Effects of cocoa products intake on cardiometabolic biomarkers of type 2 diabetes patients: a systematic review and meta-analysis based on both long-term and short-term randomised controlled trials

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ABSTRACT
Cocoa consumption as a diet has been shown to improve cardiometabolic biomarkers for T2D, but results were inconsistent. A comprehensive search from PubMed, Web of Science, Embase, and The Cochrane Library to identify the randomised controlled trials investigating the impacts of cocoa products consumption on cardiometabolic biomarkers in T2D was performed up to December 2020. Twelve trials involving 9 long-term and 3 short-term studies were included. The cocoa products significantly decreased low density lipoprotein-cholesterol (WMD: −9.955 mg/dL, 95% CI: −17.408, −2.501, p = 0.009), triglyceride (WMD: −15.364 mg/dL, 95% CI: −23.383, −7.346, p < 0.001), blood glucose (WMD: −9.105 mg/dL, 95% CI: −15.022, −3.189, p = 0.003), and C-reactive protein (WMD: −0.978 mg/L, 95% CI: −1.687, −0.269, p = 0.007) in long-term. The results indicated the beneficial long-term effects of cocoa products intake on cardiometabolic biomarkers for T2D, especially on blood glucose, lipid metabolism (LDL-C and TG), and inflammation (CRP).

Introduction
Diabetes is a major threat to global public health, increasing the risk of early death. It is estimated that approximately 4.2 million adults would die from diabetes and its complications (International Diabetes Federation 2019). Type 2 diabetes (T2D), as the most prevalent type of diabetes, is characterised by high blood sugar, low inflammation, insulin resistance and β-cell failure (Nie et al. 2019; Liang et al. 2021). T2D patients have several symptoms in common, such as increased blood glucose, decreased insulin sensitivity, obesity, dyslipidemia, and high blood pressure, which are risk factors for cardiovascular disease (CVD) (Liang et al. 2021). CVD, as a common and serious comorbidity of T2D, contributes to approximately half of all deaths in patients with T2D despite its mortality is declining overall since 1950 (Einarson et al. 2018; Zheng et al. 2018). In consideration of this condition, it is crucial to find effective strategies to prevent, delay or reverse cardiovascular complications.

Positive clinical trial evidence suggested that some methods of treatment of T2D can reduce the incidence of cardiovascular events in patients with diabetes and delay the onset of complications (Du et al. 2017; Nie et al. 2021). Conventional drug therapies for diabetes and its cardiovascular complications that are both safe and effective are insufficient to meet rising demand (Carrizzo et al. 2020; Unuofin and Lebelo 2020). Thus, developing alternative approaches for treatment as well as for prevention are imperative. Nutritional management, as a non-pharmacological approach to counter polypharmacy, is viewed as the primary intervention in the management and prevention of T2D (Dyson et al. 2018; Zheng et al. 2018), in which functional food is a promising field (Venkatakrishnan et al. 2020; Escalante-Araiza and Gutiérrez-Salmeán 2021).

Cocoa and its products, chocolate, are consumed largely in the world (Halib et al. 2020), which are rich in various bioactive compounds such as polyphenols, methylxanthine and so on (Gammone et al. 2018). Among polyphenols, flavonols are predominantly found in cocoa products (Tanghe et al. 2021). Numerous
studies have reported various positive health effects of cocoa products, such as reducing risk of T2D (Maskarinec et al. 2019), reducing blood pressure (Grassi et al. 2015; Ried et al. 2017), improving endothelial function (Sansone et al. 2015; Grone et al. 2020) and reducing inflammation factors (Goya et al. 2016).

Although cocoa products have been found to have these health benefits above, the favourable effects of cocoa products in individuals with T2D have largely been postulated studies in healthy volunteers. Recently, there are some data from controlled clinical trials that provide evidence for the potential health benefits of cocoa products for individuals with T2D (Rostami et al. 2015; Ayoobi et al. 2017; Rynarzewski et al. 2019). Nevertheless, there are inconsistencies in some biomarkers. In addition, few meta-analyses to date have simultaneous covered the short-term and long-term effects on comprehensive cardiometabolic profile biomarkers of cocoa products on T2D patients (Lin et al. 2016; Darand et al. 2021).

As a consequence, our meta-analysis was performed to determine the short-term and long-term effect cocoa products intake on cardiometabolic biomarkers of T2D patients. Furthermore, it is also likely to provide evidence base for whether cocoa products could be a part of the nutritional management of people with T2D.

**Methods**

This meta-analysis followed the guidelines from Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) (Shamseer et al. 2015) protocol was used to conduct and report this meta-analysis (Supplementary Table 1). This meta-analysis was registered in PROSPERO International Prospective Register of Systematic Reviews (ID: CRD42021236478).

**Data searches and study selection**

We systematically searched online databases including PubMed, Web of Science, Embase and The Cochrane Library with no time limitation up to 14 December 2020. Search strings can be found in the Supplementary Table 2.

All studies were selected for inclusion by 2 independent reviewers (XC and XG), subject to approval by a third reviewer (XZ). The population, intervention, comparison, outcome, study design (PICOS) criteria applied for the meta-analysis was presented in Supplementary Table 3. All clinical trials that evaluated the effect of cocoa products intake on cardiovascular health in patients with T2D were included in this meta-analysis. Studies were included if they had the following criteria: (1) the study design was randomised controlled trial (RCT) (either parallel or crossover design), (2) the participants were adults (aged ≥ 18 years) diagnosed with T2D, (3) the subjects were assigned ≥ 1 group to cocoa or chocolate and 1 group to placebo, (4) the study reported mean and standard deviation (SD) of outcomes at the final or mean changes for the intervention and the placebo group, (5) the studies were published in English. Studies were excluded if they met the following exclusion criteria: (1) non-RCTs studies, (2) done on people without T2D, or animals, (3) the primary or secondary outcome parameters we needed were not reported. (4) review papers, letters, or conference abstracts.

**Data extraction**

We designed a data collection form before the implementation of the search strategy. Two investigators (XC and XG) independently extracted the relevant information from the selected studies. Any disagreements between these two authors were resolved by a third researcher. The following information was extracted from the included RCTs: (1) general information: the first author, publication year, country of origin; (2) study characteristics: study design, sample size, intervention duration, number of intervention and control groups, the type and dose of cocoa products intake; (3) participant characteristics: age, gender; (4) outcome measures: change from baseline means and SDs of related biomarkers, including high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), total cholesterol (TC), triglyceride (TG), blood glucose (BG), glycosylated haemoglobin A1c (HbA1c), homoeostatic model assessment for insulin resistance (HOMA-IR), diastolic blood pressure (DBP), systolic blood pressure (SBP), and C-reactive protein (CRP). When displayed the results at various time points, we only considered data relating to the longest duration of treatment.

**Assessment of study quality**

Methodologic quality was assessed with the use of the Cochrane Collaborations tool for assessing the risk of bias (Higgins et al. 2011). Two authors (JD and XG) independently evaluated the quality of the studies by
the following criteria: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting. According to Cochrane Handbook, the risk of bias of studies was classified as low, high or unclear regarding each domain. Review Manager software (version 5.3) was applied in assessment of study quality.

**Data synthesis and statistical analysis**

If studies reported standard error instead of standard deviation, we would estimate the SD by \[SD = SE \times \text{square root (n)}\]. For studies reported the outcome in graphic form, we performed data extraction by using GetData Graph Digitiser 2.26. If the study only reported the mean and upper and lower quartiles, we would use some methods to estimate (Luo et al. 2018). For studies that did not report the standard deviations (SDs) of mean change, we utilised the following formula to estimate: \[SD_{\text{change}}^2 = SD_{\text{baseline}}^2 + SD_{\text{final}}^2 - (2 \times \text{corr} \times SD_{\text{baseline}} \times SD_{\text{final}})\] (Borenstein et al. 2009). Estimates of effect sizes were expressed based on weighted mean difference (WMD) and 95% confidence interval (CI) from the random effects model. Heterogeneity across studies was assessed by using Q test and \(I^2\) index, with an \(I^2\) of 25%, 50%, and 75% signifying low, medium, and high heterogeneity, respectively, and \(p < 0.05\) indicated that heterogeneity existed. The subgroup analysis was performed to find out the probable source of heterogeneity among trials. Subgroup analyses were conducted where sample size permitted and with
moderate or high heterogeneity. Studies were categorised based on region (America, Europe, Asia), study design (parallel, crossover), age (≤ 65, > 65), baseline BMI (≤ 30 kg/m², > 30 kg/m²), type of intervention (cocoa powder, high-polyphenol chocolate or dark chocolate), dose (≤ 25 g/d, > 25 g/d), and duration (≤ 8 weeks, > 8 weeks). Egger’s tests and funnel plots were formally applied to test for publication bias (Higgins et al. 2003). In addition, sensitivity analysis was executed to assess the possible effect of each single study on the pooled effect size. The statistical analyses were performed by using Stata version 12.0 (StataCorp LP). p < 0.05 was considered as statistically significant.

Results

Study selection

Among 1532 potential records, 44 articles were selected for detailed assessment. Twenty-nine studies were excluded from meta-analysis because of the following reasons: 7 articles were conference abstracts, one article was editorial comment, one was the letter to the editor, 13 articles were review, the subjects and outcomes of 7 articles did not meet inclusion criteria. Ultimately, 15 articles included 12 studies fulfilled our inclusion criteria (Balzer et al. 2008; Mellor et al. 2010; Curtis et al. 2012; 2013; Mellor et al. 2013; Parsaeyan et al. 2014; Basu et al. 2015; Rostami et al. 2015; Foster 2016; Ayoobi et al. 2017; Dicks et al. 2018; Jafarirad et al. 2018; Konya et al. 2019; Rynarzewski et al. 2019; Davis et al. 2020). The specific selection flow chart was presented in Figure 1.

| Author year | Region | Sample size T/C | Type of intervention | Study design | Dose (g/d) | Duration (w) | Parameter |
|-------------|--------|----------------|----------------------|--------------|------------|--------------|-----------|
| Balzer et al. 2008 | America | 41/21 | cocoa powder | parallel | 54 | 4 | HDL-C, LDL-C, TC, TG, BG, HbA1c, CRP |
| Mellor et al. 2010 | Europe | 12/12 | high-polyphenol chocolate or dark chocolate | crossover | 45 | 8 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP, CRP |
| Curtis et al. 2012 | Europe | 93/47/46 | high-polyphenol chocolate or dark chocolate | parallel | 27 | 52 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP |
| Parsaeyan et al. 2014 | Asia | 100/50/50 | cocoa powder | parallel | 10 | 6 | HDL-C, LDL-C, TG, BG, insulin, HbA1c, HOMA-IR, DBP, CRP |
| Rostami et al. 2015 | Asia | 60/32/28 | high-polyphenol chocolate or dark chocolate | parallel | 25 | 8 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP, CRP |
| Ayoobi et al. 2017 | Asia | 44/21/23 | high-polyphenol chocolate or dark chocolate | parallel | 30 | 8 | SBP, DBP |
| Jafarirad et al. 2018 | Asia | 44/21/23 | high-polyphenol chocolate or dark chocolate | parallel | 30 | 8 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP, CRP |
| Dicks et al. 2018 | Europe | 35/17/18 | cocoa powder | parallel | 2.5 | 12 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP |
| Konya et al.(a) 2019 | Europe | 24/11/13 | cocoa powder | parallel | 3.2 | 8 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP |
| Konya et al.(b) 2019 | Europe | 25/12/13 | cocoa powder | parallel | 3.2 | 8 | HDL-C, LDL-C, TC, TG, BG, insulin, HbA1c, HOMA-IR, DBP, SBP |

The arrow indicates an increase (↑) or decrease (↓) in the levels of the different parameters.

BG: blood glucose, C: Control, CRP: C-reactive protein, DBP: diastolic blood pressure, HbA1c: glycosylated haemoglobin A1c, HDL-C: high density lipoprotein-cholesterol, HOMA-IR: homoeostatic model assessment for insulin resistance, LDL-C: low density lipoprotein-cholesterol, SBP: systolic blood pressure, T: Treatment, TC: total cholesterol, TG: triglyceride, W: weeks.

Studies characteristics and quality assessment

Among the 15 articles, there are 12 studies, including 9 long term studies (Balzer et al. 2008; Mellor et al. 2010; Curtis et al. 2012; Parsaeyan et al. 2014; Rostami et al. 2015; Ayoobi et al. 2017; Dicks et al. 2018; Jafarirad et al. 2018; Konya et al. 2019; Rynarzewski et al. 2019; Davis et al. 2020). The specific selection flow chart was presented in Figure 1.
Long-term effects of cocoa products on cardiometabolic biomarkers in T2D patients

Long-term effects of cocoa products on lipids metabolism biomarkers in T2D patients

Among the long-term studies, a total of 8 studies including 434 participants reported lipids metabolism related indicators (HDL-C, LDL-C, TC and TG). The pooled estimates from the random-effect model indicated that cocoa products consumption had a negative significant effect on LDL-C (Figure 3(A), Table 3) (WMD: $-9.955$ mg/dL, 95% CI: $-17.408, -2.501$, $p = 0.009$) and TG (Figure 3(B), Table 3) (WMD: $-15.364$ mg/dL, 95% CI: $-23.383, -7.346$, $p < 0.001$), with significant heterogeneity among studies (LDL-C: $I^2 = 79.9\%$, $p < 0.001$, TG: $I^2 = 35.8\%$, $p = 0.131$), respectively. Nevertheless, there was a non-significant reduction in TC (Figure 3(C), Table 3) (WMD: $-7.632$ mg/dL, 95% CI: $-20.351, 5.086$, $p = 0.240$) and increase in HDL-C (Figure 3(D), Table 3) (WMD: $1.413$ mg/dL, 95% CI: $-1.117, 3.944$, $p = 0.251$).

Table 2. Characteristics of eligible studies for short-term.

| Author year | Region   | Sample size T/C | Type of intervention | Study design | Dose (g/d) | Duration (h) | Parameter                                                                 |
|-------------|----------|----------------|----------------------|--------------|------------|--------------|---------------------------------------------------------------------------|
| Mellor et al. 2013 | Europe  | 10/10            | high-polyphenol chocolate or dark chocolate | crossover   | 13.5       | 3            | BG, insulin†                                                              |
| Basu et al. 2015         | America  | 18/18            | cocoa powder         | crossover    | 20         | 6            | HDL-C†, LDL-C, TC, TG, BG, insulin†, HOMA-IR, DBP, SBP, CRP               |
| Rynarzewski et al. 2019  | Europe  | 12/12            | cocoa powder         | crossover    | 2.5        | 4            | HDL-C, LDL-C, TC, TG, insulin, HOMA-IR, DBP, SBP                         |

The arrow indicates an increase (†) or decrease (¶) in the levels of the different parameters.
BG: blood glucose, C: Control, CRP: C-reactive protein, DBP: diastolic blood pressure, h: hours, HbA1c: glycosylated haemoglobin A1c, HDL-C: high density lipoprotein-cholesterol, HOMA-IR: homoeostatic model assessment for insulin resistance, LDL-C: low density lipoprotein-cholesterol, SBP: systolic blood pressure, T: Treatment, TC: total cholesterol, TG: triglyceride.
following cocoa products consumption with significant heterogeneity among the studies (TC: $I^2 = 88.8\%, p < 0.001$, HDL-C: $I^2 = 76.9\%, p < 0.001$).

Subgroup analysis, by region, indicated no significant difference in HDL-C and TC, while LDL-C was significantly decreased in Europe/Asia and TG was significantly decreased in Asia. Subgroup analysis, by study design, showed no significant difference in HDL-C, LDL-C, TC, while TG was significantly decreased in parallel studies. As for LDL-C and TG, subgroup analysis by age indicated a greater effect size in $\leq 65$. Subgroup analysis, by baseline BMI, indicated no significant difference in all of the lipid profiles indicators. Stratified analysis of intervention types showed that the heterogeneity of the two groups was decreased, which showed that intervention types may be the source of heterogeneity for HDL-C, LDL-C, TC, and TG. Moreover, HDL-C was significantly increased and LDL-C as well as TG were decreased in subgroups of high-polyphenol chocolate or dark chocolate. Dose was likely to be the source of heterogeneity for HDL-C. LDL-C and TC were significantly reduced in $> 25$ g/d. Duration was possibly the source of heterogeneity for LDL-C, TC, and TG. LDL-C and TG significantly decreased in $\leq 8$ weeks. Results of subgroup analysis have been summarised in Supplementary Table 4.

**Long-term effects of cocoa products on glucose metabolism biomarkers in T2D patients**

Among long-term trials, seven trials including a total of 334 subjects reported BG and HbA1c as outcome measures. The long-term effects of cocoa products on insulin and HOMA-IR were reported in six and four studies, involving 293 individuals, 189 individuals and 142 individuals, respectively. The pooled estimates from the random-effect model indicated that cocoa products consumption had a
negative significant effect on BG (Figure 4(A), Table 3) (WMD: $-9.105 \text{ mg/dL}$, 95% CI: $-15.022, -3.189$, $p = 0.003$), with moderate heterogeneity ($I^2 = 41.1\%$, $p = 0.131$). Cocoa products consumption had non-significant reduction in insulin (Figure 4(B), Table 3) (WMD: $-0.833 \text{ mU/L}$, 95% CI: $-2.557, 0.891$, $p = 0.344$), HOMA-IR (Figure 4(C), Table 3) (WMD: $-0.533$, 95% CI: $-1.368, 0.302$, $p = 0.211$)

Figure 3. Forest plot of the long-term effect of cocoa products consumption on LDL-C (A), TG (B), TC (C), HDL-C (D).
and HbAlc (Figure 4(D), Table 3) (WMD: −0.168%, 95% CI: −0.360, 0.025, p = 0.088), with low heterogeneity in insulin ($I^2 = 18.3\%$, $p = 0.290$), HbAlc ($I^2 = 20.8\%$, $p = 0.265$) and medium heterogeneity in HOMA-IR ($I^2 = 26.7\%$, $p = 0.243$).

Subgroup analysis of BG, by region, indicated a significant decrease in Europe and Asia. Subgroup analysis, by study design, indicated no significant difference in BG and HOMA-IR between the subgroups. Stratified analysis by age showed that HOMA-IR was significantly decreased in subgroup of ≤ 65. Subgroup analysis, by baseline BMI, indicated no significant difference in BG and HOMA-IR. Stratified analysis of BG and HOMA-IR by type of intervention showed a significantly decreased in high-polyphenol chocolate or dark chocolate. Subgroup analysis of BG and HOMA-IR by dose indicated a significant decrease in subgroup of > 25 g/d. Stratified analysis by duration indicated that BG was significantly decreased in ≤ 8 weeks and HOMA-IR in > 8 weeks. Results of subgroup analysis have been presented in Supplementary Table 4.

### Table 3. WMDs in biomarkers in cocoa products intervention groups compared with placebo groups.

| Indicators | n | WMD (95%CI) | $P$ | $I^2$ | $P$ |
|------------|---|-------------|-----|-----|-----|
| Long-term  |   |             |     |     |     |
| HDL-C      | 9 | 1.413 (−1.117, 3.944) | 0.274 | 76.9 | < 0.001 |
| LDL-C      | 9 | −9.555 (−17.408, −2.501) | 0.009 | 79.9 | < 0.001 |
| TC         | 9 | −7.632 (−20.351, 5.086) | 0.240 | 88.8 | < 0.001 |
| TG         | 9 | −15.364 (−23.383, −7.346) | < 0.001 | 35.8 | 0.131 |
| BG         | 8 | −9.105 (−15.022, −3.189) | 0.003 | 36.5 | 0.138 |
| insulin    | 7 | −0.833 (−2.557, 0.891) | 0.344 | 18.3 | 0.290 |
| Hba1C      | 8 | −0.129 (−0.263, 0.006) | 0.060 | 20.8 | 0.265 |
| HOMA-IR    | 5 | −0.533 (−1.368, 0.302) | 0.211 | 26.7 | 0.243 |
| CRP        | 3 | −0.978 (−1.687, −0.269) | 0.070 | 0.0 | 0.420 |
| Short-term |   |             |     |     |     |
| BG         | 3 | 1.131 (−8.656, 10.918) | 0.821 | 0.0 | 0.887 |
| insulin    | 3 | 1.770 (−1.010, 4.550) | 0.212 | 0.0 | 0.747 |
| HOMA-IR    | 2 | 0.163 (−3.381, 3.707) | 0.928 | 18.4 | 0.268 |

BG: blood glucose, CRP: C-reactive protein, DBP: diastolic blood pressure, Hba1C: glycosylated haemoglobin A1c, HDL-C: high density lipoprotein-cholesterol, HOMA-IR: homeostatic model assessment for insulin resistance, LDL-C: low density lipoprotein-cholesterol, SBP: systolic blood pressure, TC: total cholesterol, TG: triglyceride.

### Table 4. The main results of cocoa products consumption on biomarkers in T2D patients.

| Parameter          | Effect | Results of subgroup analyses |
|--------------------|--------|------------------------------|
| Long-term          |        |                              |
| Lipid metabolism   |        |                              |
| HDL-C              | Down   | Possible sources of heterogeneity: type of intervention, dose |
| LDL-C              | Down   | Possible sources of heterogeneity: type of intervention, dose |
| TC                 | −      | Possible sources of heterogeneity: Baseline BMI, type of intervention, duration |
| TG                 | Down   | Down in such groups: Asia, parallel study, age ≤ 65, high–polyphenol chocolate or dark chocolate, duration ≤ 8 weeks |
| Glucose metabolism |        |                              |
| BG                 | Down   | Europe and Asia, high–polyphenol chocolate or dark chocolate, dose >25 g/d, duration ≤ 8 weeks |
| Insulin            | −      |                              |
| Hba1C              | −      |                              |
| HOMA-IR            | −      |                              |
| Blood pressure     |        |                              |
| DBP                | −      |                              |
| SBP                | −      |                              |
| Inflammation cytokines | CRP  | Down −                      |
| Short-term         |        |                              |
| Glucose metabolism |        |                              |
| BG                 | −      |                              |
| Insulin            | −      |                              |
| HOMA-IR            | −      |                              |

BG: blood glucose, CRP: C-reactive protein, DBP: diastolic blood pressure, Hba1C: glycosylated haemoglobin A1c, HDL-C: high density lipoprotein-cholesterol, HOMA-IR: homeostatic model assessment for insulin resistance, LDL-C: low density lipoprotein-cholesterol, SBP: systolic blood pressure, TC: total cholesterol, TG: triglyceride.
Figure 4. Forest plot of the long-term effect of cocoa products consumption on BG (A), insulin (B), HOMA-IR (C), HbA1c (D).
Long-term effects of cocoa products on blood pressure in T2D patients

We also inspected whether there was an effect of cocoa products long-term consumption on blood pressure in diabetic patients by extracting DBP and SBP data from the eligible studies. The effect of cocoa products on blood pressure was reported in 6 trials, involving 289 subjects. Pooled effects size of 6 trials indicated a non-significant reduction in DBP (Figure 5(A), Table 3) (WMD: −1.319 mmHg, 95% CI: −3.052, 0.414, p = 0.136) and SBP (Figure 5(B), Table 3) (WMD: −2.062 mmHg, 95% CI: −6.284, 2.160, p = 0.338), with moderate heterogeneity among trials (DBP: $I^2 = 3.2\%$, p = 0.401, SBP: $I^2 = 45.4\%$, p = 0.089).

According to the results of subgroup analysis, region, dose and duration might be the source of heterogeneity for SBP in association studies and SBP was significantly decreased in Asia, while there was no significant difference based on study design, age, baseline BMI, type of intervention, dose, and duration. Results of subgroup analysis have been presented in Supplementary Table 4.

Long-term effects of cocoa products on inflammatory biomarkers in T2D patients

There were three trials to be eligible to extract CRP data, which involved 145 participants. Quantitative analysis of CRP showed a significant reduction (Figure 6, Table 3) (WMD: −0.978 mg/L, 95% CI: −1.687, −0.269, p = 0.007), with no between-study heterogeneity ($I^2 = 0.0\%$, p = 0.420). One study analysed the tumour necrosis factor-α (TNF-α), Interleukin-6 (IL-6) (Ayoobi et al. 2017), and it was shown that dark chocolate consumption decreased the level of them compared with the control group.

Short-term effect of cocoa products on cardiometabolic biomarkers in T2D patients

Three trials reported the short-term effect of cocoa products on BG (Figure 7(A), Table 3), insulin (Figure 7(B), Table 3) and HOMA-IR (Figure 7(C), Table 3), for which our meta-analysis showed no effect (BG: WMD: 1.131 mg/dL, 95% CI: −8.656, 10.918, p = 0.821; HOMA-IR: WMD: 0.163, 95% CI: −3.381, 3.707, p = 0.928; insulin: WMD: 1.770 mU/L,
95% CI: $(-1.010, 4.550, p = 0.212)$, with low between-study heterogeneity (BG: $I^2 = 0.0\%, p = 0.887$; HOMA-IR: $I^2 = 18.4\%, p = 0.268$; insulin: $I^2 = 0.0\%, p = 0.747$).

**Sensitivity analysis**

To discover the impact of each single study on the combined effect size, each trial from the analysis was removed, step by step. No significant effect of any individual study was observed on the combined effect sizes of HDL-C, LDL-C, TC, TG, BG, HbAlc, HOMA-IR, insulin, DBP, and SBP. The specific results of sensitivity analysis were presented in Supplementary Figure 1–3.

**Publication bias**

Publication bias was performed on the index which involved more than four studies. It was roughly evaluated by visual inspection of a funnel plot (Supplementary Figure 4–6). Furthermore, Egger’s regression test was also applied to detect potential publication bias quantitatively among the eligible trials of meta-analyses. The outcomes of Egger’s regression test manifested that no significant publication biases were noticed from meta-analyses estimating the long-term effects of cocoa products consumption on HDL-C ($t = 1.15, p = 0.287$), LDL-C ($t = 2.30, p = 0.055$), TC ($t = 2.10, p = 0.074$), TG ($t = 1.68, p = 0.138$), BG ($t = 0.54, p = 0.611$), HbAlc ($t = -0.88, p = 0.411$), insulin ($t = 0.75, p = 0.486$), HOMA-IR ($t = 1.08, p = 0.361$), DBP ($t = 0.26, p = 0.806$) and SBP ($t = 0.97, p = 0.378$). However, a mild dissymmetry was observed by visual inspection in TC and TG, which indicated that there was slight publication bias. It may be caused by the small number of RCTs included, limited sample sizes.

**Discussion**

The present meta-analyses of RCTs summarised the effects of cocoa products on cardiometabolic biomarkers in T2D patients. Twelve RCTs were involved, including 9 long-term trials and 3 short-term trials. For long-term, the results indicated that cocoa products consumption significantly decreased LDL-C, TG, BG, and CRP. Nevertheless, as for short-term, it showed that there was non-significant reduction in BG, HOMA-IR and insulin.

In recent years, several large prospective cohort studies have shown that moderate consumption of cocoa products may reduce risk of T2D (Greenberg 2015; Matsumoto et al. 2015; Crichton et al. 2017). Previous systematic reviews and meta-analyses, regarding cocoa flavanol intake and biomarkers for cardiometabolic health, revealed that cocoa flavanol intake has favourable effects on select cardiometabolic biomarkers among adults, including TG, HDL-C, insulin, QUICKI and CRP. In addition, the included RCTs indicated that the consumption of cocoa products for diabetics may have a beneficial effect on blood sugar control and to a greater extent on factors related to CVD risk (Lin et al. 2016).

Many studies have explored the effect of cocoa products supplementation on lipids profile of non-diabetic population, such as the healthy individuals (Wan et al. 2001; Fraga et al. 2005; Almoosawi et al. 2012; Neufingerl et al. 2013), hypertensive (Grassi et al. 2005; Muniyappa et al. 2008), hypercholesterolemic (Baba et al. 2007; Sarria et al. 2014) and overweight (Almoosawi et al. 2012; Khan et al. 2012). Several meta-analyses have been performed to search for the effect of the intake of cocoa products on lipid metabolism. It has shown that cocoa consumption significantly reduced TC and LDL-C, even at low doses in individuals who exhibited cardiovascular risk factors.
while HDL-C and TG did not change (Jia et al. 2010). Similar outcomes were discovered by another meta-analysis (Tokede et al. 2011). In contrast, other studies (Hooper et al. 2012; Sarri/C19a et al. 2020) reported that HDL-C was increased. Similar to the results of studies on individuals without T2D, the effects of cocoa products consumption on the lipid profile in diabetic also were controversial (Table 1). The findings of our meta-analysis showed reduction of LDL-C and TG levels while no change in HDL-C and TC. In accordance with past research, different methylxanthine content of cocoa which may be partly responsible for the difference in HDL-C (Neufingerl et al. 2013). However, a kind of product tested higher intake of methylxanthines has not led to a significant increase in HDL-C and flavanols appeared to be responsible for the increase (Sarriá et al. 2015; Goya et al. 2016). In our research, only three eligible trials (Balzer et al. 2008; Basu et al. 2015; Foster 2016; Dicks et al. 2018; Davis et al. 2020) have reported the specific content of theobromine contained in cocoa intervention. Thus, it was impossible to perform the subgroup analysis stratified by content of theobromine, so it was also hard to render it possible to know whether the difference in HDL-C enhancement effect was associated with the theobromine.

Figure 7. Forest plot of the short-term effect of cocoa products consumption on BG (A), insulin (B), HOMA-IR (C).
In addition to ameliorating blood lipid metabolism, cocoa products also have a positive effect on blood glucose metabolism. In consistence with the studies on non-diabetic population (Grassi et al. 2008; Cordero-Herrera et al. 2014), our research indicated that cocoa products intake in favour of glucose homeostasis and insulin resistance in long-term. Compared with long-term effect, the results of the meta-analysis showed no improvement on blood glucose metabolism in short-term. Nevertheless, making this conclusion needs to be cautious for too few studies. Moreover, what is worrying is that the sugar and energy contained in cocoa may offset part of the beneficial effects (Mellor et al. 2015).

Cocoa has also been found to have a lowering effect on blood pressure (BP) (Ried et al. 2010; Hooper et al. 2012). However, inconsistent with these researches, our research did not find the BP lowering effect of cocoa. Some researchers have deemed that the occurrence of this condition probably related to the population’s baseline BP and age (Ried et al. 2010). They found that the individuals with hypertension or prehypertension had the most significant reduction in BP, while those with normal BP had no reduction. Besides, there was a negative correlation between cocoa consumption and BP in the elderly subjects while no beneficial effect of cocoa intake on BP was disclosed in normal BP or middle-aged subjects (Jafarnejad et al. 2020). Interestingly, the participants included in our meta-analysis were characterised by mild hypertension while no reduction in BP. This may be associated with the small number of included studies, or it may be due to the inclusion of diabetic patients. Above all, the effect of cocoa in lowering BP varies in different populations. In agreement with previous studies (di Giuseppe et al. 2008; Lin et al. 2016), our results indicated that cocoa could reduce CRP, which suggested that cocoa was likely to have anti-inflammatory effects in T2D patients.

Altogether, the findings of our meta-analysis illustrated that long-term consumption of cocoa products had positive effects on blood lipids and blood sugar and inflammatory biomarkers for T2D patients. There are numerous potential mechanisms that may explain the potential benefits of cocoa and chocolate for diabetics. First of all, in terms of lipid-lowering effects, studies have shown that oligomeric proanthocyanidins in cocoa powder were the main active ingredients that inhibited the intestinal absorption of cholesterol and bile acids by reducing the solubility of micellar cholesterol (Mellor et al. 2010; Jaramillo Flores 2019). Additionally, flavanols and tea polyphenols were found a synergistic effect, which can reduce their overall lipid-lowering effect by inhibiting the activity of pancreatic lipase (Nakai et al. 2005; Gondoin et al. 2010).

In addition, the effect of improving the homeostasis of glucose is mainly achieved by cocoa flavanols through slowing down the digestion and absorption of carbohydrates in the intestinal tract (Strat et al. 2016). Previous studies have proposed the following hypothetical mechanisms, including inhibition of the digestive enzymes α-amylase and α-glucosidase, inhibition of glucose transporter, glucose transporter 2 (GLUT2) and sodium/glucose cotransporter 1 (SGLT1), promoting glucagon-like peptide 1(GLP-1) secretion and inhibiting Dipeptidyl peptidase IV (DPP-4) (Gu et al. 2011; González-Abuin et al. 2012; Barrett et al. 2013; Strat et al. 2016). Regarding the benefits of blood glucose metabolism, in addition to improving glucose homeostasis, it can also enhance insulin resistance and increase β-cell mass and function. At molecular level, cocoa intake prevented β-cell apoptosis by increasing antiapoptotic proteins and decreasing proapoptotic proteins (Bax and caspase-3 activity) (Martin et al. 2016; Jaramillo Flores 2019). The effect of cocoa on improving insulin resistance might be mainly through regulating insulin signal transduction. The possible mechanisms might be listed as follows. Firstly, cocoa flavanols stimulate the secretion of GLP-1 and Gastric inhibitory peptide (GIP) to enhance the incretin response, thereby promoting insulin secretion. Secondly, the cocoa flavanols in cocoa play prebiotic-like effects, which can advance the intestinal barrier function, accordingly lowering lipopolysaccharide (LPS) and chronic inflammation and improving insulin signalling. Thirdly, cocoa flavanols decreased insulin resistance through insulin-dependent and insulin-independent mechanisms, including activating the insulin signal cascade in the absence of insulin (Strat et al. 2016).

Furthermore, cocoa flavonoids have also been found to inhibit the enzyme activity of lipoxygenases (LOX) in a variety of mammals (Sies et al. 2005), which possibly confer certain anti-inflammatory, vaso-protective and anti-bronchial effects. Besides, studies have illuminated that cocoa polyphenol diffused into cells and inhibited Mitogen-activated protein kinase (MAPKs), thereby blocking inflammatory transcription factors, such as nuclear factor-k-gene binding (NF-κB) and Activator protein-1 (AP-1). These signals collectively restrained the expression of a large amounts of pro-inflammatory mediators such as TNF-α, Interleukin-8 (IL-8), IL-6, monocyte
chemoattractant protein-1 (MCP-1), nitric oxide (NO) (Ali et al. 2014). In addition, cocoa flavonals also stimulated the activity of important antioxidant enzymes, such as catalase, superoxide dismutase, glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione Glycine S-transferase (GST) (Rodriguez-Ramiro et al. 2011). Research on the role of cocoa fibre in inflammation biomarkers has shown that flavonoids were not the only cocoa component with potential biological activity, and fibre was one of them (Sarriá et al. 2012).

To our best knowledge, it is the first meta-analysis summarised both short-term and long-term RCTs to date, which is conducted specifically with T2D and evaluated the effect of cocoa products on comprehensive cardiometabolic biomarkers. The detailed subgroup analyses for potential effect modifiers and a comprehensive evaluation of potential bias were performed. Although, several limitations exist in our meta-analysis. Firstly, a small number of studies were included. Only three studies investigated the short-term effect. Moreover, the eligible studies had quite small sample sizes. Secondly, on account of the limited number of available trials, studies using different blood sources for biomarker measurements were integrated, which might bring added heterogeneity. Thirdly, the search for studies was strained by English-language articles while four large databases were searched to ensure that the search is comprehensive. In addition, the types and contents of health-affecting ingredients contained in cocoa products as intervention measures vary, such as cocoa polyphenols that have a positive effect on health and sugars that may cause weight gain. Nevertheless, although the use of different types of cocoa products in each study may be a disadvantage and should be suspected, the use of different cocoa product formulations also achieved consistent beneficial effects in the same population, which is also a potential advantage. It is the same result obtained from the difference that makes the findings more robust and widespread in clinical practice. Furthermore, due to the different types of interventions, the doses are probably not comparable and consequently lead to greater heterogeneity. Indeed, heterogeneity among long-term effect on most of biomarkers was considerable, whereas we conducted a random effects meta-analysis, and performed a subgroup analysis to find populations that might benefit more than other populations.

**Conclusion**

Our findings suggested a beneficial long-term effect of different forms of cocoa products intake on cardiometabolic biomarkers for T2D patients, especially in terms of blood glucose, lipid metabolism (LDL-C and TG) and inflammation (CRP). However, more large clinical studies with different doses of cocoa products and the duration of intervention should be implemented to approve our findings.

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**Disclosure statement**

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