



# Systematic Review The Cardiovascular Benefits and Infections Risk of SGLT2i versus Metformin in Type 2 Diabetes: A Systemic Review and Meta-Analysis

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Abstract: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and metformin are both widely accepted anti-hyperglycemic agents. However, there is still no systematic review evaluating the cardiovascular benefits and risk of infections of SGLT2i versus metformin. To make that clear, we designed this study. Public databases, including the Cochrane library database, PubMed, and Embase were searched for randomized clinical trials (RCTs) fitting the inclusion criteria. Two reviewers extracted the data and appraised the study quality independently. Thirteen RCTs enrolling 4189 patients were eligible for this analysis. Our results showed that compared with metformin, SGLT2i increased the risk of genitourinary tract infections (p < 0.00001). Further subgroup analysis suggested that the occurrence of urinary tract infections (UTI) was not statistically significant (p = 0.18), but the incidence of reproductive tract infections (RTI) was significantly increased in patients in the SGLT2i group compared with that in the metformin group (p < 0.00001). In addition, SGLT2i markedly decreased the levels of cardiovascular risk factor, including body weight, blood pressure, and triglyceride level, and significantly increased the HDL-cholesterol level (p < 0.00001) in patients versus that of metformin. For type 2 diabetes patients with obesity, SGLT2i was associated with more significant reductions in weight and blood pressure compared to metformin without an increased risk of genitourinary infections, and the reduction in fasting plasma glucose was superior in the SGLT2i group; the decrease in HbA1c was similar in both groups. Additionally, no significant publication bias was seen. Based on these findings, SGLT2i provided the similar antihyperglycemic effects, additional cardiovascular benefits, and a potential RTI risk compared with that of metformin. Our results indicate that SGLT2i is a good choice for those patients with metformin intolerance or resistance.

**Keywords:** sodium-glucose cotransporter 2 inhibitors; genitourinary tract infections; cardiovascular benefits; metformin; randomized controlled trials; meta-analysis

# 1. Introduction

Diabetes mellitus which acts as one of the most common chronic diseases has caused a major public health crisis worldwide due to its high prevalence [1,2]. According to a



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**Copyright:** © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). recent cross-sectional study, type 2 diabetes mellitus (T2DM) accounts for the majority of patients in China, and the increasing proportion of young patients leads to a high morbidity, distinct from other chronic diseases and mortality [3]. Studies have found that the hazard ratio for death due to cardiovascular disease in diabetic patients is increasing year by year, and now cardiovascular disease has become the main cause of death in T2DM patients [4]. Reducing the incidence of cardiovascular disease (CVD) is so vital for T2DM patients that the American Diabetes Association recommends a glucose-lowering drug which could provide additional cardiovascular safety as a prerequisite [5]. At present, many guidelines recommend sodium-glucose cotransporter 2 inhibitors (SGLT2i) as a priority for diabetics with atherosclerotic cardiovascular disease (ASCVD).

SGT2i is an effective and widely used oral antidiabetic drug which can significantly decrease hyperglycemia by increasing urinary glucose excretion, independent of the pancreatic  $\beta$  cell function [6–9]. SGLT2i has been widely used due to its unique advantage in weight loss, renal protection, and cardiovascular benefits [10,11]. SGLT2i may be regarded as the top option of pharmacotherapy that raises new healthcare decision-making both for clinicians and policy makers. Nonetheless, large amounts of clinical trials worldwide are concerned regarding the safety of SGLT2i in patients with T2DM, as they are potentially causing urinary tract infections (UTI) and reproductive tract infections (RTI) [12–14]. In addition, sporadic skin and respiratory infections may also induce the aggravation of T2DM, which affects the quality of life of the patients. So far, there are many articles reporting the outcomes of cardiovascular and urinary systems of SGLT2i, however, most of them analyzed the benefits of SGLT2i as an add-on treatment for metformin compared with placebo [12,15–18]. Rare reports were available comparing the cardiovascular outcomes and safety of SGLT2i monotherapy with the first-line antihyperglycemic drug, metformin. Therefore, we sought to provide a comprehensive new estimate of the cardiovascular benefits, risk of infection, and glycemic efficacy of SGLT2i in T2DM patients when compared with metformin monotherapy. In view of the limited data on cardiovascular outcomes, we performed an analysis of cardiovascular risk factors as a substitute for endpoint assessment, including body weight, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, diastolic blood pressure, and systolic blood pressure [19]. It is expected to provide evidence for doctors to choose whether SGLT2i or metformin will be preferred and it will be helpful for healthcare decision-making in the future.

#### 2. Materials and Methods

#### 2.1. Data Sources and Searches

In this meta-analysis of intervention studies, we performed a systematic search of the scientific literatures according to the PRISMA statement (PROSPERO registration number: CRD42022359007). A systematic search was conducted in the Cochrane Library database, Web of Science, Embase, PubMed, China National Knowledge Infrastructure (CNKI), and Wanfang Database for scientific literatures by two independent investigators using the same search strategy, collecting all randomized clinical trials (RCTs) on humans from inception to March 1st, 2022, with no other restrictions. The relevant text words and medical subject headings comprised terms relating to "Sodium-Glucose Transporter 2" and all the idiographic drug names, metformin, and diabetes mellitus (search strategy is provided in the Supplementary File S1). Furthermore, we also searched completed studies with the drugs specified above in the www.clinicaltrials.gov register to identify possible inclusion trials.

#### 2.2. Study Selection

Two investigators independently assessed the articles by title and abstract, and studies that satisfied the inclusion criteria were retrieved for a full-text assessment, with disagreements resolved by mutual discussion.

Studies were included if the following inclusion criteria were met: (1) RCTs; (2) assessing the effects of any SGLT2i compared with metformin agent in humans with diabetes mellitus; (3) reported at least one type of infections (genitourinary tract infections, UTIs, RTIs, or other infection events); (4) reported at least one cardiometabolic or safety outcome (body weight, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, diastolic blood pressure, and systolic blood pressure level); and (5) reported blood glucose level, including glycosylated hemoglobin (HbA1c) or fasting plasma glucose (FPG). The maximum non-overlapping data were extracted if different reports on the same trial provided data on different outcomes. Likewise, there were multiple reports of a single study and the report with longest follow-up was included.

Studies were excluded if they met any of the following exclusion criteria: (1) duplicate reports; (2) non-clinical studies or randomized controlled trials; and (3) did not report the interested outcomes (genitourinary tract infection events, effect on cardiovascular system and lowering glucose, and safety outcomes).

#### 2.3. Data Extraction and Quality Assessment

Prespecified data from each trial were performed independently by two investigators using a standardized data collection form and disagreements were resolved by mutual discussion. The following items were included: first author, year of journal article publication, clinical trial registration number, number of participants, intervention and dose, study duration, gender distribution, baseline HbA1c and body weight, and other outcome measures listed below. A greater quantity of data provided by the www.clinicaltrials.gov register could be used to supplement missing data that were not reported sufficiently or not published at all from the original text. The Cochrane risk-of-bias tool for the randomized trials (Review Manager, version 5.2) was used to assess the methodological quality of the included trial. The specific assessment items of Cochrane definitions included random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias). Two of the investigators performed the quality assessment, and disagreements were resolved by discussions. Funnel plots and the Egger statistical test were generated for exploring the risk of publication bias across the studies.

## 2.4. Outcome Indicators

We grouped outcomes into four broad sets: (1) incidence of infection events; (2) effects on cardiovascular risk factors; (3) efficacy on glycemic control; and (4) incidence of hypoglycemic adverse events. The primary outcome of interest was the incidence of infections, including urinary or reproductive tract infection events and upper respiratory tract infections. Cardiovascular risk factors enrolled in this analysis included body weight, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, diastolic blood pressure, and systolic blood pressure, and these indicators were analyzed by the change from baseline. The value changes in FPG and HbA1c were used to assess the effect of SGLT2i in lowering glucose.

### 2.5. Data Synthesis and Analysis

Statistical analyses were performed with RevMan 5.4 and Stata software, version 16.0 (StataCorp, College Station, TX, USA). For dichotomous variables, relative risk (RR) with a 95% confidence interval (CI) was used to present the pooled results, and weighed mean differences (WMD) with a 95% CI were calculated for the continuous variables. The analyses were calculated with fixed-effect models when there was no significant extent of heterogeneities. Conversely, random-effects models were used. When the heterogeneities were inevitable, a prior subgroup analysis was conducted, including types of SGLT2i and different doses of the drug, treatment periods (12 weeks, 24–26 weeks, and  $\geq$ 52 weeks), and obesity (mean BMI > 28 Kg/m<sup>2</sup>) or not. The gender subgroup analysis of genitourinary tract infection events was performed for a different physiological structure of the genitourinary tract between male and female. Statistical heterogeneity was assessed with the *p*-value of

v2-based Q test (cutoff value p = 0.10) and the I<sup>2</sup> statistic (a low likelihood: 0–25%; moderate likelihood: 26–75%; and a high likelihood: 76–100%). Sensitivity analysis was performed by omitting each study sequentially to evaluate the robustness of the results of the pooled estimates. Two-tailed p values < 0.05 indicated statistically significant results.

## 3. Results

# 3.1. Search Results

Our research yielded 6498 potentially eligible studies, and 6398 articles were excluded by scanning the titles and abstracts. Eighty-seven studies were excluded because of improper article type or an inappropriate intervention or outcome measure, thus ultimately a total of 13 fulfilling studies [20–32] were identified for the meta-analysis (Figure 1).

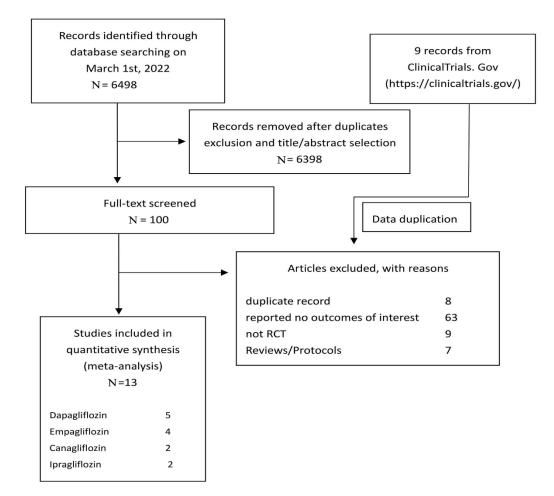


Figure 1. Flowchart for identification and selection of included trials.

## 3.2. Study Characteristics

Our search identified four types of SGLT2i with available data, including four studies of empagliflozin [20–23], five of dapagliflozin [24–28], two of canagliflozin [29,30], and two of ipragliflozin [31,32]. The baseline characteristics of the enrolled patients and the drug therapy information are illustrated in Table 1. A total of 4189 patients with T2DM were included in our study, among which 2699 patients were included in the SGLT2i group and 1490 patients in the metformin group. Among the 4189 patients, 9.24% (387/4189) cases had genitourinary tract infections, 5.67% (234/4127) cases had a UTI, 3.65% (140/3831) cases had an RTI, and 3.60% (92/2559) cases had upper respiratory tract infections. Among those patients, 57.13% (2393/4189) had their BMI > 28 Kg/m<sup>2</sup> [22,25,29,31]. In the study conducted by Araki, E. et al. in 2015 [20], in which the patients underwent a background treatment with sulfonylurea, and in the study conducted by Koshizaka, M. et al. [32] in

2019, where patients underwent a background treatment with DPP-4i, both applied SGLT2i and metformin for monotherapy. In the trial conducted by Pian Liu et al. in 2021 [27] and Jingqian Xie et al. in 2020 [30], all participants received routine congestive heart failure treatment.

]	<b>ble 1.</b> Basic characteristics of randomized controlled trials included in the meta-analysis.	

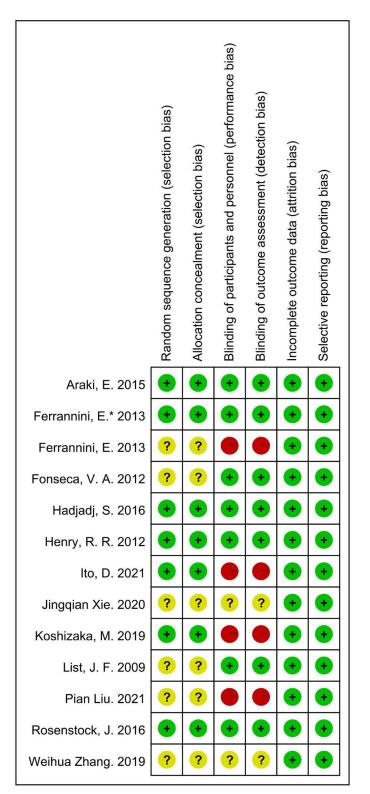
Study	Interventions	Study Duration (Weeks)	Number of Participants	Male (N)	Age (Years)	HbA1c (%)	Body Weight (Kg)	BMI (Kg/M)
Araki, E. 2015 [20] (NCT01368081)	EMPA 10 mg EMPA 25 mg MET 1111 mg <sup>§</sup>	52	136 137 63	99 96 47	$\begin{array}{c} 61.3 \pm 9.9 \\ 61.8 \pm 9.6 \\ 60.0 \pm 10.2 \end{array}$	$\begin{array}{c} 8.0 \pm 0.7 \\ 8.1 \pm 0.8 \\ 7.9 \pm 0.8 \end{array}$	$65.8 \pm 12.2$ $67.0 \pm 13.7$ $68.2 \pm 12.2$	$\begin{array}{c} 24.6 \pm 3.8 \\ 25.2 \pm 4.2 \\ 25.2 \pm 3.6 \end{array}$
Ferrannini, E.* 2013 [21] (NCT00789035)	EMPA 5 mg EMPA 10 mg EMPA 25 mg MET †	12	81 81 82 80	46 40 41 39	59.0 (37–78) * 58.0 (30–76) * 57.0 (30–79) * 58.0 (34–73) *	$\begin{array}{c} 7.9 \pm 0.8 \\ 8.0 \pm 0.8 \\ 7.8 \pm 0.8 \\ 8.1 \pm 0.9 \end{array}$	82.8 (51.9–116.0) * 76.8 (45.5–118.0) * 81.2 (49.1–130.0) * 81.1 (42.0–126.0) *	28.5 (20.5–38.8) * 28.1 (21.5–39.3) * 28.3 (20.1–38.8) * 28.6 (18.7–40.6) *
Hadjadj, S. 2016 [22] (NCT01719003)	EMPA 10 mg EMPA 25 mg MET 500 mg MET 1000 mg	24	169 164 168 164	97 83 86 92	$\begin{array}{c} 53.1 \pm 10.7 \\ 53.3 \pm 10.7 \\ 53.4 \pm 10.9 \\ 51.6 \pm 10.8 \end{array}$	$\begin{array}{c} 8.6 \pm 1.2 \\ 8.9 \pm 1.3 \\ 8.7 \pm 1.0 \\ 8.6 \pm 1.1 \end{array}$	$\begin{array}{c} 83.8 \pm 19.8 \\ 83.1 \pm 20.3 \\ 82.7 \pm 21.2 \\ 83.7 \pm 20.1 \end{array}$	$\begin{array}{c} 30.3 \pm 5.2 \\ 30.6 \pm 5.9 \\ 30.3 \pm 5.8 \\ 30.5 \pm 5.9 \end{array}$
Ferrannini, E. 2013 [23] (NCT00881530)	EMPA 10 mg EMPA 25 mg MET †	78	106 109 56	49 57 28	59 (30–76) * 59 (35–79) * 58 (35–73) *	$\begin{array}{c} 7.9 \pm 0.9 \\ 8.0 \pm 0.9 \\ 8.2 \pm 1.0 \end{array}$	$82.9 \pm 16.4$ $84.6 \pm 18.1$ $85.8 \pm 15.6$	28.9 (20.3–39.2) * 28.1 (19.3–40.0) * 28.6 (22.4–39.3) *
Henry, R.R. 2012 [24] (NCT00643851 NCT00859898)	DAPA 5 mg DAPA 10 mg MET 2000 mg	24	203 219 409	92 105 192	$\begin{array}{c} 52.3 \pm 10.2 \\ 51.1 \pm 11.5 \\ 52.3 \pm 10.1 \end{array}$	$\begin{array}{c} 9.1 \pm 1.4 \\ 9.1 \pm 1.3 \\ 9.1 \pm 1.3 \end{array}$	$86.2 \pm 21.1$ $88.5 \pm 19.3$ $86.4 \pm 19.7$	NO
List, J.F. 2009 [25] (NCT00263276)	DAPA 2.5 mg DAPA 5 mg DAPA 10 mg DAPA 20 mg DAPA 50 mg MET 1500 mg	12	59 58 47 59 56 56	29 28 25 32 25 27	$\begin{array}{c} 55.0 \pm 11.0 \\ 55.0 \pm 12.0 \\ 54.0 \pm 9.0 \\ 55.0 \pm 10.0 \\ 53.0 \pm 10.0 \\ 54.0 \pm 9.0 \end{array}$	$\begin{array}{c} 7.6 \pm 0.7 \\ 8.0 \pm 0.9 \\ 8.0 \pm 0.8 \\ 7.7 \pm 0.9 \\ 7.8 \pm 1.0 \\ 7.6 \pm 0.8 \end{array}$	$\begin{array}{c} 90.0 \pm 20.0 \\ 89.0 \pm 17.0 \\ 86.0 \pm 17.0 \\ 88.0 \pm 18.0 \\ 92.0 \pm 19.0 \\ 88.0 \pm 20.0 \end{array}$	$\begin{array}{c} 32.0\pm 5.0\\ 32.0\pm 5.0\\ 31.0\pm 5.0\\ 31.0\pm 5.0\\ 32.0\pm 4.0\\ 32.0\pm 5.0\end{array}$
Ito, D. 2021 [26]	DAPA 5 mg MET 1000 mg	12	11 10	8 9	$55.9 \pm 7.5$ $57.5 \pm 9.6$	$\begin{array}{c} 7.9\pm0.9\\ 7.9\pm0.9\end{array}$	$77.5 \pm 18.1 \\ 74.8 \pm 8.7$	$\begin{array}{c} 27.7\pm4.9\\ 26.7\pm3.4\end{array}$
Pian Liu. 2021 [27]	DAPA 10 mg MET 1000 mg	26	58 59	31 32	$66.6 \pm 8.4 \\ 66.3 \pm 9.3$	$\begin{array}{c} 8.1\pm1.2\\ 8.5\pm1.1\end{array}$	$\begin{array}{c} 70.1 \pm 7.8 \\ 68.6 \pm 7.7 \end{array}$	$\begin{array}{c} 24.7 \pm 1.8 \\ 24.1 \pm 2.3 \end{array}$
Weihua Zhang. 2019 [28]	DAPA 10 mg MET 1500 mg	12	30 30	19 20	$\begin{array}{c} 44.9\pm10.2\\ 44.1\pm10.8\end{array}$	$\begin{array}{c} 8.5\pm1.7\\ 8.3\pm1.4\end{array}$	$76.3 \pm 13.6 \\ 75.4 \pm 14.3$	$27.9 \pm 4.3 \\ 27.5 \pm 4.5$
Rosenstock, J. 2016 [29] (NCT01809327)	CANA 100 mg CANA 300 mg MET 2000 mg	26	237 238 237	105 125 116	$\begin{array}{c} 54.1 \pm 10.7 \\ 55.9 \pm 9.6 \\ 55.3 \pm 9.8 \end{array}$	$\begin{array}{c} 8.8 \pm 1.2 \\ 8.8 \pm 1.2 \\ 8.8 \pm 1.2 \end{array}$	$90.2 \pm 18.6$ $93.0 \pm 19.9$ $92.1 \pm 20.1$	$\begin{array}{c} 32.4 \pm 5.4 \\ 32.6 \pm 5.8 \\ 33.0 \pm 6.0 \end{array}$
Jingqian Xie. 2020 [30]	CANA 100 mg MET (1000–1500 mg)	12	31 31	11 13	$\begin{array}{c} 63.8 \pm 8.6 \\ 63.0 \pm 9.7 \end{array}$	$\begin{array}{c}9.1\pm1.7\\8.3\pm1.5\end{array}$	$\begin{array}{c} 73.3 \pm 10.3 \\ 72.5 \pm 10.2 \end{array}$	NO
Fonseca, V.A. 2012 [31] (NCT01071850)	IPRA 12.5 mg IPRA 50 mg IPRA 150 mg IPRA 300 mg MET 1500 mg	12	70 67 68 68 69	39 34 29 37 40	$53.9 \pm 9.6 \\ 52.6 \pm 10.7 \\ 54.2 \pm 10.3 \\ 54.2 \pm 10.7 \\ 53.1 \pm 11.7 \\$	$\begin{array}{c} 8.0 \pm 0.8 \\ 8.1 \pm 0.8 \\ 7.8 \pm 0.7 \\ 7.9 \pm 0.7 \\ 8.0 \pm 0.9 \end{array}$	$\begin{array}{c} 86.0 \pm 22.3 \\ 90.7 \pm 20.8 \\ 83.3 \pm 21.6 \\ 86.7 \pm 19.6 \\ 84.1 \pm 21.8 \end{array}$	$\begin{array}{c} 31.0 \pm 5.9 \\ 32.2 \pm 5.9 \\ 30.9 \pm 6.3 \\ 30.7 \pm 5.0 \\ 29.8 \pm 5.5 \end{array}$
Koshizaka, M. 2019 [32]	IPRA 50 mg MET 1124 mg <sup>§</sup>	12	48 50	31 28	$\begin{array}{c} 56.6 \pm 11.9 \\ 55.7 \pm 12.2 \end{array}$	$\begin{array}{c} 8.0\pm0.7\\ 8.1\pm0.9\end{array}$	$\begin{array}{c} 73.1 \pm 14.2 \\ 78.3 \pm 18.4 \end{array}$	$\begin{array}{c} 27.6 \pm 4.2 \\ 28.8 \pm 5.3 \end{array}$

EMPA, empagliflozin; DAPA, dapagliflozin; CANA, canagliflozin; IPRA, ipragliflozin; MET, metformin; BMI, body mass index. Data are mean  $\pm$  SD (standard deviation) unless indicated otherwise. Ferrannini, E.\*: Used to distinguish two articles with the same first author name and publication year (references [21,23]). \* Data are median (minimum–maximum).† MET dose < 1000 mg or up to the maximum tolerated dose. <sup>§</sup> Data are mean dose.

## 3.3. Methodological Quality

For random sequence generation, the specific method was clearly presented in seven studies [20–22,24,26,29,32], but the remaining six referred to "random" without a detailed method [23,25,27,28,30,31]. Six studies mentioned the specific allocation concealment method [20–22,24,26,32]. The blinding of the participants and personnel was concretely presented in seven studies [20–22,24,25,29,31], and four studies were open-label [23,26,27,32]. Blinding was not mentioned in the 2019 Weihua Zhang et al. trial [28] nor the 2020 Jingqian Xie et al. trial [30]. Significantly, the control group (metformin) was open-label in Araki, E. 2015 [20] and Ferrannini, E.\* 2013 [21], and double-blinding was presented in the experimental groups. Six studies had an incomplete outcome data bias [22–25,29,31]; the

remaining seven studies did not describe this bias [20,21,26–28,30,32]. None of included studies mentioned the reporting bias. The results of the methodological quality are graphically displayed in Figure 2.



**Figure 2.** Figure for methodological quality of included trials [20–32]. Green symbol: low risk of bias; Yellow symbol: unclear risk of bias; Red symbol: high risk of bias.

3.4. Outcomes3.4.1. Infection Incidence RiskGenitourinary Tract Infections

Genitourinary tract infections, one of the most common adverse effects of SGLT2i, were reported in all of the included RCTs. Compared with metformin, SGLT2i increased the risk of genitourinary tract infections (RR = 1.67, 95% CI = 1.35 to 2.07, p < 0.00001,  $I^2 = 27\%$ , Q test: p = 0.17) (Figure 3).

A further subgroup analysis of the different types of SGLT2i suggested that dapagliflozin was associated with a significant increase in the incidence of genitourinary tract infections in comparison with that of metformin (dapagliflozin: RR = 2.28, 95% CI = 1.63 to 3.18, p < 0.00001,  $I^2 = 0\%$ , N = 5) (Figure 4A). Additionally, the different doses of dapagliflozin all showed a significant increase in the incidence of genitourinary tract infections in the SGLT2i group compared to those in the metformin group (dapagliflozin 5 mg: RR = 1.73, 95% = 1.03 to 2.89, p = 0.04,  $I^2 = 0\%$ , N = 3; dapagliflozin 10 mg: RR = 2.37, 95% CI = 1.56 to 3.63, p < 0.0001,  $I^2 = 20\%$ , N = 4) (Figure 4A).

There was not any significant difference between empagliflozin and metformin (empagliflozin: RR = 1.24, 95% CI = 0.87 to 1.75, p = 0.23,  $I^2 = 0\%$ , N = 4) (Figure 4B). The following subgroup analyses of the different doses of empagliflozin versus metformin showed consistent results (empagliflozin 10 mg: RR = 1.27, 95% CI = 0.78 to 2.07, p = 0.34,  $I^2 = 0\%$ , N = 4; empagliflozin 25 mg: RR = 1.22, 95% CI = 0.74 to 2.01, p = 0.43,  $I^2 = 0\%$ , N = 4) (Figure 4B).

In addition, the subgroup analysis of canagliflozin showed a significantly increased risk of genitourinary tract infections (RR = 2.59, 95% CI = 1.19 to 5.64, p = 0.02,  $I^2 = 23\%$ , N = 2) (Figure 4C). Ipragliflozin had a similar risk increase in genitourinary tract infections, despite the moderate heterogeneity (RR = 0.86, 95% CI = 0.42 to 1.74, p = 0.67,  $I^2 = 60\%$ , N = 2) (Figure 4D).

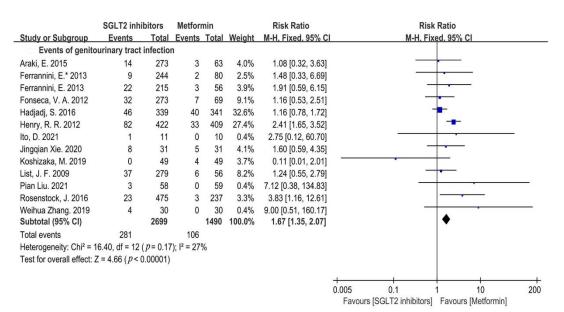
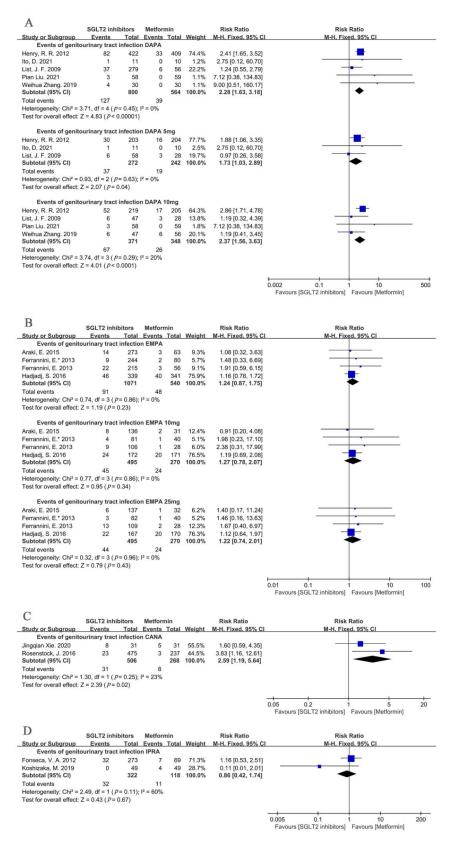


Figure 3. Risk of genitourinary tract infections of SGLT2i compared with that of metformin [20–32].

# Urinary Tract Infections (UTI)

All trials included in our meta-analysis reported the specific type of genitourinary tract infections, including UTIs and RTIs, except for one research conducted by Jingqian Xie et al. in a 2020 trial, which only reported genitourinary tract infection events [30]. Our analysis showed that the overall occurrence of UTIs was not statistically significant between the SGLT2i and metformin group (RR = 1.20, 95% CI = 0.92 to 1.58, p = 0.18,  $I^2 = 0\%$ , N = 12) (Figure 5).



**Figure 4.** (**A**) Risk of genitourinary tract infections of DAPA and its different doses compared with metformin [24–28]. (**B**) Risk of genitourinary tract infections of EMPA and its different doses compared with metformin [20–23]. (**C**) Risk of genitourinary tract infections of CANA compared with metformin [29,30]. (**D**) Risk of genitourinary tract infections of IPRA compared with metformin [31,32]. DAPA = dapagliflozin. EMPA = empagliflozin. CANA = canagliflozin. IPRA = ipragliflozin.

9 of 28

Drug types and doses were further investigated and found that there was no significant difference in the empagliflozin group compared to the metformin group, and both a low dose (10 mg) and high dose (25 mg) of empagliflozin showed a similar result (empagliflozin: RR = 0.94, 95% CI = 0.61 to 1.45, p = 0.79,  $I^2 = 0\%$ , N = 4; empagliflozin 10 mg: RR = 0.85, 95% CI = 0.46 to 1.57, p = 0.61,  $I^2 = 0\%$ , N = 4; empagliflozin 25 mg: RR = 1.03, 95% CI = 0.56 to 1.89, p = 0.94,  $I^2 = 0\%$ , N = 4) (Figure 6). Dapagliflozin resulted in a higher risk of a UTI compared to that of metformin (RR = 1.67, 95% CI = 1.11 to 2.52, p = 0.01,  $I^2 = 0\%$ , N = 5) (Figure 6). As for the influence of the dose, 10 mg of dapagliflozin significantly increased the risk of a UTI, but 5 mg of dapagliflozin had a similar risk of a UTI compared with that of metformin (dapagliflozin 5 mg: RR = 1.36, 95% CI = 0.72 to 2.59, p = 0.34,  $I^2 = 0\%$ , N = 3; dapagliflozin 10 mg: RR = 2.04, 95% CI = 1.17 to 3.56, p = 0.01,  $I^2 = 0\%$ , N = 4) (Figure 6). Only two RCTs reported canagliflozin and two RCTs reported ipragliflozin, so sub-group analyses were not performed.

As for UTIs in different genders, a sex-specific subgroup was performed in five studies with the available gender data. The results showed that no significant differences were found in a UTI incidence in the SGLT2i versus the metformin group (Male: RR = 1.55, 95% CI = 0.74 to 3.23, p = 0.24,  $I^2 = 0$ %, N = 4; Female: RR = 1.15, 95% CI = 0.81 to 1.64, p = 0.44,  $I^2 = 8\%$ , N = 4) (Figure 7). A further subgroup analysis demonstrated that empagliflozin had a similar risk of a UTI with metformin in males and females, and 10 mg and 25 mg of empagliflozin also had similar risk of a UTI compared to metformin (Male empagliflozin: RR = 1.46, 95% CI = 0.49 to 4.37, p = 0.49,  $I^2 = 0$ %, N = 3; Male empagliflozin 10 mg: RR = 1.09, 95% CI = 0.26 to 4.51, p = 0.90,  $I^2 = 0\%$ , N = 2; Male empagliflozin 25 mg: RR = 0.99, 95% CI = 0.31 to 3.21, *p* = 0.99, I<sup>2</sup> = 0%, N = 3; Female empagliflozin: RR = 0.89, 95% CI = 0.56 to 1.43, p = 0.63,  $I^2 = 0\%$ , N = 3; Female empagliflozin 10 mg: RR = 0.97, 95% CI = 0.50 to 1.88, p = 0.92,  $I^2 = 0$ %, N = 3; Female empagliflozin 25 mg: RR = 0.80, 95% CI = 0.42 to 1.53, p = 0.50,  $I^2 = 0$ %, N = 3) (Figure 7). Subgroup analysis of different treatment periods showed no significant difference in a UTI incidence between the SGLT2i and metformin group, no matter if the treatment was 12 weeks, 24-26 weeks, or  $\geq 52$  weeks (12 weeks: RR = 1.22, 95% CI = 0.69 to 2.14, p = 0.50,  $I^2 = 0\%$ , N = 5; 24–26 weeks: RR = 1.18, 95% CI = 0.86 to 1.63, p = 0.31,  $I^2 = 43\%$ , N = 5;  $\geq$ 52 weeks: RR = 1.41, 95% CI = 0.50 to 4.00, p = 0.52,  $I^2 = 0\%$ , N = 2) (Figure 8A).

	SGLT2 inhi	bitors	Metfor	min		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Events of urinar	y tract infecti	on						
Araki, E. 2015	12	273	2	63	3.6%	1.38 [0.32, 6.03]		
Ferrannini, E.* 2013	4	244	2	80	3.3%	0.66 [0.12, 3.51]		
Ferrannini, E. 2013	11	215	2	56	3.5%	1.43 [0.33, 6.28]		
Fonseca, V. A. 2012	21	273	5	69	8.8%	1.06 [0.42, 2.71]		
Hadjadj, S. 2016	27	339	31	341	33.9%	0.88 [0.53, 1.44]		
Henry, R. R. 2012	40	422	24	409	26.8%	1.62 [0.99, 2.63]		
Ito, D. 2021	1	11	0	10	0.6%	2.75 [0.12, 60.70]		
Koshizaka, M. 2019	0	49	4	49	4.9%	0.11 [0.01, 2.01]		•
List, J. F. 2009	25	279	5	56	9.1%	1.00 [0.40, 2.51]		
Pian Liu. 2021	3	58	0	59	0.5%	7.12 [0.38, 134.83]		
Rosenstock, J. 2016	8	475	3	237	4.4%	1.33 [0.36, 4.97]		
Weihua Zhang. 2019	4	30	0	30	0.5%	9.00 [0.51, 160.17]		
Subtotal (95% CI)		2668		1459	100.0%	1.20 [0.92, 1.58]		•
Total events	156		78					
Heterogeneity: Chi <sup>2</sup> = 9	9.98, df = 11 ()	p=0.53)	; l <sup>2</sup> = 0%					
Test for overall effect: 2	Z = 1.35 ( P= 0	0.18)						
							0.01	0.1 1 10 100
							0.01	0.1 1 10 100

Favours [SGLT2 inhibitors] Favours [Metformin]

**Figure 5.** Risk of urinary tract infections in patients with SGLT2i compared with that of metformin [20–29,31,32].

		_
Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H. Fixed. 95% Cl	-
1.38 [0.32, 6.03] 0.66 [0.12, 3.51] 1.43 [0.33, 6.28] 0.88 [0.53, 1.44] 0.94 [0.61, 1.45]	*	
1.37 [0.17, 10.96] 0.49 [0.03, 7.69] 1.06 [0.12, 9.08] 0.81 [0.40, 1.63] 0.85 [0.46, 1.57]		
1.40 [0.17, 11.24] 0.49 [0.03, 7.60] 1.80 [0.23, 14.02] 0.95 [0.47, 1.91] 1.03 [0.56, 1.89]		

Subtotal (95% CI)	14	495	15	270	100.0%	1.03 [0.56, 1.89]	
Total events	28		18				
Heterogeneity: Chi <sup>2</sup> = 0.70		= 0.87): l <sup>2</sup> =					
Test for overall effect: Z = 0	· · ·		0,0				
Events of urinary tr	act infecti	on DAPA					_
Henry, R. R. 2012	40	422	24	409	71.2%	1.62 [0.99, 2.63]	
lto, D. 2021	1	11	0	10	1.5%	2.75 [0.12, 60.70]	
List, J. F. 2009	25	279	5	56	24.3%	1.00 [0.40, 2.51]	<b>+</b>
Pian Liu. 2021	3	58	0	59	1.4%	7.12 [0.38, 134.83]	
Weihua Zhang. 2019	4	30	0	30	1.5%	9.00 [0.51, 160.17]	
Subtotal (95% CI)		800		564	100.0%	1.67 [1.11, 2.52]	◆
Total events	73		29				
Heterogeneity: Chi <sup>2</sup> = 3.55	, df = 4 ( p	= 0.47); l <sup>2</sup> =	= 0%				
Test for overall effect: Z = 2	2.46(p=0)	.01)					
Events of urinary tra	act infecti	on DAPA	ōmg				
Henry, R. R. 2012	16	203	12	204	78.8%	1.34 [0.65, 2.76]	
Ito, D. 2021	1	11	0	10	3.4%	2.75 [0.12, 60.70]	
List, J. F. 2009	5	58	2	28	17.8%	1.21 [0.25, 5.84]	
Subtotal (95% CI)		272		242	100.0%	1.36 [0.72, 2.59]	<b>•</b>
Total events	22		14				
Heterogeneity: Chi <sup>2</sup> = 0.22	, df = 2 ( <i>p</i>	= 0.89); l <sup>2</sup> =	= 0%				
Test for overall effect: Z =	0.95 ( <i>P</i> = 0	.34)					
Events of urinary tr	act infecti	on DAPA '	10mg				
Henry, R. R. 2012	24	219	12	205	72.3%	1.87 [0.96, 3.64]	- <b>-</b> -
List, J. F. 2009	5	47	3	28	21.9%	0.99 [0.26, 3.84]	<b>+</b>
Pian Liu. 2021	3	58	0	59	2.9%	7.12 [0.38, 134.83]	
Weihua Zhang. 2019	4	30	0	30	2.9%	9.00 [0.51, 160.17]	
Subtotal (95% CI)		354		322	100.0%	2.04 [1.17, 3.56]	-
Total events	36		15				
Heterogeneity: Chi <sup>2</sup> = 2.87	, df = 3 ( <i>p</i>	= 0.41); l <sup>2</sup> =	= 0%				
Test for overall effect: Z = 2	2.50 ( <i>P</i> = 0	0.01)					

SGLT2 inhibitors

Events

12

4

11

27

54 Heterogeneity: Chi<sup>2</sup> = 0.84, df = 3 (*P* = 0.84); l<sup>2</sup> = 0% Test for overall effect: Z = 0.26 (p = 0.79)

6

1

4

13

24

Events of urinary tract infection EMPA 25mg

6

1

7

14

Heterogeneity: Chi<sup>2</sup> = 0.41, df = 3 (*p*= 0.94); l<sup>2</sup> = 0% Test for overall effect: Z = 0.51 (p = 0.61)

Events of urinary tract infection EMPA 10mg

273

244

215

339

1071

136

81

106

172

495

137

82

109

167

Events of urinary tract infection EMPA

Study or Subaroup

Ferrannini, E.\* 2013

Ferrannini, E. 2013

Subtotal (95% CI)

Hadjadj, S. 2016

Total events

Araki, E. 2015

Ferrannini, E.\* 2013

Ferrannini, E. 2013

Hadjadj, S. 2016

Total events

Araki, E. 2015

Ferrannini, E.\* 2013

Ferrannini, E. 2013

Hadjadj, S. 2016

Subtotal (95% CI)

Araki, E. 2015

Metformin

2 63

2 80 7.5%

2

31 341 76.6%

37

1

1 40 6.5%

1 28 7.7%

16 171 77.9%

19

1

1

1 28 8.2%

15 170 76.5%

56

540 100.0%

> 31 7.9%

270 100.0%

32

40 6.9%

Total Events Total Weight

8.1%

7.9%

8.3%

Figure 6. Risk of urinary tract infections with different types and doses of SGLT2i compared with that of metformin [20–28]. DAPA = dapagliflozin, EMPA = empagliflozin.

0.01

0.1

Favours [SGLT2 inhibitors] Favours [Metformin]

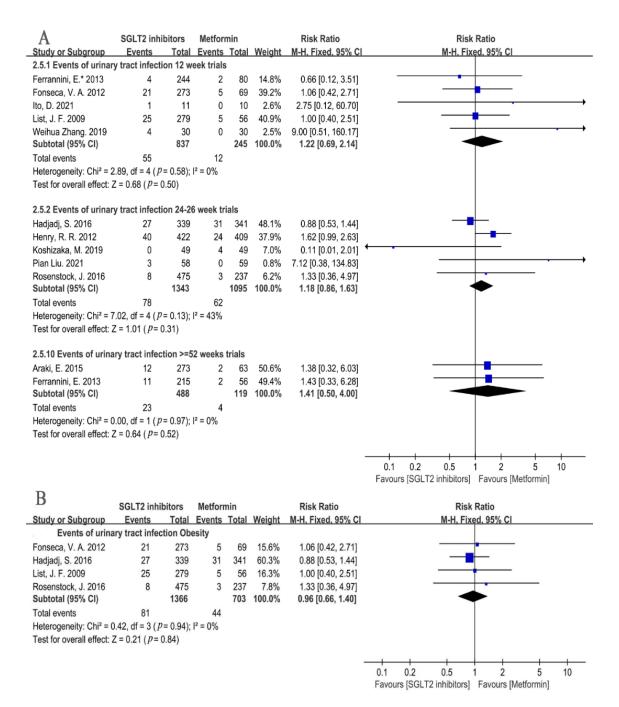
10

100

It was noted that the obesity population accounted for the most T2DM patients. In our study, four trials enrolled the obese T2DM patients. Research indicates that obese people are more likely than people of a normal weight to develop infections of various types [33]. Surprisingly, we found that SGLT2i did not result in a higher risk of a UTI compared to the metformin in the obesity subgroup (RR = 0.96, 95% CI = 0.66 to 1.40, p = 0.84,  $I^2 = 0\%$ , N = 4) (Figure 8B).

Events of uring	SGLT2 inhit Events		Metforr Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
Events of utilial	y tract infecti	on Male					
Araki, E. 2015	3	195	1	47	14.0%	0.72 [0.08, 6.80]	
Ferrannini, E. 2013	4	106	0	28	6.8%	2.44 [0.14, 44.01]	
Hadjadj, S. 2016	5	184	3	177	26.5%	1.60 [0.39, 6.61]	
Henry, R. R. 2012	10	197	6	192	52.7%	1.62 [0.60, 4.38]	
Subtotal (95% CI)		682		444	100.0%	1.55 [0.74, 3.23]	<b>•</b>
Total events	22		10				
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: 2			l² = 0%				
Events of urinar	y tract infecti	ion Male	EMPA				
Araki, E. 2015	3	195	1	47	29.5%	0.72 [0.08, 6.80]	
Ferrannini, E. 2013	4	106	0	28	14.4%	2.44 [0.14, 44.01]	
Hadjadj, S. 2016	5	184	3	177	56.0%	1.60 [0.39, 6.61]	
Subtotal (95% CI)		485		252	100.0%	1.46 [0.49, 4.37]	
Total events	12		4				
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: 2	0.52, df = 2 ( <i>p</i>		l² = 0%				
Events of uring	v traat infaati	ion Malo		Oma			
Events of urinar	•	ion iviale 99	EMPA 1	-	30 E0/	0 05 10 00 40 241	
Araki, E. 2015	2			47	38.5%	0.95 [0.09, 10.21]	
Hadjadj, S. 2016 Subtotal (95% CI)	2	100 199	3	177	61.5% 100.0%	1.18 [0.20, 6.94]	
		199		224	100.0%	1.09 [0.26, 4.51]	
Total events	4	- 0.001	4				
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: 2			1- = 0%				
Events of urinar	y tract infecti			-			_
Araki, E. 2015	1	96	1	23	30.2%	0.24 [0.02, 3.69]	
Ferrannini, E. 2013	4	57	0	14	14.9%	2.33 [0.13, 40.89]	
Hadjadj, S. 2016	3	84	3	88	54.9%	1.05 [0.22, 5.05]	
Subtotal (95% CI)		237		125	100.0%	0.99 [0.31, 3.21]	
Total events	8		4				
Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2			l² = 0%				
Events of urinar	v tract infecti	ion Fema	ale				
Araki, E. 2015	9	78	1	16	3.3%	1.85 [0.25, 13.57]	—— <del>—</del>
Ferrannini, E. 2013	7	109	2	28	6.3%	0.90 [0.20, 4.09]	
Hadjadj, S. 2016	22	155	28	164	54.0%	0.83 [0.50, 1.39]	
Henry, R. R. 2012	30	225	18	217	36.4%	1.61 [0.92, 2.80]	
Subtotal (95% CI)		567			100.0%	1.15 [0.81, 1.64]	*
Total events	68		49				
Heterogeneity: Chi <sup>2</sup> = 3 Test for overall effect: 3			l² = 8%				
	v tract infecti	ion Fem:	ale EMP/				
Events of urinar							
Events of urinar Araki E 2015	•	78	1		5 2%	1 85 [0 25 13 57]	
Araki, E. 2015	9	78 109	1	16	5.2% 9.9%	1.85 [0.25, 13.57]	
Araki, E. 2015 Ferrannini, E. 2013	9 7	109	2	16 28	9.9%	0.90 [0.20, 4.09]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016	9	109 155		16 28 164	9.9% 84.9%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI)	9 7 22	109	2 28	16 28 164	9.9%	0.90 [0.20, 4.09]	*
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events	9 7 22 38	109 155 <b>342</b>	2 28 31	16 28 164	9.9% 84.9%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	9 7 22 38 0.58, df = 2 ( <i>p</i>	109 155 <b>342</b> = 0.75);	2 28 31	16 28 164	9.9% 84.9%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39]	*
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	9 7 22 38 0.58, df = 2 ( <i>p</i> Z = 0.48 ( <i>p</i> = 0	109 155 <b>342</b> 9= 0.75); 0.63)	2 28 31 1 <sup>2</sup> = 0%	16 28 164 <b>208</b>	9.9% 84.9% <b>100.0%</b>	0.90 [0.20, 4.09] 0.83 [0.50, 1.39]	*
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: ; <b>Events of urina</b> r	9 7 22 38 0.58, df = 2 ( <i>p</i> Z = 0.48 ( <i>p</i> = 0	109 155 <b>342</b> 9= 0.75); 0.63)	2 28 31 1 <sup>2</sup> = 0%	16 28 164 <b>208</b>	9.9% 84.9% <b>100.0%</b>	0.90 [0.20, 4.09] 0.83 [0.50, 1.39]	*
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : <b>Events of urinar</b> Araki, E. 2015	9 7 22 38 0.58, df = 2 ( <i>p</i> Z = 0.48 ( <i>p</i> = 0 y tract infecti	109 155 <b>342</b> 9= 0.75); 0.63) ion Fema	2 28 31 1 <sup>2</sup> = 0%	16 28 164 <b>208</b>	9.9% 84.9% 100.0%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <i>:</i> Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016	9 7 22 38 0.58, df = 2 ( <i>p</i> Z = 0.48 ( <i>p</i> = 0 y tract infecti 4	109 155 <b>342</b> = 0.75); 0.63) ion Fema 37 57 72	2 28 1 <sup>2</sup> = 0% ale EMPA 0	16 28 164 <b>208</b> (10mg 8 14 82	9.9% 84.9% 100.0% 5.2% 10.4% 84.4%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.98 [0.12, 8.12] 0.89 [0.43, 1.84]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: <i>:</i> Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016	9 7 22 38 0.58, df = 2 ( <i>p</i> Z = 0.48 ( <i>p</i> = 0 y tract infecti 4 4	109 155 <b>342</b> = 0.75); 0.63) ion Fema 37 57	2 28 31 1 <sup>2</sup> = 0% ale EMPA 0 1	16 28 164 <b>208</b> (10mg 8 14 82	9.9% 84.9% 100.0% 5.2% 10.4%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.96 [0.12, 8.12]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : <b>Events of urinar</b> Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI)	9 7 22 38 0.58, df = 2 ( <i>p</i> Z = 0.48 ( <i>p</i> = 0 y tract infecti 4 4	109 155 <b>342</b> = 0.75); 0.63) ion Fema 37 57 72	2 28 31 1 <sup>2</sup> = 0% ale EMPA 0 1	16 28 164 <b>208</b> (10mg 8 14 82	9.9% 84.9% 100.0% 5.2% 10.4% 84.4%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.98 [0.12, 8.12] 0.89 [0.43, 1.84]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: ; Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	9 7 22 38 0.58, df = 2 (p Z = 0.48 (p = 0 C Y tract infecti441119 $0.34, df = 2 (p Z = 0.48 (p = 0 C Y C Y C Y C Y C Y C Y C Y C Y C Y C$	109 155 <b>342</b> = 0.75); 0.63) ion Fema 37 57 72 166	2 28 31 1 <sup>2</sup> = 0% ale EMPA 0 1 14 14	16 28 164 <b>208</b> (10mg 8 14 82	9.9% 84.9% 100.0% 5.2% 10.4% 84.4%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.98 [0.12, 8.12] 0.89 [0.43, 1.84]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	9 7 22 38 0.58, df = 2 ( $p$ Z = 0.48 ( $p$ = 0 y tract infecti 4 4 11 19 0.34, df = 2 ( $p$ Z = 0.09 ( $p$ = 0	109 155 342 = 0.75); 0.63) ion Fema 37 57 72 166 = 0.84); 0.92)	$2 \\ 28 \\ 31 \\ 1^2 = 0\% \\ 0 \\ 1 \\ 14 \\ 15 \\ 1^2 = 0\% \\ 15 \\ 1^2 = 0\% \\ 1 \\ 15 \\ 1^2 = 0\% \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ $	16 28 164 208 104 8 14 82 104	9.9% 84.9% 100.0% 5.2% 10.4% 84.4% 100.0%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.98 [0.12, 8.12] 0.89 [0.43, 1.84]	
Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : Events of urinar	9 7 22 38 0.58, df = 2 ( $p$ Z = 0.48 ( $p$ = 0 y tract infecti 4 4 11 19 0.34, df = 2 ( $p$ Z = 0.09 ( $p$ = 0	109 155 342 = 0.75); 0.63) ion Fema 37 57 72 166 = 0.84); 0.92)	$2 \\ 28 \\ 31 \\ 1^2 = 0\% \\ 0 \\ 1 \\ 14 \\ 15 \\ 1^2 = 0\% \\ 15 \\ 1^2 = 0\% \\ 1 \\ 15 \\ 1^2 = 0\% \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ 1 \\ $	16 28 164 208 104 8 14 82 104	9.9% 84.9% 100.0% 5.2% 10.4% 84.4% 100.0%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.98 [0.12, 8.12] 0.89 [0.43, 1.84] 0.97 [0.50, 1.88]	
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Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = ( Test for overall effect: : Events of urinar Araki, E. 2015 Ferrannini, E. 2013 Hadjadj, S. 2016 Subtotal (95% CI) Total events Hederogeneity: Chi <sup>2</sup> = ( Total events Hadjadj, S. 2016 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = (	9 7 22 38 0.58, df = 2 (p) Z = 0.48 (p = 0) q tract infecti 4 11 19 0.34, df = 2 (p) Z = 0.09 (p = 0) q tract infecti 5 3 11 19 0.04, df = 2 (p)	$\begin{array}{c} 109\\ 155\\ 342\\ \end{array}$	$\begin{array}{c} 2\\ 28\\ 31\\ 1^2=0\%\\ 0\\ 1\\ 14\\ 15\\ 15\\ 1^2=0\%\\ 1\\ 1\\ 1\\ 1\\ 1\\ 1\\ 14\\ 16\end{array}$	16 28 164 208 14 208 14 82 104 25mg 8 14 82	9.9% 84.9% 100.0% 5.2% 10.4% 84.4% 100.0% 9.7% 9.1% 81.3%	0.90 [0.20, 4.09] 0.83 [0.50, 1.39] 0.89 [0.56, 1.43] 2.13 [0.13, 36.12] 0.98 [0.12, 8.12] 0.89 [0.43, 1.84] 0.97 [0.50, 1.88] 0.98 [0.13, 7.27] 0.81 [0.09, 7.18] 0.78 [0.37, 1.61]	
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**Figure 7.** Risk of urinary tract infections with different types and doses of SGLT2i compared with that of metformin in male and female patients [20,22–24]. EMPA = empagliflozin.

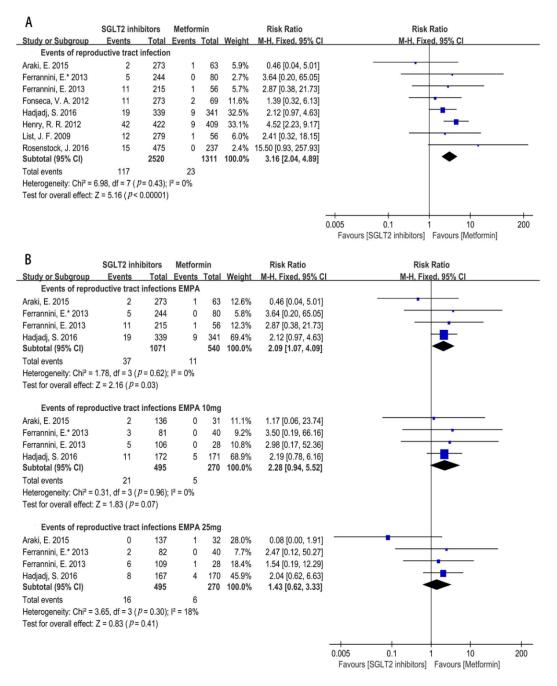


**Figure 8.** (**A**) Risk of urinary tract infections in patients with different treatment times of SGLT2i at 12 weeks, 24–26 weeks, and  $\geq$ 52 weeks compared with that of metformin [20–29,31,32]. (**B**). Risk of urinary tract infections with SGLT2i compared with of metformin in obesity patients [22,25,29,31]. Obesity = SGLT2i used in obese people.

## Reproductive Tract Infections (RTI)

For another type of genitourinary tract infections, an RTI, we also performed the corresponding analysis. The result showed that SGLT2i significantly increased the incidence of an RTI compared with that of metformin (RR = 3.16, 95% CI = 2.04 to 4.89, p < 0.00001,  $I^2 = 0\%$ , N = 8) (Figure 9A), and the incidence of an RTI induced by empagliflozin was also higher than that of metformin (RR = 2.09, 95% CI = 1.07 to 4.09, p = 0.03,  $I^2 = 0\%$ , N = 4) (Figure 9B). However, different doses of empagliflozin did not increase the risk of an RTI (empagliflozin 10 mg: RR = 2.28, 95% CI = 0.94 to 5.52, p = 0.07,  $I^2 = 0\%$ , N = 4; empagliflozin 25 mg: RR = 1.43, 95% CI = 0.62 to 3.33, p = 0.41,  $I^2 = 18\%$ , N = 4) (Figure 9B). The risk

analysis of an RTI for dapagliflozin, canagliflozin, and ipragliflozin was not performed due to the lack of included literature.



**Figure 9.** (**A**). Risk of reproductive tract infections in SGLT2i group compared with that of metformin [20-25,29,31]. (**B**). Risk of reproductive tract infections with EMPA and its different doses compared with that of metformin [20-23]. EMPA = empagliflozin.

As for the sex-specific subgroup of RTIs, the results found that SGLT2i led to a higher incidence of an RTI for both male and female subgroups (Male: RR = 4.53, 95% CI = 1.77 to 11.61, p = 0.002, I<sup>2</sup> = 13%, N = 5; Female: RR = 2.85, 95% CI = 1.68 to 4.86, p = 0.0001, I<sup>2</sup> = 53%, N = 4, Figure 10A), which was in accordance with the aforementioned results (Figure 9A). In addition, treatment with empagliflozin resulted in a higher risk of an RTI in male patients (empagliflozin: RR = 4.28, 95% CI = 1.17 to 15.58, p = 0.03, I<sup>2</sup> = 54%, N = 3) (Figure 10A).

A Study or Subgroup

Araki, E. 2015

Ferrannini, E. 2013

Hadjadj, S. 2016

Henry, R. R. 2012

Rosenstock, J. 2016

Subtotal (95% CI)

Total events

Araki, E. 2015

Ferrannini, E. 2013

SGLT2 inhibitors Metformin

195

106

184

197

230

912

195

106

3.3.2 Events of reproductive tract infections Male

2

5

9

8

7

31

Heterogeneity:  $Chi^2 = 4.58$ , df = 4 (p= 0.33); l<sup>2</sup> = 13% Test for overall effect: Z = 3.15 (p= 0.002)

3.3.3 Events of reproductive tract infections Male EMPA

2

5

Events Total Events Total Weight M-H, Fixed, 95% Cl

1

0

2

0

3

0 177

47 28.8%

28 14.1%

192 36.2%

1 47 55.4%

0 28 27.1%

	Ratio ęd. 95% Cl	
-		
-	→	
-		

	Ferrannini, E. 2013	5	106	0	28	27.1%	2.98 [0.17, 52.36]		•
	Hadjadj, S. 2016	9	184	0	177	17.5%	18.28 [1.07, 311.76]		
	Subtotal (95% CI)		485		252	100.0%	4.28 [1.17, 15.58]		
	Total events	16		1					
	Heterogeneity: Chi <sup>2</sup> = 4	.30, df = 2 ( p	= 0.12);	² = 54%					
	Test for overall effect: 2	Z = 2.20 (p = 0)	0.03)						
			,						
	3.3.5 Events of reprod	luctive tract i	infection	s Female	•				
	Ferrannini, E. 2013	6	109	1	28	8.8%	1.54 [0.19, 12.29]		
	Hadjadj, S. 2016	10	155	9	164	48.2%	1.18 [0.49, 2.82]		<b></b>
	Henry, R. R. 2012	34	225	7	217	39.3%	4.68 [2.12, 10.34]		
		8	245	0	121	3.7%	8.43 [0.49, 144.86]		
	Rosenstock, J. 2016 Subtotal (95% CI)	0	734	0	530	100.0%	2.85 [1.68, 4.86]		
		50	7.54	47	550	100.0%	2.05 [1.00, 4.00]		-
	Total events	58		17					
	Heterogeneity: Chi <sup>2</sup> = 6			$ ^2 = 53\%$					
	Test for overall effect: 2	Z = 3.87 (p = 0)	0.0001)						
								0.01 0.1	1 10 100
								Favours [SGLT2 inhibitors]	
									la avodi o [modornin]
	В								
	D	SGLT2 inhi	bitors	Metform	nin		Risk Ratio	Risk	Ratio
_	Study or Subaroup	Events	Total	Events	Total	Weight	M-H. Fixed, 95% C	M-H, Fix	ed. 95% Cl
	3.4.1 Events of reproc	luctive tract i	infection	s Obesity	v				
	Fonseca, V. A. 2012	11	273	2	, 69	22.0%	1.39 [0.32, 6.13]		
	Hadjadj, S. 2016	19	339	9	341	61.9%	2.12 [0.97, 4.63]		<b>⊢∎</b> −
	List, J. F. 2009	12	279	1	56	11.5%	2.41 [0.32, 18.15]		<b></b>
	Rosenstock, J. 2016	12	475	0	237		15.50 [0.93, 257.93]		·
	Subtotal (95% CI)	15	475 1366	0		4.0%	<b>2.61 [1.39, 4.89]</b>		
		<b>67</b>	1300	10	103	100.0%	2.01 [1.39, 4.09]		-
	Total events	57		12					
	Heterogeneity: Chi <sup>2</sup> = 2			$ ^2 = 0\%$					
	Test for overall effect: 2	Z = 2.99 (P = 0)	0.003)						
	3.4.2 Events of reproc								
	Ferrannini, E.* 2013	5	244	0	80	13.4%	3.64 [0.20, 65.05]		-
	Fonseca, V. A. 2012	11	273	2	69	56.9%	1.39 [0.32, 6.13]		
	List, J. F. 2009	12	279	1	56	29.7%	2.41 [0.32, 18.15]		
	Subtotal (95% CI)		796		205	100.0%	1.99 [0.67, 5.97]	-	
	Total events	28		3					
	Heterogeneity: Chi <sup>2</sup> = 0	.43, df = 2 ( p	9= 0.81);	<sup>2</sup> = 0%					
	Test for overall effect: 2								
		(1	,						
	3.4.3 Events of reproc	luctive tract	infection	s 24-26 v	veeks	trials			
	Hadjadj, S. 2016	19	339	9	341	47.8%	2.12 [0.97, 4.63]		<b>⊢∎</b> −
	Henry, R. R. 2012	42	422	9	409	48.7%	4.52 [2.23, 9.17]		│ <b></b>
	Rosenstock, J. 2016	15	475	0	237		15.50 [0.93, 257.93]		
	Subtotal (95% CI)	15	1236	0	987	100.0%	3.77 [2.26, 6.28]		•
		70	1230	18	301	100.076	5.77 [2.20, 0.20]		•
	Total events	76	- 0.40)						
	Heterogeneity: Chi <sup>2</sup> = 3			- 40%					
	Test for overall effect: 2	L = 5.08 (p < 0)	0.00001)						
	· · · -								
	3.4.4 Events of reproc								
	Araki, E. 2015	2	273	1	63	50.6%	0.46 [0.04, 5.01]	-	
	Ferrannini, E. 2013	11	215	1	56	49.4%	2.87 [0.38, 21.73]		
	Subtotal (95% CI)		488		119	100.0%	1.65 [0.38, 7.14]		
	Total events	13		2					
	Heterogeneity: Chi <sup>2</sup> = 1	.38, df = 1 ( p	= 0.24);	l² = 28%					
	Test for overall effect: 2	z = 0.67 ( p= 0	0.50)						
			-						
								0.005 0.1	1 10 000
									1 10 200
								Favours [SGLT2 inhibitors]	Favours [Mettormin]

**Risk Ratio** 

0.48 [0.04, 5.20]

2.98 [0.17, 52.36]

3.90 [0.84, 18.12]

0.48 [0.04, 5.20]

2.98 [0.17, 52.36]

9.1% 18.28 [1.07, 311,76]

 116
 11.9%
 7.60 [0.44, 131.88]

 560
 100.0%
 4.53 [1.77, 11.61]

**Figure 10.** (**A**). Risk of reproductive tract infections with different types and doses of SGLT2i compared with that of metformin in male or female patients [20,22-24,29]. (**B**). Risk of reproductive tract infections in SGLT2i group compared with that metformin in obesity patients and risk of reproductive tract infections in patients with different treatment times of SGLT2i at 12 weeks or 24–26 weeks compared with that metformin [20-25,29,31]. EMPA = empagliflozin.

Furthermore, SGLT2i elevated the incidence of an RTI in the obesity patients (RR = 2.61, 95% CI = 1.39 to 4.89, p = 0.003,  $I^2 = 0\%$ , N = 4) (Figure 10B). Additionally, for the time with SGLT2i therapy, the results revealed that SGLT2i treatment for 12 weeks showed a similar incidence of an RTI with that of metformin, whereas a significant increase in the incidence of an RTI in patients on SGLT2i treatment for 24–26 weeks were observed in contrast to the metformin treatment (12 weeks: RR = 1.99, 95% CI = 0.67 to 5.97, p = 0.22,  $I^2 = 0\%$ , N = 3; 24–26 weeks: RR = 3.77, 95% CI = 2.26 to 6.28, p < 0.00001,  $I^2 = 40\%$ , N = 3) (Figure 10B). Surprisingly, when using SGLT2i for more than 52 weeks, the increase in the incidence of an RTI did not quite reach a statistical significance (RR =1.65, 95% CI = 0.38 to 7.14, p = 0.50,  $I^2 = 28\%$ , N = 2) (Figure 10B).

# Non-Genitourinary Tract Infections

Four studies contributed to the risk of upper respiratory tract infections, and the result indicated no significant difference between the SGLT2i and metformin monotherapy group (RR = 0.80, 95% CI = 0.53 to 1.20, p = 0.28,  $I^2 = 0\%$ , N = 4) (Figure 11). In terms of skin infections, the occurrence of cellulitis was reported by three studies: two cases received 25 mg of empagliflozin, one case was with 5 mg of dapagliflozin, and one was with metformin. Henry, R. R. et al. reported one case of gangrene in the dapagliflozin 5 mg group. One case of herpes simplex was reported in the metformin group. Two cases of pulmonary infections were reported in the canagliflozin 10 mg group. Additionally, one case of SGLT2i on the infection types mentioned above were too few to draw reliable conclusions.

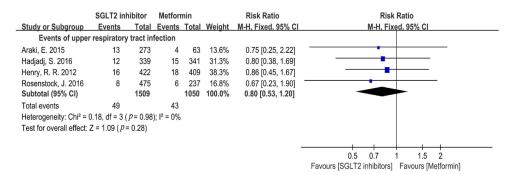


Figure 11. Risk of upper respiratory tract infections in SGLT2i group compared with that of metformin [20,22,24,29].

## 3.4.2. Effects on Cardiovascular Risk Factors

Obesity is one of the major causes of cardiovascular events [34]. Our meta-analysis showed the SGLT2i significantly reduced body weight compared with that of metformin (WMD = -1.35, 95% CI = -1.40 to -1.30, p < 0.00001, N = 10) with a moderate heterogeneity  $(I^2 = 46\%, Q \text{ test: } p = 0.05)$  (Figure 12A). Therefore, a subgroup analysis was performed and found that dapagliflozin and empagliflozin notably reduced body weight compared with that of metformin (empagliflozin: WMD = -1.47, 95% CI = -1.77 to -1.18, p < 0.00001,  $I^2 = 80\%$ , N = 4; dapagliflozin: WMD = -1.32, 95% CI = -1.77 to -0.86, p < 0.00001,  $I^2 = 0\%$ , N = 2) (Figure 12B). Due to the high heterogeneity of the empagliflozin subgroup, a sensitivity analysis was conducted and the result revealed that the source of heterogeneity mainly came from the study of Araki, E. in 2015, in which sulforylurea was added as background therapy. The sensitivity analysis suggested that empagliflozin showed more efficacy on the reduction in body weight than that of metformin with decreased heterogeneity (WMD = -1.23, 95% CI = -1.55 to -0.90, p < 0.00001,  $I^2 = 52\%$ , N = 3) (Figure 12B). Additionally, SGLT2i displayed a more significant decrease in body weight than that of metformin in obese T2DM patients (WMD = -1.35; 95% CI = -1.40 to -1.30; *p* < 0.00001,  $I^2 = 0\%$ , N = 3) (Figure 12B). Additionally, SGLT2i was superior to metform in weight loss after treatment for both 12 and 24–26 weeks (12 weeks: WMD = -0.86, 95% CI = -1.33

to -0.39, p = 0.0003,  $I^2 = 0\%$ , N = 4; 24–26 weeks: WMD = -1.35, 95% CI = -1.40 to -1.30, p < 0.0001,  $I^2 = 0\%$ , N = 4) (Figure 12B).

It is noted that hyperlipidemia is closely associated with cardiovascular disease [35]. SGLT2i presented an inferior effect on lowering the total cholesterol level compared to metformin with a high heterogeneity (WMD = 9.41, 95% CI= 4.90 to 13.92, p < 0.0001,  $I^2 = 60\%$ , N = 5), and the sensitivity analysis showed the same result after removing the study of Weihua Zhang in 2019, in which T2DM patients with metabolic syndrome were included (WMD = 10.81, 95% CI = 6.19 to 15.44, p < 0.00001,  $I^2 = 0\%$ , N = 4) (Figure 13). SGLT2i significantly increased HDL-cholesterol level compared to that of metformin with a strong heterogeneity (WMD = 3.97, 95% CI = 2.89 to 5.05, p < 0.00001,  $I^2 = 81\%$ , N = 6). Further sensitivity analysis showed that SGLT2i obviously upregulated the level of HDLcholesterol after removing the study of Araki, E. in 2015, in which sulfonylurea was used as a background therapy with a reduced heterogeneity (WMD = 2.79, 95% CI = 1.58 to 4.00, p < 0.00001,  $I^2 = 46\%$ , N = 5). Compared with metformin, SGLT2i manifested less influence on LDL-cholesterol reduction, but significantly reduced the triglyceride level in contrast to metformin monotherapy (LDL-cholesterol: WMD = 8.19, 95% CI = 5.03 to 11.35, p < 0.00001,  $I^2 = 0\%$ , N = 5; triglyceride: WMD = -17.21, 95% CI = -27.72 to -6.70, p = 0.001,  $I^2 = 40\%$ , N = 6) (Figure 13).

Hypertension is an important risk factor of CVD [36]. Our results showed that there was a significant reduction in diastolic blood pressure (DBP) in the SGLT2i group versus the metformin group (WMD = -1.66, 95% CI = -2.19 to -1.13, p < 0.00001,  $I^2 = 35\%$ , N = 10) (Figure 14A). Among different SGLT2i, empagliflozin and dapagliflozin showed the stronger efficacy in lowering DBP than that of metformin with a moderate heterogeneity (empagliflozin: WMD = -2.06, 95% CI = -2.97 to -1.16, p < 0.00001,  $I^2 = 34\%$ , N = 3; dapagliflozin: WMD = -1.93, 95% CI = -2.91 to -0.95, p = 0.0001, I<sup>2</sup> = 55%, N = 4) (Figure 14A). A subgroup analysis based on the dose of dapagliflozin was conducted, and the results demonstrated that both 5 mg and 10 mg of dapagliflozin could significantly decrease DBP (dapagliflozin5 mg: WMD= -2.10, 95% CI = -3.37 to -0.83, p = 0.001,  $I^2 = 51\%$ , N = 3; dapagliflozin 10 mg: WMD = -2.03, 95% CI = -3.17 to -0.89, p = 0.0005,  $I^2 = 30\%$ , N = 3) (Figure 14A). Additionally, there was a similar effect in reducing DBP between SGLT2i treatment for 12 weeks and metformin (WMD = -1.17, 95% CI = -2.74 to 0.40, p = 0.14,  $I^2 = 46\%$ , N = 4) (Figure 14A). Nonetheless, SGLT2i treatment for 24–26 weeks distinctly reduced DBP compared with that of metformin (WMD = -1.55, 95% CI = -2.17to -0.94, p < 0.00001,  $I^2 = 23\%$ , N = 4) (Figure 14A). Four studies provided the DBP levels in obesity patients and the results indicated that SGLT2i decreased DBP more remarkably than metformin (WMD = -1.09, 95% CI = -1.78 to  $-0.41, p = 0.002, I^2 = 0\%$ ) (Figure 14A).

In consistent with the result of DBP, SGLT2i significantly reduced systolic blood pressure (SBP) compared with metformin (WMD = -2.92, 95% CI = -3.75 to  $-2.10, p < 0.00001, I^2 = 20\%$ , N = 10) (Figure 14B). Likewise, the application of empagliflozin and dapagliflozin was more effective in reducing SBP than metformin (dapagliflozin: WMD = -3.07, 95% CI = -4.63 to -1.51, p = 0.0001,  $I^2 = 0\%$ , N = 4; empagliflozin: WMD = -3.53, 95% CI = -4.97 to -2.09, p < 0.00001,  $I^2 = 63\%$ , N = 3) (Figure 14B). Due to the non-negligible heterogeneity, a subgroup analysis based on the dose of empagliflozin was performed and the result revealed that both 10 mg and 25 mg of empagliflozin significantly reduced SBP compared with that of metformin (empagliflozin 10 mg: WMD = -3.39, 95% CI = -5.09 to -1.68, p < 0.0001,  $I^2 = 49$ %, N = 3; empagliflozin 25 mg: WMD = -3.96, 95% CI = -5.66 to -2.26, p < 0.00001,  $I^2 = 59$ %, N = 3) (Figure 14B). Considering the effect of various treatment periods of SGLT2i, we found that both SGLT2i treatment for 12 weeks and 24-26 weeks were associated with an obvious reduction in SBP compared with metformin (12 weeks: WMD = -4.61, 95% CI = -7.06 to -2.16, p = 0.0002,  $I^2 = 0\%$ , N = 4; 24–26 weeks: WMD = -2.32, 95% CI = -3.26 to -1.38, p < 0.00001,  $I^2 = 0\%$ , N = 4) (Figure 14B). In addition, for obese T2DM patients, treatment with SGLT2i significantly decreased SBP in contrast with metformin (WMD = -2.50, 95% CI = -3.53 to -1.47, p < 0.00001, $I^2 = 0\%$ , N = 4) (Figure 14B).

А	SGLT	2 inhibit	tors	Me	tformin	1		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight		IV. Fixed, 95% CI
Body weight (K	g)								
Araki, E. 2015	-2.55	2.34	273	-0.1	2.38	63	0.6%	-2.45 [-3.10, -1.80]	
Ferrannini, E.* 2013	-2.06	2.34	244	-1.32	2.33	80		-0.74 [-1.33, -0.15]	
Ferrannini, E. 2013	-2.41	3.91	168	-1.3	3.73	56	0.2%	-1.11 [-2.25, 0.03]	
Fonseca, V. A. 2012	-0.98	3.23	273	0.12	3.23	69		–1.10 [–1.95, –0.25]	
Hadjadj, S. 2016	-2.39	0.29	298	-0.9	3.61	288		-1.49 [-1.91, -1.07]	
Henry, R. R. 2012	-2.67	3.41	422	-1.33	3.41	408		-1.34 [-1.80, -0.88]	
Ito, D. 2021	-2.1	2.9	11	-1.3	2	10	0.1%	-0.80 [-2.92, 1.32]	
Jingqian Xie. 2020 Koshizaka, M. 2019	-3.26	10.1	31	-1.47	10.38	31	0.0%	-1.79 [-6.89, 3.31]	
Rosenstock, J. 2019	-2.1 -3.25	2.03 0.49	48 472	-0.49 -1.9	2.23 0.2	50 237		-1.61 [-2.45, -0.77] -1.35 [-1.40, -1.30]	
Subtotal (95% CI)	-3.20	0.49	2240	-1.9	0.2	1292		-1.35 [-1.40, -1.30]	<b>T</b>
Heterogeneity: Chi <sup>2</sup> =	16.69, df	= 9 ( <i>p</i> =		² = 46%	5				
Test for overall effect:	Z = 53.29	9 ( <i>p</i> < 0.0	00001)						
									-4 -2 0 2 4
									Favours [SGLT2 inhibitors] Favours [Metformin]
В									
-		2 inhibit			tformin			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV. Fixed, 95% Cl
Body weight (K				<i>.</i> .					
Araki, E. 2015	-2.55	2.34	273	-0.1	2.38	63		-2.45 [-3.10, -1.80]	
Ferrannini, E.* 2013	-2.06	2.34	244	-1.32	2.33	80		-0.74 [-1.33, -0.15]	
Ferrannini, E. 2013	-2.41	3.91	168	-1.3	3.73	56	6.5%	-1.11 [-2.25, 0.03]	-
Hadjadj, S. 2016 Subtotal (95% CI)	-2.39	0.29	298 983	-0.9	3.61	288 <b>487</b>		-1.49 [-1.91, -1.07] -1.47 [-1.77, -1.18]	
Heterogeneity: Chi <sup>2</sup> =	15 02 44	= 3/n-		12 - 90	0/_	-+07	100.0 /0		•
Test for overall effect:				, - 00	/0				
	_ 0.00	(F - 0.0							
Body weight (K	g) EMPA	(after d	eleting	Araki,	E. 2015	)			
Ferrannini, E.* 2013	-2.06	2.34	244	-1.32	2.33	. 80	30.8%	-0.74 [-1.33, -0.15]	
Ferrannini, E. 2013	-2.41	3.91	168	-1.3	3.73	56		-1.11 [-2.25, 0.03]	
Hadjadj, S. 2016	-2.39	0.29	298	-0.9	3.61	288		-1.49 [-1.91, -1.07]	<b>≞</b>
Subtotal (95% CI)			710			424	100.0%	-1.23 [-1.55, -0.90]	•
Heterogeneity: Chi <sup>2</sup> =	4.19, df =	:2( <i>p</i> =0	).12); l²	= 52%					
Test for overall effect:	Z = 7.37	( <i>p</i> <0.0	0001)						
Body weight (K			100		<b>.</b>			1011100 01	<b>_</b>
Henry, R. R. 2012	-2.67	3.41	422	-1.33	3.41	408		-1.34 [-1.80, -0.88]	
Ito, D. 2021	-2.1	2.9	11 433	-1.3	2	10	4.6%	-0.80 [-2.92, 1.32]	
Subtotal (95% CI) Heterogeneity: Chi <sup>2</sup> =	0.24 df -	1/n = 0		- 0%		410	100.0%	-1.32 [-1.77, -0.86]	•
Test for overall effect:				- 0%					
resciol overall effect.	2 - 5.05	(P < 0.0)	0001)						
Body weight (K	q) Obesi	tv							
Fonseca, V. A. 2012	-0.98	3.23	273	0.12	3.23	69	0.4%	_1.10 [-1.95, -0.25]	<u> </u>
Hadjadj, S. 2016	-2.39	0.29	298	-0.9	3.61	288		-1.49 [-1.91, -1.07]	<u> </u>
Rosenstock, J. 2016	-3.25	0.49	472	-1.9	0.2	237		-1.35 [-1.40, -1.30]	
Subtotal (95% CI)			1043			594		-1.35 [-1.40, -1.30]	T
Heterogeneity: Chi <sup>2</sup> =	0.76, df =	2 ( <i>p</i> = 0	).68); l²	= 0%				-	
Test for overall effect:	Z = 52.39	9 ( <i>p</i> < 0.0	00001)						
Body weight (K									
Ferrannini, E.* 2013	-2.06	2.34	244	-1.32	2.33	80		-0.74 [-1.33, -0.15]	
Fonseca, V. A. 2012	-0.98	3.23	273	0.12	3.23	69		-1.10 [-1.95, -0.25]	
Ito, D. 2021	-2.1	2.9	11	-1.3	2	10		-0.80 [-2.92, 1.32]	
Jingqian Xie. 2020	-3.26	10.1	31	-1.47	10.38	31		-1.79 [-6.89, 3.31]	•
Subtotal (95% CI)	0 50 df -	3/10-0	559 1 001-12	= 0%		190	100.0%	-0.86 [-1.33, -0.39]	▼
Heterogeneity: Chi <sup>2</sup> = Test for overall effect:				- 076					
reactor overall effect.	L - 0.09	( r = 0.0	)						
Body weight (K	g) 24-26	week tri	als						
Hadjadj, S. 2016	-2.39	0.29	298	-0.9	3.61	288	1.4%	-1.49 [-1.91, -1.07]	
Henry, R. R. 2012	-2.67	3.41		-1.33	3.41	408		-1.34 [-1.80, -0.88]	
Koshizaka, M. 2019	-2.1	2.03	48	-0.49	2.23	50		-1.61 [-2.45, -0.77]	— <u>—</u>
Rosenstock, J. 2016	-3.25	0.49	472	-1.9	0.2	237		-1.35 [-1.40, -1.30]	
Subtotal (95% CI)			1240					-1.35 [-1.40, -1.30]	
Heterogeneity: Chi <sup>2</sup> =	0.78, df =	: 3 ( <i>P</i> = 0	).85); l²	= 0%					
Test for overall effect:	Z = 52.77	7 ( <i>p</i> < 0.0	00001)						
									-4 -2 0 2 4
									Favours [SGLT2 inhibitors] Favours [Metfromin]

**Figure 12.** (**A**). Weighted mean difference in change in body weight (Kg) from baseline from SGLT2i compared with metformin [20–24,26,29–32]. (**B**). Weighted mean difference in change in body weight (Kg) from baseline from types of SGLT2i compared with metformin. Weighted mean difference in change in body weight (Kg) from baseline from SGLT2i used 12 weeks or 24–26 weeks compared with metformin and weighted mean difference in change in body weight (Kg) from baseline from SGLT2i used 12 weeks or 24–26 weeks compared with metformin and weighted mean difference in change in body weight (Kg) from baseline from SGLT2i in obesity patients [20–24,26,29–32]. DAPA = dapagliflozin, EMPA = empagliflozin. 12 weeks trials = SGLT2i used 12 weeks. Obesity = SGLT2i used in obese people.

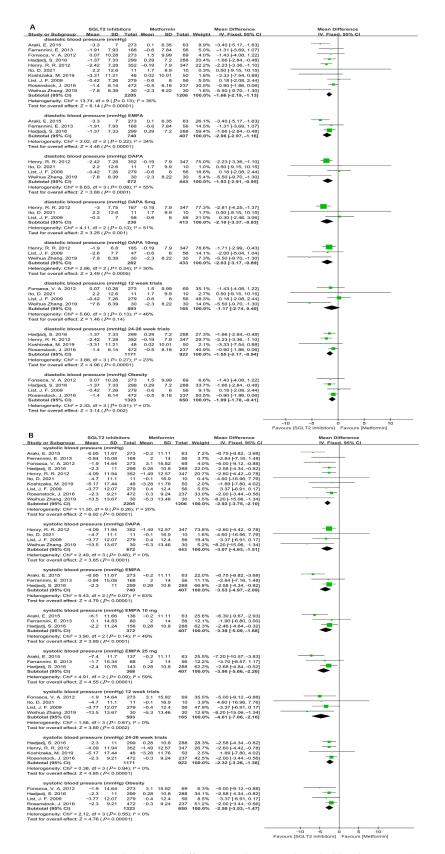
Sludy of Suburous Mean SD Total Mean SD Total Mean SD Total Melait M Fixed 95% Cl M. Fixed 95%			2 inhibi			etformin			Mean Difference	Mean Difference
$ \begin{array}{c} \operatorname{val}_{14} (E 2015 & 0.26 & 22.66 & 273 & -2.2 & 25.4 & 63 & 41.8\% & 10.25 (52.8,17.22) \\ \operatorname{wal}_{14} (E 149 & -0.25) & -1.46 & -1.26 & 23.42 & 43 & 27.0\% & -1.46 & -0.05 & -1.46 & -0.05 & -1.46 & -1.26 & 23.42 & -1.26 & -1.46 & -1.26 & $	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	I IV. Fixed, 95% CI
Terannini, E. 2013 2.21 4.8.0.4 168 -0.28 3.4.1 66 15.2% 11.4.8 ( $-000, 2.3.07$ ) to, D. 2021 -4.6 14.9 11 -6.1 15.7 10 11.0% 15.0 ( $-12.5.2$ , $-12.5.2$ , $-12.5.2$ , $-12.5.2$ 3.7.1 30 -8.5 1 41.4.4 30 5.1% -17.0 ( $+3.70.6$ , $-3.8.7$ ) We have Zhang, 2019 -255.2 3.7.1 30 -8.5 1 41.4.4 30 5.1% -7.70 ( $+3.70.6$ , $-3.8.7$ ) We have Zhang, 2019 -255.2 3.7.1 30 -8.5 1 41.4.4 30 5.1% -7.70 ( $+3.70.6$ , $-3.8.7$ ) We have Zhang, 2019 ( $+2.5.2$ , $-3.7.1$ 30 -8.5 1 41.4.4 30 5.1% -7.70 ( $+3.70.6$ , $-3.8.7$ ) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Total cholestero ( $mgddl$ ) ( $atrar$ deteting We have Zhang, 2019) Tradic 2.1% 2.2% ( $atrar$ 2.2% ( $atrar$ 2.2% 2.4% 2.4% 15.19 ( $b5.1, 2.3.8.7$ ) Subtotal ( $b9.5.7$ ( $b.2.5.8, 3.3.2$ 2.73 -2.2 2.5.8.73 63 1 9.9% 10.8.1 ( $b.15, 15.4.6.1$ ( $b.15, 15.4.6.1$ ( $b.15, 15.6.2.6.1$ ) ( $b.0.2021$ 0.8 6 11 7.3 12.6 10 15% 6.50 17.3% 1.25 ( $b.13.5, 15.1.5.1.2.4.2.0.2$ ) ( $b.0.2021$ 0.8 6 11 7.3 12.6 10 15% 6.50 ( $t.5.6.5.0.7.7.6.5$ ( $t.5.6.7.7.6.5.0.7.7.6.5$ Total characterized ( $mgddl$ ) ( $tatrar$ deteting Arabic, E.2015) HOL-cholesterol ( $mgddl$ ) ( $tatrar$ deteting Arabic, E.2017) HOL-cholesterol ( $mgddl$ ) ( $tatrar$ deteting Arabic, E.2015)				070		05.4			10.05 10.00 17.001	
Ib D. 2021 - 4.8 14.9 11 -6.1 16.7 10 110% 13.0 [-12.2, 14.89] (whuk 2may 2019 - 255.2 37.1 30 -65.1 41.44 30 51% -17.0 [-37.06, 3.34] Subtola (95% C) 530 224 200.00% 9.41 [4.90, 13.2] Hereogeneity, Ch <sup>2</sup> - 9.92, df + ( $P = 0.04$ ); $P = 60\%$ Total cholestrol(mgdd) (aff edeleting Wehux 2man, 2019) Vasik, E. 2015 8.05 25.66 273 -2.2 24.4 63 44.0% 10.25 [1.2,3, 17.22] Total cholestrol(mgdd) (aff edeleting Wehux 2man, 2019) Vasik, E. 2015 8.05 25.66 273 -2.2 24.4 63 14.0% 10.25 [1.2,3, 17.22] Total cholestrol(mgdd) (aff edeleting Wehux 2man, 2019) Vasik, E. 2015 8.05 25.66 273 -2.2 24.4 63 14.0% 10.25 [1.2,3, 17.22] (aff convariable), Ch <sup>2</sup> - 2.80, df -3 ( $P = 0.41$ ); $P = 0.\%$ Farmanni, E. 2013 2.1 48.04 168 +2.22 3.4.41 5.2 2.3.4.2 43 28.4% 15.19 [6.51, 2.3.87] Subtotal (95% C) 4.8 14.9 11 -6.1 16.7 10 11.6% 15.00 1.12% 15.16.41 Heterogeneity, Ch <sup>2</sup> - 2.80, df -3 ( $P = 0.41$ ); $P = 0.\%$ Faremanni, E. 2015 6.7 88.77 168 5.41 8.99 56 16.3% 1.36 [-1.50, 8, 2.08] (abchazka, M. 2019 1.86 11 7.3 12.6 10 1.6% -6.50 [-1.50, 8, 2.08] (abchazka, M. 2019 5.8 18.73 30 2.71 15.6 30 1.5% .3.91 [-5.15, 4.5] HOL-cholesterol (mgdd) HOL-cholesterol (mgdd) Heterogeneity, Ch <sup>2</sup> - 2.80, df -5 ( $P = 0.000$ ); $P = 81\%$ Faremanni, E. 2015 6.8 8.79 453 3.0 2.71 15.6 30 1.5% .3.91 [-5.16, 2.8, 2.8] (abchazka, M. 2019 5.8 18.73 30 2.71 15.6 30 1.5% .3.91 [-5.16, 8, 2.08] (abchazka, M. 2019 5.8 18.73 30 2.71 15.6 30 1.9% .2.95 [-1.31, 4.59] HOL-cholesterol (mgdd) HOL-cholesterol (mgdd) Heterogeneity, Ch <sup>2</sup> - 2.80, df -5 ( $P = 0.000$ ); $P = 81\%$ Faremanni, E. 2013 6.8 6 11 7.3 12.6 10 2.0% .456 [1.50, 7.15] Faremanni, E. 2013 6.8 6 17.3 30 2.71 15.6 30 1.9% .2.99 [1.31, 4.59] Heterogeneity, Ch <sup>2</sup> - 2.80, df -5 ( $P = 0.0001$ ); $P = 81\%$ Fast for overall effect: $Z = -5.70$ ( $P = 0.0001$ ); $P = 6.0\%$ Fast for overall effect: $Z = -5.70$ ( $P = 0.0001$ ); $P = 6.0\%$ Fast for overall effect: $Z = -5.70$ ( $P = 0.0001$ ); $P = 6.0\%$ Fast for overall effect: $Z = -5.70$ ( $P = 0.0001$ ); $P = 0.0\%$ Subtotal (95% C) -3.3										
$ \begin{array}{c} \mbod construction, M, 2019 & 196 & 18.15 & 48 - 13.22 & 23.42 & 43 & 27.0\% & 15.16  [55.12.3.37] \\ \mbod construction, 25.52 & 37.1 & 30 & -8.51 & 41.44 & 30 & 51.\% & -7.10  [4.57.06, 53.04] \\ \mbod construction, 25.62 & 37.1 & 30 & -8.51 & 41.44 & 30 & 51.\% & -7.10  [4.57.06, 53.04] \\ \mbod construction, 25.62 & 57.6 & 27.3 & -2.2 & 25.4 & 63 & 40.\% & 10.25  [3.28, 17.22] \\ \mbod construction, 22.1 & 64.0 & 106 & -26.2 & 34.41 & 56 & 10.0\% & 11.49  [-0.02, 23.07] \\ \mbod construction, 22.1 & 64.0 & 106 & -26.2 & 34.41 & 56 & 10.0\% & 11.49  [-0.02, 23.07] \\ \mbod construction, 22.1 & 64.0 & 166 & -26.2 & 43.41 & 26.6 & 16.0\% & 11.49  [-0.02, 23.07] \\ \mbod construction, 22.1 & 64.0 & 16.8 & -28.2 & 44.1 & 56 & 10.0\% & 10.25  [3.28, 17.22] \\ \mbod construction, 22.1 & 64.0 & 16.8 & -28.2 & 44.1 & 56 & 10.0\% & 11.49  [-0.02, 23.07] \\ \mbod construction, 22.0 & d1 = 3  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 3  (P \sim 0.011) \\ \mbod construction, 22.0 & d1 = 3  (P \sim 0.011) \\ \mbod construction, 22.0 & d1 = 3  (P \sim 0.011) \\ \mbod construction, 22.0 & d1 = 3  (P \sim 0.011) \\ \mbod construction, 22.0 & d1 = 3  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0 & d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0  d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0  d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0  d1 = 5  (P \sim 0.0001) \\ \mbod construction, 22.0  d1 = 5  (P \sim 0.0001) \\ \mbod construct$										
Weihuk Zamag, 2019       -25.2       97.1       30       -65.1       41.4       30       5.1%       -17.01       -37.06, 3.0.4]         Heterogeneity: Ch <sup>2+</sup> 9.92, df = 4 ( <i>P</i> = 0.04); P = 60%       222       100.0%       9.41 (4.90, 13.82]         Total cholesterol (mgld) (after deleting Weihua Zhang, 2019)       Total cholesterol (mgld) (after deleting Weihua Zhang, 2019)         Kraik, E. 2015       8.05       25.66       27.3       -2.2       2.8.4       63       44.0%       10.25 (3.2.8, 17.22)         Kraik, E. 2015       8.05       2.56.6       27.3       -2.2       2.8.4       15.19 (5.5), 2.3.87]         Subtrotal (95%, C)       500       17.2       10.6%       15.19 (5.5), 2.3.87]         Subtrotal (95%, C)       500       17.2       10.6%       1.55 (1.5, 15.4.4]         Heterogeneity: Ch <sup>2+</sup> = 2.8, df = 3.3       2.7.3       -2.5       50       17.3%       4.56 (1.9.7, 7.15)         Somenatok, J. 2016       6.6       48       -0.08       5.5       50       17.3%       4.56 (1.9.7, 7.15)         Somenatok, J. 2016       6.8       8.71       8.3       10.0.0%       3.39 (4.5.3, 11.45)         Weihua Zhang, 2019       6.8       17.3       12.6       10.2%       4.56 (1.9.7, 7.15)										
Subotal (PS <sup>2</sup> , C1) 530 202 100.0% 9.41 [4.90, 13.92] Heterogeneity: Ch <sup>2</sup> = 98, 2f = 4 ( $P = 0.00$ ); P = 60%; Test for overall effect: Z = 4.09 ( $P < 0.0001$ ) Total cholesterol (mg/dl) (after deleting Weihus Zhang, 2019) Avaki, E. 2015 6.05 2566 273 -2.2 254 63 441 56 16.0% 11.49 [-0.09, 23.07] to, D. 2021 -4.8 14.9 11 -6.1 167 10 11.6% 1.50 [-1.2.9, 14.89] Subotal (19%; C1) 9 196 115 46 -13.23 23.42 43 23.44 is 1519 [65.1, 33.87] Subotal (19%; C1) 9 196 115 500 172 (100.0% 10.25 [3.28, 11.17] HDL-cholesterol (mg/dl) Avaki, E. 2015 6.25 9.33 273 -2.5 8.73 63 19.9% 6.75 [6.33, 11.17] Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 16.3% 1.35 [-1.32, 4.02] Newenable, M. 2019 4.48 6.6 48 -0.08 6.5 50 17.3% 4.56 [1.97, 7.15] Subotal (19%; C1) 9 883 431 100.0% 3.97 [2.89, 5.05] Heterogeneity: Ch <sup>2</sup> = 2.80, df = 5 ( $P < 0.0001$ ); $P = 81%$ . Test for overall effect Z = -7.21 ( $P < 0.0001$ ); $P = 81%$ . HoL-cholesterol (mg/dl) (free deleting Avaki.E 2015) Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 20.44% 1.55 [-1.52, 2.08] (sochizaka, M. 2019 4.48 6.5 48 -0.08 6.5 50 2.17% 4.56 [1.57, 7.15] Subotal (19%; C1) 9 58 18.73 30 2.71 156 30 1.5% 3.09 [-5.50, 1.181] Weihua Zhang, 2019 5.8 18.73 30 2.71 156 30 1.5% 3.09 [-5.13, 1.14] Weihua Zhang, 2019 5.8 18.73 30 2.71 156 30 1.5% 3.09 [-5.13, 1.14] Subotal (19%; C1) 9 58 18.73 30 2.71 156 30 1.5% 3.09 [-1.50, 1.065] Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 20.44% 1.55 [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 156 30 1.9% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5% (Soc) [-1.50, 2.08] (sochizaka, M. 2019 5.8 18.73 30 2.71 1.53 2.31 10.5%										
Heerogeneity: Ch <sup>2</sup> = 9.92, df = 4 ( $P=0.04$ ); $P=00\%$ Total cholesterol (mg/dl) (after deleting Weihus Zhang, 2019) Araki, E. 2015 2.01 (48.04 (168 - 9.28 34.41 56 16.0% 11.49 (1.09, 23.07) (0.0, 2021 - 4.8 14.9 11 - 6.1 16.7 10 11.8% 1.30 (1-22.9.14.88) Goahizaka, M. 2019 1.96 18.15 48 - 13.23 23.42 43 28.4% 15.19 [65.1, 23.87] Subtotal (95% C) 500 172 100.0% 10.81 [6.19, 15.44] Helerogeneity: Ch <sup>2</sup> = 2.90, df = 3 ( $P=0.41$ ); $P=0\%$ Test for overall effect: 2 = 4.58 ( $P<0.0000$ )) HDL-cholesterol (mg/dl) Araki, E. 2015 6.25 9.33 273 - 2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E. 2013 6.76 8.67 1185 541 88.9 56 16.3% 1.35 [-1.32, 4.02] Ito, D. 2021 0.8 6 11 7.3 12.6 10 16.% -6.50 [-15.08, 2.08] Coshizaka, M. 2019 4.48 6.6 48 - 0.08 6.5 50 17.3% 4.58 [17.97, 71.5] Rosenatock, J. 2016 6.85 9.79 453 3.9 10.43 222 43.3% 2.28 [1.31, 4.59] Helerogeneity: Ch <sup>2</sup> = 2.0.9, df = 5 ( $P<0.0000$ )) HDL-cholesterol (mg/dl) Helerogeneity: Ch <sup>2</sup> = 2.0.9, df = 5 ( $P<0.0000$ ) HDL-cholesterol (mg/dl) (after deleting Araki, E. 2015) Ferramini, E. 2013 6.76 8.67 188 541 8.89 56 62.04% 1.35 [-1.32, 4.02] Ito, D. 2021 0.8 6 11 7.3 12.6 10 2.0% -6.50 [-15.08, 2.08] Goahizaka, M. 2019 4.48 6.56 48 -0.08 6.5 50 21.7% 4.56 [1.97, 7.15] Rosenatock, J. 2016 6.85 9.79 453 3.9 10.43 222 54.0% 2.29 [1.31, 4.59] Helerogeneity: Ch <sup>2</sup> = 2.6.7 ( $P<0.0000$ ) HDL-cholesterol (mg/dl) Hall, E. 2015 6.85 0.77 453 3.9 10.43 222 54.0% 2.29 [1.31, 4.59] Weihua Zhang, 2019 5.8 18.73 30 2.71 156 30 19% 3.96 [4.50, 10.61, 0.65] Ferramini, E. 2013 1.43 35.5 168 -5.41 2.26 55 6 2.17% 4.88 [1.97, 7.15] Rosenatock, J. 2016 6.85 9.79 453 3.9 10.43 222 54.0% 2.29 [1.31, 4.59] Weihua Zhang, 2019 5.8 18.73 30 2.71 156 30 19% 3.99 [4.53, 11.61] Helerogeneity: Ch <sup>2</sup> = 7.67 ( $P<0.00001$ ) Helerogeneity: Ch <sup>2</sup> = 7.67 ( $P<0.00$		20.02	01.11		0.01	41.44				◆
Test for overall effect: Z = 4.08 ( $P < 0.0001$ ) Total cholesterol (mg/dl) (after deleting Weihua Zhang, 2019) Naki, E. 2015 0.5 256 273 -2.2 254 63 44.0% 10.25[3.28,17.22] Ferramini, E. 2013 2.21 48.04 168 -9.28 34.41 56 16.0% 11.49 [-0.09, 23.07] No, D. 2021 - 4.8 14.9 11 - 6.1 167 10 11.6% 1.50 [-12.29, 14.89] Subtotal (95% CI) - 900 - 722 42 43 224 43 224 45 1519 [65.17, 3.87] Test for overall effect. Z = 4.58 ( $P < 0.00001$ ) HDL-cholesterol (mg/dl) Naki, E. 2015 6.25 9.33 273 -2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 16.3% 1.55 [-13.24, 0.2] Ib, D. 2021 0.8 6 11 7.3 12.6 10 16% -6.50 [-15.08, 2.08] Sochakak, M. 2019 4.48 6.6 48 -0.08 6.5 50 17.3% 4.55 [15.77, 15] Sochakak, J. 2016 6.85 9.79 453 3.9 10.43 222 43.3% 2.95 [15.1, 4.59] Heterogeneity: Ch <sup>1+</sup> = 2.00, df = 5 ( $P < 0.0001$ ); $P = 1%$ Test for overall effect. Z = 7.21 ( $P < 0.00001$ ); Heterogeneity: Ch <sup>1+</sup> = 2.00, df = 5 ( $P < 0.0001$ ; $P = 1\%$ Test for overall effect. Z = 7.21 ( $P < 0.00001$ ); HOL-cholesterol (mg/dl) Araki, E. 2015 6.7 185 5.41 8.89 56 20.4% 4.05 [1.57, 7.15] Socenatook, J. 2016 6.85 9.79 453 3.9 10.43 222 43.3% 2.95 [1.51, 4.59] Heterogeneity: Ch <sup>1+</sup> = 7.48, df = 4 ( $P = 0.0001$ ); HOL-cholesterol (mg/dl) Araki, E. 2015 7.78 455 [1.97, 7.15] Socenatook, J. 2016 6.85 9.79 185 5.41 8.89 56 20.4% 4.05 [1.57, 7.15] Socenatook, J. 2016 6.85 9.79 185 5.41 8.89 56 20.4% 4.05 [1.57, 7.15] Socenatook, J. 2016 6.85 9.79 185 5.41 8.89 56 20.4% 4.05 [1.57, 7.15] Socenatook, J. 2016 6.85 9.79 185 5.41 8.89 56 20.4% 4.05 [1.57, 7.15] Socenatook, J. 2016 6.85 9.79 185 5.41 8.89 56 20.4% 4.05 [1.57, 7.15] Socenatook, J. 2016 6.85 9.79 4.53 3.9 10.43 222 5.0% 2.36 [1.51, 4.59] Hol. D. 2021 7.74 5.4 4.74 ( $P = 0.015$ ; $P = 0.\%$ Test for overall effect. Z = 4.53 ( $P < 0.00001$ ) HEterogeneity: Ch <sup>1+</sup> = 7.74, df = 4 ( $P = 0.15$ ; $P = 0.\%$ Test for overall effect. Z = 4.53 ( $P < 0.00001$ ) Tiglycardise (mg/dl) Araki, E. 2015 - 4.58 ( $P < 0.00001$ ) Tiglycardise (mg/dl) Naki, E		9.92. df =	4 ( <i>P</i> = 0.	04);   <sup>2</sup> =	60%					
Araki, E. 2015 8.05 25.66 273 -22 25.4 63 44.0% 10.25 [3.28, 17.22] Ferramini, E. 2013 2.21 48.04 168 -42.8 34.41 66 16.09, 23.07] to, D. 2021 4.8 14.9 11 -6.1 16.7 10 11.6% 1.30 [-12.29, 14.89] (SoBhzaka, M. 2019 1.56 18.15 48 -13.23 23.42 43 28.44 56 15.90 [6.31, 23.87] to D. 2021 4.8 14.9 11 -6.1 16.7 10 11.6% 1.30 [-12.29, 14.89] Test for overall effect: Z = 4.58 ( $P < 0.0001$ ) HDL-cholesterol (mg/dl) Araki, E. 2015 6.25 9.33 273 -25 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 16.3% 1.35 [-1.32, 4.02] to, D. 2021 0.8 66 11 7.3 12.6 10 1.6% -6.50 [-15.08, 2.08] Koentock, M. 2019 4.48 6.6 48 -0.08 6.5 50 17.3% 4.56 [1.97, 7.15] Resenstock, J. 2016 6.25 9.79 453 3.9 10.43 222 43.3% 2.96 [1.31, 4.59] Wehua Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.5% 30.91 F.33, 11.81] Subtolal (9% C) 9 883 41 10.04% 3.97 [2.88, 5.05] Helerogeneity: Ch <sup>+</sup> = 2.69, df = 5 ( $P < 0.0001$ ); $P = 81\%$ Test for overall effect: Z = 7.21 ( $P < 0.00001$ ); $P = 81\%$ Test for overall effect: Z = 7.21 ( $P < 0.00001$ ); $P = 81\%$ Test for overall effect: Z = 4.53 ( $P < 0.0001$ ); $P = 81\%$ HDL-cholesterol (mg/dl) Araki, E. 2015 4.6 20.99 273 -0.2 21.43 63 29.3% 4.00 [-1.05, 10.65] Ferramini, E. 2013 1.43 351 168 -5.41 32.26 56 9.7% 6.84 [+3.30, 16.89] to, D. 2021 0.8 6 71 17.3 2.2 21.77 4.55 [1.58, 1.181] Subtolal (9% C) 710 368 100.0% 2.79 [1.58, 1.181] Subtolal (9% C) 9 39 31.47 450 -0.6 31.29 2.22 39.7 48 158 (1.163, 86, 19.60] Soenstock, J. 2016 9.39 31.74 48 -1.25 2.39.7 48 158 [1.503, 31.53] Helerogeneity: Ch <sup>+</sup> = 2.6.7, df = 4 ( $P = 0.51$ ); $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -1.34 ( $P = 0.51$ ; $P = 0\%$ Test for overall effect: Z = -										
Ferramini, E. 2013       2.21       48.04       168       -9.28       34.41       56       16.0%       11.4.9       10.00       23.07         to, D. 2021       -4.8       14.9       11       -6.1       16.7       10       11.8%       13.0       12.29       14.89       13.0       15.0       13.0       12.29       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       13.0       14.89       10.0       14.89       10.0       16.19       15.44       14.89       10.0       16.89       15.0       17.3       16.80       15.0       17.9       16.0       16.0       16.0       16.0       16.0       11.0       14.8       10.0       10.0       13.0       10.0       13.0       14.0       10.0       13.0       13.1       11.0       13.0       13.0       13.1       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0       13.0										_
by D, D2021 - 4.8 14.9 11 -6.1 16.7 10 11.6% 130 [-1.22, 14.80] ocharkak, M.2019 1.96 18.15 48 -13.23 23.42 43 244, 15.916(5.12.837] Subtotal (95% CI) 500 172 100.0% 10.81 [6.19, 15.44] Heterogeneity: Ch <sup>+</sup> = 2.6.9 ( $P = 0.41$ ); $P = 0\%$ fest for overall effect Z = 4.58 ( $P = 0.41$ ); $P = 0\%$ Ferramini, E.2015 6.25 9.33 273 -2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E.2015 6.25 9.33 273 -2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E.2015 6.25 9.33 273 -2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E.2015 6.78 8.67 168 5.41 8.89 56 10.3% -6.50 [+5.08, 2.08] Sobenstock, J.2016 6.85 9.79 453 3.9 10.43 222 43.3% 2.99 [1.31, 4.59] Vehua Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.5% 3.09 [+5.3, 11.81] Subtotal (95% C) 9 883 - 4.11 7.3 12.6 10 2.0% -6.50 [+5.08, 2.08] Ferramini, E.2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35 [+1.32, 4.02] HDL-cholesterol (mg/dl) (Aref detenting Araki, E. 2015) Ferramini, E.2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35 [+1.32, 4.02] HDL-cholesterol (mg/dl) [Aref detenting Araki, E. 2015) Ferramini, E.2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35 [+1.32, 4.02] HDL-cholesterol (mg/dl) [Aref detenting Araki, E. 2015) Ferramini, E.2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35 [+1.32, 4.02] HDL-cholesterol (mg/dl) [Aref detenting Araki, E. 2015) Ferramini, E.2013 6.78 8.73 30 2.71 15.6 30 1.9% 3.09 (+5.3, 11.81] Subtotal (95% C) 71 70 368 100.0% 2.79 [1.58, 4.00] Heterogeneity: Ch <sup>+</sup> = 2.69, gt = 11; $P = -64\%$ Fest for overall effect $Z = 4.53$ ( $P = 0.00001$ ) LDL-cholesterol (mg/dl) Triglycerides (mg/dl) Triglycerides (mg/dl) Triglycerides (mg/dl) Triglycerides (mg/dl) Hubuz 2harg, 2019 - 3.83 17.43 168 -5.51 177, 3.836 [4.44, 1.45.85] Yehua Zharg, 2019 - 3.85 98.66 48 -0.44 7 127.89 47 5.5% 15.12 [29.70, 69.44] Heterogeneity: Ch <sup>+</sup> = 2.57, df = 4.( $P = 0.61$ ; $P = 0.\%$ Ferramini, E.2013 - 4.168 294.31 168 -5.53 10.75 × 5.53 (1.51, 2]; 29.70, 69.44] Heterogeneity: Ch <sup>+</sup> = 2.85 9.866 48 -0.44 7 127.89 47 5.5% 15.12 [29.70, 69.44] Heterogeneity: Ch <sup>+</sup> = 3.83										
Konkuzak, M. 2019 1.96 18.15 48.1-323 23.42 43 28.4% 15.19 [6.51, 23.87] Methorogeneity: Ch <sup>2</sup> = 2.90, df = 3 ( $P = 0.41$ ); $P = 0\%$ Test to covarial effect: $Z = 4.58$ ( $P = 0.0001$ ) H0L-cholesterol (mg/dl) H0L-cholesterol (mg/dl) H0L-chol										
Subotal (95%, C) 500 172 100.0% 10.81 [ $\hat{n}$ : 9, 15.4d] Heterogeneity: Ch <sup>2</sup> = 2.80, df = 3 ( $P$ = 0.41); P = 0% Text for overall effect: Z = 4.58 ( $P$ < 0.00001) HDL-cholesterol (mg/dl) Araki, E. 2015 6.25 9.33 273 -2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E. 2015 6.76 8.67 168 5.41 8.89 56 16.3% 1.36 [-1.32, 4.02] Nebrabaak, D.2019 4.88 66 11 7.3 12.6 10 16% -6.50 [-15.08, 2.08] Associated al. 2019 4.88 66 44 -0.08 6.5 50 17.3% 4.56 [1.57, 7.15] Rosenstock, J. 2016 6.85 9.79 453 3.9 10.43 222 43.3% 2.95 [1.31, 4.59] Wehua Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.5% 3.09 [-5.3, 11.81] Subotal (95%, C) = 27.21 ( $P$ < 0.0001); $P = 31\%$ . Text for overall effect: Z = 7.72 ( $P$ < 0.0001); $P = 31\%$ . Heterogeneity: Ch <sup>2</sup> = 26.9, df = 5 ( $P$ < 0.0001); $P = 31\%$ . Heterogeneity: Ch <sup>2</sup> = 2.6, df = 5 ( $P$ < 0.0001); $P = 31\%$ . Text for overall effect: Z = 4.53 ( $P$ < 0.0001) HDL-cholesterol (mg/dl) (after deteling Araki, E. 2015) Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35 [-1.32, 4.02] Heterogeneity: Ch <sup>2</sup> = 7.42 ( $P$ < 0.11% P = 46\%. Text for overall effect: Z = 4.53 ( $P$ < 0.0001) LDL-cholesterol (mg/dl) Araki, E. 2015 4.6 20.99 273 -0.2 21.43 63 29.3% 4.80 [-1.05, 10.65] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 56 9.7% 6.84 [-3.30, 16.39] Ho, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% (1.01, 7.09, 19.09] Heterogeneity: Ch <sup>2</sup> = 2.67, df = 4 ( $P$ = 0.51); P = 0% Text for overall effect: Z = 4.53 ( $P$ < 0.00001) LDL-cholesterol (mg/dl) Araki, E. 2015 -13.84 68.44 273 1 69.05 63 30.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 -11.80 28.43 1 168 -75.31 187.83 56 2.5% 3.363 [-32.71, 9.937] Heterogeneity: Ch <sup>2</sup> = 2.67, df = 4 ( $P$ = 0.51); P = 0% Text for overall effect: Z = 5.07 ( $P$ = 0.00001) Triglycerides (mg/dl) Araki, E. 2015 -13.84 6.84 4.73 1 69.05 63 30.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 -14.80 28.43 1 168 -75.31 187.83 56 2.5% 3.363 [-32.71, 9.937] Heterogeneity: Ch <sup>2</sup> = 2.57, df = 4.48 1 -15.58 24 4.77 +21.89 1.77 +3.788 [-4.44, 1-5.58] Wehua 2han										_ <b>_</b>
Heterogeneity: Ch <sup>2</sup> = 2.50, df = 3 ( $P = 0.41$ ); P = 0% Test for overall effect: $Z = 4.58$ ( $P < 0.0001$ ) HDL-cholesterol (mg(d)) Araki, E. 2015 6.25 9.33 273 - 2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 16.3% 1.35 [-1.32, 4.02] Koshizaka, M. 2019 4.48 6.6 48 -0.08 6.5 50 17.3% 4.56 [1.97, 7.15] Rotenstock, J. 2016 6.85 9.79 453 3.9 10.43 222 4.3% 2.98 [1.31, 4.59] Wehua Zhang. 2019 5.8 18.73 30 2.71 15.6 30 1.5% 3.09 (-5.63, 11.81] Subtotal (95% C) 983 Heterogeneity: Ch <sup>2</sup> = 2.60, df = 5 ( $P < 0.0001$ ); P = 81% Test for overall effect: Z = 7.21 ( $P < 0.0001$ ) HDL-cholesterol (mg(d)) Araki, E. 2015 6.65 49 - 9453 3.9 10.43 222 4.3% 3.97 [2.89, 5.05] Heterogeneity: Ch <sup>2</sup> = 7.46, df = 4 ( $P = 0.11$ ); P = 46% Test for overall effect: Z = 4.53 ( $P < 0.0001$ ) HDL-cholesterol (mg(d)) Araki, E. 2015 6.48 20.99 273 -0.2 21.43 63 29.3% 4.80 [-1.05, 10.66] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 66 9.7% 6.34 [-3.30, [1.50] Normall effect: Z = 4.53 ( $P < 0.0001$ ) LDL-cholesterol (mg(d)) Araki, E. 2015 4.6 20.99 31.47 450 -0.6 31.29 223 3.4% 9.09 [4.05, 10.66] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 66 9.7% 6.34 [-3.30, [1.68] 10, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% 6.00 [7.09, 19.09] Kochizaka, M. 2019 1.38 14.78 48 -10.25 22.97 48 15.8% 11.63 [3.66, 19.00] Rosenstock, J. 2016 9.39 31.47 450 -0.6 31.29 222 3.4% 9.99 [4.55, 15.03] Subtotal (95% C) 950 399 100.0% 8.19 [5.03, 11.35] Ferramini, E. 2013 1.48 29.43 1 168 -5.41 32.86 56 30 0.9% -14.84 [-3.37, 4.07] Triglycerides (mg(d)) Araki, E. 2015 -13.84 6.84 273 1 69.05 63 30.9% -14.84 [-3.37, 5.407] Ferramini, E. 2013 1.48 29.43 1 168 -5.41 32.86 56 2.5% 3.363 [-3.27, 19.937] Triglycerides (mg(d)) Araki, E. 2015 -13.84 6.84 4 273 1 69.05 63 30.9% -14.84 [-3.37, 5.407] Ferramini, E. 2013 -14.88 29.43 1 168 -5.41 32.86 56 2.5% 3.363 [-3.27, 19.947] Heterogeneity: Ch <sup>2</sup> = 2.5.7 ( $P < 0.0001$ ) Heterogeneity: Ch <sup>2</sup> = 2.5.7 ( $P < 0.0001$ ) Heterogeneity: Ch <sup>2</sup> = 2.5.7 ( $P < 0.0001$ ) Hete		1.90	10.15		-13.23	23.42				•
Test for overall effect: $Z = 4.58$ ( $P < 0.0001$ ) HDL-sholesterol (mg/dl) Araki, E. 2015 6.25 9.33 273 -2.5 8.73 63 19.9% 8.75 [6.33, 11.17] Ferramini, E. 2015 6.76 8.67 186 5.41 8.89 56 16.3% 1.35 [-1.32, 4.02] to, D. 2021 0.8 6 11 7.3 12.6 10 1.6% -6.50 [-1.50, 2.08] Associatizaki, M.2019 4.48 6.6 48 -0.08 6.5 50 17.3% 4.56 [1.57, 7.15] Rosenstock, J. 2016 6.85 9.79 453 3.9 10.43 222 43.3% 2.95 [1.31, 4.59] Welhua Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.5% 3.09 [-5.6, 31.181] Subtolal (95% C) 9 58 18.73 30 2.71 15.6 30 1.5% 3.09 [-5.6, 31.181] Subtolal (95% C) 9 58 18.73 30 2.71 15.6 30 1.5% 3.09 [-5.6, 31.181] Subtolal (95% C) 9 58 18.73 30 2.71 15.6 30 1.5% 3.09 [-5.6, 3.1181] Subtolal (95% C) 9 71 9 81% Test for overall effect: $Z = 7.21$ ( $P < 0.0001$ ); $P = 81\%$ Rosenstock, J. 2016 6.85 9.79 453 3.9 10.43 222 54.0% 2.95 [1.31, 4.59] Welhua Zhang, 2019 5.8 18.73 30 2.71 15.8 30 1.9% 3.09 [-5.6, 3.1181] Subtolal (95% C) 7 10 388 100.0% 2.79 [1.58, 3.108] Subtolal (95% C) 7.71 15.8 30 1.9% 3.09 [-5.6, 3.1181] Subtolal (95% C) 7.71 15.8 30 1.9% 3.09 [-5.6, 3.1181] Subtolal (95% C) 9.79 453 3.9 10.43 222 54.0% 2.95 [1.31, 4.59] Welhua Zhang, 2019 5.8 18.73 30 2.71 15.8 30 1.9% 5.04 [-5.3, 11.61] Ferramini, E. 2013 1.43 35.51 168 -54.1 32.86 56 9.7% 6.84 [-3.30, 16.80] Io, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% 10.01, 7.09, 19.09] Rosenstock, J. 2016 9.39 31.47 450 -0.6 31.29 222 39.7 48 15.8% 11.63 (5.6, 19.60] Rosenstock, J. 2016 9.39 31.47 450 -0.6 31.29 222 39.7 40 5.53 (1.53, 35.6, 15.03) Subtolal (95% C) 9 399 10.00% 8.19 [5.03, 11.35] Helerogeneity: Ch <sup>2</sup> = 2.67, df = 4 ( $P = 0.51$ ); $P = 0\%$ Triglycerides (mg/dl) Mraki, E. 2015 -13.44 6.84 273 1 69.05 63 30.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 -14.88 29.43 1 168 -55.31 177, 3.58 [-4.44, 1-55.8] Welhua Zhang, 2019 -3.98 99.66 48 -24.47 121.89 47 5.5% 15.12 (-2.97), 59.44 [-4.75.48] Welhua Zhang, 2019 -3.98 75.44.8 30 -34.55 48.56 30 16.2% -53.25 (-31.44, 2.58) Subtolal (95% C) 1 = 2.87 48.44 1 -55.84 47.7 10.155 2		2 90 df =	3 ( D= 0		: 0%			100.070	10.01 [0.10, 10.44]	•
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Ferramini, E. 2013. $6.76$ $8.67$ $186$ $5.41$ $8.89$ $56$ $16.3\%$ $1.35[+1.32,4.02]$ to, D. 2021       0.8       6 $11$ $7.3$ $12.6$ $10$ $18\%$ $-6.50[+15.08,2.08]$ Goshizaka, W. 2019       4.48       6.6       48 $-0.08$ $6.5$ $50$ $7.7\%$ $4.56$ $11$ $7.3$ $224$ $43\%$ $2.06[1:31,4.59]$ Wehuz Zhang, 2019       5.8 $18.73$ $30$ $2.71$ $15.6$ $30.7\%$ $3.56[1:37,7.15]$ Subtotal (95\% C)       983 $14.3$ $222$ $43.3\%$ $10.0.9\%$ $3.97[2.89,5.05]$ Herrogeneity: Ch <sup>+</sup> = 2.60, df = 5 (P < 0.0001):										
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Weihus Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.5% 3.09 $\pm$ 58.3 11.81] Subtotal (95% Cl) 983 431 100.0% 3.97 [2.89, 5.05] Heterogeneiiy: Ch <sup>2+</sup> 2.60.9, df = 5 ( $P < 0.0001$ ); P = 81% Test for overall effect: Z = 7.21 ( $P < 0.0001$ ); P = 81% Tearamini, E. 2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35 [ $\pm$ 1.32, 4.02] to, D, 2021 0.8 6 11 7.3 12.6 10 2.0% -6.50 [ $\pm$ 15.08, 2.08] Koshizaka, M. 2019 4.48 6.56 48 -0.08 6.5 50 2.1.7% 4.56 [ $\pm$ 197, 7.15] Rosenstock, J. 2016 6.25 9.79 453 3.9 10.43 222 54.06 2.05% 2.05[ $\pm$ 1.31, 4.59] Weihus Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.9% 3.09 [ $\pm$ 5.83, 11.81] Subtotal (95% Cl) 7.10 368 100.0% 2.79 [ $\pm$ 5.8, 4.00] Heterogeneiiy: Ch <sup>2</sup> = 7.6, df = 4 ( $P = 0.11$ ); P = 46% Test for overall effect: Z = 4.53 ( $P < 0.0001$ ) LDL-cholesterol (mg/dl) Koshizaka, M. 2019 1.38 14.78 48 -10.25 23.97 48 15.8% 11.63 [ $\pm$ 36, 19.60] Rosenstock, J. 2016 9.9 31.47 450 -0.6 31.29 222 39.4% 9.99 [ $\pm$ 4.55, 15.03] Subtotal (95% Cl) 950 339 100.0% 3.279 22.21.53 3.09.9% ( $\pm$ 34.96 [ $\pm$ 10.33, 10.58] Heterogeneiiy: Ch <sup>2</sup> = 2.67, df = 4 ( $P = 0.51$ ); P = 0% Test for overall effect: Z = 4.53 ( $P < 0.0001$ ) Test for overall effect: Z = 4.53 ( $\pm$ 4.57 1 168.5 43 17 10 32% 560 2.53% 3.853 2.82] Koshizaka, M. 2019 -3.3 9.96.6 48 -24.47 121.89 47 55% 15.12 ( $\pm$ 2.70, 95.94] Heterogeneiiy: Ch <sup>2</sup> = 2.67, of = 4 ( $P = 0.51$ ); P = 0% Test for overall effect: Z = 4.58 41 115.8 44.17 10 32% 560 2.53% 3.853 2.82 ( $\pm$ 3.98 ( $\pm$ 3.98 ( $\pm$ 3.98 ( $\pm$ 3.17 ( $\pm$ 3.98 ( $\pm$ 3.17 ( $\pm$ 3.98 ( $\pm$ 3.53 ( $\pm$ 2.71, 99.84)] Heterogeneiiy: Ch <sup>2</sup> = 2.67, of = 4 ( $P = 0.51$ ); P = 0% Test for overall effect: Z = 4.58 41 1.1 -15.8 44.17 10 3.2% 5.50 ( $\pm$ 3.53 2.83 ( $\pm$ 3.24 ( $\pm$ 3.24 11 ( $\pm$ 3.24 11 ( $\pm$ 3.25 ( $\pm$ 3.24 53.24 ( $\pm$ 3.25 2.83 ( $\pm$ 3.24 ( $\pm$ 3.24 11 ( $\pm$ 3.24 11 ( $\pm$ 3.25 ( $\pm$ 3.24 ( $\pm$ 3.25 2.24 ( $\pm$ 3.24 2.23 2.24 ( $\pm$ 3.24 2.23 2.23 2.24 2.24 2.23 2.25 ( $\pm$ 3.24 2.24 2.23 2.24 2.24 2.24 2.24 2.23 2.25 ( $\pm$ 3.24 2.24 2.23 2.25 ( $\pm$										
Subtotal (95% CI) 983 431 100.0%, 3.97 [2.89, 5.05] Heterogeneity: Ch <sup>+</sup> = 260, df = 5 ( $P$ = 0.0001; P = 81% Test for overall effect: Z = 7.21 ( $P$ = 0.0001; P = 81% Test for overall effect: Z = 7.21 ( $P$ = 0.0001; D = 81% HDL-cholesterol (mg/dl) (after deleting Araki, E. 2015) Ferramini, E. 2013 6.76 8.87 168 5.41 8.89 56 20.4% 1.35 [-1.32, 4.02] Koshizaka, M. 2019 4.48 6.56 48 -0.08 6.5 50 21.7% 4.56 [1.97, 7.15] Rosenstock, J. 2016 6.58 9.79 453 3.9 10.43 222 540% 2.96 [1.31, 4.59] Weihua Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.9% 3.09 [-5.63, 11.81] Subtotal (9% Ci) 7710 386 100.0% 2.79 [1.58, 4.00] Heterogeneity: Ch <sup>+</sup> = 7.46, df = 4 ( $P$ = 0.11); P = 46% Test for overall effect: Z = 4.53 ( $P$ < 0.00001) LDL-cholesterol (mg/dl) Araki, E. 2015 4.8 20.99 273 -0.2 21.43 63 29.3% 4.80 [-1.05, 10.65] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 56 9.7% 6.84 [-3.30, 16.89] Ito, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% 10.01 (7.09, 19.09] Koshizaka, M. 2019 1.38 14.74 48 -10.22 22.397 48 15% 11.83 (3.66, 19.60] Rosenstock, J. 2016 9.39 31.47 450 -0.6 31.29 222 39.4% 9.99 [4.65, 15.03] Subtotal (9% Ci) 950 399 100.0% 8.19 [5.03, 11.35] Heterogeneity: Ch <sup>+</sup> = 2.67, df = 4 ( $P$ = 0.61]; P = 0% Test for overall effect: Z = 5.07 ( $P$ < 0.00001) Triglycerides (mg/dl) Araki, E. 2015 -13.24 48.24 1 158.41.71 10.52% 5.60 [2.38, 53.28] Koshizaka, M. 2019 -9.39 9.96.64 47 -21.47 148 47 55% 15.12 [-207, 05.94] Koshizaka, M. 2019 -9.38 9.96.64 47 -21.47 11.98 47 55% 15.12 [-207, 05.84] Koshizaka, M. 2019 -9.38 9.95.64 48.54 417 10.155 223 47.17 ** 13.86 [1.44, 1.55.8] Weihua Zhang, 2019 -3.93 9.95.64 48.54 417 10.155 223 47.17 ** 13.86 [1.44, 1.55.8] Weihua Zhang, 2019 -3.93 75 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 20.80] Subtotal (9% Ci) Ch <sup>+</sup> = 3.87, df = 5 ( $P$ = 0.14]; P = 0%										
Heterogeneity: Ch <sup>2</sup> = 26.09, df = 5 ( $P < 0.0001$ ); P = 81% Test for overall effect: Z = 7.21 ( $P < 0.0001$ ); HDL-cholesterol (mg/dl) (after deleting Araki, E. 2015) Ferramini, E. 2013 6.76 8.67 168 5.41 8.89 56 20.4% 1.35[-1.32, 4.02] to, D. 2021 0.8 67 1185 5.41 8.89 56 20.4% 1.35[-1.32, 4.02] Koshizaka, M. 2019 4.48 6.56 48 -0.08 6.5 50 21.7% 4.56 [1.97, 7.15] Sosenstock, J. 2016 6.85 9.79 4.53 3.9 10.43 222 56.0% 2.95 [1.31, 4.59] Welhua Zhang, 2019 5.8 18.73 30 2.71 15.6 30 1.9% 3.09 [5.63, 11.81] Subtotal (9% C) LDL-cholesterol (mg/dl) Heterogeneity: Ch <sup>2</sup> = 2.6, 3 ( $P < 0.0001$ ) LDL-cholesterol (mg/dl) Kashizaka, M. 2019 1.38 14.78 48 -10.25 23.97 48 15.8% 100 [-1.05, 10.65] Ferramini, E. 2013 1.43 30.51 168 -5.41 32.86 56 9.7% 6.34 [-3.30, [6.38] Koutokal (9% C) Subtotal (9% C) Ferramini, E. 2013 1.43 30.51 168 -5.41 32.86 56 9.7% 6.34 [-3.00, [9.00] Koutokal (9% C) Subtotal (9% C) Ferramini, E. 2013 1.43 30.51 168 -5.41 32.86 56 30.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 1.43 30.51 168 -5.41 32.86 56 330.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 1.43 30.51 188 -5.41 32.86 59 399 100.0% 8.19 [5.03, 11.35] Heterogeneity: Ch <sup>2</sup> = 2.6.7 ( $P < 0.0001$ ) Tiglycenides (mg/dl) Araki, E. 2015 -13.84 68.84 273 1 68.05 63 30.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 -41.86 29.43 1 168 -75.31 187.83 56 2.5% 3.836 [-32.71, 99.87] Heterogeneity: Ch <sup>2</sup> = 2.5.77 ( $P < 0.0001$ ) Tiglycenides (mg/dl) Araki, E. 2015 -13.84 68.84 273 1 69.05 63 30.9% -14.84 [-33.75, 4.07] Ferramini, E. 2013 -41.86 29.43 1 168 475.31 187.83 56 2.5% 3.836 [-32.71, 99.87] Heterogeneity: Ch <sup>2</sup> = 2.5.77 ( $P < 0.0001$ ) Tiglycenides (mg/dl) Heterogeneity: Ch <sup>2</sup> = 3.59 99.66 48 -2.447 121.89 47 5.5% 15.12 (-2.70, 59.94] Heterogeneity: Ch <sup>2</sup> = 3.3, df = 5 ( $P = 0.14$ ); $P = 0.45$ Heterogeneity: Ch <sup>2</sup> = 3.3, df = 5 ( $P = 0.14$ ); $P = 0.45$ Heterogeneity: Ch <sup>2</sup> = 3.3, df = 5 ( $P = 0.14$ ); $P = 0.45$		0.0	10.75		2.71	10.0				•
Test for overall effect: $Z = 7.21$ ( $P < 0.00001$ ) HDL-cholesterol (mg/dl) (after deleting Araki, E. 2015) Ferramini, E. 2013 6.76 8.67 166 5.41 8.89 56 20.4% 1.35 [-1.32, 4.02] Kohizaka, M. 2019 4.48 5.56 48 -0.08 6.5 50 21.7% 4.56 [1.97, 7.16] Rosenstock, J. 2016 6.55 9.74 53 3.9 10.43 222 56.0% 2.26 [5.3, 11.81] Subtotal (95% CO) Helerogeneity: Ch <sup>2</sup> = 7.46, df = 4 ( $P = 0.11$ ); P = 46% Triglycerides (mg/dl) Araki, E. 2015 4.6 20.99 273 -0.2 21.43 63 29.3% 4.80 [-1.05, 10.66] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 56 9.7% 6.34 [-3.30, 16.89] Ito, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% 6.00 [-7.09, 19.09] Koentrack, J. 2016 9.39 31.47 450 -0.6 31.29 222 39.4% 9.99 [4.55, 15.03] Subtotal (95% C) Triglycerides (mg/dl) Araki, E. 2015 -13.84 6.84 273 1 69.05 63 30.9% -14.84 [-33.75, 4.07] Triglycerides (mg/dl) Kraki, E. 2015 -13.84 6.84 1 1 -75.8 41.71 10 32% -5.00 [-3.28, 32.83 [-3.27], 9.87] Helerogeneity: Ch <sup>2</sup> = 2.5.77 ( $P < 0.0001$ ) Triglycerides (mg/dl) Kraki, E. 2015 -13.84 6.84 1 1 -75.8 41.71 10 32% -5.00 [-3.28, 32.83 [-3.27], 9.87] Konizaka, M. 2019 -9.38 99.66 48 -24.47 [21.89 47 55% 15.12], 2.970, 59.94] Konizaka, M. 2019 -9.38 554.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 1.588] Withua Zhang, 2019 -3.87 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 1.588] Withua Zhang, 2019 -3.87 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 1.588] Withua Zhang, 2019 -3.87 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 1.588] Withua Zhang, 2019 -3.87 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 1.588] Withua Zhang, 2019 -5.87 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 1.588] Withua Zhang, 2019 -5.87 54.48 30 -34.55 48.56 30 16.2% -5.32 [-31.44, 2.580] Subtotal (95% C) Ch <sup>2</sup> = 2.87, 04 (-20.54) [-8.54 41.55 (-20.54)] Ferromini, Ch <sup>2</sup> = 2.57, 07 ( $P < 0.0001$ )		26 09 df =	= 5 ( D < (		l <sup>2</sup> = 819	'n		1001070	olor [mico) oloo]	
Ferramini, E. 2013 6.76 8.87 168 5.41 8.89 56 20.4%, $135[+132,402]$ to, D. 2021 0.8 6 11 7.3 12.6 10 2.0%, $-6.50[+5.08,2.08]$ Rocentacka, N. 2019 4.48 6.56 44 -0.08 6.5 50 2.1.7%, 4.56] (1.97, 7.15] Rocentacka, N. 2019 5.8 18.73 30 2.71 15.6 30 19%, $3.09[+5.3,11.81]$ Subtotal (95%, C) $+7.46$ , $d=4(P-0.11)$ ; $P=46\%$ Test for overall effect: Z = 4.53 ( $P<0.00001$ ) LUbcholesterol (mg/dl) Araki, E. 2015 4.6 20.99 273 -0.2 21.43 63 29.3%, 4.80 [-1.05, 10.65] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 56 9.7%, 6.84 [+3.30, 16.39] to, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% 10.017-09, [9.09] Rocentacka, J. 2016 9.39 31.47 450 -0.6 31.29 222 39.4% 9.99.9 [4.95, 15.03] Subtotal (95%, C) 9.39 31.47 450 -0.6 31.29 222 39.4% 9.99.9 [4.95, 15.03] Subtotal (95%, C) 9.59 31.47 450 -0.6 31.29 222 39.4% 9.99.9 [4.95, 15.03] Subtotal (95%, C) 1.38 4 13 -75.31 187.83 56 2.5% 3.363, [-32.71, 99.97] Helerogeneity: Ch <sup>+</sup> = 2.57, df = 4 ( $P=0.61$ ); $P=0\%$ Test for overall effect: Z = 5.07 ( $P<0.00001$ ) Triglycerides (mg/dl) Konbizaka, M. 2019 -3.93 99.66 48 -24.47 121.89 47 5.5% 1512, [-2.97, 05.89.4] Konbizaka, M. 2019 -3.93 99.66 4924.47 121.89 47 5.5% 1512, [-2.97, 05.99.4] Weihua Zhang, 2019 -3.93 75.48 30 -34.55 1055 223 47.44 1.558 Subtotal (95%, C) 1.7% -3.88 [+4.41, -55.89] Weihua Zhang, 2019 -3.93, df = 5 ( $P=0.14$ ); $P=0\%$ Triglycerides (mg/dl) Weihua Zhang, 2019 -3.93, df = 5 ( $P=0.14$ ); $P=0\%$ Test ( $P=0.53$ , $P=0.44$ , $P=0.54$ , $P=0.54$ , $P=0.55$ , $P=0.56$ , $P=0.76$ , $P=0.56$ , $P=0.76$ , $P=0.57$ , $P=0.57$ , $P=0.77$ ,				,						
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Konbizaka, M. 2019 4.4 6.56 48 -0.08 6.5 50 2.17% 4.56 [197, 7.15] Rosenstock, J.2016 6.85 9.79 453 3.9 10.43 222 54.0% 2.95 [1.31, 4.59] Subtolal [95% CI) 710 30 2.71 15.6 30 19% 3.09 [4.63, 11.81] Subtolal [95% CI) 710 308 100.0% 2.79 [1.56, 4.00] Heterogeneity: Ch <sup>+</sup> = 7.46, df = ( $I = 0.11$ ); $I = 46\%$ Teart for overall effect: $Z = 4.53$ ( $I = 0.00001$ ) LDL-cholesterol (mg/dl) Araki, E. 2015 4.6 20.99 273 -0.2 21.43 63 29.3% 4.80 [-1.05, 10.65] Ferramini, E. 2013 1.43 35.51 168 -5.41 32.86 56 9.7% 6.84 [-3.30, 16.38] Io, D. 2021 -3.1 17.2 11 -9.1 13.3 10 5.8% 10.01 7.09, 19.09] Rosenstock, J. 2016 9.39 31.47 450 -0.6 31.29 222 39.4% 9.99 [4.65, 15.03] Subtolal (9% CI) 9950 399 100.0% 8.19 [5.03, 11.35] Heterogeneity: Ch <sup>+</sup> = 2.67, df = 4 ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Test for overall effect: $Z = 5.07$ ( $I = 0.61$ ); $I = 0\%$ Heterogeneity: Ch <sup>+</sup> = 2.85, 98.44 11 -15.8 441, 71 10, 75.5% 15.12 (-2.97, 0.59, 94.44, 1-55.8] Weihua Zhang, 2019 -3.98, 95.66 48 -24.47 121.89 47 55% 15.12 (-2.97, 0.59, 94.44, 1-55.81 Weihua Zhang, 2019 -3.98, 75.44, 80 -34.55 48.55 30 16.2% -5.52 (-31.44, -1.568) United (9% CI) $L = 2.67$ ( $I = 5.(I = 1.4)$ ); $I = 0.55$ Subtolal (9% CI) $L = 2.67$ ( $I = 5.(I = 1.4)$ ); $I = 0.55$ Heterogeneity: Ch <sup>+</sup> = 2.83, df = 5 ( $I = 0.14$ ); $I = 10.55$ Subtolal (9% CI) $L = 2.37, 44.85$ Subtolal (9% CI) $L = 2.37, 44.85$ Subtolal (9% CI) $L = 2.67$ ( $I = 3.56$ ) Subtolal (9% CI) $L = 2.67$ ( $I = 3.66$ ) Heterogeneity: Ch <sup>+</sup> = 2.87, df = 5 ( $I = 0.14$ ); $I = 10.55$ Test for overall effect: $I = 5.07$ ( $I = 0.14$ ); $I = 10.55$ Test for overall effect: $I = 5.07$ ( $I$										
Rosenstock, J. 2016         6.85         9.79         453         3.9         10.43         222         54.0%         2.95 [1.31, 4.59]           Weihua Zhang, 2019         5.8         18.73         30         2.71         15.6         30         1.9%         3.09 [-5.63, 11.81]           Subtolal (9% CI)         710         368         100.0%         2.79 [1.56, 4.00]         1.8%           Heterogeneity: Ch <sup>2</sup> = 7.46, df = 4 ( <i>P</i> = 0.11); F = 46%,         Test for overall effect: 2 = 4.53 ( <i>P</i> < 0.0001)										•
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Araki, E. 2015         -13.84         68.84         27.3         1         69.05         63         30.9%         -14.84         13.75, 4.071           Ferrannini, E. 2013         -41.68         294.31         168         -75.31         187.83         56         2.5%         33.63 [-3.27, 19.9.97]           No. D. 2021         -20.8         88.4         11         -15.8         41.7         10         3.2%         -50.01 [-63.28, 53.28]           Koshizaka, M. 2019         -9.35         99.66         48         -24.47         121.89         47         55%         151.2 [-29.70, 59.94]           Neenstock, J. 2016         -16.66         105.8         454.5         41.7         10         3.2%         -50.01 [-63.28, 55.28]           Wehua Zhang, 2019         -39.87         54.48         30         -14.5%         30         16.2%         -5.32 [-31.44, 15.58]           Subtolal (95% CI)         -98.44         42         20         100.0%         -17.2 [-27.72, -6.70]         -5.70]           Herrygeneily: Chi*e 3.83, df = 5 (P = 0.14); I* = 40%         42         100.0%         -17.2 [-27.72, -6.70]         -5.70]	Trialvcerides (n	na/dl)								
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Heterogeneity: Chi <sup>2</sup> = 8.39, df = 5 ( <i>P</i> = 0.14); l <sup>2</sup> = 40%		-39.87	54.48		-34.55	48.56			-5.32 [-31.44, 20.80]	•
	Heterogeneity: Chi <sup>2</sup> =			14);  ² =	40%					
	out of overall ellect.		r = 0.00	• /						
-100 -50 0 50										-100 -50 0 50 1

**Figure 13.** Weighted mean difference in change in blood lipid (mg/dL) from baseline from SGLT2i compared with metformin [20,23,26,28,29,32].

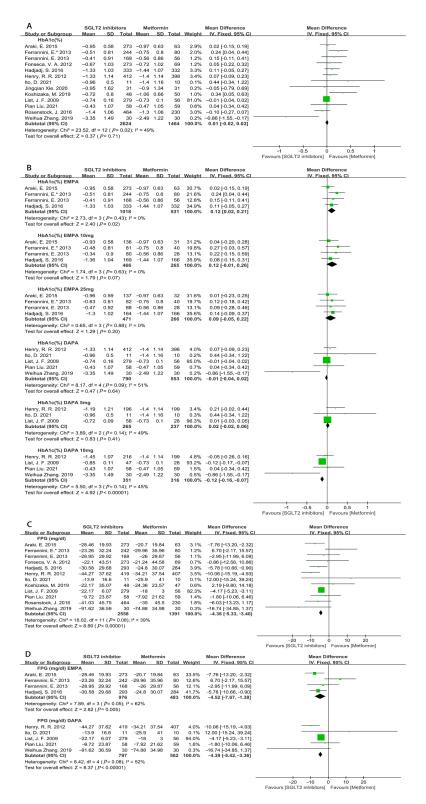
## 3.4.3. Efficacy on Glycemic Control

The antihyperglycemic effects were evaluated and the results showed that SGLT2i and metformin had a similar effect on the reduction in HbA1c (WMD = 0.01, 95% CI = -0.02 to 0.03, p = 0.71, I<sup>2</sup>= 49%, N = 13) (Figure 15A). The subgroup analysis of empagliflozin displayed a slightly poor HbA1c reduction versus metformin (WMD = 0.12, 95% CI = 0.02 to 0.21, p = 0.02, I<sup>2</sup> = 0%, N = 4) (Figure 15B). However, the doses subgroup analysis of empagliflozin showed no statistical difference between the SGLT2i and metformin groups (empagliflozin 10 mg: WMD = 0.12, 95% CI = -0.01 to 0.26, p = 0.07, I<sup>2</sup> = 0%, N = 4; empagliflozin 25 mg: WMD = 0.09, 95% CI = -0.05 to 0.22, p = 0.20, I<sup>2</sup> = 0%, N = 4; empagliflozin dapagliflozin showed the similar effect on lowering HbA1c compared with metformin (WMD = -0.01, 95% CI = -0.04 to 0.02, p = 0.64, I<sup>2</sup> = 51%, N = 5) (Figure 15B). A further dose subgroup analysis found that 10 mg of dapagliflozin significantly reduced HbA1c, and 5 mg of dapagliflozin did not show a significant difference (dapagliflozin 5 mg: WMD = 0.02, 95% CI = -0.02 to 0.06, p = 0.41, I<sup>2</sup> = 49%, N = 3; dapagliflozin 10 mg: WMD = -0.12, 95% CI = -0.16 to -0.07, p < 0.00001, I<sup>2</sup> = 45%, N = 4) (Figure 15B).

Compared to metformin monotherapy, SGLT2i significantly decreased FPG (WMD = -4.36, 95% CI = -5.33 to -3.40, p < 0.00001,  $I^2 = 39\%$ , N = 12) (Figure 15C). The subgroup analysis indicated that empagliflozin and dapagliflozin were more effective than metformin in the reduction in FPG (empagliflozin: WMD = -4.52, 95% CI = -7.67 to -1.38, p = 0.005,  $I^2 = 62\%$ , N = 4; dapagliflozin: WMD = -4.39, 95% CI = -5.42 to -3.36, p < 0.00001,  $I^2 = 52\%$ , N = 5) (Figure 15D).



**Figure 14.** (**A**). Weighted mean difference in change in diastolic blood pressure (mmHg) from baseline from SGLT2i compared with metformin [20,22–26,28,29,31,32]. (**B**). Weighted mean difference in change in systolic blood pressure (mmHg) from baseline from SGLT2i compared with metformin [20,22–26,28,29,31,32]. DAPA = dapagliflozin, EMPA = empagliflozin. 12 weeks trials = SGLT2i used 12 weeks, 24–26 weeks trials = SGLT2i used 24–26 weeks. Obesity = SGLT2i used in obese people.



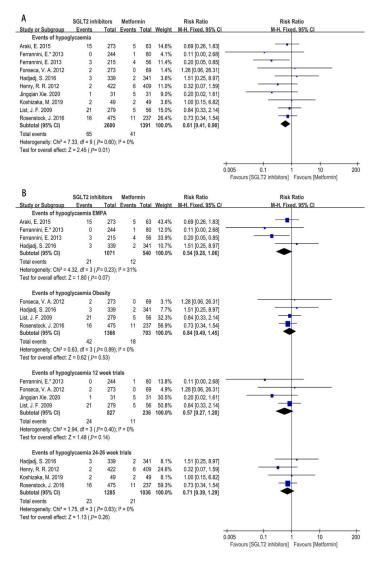
**Figure 15.** (**A**). Weighted mean differences in change in HbA1c (%) from baseline between SGLT2i and metformin [20–32]. (**B**). Weighted mean difference in change in HbA1c (%) from baseline from different types and doses of SGLT2i compared with metformin [20–28]. (**C**). Weighted mean difference in change in FPG (mg/dL) from baseline from SGLT2i compared with metformin [20–29,31,32]. (**D**). Weighted mean difference in change in FPG (mg/dL) from baseline from SGLT2i compared with metformin [20–29,31,32].

# 3.4.4. Hypoglycemia Incidence Risk

Incidence of hypoglycemia was lower in SGLT2i groups compared with metformin, which was assessed from the ten trials included (RR = 0.61, 95% CI = 0.41 to 0.90, p = 0.01,  $I^2 = 0\%$ ) (Figure 16A). A further subgroup analysis showed that the risk of hypoglycemia in the empagliflozin group was similar with that of metformin (RR = 0.54, 95% CI = 0.28 to 1.06, p = 0.07,  $I^2 = 31\%$ , N = 4) (Figure 16B). SGLT2i also showed a similar effect as metformin in the risk of hypoglycemia in obese people (RR = 0.84, 95% CI = 0.49 to 1.45, p = 0.53,  $I^2 = 0\%$ , N = 4) (Figure 16B). As for the influence of the treatment period of SGLT2i, both 12 weeks and 24–26 weeks of treatment of SGLT2i did not increase the incidence of hypoglycemia compared with metformin (12 weeks: RR = 0.57, 95% CI = 0.27 to 1.20, p = 0.14,  $I^2 = 0\%$ , N = 4; 24–26 weeks: RR = 0.71, 95% CI = 0.39 to 1.29, p = 0.26,  $I^2 = 0\%$ , N = 4) (Figure 16B).

## 3.4.5. Publication Bias

Funnel plot of genitourinary tract infection events indicated no obvious reporting bias (Figure 17). Additionally, the Egger test also revealed no significant publication bias (p = 0.92).



**Figure 16.** (A). Risk of hypoglycemia in SGLT2i group compared with that of metformin [20–25,29–32]. (B) Risk of hypoglycemia between the two groups in different subgroups [20–25,29–32]. EMPA = empagliflozin, 12 weeks trials = SGLT2i used 12 weeks, 24–26 weeks trials = SGLT2i used 24–26 weeks. Obesity = SGLT2i used in obese people.



22 of 28

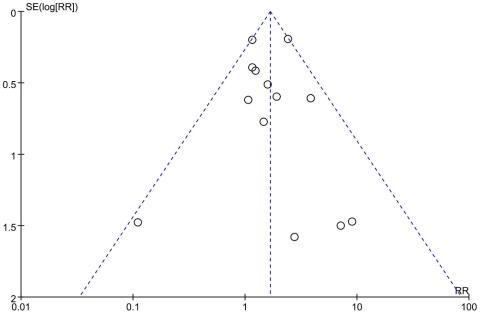


Figure 17. Funnel plot of genitourinary tract infection events.

# 4. Discussion

The prevalence of T2DM is increasing significantly in China, and oral glycemic agent therapy is still the main treatment strategy for most T2DM patients [37,38]. However, with a gradual loss of efficacy owing to the progressive loss of the  $\beta$ -cell function and the occurrence of metabolic comorbidities such as a gain in weight, CVD, and hypoglycemia, novel medications are being developed to improve the glycemic control and delay complications [39,40]. Sodium-glucose cotransporter 2 (SGLT2) mediates approximately 80–90% of renal glucose reabsorption under normal physiologic conditions, and SGLT2i can reduce 30–50% of the filtered glucose load in T2DM patients by increasing urinary glucose excretion [41]. However, the Food and Drug Administration (FDA) issued safety warnings for UTIs which may represent a leading cause of sepsis and are potentially life-threatening [42,43]. We conducted a meta-analysis to evaluate the benefit on the cardiovascular system and the potential risk of infection of SGLT2i in T2DM patients compared to metformin. Our analysis revealed strong associations between SGLT2i and the risk of genitourinary tract infections compared to metformin, and an RTI was the main cause of the difference, while there was no significant association between SGLT2i and the risk of UTI compared to metformin. This finding of our analysis is consistent with the results of previous reports, despite different trial designs and interventions of included studies from previous meta-analyses [44-46]. SGLT2i-induced increased glycosuria may predispose to mycotic colonization and bacterial overgrowth in view of the mechanism of action of the SGLT2i, in which case the enhanced risk of genitourinary tract infections is inevitable [47]. However, diuresis induced by SGLT2i may reduce urethra pathogen loads, which may be the reason for the non-obvious risk of a UTI [48,49].

Furthermore, the subgroup analysis of different types of SGLT2i indicated that empagliflozin was not associated with an increased risk of genitourinary tract infections, and a similar finding was observed in the risk of UTIs with empagliflozin. However, the increased risk of an RTI from the empagliflozin treatment was observed. Further analysis was conducted to separate the empagliflozin treatment into different dose groups, and we found neither 10 mg of empagliflozin nor 25 mg of empagliflozin increased the risk of an RTI compared to metformin. Dapagliflozin, the most commonly used SGLT2i in China, significantly increased the risk of genitourinary tract infections compared to metformin, potentially in a linearly dose-related mode. An animal study showed dapagliflozin has a more prolonged urinary glucose excretion than other SGLT2i [50]. Due to the lack of reasonable biologic mechanisms to explain this phenomenon, further research is required to decipher this finding. Canagliflozin was also associated with an increased risk of genitourinary tract infections, whereas ipragliflozin did not and the conclusions should be treated cautiously due to the small number of RCTs that reported this outcome.

It is uncertain whether there is a sex difference in the risk of UTIs and RTIs associated with SGLT2i compared to metformin because of the different physiological structure of the urogenital tract. Our analysis revealed that SGLT2i was associated with a higher risk of an RTI in the male and female population compared with metformin. The conclusions are consistent with previous studies which reported that increased genital infections associated with SGLT2i were common in females and males [51–53]. In view of various treatment periods of SGLT2i, we conducted a further subgroup analysis using Revman software to clarify the effect of the treatment period of SGLT2i on the infection incidence. We found that SGLT2i therapy for 12 weeks did not increase the risk of UTIs and RTIs, and the incidence in an RTI was higher at 24 to 26 weeks than that of metformin, which was consistent with the previous studies [54–56]. Interestingly, the subgroup analysis showed there was no difference on the risk of RTIs and UTIs between SGLT2i and metformin at 52 weeks' treatment. Due to the small number of articles included, more research is needed to confirm the long-term safety of SGLT2i on UTIs and RTIs.

T2DM works as a serious chronic metabolic disease that is characterized by insulin resistance (IR) and obesity, which accounts for 44% of diabetes cases [57,58]. Obesity is associated with the worsening of IR, and there is a 7-fold increased risk in the individuals' mortality in T2DM with obese individuals [59]. Our research indicated that obese T2DM patients treated with SGLT2i suffered a higher risk of RTI compared to metformin monotherapy. Recent studies have proved that obesity could alter immune cell function and glucose metabolism, and these obesity-related mechanisms may contribute to the predisposition to infections [60]. Therefore, weight loss supported the reduction in infection risk.

With the exception of the most common genitourinary tract infections, sporadic studies have reported that SGLT2i was associated with skin and pulmonary infections [61–63]. Urticaria, pruritus, photosensitivity, and various rashes caused by SGLT2i may be driven by a potential skin toxicity [61,62]. In addition, SGLT2i also led to an increased liquid glucose concentration of the airway surface, which translated directly to an increased proliferation of pathogenic bacteria and induced the occurrence of lung infections, for some SGLT2i bound with the SGLT-1 receptors in the lungs, such as canagliflozin and ipragliflozin [63,64]. Hence, we conducted further research to determine whether SGLT2i increased the risk of a potential extra-urogenital infection. Our research showed that SGLT2i treatment was not significantly associated with an increased risk of upper respiratory tract infections in contrast to metformin. However, due to the small number of RCTs that reported related data, further research is required to broaden the progress of this field. Additionally, rare studies focused on the influence of SGLT2i on the skin and other ectopic infections, therefore, no pooled data were analyzed to clarify the effect of SGLT2i on the cutaneous infection in our systematic review.

Due to the severe detriment and high mortality rate of diabetes-related cardiovascular complications, antidiabetic agents should be prioritized in T2DM patients complicated with cardiovascular disease, especially the drugs that could effectively improve cardiovascular outcomes [65–67]. Our findings strongly supported the use of SGLT2i in T2DM patients were related with the decreased risk of cardiovascular disease, and SGLT2i showed a potential beneficial effect on reducing cardiovascular risk factors when compared to metformin monotherapy. T2DM patients treated with SGLT2i experienced a significant body weight reduction, regardless of the type of SGLT2i, the treatment duration, and the baseline weight of the patients. The effect of SGLT2i on lowering body weight may be due to the glycosuria-mediated effect of osmotic diuresis and caloric expenditure [68,69]. Furthermore, as for the regulation of the lipid metabolism, SGLT2i could significantly enhance the level of HDL cholesterol and decrease triglyceride levels, which further lead to the decrease in cardiovascular risk. This may be explained by the fact that SGLT2i improves

IR and increases endogenous insulin secretion, which in turn increases the catabolism of very low density lipoprotein (VLDL) cholesterol and chylomicrons, ultimately leading to a reduction in triglycerides and an increase in HDL cholesterol [70]. Similarly, the beneficial effect of SGLT2i on the modulation of blood pressure was also confirmed by our meta-analysis, which was consistent with the previous reports [71,72]. Osmotic diuresis caused by increasing urinary glucose excretion induced by SGLT2i is likely to be the reason for the antihypertensive effect [73]. To sum up, the previously described beneficial effect of SGLT2i on improving the risk of cardiovascular outcomes was confirmed by our systematic review [12,72].

From the view of the antihyperglycemic effect, our research suggested that SGLT2i monotherapy, which was developed for the treatment of T2DM, showed a similar improvement of HbA1c with metformin. Moreover, we found that 10 mg of dapagliflozin appeared to produce a slightly greater reduction in HbA1c than metformin for T2DM patients. For another indicator that effectively reflects the antihyperglycemic efficacy, a significant reduction in FPG in SGLT2i monotherapy was observed in comparison with metformin. Considering the potential risk of hypoglycemia, which is considered as the acute complication of diabetes and severely threatens the life of patients [74], we conducted the analysis of adverse event about the incidence of hypoglycemia. Our research indicated that SGLT2i displayed a low risk of hypoglycemia, which showed no significant difference in each subgroup analysis compared with metformin.

Our meta-analysis firstly focused on the cardiovascular benefit and infection risk of SGLT2i compared with metformin, which filled many gaps left by those of prior work. In this analysis, we included more recent articles and focused on the comparison of the most relevant infection events and potential efficacy, including the reduction in the cardiovascular risk factor and improvement of glycemic control with the current first-line antihyperglycemic agent, metformin. Furthermore, limitations also existed in our research. First, the cardiovascular outcomes were not reported in the original trials, so the cardiovascular benefits in our study were evaluated by the risk factors. Second, the wide confidence intervals lead to a low level of certainty for some findings and need to be interpreted with care. In addition, few high-quality articles which reported the influence of canagliflozin and ipragliflozin were included, hence, more RCTs are needed to address the large evidence gap on the efficacy and safety of these SGLT2i.

## 5. Conclusions

In summary, SGLT2i showed significant benefits in the reduction in cardiovascular risk factors, such as body weight, blood pressure, triglycerides, and increasing HDL cholesterol level, and had similar antihyperglycemic efficacy, including lowering blood glucose and HbA1c without the significant elevation of UTIs compared with metformin monotherapy, especially in obese T2DM patients. In short-term trials, SGLT2i provided the similar antihyperglycemic effect with metformin and induced additional cardiovascular benefits and the potential risk of an RTI. Additional long-term trials are needed to confirm the long-term safety of SGLT2i, which is expected to be the first choice for patients with metformin intolerance.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/metabo12100979/s1, Supplementary File S1. Search Strategy (DOC).

**Author Contributions:** C.X. and L.H. did the scientific literature search and extracted data. J.Z. and L.X. did the data analyses. L.H. wrote the first draft of the report. J.D. and L.L. contributed to the study conception and design, critical revision of the manuscript for important intellectual content, and final approval of the version to be published. All authors have read and agreed to the published version of the manuscript.

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**Conflicts of Interest:** We declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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