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Evaluating the effects of dietary patterns on circulating C-reactive protein levels in the general adult population: an umbrella review of meta-analyses of interventional and observational studies

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Abstract

Adopting a healthy dietary pattern may be an initial step in combating inflammation-related chronic diseases; however, a comprehensive synthesis evaluating current evidence is lacking. This umbrella review aimed to summarise the current evidence on the effects of dietary patterns on circulating C-reactive protein (CRP) levels in adults. We conducted an exhaustive search of the Pubmed, Scopus and Epistemonikos databases, spanning from their inception to November 2023, to identify systematic reviews and meta-analyses across all study designs. Subsequently, we employed a random-effects model to recompute the pooled mean difference. Methodological quality was assessed using the A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) checklist, and evidence certainty was categorised as non-significant, weak, suggestive, highly suggestive or convincing (PROSPERO: CRD42023484917). We included twenty-seven articles with thirty meta-analyses of seven dietary patterns, fifteen of which (50 %) exhibited high methodological quality. The summary effects of randomised controlled trials (RCT) found that the Mediterranean diet was the most effective in reducing circulating CRP levels, followed by Vegetarian/Vegan and Energy-restricted diets, though the evidence was of weak quality. In contrast, Intermittent Fasting, Ketogenic, Nordic and Paleolithic diets did not show an inverse correlation with circulating CRP levels. Some results from combined interventional and observational studies, as well as solely observational studies, also agreed with these findings. These dietary patterns show the potential in reducing CRP levels in adults, yet the lack of high-quality evidence suggests future studies may alter the summary estimates. Therefore, further well-conducted studies are warranted.

Keywords: **Umbrella review: Dietary patterns: C-reactive protein: Inflammation: Chronic diseases**

Low-grade inflammation refers to a condition marked by increased levels of inflammatory indicators, including C-reactive protein (CRP)[1]. This chronic, low-grade inflammation is significantly involved in the various co-morbidities linked to numerous chronic diseases, such as type 2 diabetes[2], dyslipidemia[3], stroke[4], cardiovascular disorders[5], certain types of cancer[6] and all-cause mortality[7]. The rising prevalence of these chronic diseases among the ageing global population burdens both the economy and healthcare systems significantly[8]. Consequently, it is critical to determine intervention priorities that enhance healthy ageing and thwart or postpone the onset of chronic diseases associated with inflammation.

Dietary patterns provide an alternative perspective to the conventional analysis of single nutrient intake, potentially enabling the development of more holistic dietary guidelines for health promotion, disease prevention and treatment[9]. Indeed, dietary patterns are key in regulating chronic inflammation and influencing chronic disease risk through mechanisms such as gut microbiome modulation, oxidative stress and energy balance[10,11]. The pro- or anti-inflammatory properties of dietary patterns and their components are central to these mechanisms. Healthy dietary patterns, particularly adherence to a Mediterranean diet or consuming foods like vegetables and fruits, as well as macro/micronutrients such as *n*-3 PUFA and vitamins C and E, have been demonstrated to mitigate systemic inflammation[12,13]. Conversely, the predominant Western dietary pattern, characterised by high intake of refined grains, red meat, refined sugar and saturated fats, has been associated with a pro-inflammatory response and an increase in circulating inflammatory biomarkers[14]. Therefore, adopting a healthy dietary pattern may serve as an initial step towards mitigating inflammation-associated chronic diseases.

Abbreviations: CRP, C-reactive protein; MD, mean difference; RCT, randomised controlled trial.

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Table 1. PICOS criteria for inclusion and exclusion of studies

Parameter	Inclusion criterion	Exclusion criterion
Population	Adults aged over 18 years.	Children, adolescents, and lactating or pregnant women.
Intervention	All specific dietary patterns with designated names (e.g. the Mediterranean diet, Vegetarian diet, Vegan diet and Intermittent Fasting diet).	A study evaluating the impact of individual nutrient components, micronutrients, vitamins, phytochemicals via diets or food supplements (e.g. polyphenols, carotenoids, vitamin C, *n*-3 and *n*-3 PUFA) as well as general diets (e.g. healthy dietary patterns, Western dietary patterns and traditional dietary patterns).
Comparison	No dietary intervention or any specific diets, dietary patterns or dietary interventions.	The study employed dietary patterns combined with additional interventions in the control group (e.g. exercise)
Outcome	C-reactive protein (CRP) or/and high-sensitivity C-reactive protein (hsCRP).	Inflammatory biomarkers other than CRP, such as TNF-α.
Study design	$\geq$ 2 meta-analyses of RCT or longitudinal observational studies, including cohort studies, case–cohort studies, nested case–control and cross-sectional studies.	(1) Systematic reviews without meta-analytic evidence synthesis; (2) meta-analyses not published as peer-reviewed articles in international scientific journals; (3) meta-analyses lacking appropriate data (e.g. effect size and 95 % CI) or insufficient for quantitative synthesis; (4) absence of full-text papers (only abstracts, conference papers, letters, commentaries and notes); (5) animal and/or *in vitro* studies; (6) publications in languages other than English.

PICOS, Participants, Interventions, Control, Outcomes, Study Design; RCT, randomised controlled trial.

During the past decade, numerous systematic reviews, including meta-analyses of prospective studies, have accumulated evidence concerning the associations between various dietary patterns and circulating CRP levels[15–17]. These findings hold significant implications for advancing our understanding of preventive and therapeutic strategies for chronic diseases intricately associated with inflammation. However, as of now, no comprehensive synthesis has assessed the overall strength, precision and methodological quality of these systematic reviews and meta-analyses. Consequently, this umbrella review aims to consolidate and synthesise existing evidence from meta-analysis studies on dietary patterns and their impact on circulating CRP levels in the general adult population. Our findings bolster the evidence for the robust effectiveness of anti-inflammatory dietary patterns in lowering the incidence of chronic diseases, partially achieved by the mechanism of decreasing circulating CRP levels.

Materials and methods

The authors collectively established the protocol *a priori*, and comprehensive details of the protocol governing this systematic review were prospectively registered on PROSPERO (CRD42023484917). Adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline is observed in this umbrella review, with a corresponding PRISMA checklist provided for reference. Our research endeavour was systematically designed to address the following inquiry: *'Among adult populations, which dietary patterns, as determined through a comprehensive analysis of existing evidence, effectively mitigates circulating CRP levels, and furthermore, which of these dietary patterns demonstrates the most pronounced reduction (from both observational research and randomized controlled trials (RCTs))?'* The formulation of this specific research question was structured in accordance with the PICOS (Participants, Interventions, Control, Outcomes, Study Design) principle, with detailed specifications provided in Table 1.

Search strategy

In this study, we executed an umbrella review encompassing meta-analyses of observational studies (cross-sectional, case–control and cohort studies) as well as randomised controlled trial (RCT), with a focus on evaluating the efficacy of diverse dietary interventions on circulating CRP levels in adult populations. The lead author conducted a systematic search of the Pubmed, Scopus and Epistemonikos databases, spanning from their inception to November 15, 2023. The methodology for this search strategy was enhanced by examining the reference lists of pertinent original articles, review articles and meta-analyses. This manual scrutiny was conducted to identify publications that could potentially meet the eligibility criteria. The search algorithm utilised in the present umbrella review was collaboratively formulated by the entire research team, with details provided in the online Supplementary Table S1 for reference. All search results were then imported into Microsoft Excel® for Windows for duplicate removal. In the process of study selection, two independent investigators (VTQC and NDK) systematically conducted a three-phase parallel screening encompassing titles, abstracts and full texts of all retrieved studies, adhering to predefined inclusion and exclusion criteria. Any discrepancies in the selection process were addressed through a consensus-based approach. In instances where consensus was unattainable, a third investigator (TQD) was entrusted with making the definitive decision.

Eligibility criteria

Data extraction. Data extraction from each meta-analysis was carried out using a custom-designed spreadsheet to systematically record quantitative data. This spreadsheet, developed in Microsoft Excel® for Windows, underwent a preliminary pilot test on five randomly selected papers to ensure methodological consistency and concordance among the authors. Data extracted from each eligible article included: (1) first author's name and publication year; (2) dietary patterns studied; (3) characteristics of included publications, such as number of studies,

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case/intervention numbers, total participant count, databases searched, search period, published duration of original studies, registration status, funding sources and countries; (4) meta-analysis results, including pooled estimate size with 95 % CI, heterogeneity and publication bias assessment. In instances where this information was not readily available in the included articles, it was diligently extracted from the primary studies themselves. In cases where studies implemented supplementary interventions beyond a specified time frame, data extraction was confined exclusively to values pertinent to the dietary intervention. Regarding the inflammatory biomarker CRP, which has been quantified as either CRP or hsCRP in various studies, this work uniformly refers to both terms as CRP for consistency and clarity[16]. The data extraction process was conducted by three authors (TQD, VTQC and NDK), with independent verification carried out by two other authors (NTHH and VTQC). Any discrepancies encountered during this phase were resolved through thorough discussion among the involved authors.

Assessment of methodological quality of the systematic reviews. The methodological quality of the included systematic reviews and meta-analyses was appraised through the utilisation of A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[18]. This instrument comprises sixteen items, encompassing seven critical domains (items 2, 4, 7, 9, 11, 13 and 15) and nine non-critical domains (items 1, 3, 5, 6, 8, 10, 12, 14 and 16), specifically designed to gauge review quality and confidence. Responses to each item were assessed as 'Yes' 'No' or 'Partial Yes' (indicating partial adherence to the standard). Subsequently, the included systematic reviews and meta-analyses were classified into the following tiers: high quality (zero or one non-critical weakness); moderate quality (more than one non-critical weakness); low quality (exhibiting one critical flaw with or without non-critical weaknesses) and critically low quality (manifesting more than one critical flaw with or without non-critical weaknesses). This task of bias assessment in each included systematic reviews and meta-analysis was independently undertaken by two authors (TQD and NDK). Any discrepancies that arose during this assessment were identified and resolved through collaborative discussion.

Assessment of quality of evidence. Consistent with earlier umbrella reviews, meta-analyses that demonstrated nominally significant associations were categorised into four levels of evidence: convincing, highly suggestive, suggestive, weak or non-significant association, as per previously established critera[19,20]. In summary, these criteria endeavour to evaluate the degree of statistical significance, the amount of evidence, the consistency of findings and the absence of indications of bias. A *P*-value equal to or greater than 0·05 indicates the absence of a statistically significant association. Online Supplementary Table S2 details the exhaustive criteria utilised for ascertaining the level of evidence.

Data analysis. To ascertain the pooled effect of intervention diets *v.* control groups on the CRP inflammatory biomarker, we combined the results from meta-analysis studies by classifying diet type as a categorical variable and by study designs (RCT, observational studies and a combination of both these study designs). Consequently, we computed the effect size by evaluating the differences in means (95 % CI) of inflammatory biomarker concentrations using the DerSimonian and Laird random-effects model[21]. The intention was to conduct a meta-analysis once data from a minimum of two studies became available. Summary estimates and their corresponding 95 % CI were generated employing a random-effects model, which allocates weight to each study in accordance with its individual inverse variance. To assess the degree of inconsistency among studies or the extent of variability in the effects, also referred to as statistical heterogeneity, we employed the I^2 statistic. I^2 quantifies the proportion of variability in effect estimates attributable to heterogeneity rather than sampling error. Values of ≥ 50 % and ≥ 75 % indicate substantial and pronounced heterogeneity, respectively[21]. In order to detect potential publication bias, we generated and scrutinised a funnel plot, evaluating asymmetry through visual inspection. Furthermore, if there were three or more studies available, we conducted Egger's regression asymmetry test[22]. This test allowed us to estimate small-study effects, which refer to whether smaller studies tended to yield higher risk estimates than larger ones. A *P*-value of < 0·10 was construed as indicative of the presence of small-study effects. All statistical analyses were performed using Stata software version 17 (StataCorp).

Patient and public involvement. The inception of the research question, the structuring of the study design, the interpretation of results and the composition of the manuscript were executed without involvement from patients or the public.

Results

Identification and selection of relevant literature

Our systematic literature search yielded a total of 4850 publications, from which 2263 duplicates were subsequently removed. The process of study selection, along with the reasons for exclusion, is delineated in a flow chart presented in Fig. 1. Initial screening of titles and abstracts from the remaining 2587 citations resulted in the exclusion of 2412 citations. Further scrutiny through full-text assessment of the remaining 175 publications led to the exclusion of an additional 148 publications. Additionally, a systematic review was incorporated into our analysis following its identification in the reference list of the included reviews. Ultimately, twenty-seven meta-analyses encompassing thirty reanalysed effect sizes pertaining to seven dietary patterns were deemed appropriate for inclusion in this umbrella review.

Description of included meta-analyses

The summary presents the descriptive characteristics of included reviews related to various dietary patterns, as illustrated in Fig. 2 and online Supplementary Table S3. These reviews were published between 2011 and 2023, with more than half (*n* 14, 51·9 %) emerging post-2020 (Fig. 2(a)). The quantity of databases searched varied from a minimum of 2, comprising 10 % of the total, to a maximum of 7, accounting for 6·7 %. The

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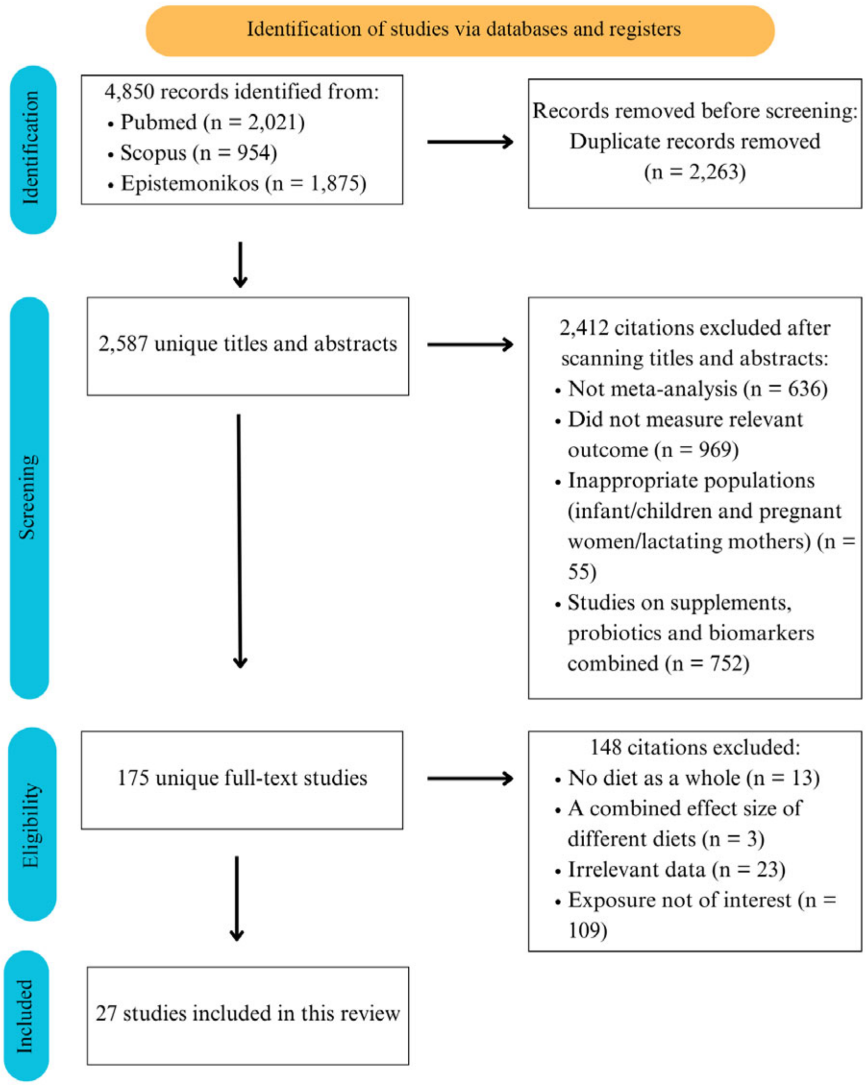

Fig. 1. PRISMA flow diagram of the literature selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

predominant number of datasets used was 4, constituting 36·7 % of the total (Fig. 2(b)). The principal databases employed for compiling research were PubMed/Medline (28·0 %), the Cochrane Library (16·8 %), Scopus (13·1 %), Embase (12·1 %) and the Web of Science (11·2 %) (Fig. 2(c)). The time frame for the primary article searches within the included review articles extended from the inception of the database until 2011–2023 (Fig. 2(d)). Additionally, nineteen reviews (63·3 %) had a registered protocol (Fig. 2(e)), and twenty reviews (66·7 %) received support from governmental or non-governmental entities (Fig. 2(f)). All reviews selected for inclusion were derived from articles published in peer-reviewed academic journals.

Online Supplementary Table S3 presents an analysis of twenty-seven reviews, indicating that the number of primary studies included in each review varied from 2 to 19. A substantial majority, twenty reviews (74·1 %), consisted of published meta-analyses of RCT. The participant cohort sizes also varied substantially, ranging from a minimum of 56 to a maximum of 7099 participants. This diversity was also mirrored in the range of intervention groups (28–3779 participants) and control groups (28–5041 participants). The mean age of participants within the primary studies ranged from 18 to 77 years, with a predominantly focus on cohorts representative of the general population. Nonetheless, a subset of the reviews specifically targeted populations afflicted with overweight or obesity[23–25], cancer[26] and various chronic diseases[27–29].

Geographically, the primary studies were distributed across six continents: Africa, Asia, Europe, North America, Oceania and South America, covering a total of thirty countries. The most substantial proportion of these studies was conducted in the USA (17·29 %), followed by Italy and Brazil (each 7·52 %), Sweden and Australia (each 6·77 %) and Germany (6·02 %), as shown in online Supplementary Table S3.

The dietary patterns explored within the intervention groups of these included reviews were classified into seven principal categories: Vegetarian/Vegan diets[16,17,24,30–32], Paleolithic diet[15,29,33], Intermittent Fasting diet[23,34–37], Energy-restricted

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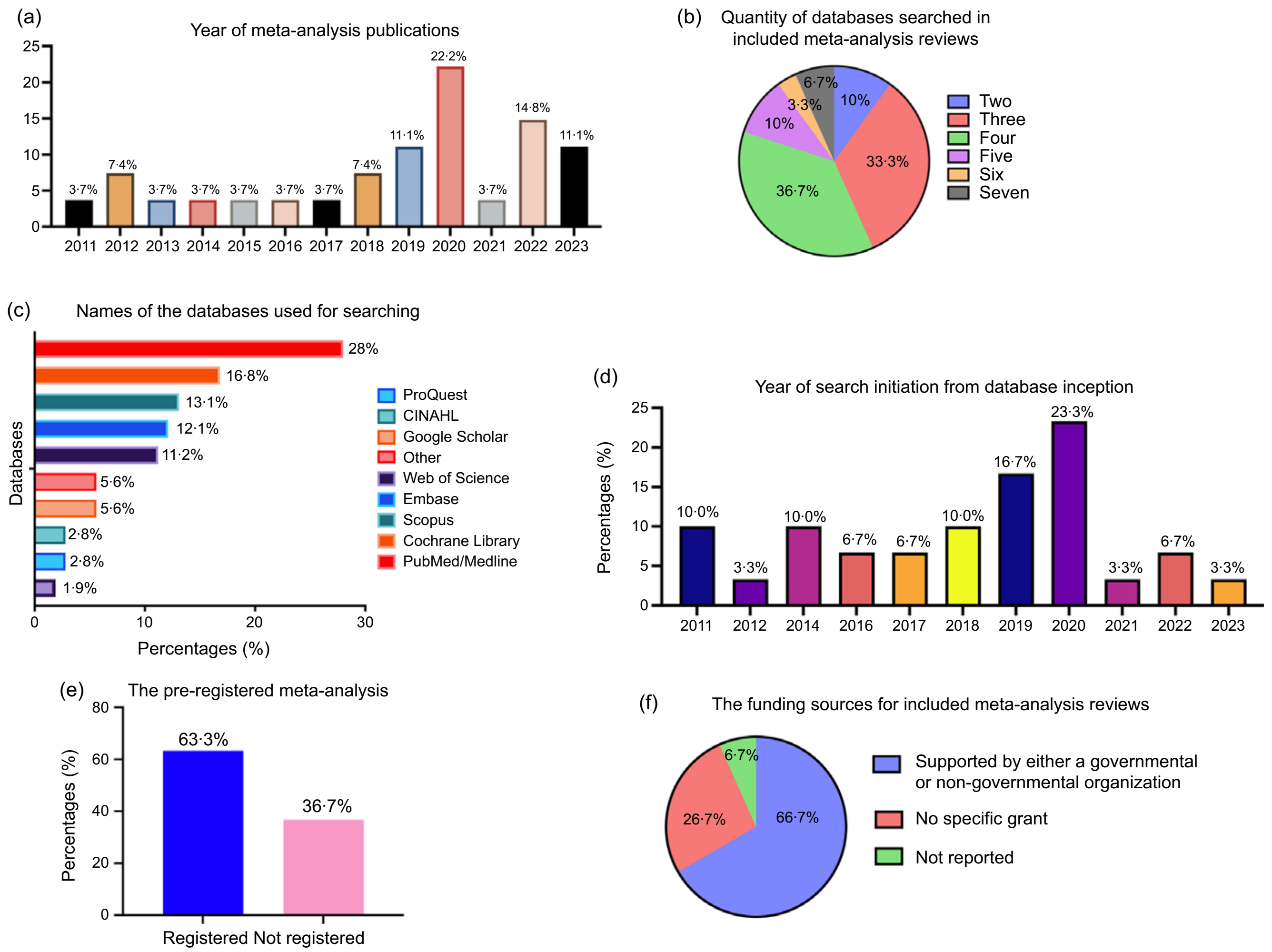

Fig. 2. General descriptive characteristics of the included meta-analyses in this umbrella review.

diet[25,34], Mediterranean diet[27,28,38–41], Nordic diet[42,43] and Ketogenic diet[26,44–46].

The methodological quality of the incorporated meta-analyses

The results of the methodological quality assessment are presented in online Supplementary Table S4 and Fig. S1. Among the retrieved meta-analyses, fifteen (50 %) were classified as having high methodological quality, five (16·7 %) as moderate, seven (23·3 %) as low and three (10 %) as critically low. The majority of the meta-analyses demonstrated either low or critically low confidence in their findings, predominantly due to non-compliance with two critical domains: first, a notable absence of a pre-established review protocol prior to execution (10 of 11, 90·9 %), and second, a lack of employed a robust technique for the evaluation and incorporation of bias risk in the individual studies during result interpretation (3 of 11, 27·3 %). Furthermore, most of the included systematic reviews and meta-analyses failed to disclose the funding sources of the included primary studies and did not sufficiently elucidate the rationale behind their selection of specific study designs for inclusion in the systematic reviews and meta-analyses.

Effects of dietary patterns on circulating C-reactive protein levels

Table 2 and online Supplementary Fig. S2–5 delineate the recalculated mean difference (MD) with their corresponding 95 % CI alongside the calibre of evidence for the correlation between dietary patterns and circulating CRP levels. Collectively, none of these associations attained classifications as either strong, highly suggestive or even suggestive in terms of evidence quality. In a detailed breakdown, weak evidence was attributed to 42·9 % (*n* 3) of the comparative analyses, whereas 57·1 % (*n* 4) were categorised under non-significant evidence.

For RCT, the Mediterranean diet exhibited the most significant reduction in adult circulating CRP levels (MD: −0·71 mg/l; 95 % CI −1·22, −0·19; $I^2 = 76{\cdot}98$ %). Following this, the Vegetarian/Vegan and Energy-restricted diets also demonstrated reductions in circulating CRP levels, although the effects were less pronounced (MD: −0·55 mg/l; 95 % CI −0·85, −0·26;

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Table 2. Summary of estimates with 95 % CI and evidence quality for the effectiveness of dietary patterns in lowering circulating CRP levels in general adult populations
(Mean difference and 95 % confidence intervals)

No.	Dietary patterns	Meta-analysis studies, *n*	Primary studies, *n*	Searching databases, *n* (mean)	Intervention groups, *n*	Control groups, *n*	Total samples	Recalculated MD*	95 % CI	*P*	I^2 (%)	Quality of the evidence
1	Mediterranean diet[a]	6	55	4·2	9074	5649	14 723	−0·61	−0·95, −0·26	<0·001	82·44	Weak evidence
2	Mediterranean diet[b]	4	37	4·4	4725	3795	8520	−0·71	−1·22, −0·19	<0·001	76·98	Weak evidence
3	Vegetarian/Vegan diets[a]	8	93	2·9	6335	12 146	18 481	−0·43	−0·60, −0·25	0·01	50·04	Weak evidence
4	Vegetarian/Vegan diets[b]	4	28	3	1075	922	1997	−0·55	−0·85, −0·26	0·05	8·52	Weak evidence
5	Vegetarian/Vegan diets[c]	4	65	2·8	5260	11 224	16 484	−0·37	−0·59, −0·15	0·02	68·39	Weak evidence
6	Energy-restricted diet[b]	2	19	4·5	624	519	1143	−0·09	−0·30, 0·12	0·02	81·73	Weak evidence
7	Intermittent Fasting diet[b]	5	27	4·0	709	578	1287	−0·03	−0·06, −0·00	0·87	0	Non-significant
8	Ketogenic diets[a]	4	19	4·3	541	641	1182	−0·05	−0·46, 0·36	0·33	27·65	Non-significant
9	Ketogenic diets[b]	2	7	5	234	247	481	0·36	−0·53, 1·25	0·36	0	Non-significant
10	Ketogenic diets[d]	2	12	3·5	307	394	701	−0·21	−0·36, −0·05	0·31	3	Non-significant
11	Nordic diet[b]	2	11	3·5	708	708	1416	−0·19	−0·71, 0·32	0·45	0	Non-significant
12	Paleolithic diet[b]	3	18	4·7	1051	1044	2095	−0·41	−0·63, −0·19	0·34	0	Non-significant

CRP, C-reactive protein; MD, mean difference.
The recalculated MD has been derived from [a] an amalgamation of both cross-sectional studies and RCT/controlled clinical trial, [b] exclusively from RCT, [c] exclusively from cross-sectional studies and [d] exclusively from controlled clinical trial. Recalculated MD along with their respective 95 % CI were computed employing random-effects models. The findings from this umbrella review were categorised into five levels: convincing, highly suggestive, suggestive, weak or non-significant association, based on criteria detailed in online Supplementary Table S2.
* Unit of CRP levels in effect size calculations: mg/l.

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$I^2 = 8·52$ % and MD: −0·09 mg/l; 95 % CI −0·30, 0·12; $I^2 = 81·73$ %, respectively). All these findings were characterised by weak evidence quality. In stark contrast, diets such as Intermittent Fasting, Ketogenic, Nordic and Paleolithic showed no inverse correlation with circulating CRP levels, with the evidence for these dietary patterns remaining consistently non-significant.

In observational studies and controlled clinical trials, the recalculated MD values were determined only for Vegetarian/Vegan and Ketogenic diets due to the limited number of included meta-analyses. Consistent with RCT findings, adherence to Vegetarian/Vegan diets was associated with a reduction in circulating CRP levels (MD: −0·37 mg/l; 95 % CI −0·59, −0·15; $I^2 = 68·39$ %), though this was supported by weak evidence quality. Conversely, Ketogenic diets did not show similar effects (MD: −0·21 mg/l; 95 % CI −0·36, −0·05; $I^2 = 3$ %).

Finally, the combined results from meta-analyses of observational studies and RCT revealed strong consistency in the order and magnitude of dietary effects on circulating CRP levels, mirroring the findings from RCT. Specifically, the Mediterranean diet showed the most significant reduction in adult circulating CRP levels (MD: −0·61 mg/l; 95 % CI −0·95, −0·26; $I^2 = 82·44$ %), while Vegetarian/Vegan diets also demonstrated reductions, though less pronounced (MD: −0·43 mg/l; 95 % CI −0·60, −0·25; $I^2 = 50·04$ %). All these findings were supported by weak evidence quality. Additionally, the Ketogenic diets exhibited limited efficacy in reducing circulating CRP levels.

Publication bias

Evidence suggestive of potential publication bias, as discerned through the asymmetry observed in the funnel plots, has been detected in relation to the associations between the Mediterranean diet and Vegetarian/Vegan diets regarding their impact on the reduction of circulating CRP levels when compared with other dietary interventions (see online Supplementary Fig. S6–7). Furthermore, except for the Energy-restricted diet, which had a limited number of reviews, we conducted an Egger test for the Mediterranean and Vegetarian/Vegan diets. The results revealed small-study effects for both diets, with P-values of 0·0082 and 0·0029, respectively.

Discussion

Principal findings

The present umbrella review has systematically synthesised evidence derived from diverse study designs, with a specific focus on elucidating the effectiveness of various dietary patterns in ameliorating circulating CRP levels. By combining our findings with the results of meta-analyses of RCT, our analysis yielded weak quality evidence suggesting that Mediterranean, Vegetarian/Vegan and Energy-restricted diets are inversely associated with circulating CRP levels in diverse adult populations with various health statuses. Furthermore, the combined results of meta-analyses from observational studies and RCT for the Mediterranean and Vegetarian/Vegan diets, as well as the meta-analyses from solely observational studies for the Vegetarian/Vegan diet, were consistent with those obtained from RCT. To the best of our knowledge, this review represents the inaugural effort to comprehensively synthesise extant meta-analyses, appraise the methodological quality of these publications and critically assess the overall quality of evidence pertaining to all relevant dietary patterns within this topic.

Interpretation in light of evidence

Adherence to the Mediterranean diet entails regular consumption of characteristic foods beneficial against inflammation and oxidation, such as fatty fish, vegetables, legumes, fresh fruits, nuts and olive oil[47]. This well-researched diet is globally recognised for its health benefits, particularly in reducing the risk of non-communicable diseases like heart disease, diabetes and cancer[48]. The elucidation of these health benefits can be partially attributed to the diet's multifaceted capability to reduce circulating levels of CRP in adult populations. This reduction is achieved through a series of biological processes, which include the modulation of lipid mediators, the alleviation of oxidative stress, alterations in gut microbiota composition and the suppression of inflammation-associated pathways. First, the Mediterranean diet, replete with n-3 fatty acids derived from sources such as salmon and mackerel, alongside oleic acid obtained from olive oil, exerts an influence on the composition of cell membrane phospholipids. This leads to a decrease in the synthesis of inflammatory eicosanoids and cytokines, thereby attenuating systemic inflammation and the levels of circulating CRP[49]. Second, the diet's abundant antioxidant constituents – comprising vitamins C and E, β-carotene, and a plethora of polyphenols present in fruits, vegetables and nuts – counteract oxidative stress. This is achieved through the neutralisation of free radicals and the inhibition of the NF-κB signalling pathway, culminating in a reduced production of pro-inflammatory cytokines and a consequent decrease in circulating CRP levels[50]. Third, the high dietary fibre content of the Mediterranean diet, sourced from legumes and whole grains, exerts a significant influence on the gut microbiota. This dietary fibre undergoes fermentation by the gut microbiota into SCFA, including butyrate, propionate and acetate. These SCFA interact with G-protein-coupled receptors on immune cells, modulating their function and diminishing the release of pro-inflammatory cytokines, which may result in a systemic reduction in inflammation and a subsequent potential decrease in circulating CRP levels[51]. Finally, the diet's rich endowment of polyphenols, particularly flavonoids, plays a pivotal role in modulating inflammatory signalling pathways. They are known to inhibit the activity of enzymes like cyclo-oxygenase-2 (COX-2) and lipoxygenase and downregulate the production of pro-inflammatory mediators like TNF-α and IL-6[52], which might be upstream of CRP synthesis in the liver.

The observed diminution in circulating CRP levels among adults adhering to Vegetarian and Vegan diets, which bear resemblance to the Mediterranean diet, can be principally ascribed to the profuse presence of antioxidants and phytochemicals. These substances are derived from a robust consumption of fruits, vegetables, nuts and whole grains, effectively attenuating oxidative stress and inflammation[53,54]. Additionally, akin to the Mediterranean dietary pattern, these dietary regimens exert a considerable influence on the composition of gut microbiota. They encourage the proliferation of beneficial bacterial strains capable of producing anti-inflammatory SCFA, which potentially contribute to the noted reduction in circulating CRP levels[55]. Distinguishing themselves from the Mediterranean diet, Vegetarian and Vegan diets often result in lower body weight and reduced adiposity compared with omnivorous diets. This difference may be illuminated by the fact that adipose tissue, especially visceral fat, is capable of producing pro-inflammatory cytokines, which elevate circulating CRP levels. Thus, the typically lower body weight and diminished fat mass associated with Vegetarian and Vegan diets are crucial in potentially reducing circulating CRP levels[56,57]. Vegetarian and, particularly, Vegan diets are characterised by a substantial intake of PUFA, notably *n*-3 fatty acids sourced from foods like flaxseeds, chia seeds and walnuts. These fatty acids possess well-documented anti-inflammatory properties, offering a potential avenue for the reduction of circulating CRP levels[58]. Furthermore, the exclusion of heme iron and N-glycolylneuraminic acid (Neu5Gc) – compounds predominantly present in red meat and linked to inflammation – marks a distinctive feature of Vegetarian and Vegan diets[59]. This avoidance may potentially contribute to the lower circulating CRP levels observed in individuals adhering to these dietary patterns. Lastly, several additional mechanisms have been postulated, encompassing enhanced insulin sensitivity[60], heightened nitric oxide production[61] and the presence of phytochemicals and alkaloids[62]. Collectively, these mechanisms play a role in attenuating inflammation and, consequently, may contribute to the reduction in circulating CRP levels.

Energy-restricted diets have been associated with the reduction of circulating CRP levels in humans, although the exact mechanisms have not been clearly elucidated. A plausible explanation for this phenomenon is the substantial weight loss frequently observed in individuals adhering to such diets. Weight loss, particularly the reduction of adipose tissue, can lead to a decrease in pro-inflammatory cytokines produced by adipocytes[63]. Additionally, energy-restricted diets are conjectured to exert a mitigative effect on cellular senescence, a phenomenon intimately associated with ageing and inflammation. This effect is thought to occur through the preservation of cellular integrity and the prevention of cellular damage. The proposed mechanisms facilitating this protective effect include the reduction of oxidative stress and inflammation, as well as the enhancement of autophagy[64]. These processes collectively contribute to the maintenance of cellular health and may thus play a role in attenuating the systemic inflammatory response, as evidenced by reduced circulating CRP levels.

Limitations of the included meta-analyses and prospective research trajectories

In this umbrella review, we systematically identify significant research gaps and underline the necessity for methodologically rigorous meta-analyses. First, an observation was made regarding the relatively limited number of meta-analytic articles available on the subject, indicating that this field of research is still nascent and merits further empirical investigation. Second, a proportion of the meta-analyses (fourteen out of thirty), each involving ≤ 5 primary studies, reveal evidence of small-study effects or the potential for publication bias[15,16,23,28,29,35,37–40,43–46]. Third, a substantial portion of these meta-analyses acknowledges the lack of clearly established criteria for inclusion and exclusion, as well as for intervention designs, which encompass critical elements such as intervention duration, age, sex, dosage and the health status of participants in their included primary studies. Furthermore, the definition of dietary patterns displayed heterogeneity and experienced variability across various geographical and cultural contexts, as exemplified by the Mediterranean diet[27], Vegetarian diet[17] and Nordic diet[43]. Dietary research encounters inherent methodological challenges such as the measurement and quantification of dietary intakes[35,36], as well as issues pertaining to recall bias, misreporting, misclassification and measurement error[16,30,32,35]. These lack of precision have led to notable heterogeneity in the assessment of dietary patterns and their influence on inflammation markers[15,23,24,26,27,30,32,35–37,40–43,45]. Fourth, the majority of both primary studies and systematic reviews omitted descriptions of dietary compliance, which has the potential to lead to an underestimation of the true intervention effects and introduce complexity in the interpretation of these studies[15,17,29,30,38]. Finally, the uniformity of isoenergetic diets across study arms was inconsistent, posing challenges in differentiating the effects of dietary pattern alterations on reduced energy intake and, consequently, their potential influence on circulating CRP levels[23,25,27,33,40,43].

Future research should prioritise harmonising methodologies to evaluate adherence to various dietary patterns and standardising assessment criteria and definitions of these diets. To facilitate this, the establishment of international research guidelines is suggested. Our analysis confirms the need for a more unified and standardised methodological approach in future studies, emphasising detailed documentation of intervention protocols, definition of dietary patterns, baseline participant characteristics, sample sizes and outcome data. Implementing this structured approach is expected to significantly enhance the accuracy of assessing how dietary patterns affect circulating CRP levels and the associated metabolic processes. Despite some methodological weaknesses in the meta-analyses reviewed, a clear trend emerges: adherence to Mediterranean, Vegetarian/Vegan and Energy-restricted diets is consistently associated with lower levels of circulating CRP, and none of the studies reviewed suggest these diets negatively affect inflammatory markers. Lastly, we recommend that researchers pre-register their study protocols on platforms like PROSPERO to ensure high methodological standards.

Strengths and limitations

Our umbrella review had several strengths. It was the first comprehensive analysis of meta-analyses assessing the effect of dietary patterns on reducing circulating CRP levels. Efforts were made to minimise bias, such as recalculating all meta-analyses using a random-effects method and having two authors independently conduct the review process. Additionally, we assessed the methodological quality and evidence strength of all identified associations using validated tools. This process helped identify significant research gaps and inform future research directions.

This umbrella review also had several limitations. First, we were unable to perform subgroup analyses (e.g. by age, sex and geographical location) and sensitivity analyses (e.g. excluding high-risk studies) due to limited subgroup data and a scarcity of available meta-analyses. Second, the quality of our umbrella review and its conclusions may be influenced by the heterogeneity among the included meta-analyses, specifically regarding the measurement of dietary exposure in the primary studies varied, leading to differences in questionnaires, analytical approaches and baseline circulating CPR levels. Furthermore, the paucity of prospective studies within these meta-analyses and our umbrella review exacerbates issues of limited statistical robustness, the risk of publication bias and the overall diminished credibility of the evidence. Consequently, further large-scale and high-quality intervention trials are needed to accurately gauge the influence of dietary patterns on the modulation of circulating CRP levels in a general adult cohort. Third, in our review, the majority of studies predominantly featured Western participants, a situation partly attributable to the exclusive inclusion of studies published in English. Additionally, numerous studies over the past decades have consistently indicated that a Western diet is associated with sustained systemic inflammation[65]. These limitations raise concerns regarding the applicability of our findings to diverse ethnic groups and communities with limited resources. Finally, the reliability of our review depended on the included meta-analyses and, indirectly, on primary studies.

Conclusions

Given the escalating prevalence of chronic diseases linked to inflammation, there exists a necessity for empirically grounded recommendations concerning the health implications of various dietary patterns. Notwithstanding the acknowledged limitations of the current literature, our findings provide further substantiation for the protective influence of dietary patterns against elevated circulating CRP levels in the diverse adult population, encompassing a range of health conditions. Specifically, our review highlights that adherence to healthy dietary patterns, encompassing the Mediterranean, Vegetarian/Vegan and Energy-restricted diets, exhibits a discernible association with reduced circulating CRP levels. These observed associations offer robust mechanistic evidence regarding the potential anti-inflammatory properties of these dietary patterns. However, none of these dietary patterns examined in our study received a high-quality evidence rating; all were deemed to have weak quality evidence, primarily attributed to the limited number of meta-analyses included. From a public health perspective, it implies that these dietary patterns accommodating individual contextual factors such as culture, food availability and taste preferences may yield analogous reductions in circulating CRP levels, mirroring the observations presented in this review.

To enhance the evidential certainty regarding the impact of dietary patterns on circulating CRP levels in adults, future studies should prioritise minimising bias. This can be achieved through increased incorporation of RCT that examine the long-term effects of dietary interventions, while also including isoenergetic comparisons between intervention and control groups. Additionally, forthcoming primary research should adhere to standardised methodologies, conduct comprehensive analyses and provide meticulous reporting of baseline participant characteristics, dietary pattern definitions, sample sizes and data collection procedures. Such measures will facilitate a more precise quantification of the association between various dietary patterns and not only circulating CRP levels but also other inflammation markers and disease outcomes in specific study populations. Finally, future systematic reviews and meta-analyses need to follow current guidelines for conducting and reporting included studies to ensure methodological rigour and transparency.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114524001648

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