Reviews in Cardiovascular Medicine

Systematic Review

Apple or apple polyphenol consumption improves cardiovascular disease risk factors: a systematic review and meta-analysis

Xiaoqing Zhu[1,†], Guanhua Xu[1,†], Wangyan Jin[1], Yingying Gu[1], Xuhua Huang[1], Lidan Ge[2,*]

[1] *Department of Critical Medicine, The First People's Hospital of Xiaoshan District, 311200 Hangzhou, Zhejiang, China*

[2] *Department of Geriatrics, The First People's Hospital of Xiaoshan District, 311200 Hangzhou, Zhejiang, China*

*Correspondence: gelidan0571@126.com (Lidan Ge)
† These authors contributed equally.

DOI:10.31083/j.rcm2203089

Submitted: 20 April 2021 Revised: 29 June 2021 Accepted: 6 July 2021 Published: 24 September 2021

Many fruits and vegetables have been found to have a protective effect against cardiovascular diseases. We conducted a systematic review and meta-analysis to determine the relationship between apple or apple polyphenol intake and cardiovascular disease risk. The PubMed, Embase, Cochrane, and Web of Science databases were searched up to August 4, 2020. Studies that had an intervention time of >1 week; used apple or apple polyphenols as the intervention; were designed as a randomized controlled trial; and measured blood pressure, cholesterol, and blood glucose levels were included. The meta-analysis showed that the group with apple or apple polyphenol intake had significantly higher high-density lipoprotein levels (standardized mean difference [SMD] = 0.34, 95% confidence interval [CI] [0.01, 0.67], p = 0.0411, I^2 = 77%, random-effects model) and significantly lower C-reactive protein levels (SMD = –0.43, 95% CI [–0.65, –0.20], p = 0.0002, I^2 = 18%, fixed-effects model) than the control group, indicating that the intervention reduced the risk of cardiovascular diseases. Apple or apple polyphenol intake is associated with a reduced risk of cardiovascular diseases. These results are consistent with the old saying that eating an apple a day can help keep the doctors away.

Keywords

Apples; Apple polyphenols; Cardiovascular disease; Blood pressure; Cholesterol level; Blood glucose level

1. Introduction

According to the World Health Organization, cardiovascular diseases (CVDs) are currently the leading cause of death worldwide [1]. High blood pressure, smoking habit, high cholesterol level, diabetes, overweight or obesity, and a sedentary lifestyle can all negatively influence cardiovascular health. Population-wide strategies to address behavioral risk factors such as an unhealthy diet and obesity can help prevent most CVDs. Some studies have shown that the consumption of plant products such as fruits and vegetables is associated with a reduction in the risk of CVD development [2]. Moreover, some studies proposed that the intake of certain single nutrients (such as vitamin C) at the level naturally present in plants is related to a reduction of disease risk; however, these associations cannot explain the protective effect of plant foods on health [2]. Therefore, it is speculated that other nonnutritive components in plants, such as polyphenols, may also play a role in the reported beneficial effects of plant foods [3, 4]. Polyphenols are naturally occurring components in many plant-derived foods [5]. Many *in vitro* and animal studies have shown that polyphenols may be beneficial for cardiovascular health [6–9].

Apples are a good source of various nutrients, including vitamin C and a variety of polyphenols [10]. For a long time, apples have been considered to have health-promoting effects, as illustrated by the old saying that "an apple a day keeps the doctor away". One previous study has reported results consistent with this old saying. The study showed that higher dietary intake and/or higher blood levels of vitamin C, carotenoids, and alpha-tocopherol (as markers of fruit and vegetable intake) are associated with a reduced risk of CVD [4]. In particular, the soluble fiber content of fruits and vegetables is related to reduced blood lipid level and has a potential to prevent CVDs.

However, some studies have also reported negative effects of consuming apples, such as blood sugar fluctuations and a craving for more sugar [11]. Thus, we are interested about whether apples can truly benefit human health and reduce the risk factors for CVD.

One meta-analysis published in 2019 has focused on our topic of interest [12]. This previous study investigated the association between apple or pear intake and CVD or cardiometabolic disease. However, several differences distinguish our study from the previous meta-analysis. First, we only included randomized controlled trials (RCTs), whereas the other meta-analysis included RCTs, non-RCTs, and prospective observational studies. One reason for including only RCTs is to reduce selection bias. In addition, comparing two groups under an RCT design allows a much more straightforward interpretation. Further, we included more key indicators to better represent the potential risk of future CVD development. Therefore, through this meta-analysis involving a more accurate study method and more comprehensive health indicators [13, 14], we aimed to elucidate the effects of apple or apple polyphenols on the risk of CVD.

2. Materials and methods

2.1 Search strategy

A comprehensive systematic literature search of studies published from inception to August 4, 2020, was conducted in the PubMed (https://pubmed.ncbi.nlm.nih.gov/), Embase (https://www.embase.com/), Cochrane (https://www.cochrane.org/), and Web of Science (https://app.webofknowledge.com/author/search) databases. Our meta-analysis was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [15]. The outcomes of our study were blood pressure, total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), blood glucose, and C-reactive protein (CRP) levels.

The search strategy was as follows: (hypertension [MeSH] OR blood pressure [MeSH] OR cholesterol [MeSH] OR low-density lipoprotein [MeSH] OR high-density lipoprotein [MeSH] OR triacylglycerol [MeSH] OR glucose blood level [MeSH] OR inflammation [MeSH] OR lipid [MeSH]) AND (apple [Title/Abstract] OR apple polyphenols [Title/Abstract]) AND ("randomized controlled trial [MeSH]" OR "random allocation [MeSH]" OR "[singl* OR doubl* OR trebl* OR tripl*]" AND "[blind* OR mask*]") [16, 17].

2.2 Inclusion criteria

The eligible studies needed to meet the following criteria: (1) had an RCT design; (2) used apples or apple polyphenols as the intervention; (3) had a control group; (4) measured blood lipids (TC, HDL, LDL, and TG), systolic and diastolic blood pressure, and blood glucose or CRP levels; and (5) had an intervention time of >1 week.

2.3 Exclusion criteria

The exclusion criteria were as follows: (1) animal experiments, case reports, and review articles; and (2) duplicate reports or reports with an unclear description of outcomes.

2.4 Screening and data extraction

After searching the literature, two reviewers independently screened the search results according to the selection criteria, and uncertainties were resolved by consensus. The collected data included basic information of the studies (e.g., first author and study country), intervention time, intervention dose, sample size, demographic data (e.g., age and sex), and outcomes (e.g., blood pressure, cholesterol, and lipoproteins).

2.5 Literature quality assessment

The Jadad scale was used to assess the quality of each study [18]. A Jadad score of ≥ 3 was considered to indicate a high-quality study, whereas a score of <3 was considered to indicate a low-quality study. The strength of the evidence was assessed using the Cochrane Collaboration tool (http://meta-analysis-with-r.org (Accessed: 19 August 2021)).

2.6 Statistical analysis

A meta-analysis was conducted on the selected studies. The baseline variables and outcomes were compared between the experimental and control groups to estimate the statistical differences, whereas the standard deviation of the variation was obtained from the original study or calculated using the standard formula [19]. I^2 was used to evaluate the heterogeneity among the studies. The random-effects model was chosen when $I^2 \geq 50\%$, indicating high heterogeneity among the data; otherwise, the fixed-effects model was used. Relative risks and standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for dichotomous and continuous data using the Mantel-Haenszel and inverse variance methods, respectively. All data analyses and funnel plot analyses were performed using the Meta package (GitHub https://github.com/guido-s/meta (Accessed: 19 August 2021)) in R version 4.0.2.

3. Results

3.1 Search results

A total of 661 records were identified through the search of the four databases: 158 in Web of Science, 287 in Embase, 89 in Cochrane, and 127 in PubMed. The titles and abstracts of 469 published articles were screened after the removal of duplicates. A total of 426 studies were irrelevant to the subject, 25 studies were not RCTs, 67 studies did not meet the inclusion criteria, and 2 studies used duplicate data. Finally, 10 studies were included in our meta-analysis [20–29] (Fig. 1, Table 1, Ref. [20–29]).

3.2 Characteristics of the included studies

A total of 626 participants were included in the 10 studies. The experimental design was mostly double blind, in which the intervention group was given an oral apple polyphenol drink, apple extract, and fresh apples. Meanwhile, the control group was given the same calories of muffins, cranberries, and *Lactobacillus*-containing probiotics in a nonblinded experiment. The duration of the experiment was 4 weeks, 8 weeks, 12 weeks, and 1 year. Participants with one or more cardiovascular risk factors, most of whom were obese, were enrolled in the trials. The details are shown in Table 1. Fig. 2 shows that there was no publication bias in the included studies.

3.3 Laboratory findings

3.3.1 Effects of apples or apple polyphenols on blood lipids

Among the included studies, eight [21–28] tested the TC levels in 277 participants who consumed apples or apple polyphenols and 258 control participants. The results showed no significant difference in TC levels between the two groups (SMD = 0.12, 95% CI [–0.06, 0.29], $p = 0.1858$, I^2 = 0%, fixed-effects model). Subgroup analysis [30] was conducted for the apple and apple polyphenol groups. Compared with the control group, neither of the intervention subgroups showed significantly reduced TC levels, as shown in Fig. 3.

Table 1. Literature characteristics.

Author	Year	Area	Sample size	Duration	Health	Treatment			Control			Jadad
						age	intervention	dose	age	intervention	dose	
Arrigo F.G. Cicero [20]	2017	Italy	62	8 wk	obese	63.3 ± 7.5	apple extract	300 mg/d	63.2 ± 11.6	Placebo	300 mg/d	5
Ashley Eisner [21]	2019	America	38	8 wk	obese children	10–16	dried apple	240 kcal/d	10–16	muffin	240 kcal/d	3
Gian Carlo Tenore [22]	2019	Italy	54	8 wk	CVD risk	45.1 ± 10.3	apple puree	125 g/d	48.2 ± 10.2	probiotic	125 g/d	5
Maria Saarenhovi [23]	2017	Finland	57	4 wk	health, blood pressure high	55.6 ± 7.9	apple extract	100 mg/d	54.9 ± 6.4	Placebo	100 m g/d	3
Mohammad Reza Vafa [24]	2011	Iran	46	8 wk	CVD risk	41.08 ± 4.19	apple	300 g/d	41.65 ± 3.79	regular dietary	300 g/d	2
Sheau C. Chai [25]	2012	America	100	1 year	postmenopausal women	55.6 ± 5.0	dried apple	75 g/d	57.5 ± 4.01	dried plum	75 g/d	4
Stephan W. Barth [26]	2012	German	68	4 wk	obese	23–69	apple juice	805.2 mg/d	23–69	Placebo	805.2 mg/d	3
Toshihiko Shoji [27]	2017	Japan	65	12 wk	health, blood glucose high	50.2 ± 1.3	apple polyphenols	600 mg/d	51.6 ± 1.1	Placebo	600 mg/d	4
Yoko Akazome [28]	2010	Japan	88	12 wk	obese	45.8 ± 8.2	apple polyphenols	600 mg/d	45.8 ± 8.2	Placebo	600 mg/d	3
Yoko NagasakoAka-zome [29]	2007	Japan	48	12 wk	obese	47.8 ± 10.8	apple polyphenols	600 mg/d	46.5 ± 10.8	Placebo	600 mg/d	3

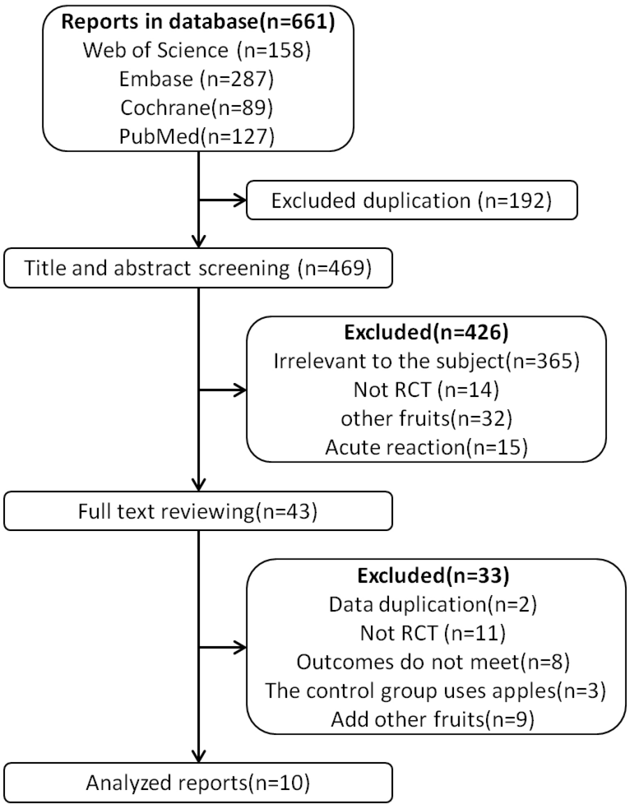

Fig. 1. Flow diagram of the inclusion of studies identified in the systematic review. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) template.

Eight studies [20–24, 26–28] tested the TG levels in 277 participants who consumed apples or apple polyphenols and 258 control participants. The results showed no significant difference in the TG levels between the two groups (SMD = 0.14, 95% CI [–0.03, 0.31], p = 0.1023, I^2 = 0%, fixed-effects model). Subgroup analysis was conducted for the apple and apple polyphenol groups. Compared with the control group, neither of the intervention subgroups showed significantly reduced TG levels, as shown in Fig. 4.

Nine studies [20–24, 26–29] tested the LDL-cholesterol (LDL-C) levels in 301 participants who consumed apples or apple polyphenols and 282 control participants. The results showed no significant difference in LDL-C levels between the two groups (SMD = 0.14, 95% CI [–0.02, 0.31], p = 0.1023, I^2 = 3%, fixed-effects model). Subgroup analysis was conducted for the apple and apple polyphenol groups. Compared with the control group, neither of the intervention subgroups showed significantly reduced LDL-C levels, as shown in Fig. 5.

Ten studies [20–29] tested the HDL-C levels in 346 participants who consumed apples or apple polyphenols and 337 control participants. Compared with the control group, the group that consumed apples or apple polyphenols showed significantly increased HDL-C levels (SMD = 0.34, 95% CI [0.01, 0.67], p = 0.0411, I^2 = 77%, random-effects model). Subgroup analysis was conducted for the apple and apple polyphenol groups. Compared with the control group, the subgroup that consumed apples showed significantly increased HDL-C levels (SMD = 0.91, 95% CI [0.48, 1.34], I^2 = 56%, random-effects model). However, there was no sig-

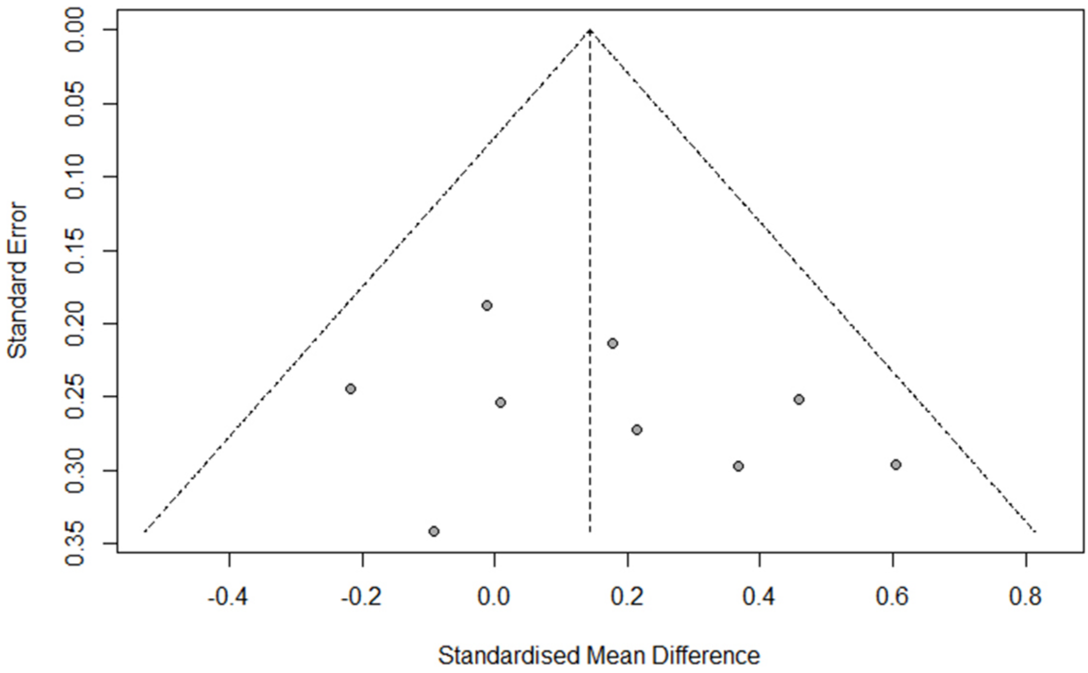

Fig. 2. Funnel plot of the meta-analysis of the included studies. The logit event rate for the standardized mean difference (horizontal axis) is presented against the standard error (vertical axis). The plot shows the absence of publication bias in the included studies.

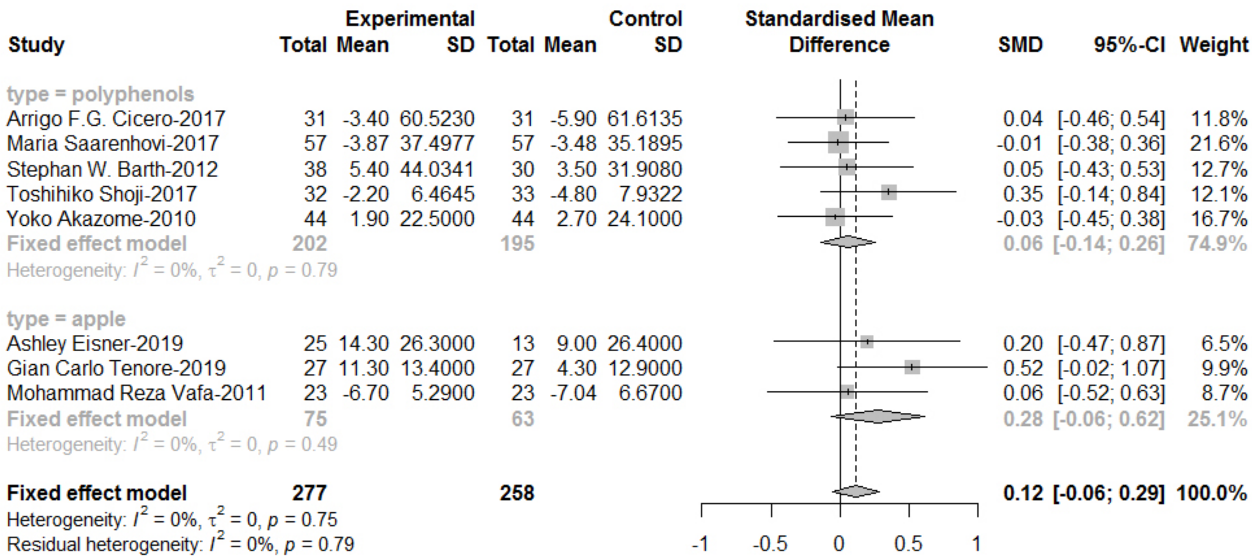

Fig. 3. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on blood lipid levels. No significant difference in total cholesterol (TC) levels was observed between the experimental and control groups.

nificant difference in HDL-C levels in the subgroup that consumed apple polyphenols (SMD = 0.01, 95% CI [–0.18, 0.19], I^2 = 0%, fixed-effects model), as shown in Fig. 6. We conducted a sensitivity analysis of these two groups to assess the stability of the meta-analysis. When any single study was removed, the relevant pooled SMDs did not radically change. This indicates the stability of the meta-analysis, as shown in Fig. 7.

3.3.2 Effects of apples or apple polyphenols on blood pressure

Two studies [20, 28] tested the systolic and diastolic blood pressure levels in 75 participants who consumed apples or apple polyphenols and 75 control participants. The results showed no significant difference in the systolic and diastolic blood pressure levels between the two groups (SMD = –0.4, 95% CI [–0.36, 0.28], $p = 0.8212$, I^2 = 0%, fixed-effects model and SMD = –0.03, 95% CI [–0.35, 0.29], $p = 0.8408$, I^2 = 0%, fixed-effects model), as shown in Figs. 8,9.

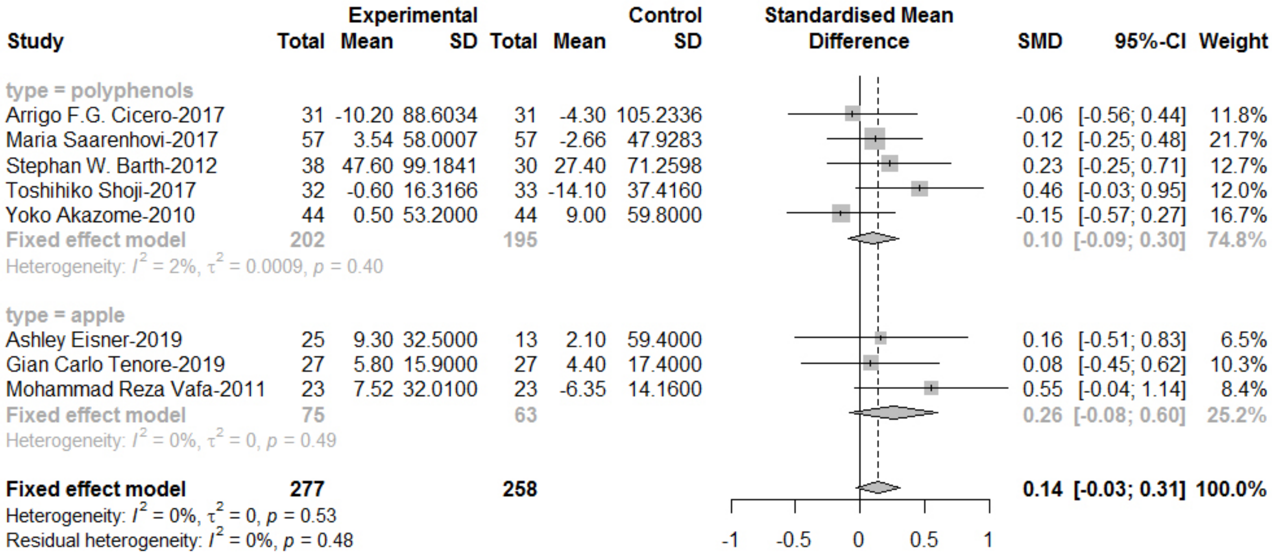

Fig. 4. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on triglyceride (TG) levels. No significant difference in TG levels was observed between the experimental and control groups.

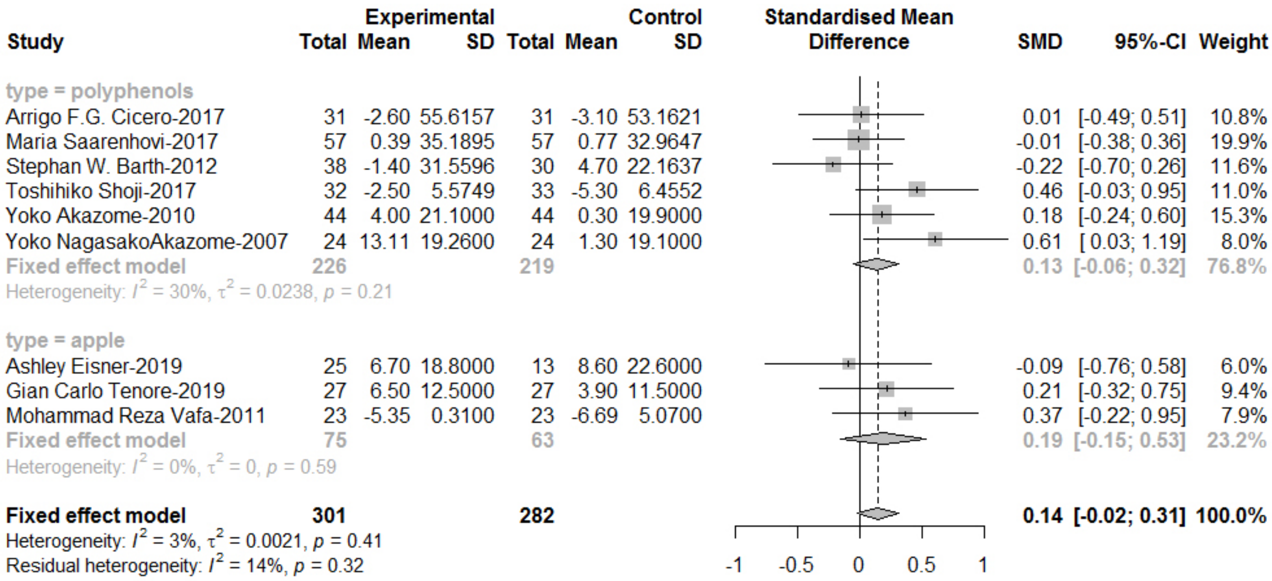

Fig. 5. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on low-density lipoprotein cholesterol (LDL-C) levels. No significant difference in LDL-C levels was observed between the experimental and control groups.

3.3.3 Effects of apples or apple polyphenols on blood glucose or CRP

Four studies [20–22, 28] tested the blood glucose levels in 127 participants who consumed apples or apple polyphenols and 115 control participants. The results showed no significant difference in the blood glucose levels between the two groups (SMD = –0.14, 95% CI [–0.40, –0.12], p = 0.2837, I^2 = 37%, fixed-effects model), as shown in Fig. 10.

Four studies [21, 23, 25, 26] tested the CRP levels in 165 participants who consumed apples or apple polyphenols and 155 control participants. Compared with the control group, the group that consumed apples or apple polyphenols showed significantly decreased CRP levels (SMD = –0.43, 95% CI [–0.65, –0.20], p = 0.0002, I^2 = 18%, fixed-effects model), as shown in Fig. 11.

4. Discussion

In 2016, an estimated 17.9 million people died of CVD, accounting for 31% of all deaths worldwide, according to the World Health Organization. In our study, we found that apple or apple polyphenol consumption can increase HDL-C levels and decrease CRP levels. This may be the reason why apples are beneficial to cardiovascular health and can potentially prevent future CVD development [3, 4].

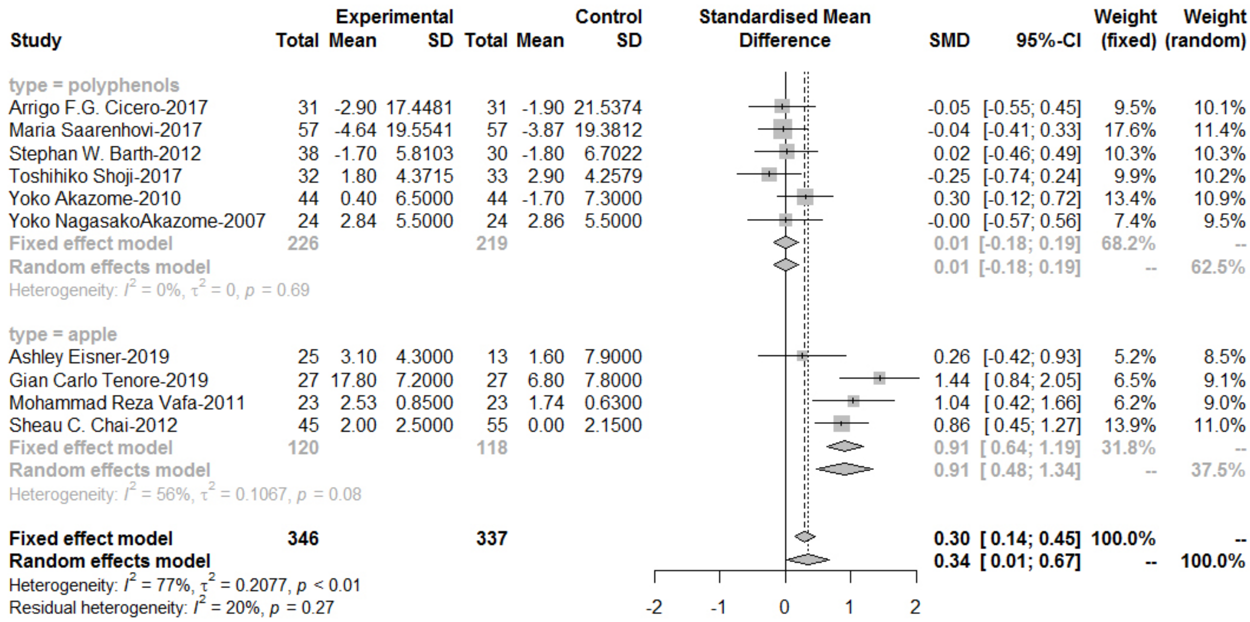

Fig. 6. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on high-density lipoprotein cholesterol (HDL-C) levels. Compared with the control group, participants who consumed apples or apple polyphenols showed significantly increased HDL-C levels.

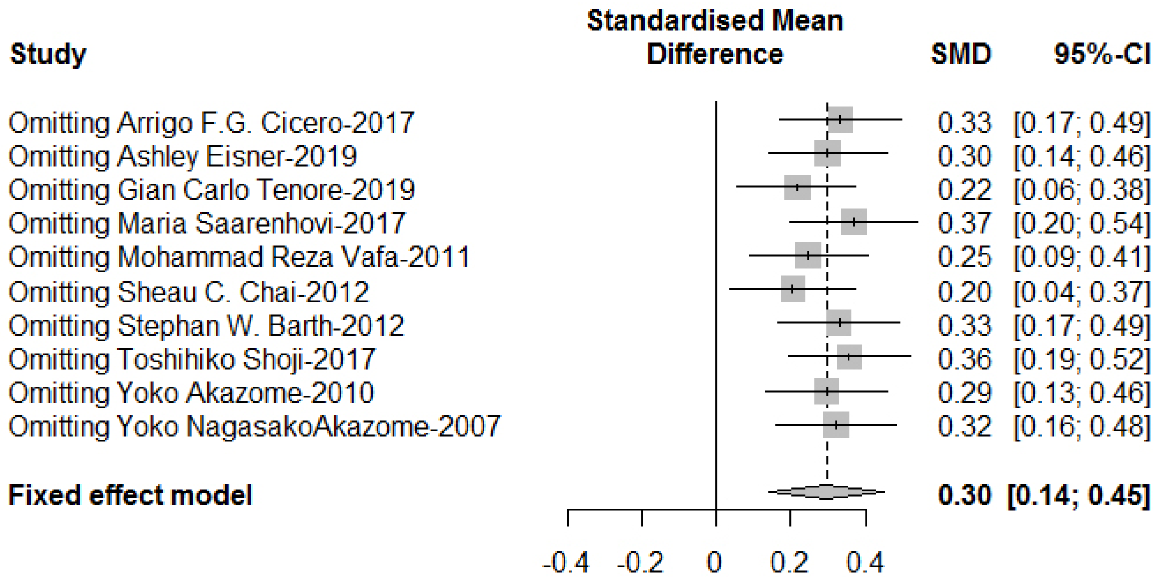

Fig. 7. Forest plots of the sensitivity analysis on the effects of apple or apple polyphenol intake on high-density lipoprotein cholesterol (HDL-C) levels. The sensitivity analysis suggested the stability of the meta-analysis.

The results of this study are consistent with previous evidence suggesting that apples fulfill the expectations from the famous saying about keeping doctors away [3, 31]. Researchers from Florida State University reported at the 2011 Experimental Biology Conference in Washington that elderly women who consumed apples daily had reduced LDL-C levels (by an average of 23%) and increased HDL-C levels (by 4%) within 6 months, illustrating those apples are indeed a "magic fruit". Nagasako-Akazome *et al.* [29] targeted healthy men and women with slightly elevated serum cholesterol levels in their study. After the administration of food tablets containing apple polyphenols for 4 weeks, the data showed that the polyphenols from apples actively inhibited the absorption and accelerated the excretion of cholesterol, resulting in a decreased serum cholesterol level. The underlying mechanism is that apple polyphenols combine with cholesterol and/or bile acids, thereby enhancing the excretion of these compounds in feces; thus, polyphenols can inhibit the enterohepatic circulation of cholesterol and bile acids. Moreover, in another study that was conducted on 40

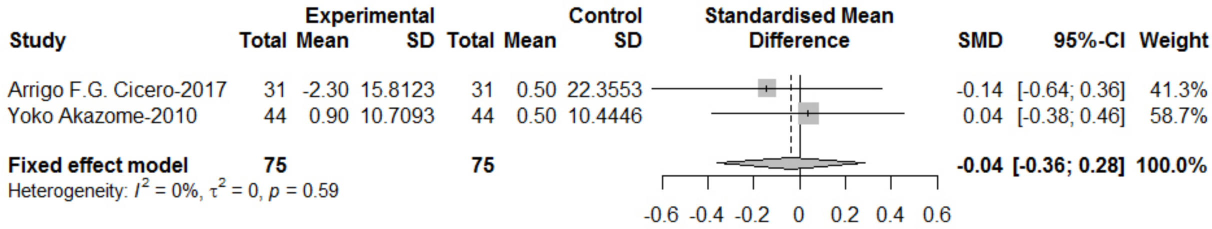

Fig. 8. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on systolic blood pressure. No significant difference in systolic blood pressure was observed between the experimental and control groups.

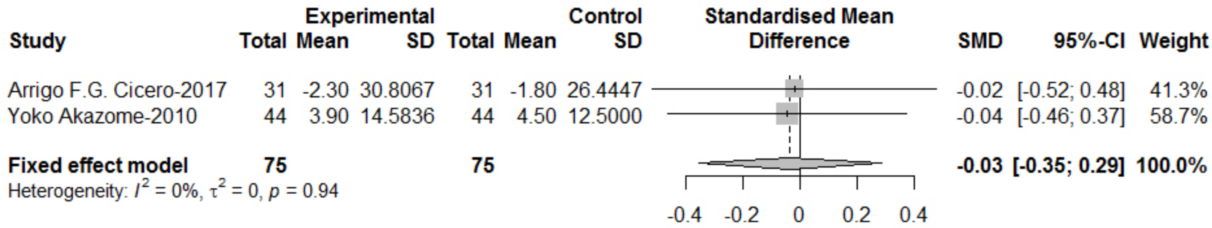

Fig. 9. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on diastolic blood pressure. No significant difference in diastolic blood pressure was observed between the experimental and control groups.

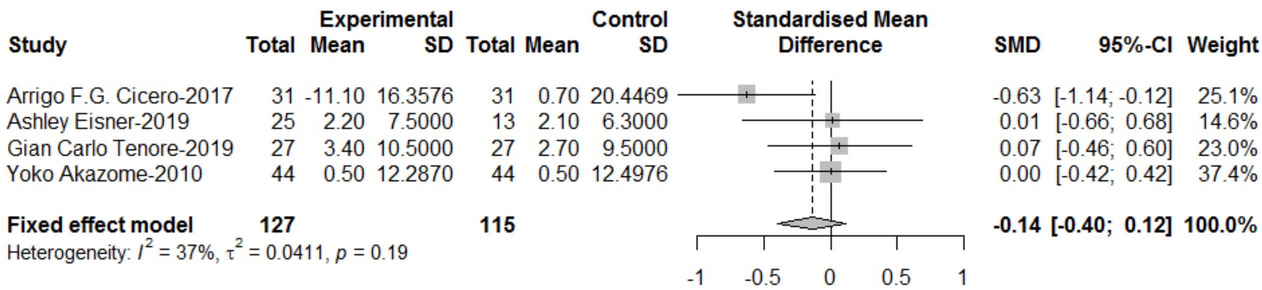

Fig. 10. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on blood glucose levels. No significant difference in blood glucose levels was observed between the experimental and control groups.

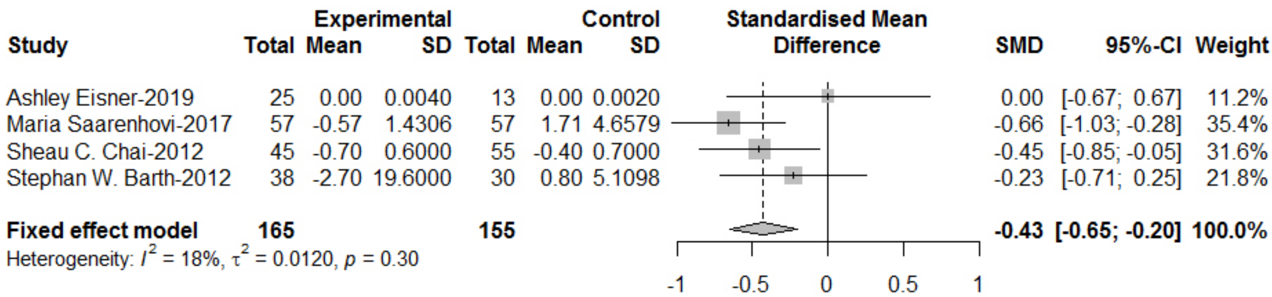

Fig. 11. Forest plots of the meta-analysis on the effects of apple or apple polyphenol intake on C-reactive protein (CRP) levels. Compared with the control group, the group that consumed apples or apple polyphenols showed significantly decreased CRP levels.

mildly hypercholesterolemic volunteers who consumed two apples per day for 8 weeks, a significant reduction was observed in serum TC, LDL-C, and plasma intercellular adhesion molecule-1 levels, with no detrimental effect on HDL-C levels, compared with sugar-matched controls [10].

The results also showed that the consumption of apple or apple polyphenols had no significant effect on the serum levels of TC and LDL-C and on blood pressure, in agreement with the results of other studies. In an early study, 28 participants with normal cholesterol levels were recruited. They were separated into two groups: one group consumed

375 mL of unsupplemented apple juice per day and the other group consumed 340 g of cored whole apple per day for 6 weeks. Thereafter, the participants were crossed over to the alternate intervention for another 6 weeks. After 12 weeks of observation, no significant difference was observed between the two groups in the serum levels of TC, LDL-C, and apolipoprotein B, whereas a low and insignificant increase was observed in fasting TG levels [32]. In another study, 15 individuals with an average age of 67–75 years consumed 2 g/kg body weight of apple daily for 1 month and showed no significant difference in the levels of serum TG, TC, LDL, HDL, and very LDL [33].

The participants included in our analysis and in other studies who showed no significant differences after the intervention were considered healthy individuals. Although some experimental participants were slightly overweight and had one or several risk factors, their physical condition was generally healthy. Therefore, daily intake of apples with low polyphenol content will not have a positive and significant effect on blood lipid levels, as in individuals with symptoms. Nagasako-Akazome *et al.* [29] reported that daily intake of 600 mg apple polyphenol extract caused a significant decrease in serum TC and LDL-C levels. This amount of apple polyphenol intake was much greater than the dose used in the other studies included in the meta-analysis. Therefore, the insufficient amount could be a possible explanation for the observed insignificances.

Moreover, we observed some insignificant increases in serum TC, TG, and LDL-C levels. The mechanisms leading to increased serum TG levels may include increased intake of fructose from the consumption of apples [34]. An increase in dietary fructose intake will increase the liver lipogenesis activity of enzymes, leading to increased TG levels.

Although we obtained some promising results from our analysis, it is important note that the included studies were performed over a relatively short period (most of the studies lasted approximately 4–8 weeks). Thus, no conclusions on the long-term effects of polyphenols can be drawn. After a careful screening, only 10 articles were included in the analysis. As this amount of literature is not very representative, our results cannot be used to generalize the effects of apple or apple polyphenols on the prevention of CVDs. The diversity of participants was also a limitation. In the studies included in our analysis, more than half of the participants were overweight. More studies including participants with normal weight or even underweight are needed to obtain comprehensive information about the effects of apple or apple polyphenols.

5. Conclusions

In conclusion, although apple or apple polyphenol consumption had no significant effect on the serum levels of TC and LDL-C and on blood pressure, we still found that apple or apple polyphenol intake can effectively increase HDL-C levels, reduce CRP levels, and potentially reduce the risk of CVD. However, because of the small number of included studies, small sample sizes, different conditions of the included participants, and short intervention periods, our findings have certain limitations. To obtain more meaningful results, future studies should consider expanding the scope of participants to include all kinds of people with different physical signs.

Author contributions

XZ and GX conceptualized the study. WJ involved in formal analysis. YG designed methodology. XH and LG collected the data. XZ and GX wrote the original draft. WJ, YG, XH and LG wrote, reviewed, and edited the manuscript. Finally, all authors read and approved this manuscript for publication.

Ethics approval and consent to participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received no external funding.

Conflict of interest

The authors declare no conflict of interest.

References

[1] World Health Organization. Global health observatory visualisations: Causes of death. Geneva: World Health Organization. 2016.
[2] Cockroft JE, Durkin M, Masding C, Cade JE. Fruit and vegetable intakes in a sample of pre-school children participating in the 'Five for all' project in Bradford. Public Health Nutrition. 2005; 8: 861–869.
[3] Aune D, Giovannucci E, Boffetta P, Fadnes LT, Keum N, Norat T, *et al.* Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. International Journal of Epidemiology. 2017; 46: 1029–1056.
[4] Aune D, Keum N, Giovannucci E, Fadnes LT, Boffetta P, Greenwood DC, *et al.* Dietary intake and blood concentrations of antioxidants and the risk of cardiovascular disease, total cancer, and all-cause mortality: A systematic review and dose-response meta-analysis of prospective studies. American Journal of Clinical Nutrition. 2018; 108: 1069–1091.
[5] Fraga CG, Croft KD, Kennedy DO, Tomás-Barberán FA. The effects of polyphenols and other bioactives on human health. Food & Function. 2019; 10: 514–528.
[6] Potì F, Santi D, Spaggiari G, Zimetti F, Zanotti I. Polyphenol Health Effects on Cardiovascular and Neurodegenerative Disorders: a Review and Meta-Analysis. International Journal of Molecular Sciences. 2019; 20: 351.
[7] Vitale M, Vaccaro O, Masulli M, Bonora E, Del Prato S, Giorda CB, *et al.* Polyphenol intake and cardiovascular risk factors in a population with type 2 diabetes: The tosca. It study. Clinical Nutrition. 2017; 36: 1686–1692.
[8] Basu A, Du M, Leyva MJ, Sanchez K, Betts NM, Wu M, *et al.* Blueberries Decrease Cardiovascular Risk Factors in Obese Men and Women with Metabolic Syndrome. Journal of Nutrition. 2010; 140: 1582–1587.

[9] Whyte AR, Cheng N, Fromentin E, Williams CM. A Randomized, Double-Blinded, Placebo-Controlled Study to Compare the Safety and Efficacy of Low Dose Enhanced Wild Blueberry Powder and Wild Blueberry Extract (ThinkBlue) in Maintenance of Episodic and Working Memory in Older Adults. Nutrients. 2018; 10: 660.

[10] Koutsos A, Riccadonna S, Ulaszewska MM, Franceschi P, Trošt K, Galvin A, *et al.* Two apples a day lower serum cholesterol and improve cardiometabolic biomarkers in mildly hypercholesterolemic adults: A randomized, controlled, crossover trial. American Journal of Clinical Nutrition. 2020; 111: 307–318.

[11] Gheflati A, Bashiri R, Ghadiri-Anari A, Reza JZ, Kord MT, Nadjarzadeh A. The effect of apple vinegar consumption on glycemic indices, blood pressure, oxidative stress, and homocysteine in patients with type 2 diabetes and dyslipidemia: A randomized controlled clinical trial. Clinical Nutrition ESPEN. 2019; 33: 132–138.

[12] Gayer BA, Avendano EE, Edelson E, Nirmala N, Johnson EJ, Raman G. Effects of Intake of Apples, Pears, or their Products on Cardiometabolic Risk Factors and Clinical Outcomes: A Systematic Review and Meta-Analysis. Current Developments in Nutrition. 2019; 3: nzz109.

[13] Cai X, Zhang Y, Li M, Wu JH, Mai L, Li J, *et al.* Association between prediabetes and risk of all cause mortality and cardiovascular disease: Updated meta-analysis. British Medical Journal. 2020; 370: m2297.

[14] Weaver SR, Rendeiro C, McGettrick HM, Philp A, Lucas SJE. Fine wine or sour grapes? A systematic review and meta-analysis of the impact of red wine polyphenols on vascular health. European Journal of Nutrition. 2021; 60: 1–28.

[15] Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, *et al.* Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: Elaboration and explanation. British Medical Journal. 2015; 350: g7647.

[16] Yang H, Lee HJ. Research Trend Visualization by MeSH Terms from PubMed. International Journal of Environmental Research and Public Health. 2018; 15: 1113.

[17] Restrepo MI, McGrath MC, Sarkar IN, Chen ES. Web-Based Visualization of MeSH-Based PubMed/Medline Statistics. Studies in Health Technology and Informatics. 2019; 264: 1490–1491.

[18] Clark HD, Wells GA, Huët C, McAlister FA, Salmi LR, Fergusson D, *et al.* Assessing the quality of randomized trials: reliability of the Jadad scale. Controlled Clinical Trials. 1999; 20: 448–452.

[19] Gao Q, Qin L, Arafa A, Eshak ES, Dong J. Effects of strawberry intervention on cardiovascular risk factors: a meta-analysis of randomised controlled trials. British Journal of Nutrition. 2020; 124: 241–246.

[20] Cicero AFG, Caliceti C, Fogacci F, Giovannini M, Calabria D, Colletti A, *et al.* Effect of apple polyphenols on vascular oxidative stress and endothelium function: A translational study. Molecular Nutrition & Food Research. 2017; 61: 1700373.

[21] Eisner A, Ramachandran P, Cabalbag C, Metti D, Shamloufard P, Kern M, *et al.* Effects of Dried Apple Consumption on Body Composition, Serum Lipid Profile, Glucose Regulation, and Inflammatory Markers in Overweight and Obese Children. Journal of Medicinal Food. 2020; 23: 242–249.

[22] Tenore GC, Caruso D, Buonomo G, D'Avino M, Ciampaglia R, Maisto M, *et al.* Lactofermented Annurca Apple Puree as a Functional Food Indicated for the Control of Plasma Lipid and Oxidative Amine Levels: Results from a Randomised Clinical Trial. Nutrients. 2019; 11: 122.

[23] Saarenhovi M, Salo P, Scheinin M, Lehto J, Lovró Z, Tiihonen K, *et al.* The effect of an apple polyphenol extract rich in epicatechin and flavan-3-ol oligomers on brachial artery flow-mediated vasodilatory function in volunteers with elevated blood pressure. Nutrition Journal. 2017; 16: 73.

[24] Vafa MR, Haghighatjoo E, Shidfar F, Afshari S, Gohari MR, Ziaee A. Effects of apple consumption on lipid profile of hyperlipidemic and overweight men. International Journal of Preventive Medicine. 2011; 2: 94–100.

[25] Chai SC, Hooshmand S, Saadat RL, Payton ME, Brummel-Smith K, Arjmandi BH. Daily apple versus dried plum: impact on cardiovascular disease risk factors in postmenopausal women. Journal of the Academy of Nutrition and Dietetics. 2012; 112: 1158–1168.

[26] Barth SW, Koch TCL, Watzl B, Dietrich H, Will F, Bub A. Moderate effects of apple juice consumption on obesity-related markers in obese men: impact of diet-gene interaction on body fat content. European Journal of Nutrition. 2012; 51: 841–850.

[27] Shoji T, Yamada M, Miura T, Nagashima K, Ogura K, Inagaki N, *et al.* Chronic administration of apple polyphenols ameliorates hyperglycaemia in high-normal and borderline subjects: A randomised, placebo-controlled trial. Diabetes Research and Clinical Practice. 2017; 129: 43–51.

[28] Akazome Y, Kametani N, Kanda T, Shimasaki H, Kobayashi S. Evaluation of safety of excessive intake and efficacy of long-term intake of beverages containing apple polyphenols. Journal of Oleo Science. 2010; 59: 321–338.

[29] Nagasako-Akazome Y, Kanda T, Ohtake Y, Shimasaki H, Kobayashi T. Apple polyphenols influence cholesterol metabolism in healthy subjects with relatively high body mass index. Journal of Oleo Science. 2007; 56: 417–428.

[30] Borenstein M, Higgins JPT. Meta-analysis and subgroups. Prevention Science. 2013; 14: 134–143.

[31] Fabiani R, Minelli L, Rosignoli P. Apple intake and cancer risk: A systematic review and meta-analysis of observational studies. Public Health Nutrition. 2016; 19: 2603–2617.

[32] Hyson D, Studebaker-Hallman D, Davis P, Gershwin M. Apple Juice Consumption Reduces Plasma Low-Density Lipoprotein Oxidation in Healthy Men and Women. Journal of Medicinal Food. 2000; 3: 159–166.

[33] Avci A, Atli T, Ergüder I, Varli M, Devrim E, Turgay S, *et al.* Effects of apple consumption on plasma and erythrocyte antioxidant parameters in elderly subjects. Experimental Aging Research. 2007; 33: 429–437.

[34] Davidson MH, Dugan LD, Stocki J, Dicklin MR, Maki KC, Coletta F, *et al.* A Low-Viscosity Soluble-Fiber Fruit Juice Supplement Fails to Lower Cholesterol in Hypercholesterolemic Men and Women. Journal of Nutrition. 1998; 128: 1927–1932.