 [-0.24, -0.05]
Test for Subgroup Differen	ces: Q _M =	1.54, df = 1,	p = 0.21			Favou	rs ITF Fav	ours control

Model for all studies: (Q = 470.31, df = 38, p < .01;
$$I^2$$
 = 84.8%, τ^2 = 0

Fav	our:	s ITF			Favours control				
				i					
-4	-3	-2	-1	0	1				
		_							

Figure 7: LDL-C - subgroup by RoB

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Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95%Cl]
Low								
Williams 2022	20	2.8	0.7	20	3.9	1	⊢	-1.10 [-1.63, -0.57]
Vandokkum 1999	24	2.82	0.55	12	2.82	0.51	⊦÷-1	0.00 [-0.36, 0.36]
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	┝╼╪╌┥	-0.10 [-0.53, 0.33]
Roshanravan 2017	15	1.99	0.96	15	2.51	0.59	⊢⊷	-0.52 [-1.09, 0.05]
Roshanravan 2017	14	2.55	0.86	15	2.12	0.7	⊢	0.43 [-0.14, 1.00]
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	H#H	-0.01 [-0.22, 0.20]
Nishimura 2015	24	0.2	1.61	24	0.03	0.9	⊢∔∙−−−∣	0.17 [-0.57, 0.91]
Machado 2019	13	2.66	0.76	13	3.02	0.9	⊢■∔∣	-0.36 [-1.00, 0.28]
Letexier 2003	8	2.9	0.62	8	2.77	0.59	⊢∔■−−	0.13 [-0.46, 0.72]
Jackson 1999	27	4	0.85	27	4.43	1.08	⊢≖⊣	-0.43 [-0.95, 0.09]
Giacco 2004	27	4.58	0.67	27	4.55	0.78	⊢∔⊣	0.03 [-0.36, 0.42]
Ghavami 2019	23	2.52	1.14	23	2.91	0.84	⊢≖∔∣	-0.39 [-0.97, 0.19]
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	⊢•́-1	0.02 [-0.47, 0.51]
Dehghan 2016	27	0.96	2.51	22	3.03	1.05	⊢	-2.07 [-3.11, -1.03]
Cronin 2016	99	2.6	1	100	2.9	1	⊦∎-I	-0.30 [-0.58, -0.02]
Clarke 2016	30	2.6	0.55	30	2.5	0.55	'≡ -	0.10 [-0.18, 0.38]
Chambers 2019	12	3.3	0.35	12	3.3	0.69	⊢ ∔-1	0.00 [-0.44, 0.44]
Causey 2000	12	3.8	0.7	12	3.88	0.83		-0.08 [-0.69, 0.53]
Bonsu 2012	12	2.4	0.8	14	2.5	0.8	⊢ •−1	-0.10 [-0.72, 0.52]
Blaedel 2016	20	3.2	0.45	19	3.1	0.57	F≢-1	0.10 [-0.22, 0.42]
Alles 1999	20	3.94	0.43	20	3.8	1.04	⊢⊸⊣	0.14 [-0.35, 0.63]
Aliasgharzadeh 2015	27	2.44	0.89	25	3.01	1.11	⊢≖⊣	-0.57 [-1.12, -0.02]
RE Model for Subgroup		72, df = 21, p	o < .01; 1 ²	= 53.7%, τ	= 0.06)		•	-0.15 [-0.29, -0.01]
High								
Wong 2010	23	-0.23	0.12	23	-0.12	0.06	<u>ii</u>	-0.11 [-0.16, -0.06]
Tovar 2012	23	0.23	0.12	23	0.23	0.58		-0.12 [-0.44, 0.20]
Tovar 2012	23 30	0.11	0.58	20	0.23	0.58		-0.09 [-0.39, 0.21]
Sorensen 2010	30 12	2.7	0.58	29 12	3	0.58		-0.30 [-0.95, 0.35]
Shakeri 2014	24	-0.19	0.7	24	-0.31	0.98		0.12 [-0.41, 0.65]
Scheid 2014	24 37	2.93	0.9	24 35	3.04	0.98		-0.11 [-0.45, 0.23]
Satoh 2013	29	2.93	0.81	27	2.82	0.07		0.12 [0.05, 0.19]
Russo 2010	29 15	2.94	1.22	15	2.82	0.13		0.10 [-0.64, 0.84]
Rajkumar 2015	15	2.02 1.43	0.35	15	1.6	0.81		-0.17 [-0.38, 0.04]
Padilla-Camberos 2018	15	3.14	0.35	15	3.14	0.23	,, 	0.00 [-0.61, 0.61]
Luo 2000	14	3.14	0.73	14	3.14	0.63	 	0.00 [-0.60, 0.60]
Hiel 2020	51							0.08 [-0.13, 0.29]
Genta 2009	20	-0.01 2.52	0.58	55 15	-0.09	0.5	,,	-0.91 [-1.29, -0.53]
Dewulf 2013			0.26		3.43	0.71		-0.91 [-1.29, -0.33] -0.13 [-0.50, 0.24]
Dewuli 2013 Davidson 1998	15	-0.1	0.33	15	0.03	0.65	.	
	21	-0.09	0.05	21	0.45	0.07	•• ; 	-0.54 [-0.58, -0.50]
Castro-Sanchez 2016 Buddington 2017	16 45	3.72 2.59	1.17	16 43	3.16 2.83	1.12		0.56 [-0.23, 1.35] -0.24 [-0.61, 0.13]
RE Model for Subgroup	45 (0 = 406	2.59 .35, df = 16,	0.89 n < 01 [·] 1 ²	$^{2} = 92.2\%$	2.83	0.89	•	-0.14 [-0.28, 0.00]
	00+			- 52.270,	2			

RE Model for all studies: (Q = 470.31, df = 38, p < .01;
$$I^2$$
 = 84.8%, τ^2 = 0.05)

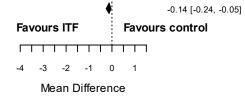


Figure 8: LDL-C - subgroup by follow-up duration

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95%Cl]
Less than 6 weeks								
Wong 2010	23	-0.23	0.12	23	-0.12	0.06		-0.11 [-0.16, -0.06]
Vandokkum 1999	24	2.82	0.55	12	2.82	0.51	⊢≑-1	0.00 [-0.36, 0.36]
Sorensen 2010	12	2.7	0.7	12	3	0.9	┝┈╺╪┥	-0.30 [-0.95, 0.35]
Russo 2010	15	2.82	1.22	15	2.72	0.81	⊢⊸−−	0.10 [-0.64, 0.84]
Pedersen 1997	64	2.38	0.67	64	2.39	0.56	I#I	-0.01 [-0.22, 0.20]
Nishimura 2015	24	0.2	1.61	24	0.03	0.9	⊢∔∙−−−Ⅰ	0.17 [-0.57, 0.91]
Luo 2000	10	3.85	0.73	10	3.85	0.63	⊢∔⊣	0.00 [-0.60, 0.60]
Letexier 2003	8	2.9	0.62	8	2.77	0.59	┝╌╍╌┥	0.13 [-0.46, 0.72]
Clarke 2016	30	2.6	0.55	30	2.5	0.55	H≡-I	0.10 [-0.18, 0.38]
Causey 2000	12	3.8	0.7	12	3.88	0.83	⊢iI	-0.08 [-0.69, 0.53]
Blaedel 2016	20	3.2	0.45	19	3.1	0.57	- <mark> =</mark> -	0.10 [-0.22, 0.42]
Alles 1999	20	3 94	0 43	20	3.8	1.04	⊢	0.14 [-0.35, 0.63]
RE Model for Subgroup	(Q = 10.9	91, df = 13,	o = 0.62; 1 ²	² = 14.9%, ²	$r^2 = 0.00$)		1	0.03 [-0.01, 0.06]
Greater than or equa	al to 6 w	eeks						
Williams 2022	20	2.8	0.7	20	3.9	1	┝╼╾┥	-1.10 [-1.63, -0.57]
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94	⊢≖	-0.10 [-0.53, 0.33]
Tovar 2012	23	0.11	0.58	28	0.23	0.58	⊢∎ -I	-0.12 [-0.44, 0.20]
Tovar 2012	30	0.21	0.58	29	0.3	0.58	⊢ ∎i I	-0.09 [-0.39, 0.21]
Shakeri 2014	24	-0.19	0.9	24	-0.31	0.98	┝╌═╌┥	0.12 [-0.41, 0.65]
Scheid 2014	37	2.93	0.81	35	3.04	0.67	⊢ ∎i-1	-0.11 [-0.45, 0.23]
Satoh 2013	29	2.94	0.12	27	2.82	0.13	ju i	0.12 [0.05, 0.19]
Roshanrav an 2017	15	1.99	0.96	15	2.51	0.59	⊢ •→j	-0.52 [-1.09, 0.05]
Roshanrav an 2017	14	2.55	0.86	15	2.12	0.7	<u> -</u>	0.43 [-0.14, 1.00]
Rajkumar 2015	15	1.43	0.35	15	1.6	0.23		-0.17 [-0.38, 0.04]
Padilla-Camberos 2018	14	3.14	0.75	14	3.14	0.88	⊢ ∔1	0.00 [-0.61, 0.61]
Machado 2019	13	2.66	0.76	13	3.02	0.9	┝━━┷┥	-0.36 [-1.00, 0.28]
Jackson 1999	27	4	0.85	27	4.43	1.08	┝━━┤	-0.43 [-0.95, 0.09]
Hiel 2020	51	-0.01	0.58	55	-0.09	0.5	i s i	0.08 [-0.13, 0.29]
Giacco 2004	27	4.58	0.67	27	4.55	0.78	⊢ ∎-1	0.03 [-0.36, 0.42]
Ghavami 2019	23	2.52	1.14	23	2.91	0.84	⊢≖∔	-0.39 [-0.97, 0.19]
Genta 2009	20	2.52	0.26	15	3.43	0.71	⊢∎⊣	-0.91 [-1.29, -0.53]
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	⊢∔-1	0.02 [-0.47, 0.51]
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	, ⊢∎-1	-0.13 [-0.50, 0.24]
Dehghan 2016	27	0.96	2.51	22	3.03	1.05 ⊢	i	-2.07 [-3.11, -1.03]
Davidson 1998	21	-0.09	0.05	21	0.45	0.07		-0.54 [-0.58, -0.50]
Cronin 2016	99	2.6	1	100	2.9	1	-■-	-0.30 [-0.58, -0.02]
Chambers 2019	99 12	3.3	0.35	100	3.3	0.69	· · ·	0.00 [-0.44, 0.44]
Castro-Sanchez 2016	12	3.72	1.17	12	3.16	1.12	<u> </u>	0.56 [-0.23, 1.35]
Buddington 2017	45	2.59	0.89	43	2.83	0.89	_∎ -	-0.24 [-0.61, 0.13]
Bonsu 2012	45 12	2.59	0.89	43 14	2.83			-0.10 [-0.72, 0.52]
Aliasgharzadeh 2015	27	2.4 2.44	0.8	14 25	2.5 3.01	0.8		-0.57 [-1.12, -0.02]
RE Model for Subgroup		2.44 .50, df = 26,	0.09 n < 01. 1	20 = 87 /0/	3.01	1.11	`▲	-0.22 [-0.35, -0.08]
	100 - 201		ייס, ד	- 07.470,	- 0.00)		•	0.22 [-0.00, -0.00]

RE Model for all studies: (Q = 470.31, df = 38, p < .01;
$$I^2$$
 = 84.8%, τ^2 = 0.05)

Test for Subgroup Differences: $Q_M = 4.40$, df = 1, p = 0.04

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Figure 9: LDL-C - subgroup by age

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown Luo 2000 Sorensen 2010	10 12	3.85 2.7	0.73 0.7	10 12	3.85 3	0.63 0.9	→ → 0.00 [−0.60, 0.60] → → → −0.30 [−0.95, 0.35]
Jackson 1999 Giacco 2004	27 27	4 4.58	0.85 0.67	27 27	4.43 4.55	1.08 0.78 0.89	−0.43 [−0.95, 0.09] −0.43 [−0.36, 0.42] −0.24 [−0.61, 0.13]
Buddington 2017 RE Model for Subgrou	up (Q = 3.99	, df = 4, p = 0	0.41; I ² = 1	$.6\%, \tau^2 = 0.0$	00)		◆ -0.06 [-0.20, 0.09]
more than 40 years Blaedel 2016	20	3.2	0.45	19	3.1	0.57	0.10 [-0.22, 0.42]
Williams 2022	20	2.8	0.45	20	3.9	1	
Castro-Sanchez 2016	16	3.72	1.17	16	3.16	1.12	
Bonsu 2012	12	2.4	0.8	14	2.5	0.8	
Machado 2019	12	2.66	0.8	13	3.02	0.8	
Rajkumar 2015	15	1.43	0.75	15	1.6	0.9	
Pedersen 1997	64	2.38	0.35	64	2.39	0.23	H = H = -0.17 [-0.38, 0.04] H = H = -0.01 [-0.22, 0.20]
Scheid 2014	37	2.30	0.87	35	2.39	0.56	
Shakeri 2014	24	-0.19	0.81	24	-0.31	0.07	-0.11[-0.43, 0.23]
Hiel 2020	24 51	-0.19	0.9	24 55		0.98	
Roshanravan 2017	15	1.99	0.56	55 15	-0.09 2.51	0.59	
Roshanravan 2017	13	2.55	0.96	15	2.12	0.59	
Aliasgharzadeh 2015	27	2.55	0.80	25	3.01	1.11	-0.57 [-1.12, -0.02]
Dehghan 2016	27	2.44	2.51	25 22	3.01	1.05	-2.07[-3.11, -1.03]
Dewulf 2013	15	-0.1	0.33	15	0.03	0.65	
Ghavami 2019	23	2.52	1.14	23	2.91	0.85	
Genta 2009	23	2.52	0.26	23 15	3.43	0.64	
Vaghef-Mehrabany 2019	20	-0.11	0.20	23	-0.01	0.71	
Satoh 2013	22						0.12 [0.05, 0.19]
Nishimura 2015	29 24	2.94	0.12	27 24	2.82	0.13 0.9	- 0.12 [0.03, 0.13]
Clarke 2016	24 30	0.2 2.6	1.61	24 30	0.03		H = 1 0.17 [-0.37, 0.91]
Russo 2010			0.55		2.5	0.55	\rightarrow 0.10 [-0.18, 0.38]
RE Model for Subgrou	15	2.82 83 df = 21 i	$1.22 = 01 \cdot 1^2 -$	- 02 8% - ²	2.72	0.81	● -0.20 [-0.34, -0.05]
	up (& = 420.	00, ui – 21, j	5 4.01,1 -	- 52.0 70, t	- 0.00)		• 0.20 [0.04, 0.03]
40 years or less							
Letexier 2003	8	2.9	0.62	8	2.77	0.59	0.13 [-0.46, 0.72]
Cronin 2016	99	2.6	1	100	2.9	1	-0.30 [-0.58, -0.02]
Chambers 2019	12	3.3	0.35	12	3.3	0.69	⊢∔→ 0.00 [−0.44, 0.44]
Padilla-Camberos 2018	14	3.14	0.75	14	3.14	0.88	⊢+→ 0.00 [−0.61, 0.61]
Tovar 2012	23	0.11	0.58	28	0.23	0.58	⊢∎⊣ −0.12 [−0.44, 0.20]
Causey 2000	12	3.8	0.7	12	3.88	0.83	-0.08 [-0.69, 0.53]
Davidson 1998	21	-0.09	0.05	21	0.45	0.07	-0.54 [-0.58, -0.50]
Alles 1999	20	3.94	0.43	20	3.8	1.04	
Wong 2010	23	-0.23	0.12	23	-0.12	0.06	-0.11 [-0.16, -0.06]
Tovar 2012	30	0.21	0.58	29	0.3	0.58	⊢■⊢ −0.09 [−0.39, 0.21]
Forcheron 2007	9	2.33	0.6	8	2.31	0.42	⊢ 0.02 [−0.47, 0.51]
Vandokkum 1999 RE Model for Subgrou	24 In (Q = 18.9	2.82 1. df = 11. p	= 0.55 = 0.06; $ ^2$ =	12 = 36.0%. τ ² :	2.82 = 0.02)	0.51	→ 0.00 [-0.36, 0.36] → -0.11 [-0.25, 0.04]
RE Model for all studies:		31, df = 38, j					-0.14 [-0.24, -0.05]
Test for Subgroup Difference				-υ4.070,τ	- 0.05)	Fore	•
	cs. QM - 1.0	z, ui – z, μ –	0.44			ravo	burs ITF Favours control

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Figure 10: LDL-C - subgroup by body mas index

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Unknown Letexier 2003 Causey 2000 Davidson 1998 Forcheron 2007 Vandokkum 1999 RE Model for Subgrou	8 12 21 9 24 up (Q = 20.1	2.9 3.8 -0.09 2.33 2.82 5, df = 4, p <	0.62 0.7 0.05 0.6 0.55 <.01; 1 ² = 7	8 12 21 8 12 1.1%, τ ² = 0	2.77 3.88 0.45 2.31 2.82 0.08)	0.59 0.83 0.07 0.42 0.51	◆ ∓ ⊥∎⊥	$\begin{array}{c} 0.13 \left[-0.46, \ 0.72\right] \\ -0.08 \left[-0.69, \ 0.53\right] \\ -0.54 \left[-0.58, \ -0.50\right] \\ 0.02 \left[-0.47, \ 0.51\right] \\ 0.00 \left[-0.36, \ 0.36\right] \\ -0.16 \left[-0.47, \ 0.14\right] \end{array}$
Obese Castro-Sanchez 2016 Bonsu 2012 Shakeri 2014 Hiel 2020 Roshanravan 2017 Roshanravan 2017 Aliasgharzadeh 2015 Dehydha 2016 Dewulf 2013 Ghavami 2019 Genta 2009 Vaghef-Mehrabany 2019 Padilla-Camberos 2018 Tovar 2012 Tovar 2012 Machado 2019 RE Model for Subgrou	16 12 24 51 15 15 27 27 27 27 27 23 20 22 14 23 30 30 13 46.8	3.72 2.4 -0.19 -0.01 2.55 2.44 0.96 -0.1 2.52 2.52 -0.11 3.14 0.21 0.21 0.21 1, df = 15, p	1.17 0.8 0.9 0.58 0.86 0.89 2.51 0.33 1.14 0.26 0.47 0.75 0.58 0.76 < .01; 1 ² = 1	16 14 25 15 15 25 22 15 23 15 23 15 23 15 23 14 29 15 23 69.1%, τ^2 =	3.16 2.5 -0.31 -0.09 2.51 2.12 3.01 3.03 0.03 2.91 3.43 -0.01 3.14 0.23 0.3 3.02 0.11)	1.12 0.8 0.5 0.5 0.7 1.11 1.05 0.84 0.71 0.94 0.88 0.58 0.58 0.9	┄╋┨┹┲╄┲╌┲┰╌┲┰┺┸┺ ┈╋┨┹┲	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
Pre-obese Scheid 2014 Cronin 2016 Chambers 2019 Alles 1999 Wong 2010 Luo 2000 Sorensen 2010 Jackson 1999 Giacco 2004 Buddington 2017 Blaedel 2016 Williams 2022 RE Model for Subgrou	37 99 12 20 23 10 12 27 45 20 20 20 20 0 u p (Q = 20.5	2.93 2.6 3.3 3.94 -0.23 3.85 2.7 4 4.58 2.59 3.2 2.8 7, df = 11, p	$\begin{array}{c} 0.81 \\ 1 \\ 0.35 \\ 0.43 \\ 0.12 \\ 0.73 \\ 0.7 \\ 0.85 \\ 0.67 \\ 0.89 \\ 0.45 \\ 0.7 \\ 0.95 \\ 0.71^2 = 0.04; 1^2 = 0.04; 1^2 = 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.04 \\ 0.$	35 100 12 20 23 10 12 27 27 43 43 19 20 ε 46.6%, τ ²	3.04 2.9 3.3 -0.12 3.85 3 4.43 4.43 4.55 2.83 3.1 3.9 = 0.02)	0.67 1 0.69 1.04 0.63 0.9 1.08 0.78 0.78 0.57 1	◆····································	$\begin{array}{c} -0.11 \left[-0.45, \ 0.23\right] \\ -0.30 \left[-0.58, -0.02\right] \\ 0.00 \left[-0.44, \ 0.44\right] \\ 0.14 \left[-0.35, \ 0.63\right] \\ -0.11 \left[-0.16, -0.06\right] \\ 0.00 \left[-0.60, \ 0.60\right] \\ -0.30 \left[-0.95, \ 0.35\right] \\ -0.43 \left[-0.95, \ 0.09\right] \\ 0.03 \left[-0.36, \ 0.42\right] \\ -0.24 \left[-0.61, \ 0.13\right] \\ 0.10 \left[-0.22, \ 0.42\right] \\ -1.10 \left[-1.63, -0.57\right] \\ -0.16 \left[-0.29, \ -0.02\right] \end{array}$
Normal Rajkumar 2015 Pedersen 1997 Satoh 2013 Nishimura 2015 Clarke 2016 Russo 2010 RE Model for Subgrou	15 64 29 24 30 15 up(Q = 7.47	1.43 2.38 2.94 0.2 2.6 2.82 , df = 5, p =	0.35 0.67 0.12 1.61 0.55 1.22 0.19; 1 ² = 4	15 64 27 24 30 15 2.4%, τ ² = 0	1.6 2.39 2.82 0.03 2.5 2.72 0.01)	0.23 0.56 0.13 0.9 0.55 0.81		$\begin{array}{c} -0.17 \begin{bmatrix} -0.38, \ 0.04 \\ -0.01 \begin{bmatrix} -0.22, \ 0.20 \end{bmatrix} \\ 0.12 \begin{bmatrix} 0.05, \ 0.19 \end{bmatrix} \\ 0.17 \begin{bmatrix} -0.57, \ 0.91 \end{bmatrix} \\ 0.10 \begin{bmatrix} -0.18, \ 0.38 \end{bmatrix} \\ 0.10 \begin{bmatrix} -0.64, \ 0.84 \end{bmatrix} \\ 0.03 \begin{bmatrix} -0.09, \ 0.16 \end{bmatrix} \end{array}$
RE Model for all studies: Test for Subgroup Difference		31, df = 38, 3, df = 3, p =		= 84.8%, τ ²	= 0.05)	Favou	Irs ITF Fa	-0.14 [-0.24, -0.05] vours control

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Figure 11: LDL-C - subgroup by diabetes status

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Unknown								
Sorensen 2010	12	2.7	0.7	12	3	0.9	L I	-0.30 [-0.95, 0.35]
Giacco 2004	27	4.58	0.67	27	4.55	0.78	· • •	0.03 [-0.36, 0.42]
Castro-Sanchez 2016	16	3.72	1.17	16	3.16	1.12	· · · · · · · · · · · · · · · · · · ·	0.56 [-0.23, 1.35]
Hiel 2020	51	-0.01	0.58	55	-0.09	0.5	, interest in the second se	0.08 [-0.13, 0.29]
Vaghef-Mehrabany 2019	22	-0.11	0.47	23	-0.01	0.94		-0.10 [-0.53, 0.33]
Machado 2019	13	2.66	0.76	13	3.02	0.9		-0.36 [-1.00, 0.28]
Causey 2000	12	3.8	0.7	12	3.88	0.83	·	-0.08 [-0.69, 0.53]
						0.07		-0.54 [-0.58, -0.50]
Davidson 1998 RE Model for Subgroup	(Q = 20.1	5, df = 4, p <	0.00 $(.00)$ $(.01)$ $(.01)$ $(.01)$ $(.01)$	$1.1\%, \tau^2 = 0$	0.45	0.07	•	-0.16 [-0.47, 0.14]
No diabetes								
Scheid 2014	37	2.93	0.81	35	3.04	0.67	H a H	-0.11 [-0.45, 0.23]
Cronin 2016	99	2.35	1	100	2.9	1		-0.30 [-0.58, -0.02]
Chambers 2019	12	3.3	0.35	12	3.3	0.69		0.00 [-0.44, 0.44]
Wong 2010	23	-0.23	0.35	23	-0.12	0.06		-0.11 [-0.16, -0.06]
Jackson 1999	27	4	0.12	27	4.43	1.08	⊢ ∎–	-0.43 [-0.95, 0.09]
Buddington 2017	45	2.59	0.85	43	2.83	0.89		-0.24 [-0.61, 0.13]
Blaedel 2016	20	3.2	0.89	19	3.1	0.57		0.10 [-0.22, 0.42]
Williams 2022	20	2.8	0.45	20	3.9	1		-1.10 [-1.63, -0.57]
Dewulf 2013	20 15	2.0 -0.1	0.33	20 15	0.03	0.65		-0.13 [-0.50, 0.24]
Genta 2009	20	2.52	0.33	15	3.43	0.05		-0.91 [-1.29, -0.53]
Padilla-Camberos 2018	20 14	2.52	0.20	15	3.43	0.88		0.00 [-0.61, 0.61]
Tovar 2012	23	0.14	0.75	28	0.23	0.68		-0.12 [-0.44, 0.20]
Tovar 2012	23 30	0.11	0.58	20	0.23	0.58		-0.09 [-0.39, 0.21]
Rajkumar 2015	30 15	1.43	0.58	29 15				-0.17 [-0.38, 0.04]
Pedersen 1997	64		0.35		1.6	0.23 0.56		-0.01 [-0.22, 0.20]
Nishimura 2015		2.38		64	2.39			0.17 [-0.57, 0.91]
Clarke 2016	24	0.2	1.61	24	0.03	0.9		0.10 [-0.18, 0.38]
Russo 2010	30 15	2.6	0.55	30	2.5	0.55		0.10 [-0.64, 0.84]
Letexier 2003		2.82	1.22	15	2.72	0.81	·	
Forcheron 2007	8	2.9	0.62	8	2.77	0.59		0.13 [-0.46, 0.72] 0.02 [-0.47, 0.51]
Vandokkum 1999	9	2.33	0.6	8	2.31	0.42		0.02 [-0.47, 0.31]
RE Model for Subgroup	24 (Q = 41.5	2.82 2, df = 20, p	0.55 < .01; l ² = 0	$12_{63.0\%, \tau^2} =$	2.82 0.03)	0.51	<u>⊢</u> ∔-1 ♦ -	-0.15 [-0.26, -0.03]
Have diabetes								. , ,
Alles 1999	00	0.04	0.40	00	0.0	4.04		0.14 [-0.35, 0.63]
Luo 2000	20 10	3.94	0.43	20	3.8	1.04		0.00[-0.60, 0.60]
Bonsu 2012		3.85	0.73	10	3.85	0.63		-0.10 [-0.72, 0.52]
Shakeri 2014	12	2.4	0.8	14	2.5	0.8	···•	
Roshanravan 2017	24	-0.19	0.9	24	-0.31	0.98		0.12 [-0.41, 0.65] -0.52 [-1.09, 0.05]
	15	1.99	0.96	15	2.51	0.59	······································	
Roshanravan 2017	14	2.55	0.86	15	2.12	0.7	· · ·	0.43 [-0.14, 1.00]
Aliasgharzadeh 2015	27	2.44	0.89	25	3.01	1.11	⊢ ∎−-(-0.57 [-1.12, -0.02]
Dehghan 2016	27	0.96	2.51	22	3.03	1.05 ⊢		-2.07 [-3.11, -1.03]
Ghavami 2019	23	2.52	1.14	23	2.91	0.84		-0.39 [-0.97, 0.19]
Satoh 2013 RE Model for Subgroup	(Q = 31.7	2.94 0, df = 9, p <	0.12 : .01; I ² = 7	$7.7\%, \tau^2 = 0$	2.82).16)	0.13	▲	0.12 [0.05, 0.19] -0.18 [-0.49, 0.12]
		31, df = 38, j					-	-0.14 [-0.24, -0.05]
RE Model for all studies: Test for Subgroup Differences				· 04.0 /0, t	- 0.03)	Favours		ours control

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Figure 12: Triglycerides - subgroup by sex

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Unknown								
Scheid 2014	37	1.5	0.78	35	1.48	0.93	+∔-	0.02 [-0.38, 0.42]
Jackson 1999	27	1.29	0.35	27	1.59	0.58	={	-0.30 [-0.56, -0.04]
Castro-Sanchez 2016	16	-0.3	0.61	16	-0.01	0.49	⊦∎∮	-0.29 [-0.67, 0.09]
RE Model for Subgroup	(Q = 1.90	-0.3 , df = 2, p =	= 0.39; I ² =	= 0.0%, τ ²	= 0.00)		•	-0.23 [-0.41, -0.04]
Both								
Williams 2022	20	1.1	0.7	20	1.2	0.4	 	-0.10 [-0.45, 0.25]
Wong 2010	23	1.64	0.14	23	1.73	0.14		-0.09 [-0.17, -0.01]
Sorensen 2010	12	1	0.4	12	1	0.7		0.00 [-0.46, 0.46]
Shakeri 2014	24	-0.3	0.68	24	-0.36	0.9	<u>++</u> -	0.06 [-0.39, 0.51]
Satoh 2013	29	1.16	0.07	27	1.06	0.08		0.10 [0.06, 0.14]
Roshanravan 2017	15	1.8	0.65	15	1.83	0.71		-0.03 [-0.52, 0.46]
Roshanravan 2017	14	1.84	0.51	15	1.78	0.68	I∔I	0.06 [-0.38, 0.50]
Rajkumar 2015	15	1.16	0.07	15	1.18	0.08		-0.02 [-0.07, 0.03]
Padilla-Camberos 2018	14	1.55	0.68	14	3.95	3.08 ⊢		-2.40 [-4.05, -0.75]
Nishimura 2015 Machado 2019	24	0.09	0.7	24	0.01	0.39	++ ++	0.08 [-0.24, 0.40]
Luo 2000	13	1.26	0.4	13	1.27	0.65		-0.01 [-0.42, 0.40] -0.09 [-0.48, 0.30]
Luo 2000 Letexier 2003	10	1.33	0.51	10	1.42	0.38		-0.15 [-0.40, 0.10]
Hiel 2020	8 51	0.77	0.23	8	0.92 -0.1	0.28	Η	-0.05 [-0.47, 0.37]
Gosmez-Rey es 2010	20	-0.15 -0.19	1.34 0.03	55 20	-0.1	0.79	.	-0.19 [-0.22, -0.16]
Ghavami 2019	20	-0.19	0.03	20	2.09	0.06 0.09	ન	-0.19 [-0.44, 0.06]
Forcheron 2007	9	0.77	0.42	8	0.64	0.03	I ∔ I	0.13 [-0.22, 0.48]
Davidson 1998	21	-0.04	0.19	21	0.04	0.16	i i i i i i i i i i i i i i i i i i i	-0.08 [-0.19, 0.03]
Daud 2014	12	1.58	1.1	10	0.97	0.38		0.61 [-0.06, 1.28]
Clarke 2016	30	1.2	0.55	30	1.3	1.64	H	-0.10 [-0.72, 0.52]
Chambers 2019	12	1	0.35	12	1.1	0.35	H	-0.10 [-0.38, 0.18]
Buddington 2017	45	1.06	0.72	43	1.16	0.69	Hel Hel	-0.10 [-0.39, 0.19]
Bonsu 2012	12	1.5	0.6	14	1.8	1.2	⊢₊∔	-0.30 [-1.01, 0.41]
Alles 1999	20	2 56	0.69	20	2 44	0.79	Fi≉-1	0.12 [-0.34, 0.58]
RE Model for Subgroup	(Q = 155.	55, df = 23,	p < .01; I	² = 68.4%	$\tau^2 = 0.01$		•	-0.05 [-0.11, 0.01]
Male								
Vandokkum 1999	24	1.3	0.53	12	1.4	0.68	⊢ i -i	-0.10 [-0.54, 0.34]
Tripkovic 2015	10	2.08	0.86	10	1.79	0.61	H	0.29 [-0.36, 0.94]
Russo 2010	15	0.85	0.3	15	0.95	0.32		-0.10 [-0.32, 0.12]
Luo 1996	12	0.83	0.55	12	0.72	0.17	, I i -I	0.11 [-0.22, 0.44]
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.17]
Blaedel 2016	20	1.27	1.03	19 2	0.96	0.31	l <u>∔</u> I	0.31 [-0.16, 0.78]
RE Model for Subgroup	(Q = 4.10	, df = 5, p =	= 0.54; 1 =	= 5.0%, τ	= 0.00)		•	0.02 [-0.15, 0.18]
Female								
Vaghef-Mehrabany 2019	22	-0.09	0.63	23	-0.16	0.57	+ ⊾	0.07 [-0.28, 0.42]
Tov ar 2012	23	-0.35	0.48	28	-0.41	0.48	별	0.06 [-0.20, 0.32]
Tov ar 2012	30	-0.36	0.48	29	-0.29	0.48	변	-0.07 [-0.31, 0.17]
Pedersen 1997	64	0.97	0.39	64	0.98	0.42		-0.01 [-0.15, 0.13]
Genta 2009	20	2.1	0.97	15	2.19	0.78	 H	-0.09 [-0.67, 0.49]
Dewulf 2013 Debahan 2016	15	-0.09	0.33	15	0.07	0.37	رجم العا:	-0.16 [-0.41, 0.09]
Dehghan 2016 Alias gharzadeb 2015	27	1.95	0.71	22	2.49	0.66	 ++¦	-0.54 [-0.92, -0.16]
Aliasgharzadeh 2015 RE Model for Subgroup	27 (Q = 12.4	2 2, df = 7, p	0.69 = 0.09; 1 ²	25 = 42.9%,	$\tau^2 = 0.01$)	0.68	•	-0.45 [-0.82, -0.08] -0.11 [-0.25, 0.02]
RE Model for all studies:		63, df = 40,			$\tau^2 = 0.01$		(-0.06 [-0.12, -0.01]
	,			2	,	_]	

Test for Subgroup Differences: $Q_M = 3.53$, df = 3, p = 0.32

Favours ITF Favours control

-4.5 -3 -1.5 0 1 2 3

Figure 13: Triglycerides - subgroup by disease

-

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
With disease								
Wong 2010	23	1.64	0.14	23	1.73	0.14	i i	-0.09 [-0.17, -0.01]
Vaghef-Mehrabany 2019	23	-0.09	0.14	23	-0.16	0.14		0.07 [-0.28, 0.42]
Tripkovic 2015	10	2.08	0.86	10	-0.10	0.57		0.29 [-0.36, 0.94]
Tov ar 2012	23	-0.35	0.48	28	-0.41	0.48	H , H	0.06 [-0.20, 0.32]
Tov ar 2012	30	-0.36	0.48	29	-0.29	0.48	I - I	-0.07 [-0.31, 0.17]
Sorensen 2010	12	1	0.4	12	1	0.7	F.∎.I	0.00 [-0.46, 0.46]
Shakeri 2014	24	-0.3	0.4	24	-0.36	0.9	I − I	0.06 [-0.39, 0.51]
Satoh 2013	29	1.16	0.00	27	1.06	0.08		0.10 [0.06, 0.14]
Roshanravan 2017	15	1.10	0.65	15	1.83	0.71	H	-0.03 [-0.52, 0.46]
Roshanravan 2017	14	1.84	0.51	15	1.78	0.68		0.06 [-0.38, 0.50]
Padilla-Camberos 2018	14	1.55	0.68	14	3.95	3.08 ⊢		-2.40 [-4.05, -0.75]
Machado 2019	13	1.26	0.4	13	1.27	0.65	141	-0.01 [-0.42, 0.40]
Luo 2000	10	1.33	0.51	10	1.42	0.38	⊢	-0.09 [-0.48, 0.30]
Hiel 2020	51	-0.15	1.34	55	-0.1	0.79	H	-0.05 [-0.47, 0.37]
Gosmez-Rey es 2010	20	-0.19	0.03	20	0	0.06	, in the second s	-0.19 [-0.22, -0.16]
Ghavami 2019	23	1.9	0.6	23	2.09	0.09	1=1	-0.19 [-0.44, 0.06]
Genta 2009	20	2.1	0.97	15	2.19	0.78	⊢•I	-0.09 [-0.67, 0.49]
Dewulf 2013	15	-0.09	0.33	15	0.07	0.37	l=i	-0.16 [-0.41, 0.09]
Dehghan 2016	27	1.95	0.71	22	2.49	0.66	+=+:	-0.54 [-0.92, -0.16]
Davidson 1998	21	-0.04	0.19	21	0.04	0.16	, ii	-0.08 [-0.19, 0.03]
Daud 2014	12	1.58	1.1	10	0.97	0.38	i −−−1	0.61 [-0.06, 1.28]
Chambers 2019	12	1	0.35	12	1.1	0.35	I-I	-0.10 [-0.38, 0.18]
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.17]
Castro-Sanchez 2016	16	-0.3	0.61	16	-0.01	0.49	⊢=÷j	-0.29 [-0.67, 0.09]
Bonsu 2012	12	1.5	0.6	14	1.8	1.2	⊢+∔4	-0.30 [-1.01, 0.41]
Blaedel 2016	20	1.27	1.03	19	0.96	0.31	ŀ ;	0.31 [-0.16, 0.78]
Alles 1999	20	2.56	0.69	20	2.44	0.79	H = -	0.12 [-0.34, 0.58]
Aliasgharzadeh 2015	27	2	0.69	25	2.45	0.68	⊢ ∎-I;	-0.45 [-0.82, -0.08]
RE Model for Subgroup	(Q = 164.	56, df = 27,	p < .01;	$1^2 = 66.5\%$	$\tau^2 = 0.01$		•	-0.07 [-0.14, -0.01]
Without disease							1	
Williams 2022	20	1.1	0.7	20	1.2	0.4	⊢⊷⊣	-0.10 [-0.45, 0.25]
Vandokkum 1999	24	1.3	0.53	12	1.4	0.68		-0.10 [-0.54, 0.34]
Scheid 2014	37	1.5	0.78	35	1.48	0.93		0.02 [-0.38, 0.42]
Russo 2010	15	0.85	0.3	15	0.95	0.32		-0.10 [-0.32, 0.12]
Rajkumar 2015	15	1.16	0.07	15	1.18	0.08		-0.02 [-0.07, 0.03]
Pedersen 1997	64	0.97	0.39	64	0.98	0.42	M	-0.01 [-0.15, 0.13]
Nishimura 2015	24	0.09	0.7	24	0.01	0.39	+ +	0.08 [-0.24, 0.40]
Luo 1996	12	0.83	0.55	12	0.72	0.17	 	0.11 [-0.22, 0.44]
Letexier 2003	8	0.77	0.23	8	0.92	0.28	r=i =f	-0.15 [-0.40, 0.10]
Jackson 1999	27	1.29	0.35	27	1.59	0.58	•	-0.30 [-0.56, -0.04]
Forcheron 2007	9	0.77	0.42	8	0.64	0.31	⊦⊷⊣ ⊦∻-1	0.13 [-0.22, 0.48]
Clarke 2016	30	1.2	0.55	30	1.3	1.64		-0.10 [-0.72, 0.52]
Buddington 2017	45	1.06 , df = 12, p	0.72	43	1.16 ² - 0.00)	0.69	H	-0.10 [-0.39, 0.19]
RE Model for Subgroup	(Q = 8.30	, ur = 12, p	= 0.76; 1	= 0.0%, τ	2 = 0.00)			-0.03 [-0.08, 0.01]
RE Model for all studies:	(Q = 177.	63, df = 40,	p < .01;	l ² = 57.5%	$\tau^2 = 0.01$		Ę	-0.06 [-0.12, -0.01]

Test for Subgroup Differences: $Q_M = 0.19$, df = 1, p = 0.66

Favours ITF Favours control

-4.5 -3 -1.5 0 1 2 3

Figure 14: Triglycerides - subgroup by dose

-

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Unknown								
Blaedel 2016	20	1.27	1.03	19	0.96	0.31	H	0.31 [-0.16, 0.78]
RE Model for Subgroup	(Q = 0.00	, df = 0, p =	: 1.00; I ² =	= 0.0%, τ ²	= 0.00)		•	0.31 [-0.16, 0.78]
Less than 10g								
Shakeri 2014	24	-0.3	0.68	24	-0.36	0.9	I+I	0.06 [-0.39, 0.51]
Scheid 2014	37	1.5	0.00	35	1.48	0.93	I.≢-I	0.02 [-0.38, 0.42]
Satoh 2013	29	1.16	0.07	27	1.40	0.08		0.10 [0.06, 0.14]
Padilla-Camberos 2018	14	1.55	0.68	14	3.95	3.08 ⊢		-2.40 [-4.05, -0.75]
Nishimura 2015	24	0.09	0.00	24	0.01	0.39	, I i I	0.08 [-0.24, 0.40]
Machado 2019	13	1.26	0.4	13	1.27	0.65	⊢ ≠-1	-0.01 [-0.42, 0.40]
Gosmez-Reyes 2010	20	-0.19	0.03	20	0	0.06		-0.19 [-0.22, -0.16]
Genta 2009	20	2.1	0.97	15	2.19	0.78	⊢÷-i	-0.09 [-0.67, 0.49]
Castro-Sanchez 2016	16	-0.3	0.61	16	-0.01	0.49	i-i	-0.29 [-0.67, 0.09]
RE Model for Subgroup	(0 = 143)	74, df = 8, j	$n < 0.01 \cdot 1^2$	= 88.2%	$\tau^2 = 0.02$)	0.40	· · · ·	-0.06 [-0.19, 0.08]
	(🗠	, u. o, j	,.	00.270,	,			
Greater than or equa	al to 10g							
Williams 2022	20	1.1	0.7	20	1.2	0.4	H	-0.10 [-0.45, 0.25]
Wong 2010	23	1.64	0.14	23	1.73	0.14		-0.09 [-0.17, -0.01]
Vandokkum 1999	24	1.3	0.53	12	1.4	0.68	H	-0.10 [-0.54, 0.34]
Vaghef-Mehrabany 2019	22	-0.09	0.63	23	-0.16	0.57		0.07 [-0.28, 0.42]
Tripkovic 2015	10	2.08	0.86	10	1.79	0.61	<u>⊢;-</u> -1	0.29 [-0.36, 0.94]
Tov ar 2012	23	-0.35	0.48	28	-0.41	0.48	 	0.06 [-0.20, 0.32]
Tov ar 2012	30	-0.36	0.48	29	-0.29	0.48	Hei I	-0.07 [-0.31, 0.17]
Sorensen 2010	12	1	0.4	12	1	0.7	F≢-I	0.00 [-0.46, 0.46]
Russo 2010	15	0.85	0.3	15	0.95	0.32	. H.	-0.10 [-0.32, 0.12]
Roshanravan 2017	15	1.8	0.65	15	1.83	0.71	F.€-1	-0.03 [-0.52, 0.46]
Roshanravan 2017	14	1.84	0.51	15	1.78	0.68	∔ -	0.06 [-0.38, 0.50]
Rajkumar 2015	15	1.16	0.07	15	1.18	0.08		-0.02 [-0.07, 0.03]
Pedersen 1997	64	0.97	0.39	64	0.98	0.42		-0.01 [-0.15, 0.13]
Luo 1996	12	0.83	0.55	12	0.72	0.17	_ ≓ 	0.11 [-0.22, 0.44]
Luo 2000	10	1.33	0.51	10	1.42	0.38	F=1	-0.09 [-0.48, 0.30]
Letexier 2003	8	0.77	0.23	8	0.92	0.28	ei,	-0.15 [-0.40, 0.10]
Jackson 1999	27	1.29	0.35	27	1.59	0.58	H=f	-0.30 [-0.56, -0.04]
Hiel 2020	51	-0.15	1.34	55	-0.1	0.79	H	-0.05 [-0.47, 0.37]
Ghavami 2019	23	1.9	0.6	23	2.09	0.09	= 1	-0.19 [-0.44, 0.06]
Forcheron 2007	9	0.77	0.42	8	0.64	0.31	1=1	0.13 [-0.22, 0.48]
Dewulf 2013	15	-0.09	0.33	15	0.07	0.37	14	-0.16 [-0.41, 0.09]
Dehghan 2016	27	1.95	0.71	22	2.49	0.66	┝╾┥┊	-0.54 [-0.92, -0.16]
Davidson 1998	21	-0.04	0.19	21	0.04	0.16	7.	-0.08 [-0.19, 0.03]
Daud 2014	12	1.58	1.1	10	0.97	0.38		0.61 [-0.06, 1.28]
Clarke 2016	30	1.2	0.55	30	1.3	1.64		-0.10 [-0.72, 0.52]
Chambers 2019	12	1	0.35	12	1.1	0.35	, I I	-0.10 [-0.38, 0.18]
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.17]
Buddington 2017	45	1.06	0.72	43	1.16	0.69	, H . .	-0.10 [-0.39, 0.19]
Bonsu 2012	12	1.5	0.6	14	1.8	1.2	H-+++	-0.30 [-1.01, 0.41]
Alles 1999	20	2.56	0.69	20	2.44	0.79	. ⊦ ≓-1	0.12 [-0.34, 0.58]
Aliasgharzadeh 2015	27	2	0.69	2 25	2.45	0.68	H+i;	-0.45 [-0.82, -0.08]
RE Model for Subgroup	(Q = 29.5	1, df = 30, j	o = 0.49; I	= 4.4%,	$\tau^{-} = 0.00)$			-0.06 [-0.10, -0.02]
RE Model for all studies:	(Q = 177.	63, df = 40,	p < .01; I	² = 57.5%,	$\tau^2 = 0.01)$		•	-0.06 [-0.12, -0.01]

RE Model for all studies: (Q = 177.63, df = 40, p < .01;
$$I^2$$
 = 57.5%, τ^2 = 0.0

01) Favours ITF Favours control

-0.06 [-0.12, -0.01]

Test for Subgroup Differences: $Q_M = 2.34$, df = 2, p = 0.31

-4.5 -3 -1.5 0 1 2 3

Figure 15: Triglycerides - subgroup by ITF type

-

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Othere								
Others Williams 2022	20		0.7	20	1.0	0.4	H-H	-0.10 [-0.45, 0.25]
Wong 2010	20	1.1	0.7	20	1.2	0.4		-0.09 [-0.17, -0.01]
Vandokkum 1999	23 24	1.64	0.14	23	1.73	0.14		-0.10 [-0.54, 0.34]
Sorensen 2010		1.3	0.53	12	1.4	0.68		0.00 [-0.46, 0.46]
Scheid 2014	12 37	1	0.4	12 35	1	0.7		
		1.5	0.78		1.48	0.93	1	0.02 [-0.38, 0.42]
Satoh 2013 Baikumar 2015	29	1.16	0.07	27	1.06	0.08	7	0.10 [0.06, 0.14]
Rajkumar 2015 Padilla-Camberos 2018	15	1.16	0.07	15	1.18	0.08		-0.02 [-0.07, 0.03]
Machado 2019	14	1.55	0.68	14	3.95	3.08 ⊢		-2.40 [-4.05, -0.75]
	13	1.26	0.4	13	1.27	0.65	- ≠	-0.01 [-0.42, 0.40]
Luo 1996	12	0.83	0.55	12	0.72	0.17	,-, ⊦	0.11 [-0.22, 0.44]
Luo 2000	10	1.33	0.51	10	1.42	0.38		-0.09 [-0.48, 0.30]
Gosmez-Reyes 2010	20	-0.19	0.03	20	0	0.06	Ē	-0.19 [-0.22, -0.16]
Genta 2009	20	2.1	0.97	15	2.19	0.78	1÷-1	-0.09 [-0.67, 0.49]
Forcheron 2007	9	0.77	0.42	8	0.64	0.31		0.13 [-0.22, 0.48]
Dewulf 2013	15	-0.09	0.33	15	0.07	0.37	,	-0.16 [-0.41, 0.09]
Dehghan 2016	27	1.95	0.71	22	2.49	0.66	гел, Е.е.)	-0.54 [-0.92, -0.16]
Daud 2014	12	1.58	1.1	10	0.97	0.38		0.61 [-0.06, 1.28]
Clarke 2016	30	1.2	0.55	30	1.3	1.64		-0.10 [-0.72, 0.52]
Buddington 2017	45	1.06	0.72	43	1.16	0.69	⊢≠⊣	-0.10 [-0.39, 0.19]
Alles 1999	20	2.56	0.69	20	2.44	0.79	⊢⊷⊓ ⊢⊷¦	0.12 [-0.34, 0.58]
Aliasgharzadeh 2015	27	2	0.69	25 2 70.00	2.45 2 0.04	0.68		-0.45 [-0.82, -0.08]
RE Model for Subgroup	(Q = 163.)	68, df = 20,	p < .01; I	= 78.3%,	τ ² = 0.01)			-0.07 [-0.15, 0.01]
Inulin								
Vaghef-Mehrabany 2019	22	-0.09	0.63	23	-0.16	0.57	ц <u>і</u> н	0.07 [-0.28, 0.42]
Tripkovic 2015	10	2.08	0.86	10	1.79	0.61	<u>⊢</u> -	0.29 [-0.36, 0.94]
Tov ar 2012	23	-0.35	0.48	28	-0.41	0.48	i i i	0.06 [-0.20, 0.32]
Tov ar 2012	30	-0.36	0.48	29	-0.29	0.48	I .	-0.07 [-0.31, 0.17]
Shakeri 2014	30 24	-0.30	0.48	29	-0.29	0.48	⊢ 1	0.06 [-0.39, 0.51]
Russo 2010	24 15	0.85	0.08	15	0.95	0.9	H	-0.10 [-0.32, 0.12]
Roshanravan 2017	15	1.8	0.65	15	1.83	0.32	Ļ.	-0.03 [-0.52, 0.46]
Roshanravan 2017	13	1.84	0.51	15	1.78	0.68	H+H	0.06 [-0.38, 0.50]
Pedersen 1997	64	0.97	0.39	64	0.98	0.42	· · · ·	-0.01 [-0.15, 0.13]
Nishimura 2015	24	0.09	0.7	24	0.00	0.39	i÷-I	0.08 [-0.24, 0.40]
Letexier 2003	24	0.09	0.23	8	0.01	0.39	H	-0.15 [-0.40, 0.10]
Jackson 1999	27	1.29	0.25	27	1.59	0.28	H=t	-0.30 [-0.56, -0.04]
Hiel 2020	51	-0.15	1.34	55	-0.1	0.38	Hiti	-0.05 [-0.47, 0.37]
Ghavami 2019	23	1.9	0.6	23	2.09	0.79	l=1	-0.19 [-0.44, 0.06]
Davidson 1998	23	-0.04	0.19	23	0.04	0.05		-0.08 [-0.19, 0.03]
Chambers 2019	12	-0.04	0.19	12	1.1	0.35	i.	-0.10 [-0.38, 0.18]
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.17]
Castro-Sanchez 2016	12	-0.3	0.61	12	-0.01	2.19 0.49	⊢=1	-0.29 [-0.67, 0.09]
Bonsu 2012	10	-0.3 1.5	0.61	16	-0.01	0.49 1.2	, , L-++1	-0.29 [-0.07, 0.09] -0.30 [-1.01, 0.41]
Blaedel 2016	20	1.5	1.03	14 19	0.96	0.31	⊢ ¦++-	-0.30 [-1.01, 0.41] 0.31 [-0.16, 0.78]
RE Model for Subgroup	20 (0 = 12 0	1.27 3, df = 19, p	1.03 - 0.70-1	$1^{2} - 0.0\%$	- 0.90 - ² - 0.00	0.51		-0.07 [-0.12, -0.01]
	10.0	5, ui – 19, þ	5 - 0.79, 1	- 0.0 %,	. – 0.00)			-0.07 [-0.12, -0.01]
RE Model for all studies:	(Q = 177.	63, df = 40,	p < .01; I	l ² = 57.5%,	$\tau^{2} = 0.01)$		ŧ	-0.06 [-0.12, -0.01]

Test for Subgroup Differences: $Q_M = 0.00$, df = 1, p = 0.98

Favours ITF Favours control

-4.5 -3 -1.5 0 1 2 3

Figure 16: Triglycerides - subgroup by RoB

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% C
Low								
Williams 2022	20	1.1	0.7	20	1.2	0.4	H	-0.10 [-0.45, 0.2
Vandokkum 1999	24	1.3	0.53	12	1.4	0.68	H	-0.10 [-0.54, 0.3
Vaghef-Mehrabany 2019	22	-0.09	0.63	23	-0.16	0.57	H-I	0.07 [-0.28, 0.4
Tripkovic 2015	10	2.08	0.86	10	1.79	0.61	⊢ 1	0.29 [-0.36, 0.9
, Roshanravan 2017	15	1.8	0.65	15	1.83	0.71	⊢ •1	-0.03 [-0.52, 0.4
Roshanravan 2017	14	1.84	0.51	15	1.78	0.68	F≢4	0.06 [-0.38, 0.5
Pedersen 1997	64	0.97	0.39	64	0.98	0.42	÷.	-0.01 [-0.15, 0.1
Nishimura 2015	24	0.09	0.7	24	0.00	0.39	I÷-I	0.08 [-0.24, 0.4
Machado 2019	13	1.26	0.4	13	1.27	0.65	H+H	-0.01 [-0.42, 0.4
Luo 1996	10	0.83	0.55	12	0.72	0.00	I=I	0.11 [-0.22, 0.4
Letexier 2003	8	0.03	0.33	8	0.92	0.28		-0.15 [-0.40, 0.1
Jackson 1999	° 27	1.29	0.23	° 27	1.59	0.28	⊢=t	-0.30 [-0.56, -0.0
Gosmez-Reyes 2010	27			27			i 🖬	-0.19 [-0.22, -0.1
Goshiez-Reyes 2010 Ghavami 2019		-0.19	0.03		0	0.06		-0.19 [-0.22, -0.1
Forcheron 2007	23	1.9	0.6	23	2.09	0.09	'-; ≠-1	-
	9	0.77	0.42	8	0.64	0.31	: :	0.13 [-0.22, 0.4
Dehghan 2016	27	1.95	0.71	22	2.49	0.66		-0.54 [-0.92, -0.1
Clarke 2016	30	1.2	0.55	30	1.3	1.64		-0.10 [-0.72, 0.5
Chambers 2019	12	1	0.35	12	1.1	0.35	. 14	-0.10 [-0.38, 0.1
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.1
Bonsu 2012	12	1.5	0.6	14	1.8	1.2	⊢•÷I	-0.30 [-1.01, 0.4
Blaedel 2016	20	1.27	1.03	19	0.96	0.31	 ∎-	0.31 [-0.16, 0.7
Alles 1999	20	2.56	0.69	20	2.44	0.79	. ⊢ ≢-1	0.12 [-0.34, 0.5
Aliasgharzadeh 2015	27	2	0.69	25	2.45	0.68	F•4	-0.45 [-0.82, -0.0
RE Model for Subgroup	(Q = 33.4	5, df = 22,	p = 0.06;	² = 33.6%	$\tau^2 = 0.01$)		•	-0.10 [-0.17, -0.0
High								
Wong 2010	23	1.64	0.14	23	1.73	0.14	, H	-0.09 [-0.17, -0.0
Tov ar 2012	23	-0.35	0.48	28	-0.41	0.48	I÷I	0.06 [-0.20, 0.3
Tov ar 2012	30	-0.36	0.48	29	-0.29	0.48	I-I	-0.07 [-0.31, 0.1
Sorensen 2010	12	1	0.4	12	1	0.7	F 4 4	0.00 [-0.46, 0.4
Shakeri 2014	24	-0.3	0.68	24	-0.36	0.9	I÷-I	0.06 [-0.39, 0.5
Scheid 2014	37	1.5	0.78	35	1.48	0.93	H	0.02 [-0.38, 0.4
Satoh 2013	29	1.16	0.07	27	1.06	0.08		0.10 [0.06, 0.1
Russo 2010	15	0.85	0.3	15	0.95	0.32	H	-0.10 [-0.32, 0.1
Rajkumar 2015	15	1.16	0.07	15	1.18	0.02	i i i	-0.02 [-0.07, 0.0
Padilla-Camberos 2018	13	1.10	0.68	13	3.95	3.08 ⊢		-2.40 [-4.05, -0.7
Luo 2000	14	1.33	0.68	14	3.95 1.42	0.38		-0.09 [-0.48, 0.3
Hiel 2020	51	-0.15	1.34	55	-0.1	0.38	H41	
Genta 2009							,,,, ⊨•÷-i	-0.05 [-0.47, 0.3
	20	2.1	0.97	15	2.19	0.78	=	-0.09 [-0.67, 0.4
Dewulf 2013	15	-0.09	0.33	15	0.07	0.37	•	-0.16 [-0.41, 0.0
Davidson 1998	21	-0.04	0.19	21	0.04	0.16	M	-0.08 [-0.19, 0.0
Daud 2014	12	1.58	1.1	10	0.97	0.38		0.61 [-0.06, 1.2
Castro-Sanchez 2016	16	-0.3	0.61	16	-0.01	0.49	- - -]	-0.29 [-0.67, 0.0
Buddington 2017	45	1.06	0.72	43	2 1.16	0.69	H	-0.10 [-0.39, 0.1
RE Model for Subgroup	(Q = 47.0	8, df = 17,	p < .01; I ⁻	= 50.7%,	τ = 0.00)		•	-0.03 [-0.09, 0.0
RE Model for all studies:	(Q = 177.	63, df = 40,	p < .01:	$^{2} = 57.5\%$	$\tau^2 = 0.01$		É T	-0.06 [-0.12, -0.0
Test for Subgroup Differe			•		,	Favou		ours control

RE Model for all studies: (Q = 177.63, df = 40, p < .01;
$$l^2$$
 = 57.5%, τ^2 = 0.01)

Test for Subgroup Differences:
$$Q_M = 1.86$$
, df = 1, p = 0.17

-4.5 -3 -1.5 0 1 2 3

Figure 17: Triglycerides - subgroup by follow-up duration

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Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
olddy	Total	Weall	30	Total	Wean	30		
Less than 6 weeks								
Wong 2010	23	1.64	0.14	23	1.73	0.14	, H	-0.09 [-0.17, -0.01]
Vandokkum 1999	24	1.3	0.53	12	1.4	0.68	F⊷i-I	-0.10 [-0.54, 0.34]
Tripkovic 2015	10	2.08	0.86	10	1.79	0.61	⊢ ∶ 1	0.29 [-0.36, 0.94]
Sorensen 2010	12	1	0.4	12	1	0.7	I . ∔1	0.00 [-0.46, 0.46]
Russo 2010	15	0.85	0.3	15	0.95	0.32	H	-0.10 [-0.32, 0.12]
Pedersen 1997	64	0.97	0.39	64	0.98	0.42	Щ.	-0.01 [-0.15, 0.13]
Nishimura 2015	24	0.09	0.7	24	0.01	0.39	I≑I	0.08 [-0.24, 0.40]
Luo 1996	12	0.83	0.55	12	0.72	0.17	I ¦− I	0.11 [-0.22, 0.44]
Luo 2000	10	1.33	0.51	10	1.42	0.38	⊢÷I	-0.09 [-0.48, 0.30]
Letexier 2003	8	0.77	0.23	8	0.92	0.28	l=i	-0.15 [-0.40, 0.10]
Clarke 2016	30	1.2	0.55	30	1.3	1.64	⊢⊷∔	-0.10 [-0.72, 0.52]
Causey 2000	12	2.75	1.83	12	3.19	2.19		-0.44 [-2.05, 1.17]
Blaedel 2016	20	1.27	1.03	19	0.96	0.31	⊬⊶	0.31 [-0.16, 0.78]
Alles 1999	20	2.56	0.69	20	2.44	0.79	I÷-I	0.12 [-0.34, 0.58]
RE Model for Subgroup	(Q = 7.77	, df = 13, p	$= 0.86: 1^2$	= 0.0%. τ	$^{2} = 0.00$		i	-0.05 [-0.11, 0.00]
0 1	(, . , p	,	, .	,			
Greater than or equa	l to 6 we	eks						
Williams 2022	20	1.1	0.7	20	1.2	0.4	I-iI	-0.10 [-0.45, 0.25]
Vaghef-Mehrabany 2019	22	-0.09	0.63	23	-0.16	0.57	н і н	0.07 [-0.28, 0.42]
Tov ar 2012	23	-0.35	0.48	28	-0.41	0.48	i i i	0.06 [-0.20, 0.32]
Tov ar 2012	30	-0.36	0.48	29	-0.29	0.48	= =	-0.07 [-0.31, 0.17]
Shakeri 2014	24	-0.3	0.68	24	-0.36	0.9	i i i	0.06 [-0.39, 0.51]
Scheid 2014	37	-0.5	0.00	35	1.48	0.93	i i i	0.02 [-0.38, 0.42]
Satoh 2013	29	1.16	0.07	27	1.40	0.08		0.10 [0.06, 0.14]
Roshanravan 2017	15	1.8	0.65	15	1.83	0.00	, r i+i	-0.03 [-0.52, 0.46]
Roshanrav an 2017	13	1.84	0.00	15	1.78	0.68	i+i	0.06 [-0.38, 0.50]
Rajkumar 2015	15	1.16	0.07	15	1.18	0.08	· · · ·	-0.02 [-0.07, 0.03]
Padilla-Camberos 2018	13	1.55	0.68	13	3.95	3.08 ⊢		-2.40 [-4.05, -0.75]
Machado 2019							⊦∔1	-0.01 [-0.42, 0.40]
Jackson 1999	13	1.26	0.4	13	1.27	0.65	i ⊨=t	
Hiel 2020	27	1.29	0.35	27	1.59	0.58	,-, ⊢+	-0.30 [-0.56, -0.04]
	51	-0.15	1.34	55	-0.1	0.79		-0.05 [-0.47, 0.37]
Gosmez-Reyes 2010	20	-0.19	0.03	20	0	0.06	Ē	-0.19 [-0.22, -0.16]
Ghavami 2019	23	1.9	0.6	23	2.09	0.09	,-, ⊢-,-	-0.19 [-0.44, 0.06]
Genta 2009	20	2.1	0.97	15	2.19	0.78	 + = -1	-0.09 [-0.67, 0.49]
Forcheron 2007	9	0.77	0.42	8	0.64	0.31		0.13 [-0.22, 0.48]
Dewulf 2013	15	-0.09	0.33	15	0.07	0.37		-0.16 [-0.41, 0.09]
Dehghan 2016	27	1.95	0.71	22	2.49	0.66	<u>⊦=</u> li	-0.54 [-0.92, -0.16]
Davidson 1998	21	-0.04	0.19	21	0.04	0.16		-0.08 [-0.19, 0.03]
Daud 2014	12	1.58	1.1	10	0.97	0.38	 	0.61 [-0.06, 1.28]
Chambers 2019	12	1	0.35	12	1.1	0.35		-0.10 [-0.38, 0.18]
Castro-Sanchez 2016	16	-0.3	0.61	16	-0.01	0.49	F=4	-0.29 [-0.67, 0.09]
Buddington 2017	45	1.06	0.72	43	1.16	0.69	, H#H	-0.10 [-0.39, 0.19]
Bonsu 2012	12	1.5	0.6	14	1.8	1.2	⊢-÷-1	-0.30 [-1.01, 0.41]
Aliasgharzadeh 2015	27	2	0.69	25	2.45	0.68	⊢•-I	-0.45 [-0.82, -0.08]
RE Model for Subgroup	(Q = 169.3	26, df = 26,	p < .01; I	⁻ = 71.4%,	τ ² = 0.01)		•	-0.08 [-0.15, -0.02]
				0	2			

RE Model for all studies: (Q = 177.63, df = 40, p < .01;
$$I^2$$
 = 57.5%, τ^2 = 0.01)

Test for Subgroup Differences:
$$Q_M = 0.87$$
, df = 1, p = 0.35

-4.5 -3 -1.5 0 1 2 3

Figure 18: Triglycerides - subgroup by age

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown Castro-Sanchez 2016 Rajkumar 2015 Pedersen 1997 Letexier 2003 Causey 2000 RE Model for Subgrou	16 15 64 8 12 Jp (Q = 3.10	-0.3 1.16 0.97 0.77 2.75 , df = 4, p = 0	0.61 0.07 0.39 0.23 1.83 0.54; 1 ² = 0	$ \begin{array}{c} 16\\ 15\\ 64\\ 8\\ 12\\ .0\%, \tau^{2}=0. \end{array} $	-0.01 1.18 0.98 0.92 3.19 00)	0.49 0.08 0.42 0.28 2.19	-0.02 [-0.67, 0.09] -0.02 [-0.07, 0.03] -0.01 [-0.15, 0.13] -0.15 [-0.40, 0.10] -0.44 [-2.05, 1.17] -0.03 [-0.08, 0.02]
more than 40 years Scheid 2014 Chambers 2019 Alles 1999 Wong 2010 Luo 2000 Sorensen 2010 Jackson 1999 Gosmez-Reyes 2010 Bonsu 2012 Shakeri 2014 Hiel 2020 Roshanravan 2017 Roshanravan 2017 Aliasqharzadeh 2015 Dehghan 2016 Dewulf 2013 Ghavami 2019 Genta 2009 Tripkovic 2015 Satoh 2013 Nishimura 2015 Davidson 1998 RE Model for Subgrou	37 20 23 10 12 27 20 12 24 51 15 14 27 27 25 23 20 10 29 24 29 24 21 150. 21 50. 21 20 21 50. 21 20 21 20 21 20 21 20 20 20 20 20 20 20 20 20 20 20 20 20	1.5 1 2.56 1.64 1.33 1 1.29 -0.19 1.5 -0.3 -0.15 1.8 1.84 2 1.95 -0.09 1.9 2.1 2.08 1.16 0.09 -0.04 69, df = 21, j	$\begin{array}{c} 0.78\\ 0.35\\ 0.69\\ 0.14\\ 0.51\\ 0.4\\ 0.35\\ 0.03\\ 0.6\\ 0.68\\ 1.34\\ 0.65\\ 0.51\\ 0.69\\ 0.71\\ 0.33\\ 0.6\\ 0.97\\ 0.86\\ 0.07\\ 0.7\\ 0.97\\ 0.86\\ 0.07\\ 0.7\\ 0.97\\ 0.98\\ 0.019\\ 0.71\\ 0.19\\ 0.97\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.19\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.7\\ 0.98\\ 0.07\\ 0.98\\ 0.07\\ 0.98\\ 0.07\\ 0.98\\ 0.07\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.07\\ 0.09\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.00\\ 0.$	35 12 20 23 10 12 27 20 14 24 55 15 25 25 25 25 25 25 25 15 15 25 25 25 25 15 15 25 25 25 25 25 25 25 25 25 25 15 25 25 27 20 20 20 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} 1.48\\ 1.1\\ 2.44\\ 1.73\\ 1.42\\ 1\\ 1.59\\ 0\\ 1.8\\ -0.36\\ -0.1\\ 1.83\\ 1.78\\ 2.45\\ 2.49\\ 0.07\\ 2.09\\ 2.19\\ 1.79\\ 1.06\\ 0.01\\ 0.04\\ = 0.01 \end{array}$	$\begin{array}{c} 0.93\\ 0.35\\ 0.79\\ 0.14\\ 0.38\\ 0.7\\ 0.58\\ 0.06\\ 1.2\\ 0.9\\ 0.71\\ 0.68\\ 0.66\\ 0.37\\ 0.68\\ 0.66\\ 0.37\\ 0.68\\ 0.66\\ 0.37\\ 0.68\\ 0.69\\ 0.78\\ 0.61\\ 0.09\\ 0.78\\ 0.61\\ 0.39\\ 0.16\\ \end{array}$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $
40 years or less Buddington 2017 Blaedel 2016 Williams 2022 Vaghef-Mehrabany 2019 Padilla-Camberos 2018 Tovar 2012 Daud 2014 Machado 2019 Clarke 2016 Luo 1996 Russo 2010 Forcheron 2007 Vandokkum 1999 RE Model for Subgrou	45 20 22 14 23 30 12 13 30 12 15 9 24 24 Q = 16.4	1.06 1.27 1.1 -0.09 1.55 -0.35 -0.36 1.58 1.26 1.2 0.83 0.85 0.77 1.3 4, df = 13, p	$\begin{array}{c} 0.72\\ 1.03\\ 0.7\\ 0.63\\ 0.68\\ 0.48\\ 0.48\\ 1.1\\ 0.4\\ 0.55\\ 0.55\\ 0.3\\ 0.42\\ 0.53\\ 0.23; ^2 = \end{array}$	43 19 20 23 14 28 29 10 13 30 12 15 8 12 15 5 8 12 τ = 0.0%, τ ² =	$\begin{array}{c} 1.16\\ 0.96\\ 1.2\\ -0.16\\ 3.95\\ -0.41\\ -0.29\\ 0.97\\ 1.27\\ 1.3\\ 0.72\\ 0.95\\ 0.64\\ 1.4\\ 0.00) \end{array}$	0.69 0.31 0.4 0.57 3.08 0.48 0.48 0.38 0.65 1.64 0.17 0.32 0.31 0.68	H=H -0.10 [-0.39, 0.19] H=H 0.31 [-0.16, 0.78] H=H -0.10 [-0.45, 0.25] H=H 0.07 [-0.28, 0.42] -2.40 [-4.05, -0.75] H=H -0.06 [-0.20, 0.32] H=H -0.06 [-0.31, 0.17] H=H -0.01 [-0.42, 0.40] H=H -0.01 [-0.42, 0.40] H=H -0.10 [-0.72, 0.52] H=H -0.10 [-0.32, 0.12] H=H -0.10 [-0.32, 0.12] H=H -0.10 [-0.32, 0.12] H=H -0.10 [-0.34, 0.34] -0.10 [-0.54, 0.34] -0.00 [-0.10, 0.09]
RE Model for all studies: Test for Subgroup Difference		63, df = 40, _l 9, df = 2, p =	,	[:] 57.5%, τ ²	= 0.01)	Fav	-0.06 [-0.12, -0.01]

Figure 19: Triglycerides - subgroup by BMI

(9)

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown Letexier 2003 Causey 2000 Davidson 1998 Forcheron 2007 Vandokkum 1999 RE Model for Subgro	8 12 21 9 oup (Q = 1.89	0.77 2.75 -0.04 0.77 1.3 , df = 4, p =	0.23 1.83 0.19 0.42 0.53 0.76; 1 ² = 0		0.92 3.19 0.04 0.64 1.4 00)	0.28 2.19 ⊢ 0.16 0.31 0.68	-0.15 [-0.40, 0.10] -0.44 [-2.05, 1.17] -0.08 [-0.19, 0.03] -0.13 [-0.22, 0.48] -0.10 [-0.54, 0.34] -0.08 [-0.17, 0.02]
Obese Castro-Sanchez 2016 Gosmez-Reyes 2010 Bonsu 2012 Shakeri 2014 Hiel 2020 Roshanravan 2017 Roshanravan 2017 Aliasqharzadeh 2015 Dehghan 2016 Dewulf 2013 Ghavami 2019 Genta 2009 Tripkovic 2015 Vaghef-Mehrabany 2019 Padilla-Camberos 2018 Tovar 2012 Tovar 2012 Daud 2014 Machado 2019 RE Model for Subgrou	16 20 12 24 51 15 27 27 27 27 27 23 20 10 22 14 23 30 22 14 23 30 22 14 30 22 13 30.2	-0.3 -0.19 1.5 -0.3 -0.15 1.8 1.84 2 1.95 -0.09 1.9 2.1 2.08 -0.09 1.55 -0.36 1.58 1.26 0, df = 18, p	$\begin{array}{c} 0.61\\ 0.03\\ 0.6\\ 0.68\\ 1.34\\ 0.65\\ 0.51\\ 0.69\\ 0.71\\ 0.3\\ 0.68\\ 0.48\\ 0.48\\ 0.48\\ 1.1\\ 0.4\\ = 0.04; 1^2 = \end{array}$	16 20 14 25 15 15 25 22 15 23 15 23 15 23 15 23 14 23 28 29 10 13 28 29 10 13 28 29 28 29 28 29 21 28 29 29 20 14 25 25 25 25 25 25 25 25 25 25 25 25 25	-0.01 0 1.8 -0.36 -0.1 1.83 1.78 2.49 0.07 2.09 2.19 1.79 -0.16 3.95 -0.41 -0.29 0.97 1.27 = 0.00)	0.49 0.06 1.2 0.9 0.71 0.68 0.68 0.66 0.37 0.09 0.78 0.61 0.57 3.68 0.48 0.48 0.48 0.48 0.38 0.65	
Pre-obese Scheid 2014 Chambers 2019 Alles 1999 Wong 2010 Luo 2000 Sorensen 2010 Jackson 1999 Buddington 2017 Blaedel 2016 Williams 2022 RE Model for Subgro	37 12 20 23 10 12 27 45 20 20 0 up (Q = 6.60	1.5 1 2.56 1.64 1.33 1 1.29 1.06 1.27 1.1 , df = 9, p =	0.78 0.35 0.69 0.14 0.51 0.4 0.35 0.72 1.03 0.72 1.03 0.7 0.68; 1 ² = 0	$\begin{array}{c} 35\\12\\20\\23\\10\\12\\27\\43\\19\\20\\.0\%, \tau^{2}=0. \end{array}$	1.48 1.1 2.44 1.73 1.42 1 1.59 1.16 0.96 1.2	$\begin{array}{c} 0.93\\ 0.35\\ 0.79\\ 0.14\\ 0.38\\ 0.7\\ 0.58\\ 0.69\\ 0.31\\ 0.4 \end{array}$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$
Normal Rajkumar 2015 Pedersen 1997 Satoh 2013 Nishimura 2015 Clarke 2016 Luo 1996 Russo 2010 RE Model for Subgro	15 64 29 24 30 12 15 9up (Q = 15.4	1.16 0.97 1.16 0.09 1.2 0.83 0.85 9, df = 6, p =	0.07 0.39 0.07 0.7 0.55 0.55 0.55 = 0.02; 1 ² =	$1564272430121557.3%, \tau^2 =$	1.18 0.98 1.06 0.01 1.3 0.72 0.95 0.00)	0.08 0.42 0.08 0.39 1.64 0.17 0.32	-0.02 [-0.07, 0.03] -0.01 [-0.15, 0.13] 0.10 [0.06, 0.14] 0.08 [-0.24, 0.40] -0.10 [-0.72, 0.52] 11 0.11 [-0.22, 0.44] + 0.11 [-0.22, 0.44] + 0.10 [-0.32, 0.12] 0.03 [-0.05, 0.10]
RE Model for all studies: $(Q = 177.63, df = 40, p < .01; l^2 = 57.5\%, \tau^2 = 0.01)$ Test for Subgroup Differences: $Q_M = 12.66, df = 3, p = 0.01$						Favours ITI	F Favours control

-3 -2 -1 0 1 2 3 Mean Difference

-4

Figure 20: Triglycerides - subgroup by diabetes status

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Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown Sorensen 2010 Castro-Sanchez 2016 Hiel 2020 Tripkovic 2015 Vaghef-Mehrabany 2019 Daud 2014 Machado 2019 Causey 2000 Davidson 1998 RE Model for Subgrou	12 16 51 10 22 12 13 12 21 21 up (Q = 1.89	1 -0.3 -0.15 2.08 -0.09 1.58 1.26 2.75 -0.04 , df = 4, p = 0	0.4 0.61 1.34 0.86 0.63 1.1 0.4 1.83 0.19 0.76; I ² = 0.	$12 \\ 16 \\ 55 \\ 10 \\ 23 \\ 10 \\ 13 \\ 12 \\ 21 \\ 0\%, \tau^{2} = 0.$	$ \begin{array}{c} 1 \\ -0.01 \\ -0.1 \\ 1.79 \\ -0.16 \\ 0.97 \\ 1.27 \\ 3.19 \\ 0.04 \\ 00) \end{array} $	0.7 0.49 0.79 0.61 0.57 0.38 0.65 2.19 0.16	↓ ↓ ↓ 0.00 [-0.46, 0.46] ↓ ↓ ↓ -0.29 [-0.67, 0.09] ↓ ↓ ↓ 0.05 [-0.47, 0.37] ↓ ↓ ↓ 0.29 [-0.36, 0.94] ↓ ↓ ↓ 0.61 [-0.06, 1.28] ↓ ↓ ↓ -0.01 [-0.42, 0.40] ↓ ↓ ↓ -0.04 [-2.05, 1.17] ↓ ↓ ↓ -0.08 [-0.19, 0.03] ↓ ↓ ↓ -0.08 [-0.17, 0.02]
No diabetes Scheid 2014 Chambers 2019 Wong 2010 Jackson 1999 Buddington 2017 Blaedel 2016 Williams 2022 Gosmez-Reyes 2010 Dewulf 2013 Genta 2009 Padilla-Camberos 2018 Tovar 2012 Tovar 2012 Rajkumar 2015 Pedersen 1997 Nishimura 2015 Clarke 2016 Luo 1996 Russo 2010 Letexier 2003 Forcheron 2007 Vandokkum 1999 RE Model for Subgrou	37 12 23 27 45 20 20 15 20 15 20 15 20 15 64 23 30 15 64 24 30 15 8 9 24 20 24 20 24 30 24 20 24 30 24 30 24 5 8 9 24 5 24 5 20 20 20 20 20 20 20 20 20 20 20 20 20	1.5 1 1.64 1.29 1.06 1.27 1.1 -0.19 -0.09 2.1 1.55 -0.35 -0.36 1.16 0.97 0.97 0.83 0.83 0.85 0.777 1.3 8, df = 21, p	0.78 0.35 0.14 0.35 0.72 1.03 0.72 0.03 0.33 0.97 0.68 0.48 0.07 0.39 0.7 0.55 0.55 0.55 0.55 0.3 0.23 0.23 0.23 0.43	35 12 23 27 43 19 20 15 15 15 15 14 28 29 15 64 24 30 12 15 8 8 21 5 8 8 12 29 15 64 24 30 12 5 64 24 30 12 27 27 27 27 20 20 15 15 14 20 20 20 20 20 20 20 20 20 20 20 20 20	$\begin{array}{c} 1.48\\ 1.1\\ 1.73\\ 1.59\\ 1.16\\ 0.96\\ 1.2\\ 0\\ 0.07\\ 2.19\\ 3.95\\ -0.41\\ -0.29\\ 1.18\\ 0.98\\ 0.01\\ 1.3\\ 0.72\\ 0.95\\ 0.92\\ 0.64\\ 1.4\\ 0.00 \end{array}$	$\begin{array}{c} 0.93\\ 0.35\\ 0.14\\ 0.58\\ 0.69\\ 0.31\\ 0.4\\ 0.06\\ 0.37\\ 0.78\\ 3.66\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ 0.48\\ $	Image: Constraint of the system 0.02 [-0.38, 0.42] Image: Constraint of the system -0.09 [-0.17, -0.01] Image: Constraint of the system -0.010 [-0.39, 0.19] Image: Constraint of the system -0.010 [-0.45, 0.25] Image: Constraint of the system -0.019 [-0.22, -0.16] Image: Constraint of the system -0.09 [-0.67, 0.49] Image: Constraint of the system -0.09 [-0.67, 0.03] Image: Constraint of the system -0.01 [-0.15, 0.13] Image: Constraint of the system -0.01 [-0.72, 0.52] Image: Constraint of the system -0.01 [-0.72, 0.52] Image: Constraint of the system -0.010 [-0.72, 0.52]
Have diabetes Alles 1999 Luo 2000 Bonsu 2012 Shakeri 2014 Roshanravan 2017 Aliasgharzadeh 2015 Dehghan 2016 Ghavami 2019 Satoh 2013 RE Model for Subgrou RE Model for all studies:	-	2.56 1.33 1.5 -0.3 1.8 1.84 2 1.95 1.16 3, df = 9, p < 63, df = 40, p				0.79 0.38 1.2 0.9 0.71 0.68 0.68 0.68 0.66 0.09 0.08	Image: Constraint of the system 0.12 [-0.34, 0.58] Image: Constraint of the system -0.09 [-0.48, 0.30] Image: Constraint of the system -0.30 [-1.01, 0.41] Image: Constraint of the system -0.06 [-0.39, 0.51] Image: Constraint of the system -0.06 [-0.38, 0.50] Image: Constraint of the system -0.45 [-0.82, -0.08] Image: Constraint of the system -0.45 [-0.82, -0.08] Image: Constraint of the system -0.19 [-0.44, 0.06] Image: Constraint of the system -0.11 [-0.27, 0.05]
Test for Subgroup Difference	-			oo,, t	0.017	Favo	

Test for Subgroup Differences: $Q_M = 0.35$, df = 2, p = 0.84

 Favours ITF
 Favours control

 -4
 -3

 -4
 -3

Figure 21: Fasting blood glucose -subgroup by sex

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95%Cl]
Unknown								
Scheid 2014	37	5.41	1.06	35	5.12	0.59	H a -1	0.29 [-0.10, 0.68]
Jackson 1999	27	4.84	0.51	27	4.99	0.49	H#H	-0.15 [-0.42, 0.12]
RE Model for Subgroup	(Q = 3.29, df =	1, p = 0.07;	$I^2 = 69.6\%$	$t_{\rm b}, \ \tau^2 = 0.07)$			+	0.05 [-0.38, 0.47]
Both								
Williams 2022	20	5.1	0.5	20	5	0.5	H#H	0.10 [-0.21, 0.41]
Mitchell 2021	13	-0.01	2.6	9	-0.05	1.33		0.04 [-1.62, 1.70]
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	⊢ •÷-1	-0.46 [-1.88, 0.96]
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	⊢∎÷	-0.30 [-0.74, 0.14]
Satoh 2013	29	6.95	0.21	27	6.52	0.3	H	0.43 [0.29, 0.57]
Roshanravan 2017	15	8.03	3.17	15	7.27	1.3	⊢ ∔-•	- 0.76 [-0.97, 2.49]
Roshanravan 2017	14	8.83	2.36	15	8.05	2.33	⊢ <u>∔</u>	- 0.78 [-0.93, 2.49]
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	i 👘 I	0.07 [-0.18, 0.32]
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	I÷I	0.04 [-0.37, 0.45]
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	i i	0.06 [-0.10, 0.22]
Machado 2019	13	5.02	0.11	13	5.05	0.11	, i	-0.03 [-0.11, 0.05]
Luo 2000	10	8.89	1.68	10	8.88	1.61	<u>↓</u>	0.01 [-1.43, 1.45]
Letexier 2003	8	4.68	0.4	8	4.62	0.2	H a -I	0.06 [-0.25, 0.37]
Hiel 2020	51	0.23	1.96	55	-0.18	0.2	⊢∎⊣	0.41 [-0.19, 1.01]
Guess 2015	20	-0.4	0.19	19	0.16	0.23		-0.56 [-0.69, -0.43]
Giacco 2004	20	-0.4 5.44	1	27	5.38	0.23		0.06 [-0.43, 0.55]
Ghav ami 2019	23	6.63	1.71	27	7.24	1.55	⊢ <u>-</u>	-0.61 [-1.55, 0.33]
Forcheron 2007	9	4.03	0.3	23	3.81	0.57	. ⊦∎⊣	0.22 [-0.22, 0.66]
Daud 2014	9 12	4.63	0.3	10	4.51	0.28	⊢,– ⊢ ⊦≢-1	0.11 [-0.21, 0.43]
Clarke 2016	30	4.62		30	4.51	0.28		0.00 [-0.28, 0.28]
Chambers 2019	30 12		0.55				,	0.00 [-0.20, 0.20]
Buddington 2017		5.3	0.69	12	5.3	0.35	⊦≕i	-0.21 [-0.61, 0.19]
Bonsu 2012	45	4.73	0.72	43	4.94	1.15	1-1	
Alles 1999	12	7.6	2.6	14	7.4	1.4		0.20 [-1.44, 1.84]
	20	8.61	0.81	20 2	8.59	2.66		0.02 [-1.20, 1.24]
RE Model for Subgroup	(Q = 117.58, di	r = 23, p < .0	(1; 1 = 72)	3%, τ = 0.0	15)		Ť	0.01 [-0.12, 0.14]
Male								
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	H#H	-0.11 [-0.40, 0.18]
Russo 2010	15	4.66	0.29	15	4.97	0.53	∎-	-0.31 [-0.62, -0.00]
Luo 1996	12	4.94	0.35	12	4.86	0.55	 ∎ 	0.08 [-0.29, 0.45]
Blaedel 2016	20	5.6	2 0.45	₂ 19	5.6	0.87	F≢-I	0.00 [-0.44, 0.44]
RE Model for Subgroup	(Q = 2.90, df =	3, p = 0.41;	I ² = 1.2%,	$\tau^2 = 0.00)$			•	-0.11 [-0.28, 0.05]
Female								
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	F≢I	0.05 [-0.39, 0.49]
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51	H , ≡-1	0.21 [-0.07, 0.49]
Tovar 2012	30	-0.03	0.51	29	-0.12	0.5	1 ,	0.09 [-0.17, 0.35]
Genta 2009	20	4.18	0.5	15	4.84	0.66	⊦∎-l	-0.66 [-1.06, -0.26]
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	H∎H	-0.17 [-0.51, 0.17]
Dehghan 2016	27	8.36	1.17	22	9.02	1	⊢≖−{	-0.66 [-1.27, -0.05]
Dehgahn 2014	27	-1.02	, 1.01	25	-0.09	0.67	⊦∎-i	-0.93 [-1.39, -0.47]
RE Model for Subgroup	(Q = 30.13, df						•	-0.26 [-0.59, 0.07]
RE Model for all studies:	(Q	= 157.45, df	= 36, p < .	.01; I ² = 72.9	9%, τ ² = 0.06))		-0.05 [-0.16, 0.05]

Test for Subgroup Differences: Q_M = 3.44, df = 3, p = 0.33

Favours control

Favours ITF

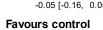
-2 -1 0 1 2 3

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Figure 22: Fasting blood glucose -subgroup by disease

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI
With disease								
Mitchell 2021	13	-0.01	2.6	9	-0.05	1.33	⊢ <u>∔</u> − 1	0.04 [-1.62, 1.70
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	⊦≑⊣	0.05 [-0.39, 0.49
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	I=I	-0.11 [-0.40, 0.18
Tov ar 2012	23	-0.02	0.52	28	-0.23	0.51	i j≡ 1	0.21 [-0.07, 0.49
Tov ar 2012	30	-0.03	0.51	29	-0.12	0.5	H	0.09 [-0.17, 0.35
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	⊢	-0.46 [-1.88, 0.96
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	⊢∎÷	-0.30 [-0.74, 0.14
Satoh 2013	29	6.95	0.21	27	6.52	0.3		0.43 [0.29, 0.57
Roshanrav an 2017	15	8.03	3.17	15	7.27	1.3	⊢	┥ 0.76 [-0.97, 2.49
Roshanrav an 2017	14	8.83	2.36	15	8.05	2.33	⊢ ; •	→ 0.78 [-0.93, 2.49
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	I∳I	0.04 [-0.37, 0.45
Machado 2019	13	5.02	0.11	13	5.05	0.11	Ŵ	-0.03 [-0.11, 0.05
Luo 2000	10	8.89	1.68	10	8.88	1.61	⊢ ∔ −1	0.01 [-1.43, 1.45
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	H;∎-1	0.41 [-0.19, 1.01
Guess 2015	20	-0.4	0.19	19	0.16	0.23	H	-0.56 [-0.69, -0.43
Giacco 2004	27	5.44	1	27	5.38	0.83	⊢ ≢-1	0.06 [-0.43, 0.55
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	⊢≖∔∣	-0.61 [-1.55, 0.33
Genta 2009	20	4.18	0.5	15	4.84	0.66	⊦ ∎i	-0.66 [-1.06, -0.26
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	H	-0.17 [-0.51, 0.17
Dehghan 2016	27	8.36	1.17	22	9.02	1	⊢≖−ŧ	-0.66 [-1.27, -0.05
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	⊢∎⊣∶	-0.93 [-1.39, -0.47
Daud 2014	12	4.62	0.48	10	4.51	0.28	H ia I	0.11 [-0.21, 0.43
Chambers 2019	12	5.3	0.69	12	5.3	0.35	⊢≑-I	0.00 [-0.44, 0.44
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	⊢	0.20 [-1.44, 1.84
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	⊢÷-I	0.00 [-0.44, 0.44
Alles 1999	20	8.61	0.81	20	8.59	2.66	⊢ i − I	0.02 [-1.20, 1.24
RE Model for Subgroup	(Q	= 144.65, df	= 25, p < .	01; $I^2 = 79.7$	7%, $\tau^2 = 0.09$		•	-0.09 [-0.25, 0.06
Without disease								
Williams 2022	20	5.1	0.5	20	5	0.5	Hiel	0.10 [-0.21, 0.41
Scheid 2014	37	5.41	1.06	35	5.12	0.59	i ; ≡-i	0.29 [-0.10, 0.68
Russo 2010	15	4.66	0.29	15	4.97	0.53	l=i	-0.31 [-0.62, -0.00
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	iși i	0.07 [-0.18, 0.32
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	i i i i i i i i i i i i i i i i i i i	0.06 [-0.10, 0.22
Luo 1996	12	4.94	0.35	12	4.86	0.55	H	0.08 [-0.29, 0.45
Letexier 2003	8	4.68	0.4	8	4.62	0.2	l ∳ l	0.06 [-0.25, 0.37
Jackson 1999	27	4.84	0.51	27	4.99	0.49	H a i	-0.15 [-0.42, 0.12
Forcheron 2007	9	4.03	0.3	8	3.81	0.57	⊦≖⊣	0.22 [-0.22, 0.66
Clarke 2016	30	4.9	0.55	30	4.9	0.55	I ≢ I	0.00 [-0.28, 0.28
Buddington 2017	45	4.73	0.72	43	4.94	1.15	H∎il	-0.21 [-0.61, 0.19
RE Model for Subgroup	(Q	= 10.72, df =	= 10, p = 0.	38; $I^2 = 0.0$	%, $\tau^2 = 0.00$)		•	0.02 [-0.07, 0.10
RE Model for all studies:	(Q	= 157.45, df	= 36, p < .	.01; I ² = 72.9	$9\%, \tau^2 = 0.06$		•	-0.05 [-0.16, 0.05

Test for Subgroup Differences: Q_M = 0.89, df = 1, p = 0.35



Favours ITF

-2 -1 0 1 2 3

Figure 23: Fasting blood glucose -subgroup by dose

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Unknown								
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	⊢∔I	0.00 [-0.44, 0.44]
RE Model for Subgroup	(Q = 0.00, df =	: 0, p = 1.00;	$I^2 = 0.0\%$	$\tau^2 = 0.00)$				0.00 [-0.44, 0.44]
				,				
Less than 10g								
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	┝━━╈╤═┥	-0.46 [-1.88, 0.96]
Scheid 2014	37	5.41	1.06	35	5.12	0.59	l ¦≡ 1	0.29 [-0.10, 0.68]
Satoh 2013	29	6.95	0.21	27	6.52	0.3		0.43 [0.29, 0.57]
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	F≢-I	0.04 [-0.37, 0.45]
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	, Militaria (Militaria) Militaria (Militaria	0.06 [-0.10, 0.22]
Machado 2019	13	5.02	0.11	13	5.05	0.11		-0.03 [-0.11, 0.05]
Genta 2009	20	4.18	2 0.5	₂ 15	4.84	0.66	⊦■┥	-0.66 [-1.06, -0.26]
RE Model for Subgroup	(Q = 46.64, df	= 6, p < .01;	I ⁻ = 90.9%	ο, τ ² = 0.10)			•	0.03 [-0.25, 0.30]
Greater than or equ								
Williams 2022	20	5.1	0.5	20	5	0.5	=	0.10 [-0.21, 0.41]
Mitchell 2021	13	-0.01	2.6	20	-0.05	1.33	L	0.04 [-1.62, 1.70]
Vaghef-Mehrabany 2019	22	-0.01	2.6	23	-0.05	0.87	· · · · ·	0.05 [-0.39, 0.49]
Tripkovic 2015	10	5.53	0.04	10	5.64	0.37	H e ri	-0.11 [-0.40, 0.18]
Tovar 2012	23	-0.02	0.20	28	-0.23	0.51		0.21 [-0.07, 0.49]
Tov ar 2012	30	-0.02	0.52	28	-0.23	0.51	· · ·	0.09 [-0.17, 0.35]
Sorensen 2010	12	-0.03	0.51	12	-0.12 5.4	0.5	⊢ ∎:	-0.30 [-0.74, 0.14]
Russo 2010	12	4.66	0.29	12	4.97	0.53	Here i	-0.31 [-0.62, -0.00]
Roshanrav an 2017	15	8.03	3.17	15	7.27	1.3	,-, 	→ 0.76 [-0.97, 2.49]
Roshanrav an 2017	13	8.83	2.36	15	8.05	2.33		→ 0.78 [-0.93, 2.49]
Rajkumar 2015	14	4.64	0.37	15	4.57	0.33	· · ·	0.07 [-0.18, 0.32]
Luo 1996	12	4.94	0.35	12	4.86	0.55	H#H	0.08 [-0.29, 0.45]
Luo 2000	12	8.89	1.68	12	8.88	1.61		0.01 [-1.43, 1.45]
Letexier 2003	8	4.68	0.4	8	4.62	0.2	i i i i i i i i i i i i i i i i i i i	0.06 [-0.25, 0.37]
Jackson 1999	27	4.84	0.51	27	4.99	0.2	I ni i	-0.15 [-0.42, 0.12]
Hiel 2020	51	0.23	1.96	55	-0.18	0.97		0.41 [-0.19, 1.01]
Guess 2015	20	-0.4	0.19	19	0.16	0.23		-0.56 [-0.69, -0.43]
Giacco 2004	20	5.44	1	27	5.38	0.83	∔	0.06 [-0.43, 0.55]
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	⊢ ∎∔1	-0.61 [-1.55, 0.33]
Forcheron 2007	9	4.03	0.3	8	3.81	0.57	F∎-1	0.22 [-0.22, 0.66]
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	⊢ ∎-j	-0.17 [-0.51, 0.17]
Dehghan 2016	27	8.36	1.17	22	9.02	1	⊢{	-0.66 [-1.27, -0.05]
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	┝╼┥┊	-0.93 [-1.39, -0.47]
Daud 2014	12	4.62	0.48	10	4.51	0.28	· · · · · · · · · · · · · · · · · · ·	0.11 [-0.21, 0.43]
Clarke 2016	30	4.9	0.55	30	4.9	0.55	Hini I	0.00 [-0.28, 0.28]
Chambers 2019	12	5.3	0.69	12	5.3	0.35	F≢-I	0.00 [-0.44, 0.44]
Buddington 2017	45	4.73	0.72	43	4.94	1.15	I ≡ I	-0.21 [-0.61, 0.19]
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	⊢	0.20 [-1.44, 1.84]
Alles 1999	20	8.61	0.81	20	8.59	2.66		0.02 [-1.20, 1.24]
RE Model for Subgroup	(Q = 85.17, df			2		2.00		-0.08 [-0.20, 0.03]
	,	· •	,	,	,			
RE Model for all studies:	(Q	= 157.45, df	= 36, p < .	01; I ² = 72.9	$9\%, \tau^2 = 0.06)$)		-0.05 [-0.16, 0.05]

del for all studies: (Q = 157.45, df = 36, p < .01;
$$I^2$$
 = 72.9%, τ^2 = 0

Test for Subgroup Differences: Q_M = 0.93, df = 2, p = 0.63

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Figure 24: Fasting blood glucose -subgroup by ITF type

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Others								
Williams 2022	20	5.1	0.5	20	5	0.5	l ⊨ l	0.10 [-0.21, 0.41]
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	⊦≖÷	-0.30 [-0.74, 0.14]
Scheid 2014	37	5.41	1.06	35	5.12	0.59	k ≡ I	0.29 [-0.10, 0.68]
Satoh 2013	29	6.95	0.21	27	6.52	0.3	H	0.43 [0.29, 0.57]
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	li∳-l	0.07 [-0.18, 0.32]
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	F∳-I	0.04 [-0.37, 0.45]
Machado 2019	13	5.02	0.11	13	5.05	0.11		-0.03 [-0.11, 0.05]
Luo 1996	12	4.94	0.35	12	4.86	0.55	Hiệ-H	0.08 [-0.29, 0.45]
Luo 2000	10	8.89	1.68	10	8.88	1.61	⊢ ÷ −1	0.01 [-1.43, 1.45]
Giacco 2004	27	5.44	1	27	5.38	0.83	⊦≢⊣	0.06 [-0.43, 0.55]
Genta 2009	20	4.18	0.5	15	4.84	0.66	⊦∎i	-0.66 [-1.06, -0.26]
Forcheron 2007	9	4.03	0.3	8	3.81	0.57	Fi≡-1	0.22 [-0.22, 0.66]
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	H∎i	-0.17 [-0.51, 0.17]
Dehghan 2016	27	8.36	1.17	22	9.02	1	⊢4	-0.66 [-1.27, -0.05]
Daud 2014	12	4.62	0.48	10	4.51	0.28	H ≢ I	0.11 [-0.21, 0.43]
Clarke 2016	30	4.9	0.55	30	4.9	0.55	I≢I	0.00 [-0.28, 0.28]
Buddington 2017	45	4.73	0.72	43	4.94	1.15	⊢= il	-0.21 [-0.61, 0.19]
Alles 1999	20	8.61	0.81	20	8.59	2.66	H	0.02 [-1.20, 1.24]
RE Model for Subgroup	(Q	= 58.59, df =	= 17, p < .0	1; I ² = 69.49	%, $\tau^2 = 0.04$)		•	-0.00 [-0.13, 0.13]
Inulin								
Mitchell 2021	13	-0.01	2.6	9	-0.05	1.33	⊢ <u>†</u> −1	0.04 [-1.62, 1.70]
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	⊦≢-1	0.05 [-0.39, 0.49]
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	I III	-0.11 [-0.40, 0.18]
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51	H e ri	0.21 [-0.07, 0.49]
Tovar 2012	30	-0.03	0.51	29	-0.12	0.5	l i ≓l	0.09 [-0.17, 0.35]
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	⊢;-1	-0.46 [-1.88, 0.96]
Russo 2010	15	4.66	0.29	15	4.97	0.53	H=-	-0.31 [-0.62, -0.00]
Roshanravan 2017	15	8.03	3.17	15	7.27	1.3	H +	H 0.76 [-0.97, 2.49]
Roshanrav an 2017	14	8.83	2.36	15	8.05	2.33	<u>⊢ ; -</u>	H 0.78 [-0.93, 2.49]
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	÷.	0.06 [-0.10, 0.22]
Letexier 2003	8	4.68	0.4	8	4.62	0.2	Hiệt	0.06 [-0.25, 0.37]
Jackson 1999	27	4.84	0.51	27	4.99	0.49	H a i	-0.15 [-0.42, 0.12]
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	l ; ∎ -l	0.41 [-0.19, 1.01]
Guess 2015	20	-0.4	0.19	19	0.16	0.23		-0.56 [-0.69, -0.43]
Ghavami 2019	23	6.63	1.71	23	7.24	1.55		-0.61 [-1.55, 0.33]
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	┝═┥	-0.93 [-1.39, -0.47]
Chambers 2019	12	5.3	0.69	12	5.3	0.35	. ⊦ ≢⊣	0.00 [-0.44, 0.44]
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	⊢ <u></u> ;	0.20 [-1.44, 1.84]
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	⊢ • +	0.00 [-0.44, 0.44]
RE Model for Subgroup	(Q	= 74.97, df =	= 18, p < .0	1; I ² = 71.09	%, $\tau^2 = 0.07$)		•	-0.10 [-0.26, 0.06]
RE Model for all studies:	(Q	= 157.45, df	= 36, p < .	01; I ² = 72.9	9%, $\tau^2 = 0.06$)	•	-0.05 [-0.16, 0.05]

(Q = 157.45, df = 36, p < .01; I^2 = 72.9%, τ^2 = 0.06)

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Test for Subgroup Differences: $Q_M = 0.81$, df = 1, p = 0.37



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Figure 25: Fasting blood glucose -subgroup by RoB

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% 0
Low							
Williams 2022	20	5.1	0.5	20	5	0.5	0.10 [-0.21, 0.4
Mitchell 2021	13	-0.01	2.6	9	-0.05	1.33	0.04 [-1.62, 1.7
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	-0.11 [-0.40, 0.1
Roshanravan 2017	15	8.03	3.17	15	7.27	1.3	⊢ − − − − − − − − − − − − − − − − − − −
Roshanravan 2017	14	8.83	2.36	15	8.05	2.33	0.78 [-0.93, 2.4
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	0.06 [-0.10, 0.2
Machado 2019	13	5.02	0.11	13	5.05	0.11	-0.03 [-0.11, 0.0
Luo 1996	12	4.94	0.35	12	4.86	0.55	0.08 [-0.29, 0.4
Letexier 2003	8	4.68	0.4	8	4.62	0.2	0.06 [-0.25, 0.3
Jackson 1999	27	4.84	0.51	27	4.99	0.49	-0.15 [-0.42, 0.
Guess 2015	20	-0.4	0.19	19	0.16	0.23	-0.56 [-0.69, -0.4
Giacco 2004	27	5.44	1	27	5.38	0.83	0.06 [-0.43, 0.5
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	-0.61 [-1.55, 0.3
Forcheron 2007	9	4.03	0.3	8	3.81	0.57	
Dehghan 2016	27	8.36	1.17	22	9.02	1	-0.66 [-1.27, -0.0
Clarke 2016	30	4.9	0.55	30	4.9	0.55	IIII 0.00 [-0.28, 0.2
Chambers 2019	12	5.3	0.69	12	5.3	0.35	
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	0.20 [-1.44, 1.8
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	+ 0.00 [-0.44, 0.4
Alles 1999	20	8.61	0.81	20	8.59	2.66	
RE Model for Subgroup	(Q = 66.73, df	= 20, p < .01	; I ² = 62.8 ^o	%, $\tau^2 = 0.03$		2.00	-0.06 [-0.18, 0.0
High							
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51	0.21 [-0.07, 0.4
Tovar 2012	30	-0.03	0.51	29	-0.12	0.5	0.09 [-0.17, 0.3
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	-0.46 [-1.88, 0.9
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	-0.30 [-0.74, 0.
Scheid 2014	37	5.41	1.06	35	5.12	0.59	₩₩ 0.29 [-0.10, 0.6
Satoh 2013	29	6.95	0.21	27	6.52	0.3	■ 0.43 [0.29, 0.5
Russo 2010	15	4.66	0.29	15	4.97	0.53	-0.31 [-0.62, -0.0
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	■ 0.07 [-0.18, 0.3
Padilla-Camberos 2018	10	4.68	0.54	10	4.64	0.57	
Luo 2000	10	8.89	1.68	10	8.88	1.61	
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	 0.41 [-0.19, 1.0
Genta 2009	20	4.18	0.5	15	4.84	0.66	-0.66 [-1.06, -0.2
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	-0.17 [-0.51, 0.7
Dehgahn 2014	27	-0.11	1.01	25	-0.09	0.3	-0.93 [-1.39, -0.4
Daud 2014	12	-1.02	0.48	25 10	-0.09 4.51	0.07	H≡I 0.11 [-0.21, 0.4
	45	4.62	0.48	43	4.51	0.28 1.15	-0.21 [-0.21, 0.2
Buddington 2017							

Test for Subgroup Differences: $Q_M = 0.01$, df = 1, p = 0.93

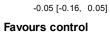
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Figure 26: Fasting blood glucose -subgroup by follow-up duration

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95%CI]
Less than 6 weeks								
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	H e i I	-0.11 [-0.40, 0.18]
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	⊢∎÷	-0.30 [-0.74, 0.14]
Russo 2010	15	4.66	0.29	15	4.97	0.53	l∎i	-0.31 [-0.62, -0.00]
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	÷.	0.06 [-0.10, 0.22]
Luo 1996	12	4.94	0.35	12	4.86	0.55	HiệH	0.08 [-0.29, 0.45]
Luo 2000	10	8.89	1.68	10	8.88	1.61	⊢ i − i	0.01 [-1.43, 1.45]
Letexier 2003	8	4.68	0.4	8	4.62	0.2	I≢I	0.06 [-0.25, 0.37]
Clarke 2016	30	4.9	0.55	30	4.9	0.55	l i și l	0.00 [-0.28, 0.28]
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	F∔I	0.00 [-0.44, 0.44]
Alles 1999	20	8.61	0.81	20	8.59	2.66		0.02 [-1.20, 1.24]
RE Model for Subgroup	(Q = 6.95, df =	9, p = 0.64;	$I^2 = 6.8\%,$	$\tau^2 = 0.00)$			•	-0.03 [-0.13, 0.07]
Greater than or equ	al to 6 week	s						
Williams 2022	20	5.1	0.5	20	5	0.5	Hiel	0.10 [-0.21, 0.41]
Mitchell 2021	13	-0.01	2.6	9	-0.05	1.33		0.04 [-1.62, 1.70]
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	⊢ ‡ -I	0.05 [-0.39, 0.49]
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51	i ,≡ i	0.21 [-0.07, 0.49]
Tov ar 2012	30	-0.03	0.51	29	-0.12	0.5	H i el	0.09 [-0.17, 0.35]
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18		-0.46 [-1.88, 0.96]
Scheid 2014	37	5.41	1.06	35	5.12	0.59	ŀ≡I	0.29 [-0.10, 0.68]
Satoh 2013	29	6.95	0.21	27	6.52	0.3	H	0.43 [0.29, 0.57]
Roshanrav an 2017	15	8.03	3.17	15	7.27	1.3	H + +	→ 0.76 [-0.97, 2.49]
Roshanrav an 2017	14	8.83	2.36	15	8.05	2.33	⊢ <u>∔</u>	→ 0.78 [-0.93, 2.49]
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	line I	0.07 [-0.18, 0.32]
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	ŀ≢I	0.04 [-0.37, 0.45]
Machado 2019	13	5.02	0.11	13	5.05	0.11	Ŵ	-0.03 [-0.11, 0.05]
Jackson 1999	27	4.84	0.51	27	4.99	0.49	H a ti	-0.15 [-0.42, 0.12]
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	l ∶ ∎ l	0.41 [-0.19, 1.01]
Guess 2015	20	-0.4	0.19	19	0.16	0.23	H	-0.56 [-0.69, -0.43]
Giacco 2004	27	5.44	1	27	5.38	0.83	⊦≞⊣	0.06 [-0.43, 0.55]
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	┝╼╶┊┤	-0.61 [-1.55, 0.33]
Genta 2009	20	4.18	0.5	15	4.84	0.66	⊦∎₁	-0.66 [-1.06, -0.26]
Forcheron 2007	9	4.03	0.3	8	3.81	0.57	F≣-1	0.22 [-0.22, 0.66]
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	⊢= :	-0.17 [-0.51, 0.17]
Dehghan 2016	27	8.36	1.17	22	9.02	1	┝╼╶┥	-0.66 [-1.27, -0.05]
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	┝━┥┊	-0.93 [-1.39, -0.47]
Daud 2014	12	4.62	0.48	10	4.51	0.28	⊢∎-1	0.11 [-0.21, 0.43]
Chambers 2019	12	5.3	0.69	12	5.3	0.35	<u> ≢ </u>	0.00 [-0.44, 0.44]
Buddington 2017	45	4.73	0.72	43	4.94	1.15	+=:	-0.21 [-0.61, 0.19]
Bonsu 2012	12	7.6	2.6	14	7.4	1.4		0.20 [-1.44, 1.84]
RE Model for Subgroup	(Q = 150.40, df	r = 26, p < .0	01; I = 80.	1%, τ ⁻ = 0.0	18)		•	-0.05 [-0.19, 0.09]
RE Model for all studies:	(Q	= 157.45, df	= 36, p < .	01; I ² = 72.	9%, $\tau^2 = 0.06$)	ė.	-0.05 [-0.16, 0.05]

Test for Subgroup Differences: $Q_M = 0.00$, df = 1, p = 0.97



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Figure 27: Fasting blood glucose - subgroup by age

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown							
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	0.07 [-0.18, 0.32]
	8	4.68	0.4	8	4.62	0.2	0.06 [-0.25, 0.37]
Letexier 2003 RE Model for Subgrou	up (Q = 0.00	, df = 1, p = ($0.96; I^2 = 0$.0%, τ ² = 0.0	00)		♦ 0.07 [−0.13, 0.26]
more than 40 years							
Scheid 2014	37	5.41	1.06	35	5.12	0.59	0.29 [-0.10, 0.68]
Chambers 2019	12	5.3	0.69	12	5.3	0.35	⊢ ∎−1 0.00 [−0.44, 0.44]
Alles 1999	20	8.61	0.81	20	8.59	2.66	0.02 [-1.20, 1.24]
Luo 2000	10	8.89	1.68	10	8.88	1.61	0.01 [-1.43, 1.45]
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	-0.30 [-0.74, 0.14]
Jackson 1999	27	4.84	0.51	27	4.99	0.49	-0.15 [-0.42, 0.12]
Giacco 2004	27	5.44	1	27	5.38	0.83	0.06 [-0.43, 0.55]
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	
Guess 2015	20	-0.4	0.19	14	0.16	0.23	-0.56 [-0.69, -0.43]
Mitchell 2021							
Tajadadi-Ebrahimi 2014	13	-0.01	2.6	9	-0.05	1.33	
	27	-0.63	3.08	27	-0.17	2.18	
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	-0.93 [-1.39, -0.47]
Roshanravan 2017	15	8.03	3.17	15	7.27	1.3	⊢ <u>-</u> 0.76 [−0.97, 2.49]
Roshanravan 2017	14	8.83	2.36	15	8.05	2.33	⊢+ 0.78 [−0.93, 2.49]
Dehghan 2016	27	8.36	1.17	22	9.02	1	-0.66 [-1.27, -0.05]
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	-0.17 [-0.51, 0.17]
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	-0.61 [-1.55, 0.33]
Genta 2009	20	4.18	0.5	15	4.84	0.66	-0.66 [-1.06, -0.26]
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	-0.11 [-0.40, 0.18]
Satoh 2013	29	6.95	0.21	27	6.52	0.3	0.43 [0.29, 0.57]
Nishimura 2015	24	0.08	03	24	0.02	0.25	0.06 [-0.10, 0.22]
RE Model for Subgrou	up (Q = 142.	88, df = 21, j	$o < .01; I^2 =$	= 79.9 ⁻ , τ ² =	= 0.11)		◆ -0.14 [-0.33, 0.05]
40 years or less							
Buddington 2017	45	4.73	0.72	43	4.94	1.15	-0.21 [-0.61, 0.19]
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	0.00 [-0.44, 0.44]
Williams 2022	20	5.1	0.5	20	5	0.5	⊢ 0.10 [−0.21, 0.41]
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	0.05 [-0.39, 0.49]
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	0.04 [-0.37, 0.45]
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51	0.21 [-0.07, 0.49]
Tovar 2012	30	-0.03	0.51	29	-0.12	0.5	0.09 [-0.17, 0.35]
Daud 2014	12	4.62	0.48	10	4.51	0.28	
Machado 2019	12	5.02	0.48	13	5.05	0.28	
Clarke 2016	30						
		4.9	0.55	30	4.9	0.55	· · · · · · · · · · · · · · · · · · ·
Luo 1996	12	4.94	0.35	12	4.86	0.55	
Russo 2010	15	4.66	0.29	15	4.97	0.53	-0.31 [-0.62, -0.00]
Forcheron 2007 RE Model for Subgrou	9 Jp(Q = 10.1	4.03 0, df = 12, p	0.3 = 0.61; l ² =	= 0.0%, τ ² =	3.81 0.00)	0.57	·····································
RE Model for all studies:	-	45, df = 36, j					-0.05 [-0.16, 0.05]
			,	-12.370, t -	- 0.00)		
Test for Subgroup Difference	es: Q _M = 2.4	4, df = 2, p =	0.30			Favou	ITS ITF Favours control

-4 -3 -2 -1 0 1 2 3

Figure 28: Fasting blood glucose - subgroup by BMI

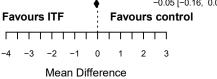
Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown							
Letexier 2003	8	4.68	0.4	8	4.62	0.2	0.06 [-0.25, 0.37]
Forcheron 2007	9	4.03	0.3	â	3.81	0.57	0.22 -0.22, 0.66
Forcheron 2007 RE Model for Subgrou	Jp (Q = 0.34	, df = 1, p = 0	$0.56; 1^2 = 0$	$.0\%, \tau^{z} = 0.$	00)		♦ 0.11 [−0.14, 0.37]
Obese							
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	······ ··· ··· · 0.20 [−1.44, 1.84
Guess 2015	20	-0.4	0.19	19	0.16	0.23	■ -0.56 [-0.69, -0.43
Vitchell 2021	13	-0.01	2.6	9	-0.05	1.33	▶ 0.04 [−1.62, 1.70
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	-0.46 [-1.88, 0.96
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	⊢;-= 0.41 [−0.19, 1.01
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	-0.93 [-1.39, -0.47
Roshanravan 2017	15	8.03	3.17	15	7.27	1.3	↓ 0.76 [−0.97, 2.49
Roshanravan 2017	14	8.83	2.36	15	8.05	2.33	↓ 0.78 [−0.93, 2.49
Dehghan 2016	27	8.36	1.17	22	9.02	1	-0.66 [-1.27, -0.05
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	–0.17 [−0.51, 0.17
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	-0.61 [-1.55, 0.33
Genta 2009	20	4.18	0.5	15	4.84	0.66	-0.66 [-1.06, -0.26
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	-0.11 [-0.40, 0.18
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	0.05 [-0.39, 0.49
Padilla-Camberos 2018	14	4.68	0.54	14	4.64	0.57	0.04 [-0.37, 0.45
Tovar 2012	23	-0.02	0.52	28	-0.23	0.51	6.21 [−0.07, 0.49
Tovar 2012	30	-0.03	0.51	29	-0.12	0.5	HEH 0.09 [-0.17, 0.35
Daud 2014	12	4.62	0.48	10	4.51	0.28	H ■ + 0.11 [−0.21, 0.43
						0.20	-0.03 [-0.11, 0.05
Machado 2019 RE Model for Subgrou	up (Q = 84.8	3, df = 18, p	< .01; l ² =	80.2%, τ ² =	0.09)	0.11	-0.15 [-0.34, 0.03
Pre-obese							
Scheid 2014	37	5.41	1.06	35	5.12	0.59	!- 0.29 [−0.10, 0.68]
Chambers 2019	12	5.3	0.69	12	5.3	0.35	⊢ 0.00 – 0.44, 0.44
Alles 1999	20	8.61	0.81	20	8.59	2.66	0.02 [-1.20, 1.24
Luo 2000	10	8.89	1.68	10	8.88	1.61	0.01 [-1.43, 1.45
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	⊢– + –0.30 [−0.74, 0.14
Jackson 1999	27	4.84	0.51	27	4.99	0.49	H ■ H −0.15 [−0.42, 0.12
Giacco 2004	27	5.44	1	27	5.38	0.83	0.06 [-0.43, 0.55
Buddington 2017	45	4.73	0.72	43	4.94	1.15	-0.21 [-0.61, 0.19
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	⊢––1 0.00 [−0.44, 0.44
Williams 2022	20	5.1	0.5	20	5	0.5	H → 0.10 [−0.21, 0.41
Williams 2022 RE Model for Subgroเ	Jp (Q = 6.37	, df = 9, p = 0	$0.70; i^2 = 0$	$.0\%, \tau^2 = 0.1$	00)	0.0	↓ −0.03 [−0.16, 0.10
Normal							
Rajkumar 2015	15	4.64	0.37	15	4.57	0.33	H → 0.07 [−0.18, 0.32
Satoh 2013	29	6.95	0.21	27	6.52	0.3	0.43 [0.29, 0.57
Nishimura 2015	24	0.08	0.3	24	0.02	0.25	0.06 [-0.10, 0.22
Clarke 2016	30	4.9	0.55	30	4.9	0.55	H H 0.00 [−0.28, 0.28
Luo 1996	12	4.94	0.35	12	4.86	0.55	0.08 [-0.29, 0.45
						0.53	-0.31 [-0.62, -0.00
Russo 2010 RE Model for Subgrou	Jp (Q = 27.5	7, df = 5, p <	.01; Î ² = 7	$8.8\%, \tau^2 = 0$	0.05)	5.00	♦ 0.08 [−0.12, 0.28
RE Model for all studies:	(Q = 157.	45, df = 36, j	$0 < .01: 1^2 =$	72.9% . τ ²	= 0.06)		-0.05 [-0.16, 0.05
Test for Subgroup Difference				, t	,	Favou	

Test for Subgroup Differences: Q_M = 3.84, df = 3, p = 0.28

Favours ITF	Favours control
-4 -3 -2 -1 (0 1 2 3

Figure 29: Fasting blood glucose - subgroup by diabetes status

Study/subgroup	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Unknown							
Sorensen 2010	12	5.1	0.5	12	5.4	0.6	-0.30 [-0.74, 0.14]
Giacco 2004	27	5.44	1	27	5.38	0.83	
Hiel 2020	51	0.23	1.96	55	-0.18	0.97	⊢ – 0.41 –0.19, 1.01
Tripkovic 2015	10	5.53	0.28	10	5.64	0.37	-0.11 [-0.40, 0.18]
Vaghef-Mehrabany 2019	22	-0.13	0.64	23	-0.18	0.87	0.05 [-0.39, 0.49]
Daud 2014	12	4.62	0.48	10	4.51	0.28	+■+ 0.11 [-0.21, 0.43]
						0.11	-0.03 [-0.11, 0.05]
Machado 2019 RE Model for Subgro	up(Q = 0.34	, df = 1, p =	$0.56; I^2 = 0$	$.0\%, \tau^2 = 0$.00)		• 0.11 [-0.14, 0.37]
No diabetes							
Scheid 2014	37	5.41	1.06	35	5.12	0.59	
Chambers 2019	12	5.3	0.69	12	5.3	0.35	0.00 [-0.44, 0.44]
Jackson 1999	27	4.84	0.51	27	4.99	0.49	-0.15 [-0.42, 0.12]
Buddington 2017	45	4.73	0.72	43	4.94	1.15	
Blaedel 2016	20	5.6	0.45	19	5.6	0.87	
Williams 2022	20	5.1	0.5	20	5	0.5	
Guess 2015	20	-0.4	0.19	19	0.16	0.23	-0.56 [-0.69, -0.43]
Mitchell 2021	13	-0.01	2.6	9	-0.05	1.33	
Dewulf 2013	15	-0.11	0.6	15	0.06	0.3	-0.17 [-0.51, 0.17]
Genta 2009	20	4.18	0.0	15	4.84	0.66	
Padilla-Camberos 2018	14	4.18	0.54	14	4.64	0.57	
Tovar 2012	23	-0.02	0.54	28	-0.23	0.57	H■H 0.04 [-0.37, 0.45] 0.21 [-0.07, 0.49]
Tovar 2012	23 30	-0.02	0.52	20 29	-0.23	0.51	
Rajkumar 2015							
Nishimura 2015	15	4.64	0.37	15	4.57	0.33	
Clarke 2016	24	0.08	0.3	24	0.02	0.25	
	30	4.9	0.55	30	4.9	0.55	H 0.00 [-0.28, 0.28]
Luo 1996	12	4.94	0.35	12	4.86	0.55	
Russo 2010	15	4.66	0.29	15	4.97	0.53	
Letexier 2003	8	4.68	0.4	8	4.62	0.2	
Forcheron 2007 RE Model for Subgrou	y = 797	4.03 6 df = 10 p	0.3	66 7% - ² -	3.81	0.57	
	up(@ - 78.7	0, ui – 19, p	< .01, 1 =	00.7 %, 1 -	0.04)		• -0.05 [-0.17, 0.07]
Have diabetes							
Alles 1999	20	8.61	0.81	20	8.59	2.66	⊢ <u>+</u> 0.02 [−1.20, 1.24]
Luo 2000	10	8.89	1.68	10	8.88	1.61	· · · · · · · · · · · · 0.01 [−1.43, 1.45]
Bonsu 2012	12	7.6	2.6	14	7.4	1.4	→ → → 0.20 [−1.44, 1.84]
Tajadadi-Ebrahimi 2014	27	-0.63	3.08	27	-0.17	2.18	
Dehgahn 2014	27	-1.02	1.01	25	-0.09	0.67	-0.93 [-1.39, -0.47]
Roshanravan 2017	15	8.03	3.17	15	7.27	1.3	······ 0.76 [−0.97, 2.49]
Roshanravan 2017	14	8.83	2.36	15	8.05	2.33	······ 0.78 [−0.93, 2.49]
Dehghan 2016	27	8.36	1.17	22	9.02	1	-0.66 [-1.27, -0.05]
Ghavami 2019	23	6.63	1.71	23	7.24	1.55	-0.61 [-1.55, 0.33]
Satoh 2013 RE Model for Subgrou	29 un (Q = 45.3	6.95 6 df=9 p <	0.21 01 · 1 ² = 6	$7.8\% \frac{27}{\tau^2} = 0$	6.52 0.25)	0.3	$-0.17 \begin{bmatrix} 0.43 & [0.29, 0.57] \\ -0.17 & [-0.62, 0.27] \end{bmatrix}$
RE Model for all studies:	,	45, df = 36,	,	= 72.9%, τ ²	= 0.06)	_	-0.05 [-0.16, 0.05]
Test for Subgroup Difference	ces: Q _M = 0.6	4, df = 2, p =	0.73			Favou	ITF Favours control

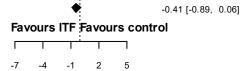


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		ITF			Control			
Study	Total	Mean	SD	Total	Mean	SD		MD [95% CI]
Bahmani 2016	25	30.8	5.9	25	29.8	5.9	⊢ − − 1	1.00 [-2.27, 4.27]
Castro-Sanchez 2016	16	34.66	5.5	16	34.5	5.5	⊢ I	0.16 [-3.65, 3.97]
Chambers 2019	12	30	3.12	12	30	3.12	⊢	0.00 [-2.50, 2.50]
Clarke 2016	30	24.2	2.74	30	24.2	2.74	F	0.00 [-1.39, 1.39]
Cronin 2016	100	28.1	5.3	100	27.1	4.6		1.00 [-0.38, 2.38]
Daud 2014	12	29.9	3.81	10	31.2	3.48	⊢_ • <u>+</u> -1	-1.30 [-4.35, 1.75]
Dehghan 2016	27	30.22	3.44	22	30.03	3.88	⊢ <u>⊨</u> −1	0.19 [-1.89, 2.27]
Dewulf 2013	15	-0.35	1.37	15	-0.22	0.87	F∰-1	-0.13 [-0.95, 0.69]
Fernandes 2016	3	0	0.1	3	0.1	0.3	i	-0.10 [-0.46, 0.26]
Genta 2009	20	28	3	15	32	4	┝━━━┥	-4.00 [-6.41, -1.59]
Ghav ami 2019	23	29.15	2.73	23	30.64	2.24	⊢≖⊣	-1.49 [-2.93, -0.05]
Gosmez-Reyes 2010	20	31.2	6.65	20	30.81	6	⊢ I	0.39 [-3.54, 4.32]
Hiel 2020	51	1	1.4	55	-1.2	2.9	H∎H	2.20 [1.34, 3.06]
Nishimura 2015	24	-0.05	0.25	24	0.23	0.98	H	-0.28 [-0.68, 0.12]
Padilla-Camberos 2018	14	34.25	2.64	14	34.75	2.64	⊢_ ∎I	-0.50 [-2.46, 1.46]
Rajkumar 2015	15	18.66	1.55	15	22.33	1.74	⊢∎⊣	-3.67 [-4.85, -2.49]
Reimer 2017	26	0.1	0.51	27	0.1	1.04	i 🙀	0.00 [-0.44, 0.44]
Reimer 2017	22	0	0.47	21	0.2	0.46	, in the second s	-0.20 [-0.48, 0.08]
Roshanrav an 2017	14	29.97	4.12	15	29.75	4.69	⊢	0.22 [-2.99, 3.43]
Roshanrav an 2017	15	30.15	2.73	15	30.64	5.24	⊢	-0.49 [-3.48, 2.50]
Salmean 2019	6	34.4	3	6	35.6	4.9	⊢	-1.20 [-5.80, 3.40]
Satoh 2013	29	25	0.7	27	26.43	0.86	H e i	-1.43 [-1.84, -1.02]
Tajadadi-Ebrahimi 2014	27	30.8	5.9	27	29.8	5.9	⊢ ∔ = →	1.00 [-2.15, 4.15]
Tripkovic 2015	10	30.39	2.71	10	30.23	2.88	⊢	0.16 [-2.29, 2.61]
Vaghef-Mehrabany 201	9 22	-1.1	0.94	23	-0.8	0.81		-0.30 [-0.81, 0.21]
Wong 2010	23	25.5	0.5	23	25.5	0.5		0.00 [-0.29, 0.29]
Crovesy 2021	11	-0.87	0.85	10	-0.25	0.86	⊢≡ }	-0.62 [-1.35, 0.11]
Williams 2022	20	24.6	3.7	20	26.9	4.8	⊢_ ∎	-2.30 [-4.96, 0.36]
Ziaei 2022	50	27.62	3.48	25	28.38	1.93	⊢ ∎ i l	-0.76 [-1.99, 0.47]

Figure 30: Forest plot displaying the effect of inulin-type fructans on body mass index

RE Model for all studies: (Q = 121.79, df = 28, p < .01; 1^2 = 88.5%, τ^2 = 1.02)



-4 -1 2 3

		ITF			Control			
Study	Total	Mean	SD	Total	Mean	SD		MD [95% CI]
Alles 1999	20	81.9	14.4	20	81.7	14	F-+-1	0.20 [-8.60, 9.00]
Bahmani 2016	25	80.1	15.3	25	75	14.4	⊢∔ • − − 1	5.10 [-3.14, 13.34]
Castro-Sanchez 2016	16	95.7	18.8	16	95.2	18.8	⊢ ∔ – I	0.50 [-12.53, 13.53]
Cronin 2016	100	72.6	13.9	100	70.3	12.4	l : 1	2.30 [-1.35, 5.95]
Daud 2014	12	84.1	16.63	10	86.3	14.23	⊢	-2.20 [-15.10, 10.70]
Dehghan 2016	27	72.07	10.13	22	71.56	10.66	H-H	0.51 [-5.36, 6.38]
Fernandes 2016	3	-0.5	0.7	3	0.5	0.9	H	-1.00 [-2.29, 0.29]
Forcheron 2007	9	62.5	7.5	8	64	8.2	⊢	-1.50 [-9.00, 6.00]
Genta 2009	20	76.2	6.1	15	92.3	10.1	⊢ ⊷⊣	-16.10 [-21.87, -10.33]
Ghavami 2019	23	81.46	11.39	23	79.4	13.91	⊢ 1	2.06 [-5.29, 9.41]
Guess 2015	20	-1.8	0.4	19	-0.5	0.3		-1.30 [-1.52, -1.08]
Guess 2016	34	-0.42	0.17	34	0.38	0.26	, i i i i i i i i i i i i i i i i i i i	-0.80 [-0.90, -0.70]
Hiel 2020	51	-2.7	4	55	-1.2	2.9	F.	-1.50 [-2.84, -0.16]
Holscher 2014	58	70.3	11.22	29	70.1	11.31	r∔-1	0.20 [-4.83, 5.23]
Luo 1996	12	68	6.93	12	67	6.93	⊢∔–-I	1.00 [-4.55, 6.55]
Machado 2019	13	-2.6	0.76	13	-1.09	0.72		-1.51 [-2.08, -0.94]
Nishimura 2015	24	-0.08	0.59	24	0.64	2.94	H	-0.72 [-1.92, 0.48]
Padilla-Camberos 2018	14	100.25	12.01	14	92.5	10.54	i − − − 1	7.75 [-0.62, 16.12]
Parnell 2009	21	-1.03	1.97	17	0.45	1.28	H	-1.48 [-2.52, -0.44]
Pol 2018	29	90.7	11.3	26	90.6	12.6	⊢∔–I	0.10 [-6.25, 6.45]
Reimer 2017	26	0.2	1.53	27	0.4	2.08		-0.20 [-1.18, 0.78]
Reimer 2017	22	0.1	1.88	21	0.7	1.83	Ĥ	-0.60 [-1.71, 0.51]
Roshanrav an 2017	14	79.96	14.57	15	80.34	12.23	⊢ ∔1	-0.38 [-10.21, 9.45]
Roshanrav an 2017	15	85.42	9.95	15	81.13	16.02	⊢∔ ∎	4.29 [-5.25, 13.83]
Salmean 2019	6	87.4	9.9	6	90.9	12.3	⊢ • • • • • •	-3.50 [-16.13, 9.13]
Satoh 2013	29	62.88	2.43	27	65.32	2.8	H.	-2.44 [-3.82, -1.06]
Tajadadi-Ebrahimi 2014	27	80.1	15.3	27	75	14.4	⊢ I	5.10 [-2.83, 13.03]
Tov ar 2012	30	-2.81	2.34	29	-2.89	2.51	i i i	0.08 [-1.16, 1.32]
Tov ar 2012	23	-3.88	2.41	28	-4.09	2.28	H	0.21 [-1.09, 1.51]
Tripkovic 2015	10	101.99	12.15	10	101.69	12.86	⊢ – − − − 1	0.30 [-10.67, 11.27]
Vaghef-Mehrabany 2019	22	-2.69	2.14	23	-2.06	2.08	μ,	-0.63 [-1.86, 0.60]
Wong 2010	23	72.9	3.1	23	72.9	3.1	н і н	0.00 [-1.79, 1.79]
Crovesy 2021	11	-2.24	2.11	10	-0.58	2.19	н н	-1.66 [-3.50, 0.18]
Mitchell 2021	13	88.59	15.43	9	87.21	9.24	⊢ ∔ I	1.38 [-8.95, 11.71]
Williams 2022	20	71.6	13.6	20	74.7	13.6	⊢∔-1	-3.10 [-11.53, 5.33]
Ziaei 2022	50	-2	2.05	25	-0.43	1.14		-1.57 [-2.29, -0.85]

Figure 31: Forest plot displaying the effect of inulin-type fructans on body weight

RE Model for all studies: (Q = 81.43, df = 35, p < .01; I^2 = 50.1%, τ^2 = 0.17) Favours ITF



-24 -12 0 12 24 Mean Difference

(

Figure 32: Forest plot displaying the effect of inulin-type fructans on waist circumference

		ITF			Control	I		
Study	Total	Mean	SD	Total	Mean	SD		MD [95% CI]
Castro-Sanchez 2016	16	107.9	15.6	16	107.8	15.49	F1	0.10 [-10.67, 10.87]
Dehghan 2016	27	97.59	6.46	22	100.47	4.29	+■-	-2.88 [-5.91, 0.15]
Genta 2009	20	95.2	4.8	15	101.9	2.4	HEH	-6.70 [-9.13, -4.27]
Ghavami 2019	23	96.28	8.03	23	93.68	9.98	⊢ ∎_1	2.60 [-2.63, 7.83]
Hiel 2020	51	-2.2	4.2	55	-2.6	4.1		0.40 [-1.18, 1.98]
Machado 2019	13	-4.93	1.35	13	-2.81	1.05		-2.12 [-3.05, -1.19]
Padilla-Camberos 2018	14	99	8.2	14	111.5	7.03	⊢ ∎→1	-12.50 [-18.16, -6.84]
Pol 2018	29	95.6	8.8	26	96.6	8.4	⊢⊷	-1.00 [-5.55, 3.55]
Reimer 2017	26	-0.8	5.61	27	-0.1	3.64	H	-0.70 [-3.26, 1.86]
Reimer 2017	22	-0.4	3.28	21	-0.7	4.12	Hart	0.30 [-1.93, 2.53]
Roshanrav an 2017	14	93.84	8.77	15	95.14	9.8	┝━━╋╧┥	-1.30 [-8.06, 5.46]
Roshanrav an 2017	15	98.5	8.42	15	95.41	12.14	⊢	3.09 [-4.39, 10.57]
Tripkovic 2015	10	105.12	6.28	10	105.89	7.4	⊢ <u>∔</u> ·	-0.77 [-6.79, 5.25]
Vaghef-Mehrabany 201	9 22	-7.07	5.47	23	-6.37	5.24	H a ri	-0.70 [-3.83, 2.43]
Wong 2010	23	89.5	2.3	23	89.1	2.2		0.40 [-0.90, 1.70]
Crovesy 2021	11	-1.8	1.96	10	-0.73	2.27		-1.07 [-2.89, 0.75]
Williams 2022	20	78.8	10.7	20	78.8	9.1	<u> </u>	0.00 [-6.16, 6.16]

RE Model for all studies:(Q = 55.18, df = 16, p < .01; I^2 = 78.0%, τ^2 = 5.27)

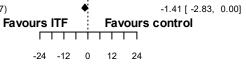




Figure 33: Forest plot displaying the effect of inulin-type fructans on waist-to-hip ratio

Study	TotalMear	ITF SD		Contro I Mean			MD [95% CI]
Daud 2014	12 0.88	0.069	10	0.83	0.095	⊢	0.05 [-0.02, 0.12]
Dehghan 2016	27 0.92	0.05	22	0.95	0.07	⊢ ∎ 1	-0.03 [-0.06, 0.00]
Dewulf 2013	15 -0.013	0.023	15	-0.004	0.032	⊢ ∎-1	-0.01 [-0.03, 0.01]
Ghavami 2019	23 0.9	0.08	23	0.87	0.05	I I	0.03 [-0.01, 0.07]
Hiel 2020	51 -0.01	0.04	55	0.01	0.03	HEN	-0.02 [-0.03, -0.01]
Machado 2019	13 0.86	0.01	13	0.88	0.01	•	-0.02 [-0.03, -0.01]
Padilla-Camberos 2018	14 0.885	0.088	14	0.9	0.064	⊢ • ÷ · ·	-0.02 [-0.07, 0.04]
Roshanrav an 2017	14 0.88	0.05	15	0.9	0.07		-0.02 [-0.06, 0.02]
Roshanrav an 2017	15 0.9	0.08	15	0.88	0.05	F	0.02 [-0.03, 0.07]
Vaghef-Mehrabany 2019	22 -0.03	0.034	23	-0.04	0.058	⊢æ -i	0.01 [-0.02, 0.04]
RE Model for all studies:	(Q = 16.	90, df =	= 9, p =	0.05; I ²	² = 51.3%, τ ² = 0.00) Fa	vours ITF Favours o	-0.01 [-0.02, 0.00] control
							.2
						Mean Difference	

Figure 34: Forest plot displaying the effect of inulin-type fructans on systolic blood pressure

Study T	otal	ITF Mean	SD	Total	Contro Mean	SD		MD [95% CI]
Bahmani 2016	25	-1.5	9.6	25	-6.4	9		4.90 [-0.26, 10.06]
Cronin 2016	99	136.8	21.7	100	133.3	26.8	⊢ <u>+</u> =ı	3.50 [-3.27, 10.27]
Dehghan 2016	27	121.67	6.65	22	134.21	13.97	⊢ ∎→1	-12.54 [-18.89, -6.19]
Gosmez-Reyes 2010	20	-3.9	0.64	20	0	0.17		-3.90 [-4.19, -3.61]
Hiel 2020	51	-4.2	13.1	55	-6.5	12.5	⊢∎→	2.30 [-2.58, 7.18]
Machado 2019	13	110.41	3.07	13	111.92	1.99		-1.51 [-3.50, 0.48]
Nishimura 2015	24	4.63	26.75	24	1.04	10.53	F I	3.59 [-7.91, 15.09]
Roshanrav an 2017	14	118.93	18.31	15	129	9.29	⊢ ■ →	-10.07 [-20.75, 0.61]
Roshanrav an 2017	15	133.33	22.49	15	128	22.34	H	5.33 [-10.71, 21.37]
Satoh 2013	29	136.37	3.49	27	134.04	2.71		2.33 [0.70, 3.96]
Tripkovic 2015	10	125.2	11.6	10	121.5	11.2	⊢┊■──┤	3.70 [-6.29, 13.69]
Vaghef-Mehrabany 2019	22	-7.5	12.7	23	-7.26	12	F	-0.24 [-7.47, 6.99]
Wong 2010	23	122	2.3	23	121.9	2.2	•	0.10 [-1.20, 1.40]
Williams 2022	20	116.3	1.9	20	112.9	9.9	₩₩ -1	3.40 [-1.02, 7.82]
Ziaei 2022	50	109.11	8.83	25	106	13.44	⊢ ∎1	3.11 [-2.70, 8.92]

Figure 35: Forest plot displaying the effect of inulin-type fructans on diastolic blood pressure

Study	Total	ITF Mean	SD	Total	Control Mean	SD	MD [95% CI]
Bahmani 2016	25	-0.5	6.7	25	-3.8	6.8	→ 3.30 [-0.44, 7.04]
Cronin 2016	99	83.1	12.2	100	82.6	11.2	0.50 [-2.75, 3.75]
Dehghan 2016	27	77.7	14.86	22	86.05	7.56	-8.35 [-14.78, -1.92]
Gosmez-Reyes 2010	20	-5.12	0.14	20	1.1	0.72	-6.22 [-6.54, -5.90]
Hiel 2020	51	-5.1	12.5	55	-1.9	10.2	-3.20 [-7.56, 1.16]
Machado 2019	13	67.25	11.21	13	66.53	5.19	0.72 [-6.00, 7.44]
Nishimura 2015	24	3.38	16.07	24	0.04	6.42	3.34 [-3.58, 10.26]
Roshanrav an 2017	14	73.57	6.63	15	78.33	8.38	-4.76 [-10.24, 0.72]
Roshanrav an 2017	15	79	8.7	15	80	8.45	-1.00 [-7.14, 5.14]
Tripkovic 2015	10	73.3	12.2	10	70.9	10.8	↓ 2.40 [-7.70, 12.50]
Vaghef-Mehrabany 20)19 22	-3.41	9.56	23	-4.78	9.47	⊢– 1.37 [-4.19, 6.93]
Wong 2010	23	75.8	1.4	23	75.8	1.5	0.00 [-0.84, 0.84]
Williams 2022	20	70.9	7.8	20	71.6	9.4	-0.70 [-6.05, 4.65]
Ziaei 2022	50	72.2	5.3	25	73.46	7.1	-1.26 [-4.41, 1.89]

RE Model for all studies: (Q = 246.66, df = 13, p < .01; I^2 = 88.3%, τ^2 = 7.56)

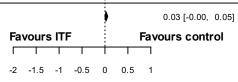
-1.28 [-3.18, 0.62] Favours ITFFavours control -15 -5 0 5 15

Mean Difference

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Aliasgharzadeh 2015	27	1.17	0.17	25	1.12	0.11	(=	0.05 [-0.03, 0.13]
Alles 1999	20	1.09	0.09	20	1.09	0.25	HŧH	0.00 [-0.12, 0.12]
Blaedel 2016	20	1.1	0.18	19	1.1	0.17	I ≜ I	0.00 [-0.11, 0.11]
Bonsu 2012	12	1.2	0.3	14	1.2	0.3	⊢•́-1	0.00 [-0.23, 0.23]
Buddington 2017	45	1.44	0.38	43	1.41	0.33	⊢∎-I	0.03 [-0.12, 0.18]
Castro-Sanchez 2016	16	0.06	0.1	16	-0.03	0.11	j=i	0.09 [0.02, 0.16]
Causey 2000	12	0.92	0.2	12	0.95	0.26	⊢ i i	-0.03 [-0.22, 0.16]
Chambers 2019	12	1.6	0.35	12	1.5	0.35	⊢⊷⊣	0.10 [-0.18, 0.38]
Clarke 2016	30	1.5	0.55	30	1.5	0.55	⊢ • −1	0.00 [-0.28, 0.28]
Daud 2014	12	1.4	0.35	10	1.1	0.32	┝━━┥	0.30 [0.02, 0.58]
Davidson 1998	21	0	0.04	21	0.11	0.04		-0.11 [-0.13, -0.09]
Dehghan 2016	27	1.21	0.2	22	1.12	0.11		0.09 [0.00, 0.18]
Dewulf 2013	15	-0.03	0.09	15	-0.03	0.14	I ,	0.00 [-0.08, 0.08]
Forcheron 2007	9	1.47	0.33	8	1.13	0.28	} ↓	0.34 [0.05, 0.63]
Genta 2009	20	1.48	0.33	15	1.3	0.3	⊢ 1	0.18 [-0.03, 0.39]
Ghavami 2019	23	1.11	0.24	23	1.09	0.24	⊦⊷⊣	0.02 [-0.12, 0.16]
Giacco 2004	27	1.29	0.34	27	1.32	0.39	⊢⊷⊣	-0.03 [-0.23, 0.17]
Gosmez-Rey es 2010	20	0.07	0.02	20	0	0.01		0.07 [0.06, 0.08]
Hiel 2020	51	-0.03	0.14	55	0.01	0.18	H,	-0.04 [-0.10, 0.02]
Jackson 1999	27	1.31	0.33	27	1.31	0.39	H+H	0.00 [-0.19, 0.19]
Letexier 2003	8	1.31	0.28	8	1.2	0.31	⊢1	0.11 [-0.18, 0.40]
Luo 2000	10	1.02	0.25	10	1.01	0.19	⊢ -1	0.01 [-0.18, 0.20]
Luo 1996	12	0.97	0.17	12	1.05	0.21	⊢ ∎-1	-0.08 [-0.23, 0.07]
Machado 2019	13	1.27	0.32	13	1.32	0.29	⊢⊷⊣	-0.05 [-0.28, 0.18]
Nishimura 2015	24	-0.01	0.14	24	0.01	0.19	Heit	-0.02 [-0.11, 0.07]
Padilla-Camberos 2018	14	1.23	0.3	14	1.12	0.27	l÷∎-1	0.11 [-0.10, 0.32]
Pedersen 1997	64	1.38	0.3	64	1.37	0.3	I=I	0.01 [-0.09, 0.11]
Rajkumar 2015	15	1.27	0.24	15	1.16	0.17	¦= -I	0.11 [-0.04, 0.26]
Roshanrav an 2017	14	1.18	0.27	15	0.88	0.17	┝╼┤	0.30 [0.13, 0.47]
Roshanrav an 2017	15	1.03	0.23	15	1.03	0.22	F≢-I	0.00 [-0.16, 0.16]
Russo 2010	15	1.35	0.32	15	1.16	0.22	┝╼┥	0.19 [-0.01, 0.39]
Satoh 2013	29	1.53	0.04	27	1.59	0.1	H.	-0.06 [-0.10, -0.02]
Scheid 2014	37	1.34	0.34	35	1.31	0.21	HH	0.03 [-0.10, 0.16]
Shakeri 2014	24	0.06	0.18	24	0.06	0.21	F≢-I	0.00 [-0.11, 0.11]
Sorensen 2010	12	1.7	0.6	12	1.9	0.7	⊢ • ÷ −1	-0.20 [-0.72, 0.32]
Tov ar 2012	30	0	0.17	29	-0.09	0.17	 =1	0.09 [0.00, 0.18]
Tov ar 2012	23	-0.09	0.17	28	-0.09	0.17	l e l	0.00 [-0.09, 0.09]
Tripkovic 2015	10	1.24	0.29	10	1.17	0.25	⊢₋	0.07 [-0.17, 0.31]
Vaghef-Mehrabany 2019	22	-0.13	0.18	23	-0.04	0.16	(=)	-0.09 [-0.19, 0.01]
Vandokkum 1999	24	1.15	0.21	12	1.14	0.22	H#H	0.01 [-0.14, 0.16]
Wong 2010	23	0.02	0.02	23	-0.03	0.02		0.05 [0.04, 0.06]
Williams 2022	20	1.5	0.3	20	1.4	0.4	F∔∎-1	0.10 [-0.12, 0.32]

Figure 36: Forest plot displaying the effect of inulin-type fructans on high-density lipoprotein

RE Model for all studies: (Q = 260.73, df = 41, p < .01; I^2 = 82.4%, τ^2 = 0.00)



Mean Difference

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Figure 37: Forest plot displaying the effect of inulin-type fructans on very low-density lipoprotein

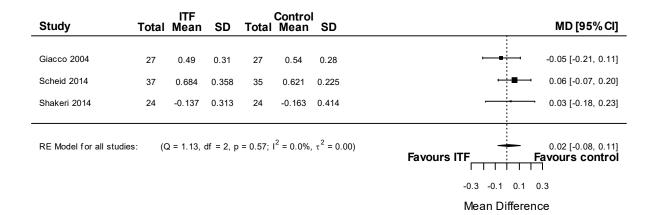
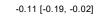


Figure 38: Forest plot displaying the effect of inulin-type fructans on total cholesterol

Study	Total	ITF Mean	SD	Total	Control Mean	SD		MD [95% CI]
Aliasgharzadeh 2015	27	4.53	0.94	25	5.25	1.18	⊢ •−4	-0.72 [-1.30, -0.14]
Alles 1999	20	6.21	0.43	20	6.01	1.18	⊢÷∎{	0.20 [-0.35, 0.75]
Blaedel 2016	20	4.4	0.45	19	4.3	0.44	F ≡ -1	0.10 [-0.18, 0.38]
Bonsu 2012	12	4.2	1	14	4.5	1.2	⊢ • ÷ · I	-0.30 [-1.15, 0.55]
Buddington 2017	45	4.52	1.01	43	4.77	1	• i l	-0.25 [-0.67, 0.17]
Castro-Sanchez 2016	16	5.59	1.09	16	5.08	1.09	⊢ • – 1	0.51 [-0.25, 1.27]
Causey 2000	12	5.7	0.82	12	5.9	0.96	⊢	-0.20 [-0.91, 0.51]
Chambers 2019	12	5.3	0.69	12	5.2	1.04	⊢-=1	0.10 [-0.61, 0.81]
Clarke 2016	30	4.7	0.55	30	4.5	0.55	⊨ =1	0.20 [-0.08, 0.48]
Cronin 2016	99	4.5	1	100	4.8	2	⊢≖∔	-0.30 [-0.74, 0.14]
Daud 2014	12	5.2	0.69	10	4.7	0.95	H <u>+</u> − − 1	0.50 [-0.21, 1.21]
Davidson 1998	21	-0.08	0.06	21	0.44	0.06		-0.52 [-0.56, -0.48]
Dehghan 2016	27	4.61	0.96	22	5.28	1.12	┝━━━┥╡	-0.67 [-1.26, -0.08]
Dewulf 2013	15	-0.18	0.42	15	0.05	0.75	⊢≖∔	-0.23 [-0.67, 0.21]
Forcheron 2007	9	4.14	0.48	8	3.73	0.45	<u>⊢</u> ∎-1	0.41 [-0.03, 0.85]
Genta 2009	20	5.17	0.97	15	5.2	1.07	⊢ ∔ – I	-0.03 [-0.72, 0.66]
Ghavami 2019	23	4.61	1.42	23	4.56	0.8		0.05 [-0.62, 0.72]
Gosmez-Reyes 2010	20	-0.05	0.03	20	0.18	0.04		-0.23 [-0.25, -0.21]
Hiel 2020	51	-0.13	0.68	55	-0.09	0.51	I 🖬	-0.04 [-0.27, 0.19]
Jackson 1999	27	5.9	0.97	27	6.46	0.91	⊢•-€	-0.56 [-1.06, -0.06]
Letexier 2003	8	4.35	0.85	8	4.12	0.91	⊢÷I	0.23 [-0.63, 1.09]
Luo 2000	10	5.13	0.85	10	5.15	0.44	⊢	-0.02 [-0.61, 0.57]
Luo 1996	12	3.96	0.76	12	3.91	0.59	⊢ ∔ -1	0.05 [-0.49, 0.59]
Machado 2019	13	4.5	0.69	13	4.93	0.97	⊢⊷∔	-0.43 [-1.08, 0.22]
Nishimura 2015	24	0.02	0.49	24	-0.01	0.46	I∳-I	0.03 [-0.24, 0.30]
Padilla-Camberos 2018	14	4.83	0.86	14	5.14	0.78	⊢∎∔∣	-0.31 [-0.92, 0.30]
Pedersen 1997	64	4.24	0.75	64	4.25	0.63	F∳I	-0.01 [-0.25, 0.23]
Rajkumar 2015	15	3.23	0.21	15	3.33	0.14	H.	-0.10 [-0.23, 0.03]
Roshanrav an 2017	14	4.75	0.98	15	4.16	0.82	, F−−−−1	0.59 [-0.07, 1.25]
Roshanrav an 2017	15	4.2	1.19	15	4.41	0.75	⊢₋∔₋₁	-0.21 [-0.92, 0.50]
Russo 2010	15	4.05	0.81	15	4.45	0.88	⊢∎∔∣	-0.40 [-1.01, 0.21]
Scheid 2014	37	4.98	0.9	35	5	0.76	⊦÷-1	-0.02 [-0.40, 0.36]
Shakeri 2014	24	-0.27	1.09	24	-0.41	1.13		0.14 [-0.49, 0.77]
Sorensen 2010	12	4.9	1.1	12	5.3	1.1	⊢≖∔⊣	-0.40 [-1.28, 0.48]
Tov ar 2012	30	0.06	0.62	29	0.08	0.62	⊦÷-1	-0.02 [-0.34, 0.30]
Tov ar 2012	23	-0.17	0.62	28	-0.01	0.62	⊢≕∔	-0.16 [-0.50, 0.18]
Tripkovic 2015	10	5.15	0.77	10	4.97	0.63	⊢ ∔∎−−1	0.18 [-0.44, 0.80]
Vaghef-Mehrabany 2019	22	-0.28	0.56	23	-0.13	0.95	⊢₌⊣	-0.15 [-0.60, 0.30]
Vandokkum 1999	24	4.51	0.58	12	4.56	0.62	⊢⊷⊣	-0.05 [-0.47, 0.37]
Wong 2010	23	-0.23	0.12	23	-0.18	0.06		-0.05 [-0.10, 0.00]
Williams 2022	20	4.3	0.7	20	4.9	0.8	┝╌ब╌┤	-0.60 [-1.07, -0.13]

RE Model for all studies: (Q = 344.26, df = 40, p < .01; l^2 = 85.6%, τ^2 = 0.03)



Favours ITF Favours control

-3 -2 -1 0 1

Mean Difference

Figure 39: Forest plot displaying the effect of inulin-type fructans on apolipoprotein A1

Study	ITF Control TotaMean SD TotaMean SD	MD [95% CI]
Causey 2000	12 1.06 0.336 12 1.099 0.379	-0.04 [-0.33, 0.25]
Jackson 1999	27 1.165 0.211 27 1.222 0.236	-0.06 [-0.18, 0.06]
Jing 2000	10 1.51 0.253 10 1.52 0.19	-0.01 [-0.21, 0.19]
Luo 1996	12 1.5 0.242 12 1.5 0.173	0.00 [-0.17, 0.17]
Vandokkum 1999	24 2.065 0.966 12 1.26 0.13	► 0.80 [0.41, 1.20]
Wong 2010	23 -0.02 0.02 23 -0.018 0.024	-0.00 [-0.01, 0.01]
RE Model for all studies:	(Q = 17.05, df = 5, p < .01; I^2 = 91.6%, τ^2 = 0. Fav	.05) 0.07 [-0.12, 0.27] ours ITF Favours control
		-0.1 0 0.1 0.2
		Mean Difference

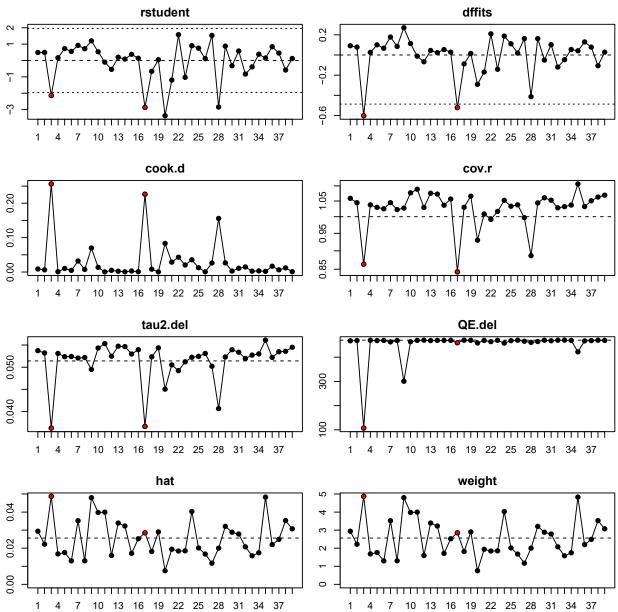
Figure 40: Forest plot displaying the effect of inulin-type fructans on apolipoprotein B

Study	Total	ITF Mean	SD	Total	Control Mean	SD						MD	[95% Cl]
Causey 2000	12	1.045	0.347	12	1.133	0.382						0-1 00 0-	.38, 0.20
Jackson 1999	27	0.869	0.142	27	1.165	0.211		-					.39, -0.20
Jing 2000	10	1.27	0.126	10	1.31	0.19		H				-	.18, 0.10
Luo 1996	12	0.82	0.277	12	0.79	0.139		-				0.03 [-0	.15, 0.21
Vandokkum 1999	24	2.885	1.718	12	0.93	0.14			F			1.95 [1	.26, 2.65
Wong 2010	23	-0.064	0.022	23	-0.05	0.015		,				-0.01 [-0	.02, -0.00
RE Model for all stu	dies: (C	Q = 64.59,	df = 5, p	o < .01; l ²	² = 99.4%, Favo	$\tau^2 = 0.51$)		_	Favo	ours co		.38, 0.79
								Ì	1	1	I		
					-3	-2	-1	0	1	2	3	4	
							Ν	lean Di	ifferenc	e			

Figure 41: Forest plot displaying the effect of inulin-type fructans on hemoglobin A1c (HbA1c).

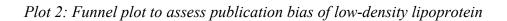
		ITF			Control			
Study	Total	Mean	SD	Total	Mean	SD		MD [95% CI]
Bonsu 2012	12	7.3	1.5	14	7.1	1.2	H=1	0.20 [-0.86, 1.26]
Chambers 2019	12	5.473	7.967	12	5.473	7.967	⊢	0.00 [-6.37, 6.37]
Dehgahn 2014	27	-0.6	0.506	25	0.1	0.606		-0.70 [-1.00, -0.40]
Dehghan 2016	27	7.74	0.75	22	8.43	1.06	-	-0.69 [-1.22, -0.16]
Dewulf 2013	15	0	0.181	15	0	0.181		0.00 [-0.13, 0.13]
Ghavami 2019	23	7.62	1.85	23	7.79	1.29	+++	-0.17 [-1.09, 0.75]
Hiel 2020	51	0	0.2	55	-0.2	1		0.20 [-0.07, 0.47]
Jing 2000	10	7.52	1.455	10	7.35	1.391	H-1	0.17 [-1.08, 1.42]
Nishimura 2015	24	-0.09	0.049	24	-0.03	0.049		-0.06 [-0.09, -0.03]
Roshanrav an 2017	14	8.579	4	15	8.041	3.4	 -1	0.54 [-2.17, 3.25]
Roshanrav an 2017	15	8.086	4.2	15	7.235	3.4	⊢ − − 1	0.85 [-1.88, 3.59]
Russo 2010	15	4.975	0.374	15	4.975	0.316		0.00 [-0.25, 0.25]
Sorensen 2010	12	5.9	0.2	12	5.9	0.2	•	0.00 [-0.16, 0.16]
RE Model for all studies:	(Q = 28.6	64, df = 12,	p < .01; I ²	= 85.0%, τ ²	² = 0.06)	F	avours ITF Favou	-0.11 [-0.31, 0.09] Irs control
							-8 -4 0 4 8	
							Mean Difference	

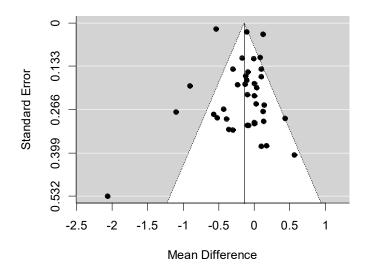
Supplementary plots

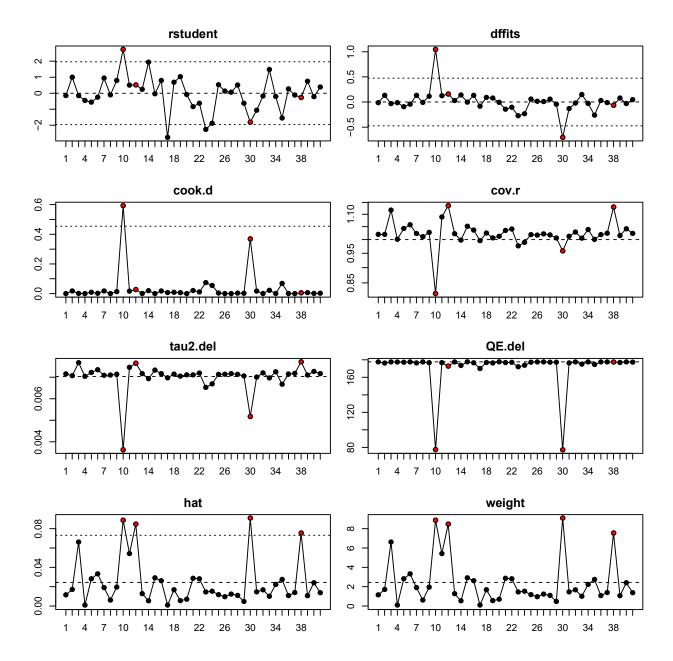


Plot 1: Influence and outlier plots for LDL-C

rstudent: studentized residuals, **dffits:** difference in fits, and **cook.d:** Cook's distance, cov.r: covariance ratio, **tau2.del:** leave-one-out estimates of the amount of heterogeneity, **QE.del** leave-one-out values of the test statistics for heterogeneity

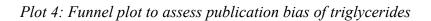


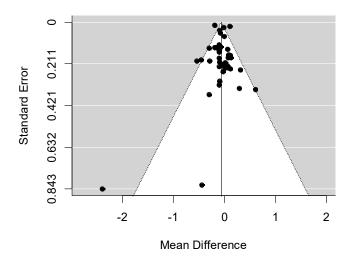


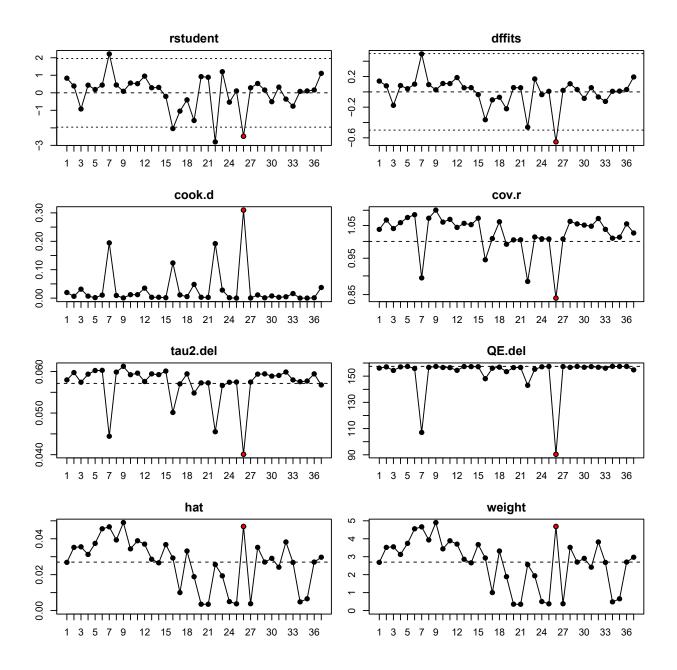


Plot 3: Influence and outlier plots for triglycerides

rstudent: studentized residuals, **dffits:** difference in fits, and **cook.d:** Cook's distance, cov.r: covariance ratio, **tau2.del:** leave-one-out estimates of the amount of heterogeneity, **QE.del** leave-one-out values of the test statistics for heterogeneity

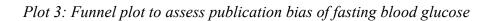


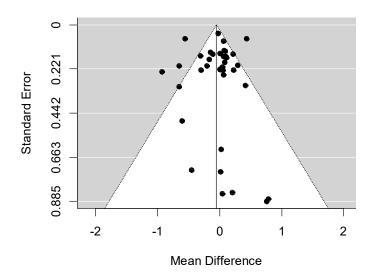




Plot 5: Influence and outlier plots for fasting blood glucose

rstudent: studentized residuals, **dffits:** difference in fits, and **cook.d:** Cook's distance, cov.r: covariance ratio, **tau2.del:** leave-one-out estimates of the amount of heterogeneity, **QE.del** leave-one-out values of the test statistics for heterogeneity





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Chapter 4: Assessment of the quality of reporting in abstracts of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey

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Assessment of the quality of reporting in abstracts of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey

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Abstract

Introduction

Sufficiently detailed reporting in the abstracts of randomized controlled trials (RCTs) is essential to judge the validity and applicability of RCTs. We assessed the reporting quality of RCT abstracts examining the effects of inulin-type fructans supplementation on cardiovascular risk factors, before and after the publication of the Consolidated Standards of Reporting Trials extension for abstracts (CONSORT-A) in 2008.

Methods

MEDLINE, EMBASE, Emcare, AMED, the Cochrane Library and CINAHL were searched for RCTs from inception to May 15, 2022, including the reference lists of selected RCTs. We screened titles and abstracts and extracted the data independently and in duplicate. We included RCTs that investigated the effects of inulin-type fructans on cardiovascular disease risk factors (e.g., low-density lipoprotein cholesterol, triglycerides, fasting blood glucose) in adults (18 years or older). The primary outcomes of this study were: the overall reporting quality of abstracts (defined as the total number of items [0 to 15] present from the CONSORT-A checklist reported in each abstract) published before and after CONSORT-A; and the study characteristics (e.g., sample size, significance of primary outcome) predictive of the CONSORT-A score. The secondary outcome was the frequency in the reporting of each CONSORT-A item before and after CONSORT-A publication. A t-test was used to estimate the mean difference in the total number of reported items in studies published before and after CONSORT-A and Poisson regression was used to explore the factors associated with the overall reporting quality of the

abstracts. We used Fisher's exact test to compare the adherence to each of the 15 items before and after CONSORT-A publication.

Results

We included 55 RCTs from 1,767 reports. Overall, the mean number of adequately reported items before the publication of CONSORT-A was 3.91 (standard deviation, [SD] 0.94) and 4.64 (SD 1.38) after. The unadjusted mean difference of 0.73 (95% CI -1.61 to 0.16) indicates that the reporting quality was not different between these two periods. We did not identify any factors associated with better quality of reporting. Studies published after the release of the CONSORT-A extension were more likely to report titles identifying them as RCTs (odds ratio [OR], 95% confidence interval [CI], not estimable [NE], p = 0.001), the number randomized (OR, 95% CI, NE, p = 0.004) and trial registration (OR, 95% CI, NE, p=0.048) but were less likely to report trial design (OR 0.12, 95% CI 0.01 to 0.68, p = 0.006) after publication of CONSORT-A.

Conclusion

Our study found a suboptimal improvement in overall reporting quality of abstracts of RCTs investigating the effects of inulin-type fructans on cardiovascular risk factors. A collaborative approach from authors, reviewers, and journal editors are needed to improve the reporting quality of RCT abstracts.

Keywords: systematic survey, CONSORT for abstract, quality of reporting, methodological study, systematic review

Abstract word count: 443

Full-text word count: 2,710

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Background

Randomized controlled trials (RCTs) are the gold standard to assess the effectiveness of health interventions (1-3). A well-conducted RCT can transform patient care. However, the reporting of the study design, conduct, analysis, and interpretation of a published RCT must be transparent and sufficiently detailed. This allows readers and practitioners to appropriately judge the validity of the trial design and conduct, as well as the applicability of the trial results to particular practice settings (4). This is hampered by inadequate trial reporting (5), which can lead to a biased estimate of the treatment effect, leading physicians to avoid truly effective treatments or promote truly ineffective treatments (6). The Consolidated Standards of Reporting Trials (CONSORT) statement intends to facilitate improved and transparent reporting of trials by authors (7).

Clinicians often make treatment decisions based on the abstracts of research articles (5, 8-10) because of time limitations, language barriers, or inaccessibility in accessing the full report (11). If the abstract of a trial is not transparent and sufficiently detailed, then it is difficult to judge the validity and generalizability of the trial (5), and the result of such an abstract can mislead the use of trial results (10). For these reasons, authors should provide sufficient information in an abstract to make it useful to the readers as a stand-alone item.

Most medical research journals introduced structured abstracts in the 1980s, but there is limited guidance for a uniform structure for a trial abstract (5). The CONSORT extension for abstracts (CONSORT-A) was published in 2008 to address this limitation (5, 9). It was intended to ensure that an abstract provides a minimum list of key details about an RCT (5). The CONSORT-A contains 15 items that cover seven domains: the title, trial design, methods (participants, interventions, objective, outcomes, randomization, blinding), results (numbers randomized,

numbers analyzed, outcome, harms), conclusions, trial registration, and funding. The CONSORT-A for conference abstracts contains two additional domains: 'authors' (contact details for the corresponding author) and 'recruitment' (trial status) (5, 9).

A scoping review by Samaan et al. 2013 (12) included systematic reviews of RCTs that assessed the adherence to one of the six reporting guidelines: Consolidated Standards of Reporting Trials (CONSORT), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Quality of Reporting of Meta-analysis (QUOROM), Transparent Reporting of Evaluations with Nonrandomized Designs (TREND), Meta-analysis Of Observational Studies in Epidemiology (MOOSE), and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE), and identified the key factors associated with better adherence to these guidelines since the publication of CONSORT in 1996. The review reported suboptimal adherence to listed guidelines. The factors associated with better adherence to guidelines included journal impact factor, endorsement of guidelines, multisite studies, funding source, publication date, pharmacological interventions and large sample size. A systematic review by Song et al. 2017 (13) assessing reporting quality of CONSORT-A in psychiatry journals also reported similar determinants of better adherence to CONSORT-A.

After the publication of CONSORT-A, many studies identified poor adherence to CONSORT-A in general medical journals (14), in medical specialties (e.g., anesthesia (15), psychiatry (13)), in a specific patient population (e.g., patients with COVID-19 (16)) or specific interventions (e.g., COVID-19 interventions (17)). To our knowledge, no studies have assessed the role of CONSORT-A in improving the quality of reporting of abstract in nutrition trials, specifically in inulin-type fructans (ITF) supplementation trials. Inulin-type fructans (e.g., fructo-

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oligosaccharides, oligofructose and inulin) are soluble dietary fibers known as prebiotics (18), which confer various cardiometabolic health effects (19).

The objectives of this study were to 1) assess the overall reporting quality in abstracts of RCTs investigating inulin-type fructans supplementation on cardiovascular disease risk factors before and after the publication of CONSORT-A; 2) assess the factors that predict the overall reporting quality; and 3) assess the reporting of each item during each period.

Methods

Study design

We conducted a systematic survey of the literature with a comparison of mean, and domainspecific CONSORT-A scores, before and after the publication of CONSORT-A (before 2008 and 2008 or later respectively) (20). We established the methods of the study *a priori* and published the protocol (21).

Data sources and study selection

We used a comprehensive search strategy developed by a librarian (LB) (see "Supplementary materials") to search for RCTs in MEDLINE, EMBASE, Emcare, AMED, the Cochrane Library, and CINAHL from inception to May 15, 2022, without language restrictions. We searched reference lists of included RCTs to identify additional reports. The detailed inclusion criteria for this study can be found in the published protocol (21). We included RCTs that investigated the effects of inulin-type fructans (ITF) on CVD risk factors (e.g., low-density lipoprotein cholesterol, triglycerides, fasting blood glucose) in adults (18 years or older). We excluded RCTs if they only reported postprandial effects of ITF or involved participants with conditions or undergoing treatment that seriously alters normal digestion or absorption of nutrients (e.g., chemotherapy, dialysis, liver disease). We also excluded RCTs that included pregnant or lactating participants.

Reviewers working in pairs (from JRT, AG, FH, LH, AC, HH, CS) screened the titles, abstracts and assessed the eligibility of full-texts independently and in duplicate. They resolved disagreements through discussion or consultation with a third reviewer (RJdS).

Data extraction

We extracted study characteristics, including the name of the journal, publication year, journals' impact factors, funding source(s), journal endorsement of the CONSORT statement, significance of the results of primary outcome, and sample size. We considered the first reported outcome as the primary outcome if the authors did not clearly define a primary outcome in the report. Among the 17 items in the CONSORT-A checklist, we extracted data related to the adherence to 15 items, as two items, 'and 'recruitment', are only applicable to conference abstracts. Pairs of reviewers (from JRT, AG, FH, LH, AC, HH, CS) underwent calibration exercises, then extracted data independently and in duplicate and resolved any disagreements through discussion or consultation with a third reviewer (RJdS).

Outcomes

The primary outcomes of this study were 1) the overall reporting quality of abstracts of RCTs based on adherence to the CONSORT-A checklist and 2) the factors associated with reporting quality. The overall reporting quality was defined as the number of items reported out of 15 items of the CONSORT-A checklist. The secondary outcome was the frequency of reporting of each item listed on the CONSORT-A checklist.

Statistical analyses

We reported study characteristics descriptively. Fisher's exact test was conducted to compare the proportion of adherence to the reporting of each of the 15 items before and after publication of CONSORT-A. Unadjusted odds ratio (OR) with 95% confidence interval (CI) were reported. We did not use chi-square test for this analysis as planned in the protocol as most of the cells had expected frequencies < 5 (22). We used Student's t-test (unpaired) to compare the mean

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difference in the number of items reported before and after CONSORT-A periods. Mean differences and 95% CIs are reported. Poisson regression was used to explore the factors associated with reporting quality. Following previous published literature (23-25), we adjusted the Poisson regression model for study publication year (before or after the publication of CONSORT-A), endorsement of the CONSORT statement by the journal (whether there are specific instructions for the authors to follow the CONSORT statement or not), journal impact factor (as a continuous variable), the statistical significance of the primary outcome (significant vs non-significant), funding status (industry-funded vs others) and sample size ($\leq 100 \text{ vs} > 100$). We hypothesized that there was an association between these factors and overall reporting quality of abstracts. The Poisson regression results was reported as incidence rate ratio (IRR) with 95% CI (26). The IRR is obtained by exponentiating the Poisson regression coefficient (27). The IRR could be interpreted similarly as odds ratio. For example, IRR 1.21 indicates that reporting quality in abstracts published before CONSORT-A is 1.21 times better than the reporting quality in abstracts published after CONSORT-A (28). We set the statistical significance at $\alpha = 0.05$. We used residual deviance to understand goodness-of-fit of the overall Poisson regression model. We compared the adjusted model with unadjusted model with Akaike information criterion (AIC). A lower value of AIC indicates better fit. We analyzed the data with R version 4.0.3 (29).

Results

Study Characteristics

We identified 1,767 citations from the database and reference search; 55 reports (see "Supplementary materials") met our eligibility criteria. Among these 55 articles, 11 were published before and 44 were published after the publication of CONSORT-A (**Figure 1**). Most of the studies reported statistically significant primary outcomes (67%), had \leq 100 samples (91%), endorsed CONSORT statement (73%) and mean (SD) impact factor was 4.95 (4.00) (**Table 1**).

The overall reporting quality in abstracts of randomized controlled trials

The mean number of items reported before and after the publication of CONSORT-A was 3.91 (SD 0.94) and 4.64 (SD 1.38) respectively. There was no statistically significant difference in the number of items reported before and after publication of CONSORT-A, unadjusted mean difference (MD) 0.73 (95% CI -1.61 to 0.16, p = 0.11).

Table 2 presents adjusted IRR for the total number of reported CONSORT-A items. We found that none of the adjusted covariates (e.g., publication year, CONSORT-A endorsement status, statistically significant results) was significantly associated with reporting more CONSORT-A items (p > 0.05). For example, IRR was 1.15 (95% CI 0.79 to 1.67) for the articles published after the publication of CONSORT-A. For the unadjusted model, the IRR was 1.19 (95% CI 0.85 to 1.65) for the same period. The unadjusted model (AIC: 208) was slightly better fit compared to adjusted model (AIC: 217).

Reporting of each item of the CONSORT-A checklist

We found statistically significant improvement in completeness of reporting in abstracts of RCTs for 3 out of 15 items after the publication of CONSORT-A (2008 and later) compared to before (2008). After publication of CONSORT-A, more abstracts could be identified as RCTs from title (OR and 95% CI not estimable [NE], p = 0.001), provided information on number of participants randomized to each group (OR and 95% CI NE, p = 0.004) and trial registration information (OR and 95% CI NE, p=0.048). However, fewer abstracts reported on trial design (OR 0.12, 95% CI 0.01 to 0.68, p = 0.006) after publication of CONSORT-A compared to before. The remaining items were reported similarly irrespective of CONSORT-A publication period. None of the 44 studies published after CONSORT-A reported eligibility criteria and study setting or provided information on blinding (masking) and sources of funding (**Table 3**). We could not estimate ORs and 95% CIs for some of the items because either none or all the studies reported the specific items when we grouped them by CONSORT-A publication periods.

Discussion

Main findings

This study provides a systematic evaluation of the quality of reporting in abstracts of RCTs by comparing studies published before and after the publication of CONSORT-A. For this study, we only considered RCTs that investigated the effects of inulin-type fructans (ITF) on CVD risk factors (e.g., low-density lipoprotein cholesterol, triglycerides, fasting blood glucose) in adults (18 years or older). We did not identify significant improvements in the overall reporting quality in abstracts of RCTs after the publication of CONSORT-A. We also did not identify any factors that predicted improved reporting quality.

Although we found that more abstracts adhered to the CONSORT-A checklist in identifying itself as an RCT in the title, reported the number of patients randomized, and reported the trial registration, fewer abstracts specified the trial design after the publication of CONSORT-A in 2008. Drafting the titles and abstracts accurately is important in that they provide initial impressions of a research paper. Most readers will read only the title and abstract of a research paper and only a few will read the full paper if they find it interesting (30). Moreover, identifying a relevant report in an electronic database largely depends on how it was indexed (20). The electronic databases and search engines retrieve research papers based on the keywords used in the titles and abstracts (30). Thus, it would be difficult to identify an RCT if the authors do not specify it as an RCT in the title (20). In abstracts, it is essential to report the number of participants randomized to each group, which can be used by the readers to understand whether all participants were included in the data analysis (20). Identifying the trial registration is also essential to minimize selective reporting of outcomes and to avoid the inclusion of results from multiple papers published on the same trial when conducting meta-analyses (20). Specifying the

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trial design (e.g., parallel group, crossover) is very important for appropriate indexing of trial in electronic databases. Moreover, if the design of a trial is not reported properly then readers might misinterpret a small sample size as the total number of participants randomized in the trial instead of the number of clusters in a cluster randomized controlled trial (20). We also found that among the 44 RCTs published after CONSORT-A, none of them reported the participant eligibility criteria, the nature of the blinding, nor the study funding, which are required for transparent reporting of a trial (20). Even after publication of CONSORT-A, none of the articles adhere the CONSORT-A checklist completely.

Relation to previous work

We did not identify any systematic survey that assessed the reporting quality in abstracts of RCTs examining the effects of ITF supplementation on CVD risk factors in adults. However, we identified a few studies assessing reporting quality in other fields. For example, a study by Sriganesh et al. (25) assessed the quality of abstracts of RCTs (based on 17-item CONSORT-A) in the top five pain journals and reported a similar mean (SD) number of items reported pre-CONSORT-A 6.12 (1.59) and post-CONSORT-A 7.06 (1.93) periods. Speich et al. (31) assessed the quality of abstracts for surgical RCTs (based on 15-item CONSORT-A) and found similar trends in reporting the mean number of items during pre-CONSORT-A (mean 6.14, SD 0.47) and post-CONSORT-A (mean 8.11, SD 0.55) periods. Similarly, Germini et al. (23) assessed the quality of reporting in abstracts of RCTs published in emergency medicine journals reported mean (SD) number of items was 6.4 (1.9) and 6.9 (1.8) in pre and post-CONSORT-A periods. The previous published paper indicate that publication of CONSORT-A did not affect reporting quality in other fields as it did not also in our study area.

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Limitations of the study

Our study has several limitations. This study required making subjective judgements to score the items as reported or not. To minimize this limitation, we provided detailed instructions to the data extractors and conducted piloting and calibration exercise. Quality of reporting in abstracts could be influenced by various factors other than adherence to CONSORT-A that we did not consider. For example, following a mandatory structure suggested by the journals or specific requirements by the funding agencies can lead to incomplete reporting. We followed published literature (23, 25) to adjust the factors that might influence incomplete reporting in abstracts. Another limitation of our study is that we defined CONSORT endorsement as whether the journal had endorsed CONSORT as of June 2022 as year of CONSORT enforcement is not available from the journal websites. We also used journal impact factors at present time (until June 2022), rather than at time of publication.

Implications

Our study presents a snapshot of the current practice of reporting in abstracts of RCTs of inulintype fructans supplementation to researchers, reviewers, and editors of journals. We highlight the well-reported and under-reported CONSORT-A items. Our study reveals suboptimal improvement in reporting of CONSORT-A items even after publication of CONSORT-A. There was improvement in reporting of only 20% of items. Almost all the studies published after CONSORT-A did not report important methodological details (e.g., randomization, blinding), which could lead to a biased reporting of treatment estimates (32). Considering the importance of reporting all the CONSORT-A items, a collaborating approach from authors, reviewers, and journal editors is needed to improve the transparent reporting of RCT abstracts.

Conclusion

Our study found a suboptimal improvement in overall reporting quality of abstracts of RCTs investigating the effects of inulin-type fructans on cardiovascular risk factors. A collaborative approach from authors, reviewers, and journal editors is needed to improve reporting quality of RCT abstracts.

Abbreviations

AIC = Akaike information criterion CONSORT = Consolidated Standards of Reporting Trials CONSORT-A = The CONSORT extension for abstract CVD = Cardiovascular disease IRR = Incidence rate ratio ITF = Inulin-type fructans MD = Mean difference RCT = Randomized controlled trial SD = Standard deviation

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Contributors

JRT, RJdS and LM conceptualized the study. JRT analyzed and drafted the manuscript. RJdS is the guarantor of the study.

Funding

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Competing interests

None

Patient and public involvement

We did not involve any patients or community people in this study.

Data sharing

The review was conducted using already published data. Data is available upon reasonable request.

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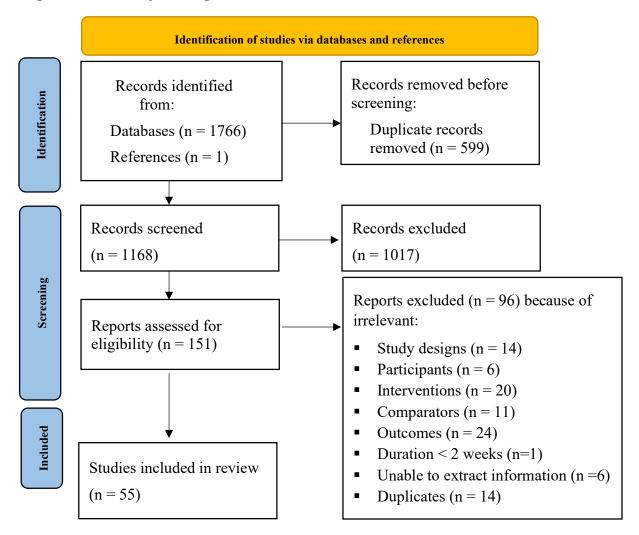
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Figures

Figure 1. PRISMA flow diagram



Flow of studies through the systematic search, assessment of eligibility and inclusion into the review (1)

Reference:

1. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

Tables

0				
	Pre-CONSORT-A Until 2007 (n = 11)	Post-CONSORT-A 2008 - 2022 (n = 44)	Total $n = 55$	
Characteristics	n (%)	n (%)	n (%)	
Statistically significant results				
Yes	5 (45)	32 (73)	37 (67)	
No	6 (55)	12 (27)	18 (33)	
Sample size				
≤100	11 (100)	39 (89)	50 (91)	
>100	0 (0)	5 (11)	5 (9)	
Funding				
Industry	4 (36)	10 (23)	14 (25.50)	
Others	2 (18)	25 (57)	27 (49)	
No information	5 (46)	9 (20)	14 (25.50)	
CONSORT endorsement				
Yes	NA	40 (73)	40 (73)	
No	NA	15 (27)	15 (27)	
Journal's impact factor Mean (SD)	5.4 (2.0)	4.8 (4.4)	4.95 (4.00)	

Table1: Characteristics of trials by period of publication

CONSORT-A = Consolidated Standards of Reporting Trials extension for abstracts; IQR = interquartile range; NA = not applicable

	IRR (95% CI)	p-value
Intercept	3.96 (2.45 to 6.42)	< 0.001
CONSORT-A		
Pre (reference)		
Post	1.15 (0.79 to 1.67)	0.46
Endorsement of CONSORT by journal		
No (reference)		
Yes	0.96 (0.71 to 1.29)	0.78
Results statistically significant		
No (reference)		
Yes	1.15 (0.86 to 1.53)	0.34
Funding source		
Industry (reference)		
Other than industry	0.94 (0.68 to 1.32)	0.73
No information	0.94 (0.65 to 1.36)	0.75
Sample size		
≤ 100 (reference)		
>100	0.87 (0.54 to 1.4)	0.57

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IRR = Incidence rate ratio; CI = Confidence interval

Note: IRR < 1 indicates better reporting in reference group compared to the other group(s). It is the opposite for IRR>1. IRR = 1 indicates similar reporting in reference and other group (s).

	CONSORT-A				
		Pre until 2007 (n = 11)	Post 2008 - 2022 (n = 44)	Univariate analysis	
Item	Description	n (%)	n (%)	OR (95% CI)	P value
Title	Identification of the study as randomized	0 (0.00)	23 (52.27)	Not estimable	0.001
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	9 (81.82)	15 (34.09)	0.12 (0.01 to 0.68)	0.006
Methods					
Participants	Eligibility criteria for participants and the settings where the data were collected	1 (9.09)	0 (0.00)	Not estimable	0.200
Interventions	Interventions intended for each group	8 (72.73)	32 (72.73)	1 (0.15 to 5.13)	>0.999
Objective	Specific objective or hypothesis	11 (100)	39 (88.64)	Not estimable	0.571
Outcome	Clearly defined primary outcome for this report	0 (0.00)	1 (2.27)	Not estimable	>0.999
Randomization	How participants were allocated to interventions	0 (0.00)	1 (2.27)	Not estimable	>0.999
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	0 (0.00)	0 (0.00)	Not estimable	
Results				Not estimable	
Numbers randomized	Number of participants randomized to each group	0 (0.00)	21 (47.73)	Not estimable	0.004
Numbers analysed	Number of participants analysed in each group	0 (0.00)	2 (4.55)	Not estimable	>0.999

Table 3: Frequency of reporting each Consolidated Standards of Reporting Trials extension for abstracts (CONSORT-A) items

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Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	2 (18.18)	10 (22.73)	1.3(0.22 to 14.49)	>0.999
	productor	2 (10.10)	10 (22.75)	1.5(0.22 to 11.15)	0.999
Harms	Important adverse events or side effects	1 (9.09)	4 (9.09)	1 (0.09 to 54.11)	>0.999
Conclusions	General interpretation of the results	10 (90.91)	42 (95.45)	2.1 (0.03 to 43.51)	0.495
Trial registration	Registration number and name of trial register	0 (0.00)	14 (31.82)	Not estimable	0.048
Funding	Source of funding	1 (9.09%	0 (0.00%	Not estimable	0.200

Supplementary materials

Assessment of the quality of reporting in abstracts of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey

Search strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

- 1 (fructooligosaccharide* or fructo oligosaccharide*).ti,ab,kf.
- 2 neosugar*.ti,ab,kf.
- 3 Fructans/
- 4 Inulin/
- 5 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kf.
- 6 inulin*.ti,ab,kf.
- 7 asteraceae.ti,ab,kf.
- 8 oligofructose*.ti,ab,kf.
- 9 chicory.ti,ab,kf.
- 10 chicory root.ti,ab,kf.
- 11 Helianthus/
- 12 jerusalem artichoke*.ti,ab,kf.
- 13 or/1-12
- 14 Lipids/
- 15 lipids.ti,ab,kf.
- 16 Lipoproteins/
- 17 Lipoproteins, IDL/
- 18 exp Lipoproteins, LDL/
- 19 exp Lipoproteins, HDL/

- 20 exp Lipoproteins, VLDL/
- 21 lipid.ti,ab,kf.
- 22 lipoprotein*.ti,ab,kf.
- 23 exp Triglycerides/
- 24 triglyceride*.ti,ab,kf.
- 25 triacetin/ or triolein/
- 26 triacylglycerol*.ti,ab,kf.
- 27 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kf.
- 28 cholesterol*.ti,ab,kf.
- 29 apolipoproteins a/ or apolipoprotein a-i/
- 30 apo* a1.ti,ab,kf.
- 31 apo* a i.ti,ab,kf.
- 32 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kf.
- 33 Apolipoproteins B/
- 34 apo* b.ti,ab,kf.
- 35 or/14-34
- 36 exp waist circumference/
- 37 (waist adj3 (circumference* or ratio*)).ti,ab,kf.
- 38 Glucose/
- 39 glucose.ti,ab,kf.
- 40 blood pressure*.ti,ab,kf.
- 41 body mass index/
- 42 (body mass ind* or BMI).ti,ab,kf.
- 43 or/36-42
- 44 random*.ti,ab,kf.
- 45 rct*.ti,ab,kf.
- 46 randomized controlled trial/
- 47 randomized controlled trial.pt.
- 48 random allocation/
- 49 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kf.
- 50 exp clinical trial/

- 51 controlled clinical trial/
- 52 clinical trial*.ti,ab,kf.
- 53 or/44-52
- 54 13 and (35 or 43) and 53
- 55 remove duplicates from 54

Database: Embase

Search Strategy:

- 1 fructose oligosaccharide/
- 2 (fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*).ti,ab,kw.
- 3 fructan/
- 4 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kw.
- 5 inulin/
- 6 inulin*.ti,ab,kw.
- 7 asteraceae.ti,ab,kw.
- 8 chicory/
- 9 chicory.ti,ab,kw.
- 10 jerusalem artichoke/
- 11 jerusalem artichoke*.ti,ab,kw.
- 12 helianthus.ti,ab,kw.
- 13 or/1-12
- 14 lipid/
- 15 (lipid or lipids).ti,ab,kw.
- 16 lipoprotein/
- 17 intermediate density lipoprotein/
- 18 low density lipoprotein/
- 19 high density lipoprotein/
- 20 very low density lipoprotein/
- 21 lipoprotein*.ti,ab,kw.
- 22 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kw.
- 23 exp triacylglycerol/
- 24 (triglyceride* or triacylglycerol* or triacetin* or triolein*).ti,ab,kw.
- 25 cholesterol/
- 26 cholesterol*.ti,ab,kw.

27 apolipoprotein/ or apolipoprotein a/ or apolipoprotein a1/ or apolipoprotein b/ or apolipoprotein b100/ or apolipoprotein b48/

- 28 (apo* a1 or apo* a 1 or apo* a i or apo* ai).ti,ab,kw.
- 29 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kw.
- 30 apo* b*.ti,ab,kw.
- 31 (proapoliprotein adj1 b*).ti,ab,kw.
- 32 or/14-31
- 33 waist circumference/
- 34 (waist adj3 (circumference* or ratio*)).ti,ab,kw.
- 35 glucose/
- 36 glucose*.ti,ab,kw.
- 37 blood pressure/
- 38 blood pressure*.ti,ab,kw.
- 39 body mass/
- 40 (body mass ind* or BMI).ti,ab,kw.
- 41 or/33-40
- 42 random*.ti,ab,kw.
- 43 rct*.ti,ab,kw.
- 44 randomized controlled trial/
- 45 exp randomization/
- 46 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kw.
- 47 clinical trial/
- 48 clinical trial*.ti,ab,kw.
- 49 controlled clinical trial/
- 50 or/42-49
- 51 13 and 41 and 50
- 52 remove duplicates from 51

Database: Ovid Emcare

Search Strategy:

- 1 fructose oligosaccharide/
- 2 (fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*).ti,ab,kw.
- 3 fructan/
- 4 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kw.
- 5 inulin/
- 6 inulin*.ti,ab,kw.
- 7 asteraceae.ti,ab,kw.
- 8 chicory/
- 9 chicory.ti,ab,kw.
- 10 jerusalem artichoke/
- 11 jerusalem artichoke*.ti,ab,kw.
- 12 helianthus.ti,ab,kw.
- 13 or/1-12
- 14 lipid/
- 15 (lipid or lipids).ti,ab,kw.
- 16 lipoprotein/
- 17 intermediate density lipoprotein/
- 18 low density lipoprotein/
- 19 high density lipoprotein/
- 20 very low density lipoprotein/
- 21 lipoprotein*.ti,ab,kw.
- 22 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kw.
- 23 exp triacylglycerol/
- 24 (triglyceride* or triacylglycerol* or triacetin* or triolein*).ti,ab,kw.
- 25 cholesterol/
- 26 cholesterol*.ti,ab,kw.

27 apolipoprotein/ or apolipoprotein a/ or apolipoprotein a1/ or apolipoprotein b/ or apolipoprotein b100/ or apolipoprotein b48/

- 28 (apo* a1 or apo* a 1 or apo* a i or apo* ai).ti,ab,kw.
- 29 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kw.
- 30 apo* b*.ti,ab,kw.
- 31 (proapoliprotein adj1 b*).ti,ab,kw.
- 32 or/14-31
- 33 waist circumference/
- 34 (waist adj3 (circumference* or ratio*)).ti,ab,kw.
- 35 glucose/
- 36 glucose*.ti,ab,kw.
- 37 blood pressure/
- 38 blood pressure*.ti,ab,kw.
- 39 body mass/
- 40 (body mass ind* or BMI).ti,ab,kw.
- 41 or/33-40
- 42 random*.ti,ab,kw.
- 43 rct*.ti,ab,kw.
- 44 randomized controlled trial/
- 45 exp randomization/
- 46 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kw.
- 47 clinical trial/
- 48 clinical trial*.ti,ab,kw.
- 49 controlled clinical trial/
- 50 or/42-49
- 51 13 and 41 and 50
- 52 remove duplicates from 51

PhD Thesis - J. R. Talukdar; McMaster University - Health Research Methodology

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

1 (fructooligosaccharide* or fructo oligosaccharide* or neosugar* or (fructan* or inutest* or oligofructan* or polyfructosan*) or inulin* or asteraceae or oligofructose* or chicory or chicory root or jerusalem artichoke*).mp. [mp=title, short title, abstract, full text, keywords, caption text]

2 (lipids or lipid or lipoprotein* or triglyceride* or triacylglycerol* or (HDL or LDL or VLDL or IDL or TG or TAG) or cholesterol* or apo* al or apo* a i or (proapoliprotein adj1 (ai or al or a i or a-1)) or apo* b or (waist adj3 (circumference* or ratio*)) or glucose or blood pressure* or (body mass ind* or BMI)).mp. [mp=title, short title, abstract, full text, keywords, caption text]

3 1 and 2

Database: AMED (Allied and Complementary Medicine)

Search Strategy:

1 (fructooligosaccharide* or fructo oligosaccharide* or neosugar* or (fructan* or inutest* or oligofructan* or polyfructosan*) or inulin* or asteraceae or oligofructose* or chicory or chicory root or jerusalem artichoke*).mp.

- 2 Lipids/
- 3 lipoproteins/
- 4 triglycerides/

5 (lipids or lipid or lipoprotein* or triglyceride* or triacylglycerol* or (HDL or LDL or VLDL or IDL or TG or TAG) or cholesterol* or apo* al or apo* a i or (proapoliprotein adj1 (ai or al or a i or a-1)) or apo* b or (waist adj3 (circumference* or ratio*)) or glucose or blood pressure* or (body mass ind* or BMI)).mp. [mp=abstract, heading words, title]

6 or/2-5

7 1 and 6

Database: CINAHL

Search Strategy:

S1 fructose oligosaccharide* or fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*

- S2 fructan* or inutest* or oligofructan* or polyfructosan*
- S3 inulin* or asteraceae
- S4 chicory
- S5 jerusalem artichoke*
- S6 helianthus
- S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
- S8 (MH "Lipids")
- S9 lipid or lipids
- S10 MH "Lipoproteins"
- S11 lipoprotein*
- S12 MH "Lipoproteins, LDL+"
- S13 MH "Lipoproteins, HDL+"
- S14 HDL or LDL or VLDL or IDL or TG or TAG
- S15 MH "Triglycerides"
- S16 triacylglycerol* or triacylglyceride*
- S17 MH "Cholesterol"
- S18 cholesterol*
- S19 MH "Apolipoproteins"
- S20 apo* a1 or apo* a 1 or apo* a i or apo* ai
- S21 proapolioprotein N1 (ai or a1 or a i or a 1)
- S22 apo* b*
- S23 proapolioprotein N1 b*

S24 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23

- S25 MH "Waist Circumference"
- S26 waist N3 (circumference* or ratio*)
- S27 MH "Glucose"

- S28 glucose*
- S29 MH "Blood Pressure"
- S30 blood pressure*
- S31 MH "Body Mass Index"
- S32 body mass ind* or BMI
- S33 S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
- S34 S7 AND S24 AND S33
- S35 S7 AND S24 AND S33

Supplementary materials: References of included studies

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Chapter 5: Assessment of the quality of reporting of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey

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Assessment of the quality of reporting of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey

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Abstract

Background

Transparent and detailed reporting of randomized controlled trials (RCTs) is essential to judge its validity and generalizability. We assessed the reporting quality of RCTs examining the effects of inulin-type fructans supplementation on cardiovascular risk factors, before and after the publication of the Consolidated Standards of Reporting Trials (CONSORT) in 2010.

Methods

We searched MEDLINE, EMBASE, Emcare, AMED, the Cochrane Library, and CINAHL from inception to May 15, 2022, including the reference lists of selected RCTs. We screened titles and abstracts and extracted the data independently and in duplicate. We included RCTs that investigated the effects of inulin-type fructans on cardiovascular disease risk factors (e.g., low-density lipoprotein cholesterol, triglycerides, fasting blood glucose) in adults (18 years or older). The primary outcomes of this study were: the overall reporting quality of RCTs (defined as the total number of items [0 to 36] present from the CONSORT checklist) published before and after CONSORT; and the study characteristics (e.g., sample size, significance of primary outcome) predictive of the CONSORT score. The secondary outcome was the reporting of each specific item of the CONSORT checklist during pre- and post-CONSORT periods. The mean difference in the total number of reported items in studies published before and after CONSORT were compared using a t-test and Poisson regression to explore the factors associated with overall reporting quality of RCTs. We used Fisher's exact test to compare the adherence to each of the 36 items during pre- and post-CONSORT periods.

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Results

We identified 1,767 citations from our systematic search, of which 55 were eligible. There was a significant increase in the reporting of CONSORT items (mean difference 8.5, 95% confidence interval [CI] 5.24 to 11.71) between studies published before and after publication of CONSORT. The sole variable that was predictive of better reporting quality of RCTs was whether the study was published before or after CONSORT (incidence rate ratio 1.67, 95% CI 1.40 to 2.02). Completeness of reporting of RCTs only improved in 15 out of 36 items (41.6%) after the publication of CONSORT.

Conclusion

The completeness of reporting in RCTs investigating inulin-type fructans supplementation on cardiovascular disease risk factors remains inadequate after the publication of CONSORT. Greater adherence to CONSORT by authors and enforcement of CONSORT by journals may improve the quality of reporting among RCTs.

Keywords: systematic survey, CONSORT, quality of reporting, methodological study, systematic review

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Background

Randomized controlled trials (RCTs) are considered the gold standard for assessing the effectiveness of health interventions (1-3). A well-conducted RCT can transform patient care. However, reporting of the study design, conduct, analysis, and interpretation of a published RCT must be transparent and sufficiently detailed, such that readers and practitioners can appropriately judge the validity and applicability of the trial to particular practice settings (4). This may be difficult to do when the reporting of trials is inadequate (5). At its extreme, inadequate reporting can lead to a biased estimate of the treatment effect, leading physicians to avoid effective treatments or promote ineffective treatments (6). The Consolidated Standards of Reporting Trials (CONSORT) statement was created in 2010 to facilitate improved and transparent reporting of trials by study authors (7). CONSORT is a 37-item checklist that authors are expected to adhere to while reporting an RCT. The checklist assesses quality of reporting in an RCT in five broad domains: title and abstract, introduction, methods, results, and discussion. Previous studies found that inadequately reported RCTs led to an overestimation of intervention effects, compared to adequately reported RCTs (6, 8). Moher and colleagues compared studies published in three journals that adopted CONSORT (The British Medical Journal, The Journal of the American Medical Association, and The Lancet) compared to one that did not (The New England Journal of Medicine), and found that the adoption of CONSORT led to an overall 10% improvement in reporting quality of RCTs (9). However, previous publications that assessed reporting quality of RCTs using CONSORT in COVID-19 (10), otolaryngologic (11), chiropractic (12), and in otorhinolaryngologic research studies (13) found inadequate reporting quality.

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There is limited evidence examining the quality of reporting in RCTs in regard to its design, analysis, and interpretation, especially in the field of nutrition. As a case example, we examined the reporting quality of published trials assessing the effects of inulin-type fructans supplementation on cardiovascular risk factors. This study is part of a two-study series that a) assessed the reporting quality of abstracts (see "Supplementary file") and b) in full-text reports of RCTs. The objectives of this study were to assess: 1) the overall reporting quality of these published RCTs before and after the publication of the CONSORT; 2) the factors that predicted reporting quality; and 3) the frequency of reporting of each item in the CONSORT checklist. The overall reporting quality was defined as the total number of items reported out of 36 items in the CONSORT checklist. We excluded one item (item 17b) as it assesses the reporting of binary outcomes, whereas the included RCTs in our study only reported continuous outcomes.

Methods

Study design

We conducted a systematic survey of the literature with a comparison of mean, and domainspecific CONSORT scores, before and after CONSORT publication (1). We established the methods of the study *a priori* and published the study protocol (14).

Data sources and study selection

A comprehensive search strategy was developed by a librarian (LB) (see "Supplementary material") to search RCTs in MEDLINE, EMBASE, Emcare, AMED, the Cochrane Library, and CINAHL from database inception to May 15, 2022, without language restriction. We supplemented the database search with a reference search of included RCTs. We reported the selection criteria for this study in detail in the published protocol (14). In brief, we included RCTs that investigated the effects of inulin-type fructans (ITF) on cardiovascular disease risk factors (e.g., low-density lipoprotein cholesterol, triglycerides, fasting blood glucose) in adults (18 years or older). We excluded trials that only reported postprandial effects of ITF, that included participants with conditions that seriously altered normal digestion or absorption of nutrients (e.g., chemotherapy, dialysis, liver disease), or included participants undergoing treatments with the same effects. We also excluded trials that included pregnant or lactating participants.

Reviewers (from JRT, AG, FC, LH, AC, HH, CS) screened the titles and abstracts, and assessed the eligibility of full-texts independently and in duplicate. Disagreements were resolved through discussion or consultation with a third reviewer (RJdS).

Data extraction

We extracted study characteristics (e.g., name of journal, publication year, journal impact factor, funding source(s), CONSORT endorsement status by the journal, significance of the results of the primary outcome, sample size). We considered the first reported outcome as the primary outcome if the authors did not clearly define a primary outcome. Among the 37 items in the CONSORT checklist, we extracted data related to the adherence to 36 of the items, as one item (item 17b) assesses the reporting of binary outcomes, whereas the included RCTs in our study only reported continuous outcomes. We extracted data independently and in duplicate (from JRT, AG, FC, LH, AC, HH, CS) and resolved any disagreement through discussion or consultation with a third reviewer (RJdS).

Outcomes

The primary outcomes of this study were 1) the overall reporting quality of RCTs based on adherence to the CONSORT checklist and 2) the factors associated with reporting quality. The overall reporting quality was defined as number of items reported out of 36 items of the CONSORT checklist. Study publication year (before vs. after the publication of CONSORT 2010), endorsement of the CONSORT statement by the journal (defined as the presence of specific instructions for the authors to follow the CONSORT statement or not during article submission), most recent journal impact factor (as a continuous variable), the statistical significance of primary outcome (significant vs. non-significant), funding status (industry-funded vs others) and sample size (≤ 100 vs > 100) were considered as predictors of reporting quality. The secondary outcomes were the reporting of each item of the CONSORT checklist.

Statistical analyses

We reported study characteristics as means and standard deviations (SD) for continuous variables and count (percent) for categorical variables. Fisher's exact test was used to compare the adherence of reporting each of the 36 items before and after publication of CONSORT statement. We reported unadjusted odds ratios (ORs) with 95% confidence interval (CI). We also used a t-test to compare the number of items reported before and after the publication of CONSORT, and report them as mean differences and 95% CIs. Poisson regression was used to explore the factors associated with overall reporting quality of RCTs. Following previous published literature (15-17), we adjusted the model for study publication year (before or after the publication of CONSORT), endorsement of the CONSORT statement by the journal (whether there are specific instructions for the authors to follow the CONSORT statement or not), journal impact factor (as a continuous variable), the statistical significance of the primary outcome (significant vs non-significant), funding status (industry-funded vs others) and sample size (\leq 100 vs > 100). We hypothesized that there was an association between these factors and overall reporting quality of RCTs. We reported results from the regression analysis as incidence rate ratios (IRR) with 95% CIs (18). The IRR is obtained by exponentiating the Poisson regression coefficient (19), and is interpreted similarly to odds ratios, in which an IRR > 1 indicates that RCTs published after CONSORT are reported at a higher quality than those published before CONSORT. For example, IRR 1.21 indicates that reporting quality of RCTs published after CONSORT is 1.21 times better than the reporting quality RCTs published before CONSORT (20). Statistical significance was set at $\alpha = 0.05$. We used residual deviance to understand goodness-of-fit of the overall Poisson regression model. We compared the adjusted model with

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unadjusted model with Akaike information criterion (AIC). A lower value of AIC indicated better fit. We analyzed the data with R version 4.0.3 (21).

Results

Study Characteristics

We identified 1,767 citations from the systematic search, of which 55 reports (see "Supplementary material") met our eligibility criteria. Among these 55 articles, 13 were published before and 42 were published after the publication of CONSORT (**Figure 1**). Sixty-seven per cent of the studies reported statistically significant primary outcomes, 91% had a sample size less than or equal to 100 participants, 73% were published in journals that currently endorsed the CONSORT statement, and the mean impact factor of the publishing journal was 4.95 (SD 4.00) (**Table 1**).

The overall quality of reporting quality in randomized controlled trials

The mean number of items reported after the publication of CONSORT (mean 20.8, SD 5.38) was greater than before its publication (mean 12.3, SD 3.90); unadjusted mean difference (MD) of 8.5 (95% CI 5.24 to 11.71).

Study publication year (IRR 1.67, 95% CI 1.40 to 2.02) was significantly associated with reporting more items from the CONSORT checklist when adjusted for the endorsement of CONSORT by the journal, statistical significance of the results, sources of funding, sample size, and the journal's impact factor. The unadjusted model also provided similar results (IRR 1.69, 95% CI 1.43 to 2.00). The unadjusted model (AIC: 337.54) had a better fit compared to the adjusted model (AIC: 345.64). **Table 2** presents the adjusted IRRs for the total number of reported CONSORT items.

Reporting of each item of the CONSORT checklist

We found statistically significant improvement in completeness of reporting of RCTs for 15 out of 36 items after the publication (2010 and later) compared to before publication (prior to 2010) of the CONSORT statement. After publication of the CONSORT statement, more studies could be identified as RCTs through the titles and abstracts (OR and 95% CI not estimable [NE], p <0.001), more RCTs reported methods for random sequence generation (OR 15.32, 95% CI 1.94 to 709.02, p=0.003), type of randomization (OR 9.59, 95% CI 1.21 to 444.60, p=0.019), allocation concealment (OR 9.59, 95% CI 1.21 to 444.60, p= 0.019), implementation of randomization (OR and 95% CI NE, p= 0.005), blinding (OR 11.57, 95% CI 1.47 to 535.36, p= 0.008), methods for additional analyses (e.g., subgroup, adjusted analyses) (OR and 95% CI NE, p < 0.001), provided participant flow diagrams (OR 13.27, 95% 2.66 to 92.57, p = < 0.001), recruitment information (OR and 95% CI NE, p= 0.011), baseline information (OR 15.82, 95% CI 2.28 to 190.78, p= 0.001), number analyzed (OR 4.27, 95% CI 1.15 to 15.95, p= 0.037), ancillary analyses (OR and 95% CI NE, p= <0.001), discussed limitations (OR 10.50, 95% CI 1.91 to 110.37, p = 0.002), registered protocols (OR 31.50 95% CI 3.89 to 1477.22, p = < 0.001), and made the protocol publicly accessible (OR 22.69, 95% 2.85 to 1055.06, p = <0.001). The remaining items were reported similarly before and after publication of the CONSORT statement. Among the five domains of CONSORT (i.e., title and abstract, introduction, methods, results and discussion), after the publication of the CONSORT statement, the items composing the results domain were the most completely reported, followed by the methods domain. Table 3 presents the frequency of reporting of each CONSORT item.

Discussion

Main findings

This study provides a systematic assessment of the reporting quality of RCTs comparing studies published before and after the publication of the CONSORT statement. This study included RCTs that investigated the effects of ITF on CVD risk factors (e.g., low-density lipoprotein cholesterol, triglycerides, fasting blood glucose) in adults (18 years or older). We found statistically significant improvement in the completeness of reporting of RCTs for 14 out of 36 items when we compared studies published before and after the publication of CONSORT. After publication of CONSORT, more studies could be identified as RCT from titles and abstracts, reported methods for random sequence generation, allocation concealment, implementation of randomization, blinding, methods for additional analyses (e.g., subgroup, adjusted analyses), provided participant flow diagram, recruitment information, baseline information, number analyzed, ancillary analyses, discussed limitations, registered protocols, and made the protocol accessible to others. In adjusted models, publication of the CONSORT statement was significantly associated with improved quality of reporting, while other factors (e.g., significance of results, funding source, sample size) did not influence the quality of reporting.

Our findings suggests that there was significant improvement in the reporting of methodological details (e.g., specification of primary outcomes, random sequence generation, blinding) of RCTs after the publication of the CONSORT statement. Methodological details are important for assessing the quality of RCTs (22). Especially, reporting approaches to sequence generation, blinding, allocation concealment, and handling of exclusions after allocation are the minimum requirement for assessing quality of RCTs (6). Although there was an improvement in the reporting quality of certain CONSORT items after the publication of CONSORT, this

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improvement was inadequate. For example, despite an improvement in the reporting of the randomization methodology (e.g., sequence generation, allocation concealment, implementation of random allocation and blinding), these items were only reported in 40.48% to 61.90% of the studies. Inadequate reporting of the randomization methodology can lead to an overestimation of the treatment effect (8).

In addition, we did not find significant improvements in many of the CONSORT items. For example, there was no significant improvement in the reporting of abstract or sources of funding. This is particularly concerning because clinicians often make treatment decisions based on the abstracts of research articles (5, 23-25) due to time limitations, language barriers, or inaccessibility in accessing the full report (26). Moreover, reporting a study's sources of funding is necessary to determine potential risks of biases, as studies funded by pharmaceutical companies are often found to report more favourable results compared to studies funded by other sources (1). Considering the impacts of the complete reporting of the CONSORT items, study authors, reviewers, and journals editors should be encouraged to collaborate to improve the reporting quality of RCTs.

Relation to previous work

This is the first study to assess the reporting quality of RCTs that assessed the effects of ITF supplementation on CVD risk factors in adults. Consistent with our findings, studies published in other fields similarly reported suboptimal reporting quality of RCTs. For example, a recent study by Yin et al. (10) assessing reporting quality of RCTs in patients with COVID-19 found that the reporting rate was 53.85% based on the CONSORT checklist with all 37 items. Our study also found similar rate of reporting (on average 15 out of 36 or 58%). Huang et al. (11) assessed the

reporting quality of RCTs in otolaryngology and reported a mean of 59% CONSORT adherence. Camm et al. (27) assessed reporting quality of RCTs relating to anti-arrhythmic agents and reported a mean score of 62% (15.4 of 25 group of items). A study by Nojomi et al. (28) assessed reporting quality of RCTs in Iranian journals and reported even lower CONSORT adherence (a mean of 43.8%).

Though our study reported similar increasing trends in the reporting quality of RCTs after the publication of the CONSORT statement, the absolute number of items reported remains concerningly low (41.6%). Observing the specific items of the CONSORT checklist, most of the items were not reported by the any of the RCTs even after publication of the CONOSRT statement.

Limitations of the study

This study has inherent limitations. This study required making subjective judgements to score the items as reported or not. To minimize this limitation, we provided detailed instructions to the data extractors and conducted piloting and calibration exercises. The quality of reporting of RCTs could be influenced by various factors other than adherence to CONSORT that were not consider. For example, following a mandatory structure suggested by the journals (e.g., word count) or specific requirements by the funding agencies can lead to incomplete reporting. We followed published literature (15, 17) to adjust the factors that might influence incomplete reporting of RCTs. Another limitation of our study is that we defined CONSORT endorsement as whether the journal had endorsed CONSORT as at until June 2022. We made this decision considering the lack of information regarding specific time for CONSORT endorsement. It is

also important to note that we used journal impact factors at present time (until June 2022), rather than at time of publication.

Implications

Our study presents a snapshot of the current practice of reporting quality of RCTs investigating inulin-type fructans supplementation, which will highlight the items that are underreported. All the items of the CONSORT statement are important to assess the validity of an RCT. This finding might help the reviewers and journal editors to identify the gaps in certain domains and encourage the authors to make improvements in the reporting of those specific domain. A collaborative approach by authors, reviewers, and journal editors might lead to a greater number of reported CONSORT items in published RCTs.

Conclusion

The completeness of reporting in RCTs investigating inulin-type fructans supplementation aon cardiovascular disease risk factors was inadequate after the publication of CONSORT. Publication of the CONSORT statement had little or no impact on improving the reporting quality of RCTs. Authors are encouraged to adhere to the CONSORT statement and journals would benefit from further enforcing its usage.

Abbreviations

AIC = Akaike information criterion CONSORT = Consolidated Standards of Reporting Trials CVD = Cardiovascular disease IRR = Incidence rate ratio ITF = Inulin-type fructans MD = Mean difference RCT = Randomized controlled trial SD = Standard deviation

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Contributors

JRT, RJdS and LM conceptualized the study. JRT analyzed and drafted the manuscript with the guidance from RJdS and LM. RJdS is the guarantor of the study.

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Competing interests

All authors declare no competing interests.

Patient and public involvement

We did not involve any patients or public partners in this study.

Data sharing

The review was conducted using published data. Data may be requested from the corresponding author.

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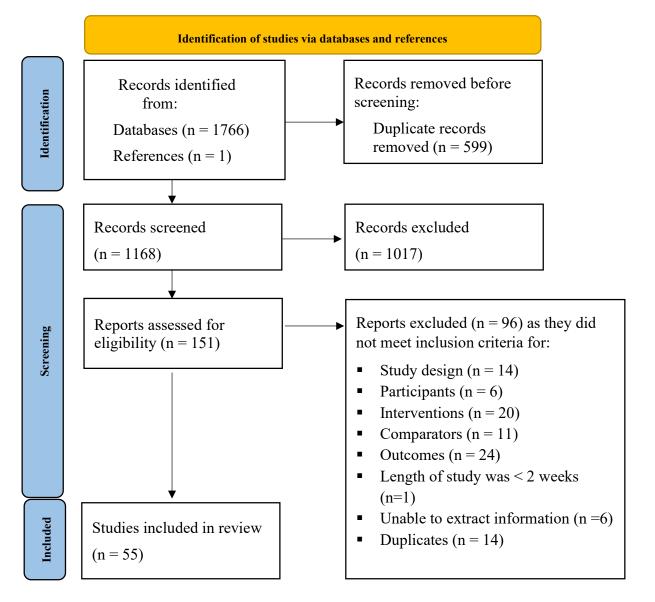
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Figures

Figure 1. PRISMA flow diagram



Flow of studies through the systematic search, assessment of eligibility and inclusion into the review (29)

Tables

Table1: Characteristics of trials by period of publication

	Pre-CONSORT Until 2009 (n = 13)	Post-CONSORT 2010 - 2022 (n = 42)	Total $n = 55$
Characteristics	n (%)	n (%)	n (%)
Statistically significant results			
Yes	7 (54)	30 (71)	37 (67)
No	6 (46)	12 (29)	18 (33)
Sample size			
≤100	13 (100)	37 (88)	50 (91)
>100	0 (0)	5 (12)	5 (9)
Funding			
Industry	5 (38.5)	9 (21.5)	14 (25.5)
Others	3 (23)	24 (57)	27 (49)
No information	5 (38.5)	9 (21.5)	14 (25.5)
*CONSORT endorsement by			
journals			
Yes	NA	40 (76)	40 (73)
No	NA	15 (24)	15 (27)
Journal's impact factor (2021- 2022)	5.68 (1.94)	4.73 (4.49)	4.95 (4.0)
Mean (SD)			

CONSORT = Consolidated Standards of Reporting Trials; NA = not applicable

*CONSORT endorsement by journals until June 2022

	IRR (95% CI)	p-value
Intercept	11.22 (8.77 TO 14.29)	< 0.001
CONSORT		
Pre (reference)		
Post	1.67 (1.40 to 2.02)	< 0.001
*CONSORT endorsement by journals		
No (reference)		
Yes	1.09 (0.94 to 1.26)	0.257
Results statistically significant		
No (reference)		
Yes	0.99 (0.86 to 1.14)	0.864
Funding source		
Industry		
Other than industry	1.07 (0.91 to 1.27)	0.407
No information	0.96 (0.80 to 1.16)	0.658
Sample size		
Less than/equal to 100		
>100	1.09 (0.88 to 1.35)	0.409
Journal's impact factor (2021-2022) (continuous)	1.00 (0.99 to 1.02)	0.748

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IRR = Incidence rate ratio; CI = Confidence interval

Note: IRR < 1 indicates better reporting in reference group compared to the other group(s). It is the opposite for IRR>1. IRR = 1 indicates similar reporting in reference and other group (s).

*CONSORT endorsement by journals until June 2022

	Item No		Pre- CONSORT Until 2009 [N=13] N (%)	Post-CONSORT 2010-2022 [N =42] N (%)	Univariate analysis OR (95% CI)	
Section/Topic		Checklist item				P value
Title and abstract						
	1a	Identification as a randomised trial in the title	0 (0.00)	23 (54.76)	NE	< 0.001
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for	0 (0.00)	25 (54.70)	INL.	~0.001
		abstracts)	0 (0.00)	3 (7.14)	NE	>0.999
Introduction						
Background and objectives	2a	Scientific background and explanation of rationale	13 (100)	42 (100)	NE	NE
objectives	2b	Specific objectives or hypotheses	13 (100)	42 (100)	NE	NE
Methods		Speenie cojeen eo er nypomeses	10 (100)	12 (100)		1,12
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	10 (76.92)	18 (42.86)	0.23 (0.04 to 1.07)	0.055
That design	3b	Important changes to methods after trial commencement (such as eligibility	10 (70.92)	10 (12:00)	3.66 (0.67 to	0.055
	4a	criteria), with reasons	2 (15.38)	17 (40.48)	38.15) 1.65 (0.03 to	0.180
Participants		Eligibility criteria for participants	12 (92.31)	40 (95.24)	34.33)	0.562
	4b	Settings and locations where the data were collected	4 (30.77)	23 (54.76)	2.67 (0.62 to 13.82)	0.205

Table 3: Frequency of reporting each Consolidated Standards of Reporting Trials (CONSORT) item

	5	The interventions for each group with sufficient details to allow replication, including how and when they were				
Interventions	6a	actually administered Completely defined pre-specified primary and secondary outcome measures,	13 (100)	42 (100)	NE	NE
		including how and when they were	0 (15 00)		4.87 (0.90 to	0.050
Outcomes	6b	assessed Any changes to trial outcomes after the	2 (15.38)	20 (47.62)	50.52)	0.053
		trial commenced, with reasons	0 (0.00)	1 (2.38)	NE	>0.999
Sample size	7a	How sample size was determined	4 (30.77)	27 (64.29)	3.94 (0.91 to 20.63)	0.054
I	7b	When applicable, explanation of any	(2011)	_/ (***_*))	
		interim analyses and stopping guidelines	0 (0.00)	0 (0.00)	NE	NE
Randomisation:						
Sequence	8a	Method used to generate the random	1(7(0))	24(5714)	15.32 (1.94 to	0.002
generation	8b	allocation sequence Type of randomisation; details of any	1 (7.69)	24 (57.14)	709.02)	0.003
	00	restriction (such as blocking and block			9.59 (1.21 to	
	0	size)	1 (7.69)	19 (45.24)	444.60)	0.019
	9	Mechanism used to implement the random allocation sequence (such as				
		sequentially numbered containers),				
Allocation		describing any steps taken to conceal the			0.50 (1.01)	
concealment mechanism		sequence until interventions were assigned	1 (7.69)	19 (45.24)	9.59 (1.21 to 444.60)	0.019
meenamsm	10	Who generated the random allocation	1 (7.07)	19 (13.21)	111.00)	0.017
		sequence, who enrolled participants, and				
Implementation		who assigned participants to interventions	0 (0.00)	17 (40.48)	NE	0.005
P	11a	If done, who was blinded after	- (0.00)		11.57 (1.47 to	0.000
Blinding		assignment to interventions (for example,	1 (7.69)	21 (50)	535.36)	0.008

		participants, care providers, those assessing outcomes) and how				
	11b	If relevant, description of the similarity of	_ /		1.01 (0.22 to	
	12a	interventions Statistical methods used to compare groups for primary and secondary	8 (61.54)	26 (61.90)	4.28)	>0.999
Statistical methods	12b	outcomes	13 (100)	42 (100)	NE	NE
	120	Methods for additional analyses, such as subgroup analyses and adjusted analyses	0 (0.00)	23 (54.76)	NE	< 0.001
Results	10					
Participant flow (a	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment,				
diagram is strongly		and were analysed for the primary	2 (22 00)	24 (00.05)	13.27 (2.66 to	-0.001
recommended)	13b	outcome For each group, losses and exclusions	3 (23.08)	34 (80.95)	92.57)	< 0.001
	-	after randomisation, together with			3.54 (0.76 to	
	14a	reasons Dates defining the periods of recruitment	7 (53.85)	34 (80.95)	16.69)	0.071
Recruitment	1 4 a	and follow-up	0 (0.00)	16 (38.10)	NE	0.011
	14b	Why the trial ended or was stopped	0 (0.00)	0 (0.00)	NE	NE
Baseline data	15 16	A table showing baseline demographic and clinical characteristics for each group For each group, number of participants	7 (53.85)	40 (95.24)	15.82 (2.28 to 190.78)	0.001
	10	(denominator) included in each analysis and whether the analysis was by original			4.27 (1.15 to	
Numbers analysed	17a	assigned groups For each primary and secondary outcome, results for each group, and the	6 (46.15)	33 (78.57)	15.95)	0.037
Outcomes and estimation		estimated effect size and its precision (such as 95% confidence interval)	13 (100)	42 (100)	NE	NE

	17b*	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA	NA	NA	NA
	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified				
Ancillary analyses		from exploratory	0 (0.00)	21 (50)	NE	< 0.001
	19	All important harms or unintended effects			0.45 (0.07)	
Harms		in each group (for specific guidance see CONSORT for harms)	10 (76.92)	25 (59.52)	0.45 (0.07 to 2.09)	0.333
Discussion			10 (70.92)	20 (09.02)	2.07)	0.555
	20	Trial limitations, addressing sources of				
		potential bias, imprecision, and, if			10.50 (1.91 to	
Limitations		relevant, multiplicity of analyses	2 (15.38)	28 (66.67)	110.37)	0.002
	21	Generalisability (external validity,				
Generalisability		applicability) of the trial findings	0 (0.00)	8 (19.05)	NE	0.176
	22	Interpretation consistent with results,			2 22 (0 04 /	
Intometation		balancing benefits and harms, and	12 (02 21)	41 (97.62)	3.32 (0.04 to	0.42
Interpretation Other information		considering other relevant evidence	12 (92.31)	41 (97.02)	273.91)	0.42
Other information	23	Registration number and name of trial			31. 50 (3.89 to	
Registration	23	registry	1 (7.69)	31 (73.81)	1477.22)	< 0.001
registration	24	Where the full trial protocol can be	1 (7.07)	51 (75.01)	22.69 (2.85 to	0.001
Protocol		accessed, if available	1 (7.69)	28 (66.67)	1055.06)	< 0.001
	25	Sources of funding and other support	~ /		<i>,</i>	
Funding		(such as supply of drugs), role of funders	0 (0.00)	3 (7.14)	NE	>0.999

NE = Not estimable, NA = Not applicable, *We excluded 17b as binary outcomes are not applicable for this study

Supplementary materials

Assessment of the quality of reporting in abstracts of randomized controlled trials investigating the effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a systematic survey

Search strategies

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

Search Strategy:

- 1 (fructooligosaccharide* or fructo oligosaccharide*).ti,ab,kf.
- 2 neosugar*.ti,ab,kf.
- 3 Fructans/
- 4 Inulin/
- 5 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kf.
- 6 inulin*.ti,ab,kf.
- 7 asteraceae.ti,ab,kf.
- 8 oligofructose*.ti,ab,kf.
- 9 chicory.ti,ab,kf.
- 10 chicory root.ti,ab,kf.
- 11 Helianthus/
- 12 jerusalem artichoke*.ti,ab,kf.
- 13 or/1-12
- 14 Lipids/
- 15 lipids.ti,ab,kf.
- 16 Lipoproteins/
- 17 Lipoproteins, IDL/
- 18 exp Lipoproteins, LDL/
- 19 exp Lipoproteins, HDL/

- 20 exp Lipoproteins, VLDL/
- 21 lipid.ti,ab,kf.
- 22 lipoprotein*.ti,ab,kf.
- 23 exp Triglycerides/
- 24 triglyceride*.ti,ab,kf.
- 25 triacetin/ or triolein/
- 26 triacylglycerol*.ti,ab,kf.
- 27 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kf.
- 28 cholesterol*.ti,ab,kf.
- 29 apolipoproteins a/ or apolipoprotein a-i/
- 30 apo* a1.ti,ab,kf.
- 31 apo* a i.ti,ab,kf.
- 32 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kf.
- 33 Apolipoproteins B/
- 34 apo* b.ti,ab,kf.
- 35 or/14-34
- 36 exp waist circumference/
- 37 (waist adj3 (circumference* or ratio*)).ti,ab,kf.
- 38 Glucose/
- 39 glucose.ti,ab,kf.
- 40 blood pressure*.ti,ab,kf.
- 41 body mass index/
- 42 (body mass ind* or BMI).ti,ab,kf.
- 43 or/36-42
- 44 random*.ti,ab,kf.
- 45 rct*.ti,ab,kf.
- 46 randomized controlled trial/
- 47 randomized controlled trial.pt.
- 48 random allocation/
- 49 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kf.
- 50 exp clinical trial/

- 51 controlled clinical trial/
- 52 clinical trial*.ti,ab,kf.
- 53 or/44-52
- 54 13 and (35 or 43) and 53
- 55 remove duplicates from 54

Database: Embase

Search Strategy:

- 1 fructose oligosaccharide/
- 2 (fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*).ti,ab,kw.
- 3 fructan/
- 4 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kw.
- 5 inulin/
- 6 inulin*.ti,ab,kw.
- 7 asteraceae.ti,ab,kw.
- 8 chicory/
- 9 chicory.ti,ab,kw.
- 10 jerusalem artichoke/
- 11 jerusalem artichoke*.ti,ab,kw.
- 12 helianthus.ti,ab,kw.
- 13 or/1-12
- 14 lipid/
- 15 (lipid or lipids).ti,ab,kw.
- 16 lipoprotein/
- 17 intermediate density lipoprotein/
- 18 low density lipoprotein/
- 19 high density lipoprotein/
- 20 very low density lipoprotein/
- 21 lipoprotein*.ti,ab,kw.
- 22 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kw.
- 23 exp triacylglycerol/
- 24 (triglyceride* or triacylglycerol* or triacetin* or triolein*).ti,ab,kw.
- 25 cholesterol/
- 26 cholesterol*.ti,ab,kw.

27 apolipoprotein/ or apolipoprotein a/ or apolipoprotein a1/ or apolipoprotein b/ or apolipoprotein b100/ or apolipoprotein b48/

- 28 (apo* a1 or apo* a 1 or apo* a i or apo* ai).ti,ab,kw.
- 29 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kw.
- 30 apo* b*.ti,ab,kw.
- 31 (proapoliprotein adj1 b*).ti,ab,kw.
- 32 or/14-31
- 33 waist circumference/
- 34 (waist adj3 (circumference* or ratio*)).ti,ab,kw.
- 35 glucose/
- 36 glucose*.ti,ab,kw.
- 37 blood pressure/
- 38 blood pressure*.ti,ab,kw.
- 39 body mass/
- 40 (body mass ind* or BMI).ti,ab,kw.
- 41 or/33-40
- 42 random*.ti,ab,kw.
- 43 rct*.ti,ab,kw.
- 44 randomized controlled trial/
- 45 exp randomization/
- 46 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kw.
- 47 clinical trial/
- 48 clinical trial*.ti,ab,kw.
- 49 controlled clinical trial/
- 50 or/42-49
- 51 13 and 41 and 50
- 52 remove duplicates from 51

Database: Ovid Emcare

Search Strategy:

- 1 fructose oligosaccharide/
- 2 (fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*).ti,ab,kw.
- 3 fructan/
- 4 (fructan* or inutest* or oligofructan* or polyfructosan*).ti,ab,kw.
- 5 inulin/
- 6 inulin*.ti,ab,kw.
- 7 asteraceae.ti,ab,kw.
- 8 chicory/
- 9 chicory.ti,ab,kw.
- 10 jerusalem artichoke/
- 11 jerusalem artichoke*.ti,ab,kw.
- 12 helianthus.ti,ab,kw.
- 13 or/1-12
- 14 lipid/
- 15 (lipid or lipids).ti,ab,kw.
- 16 lipoprotein/
- 17 intermediate density lipoprotein/
- 18 low density lipoprotein/
- 19 high density lipoprotein/
- 20 very low density lipoprotein/
- 21 lipoprotein*.ti,ab,kw.
- 22 (HDL or LDL or VLDL or IDL or TG or TAG).ti,ab,kw.
- 23 exp triacylglycerol/
- 24 (triglyceride* or triacylglycerol* or triacetin* or triolein*).ti,ab,kw.
- 25 cholesterol/
- 26 cholesterol*.ti,ab,kw.

apolipoprotein/ or apolipoprotein a/ or apolipoprotein a1/ or apolipoprotein b/ or apolipoprotein b100/ or apolipoprotein b48/

- 28 (apo* a1 or apo* a 1 or apo* a i or apo* ai).ti,ab,kw.
- 29 (proapoliprotein adj1 (ai or a1 or a i or a-1)).ti,ab,kw.
- 30 apo* b*.ti,ab,kw.
- 31 (proapoliprotein adj1 b*).ti,ab,kw.
- 32 or/14-31
- 33 waist circumference/
- 34 (waist adj3 (circumference* or ratio*)).ti,ab,kw.
- 35 glucose/
- 36 glucose*.ti,ab,kw.
- 37 blood pressure/
- 38 blood pressure*.ti,ab,kw.
- 39 body mass/
- 40 (body mass ind* or BMI).ti,ab,kw.
- 41 or/33-40
- 42 random*.ti,ab,kw.
- 43 rct*.ti,ab,kw.
- 44 randomized controlled trial/
- 45 exp randomization/
- 46 ((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask*)).ti,ab,kw.
- 47 clinical trial/
- 48 clinical trial*.ti,ab,kw.
- 49 controlled clinical trial/
- 50 or/42-49
- 51 13 and 41 and 50
- 52 remove duplicates from 51

Database: EBM Reviews - Cochrane Database of Systematic Reviews

Search Strategy:

1 (fructooligosaccharide* or fructo oligosaccharide* or neosugar* or (fructan* or inutest* or oligofructan* or polyfructosan*) or inulin* or asteraceae or oligofructose* or chicory or chicory root or jerusalem artichoke*).mp. [mp=title, short title, abstract, full text, keywords, caption text]

2 (lipids or lipid or lipoprotein* or triglyceride* or triacylglycerol* or (HDL or LDL or VLDL or IDL or TG or TAG) or cholesterol* or apo* al or apo* a i or (proapoliprotein adj1 (ai or al or a i or a-1)) or apo* b or (waist adj3 (circumference* or ratio*)) or glucose or blood pressure* or (body mass ind* or BMI)).mp. [mp=title, short title, abstract, full text, keywords, caption text]

3 1 and 2

Database: AMED (Allied and Complementary Medicine)

Search Strategy:

1 (fructooligosaccharide* or fructo oligosaccharide* or neosugar* or (fructan* or inutest* or oligofructan* or polyfructosan*) or inulin* or asteraceae or oligofructose* or chicory or chicory root or jerusalem artichoke*).mp.

- 2 Lipids/
- 3 lipoproteins/
- 4 triglycerides/

5 (lipids or lipid or lipoprotein* or triglyceride* or triacylglycerol* or (HDL or LDL or VLDL or IDL or TG or TAG) or cholesterol* or apo* al or apo* a i or (proapoliprotein adj1 (ai or al or a i or a-1)) or apo* b or (waist adj3 (circumference* or ratio*)) or glucose or blood pressure* or (body mass ind* or BMI)).mp. [mp=abstract, heading words, title]

6 or/2-5

7 1 and 6

Database: CINAHL

Search Strategy:

S1 fructose oligosaccharide* or fructooligosaccharide* or fructo oligosaccharide* or oligofructose* or neosugar*

- S2 fructan* or inutest* or oligofructan* or polyfructosan*
- S3 inulin* or asteraceae
- S4 chicory
- S5 jerusalem artichoke*
- S6 helianthus
- S7 S1 OR S2 OR S3 OR S4 OR S5 OR S6
- S8 (MH "Lipids")
- S9 lipid or lipids
- S10 MH "Lipoproteins"
- S11 lipoprotein*
- S12 MH "Lipoproteins, LDL+"
- S13 MH "Lipoproteins, HDL+"
- S14 HDL or LDL or VLDL or IDL or TG or TAG
- S15 MH "Triglycerides"
- S16 triacylglycerol* or triacylglyceride*
- S17 MH "Cholesterol"
- S18 cholesterol*
- S19 MH "Apolipoproteins"
- S20 apo* a1 or apo* a 1 or apo* a i or apo* ai
- S21 proapolioprotein N1 (ai or a1 or a i or a 1)
- S22 apo* b*
- S23 proapolioprotein N1 b*

S24 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23

- S25 MH "Waist Circumference"
- S26 waist N3 (circumference* or ratio*)
- S27 MH "Glucose"

- S28 glucose*
- S29 MH "Blood Pressure"
- S30 blood pressure*
- S31 MH "Body Mass Index"
- S32 body mass ind* or BMI
- S33 S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32
- S34 S7 AND S24 AND S33
- S35 S7 AND S24 AND S33

Supplementary materials: References of included studies

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Chapter 6: Discussion and conclusion

In this thesis, we explored the effects of inulin-type fructans supplementation on cardiovascular disease risk factors in adults in a systematic review of randomized controlled trials. We also assessed the quality of reporting in randomized controlled trials and abstracts of included trials of in the systematic review.

We included the following methodological improvements: First, we incorporated both crossover and parallel trials using Cochrane Collaboration guidance (1). Second, we conducted prespecified subgroup analyses, and third, we used the GRADE (grading of recommendations assessment, development and evaluation) approach which were lacking in previous systematic review of inulin-type fructans supplementation studies.

Our review demonstrated that inulin-type fructans supplementation probably has beneficial effects on low-density lipoprotein, triglycerides, and body weight but little to no effect on fasting blood glucose. However, we have less confidence on these results considering the low to very low certainty of evidence for these outcomes. Subgroup analysis by study duration indicated that inulin-type fructans supplementation probably had a beneficial effect on low-density lipoprotein in longer duration studies (i.e., follow-up duration of ≥ 6 weeks). In the case of triglycerides, subgroup analysis by BMI showed that inulin-type fructans supplementation possibly had beneficial effects in pre-obese (i.e., BMI 25.0 to 29.9 kg/m) and obese (i.e., BMI >30 kg/m2) participants.

The results of our review were similar to previously published systematic reviews especially for low-density lipoprotein cholesterol and triglycerides (2-5). For example, previous systematic reviews consistently reported beneficial effects of inulin-type fructans supplementation on low-density lipoprotein cholesterol (4, 5) and triglycerides (5, 6). In the case of fasting blood glucose,

the results were not consistent. For example, Wang et al. (2019) (7) and Li et al. (2021) (5) reported beneficial effects of inulin-type fructans on fasting blood glucose. However, Liu et al. (2017) (4) reported non-significant difference on fasting blood glucose after inulin-type fructans supplementation, which was similar to our result. It is important to note that our review included more recent studies in addition to the studies included in previous reviews. That is our review provided more up to date evidence on inulin-type fructans and fasting blood glucose, and this might explain some of the discrepancies.

This thesis has advanced the understanding of ITF in cardiovascular disease risk factor development through conducting an appropriate, up-to-date quantitative synthesis of RCTs, improving up on methodological limitations of previous reviews, and applying the GRADE approach to evaluating the quality of the body of evidence. The following sections briefly discussed the methodological contribution made by this thesis.

Methodological contribution

Methodologically rigorous systematic reviews are often the cornerstone for clinical practice guidelines and recommendations to reduce chronic disease risk. It is usually impractical for researchers and decision makers to assess the vast quantity of primary research and make informed health care decisions that benefit rather than harm based on up-to-date information because of the rapid increase in research literature (1). A rigorous systematic review process identifies all available relevant empirical evidence that informs a focused clinical or often broader public health problem (8). A systematic review also minimizes bias by using explicit, systematic methods to produce trustworthy findings that can be used to draw conclusions and make decisions (1, 9). It can be conducted to verify if a current clinical approach or public health guideline is supported by the best available evidence, assess the quality of this evidence, and

help resolve any uncertainty or inconsistency in practice resulting from conflicting evidence. Additionally, a systematic review can highlight methodological concerns in an existing evidence base, and provide a foundation and insight for future research in the field (9, 10).

Proper reporting of randomized trials (RCTs) especially reporting methodological details, such as the specification of primary outcomes, random sequence generation, and blinding (11) helps readers to assess the validity of RCT results (12). Insufficient reporting of RCTs can lead to categorizing a study as a high risk of bias, which can ultimately downgrade the certainty of evidence of the study.

This thesis has methodological implications that might contribute to the advancement of inulintype fructans (ITF) supplementation studies, which are relevant to the field of nutrition epidemiology as whole. Previous reviews (3-6, 13) have shown that ITF can be beneficial in improving some CVD risk factors, such as low-density lipoprotein and fasting blood glucose, in certain subgroups like females and patients with comorbidities. However, these studies have several methodological limitations. These include failing to explain statistical approaches for combining parallel and crossover trials, not following established guidance for the specification, conduct, and reporting of subgroup analyses, and not assessing the certainty of evidence. Our systematic review assessed the effects of inulin-type fructans supplementation on cardiovascular disease risk factors in adults, using the GRADE (grading of recommendations assessment, development and evaluation) approach, conducting prespecified subgroup analyses, and incorporating both crossover and parallel trials. We briefly discussed these aspects below.

Certainty (quality) of the body of evidence using GRADE approach

Authors should provide certainty of evidence in addition to providing effect estimates for an outcome (1). Cochrane suggests using the GRADE (Grading of Recommendations Assessment,

Development and Evaluation) approach for assessing the certainty of evidence (1). More than 100 organizations including the World Health Organization, the Canadian Agency for Drugs and Technology in Health has adopted this approach for assessing certainty of body of evidence (1). GRADE approach considers five domains: risk of bias, imprecision, inconsistency, indirectness, and likelihood of publication bias to assess certainty of a body of evidence. Based on these domains, this approach determines one of the four levels (i.e., high, moderate, low, or very low) of the certainty for a body of evidence for each outcome (1). Other approaches for assessing certainty of evidence include NutriGrade, Hierarchies of Evidence Applied to Lifestyle Medicine (HEALM), and the Oxford Centre for Evidence-Based Medicine Levels of Evidence (14). The suitability of applying the GRADE approach to nutrition has been questioned due to challenges in conducting randomized controlled trials (RCTs), resulting in most evidence relying on nonrandomized studies with lower certainty ratings. Proponents of an alternative approach suggest using NutriGrade for nutrition research (15). NutriGrade assigns similar weight to RCTs and cohort studies when the effect size is large (RR or HR: <0.50 and >2.00, with a statistically significant corresponding test) (15). However, GRADE is recommended if the question can be effectively addressed through RCTs (16). Moreover, it is important to ensure uniformity in the criteria used to assess the certainty of evidence across various health domains (17). Considering these aspects, we used the GRADE approach in our systematic review (please see chapter 3 for detailed assessment).

In our systematic review, based on low to very low certainty of the body of evidence, the pooled estimate demonstrated that inulin-type fructans may reduce low-density lipoprotein (mean difference [MD] -0.14 mmol/l, 95% confidence interval [CI] -0.24 to -0.05 mmol/l), triglycerides (MD -0.06 mmol/l, 95% CI -0.12 to -0.01 mmol/l), and body weight (MD -0.97 kg, 95% CI -

1.28 to -0.66). Our findings of evidence with low to very low certainty on the effects of inulintype fructans supplementation suggests further well-designed and executed trials are needed to improve the certainty of the evidence.

Subgroup analysis

In meta-analysis of RCTs, subgroup analyses are performed to understand how intervention effects differs based on study design characteristics (e.g., age distribution, sex distribution, or geographical location) (18-20). Subgroup analysis can provide misleading results if they do not follow a sound scientific process (21, 22). There are many published guidance that helps to evaluate the credibility of subgroup analyses (18, 23-26). We followed the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) approach to conduct subgroup analyses for our systematic review (18). This approach stresses the importance of hypothesising direction of subgroup effects a priori, using a test for interaction, testing only a small number of subgroups and using random effect model within subgroup in meta-analysis.

The credibility of claimed subgroup effect is higher when the investigators correctly anticipate the direction of subgroup effect *a priori* (e.g., an intervention being more effective in females), lower if they fail to anticipate the direction, and lowest if they anticipate the opposite direction. When investigators correctly anticipate an effect modification, it indicates that they had a particular hypothesis in mind, which is typically grounded in a biological or causal rationale, or in some cases, supported by external evidence (18). It is crucial to verify whether a test for interaction (usually a p-value) indicates that the observed effect modification is not likely due to chance (18). Demonstrating that an effect is significant in one subgroup and not in another is of limited value. Conducting multiple tests is a major concern in subgroup analysis. As trialists often measure numerous baseline variables, many of which they could examine for potential

effect modification, and this elevates the possibility of a chance finding; thus, credibility of subgroup analyses is higher if the investigators examine only a small number (usually \leq 5) of subgroup or effect modifiers (18, 26). Moreover, if investigators use a random effects model within subgroups to allow true effects to differ among studies, the credibility of the claimed effect modification is higher. This model enables the generalization of results beyond the studies included in the meta-analysis, and it is usually the most appropriate model to use (18).

Consistent with ICEMAN guidance, we prespecified subgroup analyses in our published protocol (please see chapter 2) and used a test for interaction and random effect model within subgroup in subgroup analyses. Subgroup analysis by study duration and BMI suggested that ITF supplementation had a beneficial effect on low-density lipoprotein cholesterol in longer duration studies (follow-up duration ≥ 6 weeks) (MD – 0.22 mmol/l, 95% CI -0.35 to -0.08 mmol/l, p = 0.04) and on triglycerides in pre-obese (BMI 25.0 to 29.9 kg/m2) (MD -0.09 mmol/l, 95% CI -0.15 to -0.02 mmol/l, p = 0.01), and obese participants (BMI >30 kg/m2) (MD -0.14 mmol/l, 95% CI -0.21 to -0.06 mmol/l, p = 0.01), respectively. These findings might have clinical implications for pre-obese and obese people for the management of their cardiovascular health, as well as for policy makers involved in managing cardiovascular diseases for the public. We have less confidence in subgroup results for triglycerides as the hypothesised direction is contradict with subgroup direction.

Parallel analysis of crossover trials

In a crossover trial, each participant receives both the treatment and the control. Since each participant receives both treatments, the measurements within each participant are correlated. If we ignore this correlation, we will overestimate the variance of the effect sizes, which will result in the trials getting very little weight in the meta-analysis. Therefore, it is essential to consider

the correlation between multiple measures in the same individual over time while conducting a meta-analysis of crossover trials to arrive at accurate conclusions (1). We did sensitivity analysis imputing correlation coefficients of 0, 0.33 and 0.66 to account for within-subject correlation in our meta-analysis based on Cochrane Collaboration guidance (1, 27). However, these sensitivity analyses did not appreciably alter the effect estimates of ITF supplementation on LDL-C, triglycerides and fasting blood glucose.

Reporting quality of abstracts of randomized controlled trials

To evaluate the validity and applicability of randomized controlled trials (RCTs), it is crucial to have detailed reporting in their abstracts. We examined the reporting quality of RCT abstracts investigating the impact of inulin-type fructans supplementation on cardiovascular risk factors, both before and after the publication of the Consolidated Standards of Reporting Trials extension for abstracts (CONSORT-A) in 2008. CONSORT-A comprises 15 items that address seven areas: the title, trial design, methods (participants, interventions, objective, outcomes, randomization, blinding), results (numbers randomized, numbers analyzed, outcome, harms), conclusions, trial registration, and funding. Our study demonstrated that the mean number of adequately reported items being 3.91 before and 4.64 after publication, indicating no significant difference (mean difference 0.73, 95% CI -1.61 to 0.16) in reporting quality between the two periods, and no factors associated with better reporting quality were identified. However, studies published after the release of CONSORT-A were more likely to report certain information such as titles identifying them as RCTs, the number of participants randomized, and trial registration, but were less likely to report trial design. In nutrition field, major journals like the American Journal of Clinical Nutrition, Clinical Nutrition and Journal of Nutrition endorse CONSORT-A. Enforcing its usage by other journals might improve the reporting quality of abstract of RCTs.

Reporting quality of randomized controlled trials

When publishing a randomized controlled trial (RCT), it is necessary to provide transparent and comprehensive reporting of the study's design, conduct, analysis, and interpretation, enabling readers and practitioners to accurately assess the trial's validity and suitability for specific practice settings. The Consolidated Standards of Reporting Trials (CONSORT) statement helps the study authors to facilitate improved and transparent reporting of trials (28). We assessed the reporting quality of RCTs examining the effects of inulin-type fructans supplementation on cardiovascular risk factors, before and after the publication of the Consolidated Standards of Reporting Trials (CONSORT) in 2010. CONSORT contains a 37-item checklist that authors are expected to follow while reporting an RCT. The checklist has five broad domains: title and abstract, introduction, methods, results, and discussion. The overall reporting quality of an RCT was defined as the total number of items reported out of 36 items in the CONSORT checklist. We omitted item 17b because it evaluates the reporting of binary outcomes, whereas the RCTs included in our study only reported continuous outcomes. Our study demonstrated that there was a significant increase in the reporting of CONSORT items, with a mean difference of 8.5 items (95% confidence interval [CI] 5.24 to 11.71) after the CONSORT publication. The only factor that predicted better reporting quality of RCTs was whether the study was published before or after CONSORT, with an incidence rate ratio of 1.67 (95% CI 1.40 to 2.02). However, only 15 out of 36 items (41.6%) showed an improvement in the completeness of reporting of RCTs after the CONSORT publication. Despite an improvement in the reporting quality of some CONSORT items following the publication of CONSORT, the improvement was insufficient. For instance, although there was an increase in the reporting of randomization methodology (such as sequence generation, allocation concealment, implementation of random allocation, and

blinding), these items were only reported in 40.48% to 61.90% of studies. Inadequate reporting of the randomization methodology can result in an overestimation of the treatment effect (29). Major journals in the field of nutrition, such as the American Journal of Clinical Nutrition, Clinical Nutrition, and Journal of Nutrition, support and endorse the use of CONSORT. Encouraging the adoption of CONSORT by other journals could enhance the quality of RCTs.

Implications for practice

Our systematic review assessed the effects of inulin-type fructans (ITF) supplementation on cardiovascular disease risk factors. This review provides low to very low certainty of evidence that ITF supplementation probably decreases low-density lipoprotein cholesterol (LDL-C), triglycerides, and body weight. The effects of ITF supplementation are more pronounced on LDL-C in longer duration study (i.e., follow-up duration \geq 6 weeks) and on triglycerides in preobese (i.e., BMI 25.0 to 29.9 kg/m2) and obese participants (i.e., BMI >30 kg/m2). Considering the low to very low certainty of evidence and as hypothesise direction is opposite to subgroup direction for triglycerides, so we have less confidence in the validity of the results. Consideration should be given to the limitations of these results in relation to routine clinical applications.

Implications for policy

The findings of our systematic review suggest that ITF supplementation may have potential implications for public health policies related to cardiovascular disease prevention and management. Policymakers could consider including ITF-rich foods or recommending ITF supplementation as part of dietary interventions, particularly for individuals at risk of developing obesity. Given the low to very low certainty of evidence, the beneficial effects of ITF supplementation need to be cautiously interpreted until evidence from more high-quality randomised trial is available. Further research is necessary to establish the efficacy and safety

profiles of ITF supplementation, which could inform the development of evidence-based guidelines.

Implications for research

Our systematic review highlights several areas for future research. Firstly, there is a need for additional well-designed and properly executed randomized controlled trials to investigate the effects of ITF supplementation compared to no supplementation on cardiovascular disease risk factors, particularly in specific populations characterized by different disease statuses. These trials should focus on ensuring longer follow-up durations and considering different subgroups based on BMI, ITF type and study duration. Future trials should reduce bias due to the randomization process, missing data, selective reporting and deviation from the intended intervention. Moreover, a priori registration, publication of protocols, and detailed data analysis plans, as well as use of appropriate reporting guidelines (e.g. CONSORT) by future trials, would also be beneficial to the quality and utility of any future research. Finally, conducting highquality systematic reviews and meta-analyses, incorporating high-quality trials in the future, would further contribute to the existing knowledge on ITF supplementation and its impact on cardiovascular health.

Conclusion

Overall, this thesis assessed the effects of inulin-type fructans supplementation on cardiovascular disease risk factors. It has contributed to the advancement of systematic review on inulin-type fructans (ITF) supplementation by addressing the limitations in previous reviews. It has also demonstrated gaps in reporting of randomized controlled trials and abstracts of randomized controlled trials and stressed the importance of improving the reporting quality of inulin-type supplementation studies.

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