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## Etiology and Pathophysiology

# Effect of plant-based diets on obesity-related inflammatory profiles: a systematic review and meta-analysis of intervention trials

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## Summary

Plant-based dietary interventions have been proposed to reduce obesity induced chronic low-grade inflammation and hence prevent chronic disease risk; however, human evidence remains unclear. This systematic review and meta-analysis of intervention trials aimed to assess the effect of plant-based diets on obesity-related inflammatory biomarker profiles. Medline, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published until January 2016 and mean differences in biomarkers of inflammatory status were assessed for: C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), soluble intercellular adhesion molecule 1 (sICAM), leptin, adiponectin and resistin. Of initially identified 2,583 publications, 29 met the meta-analysis inclusion criteria [a total of 2,689 participants]. Consumption of plant-based diets was associated with a reduction in the mean concentrations of the following biomarkers: CRP [effect size, −0.55 mg/l, 95% confidence intervals (CI): −0.78; −0.32, $I^2 = 94.4\%$], IL-6 [effect size, −0.25 ng/l, 95% CI: −0.56; 0.06, $I^2 = 74\%$], and, to some degree, sICAM (−25.07 ng/ml [95% CI: −52.32; 2.17, $I^2 = 93.2\%$]). No substantial effects were revealed for TNF-α, resistin, adiponectin and leptin. Plant-based diets are associated with an improvement in obesity-related inflammatory profiles and could provide means for therapy and prevention of chronic disease risk. © 2016 World Obesity

**Keywords:** Adipose-tissue inflammation, chronic disease, metabolic dysfunction, plant-based diets, prevention.

**Abbreviations:** DASH, Dietary Approach to Stop Hypertension; CENTRAL, Cochrane Register of Controlled Trials; CRP, c-reactive protein; IL-6, interleukin 6; TNF-α, tumour necrosis factor-alpha; sICAM, soluble intercellular adhesion molecule 1; BMI, body mass index; PREDIMED, Prevención con Dieta Mediterránea.



## Introduction

Chronic low-grade inflammation is a common condition in obese patients and has been established as an underlying etiological factor for many obesity-related chronic diseases, such as cardiovascular disease, type 2 diabetes mellitus and cancer (1). The high obesity prevalence affecting populations throughout the world and the increasing chronic disease burden necessitate the development of effective strategies to reduce risk for obesity complications and sequelae (2).

In this context, nutritional interventions targeting intermediary inflammatory pathways could be especially beneficial and warrant a focus on overall dietary patterns rather than on individual nutrients or supplements (3). Evidence from observational research has recently suggested that various plant-based diets are associated with improved inflammatory profiles, thereby lowering the risk of chronic diseases (4). Plant-based diets are defined as complex dietary patterns that emphasize foods of plant origin, particularly vegetables, grains, legumes and fruits (5). These diets generally exclude or rarely include meats, but may include dairy products, eggs and fish (5). Variations of plant-based diets include the Mediterranean style diet (6), the Nordic diet (7) and the Dietary Approaches to Stop Hypertension (DASH) diet (8), for which previous studies reported favourable associations with lower chronic disease risk. In this context, it could be hypothesized that plant-based dietary strategies may in fact prevent the generation of pro-inflammatory environment in the human organism, thereby reducing obesity-associated chronic disease risk.

To our knowledge, the available evidence regarding the association between plant-based diets and inflammatory profiles in obesity has not been subjected to a meta-analysis. To clarify the nature of this association which could prove useful in formulating dietary guidance, we performed a meta-analysis of intervention studies that had examined associations between plant-based diets and biomarkers of inflammatory status compared to non-plant-based diets in predominantly obese and metabolically afflicted patients.

## Methods

### Study protocol

The study protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42015027109).

### Data sources and search strategy

Electronic databases Medline, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for articles published in the period from January 1946 to January 2016. The search included the following keywords: (diet OR Nordic diet OR Mediterranean diet OR vegetarian diet OR plant-based diet OR Paleolithic diet OR dietary pattern OR DASH) AND (Adiponectin OR C-reactive protein (CRP) OR interleukin-6 OR IL-6 OR CRP OR inflammatory profile OR inflammation OR adipokines) and was complemented with specific search terms to identify intervention trials. No restrictions were made regarding language. We opted for using a broader search term criteria in order to allow identification of a larger number of potentially eligible studies. The reference lists of the retrieved articles were subsequently reviewed for identification of additional articles. Additionally, reference lists of related reviews and meta-analyses were further screened for potentially eligible publications. When necessary, the relevant authors were contacted by the investigators to acquire missing information.

### Study selection and eligibility criteria

Two reviewers (F.E. and K.A.) independently evaluated eligibility of studies using the following inclusion criteria: (i) use of a biosample of participants older than 18 years of age; (ii) an intervention consisting of a plant-based diet, defined as a diet consisting of plants as main source of nutrients, while small amounts of meat, fish and dairy are not excluded; (iii) collection of sufficient data to allow calculation of mean differences in inflammatory biomarkers between individuals consuming a plant-based diet and those consuming a referent or control diet (low-fat diet, habitual diet, western-type diet etc.); and (iv) use of a intervention trial study design (e.g. parallel, crossover). The exclusion criteria were (i) duration of the intervention $< 4$ weeks; (ii) using a study sample consisting of pregnant women or terminal ill patients; (iii) use of concomitant intervention in the diet intervention group (e.g. pharmacological treatment or lifestyle intervention, i.e. physical exercise); and (iv) focus on individual plant-based food components or nutrients rather than dietary pattern as a complex intervention approach. If several publications of one study reported the same outcome variables, studies with longer intervention duration or larger sample size were retained in the analysis, where duration was prioritized over sample size. With regards to outcome assessment, our initial approach was to evaluate the existing literature on all known biomarkers of inflammation. Availability of information for biomarkers not mentioned in this review was sparse and not possible to pool. Meta-analyses were therefore conducted for the following biomarkers forming inflammatory profiles: CRP, IL-6, tumour necrosis factor-alpha (TNF-α), soluble intercellular adhesion molecule 1 (sICAM), leptin, adiponectin and resistin.

### Data extraction and quality assessment

For each of the selected studies, the following information was recorded in the data extraction sheets: (i) study design and sample characteristics, including duration of trial, number of observations, mean age, gender distribution (proportion of females), mean body mass index (BMI) [calculated as weight in kilograms divided by height in metres squared]; (ii) information on dietary interventions (type and duration of intervention and control diets); and (iii) outcome assessment (biomarker measurements, adherence to diets). If studies introduced additional interventions

after a certain period of time, only values from the dietary intervention were extracted. Mean values for baseline mean age and proportion of females were calculated where not provided. Quality of individual publications was assessed based on the 'Cochrane's tool for assessing risk of bias' grading the publications according to the following criteria: (i) the risk for selection; (ii) performance; (iii) detection; (iv) attrition; and (v) reporting bias. Grading levels were 'high', 'low' and 'unclear' risk and criteria for the judgement were based on the 'Cochrane Handbook for Systematic Reviews of Interventions' (9).

### Data synthesis and statistical analysis

To estimate the pooled effect of the plant-based intervention diets compared to control diets on each respective inflammatory biomarker, estimates of the net changes in biomarker concentrations or post-intervention values were combined using a random-effects model, which assigns a weight to each study on the basis of an individual study's inverse variance. Net change values were preferred over post-intervention values, when both were available from one study. Consistency of results was evaluated based on calculation of $I^2$ index (also known as a 'heterogeneity index') which examines the null hypothesis that all studies are evaluating the same effect (10).

Stratification was preformed according to: age, sex, type of diet, disease state and geographic region and $I^2$ of each subgroup was inspected. Further, multivariable meta-regression was performed for these factors plus study size, duration of intervention, mean baseline BMI status and weight change in intervention versus control group whenever data was available. These analyses were performed whenever the number of studies was sufficient enough for this type of analysis ($n > 10$). Last, sensitivity analyses for outliers and study quality were performed to investigate single studies as potential sources of heterogeneity.

To identify publication bias, funnel plots were generated and examined. Asymmetry of generated funnel plots was assessed by visual inspection and the Egger's test (11). The trim-and-fill method was used to adjust for publication bias as previously reported (12). All analyses were performed using statistical software R (version 3.2.2) with the 'meta'-package (13).

## Results

### Data search results

The systematic literature search produced a total of 2,583 publications after exclusion of duplicates from the different databases. After initial screening, 2,496 publications were excluded and a further 58 records were excluded following full-text assessment. Reasons for exclusion after assessment of the full-text are shown in Fig. 1.

### Study characteristics

Main characteristics of the included studies are summarized in Table 1. Overall, 29 publications of 25 studies were included in the meta-analysis with a total of 2,689 participants at a median age of 53 years (range 28–68 years). Among the studies, 21 were parallel control trials among which only one study was non-randomized, three studies used a cross-over design and one study used a consecutive trial design, where participants were first standardized to a control diet and then set under the plant-based diet. The study durations ranged from 5 to 96 weeks where nine studies were of 48 weeks or longer duration. The average BMI (SD) of the included study population was 29.03 (2.47) kg/m$^2$. Of all participants, 61% had a BMI between 25 and 29.9 kg/m$^2$ and 37% had a BMI ≥30 kg/m$^2$. Only one study comprising 2% of the included participants reported mean BMI <25 kg/m$^2$. Majority of the studies were conducted among metabolically afflicted participants with 89% of the participants (18 out of 25 studies) diagnosed with metabolic syndrome, type 2 diabetes or CVD. Main choice for a plant-based dietary intervention was the Mediterranean diet ($n = 17$). Other types of diet included: Nordic diet ($n = 4$), DASH diet ($n = 2$), Vegetarian diet ($n = 1$) and the Paleolithic diet ($n = 1$). Short description of the food components composing respective diet types are provided in the supplement (Table S1). Most commonly applied types of control diets were low-fat diets characterized by reduced intake of fat enriched foods leading to <30% energy intake from fat ($n = 11$) or habitual (Western-type) diets ($n = 14$). With regards to the outcome assessment, most of the intervention trials were focused on CRP ($n = 24$; 2,008 observations) and IL-6 ($n = 8$; 975 observations) as biomarkers representing inflammatory response, whereas a restricted number of studies evaluated TNF-α ($n = 5$; 368 observations), sICAM ($n = 5$; 534 observations), resistin ($n = 3$; 275 observations), leptin ($n = 4$; 488 observations) and adiponectin ($n = 7$; 911 observations).

### Pooled effects of plant-based diets on inflammatory biomarker profiles

Among the different biomarker profiles, the most apparent effect of plant-based diets overall was observed for the biomarkers CRP, IL-6 and, to some degree, sICAM, whereas no (statistically significant) effects were revealed for the remaining biomarkers TNF-a, resistin and leptin (Table 2). Adiponectin levels showed a tendency for an increase, but also remained statistically not significant (Figure S1). Mean differences in biomarker concentrations between intervention and control groups were −0.55 mg/l [95% confidence

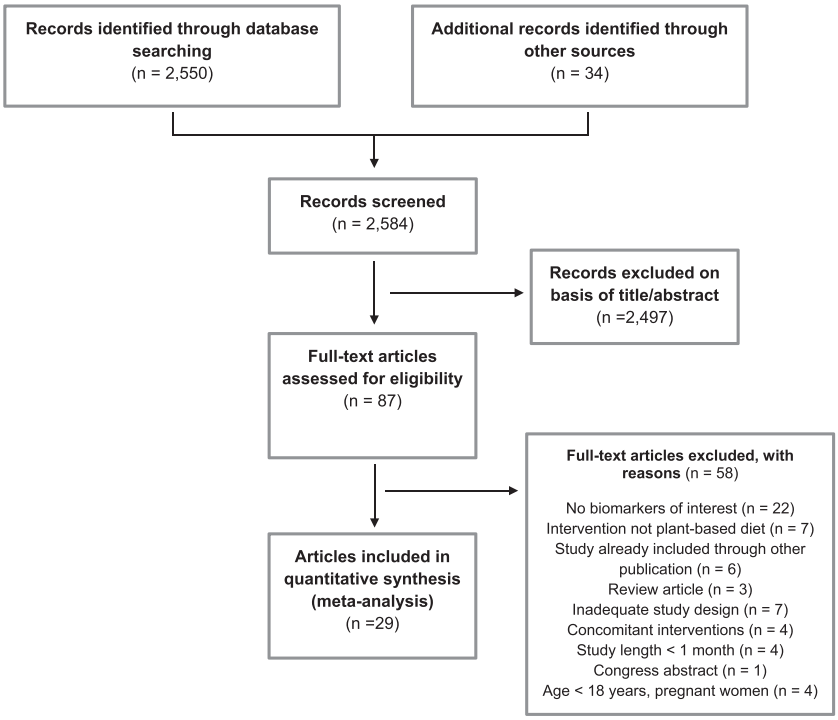


**Figure 1** PRISMA flow chart. Selection process from initial search to final number of included studies.

intervals (CI): −0.78; −0.32, $I^2 = 94.4\%$] for CRP (A), −0.25 ng/l [95% CI: −0.56; 0.06; $I^2 = 74\%$] for IL-6 (B), and −25.07 ng/ml [95% CI: −52.32; 2.17, $I^2 = 93.2\%$] for sICAM (C), respectively (Fig. 2).

### Subgroup analysis and meta-regression

In stratified analyses conducted separately for each individual biomarker, no apparent sources of observed heterogeneity of overall results have been revealed (Table S2). An exception was the suggested heterogeneity according to geographic region (*P* for group difference, 0.05, 0.006, 0.03 for CRP, IL-6 and sICAM, respectively). Studies conducted in the Southern European Countries seemed to report stronger effects compared to studies from North Europe or in the Americas (Table S2). However, because of the disproportional number of studies within sub-groups these results should be cautiously interpreted. Multivariable meta-regression yielded no significant results for CRP regarding age, study size, sex, duration of trial, BMI and reported change in weight compared to control (Table S3). The number of studies for the remaining biomarkers was too low (<10) to warrant meta-regression analysis.

### Risk of bias assessment

Results of the risk of bias assessment are summarized in Fig. 3. Overall, risk of performance bias was 'high', while a 'low' risk for attrition bias and reporting bias could be observed. Risk of bias for random sequence generation, allocation concealment and blinding of outcome assessment could not be evaluated in a number of studies because of insufficient information and lead to 'unclear risk'-ratings in most of the evaluated studies. The generated funnel plot for CRP showed no evidence for publication bias through visual inspection or Egger's test (Figure S2). The trim-and-fill method produced a theoretical pooled estimate of −0.55 mg/l [95% CI: −0.79; −0.32; $I^2 = 94\%$] after one theoretically missing study was added.

## Discussion

In this systematic review and meta-analysis of intervention trials including 2,689 predominantly obese and metabolically afflicted patients, consumption of plant-based diets was associated with overall improvement in inflammatory profiles compared with consumption of control diets. The most pronounced effects were observed for CRP, IL-6 and sICAM as biomarkers indicating chronic low-grade inflammation and activated innate immunity. No statistically significant effects of plant-based diets were identified for TNF-α, adiponectin, leptin and resistin. This meta-analysis provides the most comprehensive estimates to date summarizing the effects of plant-based diets on inflammatory biomarker profiles, including a presentation of effects by various dietary types. As such, the findings provide important evidence to support plant-based diets as means for prevention of adiposity-related chronic disease risk.

**Table 1** Designs and population characteristics of intervention trials of plant-based diets* and inflammatory profiles#

| Reference | Size % Female | Age [years]§ Drop-out rate | BMI [kg/m$^2$]§ | Study design Duration of trial | Study population Country | Intervention | Control | Application of intervention | Dietary assessment |
|---|---|---|---|---|---|---|---|---|---|
| Asemi *et al.* 2014 (47) | 48 100% | 30 ± 6.4 11% | 30.3 ± 4.7 | Parallel 8 weeks | Overweight with polycystic ovary syndrome Iran | DASH, calorie-reduction (−350 to −700 kcal) | Traditional Iranian diet | 7-day menu cycle, personalized dietary advice | 3-day food records |
| Athyros *et al.* 2011 (48) | 100 51% | 54.7 ± 3.8 0% | 27.6 ± 2.3 | Parallel 16 weeks | Individuals with mild hypercholesterolaemia Greece | Mediterranean diet, *ad libitum* | Hypolipidemic diet | 7-day menu cycle, dietary advice | Semi-quantitative questionnaire |
| Azadbakht *et al.* 2011 (49) | 31 58% | 55.0 ± 6.5 30% | - | Crossover 8 weeks | Type 2 diabetics Iran | DASH, isocaloric | Standard diet for diabetic patients | Personalized dietary advice | 3-day food records |
| Bladbjerg *et al.* 2011 (50) | 80 59% | 28 ± 4.6 16% | 31.4 ± 2.6 | Parallel 24 weeks | Healthy Obese Denmark | High-MUFA diet, *ad libitum* | Average Danish diet | Dietary advice | 3-day dietary record |
| Casas *et al.* 2014 (51) | 109 58% | 68 ± 6 1% | 28.2 ± 3.5 | Parallel 48 weeks | Patients with metabolic syndrome Spain | Mediterranean diet, *ad libitum* | Low-fat diet | Personalized dietary advice, supply with key foods | FFQ |
| Ceriello *et al.* 2014 (52) | 24 29% | – 0% | 29.5 ± 1.3 | Parallel 12 weeks | Type 2 diabetics receiving metformin Italy | Mediterranean diet, *ad libitum* | Low-fat diet | Dietary advice | Not specified |
| de Mello *et al.* 2011 (53) | 70 51% | 59 ± 7 29% | 31.0 ± 3.5 | Parallel 12 weeks | Patients with metabolic syndrome Finland | Nordic-type diet *ad libitum* | Habitual diet with restriction of fish, bilberry and whole grain | Dietary advice, supply with key foods | 4-day dietary record |
| Djuric *et al.* 2009 (54) | 60 100% | 44 13% | 24 ± 2.8 | Parallel 24 weeks | Apparently healthy United States | Mediterranean diet, *ad libitum* | Habitual diet (+ written material to correct nutritional deficiencies) | Personalized dietary advice | 7-day dietary record |
| Esposito *et al.* 2004 (55) | 180 45% | 44 ± 6 8% | 28 ± 3.3 | Parallel 96 weeks | Patients with metabolic syndrome Italy | Mediterranean diet, *ad libitum* | Habitual diet (+ written information on healthy food choices) | Personalized dietary advice | 3-day dietary record |
| Esposito *et al.* 2009 (56) | 215 51% | 52 ± 11 9% | 29.6 ± 3.5 | Parallel 48 weeks | Type 2 diabetics Italy | Mediterranean diet, calorie-restricted (♀:1500 kcal/d; ♂: 1800 kcal/d) | Low-fat diet, calorie-restricted (♀:1500 kcal/d; ♂: 1800 kcal/d) | Dietary advice | Food diary |
| Itsiopoulos *et al.* 2010 (57) | 27 41% | 59 12% | 30.7 | Crossover 24 weeks | Type 2 diabetics Australia | Mediterranean diet, *ad libitum* | Habitual diet | Dietary advice, supply with foods | Unspecified record |
| Jönsson *et al.* 2009 (58) | 13 23% | 64 ± 6 0% | 30 ± 7 | Crossover 12 weeks | Type 2 diabetics Sweden | Paleolithic diet, *ad libitum* | Standard diet for diabetic patients | Dietary advice | 4-day dietary record |
| Kahleova *et al.* 2010 (59) | 74 53% | 56 ± 6.7 16% | 35.0 ± 5.4 | Parallel 24 weeks | Type 2 diabetics Czech Republic | Vegetarian diet, calorie-reduction (−500 kcal) | Standard diet for diabetic patients | Dietary advice, supply with foods | 3-day dietary record |

(*Continues*)

**Table 1** (Continued)

| Reference | Size % Female | Age [years]§ Drop-out rate | BMI [kg/m$^2$]§ | Study design Duration of trial | Study population Country | Intervention | Control | Application of intervention | Dietary assessment |
|---|---|---|---|---|---|---|---|---|---|
| Konstantinidou *et al.* 2010 (60) | 89<br>80% | 44 ± 11<br>2% | 25.0 ± 4.0 | Parallel<br>12 weeks | Apparently healthy<br>Spain | Mediterranean diet, *ad libitum* | Habitual diet | Personalized dietary advice | FFQ |
| Lasa *et al.* 2014 (61) | 141<br>57% | 67 ± 7<br>0% | 29.6 ± 2.8 | Parallel<br>48 weeks | Patients with metabolic syndrome and without previous cardiovascular disease<br>Spain | Mediterranean diet + 50 ml/day olive oil, *ad libitum* | Low-fat diet | Personalized dietary advice | FFQ |
| Maiorino *et al.* 2016 (62) | 215<br>51% | 52 ± 11<br>7% | 29.6 ± 3.5 | Parallel<br>48 weeks | Type 2 diabetics<br>Italy | Mediterranean diet, calorie-restricted (♀:1500 kcal/d; ♂: 1800 kcal/d) | Low-fat diet, calorie-restricted (♀:1500 kcal/d; ♂: 1800 kcal/d) | Dietary advice | 3-day dietary record |
| Mekki *et al.* 2010 (63) | 40<br>45% | 61 ± 14<br>0% | 26.2 ± 5.6 | Parallel<br>13 weeks | Patients with moderate chronic renal failure and dyslipidemia<br>Algeria | Mediterranean diet, *ad libitum* | Standard diet for kidney disease | Dietary advice | 24-h recall |
| Poulsen *et al.* 2014 (64) | 181<br>71% | 42 ± 13<br>19% | 30.2 ± 4.9 | Parallel<br>26 weeks | Patients with metabolic syndrome<br>Denmark | New Nordic diet, *ad libitum* | Average Danish diet | Dietary advice | 3-day dietary record |
| Richard *et al.* 2013 (65, 66) | 26<br>0% | 49 ± 12<br>0% | 32.4 ± 5.1 | Consecutive diet phases<br>5 weeks | Patients with metabolic syndrome<br>Canada | Mediterranean diet, isocaloric | North American diet | Supply with food and meals, partially feeding under supervision | Supervised meals |
| Rokling-Andersen *et al.* 2007 (67) | 98<br>0% | 45 ± 3<br>16% | 28.6 ± 3.4 | Parallel<br>48 weeks | Patients with risk factors for diabetes and cardiovascular diseases<br>Sweden | Nordic-type diet, *ad libitum* | Habitual diet | Personalized dietary advice | Not specified |
| Sexton *et al.* 2012 (68) | 23<br>74% | 39 ± 4<br>7% | 25.7 ± 1.2 | Parallel<br>12 weeks | Patients with symptomatic asthma, clinically stable<br>New Zealand | Mediterranean diet, *ad libitum* | Habitual diet | Personalized dietary advice | FFQ |
| Shai *et al.* 2008 (46) | 322<br>14% | 52 ± 7<br>12% | 30.9 ± 3.7 | Parallel<br>96 weeks | Obese/Type 2 diabetics/CHD patients<br>Israel | Mediterranean diet, calorie-restricted (♀:1500 kcal/d; ♂: 1800 kcal/d) | Low-fat diet, calorie-restricted (♀:1500 kcal/d; ♂: 1800 kcal/d) | Personalized dietary advice | FFQ |
| Sköldstam *et al.* 2003 (69) | 51<br>80% | 59<br>8% | 27 | Parallel<br>12 weeks | Patients with rheumatoid arthritis<br>Sweden | Mediterranean diet adjusted for Sweden, *ad libitum* | Habitual diet | Dietary advice, supply with foods and meals | Diet history |
| Stachowska *et al.* 2004 (70) | 37<br>32% | 43 ± 11<br>0% | 25.5 ± 4.2 | Parallel<br>24 weeks | Kidney graft recipients<br>Poland | Mediterranean diet, isocaloric | Low-fat diet | Supply with meals | 24-h recall |
| Thomazella *et al.* 2011 (71) | 42<br>0% | 55 ± 5<br>5% | 26.4 ± 2.2 | Parallel<br>12 weeks | Patients with coronary event ≥ 1, absence of | Mediterranean diet, isocaloric | Low-fat diet | Personalized advice, supply with foods | 4-day dietary record |

(*Continues*)

**Table 1** (Continued)

| Reference | Size % Female | Age [years]§ Drop-out rate | BMI [kg/m$^2$]§ | Study design Duration of trial | Study population Country | Intervention | Control | Application of intervention | Dietary assessment |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | secondary events Brazil | | | | |
| Tuttle *et al.* 2008 (72) | 101 26% | 58 ± 9 27% | 30.5 ± 5.5 | Parallel 96 weeks | Patients with previous myocardial infarction United States | Mediterranean diet, *ad libitum* | Low-fat diet | Personalized dietary advice | 3-day dietary record |
| Urpi-Sarda *et al.* 2012 (39) | 341 49% | 67 ± 6 0% | 29.4 ± 3.4 | Parallel 48 weeks | Patients with metabolic syndrome Spain | Mediterranean diet, *ad libitum* | Low-fat diet | Personalized dietary advice, supply with key foods | FFQ |
| Uusitupa *et al.* 2013 (73) | 166 76% | 54 ± 9 17% | 31.6 ± 3.2 | Parallel 18/24 weeks | Patients with metabolic syndrome Scandinavia | Healthy Nordic diet, isocaloric | Average diet of Nordic countries | Supply with key foods, dietary advice | 4-day dietary record |

DASH, dietary approach to stop hypertension; BMI, body mass index; MUFA, monounsaturated fatty acids; FFQ, food frequency questionnaire; CHD, coronary heart disease.
*Plant-based diets are defined as dietary patterns that emphasize foods of plant origin, particularly vegetables, grains, legumes and fruits; generally exclude or rarely include meats, but may include dairy products, eggs and fish.
#Biomarkers characterizing endpoint: inflammatory profiles.
§If necessary, values were approximated using given information (e.g. range, group mean).

Current evidence suggests a central role for chronic low-grade inflammation in a number of obesity-related chronic diseases (14–17). Circulating phase reactants such as CRP, TNF-α and certain cytokines (i.e. IL-6) have been suggested not only as biomarkers of increased risk for chronic diseases, but also as direct contributors to disease pathogenesis (18–20). Inflammatory processes are known to exist in a constant interplay with adiposity associated pathogenic pathways including insulin resistance, oxidative stress and hyperlipidemia. In this vein, recent research has underscored the pro- and anti-inflammatory potential of plasma proteins excreted by adipose tissue, collectively named adipokines, such as adiponectin, leptin and resistin (21–23). Adiponectin is among the most extensively investigated and well characterized biomarkers shown to exert potent anti-inflammatory and anti-atherosclerotic properties (24). Low plasma adiponectin levels were independently associated with a higher risk of type 2 diabetes (25), myocardial infarction (26, 27) and colorectal cancer (28), whereas elevated concentrations of the adipokines—leptin and resistin—have been mostly implicated in the development of type 2 diabetes and its complications(29, 30).

Our data underscored the effect of plant-based diets in reducing concentrations of specific biomarkers indicating chronic inflammatory response and activated innate immunity including CRP, IL-6 and, to some degree, sICAM. CRP, an acute-phase reactant produced by the liver in response to IL-6, is considered to be an established biomarker of systemic low-grade inflammation proposed to link altered cytokine milieu and endothelial dysfunction associated with the metabolic syndrome (31, 32). Interestingly, the data showed an effect from plant-based diet interventions on the novel inflammatory biomarker sICAM. This trans-membrane adhesion molecule is acting as cytokine inducible member of the immunoglobulin superfamily expressed in a number of cells at sites of inflammation and immune reactivity. Polymorphisms encoded in the sICAM gene have been associated with the risk of CVD (33) and type 2 diabetes complications (34); however, functional characteristics of sICAM with regards to overall chronic disease risk are still largely unexplored. We did not observe pronounced effects for particular adiposity-associated biomarkers including adiponectin, leptin and resistin; however, it should be noted that evidence on these factors was restricted by the number and relatively low quality of available studies. More research is warranted to evaluate associations between plant-based diets and inflammatory adipokines in the future.

Our findings from intervention trials were consistent with the results of numerous observational studies demonstrating that certain components of plant-based diets such as omega-3 fatty acids, fruits, vegetables, nuts and whole grains are associated with lower levels of chronic inflammation and obesity-related inflammatory disorders (35, 36). In

**Table 2** Summary of pooled estimates for mean differences in biomarker concentrations after plant-based dietary intervention

| Biomarker | Number of studies | Pooled observations | Mean difference [95% CI] | $I^2$ [95% CI] |
|---|---|---|---|---|
| CRP [mg/l] | 24 | 2,008 | −0.55 [−0.78; −0.32] | 94.4% [92.8; 95.7] |
| IL-6 [ng/l] | 8 | 975 | −0.25 [−0.56; 0.06] | 74% [47.2; 87.2] |
| TNF-α [ng/l] | 5 | 368 | 0.02 [−0.17; 0.21] | 0% [0.0; 74.1] |
| sICAM [ng/ml] | 5 | 534 | −25.07 [−52.32; 2.17] | 93.2% [87.1; 96.4] |
| Resistin [ng/ml] | 3 | 275 | 0.00 [−0.14; 0.14] | 0% [0.0; 83.7] |
| Leptin [ng/ml] | 4 | 488 | −0.24 [−0.68; 0.21] | 0% [0.0; 0.0] |
| Adiponectin [mg/l] | 7 | 911 | 0.62 [−0.55; 1.78] | 95.5% [92.8; 97.2] |

CRP, C-reactive protein; IL-6, interleukin-6, TNF-α, tumour necrosis factor-alpha; sICAM, soluble intercellular adhesion molecule; MD, mean difference; CI, confidence interval.

contrast, dietary patterns high in refined starches, sugar, saturated and trans-fatty acids, and poor in natural antioxidants and fibre from fruits, vegetables and whole grains have been particularly suggested to induce an activation of the innate immune system, most likely by an excessive production of pro-inflammatory cytokines (35). The details provided in the studies included in the present analysis did not allow subgroup analyses to evaluate the relative influence of individual dietary factors on the observed differences in inflammatory profiles. A recent meta-analysis of prospective studies and controlled trials on Mediterranean diet and cardio-vascular outcomes suggested that the protective effects of this diet could be mostly attributable to olive oil, fruits, vegetables and legumes (37). However, overall in the literature no appreciable associations were seen for most of the individual dietary components and chronic disease incidence and mortality (35, 38) which would suggest that it may be the complex effects of multiple dietary components that may be important. Further studies are required to explore the associations between specific foods and nutrients and chronic low-grade inflammation and the potential synergistic effects of these factors.

The mechanisms by which a plant-based diet can reduce the low-grade inflammatory state are unclear. Nonetheless, current evidence allows us to speculate on the following potential explanations for the observed associations. First, plant-based diets could be associated with a lower BMI attributable to the lower energy density of the diet. Energy restriction and weight loss are associated with lower levels of inflammatory biomarkers (CRP and IL-6) suggesting that weight loss, at least in the short term, may be responsible for the reductions in most of the inflammatory biomarkers. Thus, potential confounding effects of weight loss which itself may reduce inflammation and improve endothelial function could be speculated. However, we controlled the analysis for reported weight loss and it did not explain the observed effect, for CRP in particular. Furthermore, in large and long term intervention trials such as Prevención con Dieta Mediterránea (PREDIMED), the weight differences did not entirely explain the observed differences in inflammatory biomarkers (39, 40). Second, the relation between plant-based diets and changes in inflammatory biomarkers may also be related to coinciding changes in the levels of oxidative stress that are being reduced in diets lower in saturated fatty acids and richer in polyunsaturated fatty acids (41, 42). Third, based on evidence from cross-sectional population studies and a meta-analysis of intervention trials, diets with a high glycemic load were shown to adversely affect inflammatory markers, therefore another explanation could include reduced levels of circulating glucose after plant based interventions (43, 44). Further studies are needed in order to explore these and other mechanisms (i.e. induced alterations in the gut microbiome and bacteria-produced metabolites) that may potentially underline observed associations.

We evaluated different types of plant-based diets among which the most extensively investigated appeared to be the Mediterranean-type diet. Our findings showing that the Mediterranean diet is associated with lower levels of CRP and IL-6 are consistent with those of a previous meta-analysis of intervention studies (45). However, in our analyses we extend those findings by including in addition intervention trials that evaluated different types of commonly assessed plant-based diets such as the Nordic diet, the Paleolithic diet and the DASH diet. Interestingly, the Mediterranean diet and the DASH diet seemed to have similar effects and lead to the largest changes in effect estimates. However, the number of studies for each included diet type was relatively low and does not allow judging on the superiority of one diet type over the others.

The present meta-analysis has several strengths. First, the available intervention trials provided a reasonably large overall sample size and allowed subgroup analyses in specific population groups. Second, we focused on dietary patterns rather than on the use of dietary supplements or artificial dietary approaches which allows translation of the findings to both general and clinical populations. Importantly, studies based on nutritional counseling observed similar lowering of concentrations as more intensive interventions (i.e. providing foods and drinks). The stability of the effects was sustained even after the end of the intervention (39, 46). Third, we covered a full spectrum of available biomarkers that reflect

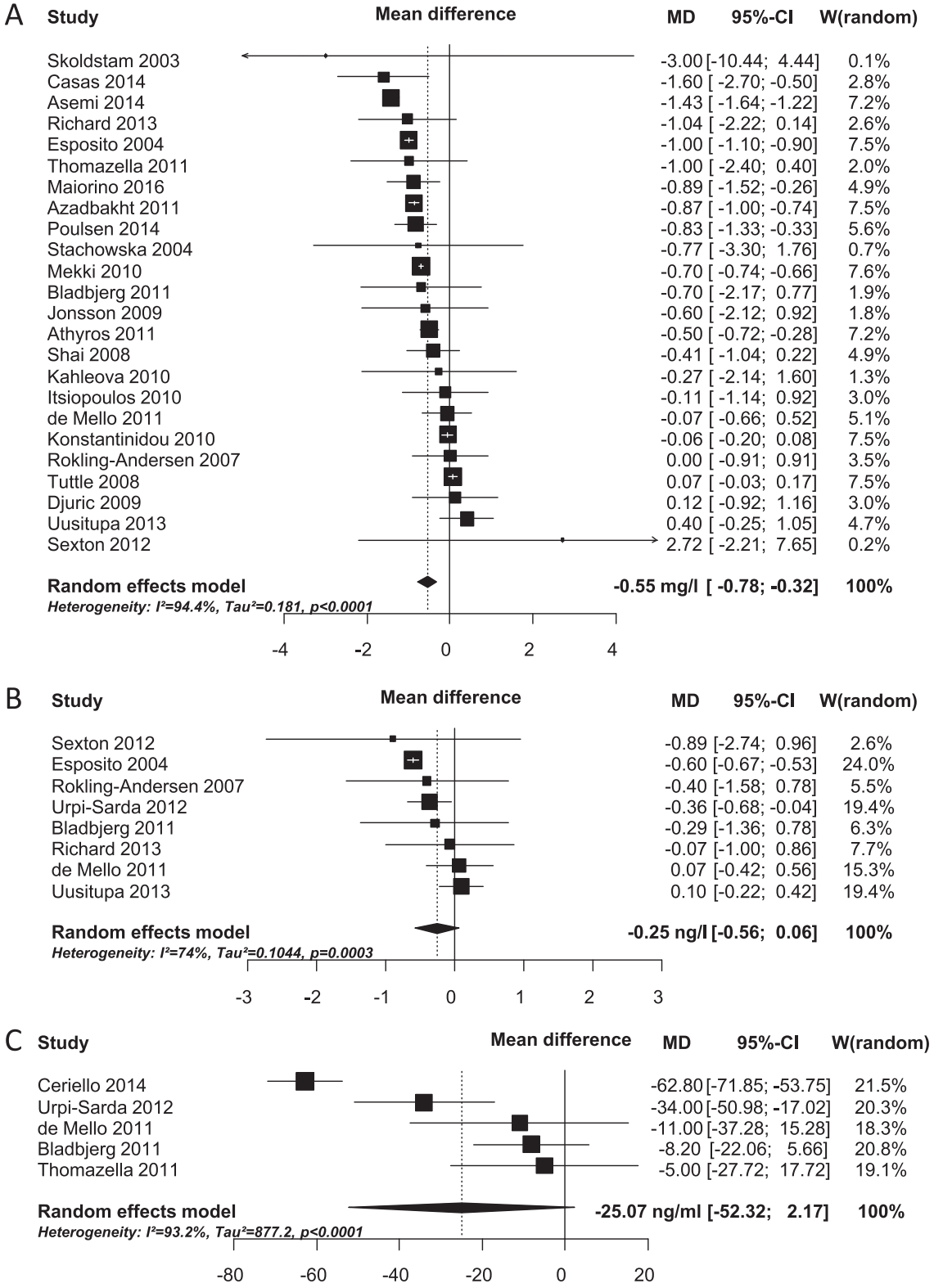


**Figure 2** Pooled estimates for differences in concentrations of CRP (Panel A), IL-6 (Panel B) and sICAM (Panel C) after intervention with plant-based diets Single study effects are depicted as squares with error bars indicating 95% confidence intervals. Pooled estimates from random effect model for each biomarker are depicted as diamonds. MD, mean difference; 95% CI, 95%confidence intervals; W(random), weight of single study in random effects model; $I^2$, measurement of inconsistency.

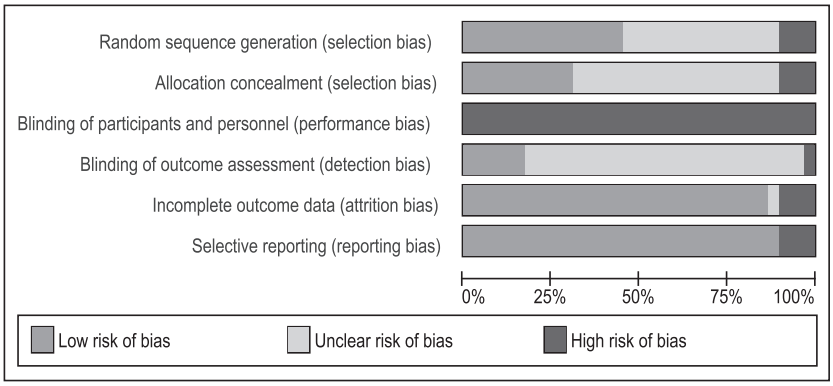


**Figure 3** Risk of bias graph.

chronic inflammation and immune reaction, including a set of novel molecules at the site of adipose-tissue induced inflammatory response.

Our study has several limitations. First, although we found statistically significant effects for several inflammatory biomarkers; we also detected a high heterogeneity among the intervention trials. However, it should be noted that we relied on variously reported food patterns that may differ from study to study. Furthermore, the measurements of biomarkers were not standardized, which appears to be a particular challenge in studies employing novel biomarkers. Second, the observed associations for some biomarkers did not reach statistical significance or if so, the strength was modest. One possible explanation could be that most of those studies did not last long enough for detecting a biological effect reflected by changes in biomarker concentrations. Further, some of the studies used another form of 'healthy diet' in the control population which may have also decreased inflammatory levels and therefore could have led to an underestimation of the true effect of the intervention diet. Finally, our analysis is restricted by the data provided within the available studies each having its own methodological characteristics and potential drawbacks. In this respect, we should acknowledge the differences in the assay quality measurements and range of investigated inflammatory biomarkers. Of note, the majority of biomarkers are mostly sharing common etiological pathways; hence we evaluated only effects on individual biomarkers. More research is needed from well-phenotyped observational studies to identify suitable targets for intervention, thereby exploring biomarkers in combinations.

In conclusion, this systematic review and meta-analysis of intervention trials suggests that consumption of plant based-diets is associated with an improvement in inflammatory profiles in metabolically afflicted patients as indicated by decreases in CRP and IL-6 concentrations. Further research is warranted to clarify which specific types of diets or individual food and nutrient components may drive these associations, and also to identify valid sets of diet-related inflammatory biomarkers. Nonetheless, these data add support to the notion that complex dietary interventions should stay in the focus of chronic disease management and prevention.

## Conflicts of interest

The authors disclose no conflict of interest.

## Acknowledgments

KA designed the study; FE and KA conducted the search and data extraction; FE analysed the data. FE and KA drafted the manuscript. All authors revised and approved the final version.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article, http://dx.doi.org/10.1111/obr.12439

Table S1: Short descriptions of diet types
Table S2. Mean difference (95% CI) in biomarker concentrations from 28 intervention trials, according to prespecified potential sources of heterogeneity

Table S3: Estimates from multivariable meta-regression for CRP

Figure S1: Pooled estimates for differences in concentrations of TNF-α (Panel A), adiponectin (Panel B), Resistin (Panel C) and Leptin (Panel D) after intervention with plant-based diets

Figure S2: Funnel plot for CRP

Figure S3: Risk of bias summary

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