Effects of fruit and vegetable consumption on inflammatory biomarkers and immune cell populations: a systematic literature review and meta-analysis

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ABSTRACT

Background: Inflammation is associated with an increased risk of a range of chronic diseases. A diet high in fruit and vegetables may help to reduce inflammation, as fruit and vegetables are rich sources of antioxidants and other biologically active substances, which may improve immune function.

Objective: To summarize the evidence, we executed a systematic review and meta-analysis examining the effects of fruit and/or vegetable intake on inflammatory biomarkers and immune cells in humans with different diseases and conditions.

Design: Electronic databases including PubMed, Cochrane, CINAHL, and EMBASE were systematically searched up to March 2018.

Results: Eighty-three studies were included. Of these, 71 (86%) were clinical trials, and 12 were observational studies ($n = 10$ cross-sectional and $n = 2$ cohort). Amongst the observational research, $n = 10$ studies found an inverse association between intakes of fruit or vegetables and inflammatory biomarkers. Similarly, the majority of the intervention studies (68%, $n = 48$) reported beneficial effects of fruit or vegetable intake on $\geq$1 biomarker of systemic or airway inflammation. A meta-analysis of included studies showed that fruit or vegetable intake decreased circulating levels of C-reactive protein and tumor necrosis factor-α ($P < 0.05$) and increased the $\gamma\delta$-T cell population ($P < 0.05$).

Conclusions: In conclusion, this review suggests that higher intakes of fruit and vegetables lead to both a reduction in proinflammatory mediators and an enhanced immune cell profile. *Am J Clin Nutr* 2018;108:136–155.

Keywords: fruits, vegetables, antioxidants, inflammation, immunity

INTRODUCTION

The relation between oxidative stress, inflammation, and the risk of a wide range of chronic health conditions has been frequently described in the literature (1–3). Inflammation is essential for protecting the body against insult and injury. However, when inflammation becomes persistent, the mediators produced by activated immune cells can lead to tissue damage and development of disease (3). A chronic inflammatory state is characterized by increased levels of circulating inflammatory biomarkers such as C-reactive protein (CRP), TNF-α, and IL-6 (4). Therapeutic strategies that target reducing inflammation have the potential to dramatically reduce the burden of many chronic diseases.

Sufficient fruit and vegetable (F&V) intake is one of the cornerstones of a healthy diet, and may provide protection against cardiovascular disease (CVD), several cancers, and other chronic diseases (5). F&Vs are rich dietary sources of various immune-protective substances such as fiber, folate, vitamins, as well as non-nutrient phytochemicals, including carotenoids and flavonoids, such as β-carotene, anthocyanins, flavanols, and flavanones (6). These substances can have profound effects on cellular growth and differentiation, and are needed for the optimal functioning of the immune system (7).

Various studies have reported that a high F&V consumption can decrease systemic inflammation (3). Some studies have examined the effect of F&V interventions on immune cell populations. Increased natural killer cell (NK cell) cytotoxicity and lymphocyte proliferation have been reported following consumption of different F&V juices (8–10). In addition, some epidemiologic studies have also reported that F&V intake is inversely associ-

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Abbreviations used: CRP, C-reactive protein; CVD, cardiovascular disease; F&V, fruit and vegetable; GPR, G protein-coupled receptor; hsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemotactic protein-1; MD, mean difference; NK cell, natural killer cell; PBMC, peripheral blood mononuclear cell; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular adhesion molecule-1; VCAM-1, vascular adhesion molecule-1; WBC, white blood cell count.

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1. fruit* OR vegetable* OR fruit and vegetable OR Mediterranean diet OR melon OR citrus OR tomato OR apple OR grapes OR kiwifruit OR banana OR broccoli OR strawberries OR spinach OR lettuce OR carrots OR pumpkin OR berries OR cherries OR mango OR barberry OR pomegranate OR apricot OR watermelon OR pomegranate OR passion fruit
2. inflammation OR inflammatory marker OR inflammation mediator OR CRP OR c reactive protein OR fibrinogen OR acute phase protein OR IL-* OR interleukin OR IL-6 OR tumour necrosis factor OR tumour necrosis factor OR TNF-α OR E-selectin OR serum amyloid A OR ICAM-1 OR intercellular adhesion molecule OR VCAM-1 OR vascular cell adhesion protein 1 OR exhaled nitric oxide OR eNO OR feNO OR interferon OR IFN OR IFN-α OR IFN-γ OR immune OR immunity OR leukocytes OR white blood cells OR macrophages OR neutrophils OR dendritic cells OR innate lymphoid cells OR mast cells OR eosinophils, basophils OR natural killer cells OR lymphocyte OR T cells OR B cells OR T helper OR T cell OR B cells OR T regulatory cell OR T helper cells OR antigen presenting cells
3. 1 AND 2
4. Filters: human

FIGURE 1 Example of search strategy with the use of PubMed for studies investigating the effect of fruit and/or vegetable on inflammatory biomarkers and immune cell population in humans. CRP, C-reactive protein; eNO, exhaled nitrico oxide; ICAM-1, intercellular adhesion molecule; IFN, interferon; VCAM-1, vascular cell adhesion protein 1.

ated with proinflammatory biomarkers, such as CRP (1, 11, 12) and TNF-α (13). However, there is heterogeneity in the literature and not all studies have reported beneficial effects (14, 15).

Although previous meta-analyses have assessed the relation between F&V intake and risk of CVD (16) or other chronic diseases such as type 2 diabetes (17), to our knowledge, there is no comprehensive study that reviews the effects of F&V intake on inflammation and immune cell populations. Hence, the aim of this systematic literature review and meta-analysis is to evaluate the association between F&V consumption and inflammation and immunity. We specifically aimed to identify and examine the available evidence for the effects of F&V intake on inflammatory biomarkers and immune cell populations in humans.

METHODS

Search strategy

A systematic search of relevant papers published before March 2017 was performed with the use of PubMed, Cochrane, CINAHL, and EMBASE with the keyword search term only (inclusion and exclusion criteria were not considered in the search strategy). Studies were limited to humans with no time restriction. In addition, the reference lists of retrieved articles and relevant systematic reviews were searched to identify other relevant studies. See **Figure 1** for an example of the search strategy used. The search was conducted again in March 2018 to ensure that any relevant articles published after the initial search were identified. The Medical Subject Headings search terms included: fruit, fruit extract, vegetable, vegetable products, fruit and vegetable juices, inflammatory markers, IL, CRP, TNF-α, IL-6, immune cells, T cells, NK cells, B cells, dendritic cells, lymphocytes, and antigen-presenting cells.

Study selection

This systematic review considered only original studies with the following designs: randomized controlled trials, cohort studies, case-control studies, before and after studies, and cross-sectional studies. Animal models, in-vitro studies, systematic reviews, narrative reviews, opinion papers, case studies, case reports, and conference abstracts were excluded. Review articles were collected for the purposes of reviewing the reference lists and did not contribute to the final number of included studies.

TABLE 1
Methodologic quality rating of each study as determined by the judgments of the authors[1]

First author (year)	Q1[2]	Q2[3]	Q3[4]	Q4[5]	Q5[6]	Q6[7]	Q7[8]	Q8[9]	Q9[10]	Q10[11]	QA
Amagase (2009) (25)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Pos
Vidal (2012) (52)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Guo (2014) (37)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Karlsen (2010) (39)	Y	Y	Y	Y	N	Y	Y	Y	Y	UC	Pos
Kolehmainen (2012) (41)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Larmo (2008) (43)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
McAnulty (2011) (45)	Y	Y	N	N	N	Y	Y	Y	Y	UC	Neu
Riso (2013) (47)	Y	N	Y	Y	NA	Y	Y	Y	Y	Y	Neu
Basu (2014) (28)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Xie (2017) (55)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Nilsson (2017) (58)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Duffey (2015) (59)	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Pos
Hosseini (2016) (2)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Asgary (2013) (26)	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Neu
Davidson (2009) (33)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Shema-Didi (2012) (49)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Sohrab (2014) (50)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Han (2016) (38)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Pos
Tomé-Carneiro (2012) (51)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Castilla (2006) (31)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Zunino (2014) (54)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Barona (2012) (27)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Bell (2014) (29)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Kelley (2013) (40)	Y	N	N	Y	NA	Y	Y	Y	Y	UC	Neu
Kent (2017) (56)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Buscemi (2012) (30)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Dalgard (2009) (32)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Pos
Sanchez-Moreno (2003) (48)	Y	Y	N	N	NA	Y	Y	Y	Y	UC	Neu
Deopurkar (2010) (34)	Y	UC	Y	NA	NA	N	Y	Y	Y	Y	Neu
Gammon (2014) (36)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Hunter (2012) (53)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Dow (2013) (35)	Y	Y	Y	N	N	Y	Y	Y	Y	UC	Neu
Leelarungrayub (2016) (44)	Y	Y	N	Y	N	Y	Y	Y	Y	UC	Neu
Kanellos (2017) (57)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Nishizawa (2011) (46)	Y	N	Y	N	Y	Y	Y	Y	Y	N	Neu
Kuntz (2014) (42)	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Neu
Bub (2003) (8)	Y	N	Y	N	N	Y	Y	Y	Y	UC	Neu
Ghavipour (2013) (4)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Watzl (2003) (9)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Neu
Watzl (1999) (10)	Y	N	N	Y	N	Y	Y	Y	Y	UC	Neu
Briviba (2004) (14)	Y	N	Y	Y	Y	Y	Y	Y	Y	UC	Neu
Watzl (2000) (15)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Aalami-Harandi (2015) (60)	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Pos
Riso (2014) (61)	Y	N	Y	Y	NA	Y	Y	Y	Y	UC	Neu
Upritchard (2000) (62)	Y	Y	Y	Y	N	Y	Y	Y	Y	UC	Pos
Inserra (1999) (65)	Y	Y	N	Y	NA	Y	Y	Y	Y	Y	Neu
Jin (2010) (3)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Macready (2014) (6)	Y	Y	Y	Y	N	Y	Y	Y	Y	UC	Pos
Baldrick (2012) (1)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Freese (2004) (11)	Y	Y	Y	NA	N	Y	Y	Y	Y	N	Pos
McCall (2011) (12)	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Pos
Lamprecht (2007) (13)	Y	N	Y	Y	Y	Y	Y	Y	Y	UC	Neu
Bobe (2010) (63)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Hunter (2012) (64)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Knab (2013) (66)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Knab (2014) (67)	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Pos
Lamprecht (2013) (68)	Y	N	Y	Y	Y	Y	Y	Y	Y	UC	Neu
Nadeem (2014) (69)	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Pos
Nantz (2006) (70)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Watzl (2005) (71)	Y	N	Y	NA	Y	Y	Y	Y	Y	UC	Neu
Williams (2017) (72)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Wood (2012) (73)	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Pos
Romieu (2009) (23)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos

(*Continued*)

TABLE 1
(*Continued*)

First author (year)	Q1[2]	Q2[3]	Q3[4]	Q4[5]	Q5[6]	Q6[7]	Q7[8]	Q8[9]	Q9[10]	Q10[11]	QA
Holt (2009) (20)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Hermsdorff (2010) (74)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Lopez-Garcia (2004) (75)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Root (2012) (76)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Wannamethee (2006) (77)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Almeida-de-souza (2017) (22)	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Pos
Rowe (2011) (80)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Kontiokari (2005) (24)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Zunino (2013) (81)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
McAnulty (2014) (78)	Y	Y	Y	N	N	Y	Y	Y	Y	UC	Pos
Nantz (2013) (79)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Bohn (2010) (82)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Nantz (2012) (84)	Y	Y	Y	Y	Y	Y	Y	Y	Y	UC	Pos
Murashima (2004) (83)	Y	N	N	Y	N	Y	Y	Y	Y	Y	Neu
Liu (2012) (85)	Y	N	Y	Y	N	Y	Y	Y	Y	UC	Neu
Gibson (2012) (5)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Pos
Winkler (2004) (86)	Y	Y	Y	Y	NA	Y	Y	Y	Y	UC	Pos
Hendricks (2008) (87)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Neu
Nettleton (2010) (88)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos
Kruzich (2004) (21)	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Pos

[1]N, no; NA, not applicable; Neu, neutral; Pos, positive; Q, question; QA, quality assessment; UC, unclear; Y, yes.
[2]Q1: Was the research question clearly stated?
[3]Q2: Was the selection of study subjects/patients free from bias?
[4]Q3: Were study groups comparable?
[5]Q4: Was the method of handling withdrawals described?
[6]Q5: Was blinding used to prevent introduction of bias?
[7]Q6: Were intervention/therapeutic regimens/exposure factor or procedure and any comparisons described in detail? Were intervening factors described?
[8]Q7: Were outcomes clearly defined and the measurements valid and reliable?
[9]Q8: Was the statistical analysis appropriate for the study design and type of outcome indicators?
[10]Q9: Are conclusions supported by results with biases and limitations taken into consideration?
[11]Q10: Is bias due to study's funding or sponsorship unlikely?

The target study population was humans of all ages, genders, or ethnicities, with any health status. The exposure of interest was consumption of whole or extracted fruit or vegetables. The study outcome measures were inflammatory biomarkers such as ILs, CRP, and TNF-α, as well as markers of immune function such as immune cell populations.

Citations from electronic databases were imported into the referencing software Endnote X8. Two reviewers (BH and AS) independently reviewed and evaluated all articles by title and abstract, and thereafter performed independent full-text assessments. A third independent reviewer (BSB) was consulted in cases where reviewers' evaluations were not in agreement.

Study quality

Eligible studies were assessed independently in terms of their methodological quality by 2 reviewers (BH and AS) based on a standardized critical appraisal checklist designed by the American Dietetic Association (18). The tool considered the reliability, validity, and generalizability of the included studies. This tool comprises 4 relevance questions that address the applicability of the study findings to practice and 10 validity questions that address scientific rigor, including risk of bias. Based on the responses to these questions as determined by the reviewers (BH and AS), each study was rated as having negative, positive, or neutral quality. The methodologic quality rating of the included studies is detailed in **Table 1**.

Data extraction and study synthesis

Study details were extracted and recorded into a custom-designed database. Data extracted included title, authors, country, study design, participant characteristics, study factor (e.g., dosage/dietary intake of fruits and vegetables), study duration, main outcome measures, findings including statistical significance, analysis with adjustment for confounding factors, and limitations. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol was followed during data extraction and study synthesis (19).

Statistical methods

A meta-analysis was performed to investigate the effects of F&V intake on inflammatory biomarkers (CRP, TNF-α, and IL-6) and immune cell population percentage ($\alpha\beta$-T cells, $\gamma\delta$-T cells, and NK cells) with Review Manager (RevMan, version 5.3, Nordic Cochrane Centre). Only studies that met the following inclusion criteria were included in the meta-analysis: *1*) F&V intake reported; *2*) the mean and SD, SE, or IQRs were reported; *3*)

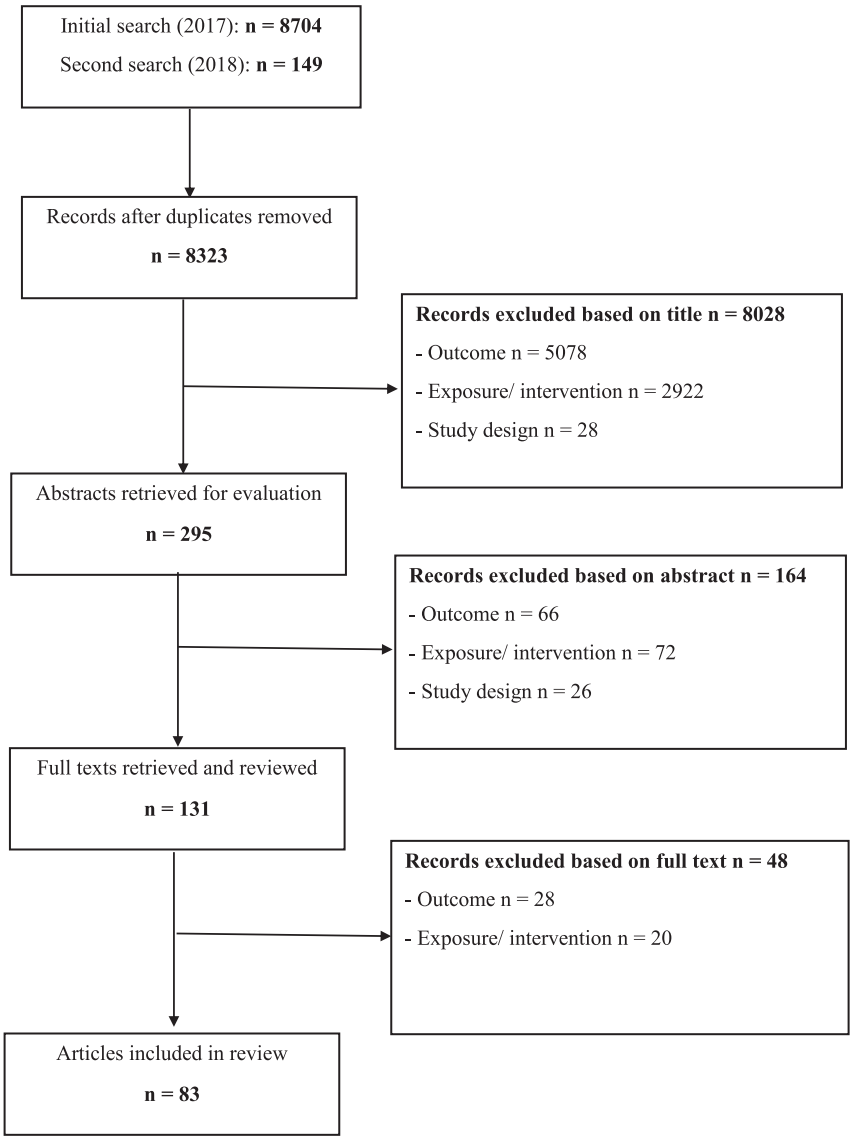

FIGURE 2 Search and inclusion process flowchart of studies for inclusion in a systematic review of the effects of fruit and vegetable intakes on inflammatory biomarkers and immune cell population.

the OR or the relative risks and the corresponding 95% CIs were reported. All reported SEs, 95% CIs, and IQRs were converted to SDs. However, due to the differences in exposure and outcome assessments, meta-analysis of all included studies was not possible. Appreciable heterogeneity was assumed if $I^2 > 50$ and $P < 0.1$. Meta-analysis was performed with the use of fixed-effect modelling if $I^2 < 50$, and random-effect modelling was used if $I^2 > 50$. Included studies used different interventions; thus meta-analysis was performed in studies with similar outcome measurements. The inverse-variance statistical method was used, and the mean difference (MD) and corresponding 95% CIs were calculated.

RESULTS

Search results

A flow chart showing the article retrieval and inclusion process is presented in **Figure 2**. A total of 8853 articles were identified with $n = 530$ duplicates identified and excluded. The titles of the remaining 8323 articles were reviewed with $n = 295$ retrieved for abstract appraisal. Abstracts from 131 articles met the inclusion criteria and full texts were retrieved for the further review. Eighty-three articles met the criteria and were included in this systematic literature review.

Study characteristics

The majority of studies (94%, $n = 78$) were performed in adults (≥18 y of age) with only 3 in adolescents (20–22) and 2 in children (23, 24). In terms of study design, experimental was the most common (86%, $n = 71$), with 10 cross-sectional studies and 2 cohort studies. A total of $n = 5420$ participants were included in clinical trials with a mean intervention period of 85 d, ranging from 6 h to 4 y. Overall, 17,710 participants were included from cross-sectional studies, and 556 individuals with a mean follow-up of 5.22 y from cohort studies. The methodological quality of

TABLE 2
Summary of included studies examining the effects of fruit and vegetable intake on inflammatory biomarkers[1]

First author (year)	Country	Design	Population, *n*	Age, y	Intervention	Effects on inflammatory biomarkers
Amagase (2009) (25)	USA	RCT	Healthy, 60	55–72	120 mL standardized barberry fruit juice (equivalent to ≥150 g fresh fruit) or placebo daily for 30 d	↑ Serum levels of IL-2
Vidal (2012) (52)	China	RCT	Healthy, 150	65–70	Lacto-wolfberry or placebo (13.7 g/d) for 3 mo	↔ Any biomarkers
Guo (2014) (37)	China	RCT	Obesity, 44	18–25	250 mL of either barberry juice or placebo twice daily for 4 wk	↓ Plasma levels of TNF-α, and IL-8
Karlsen (2010) (39)	USA	RCT	At risk of CVD, 62	30–70 y (men) and 45–70 y (women)	330 mL bilberry juice ($n = 31$) or water ($n = 31$) for 4 wk	↓ Plasma concentrations of CRP, IL-6, IL-15, and MIG, ↑ TNF-α, ↔ other biomarkers
Kolehmainen (2012) (41)	Finland	RCT	Metabolic syndrome, 27	BLB: 53 ± 6 CO: 50 ± 7	A diet rich in BLB (400 g fresh BLB) or a control diet for 8 wk	↓ Serum hsCRP, IL-6, IL-12
Larmo (2008) (43)	Finland	RCT	Healthy, 254	19–50	28 g frozen sea buckthorn puree or placebo for 90 d	↓ Serum CRP concentrations
McAnulty (2011) (45)	USA	RCT	Well trained, 25	BB (31.1 ± 12.6) CO (33.4 ± 16.0)	250 g blueberries/d for 6 wk and 375 g given 1 h prior to 2.5 h of running or placebo	↔ Any biomarkers
Riso (2013) (47)	Italy	Crossover RCT	At risk of CVD, 18	47.8 ± 9.7	A WB (25 g freeze-dried powder, providing 375 mg of ACNs) or a placebo drink for 6 wk, spaced by a 6-wk wash-out	↔ Serum levels of IL-6, TNF-α, CRP, sVCAM-1
Basu (2014) (28)	UK	RCT	Abdominal adiposity, 60	49 ± 10	One of the following 4 beverages for 12 wks: *1*) LD-FDS (25 g/d), *2*) LD control, *3*) HD-FDS (50 g/d), and *4*) HD control	↔ Serum levels of hsCRP, sICAM, and sVCAM
Xie (2017) (55)	USA	RCT	Healthy, 49	18–65	500 mg berry extract or placebo for 12 wk	↔ Any biomarkers
Nilsson (2017) (58)	Sweden	Crossover RCT	Healthy, 40	50–70	Berry beverage based on a mixture of berries (150 g blueberries, 50 g blackcurrant, 50 g elderberry, 50 g lingonberries, 50 g strawberry, and 100 g tomatoes) or a control beverage, daily for 5 wk	↔ Plasma IL-6 and IL-18 levels
Duffey (2015) (59)	USA	Cross-sectional	Healthy, 10,334	≥19	Average 404 mL of CJC vs. <404 ml	↓ Serum levels of CRP
Hosseini (2016) (2)	Iran	RCT	Overweight/obese, 42	30–60	1000 mg pomegranate extract, or a placebo, daily for 30 d	↓ Plasma levels of IL-6 and hsCRP
Asgary (2013) (26)	Iran	Experimental	13 hypertensive men	39–68	Natural PJ (150 ml/d) following a 12-h fast	↔ Blood levels of hsCRP, ICAM-1, VCAM-1, E-selectin, and IL-6
Davidson (2009) (33)	USA	RCT	At risk of CHD, 289	45–74	240 ml PJ/d or control beverage for 18 mo	↔ Blood levels of CRP
Shema-Didi (2012) (49)	Israel	RCT	Chronic hemodialysis patients, 101	>18	100 mL PJ, or matching placebo during each dialysis (3/wk) for 1 y	↓ Plasma levels of IL-6, TNF-α
Sohrab (2014) (50)	Iran	RCT	T2DM, 50	40–65	250 mL PJ/d or a control beverage for 12 wk	↓ Plasma CRP and IL-6 levels
Han (2016) (38)	Korea	RCT	Overweight/obese, 76	30–70	Control (starch, 4 g/d, $n = 24$), low-GO [low-dose GO, grape pomace extract (342.5 mg/d) + omija fruit extract (57.5 mg/d), $n = 26$], and high-GO [high-dose GO, grape pomace extract (685 mg/d) + omija fruit extract (115 mg/d), $n = 26$] groups for 10 wk	↓ Plasma IL-1b, and TNF-α levels
Tomé-Carneiro (2012) (51)	Spain	RCT	Undergoing primary prevention of CVD, 75	18–80	A: resveratrol-rich grape supplement (resveratrol 8 mg); B: conventional grape supplement lacking resveratrol; C: placebo (maltodextrin) for the first 6 mo and a double dose for the next 6 mo	A:↓ Plasma hsCRP; B: ↔ any biomarker

(*Continued*)

TABLE 2
(*Continued*)

First author (year)	Country	Design	Population, *n*	Age, y	Intervention	Effects on inflammatory biomarkers
Castilla (2006) (31)	Spain	RCT	Receiving hemodialysis, 38; healthy, 15	30–70	Hemodialytic patients: RGJ (100 mL/d) or control for 14 d. Healthy controls: 100 mL RGJ/d for 14 d	↓ Plasma levels of MCP-1, ↔ VCAM1, ICAM1, and CRP
Zunino (2014) (54)	USA	Crossover RCT	Obesity, 24	20–60	92 g grape powder (~4 servings of grape) or placebo for 9 wk	↔ Plasma levels of CRP
Barona (2012) (27)	USA	RCT	Metabolic syndrome, 24	30–70	46 g lyophilized grape powder (equivalent to 252 g fresh grapes), or placebo for 4 wk	↑ mRNA expression of IL-10, and the inducible iNOS in those individuals without dyslipidemia, ↔ plasma IL-6, IL-8, and TNF-α levels
Bell (2014) (29)	UK	RCT	Trained cyclists, 16	30 ± 8	30 mL MC or placebo, 2 times/d for 7 consecutive days	↓ Plasma levels of IL-6 and hsCRP, ↔ IL-1-β or TNF-α
Kelley (2013) (40)	USA	Before and after	Healthy, 18	45–61	Supplemented the diets with Bing sweet cherries (280 g/d) for 28 d	↓ Plasma levels of CRP, plasminogen activator inhibitor-1, endothelin-1, epidermal growth factor, and IL-18, ↑ IL-1 receptor antagonist
Kent (2017) (56)	Australia	RCT	Mild-to-moderate dementia, 49	>70	200 mL either a cherry juice or control beverage/d for 12 wk	↔ Plasma CRP and IL-6 levels
Buscemi (2012) (30)	Italy	Single-blind crossover study	At risk of CVD, 18; healthy, 12	27–56	2 periods of 7 d each with a 3-d interval, each participant alternatively randomized to receive 500 mL orange juice or placebo	↓ Plasma concentrations of hsCRP, IL-6, and TNF-α
Dalgard (2009) (32)	Denmark	2 × 2 factorial, crossover RCT	Peripheral arterial disease, 48	60.57	Juice + vitamin E, juice + placebo, reference beverage (sugar drink) + vitamin E, reference beverage + placebo for 28 d, separated by a 4-wk wash-out period	↓ Plasma levels of CRP and fibrinogen by 11% and 3%, respectively, ↔ IL-6
Sanchez-Moreno (2003) (48)	Spain	Experimental	Healthy, 12	20–32	500 mL high-pressure orange juice/d for 14 d	↓ Plasma levels of PG E2, ↔ CRP
Deopurkar (2010) (34)	USA	Trial	Healthy, 48	25–47	300-kcal drinks of either glucose, saturated fat as cream, orange juice, or only water to ingest in a fasting state	↔ Expression of TLR-4, NF-kB binding, TNF-α, IL-1β in MNCs and in plasma LPS.
Gammon (2014) (36)	New Zealand	Crossover RCT	Hyper-cholesterol, 85	27–73	4-wk healthy diet run-in, before two 4-wk interventions of 2 green kiwifruit/d plus healthy diet (intervention) or healthy diet alone (control)	↓ Serum CRP and IL-6 concentrations
Hunter (2012) (53)	New Zealand	Crossover RCT	Elderly, 32	≥65	The equivalent of 4 kiwifruit or 2 bananas/d for 4 wk, with treatments separated by a 4-wk washout period	↔ Plasma levels of hsCRP, homocysteine
Dow (2013) (35)	USA	RCT	Overweight/obese, 69; metabolic syndrome, 29	>18	A low bioactive diet plus 1.5 grapefruit/d for 6 wk ($n = 37$, $n = 14$ with MetS) or a control condition in which a low bioactive diet devoid of citrus was consumed ($n = 32$, $n = 15$ with MetS)	↓ Plasma levels of hsCRP, ↔ sVCAM-1
Leelarungrayub (2016) (44)	Thailand	Before and after	Elderly, 29	54–78	A 2-wk control period was followed by 4 wk of 100 g fresh star fruit juice consumption 2 times/d after meals	↓ Blood levels of NO, TNF-α and IL- 23, ↔ IL-2
Kanellos (2017) (57)	Greece	RCT	Healthy, 36	20–40	Raisins equal to 5 fruit servings (90 g/d) or placebo for 4 wk	↔ Plasma CRP and leptin levels
Nishizawa (2011) (46)	Japan	RCT	Runners, 20	20.6 ± 1.25	Twice-daily FRLFE (100 mg/d, or 50 mg/dose) or placebo for 2 mo	↓ Serum level of IL-6, ↔ IL-10
Kuntz (2014) (42)	Germany	Crossover RCT	Healthy, 30	23–27	330 mL beverages (placebo, fruit juice, and fruit smoothie with 8.9 ± 0.3, 983.7 ± 37, and 840.9 ± 10 mg ACN/L, respectively) over 14 d	↔ Any biomarkers
Bub (2003) (8)	Germany	Crossover RCT	Healthy, 27	35 ± 4	2 polyphenol-rich juices [236 mg (A) and 226 mg (B) polyphenols with cyanidin glycosides (A) and epigallocatechin gallate (B)] (330 mL/d) supplemented for 2 wk	↑ IL-2 secretion by activated lymphocytes

(*Continued*)

TABLE 2
(*Continued*)

First author (year)	Country	Design	Population, *n*	Age, y	Intervention	Effects on inflammatory biomarkers
Ghavipour (2013) (4)	Iran	RCT	Overweight/obese, 106	22–24	330 mL of tomato juice or water/d for 20 d	↓ Serum levels of IL-8 and TNF-α
Watzl (2003) (9)	Germany	Crossover RCT	Healthy, 22	28.7 ± 5.9	330 mL of either tomato juice (37.0 mg lycopene) or carrot juice (27.1 mg β-carotene and 13.1 mg α-carotene/d) for 2 wk on a low-carotenoid diet with a 2-wk depletion period after juice intervention	Low-carotenoid diet: ↓ IL-2; juice intervention: ↔ any biomarkers
Watzl (1999) (10)	Germany	Experimental	Healthy, 23	27–40	Weeks 1–2: low-carotenoid period, throughout weeks 3–8: daily consumption of 330 mL tomato juice (40 mg) (weeks 3–4), 330 mL carrot juice (weeks 5–6), 10 g dried spinach powder (weeks 7–8)	Low-carotenoid diet: ↓ IL-2 and IL-4 secretion; tomato juice consumption: ↑IL-2 and IL-4 secretion; carrot juice and spinach powder consumption: ↔ any biomarker
Briviba (2004) (14)	Germany	RCT	Nonsmoker, 30; smoker, 25	30–45	Three tomato oleoresin extract capsules daily (each containing 4.88 mg lycopene, 0.48 mg phytoene, 0.44 mg phytofluene, and 1.181 mg α-tocopherol) or placebo for 2 wk	↔ IL-2 and TNF-α secretion
Watzl (2000) (15)	Germany	RCT	Healthy, 50	63–86	330 mL tomato juice/d (47.1 mg lycopene/d) or mineral water for 8 wk	↔ Secretion of TNF- α, IL-2, and IL-4
Aalami-Harandi (2015) (60)	Iran	RCT	Pregnant women at 27 wk of gestation, 44	18–40	One garlic tablet (equal to 400 mg garlic and 1 mg allicin) ($n = 22$) or placebo ($n = 22$) once daily for 9 wk	↓ Serum levels of hsCRP
Riso (2014) (61)	Italy	Crossover trial	Smokers (>10 cigarettes/d), 17	21.8 ± 2.7	Broccoli diet (250 g/d)/wash-out/control diet vs. control diet/wash-out/broccoli diet. Each analysis was separated by 15 d of wash-out period	↓ Plasma CRP, ↔ TNF-α, IL-6, IL-6sR or adiponectin,
Upritchard (2000) (62)	New Zealand	RCT	T2DM, 57	<75	Tomato juice (500 mL/d), or vitamin E (800 U/d) or vitamin C (500 mg/d) or placebo for 4 wk	↑ Plasma lycopene levels, ↔ CRP, VCAM
Inserra (1999) (65)	USA	Before and after	Elderly, 53	60–86	Fruit juice supplements contained 850 mg fruit powder/capsule made from extracts of apples, oranges, pineapples, papaya, cranberries, and peaches. Vegetable supplements contained 750 mg vegetable powder/capsule and contained extracts of carrots, parsley, beets, broccoli, kale, cabbage, spinach, and tomatoes. Participants consumed extract for 80 d	↑ IL-2 secretion, ↔ TNF-α
Jin (2010) (3)	USA	RCT	Healthy, 117	22–55	Placebo, FV, or FVB capsule for a 60-d period	Both interventions: ↓ MCP-1, MIP-1b, and RANTES
Macready (2014) (6)	UK	RCT	At risk of CVD, 174	26–70	High-flavonoid FV, low-flavonoid FV, or habitual diet, with high- and low-flavonoid FV amounts sequentially increasing by 2, 4, and 6 (+2, +4, and +6) portions/d every 6 wk over habitual intakes	Low-flavonoid FV diet: ↓ CRP, E selectin, and VCAM with 14 portions/d
Baldrick (2012) (1)	UK	RCT	COPD with a habitually low FV intake (≤2 portions FV/d), 81	Low FV: 61.2 ± 8.3; High FV: 63.2 ± 9.1	≥5 portions of FV/d or ≤2 portions FV/d for 12 wk	↔ Any biomarkers
Freese (2004) (11)	Finland	RCT	Healthy, 77	19–52	A 6-wk diet containing either 810 or 196 g of vegetables, berries, and apples/d, and rich either in linoleic acid (11% energy) or oleic acid (12% energy)	↔ Plasma levels of ICAM, and hsCRP

(*Continued*)

TABLE 2
(*Continued*)

First author (year)	Country	Design	Population, *n*	Age, y	Intervention	Effects on inflammatory biomarkers
McCall (2011) (12)	UK	RCT	Hypertensive, 117	40–65	1, 3 or 6 portions of FV/d for 8 wk	↔ Serum levels of hsCRP, sICAM, VCAM
Lamprech (2007) (13)	Austria	RCT	Healthy, 41	34 ± 5	Placebo or JPC capsules for 28 wk	↓ Serum concentrations of CRP and TNF- α
Bobe (2010) (63)	USA	RCT	Colorectal adenoma, 872	52–71	Extensive dietary and behavioral counselling to achieve the PPT dietary goals of 20% of total energy from fat, 18 g/1000 kcal of dietary fiber, and 5–8 daily servings (depending on total caloric intake) of FV; or control (did not receive such counselling and were expected to continue their usual intake) groups for 4 y	↓ Serum IL-6 concentrations
Hunter (2012) (64)	New Zealand	Crossover RCT	Smokers, 42	30–63	Nonsupplemented milk, prototype milk A contained a combination of grape seed extract (0.213 g/serving), apple extract (0.213 g/serving), and tomato concentrate (0.106 g/serving), prototype milk B contained boysenberry juice concentrate (0.285 g/serving) and apple extract (0.285 g/serving) for 6 wk	↔ Any inflammatory biomarkers
Knab (2013) (66)	USA	Cross over RCT	Swimmers, 9	24.6 ± 0.7	Completed 10-d training with or without 16 fl oz of fresh FV juice (230 mg flavonoids) ingested before and afer workout	↔ Any inflammatory biomarkers
Knab (2014) (67)	USA	RCT	Cyclists, 34	In: 35.1 ± 8.0; Pl: 35.5 ± 8.2	A freeze-dried FV juice powder (230 mg flavonoids/d) or placebo for 17 d	↔ Exercise-induced alterations in inflammatory biomarkers (IL-6, IL-8, TNF-α, MCP-1, CRP)
Lamprecht (2013) (68)	Austria	RCT	Obese premenopausal, 42	41 ± 5	FVB capsules that provided 7.5 mg β-carotene, 200 mg vitamin C, 60 mg RRR-α-tocopherol, 600 mg folate and 63 kJ/d or placebo for 8 wk	↓ Serum levels of CRP and TNF-α
Nadeem (2014) (69)	UK	RCT	Hypertensive, 112	40–65	Intervention of 1, 3, or 6 portions of FV/d for 8 wk after a 4-wk washout period (1 serving FV/d)	↓ Serum amyloid A related inflammation, ↔ IL-6, hsCRP, E-selectin
Nadeem (2014) (69)	UK	RCT	Low FV intake (≤2 serving/d), 82	65–85	Intervention of 2 or 5 portions of FV/d for 16 wk	FV: ↓ serum amyloid A related inflammation, ↔ IL-6, hsCRP, E-selectin
Nantz (2006) (70)	US	RCT	Healthy, 59	21–53	FVCJ 4 capsules/d or placebo for 77 d	↓ Serum IFN-γ
Watzl (2005) (71)	Germany	RCT	Low FV intake (≤2 serving/d), 64	31 ± 9	2, 5, or 8 servings/d of carotenoid-rich vegetables and fruit for 4-wk period	8 servings FV/d: ↓ serum CRP
Williams (2017) (72)	Australia	RCT	Overweight/ obesity, 56	≥40	6 capsules of FV juice concentrate or placebo for 8 wk	↓ Plasma TNF-α level
Wood (2012) (73)	Australia	RCT	Asthma, 137	HAD: 54 ± 14; LAD: 58 ± 15	A high-antioxidant diet (5 servings of vegetables and 2 servings of fruit/d, $n = 46$) or a low-antioxidant diet (<2 servings of vegetables and 1 serving of fruit/d, $n = 91$) for 14 d, and then those who consumed the high-antioxidant diet received placebo. Subjects who consumed the low-antioxidant diet received placebo or tomato extract (45 mg lycopene/d). The intervention continued until week 14 or until an exacerbation occurred	Low-antioxidant diet: ↑ plasma CRP at week 14; tomato extract: ↔ airway or systemic inflammation
Romieu (2009) (23)	Mexico	Cohort	Asthmatic children, 158 vs. 50 healthy control followed for an average of 22 wk	6–14	>1/d vs. ≥4 times FV/mo	FVI: ↓ IL-8 levels in nasal lavage
Holt (2009) (20)	US	Cross-sectional	Healthy, 285	13–17	Highest vs. lowest serving/d	↓ Plasma levels of CRP, IL-6, and TNF-α

(*Continued*)

TABLE 2
(*Continued*)

First author (year)	Country	Design	Population, *n*	Age, y	Intervention	Effects on inflammatory biomarkers
Hermsdorff (2010) (74)	Spain	Translational	Healthy, 120	20.8 ± 2.6	Highest vs. lowest tertile	↓ Plasma levels of CRP, homocysteine, ICAM1, IL1-R1, IL-6, TNF-α; ↓ NF-κB1 gene expression in PBMC
Lopez-Garcia (2004) (75)	USA	Cross-sectional	Healthy, 732	43–69	Highest vs. lowest quartile	↓ plasma CRP and E-selectin
Root (2012) (76)	USA	Cross-sectional	Healthy, 1000	18–85	Fruit: ≤2 vs. >2 servings/d; vegetables: ≤3 vs. >3 servings/d	↓ Serum levels of CRP, IL-6, TNF-α
Wannamethee (2006) (77)	UK	Cross-sectional	Healthy, 3258	60–79	<1/wk vs. >7/wk	Fruit intake: ↓ serum CRP levels; vegetable intake: ↔
Almeida-de-souza (2017) (22)	Portugal	Cross-sectional	Healthy, 412	12–18	Highest vs. lowest tertile	Greater variety of vegetable consumption: ↓ serum levels of CRP, IL-6 and overall inflammatory score; fruit variety: ↔

[1]ACN, anthocyanin; BB, blueberries; BLB, bilberries; CHD, coronary heart disease; CJC, cranberry juice cocktail; CO, control; COPD, chronic obstructive pulmonary disease; CRP, C-Reactive Protein; CVD, cardiovascular disease; FDS, freeze-dried strawberries; fl oz, fluid ounce; FRLFE, flavonol-rich lychee fruit extract; FV, fruit and vegetable; FVB, fruit and vegetable juice powder concentrate with added berry powder; FVCJ, fruit and vegetable concentrate juice; FVI, fruit and vegetable index; GO, grape pomace and omijia fruit ethanol extracts; HAD, high antioxidant diet; HD, high dose; hsCRP, high-sensitivity C-reactive protein; ICAM, intracellular adhesion molecule; IFN, interferon; In., intervention; iNOS, isoform of nitric oxide synthase; JPC, juice powder concentrate; LAD, low antioxidant diet; LD, low dose; LPS, lipopolysaccharide; MC, Montmorency cherries; MCP-1, monocyte chemotactic protein-1; MetS, metabolic syndrome; MIG, monokine induced by interferon-gamma MIP-1b, macrophage inflammatory protein 1-b; MNC, monocytes; PBMC, peripheral blood monocyte cell; PG E2, prostaglandin E2; PJ, pomegranate juice; Pl., Placebo; PPT, polyp prevention trial; RANTES, regulated upon activation normal T cell expressed and secreted; RCT, randomized controlled trial; RGJ, red grape juice; sICAM, soluble intracellular adhesion molecule; sVCAM, soluble vascular adhesion molecule; TLR, toll-like receptor; T2DM, type 2 diabetes mellitus; VCAM, vascular adhesiono molecule; WB, wild blueberries; ↑, increase; ↓, decrease; ↔, no effect.

$n = 55$ studies was positive. These studies were methodologically strengthened by their use of random allocation to the intervention and control group or treatment arm (cross over trials), double blinding, and comparability of study group; $n = 28$ studies were neutral. Factors that limited the methodologic quality of the studies rated as neutral included, insufficient detail provided regarding the study inclusion/exclusion criteria, group comparability, intervening factors, and data collection and analysis. No study was excluded due to negative quality.

Effects of fruit and vegetable intake on systemic/airway inflammatory biomarkers

Fruit only

Thirty-six experimental trials (2, 8, 25–58), and one cross-sectional study (59) assessed the association of fruit intake and inflammatory biomarkers and circulating levels of high-sensitivity CRP (hsCRP), TNF-α, IL-6, IL-8, soluble vascular adhesion molecule-1 (sVCAM), soluble intercellular adhesion molecule-1 (sICAM), or E-selectin **(Table 2)**. Fruit intake was reported to have beneficial effects on at least 1 marker of systemic inflammation such as hsCRP or TNF-α in most of the studies (2, 8, 25, 27, 29–32, 35–41, 43–46, 48–51, 59), although some studies (26, 28, 33, 34, 42, 47, 52–58) found no significant effects. The type of fruits investigated varied, and included berries, such as strawberries, blueberries, or barberry ($n = 12$) (25, 28, 37, 39, 41, 43, 45, 47, 52, 55, 58, 59), pomegranate juice (26, 33, 49, 50) or extract (2) ($n = 5$), grape products such as grape extract (38, 51), powder (27, 54) or juice (31), and cherries (29, 40, 56). Other studies examined whether consumption of mixed-fruit juice (8, 42), orange juice (30, 32, 34, 48), kiwifruit (36, 53), grapefruit (35), star fruit (44), raisins (57), or lychee extract (46) beneficially altered circulating levels of hsCRP, TNF-α, IL-6, IL-8, sVCAM, sICAM, or E-selectin.

Amagase et al. (25) examined the effects of daily barberry juice on immune function, and reported that the intervention group had significantly decreased serum levels of IL-2 compared to baseline and the control group, whereas serum concentration of IL-4 was not altered by the treatment. In contrast, a 3-mo trial by Vidal et al. (52) found that there was no difference in CRP, IL-6, or orosomucoid following barberry supplementation compared to placebo. Guo et al. (37) described a 4-wk trial comparing bayberry juice with placebo and reported the intervention group had significantly lower plasma levels of TNF-α and IL-8 compared to placebo. Similarly, 2 studies (39, 41) showed that supplementation with bilberries resulted in decreased CRP and IL-6; however, plasma concentration of TNF-α unexpectedly increased following bilberry intervention in 1 study (39). In another trial by Larmo et al. (43) consumption of frozen sea buckthorn berries for 90 d significantly decreased serum levels of CRP compared to the baseline and placebo. Two studies (45, 47) reported that blueberry intervention did not reduce plasma levels of CRP, IL-6, TNF- α, and sVCAM. One study assessed the effects of strawberries on biomarkers of inflammation, and showed no significant change on blood levels of hsCRP, sICAM, and sVCAM (28). Two studies reported no significant changes in IL-6, CRP, IL-1β, or TNF-α following consumption of berry extract (55) or mixed-berry beverage (58). A cross-sectional study by Duffey et al. (59) reported

TABLE 3
Summary of included studies examining the effects of fruit and vegetable intake on immune function[1]

First author (year)	Country	Study design	Population, *n*	Age, y	Intervention	Effects on immune cells
Rowe (2011) (80)	USA	RCT	Healthy, 85	50–75	360 mL (12 oz) of beverage (100% grape juice or placebo) daily for 9 wk	↑ Numbers of circulating $\gamma\delta$-T, ↔ proliferation of $\gamma\delta$-T cells
Bub (2003) (8)	Germany	Crossover RCT	Nonsmoking, 27	35 ± 4	2 polyphenol-rich juices [236 mg (A) and 226 mg (B) polyphenols with cyanidin glycosides (A) and epigallocatechin gallate (B)] (330 mL/d) supplemented for 2 wk	↑ Lymphocyte proliferative responsiveness, the lytic activity of NK cells
Amagase (2009) (25)	USA	RCT	Healthy, 60	55–72	120 mL standardized barberry fruit juice (equivalent to ≥150 g fresh fruit) or placebo daily for 30 d	↑ Number of lymphocytes, ↔ number of CD4, CD8, and NK cells
McAnulty (2011) (45)	USA	RCT	Well-trained subjects, 25	BB: 31.1 ± 12.6; placebo: 33.4 ± 16.0	250 g blueberries/d for 6 wk and 375 g given 1 h prior to 2.5 h of running or placebo	↑ NK cell counts
Kontiokari (2005) (24)	Finland	RCT	341 children	4.3	Cranberry juice (5 mL/kg) or a placebo for 3 mo	↔ Carriage of respiratory bacteria
Shema-Didi (2012) (49)	Israel	RCT	Chronic hemodialysis patients, 101	>18	100 mL PJ, or matching placebo during each dialysis (3/wk) for 1 y	↓ Infection incidence rate
Nishizawa (2011) (46)	Japan	RCT	Long-distance runners, 20	20.6 ± 1.25	Twice-daily FRLFE (100 mg/d, or 50 mg/dose) or placebo for 2 mo	↔ Neutrophil or lymphocyte counts, total WBC modified
Vidal (2012) (52)	China	RCT	Elderly, 150	65–70	Lacto-wolfberry or placebo (13.7 g/d) for 3 mo	↔ Immune cells composition, autoantibodies levels
Zunino (2014) (54)	USA	Crossover RCT	Obesity, 24	20–60	92 g grape powder (~4 servings of grape) or placebo for 9 wk	↔ Proliferative responses of CD4+ or CD8+ T cells, cytokine production by activated T cells
Zunino (2013) (81)	USA	Crossover RCT	Obesity, 20	20–50	Strawberry powder (~4 servings of frozen strawberries/d) or placebo for 3 wk, and then crossed over to another treatment for the last treatment	↔ Cell counts, the overall percentage of CD4+ and CD8+ cells at 24, 48, and 72 h, cytokine production by T-lymphocyte
Hunter (2012) (53)	New Zealand	Crossover RCT	Elderly, 32	≥65	The equivalent of 4 kiwifruit or 2 bananas/d for 4 wk, with treatments separated by a 4-wk washout period	↔ Innate immune function (NK cell activity, phagocytosis)
McAnulty (2014) (78)	USA	RCT	Healthy, 25	18–50	Blueberry (equivalent to 250 g berries) or placebo daily for 6 wk	↑ Absolute NK cells
Nantz (2013) (79)	USA	RCT	Healthy, 45	21–50	Low-calorie cranberry beverage (450 mL) made with a juice-derived, powdered cranberry fraction ($n = 22$) or a placebo beverage ($n = 23$), daily for 10 wk	↑ Proliferation index of $\gamma\delta$-T cells, ↔ B cells, NK cells, $\alpha\beta$-T cells, and monocytes
Bohn (2010) (82)	Norway	Trial	Healthy smokers, 29	45–75	Antioxidant-rich diet, a kiwifruit diet (3 kiwifruits/d added to the regular diet) or a control group for 8 wk	Upregulation groups of genes involved in regulation of immune cells
Nantz (2012) (84)	USA	RCT	Healthy, 120	21–50	2.56 g garlic extract/d or placebo for 90 d	↑ Proliferation of NK cells, activation state of the NK population, $\gamma\delta$-T cells proliferation
Watzl (2003) (9)	Germany	Crossover RCT	Healthy, 22	28.7 ± 5.9	330 mL/d of either tomato juice (37.0 mg lycopene/d) or carrot juice (27.1 mg β-carotene/d and 13.1 mg α-carotene/d) for 2 wk on a low-carotenoid diet with a 2-wk depletion period after juice intervention	Low-carotenoid diet: ↓ NK cell cytotoxicity, and lymphocyte proliferation; juice intervention: ↔
Watzl (1999) (10)	Germany	Experimental	Healthy, 23	27–40	Weeks 1–2: low-carotenoid period; throughout weeks 3–8: daily consumption of 330 mL tomato juice (40 mg) (weeks 3–4), 330 mL carrot juice (weeks 5–6), 10 g dried spinach powder (weeks 7–8)	Low-carotenoid diet: ↓ proliferation of PBMCs; tomato juice consumption: ↔ lymphocyte proliferation; carrot juice and spinach powder consumption: ↔

(*Continued*)

TABLE 3
(*Continued*)

First author (year)	Country	Study design	Population, *n*	Age, y	Intervention	Effects on immune cells
Briviba (2004) (14)	Germany	RCT	Smoker, 25, nonsmoker, 30	30–45	3 tomato oleoresin extract capsules/d (each containing 4.88 mg lycopene, 0.48 mg phytoene, 0.44 mg phytofluene and 1.181 mg α-tocopherol) or placebo for 2 wk	↔ Lymphocyte proliferation, NK cell activity
Watzl (2000) (15)	Germany	RCT	Elderly, 50	63–86	330 mL tomato juice/d (47.1 mg lycopene/d) or mineral water for 8 wk	↔ Lymphocyte proliferation
Murashima (2004) (83)	Japan	Experimental	Healthy, 12	20–36	Fresh broccoli sprouts (100 g/d) for 1 wk	↔ NK cell activity
Liu (2012) (85)	USA	Self-controlled, longitudinal study	HIV-infected women, 77	≥18	"Every or almost every day" vs. "only as needed"	↔ Any immunologic markers
Inserra (1999) (65)	USA	Before and after	Elderly, 53	60–86 y	Fruit juice supplements contained 850 mg fruit powder/capsule made from extracts of apples, oranges, pineapples, papaya, cranberries, and peaches. Vegetable supplements contained 750 mg vegetable powder/capsule and contained extracts of carrots, parsley, beets, broccoli, kale, cabbage, spinach, and tomatoes. Participants consumed extract for 80 d	↑ Spontaneous proliferation of PBMCs, NK cell cytotoxicity
Gibson (2012) (5)	UK	RCT	Healthy, 83	65–85	≤2 FV portions/d or ≥5 FV portions/d for 16 wk	↑ Antibody binding to pneumococcal capsular LPS (total IgG), ↔ antibody binding to tetanus toxoid
Jin (2010) (3)	USA	RCT	Healthy, 117	22–55	Placebo, FV, or FVB capsule for a 60-d period	↔ WBC counts
Knab (2014) (67)	USA	RCT	Cyclists, 43	In: 35.1 ± 8.0; Pl: 35.5 ± 8.2	A freeze-dried FV juice powder (230 mg flavonoids/d) or placebo for 17 d	↔ Immune function (G-PHAG and M-PHAG)
Nantz (2006) (70)	USA	RCT	Healthy, 59	21–53	FVCJ 4 capsules/d or placebo for 77 d	↑ Number of $\gamma\delta$-T cells
Watzl (2005) (71)	Germany	RCT	Intake of <2 servings FV/d	31 ± 9	2, 5, or 8 servings/d of carotenoid-rich vegetables and fruit for 4-wk period	8 servings FV/d ↔ immunologic markers
Winkler (2004) (86)	Germany	RCT	HIV, 23 vs. healthy controls, 18	20–53	1 L fruit juice (group J) or 30 mL FV concentrate (group C) daily for 16 wk	Fruit juice: ↑ PHA-induced lymphocyte proliferation in HIV+ and in HIV- subject, ↔ the count of CD4+ and CD8+ cells, the CD4+:CD8+ ratio and HIV viral load
Hendricks (2008) (87)	USA	Cohort	HIV, 348	≥18	Highest vs. lowest mean intake	↑ CD4 count
Root (2012) (76)	USA	Cross-sectional	Healthy, 1000	18–85	Fruit: ≤2 vs. >2 servings/d; vegetables: ≤3 vs. >3 servings/d	↓ WBC counts
Nettleton (2010) (88)	USA	Cross-sectional	Healthy, 1101	F: 70.7 ± 5.4; M:71.8 ± 5.5	Highest vs. lowest quartile	↔ Immunologic markers
Kruzich (2004) (21)	USA	Cross-sectional	HIV-infected, 264 and HIV uninfected, 127	13–23	Maximum vs. minimum score	↔ Immunologic markers

[1] BB, blueberries; CD, cluster of differentiation; FRLFE, flavonol-rich lychee fruit extract; FV, fruit and vegetables; FVB, fruit and vegetable juice powder concentrate with added berry powder; FVCJ, fruit and vegetable concentrate juice; G-PHAG, granulocyte phagocytosis and oxidative burst activity; HD, Heart Disease; In., intervention; M-PHAG, monocyte phagocytosis and oxidative burst activity; NK cells, natural killer cells; PBMC, peripheral blood monocyte cell; PHA, phytohemagglutinin; PJ, pomegranate juice; Pl., placebo; RCT, randomized controlled trial; WBC, white blood cell; ↑, increase; ↓, decrease; ↔, no effect.

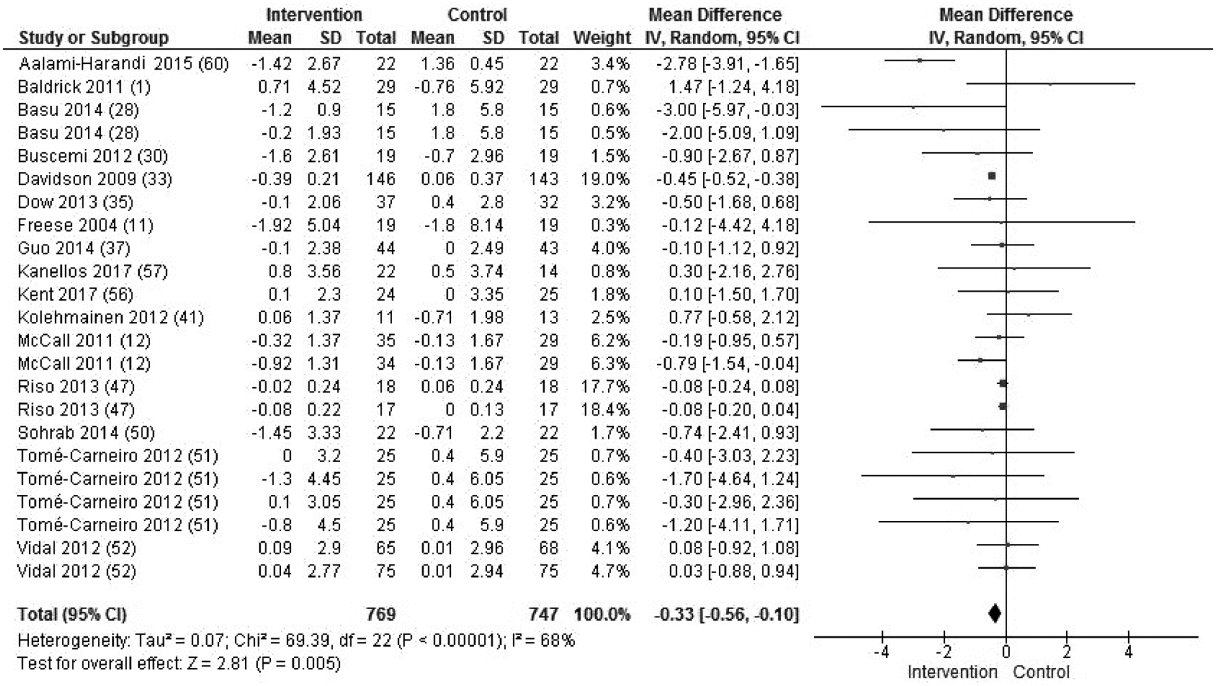

FIGURE 3 Forest plot of randomized controlled trials investigating the effects of fruit and vegetable intake on circulating C-reactive protein levels (milligrams per liter). Values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of $P < 0.10$. IV, inverse variance.

that consumption of cranberry juice was significantly associated with lower CRP levels.

We have previously investigated the effects of pomegranate extract consumption on inflammation (2), and reported that pomegranate extract intervention for 30 d reduced plasma CRP and IL-6. Similarly, consumption of pomegranate juice resulted in reduction of plasma IL-6, TNF-α, and CRP levels in 2 studies (49, 50). However, some studies (26, 33) did not observe any changes in circulating inflammatory biomarkers, such as hsCRP, intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and IL-6, following pomegranate juice consumption. Three studies reported significantly decreased levels of TNF-α (38), CRP (51), or monocyte chemotactic protein-1 (MCP-1) (31) following grape supplement intervention. In contrast, intake of grape powder for 9 wk had no significant effect on blood CRP level (54). In another trial by Barona et al. (27) consumption of grape powder for 4 wk increased expression of inducible nitric oxide synthase (iNOS) and IL-10. However, no significant changes were observed in any inflammatory biomarkers, such as IL-6 and TNF-α.

Interventions to increase cherry consumption reduced circulating levels of IL-6 and hsCRP, compared with control groups in 2 studies (29, 40); however, 1 study reported no significant change in plasma CRP and IL-6 concentrations (56). Four trials examined inflammatory responses following orange juice intake, with 3 showing a protective effect against systemic inflammation (primarily hsCRP, IL-6, or prostaglandin E2) (30, 32, 48). However, Deopurkar et al. (34) found no effect in a similar orange juice intervention trial.

Gammon et al. (36) described a 4-wk trial of 2 green kiwifruit/d plus healthy diet compared with healthy diet, and reported that kiwifruit resulted in a significant reduction in serum levels of CRP and IL-6. In another trial by Hunter et al. (53), no significant difference was observed in the serum level of hsCRP between those who received kiwifruit compared with those who received bananas daily for 4 wk.

Three studies investigated the effects of consumption of grapefruit (35), star fruit (44), or lychee extract (46), and all showed a significant reduction in either hsCRP or TNF-α compared with placebo. No changes in plasma levels of CRP and leptin were reported in a raisin intervention study (57). Two trials assessed the effects of mixed-fruit juice intake on IL-2, IL-6, IL-8, CRP, or TNF-α. One study (42) did not observe any changes, whereas the other (8) reported a significant increase in IL-2 secretion by activated lymphocytes compared with baseline.

Vegetables only

Eight trials (4, 9, 10, 14, 15, 60–62) examined anti-inflammatory responses to increased vegetable intake, with 3 showing a protective effect on inflammation including reduced hsCRP, TNF-α, and IL-6 (4, 60, 61) (Table 2). In a 9-wk trial (60), intake of garlic supplements decreased serum levels of CRP compared to placebo. In another trial (14), no change in TNF-α was observed following a low-carotenoid diet supplemented with a tomato extract for 2 wk. Daily consumption of tomato juice also had no significant effect on CRP, IL-2, IL-4, and TNF-α (9, 10, 15, 62). In contrast with these findings, we previously showed that supplementation with tomato juice for 20 d resulted in a significant reduction in serum concentrations of IL-8 and TNF-α compared to placebo and baseline (4). In another study (61), 10-d broccoli consumption significantly decreased plasma CRP levels.

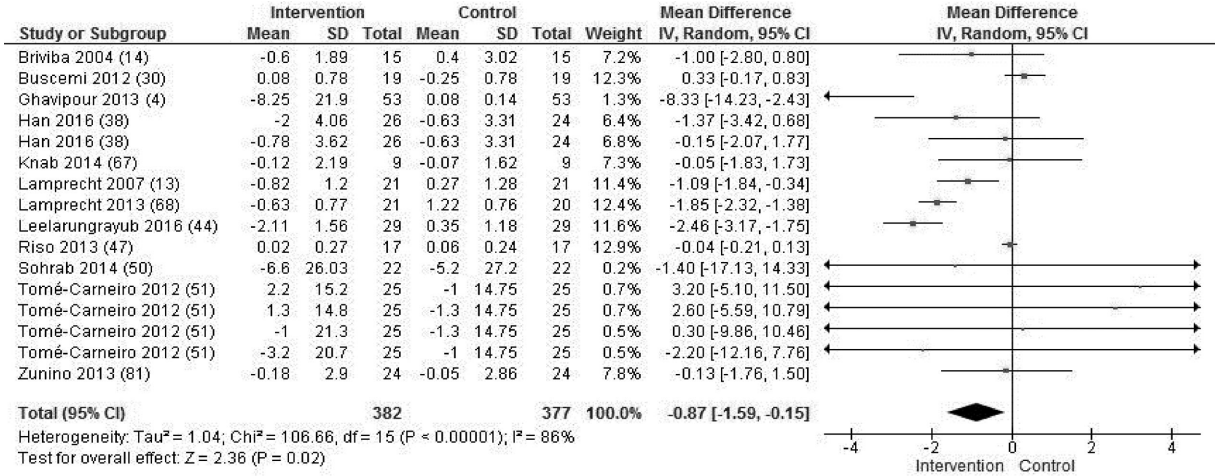

FIGURE 4 Forest plot of randomized controlled trials investigating the effects of fruit and vegetable intake on circulating TNF-α (pg/mL). Values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of $P < 0.10$. IV, inverse variance.

Fruit and vegetables

Twenty-five studies, including 17 experimental trials (1, 3, 6, 11–13, 63–73), 1 cohort (23) and 6 cross-sectional studies (20, 22, 74–77), assessed the effects of F&V intake on systemic or airway inflammation (Table 2). One cohort (23) and 5 cross-sectional studies (20, 22, 74–76) reported that F&V intake was inversely associated with circulating levels of inflammatory cytokines, such as CRP, IL-6, and TNF-α. Wannamethee et al. (77) reported that fruit intake was significantly associated with lower plasma CRP levels, though vegetable intake was not. The majority of experimental trials (3, 6, 13, 63, 65, 68–73) (66%, $n = 11$) reported a significant reduction in systemic inflammation as indicated by inflammatory biomarkers including hsCRP, TNF-α, IL-6, and E-selectin following F&V consumption, whereas 6 trials (1, 11, 12, 64, 66, 67) found no effect of F&V intake on systemic or airway inflammation.

Studies on the effects of F&V intake on immune cell populations

Fruit only

Twelve experimental trials (8, 25, 45, 46, 52–54, 78–82) examined the effects of fruit intake on immune cell function, and

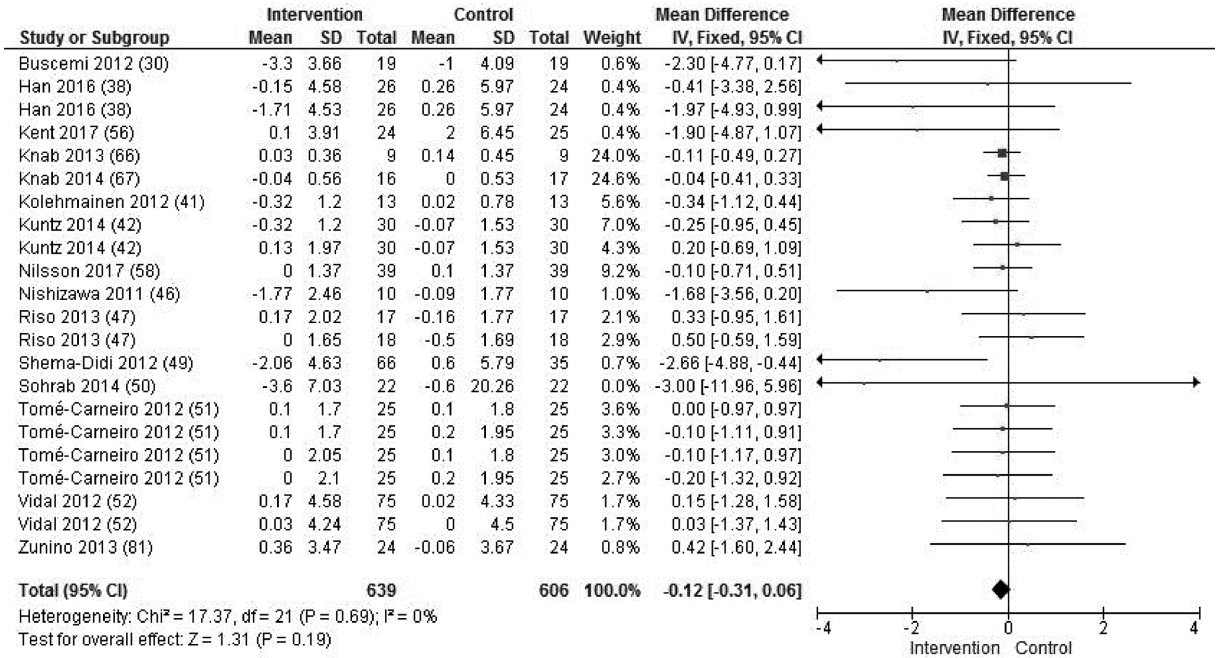

FIGURE 5 Forest plot of randomized controlled trials investigating the effects of fruit and vegetable intake on circulating IL-6 (pg/ml). Values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of $P < 0.10$. IV, inverse variance.

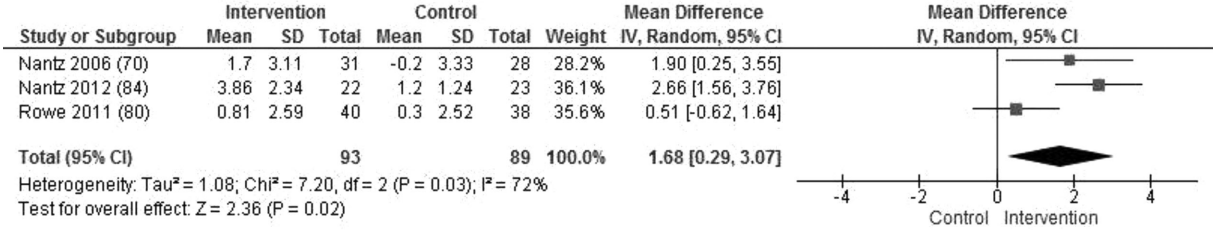

FIGURE 6 Forest plot of randomized controlled trials investigating the effects of fruit and vegetable intake on $\gamma\delta$-T cell population percentage. Values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of $P < 0.10$. IV, inverse variance.

1 study (24) assessed whether fruit intake can beneficially affect respiratory bacterial flora **(Table 3)**. Nine studies (8, 45, 46, 54, 78–82) reported that fruit consumption induced beneficial alterations in immune cell function, whereas some studies (24, 25, 52, 53) found no effect (on immune cell populations). More than 50% of studies ($n = 7$) (24, 25, 45, 52, 78, 79, 81) examined the effects of different kind of berries, mostly cranberries and blueberries, on immune cell function. Other studies tested the hypothesis that consumption of grapes (54, 80), kiwifruit (53, 82), lychee extract (46), or mixed-fruit juice (8) can modify immune function.

Two studies (45, 78) found that intake of blueberries increased the NK cell population. In another trial by Nantz et al. (79) intake of a low-calorie cranberry beverage increased the proliferation index of $\gamma\delta$-T cells. In agreement with these findings, Bub et al. (8) found that fruit juice consumption significantly increased lymphocyte proliferative responses as well as the lytic activity of NK cells. In another study (81), consumption of strawberries for 3 wk was found to increase the production of TNF-α by the monocyte population after stimulation with LPS, which may improve the effectiveness of an immune response to invading pathogens. In contrast, 3 studies examining consumption of either barberries (25), goji berries (52), or kiwifruit (53) found no significant effect on immune cell proliferation. Similarly, consumption of lychee extract (46) for 2 mo did not change proliferation of neutrophils or lymphocytes; however, total white blood cell counts were modified. Increased numbers of circulating $\gamma\delta$-T cells were reported following grape juice consumption for 9 wk (80). In contrast, in another trial (54) consumption of grape powder for 9 wk did not affect the immune cell population; however, a significant increase in the production of IL-6 and IL-1β was reported in LPS-activated monocytes.

In terms of other effects on immunity, adding kiwifruits daily to a regular diet resulted in upregulation of 11 genes involved in immune-related processes compared to baseline and control (82). Also, composition of respiratory bacteria was not altered after cranberry juice intake for 3 mo (24).

Vegetables only

Seven studies (9, 10, 14, 15, 83–85) examined immune cell populations following vegetable intake, with $n = 3$ showing modulation of immune cell function (9, 10, 84) (Table 3). In a 3-mo trial (84), intake of garlic supplements increased proliferation of NK cells and $\gamma\delta$-T cells compared to placebo, whereas garlic had no effect on immune cells in another supplementation study (85). Watzl et al. (10) found that carotenoid depletion decreased proliferation of peripheral blood mononuclear cells (PBMCs). In one study (9), supplementation with tomato juice increased lytic activity of NK cells, although no effects were seen in other studies investigating tomato extract (14) and tomato juice (15). In addition, no beneficial effect was observed on immune cell function following consumption of broccoli (83).

Fruit and vegetables

Twelve studies, including 8 experimental trials (3, 5, 65, 67, 70, 71, 82, 86), 1 cohort (87) and 3 cross-sectional studies (21, 76, 88), assessed the effects of F&V intake on immune cells (Table 3). More than 60% of studies ($n = 7$) showed a beneficial association of F&V consumption and function of immune cells (5, 65, 70, 76, 82, 86, 87). Bøhn et al. (82) reported upregulation of genes involved in the immune-related processes following consumption of a high antioxidant diet (>5 servings of F&V/d) compared to baseline and a control group. In 3 studies (65, 70, 86), increased proliferation of lymphocytes were observed in the group supplemented with F&V extract compared to placebo. Similarly, a prospective study (87) of 348 HIV-positive adults reported that F&V intake was correlated with number

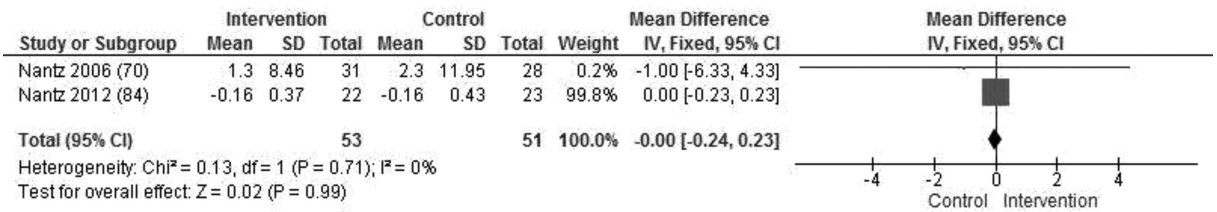

FIGURE 7 Forest plot of randomized controlled trials investigating the effects of fruit and vegetable intake on $\alpha\beta$-T cell population percentage. Values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of $P < 0.10$. IV, inverse variance.

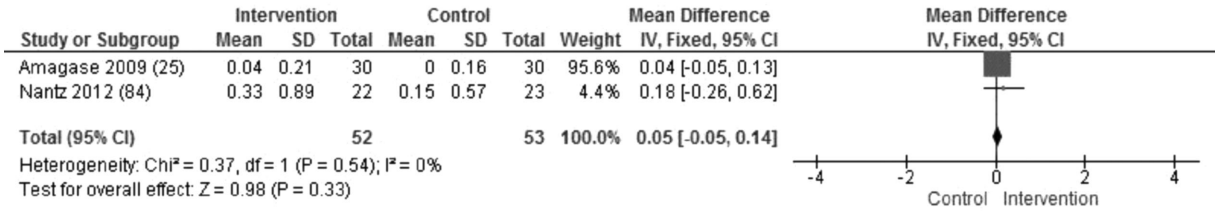

FIGURE 8 Forest plot of randomized controlled trials investigating the effects of fruit and vegetable intake on NK cell population percentage. Values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of $P < 0.10$. IV, inverse variance.

of CD4+ T lymphocyte cells. A cross-sectional study by Root et al. (76) showed that fruit intake was inversely associated with white blood cell count (WBC), although, they did not find any association between vegetable intake and WBC. In contrast, 5 cross-sectional studies (3, 21, 67, 71, 88) found no significant association between F&V intake and immune function.

Findings from meta-analysis

Through the use of meta-analysis, we examined changes in circulating levels of the most commonly evaluated inflammatory biomarkers, including CRP, TNF-α, and IL-6, following F&V intervention. Higher F&V intake was correlated with lower blood levels of CRP (MD: –0.34; 95% CI: –0.58, –0.11; $P < 0.01$; $I^2 = 71\%$) **(Figure 3)** and TNF-α (MD: –0.87; 95% CI: –1.59, –0.15; $P = 0.02$; $I^2 = 86$) **(Figure 4)**. However, the meta-analysis showed F&V intervention did not have a significant effect on IL-6 levels (MD: –0.12; 95% CI: –0.31, 0.08; $P = 0.2$; $I^2 = 0$) **(Figure 5)**. Changes in immune cell populations following F&V consumption were also analyzed. F&V intake was associated with a higher percentage of $\gamma\delta$-T cells (MD: 1.68; 95% CI: 0.29, 3.07; $P = 0.02$; $I^2 = 72$) **(Figure 6)**, although F&V intake had no significant effect on other immune cell populations **(Figures 7** and **8)**. No meta-analysis was possible on the observational research, as the studies used heterogeneous methods in reporting outcomes of interest.

DISCUSSION

This systematic review and meta-analysis supports the epidemiologic evidence that higher consumption of F&V is associated with reduced inflammation. We found that the majority of studies ($n = 56$; 71%) reported protective effects of F&V intake on inflammation or immune function. The meta-analysis showed that higher intake of F&V is associated with lower levels of CRP and TNF-α ($P < 0.05$) **(Figure 9)**. The effect of F&V intake on immune cell function was less clear due to the limited number of available studies; however, meta-analysis showed that higher consumption of F&V was associated with an increased $\gamma\delta$-T cell population ($P < 0.05$) **(Figure 10)**.

Chronic systemic inflammation leads to reduced human life span, because it increases the prevalence of various diseases predominantly found in developed countries, including obesity (4), diabetes (50), and some cancers (63). The ability of F&V to protect against the development of these chronic conditions is well documented (3, 16, 17, 89, 90). The mechanisms of protection are not yet clear; however, there are numerous beneficial nutrients in F&V that have antioxidant and anti-inflammatory properties, such as carotenoids, vitamin C, vitamin E, flavonoids, and soluble fiber. Individually these nutrients have been shown to be protective against systemic inflammation. For example, a cross-sectional study (77) of 3254 elderly participants found an inverse association between vitamin C intake and plasma CRP levels. Similarly, in another study, high plasma vitamin C levels were correlated with a reduced circulatory CRP concentration (91). Another study reported that supplementation with vitamin E (800 IU/d) significantly decreased CRP levels in diabetic patients (62). Hence, it is likely that the positive effects of F&V can be attributed to the combination of these nutrients and subsequent displacement of proinflammatory nutrients from the diet, such as dietary fat.

Epidemiologic data across the general population has demonstrated that plasma lycopene and β-carotene were inversely associated with inflammatory biomarkers, including CRP and

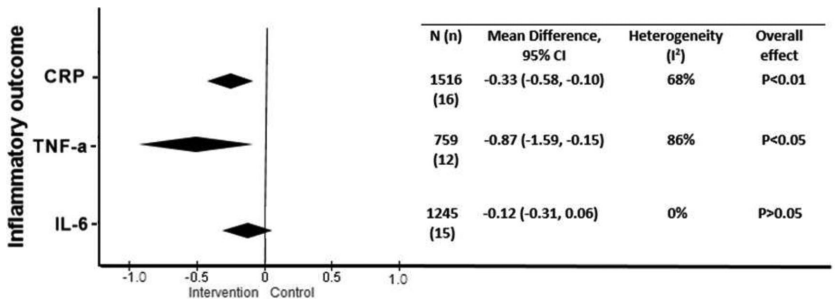

FIGURE 9 Overall effects of fruit and vegetable intake on inflammatory biomarkers. CRP, C-reactive protein; *N*, number of participants included in the meta-analysis; *n*, number of studies included in the meta-analysis.

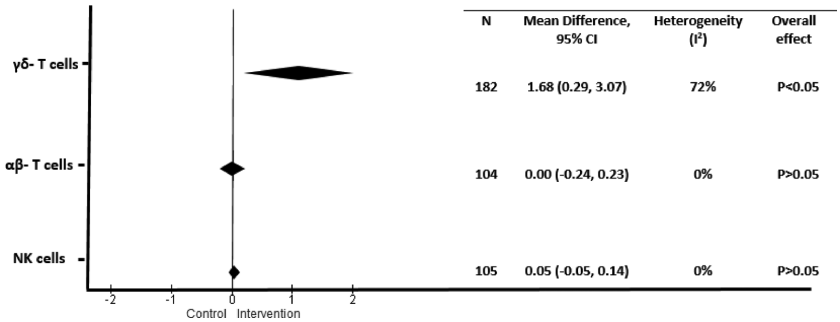

FIGURE 10 Overall effects of fruit and vegetable intake on different immune cell population percentage. *N*, number of participants included in the meta-analysis; *n*, number of studies included in the meta-analysis; NK cells, natural killer cells.

sICAM (92). In addition, consumption of carotenoid-rich food has been shown to reduce systemic inflammation in overweight and obese people (4). In another study, lycopene inhibited TNF-α–induced endothelial ICAM expression (93). Flavonoids are a group of polyphenols found in F&V with antioxidant and anti-inflammatory effects (94). Short-term supplementation of pure flavonoids, including quercetin and epicatechin, decreased IL-1β and E-selection (95). The exact mechanism by which flavonoids inhibit inflammation is not clear. It has been suggested that quercetin, in particular, inhibits both cyclo-oxygenase and lipoxygenase activities, thus diminishing the formation of inflammatory metabolites (96). Another immune-protective compound of F&V is fiber. Recently, we reported that dietary fiber was inversely associated with airway inflammation (97). In line with these findings, several studies in the general population reported that dietary fiber intake was inversely related to systemic inflammation (98, 99). It has been suggested that dietary soluble fiber intake can modulate inflammatory responses, due to production of short-chain fatty acids, which activate the free fatty acid receptors G protein–coupled receptor 41 and 43 (GPR41 and GPR43), and inhibit histone deactylases, with both of these mechanisms having anti-inflammatory actions (100, 101). Since various phytochemicals have mutually beneficial effects, it has been suggested that combinations of such nutrients, found in F&V, can enhance their roles in immune responses to inflammation (102).

To our knowledge, the present systematic literature review and meta-analysis is the first to assess the effects of F&V consumption on inflammation and immune function. Previous meta-analyses have investigated the effects of F&V intake on the risk of chronic diseases such as type 2 diabetes (89, 90), and coronary heart disease (16). A meta-analysis of 5 clinical trials (103) assessed the effects of pomegranate juice consumption on plasma CRP levels, and showed no significant effect, which may be a result of the small number of studies.

The strengths of this review include the broad systematic literature search, defined inclusion criteria and clear approach to collecting data, thorough assessment of the evidence, inclusion of studies with various designs, and meta-analysis. Furthermore, all studies were assessed for quality and validity.

However, our study has some limitations worth noting that are common to analysis of dietary interventions. First, the included studies were heterogeneous with respect to the intervention or the diet exposure, design, study size, and duration of follow-up. Some studies assessed the effects of specific types of F&V, whereas others investigated the effects of total F&V intake. However, this limitation has been addressed by presenting the results according to study exposure. The meta-analysis was also performed based on the intervention employed. Second, dissimilar populations in terms of age and health condition were observed among the studies. Some studies were performed in healthy populations (11, 14, 25, 34), whereas other studies were conducted in patients with type 2 diabetes (50), metabolic syndrome (27), high blood pressure (26), high risk of CVD (30), or in other conditions such as pregnancy (60). Due to the limited number of studies available for inclusion in the meta-analysis, separating the analysis according to health status was not possible. Moreover, different studies used different methods of dietary assessments, such as 24-h recall, food record, or food-frequency questionnaire. Finally, the possibility of publication bias exists, as studies with positive findings are more likely to be published.

In conclusion, this systematic review of the literature suggests that a higher intake of F&V decreases inflammation, and also enhances immune cell populations. These findings support recommendations to increase F&V intake for the primary prevention of many chronic diseases. However, well-designed randomized controlled trials are needed to confirm our results. Future research is also required to explore potential mechanisms underlying the observed associations.

The authors' responsibilities were as follows—BH, BSB, and LGW: designed the study; BH and AS: conducted the search; BH: analyzed the data and wrote the paper; BSB, AS, and LGW: revised the paper; MRS, AC, and PABW: reviewed the paper; LGW: had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest.

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