The effects and associations of whole-apple intake on diverse cardiovascular risk factors. A narrative review

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REVIEW

The effects and associations of whole-apple intake on diverse cardiovascular risk factors. A narrative review

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ABSTRACT

Apples are among the world's most consumed fruits. However, while the impact of whole-apple intake on cardiovascular disease (CVD) remains unknown. This narrative review summarizes a novel integrated view of whole-apple intake, CVD risk association (through observational studies; OSs), and the effects on CVD risk factors (randomized trials; RTs). In 8 OSs, whole-apple intake was associated with a reduced risk of CVD mortality, ischemic heart disease mortality, stroke mortality, all-cause mortality, and severe abdominal aortic calcification, as well as with lower C-reactive protein (CRP) concentrations. In 8 RTs, whole-apple consumption reduced total cholesterol, low-density lipoprotein cholesterol, systolic blood pressure, pulse pressure, and plasma inflammatory cytokines, and noticeably reduced CRP, whereas it increased high-density lipoprotein cholesterol (HDLc) and improved endothelial function. Thus, consuming between 100 and 150 g/day of whole apples is associated with a lower CVD risk and decreases in blood pressure, pulse pressure, total cholesterol, low-density lipoprotein cholesterol, and inflammation status as well as with increases in HDLc and endothelial function. These results, support the regular consumption of whole apples as an aid in the prevention of CVD.

Introduction

Cardiovascular disease (CVD) is the current leading cause of death worldwide, despite the important efforts toward the prevention of cardiovascular events through the implementation of healthy lifestyles (Onor et al. 2017; Warburton and Bredin 2017; Joseph et al. 2017), which include dietary management and physical activity (Martínez-González et al. 2015). Consequently, more strategies are needed to address the management and prevention of CVD. Additionally, consuming high amounts of fruits and vegetables is associated with diverse cardiovascular health benefits, such as the reduction in various cardiovascular risk factors and the associated risk of cardiovascular events and CVD mortality (Slavin and Lloyd 2012; Miller, Thangthaeng, et al. 2017; Alissa and Ferns 2017; Collese et al. 2017). Apples are one of the most popular fruits worldwide due to their seasonal availability, geographical distribution and organoleptic properties (Wang et al. 2018). Currently, apples' health effects are attributed mostly to their high content of phenolic compounds (PCs) (GutiErrez-Grijalva et al. 2016; Guasch-Ferré

et al. 2017; Dias et al. 2017) and fiber (Veronese et al. 2018). However, the total phenolic composition, pattern, and content of apples differ significantly between varieties (Kalinowska et al. 2014). Furthermore, apple diversity is influenced by a set of environmental factors including the soil, growing season, and harvest season, as well as their storage conditions and maturity status (Kalinowska et al. 2014; Stirpe et al. 2017). Despite these differences, the most frequently found PCs in apples are hydroxycinnamic acids (0.05–3 g/kg), flavanols (4.6–25.48 g/kg), dihydrochalcones (0.049–0.434 g/kg), and anthocyanins, which are mainly in the red peel (0.010–0.551 g/kg), which contribute to a total phenolic content that ranges between 5.23 and 27.24 g/kg of their dry weight (Hyson 2011; Gerhauser 2008). In addition, apples contain by a complex set of components such as vitamins A, B1, B2, C, and K, and minerals including iron, phosphorus, and potassium, as well as natural sugars (Stirpe et al. 2017). Therefore, to reveal the impact of whole-apple consumption on CVD risk factors, information from observational studies (OSs) and randomized trials (RTs) was
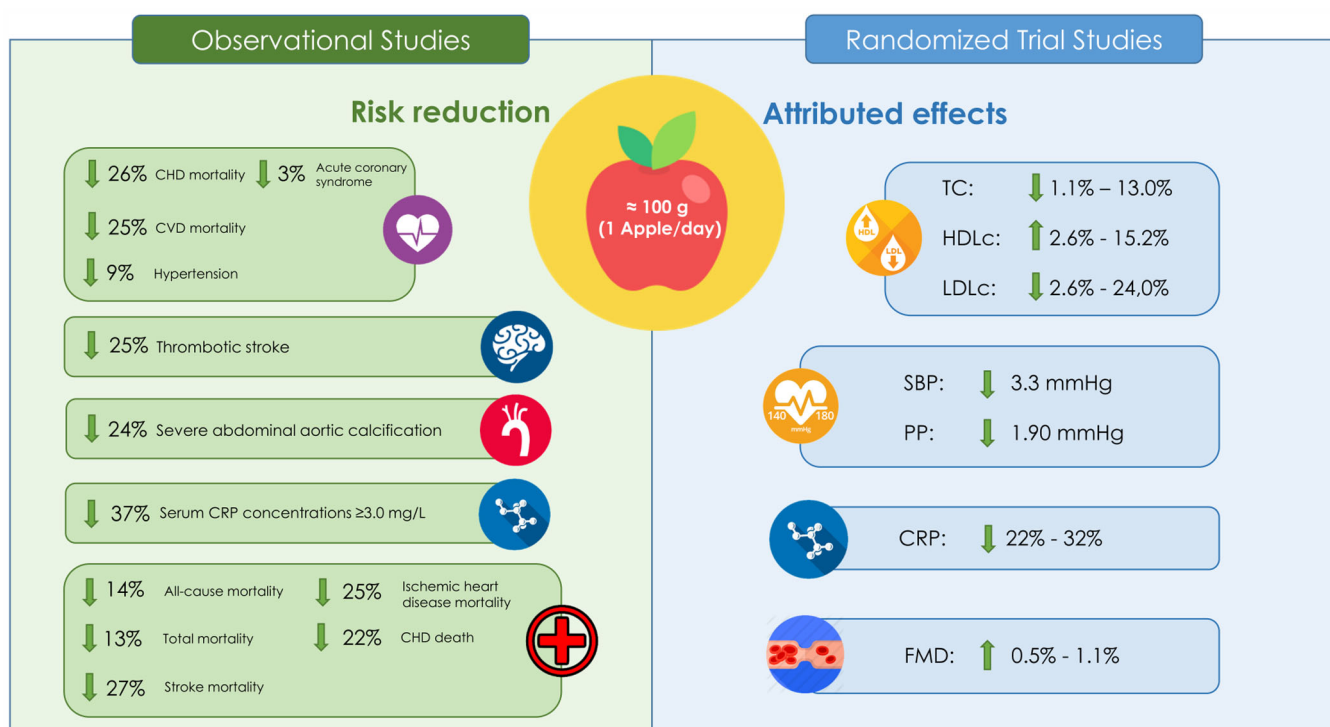
Figure 1. Beneficial effects of whole-apple consumption from observational studies (associated risk reductions) and randomized trial studies (attributed effects). The figure showed the health benefits of the consumption of approximately 100 g of whole-apple, corresponding to 1 apple a day, on diverse cardiovascular risk factors. Low-density lipoprotein cholesterol (LDLc), total cholesterol (TC), high-density lipoprotein cholesterol (HDLc), C-reactive protein (CRP), millimeters of mercury (mmHg), systolic blood pressure (SBP), pulse pressure (PP), coronary heart disease (CHD), cardiovascular disease (CVD), flow-mediated dilatation (FMD). All values presented, are statistically significant ($p < 0.05$) with the exception of the CRP values in randomized clinical trials.

analyzed. First, the associations between whole-apple consumption and CVD risk protection were assessed based on the analysis of OS. Second, the causal effects of whole-apple consumption on CVD risk factors were assessed through RTs. As a food, the causal effects of whole-apple consumption on CVD risk factors in humans should be considered with attention to particular methodological considerations regarding the compliance of different key quality characteristics of randomized controlled trials (RCTs) such as the impossibility for a double-blinded trial and the lack of adequate controls and/or placebos (Kalinowska et al. 2014; Hébert et al. 2016).

Such is the case of the seminal study by Gormley et al. conducted in 1977, which involved noncontrolled and nonrandomized parallel intervention trial design, on 76 free-living male volunteers aged between 30 and 50 years old (Gormley et al. 1977). The participants were divided into two groups based on similar cholesterol levels: Group 1 consumed between 2 and 3 Irish Golden Delicious (GD) apples/day whereas Group 2 consumed only 3 Irish GD apples/week. Both groups were evaluated before and after a period of 4 months (Gormley et al. 1977). Despite the positive results reported by the authors regarding a serum cholesterol reduction of 8.1% when comparing both groups at the end of the intervention (Gormley et al. 1977), the study design does not comply with the present-day quality standards of an RCT (Schulz, Altman, and Moher 2010). Moreover, since there is a current interest in assessing the effects of whole-food intake, we focused on the effects of the intake of whole apples instead of their individual components, extracts or

juices. In that context, the objective of this narrative review is to render a novel and integrated view of whole-apple consumption by summarizing its associations with different CVD risk factors through OSs as well as the effects of whole-apple intake on CVD risk factors such as blood pressure, endothelial function, lipids, and inflammation in RTs.

Literature search

This narrative review is structured based on the criteria proposed by different authors (Green, Johnson, and Adams 2006; Ferrari 2015) and utilizes a methodological systematic approach to the literature search based on the general principles published in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2009). The PRISMA flowchart (Supplementary material, Figure 1) and checklist (Supplementary material, Table 1) for the present narrative review are provided. The Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung and Blood Institute (NHLBI) was used to assess the included observational studies (National Institutes of Health 2014) for the OSs included in this narrative review (Supplementary material, Table 2). For the included RTs, the Revised Tool to Assess Risk of Bias in Randomized Trials (RoB 2) (Higgins et al. 2011) was employed (Supplementary material, Table 3 and Supplementary Data).

Information sources and search strategy

The scientific web libraries SCOPUS (https://www.scopus.com), Cochrane Library (https://www.cochranelibrary.com/), and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) were explored using the following search terms for this narrative review: "(Apples OR malus) AND (health OR health outcome) AND (RCT OR randomized clinical trial OR epidemiological OR observational OR randomized control* trial OR cohort OR cohort studies OR case-control studies) NOT (review)". Only studies published in the last 20 years, from January 1999 to April 2019 were finally selected.

Article's selection criteria employed

Our group identified 802 articles from the database search after duplicates were removed, and no additional articles were found by hand-searching. Only peer-reviewed articles written in English were included. Two independent authors (B.A.S.-R. and Ú.C.) extracted the published data and a third reviewer (R.S.) resolved all differences. After the analysis of the titles and abstracts, a total of 16 articles (Arts et al. 2001; Mink et al. 2007; Hodgson et al. 2016; Bondonno et al. 2012; Bondonno et al. 2018; 2016; Knekt et al. 2002; Chun et al. 2008; Chai et al. 2012; Hansen et al. 2010; Borgi et al. 2016; Tenore et al. 2017; Vafa et al. 2011; Ravn-Haren et al. 2013; Auclair et al. 2010; Liddle et al. 2019) were included according to our search strategy for this narrative review.

The effects and associations of whole-apple intake on cardiovascular risk factors

The information regarding the associations between whole-apple consumption and cardiovascular risk factors provided by the OSs and the beneficial effects attributed to whole-apple intake on CVD risk factors, acquired from the RTs, are shown in Table 1.

Observational studies

Our research strategy identified 8 OSs that reported associations between whole-apple intake and variouscardiovascular risk factors (Mink et al. 2007; Hodgson et al. 2016; Bondonno et al. 2016; Knekt et al. 2002; Arts et al. 2001; Chun et al. 2008; Hansen et al. 2010; Borgi et al. 2016). Of these articles, 7 were cohort studies (Mink et al. 2007; Hodgson et al. 2016; Bondonno et al. 2016; Knekt et al. 2002; Arts et al. 2001; Hansen et al. 2010; Borgi et al. 2016), and 1 was a cross-sectional study, which was included in our analysis due to scarce data (Chun et al. 2008).

Observed cardiovascular effects of whole-apple intake

Many beneficial associations have been consistently demonstrated in OSs between higher intakes of PCs, obtained through fruit consumption, and various CVD risk factors (Aune et al. 2017; Miller, Thangthaeng, et al. 2017). However, to the best of our knowledge, a comprehensive analysis on the associations between whole-apple intake and different CVD risk factors has not been performed to date. In that context, the Iowa Women's Health Study, a prospective cohort study performed on a total sample of 34,489 postmenopausal women aged between 55 and 69 years old, between 1986 and 2002, sought to unveil the possible health-related associations between the fruit and vegetable intake, determined through food-frequency questionnaires (FFQ), and various cardiovascular outcomes (Mink et al. 2007). The authors reported that the postmenopausal women who consumed >1 whole-apple/day reported a significant 25% reduction in CVD mortality [hazard rate ratio (HRR) (95% confidence interval; CI)] [0.75 (0.68, 0.82; $p < 0.001$)] (Mink et al. 2007). Additionally, it was demonstrated that consuming >1 whole-apple/day is also associated with a 26% reduction in coronary heart disease (CHD) mortality [0.74 (0.65, 0.84; $p < 0.001$)] and with a 27% reduction in stroke mortality [0.73 (0.59, 0.90; $p = 0.018$)] compared with postmenopausal women who consumed <1 apple/week (Mink et al. 2007). Additionally, in another cohort study in which the total fruit intake of 1,456 elderly women (>70 years old) was assessed through FFQs for a period of 15 years (Hodgson et al. 2016), the results of the study reveal that, after multivariable adjustments, for each 53 g/day increase in whole-apple intake there is a significant 14% risk reduction in the all-cause mortality among the nonsmoking population [HR = 0.86 (0.75, 0.97; $p < 0.05$)]. However, the same effects were not observed for the smoking population (Hodgson et al. 2016).

Furthermore, in the "Calcium Intake Fracture Outcome Study" (CAIFOS), a five-year-long (1998–2003) prospective cohort study, in which the whole-apple consumption was assessed through FFQs on a sample of 1052 elderly women (over 70 years old), and abdominal aortic calcification (AAC) was assessed as a biomarker for subclinical vascular disease (N. P. Bondonno et al. 2016). After multivariable adjustments, the results showedthat for each extra 50 g/day of whole-apple intake there was a 24% lower odds of having severe abdominal aortic calcification [odds ratio (OR): 0.76 (0.62, 0.93), $p = 0.009$)] (N. P. Bondonno et al. 2016).

Similar results have also been published in a 6 year (1966–1972) cohort study in which the flavonoid intake of 10,054 Finnish men and women between 52 and 65 years old was determined through dietary history (Knekt et al. 2002). The results showed that in comparisons between the highest and lowest quartiles of consumption, the ingestion of quercetin, an apple-attributed flavanol, reduced the total mortality relative risk (RR) by 13% [0.87 (0.77, 0.99; $p = 0.003$)], the RR for ischemic heart disease mortality by 25% [0.75 (0.60, 0.94; $p = 0.007$)], and the RR of thrombotic stroke by 25% [0.75 (0.57, 0.99; $p = 0.009$)] (Knekt et al. 2002) following multivariable adjustment. Moreover, the association between total mortality and the whole-apple consumption was further described in the Iowa Women's Health Study population (Arts et al. 2001). In this cohort study, the whole-apple intakes of 34,492 postmenopausal women (55–69 years old) were assessed for a 12-year period (1986–1998) through FFQs (Arts et al. 2001). The results

Table 1. General information on studies that assessed the effect of whole-apple intake on cardiovascular risk factors.

Title	Author	N	Population	Duration of the intervention/follow-up period	Study type	Observational evaluation method/Clinical intervention	Associations or effects between whole-apple intake and cardiovascular risk factors
Observational studies							
Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women	Mink et al. (2007)	34,489	55–69 year-old post-menopausal women	16 years	Prospective cohort	Food-frequency questionnaire	HRR demonstrates that consuming >1 apples/week has a significant inverse association (HR (95% CI)) of stroke mortality 0.73 (0.59, 0.90) p = 0.018, CHD mortality 0.74 (0.65, 0.84) p < 0.001, and CVD mortality 0.75 (0.68, 0.82) p < 0.001, when adjusted for age and energy.
Apple intake is inversely associated with all-cause and disease-specific mortality in elderly women.	Hodgson et al. (2016)	1,456	> 70-year-old elderly women	15 years	Cohort	Food-frequency questionnaire	HR demonstrates that for each standard deviation increase of 53 g/day of apple intake is associated (HR (95% CI)) with a lower risk of all-cause mortality in nonsmokers 0.86 (0.75, 0.979) p < 0.05.
Fruit intake and abdominal aortic calcification in elderly women: A prospective cohort study	Bondonno et al. (2016)	1,052	> 70-year-old elderly women	5 years	Prospective cohort	Food-frequency questionnaire	Each standard deviation (SD; 50 g/day) increase in apple intake was associated with a 24% lower odds of having severe AAC (AAC score >5) OR (95% CI): 0.76 (0.62, 0.93), p = 0.009 after a multivariable-adjusted logistic regression.
Flavonoid intake and risk of chronic diseases.	Knekt et al. (2002)	10,054	52–65 year-old men and women	6 years	Cohort	Dietary history	The RR (95% CI) between highest and lowest quartiles of quercetin consumption, attributed to apple intake after a multivariable adjustment was of 0.87 (0.77, 0.99) p = 0.003, for total mortality; 0.75 (0.60, 0.94) p = 0.007; for mortality from ischemic heart disease; and 0.75 (0.57, 0.99) p = 0.009, for thrombotic stroke.
Dietary catechins in relation to coronary heart disease death among postmenopausal women	Arts et al. (2001)	34,492	55–69-year-old post-menopausal women	12 years	Prospective cohort	Food-frequency questionnaire	Apples are inversely associated with CHD death (Risk ratio (95% CI)) 0.78 (0.62, 0.98) p < 0.05, after multivariable-adjusted.
Serum C-Reactive Protein Concentrations Are Inversely Associated with Dietary Flavonoid Intake in U.S	Chun et al. (2008)	8,335	≥19 year-old adults	3 years	Cross-sectional	24 hour dietary recall	Individuals who consumed more than 138g/apple/day had a significant decrease in serum C-reactive protein concentration of 1.49 (0.10) mg/L with and an OR for CRP ≥ 3 mg/L (OR (95% CI)) 0.63 (0.39, 1.04) p < 0.05.
Fruit and vegetable intake and risk of the acute coronary syndrome.	Hansen et al. (2010)	53,383	50–64-year-old men and women	7.7 years	Prospective cohort	Food-frequency questionnaire	An inverse association for apple intake and the risk of the acute coronary syndrome was noted for men with a multivariable-adjusted IRR (95% CI) of 0.97 (0.94, 0.99) p < 0.05, per each 25 g/day of apple consumed. The same trend was observed in women, although not significant.
Fruit and Vegetable Consumption and the Incidence of Hypertension in Three Prospective Cohort Studies	Borgi et al. (2016)	123,059	25–55-year-old women 40–75-year-old men	8 years	Cohort	Semi-quantitative food-frequency questionnaire	Consumption levels of ≥4 apples/week were associated with a decreased risk of hypertension after a multivariable pooled HR (95% CI) analysis of 0.91 (0.88–0.95) p < 0.001.

Randomized trial studies
Lipid profile

Title	Reference	n	Duration	Study type	Groups	Results
Annurca (*Malus pumila* Miller cv. Annurca) apple as a functional food for the contribution to a healthy balance of plasma cholesterol levels: results of a randomized clinical trial	Tenore et al. (2016)	250	2 months	Chronic RT	**Group 1:** 1 RD apple/day **Group 2:** 1 GS apple/day **Group 3:** 1 F apple/day **Group 4:** 1 GD apple/day **Group 5:** 2 ANN apples/day	The significant difference ($p < 0.05$) between the end of the intervention study ($t = 2$ months) and the baseline ($t = 0$) of each group on plasma biochemical parameters: **TC reduction:** ANN (-8.4%)> GS (-4.5%)>RD (-2.9%)>F (-2.3%)>GD (-1.1%) **LDLc reduction:** ANN (-14.5%)> GS (-8.3%)>RD (-5.8%)>F (-4.7%)>GD (-2.6%) **HDLc increase:** ANN ($+15.2\%$)> GS ($+4.5\%$)>RD ($+4.2\%$)>F ($+4.1\%$)>GD ($+2.6\%$) **TG increase:** GS ($+12.7\%$)>F ($+10.8\%$)>GD ($+9.3\%$)>RD ($+8.3\%$) >ANN ($+6.1\%$)
Effects of apple consumption on lipid profile of hyperlipidemic and overweight men	Vafa et al. (2011)	46	2 months	Chronic RCT	**Group 1:** control group **Group 2:** 300 g GD apple/day	No significant differences were observed regarding TC, LDLc, HDLc, LDL/HDL ratio, Lp(a), and ApoB serum levels. There was an observed increase of TG and VLDL at the end of the study when compared to the baseline in Group 2, although not significant. Moreover, there was an observed increase in TG and VLDL when comparing Group 2 against Group 1 at the end of the study ($p < 0.05$).
Daily apple versus dried plum: impact on cardiovascular disease risk factors in postmenopausal women	Chai et al. (2012)	160	12 months	Chronic RCT	**Group 1:** Dried apple 75 g/day **Group 2:** Dried plum 100 g/day (comparative control)	In Group 1, after 3 months, there was a 9% reduction in serum TC and a 16% reduction of LDLc when compared to baseline, these reductions were further increased to 13% and 24% respectively at the end of the study ($p < 0.05$). Moreover, there was a reduction in TC values but not in LDLc, when comparing Group 1 versus Group 2 at 6 months ($p < 0.05$). There were no significant differences between HDLc and TG, and HDLc/LDLc ratio between and within the groups. Moreover, after dried apple consumption, HDLc increased by 3%, TG decreased by 9%, and the ratio HDL/LDL increased after 12 months when compared to the baseline, although non-significant.
Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers	Ravn-Haren et al. (2013)	23	4 week each intervention + 1-week wash-out	Crossover chronic RCT	**Group 1:** Control period **Group 2:** 550 g/day of Shampion whole fresh apple **Group 3:** 22 g/day of Shampion apple pomace **Group 4:** 500 ml/day of Shampion cloudy apple juice **Group 5:** 500 ml/day of Shampion clear apple juice.	After 4 weeks, Group 2 showed a reduction in plasma TC and in LDLc of 5.6% and 6.7% respectively when compared to Group 1, although non-significant. Group 2 did not show any differences in TG, HDLc, and TC/HDLc ratio when compared to Group 1.

(continued)

Table 1. Continued.

Title	Author	N	Population	Duration of the intervention/follow-up period	Study type	Observational evaluation method/Clinical intervention	Associations or effects between whole-apple intake and cardiovascular risk factors
The regular consumption of a polyphenol-rich apple does not influence endothelial function: a randomized double-blind trial in hypercholesterolemic adults.	Auclair et al. (2010)	30	47–60-year-old hypercholesterolemic men	4 week	Crossover chronic RT	**Group 1:** 40 g of lyophilized MD apple (polyphenol-poor; = 2 MD fresh apples (270 g)) **Group 2:** 40 g of lyophilized MD apple (polyphenol-rich; = 2 MD fresh apples (270 g))	After 4 weeks of intervention, Group 2 showed no significant differences in TC, TG, LDLc, HDLc, Apo A1, Apo B, and Apo B/Apo A1 ratio when compared to Group 1 and when compared the baseline versus the end of the study
Inflammation							
Daily apple versus dried plum: impact on cardiovascular disease risk factors in postmenopausal women	Chai et al. (2012)	160	50–61-year-old healthy post-menopausal women	12 months	Chronic RCT	**Group 1:** Dried apple 75 g/day **Group 2:** Dried plum 100 g/day (comparative control)	Serum CRP levels noticeably decreased by 22% and 32% in Group 1 after 6 months and 12 months of intervention respectively when compared to baseline.
Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers	Ravn-Haren et al. (2013)	23	18–69-year-old healthy volunteers	5 × 4 week	Crossover RCT	**Group 1:** Control period **Group 2:** 550 g/day of Shampion whole fresh apple **Group 3:** 22 g/day of Shampion apple pomace **Group 4:** 500 ml/day of Shampion cloudy apple juice **Group 5:** 500 ml/day of Shampion clear apple juice.	Group 2 showed no significant reduction in serum hs-CRP after 4 weeks when compared to Group 1.
Assessing the Effects of Acute and Chronic Whole Apple Consumption on Biomarkers of Inflammation in Overweight and Obese Adults (P21-011-19)	Liddle et al. (2019)	46	44–48-year-old overweight and obese adults	6 weeks	Chronic RCT	**Group 1:** Control **Group 2:** 3 Gala apples (200 g) /day	Group 2, consisting of chronic apple consumption, decreased fasting unstimulated (IL-6) and LPS-stimulated (IL-6, INF-γ, TNF-α) PBMC-secreted inflammatory cytokines (P < 0.05), as well as plasma IL-6 (P < 0.05).
Assessing the Effects of Acute and Chronic Whole Apple Consumption on Biomarkers of Inflammation in Overweight and Obese Adults (P21-011-19)	Liddle et al. (2019)	26	42–48-year-old overweight and obese adults	1 dose (4 h and 6 h)	Crossover acute RCT	**Group 1:** 3 Gala apples (200 g)	Acute apple consumption decreased 4 h postprandial unstimulated (IL-1β, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein (MIP)-1β, TNF-α) and LPS-stimulated (IL-6, TNF-α) PBMC-secreted inflammatory cytokines (P < 0.05).
The regular consumption of a polyphenol-rich apple does not influence endothelial function: a randomized double-blind trial in hypercholesterolemic adults.	Auclair et al. (2010)	30	47–60-year-old hypercholesterolemic men	4 week	Crossover chronic RT	**Group 1:** 40 g of lyophilized MD apple (polyphenol-poor; = 2 MD fresh apples (270 g)) **Group 2:** 40 g of lyophilized MD apple (polyphenol-rich; = 2 MD fresh apples (270 g))	Apple intake showed no significant differences in CRP after 4 weeks of intervention between both groups, nor when comparing the end of the intervention with their respective baselines.
Blood pressure and endothelial function							
Flavonoid-rich apples and nitrate-rich spinach augment nitric	Bondonno et al. (2012)	30	33–70-year-old healthy men and women	1 dose	Crossover acute RCT	**Group 1:** Control (CP apple flesh)	Group 2 significantly reduced SBP in 3.3 mmHg (95% CI), 4.6, 1.8 (p < 0.001) and

Title	Reference	N	Participants	Study type	Duration	Groups	Results
oxide status and improve endothelial function in healthy men and women: A randomized controlled trial.						**Group 2:** Apple (120g CP apple flesh + 80g CP apple skin) **Group 3:** Spinach (200g) **Group 4:** Apple+Spinach (120g CP apple flesh + 80g CP apple skin + 200g spinach)	showed a non-significant tendency to lower DBPs when compared to Group 1. Moreover, Group 2 also decreased PP in 1.9 mmHg (95% CI), 3.2, 0.3 ($p = 0.02$) and showed a significant increase in brachial artery FMD in 1.1% (95% CI), 0.7, 1.5 ($p < 0.0001$) when compared to Group 1.
Flavonoid-Rich Apple Improves Endothelial Function in Individuals at Risk for Cardiovascular Disease: A Randomized Controlled Clinical Trial.	Bondonno et al. (2018)	30	47–70-year-old men and women	Acute RCT	12 h	**Group 1:** Control (2 CP apple flesh) **Group 2:** Apple (2 CP whole-apple + CP apple skin)	Group 2 improved brachial FMD at 1 h in 1% (95% CI), 0.8, 1.3 ($p < 0.001$), and at 2 h in 0.8% (95% CI), 0.6, 0.9 ($p < 0.001$) post intervention. Moreover, there were no significant differences in SBD or DBP between both groups after the acute intervention.
Flavonoid-Rich Apple Improves Endothelial Function in Individuals at Risk for Cardiovascular Disease: A Randomized Controlled Clinical Trial.	Bondonno et al. (2018)	30	47–70-year-old men and women	Crossover Chronic RCT	4 week each intervention + 2-week wash-out	**Group 1:** Control (2 CP apple flesh/day) **Group 2:** Apple (2 CP whole-apple + CP apple skin/day)	Group 2 significantly improved brachial artery FMD in 0.5% (95% CI), 0.4, 0.7 ($p < 0.001$) after 4 weeks of intervention. There were no significant differences in SBP and DBP between groups at the end of the chronic intervention.
The regular consumption of a polyphenol-rich apple does not influence endothelial function: a randomized double-blind trial in hypercholesterolemic adults.	Auclair et al. (2010)	30	47–60-year-old hypercholesterolemic men	Crossover chronic RT	4 week	**Group 1:** 40 g of lyophilized MD apple (polyphenol-poor; = 2 MD fresh apples (270 g)) **Group 2:** 40 g of lyophilized MD apple (polyphenol-rich; = 2 MD fresh apples (270 g))	Apple intake showed no significant differences in brachial artery FMD after 4 weeks of intervention between both groups, nor when comparing the end of the intervention with their respective baselines. Moreover, apple intake showed no differences in SBP, DBP, and PP.
Intake of whole apples or clear apple juice has contrasting effects on plasma lipids in healthy volunteers	Ravn-Haren et al. (2013)	23	18–69-year-old healthy volunteers	Crossover chronic RCT	5x4 week	**Group 1:** Control period **Group 2:** 550 g/day of Shampion whole fresh apple **Group 3:** 22 g/day of Shampion apple pomace **Group 4:** 500 ml/day of Shampion cloudy apple juice **Group 5:** 500 ml/day of Shampion clear apple juice.	Group 2 showed no differences in SBP and DBP when compared to Group 1 at the end of the intervention.

RT, randomized trial; RCT, randomized controlled trial; HRR, hazard rate ratio; HR, hazard ratio; RR, relative risk; OR, odds ratio; IRR, incidence rate ratio; CHD, Coronary heart disease; CVD, cardiovascular disease; TC, total cholesterol; LDLc, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; TG, triglycerides; VLDLc, very-low-density lipoprotein cholesterol; CRP, C-reactive protein; BP, blood pressure; RCT, Randomized Clinical Trial; IL-6, Interleukin-6; TNF-α, Tumoral nuclear factor-alpha; INF-γ, Interferon-gamma; LPS, lipopolysaccharide; AAC, abdominal aortic calcification; RD, red delicious; GS, granny smith; ANN, Annurca; F, Fuji; GD, golden delicious; hs-CRP, high sensitivity C-reactive protein; CP, Cripps Pink; DBP, diastolic blood pressure; SBP, systolic blood pressure; FMD, flow-mediated dilatation; PP, pulse pressure; MD, Malus Domestica.

following multivariable adjustments showed that the whole-apple consumption was associated with a 12% lower risk ratio of CHD mortality [0.78 (0.62, 0.98; $p < 0.05$)] (Arts et al. 2001).

Furthermore, the cardiovascular effects of the whole-apple intake were also assessed through FFQs, for a mean of 7.7 years (1993–2000), in a sample of 53,383 men and women that were a part of the "Diet, Cancer, and Health Prospective Cohort Study" (Hansen et al. 2010). The volunteers were aged between 50 and 64 years old and had no previous diagnosis of cancer in the Danish Cancer Registry (Hansen et al. 2010). The researchers found that for each 25 g/day of whole-apple that was consumed there was an associated 3% reduction in the incidence rate ratio (IRR) of the acute coronary syndrome in men [0.97 (0.94, 0.99; $p < 0.05$)] (Hansen et al. 2010). The same trend was observed in women, although the results were borderline significant (Hansen et al. 2010).

Similarly, other health benefits of whole-apple intake on the risk of hypertension were noted in the OSs. For instance, a prospective study included the volunteers who were recruited in the following three large longitudinal cohorts: the Nurses' Health Study (NHS; $n = 62,175$ women), the Nurses' Health Study II (NHS II; $n = 88,475$ women), and the Health Professionals Follow-up Study (HPFS; $n = 36,803$ men) (Borgi et al. 2016). The resulting sample of 123,059 participants was followed for 8 years, and the results following multivariable pooled HRR demonstrated that consuming ≥4 apples/week is associated with a 9% reduction in the risk of hypertension [0.91 (0.88, 0.95; $p < 0.001$)] (Borgi et al. 2016).

Additional benefits were noted for the inflammatory status, as was demonstrated in a cross-sectional study in which the serum C-reactive protein (CRP) concentrations were determined for 8,335 adults over 19 years old who were enrolled and followed in the National Health and Nutrition Examination Survey (NHANES) between 1999 and 2002 (3 years). Whole-apple intake was estimated with the USDA flavonoid databases matched with a 24-h dietary recall (Chun et al. 2008). As a part of the methodology, the individuals were divided into tertiles according to their whole-apple intake as the following: nonconsumers, individuals who consumed between 0 g and 106 g of whole-apple/day (low consumers), and individuals consuming between 106 g and 138 g of whole-apple/day (medium consumers). The reported CRP concentrations (means ± standard error of the mean; SEM) were 1.90 ± 0.02 mg/L for nonconsumers, 1.84 ± 0.12 mg/L for low consumers, and 1.49 ± 0.08 g/L for medium consumers (Chun et al. 2008). In addition, individuals who consumed more than 138 g of whole-apple/day (high consumers) showed significantly lower values of serum CRP concentrations of 1.49 ± 0.10 mg/L ($p < 0.05$) (Chun et al. 2008), similar to the concentrations for the medium consumers, and reported a clinically relevant OR of 0.63 (0.39, 1.04; $p < 0.05$) for CRP ≥3.0 mg/L (Chun et al. 2008). The authors observed the presence of a linear trend in a decrease of the serum CRP concentrations for whole-apple consumption in the range of 0–138 g ($p < 0.05$).

Randomized trials

Our screening identified 8 articles that described RTs (Tenore et al. 2017; Vafa et al. 2011; Chai et al. 2012; Ravn-Haren et al. 2013; Auclair et al. 2010; Liddle et al. 2019; Bondonno et al. 2012; Bondonno et al. 2018). Of these, 2 were not controlled trials (Auclair et al. 2010; Tenore et al. 2017), whereas 6 were RCTs (Vafa et al. 2011; Chai et al. 2012; Ravn-Haren et al. 2013; Liddle et al. 2019; Bondonno et al. 2012; Bondonno et al. 2018) according to the information that the authors declared in the content of the article. Moreover, out of the 8 included RTs, 5 articles reported the effects of whole-apple intake on serum or plasma lipid profiles (Tenore et al. 2017; Vafa et al. 2011; Chai et al. 2012; Ravn-Haren et al. 2013; Auclair et al. 2010), 4 described the effects of whole-apples on inflammation (Chai et al. 2012; Ravn-Haren et al. 2013; Liddle et al. 2019; Auclair et al. 2010), and 4 articles assessed the effects of whole-apple intake on, blood pressure and vascular health effects (Bondonno et al. 2012; Bondonno et al. 2018; Auclair et al. 2010; Ravn-Haren et al. 2013). Additionally, out of the 8 RTs included, 5 involved only a chronic intervention (Tenore et al. 2017; Vafa et al. 2011; Chai et al. 2012; Ravn-Haren et al. 2013; Auclair et al. 2010), 1 RT involved only an acute intervention (Bondonno et al. 2012); and 2 RTs reported results on both acute and a chronic interventions (Liddle et al. 2019; Bondonno et al. 2018). Additionally, out of these 8 studies, 5 RTs used a crossover design intervention (Ravn-Haren et al. 2013; Auclair et al. 2010; Liddle et al. 2019; Bondonno et al. 2012; Bondonno et al. 2018).

Lipid profile

The impact of serum or plasma cholesterol levels on CVD is well-established and is recognized as an independent risk factor for CVD (Goldstein and Brown 2015). According to the American Heart Association (AHA) and the American College of Cardiologists (ACC), total cholesterol (TC) levels ≤150 mg/dL, and/or low-density lipoprotein cholesterol levels (LDLc) ≤100 mg/dL, are considered to be optimal for humans (Grundy et al. 2019). Accordingly, the AHA and the ACC recommended in their latest guidelines, published in 2018, that individuals with an established atherosclerotic CVD are considered to be at high risk of cardiac complications, and should reach an LDLc target of ≤70 mg/dL (Grundy et al. 2019). Moreover, it has been demonstrated that each 38.67 mg/dL (1 mmol/L) decrease in the plasma LDLc concentrations is associated with a 30% reduction in CVD risk (Joseph et al. 2017). In this context, 5 RTs that assessed the effects of whole-apple consumption on the lipid profile in humans were identified through our screening (Tenore et al. 2017; Vafa et al. 2011; Chai et al. 2012; Ravn-Haren et al. 2013; Auclair et al. 2010).

In a recent single-blinded and placebo-controlled RCT, a group of 250 volunteers between 31 and 56 years old were randomly divided into 5 groups of 50 subjects each (22 women and 28 men per group) to determine the effects of the whole-apple consumption on the following CVD risk factors: TC, LDLc, high-density cholesterol (HDLc), and

triglycerides (TG) (Tenore et al. 2017). For a period of 60 days, four of the five groups consumed one apple a day of one of the following apple varieties, (1) red delicious (RD), (2) granny smith (GS), (3) GD and (4) Fuji (F), while the fifth group was assigned to consume 2 Annurca (ANN) apples/day (Tenore et al. 2017). The authors justify the use of two ANN apples instead of oneas an attempt to match the different apple's overall macronutrient composition. At the end of 2 months, ANN apples demonstrated the most beneficial lipid profile changes when compared to the RD, GS, GD, and F apple varieties. The summary of the results are presented in decreasing order as follows, for TC: ANN (-8.4%), GS (-4.5%), RD (-2.9%), F (-2.3%), and GD (-1.1%), $p < 0.05$ (Tenore et al. 2017). For the LDLc reduction: ANN (-14.5%), GS (-8.3%), RD (-5.8%), F (-4.7%), and GD (-2.6%), $p < 0.05$ (Tenore et al. 2017). Furthermore, all apples showed a significant increase in HDLc as follows: ANN ($+15.2\%$), GS ($+4.5\%$), RD ($+4.2\%$), F ($+4.1\%$), and GD ($+2.6\%$), $p < 0.05$ (Tenore et al. 2017). In addition, all apples showed an increase in the TG values at different rates: GS ($+12.7\%$), F ($+10.8\%$), GD ($+9.3\%$), RD ($+8.3\%$), and ANN ($+6.1\%$), $p < 0.05$ (Tenore et al. 2017). In summary, this intervention demonstrated that the overall effectiveness of apples, as modulators of plasma lipids differs depending on the apple variety consumed. Thus, the assessed whole apples were able to reduce TC values between 1.1% (GD) and 8.4% (ANN) and LDLc between 2.6% (GD) and 14.5% (ANN), while raising HDLc values between 2.6% (GD) and 15.2% (ANN), and TG values between 6.1% (ANN) and 12.7% (GS) (Tenore et al. 2017). The ANN apple effects on the lipid profile can be explained, at least in part, by their higher concentration of PCs in comparison with the rest of the compared apples (Stirpe et al. 2017). ANN apples are known to have approximately 146 ± 2.64 mg/100 g of total polyphenols, as well as high concentrations of procyanidins, quercetin, and phloretin which are known for their positive health properties (Mari et al. 2010).

In another chronic RCT study, the effects of consuming 75 g/day of a nondescribed dried apple variety on the plasma lipid profile were compared against the effects of consuming 100 g/day of dried plums (Chai et al. 2012). The intervention was performed on 160 postmenopausal women aged between 50 and 61 years old for a total of 12 months (Chai et al. 2012). As stated by the authors, the dry plum dosage was chosen based on a comparable amount of energy, fiber, carbohydrates and fat, while providing a different phenolic profile than that of the dried apple (Chai et al. 2012). The results at 3 months demonstrated a significant 9% reduction in TC and 16% in LDLc in the dried apple group compared to baseline ($p < 0.05$) (Chai et al. 2012). Moreover, at the end of the study (12 months), these reductions were further increased to 13% for TC and 24% for LDLc ($p < 0.05$) (Chai et al. 2012). However, the researchers observed no significant differences in HDLc, TG, or the HDLc/LDLc ratio, neither between nor within groups (Chai et al. 2012).

Furthermore, the effects of whole-apple consumption on the lipid profile in humans were also assessed in a crossover

RCT performed on 23 healthy volunteers between 18 and 69 years old (Ravn-Haren et al. 2013). For the study, the volunteers were randomly assigned to one of five different intervention arms for a period of 4 weeks with a one-week wash-out after completing each intervention. This process was repeated until all the volunteers completed all the interventions (Ravn-Haren et al. 2013). The interventions were as follows: Intervention 1 was used as a control period; for intervention 2, the volunteers ingested 550 g/day of whole Shampion apples; for intervention 3, the volunteers consumed 22 g/day of Shampion apple pomace; for intervention 4, the volunteers drank 500 mL/day of cloudy Shampion juice; and for intervention 5, the volunteers drank 500 mL/day of clear Shampion juice (Ravn-Haren et al. 2013). The result showed that eating 550 g/day of Shampion whole-apple caused a borderline statistically significant reduction in plasma TC of 5.6% ($p = 0.066$) whereas LDLc showed a nonsignificant reduction of 6.7% ($p = 0.12$) when compared against the control intervention after four weeks (Ravn-Haren et al. 2013).

However, two of the included studies reported no significant effects of whole apples on diverse cardiovascular risk factors. In the first study, 46 overweight and hyperlipidemic men between 30 and 50 years old were divided into two groups. The first group was asked to consume 300 g/day of fresh whole Golden Delicious (GD) apples for a period of 2 months and the second group acted as a control (Vafa et al. 2011). The results showed no significant differences with respect to the TC, LDLc, HDLc, LDL/HDL ratio, Lp (a), or ApoB serum levels. However, the GD apple intake was significantly associated with an increase in the plasma TG and VLDL values when compared against the control group at the end of the study ($p < 0.05$) (Vafa et al. 2011).

Furthermore, in a 4-week crossover chronic RCT on 30 hypercholesterolemic men between 47 and 60 years old, the participants were randomly assigned into one of two groups: Group 1 was assigned to consume 40 g/day of lyophilized "polyphenol-rich" Malus Domestica (MD) apples (≈ 2 whole-apples), while Group 2 consumed 40 g of lyophilized "polyphenol-poor" MD apples (Auclair et al. 2010). After 4 weeks of intervention, Group 1 did not show any significant differences in TC, TG, LDLc, HDLc, apolipoprotein (Apo) A1, Apo B, and Apo A1/Apo B ratio when compared against Group 2or when compared to baseline values (Auclair et al. 2010).

Inflammation

There is a current focus on so-called low-grade inflammation, based on the concept that the steady production of pro-inflammatory cytokines can alter the correct and normal metabolic functions of the human body (Minihane et al. 2015). This low-grade inflammation is known to play a central role in the pathophysiology of a vast number of human diseases including CVD, obesity, osteoarthritis, cancer and other illnesses (Grandl and Wolfrum 2018; Guzik and Touyz 2017; Corte et al. 2016; Asghar and Sheikh 2017; Guarner and Rubio-Ruiz 2015). The effect of whole-apple intake on low-grade inflammation has been examined in 4

RCTs (Chai et al. 2012; Ravn-Haren et al. 2013; Liddle et al. 2019; Auclair et al. 2010) to date. Among the included articles, 1 RCT reported both an acute and a chronic intervention (Liddle et al. 2019), while the remaining 3 RCTs described only chronic interventions (Chai et al. 2012; Ravn-Haren et al. 2013; Auclair et al. 2010).

In a combined study that included both an acute and a chronic intervention, the effects of whole-apple intake on diverse low-grade inflammation biomarkers other than CRP were assessed (Liddle et al. 2019). For the acute intervention, 200 g of Gala apples were given in a postprandial study to 26 overweight or obese adults (Liddle et al. 2019). The results showed that acute apple consumption significantly decreased fasting unstimulated interleukin (IL)-1β, granulo-cyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein (MIP)-1β, and tumor necrosis factor α (TNF-α; $p < 0.05$) (Liddle et al. 2019). Furthermore, the acute whole-apple intake produced significant reductions in the IL-6 and TNF-α inflammatory cytokines that were secreted from postprandial peripheral blood mononuclear cells (PBMC) isolated from whole blood and stimulated with 10 ng/mL lipopolysaccharide (LPS) for 24 h ($p < 0.05$) (Liddle et al. 2019). In the chronic intervention, 46 overweight or obese adults were randomly assigned to either Group 1 (the control group) or to Group 2, in which the volunteers consumed 3 whole Gala apples per day ($\sim$200 g) for a 6-week intervention period (Liddle et al. 2019). The results demonstrated, a significant decrease in the fasting unstimulated IL-6 and the LPS-stimulated IL-6, interferon-γ, and TNF-α, as well as plasma IL-6 in the intervention group, Group 2 (Liddle et al. 2019).

CRP, one of the traditional inflammation biomarkers, was assessed in one RCT in which 160 postmenopausal women (50–61 years old) who were recruited in the United States from 2007 to 2009 were randomly assigned into one of two groups. Group 1 was assigned to consume 75 g/day of a nondescribed variety of whole dried apples whereas in Group 2, the volunteers consumed 100 g/day of dried plums (Chai et al. 2012). To assess the effects of the whole-apple intake on various cardiovascular risk factors, blood samples were analyzed at 0, 3, 6, and 12 months. Compared to the baseline, Group 1 showed noticeable decreases in the serum CRP concentration levels of 22% and 32%, after 6 and 12 months of intervention respectively ($p < 0.05$) (Chai et al. 2012).

However, CRP was also evaluated in the study conducted by Ravn-Haren et al. that has already been described in this article's section "Lipid profile". Lipid Profile section (Ravn-Haren et al. 2013). The results showed that consuming 550 g/day of fresh whole Shampion apples caused no significant reductions in serum high-sensitive CRP when compared to the control group after 4 weeks of intervention (Ravn-Haren et al. 2013). Similarly, another study reported negative results for the effects of whole-apple intake on CRP. In the crossover RCT conducted by Auclair et al., also described in this review's section "Lipid profile". Lipid Profile section (Auclair et al. 2010), the intake of 40 g of lyophilized MD apple, equivalent to two fresh whole apples,

had no significant effect on CRP after 4 weeks of intervention, neither when compared with the control group nor when compared with the baseline values (Auclair et al. 2010).

Blood pressure and endothelial function

High blood pressure and endothelial function are considered to be modifiable risk factors for CVD (James 2017; Ettehad et al. 2016). High blood pressure is one of the most studied parameters implicated in the development of CVD. For every reduction of 10 mmHg in systolic blood pressure, there is an associated 20% (RR 0.80; CI 95% 0.77–0.83) reduction in CVD events (Ettehad et al. 2016). Moreover, endothelial function also plays a key role in all stages of atherosclerosis (Gimbrone and García-Cardeña 2016; Matsuzawa et al. 2015). Hence, endothelial function is now considered to be one of the earliest predictors of CVD and has been proposed as an independent CVD risk factor due to its profound association with cardiovascular pathologies (Gimbrone and García-Cardeña 2016; Matsuzawa et al. 2015; Daiber et al. 2017). Furthermore, high values of pulse pressure (PP), defined as the difference between the systolic and the diastolic blood pressures (Homan and Cichowski 2019) are associated with a significant risk for the development of CVD (Homan and Cichowski 2019).

In the present narrative review, 4 RTs were included that addressed the effects of whole-apple intake on the blood pressure or PP and endothelial function (Bondonno et al. 2012; Auclair et al. 2010; Bondonno et al. 2018; Ravn-Haren et al. 2013). Of the 4 included RTs, 1 RCT showed a significant reduction in blood pressure and PP (Bondonno et al. 2012) whereas 2 RCTs reported a significant increase in endothelial function (Bondonno et al. 2012; Bondonno et al. 2018).

In a crossover acute RCT performed on 30 healthy men and women aged between 33 and 70 years old, the researchers assessed the acute effects of whole apple's flavonoid intake on blood pressure and flow-mediated dilatation (FMD) of the brachial artery as primary outcomes and assessed the nitrosylated species (RXNO) and nitric oxide (NO) concentrations as secondary outcomes (Bondonno et al. 2012). For these purposes, the participants were randomly assigned into one of the following intervention groups: Group 1 consumed 120 g of Cripps Pink (CP) apple flesh as a control; Group 2 consumed 120 g of CP apple flesh + 80 g of CP apple skin; Group 3 was asked to consume 200 g of spinach; and Group 4 consumed 120 g of CP apple flesh + 80 g of CP apple skin + 200 g of spinach (Bondonno et al. 2012). The results showed that the acute intake of Group 2 significantly reduced the systolic blood pressure (SBP) mean values by 3.3 mmHg [95% CI, 4.6, 1.8 ($p < 0.001$)] and showed a nonsignificant tendency to lower diastolic blood pressure (DBP) values when compared to Group 1, the control group (C. P. Bondonno et al. 2012). Moreover, in Group 2, the PP values also decreased by 1.9 mmHg [95% CI, 3.2, 0.3 ($p = 0.02$)], and there was a significant increase in brachial artery FMD of 1.1% [95% CI,

0.7, 1.5 ($p < 0.0001$)] compared to the control Group 1 (Bondonno et al. 2012).

Additionally, another study consisted of both an acute 12 h intervention and a chronic crossover study comprising two four-week intervention periods plus a two-week wash-out period (Bondonno et al. 2018). To assess the effects of whole-apple intake on endothelial function, 30 men and women aged between 47 and 70 years old were randomly assigned to one of two groups. Group 1, was assigned to eat only the flesh of 2 CP apples/day (as a control), while Group 2 was assigned to eat 2 whole CP apples/day plus the skin of a second CP apple blended with water (Bondonno et al. 2018). As a result, for the acute intervention, Group 2 improved the brachial artery FMD by 1% [95% CI; 0.8, 1.3 ($p < 0.001$)] 1 h after the intervention and by 0.8% [95% CI; 0.6, 0.9 ($p < 0.001$)] 2 h after the intervention (N. P. Bondonno et al. 2018). Furthermore, as a result of the chronic intervention, Group 2 significantly improved the brachial artery FMD by 0.5% [95% CI; 0.4, 0.7 ($p < 0.001$)] after 4 weeks of intervention compared to the baseline values (Bondonno et al. 2018). However, despite the positive effects of the acute or chronic intake of whole-apples on brachial artery FMD (Group 2), there were no significant differences in the SBP nor in DBP between groups at the end of either the acute and the chronic interventions (Bondonno et al. 2018).

However, two trials did not report positive effects regarding whole-apple intake and vascular health or endothelial function (Ravn-Haren et al. 2013; Auclair et al. 2010). In the first study, a double-blinded crossover chronic RT performed by Auclair et al. and already described in section "Lipid profile". Lipid Profile section (Auclair et al. 2010), it was reported that for hypercholesterolemic males, neither consuming 40 g/day of a polyphenol-rich apple nor consuming 40 g/day of a polyphenol-poor apple caused any significant differences between the two groups in brachial artery FMD, SBP, DBP or PP or in comparisons against their respective baselines (Auclair et al. 2010). Moreover, in the final study, another crossover chronic RCT that has also been described in this paper's section "Lipid profile". Lipid Section (Ravn-Haren et al. 2013), it was reported that consuming 550 g/day of whole-fresh Shampion apple showed no significant differences in either SBP and DBP compared to those of the control group at the end of the intervention (Ravn-Haren et al. 2013).

Final remarks

The analysis of the observational evidence provided by these studies demonstrated that the intake of at least 1 whole-apple/day ($\approx$100 g/day) is significantly associated with a reduction in the all-cause mortality risk by 14% (Hodgson et al. 2016), the stroke mortality risk by 27% (Mink et al. 2007), the ischemic heart disease mortality risk by 25% (Knekt et al. 2002), the CHD mortality risk by 26% (Mink et al. 2007), the CVD mortality risk by 25% (Mink et al. 2007), the hypertension risk by 9% (Borgi et al. 2016), the thrombotic stroke event risk by 25% (Knekt et al. 2002), and

the risk of severe abdominal aortic calcification by 24% (Bondonno et al. 2016). Moreover, whole-apple consumption is associated with a 37% reduction in the risk of high serum CRP concentrations ($\geq$3.0 mg/L) (Chun et al. 2008). Furthermore, the whole-apple intake effects tested in RTs showed an overall hypocholesterolemic effect. In particular, intake of the whole ANN variety apples reduced TC by 8.4% and LDLc by 14.7%, while increasing HDLc by 15.2%, whereas the GS, F, RD, and GD apple varieties (listed from higher to lower efficacy) were able to reduce TC and LDLc to various degrees (Tenore et al. 2017). These results suggest that at least some of the noted beneficial effects of whole apples are not primarily driven by a matrix effect as much as they are by its phenolic content. Moreover, eating 200 g/day of Gala apples for at least 6 weeks significantly decreases the production of various pro-inflammatory cytokines such as the fasting unstimulated IL-6, as well as the LPS-stimulated IL-6, INF-γ, and TNF-α in PMBCs. Additionally, the intake of 75 g/day of whole apples for 12 months noticeably reduced the inflammatory status by decreasing the CRP serum levels by 32% (Chai et al. 2012). Likewise, whole-apple intake caused a reduction of 3.3 mmHg in SBP and a reduction of 1.9 mmHg in PP (Bondonno et al. 2012), while improving the endothelial function in 1.1% as assessed using brachial artery FMD (Bondonno et al. 2012; Bondonno et al. 2018). A summary of the beneficial risk associations and effects of whole-apple consumption as shown by the OSs and RTs are displayed in Figure 1.

Additionally, most of the articles included in the present work described neither the geographical origin nor the nutritional composition of the apples used. In particular, the geographical origin of most of the apple varieties included in the present review was diverse (ANN, Italy; RD, Peru/Iowa; GS, Australia; GD, United States; F, Japan; Shampion, Czech Republic; Gala, New Zealand; CP, Australia) and was not available in all cases from the original authors. The geographical origin of apples seems to be of paramount importance when analyzing their health properties, since conditions such as the weather, the harvest season, and the type of soil significantly change the apple's nutritional composition (i.e., phenolic content or their mineral, fiber and vitamin content) (Wang et al. 2018; Kalinowska et al. 2014; Stirpe et al. 2017), which affect the various health effects on CVD. Furthermore, quality labels such as the "Protected Geographical Indication" product, given to ANN apples, ensures a specific nutritional composition linked to their geographical origin, which guarantees a standardized apple and the positive cardiovascular effects associated with their consumption.

Therefore, the common English-language proverb of Welsh origin "one apple a day keeps the doctor away," is currently being scientifically demonstrated in the context of the prevention of CVD.

Future considerations

The authors of the present narrative review consider that performing RCTs to explore the properties of foods

consumed as a whole and not only their extracts is of paramount importance for both the scientific community and general society to increase the applicability and quality of the evidence-based clinical recommendations for a healthy lifestyle, not only for disease prevention but also for individuals suffering from diverse metabolic pathologies. Moreover, we argue that the generalization of the conclusions acquired from clinical trials that use apple extracts to infer part of the properties of whole-foods can only provide researchers with partial information of their effects, due to the frequently unaccounted properties of the food matrix, which is known for its capacity to modify the bioavailability of phenols and other compounds among other possible variables (Gleize et al. 2016; Cusack, Fernandez, and Volek 2013). Additionally, our group contends that the combination of the causal evidence acquired from RCTs along with the associations obtained from OSs is the most appropriate way to determine the properties of chronic intake of whole apples and other whole foods.

Conclusion

The regular consumption of 100–150 g/day of whole apples, corresponding to one regular fresh apple, can be considered a positive action for the prevention of CVD and CVD mortality. Additionally, whole-apple intake improves different CVD risk factors through the reduction of blood pressure, PP, TC, LDLc, and inflammation status, while increasing HDLc and improving the endothelial function. This information supports regular whole-apple consumption as an effective tool in the management of CVD.

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The authors have declared no conflicts of interest. Complete Declaration of Interest forms for each author has been uploaded at the time of manuscript submission.

Author's Contributions

Study conception and design: B.A.S-R., Ú.C., L.C., J.C., L.P., and R.S.
Acquisition of data: B.A.S-R., and Ú.C.
Analysis and interpretation of data: B.A.S-R., Ú.C., and R.S.
Drafting of the manuscript: B.A.S-R, and Ú.C.
Critical revision: Ú.C., M-P.R., I.L., and R.S.

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