Inulin-type fructans supplementation and cardiovascular disease risk factors

Inulin-type fructans supplementation and cardiovascular disease risk factors

By

Jhalok Ronjan Talukdar, MSS, MPH, MSc

A thesis submitted to the School of Graduate Studies

in partial fulfillment of the requirements for the Degree

Doctor of Philosophy

in Health Research Methodology,

McMaster University

Doctor of Philosophy (2023)

Health Research Methodology, McMaster University, Hamilton, Ontario, Canada

Title: Inulin-type fructans supplementation and cardiovascular disease risk factors

Author: Jhalok Ronjan Talukdar, BSS & MSS (Shahjalal University of Science and Technology, Bangladesh), MPH (BRAC University, Bangladesh), MSc (McMaster University, Canada)

Supervisors: Dr. Russell Jude de Souza and Dr. Lawrence Mbuagbaw

Number of pages: xiv, 242

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 peer-reviewed 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.

ACKNOWLEDGEMENTS

Success in health research requires a dedicated team of professionals from diverse backgrounds, and I was fortunate enough to have such a team. I am grateful to every one of them who helped me achieve my goal of completing my PhD.

I owe a special debt of gratitude to my supervisors, Dr. Lawrence Mbuagbaw and Dr. Russell Jude de Souza, who played an instrumental role in transforming my PhD experience from one of struggle and despair to one of triumph and success. They provided me with the mentorship and support that I needed to thrive, taking the time to provide insightful feedback that helped me refine my ideas and approach. They also challenged me when needed, to show me what I could achieve. I will never forget their belief in me and their willingness to challenge and inspire me to achieve my full potential.

I would also like to express my sincere gratitude to Dr. Behnam Sadeghirad, who served as the third member of my thesis committee and provided insightful feedback and guidance that greatly improved the quality of my research. Dr. Sadeghirad also served as my independent study supervisor and dedicated a significant amount of time to ensuring my success.

In addition to my supervisors, I am indebted to Dr. Lehana Thabane, Dr. Bradley Johnston, and Dr. Sameer Parpia for their invaluable guidance and mentorship during different phases of my PhD, shaping my research and academic growth.

I must also acknowledge the unwavering support of my family and friends, who have been a constant source of encouragement and inspiration. Specifically, I thank my brothers - Bidyut, Pradyut, Pulak, and Rupak, my cousin Lipi and my wife Priyanka, whose constant support and guidance helped me navigate the highs and lows of graduate school.

Finally, I am grateful to my colleagues, faculty, and staff in the Health Research Methodology program who supported me when needed. I feel fortunate to have been surrounded by such an incredible group of individuals throughout my academic journey. Your unwavering support, encouragement, and guidance have played a vital role in shaping my academic career, and for that, I am eternally grateful. Thank you all for being an integral part of my journey.

TABLE OF CONTENTS

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 inulin-type 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.

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

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

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 well-developed 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

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 meta-analyst 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

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 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. 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.

References

1. Vaduganathan M, Mensah George A, Turco Justine V, Fuster V, Roth Gregory A. The Global Burden of Cardiovascular Diseases and Risk. Journal of the American College of Cardiology. 2022;80(25):2361-71.

2. Cardiovascular diseases — Level 2 cause [Internet]. 2019 [cited September 22, 2021]. Available from: http://www.healthdata.org/results/gbd_summaries/2019/cardiovascular-diseases-level-2-cause.

3. Frostegård J. Immunity, atherosclerosis and cardiovascular disease. BMC Med. 2013;11:117-.

4. Francula-Zaninovic S, Nola IA. Management of Measurable Variable Cardiovascular Disease' Risk Factors. Curr Cardiol Rev. 2018;14(3):153-63.

5. World Health Organization. Cardiovascular diseases (CVDs) 2021 [cited 2021 September 01]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

6. National Health Service (NHS). Cardiovascular disease 2018 [Available from: https://www.nhs.uk/conditions/cardiovascular-disease/.

7. American Heart Association. Health Threats from High Blood Pressure 2023 [cited 2023 June 18]. Available from: https://www.heart.org/en/health-topics/high-blood-pressure/health-threats-from-high-blood-pressure.

8. American Heart Association. HDL (Good), LDL (Bad) Cholesterol and Triglycerides 2023 [Available from: https://www.heart.org/en/health-topics/cholesterol/hdl-good-ldl-bad-cholesterol-and-triglycerides.

9. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. Int J Mol Sci. 2014;15(4):6184-223.

10. Duca L, Sippl R, Snell-Bergeon JK. Is the risk and nature of CVD the same in type 1 and type 2 diabetes? Curr Diab Rep. 2013;13(3):350-61.

11. National Institute of Diabetes and Digestive and Kidney Diseases. Diabetes, Heart Disease, & Stroke 2021 [Available from: https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/heart-disease-stroke.

12. Rakhra V, Galappaththy SL, Bulchandani S, Cabandugama PK. Obesity and the Western Diet: How We Got Here. Mo Med. 2020;117(6):536-8.

13. Afshin A, Sur PJ, Fay KA, Cornaby L, Ferrara G, Salama JS, et al. Health effects of dietary risks in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet. 2019;393(10184):1958-72.

14. World Health Organization. Healthy diet 2020 [cited 2023 June 18]. Available from: https://www.who.int/news-room/fact-sheets/detail/healthy-diet.

15. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism: clinical and experimental. 2022;133:155217.

16. Anand SS, Hawkes C, de Souza RJ, Mente A, Dehghan M, Nugent R, et al. Food Consumption and its Impact on Cardiovascular Disease: Importance of Solutions Focused on the Globalized Food System: A Report From the Workshop Convened by the World Heart Federation. J Am Coll Cardiol. 2015;66(14):1590-614.

17. Roberfroid MB. Functional foods: concepts and application to inulin and oligofructose. British Journal of Nutrition. 2002;87(S2):S139-S43.

18. Mirmiran P, Bahadoran Z, Azizi F. Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: A review. World J Diabetes. 2014;5(3):267-81.

19. Ballali S, Lanciai F. Functional food and diabetes: a natural way in diabetes prevention? International Journal of Food Sciences and Nutrition. 2012;63(sup1):51-61.

20. Roberfroid MB. Inulin-Type Fructans: Functional Food Ingredients. The Journal of Nutrition. 2007;137(11):2493S-502S.

21. Gregori D, Gafare CE. Multifunctional food: medical evidence and methodological notes on substantiating health claims. International Journal of Food Sciences and Nutrition. 2012;63(sup1):29-36.

22. Al-Sheraji SH, Ismail A, Manap MY, Mustafa S, Yusof RM, Hassan FA. Prebiotics as functional foods: A review. Journal of Functional Foods. 2013;5(4):1542-53.

23. Alkhatib A, Tsang C, Tiss A, Bahorun T, Arefanian H, Barake R, et al. Functional Foods and Lifestyle Approaches for Diabetes Prevention and Management. Nutrients. 2017;9(12).

24. Roberfroid MB. Concepts in functional foods: the case of inulin and oligofructose. J Nutr. 1999;129(7 Suppl):1398s-401s.

25. Pandey KR, Naik SR, Vakil BV. Probiotics, prebiotics and synbiotics- a review. J Food Sci Technol. 2015;52(12):7577-87.

26. Grajek W, Olejnik A, Sip A. Probiotics, prebiotics and antioxidants as functional foods. Acta Biochim Pol. 2005;52(3):665-71.

27. Florowska A, Krygier K, Florowski T, Dłużewska E. Prebiotics as functional food ingredients preventing diet-related diseases. Food Funct. 2016;7(5):2147-55.

28. Van Loo J, Bosscher D. Inulin-Type Fructans. Therapeutic Microbiology2008. p. 147-57.

29. Wilson B, Whelan K. Prebiotic inulin-type fructans and galacto-oligosaccharides: definition, specificity, function, and application in gastrointestinal disorders. Journal of Gastroenterology and Hepatology. 2017;32(S1):64-8.

30. Man S, Liu T, Yao Y, Lu Y, Ma L, Lu F. Friend or foe? The roles of inulin-type fructans. Carbohydrate Polymers. 2021;252:117155.

31. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, et al. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods. 2019;8(3).

32. Kolida S, Gibson GR. Prebiotic Capacity of Inulin-Type Fructans. The Journal of Nutrition. 2007;137(11):2503S-6S.

33. Roberfroid MB. Prebiotics and probiotics: are they functional foods? The American Journal of Clinical Nutrition. 2000;71(6):1682S-7S.

34. Roberfroid M, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, et al. Prebiotic effects: metabolic and health benefits. British Journal of Nutrition. 2010;104(S2):S1-S63.

35. Niness KR. Inulin and Oligofructose: What Are They? The Journal of Nutrition. 1999;129(7):1402S-6S.

36. Bosscher D. Fructan Prebiotics Derived from Inulin. In: Charalampopoulos D, Rastall RA, editors. Prebiotics and Probiotics Science and Technology. New York, NY: Springer New York; 2009. p. 163-205.

37. Jackson PPJ, Wijeyesekera A, Rastall RA. Inulin-type fructans and short-chain fructooligosaccharides—their role within the food industry as fat and sugar replacers and texture modifiers—what needs to be considered! Food Science & Nutrition. 2023;11(1):17-38.

38. Ramos Meyers G, Samouda H, Bohn T. Short Chain Fatty Acid Metabolism in Relation to Gut Microbiota and Genetic Variability. Nutrients. 2022;14(24).

39. Hu T, Wu Q, Yao Q, Jiang K, Yu J, Tang Q. Short-chain fatty acid metabolism and multiple effects on cardiovascular diseases. Ageing Res Rev. 2022;81:101706.

40. Li L, Li P, Xu L. Assessing the effects of inulin-type fructan intake on body weight, blood glucose, and lipid profile: A systematic review and meta-analysis of randomized controlled trials. Food Sci Nutr. 2021;9(8):4598-616.

41. Liu F, Prabhakar M, Ju J, Long H, Zhou HW. Effect of inulin-type fructans on blood lipid profile and glucose level: a systematic review and meta-analysis of randomized controlled trials. European journal of clinical nutrition. 2017;71(1):9-20.

42. Beserra BT, Fernandes R, do Rosario VA, Mocellin MC, Kuntz MG, Trindade EB. A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. Clinical nutrition (Edinburgh, Scotland). 2015;34(5):845-58.

43. Wang L, Yang H, Huang H, Zhang C, Zuo HX, Xu P, et al. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose-response meta-analysis of 33 randomized controlled trials. J Transl Med. 2019;17(1):410.

44. Brighenti F. Dietary Fructans and Serum Triacylglycerols: A Meta-Analysis of Randomized Controlled Trials. The Journal of Nutrition. 2007;137(11):2552S-6S.

45. Faghihimani Z, Namazi N, Ghaffari S, Rezaei Kelishadi M, Sharifi S, Nattagh-Eshtivani E, et al. Effects of Inulin Type-Carbohydrates on blood pressure: a systematic review and meta-analysis. International Journal of Food Properties. 2021;24(1):129-39.

46. Wang L, Yang H, Huang H, Zhang C, Zuo H-X, Xu P, et al. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose–response meta-analysis of 33 randomized controlled trials. Journal of Translational Medicine. 2019;17(1):410.

47. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane, 2021. Available from www.training.cochrane.org/handbook.; 2021.

48. Katz DL, Karlsen MC, Chung M, Shams-White MM, Green LW, Fielding J, et al. Hierarchies of evidence applied to lifestyle Medicine (HEALM): introduction of a strength-of-evidence approach based on a methodological systematic review. BMC Med Res Methodol. 2019;19(1):178.

49. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019): Cochrane, 2019. Available from www.training.cochrane.org/handbook.; 2019.

50. Schandelmaier S, Briel M, Varadhan R, Schmid CH, Devasenapathy N, Hayward RA, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. Canadian Medical Association Journal. 2020;192(32):E901.

51. Chan A-W, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. The Lancet. 2005;365(9465):1159-62.

52. DeMauro SB, Giaccone A, Kirpalani H, Schmidt B. Quality of reporting of neonatal and infant trials in high-impact journals. Pediatrics. 2011;128(3):e639-44.

53. Soares HP, Daniels S, Kumar A, Clarke M, Scott C, Swann S, et al. Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group. Bmj. 2004;328(7430):22-4.

54. Talukdar JR, Cooper MA, Lyutvyn L, Zeraatkar D, Ali R, Bierbrier R, et al. Effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2022;12(7):e058875.

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.

Open access 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

Jhalok Ronjan Talukdar ,[1] Matthew Adam Cooper,[2] Lyuba Lyutvyn,[1] Dena Zeraatkar ,[1,3] Rahim Ali,[4] Rachel Bierbrier,[5] Sabrina Janes,[6] Vanessa Ha,[7] Pauline B Darling,[8] John L Sievenpiper,[9,10] David J A Jenkins ,[9,10,11] Laura Banfield,[12] Lawrence Mbuagbaw ,[1,13,14,15,16,17] Russell J de Souza [1,18,19]

To cite: Talukdar JR, Cooper MA, Lyutvyn L, *et al*. Effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a protocol for a systematic review and meta-analysis of **randomised** controlled trials. *BMJ Open* 2022;**12**:e058875. doi:10.1136/bmjopen-2021-058875

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-058875).

Received 03 November 2021
Accepted 24 March 2022

For numbered affiliations see end of article.

Correspondence to
Dr Russell J de Souza; desouzrj@mcmaster.ca

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 ITF; (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.

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.
⇒ 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.

INTRODUCTION

Cardiovascular disease (CVD) is a major cause of death worldwide.[1] In 2019, CVD caused an estimated 17.9 million deaths globally[1] 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) 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.[5 6] 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.[7 8] Some of the well-established risk factors for CVD include high blood pressure, high cholesterol, diabetes, and excess body fat.[9]

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

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.[14 15] 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.[17–19]

Inulin-type fructans (ITF) are carbohydrates[20] 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 bacteria[24] 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*[31] 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 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 tool[34] 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

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:

1. 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 ≥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 well-conducted 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 1996[45] 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.[42 45 46 52] 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 CONSORT-A 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.

Author affiliations
[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
[2]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[3]Department of Biomedical Informatics, Harvard Medical School, Boston, Massachusetts, USA
[4]Faculty of Law (Common Law Section), University of Ottawa, Ottawa, Ontario, Canada
[5]Department of Dermatology, McGill University Health Centre, Montreal, Québec, Canada
[6]St Michael's Hospital, Toronto, Ontario, Canada
[7]School of Medicine, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada
[8]School of Nutrition Sciences, University of Ottawa, Ottawa, Ontario, Canada
[9]Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[10]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition and Risk Factor Modification centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
[11]Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[12]Health Sciences Library, McMaster University, Hamilton, Ontario, Canada
[13]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada
[14]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada
[15]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
[16]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon
[17]Department of Global Health, Stellenbosch University, Cape Town, South Africa
[18]Global Health Graduate Program, McMaster University, Hamilton, Ontario, Canada
[19]Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada

Twitter Rahim Ali @rahimalii and Russell J de Souza @DrRussRD

Contributors RJdS conceived the work. JRT drafted the manuscript. RJdS, LM, JRT, DZ, MAC, LL, RA, RB, SJ, VH, PBD, JLS and DJAJ contributed to the data analysis plan. LB contributed to the search strategy development. RJdS, LM, JRT, DZ, MAC, LL, RA, RB, SJ, VH, PBD, JLS, DJAJ and LB will collaborate on data interpretation. RJdS is the guarantor of this study. RJdS, LM, DZ, MC, LL, RA, RB, SJ, VH, PBD, JLS and DJAJ revised the manuscript critically for important intellectual content.

Funding No financial support was received for preparation of this manuscript.

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 Soybean Board (the USDA soy '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,

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 Coie, 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. 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 scientific advisor for the Food, Nutrition and Safety Program (FNSP) and the Technical Committee on Carbohydrates of 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 wife is an employee of AB InBev.DJAJ received salary support and discretionary funding from the Canada Research Chair (CRC) endowment of the federal government of Canada. He has received research grants from Saskatchewan & Alberta Pulse Growers Associations, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies, Unilever Canada and 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, Bayer Consumer Care, Springfield, New Jersey, 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, 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, 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. He received an honorarium from the US 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 two daughters, Wendy Jenkins and Amy Jenkins, have published a vegetarian book, 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.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Jhalok Ronjan Talukdar http://orcid.org/0000-0001-9739-5632
Dena Zeraatkar http://orcid.org/0000-0003-4287-0541
David J A Jenkins http://orcid.org/0000-0003-1192-9571
Lawrence Mbuagbaw http://orcid.org/0000-0001-5855-5461
Russell J de Souza http://orcid.org/0000-0001-8945-513X

REFERENCES

1 World Health Organization. Cardiovascular diseases (CVDs), 2021. Available: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)
2 Francula-Zaninovic S, Nola IA. Management of measurable variable cardiovascular disease' risk factors. *Curr Cardiol Rev* 2018;14:153–63.
3 Cardiovascular diseases — Level 2 cause [online], 2019. Available: http://www.healthdata.org/results/gbd_summaries/2019/cardiovascular-diseases-level-2-cause [Accessed 22 Sep 2021].
4 Frostegård J. Immunity, atherosclerosis and cardiovascular disease. *BMC Med* 2013;11:117.
5 National Heart Lung and Blood Institute (NHLB), 2021. Available: https://www.nhlbi.nih.gov/health-topics/atherosclerosis [Accessed 1 Sep 2021].
6 National Health Service (NHS). Atherosclerosis, 2019. Available: https://www.nhs.uk/conditions/atherosclerosis/ [Accessed 1 Sep 2019].
7 Johns Hopkins Medicine. Fight inflammation to help prevent heart disease, 2021. Available: https://www.hopkinsmedicine.org/health/wellness-and-prevention/fight-inflammation-to-help-prevent-heart-disease [Accessed 21 Oct 2021].
8 American Heart Association. Inflammation and heart disease, 2021. Available: https://www.heart.org/en/health-topics/consumer-healthcare/what-is-cardiovascular-disease/inflammation-and-heart-disease [Accessed 21 Oct 2021].
9 National Health Service (NHS). Cardiovascular disease, 2018. Available: https://www.nhs.uk/conditions/cardiovascular-disease/ [Accessed 1 Sep 2021].
10 Threapleton DE, Greenwood DC, Evans CEL, *et al*. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. *BMJ* 2013;347:f6879.
11 Brown L, Rosner B, Willett WW, *et al*. Cholesterol-lowering effects of dietary fiber: a meta-analysis. *Am J Clin Nutr* 1999;69:30–42.
12 Streppel MT, Arends LR, van 't Veer P, *et al*. Dietary fiber and blood pressure: a meta-analysis of randomized placebo-controlled trials. *Arch Intern Med* 2005;165:150–6.
13 Sánchez-Muniz FJ. Dietary fibre and cardiovascular health. *Nutr Hosp* 2012;27:31–45.
14 Wong JMW, de Souza R, Kendall CWC, *et al*. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol* 2006;40:235–43.

15 Bernstein AM, Titgemeier B, Kirkpatrick K, *et al*. Major cereal grain fibers and psyllium in relation to cardiovascular health. *Nutrients* 2013;5:1471–87.
16 Tobe SW, Stone JA, Anderson T, *et al*. Canadian cardiovascular harmonized national guidelines endeavour (C-CHANGE) guideline for the prevention and management of cardiovascular disease in primary care: 2018 update. *CMAJ* 2018;190:E1192–206.
17 Kim Y, Je Y. Dietary fiber intake and total mortality: a meta-analysis of prospective cohort studies. *Am J Epidemiol* 2014;180:565–73.
18 Yang Y, Zhao L-G, Wu Q-J, *et al*. Association between dietary fiber and lower risk of all-cause mortality: a meta-analysis of cohort studies. *Am J Epidemiol* 2015;181:83–91.
19 Huang T, Xu M, Lee A, *et al*. Consumption of whole grains and cereal fiber and total and cause-specific mortality: prospective analysis of 367,442 individuals. *BMC Med* 2015;13:59.
20 Roberfroid MB. Inulin-type fructans: functional food ingredients. *J Nutr* 2007;137:2493S–502.
21 Niness KR, Inulin NKR. Inulin and oligofructose: what are they? *J Nutr* 1999;129:1402S–6.
22 Bosscher D. Fructan prebiotics derived from inulin. In: Charalampopoulos D, Rastall RA, eds. *Prebiotics and probiotics science and technology*. New York, NY: Springer, 2009: 163–205.
23 Man S, Liu T, Yao Y, *et al*. Friend or foe? The roles of inulin-type fructans. *Carbohydr Polym* 2021;252:117155.
24 Liu F, Prabhakar M, Ju J, *et al*. Effect of inulin-type fructans on blood lipid profile and glucose level: a systematic review and meta-analysis of randomized controlled trials. *Eur J Clin Nutr* 2017;71:9–20.
25 Davani-Davari D, Negahdaripour M, Karimzadeh I, *et al*. Prebiotics: definition, types, sources, mechanisms, and clinical applications. *Foods* 2019;8:92.
26 Beserra BTS, Fernandes R, do Rosario VA, *et al*. A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. *Clin Nutr* 2015;34:845–58.
27 Wang L, Yang H, Huang H, *et al*. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose-response meta-analysis of 33 randomized controlled trials. *J Transl Med* 2019;17:410.
28 Liber A, Szajewska H. Effects of inulin-type fructans on appetite, energy intake, and body weight in children and adults: systematic review of randomized controlled trials. *Ann Nutr Metab* 2013;63:42–54.
29 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
30 Higgins JPT, Thomas J, Chandler J. Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021), 2021. Available: www.training.cochrane.org/handbook
31 Roshanravan N, Mahdavi R, Alizadeh E, *et al*. Effect of butyrate and inulin supplementation on glycemic status, lipid profile and glucagon-like peptide 1 level in patients with type 2 diabetes: a randomized double-blind, placebo-controlled trial. *Horm Metab Res* 2017;49:886–91.
32 Elbourne DR, Altman DG, Higgins JPT, *et al*. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;31:140–9.
33 Curtin F, Altman DG, Elbourne D. Meta-analysis combining parallel and cross-over clinical trials. I: continuous outcomes. *Stat Med* 2002;21:2131–44.
34 Higgins JPT, Savović J, Page MJ. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, *et al*, eds. *Cochrane Handbook for systematic reviews of interventions version 6.2 (updated February 2021)*, 2021. www.training.cochrane.org/handbook
35 Ebrahim S, Akl EA, Mustafa RA, *et al*. Addressing continuous data for participants excluded from trial analysis: a guide for systematic reviewers. *J Clin Epidemiol* 2013;66:1014–21.
36 Guyatt GH, Ebrahim S, Alonso-Coello P, *et al*. GRADE guidelines 17: assessing the risk of bias associated with missing participant outcome data in a body of evidence. *J Clin Epidemiol* 2017;87:14–22.
37 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
38 Schandelmaier S, Briel M, Varadhan R, *et al*. Development of the instrument to assess the credibility of effect modification analyses (ICEMAN) in randomized controlled trials and meta-analyses. *CMAJ* 2020;192:E901–6.
39 Savović J, Turner RM, Mawdsley D, *et al*. Association between risk-of-bias assessments and results of randomized trials in Cochrane reviews: the ROBES meta-epidemiologic study. *Am J Epidemiol* 2018;187:1113–22.
40 Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924.
41 Guyatt G, Oxman AD, Akl EA, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011;64:383–94.
42 Schulz KF, Altman DG, Moher D, *et al*. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
43 Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. *BJOG* 2018;125:1716.
44 Akobeng AK. Understanding randomised controlled trials. *Arch Dis Child* 2005;90:840.
45 Begg C, Cho M, Eastwood S, *et al*. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* 1996;276:637–9.
46 Hopewell S, Clarke M, Moher D, *et al*. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008a;371:281–3.
47 Schulz KF, Chalmers I, Hayes RJ, *et al*. Empirical evidence of bias. dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;273:408–12.
48 Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;357:1191–4.
49 Barry HC, Ebell MH, Shaughnessy AF, *et al*. Family physicians' use of medical abstracts to guide decision making: style or substance? *J Am Board Fam Pract* 2001;14:437–42.
50 Hopewell S, Clarke M, Moher D, *et al*. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 2008b;5:e20.
51 Sriganesh K, Bharadwaj S, Wang M, *et al*. Quality of abstracts of randomized control trials in five top pain journals: a systematic survey. *Contemp Clin Trials Commun* 2017;7:64–8.
52 Moher D, Schulz KF, Altman D, *et al*. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *JAMA* 2001;285:1987–91.

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

Citation:

Talukdar JR, Cooper M, Lyutvyn L, Zeraatkar D, Ali R, Berbrier R, Janes R, Ha V, Darling R, Xue M, Chu A, Chowdhury F, Harnack HE, Huang L, Malik M, Powless J, Lavergne FV, Zhang X, Ehrlich S, Jenkins DJA, Sievenpiper JL, Banfield L, Mbuagbaw L, de Souza RJ. The effects of inulin-type fructans on cardiovascular disease risk factors: A systematic review and meta-analysis of randomized controlled trials (submitted to The American Journal of Clinical Nutrition, under review)

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

A systematic review and meta-analysis of randomized controlled trials

Jhalok Ronjan Talukdar[1], Matthew Cooper[2], Lyuba Lyutvyn[1], Dena Zeraatkar[1,3], Rahim Ali[4], Rachel Berbrier[5], Sabrina Janes[6], Vanessa Ha[7], Pauline B. Darling[8], Michael Xue[9], Alexandro Chu[10], Fariha Chowdhury[11], Hope E. Harnack[12], Louise Huang[9], Mikail Malik[9], Jacqui Powless[1], Florence V. Lavergne[13], Xuehong Zhang[14,15], Shelley Ehrlich[16], David JA Jenkins[17,18,19,20], John L Sievenpiper[21,22,23,24,25,26], Laura Banfield[27,28], Lawrence Mbuagbaw[1,29,30,31,32,33], Russell J de Souza[1,23,26,29,34]

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada
[2]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada
[3]Blavatnik Institute, Harvard Medical School, Boston, Massachusetts, USA
[4]Faculty of Law, Common Law Section, University of Ottawa, Ottawa, Ontario, Canada
[5]Division of Dermatology, McGill University Health Centre, Montreal, Quebec, Canada
[6]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada
[7]School of Medicine, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada
[8]School of Nutrition Sciences, University of Ottawa, Ottawa, Ontario, Canada
[9]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada
[10]Department of Medicine, McMaster University, Hamilton, Ontario, Canada
[11] School of Rehabilitation Science, McMaster University, Hamilton, Ontario, Canada
[12]Department of Kinesiology, Faculty of Science, McMaster University, Hamilton, Ontario, Canada
[13]School of Nutrition Sciences, Faculty of Health Sciences, University of Ottawa, Ontario, Canada
[14]Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA
[15]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, USA
[16]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA
[17]Departments of Nutritional Sciences and Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada
[18]Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, ON, Canada
[19]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada
[20]Division of Endocrinology, Department of Medicine, St. Michael's Hospital, Toronto, ON, Canada

[21]Department of Nutritional Sciences, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[22]Department of Medicine, Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada
[23]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital, Toronto, Ontario, Canada
[24]Clinical Nutrition and Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada
[25]Division of Endocrinology and Metabolism, Department of Medicine, St. Michael's Hospital, Toronto, Ontario, Canada
[26]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada
[27]Health Sciences Library, McMaster University, Hamilton, Ontario, Canada
[28]Global Health Graduate Program, McMaster University, Hamilton, Ontario, Canada
[29]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada
[30]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada
[31]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada
[32]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon
[33]Department of Global Health, Stellenbosch University, Cape Town, South Africa
[34]Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada

Corresponding author:
Russell J de Souza
Associate Professor
Department of Health Research Methods, Evidence, and Impact
McMaster University
MDCL, Room 3210
1280 Main Street West
Hamilton, ON, Canada, L8S 4K1
desouzrj@mcmaster.ca

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 ≥ 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.

Full-text word count: 4,087

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

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) very-low-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 ≥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).

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 (http://plotdigitizer.sourceforge.net/). 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 I^2 statistic. We considered that an I^2 value ≤ 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and ≥ 75% may represent considerable heterogeneity (13). If I^2 was ≥ 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 ≥ 10 g/day), risk of bias (low vs high or unclear), duration of intervention (< 6 weeks vs ≥ 6 weeks). We conducted three post-hoc subgroup analyses: 1) age (young: <40 years, old: ≥ 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 ≤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 ≥ 0.1) (**Supplementary Figures 12 - 20**). The substantial heterogeneity was explained by this subgroup (pre-obese: I^2 = 0%, obese: I^2 = 17%, normal: I^2 = 53.7%).

Sensitivity analyses excluding influential (39, 57) (MD -0.08, 95% CI -0.12 to -0.03 mmol/l, I^2 = 32%) and outliers (39, 45, 51, 57) RCTs (MD -0.05, 95% CI -0.09 to -0.02 mmol/l, I^2 = 1.2%) (**supplementary plot 3)** explained the heterogeneity and improved precisions of estimates without changing the conclusion (**Figure 2**). Including older (age on average ≥ 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 ($p \geq 0.1$) (**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

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-, low- and 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 LDL-C; and BMI 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

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 ≥ 6 weeks) and on TG in pre-obese (BMI 25.0 to 29.9 kg/m^2) and obese participants (BMI >30 kg/m^2) 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 well-designed 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

Acknowledgments

None

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.

Funding

No financial support was received for preparation of this manuscript.

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).

DJAJ has received research grants from Saskatchewan & Alberta Pulse Growers Associations, the Agricultural Bioproducts Innovation Program through the Pulse Research Network, the Advanced Foods and Material Network, Loblaw Companies Ltd., Unilever Canada and

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, 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. 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.

1. Roberfroid MB. Inulin-Type Fructans: Functional Food Ingredients. The Journal of Nutrition. 2007;137(11):2493S-502S.

2. Niness KR. Inulin and Oligofructose: What Are They? The Journal of Nutrition. 1999;129(7):1402S-6S.

3. Bosscher D. Fructan Prebiotics Derived from Inulin. In: Charalampopoulos D, Rastall RA, editors. Prebiotics and Probiotics Science and Technology. New York, NY: Springer New York; 2009. p. 163-205.

4. Man S, Liu T, Yao Y, Lu Y, Ma L, Lu F. Friend or foe? The roles of inulin-type fructans. Carbohydrate Polymers. 2021;252:117155.

5. Liu F, Prabhakar M, Ju J, Long H, Zhou HW. Effect of inulin-type fructans on blood lipid profile and glucose level: a systematic review and meta-analysis of randomized controlled trials. European journal of clinical nutrition. 2017;71(1):9-20.

6. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, et al. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods. 2019;8(3):92.

7. Shoaib M, Shehzad A, Omar M, Rakha A, Raza H, Sharif HR, et al. Inulin: Properties, health benefits and food applications. Carbohydrate Polymers. 2016;147:444-54.

8. Ward NC, Watts GF, Eckel RH. Statin Toxicity. Circulation Research. 2019;124(2):328-50.

9. Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, et al. Patient-Reported Reasons for Declining or Discontinuing Statin Therapy: Insights From the PALM Registry. Journal of the American Heart Association. 2019;8(7):e011765.

10. Beserra BT, Fernandes R, do Rosario VA, Mocellin MC, Kuntz MG, Trindade EB. A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. Clinical nutrition (Edinburgh, Scotland). 2015;34(5):845-58.

11. Wang L, Yang H, Huang H, Zhang C, Zuo HX, Xu P, et al. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose-response meta-analysis of 33 randomized controlled trials. J Transl Med. 2019;17(1):410.

12. Liber A, Szajewska H. Effects of inulin-type fructans on appetite, energy intake, and body weight in children and adults: systematic review of randomized controlled trials. Annals of nutrition & metabolism. 2013;63(1-2):42-54.

13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane, 2021. Available from www.training.cochrane.org/handbook.; 2021.

14. 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.

15. Talukdar JR, Cooper M, Lyutvyn L, Zeraatkar D, Ali R, Berbrier R, et al. 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 (accepted).

16. Dudum R, Juraschek SP, Appel LJ. Dose-dependent effects of lifestyle interventions on blood lipid levels: Results from the PREMIER trial. Patient Educ Couns. 2019;102(10):1882-91.

17. Packard C, Chapman MJ, Sibartie M, Laufs U, Masana L. Intensive low-density lipoprotein cholesterol lowering in cardiovascular disease prevention: opportunities and challenges. Heart. 2021;107(17):1369.

18. Esan O, Wierzbicki AS. Triglycerides and cardiovascular disease. Curr Opin Cardiol. 2021;36(4):469-77.

19. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet (London, England). 2014;384(9943):626-35.

20. Shi H, Ge Y, Wang H, Zhang Y, Teng W, Tian L. Fasting blood glucose and risk of Stroke: A Dose–Response meta-analysis. Clinical Nutrition. 2021;40(5):3296-304.

21. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

22. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010;36(3):1 - 48.

23. R Core Team. R: A language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria; 2020 [cited 2022 March 10]. Available from: https://www.R-project.org/.

24. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002.

25. Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Research Synthesis Methods. 2010;1(2):112-25.

26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

27. McMaster University and Evidence Prime. GRADEpro GDT: GRADEpro Guideline Development Tool [Software] 2021 [cited 2022 May 2]. Available from: gradepro.org.

28. Aliasgharzadeh A, Khalili M, Mirtaheri E, Pourghassem Gargari B, Tavakoli F, Abbasalizad Farhangi M, et al. A Combination of Prebiotic Inulin and Oligofructose Improve Some of

Cardiovascular Disease Risk Factors in Women with Type 2 Diabetes: A Randomized Controlled Clinical Trial. Advanced pharmaceutical bulletin. 2015;5(4):507-14.

29. Alles MS, de Roos NM, Bakx JC, van de Lisdonk E, Zock PL, Hautvast GA. Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. The American journal of clinical nutrition. 1999;69(1):64-9.

30. Bahmani F, Tajadadi-Ebrahimi M, Kolahdooz F, Mazouchi M, Hadaegh H, Jamal AS, et al. The Consumption of Synbiotic Bread Containing Lactobacillus sporogenes and Inulin Affects Nitric Oxide and Malondialdehyde in Patients with Type 2 Diabetes Mellitus: Randomized, Double-Blind, Placebo-Controlled Trial. Journal of the American College of Nutrition. 2016;35(6):506-13.

31. Blædel T, Holm JB, Sundekilde UK, Schmedes MS, Hess AL, Lorenzen JK, et al. A randomised, controlled, crossover study of the effect of diet on angiopoietin-like protein 4 (ANGPTL4) through modification of the gut microbiome. Journal of nutritional science. 2016;5:e45.

32. Bonsu NK, Johnson SJIJD, Metab. Effects of inulin fibre supplementation on serum glucose and lipid concentration in patients with type 2 diabetes. 2012;21:80-6.

33. Castro-Sanchez F, Ochoa-Acosta D, Valenzuela-Rubio N, Domínguez-Rodríguez M, Fierros-Valdez J, Vergara-Jiménez MJAJNM. Inulin effect on weight loss and associated parameters with the development of cardiovascular disease in obese dyslipidemic subjects. 2017;4(1):1044.

34. Causey JL, Feirtag JM, Gallaher DD, Tungland BC, Slavin JL. Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. Nutrition Research. 2000;20(2):191-201.

35. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019;68(8):1430-8.

36. Cronin BE, Allsopp PJ, Slevin MM, Magee PJ, Livingstone MB, Strain JJ, et al. Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain fructo-oligosaccharides on serum lipids in postmenopausal women. The British journal of nutrition. 2016;115(4):658-65.

37. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, et al. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity (Silver Spring, Md). 2014;22(6):1430-8.

38. Davidson MH, Maki KC, Synecki C, Torri SA, Drennan KBJNR. Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. 1998;18:503-17.

39. Dehghan P, Farhangi MA, Tavakoli F, Aliasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: A randomized placebo-controlled Trial. Complementary therapies in medicine. 2016;24:96-102.

40. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. International journal of food sciences and nutrition. 2014;65(1):117-23.

41. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62(8):1112-21.

42. Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clinical nutrition (Edinburgh, Scotland). 2009;28(2):182-7.

43. Ghavami A, Roshanravan N, Nattagh-Eshtivani E, Sharifi S, Arzhang P, Sani MA, et al. The effect of high performance inulin on appetite, energy in-take and anthropometric indices in patient with type 2 diabetes. 2019;21:121-6.

44. Giacco R, Clemente G, Luongo D, Lasorella G, Fiume I, Brouns F, et al. Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. Clinical nutrition (Edinburgh, Scotland). 2004;23(3):331-40.

45. Gómez-Reyes E, Orea-Tejeda A, Castillo-Martínez L, Cassis-Nosthas L, Vargas-Voracková FJE. Prebiotics consumption modifies diastolic blood pressure, but does not affect serum lipids concentration in volunteers with ischemic heart disease. 2010;128:139.

46. Guess ND, Dornhorst A, Oliver N, Bell JD, Thomas EL, Frost GS. A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. Nutrition & metabolism. 2015;12:36.

47. Guess ND, Dornhorst A, Oliver N, Frost GS. A Randomised Crossover Trial: The Effect of Inulin on Glucose Homeostasis in Subtypes of Prediabetes. Annals of nutrition & metabolism. 2016;68(1):26-34.

48. Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clinical nutrition (Edinburgh, Scotland). 2020;39(12):3618-28.

49. Luo J, Van Yperselle M, Rizkalla SW, Rossi F, Bornet FR, Slama G. Chronic consumption of short-chain fructooligosaccharides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. J Nutr. 2000;130(6):1572-7.

50. Machado AM, da Silva NBM, Chaves JBP, Alfenas RCG. Consumption of yacon flour improves body composition and intestinal function in overweight adults: A randomized, double-blind, placebo-controlled clinical trial. Clinical nutrition ESPEN. 2019;29:22-9.

51. Padilla-Camberos E, Barragán-Álvarez CP, Diaz-Martinez NE, Rathod V, Flores-Fernández JM. Effects of Agave fructans (Agave tequilana Weber var. azul) on Body Fat and Serum Lipids in Obesity. Plant foods for human nutrition (Dordrecht, Netherlands). 2018;73(1):34-9.

52. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. The American journal of clinical nutrition. 2009;89(6):1751-9.

53. Pol K, de Graaf C, Meyer D, Mars M. The efficacy of daily snack replacement with oligofructose-enriched granola bars in overweight and obese adults: a 12-week randomised controlled trial. British Journal of Nutrition. 2018;119(9):1076-86.

54. Reimer RA, Willis HJ, Tunnicliffe JM, Park H, Madsen KL, Soto-Vaca A. Inulin-type fructans and whey protein both modulate appetite but only fructans alter gut microbiota in adults with overweight/obesity: A randomized controlled trial. Molecular nutrition & food research. 2017;61(11).

55. Roshanravan N, Mahdavi R, Alizadeh E, Ghavami A, Rahbar Saadat Y, Mesri Alamdari N, et al. The effects of sodium butyrate and inulin supplementation on angiotensin signaling pathway via promotion of Akkermansia muciniphila abundance in type 2 diabetes; A randomized, double-blind, placebo-controlled trial. J Cardiovasc Thorac Res. 2017;9(4):183-90.

56. Salmean YAJPIN. Using inulin fiber supplementation with MyPlate recommendations promotes greater weight loss in obese women. 2019;21:81-5.

57. Satoh H, Kudoh A, Hasegawa K, Hirai H, Watanabe T. Yacon supplementation reduces serum free fatty acids and tumor necrosis factor alpha concentrations in patients with type 2 diabetes. Diabetology International. 2014;5(3):165-74.

58. Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, et al. Consumption of synbiotic bread decreases triacylglycerol and VLDL levels while increasing HDL levels in serum from patients with type-2 diabetes. Lipids. 2014;49(7):695-701.

59. Tajadadi-Ebrahimi M, Bahmani F, Shakeri H, Hadaegh H, Hijijafari M, Abedi F, et al. Effects of daily consumption of synbiotic bread on insulin metabolism and serum high-sensitivity C-reactive protein among diabetic patients: a double-blind, randomized, controlled clinical trial. Annals of nutrition & metabolism. 2014;65(1):34-41.

60. Tovar AR, Caamaño Mdel C, Garcia-Padilla S, García OP, Duarte MA, Rosado JL. The inclusion of a partial meal replacement with or without inulin to a calorie restricted diet contributes to reach recommended intakes of micronutrients and decrease plasma triglycerides: a randomized clinical trial in obese Mexican women. Nutrition journal. 2012;11:44.

61. Tripkovic L, Muirhead NC, Hart KH, Frost GS, Lodge JK. The effects of a diet rich in inulin or wheat fibre on markers of cardiovascular disease in overweight male subjects. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2015;28(5):476-85.

62. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. Nutritional neuroscience. 2021;24(5):339-53.

63. Wong JM, Kendall CW, de Souza R, Emam A, Marchie A, Vidgen E, et al. The effect on the blood lipid profile of soy foods combined with a prebiotic: a randomized controlled trial. Metabolism: clinical and experimental. 2010;59(9):1331-40.

64. Sørensen M, Johansen OE. Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. Scandinavian journal of clinical and laboratory investigation. 2010;70(6):385-91.

65. Buddington RK, Kapadia C, Neumer F, Theis S. Oligofructose Provides Laxation for Irregularity Associated with Low Fiber Intake. Nutrients. 2017;9(12).

66. Clarke ST, Green-Johnson JM, Brooks SP, Ramdath DD, Bercik P, Avila C, et al. β2-1 Fructan supplementation alters host immune responses in a manner consistent with increased exposure to microbial components: results from a double-blinded, randomised, cross-over study in healthy adults. The British journal of nutrition. 2016;115(10):1748-59.

67. Fernandes R, Beserra BT, Mocellin MC, Kuntz MG, da Rosa JS, de Miranda RC, et al. Effects of Prebiotic and Synbiotic Supplementation on Inflammatory Markers and Anthropometric Indices After Roux-en-Y Gastric Bypass: A Randomized, Triple-blind, Placebo-controlled Pilot Study. Journal of clinical gastroenterology. 2016;50(3):208-17.

68. Forcheron F, Beylot M. Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. Metabolism: clinical and experimental. 2007;56(8):1093-8.

69. Holscher HD, Doligale JL, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, et al. Gastrointestinal tolerance and utilization of agave inulin by healthy adults. Food & function. 2014;5(6):1142-9.

70. Jackson KG, Taylor GR, Clohessy AM, Williams CM. The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. The British journal of nutrition. 1999;82(1):23-30.

71. Letexier D, Diraison F, Beylot M. Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. The American journal of clinical nutrition. 2003;77(3):559-64.

72. Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry JL, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. The American journal of clinical nutrition. 1996;63(6):939-45.

73. Nishimura M, Ohkawara T, Kanayama T, Kitagawa K, Nishimura H, Nishihira J. Effects of the extract from roasted chicory (Cichorium intybus L.) root containing inulin-type fructans on blood glucose, lipid metabolism, and fecal properties. Journal of traditional and complementary medicine. 2015;5(3):161-7.

74. Pedersen A, Sandström B, Van Amelsvoort JM. The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. The British journal of nutrition. 1997;78(2):215-22.

75. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. Journal of cardiovascular pharmacology and therapeutics. 2015;20(3):289-98.

76. Russo F, Clemente C, Linsalata M, Chiloiro M, Orlando A, Marconi E, et al. Effects of a diet with inulin-enriched pasta on gut peptides and gastric emptying rates in healthy young volunteers. European journal of nutrition. 2011;50(4):271-7.

77. Scheid MM, Genaro PS, Moreno YM, Pastore GM. Freeze-dried powdered yacon: effects of FOS on serum glucose, lipids and intestinal transit in the elderly. European journal of nutrition. 2014;53(7):1457-64.

78. van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EG. Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. European journal of clinical nutrition. 1999;53(1):1-7.

79. Mitchell CM, Davy BM, Ponder MA, McMillan RP, Hughes MD, Hulver MW, et al. Prebiotic inulin supplementation and peripheral insulin sensitivity in adults at elevated risk for type 2 diabetes: A pilot randomized controlled trial. Nutrients. 2021;13(9):3235.

80. Williams CJ, Torquati L, Li Z, Lea RA, Croci I, Keating E, et al. Oligofructose-Enriched Inulin Intake, Gut Microbiome Characteristics, and the VO2Peak Response to High-Intensity Interval Training in Healthy Inactive Adults. Journal of Nutrition. 2022;152(3):680-9.

81. Ziaei R, Shahshahan Z, Ghasemi-Tehrani H, Heidari Z, Ghiasvand R. Effects of inulin-type fructans with different degrees of polymerization on inflammation, oxidative stress and endothelial dysfunction in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clinical Endocrinology. 2022.

82. Crovesy L, El-Bacha T, Rosado EL. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: a double-blind randomized controlled clinical trial in women with obesity. Food & function. 2021;12(5):2161-70.

83. Brighenti F. Dietary fructans and serum triacylglycerols: a meta-analysis of randomized controlled trials. J Nutr. 2007;137(11 Suppl):2552s-6s.

84. Faghihimani Z, Namazi N, Ghaffari S, Rezaei Kelishadi M, Sharifi S, Nattagh-Eshtivani E, et al. Effects of Inulin Type-Carbohydrates on blood pressure: a systematic review and meta-analysis. International Journal of Food Properties. 2021;24(1):129-39.

85. Li L, Li P, Xu L. Assessing the effects of inulin-type fructan intake on body weight, blood glucose, and lipid profile: A systematic review and meta-analysis of randomized controlled trials. Food Sci Nutr. 2021;9(8):4598-616.

86. Zeraatkar D, Bhasin A, Morassut RE, Churchill I, Gupta A, Lawson DO, et al. Characteristics and quality of systematic reviews and meta-analyses of observational nutritional epidemiology: a cross-sectional study. The American journal of clinical nutrition. 2021;113(6):1578-92.

87. Dou Y, Yu X, Luo Y, Chen B, Ma D, Zhu J. Effect of Fructooligosaccharides Supplementation on the Gut Microbiota in Human: A Systematic Review and Meta-Analysis. Nutrients. 2022;14(16).

88. Megur A, Daliri EB, Baltriukienė D, Burokas A. Prebiotics as a Tool for the Prevention and Treatment of Obesity and Diabetes: Classification and Ability to Modulate the Gut Microbiota. Int J Mol Sci. 2022;23(11).

89. Fu R, Vandermeer BW, Shamliyan TA, O'Neil ME, Yazdi F, Fox SH, et al. AHRQ Methods for Effective Health Care

Handling Continuous Outcomes in Quantitative Synthesis. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.

90. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International Journal of Epidemiology. 2002;31(1):140-9.

91. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. Annals of internal medicine. 2012;156(4):291-304.

92. Tawfick MM, Xie H, Zhao C, Shao P, Farag MA. Inulin fructans in diet: Role in gut homeostasis, immunity, health outcomes and potential therapeutics. International Journal of Biological Macromolecules. 2022;208:948-61.

93. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov. 2020.

94. Government of Canada. Nutrients in food: Fibre 2015 [cited 2022 April 8]. Available from: https://www.canada.ca/en/health-canada/services/nutrients.html.

95. Healey G, Murphy R, Butts C, Brough L, Whelan K, Coad J. Habitual dietary fibre intake influences gut microbiota response to an inulin-type fructan prebiotic: a randomised, double-blind, placebo-controlled, cross-over, human intervention study. The British journal of nutrition. 2018;119(2):176-89.

96. Tandon D, Haque MM, Gote M, Jain M, Bhaduri A, Dubey AK, et al. A prospective randomized, double-blind, placebo-controlled, dose-response relationship study to investigate efficacy of fructo-oligosaccharides (FOS) on human gut microflora. Sci Rep. 2019;9(1):5473-.

97. Salazar N, Dewulf EM, Neyrinck AM, Bindels LB, Cani PD, Mahillon J, et al. Inulin-type fructans modulate intestinal Bifidobacterium species populations and decrease fecal short-chain fatty acids in obese women. Clinical nutrition (Edinburgh, Scotland). 2015;34(3):501-7.

References

1. Roberfroid MB. Inulin-Type Fructans: Functional Food Ingredients. The Journal of Nutrition. 2007;137(11):2493S-502S.
2. Niness KR. Inulin and Oligofructose: What Are They? The Journal of Nutrition. 1999;129(7):1402S-6S.
3. Bosscher D. Fructan Prebiotics Derived from Inulin. In: Charalampopoulos D, Rastall RA, eds. Prebiotics and Probiotics Science and Technology. New York, NY: Springer New York; 2009:163-205.
4. Man S, Liu T, Yao Y, Lu Y, Ma L, Lu F. Friend or foe? The roles of inulin-type fructans. Carbohydrate Polymers. 2021;252:117155.
5. Liu F, Prabhakar M, Ju J, Long H, Zhou HW. Effect of inulin-type fructans on blood lipid profile and glucose level: a systematic review and meta-analysis of randomized controlled trials. Eur J Clin Nutr. 2017;71(1):9-20.
6. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, et al. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods (Basel, Switzerland). 2019;8(3):92.
7. Shoaib M, Shehzad A, Omar M, Rakha A, Raza H, Sharif HR, et al. Inulin: Properties, health benefits and food applications. Carbohydrate Polymers. 2016;147:444-54.
8. Ward NC, Watts GF, Eckel RH. Statin Toxicity. Circulation Research. 2019;124(2):328-50.
9. Bradley CK, Wang TY, Li S, Robinson JG, Roger VL, Goldberg AC, et al. Patient-Reported Reasons for Declining or Discontinuing Statin Therapy: Insights From the PALM Registry. Journal of the American Heart Association. 2019;8(7):e011765.
10. Beserra BT, Fernandes R, do Rosario VA, Mocellin MC, Kuntz MG, Trindade EB. A systematic review and meta-analysis of the prebiotics and synbiotics effects on glycaemia, insulin concentrations and lipid parameters in adult patients with overweight or obesity. Clin Nutr. 2015;34(5):845-58.
11. Wang L, Yang H, Huang H, Zhang C, Zuo HX, Xu P, et al. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose-response meta-analysis of 33 randomized controlled trials. J Transl Med. 2019;17(1):410.
12. Liber A, Szajewska H. Effects of inulin-type fructans on appetite, energy intake, and body weight in children and adults: systematic review of randomized controlled trials. Ann Nutr Metab. 2013;63(1-2):42-54.
13. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane, 2021. Available from www.training.cochrane.org/handbook.; 2021.
14. 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.
15. Talukdar JR, Cooper M, Lyutvyn L, Zeraatkar D, Ali R, Berbrier R, et al. 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 (accepted).
16. Dudum R, Juraschek SP, Appel LJ. Dose-dependent effects of lifestyle interventions on blood lipid levels: Results from the PREMIER trial. Patient Educ Couns. 2019;102(10):1882-91.

17. Packard C, Chapman MJ, Sibartie M, Laufs U, Masana L. Intensive low-density lipoprotein cholesterol lowering in cardiovascular disease prevention: opportunities and challenges. Heart. 2021;107(17):1369.
18. Esan O, Wierzbicki AS. Triglycerides and cardiovascular disease. Curr Opin Cardiol. 2021;36(4):469-77.
19. Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. Lancet. 2014;384(9943):626-35.
20. Shi H, Ge Y, Wang H, Zhang Y, Teng W, Tian L. Fasting blood glucose and risk of Stroke: A Dose–Response meta-analysis. Clinical Nutrition. 2021;40(5):3296-304.
21. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
22. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010;36(3):1 - 48.
23. R Core Team 2020;Pages. Accessed at R Foundation for Statistical Computing, Vienna, Austria at https://www.R-project.org/.
24. Sterne JAC, Sutton AJ, Ioannidis JPA, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002.
25. Viechtbauer W, Cheung MWL. Outlier and influence diagnostics for meta-analysis. Research Synthesis Methods. 2010;1(2):112-25.
26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.
27. McMaster University and Evidence Prime 2021;Pages gradepro.org on May 2 2022.
28. Aliasgharzadeh A, Khalili M, Mirtaheri E, Pourghassem Gargari B, Tavakoli F, Abbasalizad Farhangi M, et al. A Combination of Prebiotic Inulin and Oligofructose Improve Some of Cardiovascular Disease Risk Factors in Women with Type 2 Diabetes: A Randomized Controlled Clinical Trial. Adv Pharm Bull. 2015;5(4):507-14.
29. Alles MS, de Roos NM, Bakx JC, van de Lisdonk E, Zock PL, Hautvast GA. Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. Am J Clin Nutr. 1999;69(1):64-9.
30. Bahmani F, Tajadadi-Ebrahimi M, Kolahdooz F, Mazouchi M, Hadaegh H, Jamal AS, et al. The Consumption of Synbiotic Bread Containing Lactobacillus sporogenes and Inulin Affects Nitric Oxide and Malondialdehyde in Patients with Type 2 Diabetes Mellitus: Randomized, Double-Blind, Placebo-Controlled Trial. J Am Coll Nutr. 2016;35(6):506-13.
31. Blædel T, Holm JB, Sundekilde UK, Schmedes MS, Hess AL, Lorenzen JK, et al. A randomised, controlled, crossover study of the effect of diet on angiopoietin-like protein 4 (ANGPTL4) through modification of the gut microbiome. J Nutr Sci. 2016;5:e45.
32. Bonsu NK, Johnson SJIJD, Metab. Effects of inulin fibre supplementation on serum glucose and lipid concentration in patients with type 2 diabetes. 2012;21:80-6.
33. Castro-Sanchez F, Ochoa-Acosta D, Valenzuela-Rubio N, Domínguez-Rodríguez M, Fierros-Valdez J, Vergara-Jiménez MJAJNM. Inulin effect on weight loss and associated parameters with the development of cardiovascular disease in obese dyslipidemic subjects. 2017;4(1):1044.
34. Causey JL, Feirtag JM, Gallaher DD, Tungland BC, Slavin JL. Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. Nutrition Research. 2000;20(2):191-201.
35. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma

metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019;68(8):1430-8.
36. Cronin BE, Allsopp PJ, Slevin MM, Magee PJ, Livingstone MB, Strain JJ, et al. Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain fructo-oligosaccharides on serum lipids in postmenopausal women. Br J Nutr. 2016;115(4):658-65.
37. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, et al. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity (Silver Spring). 2014;22(6):1430-8.
38. Davidson MH, Maki KC, Synecki C, Torri SA, Drennan KBJNR. Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. 1998;18:503-17.
39. Dehghan P, Farhangi MA, Tavakoli F, Aliasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: A randomized placebo-controlled Trial. Complement Ther Med. 2016;24:96-102.
40. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. Int J Food Sci Nutr. 2014;65(1):117-23.
41. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62(8):1112-21.
42. Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clin Nutr. 2009;28(2):182-7.
43. Ghavami A, Roshanravan N, Nattagh-Eshtivani E, Sharifi S, Arzhang P, Sani MA, et al. The effect of high performance inulin on appetite, energy in-take and anthropometric indices in patient with type 2 diabetes. 2019;21:121-6.
44. Giacco R, Clemente G, Luongo D, Lasorella G, Fiume I, Brouns F, et al. Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. Clin Nutr. 2004;23(3):331-40.
45. Gómez-Reyes E, Orea-Tejeda A, Castillo-Martínez L, Cassis-Nosthas L, Vargas-Voráckova FJE. Prebiotics consumption modifies diastolic blood pressure, but does not affect serum lipids concentration in volunteers with ischemic heart disease. 2010;128:139.
46. Guess ND, Dornhorst A, Oliver N, Bell JD, Thomas EL, Frost GS. A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. Nutr Metab (Lond). 2015;12:36.
47. Guess ND, Dornhorst A, Oliver N, Frost GS. A Randomised Crossover Trial: The Effect of Inulin on Glucose Homeostasis in Subtypes of Prediabetes. Ann Nutr Metab. 2016;68(1):26-34.
48. Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clin Nutr. 2020;39(12):3618-28.
49. Luo J, Van Yperselle M, Rizkalla SW, Rossi F, Bornet FR, Slama G. Chronic consumption of short-chain fructooligosaccharides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. J Nutr. 2000;130(6):1572-7.
50. Machado AM, da Silva NBM, Chaves JBP, Alfenas RCG. Consumption of yacon flour improves body composition and intestinal function in overweight adults: A randomized, double-blind, placebo-controlled clinical trial. Clin Nutr ESPEN. 2019;29:22-9.

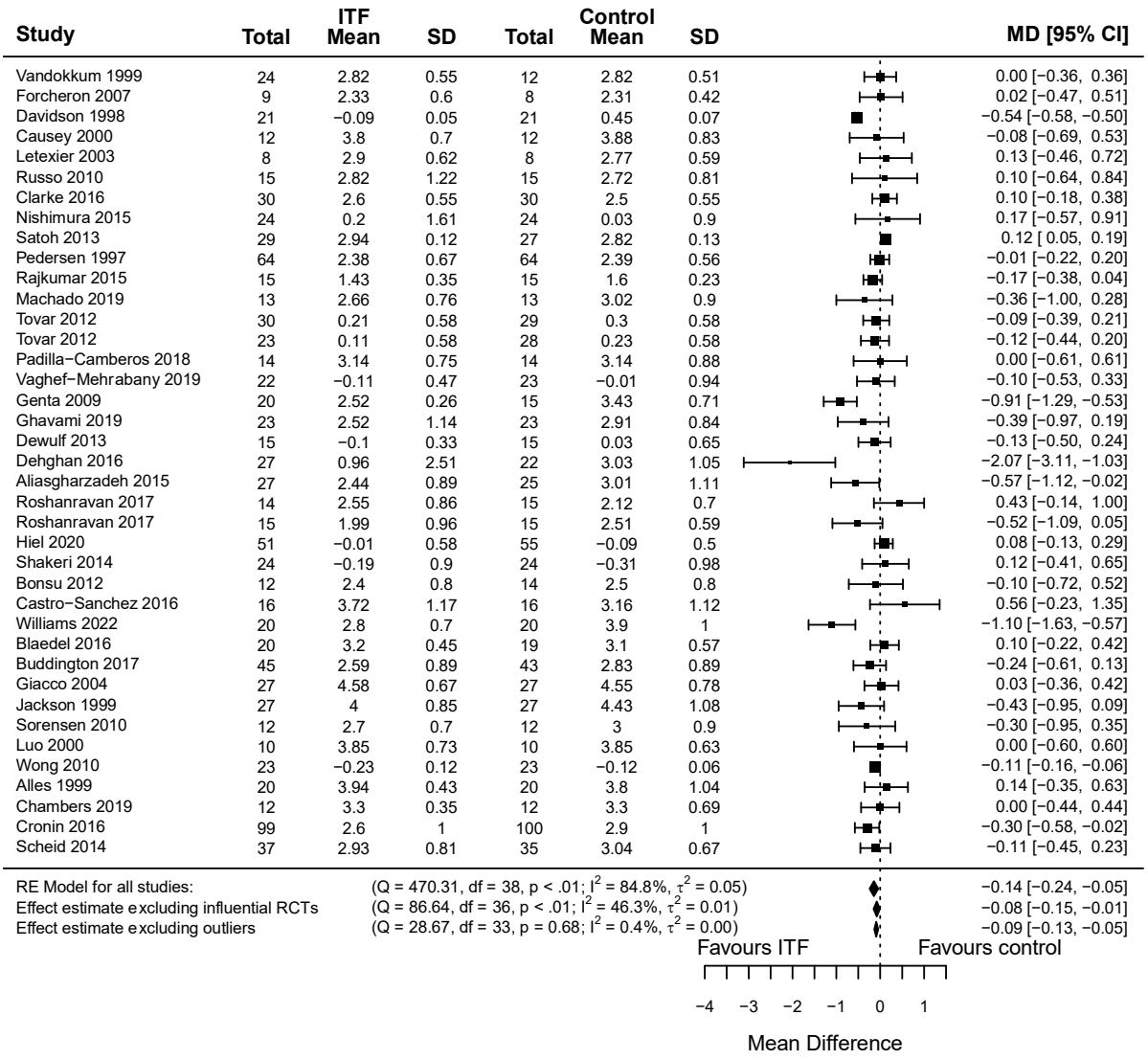
51. Padilla-Camberos E, Barragán-Álvarez CP, Diaz-Martinez NE, Rathod V, Flores-Fernández JM. Effects of Agave fructans (Agave tequilana Weber var. azul) on Body Fat and Serum Lipids in Obesity. Plant Foods Hum Nutr. 2018;73(1):34-9.
52. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. Am J Clin Nutr. 2009;89(6):1751-9.
53. Pol K, de Graaf C, Meyer D, Mars M. The efficacy of daily snack replacement with oligofructose-enriched granola bars in overweight and obese adults: a 12-week randomised controlled trial. British Journal of Nutrition. 2018;119(9):1076-86.
54. Reimer RA, Willis HJ, Tunnicliffe JM, Park H, Madsen KL, Soto-Vaca A. Inulin-type fructans and whey protein both modulate appetite but only fructans alter gut microbiota in adults with overweight/obesity: A randomized controlled trial. Mol Nutr Food Res. 2017;61(11).
55. Roshanravan N, Mahdavi R, Alizadeh E, Ghavami A, Rahbar Saadat Y, Mesri Alamdari N, et al. The effects of sodium butyrate and inulin supplementation on angiotensin signaling pathway via promotion of Akkermansia muciniphila abundance in type 2 diabetes; A randomized, double-blind, placebo-controlled trial. Journal of cardiovascular and thoracic research. 2017;9(4):183-90.
56. Salmean YAJPIN. Using inulin fiber supplementation with MyPlate recommendations promotes greater weight loss in obese women. 2019;21:81-5.
57. Satoh H, Kudoh A, Hasegawa K, Hirai H, Watanabe T. Yacon supplementation reduces serum free fatty acids and tumor necrosis factor alpha concentrations in patients with type 2 diabetes. Diabetology International. 2014;5(3):165-74.
58. Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, et al. Consumption of synbiotic bread decreases triacylglycerol and VLDL levels while increasing HDL levels in serum from patients with type-2 diabetes. Lipids. 2014;49(7):695-701.
59. Tajadadi-Ebrahimi M, Bahmani F, Shakeri H, Hadaegh H, Hijijafari M, Abedi F, et al. Effects of daily consumption of synbiotic bread on insulin metabolism and serum high-sensitivity C-reactive protein among diabetic patients: a double-blind, randomized, controlled clinical trial. Ann Nutr Metab. 2014;65(1):34-41.
60. Tovar AR, Caamaño Mdel C, Garcia-Padilla S, García OP, Duarte MA, Rosado JL. The inclusion of a partial meal replacement with or without inulin to a calorie restricted diet contributes to reach recommended intakes of micronutrients and decrease plasma triglycerides: a randomized clinical trial in obese Mexican women. Nutr J. 2012;11:44.
61. Tripkovic L, Muirhead NC, Hart KH, Frost GS, Lodge JK. The effects of a diet rich in inulin or wheat fibre on markers of cardiovascular disease in overweight male subjects. J Hum Nutr Diet. 2015;28(5):476-85.
62. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. Nutr Neurosci. 2021;24(5):339-53.
63. Wong JM, Kendall CW, de Souza R, Emam A, Marchie A, Vidgen E, et al. The effect on the blood lipid profile of soy foods combined with a prebiotic: a randomized controlled trial. Metabolism. 2010;59(9):1331-40.
64. Sørensen M, Johansen OE. Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. Scand J Clin Lab Invest. 2010;70(6):385-91.
65. Buddington RK, Kapadia C, Neumer F, Theis S. Oligofructose Provides Laxation for Irregularity Associated with Low Fiber Intake. Nutrients. 2017;9(12).
66. Clarke ST, Green-Johnson JM, Brooks SP, Ramdath DD, Bercik P, Avila C, et al. β2-1 Fructan supplementation alters host immune responses in a manner consistent with

increased exposure to microbial components: results from a double-blinded, randomised, cross-over study in healthy adults. Br J Nutr. 2016;115(10):1748-59.
67. Fernandes R, Beserra BT, Mocellin MC, Kuntz MG, da Rosa JS, de Miranda RC, et al. Effects of Prebiotic and Synbiotic Supplementation on Inflammatory Markers and Anthropometric Indices After Roux-en-Y Gastric Bypass: A Randomized, Triple-blind, Placebo-controlled Pilot Study. J Clin Gastroenterol. 2016;50(3):208-17.
68. Forcheron F, Beylot M**.** Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. Metabolism. 2007;56(8):1093-8.
69. Holscher HD, Doligale JL, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, et al. Gastrointestinal tolerance and utilization of agave inulin by healthy adults. Food Funct. 2014;5(6):1142-9.
70. Jackson KG, Taylor GR, Clohessy AM, Williams CM**.** The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. Br J Nutr. 1999;82(1):23-30.
71. Letexier D, Diraison F, Beylot M**.** Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. Am J Clin Nutr. 2003;77(3):559-64.
72. Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry JL, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. Am J Clin Nutr. 1996;63(6):939-45.
73. Nishimura M, Ohkawara T, Kanayama T, Kitagawa K, Nishimura H, Nishihira J**.** Effects of the extract from roasted chicory (Cichorium intybus L.) root containing inulin-type fructans on blood glucose, lipid metabolism, and fecal properties. J Tradit Complement Med. 2015;5(3):161-7.
74. Pedersen A, Sandström B, Van Amelsvoort JM**.** The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. Br J Nutr. 1997;78(2):215-22.
75. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R**.** Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. J Cardiovasc Pharmacol Ther. 2015;20(3):289-98.
76. Russo F, Clemente C, Linsalata M, Chiloiro M, Orlando A, Marconi E, et al. Effects of a diet with inulin-enriched pasta on gut peptides and gastric emptying rates in healthy young volunteers. Eur J Nutr. 2011;50(4):271-7.
77. Scheid MM, Genaro PS, Moreno YM, Pastore GM**.** Freeze-dried powdered yacon: effects of FOS on serum glucose, lipids and intestinal transit in the elderly. Eur J Nutr. 2014;53(7):1457-64.
78. van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EG**.** Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. Eur J Clin Nutr. 1999;53(1):1-7.
79. Mitchell CM, Davy BM, Ponder MA, McMillan RP, Hughes MD, Hulver MW, et al. Prebiotic inulin supplementation and peripheral insulin sensitivity in adults at elevated risk for type 2 diabetes: A pilot randomized controlled trial. Nutrients. 2021;13(9):3235.
80. Williams CJ, Torquati L, Li Z, Lea RA, Croci I, Keating E, et al. Oligofructose-Enriched Inulin Intake, Gut Microbiome Characteristics, and the VO2Peak Response to High-Intensity Interval Training in Healthy Inactive Adults. Journal of Nutrition. 2022;152(3):680-9.
81. Ziaei R, Shahshahan Z, Ghasemi-Tehrani H, Heidari Z, Ghiasvand R**.** Effects of inulin-type fructans with different degrees of polymerization on inflammation, oxidative stress

and endothelial dysfunction in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clinical Endocrinology. 2022.
82. Crovesy L, El-Bacha T, Rosado EL. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: a double-blind randomized controlled clinical trial in women with obesity. Food & function. 2021;12(5):2161-70.
83. Brighenti F. Dietary fructans and serum triacylglycerols: a meta-analysis of randomized controlled trials. J Nutr. 2007;137(11 Suppl):2552s-6s.
84. Faghihimani Z, Namazi N, Ghaffari S, Rezaei Kelishadi M, Sharifi S, Nattagh-Eshtivani E, et al. Effects of Inulin Type-Carbohydrates on blood pressure: a systematic review and meta-analysis. International Journal of Food Properties. 2021;24(1):129-39.
85. Li L, Li P, Xu L. Assessing the effects of inulin-type fructan intake on body weight, blood glucose, and lipid profile: A systematic review and meta-analysis of randomized controlled trials. Food Sci Nutr. 2021;9(8):4598-616.
86. Zeraatkar D, Bhasin A, Morassut RE, Churchill I, Gupta A, Lawson DO, et al. Characteristics and quality of systematic reviews and meta-analyses of observational nutritional epidemiology: a cross-sectional study. Am J Clin Nutr. 2021;113(6):1578-92.
87. Fu R, Vandermeer BW, Shamliyan TA, O'Neil ME, Yazdi F, Fox SH, et al. AHRQ Methods for Effective Health Care
Handling Continuous Outcomes in Quantitative Synthesis. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
88. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. International Journal of Epidemiology. 2002;31(1):140-9.
89. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. Ann Intern Med. 2012;156(4):291-304.
90. Tawfick MM, Xie H, Zhao C, Shao P, Farag MA. Inulin fructans in diet: Role in gut homeostasis, immunity, health outcomes and potential therapeutics. International Journal of Biological Macromolecules. 2022;208:948-61.
91. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov.; 2020.
92. Government of Canada 2015;Pageshttps://www.canada.ca/en/health-canada/services/nutrients.html.
93. Healey G, Murphy R, Butts C, Brough L, Whelan K, Coad J. Habitual dietary fibre intake influences gut microbiota response to an inulin-type fructan prebiotic: a randomised, double-blind, placebo-controlled, cross-over, human intervention study. Br J Nutr. 2018;119(2):176-89.
94. Tandon D, Haque MM, Gote M, Jain M, Bhaduri A, Dubey AK, et al. A prospective randomized, double-blind, placebo-controlled, dose-response relationship study to investigate efficacy of fructo-oligosaccharides (FOS) on human gut microflora. Scientific reports. 2019;9(1):5473-.
95. Salazar N, Dewulf EM, Neyrinck AM, Bindels LB, Cani PD, Mahillon J, et al. Inulin-type fructans modulate intestinal Bifidobacterium species populations and decrease fecal short-chain fatty acids in obese women. Clin Nutr. 2015;34(3):501-7.

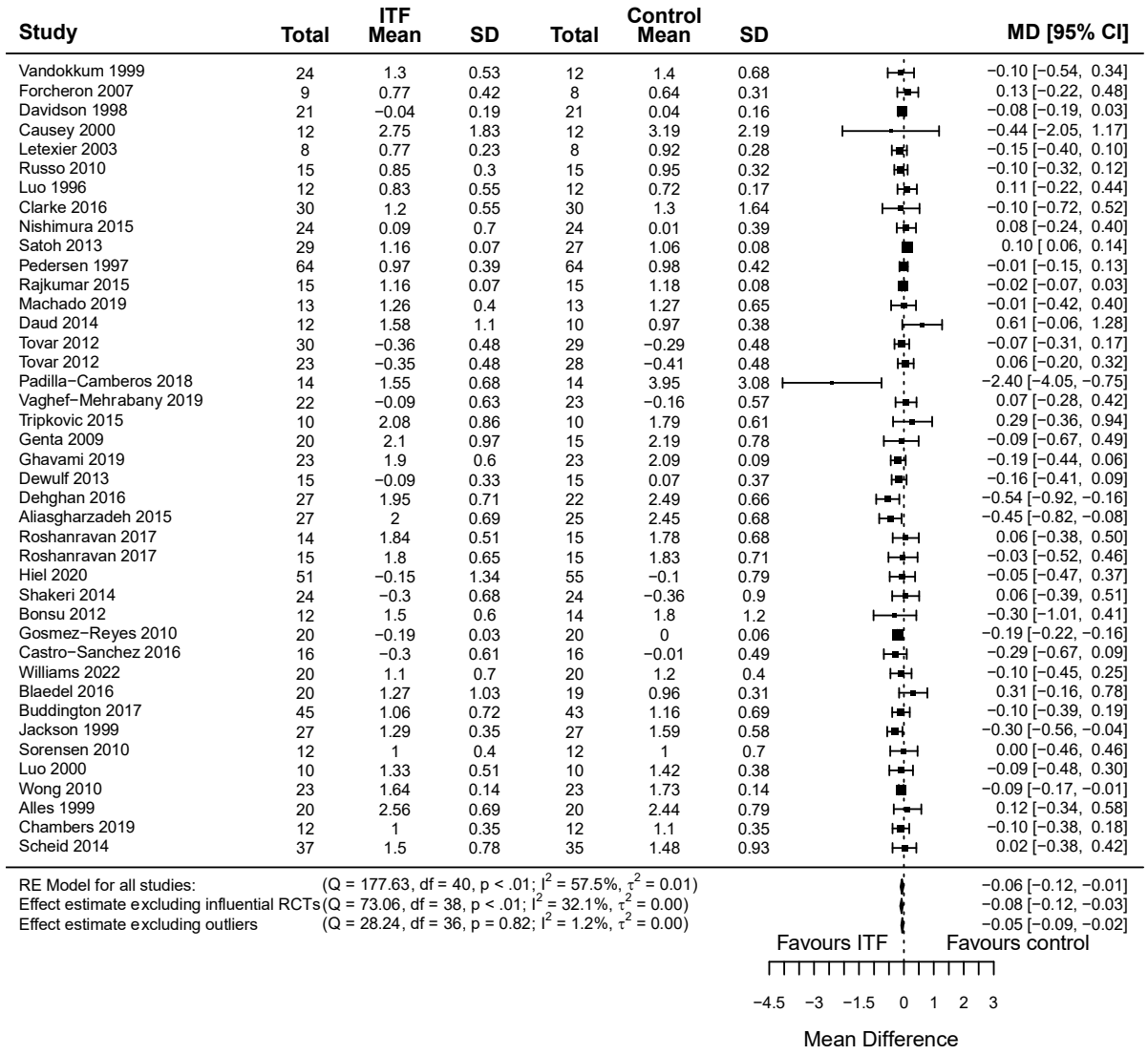
Figures

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



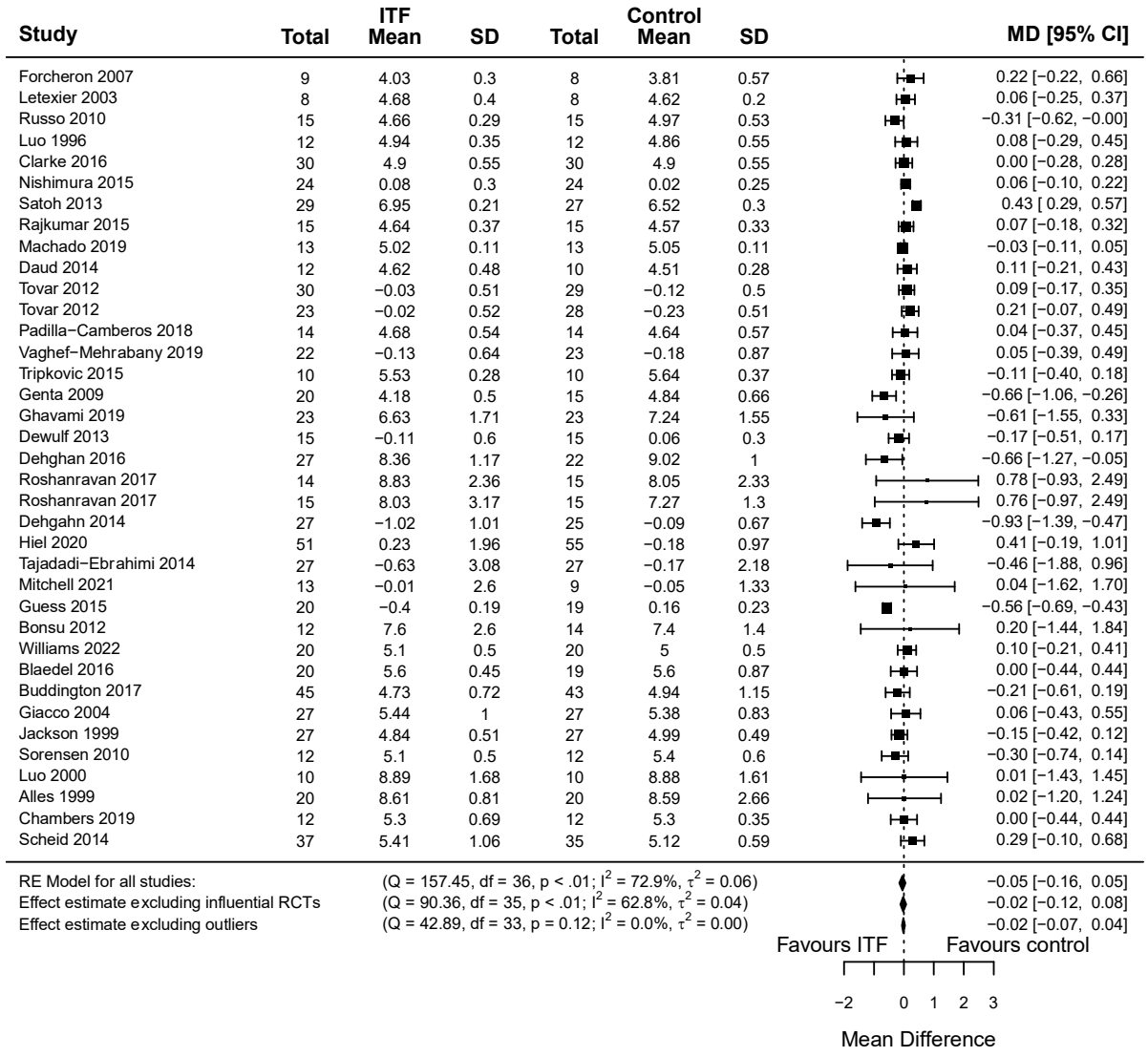
Note: Total = total number of participants completed the study, ITF = inulin-type fructans, SD = standard deviation, MD = mean

Figure 2: Forest plot displaying the effect of inulin-type fructans on triglycerides



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



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
Aliasgharzadeh 2015, Iran (1)	P	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)	C	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)	P	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)	C	-	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)	P	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)	P	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)	C	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)	C	-	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)	C	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)	C	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)	P	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)	P	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)	C	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)	P	100	42	49	Ow/Ob, T2DM	Inulin supplement	10 g/day (8 weeks)	maltodextrin	BMI, FBG, HbA1C, W
Dehghan 2016, Iran (15)	P	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)	P	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)	P	100	30	31	Healthy	FOS synbiotic	6 g/day (15 days)	maltodextrin or FOS probiotic	BMI, W

Forcheron 2007, France (18)	P	67	6	32	Healthy	Fructans supplement	10 g/day (6 months)	placebo	FBG, HDL-C, LDL-C, TC, TG, W
Genta 2009, Argentina (19)	P	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)	P	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)	C	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)	P	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)	P	40	40	59	Pre-DM	Inulin supplement	30 g/day (18 weeks)	cellulose	FBG, W
Guess 2016, UK (24)	C	NR	39	62	Pre-DM	Inulin supplement	30 g/day (14 days)	cellulose	W
Hiel 2020, Belgium (25)	P	67	68	51	Ob/$\geq$1 of pre-DM/DM/dys/HTN/elevated 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)	C	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)	P	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)	C	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)	C	50	20	23-32	Healthy	Inulin supplement	10 g/day (21 days)	maltodextrin	FBG, HDL-C, LDL-C, TC, TG
Luo 1996, France (30)	C	-	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)	P	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)	P	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,Mexico (33)	P	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)	P	81	48	40	Ow/Ob	OFS supplement	21 g/day (12 weeks)	maltodextrin in drink	BMI, FBG, W
Pedersen 1997, Denmark (35)	C	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

Pol 2018, Netherlands (36)	P	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)	P	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)	P	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)	P	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)	C	-	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)	P	100	29	23	Ob	Inulin supplement + dietary recommendations	21 g/day (42 days)	recommendation w/o inulin	BMI,W
Satoh 2013, Japan (42)	P	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)	P	NR	12	67	Healthy	FOS/yacon supplement	7.4 g/day (9 weeks)	maltodextrin	FBG, HDL-C, LDL-C, TC, TG, VLDL-C

Shakeri 2014, Iran (44)	P	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)	C	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)	P	81	48	52	T2DM	Inulin synbiotic bread	8.4 g/d (8 weeks)	Control or probiotic bread	BMI, FBG, W
Tovar 2012, Mexico (47)	P	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)	C	-	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)	P	100	51	39	Ob/MDD	Inulin supplement + weightloss diet	10 g/d (8 weeks)	maltodextrin + weightloss diet	BMI, DBP, FBG, HDL-C, LDL-C, SBP, TC, TG, WC, W, WHR
Vandokkum 1999, Netherlands (50)	C	-	20	23	Healthy	FOS or inulin supplement	15 g/d (3 weeks)	basal diet w/o non-digestible oligosaccharide or galactooligosaccharide	HDL-C, LDL-C, TC, TG, ApoA, ApoB
Wong 2010, Canada (51)	C	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

Crovesy 2021, Brazil (52)	P	100	36	34	Ob	Synbiotics	5 g/d (8 weeks)	placebo	BMI, WC, W
Mitchell 2021, USA (53)	P	65	40	54	Ob	Inulin	10 g/day (6 weeks)	placebo	FBG, W
Williams 2022, Australia (54)	P	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
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

References of included randomized controlled trials

1. Aliasgharzadeh A, Khalili M, Mirtaheri E, Pourghassem Gargari B, Tavakoli F, Abbasalizad Farhangi M, et al. A Combination of Prebiotic Inulin and Oligofructose Improve Some of Cardiovascular Disease Risk Factors in Women with Type 2 Diabetes: A Randomized Controlled Clinical Trial. Advanced pharmaceutical bulletin. 2015;5(4):507-14.

2. Alles MS, de Roos NM, Bakx JC, van de Lisdonk E, Zock PL, Hautvast GA. Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. The American journal of clinical nutrition. 1999;69(1):64-9.

3. Bahmani F, Tajadadi-Ebrahimi M, Kolahdooz F, Mazouchi M, Hadaegh H, Jamal AS, et al. The Consumption of Synbiotic Bread Containing Lactobacillus sporogenes and Inulin Affects Nitric Oxide and Malondialdehyde in Patients with Type 2 Diabetes Mellitus: Randomized, Double-Blind, Placebo-Controlled Trial. Journal of the American College of Nutrition. 2016;35(6):506-13.

4. Blædel T, Holm JB, Sundekilde UK, Schmedes MS, Hess AL, Lorenzen JK, et al. A randomised, controlled, crossover study of the effect of diet on angiopoietin-like protein 4 (ANGPTL4) through modification of the gut microbiome. Journal of nutritional science. 2016;5:e45.

5. Bonsu NK, Johnson SJIJD, Metab. Effects of inulin fibre supplementation on serum glucose and lipid concentration in patients with type 2 diabetes. 2012;21:80-6.

6. Buddington RK, Kapadia C, Neumer F, Theis S. Oligofructose Provides Laxation for Irregularity Associated with Low Fiber Intake. Nutrients. 2017;9(12).

7. Castro-Sanchez F, Ochoa-Acosta D, Valenzuela-Rubio N, Domínguez-Rodríguez M, Fierros-Valdez J, Vergara-Jiménez MJAJNM. Inulin effect on weight loss and associated parameters with the development of cardiovascular disease in obese dyslipidemic subjects. 2017;4(1):1044.

8. Causey JL, Feirtag JM, Gallaher DD, Tungland BC, Slavin JL. Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. Nutrition Research. 2000;20(2):191-201.

9. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019;68(8):1430-8.

10. Clarke ST, Green-Johnson JM, Brooks SP, Ramdath DD, Bercik P, Avila C, et al. β2-1 Fructan supplementation alters host immune responses in a manner consistent with increased exposure to microbial components: results from a double-blinded, randomised, cross-over study in healthy adults. The British journal of nutrition. 2016;115(10):1748-59.

11. Cronin BE, Allsopp PJ, Slevin MM, Magee PJ, Livingstone MB, Strain JJ, et al. Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain

fructo-oligosaccharides on serum lipids in postmenopausal women. The British journal of nutrition. 2016;115(4):658-65.

12. Crovesy L, El-Bacha T, Rosado EL. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: a double-blind randomized controlled clinical trial in women with obesity. Food & function. 2021;12(5):2161-70.

13. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, et al. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity (Silver Spring, Md). 2014;22(6):1430-8.

14. Davidson MH, Maki KC, Synecki C, Torri SA, Drennan KBJNR. Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. 1998;18:503-17.

15. Dehghan P, Farhangi MA, Tavakoli F, Aliasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: A randomized placebo-controlled Trial. Complementary therapies in medicine. 2016;24:96-102.

16. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. International journal of food sciences and nutrition. 2014;65(1):117-23.

17. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62(8):1112-21.

18. Fernandes R, Beserra BT, Mocellin MC, Kuntz MG, da Rosa JS, de Miranda RC, et al. Effects of Prebiotic and Synbiotic Supplementation on Inflammatory Markers and Anthropometric Indices After Roux-en-Y Gastric Bypass: A Randomized, Triple-blind, Placebo-controlled Pilot Study. Journal of clinical gastroenterology. 2016;50(3):208-17.

19. Forcheron F, Beylot M. Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. Metabolism: clinical and experimental. 2007;56(8):1093-8.

20. Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clinical nutrition (Edinburgh, Scotland). 2009;28(2):182-7.

21. Ghavami A, Roshanravan N, Nattagh-Eshtivani E, Sharifi S, Arzhang P, Sani MA, et al. The effect of high performance inulin on appetite, energy in-take and anthropometric indices in patient with type 2 diabetes. 2019;21:121-6.

22. Giacco R, Clemente G, Luongo D, Lasorella G, Fiume I, Brouns F, et al. Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. Clinical nutrition (Edinburgh, Scotland). 2004;23(3):331-40.

23. Gómez-Reyes E, Orea-Tejeda A, Castillo-Martínez L, Cassis-Nosthas L, Vargas-Voráckova FJE. Prebiotics consumption modifies diastolic blood pressure, but does not affect serum lipids concentration in volunteers with ischemic heart disease. 2010;128:139.

24. Guess ND, Dornhorst A, Oliver N, Bell JD, Thomas EL, Frost GS. A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. Nutrition & metabolism. 2015;12:36.

25. Guess ND, Dornhorst A, Oliver N, Frost GS. A Randomised Crossover Trial: The Effect of Inulin on Glucose Homeostasis in Subtypes of Prediabetes. Annals of nutrition & metabolism. 2016;68(1):26-34.

26. Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clinical nutrition (Edinburgh, Scotland). 2020;39(12):3618-28.

27. Holscher HD, Doligale JL, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, et al. Gastrointestinal tolerance and utilization of agave inulin by healthy adults. Food & function. 2014;5(6):1142-9.

28. Jackson KG, Taylor GR, Clohessy AM, Williams CM. The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. The British journal of nutrition. 1999;82(1):23-30.

29. Letexier D, Diraison F, Beylot M. Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. The American journal of clinical nutrition. 2003;77(3):559-64.

30. Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry JL, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. The American journal of clinical nutrition. 1996;63(6):939-45.

31. Luo J, Van Yperselle M, Rizkalla SW, Rossi F, Bornet FR, Slama G. Chronic consumption of short-chain fructooligosaccharides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. J Nutr. 2000;130(6):1572-7.

32. Machado AM, da Silva NBM, Chaves JBP, Alfenas RCG. Consumption of yacon flour improves body composition and intestinal function in overweight adults: A randomized, double-blind, placebo-controlled clinical trial. Clinical nutrition ESPEN. 2019;29:22-9.

33. Mitchell CM, Davy BM, Ponder MA, McMillan RP, Hughes MD, Hulver MW, et al. Prebiotic inulin supplementation and peripheral insulin sensitivity in adults at elevated risk for type 2 diabetes: A pilot randomized controlled trial. Nutrients. 2021;13(9):3235.

34. Nishimura M, Ohkawara T, Kanayama T, Kitagawa K, Nishimura H, Nishihira J. Effects of the extract from roasted chicory (Cichorium intybus L.) root containing inulin-type fructans on blood glucose, lipid metabolism, and fecal properties. Journal of traditional and complementary medicine. 2015;5(3):161-7.

35. Padilla-Camberos E, Barragán-Álvarez CP, Diaz-Martinez NE, Rathod V, Flores-Fernández JM. Effects of Agave fructans (Agave tequilana Weber var. azul) on Body Fat and Serum Lipids in Obesity. Plant foods for human nutrition (Dordrecht, Netherlands). 2018;73(1):34-9.

36. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. The American journal of clinical nutrition. 2009;89(6):1751-9.

37. Pedersen A, Sandström B, Van Amelsvoort JM. The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. The British journal of nutrition. 1997;78(2):215-22.

38. Pol K, de Graaf C, Meyer D, Mars M. The efficacy of daily snack replacement with oligofructose-enriched granola bars in overweight and obese adults: a 12-week randomised controlled trial. British Journal of Nutrition. 2018;119(9):1076-86.

39. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. Journal of cardiovascular pharmacology and therapeutics. 2015;20(3):289-98.

40. Reimer RA, Willis HJ, Tunnicliffe JM, Park H, Madsen KL, Soto-Vaca A. Inulin-type fructans and whey protein both modulate appetite but only fructans alter gut microbiota in adults with overweight/obesity: A randomized controlled trial. Molecular nutrition & food research. 2017;61(11).

41. Roshanravan N, Mahdavi R, Alizadeh E, Ghavami A, Rahbar Saadat Y, Mesri Alamdari N, et al. The effects of sodium butyrate and inulin supplementation on angiotensin signaling pathway via promotion of Akkermansia muciniphila abundance in type 2 diabetes; A randomized, double-blind, placebo-controlled trial. J Cardiovasc Thorac Res. 2017;9(4):183-90.

42. Russo F, Clemente C, Linsalata M, Chiloiro M, Orlando A, Marconi E, et al. Effects of a diet with inulin-enriched pasta on gut peptides and gastric emptying rates in healthy young volunteers. European journal of nutrition. 2011;50(4):271-7.

43. Salmean YAJPIN. Using inulin fiber supplementation with MyPlate recommendations promotes greater weight loss in obese women. 2019;21:81-5.

44. Satoh H, Kudoh A, Hasegawa K, Hirai H, Watanabe T. Yacon supplementation reduces serum free fatty acids and tumor necrosis factor alpha concentrations in patients with type 2 diabetes. Diabetology International. 2014;5(3):165-74.

45. Scheid MM, Genaro PS, Moreno YM, Pastore GM. Freeze-dried powdered yacon: effects of FOS on serum glucose, lipids and intestinal transit in the elderly. European journal of nutrition. 2014;53(7):1457-64.

46. Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, et al. Consumption of synbiotic bread decreases triacylglycerol and VLDL levels while increasing HDL levels in serum from patients with type-2 diabetes. Lipids. 2014;49(7):695-701.

47. Sørensen M, Johansen OE. Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. Scandinavian journal of clinical and laboratory investigation. 2010;70(6):385-91.

48. Tajadadi-Ebrahimi M, Bahmani F, Shakeri H, Hadaegh H, Hijijafari M, Abedi F, et al. Effects of daily consumption of synbiotic bread on insulin metabolism and serum high-sensitivity C-reactive protein among diabetic patients: a double-blind, randomized, controlled clinical trial. Annals of nutrition & metabolism. 2014;65(1):34-41.

49. Tovar AR, Caamaño Mdel C, Garcia-Padilla S, García OP, Duarte MA, Rosado JL. The inclusion of a partial meal replacement with or without inulin to a calorie restricted diet contributes to reach recommended intakes of micronutrients and decrease plasma triglycerides: a randomized clinical trial in obese Mexican women. Nutrition journal. 2012;11:44.

50. Tripkovic L, Muirhead NC, Hart KH, Frost GS, Lodge JK. The effects of a diet rich in inulin or wheat fibre on markers of cardiovascular disease in overweight male subjects. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2015;28(5):476-85.

51. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. Nutritional neuroscience. 2021;24(5):339-53.

52. van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EG. Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. European journal of clinical nutrition. 1999;53(1):1-7.

53. Williams CJ, Torquati L, Li Z, Lea RA, Croci I, Keating E, et al. Oligofructose-Enriched Inulin Intake, Gut Microbiome Characteristics, and the VO2Peak Response to High-Intensity Interval Training in Healthy Inactive Adults. Journal of Nutrition. 2022;152(3):680-9.

54. Wong JM, Kendall CW, de Souza R, Emam A, Marchie A, Vidgen E, et al. The effect on the blood lipid profile of soy foods combined with a prebiotic: a randomized controlled trial. Metabolism: clinical and experimental. 2010;59(9):1331-40.

55. Ziaei R, Shahshahan Z, Ghasemi-Tehrani H, Heidari Z, Ghiasvand R. Effects of inulin-type fructans with different degrees of polymerization on inflammation, oxidative stress and endothelial dysfunction in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clinical Endocrinology. 2022.

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

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

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)	⊕⊕◯◯ Low[a,c]
Fasting blood glucose	MD **0.05 mmol/L lower** (0.16 lower to 0.05 higher)	1505 (36 RCTs)	⊕◯◯◯ Very low[a,d,e]

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

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

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

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* a1 or apo* a i or (proapoliprotein adj1 (ai or a1 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* a1 or apo* a i or (proapoliprotein adj1 (ai or a1 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 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:

1. Fasting blood glucose was converted from mg/dl to mmol/l by dividing by 18 that is mmol/l = mg/dl / 18 (1).
2. 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).
5. 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).
7. 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)

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

Methodology decisions in data extraction:

1. 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.
5. 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 index (BMI)	MD **0.41 kg lower** (0.89 lower to 0.06 higher)	1330 (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)	⊕◯◯◯ Very low[c,k,l]
Waist-to-hip ratio	MD **0.01 ratio lower** (0.02 lower to 0)	411 (10 RCTs)	⊕⊕◯◯ Low[k,n]
Systolic blood pressure	MD **0.09 mmHg higher** (2.23 lower to 2.42 higher)	859 (15 RCTs)	⊕⊕◯◯ Low[c,h]
Diastolic blood pressure (DBP)	MD **1.28 mmHg lower** (3.18 lower to 0.62 higher)	803 (14 RCTs)	⊕◯◯◯ Very low[c,d,e]
High-density lipoprotein	MD **0.03 mmol/L higher** (0 to 0.05 higher)	1786 (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)	⊕⊕◯◯ Low[c,s]
Total cholesterol	MD **0.11 mmol/L lower** (0.19 to 0.02 lower)	1875 (40 RCTs)	⊕◯◯◯ Very low[c,f,i,j]
Lipoprotein A1	MD **0.07 g/L higher** (0.12 lower to 0.27 higher)	204 (6 RCTs)	⊕⊕◯◯ Low[c,o]
Lipoprotein B	MD **0.2 g/L higher** (0.38 lower to 0.79 higher)	204 (6 RCTs)	⊕⊕◯◯ Low[c,p]

Glucose hemoglobin A1c	**0.11 % lower** (0.31 lower to 0.09 higher)	514 (13 RCTs)	⊕◯◯◯ Very low[c,q,r]

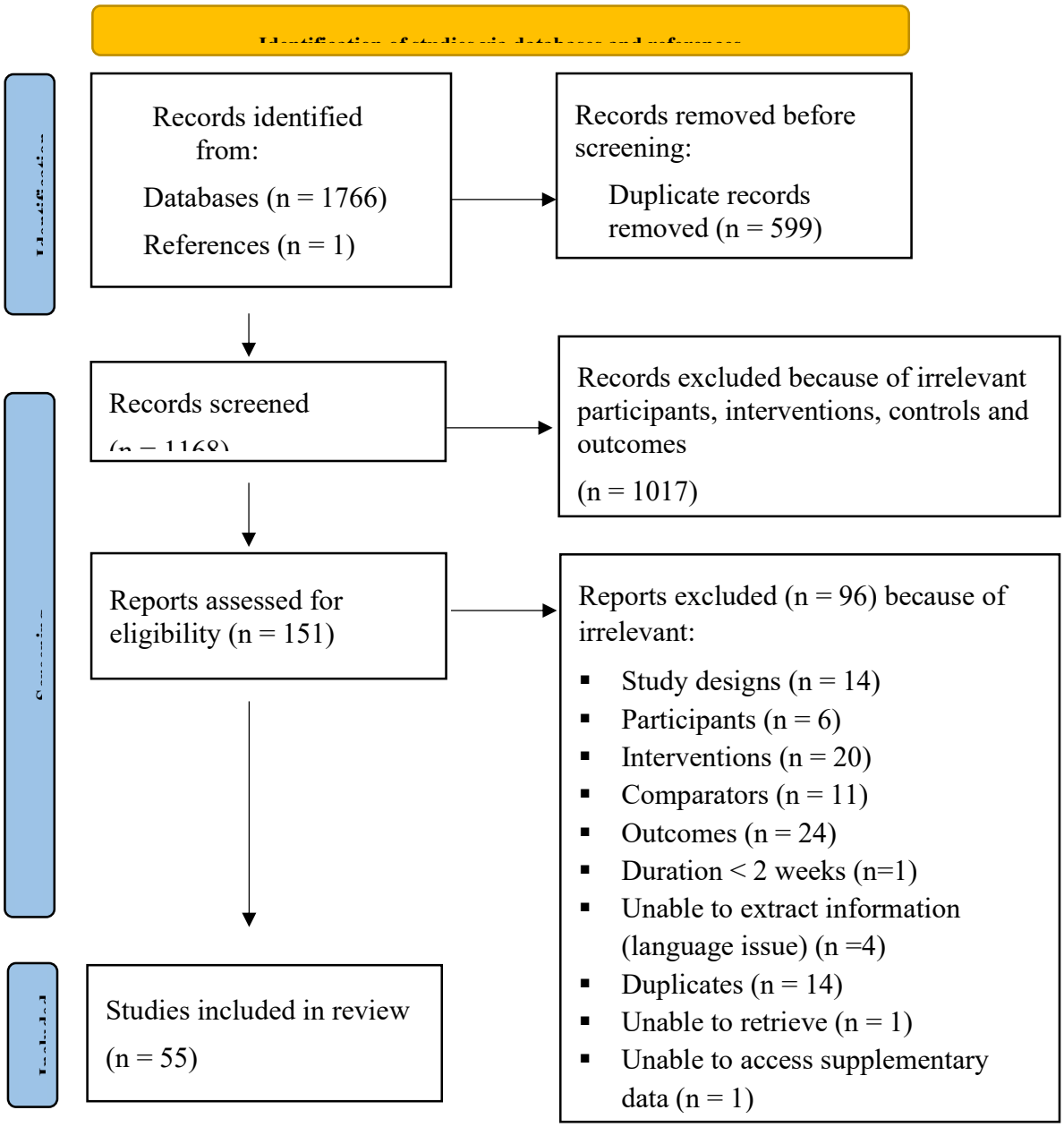
MD: mean difference

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
l. 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

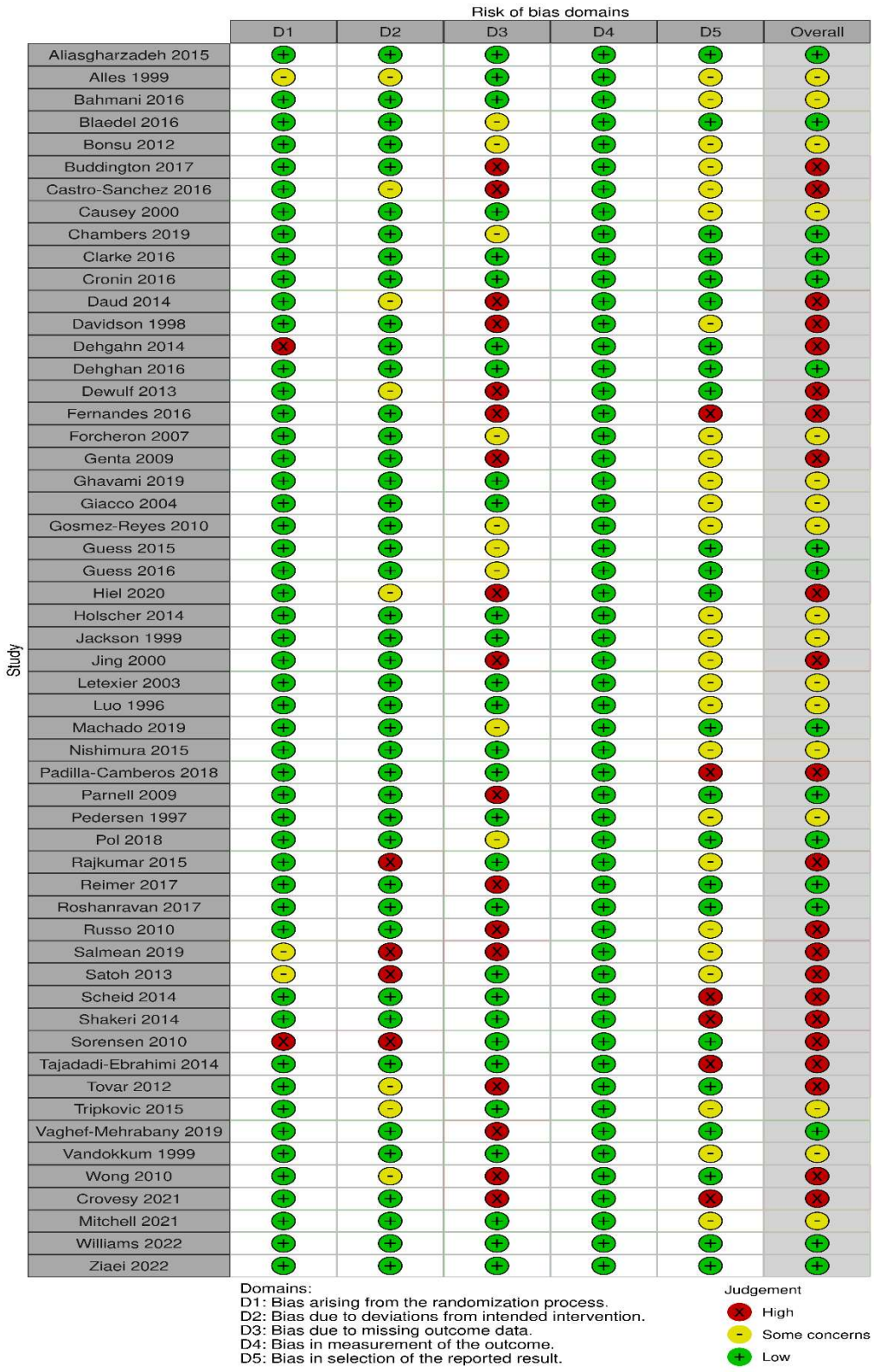
Figure 1. PRISMA flow diagram



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)



Risk of bias (continued): summary risk of bias

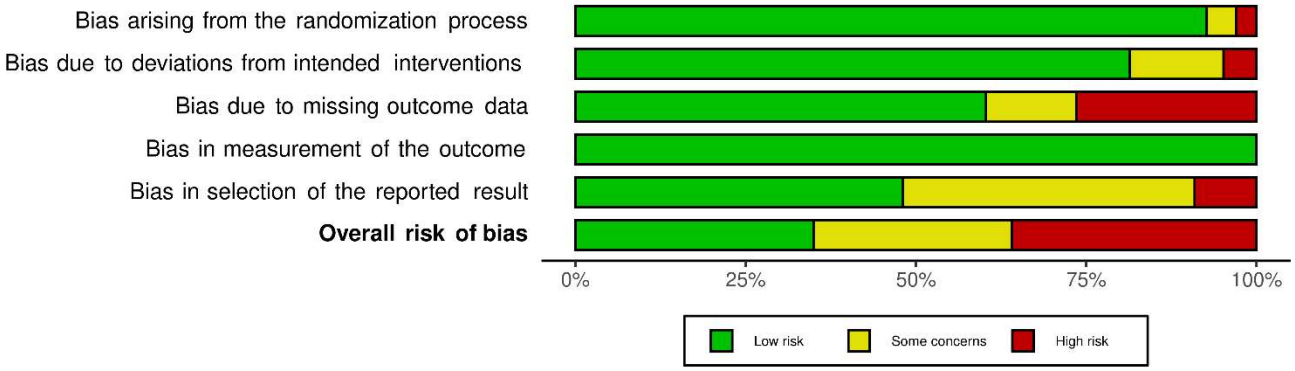


Figure 3: LDL-C - subgroup by sex

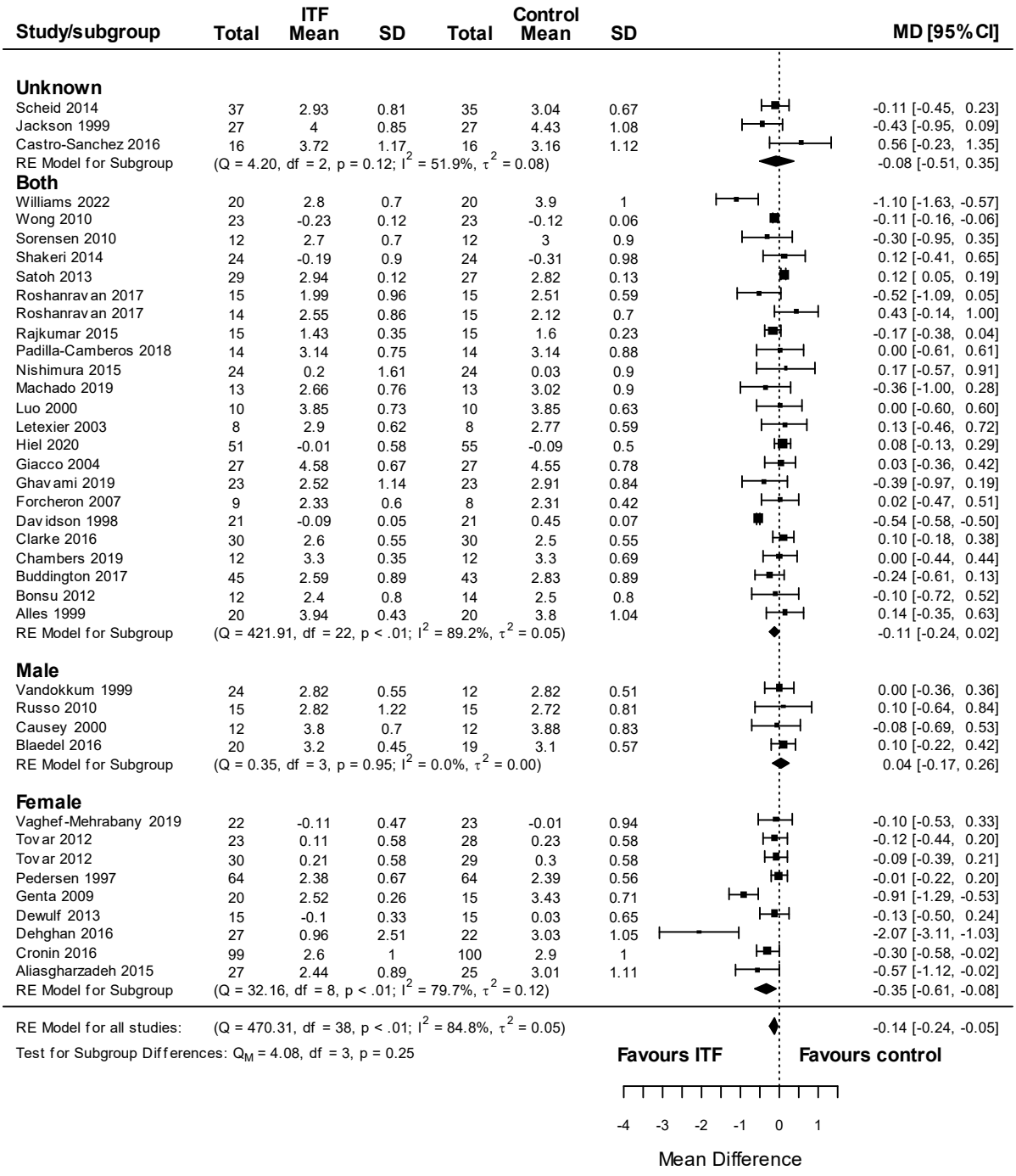


Figure 4: LDL-C - subgroup by disease

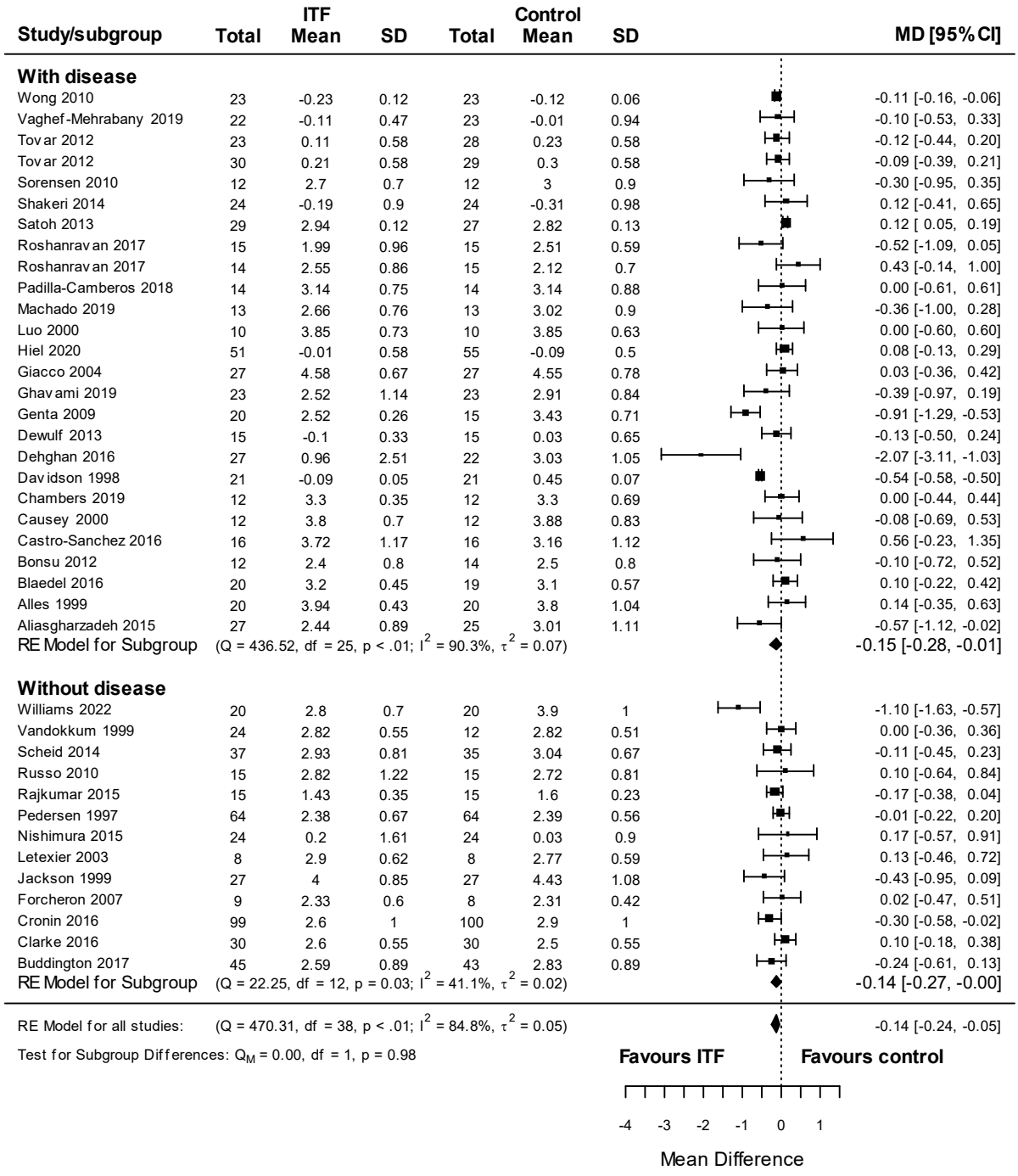


Figure 5: LDL-C - subgroup by dose

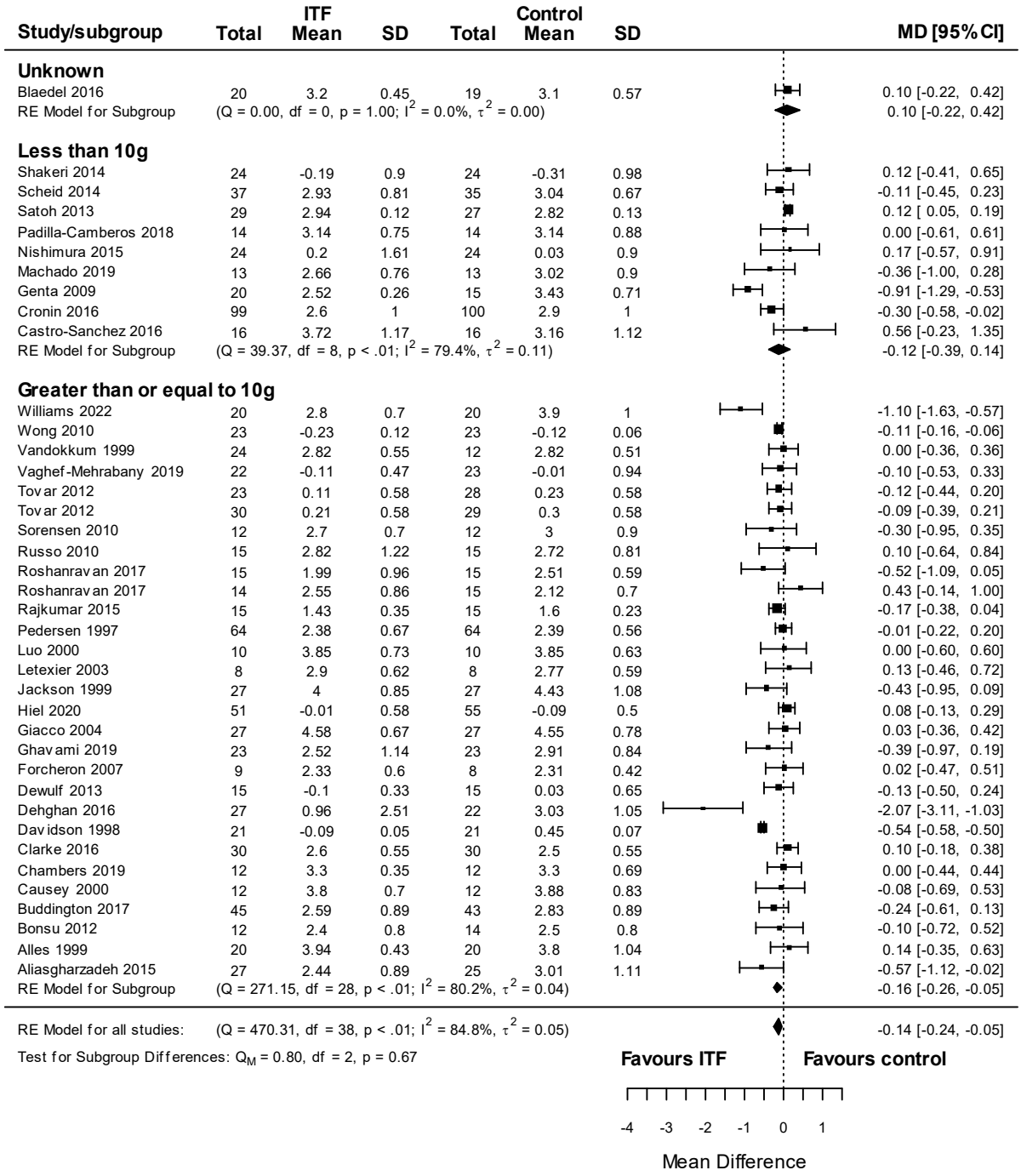


Figure 6: LDL-C - subgroup by ITF type

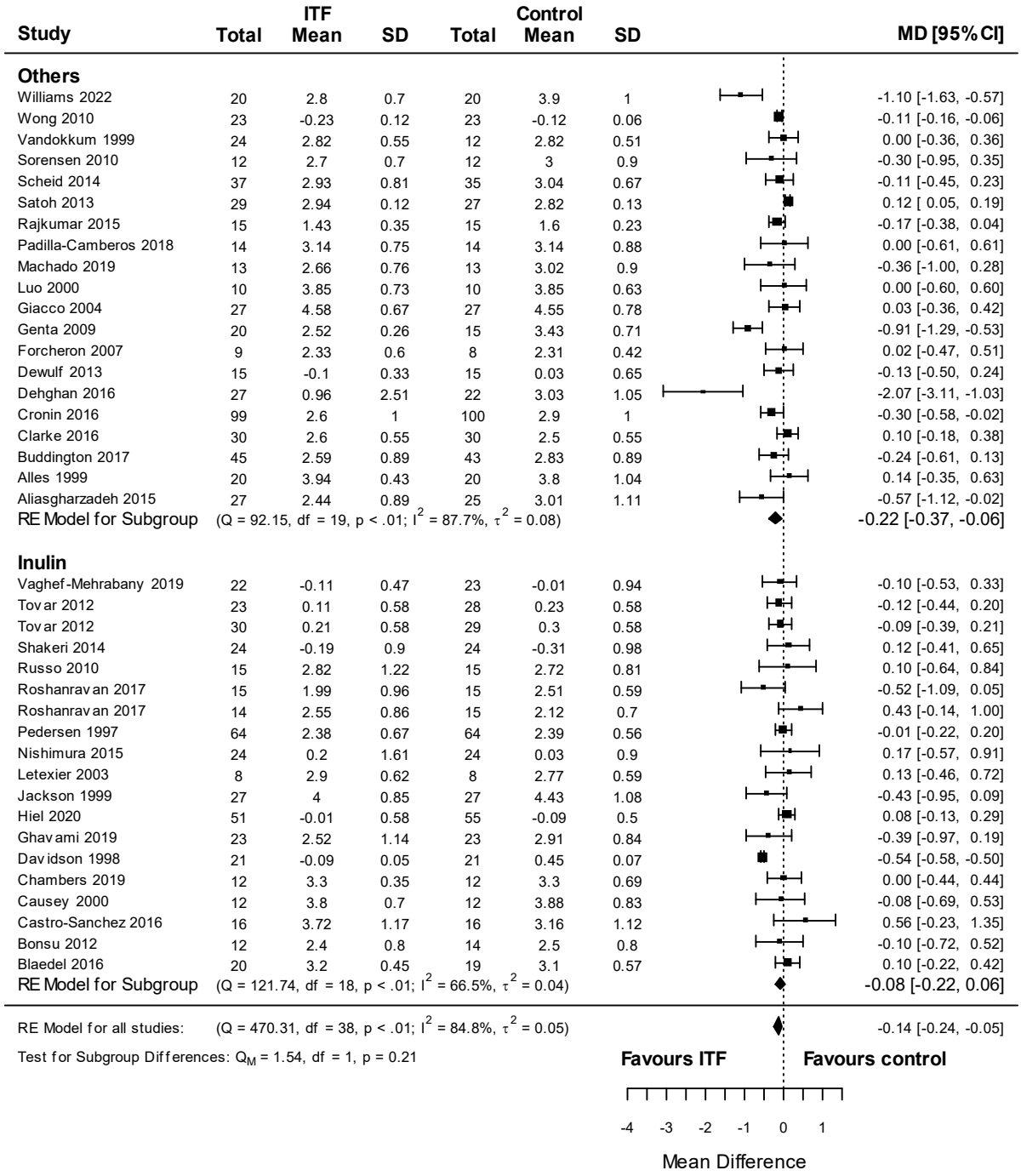


Figure 7: LDL-C - subgroup by RoB

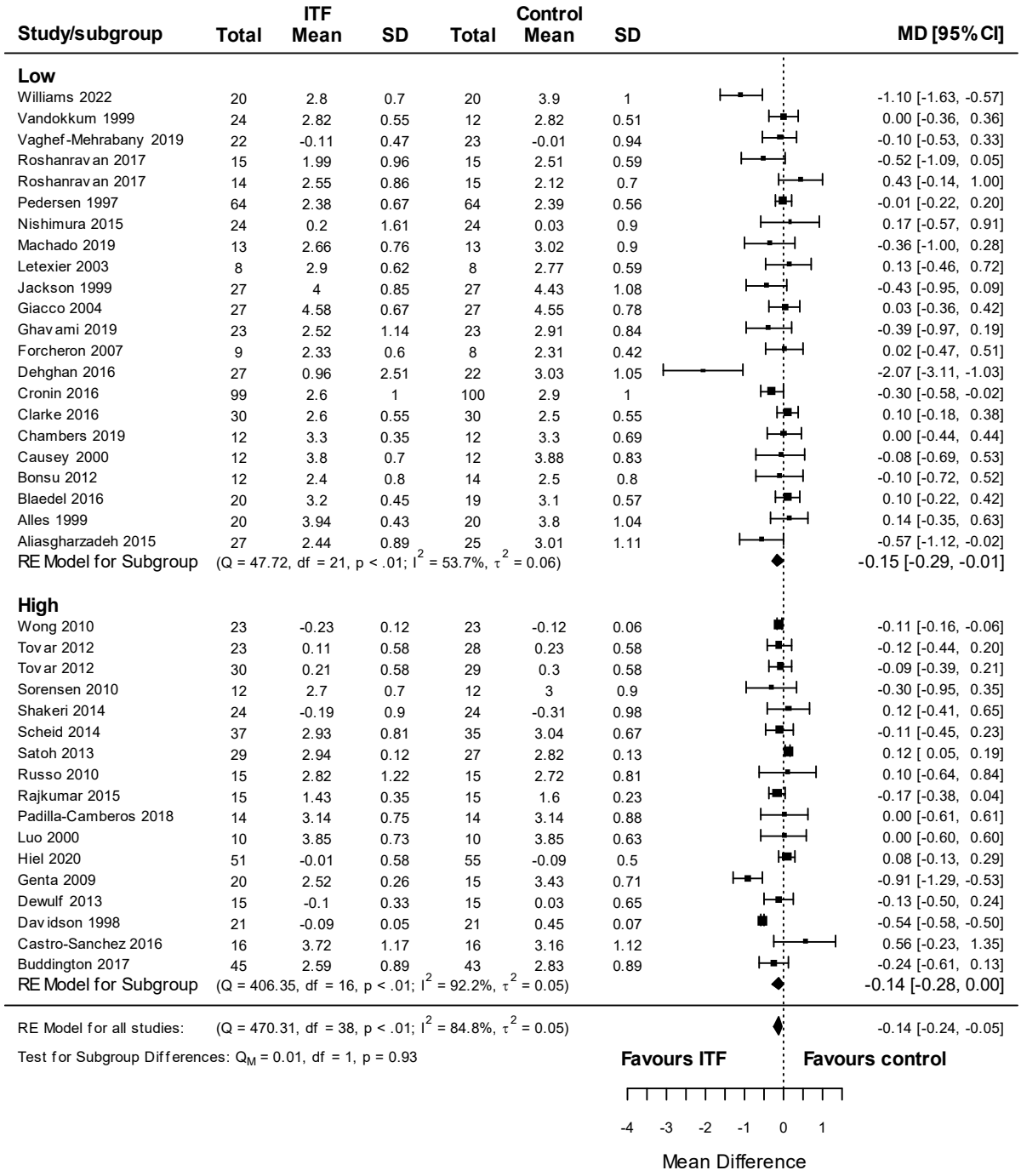


Figure 8: LDL-C - subgroup by follow-up duration

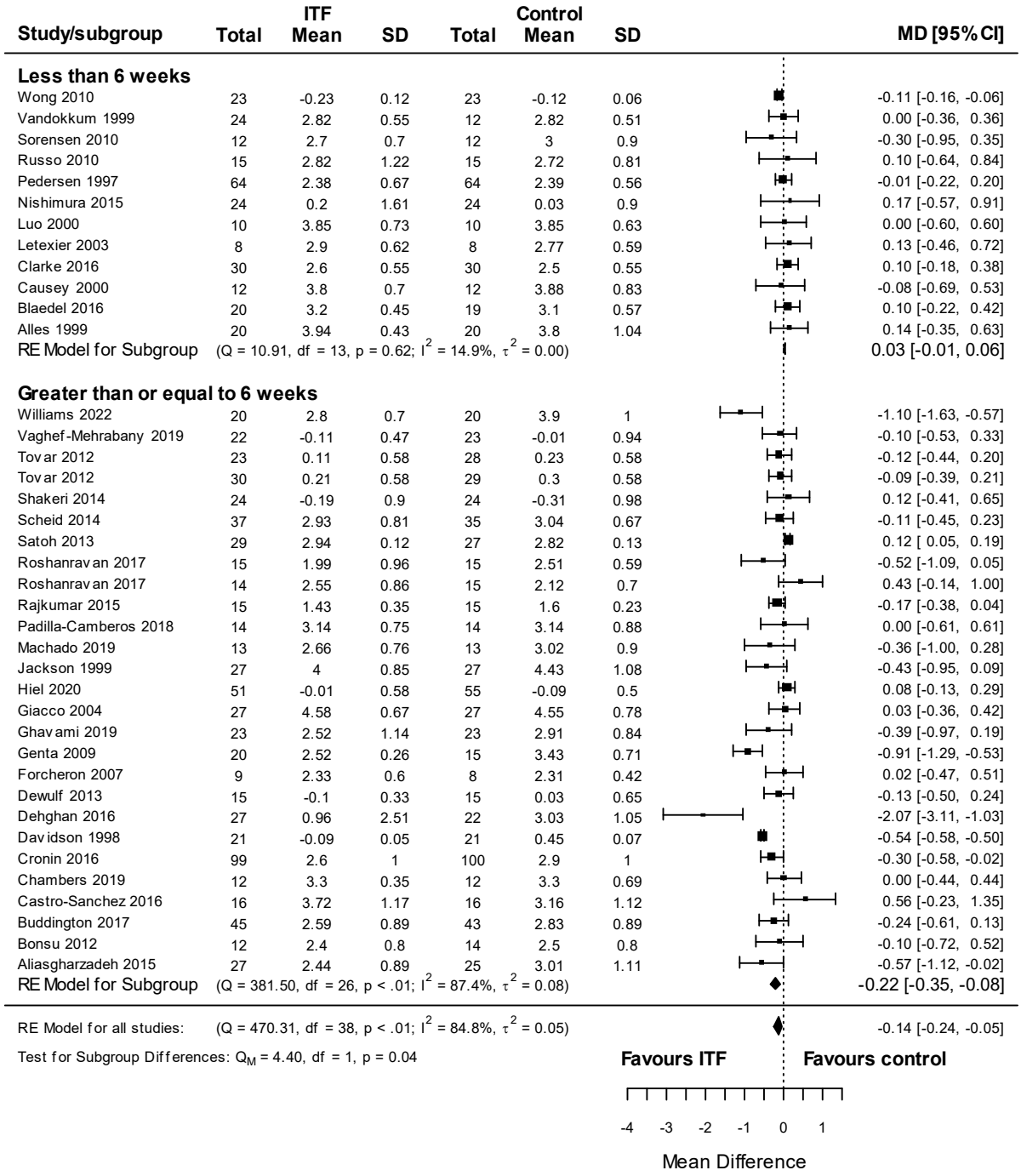


Figure 9: LDL-C - subgroup by age

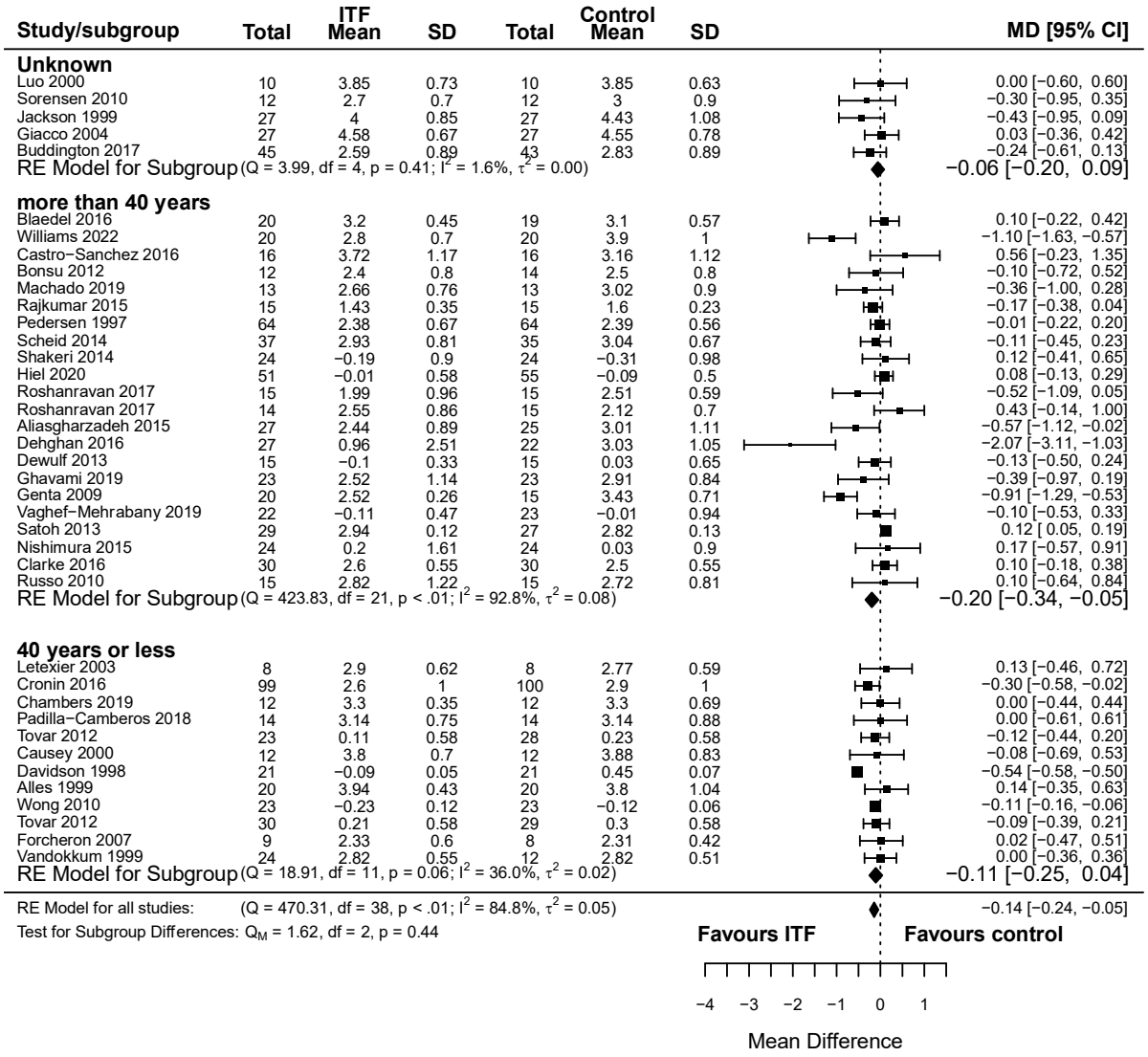


Figure 10: LDL-C - subgroup by body mas index

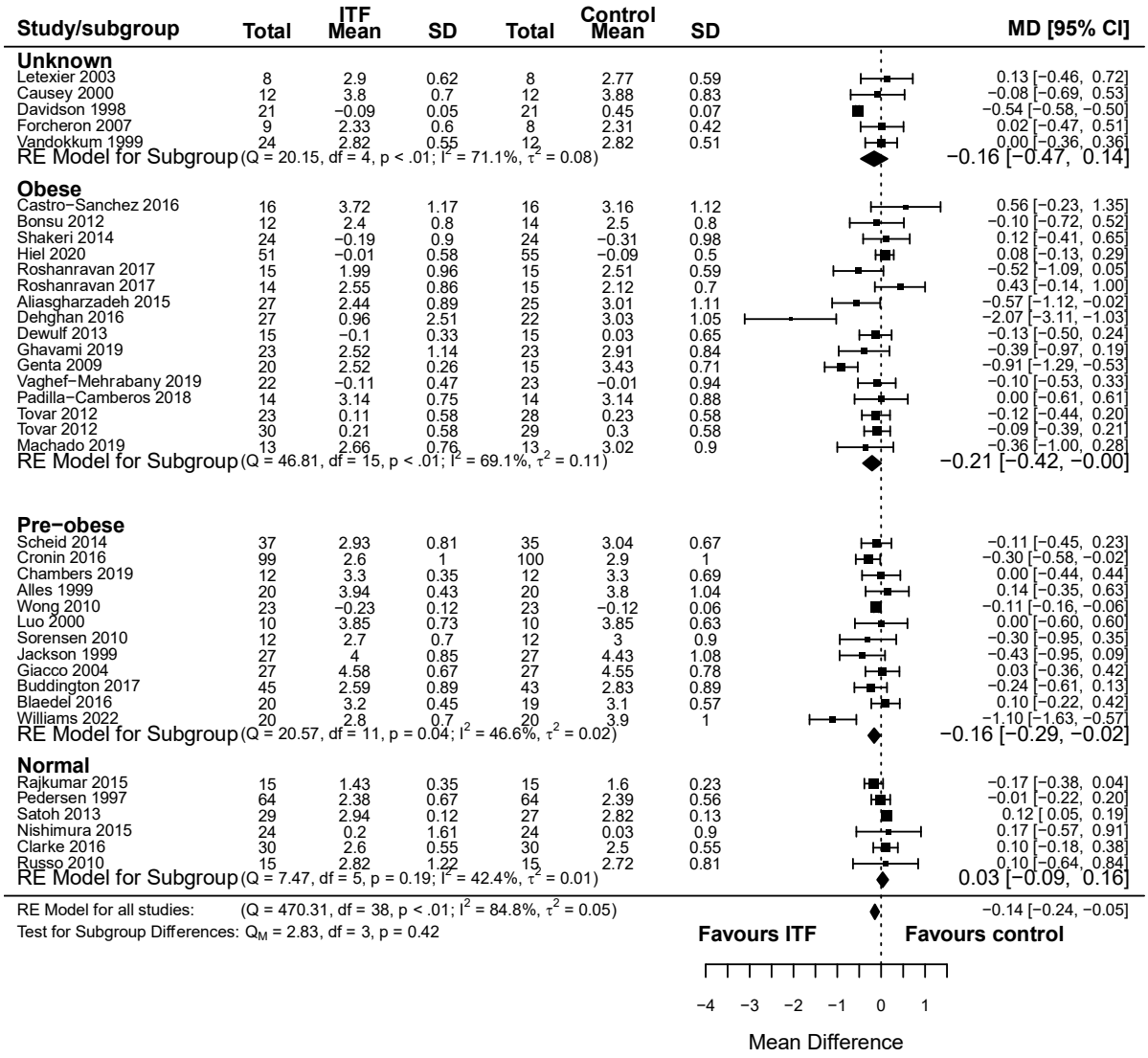


Figure 11: LDL-C - subgroup by diabetes status

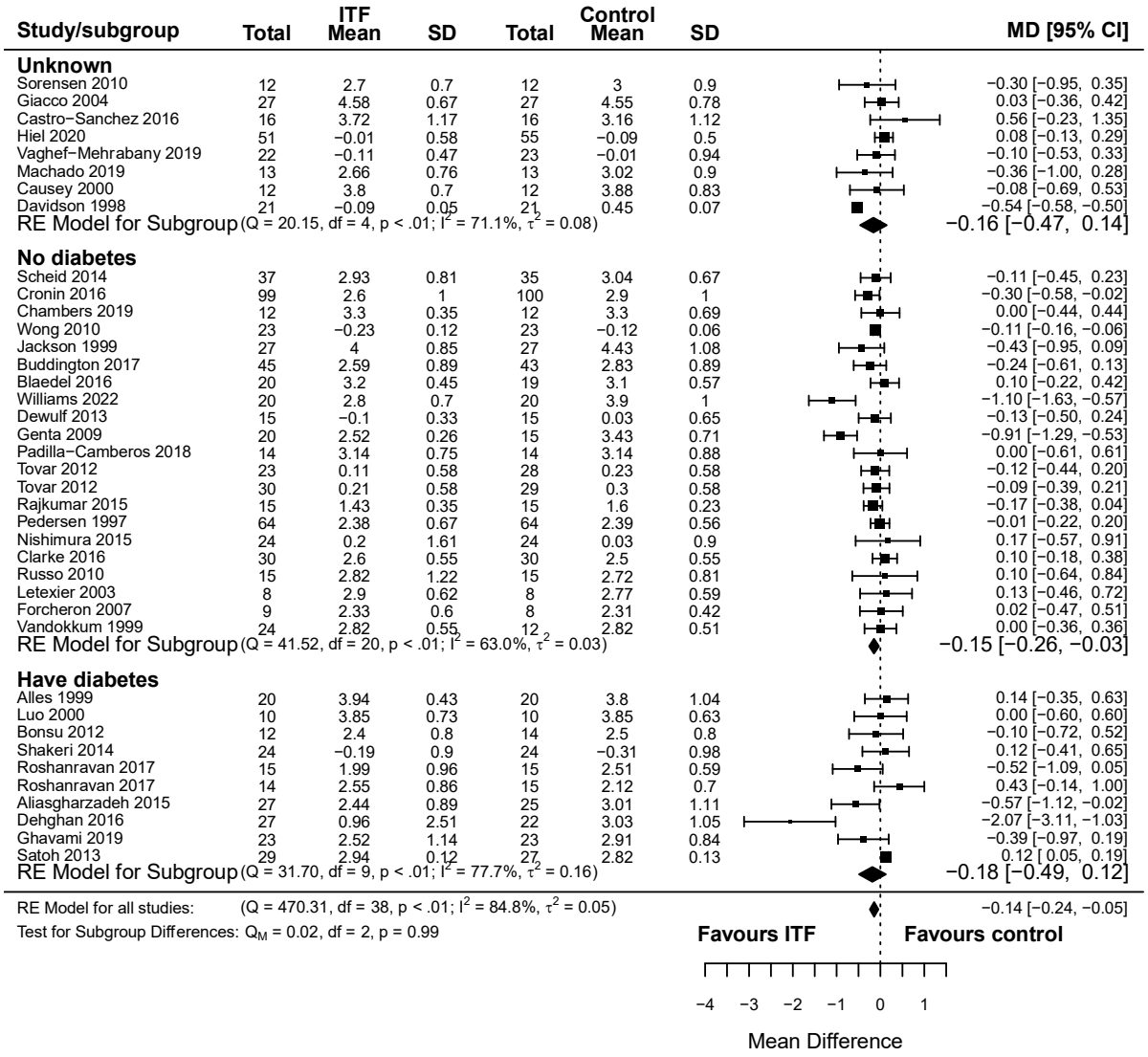


Figure 12: Triglycerides - subgroup by sex

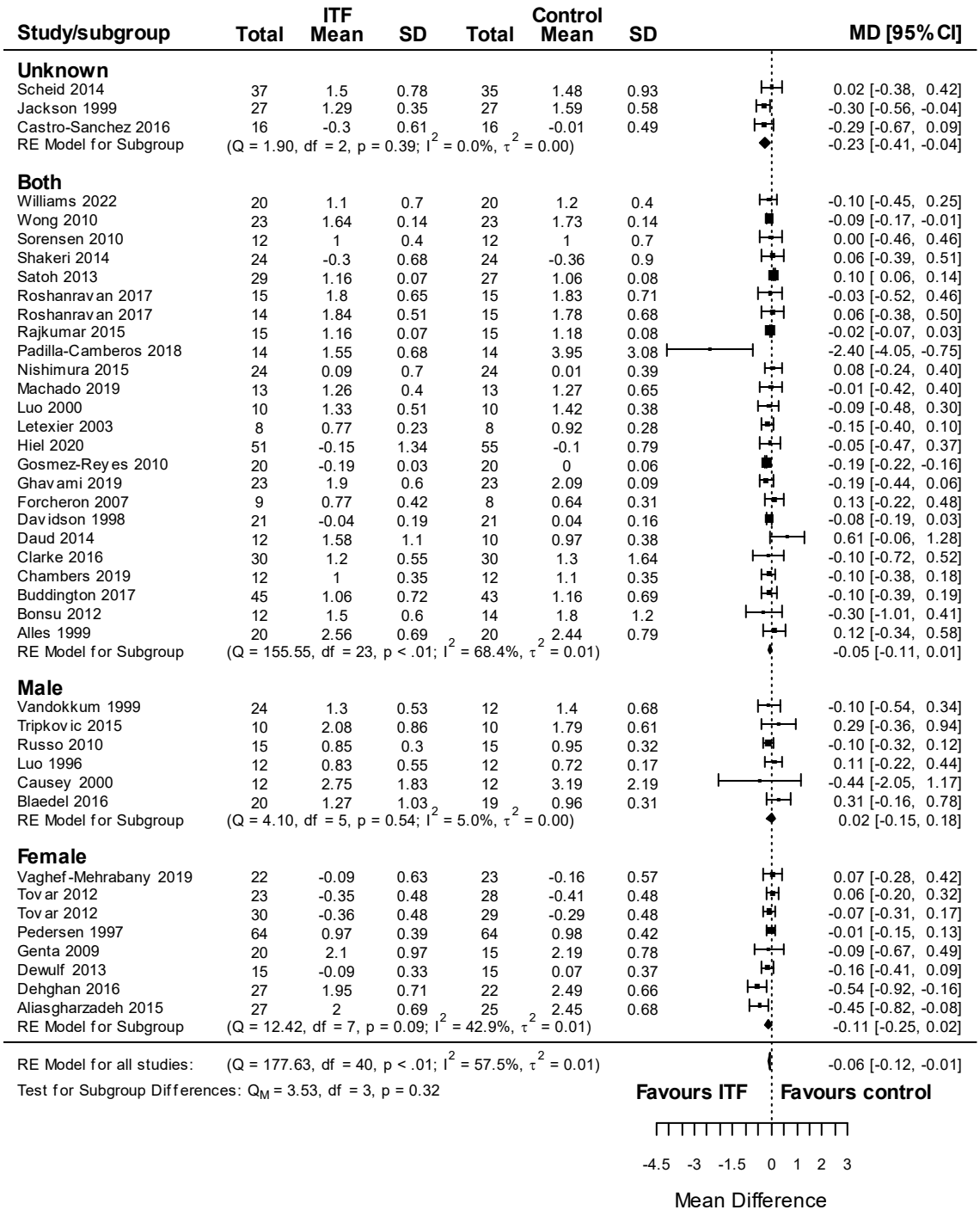


Figure 13: Triglycerides - subgroup by disease

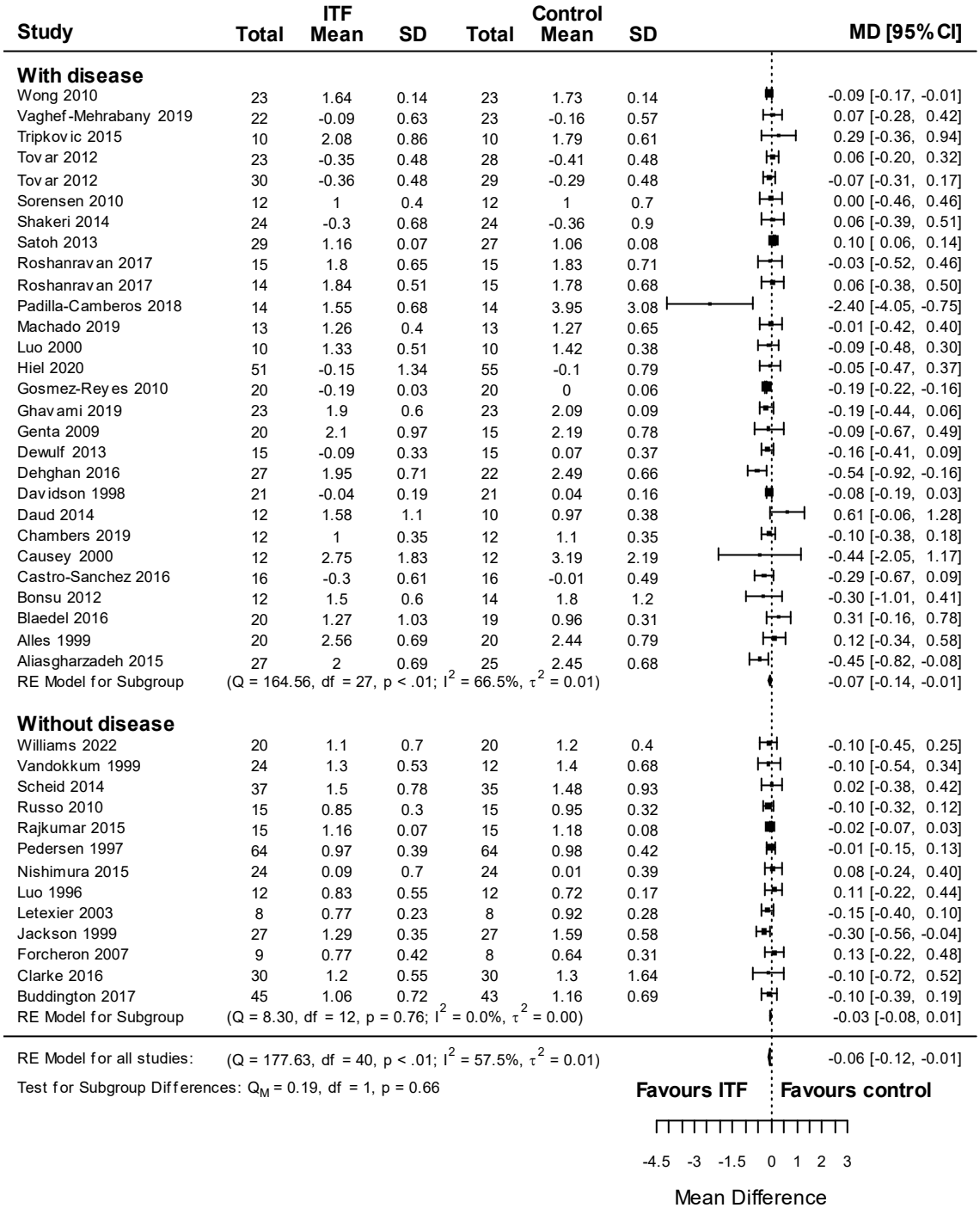


Figure 14: Triglycerides - subgroup by dose

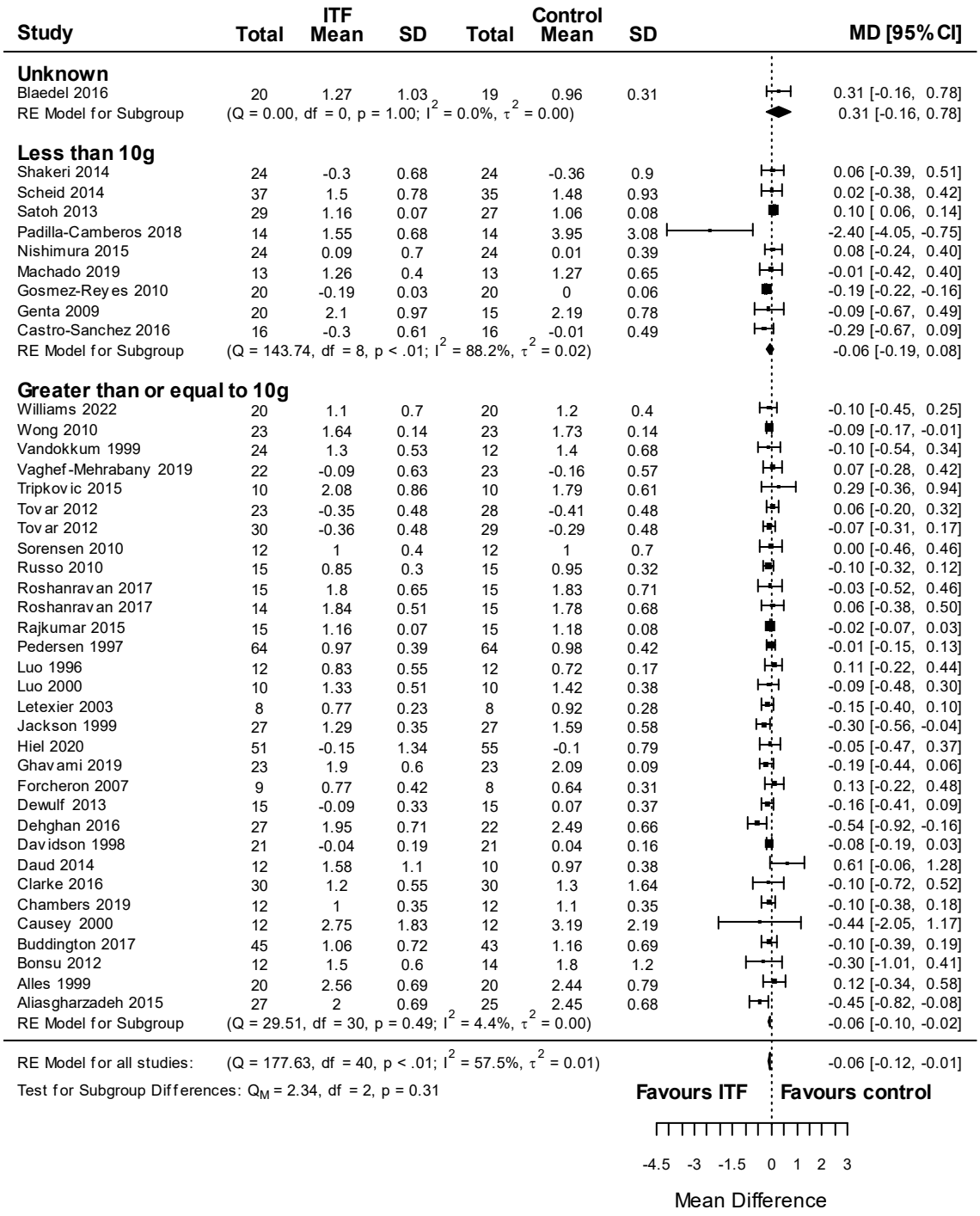


Figure 15: Triglycerides - subgroup by ITF type

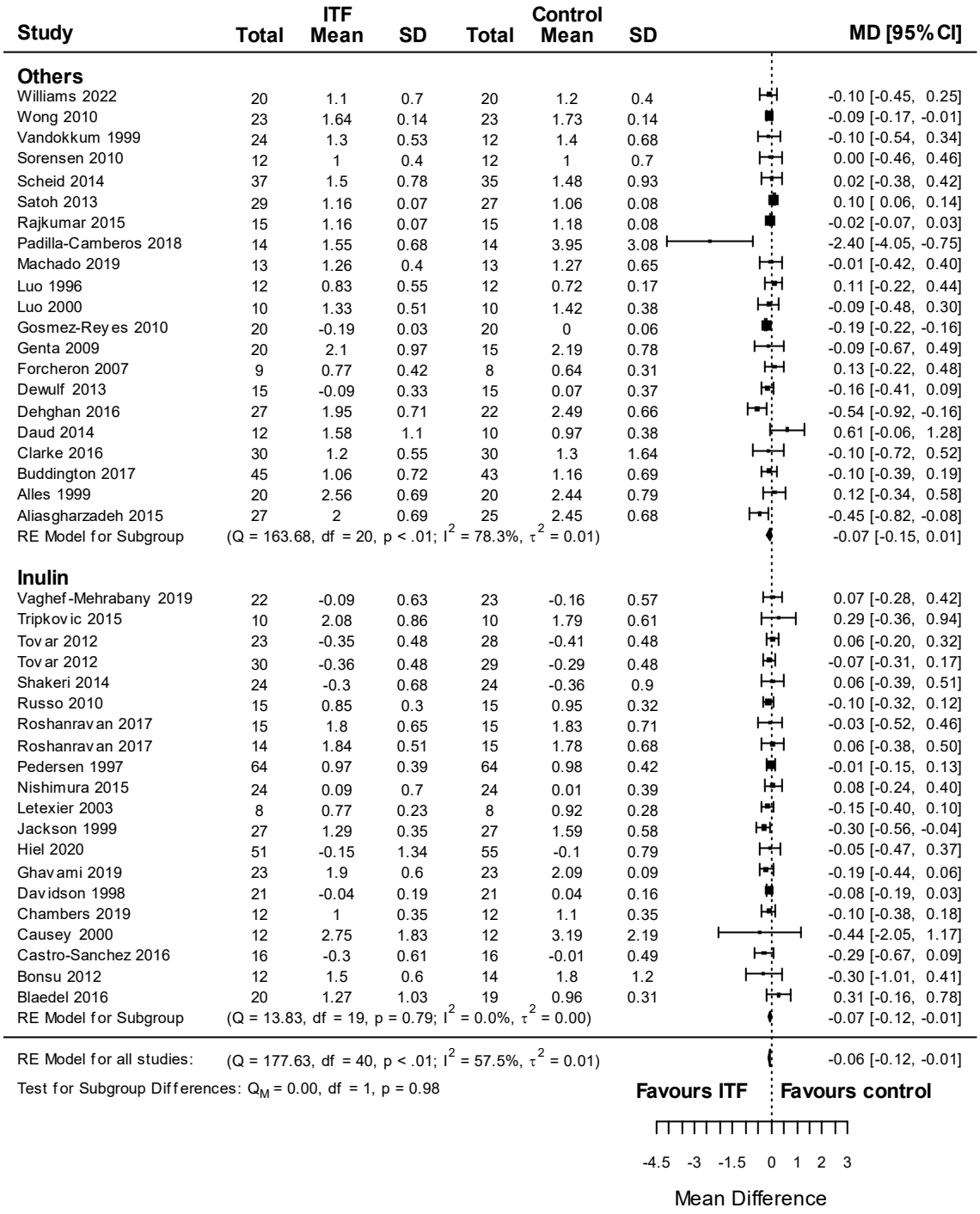


Figure 16: Triglycerides - subgroup by RoB

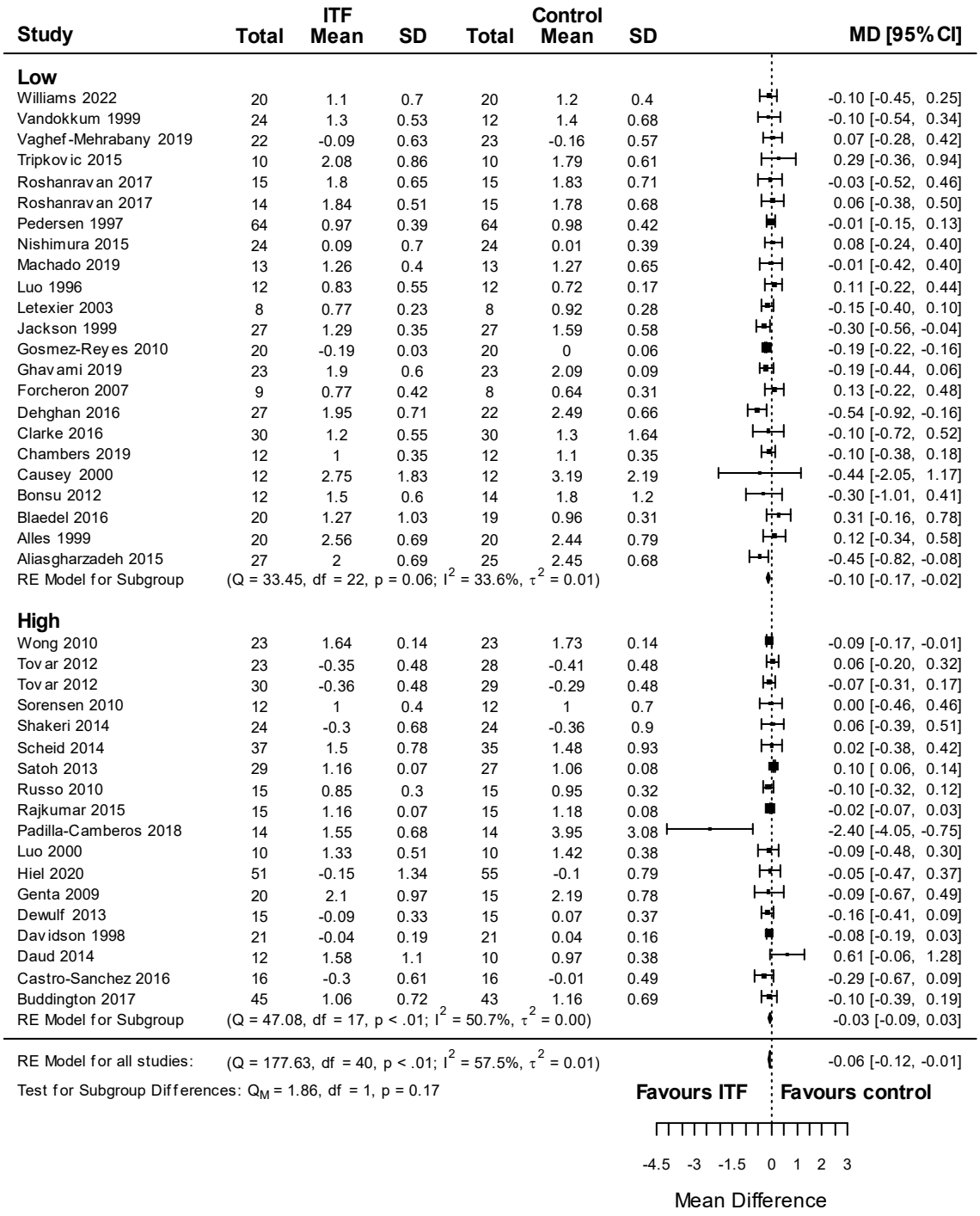


Figure 17: Triglycerides - subgroup by follow-up duration

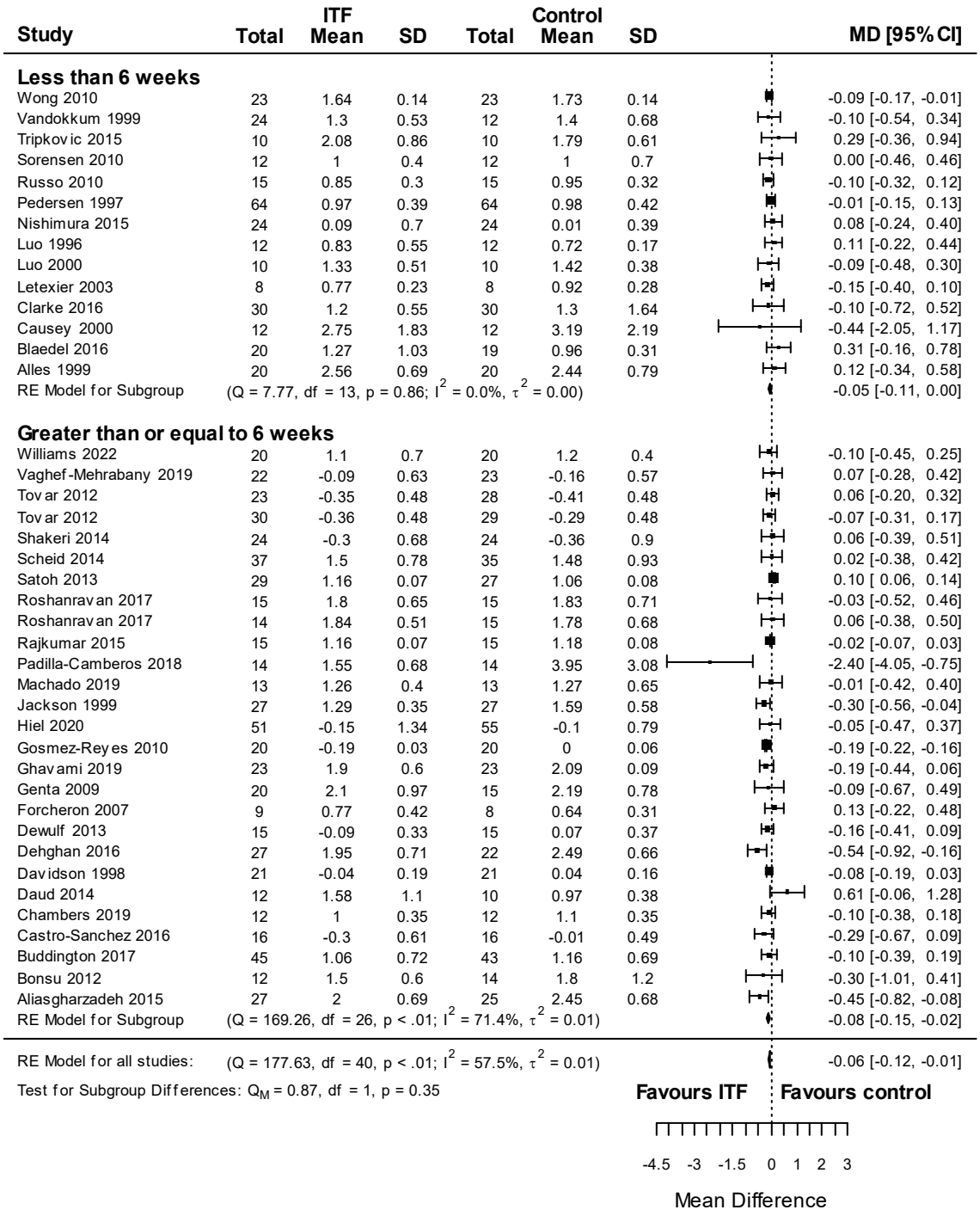


Figure 18: Triglycerides - subgroup by age

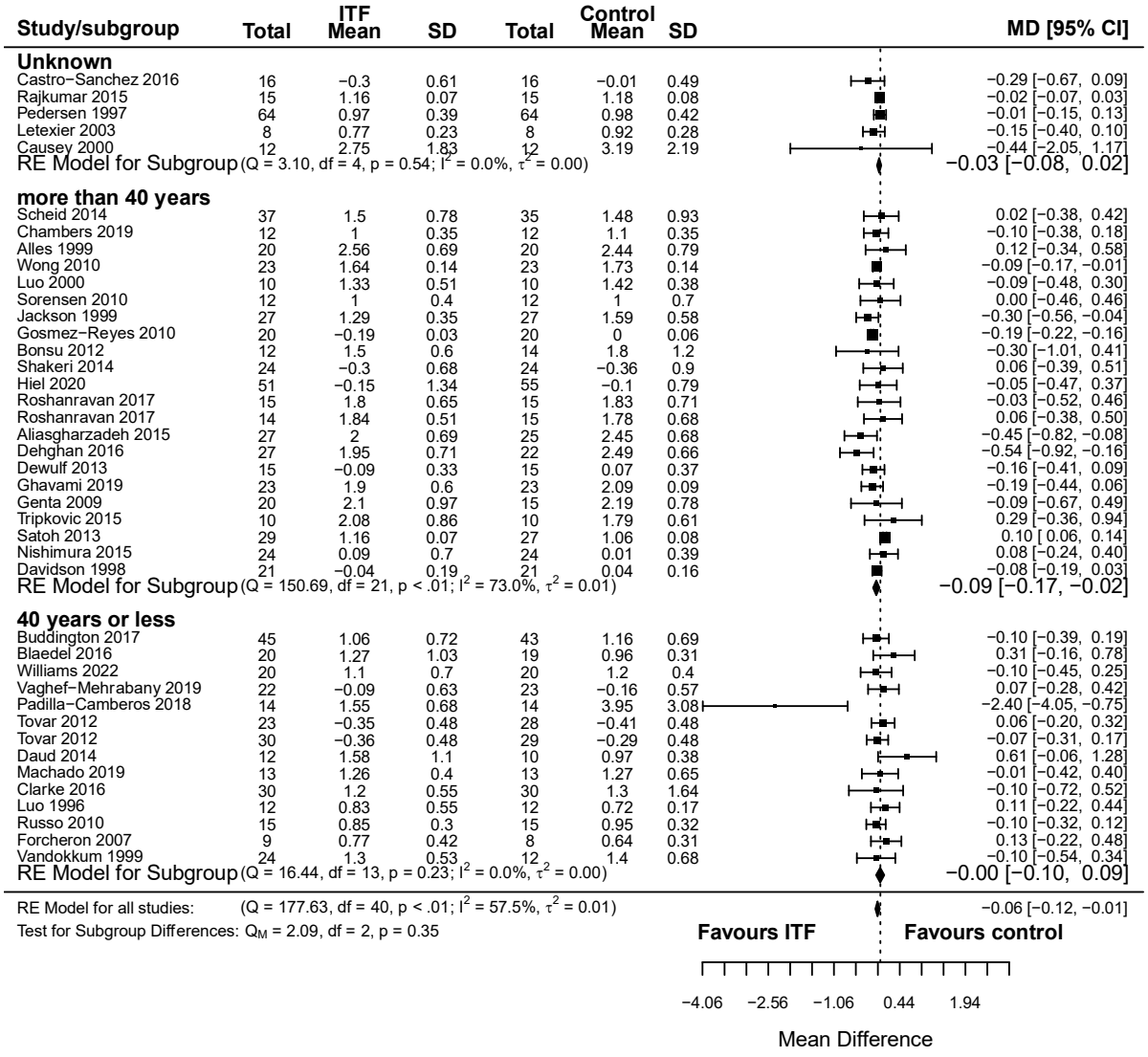


Figure 19: Triglycerides - subgroup by BMI

(9)

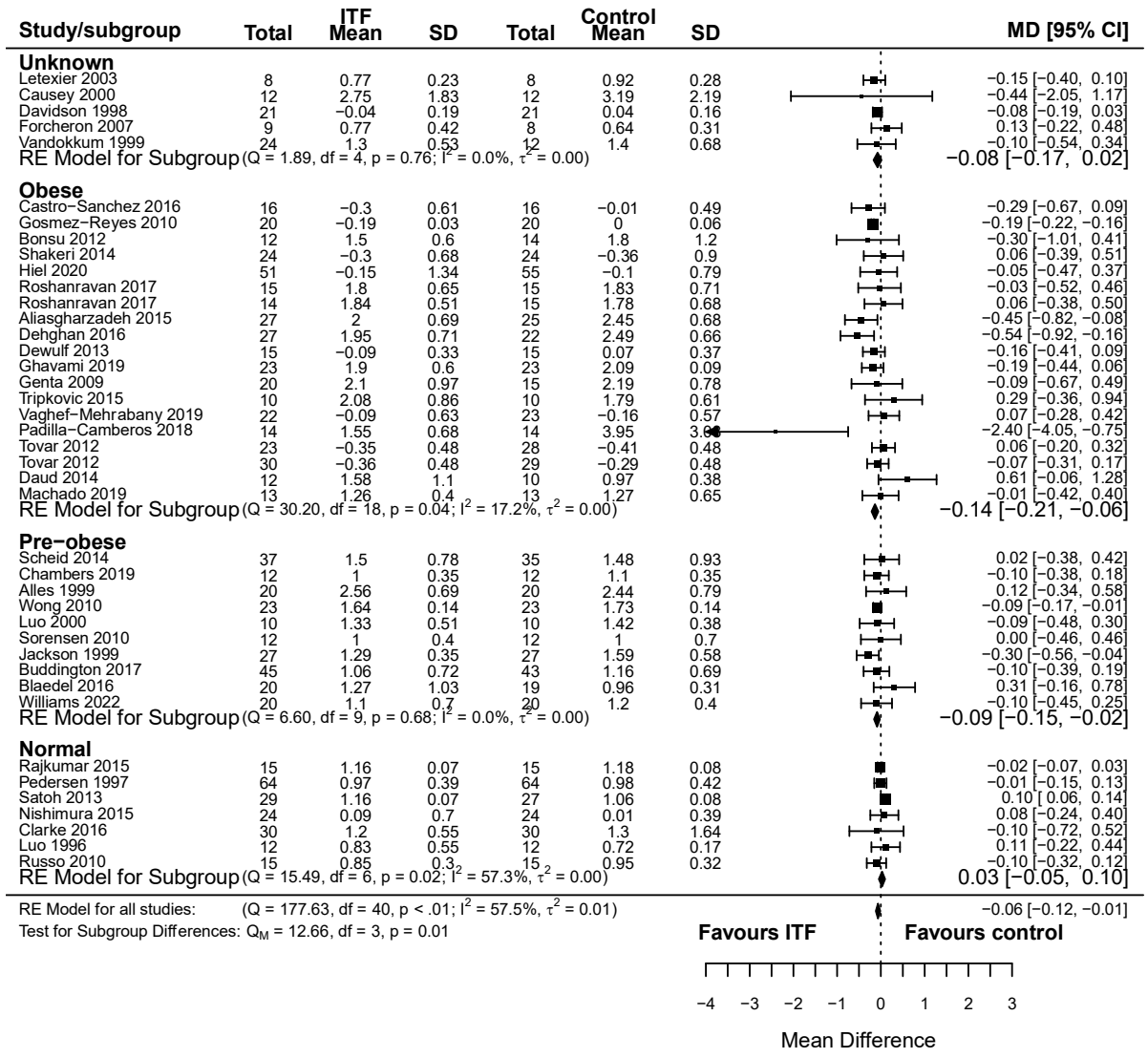


Figure 20: Triglycerides - subgroup by diabetes status

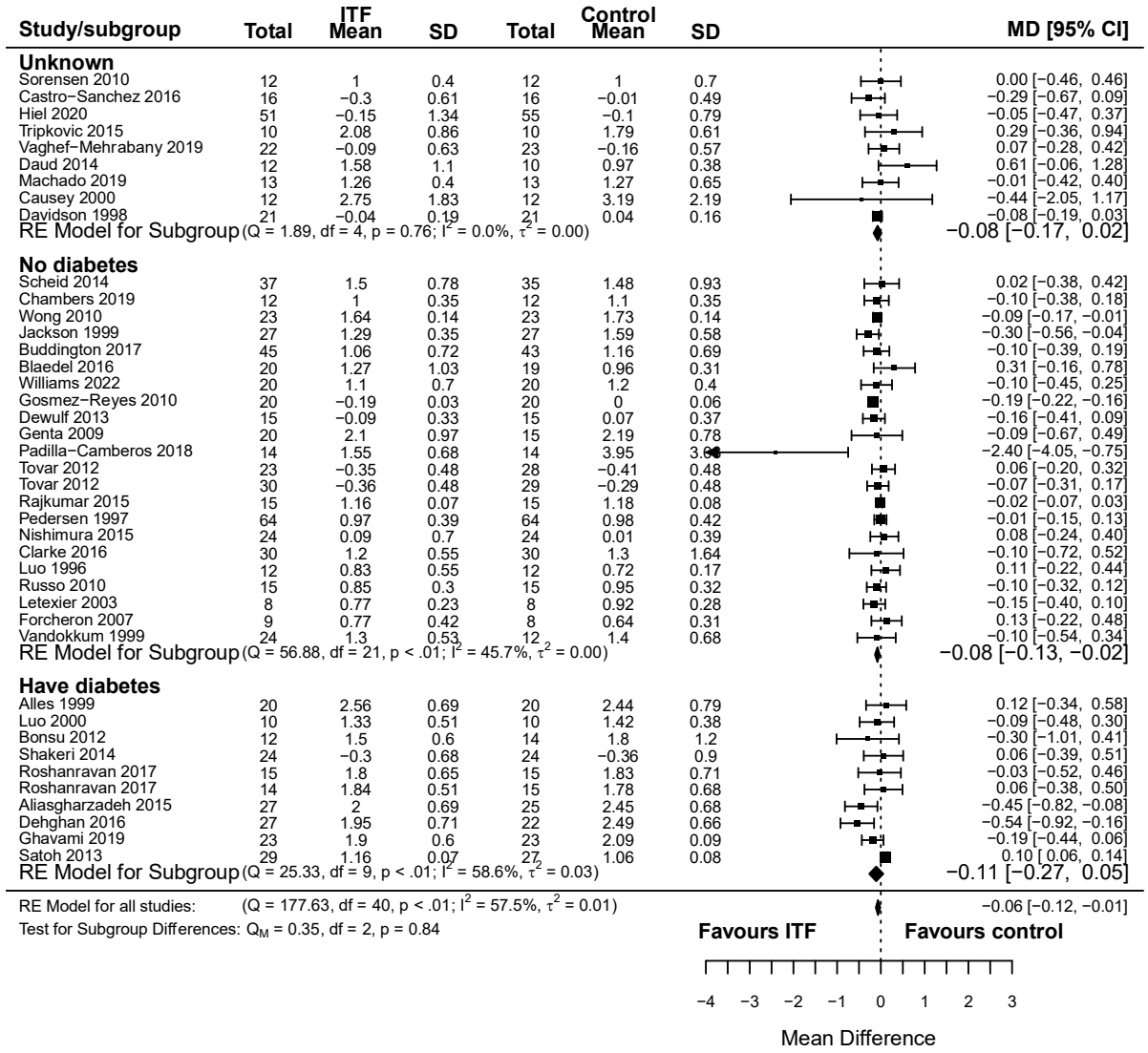


Figure 21: Fasting blood glucose -subgroup by sex

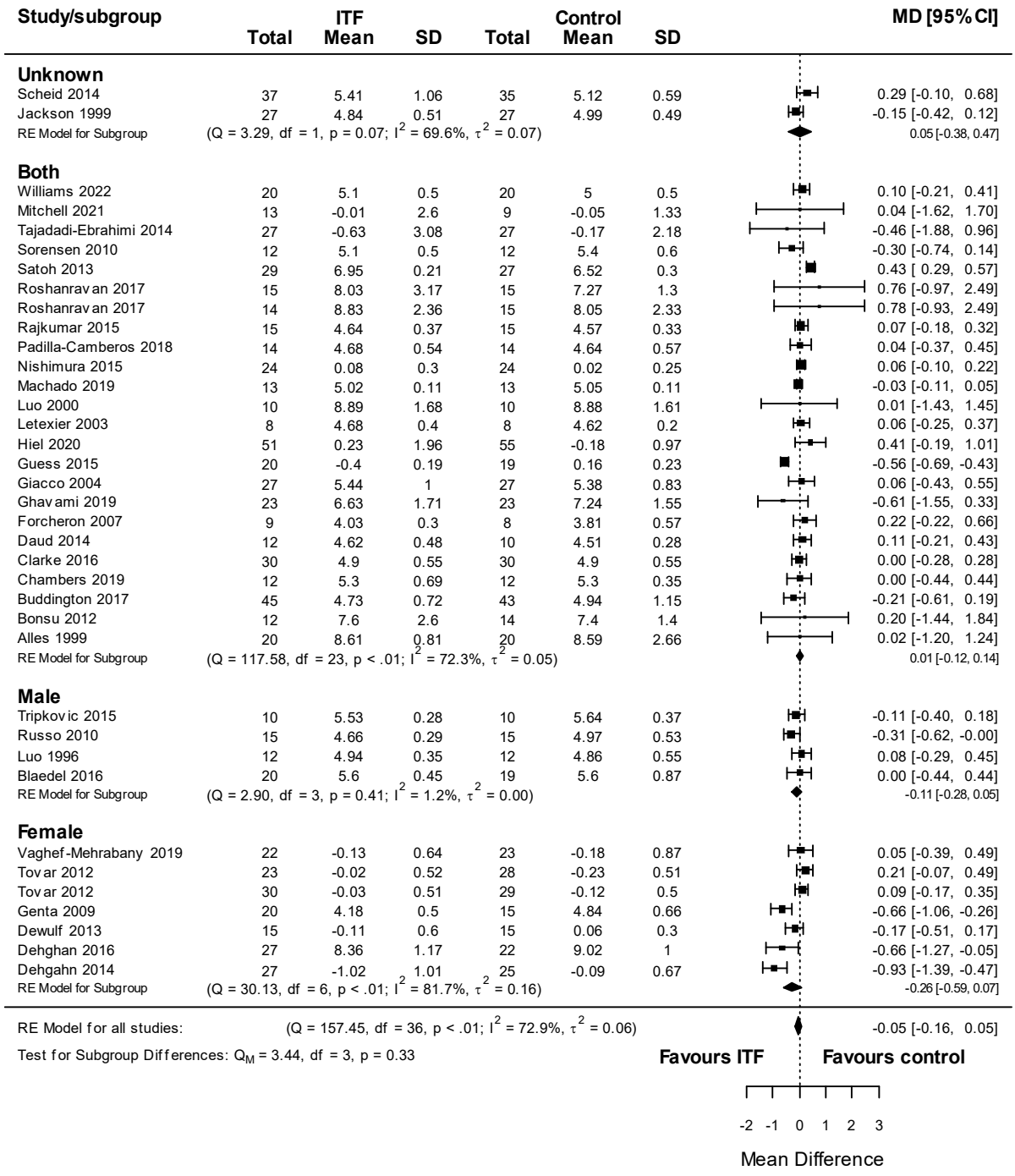


Figure 22: Fasting blood glucose -subgroup by disease

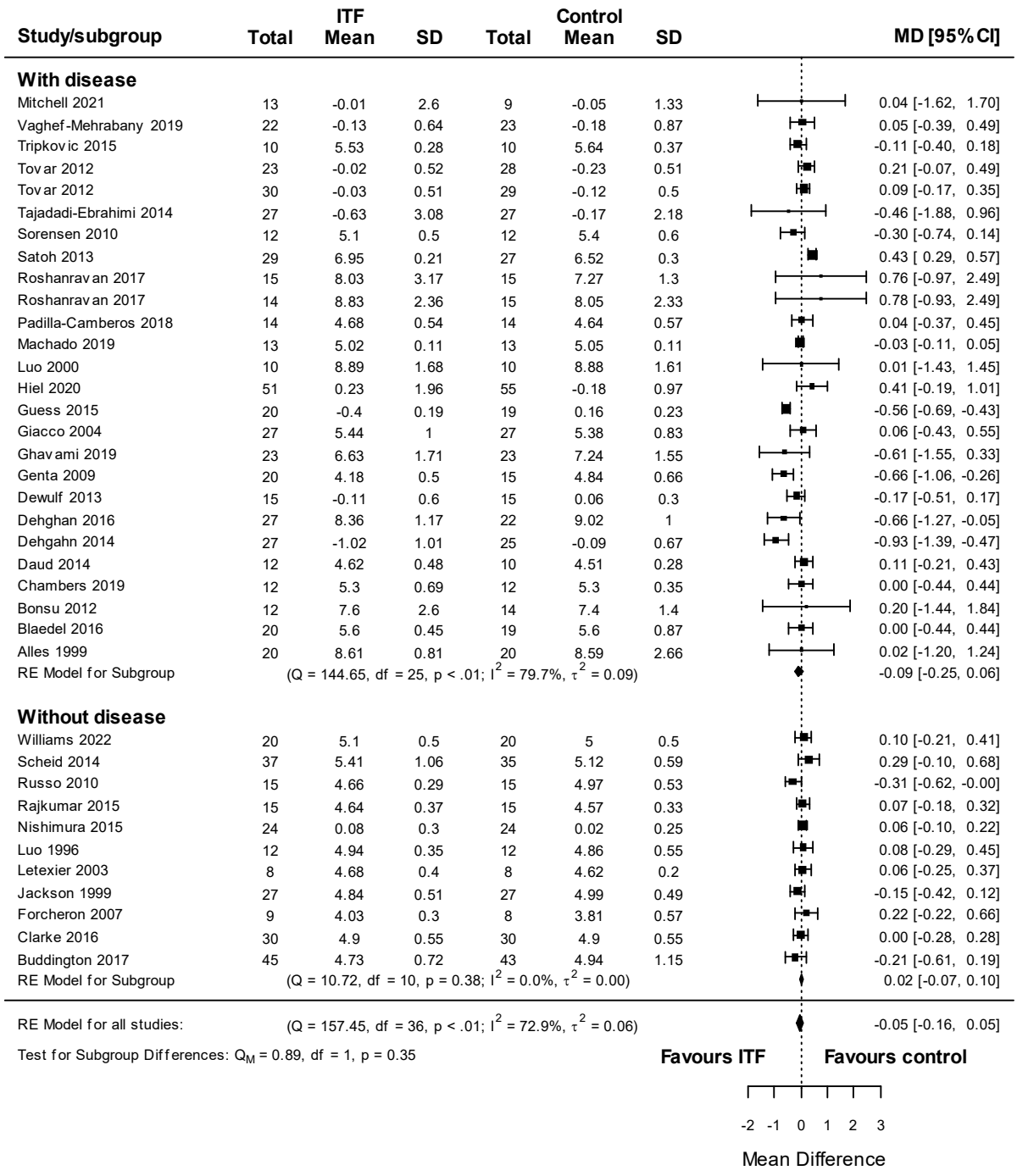


Figure 23: Fasting blood glucose -subgroup by dose

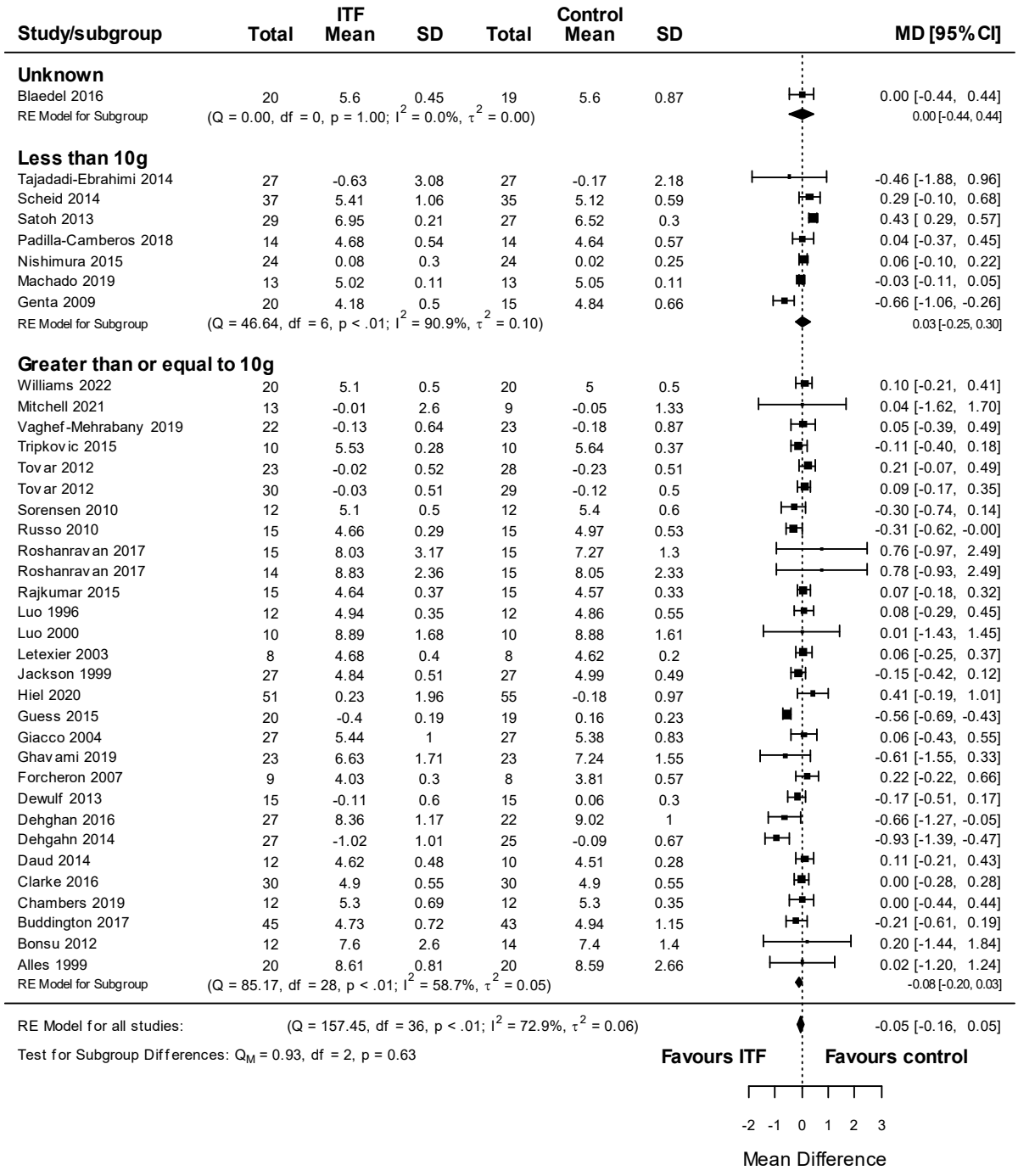


Figure 24: Fasting blood glucose -subgroup by ITF type

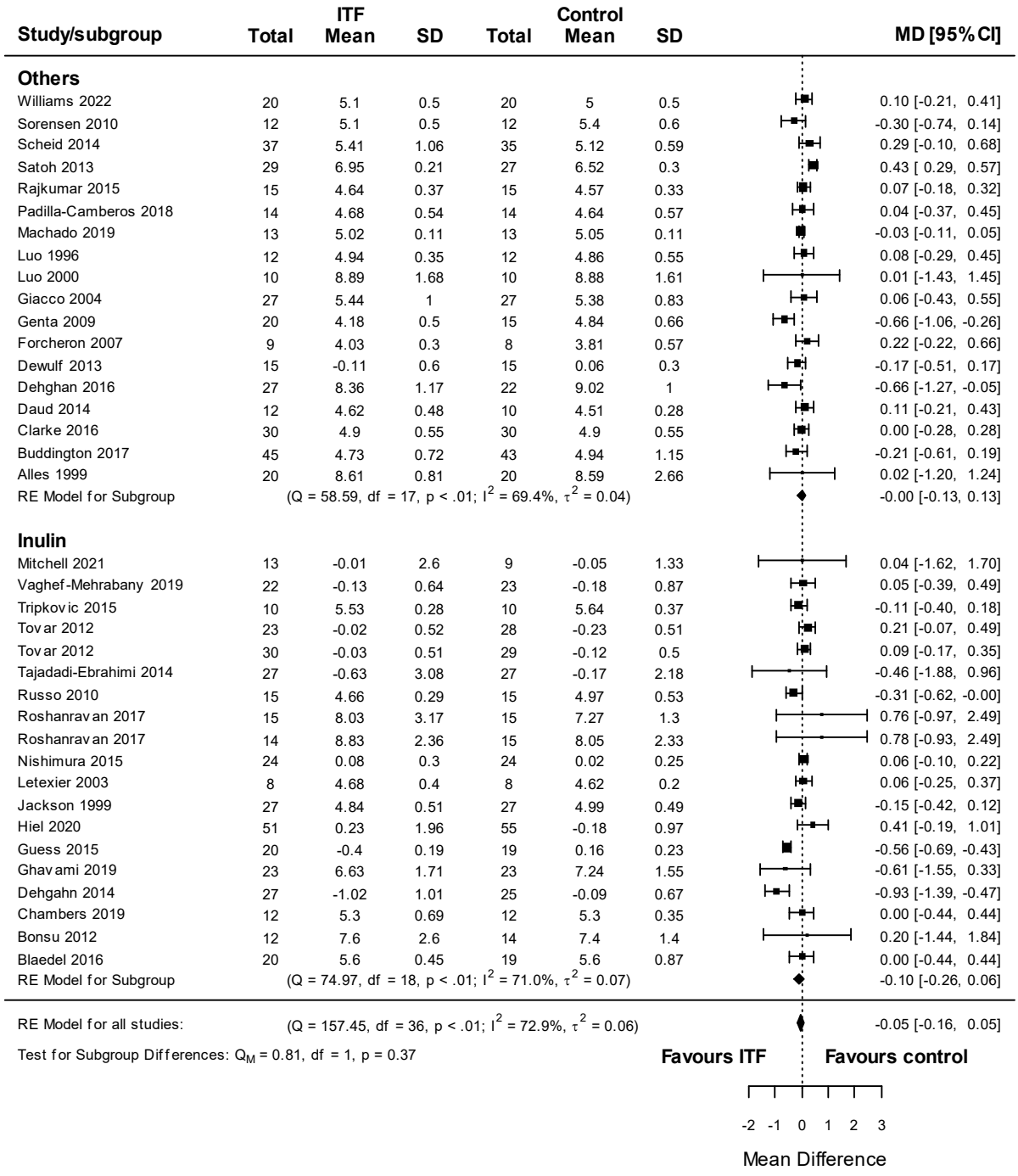


Figure 25: Fasting blood glucose -subgroup by RoB

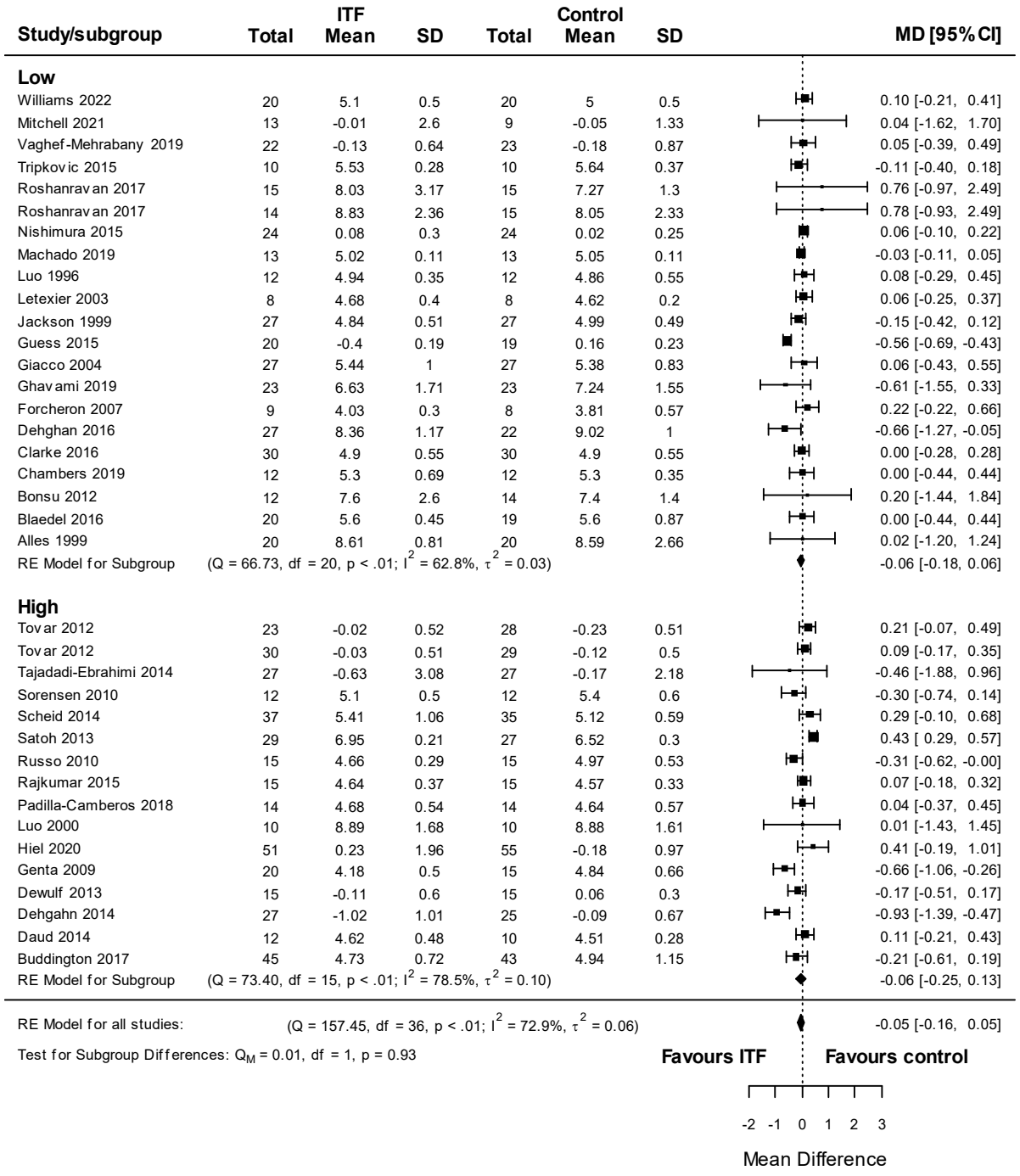


Figure 26: Fasting blood glucose -subgroup by follow-up duration

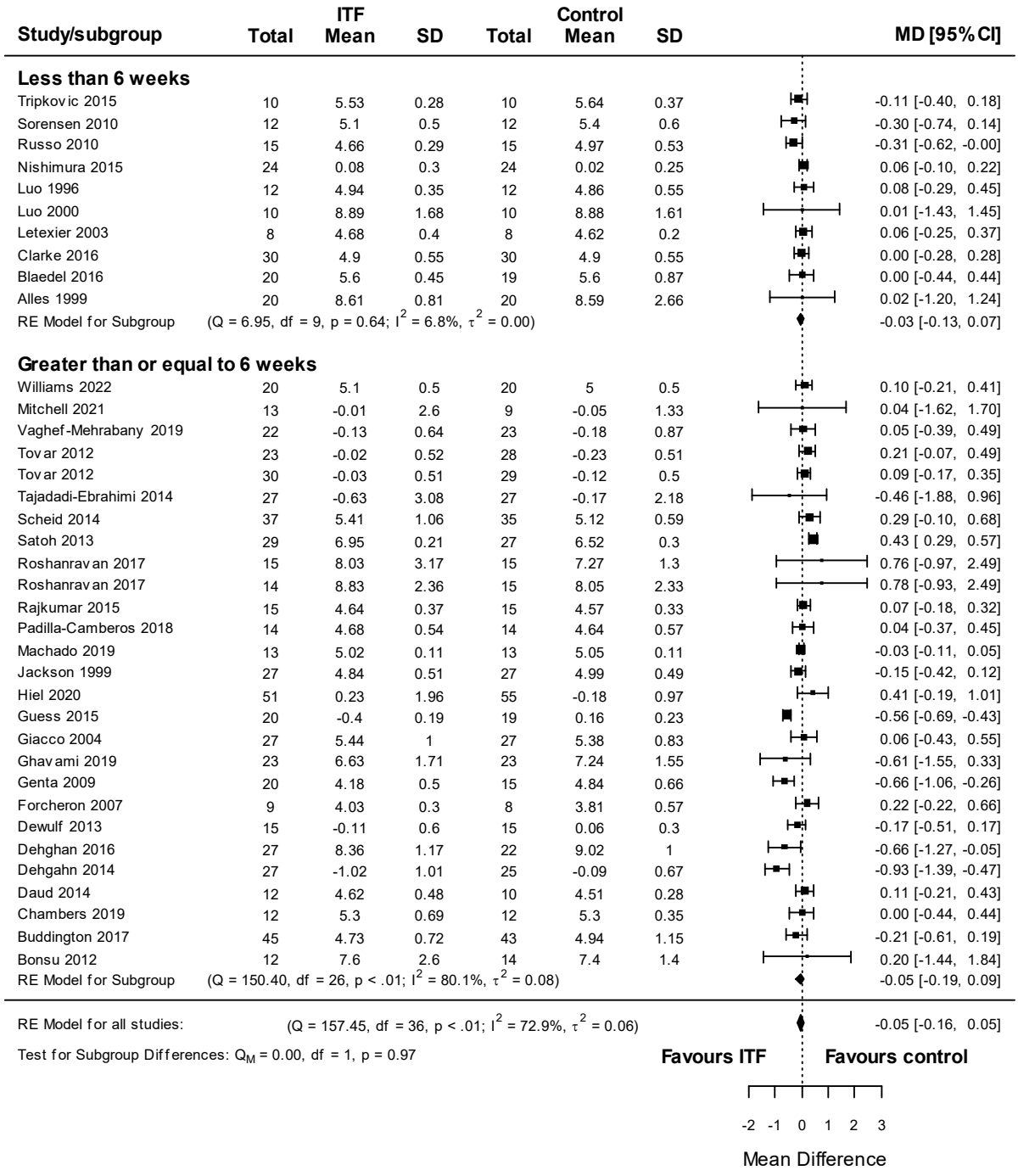


Figure 27: Fasting blood glucose - subgroup by age

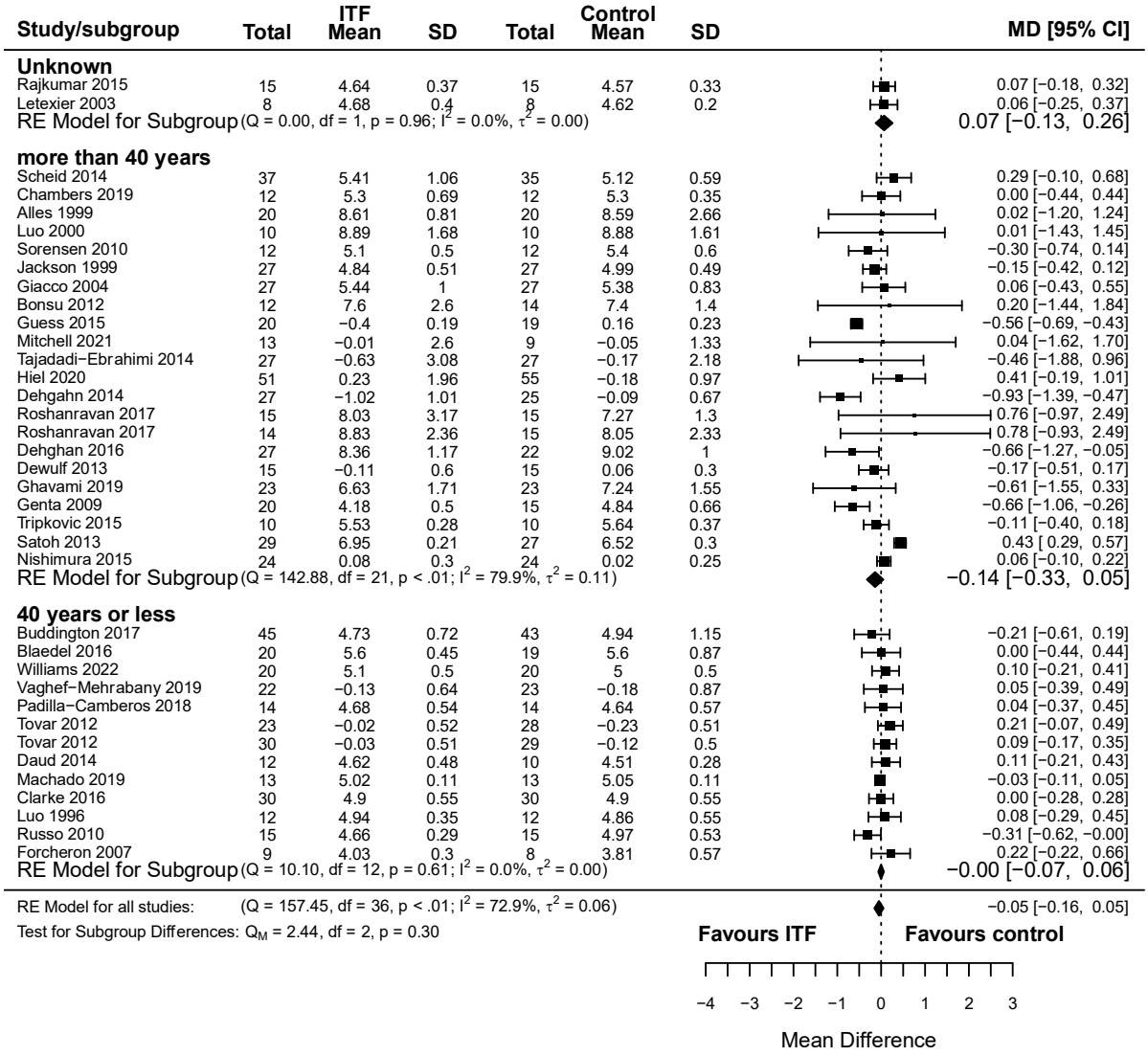


Figure 28: Fasting blood glucose - subgroup by BMI

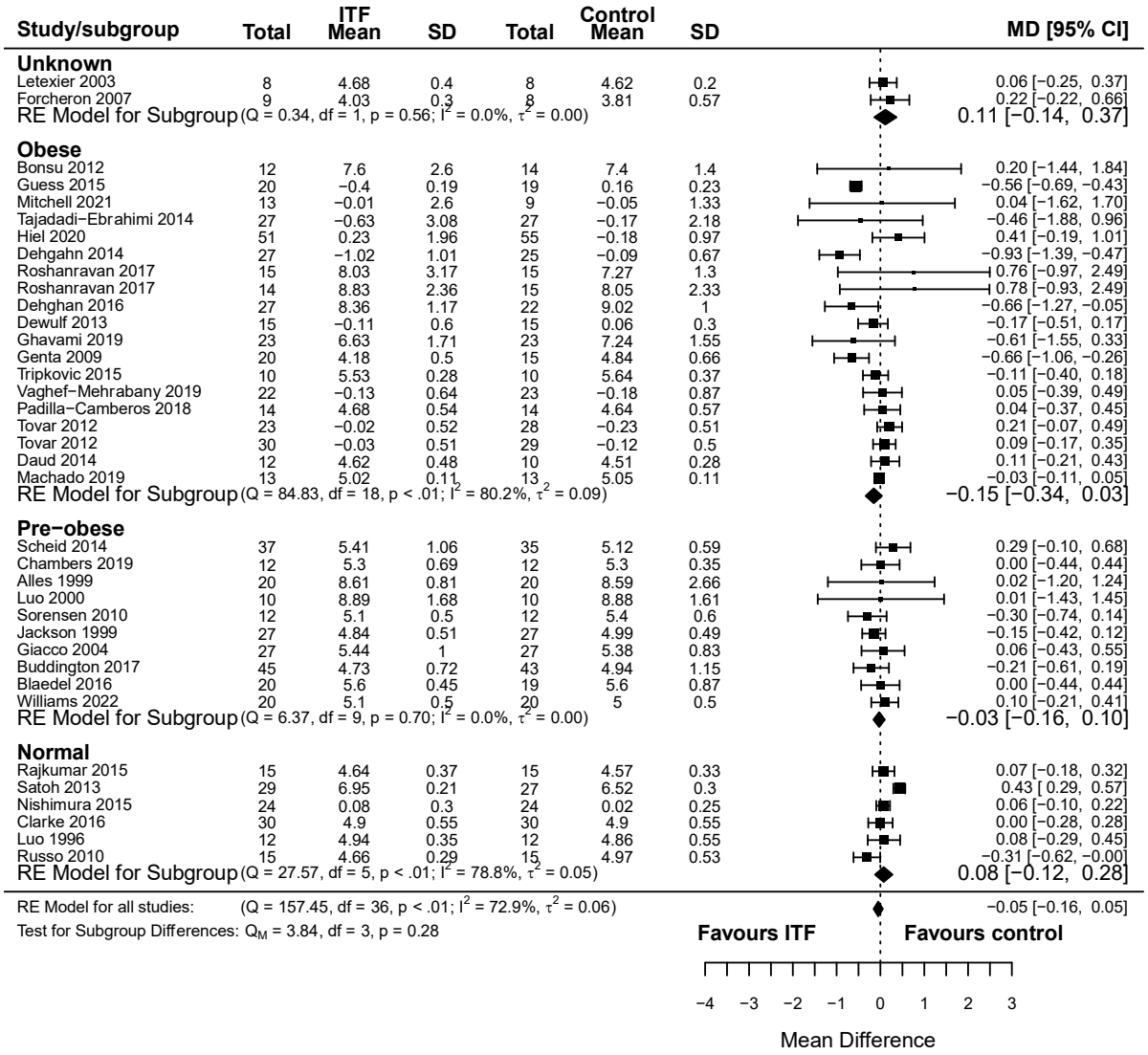


Figure 29: Fasting blood glucose - subgroup by diabetes status

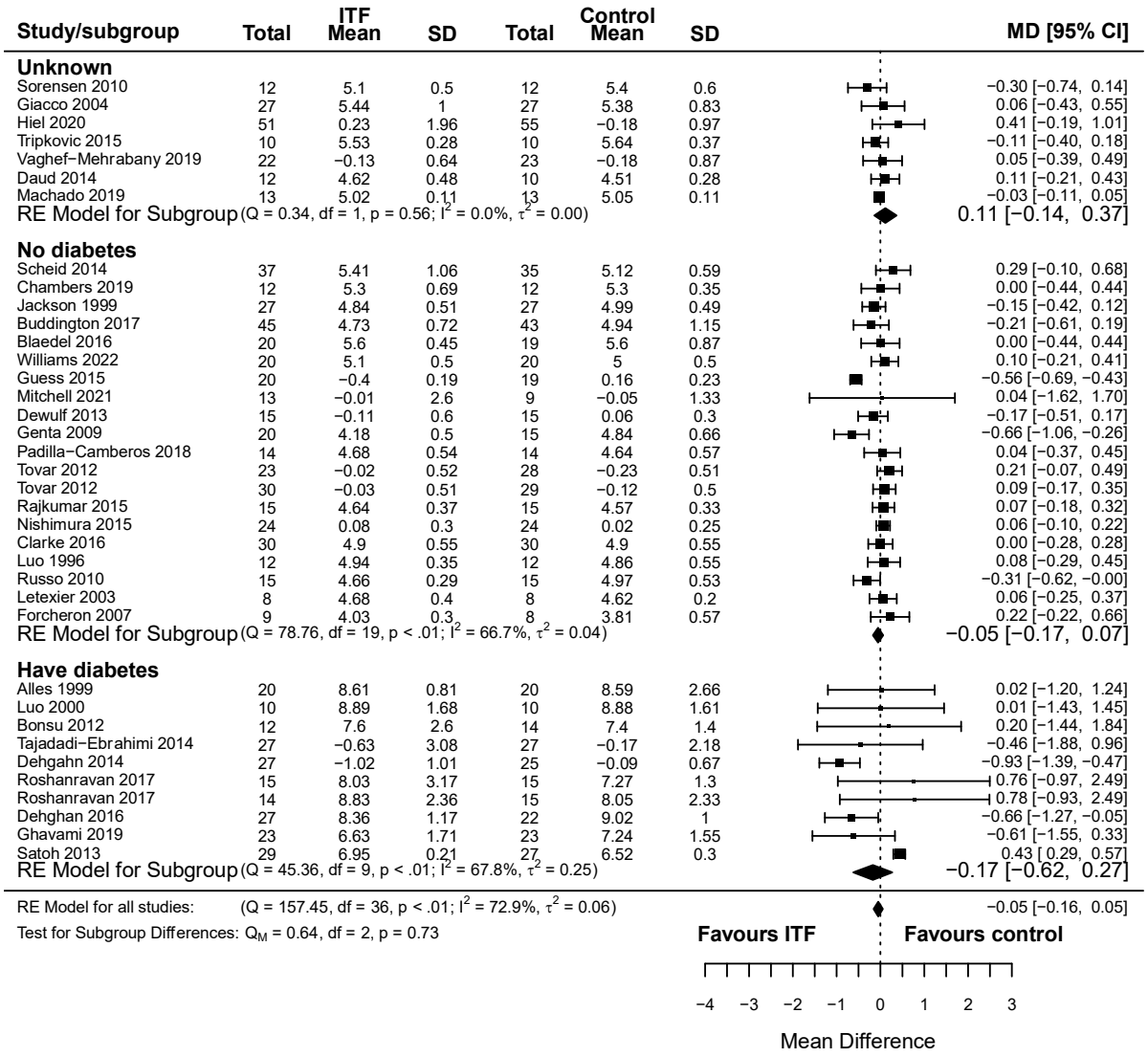


Figure 30: Forest plot displaying the effect of inulin-type fructans on body mass index

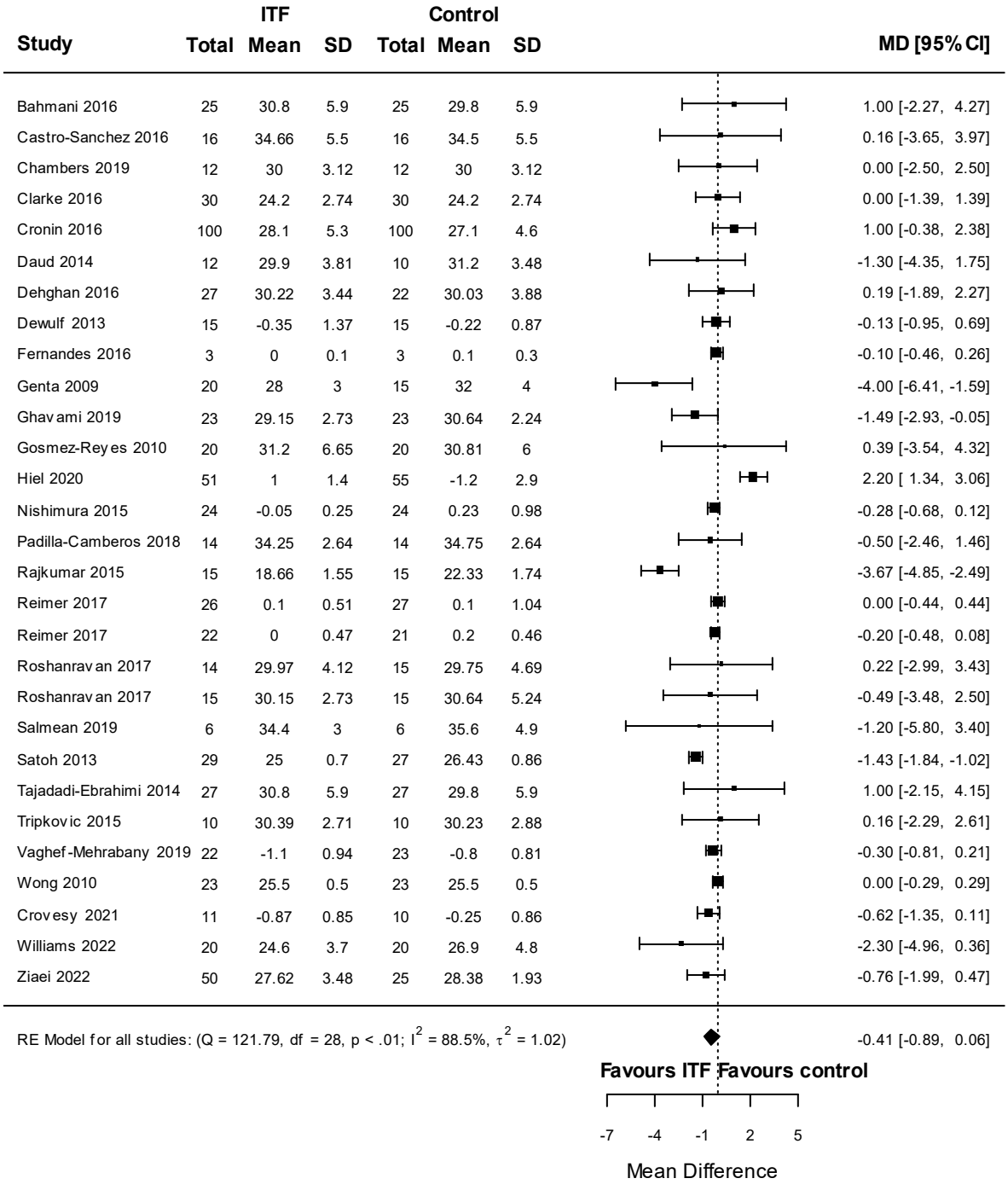


Figure 31: Forest plot displaying the effect of inulin-type fructans on body weight

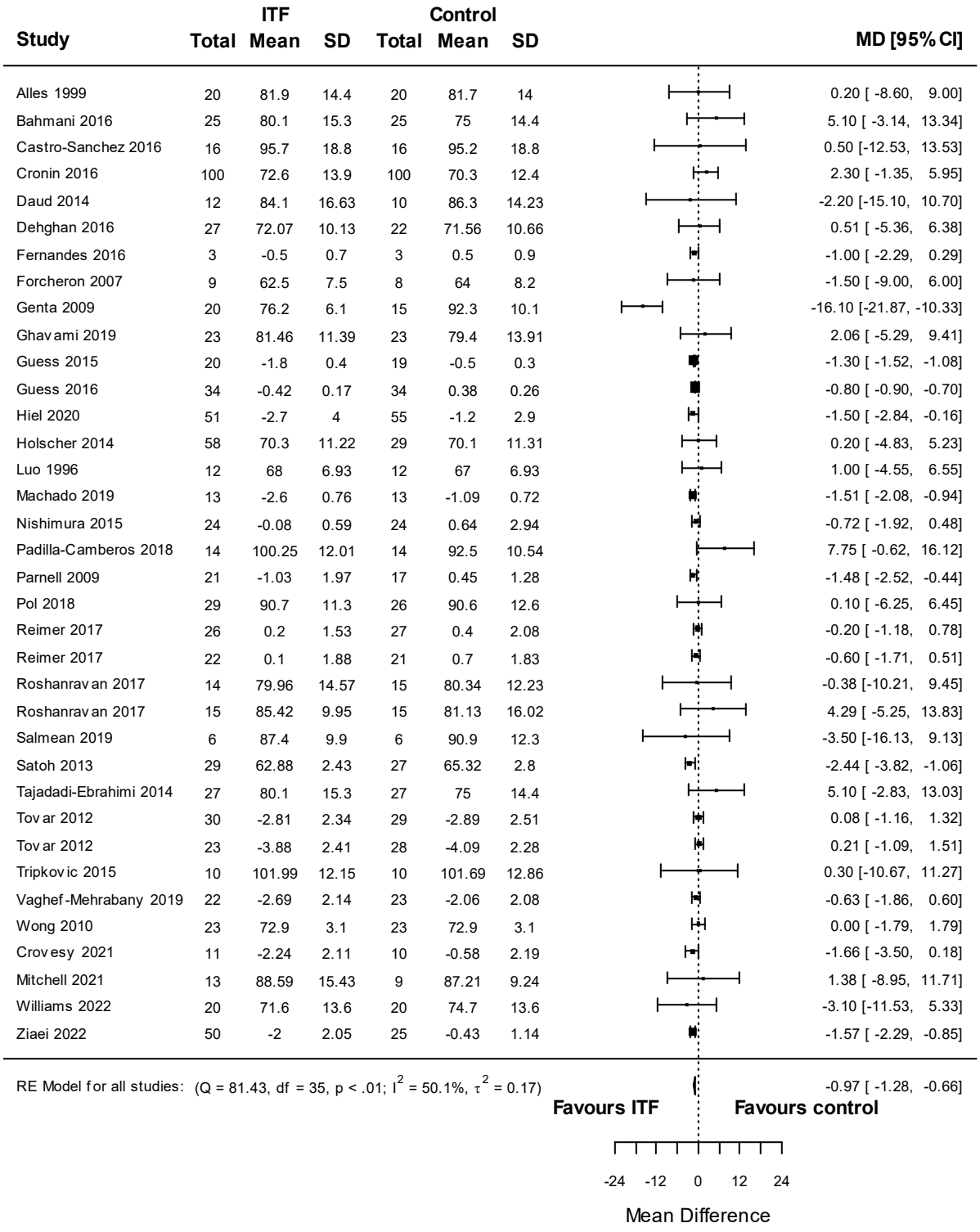


Figure 32: Forest plot displaying the effect of inulin-type fructans on waist circumference

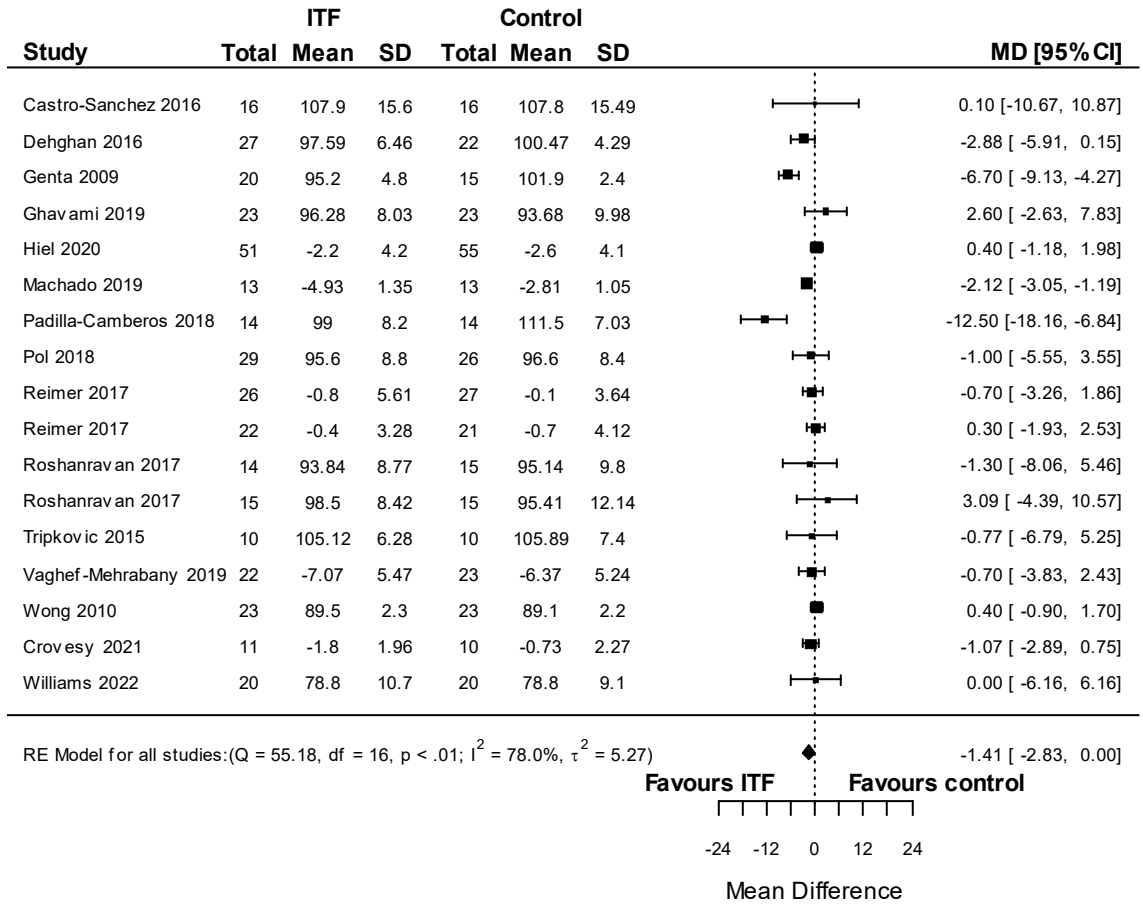


Figure 33: Forest plot displaying the effect of inulin-type fructans on waist-to-hip ratio

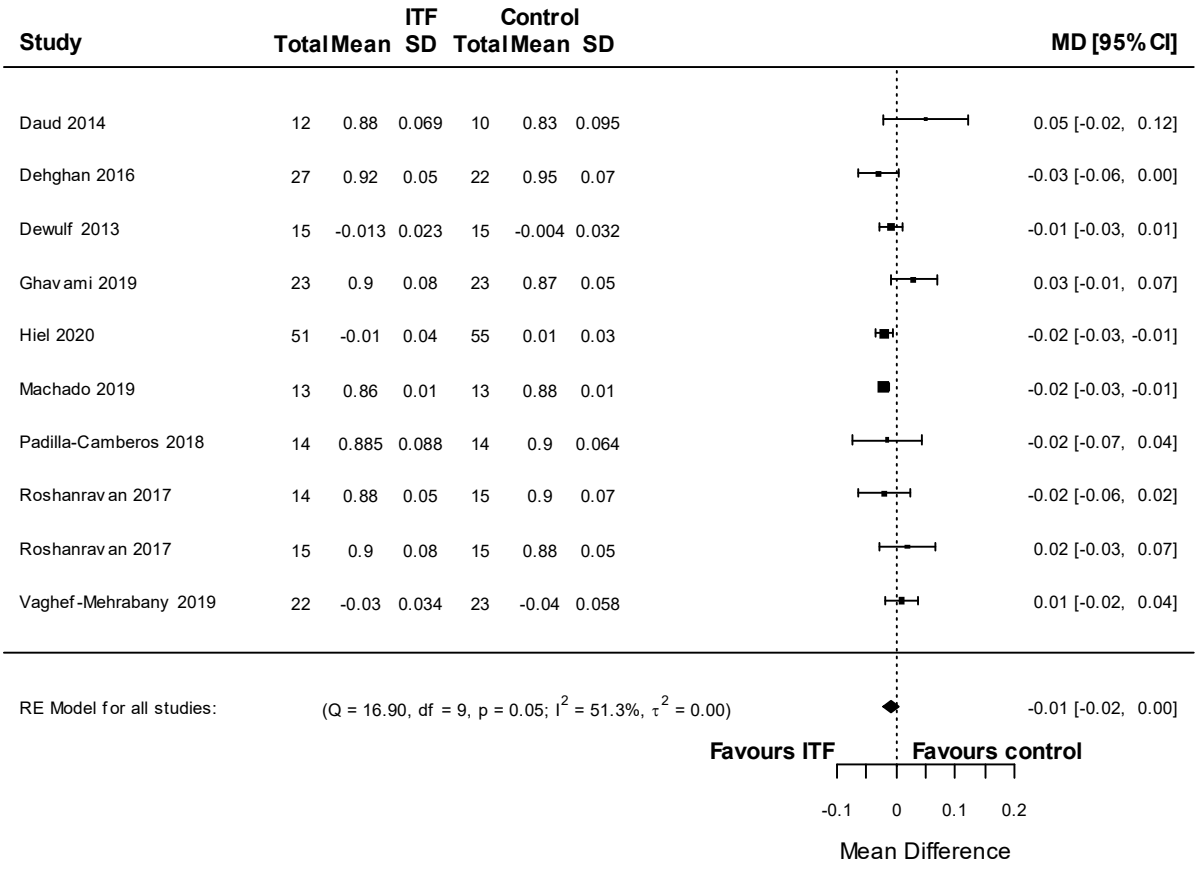


Figure 34: Forest plot displaying the effect of inulin-type fructans on systolic blood pressure

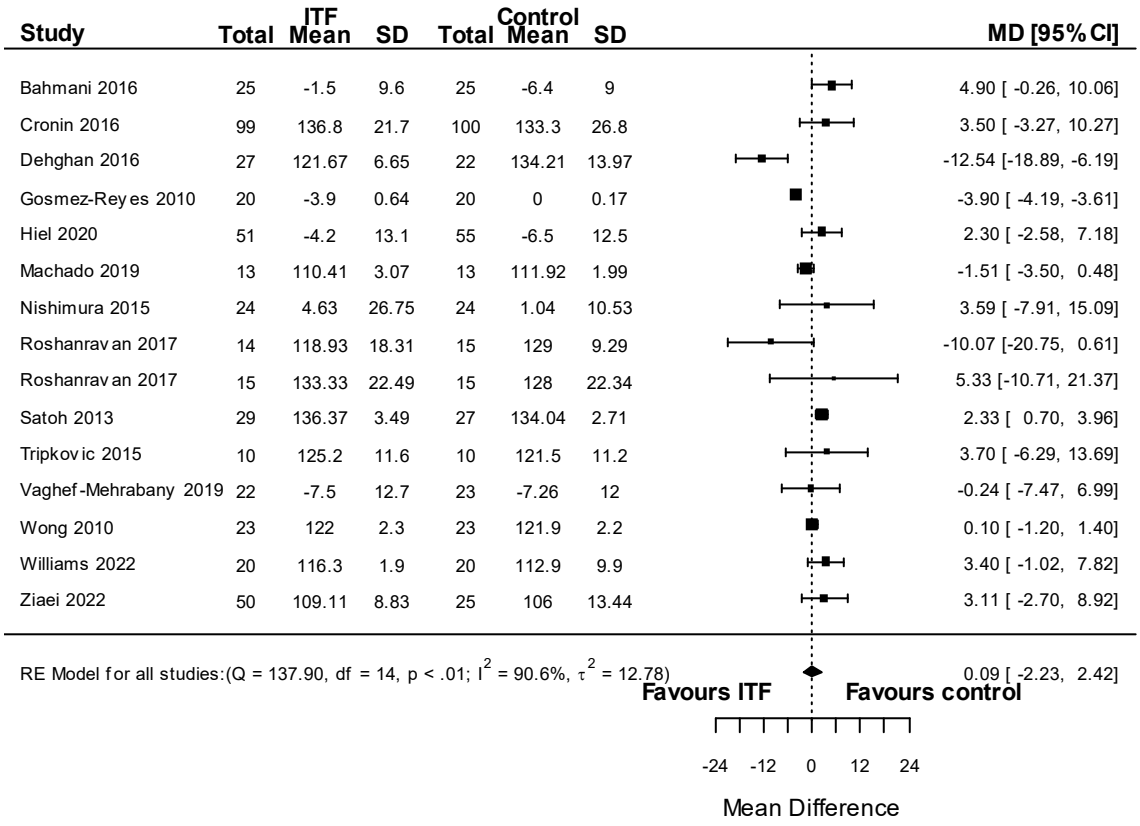


Figure 35: Forest plot displaying the effect of inulin-type fructans on diastolic blood pressure

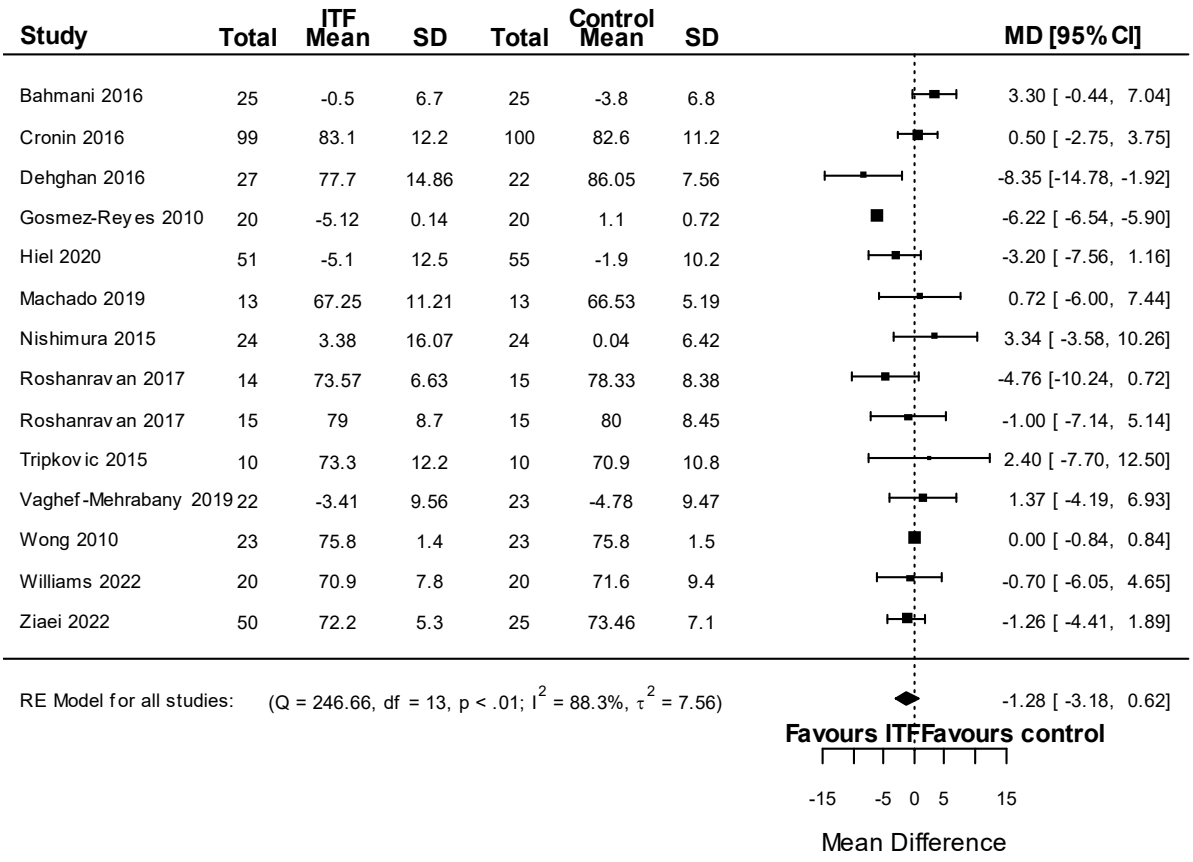


Figure 36: Forest plot displaying the effect of inulin-type fructans on high-density lipoprotein

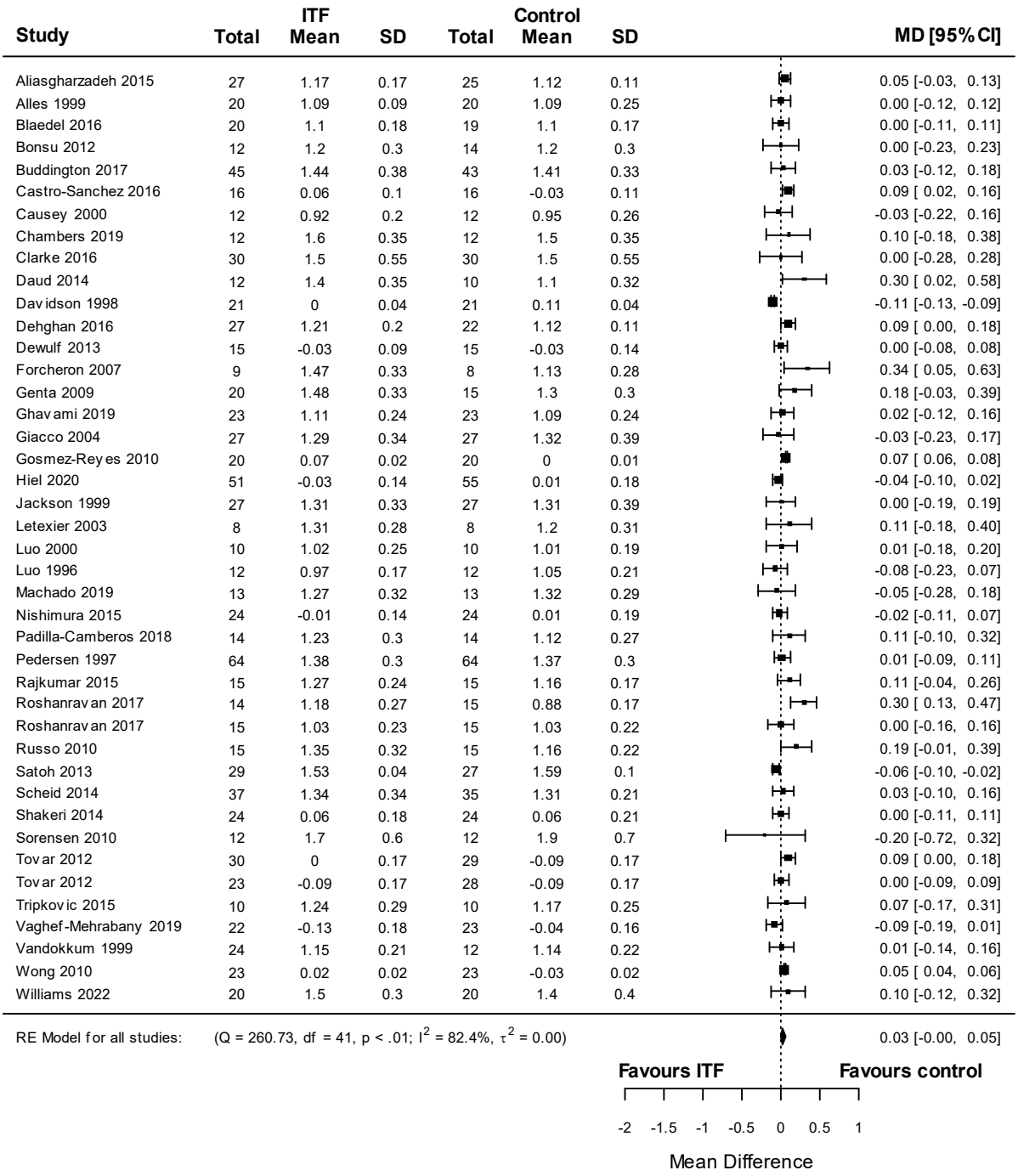


Figure 37: Forest plot displaying the effect of inulin-type fructans on very low-density lipoprotein

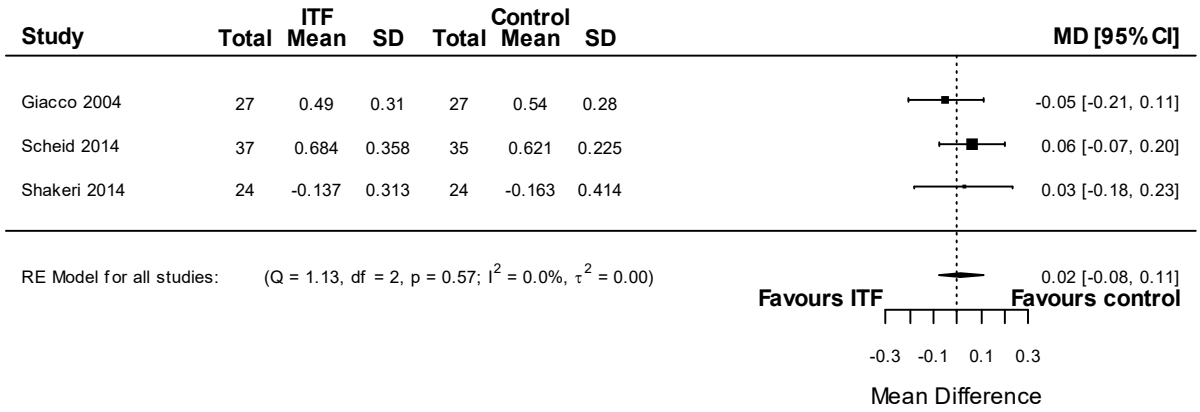


Figure 38: Forest plot displaying the effect of inulin-type fructans on total cholesterol

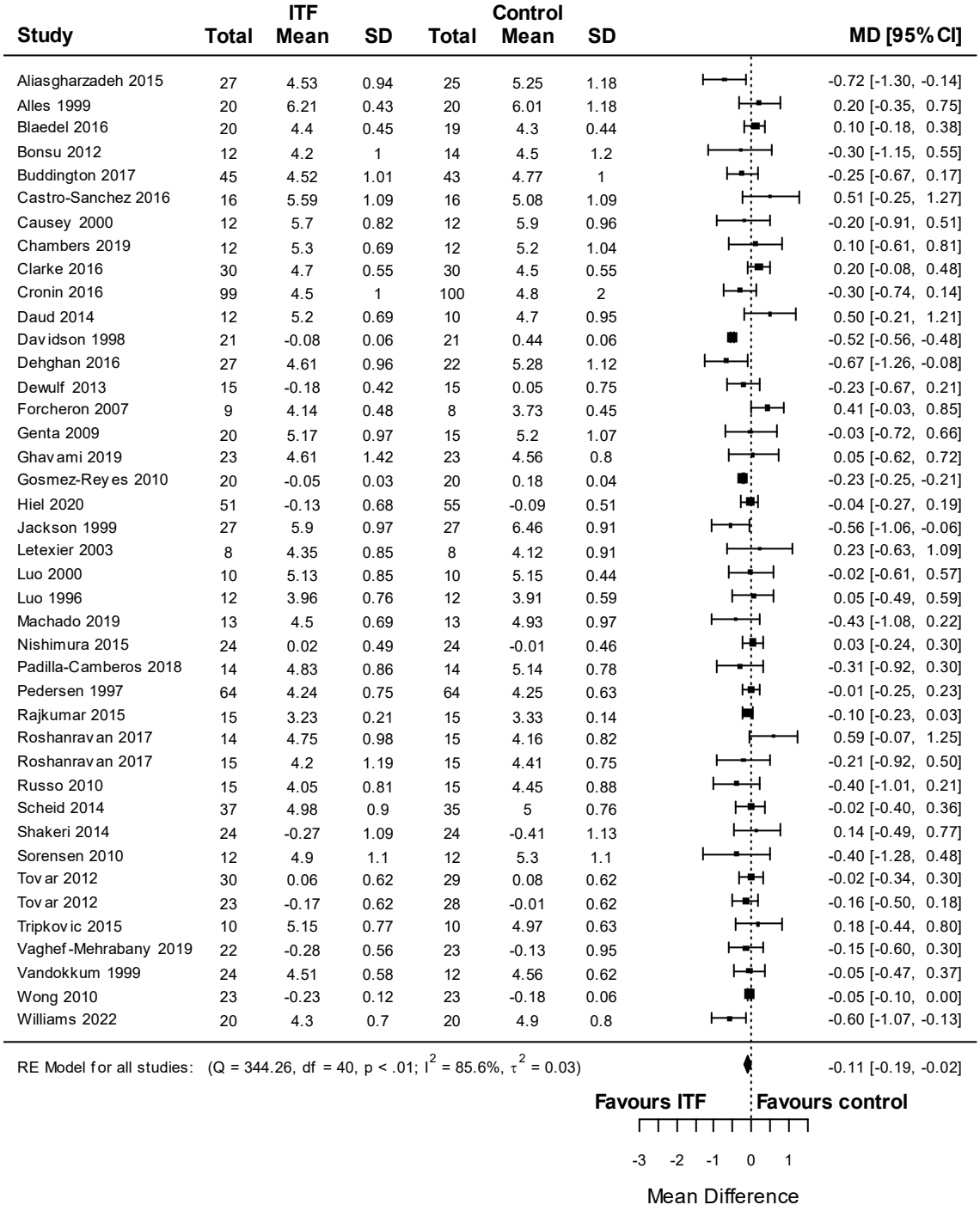


Figure 39: Forest plot displaying the effect of inulin-type fructans on apolipoprotein A1

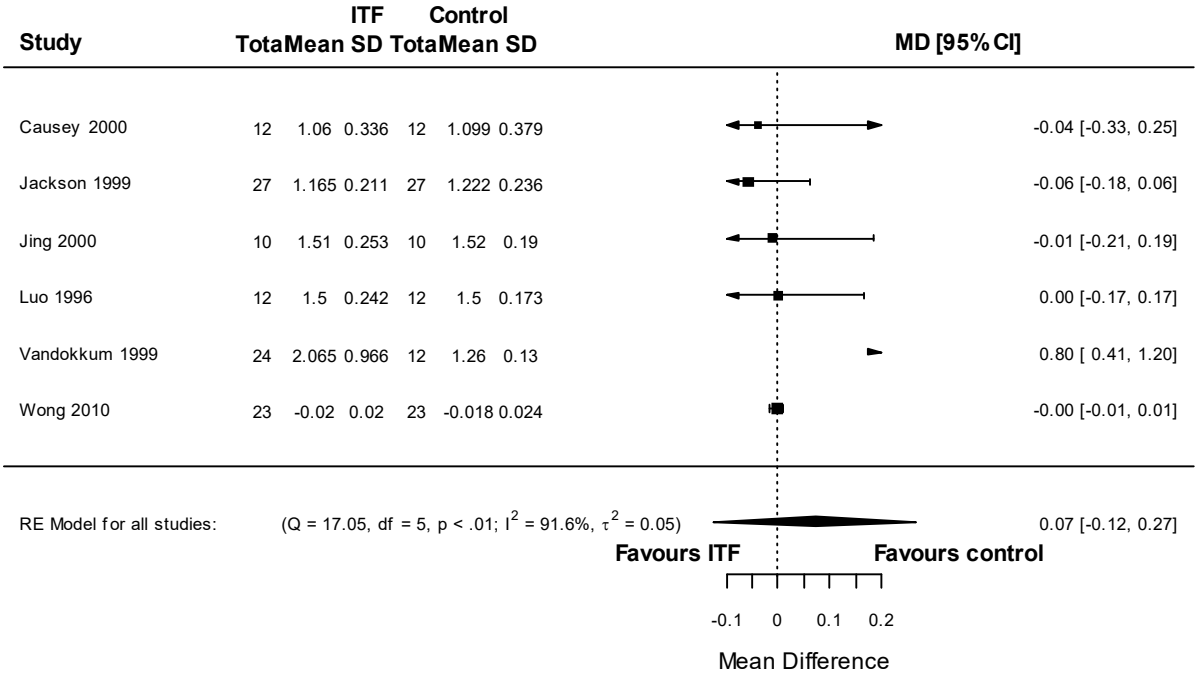


Figure 40: Forest plot displaying the effect of inulin-type fructans on apolipoprotein B

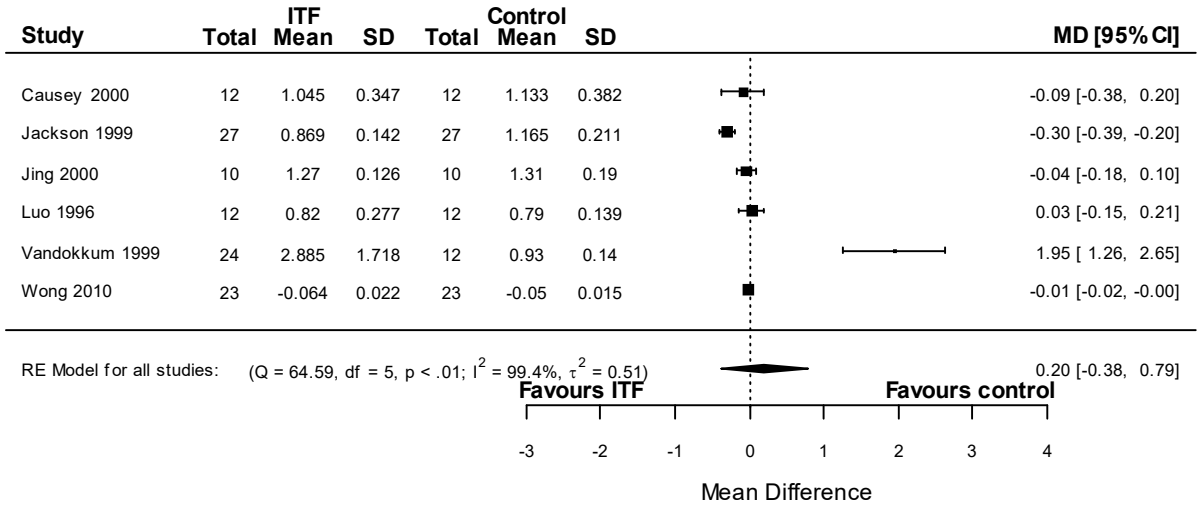
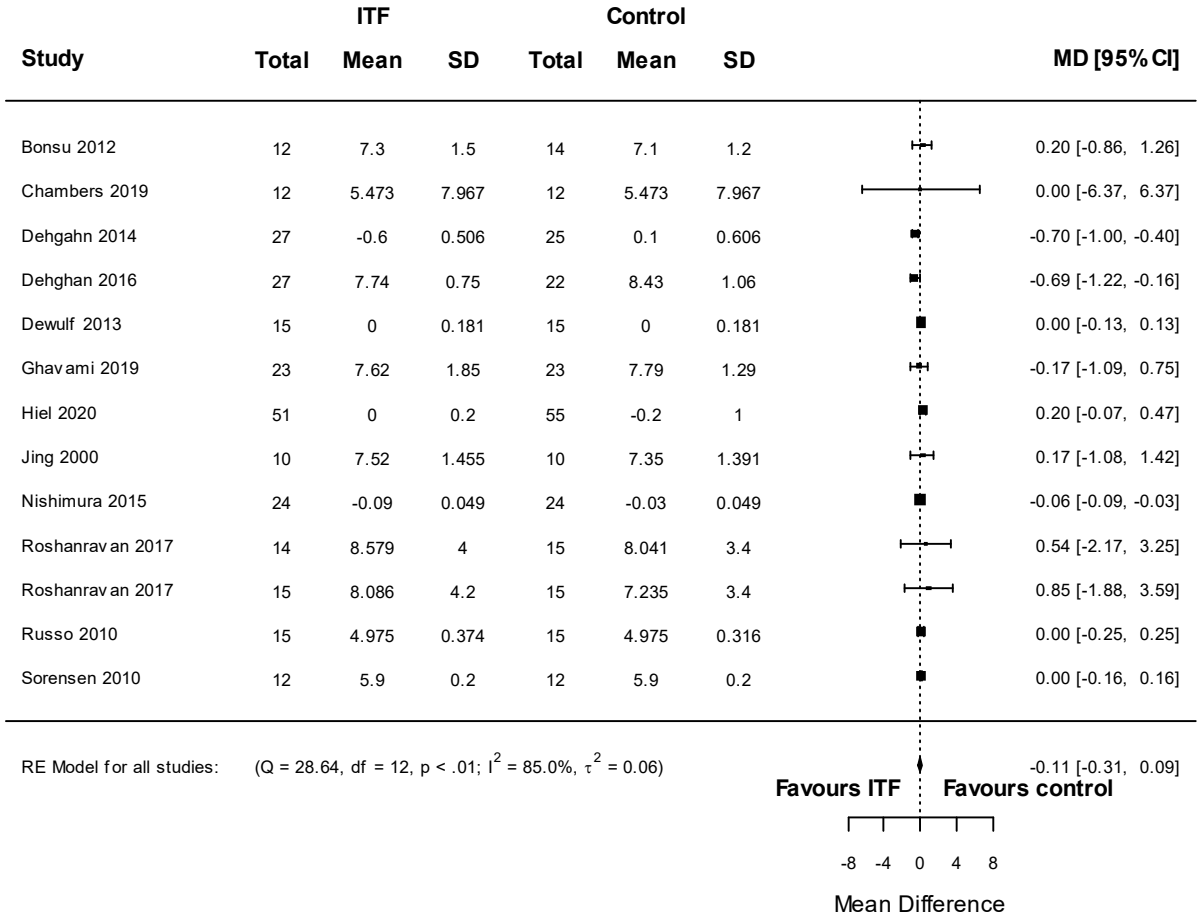
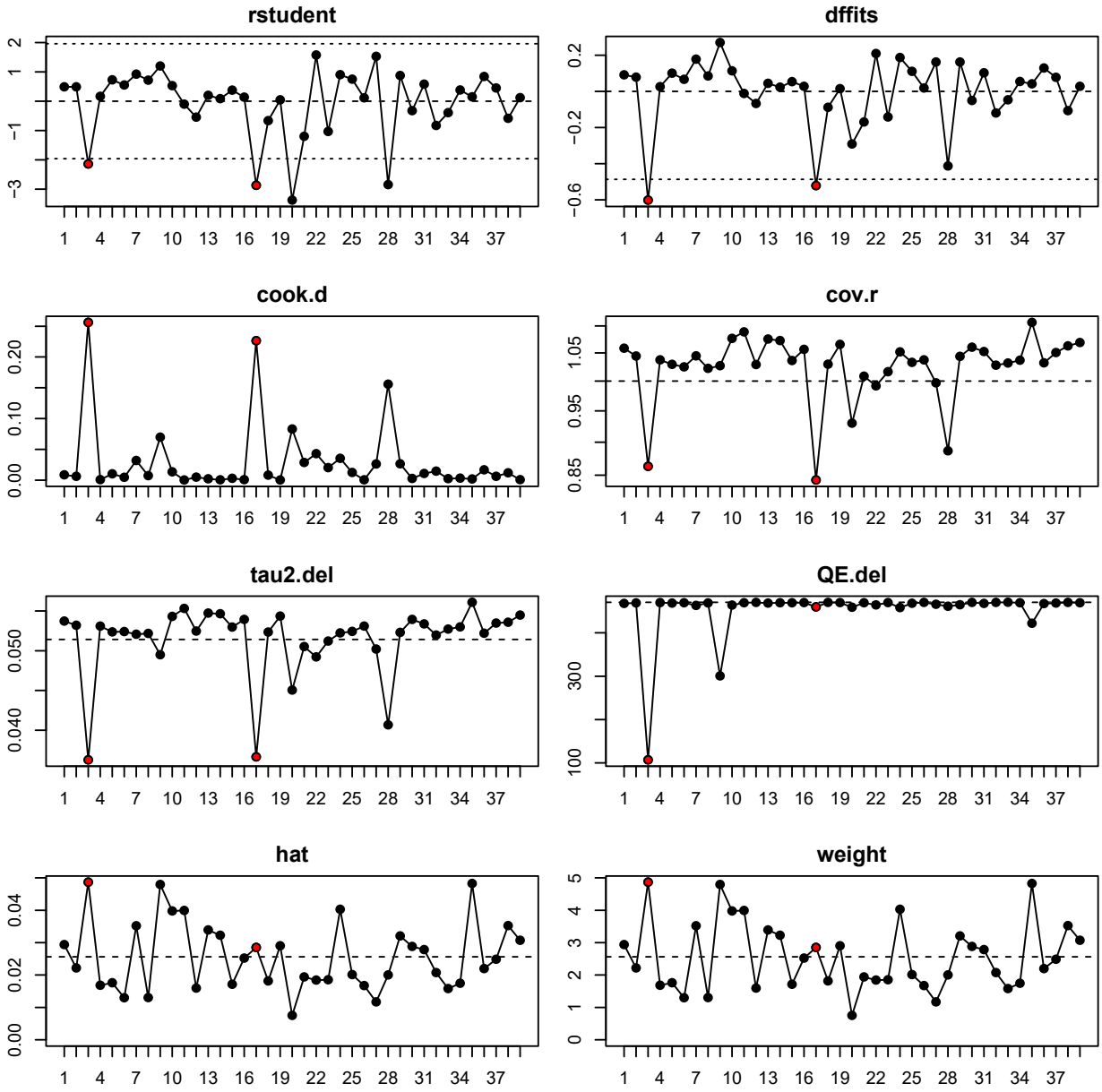


Figure 41: Forest plot displaying the effect of inulin-type fructans on hemoglobin A1c (HbA1c).



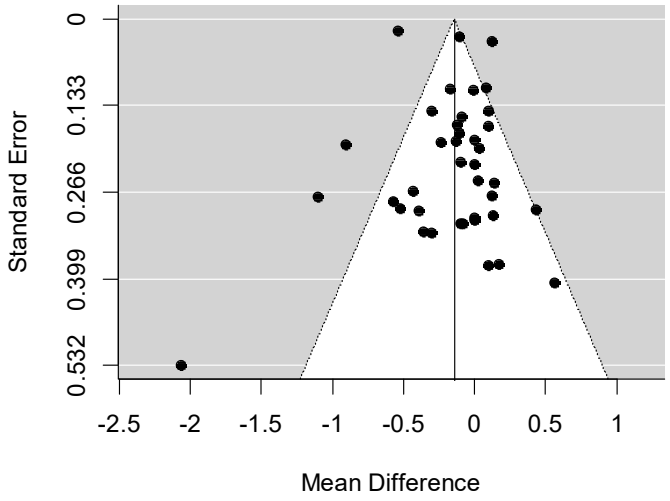
Supplementary plots

Plot 1: Influence and outlier plots for LDL-C

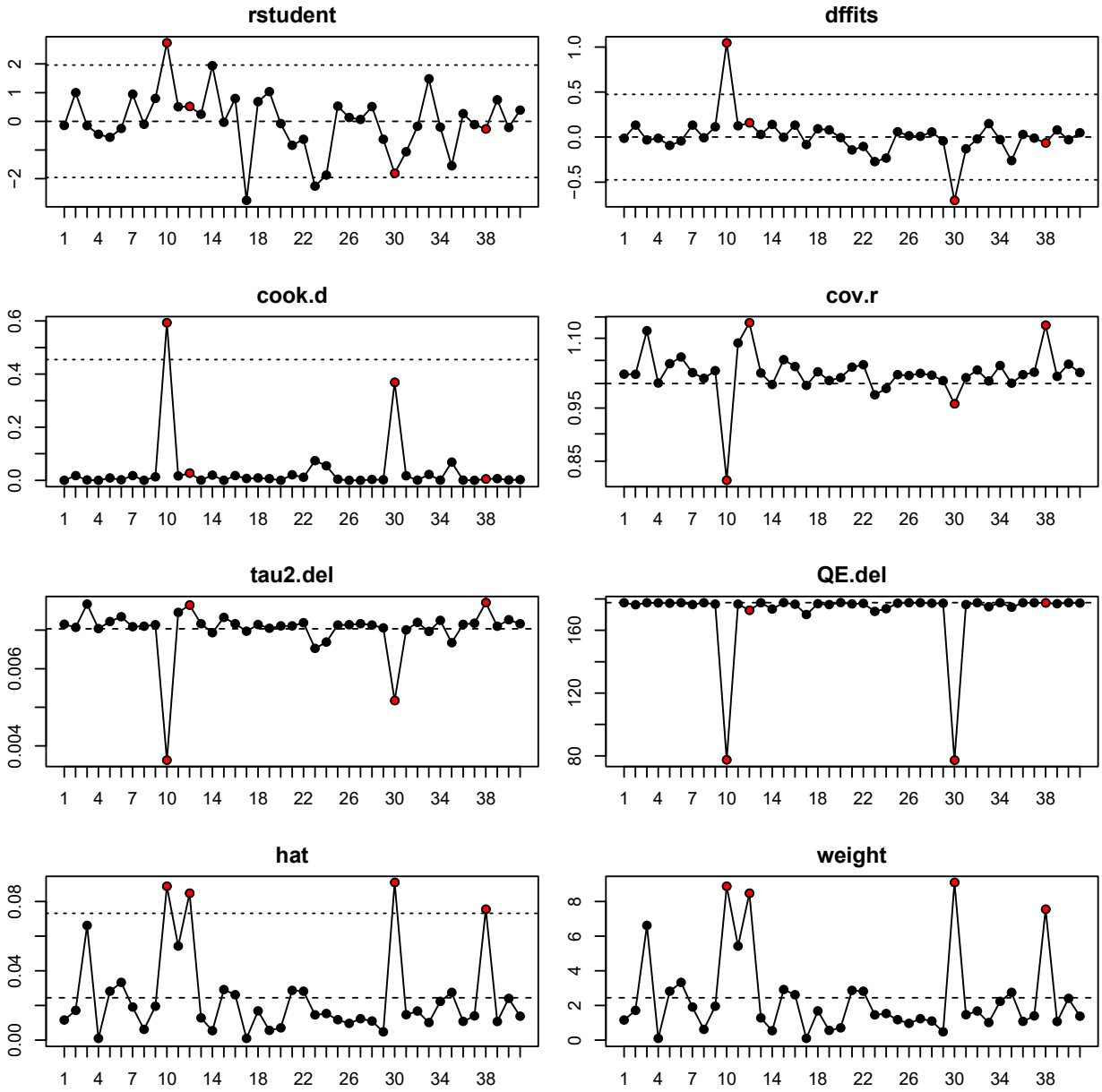


rstudent: studentized residuals, **dffits:** difference in fits, and **cook.d:** Cook's distance, cov.r: covariance ratio, **tau2.del:** leave-one-out estimates of the amount of heterogeneity, **QE.del** leave-one-out values of the test statistics for heterogeneity

Plot 2: Funnel plot to assess publication bias of low-density lipoprotein

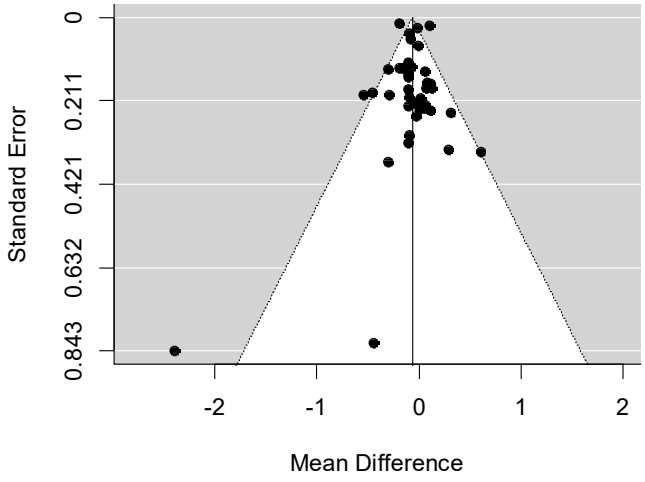


Plot 3: Influence and outlier plots for triglycerides

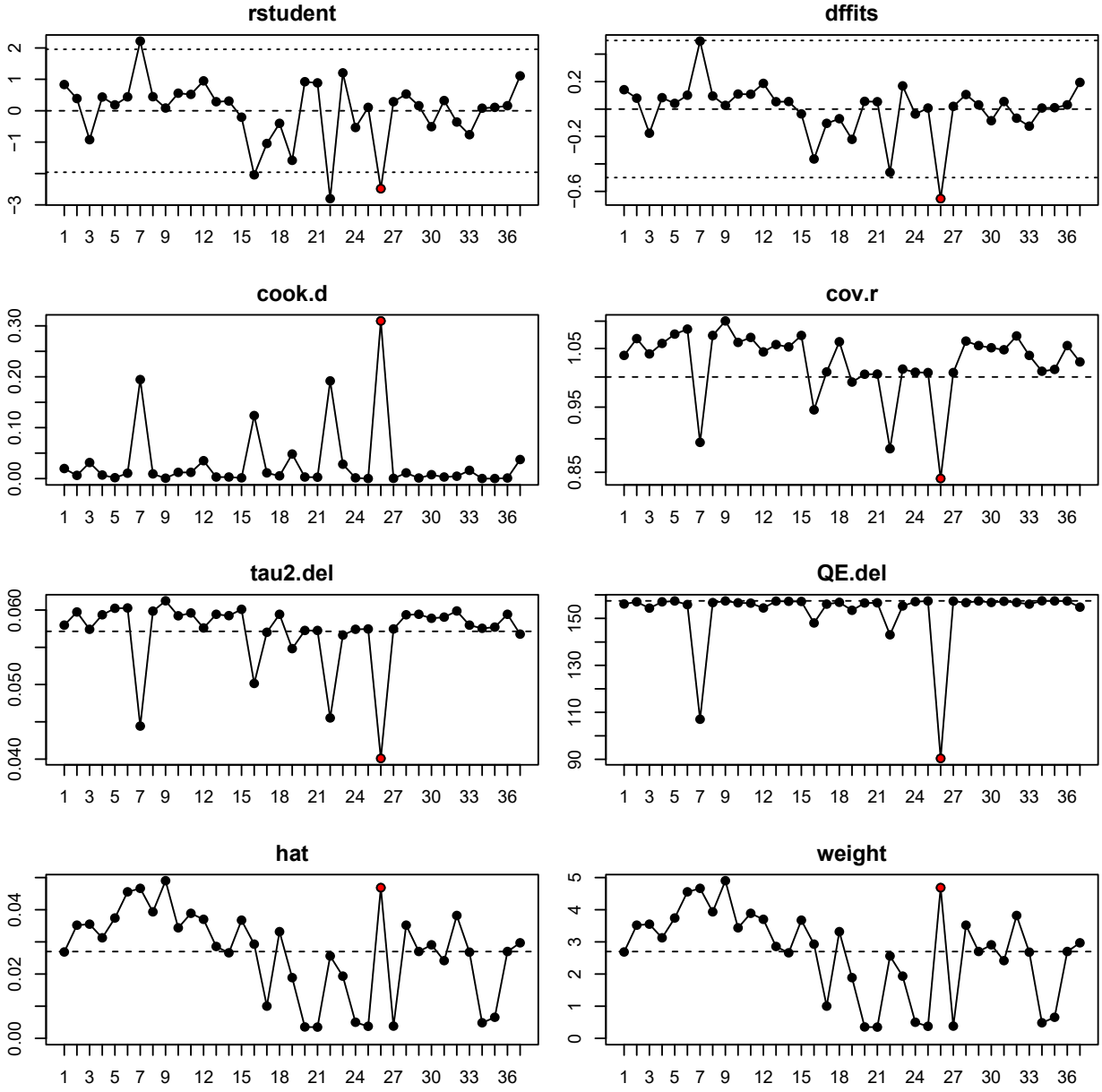


rstudent: studentized residuals, **dffits:** difference in fits, and **cook.d:** Cook's distance, cov.r: covariance ratio, **tau2.del:** leave-one-out estimates of the amount of heterogeneity, **QE.del** leave-one-out values of the test statistics for heterogeneity

Plot 4: Funnel plot to assess publication bias of triglycerides

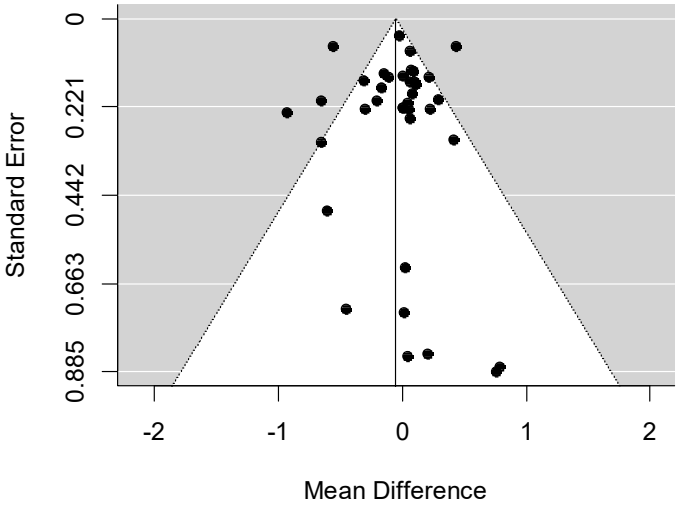


Plot 5: Influence and outlier plots for fasting blood glucose



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

Plot 3: Funnel plot to assess publication bias of fasting blood glucose



References

1. Society for Biomedical Diabetes Research. SI Unit Conversion Calculator 2015 [cited 2022 February 22]. Available from: http://www.soc-bdr.org/rds/authors/unit_tables_conversions_and_genetic_dictionaries/e5196/index_en.html.

2. National Glycohemoglobin Standardization Program [NGSP]. IFCC Standardization of HbA1c 2010 [cited 2022 February 22]. Available from: http://www.ngsp.org/ifccngsp.asp#:~:text=In%202007%2C%20the%20IFCC%20recommended,between%20NGSP%20and%20IFCC%20results.

3. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Medical Research Methodology. 2005;5(1):13.

4. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane, 2021. Available from www.training.cochrane.org/handbook.; 2021.

5. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology. 2014;14(1):135.

6. Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. Statistics in medicine. 2008;27(29):6072-92.

7. 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.

8. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Research Synthesis Methods. 2020;n/a(n/a).

9. Shi H, Ge Y, Wang H, Zhang Y, Teng W, Tian L. Fasting blood glucose and risk of Stroke: A Dose–Response meta-analysis. Clinical Nutrition. 2021;40(5):3296-304.

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

Citation:

Talukdar JR, Chu A, Garg A, Chowdhury F, Harnack HE, Huang L, Sikorski C, Mbuagbaw L, de Souza RJ. 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)

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

Jhalok Ronjan Talukdar[1], Alexandro Chu[2], Anika Garg[3], Fariha Chowdhury[4], Hope E. Harnack[5], Louise Huang[3], Claudia Sikorski[1, 15], Lawrence Mbuagbaw[1, 6, 7, 8, 9, 10,], Russell J de Souza[1, 11, 12, 13, 14, 15]

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[2]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[3]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

[4]School of Rehabilitation Sciences, McMaster University, Hamilton, Ontario, Canada

[5]Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada

[6]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

[7]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

[8]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada

[9]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon

[10]Department of Global Health, Stellenbosch University, Cape Town, South Africa

[11]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition, St Michael's Hospital, Toronto, ON, Canada

[12]Clinical Nutrition & Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada

[13]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

[14]Global Health Graduate Program, McMaster University, Hamilton, Ontario, Canada

[15]Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada

Corresponding author:
Russell J de Souza
Associate Professor
Department of Health Research Methods, Evidence, and Impact
McMaster University
MDCL, Room 3210
1280 Main Street West
Hamilton, ON, Canada
L8S 4K1
desouzrj@mcmaster.ca

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

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-

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 domain-specific 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

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 (≤ 100 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 ≤ 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

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.

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 inulin-type 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

Acknowledgments

We are grateful to Laura Banfield (librarian in Health Sciences Library at McMaster University) who helped us to develop the search strategy for this study.

Contributors

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

Funding

No financial support was received for preparation of this manuscript.

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.

References

1. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

2. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. BJOG. 2018;125(13):1716-.

3. Akobeng AK. Understanding randomised controlled trials. Archives of Disease in Childhood. 2005;90(8):840.

4. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the Quality of Reporting of Randomized Controlled Trials: The CONSORT Statement. JAMA. 1996;276(8):637-9.

5. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. The Lancet. 2008a;371(9609):281-3.

6. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical Evidence of Bias: Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials. JAMA. 1995;273(5):408-12.

7. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet (London, England). 2001;357(9263):1191-4.

8. Barry HC, Ebell MH, Shaughnessy AF, Slawson DC, Nietzke F. Family physicians' use of medical abstracts to guide decision making: style or substance? The Journal of the American Board of Family Practice. 2001;14(6):437-42.

9. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. PLoS medicine. 2008b;5(1):e20.

10. The PME. The Impact of Open Access upon Public Health. PLoS medicine. 2006;3(5):e252.

11. Sriganesh K, Bharadwaj S, Wang M, Abbade LPF, Jin Y, Philip M, et al. Quality of abstracts of randomized control trials in five top pain journals: A systematic survey. Contemporary clinical trials communications. 2017;7:64-8.

12. Samaan Z, Mbuagbaw L, Kosa D, Borg Debono V, Dillenburg R, Zhang S, et al. A systematic scoping review of adherence to reporting guidelines in health care literature. J Multidiscip Healthc. 2013;6:169-88.

13. Song SY, Kim B, Kim I, Kim S, Kwon M, Han C, et al. Assessing reporting quality of randomized controlled trial abstracts in psychiatry: Adherence to CONSORT for abstracts: A systematic review. PLOS ONE. 2017;12(11):e0187807.

14. Ghimire S, Kyung E, Kang W, Kim E. Assessment of adherence to the CONSORT statement for quality of reports on randomized controlled trial abstracts from four high-impact general medical journals. Trials. 2012;13(1):77.

15. Chow JTY, Turkstra TP, Yim E, Jones PM. The degree of adherence to CONSORT reporting guidelines for the abstracts of randomised clinical trials published in anaesthesia journals: A cross-sectional study of reporting adherence in 2010 and 2016. European journal of anaesthesiology. 2018:942-8.

16. Yin Y, Gao J, Zhang Y, Zhang X, Ye J, Zhang J. Evaluation of reporting quality of abstracts of randomized controlled trials regarding patients with COVID-19 using the CONSORT statement for abstracts. International Journal of Infectious Diseases. 2022;116:122-9.

17. Wang D, Chen L, Wang L, Hua F, Li J, Li Y, et al. Abstracts for reports of randomised trials of COVID-19 interventions had low quality and high spin. Journal of clinical epidemiology. 2021;139:107-20.

18. Man S, Liu T, Yao Y, Lu Y, Ma L, Lu F. Friend or foe? The roles of inulin-type fructans. Carbohydrate Polymers. 2021;252:117155.

19. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, et al. Prebiotics: Definition, Types, Sources, Mechanisms, and Clinical Applications. Foods. 2019;8(3):92.

20. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. PLoS medicine. 2008;5(1):e20.

21. Talukdar JR, Cooper M, Lyutvyn L, Zeraatkar D, Ali R, Berbrier R, et al. 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 (accepted).

22. Kim HY. Statistical notes for clinical researchers: Chi-squared test and Fisher's exact test. Restor Dent Endod. 2017;42(2):152-5.

23. Germini F, Marcucci M, Fedele M, Galli MG, Heath T, Mbuagbaw L, et al. Quality of reporting in abstracts of RCTs published in emergency medicine journals: a systematic survey of the literature suggests we can do better. Emergency Medicine Journal. 2020;37(11):660.

24. Kumar S, Mohammad H, Vora H, Kar K. Reporting Quality of Randomized Controlled Trials of Periodontal Diseases in Journal Abstracts-A Cross-sectional Survey and Bibliometric Analysis. J Evid Based Dent Pract. 2018;18(2):130-41.e22.

25. Sriganesh K, Bharadwaj S, Wang M, Abbade LPF, Jin Y, Philip M, et al. Quality of abstracts of randomized control trials in five top pain journals: A systematic survey. Contemp Clin Trials Commun. 2017;7:64-8.

26. Piza EL. Using Poisson and Negative Binomial Regression Models to Measure the Influence of Risk on Crime Incident Counts2012 [cited 2022 October 11]. Available from: https://www.rutgerscps.org/uploads/2/7/3/7/27370595/countregressionmodels.pdf.

27. UCLA: Statistical Consulting Group. Poisson Regression: STATA annotated output 2022 [cited 2022 October 11]. Available from: https://stats.oarc.ucla.edu/stata/output/poisson-regression/.

28. Sedgwick P. Incidence rate ratio. BMJ. 2010;341:c4804.

29. R Core Team. R: A language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria; 2020 [cited 2022 March 10]. Available from: https://www.R-project.org/.

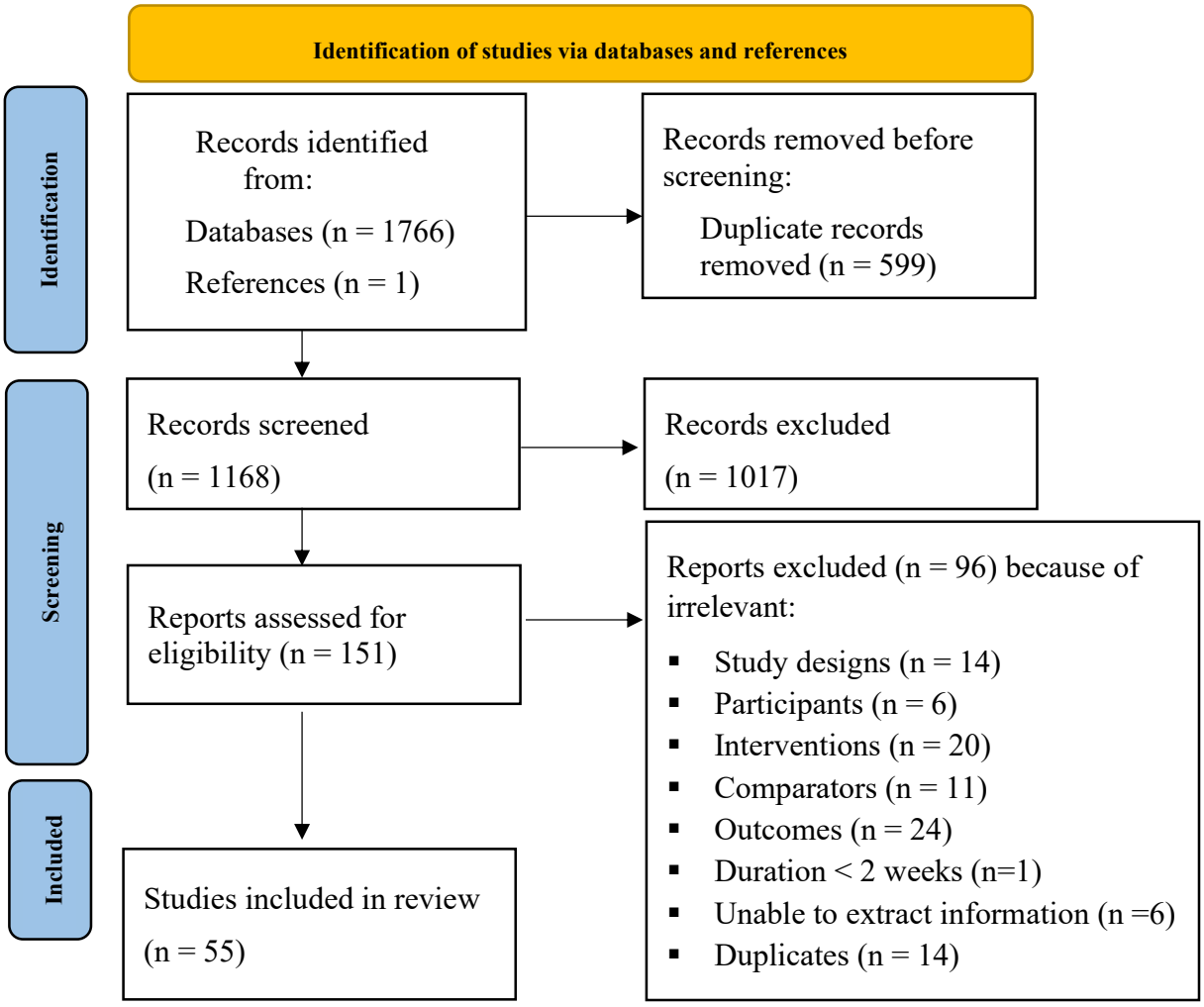
30. Tullu MS. Writing the title and abstract for a research paper: Being concise, precise, and meticulous is the key. Saudi J Anaesth. 2019;13(Suppl 1):S12-s7.

31. Speich B, Mc Cord KA, Agarwal A, Gloy V, Gryaznov D, Moffa G, et al. Reporting Quality of Journal Abstracts for Surgical Randomized Controlled Trials Before and After the Implementation of the CONSORT Extension for Abstracts. World J Surg. 2019;43(10):2371-8.

32. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? The Lancet. 1998;352(9128):609-13.

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

Table1: Characteristics of trials by period of publication

	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)

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

Table 2: Adjusted incidence rate ratios for total number of CONSORT-A items

	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

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).

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

		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

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
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

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* a1 or apo* a i or (proapoliprotein adj1 (ai or a1 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* a1 or apo* a i or (proapoliprotein adj1 (ai or a1 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

1. Aliasgharzadeh A, Khalili M, Mirtaheri E, Pourghassem Gargari B, Tavakoli F, Abbasalizad Farhangi M, et al. A Combination of Prebiotic Inulin and Oligofructose Improve Some of Cardiovascular Disease Risk Factors in Women with Type 2 Diabetes: A Randomized Controlled Clinical Trial. Advanced pharmaceutical bulletin. 2015;5(4):507-14.

2. Alles MS, de Roos NM, Bakx JC, van de Lisdonk E, Zock PL, Hautvast GA. Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. The American journal of clinical nutrition. 1999;69(1):64-9.

3. Bahmani F, Tajadadi-Ebrahimi M, Kolahdooz F, Mazouchi M, Hadaegh H, Jamal AS, et al. The Consumption of Synbiotic Bread Containing Lactobacillus sporogenes and Inulin Affects Nitric Oxide and Malondialdehyde in Patients with Type 2 Diabetes Mellitus: Randomized, Double-Blind, Placebo-Controlled Trial. Journal of the American College of Nutrition. 2016;35(6):506-13.

4. Blædel T, Holm JB, Sundekilde UK, Schmedes MS, Hess AL, Lorenzen JK, et al. A randomised, controlled, crossover study of the effect of diet on angiopoietin-like protein 4 (ANGPTL4) through modification of the gut microbiome. Journal of nutritional science. 2016;5:e45.

5. Bonsu NK, Johnson SJIJD, Metab. Effects of inulin fibre supplementation on serum glucose and lipid concentration in patients with type 2 diabetes. 2012;21:80-6.

6. Buddington RK, Kapadia C, Neumer F, Theis S. Oligofructose Provides Laxation for Irregularity Associated with Low Fiber Intake. Nutrients. 2017;9(12).

7. Castro-Sanchez F, Ochoa-Acosta D, Valenzuela-Rubio N, Domínguez-Rodríguez M, Fierros-Valdez J, Vergara-Jiménez MJAJNM. Inulin effect on weight loss and associated parameters with the development of cardiovascular disease in obese dyslipidemic subjects. 2017;4(1):1044.

8. Causey JL, Feirtag JM, Gallaher DD, Tungland BC, Slavin JL. Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. Nutrition Research. 2000;20(2):191-201.

9. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019;68(8):1430-8.

10. Clarke ST, Green-Johnson JM, Brooks SP, Ramdath DD, Bercik P, Avila C, et al. β2-1 Fructan supplementation alters host immune responses in a manner consistent with increased exposure to microbial components: results from a double-blinded, randomised, cross-over study in healthy adults. The British journal of nutrition. 2016;115(10):1748-59.

11. Cronin BE, Allsopp PJ, Slevin MM, Magee PJ, Livingstone MB, Strain JJ, et al. Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain fructo-oligosaccharides on serum lipids in postmenopausal women. The British journal of nutrition. 2016;115(4):658-65.

12. Crovesy L, El-Bacha T, Rosado EL. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: a double-blind randomized controlled clinical trial in women with obesity. Food & function. 2021;12(5):2161-70.

13. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, et al. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity (Silver Spring, Md). 2014;22(6):1430-8.

14. Davidson MH, Maki KC, Synecki C, Torri SA, Drennan KBJNR. Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. 1998;18:503-17.

15. Dehghan P, Farhangi MA, Tavakoli F, Aliasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: A randomized placebo-controlled Trial. Complementary therapies in medicine. 2016;24:96-102.

16. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. International journal of food sciences and nutrition. 2014;65(1):117-23.

17. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62(8):1112-21.

18. Fernandes R, Beserra BT, Mocellin MC, Kuntz MG, da Rosa JS, de Miranda RC, et al. Effects of Prebiotic and Synbiotic Supplementation on Inflammatory Markers and Anthropometric Indices After Roux-en-Y Gastric Bypass: A Randomized, Triple-blind, Placebo-controlled Pilot Study. Journal of clinical gastroenterology. 2016;50(3):208-17.

19. Forcheron F, Beylot M. Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. Metabolism: clinical and experimental. 2007;56(8):1093-8.

20. Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clinical nutrition (Edinburgh, Scotland). 2009;28(2):182-7.

21. Ghavami A, Roshanravan N, Nattagh-Eshtivani E, Sharifi S, Arzhang P, Sani MA, et al. The effect of high performance inulin on appetite, energy in-take and anthropometric indices in patient with type 2 diabetes. 2019;21:121-6.

22. Giacco R, Clemente G, Luongo D, Lasorella G, Fiume I, Brouns F, et al. Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. Clinical nutrition (Edinburgh, Scotland). 2004;23(3):331-40.

23. Gómez-Reyes E, Orea-Tejeda A, Castillo-Martínez L, Cassis-Nosthas L, Vargas-Voracková FJE. Prebiotics consumption modifies diastolic blood pressure, but does not affect serum lipids concentration in volunteers with ischemic heart disease. 2010;128:139.

24. Guess ND, Dornhorst A, Oliver N, Bell JD, Thomas EL, Frost GS. A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. Nutrition & metabolism. 2015;12:36.

25. Guess ND, Dornhorst A, Oliver N, Frost GS. A Randomised Crossover Trial: The Effect of Inulin on Glucose Homeostasis in Subtypes of Prediabetes. Annals of nutrition & metabolism. 2016;68(1):26-34.

26. Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clinical nutrition (Edinburgh, Scotland). 2020;39(12):3618-28.

27. Holscher HD, Doligale JL, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, et al. Gastrointestinal tolerance and utilization of agave inulin by healthy adults. Food & function. 2014;5(6):1142-9.

28. Jackson KG, Taylor GR, Clohessy AM, Williams CM. The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. The British journal of nutrition. 1999;82(1):23-30.

29. Letexier D, Diraison F, Beylot M. Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. The American journal of clinical nutrition. 2003;77(3):559-64.

30. Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry JL, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. The American journal of clinical nutrition. 1996;63(6):939-45.

31. Luo J, Van Yperselle M, Rizkalla SW, Rossi F, Bornet FR, Slama G. Chronic consumption of short-chain fructooligosaccharides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. J Nutr. 2000;130(6):1572-7.

32. Machado AM, da Silva NBM, Chaves JBP, Alfenas RCG. Consumption of yacon flour improves body composition and intestinal function in overweight adults: A randomized, double-blind, placebo-controlled clinical trial. Clinical nutrition ESPEN. 2019;29:22-9.

33. Mitchell CM, Davy BM, Ponder MA, McMillan RP, Hughes MD, Hulver MW, et al. Prebiotic inulin supplementation and peripheral insulin sensitivity in adults at elevated risk for type 2 diabetes: A pilot randomized controlled trial. Nutrients. 2021;13(9):3235.

34. Nishimura M, Ohkawara T, Kanayama T, Kitagawa K, Nishimura H, Nishihira J. Effects of the extract from roasted chicory (Cichorium intybus L.) root containing inulin-type fructans on blood glucose, lipid metabolism, and fecal properties. Journal of traditional and complementary medicine. 2015;5(3):161-7.

35. Padilla-Camberos E, Barragán-Álvarez CP, Diaz-Martinez NE, Rathod V, Flores-Fernández JM. Effects of Agave fructans (Agave tequilana Weber var. azul) on Body Fat and Serum Lipids in Obesity. Plant foods for human nutrition (Dordrecht, Netherlands). 2018;73(1):34-9.

36. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. The American journal of clinical nutrition. 2009;89(6):1751-9.

37. Pedersen A, Sandström B, Van Amelsvoort JM. The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. The British journal of nutrition. 1997;78(2):215-22.

38. Pol K, de Graaf C, Meyer D, Mars M. The efficacy of daily snack replacement with oligofructose-enriched granola bars in overweight and obese adults: a 12-week randomised controlled trial. British Journal of Nutrition. 2018;119(9):1076-86.

39. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. Journal of cardiovascular pharmacology and therapeutics. 2015;20(3):289-98.

40. Reimer RA, Willis HJ, Tunnicliffe JM, Park H, Madsen KL, Soto-Vaca A. Inulin-type fructans and whey protein both modulate appetite but only fructans alter gut microbiota in adults with overweight/obesity: A randomized controlled trial. Molecular nutrition & food research. 2017;61(11).

41. Roshanravan N, Mahdavi R, Alizadeh E, Ghavami A, Rahbar Saadat Y, Mesri Alamdari N, et al. The effects of sodium butyrate and inulin supplementation on angiotensin signaling pathway via promotion of Akkermansia muciniphila abundance in type 2 diabetes; A randomized, double-blind, placebo-controlled trial. J Cardiovasc Thorac Res. 2017;9(4):183-90.

42. Russo F, Clemente C, Linsalata M, Chiloiro M, Orlando A, Marconi E, et al. Effects of a diet with inulin-enriched pasta on gut peptides and gastric emptying rates in healthy young volunteers. European journal of nutrition. 2011;50(4):271-7.

43. Salmean YAJPIN. Using inulin fiber supplementation with MyPlate recommendations promotes greater weight loss in obese women. 2019;21:81-5.

44. Satoh H, Kudoh A, Hasegawa K, Hirai H, Watanabe T. Yacon supplementation reduces serum free fatty acids and tumor necrosis factor alpha concentrations in patients with type 2 diabetes. Diabetology International. 2014;5(3):165-74.

45. Scheid MM, Genaro PS, Moreno YM, Pastore GM. Freeze-dried powdered yacon: effects of FOS on serum glucose, lipids and intestinal transit in the elderly. European journal of nutrition. 2014;53(7):1457-64.

46. Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, et al. Consumption of synbiotic bread decreases triacylglycerol and VLDL levels while increasing HDL levels in serum from patients with type-2 diabetes. Lipids. 2014;49(7):695-701.

47. Sørensen M, Johansen OE. Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. Scandinavian journal of clinical and laboratory investigation. 2010;70(6):385-91.

48. Tajadadi-Ebrahimi M, Bahmani F, Shakeri H, Hadaegh H, Hijijafari M, Abedi F, et al. Effects of daily consumption of synbiotic bread on insulin metabolism and serum high-sensitivity C-reactive protein among diabetic patients: a double-blind, randomized, controlled clinical trial. Annals of nutrition & metabolism. 2014;65(1):34-41.

49. Tovar AR, Caamaño Mdel C, Garcia-Padilla S, García OP, Duarte MA, Rosado JL. The inclusion of a partial meal replacement with or without inulin to a calorie restricted diet contributes to reach recommended intakes of micronutrients and decrease plasma triglycerides: a randomized clinical trial in obese Mexican women. Nutrition journal. 2012;11:44.

50. Tripkovic L, Muirhead NC, Hart KH, Frost GS, Lodge JK. The effects of a diet rich in inulin or wheat fibre on markers of cardiovascular disease in overweight male subjects. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2015;28(5):476-85.

51. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. Nutritional neuroscience. 2021;24(5):339-53.

52. van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EG. Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. European journal of clinical nutrition. 1999;53(1):1-7.

53. Williams CJ, Torquati L, Li Z, Lea RA, Croci I, Keating E, et al. Oligofructose-Enriched Inulin Intake, Gut Microbiome Characteristics, and the VO2Peak Response to High-Intensity Interval Training in Healthy Inactive Adults. Journal of Nutrition. 2022;152(3):680-9.

54. Wong JM, Kendall CW, de Souza R, Emam A, Marchie A, Vidgen E, et al. The effect on the blood lipid profile of soy foods combined with a prebiotic: a randomized controlled trial. Metabolism: clinical and experimental. 2010;59(9):1331-40.

55. Ziaei R, Shahshahan Z, Ghasemi-Tehrani H, Heidari Z, Ghiasvand R. Effects of inulin-type fructans with different degrees of polymerization on inflammation, oxidative stress and endothelial dysfunction in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clinical Endocrinology. 2022.

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

Citation:

Talukdar JR, Chu A, Garg A, Chowdhury F, Harnack HE, Huang L, Sikorski C, Mbuagbaw L, de Souza RJ. 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 (accepted conditional on minor revision)

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

Jhalok Ronjan Talukdar[1], Alexandro Chu[2], Anika Garg[3], Fariha Chowdhury[4], Hope E. Harnack[5], Louise Huang[3], Claudia Sikorski[1, 15], Lawrence Mbuagbaw[1, 6, 7, 8, 9, 10,], Russell J de Souza[1, 11, 12, 13, 14, 15]

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[2]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[3]Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

[4]School of Rehabilitation Sciences, McMaster University, Hamilton, Ontario, Canada

[5]Department of Kinesiology, McMaster University, Hamilton, Ontario, Canada

[6]Department of Anesthesia, McMaster University, Hamilton, Ontario, Canada

[7]Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

[8]Biostatistics Unit, Father Sean O'Sullivan Research Centre, St Joseph's Healthcare, Hamilton, Ontario, Canada

[9]Centre for Development of Best Practices in Health (CDBPH), Yaoundé Central Hospital, Yaoundé, Cameroon

[10]Department of Global Health, Stellenbosch University, Cape Town, South Africa

[11]Toronto 3D Knowledge Synthesis and Clinical Trials Unit, Clinical Nutrition, St Michael's Hospital, Toronto, ON, Canada

[12]Clinical Nutrition & Risk Factor Modification Centre, St. Michael's Hospital, Toronto, Ontario, Canada

[13]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario, Canada

[14]Global Health Graduate Program, McMaster University, Hamilton, Ontario, Canada

[15]Population Health Research Institute, Hamilton Health Sciences Corporation, Hamilton, Ontario, Canada

Corresponding author:
Russell J de Souza
Associate Professor
Department of Health Research Methods, Evidence, and Impact
McMaster University
MDCL, Room 3210
1280 Main Street West
Hamilton, ON, Canada
L8S 4K1
desouzrj@mcmaster.ca

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.

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

Abstract word count: 379

Full-text word count: 2,781

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.

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 domain-specific 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 (≤ 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

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

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

Acknowledgments

We are grateful to Laura Banfield (librarian in Health Sciences Library at McMaster University) who helped us develop the search strategy for this study.

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.

Funding

No financial support was received for the preparation of this manuscript.

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.

References

1. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.

2. Hariton E, Locascio JJ. Randomised controlled trials - the gold standard for effectiveness research: Study design: randomised controlled trials. BJOG. 2018;125(13):1716-.

3. Akobeng AK. Understanding randomised controlled trials. Archives of Disease in Childhood. 2005;90(8):840.

4. Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the Quality of Reporting of Randomized Controlled Trials: The CONSORT Statement. JAMA. 1996;276(8):637-9.

5. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. The Lancet. 2008a;371(9609):281-3.

6. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical Evidence of Bias: Dimensions of Methodological Quality Associated With Estimates of Treatment Effects in Controlled Trials. JAMA. 1995;273(5):408-12.

7. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet (London, England). 2001;357(9263):1191-4.

8. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? The Lancet. 1998;352(9128):609-13.

9. Moher D, Jones A, Lepage L, Group ftC. Use of the CONSORT Statement and Quality of Reports of Randomized TrialsA Comparative Before-and-After Evaluation. JAMA. 2001;285(15):1992-5.

10. Yin Y, Shi F, Zhang Y, Zhang X, Ye J, Zhang J. Evaluation of reporting quality of randomized controlled trials in patients with COVID-19 using the CONSORT statement. PLoS One. 2021;16(9):e0257093.

11. Huang YQ, Traore K, Ibrahim B, Sewitch MJ, Nguyen LHP. Reporting quality of randomized controlled trials in otolaryngology: review of adherence to the CONSORT statement. Journal of Otolaryngology - Head & Neck Surgery. 2018;47(1):34.

12. Karpouzis F, Bonello R, Pribicevic M, Kalamir A, Brown BT. Quality of reporting of randomised controlled trials in chiropractic using the CONSORT checklist. Chiropractic & Manual Therapies. 2016;24(1):19.

13. Peters JP, Hooft L, Grolman W, Stegeman I. Assessment of the quality of reporting of randomised controlled trials in otorhinolaryngologic literature - adherence to the CONSORT statement. PLoS One. 2015;10(3):e0122328.

14. Talukdar JR, Cooper MA, Lyutvyn L, Zeraatkar D, Ali R, Bierbrier R, et al. Effects of inulin-type fructans supplementation on cardiovascular disease risk factors: a protocol for a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2022;12(7):e058875.

15. Germini F, Marcucci M, Fedele M, Galli MG, Heath T, Mbuagbaw L, et al. Quality of reporting in abstracts of RCTs published in emergency medicine journals: a systematic survey of the literature suggests we can do better. Emergency Medicine Journal. 2020;37(11):660.

16. Kumar S, Mohammad H, Vora H, Kar K. Reporting Quality of Randomized Controlled Trials of Periodontal Diseases in Journal Abstracts-A Cross-sectional Survey and Bibliometric Analysis. J Evid Based Dent Pract. 2018;18(2):130-41.e22.

17. Sriganesh K, Bharadwaj S, Wang M, Abbade LPF, Jin Y, Philip M, et al. Quality of abstracts of randomized control trials in five top pain journals: A systematic survey. Contemp Clin Trials Commun. 2017;7:64-8.

18. Piza EL. Using Poisson and Negative Binomial Regression Models to Measure the Influence of Risk on Crime Incident Counts2012 [cited 2022 October 11]. Available from: https://www.rutgerscps.org/uploads/2/7/3/7/27370595/countregressionmodels.pdf.

19. UCLA: Statistical Consulting Group. Poisson Regression: STATA annotated output 2022 [cited 2022 October 11]. Available from: https://stats.oarc.ucla.edu/stata/output/poisson-regression/.

20. Sedgwick P. Incidence rate ratio. BMJ. 2010;341:c4804.

21. R Core Team. R: A language and environment for statistical computing: R Foundation for Statistical Computing, Vienna, Austria; 2020 [cited 2022 March 10]. Available from: https://www.R-project.org/.

22. Chan A-W, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. The Lancet. 2005;365(9465):1159-62.

23. Barry HC, Ebell MH, Shaughnessy AF, Slawson DC, Nietzke F. Family physicians' use of medical abstracts to guide decision making: style or substance? The Journal of the American Board of Family Practice. 2001;14(6):437-42.

24. Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. PLoS medicine. 2008b;5(1):e20.

25. The PME. The Impact of Open Access upon Public Health. PLoS medicine. 2006;3(5):e252.

26. Sriganesh K, Bharadwaj S, Wang M, Abbade LPF, Jin Y, Philip M, et al. Quality of abstracts of randomized control trials in five top pain journals: A systematic survey. Contemporary clinical trials communications. 2017;7:64-8.

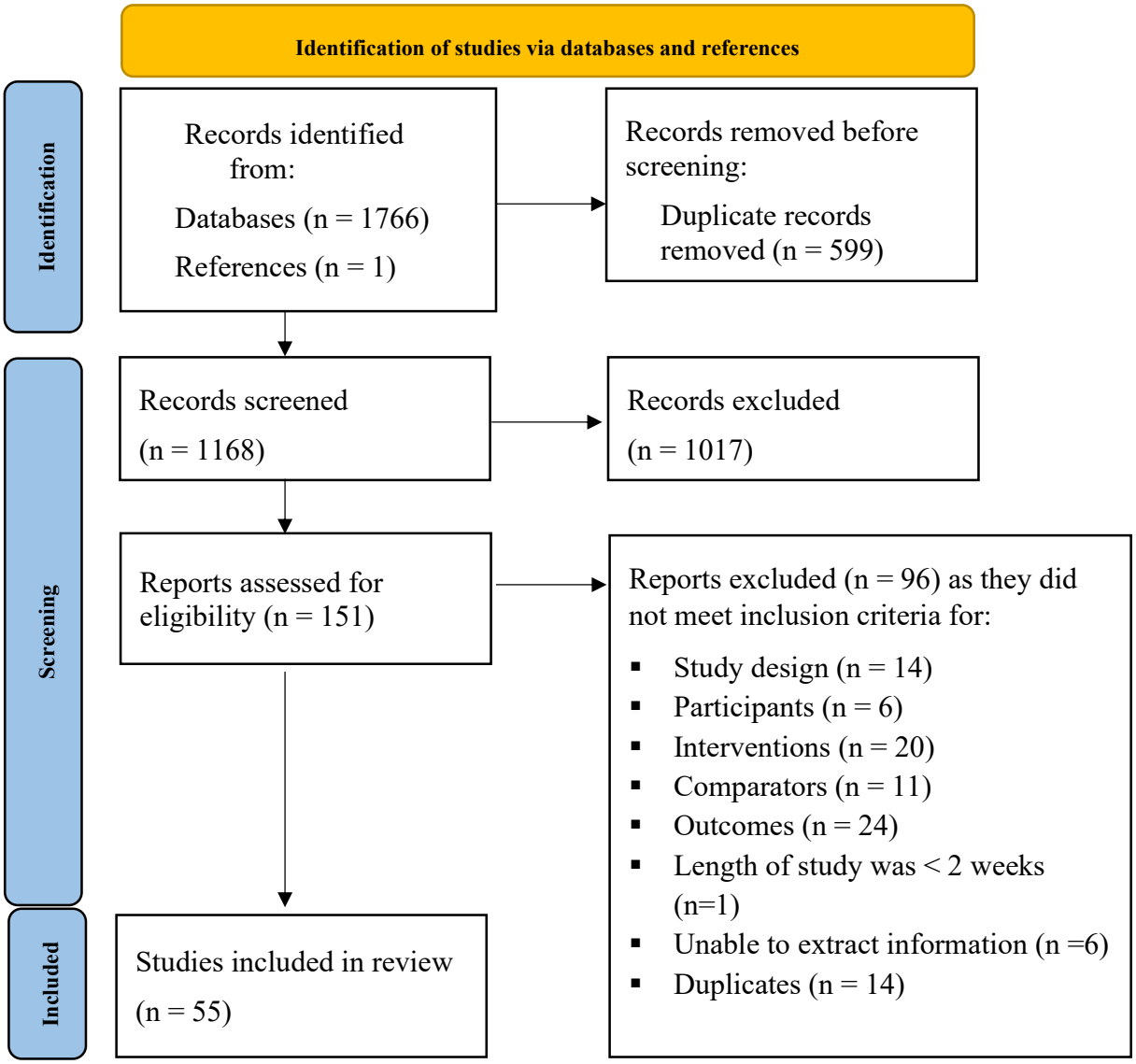
27. Camm CF, Chen Y, Sunderland N, Nagendran M, Maruthappu M, Camm AJ. An assessment of the reporting quality of randomised controlled trials relating to anti-arrhythmic agents (2002-2011). Int J Cardiol. 2013;168(2):1393-6.

28. Nojomi M, Ramezani M, Ghafari-Anvar A. Quality of reports on randomized controlled trials published in Iranian journals: application of the new version of consolidated standards of reporting trials (CONSORT). Arch Iran Med. 2013;16(1):20-2.

29. 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.

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) Mean (SD)	5.68 (1.94)	4.73 (4.49)	4.95 (4.0)

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

*CONSORT endorsement by journals until June 2022

Table 2: Adjusted incidence rate ratios for total number of CONSORT items

	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

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

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

Section/Topic	Item No	Checklist item	Pre-CONSORT Until 2009 [N=13] N (%)	Post-CONSORT 2010-2022 [N =42] N (%)	Univariate analysis OR (95% CI)	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 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
	2b	Specific objectives or hypotheses	13 (100)	42 (100)	NE	NE
Methods						
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
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	2 (15.38)	17 (40.48)	3.66 (0.67 to 38.15)	0.180
Participants	4a	Eligibility criteria for participants	12 (92.31)	40 (95.24)	1.65 (0.03 to 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

Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	13 (100)	42 (100)	NE	NE
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	2 (15.38)	20 (47.62)	4.87 (0.90 to 50.52)	0.053
	6b	Any changes to trial outcomes after the 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
	7b	When applicable, explanation of any interim analyses and stopping guidelines	0 (0.00)	0 (0.00)	NE	NE
Randomisation:						
Sequence generation	8a	Method used to generate the random allocation sequence	1 (7.69)	24 (57.14)	15.32 (1.94 to 709.02)	0.003
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	1 (7.69)	19 (45.24)	9.59 (1.21 to 444.60)	0.019
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	1 (7.69)	19 (45.24)	9.59 (1.21 to 444.60)	0.019
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	0 (0.00)	17 (40.48)	NE	0.005
Blinding	11a	If done, who was blinded after assignment to interventions (for example,	1 (7.69)	21 (50)	11.57 (1.47 to 535.36)	0.008

		participants, care providers, those assessing outcomes) and how				
	11b	If relevant, description of the similarity of interventions	8 (61.54)	26 (61.90)	1.01 (0.22 to 4.28)	>0.999
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13 (100)	42 (100)	NE	NE
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	0 (0.00)	23 (54.76)	NE	<0.001
Results						
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3 (23.08)	34 (80.95)	13.27 (2.66 to 92.57)	<0.001
	13b	For each group, losses and exclusions after randomisation, together with reasons	7 (53.85)	34 (80.95)	3.54 (0.76 to 16.69)	0.071
Recruitment	14a	Dates defining the periods of recruitment 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	A table showing baseline demographic and clinical characteristics for each group	7 (53.85)	40 (95.24)	15.82 (2.28 to 190.78)	0.001
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6 (46.15)	33 (78.57)	4.27 (1.15 to 15.95)	0.037
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the 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 in each group (for specific guidance see				
Harms		CONSORT for harms)	10 (76.92)	25 (59.52)	0.45 (0.07 to 2.09)	0.333
Discussion						
	20	Trial limitations, addressing sources of potential bias, imprecision, and, if				
Limitations		relevant, multiplicity of analyses	2 (15.38)	28 (66.67)	10.50 (1.91 to 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, balancing benefits and harms, and				
Interpretation		considering other relevant evidence	12 (92.31)	41 (97.62)	3.32 (0.04 to 273.91)	0.42
Other information						
	23	Registration number and name of trial				
Registration		registry	1 (7.69)	31 (73.81)	31. 50 (3.89 to 1477.22)	<0.001
	24	Where the full trial protocol can be				
Protocol		accessed, if available	1 (7.69)	28 (66.67)	22.69 (2.85 to 1055.06)	<0.001
	25	Sources of funding and other support				
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.

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: 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* a1 or apo* a i or (proapoliprotein adj1 (ai or a1 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* a1 or apo* a i or (proapoliprotein adj1 (ai or a1 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

1. Aliasgharzadeh A, Khalili M, Mirtaheri E, Pourghassem Gargari B, Tavakoli F, Abbasalizad Farhangi M, et al. A Combination of Prebiotic Inulin and Oligofructose Improve Some of Cardiovascular Disease Risk Factors in Women with Type 2 Diabetes: A Randomized Controlled Clinical Trial. Advanced pharmaceutical bulletin. 2015;5(4):507-14.

2. Alles MS, de Roos NM, Bakx JC, van de Lisdonk E, Zock PL, Hautvast GA. Consumption of fructooligosaccharides does not favorably affect blood glucose and serum lipid concentrations in patients with type 2 diabetes. The American journal of clinical nutrition. 1999;69(1):64-9.

3. Bahmani F, Tajadadi-Ebrahimi M, Kolahdooz F, Mazouchi M, Hadaegh H, Jamal AS, et al. The Consumption of Synbiotic Bread Containing Lactobacillus sporogenes and Inulin Affects Nitric Oxide and Malondialdehyde in Patients with Type 2 Diabetes Mellitus: Randomized, Double-Blind, Placebo-Controlled Trial. Journal of the American College of Nutrition. 2016;35(6):506-13.

4. Blædel T, Holm JB, Sundekilde UK, Schmedes MS, Hess AL, Lorenzen JK, et al. A randomised, controlled, crossover study of the effect of diet on angiopoietin-like protein 4 (ANGPTL4) through modification of the gut microbiome. Journal of nutritional science. 2016;5:e45.

5. Bonsu NK, Johnson SJIJD, Metab. Effects of inulin fibre supplementation on serum glucose and lipid concentration in patients with type 2 diabetes. 2012;21:80-6.

6. Buddington RK, Kapadia C, Neumer F, Theis S. Oligofructose Provides Laxation for Irregularity Associated with Low Fiber Intake. Nutrients. 2017;9(12).

7. Castro-Sanchez F, Ochoa-Acosta D, Valenzuela-Rubio N, Domínguez-Rodríguez M, Fierros-Valdez J, Vergara-Jiménez MJAJNM. Inulin effect on weight loss and associated parameters with the development of cardiovascular disease in obese dyslipidemic subjects. 2017;4(1):1044.

8. Causey JL, Feirtag JM, Gallaher DD, Tungland BC, Slavin JL. Effects of dietary inulin on serum lipids, blood glucose and the gastrointestinal environment in hypercholesterolemic men. Nutrition Research. 2000;20(2):191-201.

9. Chambers ES, Byrne CS, Morrison DJ, Murphy KG, Preston T, Tedford C, et al. Dietary supplementation with inulin-propionate ester or inulin improves insulin sensitivity in adults with overweight and obesity with distinct effects on the gut microbiota, plasma metabolome and systemic inflammatory responses: a randomised cross-over trial. Gut. 2019;68(8):1430-8.

10. Clarke ST, Green-Johnson JM, Brooks SP, Ramdath DD, Bercik P, Avila C, et al. β2-1 Fructan supplementation alters host immune responses in a manner consistent with increased exposure to microbial components: results from a double-blinded, randomised, cross-over study in healthy adults. The British journal of nutrition. 2016;115(10):1748-59.

11. Cronin BE, Allsopp PJ, Slevin MM, Magee PJ, Livingstone MB, Strain JJ, et al. Effects of supplementation with a calcium-rich marine-derived multi-mineral supplement and short-chain fructo-oligosaccharides on serum lipids in postmenopausal women. The British journal of nutrition. 2016;115(4):658-65.

12. Crovesy L, El-Bacha T, Rosado EL. Modulation of the gut microbiota by probiotics and symbiotics is associated with changes in serum metabolite profile related to a decrease in inflammation and overall benefits to metabolic health: a double-blind randomized controlled clinical trial in women with obesity. Food & function. 2021;12(5):2161-70.

13. Daud NM, Ismail NA, Thomas EL, Fitzpatrick JA, Bell JD, Swann JR, et al. The impact of oligofructose on stimulation of gut hormones, appetite regulation and adiposity. Obesity (Silver Spring, Md). 2014;22(6):1430-8.

14. Davidson MH, Maki KC, Synecki C, Torri SA, Drennan KBJNR. Effects of dietary inulin on serum lipids in men and women with hypercholesterolemia. 1998;18:503-17.

15. Dehghan P, Farhangi MA, Tavakoli F, Aliasgarzadeh A, Akbari AM. Impact of prebiotic supplementation on T-cell subsets and their related cytokines, anthropometric features and blood pressure in patients with type 2 diabetes mellitus: A randomized placebo-controlled Trial. Complementary therapies in medicine. 2016;24:96-102.

16. Dehghan P, Gargari BP, Jafar-Abadi MA, Aliasgharzadeh A. Inulin controls inflammation and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized-controlled clinical trial. International journal of food sciences and nutrition. 2014;65(1):117-23.

17. Dewulf EM, Cani PD, Claus SP, Fuentes S, Puylaert PG, Neyrinck AM, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. Gut. 2013;62(8):1112-21.

18. Fernandes R, Beserra BT, Mocellin MC, Kuntz MG, da Rosa JS, de Miranda RC, et al. Effects of Prebiotic and Synbiotic Supplementation on Inflammatory Markers and Anthropometric Indices After Roux-en-Y Gastric Bypass: A Randomized, Triple-blind, Placebo-controlled Pilot Study. Journal of clinical gastroenterology. 2016;50(3):208-17.

19. Forcheron F, Beylot M. Long-term administration of inulin-type fructans has no significant lipid-lowering effect in normolipidemic humans. Metabolism: clinical and experimental. 2007;56(8):1093-8.

20. Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clinical nutrition (Edinburgh, Scotland). 2009;28(2):182-7.

21. Ghavami A, Roshanravan N, Nattagh-Eshtivani E, Sharifi S, Arzhang P, Sani MA, et al. The effect of high performance inulin on appetite, energy in-take and anthropometric indices in patient with type 2 diabetes. 2019;21:121-6.

22. Giacco R, Clemente G, Luongo D, Lasorella G, Fiume I, Brouns F, et al. Effects of short-chain fructo-oligosaccharides on glucose and lipid metabolism in mild hypercholesterolaemic individuals. Clinical nutrition (Edinburgh, Scotland). 2004;23(3):331-40.

23. Gómez-Reyes E, Orea-Tejeda A, Castillo-Martínez L, Cassis-Nosthas L, Vargas-Voracková FJE. Prebiotics consumption modifies diastolic blood pressure, but does not affect serum lipids concentration in volunteers with ischemic heart disease. 2010;128:139.

24. Guess ND, Dornhorst A, Oliver N, Bell JD, Thomas EL, Frost GS. A randomized controlled trial: the effect of inulin on weight management and ectopic fat in subjects with prediabetes. Nutrition & metabolism. 2015;12:36.

25. Guess ND, Dornhorst A, Oliver N, Frost GS. A Randomised Crossover Trial: The Effect of Inulin on Glucose Homeostasis in Subtypes of Prediabetes. Annals of nutrition & metabolism. 2016;68(1):26-34.

26. Hiel S, Gianfrancesco MA, Rodriguez J, Portheault D, Leyrolle Q, Bindels LB, et al. Link between gut microbiota and health outcomes in inulin -treated obese patients: Lessons from the Food4Gut multicenter randomized placebo-controlled trial. Clinical nutrition (Edinburgh, Scotland). 2020;39(12):3618-28.

27. Holscher HD, Doligale JL, Bauer LL, Gourineni V, Pelkman CL, Fahey GC, et al. Gastrointestinal tolerance and utilization of agave inulin by healthy adults. Food & function. 2014;5(6):1142-9.

28. Jackson KG, Taylor GR, Clohessy AM, Williams CM. The effect of the daily intake of inulin on fasting lipid, insulin and glucose concentrations in middle-aged men and women. The British journal of nutrition. 1999;82(1):23-30.

29. Letexier D, Diraison F, Beylot M. Addition of inulin to a moderately high-carbohydrate diet reduces hepatic lipogenesis and plasma triacylglycerol concentrations in humans. The American journal of clinical nutrition. 2003;77(3):559-64.

30. Luo J, Rizkalla SW, Alamowitch C, Boussairi A, Blayo A, Barry JL, et al. Chronic consumption of short-chain fructooligosaccharides by healthy subjects decreased basal hepatic glucose production but had no effect on insulin-stimulated glucose metabolism. The American journal of clinical nutrition. 1996;63(6):939-45.

31. Luo J, Van Yperselle M, Rizkalla SW, Rossi F, Bornet FR, Slama G. Chronic consumption of short-chain fructooligosaccharides does not affect basal hepatic glucose production or insulin resistance in type 2 diabetics. J Nutr. 2000;130(6):1572-7.

32. Machado AM, da Silva NBM, Chaves JBP, Alfenas RCG. Consumption of yacon flour improves body composition and intestinal function in overweight adults: A randomized, double-blind, placebo-controlled clinical trial. Clinical nutrition ESPEN. 2019;29:22-9.

33. Mitchell CM, Davy BM, Ponder MA, McMillan RP, Hughes MD, Hulver MW, et al. Prebiotic inulin supplementation and peripheral insulin sensitivity in adults at elevated risk for type 2 diabetes: A pilot randomized controlled trial. Nutrients. 2021;13(9):3235.

34. Nishimura M, Ohkawara T, Kanayama T, Kitagawa K, Nishimura H, Nishihira J. Effects of the extract from roasted chicory (Cichorium intybus L.) root containing inulin-type fructans on blood glucose, lipid metabolism, and fecal properties. Journal of traditional and complementary medicine. 2015;5(3):161-7.

35. Padilla-Camberos E, Barragán-Álvarez CP, Diaz-Martinez NE, Rathod V, Flores-Fernández JM. Effects of Agave fructans (Agave tequilana Weber var. azul) on Body Fat and Serum Lipids in Obesity. Plant foods for human nutrition (Dordrecht, Netherlands). 2018;73(1):34-9.

36. Parnell JA, Reimer RA. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. The American journal of clinical nutrition. 2009;89(6):1751-9.

37. Pedersen A, Sandström B, Van Amelsvoort JM. The effect of ingestion of inulin on blood lipids and gastrointestinal symptoms in healthy females. The British journal of nutrition. 1997;78(2):215-22.

38. Pol K, de Graaf C, Meyer D, Mars M. The efficacy of daily snack replacement with oligofructose-enriched granola bars in overweight and obese adults: a 12-week randomised controlled trial. British Journal of Nutrition. 2018;119(9):1076-86.

39. Rajkumar H, Kumar M, Das N, Kumar SN, Challa HR, Nagpal R. Effect of Probiotic Lactobacillus salivarius UBL S22 and Prebiotic Fructo-oligosaccharide on Serum Lipids, Inflammatory Markers, Insulin Sensitivity, and Gut Bacteria in Healthy Young Volunteers: A Randomized Controlled Single-Blind Pilot Study. Journal of cardiovascular pharmacology and therapeutics. 2015;20(3):289-98.

40. Reimer RA, Willis HJ, Tunnicliffe JM, Park H, Madsen KL, Soto-Vaca A. Inulin-type fructans and whey protein both modulate appetite but only fructans alter gut microbiota in adults with overweight/obesity: A randomized controlled trial. Molecular nutrition & food research. 2017;61(11).

41. Roshanravan N, Mahdavi R, Alizadeh E, Ghavami A, Rahbar Saadat Y, Mesri Alamdari N, et al. The effects of sodium butyrate and inulin supplementation on angiotensin signaling pathway via promotion of Akkermansia muciniphila abundance in type 2 diabetes; A randomized, double-blind, placebo-controlled trial. J Cardiovasc Thorac Res. 2017;9(4):183-90.

42. Russo F, Clemente C, Linsalata M, Chiloiro M, Orlando A, Marconi E, et al. Effects of a diet with inulin-enriched pasta on gut peptides and gastric emptying rates in healthy young volunteers. European journal of nutrition. 2011;50(4):271-7.

43. Salmean YAJPIN. Using inulin fiber supplementation with MyPlate recommendations promotes greater weight loss in obese women. 2019;21:81-5.

44. Satoh H, Kudoh A, Hasegawa K, Hirai H, Watanabe T. Yacon supplementation reduces serum free fatty acids and tumor necrosis factor alpha concentrations in patients with type 2 diabetes. Diabetology International. 2014;5(3):165-74.

45. Scheid MM, Genaro PS, Moreno YM, Pastore GM. Freeze-dried powdered yacon: effects of FOS on serum glucose, lipids and intestinal transit in the elderly. European journal of nutrition. 2014;53(7):1457-64.

46. Shakeri H, Hadaegh H, Abedi F, Tajabadi-Ebrahimi M, Mazroii N, Ghandi Y, et al. Consumption of synbiotic bread decreases triacylglycerol and VLDL levels while increasing HDL levels in serum from patients with type-2 diabetes. Lipids. 2014;49(7):695-701.

47. Sørensen M, Johansen OE. Idiopathic reactive hypoglycaemia - prevalence and effect of fibre on glucose excursions. Scandinavian journal of clinical and laboratory investigation. 2010;70(6):385-91.

48. Tajadadi-Ebrahimi M, Bahmani F, Shakeri H, Hadaegh H, Hijijafari M, Abedi F, et al. Effects of daily consumption of synbiotic bread on insulin metabolism and serum high-sensitivity C-reactive protein among diabetic patients: a double-blind, randomized, controlled clinical trial. Annals of nutrition & metabolism. 2014;65(1):34-41.

49. Tovar AR, Caamaño Mdel C, Garcia-Padilla S, García OP, Duarte MA, Rosado JL. The inclusion of a partial meal replacement with or without inulin to a calorie restricted diet contributes to reach recommended intakes of micronutrients and decrease plasma triglycerides: a randomized clinical trial in obese Mexican women. Nutrition journal. 2012;11:44.

50. Tripkovic L, Muirhead NC, Hart KH, Frost GS, Lodge JK. The effects of a diet rich in inulin or wheat fibre on markers of cardiovascular disease in overweight male subjects. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2015;28(5):476-85.

51. Vaghef-Mehrabany E, Ranjbar F, Asghari-Jafarabadi M, Hosseinpour-Arjmand S, Ebrahimi-Mameghani M. Calorie restriction in combination with prebiotic supplementation in obese women with depression: effects on metabolic and clinical response. Nutritional neuroscience. 2021;24(5):339-53.

52. van Dokkum W, Wezendonk B, Srikumar TS, van den Heuvel EG. Effect of nondigestible oligosaccharides on large-bowel functions, blood lipid concentrations and glucose absorption in young healthy male subjects. European journal of clinical nutrition. 1999;53(1):1-7.

53. Williams CJ, Torquati L, Li Z, Lea RA, Croci I, Keating E, et al. Oligofructose-Enriched Inulin Intake, Gut Microbiome Characteristics, and the VO2Peak Response to High-Intensity Interval Training in Healthy Inactive Adults. Journal of Nutrition. 2022;152(3):680-9.

54. Wong JM, Kendall CW, de Souza R, Emam A, Marchie A, Vidgen E, et al. The effect on the blood lipid profile of soy foods combined with a prebiotic: a randomized controlled trial. Metabolism: clinical and experimental. 2010;59(9):1331-40.

55. Ziaei R, Shahshahan Z, Ghasemi-Tehrani H, Heidari Z, Ghiasvand R. Effects of inulin-type fructans with different degrees of polymerization on inflammation, oxidative stress and endothelial dysfunction in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial. Clinical Endocrinology. 2022.

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 inulin-type 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 inulin-type 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 ≤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 ≥ 6 weeks) and on triglycerides in pre-obese (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 high-quality 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.

References

1. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane, 2021. Available from www.training.cochrane.org/handbook.; 2021.

2. Brighenti F. Dietary fructans and serum triacylglycerols: a meta-analysis of randomized controlled trials. J Nutr. 2007;137(11 Suppl):2552s-6s.

3. Faghihimani Z, Namazi N, Ghaffari S, Rezaei Kelishadi M, Sharifi S, Nattagh-Eshtivani E, et al. Effects of Inulin Type-Carbohydrates on blood pressure: a systematic review and meta-analysis. International Journal of Food Properties. 2021;24(1):129-39.

4. Liu F, Prabhakar M, Ju J, Long H, Zhou HW. Effect of inulin-type fructans on blood lipid profile and glucose level: a systematic review and meta-analysis of randomized controlled trials. European journal of clinical nutrition. 2017;71(1):9-20.

5. Li L, Li P, Xu L. Assessing the effects of inulin-type fructan intake on body weight, blood glucose, and lipid profile: A systematic review and meta-analysis of randomized controlled trials. Food Sci Nutr. 2021;9(8):4598-616.

6. Brighenti F. Dietary Fructans and Serum Triacylglycerols: A Meta-Analysis of Randomized Controlled Trials. The Journal of Nutrition. 2007;137(11):2552S-6S.

7. Wang L, Yang H, Huang H, Zhang C, Zuo HX, Xu P, et al. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose-response meta-analysis of 33 randomized controlled trials. J Transl Med. 2019;17(1):410.

8. Gopalakrishnan S, Ganeshkumar P. Systematic Reviews and Meta-analysis: Understanding the Best Evidence in Primary Healthcare. J Family Med Prim Care. 2013;2(1):9-14.

9. Munn Z, Peters MDJ, Stern C, Tufanaru C, McArthur A, Aromataris E. Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. BMC Medical Research Methodology. 2018;18(1):143.

10. Peričić TP, Tanveer S. Why systematic reviews matter2019 March 6, 2023 [cited 2023 March 6]. Available from: https://www.elsevier.com/connect/authors-update/why-systematic-reviews-matter.

11. Chan A-W, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. The Lancet. 2005;365(9465):1159-62.

12. DeMauro SB, Giaccone A, Kirpalani H, Schmidt B. Quality of reporting of neonatal and infant trials in high-impact journals. Pediatrics. 2011;128(3):e639-44.

13. Wang L, Yang H, Huang H, Zhang C, Zuo H-X, Xu P, et al. Inulin-type fructans supplementation improves glycemic control for the prediabetes and type 2 diabetes populations: results from a GRADE-assessed systematic review and dose–response meta-analysis of 33 randomized controlled trials. Journal of Translational Medicine. 2019;17(1):410.

14. Katz DL, Karlsen MC, Chung M, Shams-White MM, Green LW, Fielding J, et al. Hierarchies of evidence applied to lifestyle Medicine (HEALM): introduction of a strength-of-

evidence approach based on a methodological systematic review. BMC Med Res Methodol. 2019;19(1):178.

15. Schwingshackl L, Knüppel S, Schwedhelm C, Hoffmann G, Missbach B, Stelmach-Mardas M, et al. Perspective: NutriGrade: A Scoring System to Assess and Judge the Meta-Evidence of Randomized Controlled Trials and Cohort Studies in Nutrition Research. Advances in Nutrition. 2016;7(6):994-1004.

16. Katz DL, Karlsen MC, Chung M, Shams-White MM, Green LW, Fielding J, et al. Hierarchies of evidence applied to lifestyle Medicine (HEALM): introduction of a strength-of-evidence approach based on a methodological systematic review. BMC Medical Research Methodology. 2019;19(1):178.

17. Zeraatkar D, Bhasin A, Morassut RE, Churchill I, Gupta A, Lawson DO, et al. Characteristics and quality of systematic reviews and meta-analyses of observational nutritional epidemiology: a cross-sectional study. The American journal of clinical nutrition. 2021;113(6):1578-92.

18. Stefan S, Matthias B, Ravi V, Christopher HS, Niveditha D, Rodney AH, et al. Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analyses. Canadian Medical Association Journal. 2020;192(32):E901.

19. Richardson M, Garner P, Donegan S. Interpretation of subgroup analyses in systematic reviews: A tutorial. Clinical Epidemiology and Global Health. 2019;7(2):192-8.

20. Cuijpers P, Griffin JW, Furukawa TA. The lack of statistical power of subgroup analyses in meta-analyses: a cautionary note. Epidemiol Psychiatr Sci. 2021;30:e78.

21. Burke JF, Sussman JB, Kent DM, Hayward RA. Three simple rules to ensure reasonably credible subgroup analyses. BMJ : British Medical Journal. 2015;351:h5651.

22. Inglis G, Archibald D, Doi L, Laird Y, Malden S, Marryat L, et al. Credibility of subgroup analyses by socioeconomic status in public health intervention evaluations: An underappreciated problem? SSM Popul Health. 2018;6:245-51.

23. Oxman AD, Guyatt GH. A consumer's guide to subgroup analyses. Annals of internal medicine. 1992;116(1):78-84.

24. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ. 2010;340:c117.

25. Sun X, Ioannidis JP, Agoritsas T, Alba AC, Guyatt G. How to use a subgroup analysis: users' guide to the medical literature. Jama. 2014;311(4):405-11.

26. Schühlen H. Pre-specified vs. post-hoc subgroup analyses: are we wiser before or after a trial has been performed? European Heart Journal. 2014;35(31):2055-7.

27. Sievenpiper JL, de Souza RJ, Mirrahimi A, Yu ME, Carleton AJ, Beyene J, et al. Effect of fructose on body weight in controlled feeding trials: a systematic review and meta-analysis. Annals of internal medicine. 2012;156(4):291-304.

28. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. Lancet (London, England). 2001;357(9263):1191-4.

29. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? The Lancet. 1998;352(9128):609-13.