Short-term effect of cocoa product consumption on lipid profile: a meta-analysis of randomized controlled trials

Lei Jia, Xuan Liu, Yong Yi Bai, Shao Hua Li, Kai Sun, Chen He, and Rutai Hui

ABSTRACT
Background: The effect of cocoa products on lipid changes is controversial.
Objectives: We aimed to identify and quantify the effect of cocoa on total cholesterol, LDL cholesterol, and HDL cholesterol.
Design: A comprehensive literature search was conducted for relevant trials of cocoa on lipid profile. Weighted mean differences were calculated for net changes in lipid concentrations by using fixed-effects or random-effects models. Previously defined subgroup analyses were performed to identify the source of heterogeneity.
Results: Eight trials (involving 215 participants) were included and evaluated. Because there was only one relatively longer-term study, we focused on the short-term data to evaluate the effects of cocoa on plasma lipid. Cocoa consumption significantly lowered LDL cholesterol by 5.87 mg/dL (95% CI: −11.13, −0.61; P < 0.05) and marginally lowered total cholesterol by 5.82 mg/dL (95% CI: −12.39, 0.76; P = 0.08). However, no significant change was seen in LDL cholesterol in high-quality studies (3 studies included; −4.98 mg/dL; 95% CI: −13.18, 3.21; P = 0.23). Subgroup analyses suggested a cholesterol-lowering effect only in those subjects who consumed a low dose of cocoa and with cardiovascular disease risks. There was no evidence of a dose-effect relation, of any effect in healthy subjects, or of any change in HDL cholesterol.
Conclusions: Short-term cocoa consumption significantly reduced blood cholesterol, but the changes were dependent on the dose of cocoa consumption and the healthy status of participants. There was no dose response and no effect in healthy participants. Future high-quality studies are needed to determine the efficiency of moderate cocoa consumption on lipid profile in long-term intervention and in subjects with other cardiometabolic risk factors. Am J Clin Nutr 2010;92:218–25.

INTRODUCTION
Coronary artery disease (CAD) is one of the leading causes of morbidity, mortality, and disability in many parts of the world, especially in Western countries, and accounts for one-fifth of all mortality in the United States (1). The World Health Organization has highlighted the importance of raised blood cholesterol as a risk factor for CAD. The INTERHEART study reports that those with abnormal blood lipids have a 3-fold risk of heart attack compared with those with normal concentrations (2). CAD is a disease that has a close relation to lifestyle, and diet is one of the major factors affecting people’s blood cholesterol profiles (3). Data from the National Health and Nutrition Examination Survey (2005–2006) show that 16% of American adults have serum total cholesterol concentrations of ≥240 mg/dL. (1). So, not surprisingly, increasing numbers of consumers are more careful about what they eat and whether these foods are healthy.

Cocoa and its products, such as cocoa-rich chocolate, have been known for their good taste. The affection for chocolate has expanded to a global scale: >75% of American and Spanish children report chocolate cravings (4), with the average American consuming ~5.3 kg of chocolate each year (5). Cocoa products contain more polyphenols than teas and red wines. A prospective study, involving 470 elderly men, highlights the protective effects of cocoa intake in decreasing blood pressure and reducing cardiovascular disease and all-cause mortality (6).

To date, a substantial number of observational trials have reported that the supplementation of cocoa products affects lipid profiles in subjects with cardiovascular-related diseases such as hypercholesterolemia, glucose intolerance, and hypertension as well as healthy individuals (7–31). However, the sample sizes of these studies are relatively small and the conclusions are inconsistent. Therefore, we conducted a systemic review of the scientific literature and a meta-analysis of all published randomized controlled trials that investigated the effects of cocoa on blood cholesterol. The result of our analysis may be incorporated into a targeted dietary program as part of public health policy to improve cardiovascular health.

METHODS

Literature search

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nml.nih.gov/pubmed; from 1950 to May 2009), Embase (http://www.embase.com; from 1966 up to May 2009), the Cochrane Library database (http://www.cochrane.org), and reviews of relevant articles using the relevant text keywords “cocoa” and “chocolate,” which were paired with the following: “blood lipid,” “blood cholesterol,” “low-density lipoprotein cholesterol,” “high-density lipoprotein cholesterol,” or “cardiovascular.” The search was restricted to clinical trials. No language restrictions were imposed. In addition, a manual search of references from reports of clinical trials or review articles was performed to identify relevant trials.

Study selection

We selected completed and nonconfounded randomized controlled trials from studies if they met the following inclusion criteria: 1) used cocoa products such as cocoa drink or chocolate as supplementation that were matched by a suitable control arm that allowed any observed effects to be reasonably ascribed to cocoa; 2) excluded children or critically ill participants with any degree of cardiovascular disease; 3) had assignable designs (crossover, parallel, etc) that specified the treatment type, dose, and duration; 4) evaluated blood lipids by estimating the concentrations of total cholesterol (TC), LDL cholesterol, and HDL cholesterol; and 5) assigned one of the following methods about food intake control: deducted wastage food with nothing else to be eaten, given food choice advice and assessed intake via diary or other recordings, and maintained usual food intake and avoided cocoa-related diet. The authors of any published studies in which data were insufficient were contacted to confirm their eligibility and to obtain additional study details.

Quality assessment

Each individual intervention was assessed for quality of randomization, blinding, reporting of withdrawals, generation of random numbers, and concealment of allocation. Trials scored one point for each area addressed, with a possible score of between 0 and 5 (highest level of quality) (32).

Data extraction

Two authors (LJ and XL) independently assessed and abstracted relevant trials that met the standardized, predefined criteria. Disagreements were identified computationally. Each was checked independently. If data could not be extracted or calculated from the article with confidence, no data were entered. Any discrepancies between the 2 reviewers were resolved through discussion. Extracted data included study characteristics (author, publication year, sample size, study design, type of intervention, and study duration), population information (sex and healthy status), and baseline and final concentrations or net changes of TC, LDL cholesterol, and HDL cholesterol. Data initially extracted were converted to conventional units (eg, TC: 1 mmol/L converted to 38.6 mg/dL). For trials in which blood lipid measurements were recorded at several points in time, we abstracted the value closest to the time point used in the other studies for our primary analysis.

Data synthesis and analysis

The estimate of the principal effect was defined as the net changes in each of these study variables, which were calculated as the mean difference (active treatment minus control) in the changes (follow-up minus baseline). In instances in which variances for net changes were not reported directly, they were calculated from $P$ values, CIs, or individual variances from the cocoa group and the control group. For trials in which variances for paired differences were reported separately for each group, we calculated a pooled variance for net change by using standard methods. Missing variances for paired differences were calculated from variances at baseline and at the end of follow-up for each measure by using correlation coefficient methods according to the Cochrane Handbook for Systemic Review and the theory by Follmann et al (33). We assumed equal variances during the trial and between intervention and control groups.

Our meta-analysis and statistical analyses were performed with Stata software (version 10.0; Stata Corporation, College Station, TX) and REVMAN software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom). Weighted mean differences and 95% CIs were calculated for net changes in lipid values. Statistical heterogeneity of treatment effects between studies was formally tested with Cochran’s test ($P < 0.1$). The $I^2$ statistic was also examined, and we considered $I^2 > 50\%$ to indicate significant heterogeneity between the trials (34). The result was obtained from a fixed-effects model if no significant heterogeneity was shown. If significant heterogeneity was shown, a random-effects model was selected for the analysis (35). Publication bias was assessed with funnel plots and the Egger regression test.

To examine the effect on various covariants and identify the possible source of heterogeneity within these studies, previously defined subgroup analyses were performed (cocoa dose, study duration, healthy status, and study design). Because these previous studies did not measure cocoa as a whole and because it had been reported that polyphenol content varied in different types of chocolate on the basis of the percentage of cocoa used in the formulation (36, 37), we subgrouped the trials on the basis of the dose of polyphenols in the included trials. In addition, more sensitivity analyses were performed according to the Cochrane Handbook for Systemic Review.

RESULTS

Results of the literature search

We initially identified 1211 potentially eligible studies, the majority of which were excluded because they were not clinical trials or because the interventions were not relevant to the purpose of this meta-analysis. Full-text assessment of the 25 potentially relevant articles resulted in 8 eligible randomized controlled studies (11, 12, 14, 15, 17–20). The most common reasons for exclusion were as follows: 7 trials were not randomized controlled trials (23, 24, 26, 27, 29–31), in 2 trials cocoa product was given as part of a multi-component supplement (10, 25), and 3 studies did not report enough detail for inclusion in meta-analysis (21, 22, 28). Although we could obtain the specific data of 2 studies (9, 13), we were unable to confirm their eligibility, so we excluded these 2 studies. Two studies did not have a comparable control arm (8, 16). We excluded another trial because the result may have been confounded by the inappropriate study design (7). A flowchart showing the number of
citations retrieved by individual searches as well as the number of trials included in the review is presented in Figure 1.

Study characteristics

We identified 8 trials with 215 subjects (11, 12, 14, 15, 17–20) in our study. The characteristics of the trials are shown in Table 1. All of the subjects were asked to maintain their usual diet in all 8 trials. The main sources of cocoa were dark chocolate and cocoa powder. The trials varied in size from 15 to 44 subjects. As for the 8 studies that evaluated blood lipid concentrations, 4 trials (12, 14, 17, 18) investigated the effect of cocoa on healthy subjects. The other studies investigated the effects of chocolate consumption in patients with cardiovascular risks such as prehypertension and hypertension (11, 15, 20) or diabetes (19). All of the studies reported the types of cocoa products, and different types of cocoa products varied in their polyphenol contents on the basis of the percentage of cocoa used in the formulation. Doses of polyphenols in the studies ranged from 30 to 963 mg/d, and the treatment duration varied from 2 to 18 wk.

![Flow chart showing the number of citations retrieved by individual searches and the number of trials included in the review.](FIGURE 1)

**TABLE 1**
Characteristics of study populations, type of interventions, and study designs in the included trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No. of subjects (M/F)</th>
<th>Status</th>
<th>Intervention (treatment group/control group)</th>
<th>Daily doses of polyphenol in cocoa product (mg)</th>
<th>Duration</th>
<th>Losses to follow-up</th>
<th>Study design</th>
<th>Jadad score</th>
<th>Type of diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grassi et al (11)</td>
<td>2005</td>
<td>20 (10/10)</td>
<td>EH</td>
<td>Dark chocolate/white chocolate</td>
<td>88</td>
<td>15 d</td>
<td>NA</td>
<td>R, CO</td>
<td>2</td>
<td>Usual diet</td>
</tr>
<tr>
<td>Baba et al (12)</td>
<td>2007</td>
<td>25 (25/0)</td>
<td>Healthy</td>
<td>Cocoa powder/sugar</td>
<td>766.1</td>
<td>12 wk</td>
<td>NA</td>
<td>R, PC</td>
<td>2</td>
<td>Usual diet</td>
</tr>
<tr>
<td>Wan et al (14)</td>
<td>2001</td>
<td>23 (10/13)</td>
<td>Healthy</td>
<td>Cocoa powder and dark chocolate/</td>
<td>466</td>
<td>4 wk</td>
<td>NA</td>
<td>R, CO</td>
<td>2</td>
<td>Controlled diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nutrient-matched control</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taubert et al (15)</td>
<td>2007</td>
<td>44 (20/24)</td>
<td>Pre-EH</td>
<td>Dark chocolate/white chocolate</td>
<td>30</td>
<td>6–18 wk</td>
<td>Yes</td>
<td>R, DB, PC</td>
<td>5</td>
<td>Usual diet</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and EH</td>
<td>Dark chocolate/white chocolate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fraga et al (17)</td>
<td>2005</td>
<td>27 (27/0)</td>
<td>Healthy</td>
<td>Dark chocolate/white chocolate</td>
<td>168</td>
<td>2 wk</td>
<td>Yes</td>
<td>R, CO</td>
<td>2</td>
<td>Usual diet</td>
</tr>
<tr>
<td>Balzer et al (19)</td>
<td>2008</td>
<td>41 (29/12)</td>
<td>DM</td>
<td>Cocoa drink/nutrient-matched control</td>
<td>963</td>
<td>30 d</td>
<td>Yes</td>
<td>R, DB, PC</td>
<td>5</td>
<td>Usual diet</td>
</tr>
<tr>
<td>Muniyappa et al (20)</td>
<td>2008</td>
<td>20 (8/12)</td>
<td>EH</td>
<td>Cocoa drink/nutrient-matched control</td>
<td>900</td>
<td>2 wk</td>
<td>Yes</td>
<td>R, DB, PC, CO</td>
<td>5</td>
<td>Usual diet</td>
</tr>
</tbody>
</table>

1. EH, essential hypertension; Pre-EH, prehypertension; DM, diabetes; NA, not available; R, randomized; PC, placebo controlled; DB, double-blind; CO, crossover.
Data quality

All included trials were randomized, prospective, and placebo-controlled. Three of the trials were double-blinded (15, 19, 20), and 5 were crossover trials (11, 14, 17, 18, 20). Four trials reported the details of withdrawals (15, 17, 19, 20), whereas the others did not. The quality of these trials varied from low to high. Only 3 of the trials were classified as high quality (a Jadad score of 4 or 5); and 5 studies were low quality (a Jadad score <3) (Table 1).

Effect of cocoa product supplementation on lipid concentrations

The primary outcome was changes in TC, LDL cholesterol, and HDL cholesterol between baseline and final concentrations due to cocoa supplementation. The effect of cocoa consumption on blood cholesterol was well investigated by 8 trials. Two studies (17, 19) reported the paired differences in the 3 blood cholesterol variables separately for each group, one study (15) reported only changes from the baseline of each variable, and 5 other trials provided only the baseline and final blood lipid concentrations due to cocoa product or placebo consumption. Therefore, the changes in each measure in the 5 trials were calculated according to the Cochrane Handbook for Systemic Review and the theory by Follmann et al (33).

The trial reported by Taubert et al (15) was the only study that evaluated the relatively longer-term effectiveness of cocoa supplementation in over 4 mo. However, this study also reported related short-term data. Therefore, we focused on the short-term data (6 wk) to evaluate the short-term effects of cocoa on blood lipid, being more homogeneous with other included trials. Moreover, Taubert et al mistakenly labeled SEs as SDs, so we converted the SEs into SDs in our meta-analyses.

First, the short-term data were pooled from the 8 trials. The mean change in TC was marginally affected in subjects supplemented with cocoa products (−5.82 mg/dL; 95% CI: −12.39, 0.76; P = 0.08; percentage reduction of mean difference: 3.07%) compared with controls. Heterogeneity was observed for this outcome (heterogeneity chi-square = 13.74, F = 49%, P = 0.06) (Figure 2). LDL cholesterol was significantly lower in the cocoa product-supplemented subjects than in the placebo-treated subjects. The standardized difference in mean LDL cholesterol decreased by −5.87 mg/dL (95% CI: −11.13, −0.61; P = 0.03; percentage reduction of mean difference: 4.82%) (Figure 3).

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We conducted subgroup analyses according to cocoa dosage. To explore the dose-effect relation, cocoa doses (from 30 to 963 mg polyphenols) were divided into 3 categories. We calculated the first tertile of polyphenol dosage for all included trials to be the low cocoa consumption group, which was defined as “daily consuming polyphenols <260 mg.” The high cocoa consumption group, the third tertile of polyphenol dosage, was defined as “daily consuming from 260 to 665 mg polyphenols.” The high cocoa consumption group compared with their controls, which is much lower than that in pooled whole trials (TC: −9.92 mg/dL; 95% CI: −15.71, −4.14; P = 0.0008; percentage reduction of mean difference: 5.24%; LDL cholesterol: −8.07 mg/dL; 95% CI: −15.15, −0.99; P = 0.03; percentage reduction of mean difference: 6.63%), whereas TC and LDL cholesterol were not significantly reduced in the middle and high consumption groups compared with their corresponding controls. Meanwhile, no heterogeneity of effect size was observed in each subgroup (data are shown in Table 2).

Subgroup analyses according to healthy status showed that cocoa consumption could significantly reduce TC and LDL cholesterol in participants with cardiovascular risks compared with controls (TC: −8.01 mg/dL, 95% CI: −13.83, −2.20, P = 0.007; percentage reduction of mean difference: 4.23%; LDL cholesterol: −7.60 mg/dL, 95% CI: −14.70, −0.51; P = 0.04; percentage reduction of mean difference: 6.25%); however, cocoa did not affect blood cholesterol in the healthy people group.

Because the usual follow-up periods in assessments of lipiddowering therapy were 4–6 wk (38–40), we did a subgroup analysis by duration of ≤6 and >6 wk, with the latest data available for each study in each subgroup. We included the Taubert’s 6-wk data (15) and the data from 6 other trials (11, 14, 17–20) in the shorter-term subgroup and Baba’s data (12 wk) (12) and Taubert’s 18-wk (15) data in the longer-term subgroup. A marginally significant reduction of LDL cholesterol was shown...
in the shorter-term subgroup (−5.18 mg/dL; 95% CI: −10.80, 0.44, P = 0.07), but not in the longer-term subgroup (0.22 mg/dL; 95% CI: −6.20, 6.64, P = 0.95). Cocoa also had the tendency to decrease TC in the shorter-term subgroup (−6.16 mg/dL; 95% CI: −13.73, 1.42, P = 0.11), but not in the longer-term group (1.52 mg/dL; 95% CI: −5.75, 8.79; P = 0.68). We determined that study design was not an effect modifier. No significant changes in HDL cholesterol were observed across any subgroup (Table 2).

Sensitivity analysis showed that the significance in the pooled changes in TC, LDL cholesterol, and HDL cholesterol were not altered after the imputation correlation coefficient of 0.5 according to Follmann et al (33). Exclusion of the trial by Taubert et al (15) did not alter the final results. However, when the analyses were carried out by combining Taubert’s data at the time point of 12 or 18 wk, the effects disappeared (Table 2). Sensitivity analysis that excluded the lower-quality studies (11, 12, 14, 17, 18) indicated that cocoa consumption did not significantly affect plasma lipid (TC: −6.08 mg/dL; 95% CI: −12.61, 0.45; P = 0.07; LDL cholesterol: −4.98 mg/dL; 95% CI: −13.18, 3.21; P = 0.23). Inclusion of the trials by Crews et al (7) and Engler et al (16), which had some deficiencies in food intake control, did not affect results.

Publication bias

Funnel plots and Egger tests suggested no significant asymmetry in the meta-analyses of TC, LDL cholesterol, and HDL cholesterol (TC Egger test: P = 0.65; LDL cholesterol Egger test: P = 0.79; HDL cholesterol Egger test: P = 0.15).

**DISCUSSION**

Our meta-analysis showed that short-term supplementation with cocoa products was associated with a decrease in LDL cholesterol, but had no significant effect on TC and HDL cholesterol compared with controls. However, the significant heterogeneity detected among the 8 trials in TC and HDL cholesterol analyses might influence the confidence of final results. Therefore, we performed a subgroup analysis on the basis of our predetermined variances to find the source of heterogeneity. The subgroup analyses indicated that cocoa consumption significantly decreased both LDL cholesterol and TC in the low-dose cocoa group and in participants with cardiovascular risks, whereas it had no effect on blood lipid if the cocoa dose was middle to high or in healthy people. No heterogeneity was observed in 3 of the different cocoa dose subgroups and in the cardiovascular risk subgroup. This conclusion may influence the eating habits of many people who are hesitant to eat chocolate or are addicted to chocolate. In other words, it appears to support the idea that it is good to eat moderate amounts of cocoa or dark chocolate, which may potentially benefit our health, and that cocoa products might not be “forbidden fruit” to subjects with cardiovascular risks. Moderate cocoa consumption may make blood cholesterol move in a healthy direction, whereas higher cocoa consumption may not affect lipid profile. Polyphenols have been shown to inhibit cholesterol absorption and biosynthesis and to promote

![FIGURE 3. Meta-analysis of the effect of cocoa consumption on LDL cholesterol as compared with placebo. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance.](image-url)

![FIGURE 4. Meta-analysis of the effect of cocoa consumption on HDL cholesterol as compared with placebo. The sizes of the data markers indicate the weight of each study in the analysis. IV, inverse variance.](image-url)
the expression of LDL cholesterol receptors. Cocoa butter also contains \( \approx 33\% \) monounsaturated oleic acid, which has been shown to favor an ideal lipid profile (41). However, a high dose of polyphenols has been shown to exert cytotoxic effects on liver cells, a major metabolic organ in our body (42). The adverse effect is mainly due to (−)-epigallocatechin-3-gallate, a component of polyphenols, which exists in cocoa as well, acts as a pro-oxidant, and is cytotoxic in hepatoma cells (43). Therefore, higher polyphenol supplementation may counteract its beneficial biological effects on lipid metabolism. Moreover, an animal study (44) shows that a low amount of cocoa supplementation can significantly reduce plaque, but a high amount of cocoa supplementation does not.

According to the results of this meta-analysis, it appears that a healthy status exerts a powerful moderating effect on changes in lipid concentrations: the beneficial effects of cocoa were observed only among those with cardiovascular risks. Therefore, we speculate that a high-risk status made the subjects more likely to be influenced by the intervention. It is well acknowledged that patients with cardiovascular disease or cardiovascular-related diseases such as hypertension and diabetes commonly have dyslipidemia or lipid metabolism dysfunction (45). Until now, both human and animal studies have indicated that cocoa reduced blood cholesterol more significantly in hypercholesterolemic subjects or in animals fed a high-fat diet (30, 46). A newly released study showed that polyphenols specifically targeted the pathogenesis of hyperlipidemia in diabetes to lower blood cholesterol (47). Moreover, in general, cardiovascular disease or cardiovascular-related diseases share some similar pathological mechanisms such as inflammation, insulin resistance, lipid metabolism dysfunction, and oxidative stress. Previous studies indicated that cocoa could improve insulin sensitivity and antagonize inflammatory activity and oxidative stress, which are helpful in balancing lipid metabolism (41). Therefore, cocoa consumption might significantly improve lipid profiles in subjects with cardiovascular-related disease. More studies focusing on patients with cardiovascular risks should be performed in the future to confirm our results.

Our outcomes are partially inconsistent with a recent meta-analysis that shows that cocoa supplementation has no effect on LDL-cholesterol and HDL-cholesterol concentrations (48). This is because Hooper et al (48) set more rigorous inclusion criteria; for example, they excluded studies that did not provide data on CVD or CVD risk factors. We included another 3 randomized studies with relatively high quality (12, 19, 20), which measured LDL-cholesterol and HDL-cholesterol concentrations (48). This analysis that shows that cocoa supplementation has no effect on patients with cardiovascular-related disease. More studies focusing on patients with cardiovascular risks should be performed in the future to confirm our results.

The importance of plasma lipids in cardiovascular disease has been very well documented by human and animal studies. A 1% reduction in LDL cholesterol can reduce CAD risk by \( \approx 2\% \). Each milligram (per deciliter) reduction of LDL cholesterol can reduce CAD risk by 1%. Thus, our meta-analysis shows that cocoa might significantly improve lipid profiles in subjects with cardiovascular-related disease. More studies focusing on patients with cardiovascular risks should be performed in the future to confirm our results.

Although we believe that this meta-analysis provides useful information, the finding must be interpreted with caution because
of the following weakness. First, until now, no report had been found for the effectiveness of long-term supplementation with cocoa product on lipid profile. The study duration of our included 8 trials varied from 2 to 18 wk. Following the studies by Banel et al (49) and Upadhyay et al (50), we included the data closest to the time point used in the other studies for our primary analysis when more than one time point for follow-up was reported. In our sensitivity analysis, we reanalyzed the study by Taubert et al (15). Exclusion of the trial (15) did not alter the final results. However, the effects disappeared when the analysis was carried out at the time point of 12 or 18 wk. We cannot draw a conclusion about the real effects of cocoa on lipid metabolism in the long term because (1) only one trial was conducted for >4 mo, and most of the studies were ≈1 mo, making it difficult to extrapolate beyond the duration of these studies (2). Because lipid profiles change soon after changing diets, cocoa consumption would need to be maintained indefinitely to maintain lower lipid concentrations. Long-term adherence is often a difficulty with dietary interventions (3). We still do not know the optimal daily consumption of cocoa for improving lipid metabolism or vascular health. Therefore, long-term, high-quality, double-blind, randomized clinical trials are needed to verify the long-term effects of cocoa supplementation on lipid metabolism.

Second, the subgroup analyses showed that cocoa consumption did not affect blood cholesterol significantly in the healthy subject group. This result might be ascribed to the limited studies with a large span of cocoa consumption that ranged from 168 to 766 mg polyphenols/d. Thus, before we ignore a beneficial effect of cocoa consumption on blood cholesterol in healthy persons, additional studies on the basis of more high-quality, double-blind, randomized clinical trials are needed.

Third, the results showed that the quality of the studies included in our meta-analysis varied from low to high. According to the standard for clinical trials of prescribed medicine, of the 8 trials, only 3 trials (15, 19, 20) were high-quality studies (Jadad score ≥4), whereas the other 5 studies were low quality. After the sensitivity analysis excluded low-quality studies, only 3 studies remained, and the result indicated that cocoa consumption did not significantly affect plasma lipid. This result may be attributed to the high doses of cocoa consumption (900–963 mg polyphenols) in 2 of the studies. Although none of the other 5 studies attempted a double-blind study design, all trials achieved a good balance in the relevant baseline characteristics, and most of the studies were crossover studies. With the available randomized trials, our finding may have implications. We could find the right direction to do further and deeper scientific research. Therefore, more high-quality, double-blinded, large, randomized studies are needed to elucidate this issue.

Fourth, some evidence from human and animal experiments shows that the effect of cocoa varies depending on the pre-treatment concentration of total cholesterol. However, until now, no randomized trial had been done to assess the effect of cocoa in dyslipidemia patients. More studies focusing on hypercholesterolemic subjects should be performed in the future to clarify this important issue. Finally, soft endpoints (cholesterol changes from baseline) were used in these studies, whereas the effects of treatment on clinical outcomes were not examined.

In this meta-analysis, we assessed the short-term effectiveness of cocoa product on plasma lipid concentration by reviewing available randomized controlled trials. Despite certain limitations, our findings may have potential implications. The results suggested that short-term of cocoa consumption reduced blood cholesterol, and this effect was more evident in studies with low-dose cocoa supplementation and in subjects with cardiovascular risks. Therefore, moderate cocoa consumption might be a worthwhile dietary approach for preventing hypercholesterolemia, particularly in specific patient subgroups. However, no statistically significant effect was seen by excluding the low-quality studies with only 3 studies retained. There was no evidence of dose-effect relation and no effect in healthy subjects. The long-term effectiveness and appropriate dose range of cocoa consumption are not clear. Future research efforts should concentrate on higher-quality and more rigorous randomized trials with longer follow-ups to resolve the uncertainty regarding the clinical effectiveness. Then we can really eat chocolate without feeling guilty.

We express our gratitude to Hai Wang for his assistance. The authors’ responsibilities were as follows—LJ, XL, and RH: conceived the idea for the study and developed the search strategy; and LJ and XL: summarized the data and conducted the data analyses. All authors contributed to the data analysis, verification, and writing and revision of the manuscript. None of the authors had a conflict of interest.

REFERENCES
12. Baba S, Osakabe N, Kato Y, et al. Continuous intake of polyphenolic compounds containing cocoa powder reduces LDL oxidative susceptibility...