

Review Article

Association of vegetarian diet with inflammatory biomarkers: a systematic review and meta-analysis of observational studies

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Abstract*Objective:* Vegetarian diets contain various anti-inflammatory components. We aimed to investigate the effects of vegetarianism on inflammatory biomarkers when compared with omnivores.*Design:* Systematic review and meta-analysis.*Setting:* Literature search was conducted in Science Direct, Proquest, MEDLINE and Google Scholar up to June 2016. Summary estimates and corresponding 95% CI were derived via the DerSimonian and Laird method using random effects, subgroup analyses were run to find the source of heterogeneity and a fixed-effect model examined between-subgroup heterogeneity.*Subjects:* Studies were included if they evaluated effects of any type of vegetarianism compared with omnivores on circulating levels of inflammatory biomarkers. No restriction was made in terms of language or the date of study publications.*Results:* Eighteen articles were included. Pooled effect size showed no difference in high-sensitivity C-reactive protein (hs-CRP) levels in vegetarians *v.* omnivores (Hedges' $g = -0.15$; 95% CI $-0.35, 0.05$), with high heterogeneity ($I^2 = 75.6\%$, $P < 0.01$). A subgroup analysis by minimum duration of vegetarianism showed that a minimum duration of 2 years vegetarianism was associated with lower hs-CRP levels *v.* omnivores (Hedges' $g = -0.29$; 95% CI $-0.59, 0.01$), with moderate heterogeneity ($I^2 = 68.9\%$, $P < 0.01$). No significant effect was found in studies using a minimum duration of 6 months of vegetarianism, with low heterogeneity. Vegetarianism was associated with increased IL-6 concentrations (0.21 pg/ml; 95% CI 0.18, 0.25), with no heterogeneity ($I^2 = 0.0\%$, $P = 0.60$).*Conclusions:* The meta-analysis provides evidence that vegetarianism is associated with lower serum concentrations of hs-CRP when individuals follow a vegetarian diet for at least 2 years. Further research is necessary to draw appropriate conclusions regarding potential associations between vegetarianism and IL-6 levels. A vegetarian diet might be a useful approach to manage inflammaging in the long term.**Keywords**
Vegetarianism
Omnivores
Inflammation
C-reactive protein
IL-6

Low-grade chronic inflammation (inflammaging) is a known risk factor for the development of age-related diseases such as CVD, diabetes and some cancers. Inflammaging can occur as a result of cell damage and/or from environmental factors such as dietary intakes, gut microbiota and obesity⁽¹⁾. Elevated levels of high-sensitivity C-reactive protein (hs-CRP), TNF- α and IL-6 contribute to the pathogenesis of these age-related diseases⁽¹⁾ and can be used to predict 10-year all-cause mortality in older adults⁽²⁾.

Vegetarian diets have been shown to effectively reduce the risk of obesity, hypertension⁽³⁾, type 2 diabetes and insulin resistance^(3–5), dyslipidaemia (particularly elevated cholesterol levels)⁽⁶⁾, CVD⁽⁷⁾ and mortality (from either CVD or cancer)⁽⁸⁾. While the definition of vegetarianism varies, when compared with omnivores diets, vegetarian diets typically have larger amounts of antioxidant micronutrients such as vitamins C and E, phytochemicals and fibre⁽⁹⁾. These healthful components may ameliorate inflammatory processes and decrease circulating levels of inflammatory biomarkers, thereby reducing the

risk of age-related diseases. Numerous studies have reported lower serum concentrations of inflammatory biomarkers among vegetarians compared with omnivores^(10–14), and vegan and vegetarian diets have been shown to substantially alter faecal flora⁽¹⁵⁾ that play an important role in the inflammatory response⁽¹⁶⁾. A recent lifestyle intervention study indicated that vegans and vegetarians have lower levels of systematic inflammation compared with omnivores⁽¹⁷⁾.

Most of the available evidence regarding vegetarianism and chronic inflammation comes from observational studies, and their results are inconsistent. The majority of studies suggest lower levels of inflammation in vegetarians *v.* omnivores^(9–13), while other investigations have not found significant differences between groups^(18,19) or have reported greater levels of inflammatory markers (e.g. IL-6 and hs-CRP) in vegetarians⁽²⁰⁾. Two meta-analyses from 2012 and 2015 suggested a lower risk of mortality from IHD and cancer⁽⁸⁾, and lower serum levels of total cholesterol, LDL cholesterol and HDL cholesterol⁽⁶⁾, in vegetarians compared with non-vegetarians, respectively; however, no systematic review or meta-analysis has evaluated the role of vegetarianism on serum levels of inflammatory biomarkers. Since chronic inflammation plays an important role in the pathogenesis of chronic diseases and premature mortality, it is possible that the beneficial effects from a vegetarian diet are mediated by lower inflammation. The present meta-analysis was conducted using published data from observational studies to assess the effects of a vegetarian diet on serum levels of selected inflammatory biomarkers.

Materials and methods

The meta-analysis was planned, conducted and reported according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement⁽²¹⁾.

Search strategy

A systematic search was conducted to identify relevant articles using Science Direct (www.sciencedirect.com/science/journals), Proquest (www.proquest.com), MEDLINE (www.pubmed.com) and Google Scholar (scholar.google.com) databases up to June 2016. No restriction was made in terms of language or the date of study publications. The following search terms were used in literature search: 'vegetarian' OR 'vegan' OR 'plant based diet' OR 'vegetarianism' in combination with 'acute-phase proteins' OR 'Inflammation' OR 'C-reactive protein' OR 'interleukins' OR 'tumor necrosis factor-alpha' OR 'inflammatory'. The reference lists of related original and review articles were checked for additional relevant articles using a manual approach.

Eligibility criteria

Studies were eligible for inclusion in the meta-analysis if they reported effects of any type of vegetarianism

(vegan, vegetarian, lactovegetarian, ovovegetarian and lacto-ovo-vegetarian), in comparison with an omnivorous diet, on circulating levels of inflammatory biomarkers in adults. No specific criterion was considered for the duration of being on a vegetarian diet. Studies were excluded if they assessed the effects of a general healthy lifestyle that included a vegetarian diet as one component. Two independent assessors (F.H. and M.H.R.) read titles and abstracts of the retrieved articles for inclusion and exclusion criteria; disagreements were resolved by consensus (Table 1).

Data extraction and quality assessment

The following information was extracted from each article: first author's last name, publication year, sample size, sex and age of subjects, study design, duration of being on a vegetarian diet, type of vegetarianism and inflammatory biomarker values (mean with SD or SE) for both vegetarians and omnivores. Two assessors (F.H. and M.H.R.) evaluated study quality independently using the Newcastle–Ottawa scale for non-randomized studies⁽²²⁾ and any discrepancy was resolved by discussion to reach consensus.

Statistical analyses

Effect size was calculated via Hedges' g ⁽²³⁾ using the differences between means of serum levels of inflammatory markers (vegetarians *v.* omnivores) divided by their corresponding SD.

The difference in means and SD for all inflammatory markers were extracted from each eligible study and used in the meta-analysis (vegetarians *v.* omnivores). Summary estimates and corresponding 95% CI were derived via the DerSimonian and Laird method using a random-effects model incorporating the between-study variation⁽²⁴⁾. The I^2 statistic was used to evaluate the heterogeneity among the studies⁽²⁵⁾, and H^2 was calculated as another measurement for assessing heterogeneity by dividing Q by degrees of freedom⁽²⁶⁾. Subgroup analyses were run to find the source of heterogeneity, and fixed-effect models used to examine between-subgroup heterogeneity. Sensitivity analysis was used to explore the extent to which summary estimates might be related to one particular study or a group of studies, done in accordance with the Cochrane handbook for systematic reviews of observational studies⁽²⁷⁾. Publication bias was evaluated by Egger's regression asymmetry test and Begg's adjusted rank correlation test only for hs-CRP, but not for IL-6 due to limited number of studies. Statistical analyses were done using the statistical software package Stata version 11.2 and P values of <0.05 were considered statistically significant.

Results

Systematic review

Our search retrieved 855 articles, eighteen of which were selected following screening the titles and abstracts^(9–13,18–20,28–37) (Fig. 1). Characteristics of studies

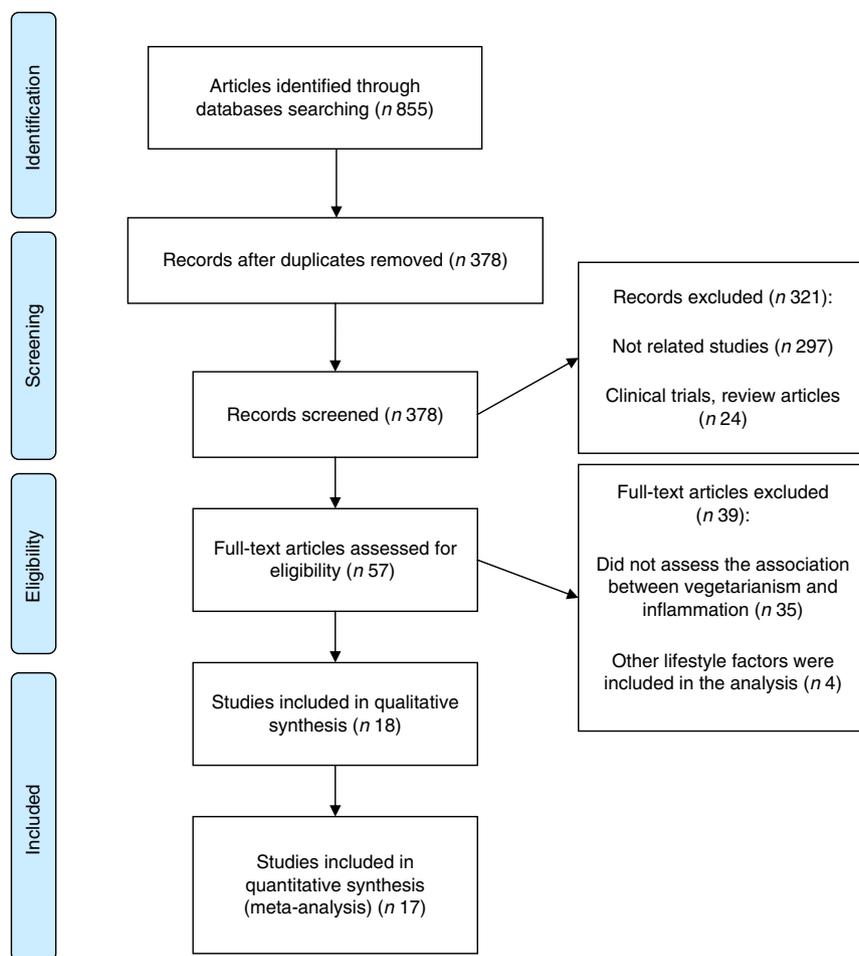


Fig. 1 Flowchart of the process of study selection

included in the systematic review are displayed in Table 1. The design of all studies was cross-sectional. Subjects were in the age range of 31 to 68 years, and duration of vegetarian diet ranged from >6 months to >5 years. Ten studies used matched groups or multivariate-adjusted models to report associations between vegetarianism and inflammatory marker(s) compared with omnivores^(12,13,18,19,29–33,35). Seven studies implemented a >2-year duration of vegetarianism^(10–13,29,32,33). Eight studies reported lower concentrations of inflammatory marker(s) in vegetarians *v.* omnivores^(9–13,28,29,31), seven studies found no difference between groups^(19,30,32–36), and three studies reported higher concentrations of inflammatory marker(s) in vegetarians *v.* omnivores^(18,20,37).

Meta-analysis

A meta-analysis was performed on seventeen studies including a total of 2398 subjects^(9–13,18–20,28–30,32–37); the study by Paalani *et al.*⁽³¹⁾ was not included in the meta-analysis because data were reported as median and interquartile range. Pooled effect size showed that there was no difference in hs-CRP levels in vegetarians *v.* omnivores (Hedges' $g = -0.15$; 95% CI $-0.35, 0.05$;

$P = 0.20$; Fig. 2). However, since heterogeneity was high ($I^2 = 75.6\%$ and $H^2 = 3.65$, $P < 0.01$ for both), subgroup analysis was run using minimum duration of vegetarianism (Fig. 3). Overall effect size of studies employing a minimum duration of ≥ 2 years of vegetarianism showed a trend towards lower hs-CRP level in vegetarians *v.* omnivores (Hedges' $g = -0.29$; 95% CI $-0.59, 0.01$; $P = 0.06$). No significant difference in hs-CRP levels between groups was found for studies employing a minimum duration of ≥ 6 months of vegetarianism (Hedges' $g = -0.00$; 95% CI $-0.17, 0.17$; $P = 0.98$). Heterogeneity was high in the ≥ 2 years of vegetarianism subgroup ($I^2 = 68.9\%$ and $H^2 = 3.22$, $P < 0.01$ for both) and low in the ≥ 6 months of vegetarianism subgroup ($I^2 = 48.4\%$ and $H^2 = 1.94$, $P = 0.06$ for both). Between-subgroup heterogeneity was significant ($P < 0.01$). Subgroup analyses based on the type of vegetarian diet (vegan, vegetarian, lactovegetarian, ovovegetarian and lacto-ovovegetarian) provided no evidence indicating that it might be the source of heterogeneity (P between subgroups = 0.363 ; see online supplementary material, Supplemental Fig. 1).

Comparison of IL-6 levels in vegetarians *v.* omnivores is shown in Fig. 4. Results suggest that vegetarians had

Table 1 Characteristics of reviewed studies on the association of vegetarian diet with inflammatory biomarkers

First author's last name (year/ country) and reference	No. of subjects (sex)	Mean age (years)	Design	Diets		Duration of vegetarian diet	Adjusted variables	Result	Study quality score
				Vegetarian	Omnivores				
Montalcini (2015/Italy) ⁽³⁰⁾	52 (M)	30	Cross-sectional	NR	NR	>3 years	BMI and age	No significant difference in most cytokines between vegetarians and omnivores	8
Yu (2014/China) ⁽³⁷⁾	195 (M)	35	Cross-sectional	Lacto-ovo	Meat intake \geq 5 times/week	>6 months	Unadjusted	Vegetarians had higher IL-6 level	6
Yang (2011/China) ⁽³⁵⁾	229 (M)	33	Cross-sectional	Lacto-ovo	NR	>1 year	Age	No significant difference in CRP between vegetarians and omnivores	8
Su (2011/Taiwan) ⁽³³⁾	90 (F)	58	Cross-sectional	Lacto-ovo	NR	>5 years	Age	No significant difference in CRP between vegetarians and omnivores	7
Paalani (2011/USA) ⁽³¹⁾	216 (NR)	69	Cross-sectional	Lacto-ovo	NR	>1 year	Multivariate	Lower CRP (not IL-6) in vegetarians	7
Krajcovicova-Kudlackova (2011/Slovakia) ⁽²⁹⁾	83 (F)	65	Cross-sectional	Lacto-ovo	NR	Long-term	Age	Lower CRP in vegetarians	7
Chen (2011/Taiwan) ⁽²⁸⁾	363 (NR)	52	Cross-sectional	Lacto-ovo	NR	>1 year	Unadjusted	Lower CRP in vegetarians	7
Yen (2010/Taiwan) ⁽³⁶⁾	49 (both)	35	Cross-sectional	All types	NR	>6 months	Unadjusted	No significant difference in CRP between vegetarians and omnivores	7
Tiahou (2009/Ivory Coast) ⁽³⁴⁾	112 (both)	30	Cross-sectional	NR	Fish consumers	>1 year	Unadjusted	No significant difference in CRP between vegetarians and omnivores	6
Chen (2008/Taiwan) ⁽¹⁰⁾	198 (both)	50	Cross-sectional	Lacto-ovo	NR	>1 year	Unadjusted	Lower CRP in vegetarians	6
Sebeková (2001/Germany) ⁽³²⁾	61 (both)	32	Cross-sectional	All types	Western mixed diet	>5 years	Age	No significant difference in CRP between vegetarians and omnivores	8
Szeto (2004/China) ⁽¹⁴⁾	60 (both)	44	Cross-sectional	Lacto-ovo	NR	>5 years	Age and sex	Vegetarians had lower CRP level	7
Fontana (2005/USA) ⁽¹³⁾	36 (both)	55	Cross-sectional	Exclusively plant food	Typical American diet	>18 months	Age, sex and socio-economic status	Vegetarians had lower CRP level	8
Sebekova (2006/Slovakia) ⁽¹⁸⁾	136 (both)	30	Cross-sectional	Lacto-ovo	NR	NR	Physical activity and education	Vegetarians had higher CRP level	8
Krajcovicova-Kudlackova (2005/Slovakia) ⁽¹²⁾	270 (both)	46	Cross-sectional	Lacto-ovo	Traditional mixed diet	>1 year	Unadjusted	Vegetarians had lower CRP level	6
Fontana (2007/Italy) ⁽¹¹⁾	42 (both)	53	Cross-sectional	Low-energy low-protein vegetarian diet	NR	>3 years	Unadjusted	Vegetarians had lower CRP level	7
Mezzano (1999/Chile) ⁽¹⁹⁾	52 (both)	31	Cross-sectional	Lacto-ovo	NR	>1 year	Age, sex and socio-economic status	No significant difference in CRP between vegetarians and omnivores	7
Lee (2016/Taiwan) ⁽²⁰⁾	154 (both)	61	Cross-sectional	Lacto-ovo	NR	>1 year	Unadjusted	Vegetarians had higher CRP and IL-6 levels	7

M, male; F, female; NR, not reported; CRP, C-reactive protein.

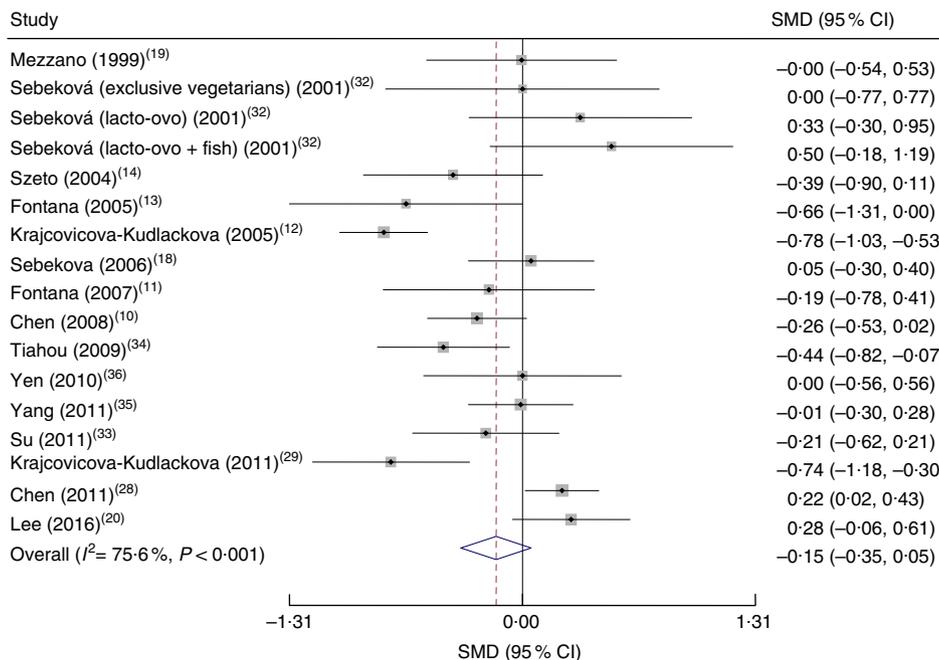


Fig. 2 Forest plot showing the overall effect of vegetarianism on C-reactive protein levels compared with omnivores. Results are effect size, presented as summarized mean difference (SMD), and 95% CI. The study-specific SMD and 95% CI are represented by the black diamond and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the overall effect size of all studies; the width of the diamond represents the overall pooled 95% CI

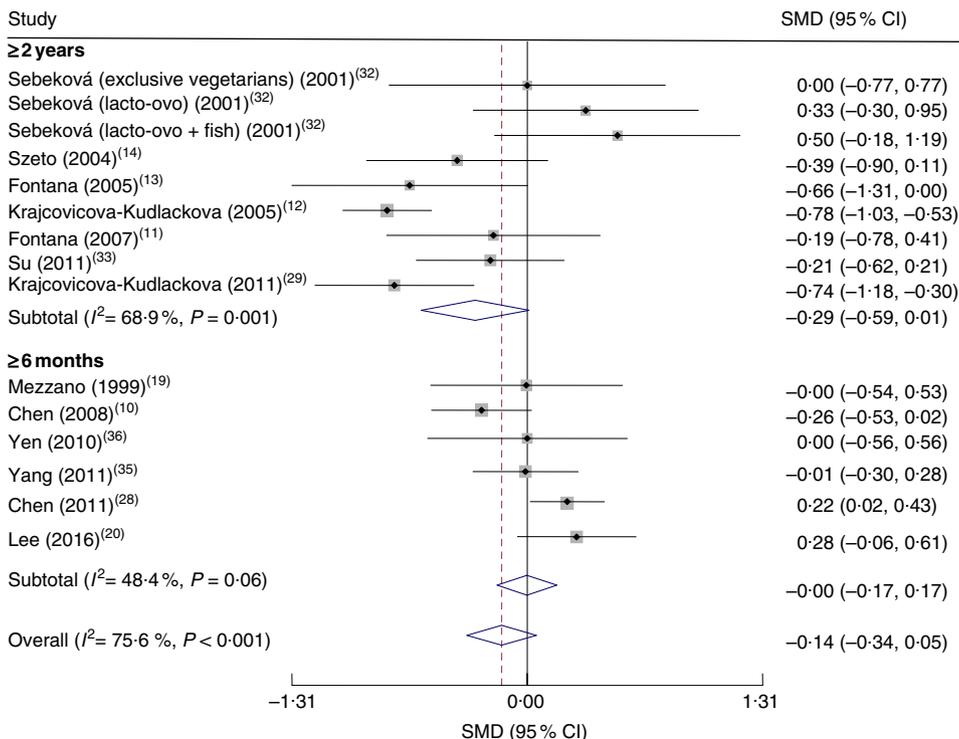


Fig. 3 Forest plot showing the overall effect of vegetarianism on C-reactive protein levels compared with omnivores by minimum duration of vegetarianism. Results are effect size, presented as summarized mean difference (SMD), and 95% CI. The study-specific SMD and 95% CI are represented by the black diamond and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the overall effect size of all studies; the width of the diamond represents the overall pooled 95% CI

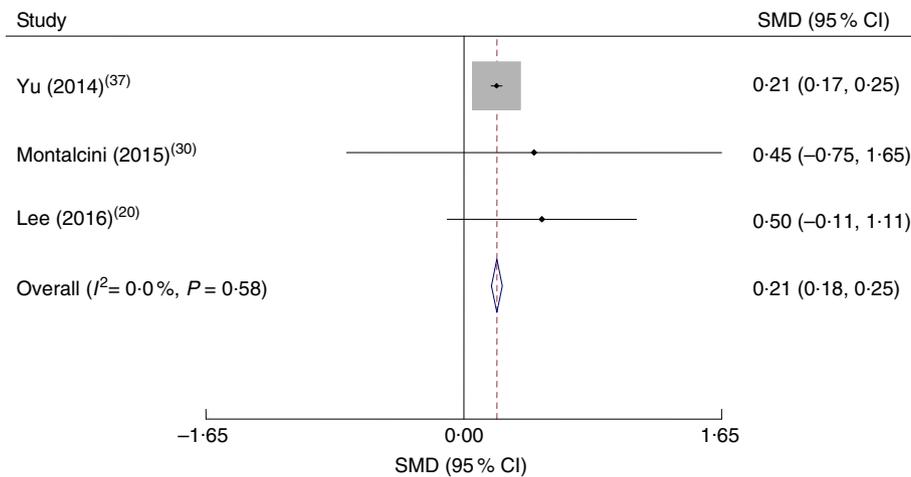


Fig. 4 Forest plot showing the overall effect of vegetarianism on IL-6 levels compared with omnivores. Results are effect size, presented as summarized mean difference (SMD), and 95% CI. The study-specific SMD and 95% CI are represented by the black diamond and horizontal line, respectively; the area of the grey square is proportional to the specific-study weight to the overall meta-analysis. The centre of the open diamond and the vertical dashed line represent the overall effect size of all studies; the width of the diamond represents the overall pooled 95% CI

higher IL-6 levels *v.* omnivores (0.21 pg/ml, 95% CI 0.18, 0.25; $P < 0.01$), with no heterogeneity ($I^2 = 0.0\%$ and $H^2 = 0.52$, $P = 0.60$).

Sensitivity analysis and publication bias

Sensitivity analysis was performed to determine the influence of each study on pooled effect size. The overall effect size of hs-CRP levels did not substantially change when individual studies were removed. In contrast, the pooled effect of IL-6 levels became insignificant after omission of the study by Yu *et al.*⁽³⁷⁾. Begg's test and Egger's test did not find evidence of publication bias in hs-CRP (Begg's: $P = 0.60$; Egger's: $P = 0.26$; see online supplementary material, Supplemental Fig. 2).

Study quality

Studies were categorized into high-quality or low-quality studies using a cut-off point of 7. Accordingly, four studies scored 6 stars and had low quality^(9,11,34,37), nine studies scored 7 stars, and five studies scored 8 stars which categorized them as having high quality (Table 1).

Discussion

Vegetarians consume large amounts of grains, fruits, vegetables, legumes and nuts. Although the health outcomes of these food components have been widely assessed, there is no consensus regarding their anti-inflammatory effects. The present study found a trend towards lower hs-CRP concentrations in subjects who were on a vegetarian diet for at least 2 years, and higher IL-6 concentrations were observed in vegetarians *v.* omnivores.

Although one study reported an association between mixed grains and hs-CRP levels⁽³⁸⁾, the majority of studies

assessed the effects of whole grains on hs-CRP. Two studies reported whole grains consumption had beneficial effects^(39,40), while two others found no favourable effects of whole grains *v.* refined grains on inflammation^(41,42). Similar discrepancies were observed for associations of fruits and vegetables with inflammation: some studies reported inverse relationships^(43,44) while others found no association between vegetable consumption and hs-CRP levels^(45,46). Several studies reported indirect associations between fruit intake and inflammatory markers^(38,45,46); however, one study reported that hs-CRP levels depend on the type of fruit consumed⁽³⁸⁾. Further, it seems that sex and BMI may influence the association between fruit and vegetable intake and hs-CRP levels⁽⁴⁷⁾.

Several studies reported that nuts have a favourable effect on inflammation^(48,49), related to the large amounts of Mg, fibre, α -linolenic acid, L-arginine, antioxidants and MUFA⁽⁵⁰⁾. Other studies reported that nuts had no beneficial effect on inflammatory markers⁽⁵¹⁻⁵³⁾. As the composition of various nuts differs⁽⁵⁴⁾, the type of nuts consumed may play an important role in the observed anti-inflammatory effects of nut intake.

Similar to other components of vegetarian diets, findings regarding the effects of legumes on inflammatory markers are not consistent. Some studies reported no association between legumes and hs-CRP levels^(45,55), while Saraf-Bank *et al.* showed that high legume intake may reduce hs-CRP concentrations after 6 weeks⁽⁵⁶⁾.

There are several agents in vegetarian diets (e.g. phytochemicals, spices, salicylic acid and dietary fibre) that may mediate the anti-inflammatory effect of vegetarianism. Phytosterols are strong anti-inflammatory agents that reduce inflammatory markers⁽⁵⁷⁻⁵⁹⁾. Some spices typical in vegetarian diets have an anti-inflammatory effect through their inhibition of pro-inflammatory marker production^(60,61).

Fruits and vegetables are known as dietary sources of salicylic acid^(62,63), an active ingredient of anti-inflammatory medications⁽⁶⁴⁾. Further, fruits and vegetables may modulate gut microbiota via dietary fibre. The ratio of the anti-inflammatory bacterium, *Faecalibacterium prausnitzii*, is higher in vegetarian diets⁽¹⁵⁾. In addition, it has been suggested that vegetarian diets improve rheumatoid arthritis, an inflammatory disease, via changes in faecal flora⁽⁶⁵⁾.

Subgroup analyses revealed that duration of vegetarianism was a source of heterogeneity. Lower hs-CRP concentrations were observed in subjects who had been on a vegetarian diet for at least 2 years, while studies including 'new' vegetarians (minimum duration of vegetarianism was 6 months) did not report any significant difference in hs-CRP levels when compared with omnivores. It seems there is a time interval between starting a vegetarian diet and reduction in hs-CRP level. Since beneficial effects of fruit and vegetable intake are in part mediated by changes in gut microbiota, perhaps longer durations are needed to observe beneficial health outcomes⁽⁶⁶⁾.

The results of a sensitivity analysis revealed that pooled effects of IL-6 levels became non-significant after omission of the study by Yu *et al.*⁽³⁷⁾. A closer look at the study design of these three reports revealed that Yu *et al.*⁽³⁷⁾ included subjects who had been vegetarians for a minimum of 6 months, while the other two studies^(20,30) assessed IL-6 levels in subjects who were on a vegetarian diet for at least 2 years. It appears that duration of vegetarianism should be considered when interpreting its effects on inflammation. Evaluating publication bias is relevant when the number of studies is larger than ten; since only three studies investigated IL-6 levels, publication bias was not evaluated and the results of this meta-analysis should be interpreted with caution.

The type of vegetarian diet in most studies included in the current systematic review and meta-analysis was lacto-ovo. Dairy products in vegetarian diet can be a double-edged sword. Although dairy products are sources of SFA, a pro-inflammatory fatty acid⁽⁶⁷⁾, they are important to meet Ca requirements⁽⁶⁸⁾. To minimize unfavourable effects of dairy products in vegetarians, dairy products can be replaced by a rich source of dietary Ca.

Several limitations should be addressed. First, although we observed elevated IL-6 levels in vegetarians *v.* omnivores, the number of studies included in the meta-analysis ($n = 3$) was not sufficient to draw reliable conclusions. Further studies should be conducted to determine the association between vegetarianism and IL-6 levels. Second, our findings were drawn from cross-sectional data; longitudinal and intervention study designs may provide additional insight into the effects of vegetarianism on inflammation. Third, dietary intakes among omnivores were not assessed. It is possible that omnivores adhered to healthy diets rich in fruits and vegetables (e.g. the DASH (Dietary Approaches to Stop Hypertension) diet). Although all studies included in the present meta-analysis used meat consumers as

omnivores, they did not focus on the type of meat consumed. There is evidence that fish intake reduces serum levels of inflammatory markers^(69,70), whereas red meat increases inflammation^(71,72). Fourth, the definition of vegetarianism was not same across studies. Inconsistencies in the definition of a vegetarian diet in the literature limit generalizability of results. Fifth, the studies included did not assess food preparation methods; food preparation methods have an important role in the context of beneficial health effects of vegetables. For example, there is an inverse association between frying temperature and anti-inflammation phytochemical contents of carrots (e.g. α -carotene, β -carotene and total carotenoids)⁽⁷³⁾. Most studies included in the present systematic review and meta-analyses were conducted in China or Taiwan. Previous studies have reported that frying foods, especially vegetables, in oil is a common cooking method in China and Taiwan⁽⁷⁴⁾. Vegetarians residing in the USA consumed more healthy foods than vegetarians residing in South Asia⁽⁷⁵⁾.

Although there are several limitations, the strengths of the current meta-analysis should be considered. To the best of our knowledge, it is the first meta-analysis that systematically reviewed and summarized associations of vegetarian diets with inflammatory biomarkers. Moreover, both Begg's rank correlation test and Egger's linear regression test demonstrated no evidence for publication bias.

Conclusion

In conclusion, results from the present study showed that those who followed a vegetarian diet for at least 2 years had lower serum concentrations of hs-CRP and increased concentrations of IL-6 in comparison with omnivores. However, only three studies assessed associations between vegetarians and IL-6; thus, findings regarding IL-6 should be interpreted with caution and further evidence should be provided to draw a valid conclusion. In contrast, fifteen studies focused on hs-CRP levels; it can be concluded that vegetarianism has a favourable effect on hs-CRP levels. Future studies should compare different types of vegetarian diets.

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Supplementary material

To view supplementary material for this article, please visit <https://doi.org/10.1017/S1368980017001768>

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