REVIEW

Vegetarian-Based Dietary Patterns and their Relation with Inflammatory and Immune Biomarkers: A Systematic Review and Meta-Analysis

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ABSTRACT

Dietary patterns with substantial proportions of energy from plant sources have been associated with favorable biomarkers of low-grade inflammation. Less is known of the relation between vegetarian-based dietary patterns and markers of inflammation and immune status. This systematic review and meta-analysis aimed to determine the relation between vegetarian-based dietary patterns and inflammatory and immune markers (C-reactive protein, tumour necrosis factor α, fibrinogen, natural killer cells, leukocytes, lymphocytes, thrombocytes, interleukins, and immunoglobulins). PubMed, Medline, and Cochrane scientific databases were searched to identify relevant studies. Random effects meta-analyses were conducted to assess the weighted mean differences (WMDs) for each outcome variable between vegetarian and non-vegetarian groups. Thirty observational and 10 intervention studies were included in the review. Pooled effects of vegetarian-based dietary patterns were associated with significantly lower concentrations of CRP (WMD: −0.61 mg/L; 95% CI: −0.91, −0.32 mg/L; $P = 0.0001$), fibrinogen (WMD: −0.22 g/L; 95% CI: −0.41, −0.04 mg/L; $P = 0.02$), and total leukocyte (WMD: $-0.62 \times 10^3/\mu$L; 95% CI -1.13×10^3, $-0.10 \times 10^3/\mu$L; $P = 0.02$) compared with those following non-vegetarian dietary patterns in observational studies. Insufficient data were identified for a meta-analysis of intervention studies. This study provides evidence that vegetarian-based dietary patterns are associated with lowered serum C-reactive protein, fibrinogen, and total leukocyte concentrations. Future research should focus on large-scale intervention trials, contrasting differences in inflammation and immune status and function between vegetarian and non-vegetarian-based populations. *Adv Nutr* 2019;10:433–451.

Keywords: inflammation, immune function, vegetarian, vegan, diet, dietary patterns, CRP, IL-6, meta-analysis, systematic review

Introduction

Nutritional epidemiology has seen a shift away from single nutrient analyses to a complementary approach in the form of dietary pattern analysis (1). Evaluating dietary patterns may provide a more holistic and clinically relevant approach to assessing diet-disease relations as nutrients are not eaten in isolation and synergistic effects of multiple components can have a concerted effect (2). Vegetarian-based dietary patterns are typically higher in fruits, vegetables, whole grains, nuts, seeds, and legumes, all of which are naturally higher in phytochemicals and some vitamins compared to non-vegetarian dietary patterns (3, 4). A variety of vegetarian-based eating patterns exist based on the inclusion or exclusion of animal products. For example, individuals who omit all animal products are classically described as vegan, whilst those who include eggs and dairy products are referred to as lacto-ovo-vegetarian (LOV) (5). Consumption of these dietary patterns are protective against many chronic diseases, including coronary heart disease, type 2 diabetes mellitus (T2DM), some cancers, and are associated with lower all-cause mortality (6–9).

An array of mechanisms are likely responsible for the protective effects observed in vegetarian-based dietary patterns,

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Supplemental Tables 1–4 and Supplemental Figures 1–7 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.

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Abbreviations used: CRP, C-reactive protein; CVD, cardiovascular disease; LOV, lacto-ovo-vegetarian; LV, lacto-vegetarian; PRISMA, Preferred Reporting of Systematic Reviews and Meta-analyses; PROSPERO, Prospective Register of Systematic Reviews; RCT randomized controlled trial; T2DM, type 2 diabetes mellitus; WMD, weighted mean difference.

including improved inflammatory and immune responses. These systems can be modulated by various dietary patterns and food components, demonstrating that plant-based foods can provide favorable outcomes (10–13). When considering inflammation, and immune status, it is important to recognize that these systems are inherently linked and work synergistically. For instance, C-reactive protein (CRP), a nonspecific systemic marker of inflammation, may be elevated in response to cytokines released by phagocytes during an infection or when tissue is damaged (14).

Without a sufficient exogenous supply of nutrients the immune system will be jeopardized (15). In addition, the impact of "non-nutritive" components of food on immune function has been acknowledged (16–18). For example, polyphenolic compounds are shown to improve lymphocyte responsiveness and natural killer cell function (19), while carotenoids can have an immune-modulating effect (20). When considering the implications of these findings, it should be noted that we do not consume these components in isolation (2). As such, exploration of the impact of consuming a whole dietary pattern that is likely to be high in these components seems indicated.

The influence of diet on inflammation has also been examined and clear associations found (12, 21). The inflammatory response is a complex biological response used for protection against mechanical, environmental, and pathological challenges, and is associated with intracellular signaling molecules which can influence both immune and inflammation responses (22, 23). Research has demonstrated links between chronic low-grade inflammation and increased risk of various diseases, with inflammation hypothesized as an underlying pathophysiologic mechanism. For instance, chronic elevation of the inflammatory markers CRP, IL-6, and fibrinogen is shown to predict the risk of cardiovascular disease (CVD) (24), all-cause mortality (25), T2DM (26), and some cancers (27).

There is evidence to suggest that plant-based diets may have favorable effects on inflammation. Consumption of dietary patterns with substantive nutrients obtained from plant rather than animal sources has been shown to attenuate markers of chronic inflammation such as CRP, IL-6, and fibrinogen (12, 13, 21, 28). Similarly, a meta-analysis recently suggested that vegetarianism was associated with lowered serum CRP concentrations and may be a useful dietary approach to manage "inflammaging," or the increased levels of chronic inflammation associated with aging (29). However, the review may be affected by their inclusion of participants who use statins [which can affect inflammatory markers such as CRP (30, 31)] and inclusion of intervention groups which may have incorporated consumption of some meat. In addition, consideration of the evidence base from randomized controlled trials (RCTs) is required to explore the effect of consuming a plant-based diet, hereinafter referred to as a vegetarian-based diet, on specific inflammatory and immune markers.

This systematic literature review aims to determine if vegetarian-based eating patterns in humans are associated with, or able to modulate, inflammation or immune biomarkers compared with those following non-vegetarian dietary patterns. A meta-analysis will further explore the effect of vegetarian-based eating patterns on common inflammation and immune biomarkers compared with non-vegetarian dietary patterns.

Methods

Study protocol

The systematic review followed the requirements of the Preferred Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (32) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42016039043; 12 May 2016). A systematic search of the PubMed, MEDLINE, and Cochrane Central Register of Controlled Trials scientific databases (all years to December 2017) was conducted to answer the research question. Scientific database searches were conducted by 1 reviewer (JC). The search strategy used the following key words, with Medical Subject Heading terms used where available: ("Immunoglobulin∗" OR "IgE" OR "IgD" OR "IgM" OR "IgA" OR "IgG" OR "Platelet∗" OR "Basophil∗" OR "Eosinophil∗" OR "t lymphocyte subsets" OR "t cell∗" OR "b lymphocyte subsets" OR "B cell∗" OR "Monocyte∗" OR "Neutrophil∗" OR "Lymphocyte∗" OR "Leukocyte∗" OR "white blood cell∗" OR "NK" OR "natural killer t cell∗" OR "natural killer cell∗" OR "immunity" OR "immune" OR "tumor necrosis factor" OR "tumour necrosis factor" OR "TNF" OR "interleukin" OR "IL-6" OR "fibrinogen" OR "CRP" OR "c reactive protein" OR "C-Reactive Protein" OR "inflammat∗") AND ("plant based" OR "plant-based" OR "vegan∗" OR "∗vegetarian" OR "vegetarian∗"). An example of the search strategy in its entirety is shown in **Supplemental Table 1**. This review considered any dietary pattern including animal meats (including fish) to be non-vegetarian based, and dietary patterns excluding all animal meats to be vegetarian based.

Inclusion criteria

Studies were included if they examined the relationship (observational studies) or effect (intervention studies) of vegetarian-based dietary patterns compared with a non-vegetarian-based control dietary pattern on an outcome of interest [CRP, ILs (all), TNF (all), fibrinogen, natural killer cells, white blood cell counts (leukocytes, lymphocytes, neutrophils, monocytes, eosinophils, basophils, thrombocytes), immunoglobulins (IgG, IgA, IgE, IgD, and IgM)], and were conducted in human populations of all ages.

Observational studies were defined a priori to include any studies in which there was no direct intervention, and could include cross-sectional, case-control, prospective cohort, and retrospective cohort studies. They had to additionally involve participants who had adhered to a vegetarian-based diet (vegetarian group only) for $\geq$1 y. This timeframe was chosen to represent a habitual dietary pattern.

Intervention studies were also defined a priori to include any studies where a vegetarian-based diet was used as an intervention with a control group and could include RCT, non-RCTs, and pre-post studies. Intervention studies had to additionally study the vegetarian-based diet for a period >4 wk. This timeframe was selected as changes in some serum inflammatory markers such as IL-6 and CRP can take several weeks to become physiologically apparent (33–35).

Exclusion criteria

Observational and intervention studies were excluded for the following reasons: *1*) they were not published in the English language; *2*) they were conference abstracts, editorials, book series, errata, or conference proceedings; *3*) they did not complete between-group analyses or provide raw data to allow these to be calculated; *4*) they were animal or cellular models; *5*) they were analyzing consumption of single foods or food groups rather than dietary patterns (e.g., exploring legume intake rather than vegetarian diets); *6*) they used drugs that could alter biomarker outcomes, i.e. metformin (CRP) (30, 31); *7*) they were assessing antibodies to food antigens rather than disease or general blood immunoglobulins; *8*) they included any type of animal meat (including fish) in the vegetarian-based groups; or *9*) they examined a single diet component/supplement only (e.g., cheese compared with vegan cheese alternative).

Intervention studies were additionally omitted if: *1*) they used lifestyle interventions in conjunction with diet intervention, i.e. exercise or stress management; or *2*) they used intervention diets containing any type of meat or did not report to controlling/discouraging meat intake.

Duplicate articles were initially removed with the use of EndNote referencing software (version X7, 2013; Thomson Reuters) with any remaining duplicates removed manually. Articles were firstly screened based on title and abstract. Full-text articles were obtained if the abstract was unavailable, or if it was unclear if the article met the inclusion criteria. Screening was performed by reviewer JCC with articles of concern discussed amongst the research team (YCP, EPN, GEP) until consensus was reached. Where results from the same study were reported in multiple articles, the most recent article was included to avoid duplication of results. Reference lists of included articles were hand searched to identify additional relevant articles.

Data extraction

Data extraction was performed by reviewer JCC in consultation with the research team, and included information related to author, date, study design, level of evidence, study population (including age, gender, country, and comorbidities), sample size, length of vegetarianism (observational studies), type of vegetarianism, details of intervention and control groups (intervention studies), outcomes investigated, and significant differences in biomarkers. Study authors were contacted for additional details if the required data were not available in the published article.

Statistical analysis

Meta-analyses were performed when >3 studies reported on a biomarker, median/mean with SD could be obtained or calculated from raw data, and the units of measurement could be made uniform. Meta-analyses were conducted separately for observational and intervention study results. Review Manager software (Review Manager version 5.3; The Nordic Cochrane Centre, Cochrane Collaboration, 2014) was used to estimate the pooled effect of inflammation and immune markers between vegetarian and non-vegetarian diets. Random effect meta-analyses were conducted to determine weighted mean differences (WMDs) by assigning a weight to each study on the basis of an individual study's inverse variance (36), and 95% CIs were used for each outcome. If a study involved >1 intervention group meeting the inclusion criteria, data for all intervention groups were combined as recommended by the Cochrane Handbook (37). For the intervention analysis, crossover studies were initially analyzed as parallel studies through the use of a paired analysis, the most conservative approach to managing crossover studies (37). Paired analyses of crossover studies with correlation coefficients of 0.25, 0.5, and 0.75 were then conducted as sensitivity analyses to determine if this influenced the results (37). The I^2 statistic was used to evaluate heterogeneity, with a score 50–90% likely indicating substantial heterogeneity, and a score of 75–100% considerable heterogeneity (37). Where ≥10 studies reported on a biomarker outcome, funnel plots were generated and Egger's test was applied to assess studies for small study effects (38) with the use of StatsDirect statistical software (version 3.1, 2013; StatsDirect Ltd) (39).

Where median and ranges were reported, the Hozo et al. (40) formula was used to calculate SD and mean (when the population was <25 persons). When IQR was given, IQR/1.35 was used to calculate the SD (37). Where insufficient information was described in the published article and raw data were provided by authors, statistical analyses were performed with SPSS software (version 21, 2012; SPSS Inc.). Shapiro-Wilk tests on raw data determined if biomarker outcomes were normally distributed. One-way ANOVA (parametric) or Kruskal-Wallis (nonparametric) tests determined if differences existed between dietary patterns for inclusion in the summary table. P values <0.05 were considered to be statistically significant.

Sensitivity analyses were performed by excluding each study individually to investigate the influence on overall estimates (37). Additionally, sensitivity analyses were conducted by excluding studies where participants suffered from a chronic condition. When sufficient data were available on the type of vegetarianism (LOV or vegan dietary patterns) (≥3 studies), subgroup analyses were performed.

Risk of bias

Study quality for the nonrandomized studies was assessed independently with the use of a modified version of the Newcastle-Ottawa Scale by 2 reviewers (JCC, EPN). Where discrepancies occurred, a third reviewer (YCP) was consulted

until a consensus was reached. The Newcastle-Ottawa Scale score for each study was based on the primary outcome of the present study (CRP) if available. For intervention studies, risk of bias was assessed with the use of the Cochrane Collaboration's tool (37). To determine the quality of the body of evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method was applied to both observational and intervention studies (41).

Results

The literature search identified 2040 articles. After the exclusion criteria were applied, 39 studies [30 observational articles (42–71) describing 29 studies (2 separate articles were identified reporting on same study participants, with different outcome markers) and 8 intervention studies] were included in the review. A further 2 studies were identified via hand searching of reference lists, resulting in a total of 10 intervention studies (72–81). **Figure 1** displays the complete process of study selection, including identification, screening, eligibility, and inclusion.

Observational studies

Description of the included studies.

The included studies were cross-sectional or matched-cohort studies (**Table 1**). Types of vegetarianism included LOV (8), lacto-vegetarian (2), vegan (5), and combinations of these with comparison groups typically consuming mixed omnivorous non-vegetarian diets. Participants in 2 of the included studies had chronic conditions, with 1 receiving dialysis therapy (59, 70), and participants in the other study having CVD, diabetes mellitus, or a combination of both (63). One study (63) reported on participants whose ages ranged between 2 and 18 y old, whereas the remainder reported on adults aged ≥18 y (Table 1). Studies were conducted in a range of continents, including Asia (44–46, 59, 62, 63, 66–71), Africa (49), North America (47, 50, 51, 54, 60), South America (42, 48, 52, 57), and Europe (43, 53, 55, 56, 58, 61, 64, 65). Study quality ranged from 2–6 out of a possible 7 with the use of the modified Newcastle-Ottawa Score tool (**Supplemental Table 2**).

CRP concentrations were significantly lower in 9 out of 19 studies in the vegetarian-based groups, with no difference in

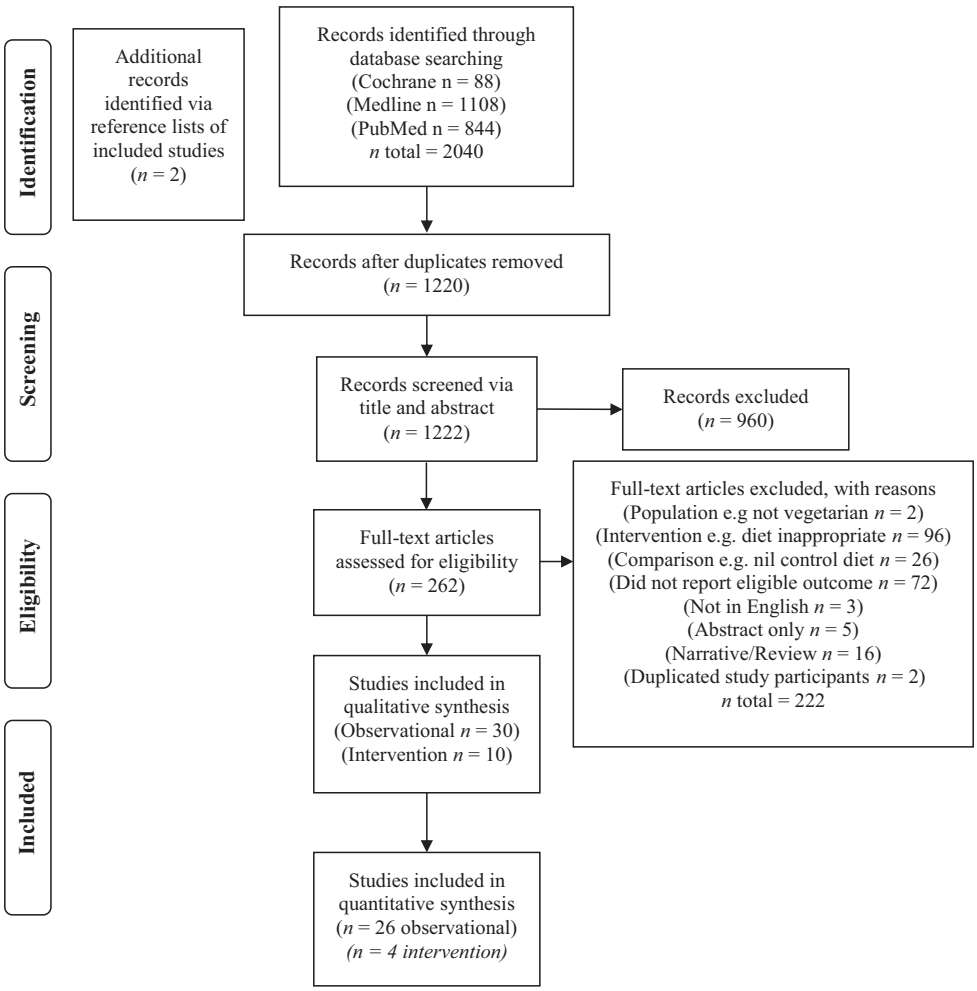

FIGURE 1 Flowchart of study selection.

TABLE 1 Characteristics of observational studies examining the association of participants following vegetarian-based or non-vegetarian dietary patterns and common biomarkers of inflammation and immune function[1]

Study (ref.)	Design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Years on vegetarian diet	Biomarker investigated	Study quality/7	Matched (NS different at baseline)	Difference in biomarker (significance $P < 0.05$)
Acosta-Navarro et al. (42)	Cross-sectional	V = 44	Nil	Brazil	V[3] = 45.5	>4	hs-CRP	5	Age	• hs-CRP (NS)[4]
Navarro et al.[2] (48)		NV = 44			NV = 46.8		Leukocytes		Gender	• Leukocytes significantly ↓ in V group
		M					Neutrophils		Smoking status	• Neutrophils significantly ↓ in V group
									hx of disease	
Ambroszkiewicz et al. (43)	Cross-sectional	LOV = 43	Nil	Poland	4.5–9.0	>4.5	CRP	4	Age	• CRP (NS)
		NV = 46							BMI	
		M and F								
Chen et al. (45)	Cross-sectional	V = 99	Nil	Taiwan	V = 51.24	>1	Leukocytes	4	Age	• CRP significantly ↑ in NV group
		NV = 99			NV = 49.38		hs-CRP		BMI	
		M and F								
Chen et al. (44)	Cross-sectional	LOV = 173	Nil	Taiwan	LOV = 54.00	>1	hs-CRP	5	BMI	• hs-CRP (NS)
		NV = 190			NV = 49.94		Leukocytes			• Leukocytes (NS)
		F					Thrombocytes			• Thrombocytes (NS)
Chuang et al. (46)	Matched cohort/ cross-sectional	V = 686	Nil	Taipei and Taiwan	V = 45.2	Long-term	CRP	5	Age	• CRP significantly ↑ in NV group
		NV = 3423			O = 45.1				Location	
		M and F							Sex	
Dong and Scott (47)	Cross-sectional	Ve = 13	Nil	USA	Ve: M = 57; F = 40	>1	Leukocytes	1	Nil	• Significance not reported
		LV = 28			LV: M = 45; F = 42					
		LOV = 15			LOV: M = 43; F = 35					
		NV = 4			NV: M = 31; F = 55					
		M and F								
Famodu et al. (49)	Cross-sectional	Ve = 8	Nil	Nigeria	Ve = 47.1	Long-term	Fibrinogen	3	Age	• Fibrinogen significantly ↑ in NV group compared with LOV and Ve group
		LOV = 28			LOV = 49.0				BMI	• Fibrinogen significantly ↑ in LOV group compared with Ve group
		NV = 40			NV = 48.7					
		M and F								
Fontana et al. (50)	Matched cohort/cross-sectional	Ve = 21	Nil	USA	Ve = 53.1	>2	hs-CRP	2	Age	• CRP significantly ↑ in NV group

(*Continued*)

TABLE 1 (*Continued*)

Study (ref.)	Design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Years on vegetarian diet	Biomarker investigated	Study quality/7	Matched (NS different at baseline)	Difference in biomarker (significance $P < 0.05$)
		NV = 21 M and F			NV = 53.1					
Fontana et al. (51)	Matched cohort/cross-sectional	Ve = 18	Nil	USA	54.2	1.5–10 (range)	hs-CRP	2	Age	• hs-CRP significantly ↑ in NV group
		NV = 18 M and F							Sex SES	
Franco-de-Moraes (52)	Cross-sectional	Ve = 66	Nil	Brazil	Ve = 49.6	>1	TNF-α	3	Age	• TNF-α (NS)
		LOV = 102 NV = 100			LOV = 49.6 NV = 49.1		CRP IL-10		Sex	• hs-CRP significantly ↑ in NV group • IL-10 (NS)
Gorczyca et al. (53)	Cross-sectional	V = 22 NV = 18	Nil	Poland	V = 4 NV = 9 (range 2–18)	>1	IgA IgM	3	Age Body weight	• IgA (NS) • IgM (NS)
		M and F					IgG		Height	• IgG (NS)
Haddad et al. (54)	Cross-sectional	Ve = 25	Nil	USA	Ve = 36.0	>1	Leukocytes	3	Age Physical activity level	• Leukocytes significantly ↓ in Ve group
		NV = 20			O = 33.5		Lymphocytes		Blood lipid concentrations	• Lymphocytes significantly ↓ in Ve group
		M and F					Neutrophils Monocytes Eosinophils Basophils Thrombocytes			• Neutrophils (NS) • Monocytes (NS) • Eosinophils (NS) • Basophils (NS) • Thrombocytes significantly ↓ in Ve group
							IgA IgG IgM CRP NK cell cytotoxic activity			• IgA (NS) • IgG (NS) • IgM (NS) • CRP (NS) • NK cell cytotoxic activity (NS)
Krajcovicova-Kudlackova and Blazicek (55)	Cross-sectional	LOV = 133	Nil	Slovakia	LOV = 46.2	>1	hs-CRP	2	Age	• hs-CRP significantly ↑ in NV group.
		NV = 137 M and F			NV = 47.2					
Malter et al. (56)	Cross-sectional	V = 22	Nil	Germany	V = 28–50	>1	Thrombocytes	2	Age	• Thrombocytes (NS)

(*Continued*)

TABLE 1 (*Continued*)

Study (ref.)	Design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Years on vegetarian diet	Biomarker investigated	Study quality/7	Matched (NS different at baseline)	Difference in biomarker (significance $P < 0.05$)
		O = 22 M					Leucocytes Lymphocytes Monocytes Basophilic granulocytes Eosinophilic granulocytes NK cell cytotoxic activity		Gender	• Leucocytes (NS) • Lymphocytes (NS) • Monocytes (NS) • Basophilic granulocytes (NS) • Eosinophilic granulocytes (NS) • NK cell activity of peripheral blood lymphocytes significantly ↑ in V group.
Mezzano et al. (57)	Cross-sectional	V = 26 NV = 26 M and F	Nil	Chile	V = 39	>1	Platelet count Fibrinogen CRP	3	Age Sex SES	• Thrombocytes significantly ↓ in NV group • Fibrinogen significantly ↑ in NV group • CRP (NS)
Montalcini et al. (58)	Cross-sectional	LOV = 26 NV = 26 M and F	Nil	Italy	LOV = 32.6 NV = 30.5	≥3	IL-2 IL-4 IL-6 IL-8 IL-10 TNF-α IL-1α IL-1β	5	Age BMI Gender	• IL-2 (NS) • IL-4 (NS) • IL-6 (NS) • IL-8 (NS) • IL-10 (NS) • TNF-α (NS) • IL-1α (NS) • Interleukin-β significantly ↑ in LOV group
Ou et al. (59)	Case control/cross-sectional	V = 21 NV = 42 M and F	Patients on dialysis therapy for >6 mo	Taiwan	V = 56.27 O = 56.29	≥1.5	hs-CRP	2	Age Sex	• hs-CRP (NS)
Paalani et al. (60)	Cross-sectional	V = 216 NV = 289 M and F	Nil	USA	68.8	>1	CRP IL-6 IL-10 TNF-α	4	Not reported	• CRP significantly ↑ in NV group
Pinto et al. (61)	Matched cohort/cross-sectional	Ve = 23 NV = 24 F	Nil	UK	Ve = 49 NV = 54	>2	IL-6	6	Age Sex BMI	• IL-6 (NS)
Pongstaporn et al. (62)	Cross-sectional	V = 179 NV = 58 M and F	Nil	Thailand	V = 18+	>1	Leukocytes Thrombocytes Neutrophils Lymphocytes	2	Nil	• Leukocytes significantly ↓ in Ve group • Thrombocytes (NS) • Neutrophils (NS) • Lymphocytes (NS)
Refsum et al. (63)	Cross-sectional	V = 78 NV = 126 M and F	100 CVD (42 of which DM) 104 without CVD (41 DM)	India	V = 27–55	Long-term	Thrombocytes	3	Nil	• Thrombocytes (NS)
Sebekova et al. (64)	Cross-sectional	LOV = 90	Nil	Slovakia	LOV = 37.7	>2	Hs-CRP	2	Age	• Hs-CRP (NS)

(*Continued*)

TABLE 1 (*Continued*)

Study (ref.)	Design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Years on vegetarian diet	Biomarker investigated	Study quality/7	Matched (NS different at baseline)	Difference in biomarker (significance $P < 0.05$)
		NV = 46 M and F			O = 37.1		Leukocytes		Gender BMI	• Leukocytes (NS
Sebekova et al. (65)	Cross-sectional	Ve = 19 LOV = 19 NV = 9 M and F	Nil	Slovakia	Ve = 39.6 LOV = 36.1 NV = 30.5	Ve = 7.2 LOV = 8.2	CRP	2	Age	• CRP (NS)
Su et al. (66)	Cross-sectional	LOV = 49 NV = 41 F	Nil	Taiwan	LOV = 58.6 ± 6.0 O = 57.2 ± 5.4	10.8	hs-CRP	3	Age Gender	• hs-CRP (NS)
Suwannuruks et al. (67)	Cross-sectional	LOV = 50	Nil	Thailand	LOV 18–50	>1	Fibrinogen	1	Nil	• Fibrinogen (NS)
		NV = 30 M and F					Leukocytes Thrombocytes			• Leukocytes (NS) • Thrombocytes (NS)
Szeto et al. (68)	Cross-sectional	LOV = 30	Nil	Hong Kong	LOV = 44.2	5–55 (range)	hs-CRP	2	Age	• CRP significantly ↑ in NV group
		NV = 30 M and F			NV = 44.0				Sex	
Tungtrongchitr et al. (69)	Cross-sectional	LV = 132 NV = 47 M and F	Nil	Thailand	LV: M = 35.5; F = 33 NV: M = 32.5; F = 32 Median	>1	Leukocytes	2	Age	• Leukocytes (NS)
							Neutrophils Lymphocytes		Sex SES	• Neutrophils (NS) • Lymphocytes significantly ↓ in LV group
							Monocytes Eosinophil		Ethnic origin	• Monocytes (NS) • Eosinophils significantly ↓ in female LV group compared with male LV and NV group
							Basophil			• Eosinophils significantly ↑ in male LV group compared with female LV group and NV group
							Thrombocytes			• Basophils (NS) • Thrombocytes (NS)
Wu et al. (70)	Cross-sectional	V = 19	Patients receiving dialysis therapy > 6 mo	Taiwan	V = 63.3	Long before HD—note mean length of HD = 5.9	hs-CRP	4	Age	• hs-CRP significantly ↑ in NV group
		NV = 299 M and F			NV = 57.5		Leukocytes		Sex	• Leukocytes significantly ↓ in V group
Yang et al. (71)	Matched cohort/cross-sectional	V = 171	Nil	China	V = 32.6	> 1	CRP	4	Mean HD length age	• CRP (NS)
		NV = 12 M			NV = 34.2					

[1] (hs-)CRP, (high-sensitivity) C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; F, female, HD, hemodialysis; Hx, History; LOV, lacto-ovo-vegetarian; LV, lacto-vegetarian; M, male, NR, not reported; NS, not significant; NV, non-vegetarian; SES, socioeconomic status; Ve, vegan.

[2] Two separate papers identified reporting on same study participants, with different outcome markers; slight difference in Navaro et al.'s population: V = 43, NV = 41; age, V = 45.0 y; NV = 46.5 y; and study quality = 4 between studies.

[3] V, participants followed combinations of Ve, LV, or LOV diets.

[4] NS, $P > 0.05$.

10 out of 19 studies (42–46, 50–52, 54, 55, 57, 59, 60, 64–66, 68, 70, 71). Leukocyte counts were significantly lower in 6 out of 11 studies in the vegetarian-based groups with no difference in 5 out of 11 studies (44, 45, 47, 48, 54, 56, 62, 64, 67, 69, 70) (**Table 2**). Four studies reported on lymphocyte counts with vegetarian groups displaying significantly lower counts in 2 of the studies (54, 56, 62, 69). Only 2 studies reported on NK cell cytotoxic activity as a function of applied immunecompetence and found improved function in the vegetarian-based group (56) or no difference between groups (54). One study reported lower neutrophil counts in vegetarian-based groups (48), whereas the other 3 studies found no difference between groups (54, 62, 69). Fibrinogen was observed to be lower in vegetarian-based groups in 2 out of 3 studies (49, 57, 67). Table 2 shows the number of included studies identified for each biomarker and summarizes the number of studies reporting significant and nonsignificant differences in outcomes between vegetarian and non-vegetarian groups.

Relation between vegetarian-based diets on inflammatory and immune biomarkers.

Twenty-six observational studies were included in the meta-analysis reporting on 4 outcomes: CRP, thrombocytes, leukocytes, and fibrinogen (**Table 3**). Consumption of a vegetarian-based dietary pattern was associated with significantly lower CRP ($P = 0.001$; **Figure 2**), fibrinogen ($P = 0.02$; **Figure 3**), and leukocyte ($P = 0.02$; **Figure 4**) levels compared with those following a mixed omnivorous non-vegetarian comparison diet. No significant difference was observed for thrombocytes between groups ($P = 0.16$; **Figure 5**). The quality of body of evidence for the observational studies was deemed to be "very low" after a 1-level downgrade was applied for each outcome as per the GRADE guidelines (41) (**Supplemental Table 3**). Funnel plots were generated for CRP and leukocyte concentrations. Egger's test indicated no significant asymmetry (**Supplemental Figure 1**).

Sensitivity analysis and subgroup analysis.

When sensitivity analyses were applied, the pooled effect on CRP remained significant. The pooled effect on leukocytes became nonsignificant when Pongstaporn et al. (62) was omitted ($P = 0.08$). Conversely, thrombocytes were significantly higher in the vegetarian group with the omission of Haddad et al. (54) ($P = 0.01$) (**Supplemental Figure 2**). Lower leukocyte and CRP levels in vegetarian-based populations continued to be found when sensitivity analyses were applied excluding studies with participants receiving hemodialysis treatment, or suffering from cardiovascular disease (CVD) or T2DM ($P = 0.01$) (**Supplemental Figure 3**).

Because of the considerable heterogeneity observed ($I^2 = 100\%$) for CRP concentrations between dietary groups, meta-analyses were performed on specific dietary groups in an attempt to identify the source of heterogeneity. No significant subgroup differences were observed between vegan, LOV groups, and non-vegetarian groups for CRP. Neither subgroup analysis accounted for the high heterogeneity

TABLE 2 Overview of included studies reporting on biomarkers and significant differences between participants following vegetarian-based or non-vegetarian dietary patterns in observational studies[1]

Biomarker	Studies included	Differences between groups (significance, $P < 0.05$)
Lymphocytes (54, 56, 62, 69)	4	↓ in V group in 2/4 studies; NS 2/4 studies
Neutrophils (48, 54, 62, 69)	4	↓ in NV group in 1/4 studies; NS 3/4 studies
Basophils (54, 56, 69)	3	NS 3/3 studies
Monocytes (54, 56, 69)	3	NS 3/3 studies
Eosinophils[3] (54, 56, 69)	3	NS 3/3 studies
NK cell cytotoxic activity (54, 56)	2	↑ in V group in 1/2 studies; NS 1/2 studies
Leukocytes (44, 45, 47, 48, 54, 56, 62, 64, 67, 69, 70)	11	↓ in V group in 6/11 studies; NS 5/11 studies
Thrombocytes (44, 54, 56, 62, 63, 67, 69)	7	↓ in V group in 1/7 studies; ↑ in V group in 1/7 studies; NS 5/7 studies
CRP (42–46, 50–52, 54, 55, 57, 59, 60, 64–66, 68, 70, 71)	19	CRP ↓ in veg group in 9/19; NS 10/19 studies
TNF-α[4] (52, 58, 60)	3	NS[2]
Fibrinogen (49, 57, 67)	3	↑ in NV group in 2/3 studies; NS 1/3 studies
Interleukins		
IL-10 (52, 58, 60)	3	NS
IL-6 (58, 60, 61)	3	NS
IL-2, IL-4, IL-8, IL-1α,IL-1β (58)	1	IL-1β ↑ in V group in 1/1 study
Immunoglobulins		
IgA, IgM, IgG (53, 54)	2	NS

[1] NV, non-vegetarian; V, vegetarian-based.
[2] NS, not significant between groups ($P > 0.05$).
[3] Tungtrongchitr et al. (69) compared medians between groups and genders. Eosinophils were significantly ↓ in the NV group compared with the male LV group but significantly ↑ compared with the female LV group.
[4] Significance not reported in 1 study.

TABLE 3 Meta-analysis summary of observational studies comparing CRP, thrombocytes, fibrinogen, and leukocytes between vegetarian-based and non-vegetarian-based dietary patterns[1]

Outcome	Number of analyses	Number of vegetarian participants	Number of control participants	Effect Estimate (95% CI)	*P* value	Inconsistency (I^2)	GRADE quality
CRP, mg/L	18	1844	4736	−0.61 (−0.91, −0.32)	0.001	100%	Very low
Thrombocytes, × 10^9/L	7	663	507	8.24 (−3.35, 19.82)	0.16	35%	Very low
Fibrinogen, g/L	3	112	96	−0.22 (−0.41, −0.04)	0.02	17%	Very low
Leukocytes, $10^3/\mu$L	11	944	970	−0.62 (−1.13, −0.10)	0.02	96%	Very low

[1] CRP, C-reactive protein.

(I^2 for both vegan and LOV groups 87%; **Supplemental Figure 4**).

Intervention studies

Ten intervention studies were identified exploring the effect of vegetarian-based eating patterns on common markers of inflammation or immune function (72–81). They included 7 parallel and 3 crossover intervention study designs. Of the included studies, 7 were randomized (72–77, 81), and the remaining 3 were unable to be confirmed as being randomized or nonrandomized (78–80) as authors could not be contacted. Vegetarian-based intervention diets included LOV (n = 3), LV (n = 1), and vegan (n = 6) with varying macronutrient percentages (**Table 4**). Control diets varied, and included a well-balanced mixed diet from the 5 food groups (72), a conventional T2DM diet recommended by the European Association for the Study of Diabetes (73), habitual mixed diets (74, 75, 77, 79, 80), and an American Heart Association diet (fat total 30%, 7% saturated fat, <300 mg of cholesterol, <1500 mg of sodium daily) (76). Intervention diet duration ranged from 4 to 56 wk. Studies were from North America (76, 81) and Europe (72–75, 77–80). The populations examined in the included studies were mixed. For instance, in 4 studies the participants had rheumatoid arthritis, 1 study population exhibited T2DM, in 1 study the participants were overweight or obese (class 1; as measured by BMI), and in 1 study the participants were children >95% of BMI for age. The biomarkers investigated varied between studies (Table 4).

CRP levels were found to be significantly lower in vegetarian-based groups than in non-vegetarian groups in 4 out of 7 studies, with no significant difference in 3 out of 7 intervention studies (**Table 5**). Lymphocytes, monocytes, pan T cells (CD3+), T suppressor cells (CD8+), T helper cells (CD4+), NK cells, TNF-α, fibrinogen, IL-6, and IgA were reported by only 1 intervention study, with no significant difference between vegetarian and non-vegetarian groups found. Table 5 shows a summary of the included intervention studies and corresponding biomarker outcomes with significant and nonsignificant differences between study groups.

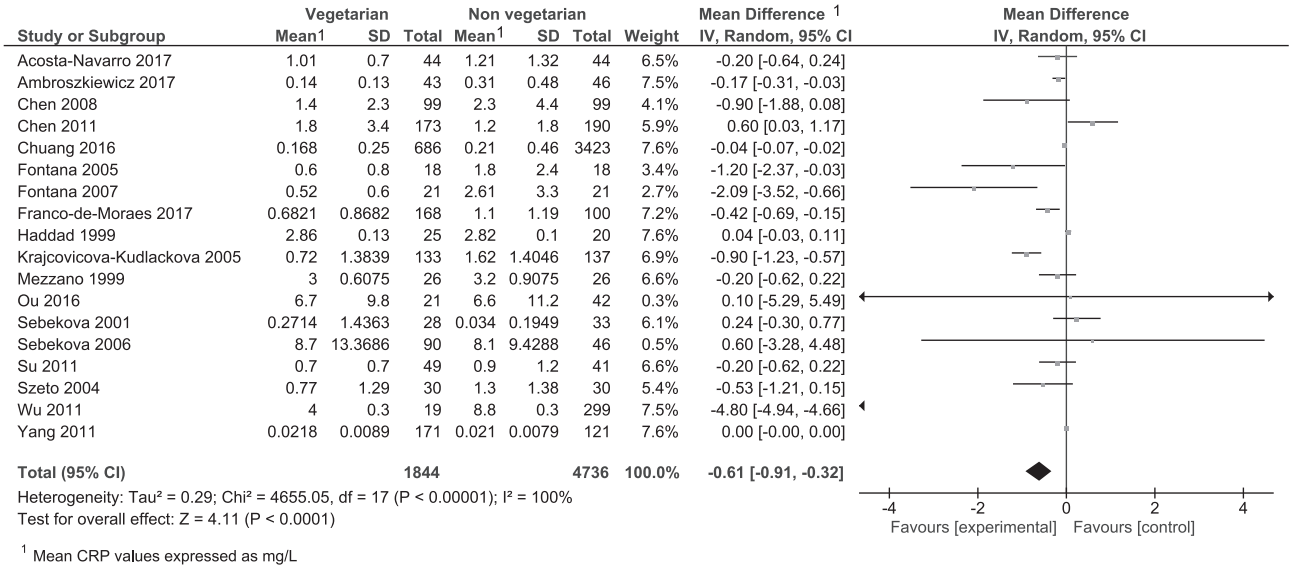

FIGURE 2 Difference in CRP values between participants following vegetarian-based dietary patterns and non-vegetarian dietary patterns (cross-sectional studies). Diamond indicates WMD with 95% CI. CRP, C-reactive protein; WMD, weighted mean difference.

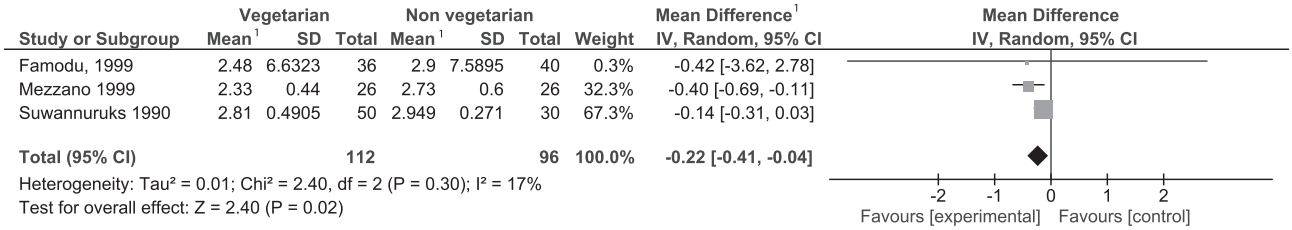

FIGURE 3 Difference in fibrinogen values between participants following vegetarian-based dietary patterns and non-vegetarian dietary patterns (cross-sectional studies). Diamond indicates WMD with 95% CI. WMD, weighted mean difference.

The quality of body of evidence for the intervention studies was rated as "very low" according to GRADE (**Supplemental Figure 5**) (41).

Pooled effects and subgroup analysis of vegetarian-based diets on inflammatory and immune biomarkers

Of the 10 studies identified, only 4 were eligible for a meta-analysis examining vegetarian-based dietary patterns and their effect on CRP (vegetarian, n = 116; non-vegetarian, n = 114). Due to the small population pool, varied population demographics (patients with rheumatoid arthritis, women, children with a BMI >95th percentile for age/sex with cholesterol >169 mg/dL and patients with T2DM), and varying intervention diets, the meta-analysis has been included as supplementary data to avoid potentially misleading conclusions common in nutritional meta-analyses (82) (**Supplemental Figure 6**). The Cochrane risk of bias assessment (**Supplemental Table 4**) and risk of bias graph (**Supplemental Figure 7**) are available as supplementary data. As a result of insufficient data, studies, or both, it was not possible to perform meta-analyses for the other outcomes.

Discussion

To the authors' knowledge, this review and meta-analysis is the first to explore both the association and effect of consuming a vegetarian-based dietary pattern on biomarkers of inflammation and immune status. The results of the analysis of observational studies suggest that individuals following vegetarian-based diets may have lower levels of CRP and fibrinogen, 2 prominent markers of inflammation, than their non-vegetarian-based counterparts. Given that CRP is implicated in the development of atherosclerosis (83) and is an independent risk predictor of cardiovascular events (84, 85), the results of this review may partly explain the lowered incidence of cardiovascular events observed in vegetarian populations (86, 87). The lowered leukocyte and fibrinogen concentrations observed in vegetarian-based eating patterns appears to be favorable as elevated leukocyte and fibrinogen biomarkers have been associated with increased risk of all-cause mortality (88), T2DM (89), metabolic syndrome (90), and coronary heart disease (91).

Our results are in contrast to those of a recent meta-analysis, which found nonsignificant differences in CRP concentrations between vegetarian- and non-vegetarian-based dietary patterns (Hedges' $g = -0{\cdot}15$; 95% CI: 0.35, 0.05) (29).

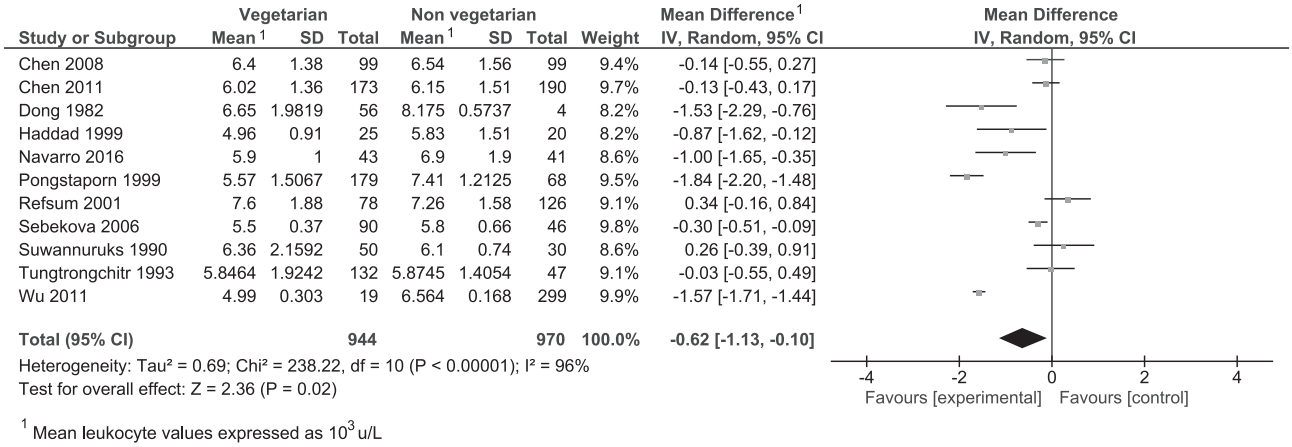

FIGURE 4 Difference in leukocyte values between participants following vegetarian-based dietary patterns and non-vegetarian dietary patterns (cross-sectional studies). Diamond indicates WMD with 95% CI. WMD, weighted mean difference.

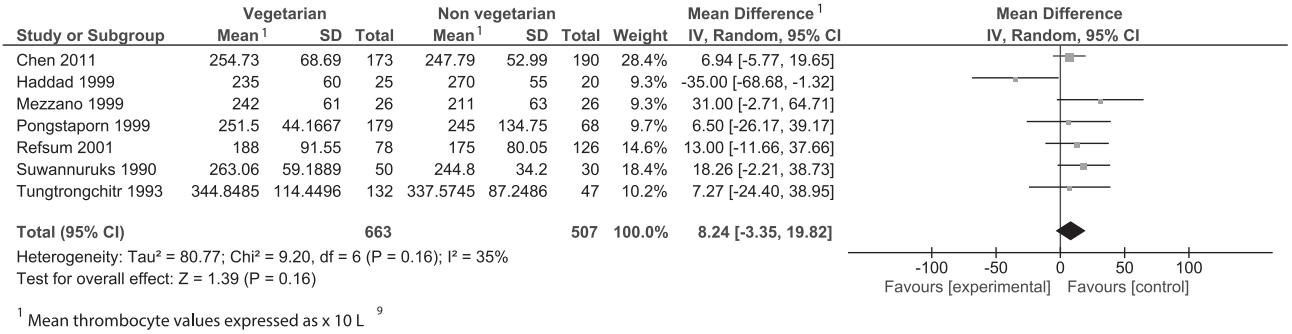

FIGURE 5 Difference in thrombocyte values between participants following vegetarian-based dietary patterns and non-vegetarian dietary patterns (cross-sectional studies). Diamond indicates WMD with 95% CI. WMD, weighted mean difference.

There are several explanations for the inconsistency. Firstly, the present review excluded studies where statins were used by participants as these are known to reduce inflammation (30, 31), whereas the previous analysis included 1 study where statin use was significantly different between groups (92). Secondly, the previous review (29) included studies that included small amounts of animal flesh in the vegetarian group (93) or where the vegetarian dietary pattern was not adequately described (94), whereas these studies were excluded from our review. We also only included studies with a duration of vegetarianism of $\geq$1 y, aligning with the suggestion that there may be a time interval between starting a vegetarian diet and a reduction in CRP (29). Finally, this review has included recently published studies not available at the time of the previous review (42, 43, 52).

Despite 10 intervention studies being identified for inclusion in this review, many biomarkers of interest were not reported upon, or were only explored in a single study, thereby limiting conclusions regarding the effect of vegetarian-based dietary patterns on these outcomes. CRP was explored in 7 studies, however, with significantly lowered concentrations following consumption of a vegetarian-based diet observed in 4/7 studies, which aligns with the results of the observational meta-analysis presented here. The limited body of evidence identified in the intervention studies highlights the need for further RCTs to confirm the results of the observational meta-analysis.

An array of nutrients and "nonnutritive" components of the vegetarian diet may be responsible for the trend for lowered inflammation biomarkers following consumption of a vegetarian-based dietary pattern (95). Consumption of flavonoids such as quercetin, kaempferol, malvidin, peonidin, daidzein, and genistein have been inversely associated with serum CRP even after adjustment for covariates including vitamin C, vitamin E, carotenes, and fruit and vegetable consumption (96). The antioxidant properties of flavonoids have been hypothesized to prevent LDL oxidation—an early inflammatory event in the development of atherosclerosis (97). Similarly, carotenoids are potent antioxidants embedded within the lipid bilayer that scavenge free radicals, and have been inversely associated with markers of inflammation (98, 99). Both flavonoids and carotenoids are typically found in higher concentrations in those following vegetarian-based dietary patterns (100), and may contribute to the observed attenuation of inflammation in vegetarian-based groups. Phytochemicals, which tend to be more plentiful in vegetarian-based eating patterns (100), may act as antioxidant, antibacterial, antifungal, anti-inflammatory, antiallergic, hypotensive, chemopreventive agents (11, 101), and may modulate inflammatory and immune function (11, 17, 18). Quantifying phytochemical intakes between vegetarian and non-vegetarian groups may be a target for future research.

Type and quantity of dietary fat intake may also influence low-grade inflammation concentrations. Several studies have linked dietary saturated fatty acids with increased serum high-sensitivity CRP and fibrinogen levels (102, 103). Saturated fatty acid intake is typically higher in non-vegetarian-based dietary patterns due to the increased consumption of animal-based products (100) and may contribute to the increased concentration of serum CRP and fibrinogen observed in non-vegetarian-based populations. Vegetarian-based populations typically consume a greater proportion of their dietary fat in the form of unsaturated fatty acids than non-vegetarians (104), a trend that is inversely associated with inflammation (105).

It is important to note that overweight and obesity are associated with elevated inflammation markers including TNF-α and IL-6 (106). Vegetarian-based populations typically exhibit lower BMIs than non-vegetarian populations (107), which may in part account for the lower CRP, fibrinogen, and total leukocyte concentrations in the vegetarian-based than in the non-vegetarian-based populations observed in this review.

Due to the limited number of studies, quantitative analysis was not possible for many biomarkers in both observational and intervention studies including interleukins (all), TNF-α, NK cell activity, lymphocytes, neutrophils, monocytes, eosinophils, basophils, IgG, IgA, IgD, IgE, and IgM. Future research should concentrate on investigating potential differences in these biomarkers with a particular focus on immune biomarkers and function between dietary groups

TABLE 4 Characteristics of interventional studies examining the effect of vegetarian dietary patterns and non-vegetarian dietary patterns on common biomarkers of inflammation and immune function[1]

Study/year	Study design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Duration of vegetarian diet, wk	Intervention vegetarian dietary pattern	Control non-vegetarian	Biomarker investigated	Matched (baseline participant characteristics matched)	Difference in biomarker (significance, $P < 0.05$)
Elkan et al. (72)	RCT (level II)[2]	Ve = 30	Patients with RA (2 and 10 y duration)	Sweden	Ve = 49.9	52	Ve	Well-balanced mixed diet from 5 food groups	CRP	Age	hs-CRP significantly ↓ within LV group
		NV = 28			NV = 50.8		Gluten free	(CHO 55–60%, pro 10–15%, fat <30% with <10% saturated)		Weight	
		M and F					(CHO 60%, pro 10%, fat 30%)			BMI	
										Disease duration	
										Concomitant treatment	
Hunt and Roughead (81)	RCT (level II; crossover)	$n = 21$	Nil	USA	33.2	8 (nil washout)	LOV	LOV with ~184 g meat (3 parts beef and 1 part chicken)/d	CRP	NA (crossover)	CRP (NS)
		F					↑ amounts of legumes, whole grains, breads/cereals fruits and vegetables				
							Cessation of supplements				
Kahleova et al. (73)	RCT (level II)	LV = 37	Patients with T2DM	Czech Republic	LV = 54.6	12	LV	Conventional T2DM diet as per DNSG of the EASD	hs-CRP	Significant differences between groups not reported at baseline	hs-CRP significantly ↓ in LV group

(*Continued*)

TABLE 4 (*Continued*)

Study/year	Study design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Duration of vegetarian diet, wk	Intervention vegetarian dietary pattern	Control non-vegetarian	Biomarker investigated	Matched (baseline participant characteristics matched)	Difference in biomarker (significance, $P < 0.05$)
		NV = 37			NV = 57.7		Animal products were limited to 1 low-fat yogurt a day	(CHO 50%, pro 20%,fat <30% with ≤7% saturated, <200 mg cholesterol / d)	Fibrinogen		Fibrinogen (NS)
		M and F					(CHO 60%, pro 15%, fat 25%)				
Kjeldsen-Kragh et al.[3] (74, 75)	RCT (Level II)	Ve = 27	Classic or definite RA	Norway	Ve = 53	56	Ve	Habitual mixed diet	CRP Thrombocytes Leukocytes TNF-α IgM IgA IgG	Significant differences between groups not reported at baseline	hs-CRP significantly ↓ in Ve group Thrombocytes significantly ↓ in Ve group Leukocytes significantly ↓ in Ve group TNF-α (NS) IgM significantly ↓ in Ve group IgA (NS) IgG significantly ↓ Ve group (after 1 month
		NV = 26			NV = 56		Gluten-free Ve for 3.5 mo		Thrombocytes		
		M and F					Followed by LOV for 9.5 m		Leukocytes TNF-α igM igA igG		
Macknin et al. (76)	RCT (level II)	Ve = 14	Children BMI >95th percentile for age/sex, cholesterol >169 mg/dL	USA	Children Ve = 15.0 O = 15.0	4	Ve	American Heart Association diet	hs-CRP	No significant difference in biomarkers at baseline	hs-CRP significantly ↓ in children on Ve
		NV = 14			Adults Ve = 46.5 O = 46.0		Avoidance of added fat and limited intake of nuts and avocado	(Fat total 30%, 7% saturated fat, <300 mg cholesterol, <1500 mg of sodium daily)	IL-6		IL-6 (NS)
		Overweight children with 1 × accompanying parent M and F									
Nenonen et al. (77)	RCT (level II)	Ve = 22	Chronic and active RA	Finland	Ve = 49.1	12	Ve	Habitual mixed diet	CRP	Height	CRP (NS)

(*Continued*)

TABLE 4 (*Continued*)

Study/year	Study design/level of evidence	Population/ gender	Comorbidities	Country	Age, y (mean or range)	Duration of vegetarian diet, wk	Intervention vegetarian dietary pattern	Control non-vegetarian	Biomarker investigated	Matched (baseline participant characteristics matched)	Difference in biomarker (significance, $P < 0.05$)
		NV = 21 M and F	CRP >10 mg/L		NV = 55.6		Rich in lactobacilli			Weight BMI Duration of RA Seropositivity Medication	
Richter et al. (78)	Nonrandomized crossover design (level III-2)[4]	*n* = 8	Nil	Denmark	21–28	12 (2 × 6 (crosover; 4 wk washout)	LOV	High amounts of animal protein (CHO 57%, pro 14%, lipids 29%)	Monocyte concentrations	NA (crossover)	Monocytes
		Well-trained athletes M					High in vegetable protein sources (CHO 57%, pro 14%, lipids 29%)		Monocytes (CD14+) NK cells (CD16+) Pan T cells (CD3+) T suppressor cells (CD8+) T helper cells (CD4+)		Monocytes (CD14+) (NS) NK cells (CD16+) (NS) Pan T cells (CD3+) (NS) T suppressor cells (CD8+) (NS) T helper cells (CD4+) (NS)
Sköldstam et al. (80)	RCT (level II)	LOV = 15	Classical RA	Sweden	LOV = 35–56	12	LOV	Habitual mixed diet	Leukocytes T lymphocytes B lymphocytes IgG IgA IgM	Not reported	Leukocytes (NS) T lymphocytes (NS) B lymphocytes (NS) IgG (NS) IgA (NS) IgM significantly ↑ within LOV group
		NV = 10			NV = 43–66		Nil alcohol, tobacco, coffee/tea Limited salt, sugar, white flour and grain products		T lymphocytes		T lymphocytes (NS)
		M and F							B lymphocytes IgG IgA IgM		B lymphocytes (NS) IgG (NS) IgA (NS) IgM significantly ↑ within LOV group T lymphocytes (NS)
Sköldstam (79)	Nonrandomized crossover design (Level III-2)	*n* = 20 NR	Classical or definite RA	Sweden	35–68	16	Ve	Habitual mixed diet	CRP	NA (crossover)	CRP (NS)

[1] (hs-)CRP, high-sensitivity C-reactive protein; CHO, carbohydrates; F, female; LOV, lacto-ovo-vegetarian; LV, lacto-vegetarian; M, male; NR, not reported; NS, not significant ($P > 0.05$); NV, non-vegetarian; pro, Protein; RA, rheumatoid arthritis; T2DM, type 2 diabetes mellitus; Ve, vegan.
[2] RCT (level II), randomized controlled trial.
[3] Same study/participants—different outcomes investigated.
[4] Level III-2, a comparative study with concurrent controls: nonrandomized, experimental trial.

TABLE 5 Overview of included studies reporting on biomarkers and significant differences between vegetarian- and non-vegetarian-based dietary patterns in intervention studies[1]

Biomarker	Studies included	Differences between groups (significance, $P < 0.05$)
Lymphocytes (80)	1	NS
Monocytes (78)	1	NS
Monocytes (CD14+) (78)	1	NS
Pan T cells (CD3+) (78)	1	NS
T suppressor cells (CD8+) (78)	1	NS
T helper cells (CD4+) (78)	1	NS
NK cells (78)	1	NS
Leukocytes (74, 80)	2	↓ in V group in 1/2 studies; NS 1/2 studies
Thrombocytes (74)	1	↓ in V group in 1/1 studies
CRP (72–74, 76, 77, 79, 81)	7	↓ in V group in 4/7; NS 3/7 studies
TNF-α (75)	1	NS
Fibrinogen (73)	1	NS
Interleukins		
IL-6 (76)	1	NS
Immunoglobulins		
IgM (75, 80)	2	↓ in V group in 1/2 studies; ↑ *within* V group in 1/2 studies;
IgA (75, 80)		NS
IgG (75, 80)		↓ in V group in 1/2 studies; NS 1/2 studies

[1] NS, not significant ($P > 0.05$); V, vegetarian-based.

given the encouraging, but limited, findings of this review, which included lowered total leukocyte and lymphocyte (in 2 out of 4 studies) concentrations in addition to improved NK cell activity in 1 out of 2 studies in vegetarian-based groups. Interestingly, of the 2 out of 4 studies which reported lowered total lymphocyte concentrations in vegetarian-based groups, both lymphocyte counts were within normal reference ranges [Haddad et al. (54): $3.04 \pm 0.83 \times 10^9$/L, normal reference range $1.170–4.698 \times 10^9$/L (108); and Tungtrongchitr (69) et al.: 30% and 33% white blood cells (median), normal reference range 18–54% (108)]. If lymphocyte counts are reduced in vegetarian-based populations, yet NK cell cytotoxic activity is improved, the overall effect on immune function may be favorable. Further exploration of lymphocyte concentrations and NK cell activity in vegetarian-based populations is required.

Although our review was comprehensive and systematic in nature, some limitations must be noted. Our analysis was limited by the small number of studies assessing the effect of vegetarian-based dietary patterns on fibrinogen ($n = 3$) and thrombocytes ($n = 7$) in observational studies, and on CRP ($n = 5$) in intervention studies. Furthermore, cross-sectional studies provide a high risk of bias and lower levels of study quality (compared to RCTs) (37). However, inclusion of cross-sectional studies was warranted in this review to provide an estimate of vegetarian-based eating patterns and their relation with a wide range of outcomes across a large population sample. In the case of this review, many studies used unit reporting methods which could not be converted to a common unit, preventing their use in the meta-analysis, had limited sample sizes, and often failed to control for risk factors that may have influenced inflammatory markers (e.g. BMI, physical activity, and smoking status), which may have increased the risk of bias in these studies. Moreover, many of the observational studies lacked detail on the types and quality of diet in both vegetarian and non-vegetarian groups, which presents challenges when interpreting the results of these studies. As mentioned, there was substantial variation between population groups and a small population sample pool in the intervention study quantitative analysis, limiting the generalizability of the results. Furthermore, it was unclear if 3 of the intervention studies were randomized or not.

There are also several strengths of this review. This meta-analysis is the first, to the authors' knowledge, to systematically and quantitatively assess the relation between vegetarian-based dietary patterns and biomarkers of inflammation and immune status in both observational and intervention studies. Previous studies have investigated the effects of specific nutrients and foods on markers of low-grade inflammation; however, nutrients and foods are seldom eaten in isolation (13, 95). A further strength of this review is that dietary patterns were considered as a whole, thereby taking into account the complex synergistic and antagonistic biochemical interactions, and enhancing the applicability of the findings to real-life eating patterns (1).

Conclusion

This study systematically assessed the evidence from observational and intervention studies in order to compare common biomarkers of inflammation and immune status in vegetarian-based and mixed non-vegetarian dietary patterns. Vegetarian-based dietary patterns appeared to be favorable in all quantitative syntheses; however, results should be interpreted with caution due to the limited number of studies and substantial variation between studies. Future research should focus on large-scale intervention studies, exploring differences in immune function between

vegetarian-based and non-vegetarian-based groups. This is justified given the increased consumption of "nonnutritive" immune-modulating phytochemicals typically consumed in vegetarian-based dietary patterns. Furthermore, because it appears there are favorable inflammatory profiles in vegetarian-based populations, it is plausible that immune function may also be improved given the inherent link between the two physiologic systems.

Acknowledgments

The authors' contributions were as follows—all authors: contributed to the conceptual idea of the review; JCC, EPN, and YCP: collected and analyzed the data; JCC, EPN, and YCP: interpreted the data; and all authors: contributed to the manuscript preparation, and have read and approved the final manuscript.

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