# RESEARCH

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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

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# Abstract

**Background:** Currently, many clinical trials have shown that inulin-type fructans (ITF) supplementation is associated with glycemic control; nevertheless, the results are inconclusive. The aim of this meta-analysis of randomized controlled trials was to assess the effects of ITF supplementation on glycemic control.

**Methods:** PubMed, EMBASE and the Cochrane Library were searched for eligible articles up to March 6, 2019. A random-effects model was used to analyze the pooled results, and the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was applied to assess the quality of evidence. The dose–response model was used to recommend the daily dose and duration for ITF supplementation.

**Results:** Thirty-three trials involving 1346 participants were included. Overall, ITF supplementation could significantly reduce concentrations of fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS) and homeostasis model assessment-insulin resistance (HOMA-IR). In the prediabetes and type 2 diabetes (T2DM) population, a more significant reduction in FBG [weighted mean difference (WMD): -0.60 mmol/; 95% CI -0.71, -0.48 mmol/; high rate], HbA1c (WMD: -0.58%; 95% CI -0.83, -0.32%; high rate), FINS (WMD:  $-1.75 \mu$ U/ml; 95% CI -2.87,  $-0.63 \mu$ U/ml; low rate), and HOMA-IR (WMD: -0.69; 95% CI -1.10, -0.28; low rate) were observed, and ITF supplementation with a daily dose of 10 g for a duration of 6 weeks and longer was recommended. Moreover, subgroup analyses suggested that the effects of glycemic control were significantly influenced by the sex of the subjects and the type and the method of intake of ITF.

**Conclusions:** Our analyses confirmed that these four main glycemic indicators were significantly reduced by ITF supplementation, particularly in the prediabetes and T2DM population. Evidence supports that reasonable

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administration of ITF supplementation may have potential clinical value as an adjuvant therapy for prediabetes and T2DM management.

*Trial registration* The trial was registered at PROSPERO as CRD42018115875 on November 23, 2018.

Keywords: Inulin-type fructans supplementation, Glycemic control, Type 2 diabetes, Prediabetes, Meta-analysis

### Background

Recently, abnormal blood glucose metabolism is experiencing rapid growth around the world, and there are more than 463 million adults with diabetes and an additional 374 million adults with impaired glucose tolerance worldwide [1]. Studies have shown that abnormal blood glucose is related to the development and prognosis of some chronic diseases, including type 2 diabetes (T2DM) and cardiovascular diseases [2–4]; thus, glycemic control is necessary. Except for regulatory control by hypoglycemic agents, dietary regulation and lifestyle modification have also been reported to be effective in glycemic control [5]. Studies have shown that intake of some dietary supplements, including omega-3 fatty acids [6], zinc [7] and coffee [8], could enhance glycemic control and reduce the risk of diabetes and its related complications. Moreover, the epidemiological data in some relevant studies suggest an association between glycemic control and inulin-type fructans (ITF) supplementation [9].

ITF, mainly composed of inulin, fructooligosaccharides (FOS) and galactooligosaccharides (GOS), is a class of linear fructans that is connected with  $\beta$  (2-1) bonds and is often defined as one kind of prebiotic [10, 11]. Many studies have provided evidence that ITF has many health benefits, such as improving immune function [12], lowering blood pressure [13], and improving blood lipids [14] if taken at a moderate dose. Although a growing body of human clinical trials, including randomized controlled trials (RCTs), support that ITF intake plays an important role in glycemic control, the results have remained controversial [15].

A previous meta-analysis conducted by Liu [14] studied ITF effects on blood lipid profiles and two glycemic indicators [fasting blood glucose (FBG) and fasting insulin (FINS)] in 2016, but no significant result was found for FBG concentration. With more trials performed in recent years, ITF has shown a more strongly linked ability to improve glycemic control and insulin resistance. Moreover, there have been no studies systematically evaluating the association between ITF supplementation and two important glycemic indicators, glycosylated hemoglobin (HbA1c) and homeostasis model assessment-insulin resistance (HOMA-IR), which were related to long-term glycemic regulation and insulin sensitivity, respectively.

Therefore, we conducted a meta-analysis of all relevant RCTs to systematically assess the effects of ITF supplementation on the four main glycemic indicators (FBG, FINS, HbA1c and HOMA-IR), aiming at providing an evidence-based medical strategy for prediabetes and T2DM management in the clinic practice.

# **Materials and methods**

#### Literature search

A systematic search was performed according to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement in the online databases PubMed, EMBASE, and the Cochrane Library until March 6, 2019. The following terms were used to search for related publications in titles and abstracts: (oligosaccharide OR fructooligosaccharide OR oligofructose OR inulin) AND (glycosylated hemoglobin OR HbA1c OR glucose OR fasting plasma glucose OR insulin resistance OR glycemic OR "HOMA"). The synonyms of terms, MESH terms and the wild card term "\*" were also used in the search. The type of study was defined as a "clinical trial". The language was restricted to English. The search strategies of the online databases are shown in Additional file 1: Table S1. If necessary, manual retrieval was also conducted to obtain additional relevant articles. The protocol was registered at PROSPERO (Registration Number: CRD42018115875).

#### Study selection

Studies were included according to the following criteria: (i) primary RCT with either a parallel or crossover design; (ii) investigation of the impact of ITF supplementation on plasma/serum glycemic indicators (FBG, HbA1c, FINS, or HOMA-IR); (iii) treatment duration longer than 7 days; and (iv) sufficient glycemic index information at baseline and at the end of follow-up, or the net change values in each group needed to be provided.

Studies were excluded according to the following criteria: (i) intervention group used other carbohydrates than ITF, such as arabino-xylan and  $\beta$ -glucan; (ii) no appropriate control group for assessing the effect of ITF supplementation; (iii) duplicate studies; (iv) observational study design; or (v) the article was a meeting abstract.

With the inclusion criteria and exclusion criteria decided in advance, we completed the screening step by step: two authors (HH and PX) conducted the preliminary screening of the searched studies based on their titles and abstracts; then, they reviewed the full text to assess eligibility criteria independently. Final eligibility was determined through agreement between the 2 reviewers, with any disagreement resolved in consultation with LW.

### **Data extraction**

HH and PX independently extracted and cross-checked the following information from the included studies: basic information about the research (first author's name, year of publication, study region, underlying disease of the study population and eligibility, study design, sponsor, sample size, numbers of participants who completed the study, numbers of participants used for analysis); subjects' characteristic information (age, sex, body mass index, baseline glycemic parameters, and antidiabetic medication use); data on the intervention and control groups (kinds of ITF and control, food carrier, daily dose, duration of intervention); and outcomes of biomarkers for glucose and insulin homeostasis (FBG, HbA1c, FINS, and HOMA-IR); adverse reactions and reasons for loss of follow-up were also collected. Notably, if the necessary original data were not given but were presented by a column graph, we extracted the data according to the graph.

### **Quality assessment**

The methodological quality and the risk of bias of the included trials were independently assessed by two authors (HH and PX) using the Cochrane criteria. The seven assessment items used for the assessment of each study were as follows: adequacy of random sequence generation, allocation concealment, blinding of participants and personnel, outcome assessment, addressing of dropouts (incomplete outcome data), selective outcome reporting, and other potential sources of bias. These seven criteria were rated as 'low risk', 'unclear risk' or 'high risk' depending on the characteristics of each criterion reported in the study.

#### Quantitative data synthesis

The meta-analysis was conducted using RevMan software version 5.2 (Cochrane Collaboration, Oxford, UK). The effect sizes were expressed as the weighted mean difference (WMD) and 95% confidence interval (CI). The WMD was estimated by calculating the net change of the mean difference by subtracting the baseline value after treatment in the intervention and control groups. The standard deviation (SD) was calculated using the method described by Hozo et al. [16] and Simental-Mendía et al. [17]. If there were different reporting units for the indexes in the original studies, a unit conversion calculation was performed.

Considering the included studies mainly performed according to health status, we categorized the participants into four groups: healthy, prediabetes and T2DM, overweight and obesity, and others. A randomeffects model (using the DerSimonian-Laird method) and the generic inverse variance method were used to compensate for the heterogeneity of the studies in terms of the different groups. Interstudy heterogeneity was assessed using the Cochran Q test and I<sup>2</sup> index and was regarded as substantial if I<sup>2</sup>>50% and *P* value was low (<0.10).

### Nonlinear dose-response analysis

We tested the dose–response relationship between ITF supplementation and the glycemic indicators with the nonlinear robust error meta-regression (REMR) model, which is mainly based on the inverse variance-weighted least squares regression and cluster robust error variances for dealing with the synthesis of correlated dose–response data from different studies. A detailed theoretical rationale and Stata codes can be found in the methodological paper of Xu and Doi [18].

### Subgroup analyses

Subgroup analyses were performed to estimate the effect size of ITF supplementation on glycemic indicators in different subsets of studies categorized according to the presence of potential confounders. Apart from the aforementioned healthy status, the studies were also categorized according to sex (male versus female), type of ITF (inulin versus other kinds), method of ITF intake (in drinks versus other kinds), intervention-control design (an ITF versus non-ITF design versus a synbiotic versus probiotic design), study design (parallel versus crossover), country of study (Iran versus other countries), and sponsor referred (no versus yes).

### Publication bias and sensitivity analysis

The potential publication bias was explored by using visual inspection of funnel plot asymmetry with RevMan software and Egger's weighted regression for quantitative assessment with Stata 12.0 software (College Station, Texas 77845 USA).

To evaluate the influence of each study on the overall effect size, a sensitivity analysis was conducted using the leave-one-out method, i.e., iteratively removing one study and repeating the analysis. To further test the robustness of the results, sensitivity analyses were also used for excluding studies of high heterogeneity that changed the pooled result more than 10%, and data were reanalyzed using a fix-effects model for  $1^2 < 50\%$ .

### GRADE certainty of the body of evidence

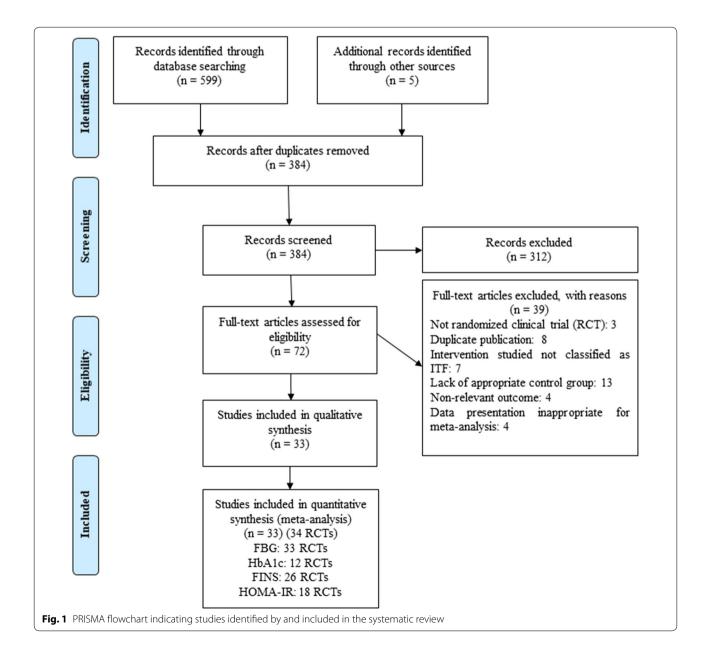
The overall certainty of evidence across the studies was graded according to the guidelines of the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) Working Group [19]. The quality of evidence could be classified into four categories according to the corresponding evaluation criteria: high, moderate, low, and very low [20].

# Results

### Flow and characteristics of the included studies

The detailed process of the PRISMA flowchart is presented in Fig. 1. Initially, 599 published studies were identified after searching multiple databases, and 5 additional records were identified through other sources. After carefully screening and assessing eligibility, 33 studies [21–53] were found eligible and were included in the systematic review. It was noteworthy that one trial [47] included two well-matched RCTs and actually counted as 2 RCTs in our meta-analysis. Therefore, 33 trials (34 RCTs) were included in all.

The study characteristics are presented in Table 1. Thirty-three clinical trials [21–53] involving 1346 participants were included, among which 23 trials were parallel RCTs [22–26, 28–35, 37, 39, 40, 44–47, 49–51] and 10 were crossover RCTs [21, 27, 36, 38, 41–43, 48, 52, 53]. Five studies [33, 39, 41, 46, 48] were conducted in healthy subjects, 7 studies [26, 28, 32, 44, 51–53] in the overweight and obesity populations and 14 studies (15



References,	Participants	nts				Intervention		Comparison	Outcome <sup>a</sup>	Study design
country	N (I/C)	Age	Gender	BMI	Population	Type	Dosage			
Alles [21], Nether- lands	20 (20/20)	59	M-9 F-11	28.3 ± 3.5	T2DM	FOS	15 g/days (20 days)	Glucose	⇔FBG	C, RCT, SB
Asemi [22], Iran	54 (27/27)	35-70	M and F	30.4±5.3	T2DM	Inulin and <i>Lactoba-</i> <i>cillus sporogenes</i>	8.4 g/days (56 days)	L. sporogenes bread	↔FBG, ↓FINS, HbA1c	P, RCT, DB
Behrouz [23], Iran	59 (29/30)	20-60	M and F	25-40	Nonalcoholic fatty liver disease	Oligofructose and probiotic	16 g/days (84 days)	Maltodextrin	↔FBG, FINS, HbA1c	P, RCT, DB
Bomhof [24], Canada 14 (8/6)	14 (8/6)	V 18	M-8 F-6	> 25	non-alcoholic stea- tohepatitis with overweight	Oligofructose	16 g/days (252 days)	Maltodextrin	↔ FINS, HOMA-IR, ↑FBG	P, RCT, DB
Bonsu [ <mark>25</mark> ], Canada	26 (12/14)	> 40	M and F	30.3 土 4.4	T2DM	Inulin	10 g/days (84 days)	Xylitol	↔FBG, HOMA-IR	P, RCT, DB
Canfora [26], Neth- erlands	44 (21/23)	45-70	M and F	28-40	Overweight or obese	GOS	15 g/days (84 days)	Maltodextrin	↔FBG, FINS	P, RCT, DB
Daubioul [27], Italy	7 (7/7)	48–60	M and F	21.7–37.6	Non-alcoholic stea- tohepatitis	FOS	16 g/days (56 days)	Maltodextrin	↔FBG, FINS	C, RCT, DB
de Luis [28], Spain	32 (16/16)	25-60	M and F	30-35	Obese	FOS	9.84 g/days (30 days)	Control cookie	↔FBG, FINS, HbA1c	P, RCT, DB
Dehghan [31], Iran	52 (27/25)	20-65	F-only	25–34.99	T2DM	Oligofructose and inulin	10 g/days (56 days)	Maltodextrin	↓FBG, HOMA-IR	P, RCT, TB
Dehghan [32], Iran	49 (24/25)	20-65	F-only	> 25	T2DM	Inulin	10 g/days (56 days)	Maltodextrin	<pre>↓FBG, FINS, HbA1c, HOMA-IR</pre>	P, RCT, DB
Dehghan [29], Iran	49 (27/22) 30–65	30-65	F-only	25–34.99	T2DM	Oligofructose and inulin	10 g/days (60 days)	Maltodextrin	↓FBG, HOMA-IR, ↔ FINS	P, RCT, DB
Dewulf [32], Belgium	30 (15/15) 18–65	) 18–65	F-only	> 30	Obese	Inulin and oligofruc- tose	16 g/days (90 days)	Maltodextrin	↔FBG, FINS, HbA1c, HOMA-IR	P, RCT, DB
Forcheron [33], France	17 (9/8)	31.7 土 4.0	M-6 F-11	ND	Healthy	Inulin and oligofruc- tose	10 g/days (180 days)	Maltodextrin	↔FBG, FINS	P, RCT, DB
Gargari [34], Iran	49 (24/25)	) 20–65	F-only	25–35	T2DM	Inulin	10 g/days (60 days)	Maltodextrin	↓FBG, FINS, HbA1c, HOMA-IR	P, RCT, TB
Ghavami [ <mark>35</mark> ], Iran	46 (23/23)	30-50	M and F	25–35	T2DM	Inulin	10 g/days (42 days)	Starch	↔FBG, FINS, HbA1c, ↓HOMA-IR	P, RCT, DB
Giacco [ <b>36</b> ], Italy	30 (30/30)	) 45.5±9.9	M-20 F-10	26.6±2.2	Mild hypercholester- olaemia	FOS	10.6 g/days (60 days)	Maltodextrine plus aspartame	↔FBG	C, RCT, DB
Guess [37], UK	38 (20/18)	) >18	M and F	25–35	Prediabetes	Inulin	30 g/days (126 days)	Cellulose	↓FBG, FINS, HbA1c	P, RCT, DB
Guess [38], UK	34 (34/34)	18 18	M and F	25–35	Overweight subjects with prediabetes	Inulin	30 g/days (42 days)	Cellulose	↔ FINS, ↓HbA1c	C, RCT, DB
Jackson [39], UK	54 (27/27)	) 35–65	M and F	20-32	Healthy	Inulin	10 g/days (56 days)	Maltodextrin	↔ FBG, FINS	P, RCT, DB
Javadi [40], Iran	38 (19/19)	) 20–60	M and F	30.7±3.7	Non-alcoholic stea- tohepatitis	Inulin	10 g/days (90 days)	Maltodextrin	↔ FBG, ↓ FINS, HbA1c	P, RCT, DB

References,	Participants	ıts				Intervention		Comparison	Outcome <sup>a</sup>	Study design
country	N (I/C)	Age	Gender	BMI	Population	Type	Dosage			
Luo [41], France	12 (12/12) 19–32	19–32	M-only	21.0±1.7	Healthy	FOS	20 g/days (28 days)	Sucrose	↔ FBG, FINS	C, RCT, DB
Luo [42], Belgium	10 (10/10)	10 (10/10) 57.0 ± 6.3 M-6 F-4	M-6 F-4	28.0±3.2	T2DM	FOS	20 g/days (28 days)	Sucrose	↔FBG, FINS, HOMA- IR	C, RCT, DB
Meksawan [43], Thailand	(6/6) 6	> 50	M-5 F-4	QN	Elderly CAPD patients	FOS	20 g/days (30 days)	Sucrose	↔FBG	C, RCT, DB
Parnell [44], Canada	39 (21/18) 20-70	20-70	M and F	>25	Overweight or obese	Oligofructose	21 g/days (84 days)	Maltodextrin	↔FBG	P, RCT, DB
Pedersen [45], UK	29 (14/15) 42–65	42-65	M-only	28.2 ± 1.0	T2DM	GOS	5.5 g/days (84 days)	Maltodextrin	↔FBG, FINS, HbA1c, HOMA-IR	P, RCT, DB
Rajkumar [46], India	30 (15/15) 20-25	20-25	M-14 F-16	M-14 F-16 18.5-24.9	Healthy	FOS and L. salivarius	10 g/days (42 days)	L. salivarius	↔FBG, FINS, HbA1c	P, RCT, SB
Roshanravan [ <mark>47</mark> ], Iran	30 (15/15) 30–55	30-55	M and F	27–35	T2DM	Inulin	10 g/days (45 days)	Starch	↔FBG, FINS, HbA1c, HOMA-IR	P, RCT, DB
Russo [48], Italy	15 (15/15)	15 (15/15) 18.8±0.7 M-only	M-only	22.8±2.3	Healthy	Inulin	11 g/days (35 days)	Control pasta	↔FBG, HbA1c, HOMA-IR, ↑FINS	C, RCT, DB
Scheid [49], Brazil	72 (35/37)	72 (35/37) 67.1 ±6.1 M and F	M and F	27.9 ± 5.0	Elderly	FOS	7.4 g/days (63 days)	Maltodextrin	↔FBG, FINS, HbA1c	P, RCT, DB
Shakeri [50], Iran	52 (26/26) 53	53	M and F	30.3 ± 5.3	T2DM	Inulin and Lactoba- cillus sporogenes	8.4 g/days (56 days)	Lactobacillus sporo- genes control breads	↔FBG	P, RCT, DB
Tovar [51], Mexican	59 (30/29) 18-50	18-50	F-only	25	Obese	Inulin	10 g/days (90 days)	No treatment	↔FBG	P, RCT, DB
Tripkovic [52], UK	10 (10/10) 30-55	30-55	M-only	25-35	Overweight	Inulin	15 g/days (28 days)	Control bread rolls	↔FBG, FINS, HbA1c	C, RCT, DB
Vulevic [53], UK	45 (45/45) 18–65	18-65	M-16 F-29 >2	> 25	Overweight	GOS	5.5 g/days (84 days)	Maltodextrin	↔FBG, ↓FINS	C, RCT, DB
C Cross-over, CAPD continuous ambulatory peritoneal dialysis, DB dihemoglobin, HOMA-IR homeostasis model assessment-insulin resist a $\uparrow$ : means the glycemic indicator(s) in the ITF intervention group with their control groups.	ntinuous ambu R homeostasis r nic indicator(s) Jed while comp	latory peritor model assessr in the ITF inte aared with th	neal dialysis, ment-insulin I ervention gro	DB double-bli resistance, ND up was (were oup; ↓, means	C Cross-over, CAPD continuous ambulatory peritoneal dialysis, DB double-blinded, FBG fasting blood glucose, FINS fasting insulin, FOS fructooligosaccharide, GOS galactooligosaccharides, hemoglobin, HOMA-IR homeostasis model assessment-insulin resistance, ND no data, PP arallel, RCT randomized controlled trial, SB single-blinded, TB triple-blinded, T2DM Type 2 diabetes and the glycemic indicator(s) in the ITF intervention group was (were) significantly increased while compared with their control group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; ↔, means the glycemic indicator(s) in the ITF intervention group; was (were) significantly decreased while compared with the com	Jucose, <i>FINS</i> fasting insul andomized controlled tria <i>h</i> ile compared with their ) in the ITF intervention g <sub>1</sub>	in, FOS fructooligosaccha II, 5B single-blinded, TB tri control group; ↔, means roup was (were) significar	ride, GOS galactooligosac iple-blinded, <i>T2DM</i> Type 2 s the glycemic indicator(s) ntly decreased while com	Cross-over, CAPD continuous ambulatory peritoneal dialysis, DB double-blinded, FBG fasting blood glucose, FINS fasting insulin, FOS fructooligosaccharide, GOS galactooligosaccharides, HBA Tc glycosylated hemoglobin, HOMA-IR homeostasis model assessment-insulin resistance, ND no data, P Parallel, RCT randomized controlled trial, SB single-blinded, TB triple-blinded, T2DM Type 2 diabetes a "	ted oup was (were) oup

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RCTs) [21, 22, 25, 29-31, 34, 35, 37, 38, 42, 45, 47, 49] in the prediabetes and T2DM population, and 7 studies [23, 24, 27, 36, 40, 43, 49] in the other group were performed mainly in non-alcoholic steatohepatitis patients [23, 24, 27, 40] or the elderly [43, 49]. The intervention substances varied among the included studies: 12 studies [25, 30, 34, 35, 37-40, 47, 48, 51, 52] used inulin only, and 4 studies [22, 23, 46, 50] used synbiotic (a combination of ITF and probiotics). The daily dose and duration of the intervention period varied between studies. The daily dose of ITF ranged from 5.5 to 30 g (median dose: 10 g/day), and the duration of the intervention periods ranged from 20 to 252 days (median duration: 56 days). Eligible outcomes of glycemic indicators were reported: FBG in 32 studies (33 RCTs) [21-37, 39-53], HbA1c in 11 studies (12 RCTs) [25, 29-31, 34, 35, 42, 45, 47], FINS in 25 studies (26 RCTs) [22-24, 26-30, 32-35, 37-42, 45-49, 52, 53], and HOMA-IR in 17 studies (18 RCTs) [22-24, 28, 30, 32, 34, 35, 37, 38, 40, 45-49, 52]. Except for one study [23], in which subjects were instructed to modify dietary intake in both the intervention and control groups, participants were advised to maintain their usual diet. The side effects were studied in 26 trials, and not mentioned in 7 others. Of the 26 trials, 19 explicitly reported all participants in the intervention and control groups had no adverse effects after substances supplementation, 5 showed no significant difference in the incidence of adverse effects between participants of the intervention and control groups, except some subjects in 2 studies [43, 44] were reported to suffer intestinal pressure, flatulence or abdominal discomfort.

### Study quality

The quality of bias assessment of the included studies is shown in Additional file 2: Figure S1. According to the seven assessment criteria of the Cochrane Handbook for Systematic Review of Interventions, most of the studies had good quality although some were characterized by insufficient information among the random sequence generation, allocation concealment, binding of outcome assessment and other bias, which was on account of the financial or food assistance provided by companies. In addition, bias may exist in some studies because 3 trials [25, 32, 48] had a high dropout rate.

## Main outcomes and GRADE certainty

We conducted a meta-analysis to assess the effect of ITF on glycemic indicators, including FBG, HbA1c, FINS, and HOMA-IR, and used GRADE to assess the results. The GRADE evidence profile for the summary of findings is presented in Table 2.

To explore whether ITF supplementation affected hyperglycemia, FBG data were analyzed. The effects of ITF on FBG were reported in 33 RCTs, including 14 RCTs in the prediabetes and T2DM population. The overall meta-analysis showed that ITF supplementation significantly reduced FBG with a WMD of -0.21 mmol/l (95% CI -0.33, -0.09 mmol/l; P=0.0005) (moderate rate). However, significant heterogeneity was observed between studies (I<sup>2</sup>=59%, P < 0.0001) (Fig. 2). Importantly, we found a more significant reduction in FBG based on the prediabetes and T2DM population (WMD: -0.60 mmol/l; 95% CI -0.71, -0.48 mmol/l; P < 0.00001) (high rate), but the reduction was not significant in other populations. Moreover, no heterogeneity was observed in the grouped analyses with all  $I^2 = 0\%$ .

Next, we examined whether ITF supplementation affected long-term glycemic regulation by analyzing HbA1c data. The effect of ITF on HbA1c was reported in 12 RCTs, including 10 RCTs in the prediabetes and T2DM population. The overall analysis revealed that HbA1c was reduced significantly (WMD: -0.39%; 95% CI -0.65, -0.13%; P=0.003) (moderate rate). Notably, in the T2DM population, HbA1c showed a significant reduction with a WMD of -0.58% (95% CI -0.83, -0.32%; P<0.00001) (high rate), and no significant heterogeneity was observed across studies (I<sup>2</sup>=14\%, P=0.31) (Fig. 3).

Next, we analyzed the effect of ITF on the fasting insulin concentration. Twenty-six RCTs reported changes in FINS after ITF supplementation, including 11 RCTs in the prediabetes and T2DM population. Overall, ITF supplementation reduced FINS significantly with a WMD of  $-1.22 \mu$ U/ml (95% CI  $-1.90, -0.54 \mu$ U/ml; P=0.0005) (very low rate) (Fig. 4). In the prediabetes and T2DM population, FINS showed a more significant reduction (WMD:  $-1.75 \mu$ U/ml; 95% CI  $-2.87, -0.63 \mu$ U/ml; P=0.002) (low rate), and the reduction was not significant or was modestly significant in the other populations.

Last, we also examined whether ITF supplementation affected insulin sensitivity by analyzing HOMA-IR. The effect of ITF on HOMA-IR was reported in 18 RCTs, among which 9 RCTs were based on the prediabetes and T2DM population. The overall analysis revealed that ITF supplementation significantly reduced HOMA-IR with a WMD of -0.57 (95% CI -0.84, -0.31; P < 0.0001) (low rate) (Fig. 5). In the prediabetes or T2DM subgroup, HOMA-IR also showed a significant reduction (WMD: -0.69, 95% CI -1.10, -0.28, P = 0.001;  $I^2 = 81\%$ ) (low rate).

In addition, to analyze the relative hypoglycemic effects, we calculated the weighted mean of the baseline

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Quality assessment	int					Summary of findings			Quality
Outcomes	Risk of bias	Risk of bias Inconsistency	Indirectness	Imprecision	Publication Bias	Number of intervention/control	Absolute effect (95% CI)	Absolute effect Relative effect <sup>a</sup> (95% Cl) intervention/control	of evidence
FBG (Total popu- lation)	No serious limitations	Serious limitations <sup>b</sup>	No serious limitations No serious limita- tions	No serious limita- tions	No serious limitations 656/651	656/651	- 0.21 (- 0.33, - 0.09) mmol/I	- 4.32%/0.36%	⊕ ⊕ ⊕O moder- ate
HbA1C (Total population)	No serious limitations	Serious limitations <sup>c</sup>	No serious limitations No serious limita- tions	No serious limita- tions	No serious limitations 220/219	220/219	- 0.39 (-0.65, - 0.13) %	- 4.93%/1.20%	⊕ ⊕ ⊕O moder- ate
FINS (Total popu- lation)	No serious limitations	Very serious limitations <sup>d</sup>	No serious limitations No serious limita- tions	No serious limita- tions	Strongly suspected <sup>e</sup>	515/514	— 1.22 (— 1.90, — 0.54) μU/ml	- 12.62%/0.44%	⊕ OOO very low
HOMA-IR (Total population)	No serious limitations	Very serious imitations <sup>f</sup>	Very serious imitations <sup>f</sup> No serious limitations No serious limita- tions	No serious limita- tions	No serious limitations 357/360	357/360	- 0.57 (- 0.84, - 0.31)	- 19.10%/- 1.27%	wol OO ⊕ ⊕
FBG (T2DM and prediabetes)	No serious limitations	No serious limitations	No serious limitations	No serious limita- tions	No serious limitations 283/280	283/280	— 0.60 (— 0.71, — 0.48) mmol/I	- 7.41%/- 0.26%	⊕ ⊕ ⊕ high
HbA1C (T2DM and predia- betes)	No serious limitations	No serious limitations	No serious limitations	No serious limita- tions	No serious limitations 190/189	190/189	— 0.58 (— 0.83, — 0.32) %	- 5.15%/1.55%	⊕ ⊕ ⊕ high
FINS (T2DM and prediabetes)	No serious limitations	Very serious limitations <sup>g</sup>	No serious limitations	No serious limita- tions	No serious limitations 232/229	232/229	— 1.75 (-2.87, — 0.63) μU/ml	- 20.08%/- 3.50%	⊕ ⊕ OO low
HOMA-IR (T2DM and predia- betes)	No serious limitations	Very serious limitations <sup>h</sup> No serious limitations	No serious limitations	No serious limita- tions	No serious limitations 195/197	195/197	- 0.69 (-1.10, - 0.28)	- 27.63%/- 2.29%	₩0 OO ⊕ ⊕

FBG fasting blood glucose, FINS fasting insulin, HBA1 cglycosylated hemoglobin, HOMA-IR homeostasis model assessment- insulin resistance, 720M type 2 diabetes mellitus

<sup>a</sup> The relative effect is computed by calculating the weighted mean of the baseline and hypoglycemic effects

 $^{\rm b}\,$  The test for heterogeneity is significant, and the I  $^2$  is moderate, 59%

 $^{\rm c}\,$  The test for heterogeneity is significant, and the  ${\rm l}^2$  is moderate, 51%

 $^{
m d}\,$  The test for heterogeneity is significant, and the I<sup>2</sup> represent substantial heterogeneity, 69%

<sup>e</sup> The Egger's test for publication bias is significant (P = 0.0035)

 $^{f}$  The test for heterogeneity is significant, and the l $^{2}$  represent substantial heterogeneity, 64%

 $^9\,$  The test for heterogeneity is significant, and the I $^2$  represent substantial heterogeneity, 78%

 $^{\rm h}\,$  The test for heterogeneity is significant, and the  ${
m l}^2$  represent substantial heterogeneity, 81%

	Evn	erimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean		Total	Moight	Nean Difference	IV, Random, 95% Cl
1.1.1 Healthy-subjects	mean	50	TULAI	mean	50	TULAI	weight	IV, Ranuom, 95% CI	IV, Kandolli, 95% Cl
Forcheron 2007	-0.3	0.334	9	-0.16	0.556	8	3.6%	0441050 0201	
Jackson 1999	-0.3	0.334	27	-0.16	0.556	-	5.4%	-0.14 [-0.58, 0.30]	
						27		0.04 [-0.22, 0.30]	
Luo 1996 Beilgumer 2015	-0.3 -0.03	0.35 0.38	12 15	-0.02 -0.11	0.488 0.301	12 15	4.5% 5.5%	-0.28 [-0.62, 0.06]	
Rajkumar 2015								0.08 [-0.17, 0.33]	
Russo 2010	-0.15	0.416	15	-0.02	0.47	15	4.7%	-0.13 [-0.45, 0.19]	
Subtotal (95% CI)	0.01.2-03	24 - 1 (D -	78	17 - 0.0/		77	23.6%	-0.04 [-0.18, 0.09]	•
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =			0.45);	r= 0%					
1.1.2 Prediabetes and T	2DM								
Alles 1999	0.2	2.365	20	0.18	2.399	20	0.6%	0.02 [-1.46, 1.50]	
Asemi 2016	-0.62778	3.083333	27	-0.20556	2.183333	27	0.6%	-0.42 [-1.85, 1.00]	
Bonsu 2012	0.1	2.252	12	-0.2	1.51	14	0.6%	0.30 [-1.20, 1.80]	
Dehghan 2014-a	-1.02	1.189	27	-0.1	0.711	25	3.0%	-0.92 [-1.45, -0.39]	
Dehghan 2014-b	-0.83889	1.003	24	-0.09444	0.711	25	3.2%	-0.74 [-1.23, -0.26]	
Dehghan 2016	-0.8	1.123	27	0.14	0.883	22	2.7%	-0.94 [-1.50, -0.38]	
Gargari 2013	-0.84	1.003	24	-0.09	0.711	25	3.2%	-0.75 [-1.24, -0.26]	
Ghavami 2018	-0.59	1.878	23	0.15	1.456	23	1.2%	-0.74 [-1.71, 0.23]	
Guess 2015	-0.4	0.19	20	0.16	0.23	18	6.5%	-0.56 [-0.69, -0.43]	+
Luo 2000	-0.52	2.026	10	-0.02	1.48	10	0.5%	-0.50 [-2.06, 1.06]	
Pedersen 2016	0.7	1.485	14	0.3	1.16	15	1.2%	0.40 [-0.57, 1.37]	
Roshanravan 2017(1)	-1.25	4.055	15	0.07	1.393	15	0.3%	-1.32 [-3.49, 0.85]	
Roshanravan 2017(2)		2.8142292	14	0.01	2.29	15	0.4%	-1.01 [-2.89, 0.87]	
Shakeri 2014	-0.86667	2.911111	26	-0.33333	2.127778	26	0.7%	-0.53 [-1.92, 0.85]	
Subtotal (95% CI)			283		22	280	24.8%	-0.60 [-0.71, -0.48]	•
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =			P = 0.63	3); I² = 0%					
1.1.3 Overweight and ob	esitv								
Canfora 2017	0	0.5	21	0	0.458	23	5.1%	0.00 [-0.28, 0.28]	+
de Luis 2013	0.05	0.82	16	0.06	0.763	16	2.8%	-0.01 [-0.56, 0.54]	
Dewulf 2013	-0.11111	0.333333	15	0.055556	0.166667	15	6.0%	-0.17 [-0.36, 0.02]	-
Parnell 2009	-0.2	0.436	21	-0.14	0.4	18	5.3%	-0.06 [-0.32, 0.20]	+
Tovar 2012	-0.033333	0.505556	30	-0.122222	0.5	29	5.4%	0.09 [-0.17, 0.35]	+
Tripkovic 2015	0.08	0.296	10	0.19	0.344	10	5.1%	-0.11 [-0.39, 0.17]	-+
Vulevic 2013		0.6557439	45		0.8544004	45	4.8%	-0.20 [-0.51, 0.11]	
Subtotal (95% CI)	0.2	0.0001 100	158	0.4	0.0011001	156	34.4%	-0.08 [-0.18, 0.02]	•
Heterogeneity: Tau <sup>2</sup> = 0.0	$10^{\circ}$ Chi <sup>2</sup> = 3.4	17 df = 6 (P =		I <sup>2</sup> = 0%		100	01111	-0.00 [-0.10, 0.02]	
Test for overall effect: Z =			0.1 0/,						
1.1.4 Others									
Behrouz 2017	-0.33	0.956	29	-0.11	1.256	30	2.7%	-0.22 [-0.79, 0.35]	
Bomhof 2018	0.62	0.523737	8	0.26	0.809506	6	1.9%	0.36 [-0.38, 1.10]	
Daubioul 2005	-0.67	2.584	7	0.55	2.176	7	0.2%	-1.22 [-3.72, 1.28]	
Giacco 2004	0.22	0.95	30	0.16	0.862	30	3.5%	0.06 [-0.40, 0.52]	+-
Javadi 2017	-0.09	0.516	19	0.03	0.454	19	4.8%	-0.12 [-0.43, 0.19]	-+
Meksawan 2016	0.45	3.05	9	0.64	2.406	9	0.2%	-0.19 [-2.73, 2.35]	
Scheid 2014	-0.33	1.102	35	-0.18	0.571	37	3.9%	-0.15 [-0.56, 0.26]	-+-
Subtotal (95% CI)	0.00	1.102	137	0.10	0.011	138	17.1%	-0.08 [-0.27, 0.11]	
Heterogeneity: Tau <sup>2</sup> = 0.0 Test for overall effect: Z =			0.82);	I² = 0%					
Total (05% CI)			GEC			664	100.0%	0.241.0.22 0.001	•
Total (95% Cl)	5. Ohiz - 77	57 df - 00 (	656	043-12-504	v	051	100.0%	-0.21 [-0.33, -0.09]	• • • • • • • • • • • • • • • • • • •
Heterogeneity: Tau <sup>2</sup> = 0.0			< U.Ul	101); 1= 59	70				-4 -2 0 2 4
Test for overall effect: Z = Test for subgroup differe			(P < 0.	00001). I <sup>2</sup> =	94.7%				Favours [ITF] Favours [control]
Fig. 2 Forest plot disp						ng blo	od gluco	ose (mmol/l) by su	bgroup

and the hypoglycemic results of the four glycemic indicators (FBG, HbA1c, FINS, and HOMA-IR). In the prediabetes and T2DM population, compared with their control groups, the relative reduction of the four indicators reached -7.15%, -7.00%, -16.58%, and -25.34%of their baseline values in the supplementation group, which were -4.68%, -6.13%, -13.06%, and -17.83%in the total population, respectively. The relative effects in both the intervention and control groups are shown in Table 2.

### Nonlinear dose-response analysis

We explored the recommended daily dose and duration of ITF for glycemic control by dose–response analysis. As shown in Fig. 6, in the prediabetes and T2DM population, the relationship curves suggested that ITF supplementation had effects on the glycemic indicators, and the effects were different with different daily doses, durations and total doses of ITF. When the daily dose was 10 g and the duration reached 42 days and longer, these four glycemic indicators were significantly reduced, and the effect

	Fa	vours [ITF]		Favo	urs [control]			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
1.2.1 T2DM									
Bonsu 2012	0.2	1.375	12	-0.2	1.539	14	4.2%	0.40 [-0.72, 1.52]	<del></del>
Dehghan 2014-a	-0.6	0.954	27	0.1	1.015	25	10.8%	-0.70 [-1.24, -0.16]	
Dehghan 2014-b	-0.7	0.819	24	0.1	1.015	25	11.2%	-0.80 [-1.32, -0.28]	
Dehghan 2016	-0.51	0.835	27	0.21	0.99	22	11.1%	-0.72 [-1.24, -0.20]	
Gargari 2013	-0.7	0.843	24	0.1	1.023	25	11.0%	-0.80 [-1.32, -0.28]	
Ghavami 2018	-0.42	2.212	23	0.77	1.47	23	4.4%	-1.19 [-2.28, -0.10]	
Luo 2000	-0.18	1.524	10	-0.35	1.494	10	3.2%	0.17 [-1.15, 1.49]	
Pedersen 2016	0.2	1.12	14	0.2	0.78	15	8.0%	0.00 [-0.71, 0.71]	
Roshanravan 2017(1)	-0.53	4.584	15	-0.2	3.701	15	0.7%	-0.33 [-3.31, 2.65]	
Roshanravan 2017(2)	-0.1281	2.0419414	14	-0.06039	1.2086107	15	3.6%	-0.07 [-1.30, 1.16]	
Subtotal (95% CI)			190			189	68.2%	-0.58 [-0.83, -0.32]	◆
Heterogeneity: Tau <sup>2</sup> = 0.	02; Chi <sup>2</sup> =	10.49, df = 9	(P = 0.3)	31); <b>i²</b> = 149	Хо				
Test for overall effect: Z	= 4.44 (P <	0.00001)							
1.2.2 Others									
Dewulf 2013	0.1	0.5	15	0	0.5	15	14.6%	0.10 [-0.26, 0.46]	+-
Russo 2010	-0.4	0.358	15	-0.2	0.308	15	17.3%	-0.20 [-0.44, 0.04]	
Subtotal (95% CI)			30			30	31.8%	-0.08 [-0.37, 0.21]	•
Heterogeneity: Tau <sup>2</sup> = 0. Test for overall effect: Z :	•		P = 0.1	7); I² = 46%					
Total (95% CI)			220			219	100.0%	-0.39 [-0.65, -0.13]	•
Heterogeneity: Tau <sup>2</sup> = 0.	08; Chi <sup>2</sup> =	22.55, df = 1	1 (P = 0	).02); I <sup>2</sup> = 51	%				
Test for overall effect: Z:	= 2.95 (P =	0.003)							
Test for subaroup differe	ences: Chi	<sup>2</sup> = 6.40. df =	1 (P = )	0.01). I <sup>2</sup> = 8	4.4%				Favours (ITF) Favours (control)
ig. 3 Forest plot disp	laying th	e effects of	inulin	-type fruc	tans on gly	cosyla	ted hem	oglobin (%) by subgrou	ıp

of glycemic control was satisfactory; the results were robust because the number of supporting studies was relatively large. Figure 6g, j, although FINS and HOMA-IR kept a decreasing trend when the daily dose was above 10 g, the supporting studies were fewer, and the results were not as credible. In the duration relationship curve, a similar situation existed.

These analyses were also performed in the total population (Additional file 3: Figure S2). The figure suggested that the overall trends of the curves were consistent with those of the prediabetes and T2DM population. For the HbA1c indicator, the trend of the dose–response relationship curves decreased rapidly at first and then rose gradually at some point.

### Subgroup analyses

The subgroup analysis results are presented in Table 3. The results showed that the female subgroup had reductions in FBG, HbA1c, FINS and HOMA-IR, while only FINS was significantly reduced in the male subgroup. The subgroup results showed that inulin had better effects on HbA1c and HOMA-IR than other kinds of ITF and that ITF supplementation in drinks had better effects on the four glycemic indicators than that in other foods, such as cookies, bread and so on. The pooled results of 4 studies examining symbiotic (ITF and probiotic) supplementation showed a significant reduction in FINS and HOMA-IR but no significant effects on the other two indicators. The study design, study country, and whether the mentioned sponsor might also be factors influencing the differences in the results between the studies.

## Sensitivity analysis

The results of the leave-one-out sensitivity analysis suggested that the effects of ITF supplementation on all four glycemic indicators were robust and not significantly driven by any single study (Additional file 4: Figure S3).

In further sensitivity analyses, after the removal of high potential outlier studies that shifted the pooled mean difference more than 10%, the reanalysis results from the fixed effect model revealed no significant change after the exclusion compared with before. All the reanalysis results are summarized in Table 4.

### **Publication bias analyses**

The publication bias of the included studies on the four indicators was inspected with a funnel plot and Egger's test, and the results are shown in Additional file 5: Figure S4. The funnel plots of FBG, HbA1c and HOMA-IR were symmetrical, which may be interpreted as no publication bias and the same results were shown in Egger's test (P > 0.05). However, the funnel plot and Egger's test showed that there might be publication bias in the FINS results (t = -2.24; 95% CI -2.28, -0.09; P = 0.035).

## Discussion

In this systematic review and meta-analysis of 33 RCTs involving a total of 1346 participants, we assessed the effects of ITF supplementation on four glycemic indicators, including FBG, HbA1c, FINS and HOMA-IR scores. In this regard, this meta-analysis provides the most up-to-date evidence supporting the putative favorable effects of ITF supplementation on glycemic control. Indeed, the results of

Study or Subgroup         Mean         SD         Total         SD <ths< th=""><th></th><th>Fav</th><th>ours [ITF]</th><th></th><th>Favou</th><th>rs [control]</th><th></th><th></th><th>Mean Difference</th><th>Mean Difference</th></ths<>		Fav	ours [ITF]		Favou	rs [control]			Mean Difference	Mean Difference
<b>1.3.1</b> Healthy-subjects Forcheron 2007 0.6 3.3 9 0.2 2.727 8 3.4% 0.40 [-2.47, 3.27] Jackson 1999 -0.58 2.337 27 0.52 3.7.45 27 5.2% -1.10 [-2.90, 0.7] Jackson 1999 -0.58 6.5522 12 -1.87 4.333 12.18% 1.01 [-3.4, 5.44] Rajkumsz 2015 -3.4 1.251 15 -2.26 1.899 15 6.2% -1.14 [-2.5, 0.4] Rowso 2010 0.78 0.885 15 -0.11 0.926 15 7.7% 0.89 [0.27, 1.51] Subtotal (95% C) -78 -9.95, df = 4 ( $P = 0.04$ ), $P = 0.05$ Tast tor overall effect Z = 0.16 ( $P = 0.87$ ) <b>1.3.2</b> Prediabetes and TZDM Assem 2016 -3.2 5.4 27 -0.3 3.4 27 4.1% -2.90 [-5.31, 0.46] Dengtan 2016 -4.8 3.866 2.4 0.2 3.8 25 4.5% -5.00 [-7.15, 2.85] Dengtan 2016 -2.78 4.851 27 0.25 9.55 2.2 1.05 +5.50 2.10 [-7.15, 2.85] Ouess 2016 -5.06 (P = 0.87) Guess 2016 -5.06 (P = 0.87) Total (95% C) -1.05 1.373 3.4 1.162712 1.737258 3.4 7.4% -5.072 [+3.6, 1.0] Dengtan 2016 -1.51 9.166 14 -1.85 7.948 15 1.04% -1.771 12.26, 8.00] Pedersen 2016 1.51 9.166 14 -1.65 7.948 15 1.0% -3.774 2.26, 8.01 Pedersen 2016 1.51 9.166 14 0.1537 15 0.64 [-5.64 -0.28] Pedersen 2016 1.51 9.166 14 0.1537 15 0.64 [-5.64 -0.28] Heterogeneity Tau" = 2.18 (Chi = 4.67.2 1 -0.0 (Chi = 0.28) <b>1.3.0 Verweight and obesity</b> Cardina 2017 -1.8 8.561 21 -0.8 15.052 23 0.8% -1.00 [+3.6, 5.16] de Luis 2010 -0.79 9.493 16 1.3 8.433 15 3.2% -0.08 [+3.5, 0.47] Meterogeneity Tau" = 2.18 (Chi = 4.67.2 4.9 (-0.02) <b>1.3.0 Verweight and obesity</b> Cardina 2017 -1.8 8.561 21 -0.8 (Tau 20, 0.01) [= 7.8%, 10.9 (-3.01001), [P = 7.8%, 10.9 (-3.012, 0.51, 16.2, 2.4] Heterogeneity Tau" = 2.13 (Chi = -4.61, 2.4] (= 0.02) <b>1.3.0 Verweight and obesity</b> Cardina 2017 -1.8 (0.592 29 1.05 1.52.47 30 1.18% -4.69 (-9.52, 0.14] Bombroz 2017 -1.52 3.16 (Chi = 0.60), [P = 0.8] <b>1.4.16</b> (7.14, 2.75, 1.4] Heterogeneity Tau" = 0.00, Chi = 1.40, df = 4 (P = 0.80), [P = 0.8] <b>1.5.1</b> (1.00, 1.122 [-1.90, 0.51] <b>1.5.2</b> 1.14 [-1.93, 0.34] Heterogeneity Tau" = 0.00, Chi = 2.44, df = 4 (P = 0.60), [P = 0.8] <b>1.5.4</b> (1.14 [-1.93, 0.34] Heterogeneity Tau" = 0.00, Chi = 2.44, df = 4 (P = 0.60), [P = 0.8] <b>1.5.4</b>	Study or Subaroup			Total			Total	Weight		
Forcheron $\frac{1}{2007}$ 0.6 2.33 9 0.2 2.727 8 3.4% 0.40 [2.47, 2.27] Jackson 1996 0.68 6.522 12 0.16 ( $r$ 2.37.45 27 52% 0.10 [2.20, 0.70] Lio 1996 0.086 6.522 12 0.16 ( $r$ 1.47 4.33 12 1.8% 1.01 [2.32, 0.24] Response 2010 0.78 0.805 15 0.011 0.926 15 7.7% 0.89 [0.27, 1.51] Stubtical (95% C) 78 77 2.4% 0.89 [0.27, 1.51] Test for overall effect 2 - 0.16 ( $r$ = 0.67) <b>1.3.2 Prediabetes and 120M</b> Asemi 2016 -2.78 4.951 27 0.25 9.565 22 1.8% -3.03 [7.45, 2.85] Dehylina 2016 -2.78 4.951 27 0.25 9.565 22 1.8% -3.03 [7.45, 2.85] Dehylina 2016 -2.76 4.951 27 0.25 9.565 22 1.8% -3.03 [7.45, 2.85] Dehylina 2016 -2.76 4.951 27 0.25 9.565 22 1.8% -3.03 [7.45, 2.85] Dehylina 2016 -2.6699 1.507:38 3.4 1.85212 1.737258 34 7.4% -0.72 [1.48, 0.47] Gargan 2017 0.25 1.7780 12.8 (1.56 2.37, 2.4% -0.72 [1.48, 0.47] Gargan 2017 0.25 1.7780 12.8 (1.56 2.37, 2.4% -0.72 [1.48, 0.47] Stubtical (95% C) -18 ( $r$ = 0.002) <b>1.3.2 Ore weight and obesity</b> Cardrox 2017 (1) -0.35 1.77 13 0.44 1.3612127 15 6.6% 0.03 [1.18, 0.47] Stubtical (95% C) -18 ( $r$ = 0.002) <b>1.3.3 Ore weight and obesity</b> Cardrox 2017 (1) -0.35 1.77 14 0.44 1.3612127 15 6.6% 0.03 [1.48, 0.47] Stubtical (95% C) -18 ( $r$ = 0.04), $r$ = 0.8 Test for overall effect 2 = 3.05 ( $r$ = 0.049), $r$ = 0.8 Test for overall effect 2 = 3.05 ( $r$ = 0.049), $r$ = 0.8 Test for overall effect 2 = 3.05 ( $r$ = 0.049), $r$ = 0.8 Test for overall effect 2 = 3.05 ( $r$ = 0.009) <b>1.3.4 Others</b> Behrous 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.68 [4.52, 0.14] Stubtical (95% C) -1.09 5.152 19 -0.03 1.779 19 7.18 -1.05 [1.92, 0.3] Stubtical (95% C) -2.31 4.64 f.0 7.14 4.7 .375 7.03% .3770 (1.52, 8.4] Javaid 2017 -1.09 1.552 19 -0.030 1.77 109 1.13 .105 [1.92, 0.13] Stubtical (95% C) -2.3 14.64 7.74 4.7 .275 7.03% .3770 (1.52, 8.4] Javaid 2017 -1.09 5.152 19 -0.030 1.373 19 7.1% .106 [1.99, 0.13] Stubtical (95% C) -2.3 14.64 7.74 3.66 7.98 9.977 2.22, 0.48 9.013 9.977 2.23, 0.48 9.917 2.24, 0.40 1.91 9.917 2.24, 0.40 1.91 9.917 2.24, 0.40 1.91 9.917 2.24, 0.40 1.91 9.										
Jackson 1999 -0.68 2.937 27 0.52 37.45 27 5.2% -1.10 [2.90, 70] Los 1996 -0.68 6.65.22 12 -1.87 4.333 12 1.8% 10.10 [2.34, 2.54] Rajkumar 2015 -3.4 1.351 15 -2.26 18.99 15 6.2% -1.14 [2.52, 0.4] Pietorgonety, Tarl= 0.36, Ch= 9.85, df= 4 (P=0.04), P=60% Test for overall effect Z= 0.16 (P=0.87) <b>1.2. Prediabets and T2DM</b> Asem 2016 -3.2 5.4 27 -0.3 3.4 27 4.1% -2.90 [5.31, 0.49] Dehphan 2014-b -4.8 3.869 24 0.2 3.8 25 4.5% -500 [7.15, 1.39] Gargan 2013 -4.74 3.869 24 0.28 4.386 25 4.2% -500 [7.15, 1.39] Gargan 2013 -4.74 3.869 24 0.28 4.386 25 4.2% -500 [7.15, 2.86] Dehphan 2014-b -4.8 3.869 24 0.28 4.386 25 4.2% -500 [7.15, 2.86] Dehphan 2016 -2.76 4.451 27 0.25 9.565 21 2.72, 2% 0.25 [6.07, 1.17] Guess 2015 -509691 2.55635 20 -2.11055 2.684653 18 5.5% -2.99 [4.66, 1.32] Guess 2015 -509691 5.07538 4 -18.521 1.77256 3.4 1.56 7.948 15 0.9% 3.177, 2.09, 8.43] Roshanavan 2017(1) -0.36 1.77 15 -0.4 1.537 15 6.6% 0.048 [1.85, 0.47] Subtoal (9% C) -2.5 1.7907 23 44 0.44 1.50127 15 6.6% 0.048 [1.85, 0.47] Subtoal (9% C) -2.5 1.7907 23 44 0.44 1.50127 15 6.6% 0.048 [1.85, 0.47] Subtoal (9% C) -2.5 1.7907 23 44 0.8 1.5052 23 0.8% -1.00 [8.16, 6.16] de Luis 2013 0.7 9.443 16 1.3 8.433 16 1.0% 0.031 [4.52, 5.61] Dewulf 2013 -2.5 15 -1 -3 13 15 0.2% -0.000 [4.85, 6.16] Dewulf 2013 0.7 9.443 16 1.3 8.433 16 1.0% 0.031 [4.52, 2.61] <b>1.3. Overweight and doesily</b> Cardroa 2017 -1.8 8.561 21 0.08 15.052 23 0.8% -1.00 [8.16, 6.16] de Luis 2013 0.7 9.443 16 1.3 8.433 16 1.0% 0.031 [4.52, 5.62] Dewulf 2013 -2.5 15 -1 -3 15 1.5 15 5 1.5 15 5 5.5 0.097 [2.62, 0.63] <b>1.4. Others</b> Test for overall effect Z= 1.33 (P = 0.05) <b>1.3. Others</b> 1.40, df= 4 (P = 0.84), P=0.8 Test for overall effect Z= 1.33 (P = 0.05) <b>1.3. Others</b> 4.3 (F = 0.86), P=0.8 Test for overall effect Z= 2.30 (P = 0.0005) <b>1.3. Other</b> 4.40, df= 4 (P = 0.84), P=0.8 Test for overall effect Z= 2.30 (P = 0.0005) <b>1.3. Other</b> 4.40, df= 4 (P = 0.84), P=0.8 Test for overall effect Z= 2.30 (P = 0.0005) <b>1.3. Other</b> 4.40, df= 4 (P = 0.84), P=0.48		0.6	3.3	9	0.2	2,727	8	3.4%	0.40 (-2.47, 3.27)	
Luc 1996 $-0.066 - 6522 12 -1.87 + 4.333 12 19\% + 101 [3.42,5.44]$ Rajkumar 2015 $-3.4 + 1951 15 -2.26 + 1899 - 10.7 + 1.44 + 25.0.24]$ Russo 2010 $0.78 - 0.805 + 15 - 0.11 - 0.926 + 15 - 7.7\% + 0.89 [0.27, 1.51]$ Russo 2010 $0.78 - 0.895 + 0.17 + 9.8, df = 4 (P = 0.04), P = 60\%$ Test for overall effect Z = 0.16 (P = 0.87) <b>1.3.2 Prediabetes and T2DM</b> Asemi 2016 $-3.2 - 5.4 - 27 - 0.3 - 3.4 + 27 - 4.1\% - 2.90 [-5.31, -0.49]$ Dehghan 2016 $-2.78 - 4.955 + 27 - 0.23 - 5.4 + 25 - 5.5 + 5.5 - 5.00 [-7.15, 2.85]$ Dehghan 2016 $-2.78 - 4.955 + 27 - 0.23 - 5.4 + 25 - 5.5 + 5.5 + 2.50 [-7.15, 2.85]$ Dehghan 2016 $-2.78 - 4.955 + 27 - 0.23 - 2.048 - 1.365 + 2.25 + 2.5\% - 5.00 [-7.15, 2.85]$ Dehghan 2016 $-2.78 - 4.955 + 27 - 0.23 - 0.04 + 1.56 + 23 - 7.2\% - 0.25 [-3.3, 2.71]$ Gives 2015 $-5.00091 - 2.5565 + 20 - 2.1155 + 2.684633 + 18 - 555 - 2.99 [-4.66, 1.32]$ Guess 2016 $-2.6999 + 1.507538 - 34 - 1.8521 2 - 1.73228 + 34 - 7.4\% - 0.72 [+3.0, 0.66]$ Pedersen 2016 $1.51 - 8.166 + 14 - 1.66 - 7.948 + 15 - 10.9\% - 3.17 [-3.09 [+3.8], 0.47]$ Roshararwan 2017(2) $-0.25 + 1.7790728 + 14 - 0.44 + 1.3512127 + 15 - 6.8\% - 0.89 [+3.5, 0.47]$ Roshararwan 2017(2) $-0.25 + 1.7790728 + 14 - 0.44 + 1.3512127 + 15 - 6.8\% - 0.89 [+3.5, 0.47]$ Heterogenehy, Tau" = 2.00, (-0.16 + 1.40, df = 4 (P = 0.84); P = 0\% Test for overall effect Z = 3.0 (P = 0.002) <b>1.3.0 Overweight and obesity</b> Cardions 2017 $-3.84 - 5.592 - 29 - 1.05 + 1.2247 - 30 - 1.6\% - 4.69 [+9.52, 0.14] Bomoto 2018 -0.33333 - 5.052964 + 45 - 1.8525615 - 6 - 5.5\% - 0.07 [-15.2, 0.49]1.1.1 -1.54 [-3.11, 0.03]Heterogenehy, Tau" = 0.00, Ch" = 1.44, df = 4 (P = 0.84); P = 0\%$ Test for overall effect Z = 2.30 (P = 0.005) <b>1.3.4 Others</b> Test for overall effect Z = 2.44, df = 4 (P = 0.84); P = 0\% Test for overall effect Z = 2.44, df = 4 (P = 0.84); P = 0\% Test for overall effect Z = 2.5 (P = 0.005) <b>1.3.4 0005</b> $-1.22 [-190, 0.54]$ <b>1.4 (-193, 0.34]</b> <b>4 (-10, -5 - 0.5 + 5.5 - 5.5 - 5.5 - 5.5 - 5.5 - 5.5 - 5.14 - 1.06 [+9.9, -1.3] Subtotal </b>										
Rajkumar 2015 $3.4$ 1951       15 $2.26$ 1899       15 $6.2\%$ $1.14[2.20.4]$ Russo 2010       0.78       0.080       10       0.926       17 $24.3\%$ $0.08[0.27, 1.51]$ Subtrail (95% C)       78 $0.00[1, 1.29, 1.10]$ $77$ $24.3\%$ $0.10[-1.29, 1.10]$ Haterogeneity Tau" = 0.95; $CH^{2} = 9.95$ , $df = 4$ $P = 0.04$ , $P = 60\%$ $77$ $24.3\%$ $0.10[-1.29, 1.10]$ Asemi 2016 $-3.2$ $5.4$ $27$ $0.3$ $2.5$ $4.5\%$ $5.00[+7.5, 2.86]$ Dehphan 2014-b $-4.8$ $3.869$ $24$ $0.23$ $3.42$ $27$ $4.1\%$ $2.20[+5.31, -0.49]$ Garant 2016 $-2.78$ $4.951$ $270.25$ $5.5\%$ $2.29[+6.6, 1.32]$ Garant 2017 $0.255693$ $2021.1055$ $2.684653$ $18$ $5.5\%$ $2.29[+6.6, 1.32]$ Guess 2016 $-2.56999$ $1.507.33$ $44$ $1.322$ $177.30.9, 9.43$ $78.3717.30.9, 9.43$ Rosharawan 2017(1) $0.36$ $1.77$ $15$ $0.44$ $1.512.237$ $0.06[8.5, 6.7]$ $0.02$										<u> </u>
Process 2010       0.78       0.805 15       -0.11       0.926       15       7.7%       0.89 [0.27, 151]         Heterogeneth: Tau" = 0.95; Ch <sup>2</sup> = 9.8; diff = 4 (P = 0.04); P = 60%       77       24.3%       -0.10 [-1.29, 1.10]         Asemi 2016       -3.2       5.4       27       -0.3       3.4       27       41%       -2.90 [5.31, -0.49]         Dehgha 2016       -3.2       5.4       27       -0.3       3.4       27       41%       -2.90 [5.31, -0.49]         Gargari 2016       -3.2       5.4       27       0.25       5.55       22       1.8%       -3.01 [7.5, -2.85]         Openson 2016       -0.27       0.26       9.55       22       1.8%       -0.01 [-1.29, 1.30]         Gargari 2018       0.21       1.607       23       -0.04       1.56       23       7.2%       0.25 (0.47.3, -271)         Guess 2016       -1.5075.83       34       -1.86 7.7948       15       1.0%       0.721 [+3.08]										
Subtotal (95% C) 78 77 24.3% -0.10 [-1.29, 1.10] Heterogenety Tau" 20 5(: 0) <sup>10</sup> 9 95, df = 4 ( $P = 0.04$ ); $P = 60\%$ Test for overall effect Z = 0.16 ( $P = 0.87$ ) <b>1.3.2</b> Prediabetes and T2DM Asemi 2016 -2.78 4.961 27 0.25 9.565 22 1.8% -0.00 [-7.3, 2.71] Obsphan 2014 - 4.8 3.869 24 0.2 3.8 25 4.5% -5.00 [-7.15, 2.56] Desphan 2016 -2.78 4.961 25 0.25 9.565 22 1.8% -0.30 [-7.45, 1.30] Ouess 2016 -2.26999 1.507538 34 -1.8521 21.73728 34 7.4% -0.72 [+4.9, 0.66] Luo 2000 0.57 13.03 1.0 2.3 10.9 10 4.4% -7.3 [+2.26, 8.80] Pedersen 2016 1.51 9.166 14 -1.66 7.948 15 1.0% 3.17 [-3.09, 4.30] Pedersen 2017 1.51 9.166 14 -1.65 7.948 15 1.0% 3.17 [-3.09, 4.3] Rosharawan 2017(2) -0.25 1.7790728 14 0.44 1.351227 15 6.8% 0.408 [+3.52, 0.47] Subtotal (95% C) 2.25 1.50 0.00001; P = 78% Test for overall effect Z = 3.06 (P = 0.002) <b>1.3.3 Overweight and obesity</b> Cantora 2017 -1.8 6.561 21 -0.8 15.052 23 0.8% -1.00 [-8.16, 6.16] de Luis 2013 0.7 9.433 16 1.3 8.433 16 1.0% -0.80 [-8.25, 5.27] Dewntof 2015 0.66 5.672 10 0.35 5.346 1 1.6% -0.80 [-8.25, 5.27] Dewntof 2015 0.66 5.672 10 0.35 5.346 1 1.6% -0.80 [-8.25, 5.27] Dewntof 2015 0.66 5.672 10 0.35 5.346 1 1.6% -0.80 [-8.25, 5.27] Dewntof 2016 0.65 5.72 10 0.35 5.346 1 1.6% -0.80 [-8.25, 5.27] Dewntof 2017 -1.8 0.65 121 -0.8 15.052 23 0.8% -1.00 [-8.16, 6.16] de Luis 2013 0.7 9.433 16 1.3 8.433 16 1.0% -0.80 [-8.25, 5.27] Dewntof 2016 0.65 5.72 10 0.35 5.346 1 1.6% -0.80 [-8.25, 5.27] Dewntof 2016 0.65 5.72 10 0.33 5.35 (-7.45 4.4% -2.42 [-4.64, -0.19] Dettoragenety. Tau" = 0.00; Ch" = 1.40, df = 4.(P = 0.84); P = 0.% Test for overall effect Z = 1.93 (P = 0.050) <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 1.2247 30 1.6% -4.89 [-9.52, 0.14] Dettoragenety. Tau" = 0.00; Ch" = 1.44, df = 4.(P = 0.66); P = 0.% Test for overall effect Z = 1.93 (P = 0.050) <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 1.2247 30 1.6% -4.69 [-9.52, 0.44] Dettoragenety. Tau" = 0.00; Ch" = 2.44, df = 4.(P = 0.66); P = 0.% Test for overall effect Z = 2.79 (P = 0.050	,									-
Heterogenety: Tau" = 0.65; Ch <sup>2</sup> = 0.65; Ch <sup>2</sup> = 0.60; Test for overall effect Z = 0.16 ( $P = 0.87$ ) <b>1.3.2 Prediables and T2DM</b> Asemi 2016 -3.2 5.4 27 -0.3 3.4 27 4.1% -2.90 [5.31, -0.49] Dehghan 2014-b -4.8 3.869 24 0.2 3.8 25 4.5% -5.00 [7.15, 2.85] Dehghan 2016 -2.78 4.4561 27 0.28 9.585 22 1.8% -5.00 [7.15, 2.85] Gargan 2013 -4.74 3.869 24 0.28 4.386 25 4.2% -5.02 [7.33, 2.71] Ghavami 2016 -2.50991 5.07538 34 -1.8521 1.73728 4 Gaves 2015 -5.09991 5.07538 34 -1.8521 1.73728 4 Guess 2015 -5.09991 5.07538 34 -1.8521 1.73728 4 Guess 2016 -2.50991 5.07538 34 -1.4521 1.73728 4 Guess 2016 -2.50991 5.07538 34 -1.4521 1.73728 4 Guess 2016 -2.50991 5.07538 34 -1.4521 1.73728 4 Guess 2016 -2.50991 5.07538 14 0.044 1.36121 2.727 29 49.4% -1.7512.88.00] Heterogenety: Tau" = 2.18; Chr# = 4.812, dir = 1.0 (P < 0.00001); P = 78% Test for overall effect Z = 3.06 (P = 0.002) <b>1.3.3 Overweight and obesity</b> Gardona 2017 -1.8 8.661 21 -0.8 15.052 23 0.8% -1.00 [e316, 6116] de Luis 2013 0.7 9.493 16 1.3 8.433 16 1.0% -0.60 [e32, 562] Dewuit 2013 -2 5 15 -1 3 31 15 3.2% -1.00 [s31, 593, 196] Trapkore 2015 -0.66 5.672 10 0.35 5.346 10 1.6% -0.69 [+35, 0.41] Wiler(2013 -1.43, 0.65 5.672 10 0.35 5.346 10 1.6% -0.47 [+2.62, 0.69] Heterogenety: Tau" = 0.00; Chr = 1.40, dir = 4 (P = 0.86); P = 0.8; Test for overall effect Z = 1.93 (P = 0.05) <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 1.2.247 30 1.8% -4.69 [+9.52, 0.14] Behrouz 2017 -3.64 5.592 29 1.05 1.2.247 30 1.8% -4.69 [+9.52, 0.14] Demid 2016 5.5333 5.61264 8 1.5 1.525615 6 5.58, -0.97 [+2.2, 0.69] Daubiol 2005 -2.3 14.61 7 1.4 7.7375 7 0.3% -3.70 [+5.2, 8.42] Javad 2017 -1.09 1.552 9 35 2.22 17.269 37 0.7% 0.31 [+7.7, 8.39] 99 15.2% -1.14 [-1.93, 0.34] Heterogenety: Tau" = 1.47; Chr <sup>2</sup> = 4.59 (+ 0					••••					◆
Testfor overall effect $Z = 0.16$ ( $P = 0.87$ ) 1.3.2 Prediabetes and T2DM Asem 2016 $-3.2$ 5.4 27 $-0.3$ 3.4 27 41% $-2.90$ [ $5.31, -0.49$ ] Dehghan 2014-b $-4.8$ 3.869 24 0.2 3.8 25 4.5% $-500$ ( $7.15, -2.65$ ] Dehghan 2016 $-2.78$ 4.961 27 0.25 9.565 22 1.8% $-500$ ( $7.15, -2.65$ ] Gargari 2013 $-4.74$ 3.869 24 0.28 4.366 25 4.2% $-602$ ( $7.13, -2.71$ ] Gharani 2016 $-2.509891$ 2.555635 20 $-2.11055$ 2.684853 18 5.5% $-2.99$ ( $4.66, -1.32$ ] Quess 2015 $-5.09691$ 2.555635 20 $-2.11055$ 2.684853 18 5.5% $-2.99$ ( $4.66, -1.32$ ] Quess 2016 $-2.509891$ 2.555635 20 $-2.11055$ 2.684853 18 5.5% $-2.99$ ( $4.66, -1.32$ ] Quess 2016 $-2.509891$ 2.5738 34 $-1.85212$ 1.73728 34 $7.4\%$ $-0.72$ ( $1.48, 0.06$ ] Pedersen 2016 1.51 9.166 14 $-1.66$ 7.948 15 1.0% $3.17$ ( $3.20, 9.43$ ] Rosharravan 2017(1) $-0.36$ 1.77 15 $-0.4$ 1.537 15 6.6% $-0.04$ ( $1.15, 1.23$ ] Rosharravan 2017(2) $-0.25$ 1.7790728 14 $0.44$ 1.3612127 15 6.6% $-0.04$ ( $1.15, 1.23$ ] Rosharravan 2017(2) $-0.25$ 1.7790728 14 $0.44$ 1.3612127 15 6.6% $-0.04$ ( $1.15, 1.23$ ] Rosharravan 2017(2) $-0.25$ 1.7790728 14 $0.44$ 1.3612127 15 6.6% $-0.04$ ( $1.15, 1.23$ ] Rosharravan 2017(2) $-0.25$ 1.7790728 14 $0.44$ 1.3612127 15 6.6% $-0.04$ ( $1.52, 1.6, 0.68$ ] Lastfor overall effect $Z = 3.06$ ( $P = 0.002$ ) <b>1.3.3 Overweight and obesity</b> Cantors 2017 $-1.8$ 8.561 21 $-0.8$ 15.052 23 $0.8\%$ $-1.00$ ( $8.16, 6.16$ ] de Luis 2013 $0.7$ 9.443 16 1.3 8.433 16 1.0% $-0.016$ ( $8.25, 562$ ] Dewut 2013 $-2$ 5 15 $-1$ 3 15 $3.2\%$ $-1.006$ ( $8.25, 562$ ] Dewut 2013 $-1.53333$ 5.6029694 45 $0.8083333$ 5.6875107 45 $4.4\%$ $-2.42$ ( $4.64, -0.19$ ] Subtotal ( $95\%$ C) 107 Heterogeneity. Tau' = 0.00; Ch <sup>2</sup> = 2.44, df = 4 ( $P = 0.86$ ); $P = 0\%$ Testfor overall effect $Z = 1.93$ ( $P = 0.05$ ) <b>1.3.4 Othes</b> Behrouz 2017 $-3.64$ $5.592$ 29 $1.05$ $1.2247$ 30 $1.6\%$ $-4.69$ ( $9.62, 0.14$ ] Doubtotal ( $95\%$ C) $98$ 99 $1.5\%$ $-3.77\%$ $0.34\%$ $-3.04$ ( $1.52$ ( $2.19, 0.54$ )] Heterogeneity. Tau' = 1.00; Ch <sup>2</sup> = 2.44, df = 4 ( $P = 0.86$ ); $P = 0\%$ Testfor overall effect $Z = 1.93$	. ,	5: Chi <sup>2</sup> = 9.9	35. df = 4 (P =	0.04)	I <sup>2</sup> = 60%					
A serior 2016 - 3.2 5.4 27 -0.3 3.4 27 4.1% -2005 531.0.49] Dehghan 2016 - 3.2 5.4 27 0.25 9.595 22 19% -3.021,745, 1.39] Gargani 2013 - 4.74 3.869 24 0.2 3.4 2.36 $\frac{5}{25}$ 4.2% -5.02[7.3, 2.71] Guess 2015 -5.09691 2.55653 20 -2.11055 2.84463 18 5.5% -2.99[4.66, 1.32] Guess 2015 -5.09691 2.55653 20 -2.11055 2.84463 18 5.5% -2.99[4.66, 1.32] Guess 2015 -5.09691 3.50753 34 -1.8521 2.173728 83 47 7.4% -0.72[1:48, 0.06] Luo 2000 0.57 13.031 10 2.3 10.9 10 0.4% -1.73[1:20, 8.80] Pedersen 2016 1.51 9.166 14 -1.66 7.944 15 10.3% 317[3.09, 8,4] Roshanrava 2017(1) -0.36 1.77 15 -0.4 1.537 15 6.6% 0.04[1.15, 1.23] Roshanrava 2017(1) -0.36 1.77 15 -0.4 1.537 15 6.6% 0.04[1.15, 1.23] Roshanrava 2017(2) -0.25 1.77072 81 44 0.44 1.3812127 15 6.6% 0.04[1.15, 1.23] Roshanrava 2017(2) -0.25 1.77072 81 44 0.44 1.3812127 15 6.6% 0.04[1.15, 0.47] Heterogeneity Tar# 2.14; ChiP = 46.12, df =10 (P < 0.0001); P = 78% Test for overall effect Z = 3.06 (P = 0.002) <b>1.3.0 Verweight and obesity</b> Cardrora 2017 - 1.8 8.561 21 -0.8 15.052 23 0.8% -1.00[8.8, 6.16] de Luis 2013 0.7 9.493 16 1.3 8.433 16 10.16% 0.31[4.52, 5.14] View 2013 -1.533333 5.0523694 45 0.803333 5.6875107 45 4.4%, -2.42[4.64, 0.18] Dewulf 2013 -2 5 15 -1 3 3 15 2.2% -1.00[8.85, 6.50] Dewulf 2015 -1.686 5.672 10 0.35 5.346 110 1.6% 0.31[4.52, 5.14] View 2013 -1.533333 5.0523694 45 0.803333 5.6875107 45 4.4%, -2.42[4.64, 0.18] Dewulf 2013 -1.533333 5.0523694 45 0.803333 5.6875107 45 4.4%, -2.42[4.64, 0.18] Datiotal (65% Cl) 107 109 11.1%, 1.54[1.31, 0.03] Heterogeneity: Tar# = 0.00; ChiP = 1.40, df = 4 (P = 0.66); P = 0% Test for overall effect Z = 1.93 (P = 0.05) <b>1.3.4 Others</b> Behnouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6%, -4.69[9.52, 0.14] Behnouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6%, -4.69[9.52, 0.14] Heterogeneity: Tar# = 0.00; ChiP = 2.44, df = 4 (P = 0.66); P = 0% Test for overall effect Z = 1.93 (P = 0.25), P = 0.4%, F = 0% Test for overall effect Z = 3.05 (P = 0.0005) Total (65% Cl) 98 91 5.2%, -1.14[1.193, 0.34] Heterogeneit		•								
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Dehphan 2016 - 2.78 4 951 27 0.25 9.565 22 1 8% -3017 45, 1.39 Gargan 2013 - 4.74 3 369 24 0.28 4.36 25 4.3% -5017 3.271 Ghavam 2018 0.21 1.607 23 -0.04 1.56 23 7.2% 0.25(0.67, 1.17) Guess 2015 - 5.0899 1.50738 34 -1.56212 1.73728 34 7.4% -0.72(1.49, 0.06) Luo 2000 0.57 13.031 10 2.3 10.9 10 0.4% -1.73[12.26, 8.60] Pedersen 2015 1.51 9.166 14 -1.66 7.948 15 10.% 3.17[3.09, 9.43] Roshamavan 2017(1) -0.36 1.77 15 -0.4 1.537 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.7790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.7790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.7790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 0017(2) -0.25 1.790728 14 0.44 1.361212 7 15 6.6% -0.68[1.65, 0.47] Subhara 000 Ch <sup>2</sup> = 0.002) 1.3.3 Overweight and obesity Cantors 2017 -1.8 8.561 21 -0.8 15.052 23 0.8% -1.00[8.16, 6.16] de Luis 2013 0.7 9.493 16 1.3 8.433 161 10% -0.68[6.62, 5.62] Dewulf 2013 -2 5 15 -1 3 31 5 3.2% -1.00[3.85, 1.96] Meterogeneity: Tau <sup>2</sup> = 0.00, Ch <sup>2</sup> = 1.40, df = 4 (P = 0.84); P = 0% Test for overall effect Z = 1.93 (P = 0.05) 1.3.4 Others Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.68[9.52, 0.14] Bomhod 2018 0.533333 1.616924 8 1.5 1.526615 6 5.5% -0.97[2.62, 0.69] Daubioul 2005 -2.3 1.461 7 1.4 7.375 7 0.3% -3.70[1.68, 2.82] Jarval 2017 -1.08 1.552 19 -0.03 1.379 19 7.1% -1.06[1.69, 0.03] Scheid 2014 2.33 17.552 35 2.22 17.269 37 0.7% 0.31[7.74, 8.30] Daubioul 2005 -2.3 1.661; P = 0.% Test for overall effect Z = 7.9 (P = 0.005); P = 0% Test for overall effect Z = 7.9 (P = 0.005); P = 0% Test for overall effect Z = 3.50 (P = 0.0005); P = 0% Test for overall effect Z = 3.50 (P = 0.0005); P = 0.4%;	Asemi 2016		5.4	27				4.1%	-2.90 [-5.31, -0.49]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Dehghan 2014-b		3.869					4.5%	-5.00 [-7.15, -2.85]	(
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $										
Guess 2015       -5.09691       2.556635       20       -2.11055       2.284463       18       5.5%       -2.99 (4.66, -1.32)         Guess 2016       -2.66999       1.507538       34       -1.65212       1.737258       34       7.4%       -0.72 [1.49, 0.06]         Luo 2000       0.57       13.031       10       23       10.9       10       0.4%       -1.72 [1.49, 0.06]         Pedersen 2016       1.51       9.166       1.4       -1.66       7.948       15       1.0%       3.17 [-2.09, 9.43]         Roshanravan 2017(2)       -0.25       1.7790728       14       0.44       1.3612127       15       6.6%       -0.69 [+185, 0.47]         Subtotal (95% CI)       232       49.4%       -1.75 [-2.87, -0.63]       +       -	-									
Guess 2016 $-2.66999$ $1.507538$ $34$ $-1.85212$ $1.737258$ $34$ $7.4\%$ $-0.72[+1.40, 0.06]$ Luo 2000 $0.57$ $13.031$ $10$ $2.3$ $10.9$ $10$ $0.4\%$ $-1.73[+12.26, 8.80]$ Pedersen 2016 $1.51$ $9.166$ $14$ $1.66$ $7.948$ $1.73[+12.26, 8.80]$ Roshanravan 2017(1) $-0.36$ $1.77$ $15$ $-0.4$ $1.537$ $15$ $6.6\%$ $0.69[+185, 0.47]$ Roshanravan 2017(2) $-0.25$ $1.79728$ $14$ $0.44$ $1.3612127$ $15$ $6.6\%$ $0.69[+185, 0.47]$ Hetorogeneity. Tau" = 2.18; Chi <sup>2</sup> = 4612, df = 10 (P < 0.00001); P = 78%										+
Luc 2000 0.57 13.031 10 2.3 10.9 10 0.4% -17.3 $[12.26, 8.0]$ Pedersen 2016 1.51 9.166 14 -1.66 7.948 15 1.0% 3.17 [3.09, 9.43] Roshanravan 2017(1) -0.36 1.77 15 -0.4 1.537 15 6.6% 0.04 [+1.15, 1.23] Roshanravan 2017(2) -0.25 1.7.790728 14 0.44 1.3612127 15 6.6% -0.68 [+1.85, 0.47] Subtotal (95% C1) 232 22 29 49.4% -1.75 [-2.87, -0.63] Heterogeneity. Tau" = 2.18; Ch" = 46.12, df = 10 (P < 0.00001); P = 78% Test for overall effect Z = 3.06 (P = 0.002) <b>1.3.0 Over weight and obesity</b> Carfora 2017 -1.8 8.561 21 -0.8 15.052 23 0.8% -1.00 [-8.16, 6.16] de Luis 2013 0.7 9.493 16 1.3 8.433 16 1.0% -0.60 [-8.82, 5.62] Dewulf 2013 -2 5 15 -1 3 15 3.2% -1.00 [-8.15, 6.16] de Luis 2013 -1.53333 5.0529694 45 0.883333 5.687510 45 4.4% -2.42 [-4.64, 0.19] Subtotal (95% C1) -107 107 11.1% -1.54 [-3.11, 0.03] Heterogeneity. Tau" = 0.00; Ch" = 1.40, df = 4 (P = 0.84); P = 0% Test for overall effect Z = 1.93 (P = 0.05) <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bomhof 2018 0.533333 1.616924 8 1.5 1.525615 6 55% -0.97 [-1.52, 0.68] <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bomhof 2018 0.533333 1.616924 8 1.5 1.525615 6 55% -0.97 [-1.52, 0.68] <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bomhof 2018 0.533333 1.616924 8 1.5 1.525615 6 55% -0.97 [-1.52, 0.68] <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bomhof 2018 0.533333 1.616924 8 1.5 1.525615 6 55% -0.97 [-1.52, 0.68] <b>1.3.4 Others</b> Behrouz 2017 -1.09 1.552 19 -0.03 1.379 19 7.1% -1.06 [-1.99, -0.13] Subtotal (95% C1) 98 99 15.2% -1.14 [-1.93, -0.34] Heterogeneity. Tau" = 0.00; Ch" = 2.44, df = 4 (P = 0.66); P = 0% Test for overall effect Z = 2.79 (P = 0.005) Total (95% C1) 515 514 100.0% -1.22 [-1.90, -0.54] Heterogeneity. Tau" = 1.47; Ch" = 79.46, df = 25 (P < 0.00001); P = 69% Test for overall effect Z = 3.50 (P = 0.0000) Test for suboroud differences: Ch" = 4.31, df = 3 (P = 0.23), P							18		-2.99 [-4.66, -1.32]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Guess 2016	-2.56999							-0.72 [-1.49, 0.06]	
Roshanravan 2017(1) $-0.36$ $1.77$ $15$ $-0.4$ $1.537$ $15$ $6.6\%$ $0.04[1.15, 1.23]$ Roshanravan 2017(2) $-0.25$ $1.7790728$ $14$ $0.44$ $1.361227$ $15$ $6.6\%$ $0.08[1.85, 0.47]$ Subtotal (95% CI) $232$ $229$ $94.\%$ $-1.75[-2.87, -0.63]$ Heterogeneity. Tau" = 2.18; Chi" = 46.12, df = 10 (P < 0.00001); P = 78% $229$ $94.\%$ $-1.75[-2.87, -0.63]$ Canfora 2017 $-1.8$ $8.561$ $21$ $-0.8$ $15.052$ $23$ $0.8\%$ $-1.00[-8.16, 6.16]$ de Luis 2013 $0.7$ $9.493$ $16$ $1.3$ $8.433$ $16$ $1.0\%$ $-0.60[-6.82, 5.62]$ Dewnld 2013 $-1.533333$ $50529644$ $50833333$ $56875107$ $45$ $4.4\%$ $-2.42[-4.64, -0.19]$ Subtotal (95% CI) $0.00$ ; Chi" = 1.40, df = 4 (P = 0.84); I" = 0\% $11.1\%$ $-1.54[-3.11, 0.03]$ $-1.533333$ $1.618924$ $8$ $1.5$ $1.52615$ $6$ $5.5\%$ $-0.97[-2.62, 0.69]$ Daviduid (95% CI) $-3.64$ $5.592$ $29$ $1.52$	Luo 2000	0.57	13.031	10			10	0.4%	-1.73 [-12.26, 8.80]	
Roshanravan 2017(2) $-0.25$ $1.7790728$ $14$ $0.44$ $1.3612127$ $15$ $6.6\%$ $-0.69[1.85, 0.47]$ Subtotal (95% CI) $232$ $229$ $49.4\%$ $-1.75[2.87, -0.63]$ Heterogeneity: Tau" = 218; Chi" = 46.12, df = 10 (P < 0.00001); P = 78% $229$ $49.4\%$ $-1.75[2.87, -0.63]$ 1.33 Overweight and obesity       Canfora 2017 $-1.8$ $8.561$ $21$ $-0.8$ $15.052$ $23$ $0.8\%$ $-1.00[8.16, 6.16]$ Dewuif 2013 $-2$ $5$ $1$ $3$ $8.433$ $16$ $1.0\%$ $0.60[6.82, 5.62]$ Dewuif 2013 $-2$ $5$ $1$ $3$ $8.433$ $16$ $10.\%$ $-325(5.2)$ Dewuif 2013 $-1.533333$ $50.529694$ $107$ $109$ $11.1\%$ $-1.54[3.311, 0.03]$ Heterogeneity: Tau" = 0.00; Chi" = 1.40, df = 4 (P = 0.84); P = 0\%       Test for overall effect: Z = 1.93 (P = 0.05) $1.2247$ $30$ $1.6\%$ $-4.69[.9.52, 0.14]$ Bomhof 2018 $0.533333$ $1.61924$ $8$ $1.5$ $1.525615$ $6$ $5.5\%$ $0.97[2.82, 0.69]$ Daviou	Pedersen 2016								3.17 [-3.09, 9.43]	
Subtotal (95% (1)       232       229       49.4% $-1.75 [-2.87, -0.63]$ Hetrogeneihy: Tau" = 2.18; Chi" = 46.12; df = 10 (P < 0.00001); P = 78%	Roshanravan 2017(1)	-0.36	1.77	15	-0.4	1.537	15	6.6%	0.04 [-1.15, 1.23]	+
Heterogeneily: Tau <sup>2</sup> = 2.18; Chi <sup>2</sup> = 4.61.2; df = 10 (P < 0.0001); P = 78% Test for overall effect Z = 3.06 (P = 0.002) <b>1.3.3 Overweight and obesity</b> Canfora 2017 - 1.8 8.561 21 -0.8 15.052 23 0.8% -1.00 [-8.16, 6.16] de Luis 2013 0.7 9.493 16 1.3 8.433 16 1.0% -0.60 [-6.82, 5.62] Dewulf 2013 -2 5 15 -1 3 15 3.2% -1.00 [-3.95, 1.95] Tripkovic 2015 0.66 5.672 10 0.35 5.346 10 1.6% 0.31 [+5.2, 5.14] Vulewic 2013 -1.53333 5.0529694 45 0.883333 5.6875107 45 4.4% -2.42 [+4.4, -0.19] Subtotal (95% CI) 107 109 11.1% -1.54 [-3.11, 0.03] Heterogeneily: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.40, df = 4 (P = 0.84); P = 0% Test for overall effect Z = 1.93 (P = 0.05) <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bombof 2018 0.53333 1.816924 8 1.5 1.525615 6 5.5% -0.07 [-2.62, 0.69] Daubioul 2005 -2.3 14.61 7 1.4 7.375 7 0.3% -3.70 [-1.582, 8.42] Javadi 2017 -1.09 1.552 19 -0.03 1.379 19 7.1% -1.06 [-1.99, -0.13] Subtotal (95% CI) 98 99 15.2% -1.14 [-1.93, -0.34] Heterogeneily: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); P = 0% Test for overall effect Z = 2.79 (P = 0.005) Total (95% CI) 515 514 100.0% -1.22 [-1.90, -0.54] Heterogeneily: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); P = 69% Test for overall effect Z = 2.50 (P = 0.0005) Total (95% CI) 515 514 100.0% -1.22 [-1.90, -0.54] Heterogeneily: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 2 (P = 0.23), P = 30.4% Favours [ITF] Favours [control]		-0.25	1.7790728		0.44	1.3612127				
Test for overall effect: $Z = 3.06 (P = 0.002)$ <b>1.3.3 Overweight and obesity</b> Canfora 2017 - 1.8 8.561 21 -0.8 15.052 23 0.8% -1.00 [-8.16, 6.16] de Luis 2013 0.7 9.493 16 1.3 8.433 16 1.0% -0.60 [-6.82, 5.62] Dewuif 2013 -2 5 15 -1 3 15 3.2% -1.00 [-3.95, 1.95] Tripkovic 2015 0.66 5.672 10 0.35 5.346 10 1.6% 0.31 [-4.52, 5.14] Vulevic 2013 -1.53333 5.0529694 45 0.883333 5.6875107 45 4.4% -2.42 [-4.64, -0.19] Subtotal (95% CI) 107 109 11.1% -1.54 [-3.11, 0.03] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.40, df = 4 (P = 0.84); P = 0% Test for overall effect: $Z = 1.93 (P = 0.05)$ <b>1.3.4 Others</b> Behrouz 2017 -3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bomhof 2018 0.53333 1.616924 8 1.5 1.526615 6 5.5% -0.97 [-2.62, 0.69] Daubioul 2005 -2.3 14.61 7 1.4 7.375 7 0.3% -3.70 [-15.82, 8.42] Javadi 2017 -1.09 1.552 19 -0.03 1.379 19 7.1% -1.06 [-1.99, -0.13] Scheid 2014 2.53 17.562 35 2.22 17.269 37 0.7% 0.31 [-7.74, 8.36] Pheterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); P = 0% Test for overall effect: $Z = 2.79 (P = 0.005)$ Total (95% CI) 515 514 100.0% -1.22 [-1.90, -0.54] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); P = 0% Test for overall effect: $Z = 2.79 (P = 0.005)$ Total (95% CI) 515 514 100.0% -1.22 [-1.90, -0.54] Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 73.46, df = 2.5 (P < 0.0005); P = 69% Test for overall effect: $Z = 3.50 (P = 0.0005)$ Total (95% CI) 515 510 Test for subaroup differences: Chi <sup>2</sup> = 4.31, df = 3 (P = 0.23), P = 30.4% Favours [CTF] Favours [control]	Subtotal (95% Cl)			232			229	49.4%	-1.75 [-2.87, -0.63]	•
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Test for overall effect: Z =	3.06 (P = 0.		~ < 0.00	JUUT), I <sup>-</sup> = 78	70				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	-	-	8,561	21	-0.8	15.052	23	0.8%	-1.00 [-8.16, 6.16]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $										
Tripkovic 2015 $0.66$ $5.672$ $10$ $0.35$ $5.346$ $10$ $1.6\%$ $0.31$ $(4.52)$ $5.14$ Vulevic 2013 $-1.533333$ $5.0529694$ $45$ $0.8833333$ $5.6875107$ $45$ $4.4\%$ $-2.42$ $[-4.64, -0.19]$ Subtotal (95% CI) $107$ $107$ $109$ $11.1\%$ $-1.54$ $-3.11, 0.03$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.40, df = 4 (P = 0.84); P <sup>2</sup> = 0%       Test for overall effect: $Z = 1.93$ (P = 0.05) $1.34$ $0.5922$ $29$ $1.05$ $12.247$ $30$ $1.6\%$ $-4.69$ $[-9.52, 0.14]$ Bornhouz 2017 $-3.64$ $5.592$ $29$ $1.05$ $12.247$ $30$ $1.6\%$ $-4.69$ $[-9.52, 0.14]$ $-4.69$ $-9.52, 0.14$ $-4.69$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.14$ $-9.52, 0.52, 0.14$ $-9.52, 0.52, 0.14$									• • •	
Vulevic 2013 $-1.533333$ $5.0529694$ $45$ $0.8933333$ $5.6875107$ $45$ $4.4\%$ $-2.42[4.64, -0.19]$ Subtotal (95% Cl)       107       109       11.1% $-1.54[-3.11, 0.03]$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.40, df = 4 (P = 0.84); l <sup>2</sup> = 0%       Test for overall effect: Z = 1.93 (P = 0.05)       1.3.4       Others         Behrouz 2017 $-3.64$ $5.592$ $29$ $1.05$ $12.247$ $30$ $1.6\%$ $-4.69[-9.52, 0.14]$ Bomhof 2018 $0.533333$ $1.616924$ $8$ $1.5$ $1.525615$ $6$ $5.5\%$ $-0.97[-2.62, 0.69]$ Daubioul 2005 $-2.3$ $14.61$ $7$ $1.4$ $7.375$ $7$ $0.3\%$ $-3.70[-15.82, 8.42]$ Javadi 2017 $-1.09$ $1.552$ $19$ $-0.03$ $1.379$ $19$ $7.1\%$ $-1.06[-1.99, -0.13]$ Scheid 2014 $2.53$ $17.52$ $35$ $2.22$ $17.269$ $37$ $0.7\%$ $0.31[-7.74, 8.36]$ Subtotal (95% Cl)       98       99 $15.2\%$ $-1.14[-1.93, -0.34]$ $-10$ $-5$ $0$ $5$ $10$		0.66			0.35				• • •	
Subtotal (95% Cl)       107       109       11.1% $-1.54$ [ $-3.11$ , $0.03$ ]         Heterogeneity: Tau <sup>2</sup> = 0.00; Ch <sup>2</sup> = 1.40, df = 4 (P = 0.84); I <sup>2</sup> = 0%       Test for overall effect: Z = 1.93 (P = 0.05)       Image: Character Structure       Image: Charaateer Structure		-1.533333	5.0529694	45	0.8833333	5.6875107	45			
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 1.40, df = 4 (P = 0.84); I <sup>2</sup> = 0% Test for overall effect: $Z = 1.93$ (P = 0.05) <b>1.3.4 Others</b> Behrouz 2017 - 3.64 5.592 29 1.05 12.247 30 1.6% -4.69 [-9.52, 0.14] Bomhof 2018 0.533333 1.616924 8 1.5 1.525615 6 5.5% -0.97 [-2.62, 0.69] Daubioul 2005 -2.3 14.61 7 1.4 7.375 7 0.3% -3.70 [-15.82, 8.42] Javadi 2017 -1.09 1.552 19 -0.03 1.379 19 7.1% -1.06 [-1.99, -0.13] Scheid 2014 2.53 17.552 35 2.22 17.269 37 0.7% 0.31 [-7.74, 8.36] Subtotal (95% CI) 98 99 15.2% -1.14 [-1.93, -0.34] Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); I <sup>2</sup> = 0% Test for overall effect: $Z = 2.79$ (P = 0.0005) Total (95% CI) 515 514 100.0% -1.22 [-1.90, -0.54] Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); I <sup>2</sup> = 69% Test for overall effect: $Z = 3.50$ (P = 0.0005) Test for suboroub differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23), I <sup>2</sup> = 30.4% Favours [ITF] Favours [control]				107			109	11.1%		•
$\begin{array}{c c c c c c c c c c c c c c c c c c c $				0.84);	I² = 0%					
Bornhof 2018 $0.533333$ $1.616924$ 8 $1.5$ $1.525615$ 6 $5.5\%$ $-0.97$ $[2.62, 0.69]$ Daubioul 2005 $-2.3$ $14.61$ 7 $1.4$ $7.375$ 7 $0.3\%$ $-3.70$ $[-15.82, 8.42]$ Javadi 2017 $-1.09$ $1.552$ $19$ $-0.03$ $1.379$ $19$ $7.1\%$ $-1.06$ $[-1.99, -0.13]$ Scheid 2014 $2.53$ $17.52$ $35$ $2.22$ $17.269$ $37$ $0.7\%$ $0.31$ $[-7.74, 8.36]$ Subtotal (95% CI)       98       99 $15.2\%$ $-1.14$ $[-1.93, -0.34]$ $\bullet$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); l <sup>2</sup> = 0.% $514$ $100.0\%$ $-1.22$ $[-1.90, -0.54]$ $\bullet$ Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69\% $514$ $100.0\%$ $-1.22$ $[-1.90, -0.54]$ $-10$ $-5$ $0$ $5$ $10$ Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69\% $Test$ for overall effect: Z = 3.50 (P = 0.0005) $-10$ $-5$ $0$ $5$ $10$ $-10$ <										
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Behrouz 2017		5.592	29	1.05	12.247	30	1.6%	-4.69 [-9.52, 0.14]	
Javadi 2017       -1.09       1.552       19       -0.03       1.379       19       7.1%       -1.06 [-1.99, -0.13]         Scheid 2014       2.53       17.552       35       2.22       17.269       37       0.7%       0.31 [-7.74, 8.36]         Subtotal (95% CI)       98       99       15.2%       -1.14 [-1.93, -0.34]       -         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); l <sup>2</sup> = 0%       514       100.0%       -1.22 [-1.90, -0.54]         Total (95% CI)       515       514       100.0%       -1.22 [-1.90, -0.54]         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%       514       100.0%       -1.22 [-1.90, -0.54]         Test for overall effect: Z = 3.50 (P = 0.0005)       Test for suboroup differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23). l <sup>2</sup> = 30.4%       Favours [ITF] Favours [control]	Bomhof 2018		1.616924		1.5	1.525615		5.5%	-0.97 [-2.62, 0.69]	
Scheid 2014       2.53       17.552       35       2.22       17.269       37 $0.7\%$ $0.31$ [-7.74, 8.36]         Subtotal (95% CI)       98       99       15.2%       -1.14 [-1.93, -0.34]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); l <sup>2</sup> = 0%       515       514       100.0%       -1.22 [-1.90, -0.54]         Total (95% CI)       515       514       100.0%       -1.22 [-1.90, -0.54]         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%       514       100.0%       -1.22 [-1.90, -0.54]         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%       514       100.0%       -1.22 [-1.90, -0.54]         Test for overall effect: Z = 3.50 (P = 0.0005)       51       514       100.0%       -1.22 [-1.90, -0.54]         Test for suboroub differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23), l <sup>2</sup> = 30.4%       Favours [ITF]       Favours [control]	Daubioul 2005	-2.3	14.61	7	1.4	7.375	7	0.3%	-3.70 [-15.82, 8.42]	
Subtotal (95% CI)       98       99       15.2%       -1.14 [-1.93, -0.34]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); l <sup>2</sup> = 0%       7       7       7         Test for overall effect: Z = 2.79 (P = 0.005)       515       514       100.0%       -1.22 [-1.90, -0.54]         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%       514       100.0%       -1.22 [-1.90, -0.54]         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%       514       100.0%       -1.22 [-1.90, -0.54]         Test for overall effect: Z = 3.50 (P = 0.0005)       Test for suboroub differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23), l <sup>2</sup> = 30.4%       Favours [ITF]       Favours [control]	Javadi 2017								-1.06 [-1.99, -0.13]	
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 2.44, df = 4 (P = 0.66); l <sup>2</sup> = 0%         Test for overall effect: Z = 2.79 (P = 0.005)         Total (95% Cl)       515         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%         Test for overall effect: Z = 3.50 (P = 0.005)         Test for suboroub differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23). l <sup>2</sup> = 30.4%         Favours [ITF]         Favours [ITF]	Scheid 2014	2.53	17.552	35	2.22	17.269			0.31 [-7.74, 8.36]	
Test for overall effect: Z = 2.79 (P = 0.005)         Total (95% Cl)       515         Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%         Test for overall effect: Z = 3.50 (P = 0.0005)         Test for subgroup differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23). l <sup>2</sup> = 30.4%	Subtotal (95% CI)			98			99	15.2%	-1.14 [-1.93, -0.34]	•
Heterogeneity: Tau <sup>2</sup> = 1.47; Chi <sup>2</sup> = 79.46, df = 25 (P < 0.00001); l <sup>2</sup> = 69%         -10         -5         0         5         10           Test for overall effect: Z = 3.50 (P = 0.0005)         -10         -5         0         5         10           Test for subgroup differences: Chi <sup>2</sup> = 4.31. df = 3 (P = 0.23). l <sup>2</sup> = 30.4%         Favours [ITF]         Favours [control]		•		0.66);	I² = 0%					
Test for overall effect: Z = 3.50 (P = 0.0005)         -10         -5         0         5         10           Test for subgroup differences: Chi <sup>2</sup> = 4.31, df = 3 (P = 0.23), i <sup>2</sup> = 30.4%         Favours [ITF]         Favours [control]	Total (95% CI)			515			514	100.0%	-1.22 [-1.90, -0.54]	•
Test for overall effect: Z = 3.50 (P = 0.0005)         -10         -5         0         5         10           Test for subgroup differences: Chi <sup>2</sup> = 4.31, df = 3 (P = 0.23), i <sup>2</sup> = 30.4%         Favours [ITF]         Favours [control]	Heterogeneity: Tau <sup>2</sup> = 1.4	7; Chi² = 79	.46, df = 25 (F	o < 0.00	0001); I <sup>2</sup> = 69	%				
Test for subgroup differences: Chi <sup>2</sup> = 4.31, df = 3 (P = 0.23), I <sup>2</sup> = 30.4% Favours [ITF] Favours [control]	Test for overall effect: Z =	3.50 (P = 0.	0005)							
Fig. 4 Forest plot displaying the effects of inulin-type fructans on fasting insulin ( $\mu$ U/ml) by subgroup				P = 0.2	3). I <sup>z</sup> = 30.4%	5				Favours (ITF) Favours (control)
	Fig. 4 Forest plot displ	aying the	effects of ir	nulin-t	ype fructa	ns on fastin	ig insu	lin (µU/ı	ml) by subgroup	

our study showed that ITF supplementation could modulate glycemic control in the total population, and better effects were found in the prediabetes and T2DM population. The REMR results revealed that when supplementing ITF with a daily dosage of 10 g and a duration of 6 weeks and longer, the glycemic indicators of the prediabetes and T2DM population were well controlled and that ITF supplementation was suitable for the total population with only modest albeit significant effects. In addition, the subgroup results showed that the sex of the subjects and the type and the method of intake of ITF were all important factors influencing the hypoglycemic effect of ITF.

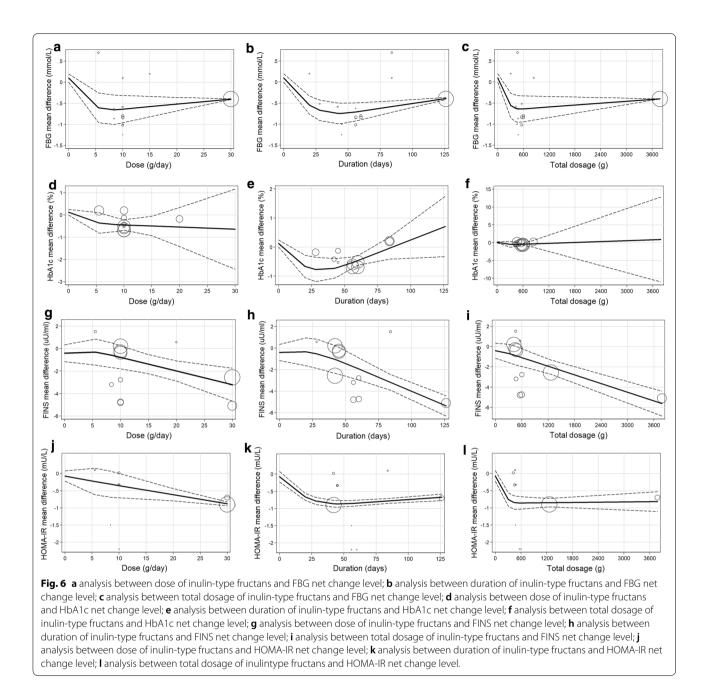
Soluble dietary fiber, one kind of nondigestible carbohydrate, has been widely considered to play an important role in glycemic control, and recently, two meta-analyses (Thompson [54] and Silva [55]) both confirmed its effect on improving glycemic control. ITF, a common but important soluble dietary fiber, has also received much attention. In recent years, interest in the effects of ITF on glycemic control has increased considerably. From the current research results, the hypoglycemic effect of ITF may have several mechanisms. ITF, which is fermented in the intestine, delays the rate of gastric emptying, thereby slowing the flow of glucose into the bloodstream and reducing the extent of postprandial blood glucose elevation [56]. At the same time, the short-chain fatty acids of the fermentation products after ingestion, especially propionic acid, may reduce or

	Ex	perimental			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
1.4.1 Healthy-subjects									
Rajkumar 2015	-1.61	2.347	15	-0.7	2.1	15	2.3%	-0.91 [-2.50, 0.68]	
Russo 2010	-0.93	1.23	15	-0.22	1.257	15	5.2%	-0.71 [-1.60, 0.18]	
Subtotal (95% CI)			30			30	7.5%	-0.76 [-1.53, 0.02]	-
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi²	= 0.05, df =	1 (P =	0.83); I²	= 0%				
Test for overall effect: Z =	= 1.91 (F	P = 0.06)							
1.4.2 Prediabetes and T	2DM								
Asemi 2016	-1.5	2.7	27	-0.2	1.6	27	3.6%	-1.30 [-2.48, -0.12]	
Dehghan 2014-b	-2.2	1.778	24	0.1	1.6	25	4.8%	-2.30 [-3.25, -1.35]	
Gargari 2013	-2.2	1.778	24	0.05	1.6	25	4.8%	-2.25 [-3.20, -1.30]	
Ghavami 2018	0.02	0.626	23	0.01	0.605	23	10.1%	0.01 [-0.35, 0.37]	+
Guess 2015	-0.7	0.3	20	-0.2	0.4	18	11.3%	-0.50 [-0.73, -0.27]	+
Guess 2016	-0.9	0.1	34	-0.2	1.6	34	8.2%	-0.70 [-1.24, -0.16]	
Pedersen 2016	0.1	1.062	14	-0.3	1.1	15	5.9%	0.40 [-0.39, 1.19]	-+
Roshanravan 2017(1)	-0.33	0.89	15	-0.11	0.591	15	8.2%	-0.22 [-0.76, 0.32]	-+
Roshanravan 2017(2)		0.628649	14		0.572975	15	9.2%	-0.53 [-0.97, -0.09]	
Subtotal (95% CI)			195			197	66.1%	-0.69 [-1.10, -0.28]	◆
Heterogeneity: Tau <sup>2</sup> = 0.	28; Chi <sup>z</sup>	= 43.07, df	= 8 (P <	< 0.0000	01); I <sup>2</sup> = 81%				
Test for overall effect: Z =	= 3.30 (F	P = 0.0010)							
1.4.3 Overweight and ol	besity								
de Luis 2013	0.5	3.551	16	-0.1	2.718	16	1.3%	0.60 [-1.59, 2.79]	
Dewulf 2013	-0.8	2.04	15		0.69	15	4.0%	-0.87 [-1.96, 0.22]	
Tripkovic 2015	0.28	1.727	10	0.23	1.602	10	2.6%	0.05 [-1.41, 1.51]	
Subtotal (95% CI)		0.000	41			41	8.0%	-0.38 [-1.20, 0.43]	
Heterogeneity: Tau <sup>2</sup> = 0.	00; Chi <sup>z</sup>	= 1.88, df =	2 (P =	0.39); I <sup>z</sup>	= 0%				
Test for overall effect: Z =									
1.4.4 Others									
Behrouz 2017	-1.04	1.686	29	0.1	5.672	30	1.4%	-1.14 [-3.26, 0.98]	
Bomhof 2018		0.995942	- 8		0.927739	6	4.4%	-0.39 [-1.40, 0.62]	
Javadi 2017	-0.3	0.427	19	0.00	0.348	19	11.1%	-0.30 [-0.55, -0.05]	
Scheid 2014	-0.05	5.254	35	0.05	3.113	37	1.5%	-0.10 [-2.11, 1.91]	
Subtotal (95% CI)	0.00	0.204	91	0.00	0.110	92	18.5%	-0.31 [-0.55, -0.08]	•
Heterogeneity: Tau <sup>2</sup> = 0.	00: Chi <sup>z</sup>	= 0.66. df =	3 (P =	0.88); I <sup>z</sup>	= 0%				
Test for overall effect: Z =									
Total (95% CI)			357			360	100.0%	-0.57 [-0.84, -0.31]	•
Heterogeneity: Tau <sup>2</sup> = 0.	15: Chi <b></b> ²	= 47.63, df		< 0.000	01); I <sup>2</sup> = 64%				
Test for overall effect: Z =									-4 -2 0 2 4
Test for subaroup differe			if = 3 (P	P = 0.37	), l² = 5.5%				Favours (ITF) Favours (control)
						home	ostasis r	nodel assessment-in	sulin resistance (arbitrary units) by subgroup
	iying th		i inum	i type i		nome	.03(03)31		

inhibit hepatic gluconeogenesis. On the other hand, propionic acid enhances glucose utilization by consuming liver citric acid. Propionic acid may also indirectly affect hepatic glucose metabolism by reducing the concentration of plasma fatty acids, a known factor closely related to gluconeogenesis [57]. In addition, studies have shown that oligofructose can improve blood glucose metabolism by increasing the levels of glucagon-like peptide (GLP-1) and glucagon-like peptide 2 (GLP-2) [58, 59]. Jafarnejad et al. [60] reported that ITF, a type of prebiotic, could significantly reduce blood glucose by promoting probiotic regulatory immune responses and systemic lowering of inflammation.

The side effects are important to mention. In the included RCTs, 26 of which studied the side effects in both intervention and control groups, and seven did not mention. Among the 26 trials, most of which reported that ITF were well tolerated by all subjects, and only

two studies [43, 44] reported that ITF were associated with minor side effects, such as slight abdominal flatulence or bloating, which may be important functional expressions of prebiotics as they are the result of gas and acid produced by fermentation by gut microbiota in the colon. None of these side effects were considered serious or harmful to health, and the side effects subsided with adaptation over time. Recently, one study [61] revealed that inulin supplementation was associated with liver damage and might even lead to liver cancer. However, in our included trials, even adverse effects on liver function were not reported. The reason might be that the subjects in these studies were mice, a different species from humans. In addition, inulin dosage might also be an important factor to consider. The China Ministry of Health Announcement No. 5 of 2009 approved inulin and polyfructose as new resource foods and stated that the recommended consumption was less than 15 g per



day. The Generally Recognized as Safe Notice (GRN) No. 605 mentioned that, in the general population, exposure to FOS in food at levels up to 20 g/day was considered safe. In addition, the taste of inulin was generally accepted, and the price was relatively low, which might make it a possible substitute for sugar in the diet.

In 2017, one meta-analysis conducted by Liu [14] studied the effects of ITF on blood lipid and blood sugar levels. Their meta-analysis mainly focused on the effect of ITF in a narrow population of individuals with dyslipidemia, which resulted in a limited number of trials and a small sample of glycemic control studies. Their results showed that ITF supplementation significantly reduced blood lipid parameters. However, no significant reduction in FBG was identified in the T2DM population (MD: -0.42 mmol/l; 95% CI -0.90, 0.06 mmol/l; P=0.09), with only three RCTs included in the T2DM subgroup analysis. In addition, HbA1c and HOMA-IR, both of which are quite important in glycemic control, were not included in their meta-analysis. Recently, more and more relevant well-designed RCTs have been reported, allowing us to perform a more specific and comprehensive

Subgroups	Subgroups Fasting blood glucose (mmol/l)	cose (mm	(I/Io	HbA1c (%) FINS (μU/ml) HC	HbA	HbA1c (%)				FINS (µU/ml)			HOMA-IR			
	n WMD (95% CI)	ъ	l <sup>2</sup> (%) p <sup>b</sup>			WMD (95% CI)	pa  2	l <sup>2</sup> (%) <i>F</i>	_ط ا	n WMD (95% CI)	р <sup>а</sup> I <sup>2</sup> (%)	đ	n WMD (95% CI)	ed.	l <sup>2</sup> (%)	æ
Sex																
Male	4 -0.15 (-0.32, 0 0.03)	0.106 0.0	0.0	0.599	7	- 0.18 (- 0.41, 0.05)	0.120 0	0.0	0.599	4 0.90 (0.30, 1.51)	0.004 71.2	< 0.001	3 -0.09 (-0.83, 0.66)	0.819 40.9	40.9	0.184
Female	6 -0.51 (-0.87, -0.16)	0.004 81.7	81.7	< 0.001	Ś	-0.56 (-0.97, -0.15)	0.008 7	72.3 0	0.006	4 -0.37 (-5.70, -1.86)	< 0.001 47.7	0.125	3 -1.84 (-2.72, -0.97)	< 0.001	56.9	0.098
ITF type																
Inulin	12 -0.28 (-0.51, -0.06)	0.012 74.5	74.5	< 0.001	$\sim$	- 0.48 (- 0.85, - 0.12)	0.010 4	47.6 0	0.076	11 - 1.20 (- 2.14, - 0.27)	0.012 84.5	< 0.001	10 - 0.63 (- 0.94, - 0.31)	< 0.001	76.9	< 0.001
Other kinds	21 -0.15 (-0.27, -0.03)	0.011 25.3	25.3	0.142	Ŝ	-0.28 (-0.71, 0.14)	0.193 6	61.5 0	0.035	15 - 1.32 (- 2.07, - 0.56)	0.001 0.0	0.754	8 - 0.42 (- 0.92, 0.09)	0.108 18.9	18.9	0.281
Food based																
ITF in drink	25 -0.24 (-0.39, -0.09)	0.002 66.9	66.9	< 0.001	1	0.42 ( 0.74, 0.11)	0.008 5	52.2 0	0.022	20 -1.38 (-2.06, -0.70)	< 0.001 61.1	< 0.001 14	14 -0.58 (-0.87, -0.28)	< 0.001 70.4	70.4	< 0.001
Others	8 -0.12 (-0.26, 0.03)	0.114	0.0	0.945	-	- 0.20 (- 0.44, 0.04)	0.101 ~		ì	6 -0.28 (-2.08, 1.51)	0.757 46.4	0.097	4 -0.62 (-1.27, 0.04)	0.067	9.2	0.347
Intervention type	'pe															
ITF vs non- 29 ITF	29 -0.22 (-0.35, -0.10)	0.001 60.5	60.5	< 0.001	12	— 0.39 (— 0.65, — 0.13)	0.004 5	51.2 0	0.020	23 - 1.08 (- 1.81, - 0.36)	0.003 69.4	< 0.001	15 -0.53 (-0.81, -0.25)	< 0.001 68.7	68.7	< 0.001
Synbiotics vs. probi- otic	4 0.01 (-0.21, 0.23)	0.944	0.0	0.697						3 – 2.10 (– 3.80, – 0.39)	0.016 34.5	0.217	3 - 1.16 (-2.02, -0.29)	0.009	0.0	0.928
Study design																
Parallel	24 - 0.23 (- 0.39, - 0.08)	0.003	68.9	< 0.001	10	- 0.45 (- 0.77, - 0.13)	0.006 5	55.4 0	0.017	19 -1.48 (-2.25, -0.71)	< 0.001 63.2	< 0.001	15 - 0.58 (- 0.89, - 0.28)	< 0.001	69.5	< 0.001
Cross-over	9 -0.15 (-0.30, -0.01)	0.038	0.0	0.962	7	- 0.19 (- 0.42, 0.05)	0.117 0.0		0.590	7 -0.32 (-1.57, 0.92)	0.612 62.7	0.013	3 - 0.63 (- 1.07, - 0.19)	0.005	0.0	0.629

Subgroups Fasting blood glucose (mmol/l)	Fastin	g blood gluc	ose (mmo	(1/1	ſΨ	HbA1c (%)			FIN	FINS (µU/ml)			HOMA-IR			
	G M	n WMD (95% P <sup>a</sup> CI)		l <sup>2</sup> (%) p <sup>b</sup>	<u>-</u>	WMD (95% CI)	ъ	l <sup>2</sup> (%) p <sup>b</sup>	<u>-</u>	n WMD (95% CI)	pa 1 <sup>2</sup> (%) pb		n WMD (95% CI)	ъ	1 <sup>2</sup> (%) 1	đ
Country of study Iran 1	11 -	ly 11 -0.59(-0.83, <0.001 31.1 -0.35)	< 0.001 3	1.1 0.151	51 7	- 0.75 (- 1.00,	< 0.001 0.0		6	0.919 9 -1.95 (-3.18, -0.721	0.002 80.4	< 0.001	8 – 0.82 (- 1.30, - 0.30)	0.001 82.1	82.1	< 0.001
Other coun- 22 -0.10 tries (-0.2 0.02)	- 22	— 0.10 (— 0.22, 0.02)	0.116 58.8	8.8 < 0.001	01 5	(00.0 - 0.08 (- 0.27, 0.11)	0.399 0.0		0.586 17	-0.76 -0.76 (-1.56, 0.04)	0.062 52.8	0.006 10	10 - 0.248 (- 0.66, - 0.29)	< 0.001	0.0	0.523
Sponsor referred No 2.	ed 25 –	d 25 -0.27 (-0.41, <0.001 60.0	< 0.001 6	0.0 < 0.001	11 10	- 0.42	0.003 54.0	.0 0.017	20	- 1.32 (	0.001 74.0	< 0.001 13		< 0.001	70.2	< 0.001
Yes	0	- 0.01 - 0.01 - 0.14,	0.920 0.0	0.0 0.791	1 16	0.00 (- 0.71, 0.71)	1.000 ∼	٢	9		0.093 7.9	0.366 5		0.422 37.8	37.8	0.169
		0.13)								0.17)			0.44)			

Table 3 (continued)

<sup>a</sup> P value for subgroup differences between groups
<sup>b</sup> P value for heterogeneity within each subgroup

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Subgroups <sup>a</sup>	FBG (mmol/l)		I	HbA1c (%)		-	FINS (µU/ml)			HOMA-IR			
	n WMD (95% Cl) P <sup>b</sup>	p <sup>b</sup> l <sup>2</sup> (%) p <sup>c</sup>	рс Рс	WMD (95% CI) P <sup>b</sup> l <sup>2</sup> (%) P <sup>c</sup>	p <sup>b</sup> l <sup>2</sup> (		n WMD (95% CI) P <sup>b</sup> I <sup>2</sup> (%) P <sup>c</sup>	) p <sup>b</sup> l <sup>2</sup> (9	6) P <sup>c</sup>	n WMD (95% Cl) P <sup>b</sup>	6 CI) Рb	l <sup>2</sup> (9	l² (%) Ρ <sup>c</sup>
Healthy-sub- jects	5 -0.04 (-0.18,0.09)	0.513 0.0 0.447	0.447				5 - 0.10 (-1.29, 1.10)		0.041	0.874 59.8 0.041 2 -0.76 (-1.53,0.02)		56 0.0	0.056 0.0 0.830
T2DM and prediabetes	11 -0.58 (-0.86, -0.31)	< 0.001 0.0	0.672 7	-0.37 (-0.71, 0.036 18.7 0.287 -0.02)	0.036 18.7	7 0.287	8 - 1.14 (-2.05, -0.23)	0.014 49.7 0.052 23)	0.052	6 -0.47 (-0.64, -0.30)		< 0.001 39.3	0.143
Overweight and obesity	7 -0.08 (-0.18, 0.02)	0.126 0.0	0.748				5 - 1.54 (- 3.11, 0.03)	0.054 0.0 0.844	0.844	3 - 0.38 (- 1.20, 0.43)		53 0.0	0.353 0.0 0.391
Others	7 - 0.08 (-0.18, 0.02)	0.419 0.0	0.748 1	- 0.20 (- 0.44, 0.101 0.04)	0.101 ~	٤	5 -1.14 (-1.93, -0.34)		0.655	0.005 0.0 0.655 4 - 0.31 (-0.55, -0.08)		10 0.0	0.010 0.0 0.883
Total	30 -0.10 (-0.18, -0.03)	0.005 4.4	0.397 8	-0.25 (-0.45, 0.011 12.5 0.333 23 -0.89 -0.06) (-1.50	0.011 12.5	0.333	23 -0.89 (-1.50, -0.28)	0.004 51.6	0.002	0.004 51.6 0.002 15 - 0.43 (-0.56, -0.29)		< 0.001 0.0	0.553

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<sup>a</sup> Excluded trials: FBG: Dehghan [30], Dehghan [29], and Guess [37]; HbA1c: Dehghan [31], Dehghan [31], Gargari [34] and Dewulf [32]; FINS: Dehghan [31], Gargari [34] and Ghavami [35]; HOMA-IR: Dehghan [31], Gargari [34] and Ghavami [35]
 <sup>b</sup> Pvalue for subgroup differences between groups
 <sup>c</sup> Pvalue for heterogeneity within each subgroup

meta-analysis to investigate the effects of ITF supplementation on glycemic control.

Our updated meta-analysis included 33 RCTs that evaluated the effect of ITF supplementation in all kinds of populations, especially prediabetes or T2DM subjects. First, the pooled results of our meta-analysis showed that ITF supplementation could improve glycemic control in the total population or in the prediabetes and T2DM population and that the results had good quality and recommendation levels after being assessed by GRADE. Moreover, except for FBG and FINS, we analyzed two other important glycemic indicators, HbA1c and HOMA-IR. HbA1c can reflect longterm glycemic control in diabetic patients, and a large number of studies have shown that a high level of HbA1c is a risk factor for diabetic complications [62, 63]. Importantly, the WMD calculated by net change was used in our study, which balanced the baseline difference among studies, making our results more accurate. Second, we analyzed and looked for causes of heterogeneity and appropriately conducted a subgroup analysis, which effectively reduced the effect of heterogeneity on the results. Notably, the effects of ITF were much stronger on glycemic control in the prediabetes and T2DM population. For example, the FBG concentration in the diabetic subgroup was significantly reduced by -0.72 mmol/l, which was 6 to 7 times greater than the reduction in the total population (-0.11 mmol/l). Finally, and notably, we performed a dose-response metaanalysis to provide specific suggestions for ITF intake for the prediabetes and T2DM population.

Several limitations of the present study deserve to be mentioned. (i) Some included studies had a small sample size, which may make them likely to report extremely large beneficial effects and have low methodological quality. However, a sensitivity analysis was conducted to exclude the outlier effects studies, and the remainder of the reanalysis results did not show any significant change with the omission of the studies from our meta-analysis. Moreover, the quality of the small trials was also critically analyzed, and only the high-quality studies were included in our analysis. (ii) Medication usage in the included studies may not have been the same, and more medical usage information could not be obtained, which may have caused bias in this meta-analysis, although ITF supplementation does not influence medication use. We performed a subgroup analysis, and no heterogeneity was found, with an  $I^2$  of 0%. (iii) Some studies did not meet the inclusion criteria because they did not report baseline characteristics (WMD could not be computed) and were not in English, which may improve the publication bias; fortunately, only the HbA1c index showed a slight bias. (iv) Though some articles have shown that glucose iAUC levels were also reduced after ITF supplementation, this blood glucose indicator was not analyzed in this study due to differences in implementation criteria and the relatively small numbers of studies. Our team will continue to focus on the impact of ITF on this indicator and conduct another meta-analysis after more high-quality studies are reported. Despite some shortcomings, this study was the most extensive meta-analysis evaluating the effects of ITF on glycemic metabolism.

# Conclusions

Our comprehensive meta-analysis indicated that ITF supplementation reduced the four main glycemic indicators significantly, thus improving glycemic control, especially for the prediabetes and T2DM population. Importantly, we first conducted a dose–response meta-analysis, and recommended an ITF supplementation of 10 g per day for 6 weeks and longer for the prediabetes and T2DM population. In addition, our subgroup analyses revealed that there were more beneficial effects on the glycemic indicators in subjects who were females, in subjects who took inulin (one type of ITF) and in subjects who took ITF as a drink. Therefore, all these important findings provide practical information and indicate that ITF can be used as an adjuvant therapy for glycemic control, especially for the patients with prediabetes or T2DM in clinical practice.

### Supplementary information

Supplementary information accompanies this paper at https://doi. org/10.1186/s12967-019-02159-0.

Additional file 1: Table S1. Search strategies in the online databases.

Additional file 2: Figure S1. Risk of bias graph (A) and risk of bias summary (B) in 33randomized controlled trials.

Additional file 3: Figure S2. Non-linear dose-response analysis between ITF supplement (dose, duration, and total dosage) and glycemic parameters (FBG, HbA1c, FINS, HOMA-IR) levels in the total population. The dose-response analysis was conducted using the nonlinear robust error meta-regression (REMR) model, which is mainly based on the inverse variance-weighted least squares regression and cluster robust error variances for dealing with the synthesis of correlated dose-response data from different studies. The solid line represents weighted mean difference and the dotted lines represent the 95% confidence intervals (Cls). Abbreviations: FBG, fasting blood glucose; FINS, fasting insulin; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance; T2DM, type2 diabetes mellitus.

Additional file 4: Figure S3. Sensitivity analysis of the included studies of FBG (A), HbA1c (B), FINS (C), and HOMA-IR (D).FBG, fasting blood glucose; FINS, fasting insulin; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance.

Additional file 5: Figure S4. Funnel plots for meta-analysis of inulin-type fructans on FBG (A), HbA1c (B), FINS (C), and HOMA-IR (D). FBG, fasting blood glucose; FINS, fasting insulin; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance.

#### Abbreviations

CI: confidence interval; FBG: fasting blood glucose; FINS: fasting insulin; HbA1c: glycosylated hemoglobin; HOMA-IR: homeostasis model assessmentinsulin resistance; ITF: inulin-type fructans; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs: randomized controlled trials; T2DM: type 2 diabetes; WMD: weighted mean difference.

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None.

### Authors' contributions

SSW and YMN conceived and designed the research, drafted the first draft, and critically reviewed the manuscript. LW and SSW had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. LW, HH, HY and PX developed and tested the data collection forms. HH and PX acquired the data. CZ and HXZ conducted the analysis and interpreted the data. All authors read and approved the final manuscript.

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#### Availability of data and materials

Not applicable.

### Ethics approval and consent to participate

Not applicable.

#### **Consent for publication**

All the authors have read and approved the paper and declare no potential conflicts of interest in the paper. If their paper is accepted, all the authors will observe the terms of the publishing license.

#### **Competing interests**

The authors declare that they have no competing interests.

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#### References

- 1. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, Belgium: 2019. http://www.diabetesatlas.org.
- Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: a systematic overview and meta-analysis of prospective studies. Diabetes Res Clin Pract. 2007;78(3):305–12.
- Norhammar A, Mellbin L, Cosentino F. Diabetes: Prevalence, prognosis and management of a potent cardiovascular risk factor. Eur J Prev Cardiol. 2017;24(3\_suppl):52–60.
- Kiviniemi AM, Lepojärvi ES, Tulppo MP, Piira OP, Kenttä TV, Perkiömäki JS, et al. Prediabetes and risk for cardiac death among patients with coronary artery disease: The ARTEMIS Study. Diabetes Care. 2019;42(7):1319–25.
- Aguiar EJ, Morgan PJ, Collins CE, Plotnikoff RC, Callister R. Efficacy of interventions that include diet, aerobic and resistance training components for type 2 diabetes prevention: a systematic review with meta-analysis. Int J Behav Nutr Phys Act. 2014;11:2.
- Moosheer SM, Waldschütz W, Itariu BK, Brath H, Stulnig TM. A proteinenriched low glycemic index diet with omega-3 polyunsaturated fatty

acid supplementation exerts beneficial effects on metabolic control in type 2 diabetes. Prim Care Diabetes. 2014;8(4):308–14.

- Wang X, Wu W, Zheng W, Fang X, Chen L, Rink L, et al. Zinc supplementation improves glycemic control for diabetes prevention and management: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2019;110(1):76–90.
- Nordestgaard AT, Thomsen M, Nordestgaard BG. Coffee intake and risk of obesity, metabolic syndrome and type 2 diabetes: a Mendelian randomization study. Int J Epidemiol. 2015;44(2):551–65.
- Lightowler H, Thondre S, Holz A, Theis S. Replacement of glycaemic carbohydrates by inulin-type fructans from chicory (oligofructose, inulin) reduces the postprandial blood glucose and insulin response to foods: report of two double-blind, randomized, controlled trials. Eur J Nutr. 2018;57(3):1259–68.
- 10. Roberfroid MB. Introducing inulin-type fructans. Br J Nutr. 2005;93(Suppl 1):S13–25.
- 11. Wilson B, Whelan K. Prebiotic inulin-type fructans and galacto-oligosaccharides: definition, specificity, function, and application in gastrointestinal disorders. J Gastroenterol Hepatol. 2017;32(Suppl 1):64–8.
- Chen K, Chen H, Faas MM, de Haan BJ, Li J, Xiao P, et al. Specific inulintype fructan fibers protect against autoimmune diabetes by modulating gut immunity, barrier function, and microbiota homeostasis. Mol Nutr Food Res. 2017;61(8):1601006.
- 13. Rault-Nania MH, Demougeot C, Gueux E, Berthelot A, Dzimira S, Rayssiguier Y, et al. Inulin supplementation prevents high fructose diet-induced hypertension in rats. Clin Nutr. 2008;27(2):276–82.
- 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 metaanalysis of randomized controlled trials. Eur J Clin Nutr. 2017;71(1):9–20.
- 15. Bonsu NK, Johnson CS, McLeod KM. Can dietary fructans lower serum glucose. J Diabetes. 2011;3(1):58–66.
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 2005;5:13.
- 17. Simental-Mendía LE, Sahebkar A, Rodríguez-Morán M, Guerrero-Romero F. A systematic review and meta-analysis of randomized controlled trials on the effects of magnesium supplementation on insulin sensitivity and glucose control. Pharmacol Res. 2016;111:272–82.
- 18. Xu C, Sar D. The robust error meta-regression method for dose-response meta-analysis. Int J Evid Based Healthc. 2018;16(3):138–44.
- Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.
- Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401–6.
- Alles MS, Roos NM, Bakx JC, 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.
- Asemi Z, Alizadeh SA, Ahmad K, Goli M, Esmaillzadeh A. Effects of beta-carotene fortified synbiotic food on metabolic control of patients with type 2 diabetes mellitus: a double-blind randomized cross-over controlled clinical trial. Clin Nutr. 2016;35(4):819–25.
- Behrouz V, Jazayeri S, Aryaeian N, Zahedi MJ, Hosseini F. Effects of probiotic and prebiotic supplementation on leptin, adiponectin, and glycemic parameters in non-alcoholic fatty liver disease: a randomized clinical trial. Middle East J Dig Dis. 2017;9(3):151–9.
- Bomhof MR, Parnell JA, Ramay HR, Crotty P, Rioux KP, Probert CS, et al. Histological improvement of non-alcoholic steatohepatitis with a prebiotic: a pilot clinical trial. Eur J Nutr. 2019;58(4):1735–45.
- Bonsu NKA, Johnson S. Effects of inulin fibre supplementation on serum glucose and lipid concentration in patients with type 2 diabetes. Diabetes Metab. 2012;21(3):80–6.
- Canfora EE, Beek CM, Hermes GDA, Goossens GH, Jocken JWE, Holst JJ, et al. Supplementation of diet with galacto-oligosaccharides increases bifidobacteria, but not insulin sensitivity, obese prediabetic individuals. Gastroenterology. 2017;153(1):87–97.
- 27. Daubioul CA, Horsmans Y, Lambert P, Danse E, Delzenne NM. Effects of oligofructose on glucose and lipid metabolism in patients with

nonalcoholic steatohepatitis: results of a pilot study. Eur J Clin Nutr. 2005;59(5):723–6.

- De Luis DA, de la Fuente B, Izaola O, Aller R, Gutierrez S, Morillo M. Double blind randomized clinical trial controlled by placebo with a fos enriched cookie on saciety and cardiovascular risk factors in obese patients. Nutr Hosp. 2013;28(1):78–85.
- 29. 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.
- 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.
- Dehghan P, Pourghassem GB, Asghari JM. Oligofructose-enriched inulin improves some inflammatory markers and metabolic endotoxemia in women with type 2 diabetes mellitus: a randomized controlled clinical trial. Nutrition. 2014;30(4):418–23.
- 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.
- 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.
- Gargari BP, Dehghan P, Aliasgharzadeh A, Jafar-Abadi MA. Effects of high performance inulin supplementation on glycemic control and antioxidant status in women with type 2 diabetes. Diabetes Metab J. 2013;37(2):140–8.
- 35. Ghavami A, Roshanravan N, Alipour S, Barati M, Mansoori B, Ghalichi F, et al. Assessing the effect of high performance inulin supplementation via KLF5 mRNA expression in adults with type 2 diabetes: a randomized placebo controlled clinical trail. Adv Pharm Bull. 2018;8(1):39–47.
- 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.
- 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. 2015;12(1):36.
- 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.
- 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.
- 40. Javadi L, Ghavami M, Khoshbaten M, Safaiyan A, Barzegari A, Gargari BP. The potential role of probiotics or/and prebiotic on serum lipid profile and insulin resistance in alcoholic fatty liver disease: a double blind randomized clinical trial. Crescent J Med Biol Sci. 2017;4(3):131–8.
- 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.
- Luo J, 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.
- Meksawan K, Chaotrakul C, Leeaphorn N, Gonlchanvit S, Eiam-Ong S, Kanjanabuch T. Effects of fructo-oligosaccharide supplementation on constipation in elderly continuous ambulatory peritoneal dialysis patients. Perit Dial Int. 2016;36(1):60–6.
- 44. 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.
- Pedersen C, Gallagher E, Horton F, Ellis RJ, Ijaz UZ, Wu H, et al. Host-microbiome interactions in human type 2 diabetes following prebiotic fibre (galacto-oligosaccharide) intake. Br J Nutr. 2016;116(11):1869–77.

- 46. 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 singleblind pilot study. J Cardiovasc Pharmacol Ther. 2015;20(3):289–98.
- 47. Roshanravan N, Mahdavi R, Alizadeh E, Jafarabadi MA, Hedayati M, Ghavami A, 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(11):886–91.
- Russo F, Riezzo G, Chiloiro M, De Michele G, Chimienti G, Marconi E, et al. Metabolic effects of a diet with inulin-enriched pasta in healthy young volunteers. Curr Pharm Des. 2010;16(7):825–31.
- 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.
- 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.
- 51. Tovar AR, Caamão MDC, 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(1):44.
- 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.
- Vulevic J, Juric A, Tzortzis G, Gibson GR. A mixture of trans-galactooligosaccharides reduces markers of metabolic syndrome and modulates the fecal microbiota and immune function of overweight adults. J Nutr. 2013;143(3):324–31.
- 54. Thompson SV, Hannon BA, An R, Holscher HD. Effects of isolated soluble fiber supplementation on body weight, glycemia, and insulinemia in adults with overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr. 2017;106(6):1514–28.
- Silva FM, Kramer CK, de Almeida JC, Steemburgo T, Gross JL, Azevedo MJ. Fiber intake and glycemic control in patients with type 2 diabetes mellitus: a systematic review with meta-analysis of randomized controlled trials. Nutr Rev. 2013;71(12):790–801.
- 56. Ahmed W, Rashid S. Functional and therapeutic potential of inulin: a comprehensive review. Crit Rev Food Sci Nutr. 2019;59(1):1–13.
- Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. Br J Nutr. 2014;111(7):1147–61.
- Jayashree B, Bibin YS, Prabhu D, Shanthirani CS, Gokulakrishnan K, Lakshmi BS, et al. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes. Mol Cell Biochem. 2014;388(1–2):203–10.
- 59. Cherbut C. Motor effects of short-chain fatty acids and lactate in the gastrointestinal tract. Proc Nutr Soc. 2003;62(1):95–9.
- Jafarnejad S, Saremi S, Jafarnejad F, Arab A. Effects of a multispecies probiotic mixture on glycemic control and inflammatory status in women with gestational diabetes: a randomized controlled clinical trial. J Nutr Metab. 2016;2016:5190846.
- Singh V, Yeoh BS, Chassaing B, Xiao X, Saha P, Aguilera OR, et al. Dysregulated microbial fermentation of soluble fiber induces cholestatic liver cancer. Cell. 2018;175(3):679–94.e22.
- Nordwall M, Abrahamsson M, Dhir M, Fredrikson M, Ludvigsson J, Arnqvist HJ. Impact of HbA1c, followed from onset of type 1 diabetes, on the development of severe retinopathy and nephropathy: the VISS Study (Vascular Diabetic Complications in Southeast Sweden). Diabetes Care. 2015;38(2):308–15.
- 63. Arnold LW, Wang Z. The HbA1c and all-cause mortality relationship in patients with type 2 diabetes is J-shaped: a meta-analysis of observational studies. Rev Diabet Stud. 2014;11(2):138–52.

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