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Review

The healthy Nordic dietary pattern has no effect on inflammatory markers: A systematic review and meta-analysis of randomized controlled clinical trials

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ABSTRACT

Objectives: The Nordic diet (ND) is regarded as a healthy dietary pattern that might beneficially affect systemic chronic inflammation; however, the results of published studies are conflicting. The present systematic review and meta-analysis aimed to summarize the published evidence by randomized controlled clinical trials with regard to the effect of the ND pattern on circulating inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF-α).
Methods: PubMed, ISI Web of Science, Scopus, and Google Scholar were searched up to October 2017 to identify relevant studies. The risk of bias in the included studies was assessed using Cochrane's collaboration tool. The overall effects were calculated using the random effects model.
Results: Seven studies were eligible to be included in the systematic review. All studies were conducted in Nordic countries. The meta-analysis of six eligible clinical trials included 613 adult participants and showed that adherence to the ND does not significantly affect circulating CRP levels (weighted mean difference [WMD]: −0.17 mg/L; 95% confidence interval [CI], −0.69 to 0.35; $P = 0.529$). The meta-analysis of three studies that reported on the effect on other inflammatory makers also failed to find any significant effect on TNF-α (WMD: 0.23 mg/L; 95% CI, −0.75 to 1.21; $P = 0.645$) and IL-6 (WMD: 0.13 mg/L, 95% CI, −0.29 to 0.56; $P = 0.539$) concentrations.
Conclusions: Adherence to the ND pattern does not seem to affect circulating CRP, IL-6, and TNF-α levels. Clinical trials with longer follow-up periods and including participants in other regions are highly recommended.

Introduction

The chronic, increased, circulatory C-reactive protein (CRP) or proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) [1] are associated with the development of several chronic diseases, including metabolic syndrome (MetS) [2], atherosclerosis [3], cardiovascular diseases [4–6], and cancers [7].

A number of factors including smoking status, obesity, hypercholesterolemia, and sedentary lifestyle have been proposed as associated with increased inflammatory markers [8–10]. Lifestyle modifications and especially dietary interventions are also considered effective to regulate inflammatory responses [11]. Single nutrients or dietary food items or food groups have been widely studied with regard to their potential antiinflammatory effects. For instance, studies have revealed that the consumption of dietary fiber [12], olive oil [13,14], soy [15], and vitamin E [16] might be associated with decreased circulatory levels of inflammatory biomarkers. A meta-analysis also showed a borderline effect of coenzyme Q10 supplementation on serum CRP levels and its significant reducing effect on IL-6 levels [17]. Furthermore, magnesium supplementation has been proposed as beneficial to reduce CRP levels among individuals with inflammation [18].

Dietary patterns have been also investigated in recent years for their effect on inflammatory markers [19]. A diet that includes a

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number of healthy food items/groups might better affect inflammatory markers than intake modification of just a single nutrient or food group. For instance, a recently published systematic review and meta-analysis of randomized clinical trials reported that adherence to the Dietary Approaches to Stop Hypertension (DASH) diet improves the circulating inflammatory biomarkers in adults compared with a typical diet [20]. The DASH diet is characterized by high intakes of whole grains, fruits, vegetables, nuts, legumes, poultry, and fish and low amounts of red meat, saturated fat, and sweetened beverages [21]. The Mediterranean diet is another healthy dietary pattern that is high in vegetables, legumes, fruits, nuts, olive oil (i.e., main source of fat), and low amounts of red meat and dairy [22]. This dietary pattern is also associated with improved inflammatory state [23].

The Nordic diet (ND) is also a healthy dietary pattern that is characterized by high intakes of traditional and locally sourced foods from Nordic countries such as Norway, Denmark, Sweden, and Finland [24]. The ND is high in fruits and vegetables (especially berries, cabbages, and root vegetables), legumes, potatoes, fresh herbs, plants and mushrooms gathered from the wild, nuts, whole grains, low-fat dairy products, the meat of livestock and game, fish, shellfish, and seaweed [24,25]. A number of studies have shown the beneficial effect of the ND on weight loss [26] and insulin sensitivity [27]. Moreover, the ND has been proposed to improve adipose tissue metabolism, lipid profile, and systemic inflammation [28–30]. Randomized clinical trials have led to different results when examining the effect of the ND on inflammatory markers. For instance, a randomized intervention trial has shown the beneficial effects of the ND pattern on low-grade inflammation [26]. However, other studies could not confirm the effect of the ND on the reduction of inflammatory markers [27,31,32].

To our knowledge, there is no systematic review that focuses on the effectiveness of the ND pattern on chronic inflammation. Therefore, the present study aimed to systematically review available data from clinical trials with regard to the effect of adherence to the ND on circulating inflammatory markers and summarize the results using a meta-analysis.

Methods

The study reports in accordance with the preferred reporting items for systematic reviews and meta-analyses guidelines [33]. A detailed protocol was registered and published in PROSPERO, which is an international prospective register of systematic reviews (www.crd.york.ac.uk/PROSPERO; registration no: CRD42017058095) in March 2017 [34].

Search strategy

To retrieve potentially related studies, we searched PubMed (www.pubmed.com), Scopus (www.scopus.com), ISI Web of Science (www.isiknowledge.com), and Google Scholar (www.scholar.google.com) up to October 2017. The search was conducted without limitation on language or publication year, using the following subsequent keywords: “Nordic diet” OR “Nordiet” OR “Baltic sea diet”.

The initial screening of the titles and abstracts was done by two independent investigators (NRJ, MM), and the full texts of the remaining papers were also examined for eligibility. A third author (ASA) resolved any disagreements between the reviewers. The reference lists of the related literature were also checked to maximize the selection of related papers.

Eligibility criteria

We included randomized controlled trials (RCTs) that were conducted in human adults if: 1) Dietary advice according to the ND or Nordic nutrition recommendations had been used for the intervention (trials that stated the use of the ND pattern for the intervention and food items provided/recommended on the basis of the healthy ND pattern), and 2) the circulating inflammatory markers evaluated (e.g., CRP, IL-6, TNF-α, and other possible markers such as E-selectin, intercellular adhesion molecule-1, and vascular adhesion molecule-1). Trials with the following characteristics were excluded from the systematic review: 1) Without control group; 2) including participants age <18 y; 3) focused on the effects of the ND components rather than the entire dietary pattern; and 4) duplicate data (duplicate publication studies with more sample size and/or complete representation of the targeted outcome variables were selected).

Data extraction

Three independent authors (NRJ, MM, and RS) abstracted the following data from eligible articles: Authors’ last name, publication year, country in which the study was conducted, sample size, participants’ age (mean or range), sex (female/male/both), intervention duration (wk), participants' health condition, components of the recommended dietary patterns, and outcome data (inflammatory markers levels at the start and end of the study, or change values from baseline). To diminish potential errors, another reviewer (ASA) rechecked the data and discrepancies were resolved through consensus. If complete data could not be extracted from the original articles, any relevant missing information was requested from the authors via e-mail.

Assessment of risk of bias in individual studies

The methodological risk of bias in the included studies was assessed with the Cochrane's collaboration tool to assess the risk of bias, which considers a range of domains including random sequence generation, allocation concealment, blinding of the participants and the personnel, blinding of the outcome assessment, incomplete outcome data, and selective reporting. Each domain was evaluated as “yes” (low risk of bias), “no” (high risk of bias), or “unclear” (uncertain risk of bias) [35]. Blinding is not feasible in dietary interventions; therefore, we did not consider this a key domain for the evaluation of the risk of bias. In total, a study was graded as "good" (low risk for >2 domains), "fair" (low-risk for 2 domains), or "weak" (low-risk for <2 domains).

Assessment of overall quality of the meta-analysis

The NutriGrade scoring system was applied to evaluate the overall quality of the present meta-analysis [36]. NutriGrade is a tool that considers the following criteria to assess the overall quality of a meta-analysis on RCTs conducted in the field of nutrition: Risk of bias/study quality/study limitations (3 points), precision (1 point), heterogeneity (1 point), directness (1 point), publication bias (1 point), funding bias (1 point), and study design (2 points). An overall calculated score of ≥8 points means that the review might be considered as high in meta-evidence. Scores of 6 to 7.99, 4 to 5.99, and 0 to 3.99 points denote moderate, low, and very low meta-evidence, respectively.

Statistical analysis

Mean change in serum inflammatory markers and its standard deviation (SD) for the ND and the control groups were extracted from each study to calculate the difference in mean and standard error (SE), which was used as effect size for the meta-analysis. To calculate the SD for mean change values, we selected 0.5 as the correlation coefficient. To ensure that our meta-analyses were not sensitive to the selected correlation coefficient, all analyses were also performed with correlation coefficients of 0.1 and 0.9.

The random effects model to take between-study heterogeneity into account was used to calculate weighted mean difference (WMD) and 95% confidence interval (CI) [37]. Between-study heterogeneity was assessed using Cochran's Q test and I-squared (I^2) [38]. If heterogeneity was observed, we performed several subgroup analyses based on different possible sources of heterogeneity including sex (male, female, or both), participants’ age (≤50 and >50 y), intervention period (<3, 3–6, and >6 mo), feeding trial status (yes/no), diet selected for the control group (Paleolithic/other diet such as typical diets or the average Danish diet), and participants’ health status (with/without MetS). We conducted a sensitivity analysis to evaluate the possible effect of each study on the overall effect size [39]. Publication bias was tested by inspecting the funnel plots and use of statistical asymmetry tests (Egger's regression asymmetry test and Begg's adjusted rank correlation test) [40]. The analyses were performed using STATA, version 11.2 (Stata Corp, College Station, TX). *P*-values of <0.05 were considered statistically significant.

Results

Included studies and their characteristics

The initial search of the online databases led to 2568 potentially relevant articles, of which 427 publications were duplicates and the remaining citations were screened based on their title and abstract. Eventually, 48 full texts of potentially relevant articles were carefully reviewed, of which 41 items were excluded because of subsequent reasons: Ten studies were conducted on children [41–50]; 21 studies had no report on the effect of the ND pattern on the inflammatory markers [28,51–70]; 4 studies investigated the individual food items of the ND rather than the effect of the whole dietary pattern [71–74], and 1 study did not have a control group [75]. Five studies were also excluded [72,76–79] because they were duplicate reports of other studies that were already included in the analysis [32,80]. Figure 1 shows the flow diagram of the study selection process.

A total of seven RCTs were included in the present systematic review and meta-analysis [25–27,31,32,80,81]. Three studies were conducted in Sweden [27,80,81], two in Denmark [25,26], one in Finland [31], and a multicenter study was carried out in four different locations of Europe [32]. The studies were published between 2011 and 2017 [25–27,31,32,80,81]. All trials were designed as parallel-group studies, and the duration of the intervention ranged between 6 wk to 2 y. One study reported data on two different time periods, and we considered the longest intervention period to calculate the overall pooled estimate [80,81]. Both men and women were included in the five clinical trials, and one study provided data separately for men and women [26]; therefore, two effect sizes were extracted for this study.

Two trials included only female participants [80,81]. The mean age of the participants varied from 39 to 60.3 y. The eligible trials included different groups of participants in their study: Moderately obese subjects [26]; participants with mild hypercholesterolemia [27]; postmenopausal non-smoking women [80,81], and subjects with ≥1 criteria for MetS [25,31,32]. The body mass index (BMI) distribution among these participants was ranged between 20 and 47.3 kg/m^2. The characteristics of the eligible studies are provided in Table 1.

Definition of the Nordic diet

Five studies [25–27,31,32] were feeding trials and participants received the ND food items including high amounts of fruits and vegetables (especially berries, cabbages, and root vegetables), whole grains, rapeseed oil, fatty fish, shellfish and seaweed, and also low-to-fat dairy products and meat, poultry, and game as well as the avoidance of sugar and sweetened beverages. Other studies were nonfeeding trials [80,81] and recommended adherence to the Nordic Nutrition Recommendations for participants in the intervention group. Typical [27,31,32], average Danish [25,26], and Paleolithic [80, 81] diets were used for participants in the control groups (Table 1).

Assessment of risk of bias

The assessment of the risk of bias in seven included studies using Cochrane's collaboration tool showed that six trials were low risk for at least three domains [25,27,29,32,80,81], and one study was low risk for two domains [26]. Allocation concealment was reported in only one study [25], and four studies reported random sequence generation [25,27,80,81], whereas these items were unclear in other studies. Since all included studies were dietary intervention trials, the blinding of participants and personnel was not reported. Details of the risk of bias assessment in individual studies are presented in Table 2.

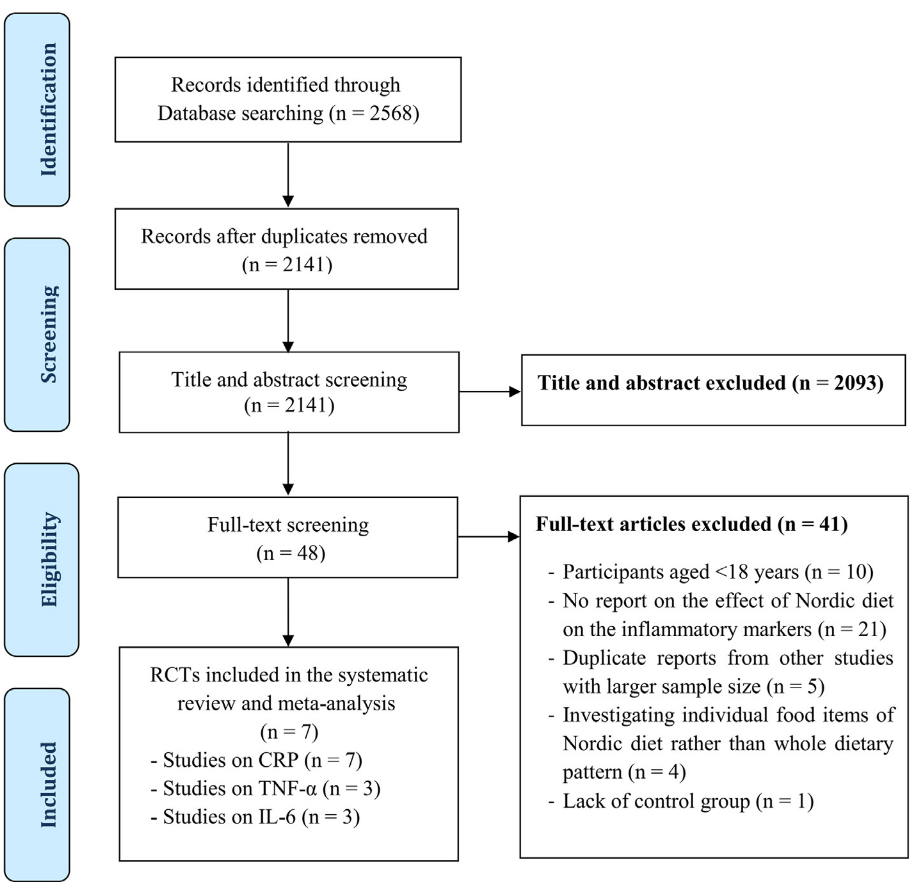

Fig. 1. Flow diagram of the study selection process

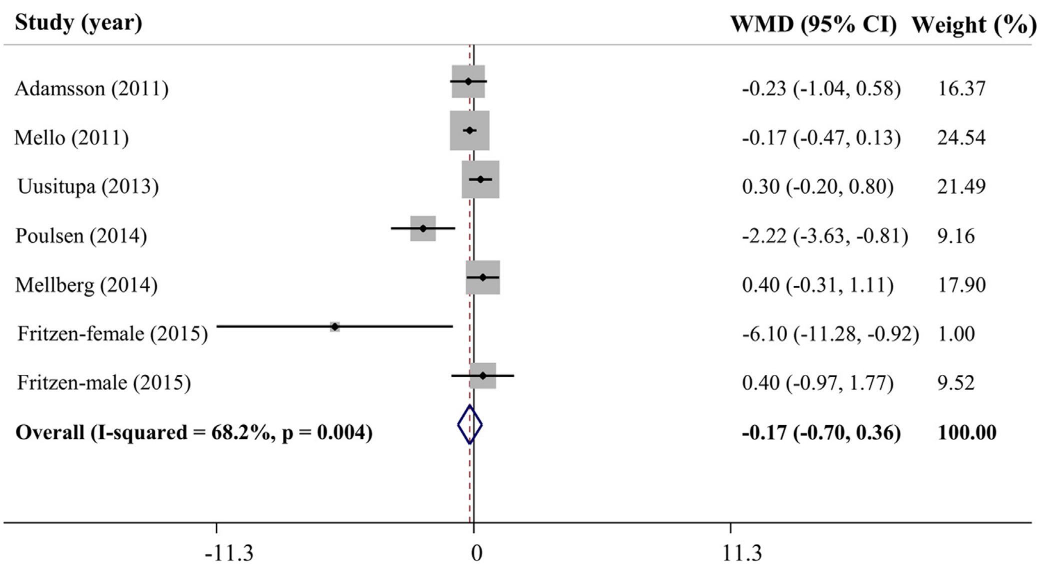

Fig. 2. Forest plot of controlled clinical trials illustrating that the Nordic diet had no significant effect on C-reactive protein levels

Meta-analysis

Effect of the Nordic diet on circulatory C-reactive protein levels

In total, six studies (seven effect sizes) with 613 participants investigated the effect of the ND pattern on CRP levels [25–27,31,32,80,81]. The result of the meta-analysis indicated that adherence to the ND does not significantly affect serum CRP concentrations (WMD: −0.17 mg/L; 95% CI, −0.69 to 0.35, $P = 0.529$) (Figure 2). The heterogeneity between the included studies was high (Cochran's Q test, Q statistic = 18.90, $P = 0.004$, $I^2 = 68.2\%$). Therefore, different subgroup analyses were conducted to determine the potential sources of heterogeneity between the studies. The results of the overall and subgroup analyses are represented in Table 3.

The subgroup analysis revealed that a reduction in circulatory CRP levels was significant neither in women (WMD: −2.32 mg/L; 95% CI, −8.6 to 3.96; $P = 0.469$) nor in men (WMD: 0.40 mg/L; 95% CI, −0.97 to 1.77; $P = 0.568$). Also, no significant changes in serum CRP concentrations were seen after adherence to the ND in any other subgroups. The subgroup analyses showed that heterogeneity was lower in studies that were conducted among participants ages >50 y (Cochran's Q test, Q statistic: 4.14; $P = 0.247$; $I^2 = 27.5\%$) compared with those age <50 y (Cochran's Q test, Q statistic: 10.57; $P = 0.005$; $I^2 = 81.1\%$; Table 3). The between-group heterogeneity was significant (Cochran's Q test, $P = 0.041$).

Effect of the Nordic diet on tumor necrosis factor alpha and interleukin-6 levels

Three studies with 195 participants investigated the effect of the ND pattern on circulating TNF-α levels [26,31,81]. The meta-analysis failed to find any significant effect (WMD: 0.23 mg/L; 95% CI, −0.75 to 1.21; $P = 0.645$). Furthermore, three clinical trials including 320 participants evaluated serum IL-6 levels [31,32,81] but the meta-analysis revealed that the ND does not affect circulating IL-6 levels (WMD: 0.13 mg/L; 95% CI, −0.29 to 0.56; $P = 0.539$).

Sensitivity analysis and publication bias

A sensitivity analysis demonstrated that the overall effects were not sensitive to removal of any individual studies. There was no evidence of publication bias among the included articles that assessed the effect of the ND on serum CRP levels using Begg's and Egger's tests (Begg's test $P = 0.230$; Egger's test $P = 0.333$). Because of the small number of studies that examined other inflammatory markers, the assessment of publication bias was done by visual inspection of funnel plots and no asymmetry was found when depicting the mean differences in serum IL-6 or TNF-α against their standard errors.

Overall quality of meta-analysis

The overall quality of the present meta-analysis using the NutriGrade scoring system resulted in a total score of 6.5 for the meta-analysis of the effect on circulating CRP levels. This score indicates moderate confidence for the overall estimate found in the current analysis.

Discussion

The current systematic review and meta-analysis of randomized controlled clinical trials revealed that the ND pattern does not significantly affect a number of inflammatory markers such as IL-6, TNF-α, and CRP. To the best our knowledge, this study is the first report on the effect of the ND pattern on chronic inflammation. Most of the included RCTs were low risk according to Cochrane's collaboration tool to assess risk of bias. In the present study, we tried to perform sensitivity and subgroup analysis to check the robustness of the results. Moreover, no evidence of potential publication bias was observed in the present study.

The majority of the included studies compared the effect of the ND with a typical diet in which subjects were advised to follow their habitual diet or an average Danish diet, which is commonly consumed by the Danish population. This dietary pattern contains refined grains including pasta and rice, meat, dairy and cheese, sugary products and fewer amounts of fiber, and vegetables and fruits, and provides approximately 50% of the energy from carbohydrate, 35% from fat, and 15% from protein [25]. Moreover, two studies compared the ND with the Paleolithic diet, which contains high amounts of vegetables, fruits, nuts, and lean meat, and provides 30% of energy from carbohydrate, 30% from protein, and 40% from fat [80,81]. The ND did not significantly affect serum CRP levels compared with all these control diets.

Table 1
Characteristics of eligible randomized controlled clinical trials

First author (y)	Country	Number/sex	Mean age (y)	RCT design	Feeding trial	Duration (wk)	Intervention diet	Control diet	Reported data	Notes about participants
Adamson (2011) [27]	Sweden	52 F/32 M	Intervention 52.6 Control 53.4	Parallel	Yes	6	Nordic diet CHO: 52% Fat: 27% Pro: 19%	Typical diet CHO: 46% Fat: 34% Pro: 17%	CRP	Mildly hypercholesterolaemic (BMI ≥20 and ≤31)
De Mello (2011) [31]	Finland	36 F/34 M	Intervention 59 Control 59	Parallel	Yes	12	Healthy Nordic-like diet (Fatty fish, vegetable oil and vegetable oil-based products in fish preparation, bilberries)	Control diet (avoid whole grain cereals, replace breads usually consumed with refined wheat breads and other cereal products, avoid bilberries, consumption of fatty fish once a week only)	CRP IL-6 TNF-α	Individuals with impaired glucose metabolism and features of the MetS (BMI: 26–39)
Uusitupa (2013) [32]	Multicenter (Finland, Sweden, Denmark, Iceland)	126 F/63 M	Intervention 54 Control 54.9	Parallel	Yes	24	Healthy Nordic diet CHO: 46.8% Fat: 31.7% Pro: 17.5%	Typical diet CHO: 44.6% Fat: 35.2% Pro: 16.2%	CRP IL-6	Subjects with two IDF criteria for MetS (BMI: 27–38)
Poulsen (2014) [25]	Denmark	146 F/M	Intervention 42.7 Control 41	Parallel	Yes	26	New Nordic diet [percent changes of NND vs. ADD] CHO: 3.2% Fat: –5.1% Pro: 2.1%	Average Danish diet	CRP	Subjects with one or more IDF criteria for MetS, centrally obese (BMI: 22.6–47.3 ~30)
Mellberg (2014) [80]	Sweden	61 F	Intervention 60.3 Control 59.5	Parallel	No	26 and 103	Nordic nutrition recommendations CHO: 55 to 60% Fat: 25 to 30% Pro: 15%	Paleolithic diet CHO: 30% Fat: 40% Pro: 30%	CRP	Postmenopausal, nonsmoking women (BMI ≥27)
Fritzen (2015) [26]	Denmark	43 F/21 M	Intervention F: 47, M: 44 Control F: 39, M: 40	Parallel	Yes	26	New Nordic diet CHO: 54.4% Fat: 30.6% Pro: 18%	Average Danish diet CHO: 50.9% Fat: 34.4% Pro: 16.6%	CRP TNF-α	Moderately obese individuals (BMI: 22.6–47.3 ~30.2)
Blomquist (2017) [81]	Sweden	61 F	Intervention 60.3 Control 59.5	Parallel	No	26 and 103	Nordic nutrition recommendations CHO: 55 to 60% Fat: 25–30% Pro: 15%	Paleolithic diet CHO: 30% Fat: 40% Pro: 30%	IL-6 TNF-α	Postmenopausal, nonsmoking women (BMI ≥27)

BMI, body mass index; CRP, C-reactive protein; CHO, carbohydrate; F, female; IL-6, interleukin-6; M, male; MetS, metabolic syndrome, Pro, protein; RCT, randomized clinical trial; TNF-α, tumor necrosis factor alpha, IDF, International Diabetes Federation

Table 2
Assessment of risk of bias in included studies using Cochrane's collaboration tool

First author(y)	Random sequence generation **(selection bias)**	Allocation concealment **(selection bias)**	Blinding of participants and personnel **(Performance bias)**	Blinding of outcome assessment **(Detection bias)**	Incomplete outcome data **(Attrition bias)**	Selective reporting **(Reporting bias)**	Overall quality
Adamson (2011) [27]	+	?	–	?	+	+	Good
Mello (2011) [31]	?	?	–	+	+	+	Good
Uusitupa (2013) [32]	?	?	–	+	+	+	Good
Poulsen (2014) [25]	+	+	–	?	+	+	Good
Mellberg (2014) [80]	+	?	–	+	+	+	Good
Fritzen (2015) [26]	?	?	–	?	+	+	Fair
Blomquist (2017) [81]	+	?	–	+	+	+	Good

Elevated levels of inflammatory markers are associated with the development of several chronic diseases including cardiovascular diseases, type 2 diabetes, lipid abnormalities, and cancers [4,5,7,82]. Therefore, applying different strategies to reduce inflammation is considered an important issue when dealing with inflammation [83], and dietary modifications are one of the effective approaches in this regard [84,85]. Recently, a meta-analysis demonstrated that adherence to healthy dietary patterns such as the Mediterranean, Nordic, Tibetan, and DASH diets is associated with a significant reduction in CRP concentrations [86]. However, the small number of included studies and combining all healthy dietary patterns in this review led to inconclusive and unreliable results.

The ND is regarded as a healthy diet that contains high amounts of fiber from vegetables, fruits, berries, potatoes, whole grains, and herbs. Although high amounts of fiber are generally associated with lower concentrations of inflammatory markers [87,88], research findings are inconsistent in this regard. Some studies indicated that there is an inverse association between fiber intake and inflammatory markers such as IL-6 and TNF-α, and no association with CRP levels [89,90]. Moreover, observational studies have demonstrated that the consumption of whole grains could have antiinflammatory effects [91–93], but the results of some dietary interventions were conflicting [94,95]. Additionally, the ND is a dietary pattern that is rich in bilberries, raspberries, and cranberries that contain high amounts of polyphenols such as anthocyanins, which may confer health benefits for inflammatory diseases [96]. There is evidence that the substantial antiinflammatory effects of polyphenols might be attributed to a reduction in oxidative stress and an inhibition of inflammatory gene expression and foam cell formation [97]. The main source of fat in the ND is rapeseed oil, which is rich in n-3 polyunsaturated and monounsaturated fatty acids. Fish and shellfish, which are found in high levels in the ND, are also good sources of n-3 fatty acids [24,98]. The results of a meta-analysis provided evidence that indicates that marine-derived n-3 polyunsaturated fatty acid supplementation significantly reduces circulating CRP, IL-6, and TNF-α levels [99].

Nevertheless, in the present study, no significant effect of the ND pattern on CRP, TNF-α, and IL-6 concentrations was observed. In a study by Fritzen et al., there was a remarkable reduction of CRP among female subjects and the authors assumed it might be attributed to weight loss and low glycemic index of the Nordic food items [26]. Blomquist et al. have also suggested that the improvement in inflammatory markers is linked to the reduction in abdominal adiposity [81]. However, no significant changes of inflammatory markers were observed in other studies, despite a weight loss in subjects who consumed the ND compared with controls [25,27,31]. Therefore, the improved inflammatory state cannot be attributed to weight loss and the non-significant effect of the ND on inflammatory markers might be associated with other factors rather than weight loss.

The ND appears to have less beneficial effects on reducing inflammation compared with other healthy dietary patterns such as the Mediterranean diet, as a meta-analysis has provided evidence that this diet might reduce inflammation and improve endothelial function [23]. Although the ND is largely similar to the Mediterranean diet, the type of consumed oil (rapeseed vs olive oil) is the main difference between the two dietary patterns. Indeed, olive oil is the major component in the Mediterranean diet, which results in higher amounts of monounsaturated fatty acids and lower saturated fatty acids and can lead to improved inflammation [100]. A meta-analysis also showed the beneficial effect of

Table 3
Meta-analysis on effect of Nordic diet on CRP levels (mg/L) based on several subgroups and all included studies (all analyses conducted using random effects model)

Study group	Effect sizes (n)	WMD (95% CI)	*P* effect	Q statistic	*P* within group	I^2 (%)	*P* between groups
Sex							
Female	2	- 2.32 (−8.60 to 3.96)	0.469	5.93	0.015	83.1	0.451
Male	1	0.40 (−0.97 to 1.77)	0.568	0.00	–	–	
Both	4	−0.29 (−0.89 to 0.30)	0.339	11.37	0.010	73.6	
Mean age, y							
≤50	3	−1.78 (−4.43 to 0.87)	0.189	10.57	0.005	81.1	0.041
>50	4	0.02 (−0.27 to 0.33)	0.852	4.14	0.247	27.5	
Duration, mo							
<3	2	- 0.17 (−0.45 to 0.10)	0.213	0.02	0.892	0	0.260
3–6	2	0.25 (−0.11 to 0.61)	0.172	0.07	0.788	0	
>6	4	−0.90 (−2.62 to 0.82)	0.304	16.18	0.001	81.5	
Feeding							
Yes	6	−0.31 (−0.93 to 0.30)	0.319	17.04	0.004	70.7	0.173
No	1	0.40 (−0.31 to 1.11)	0.272	0.00	–	–	
MetS							
Yes	3	−0.37 (−1.16 to 0.42)	0.360	6.99	0.072	57.1	0.440
No	4	−0.01 (−0.91 to 0.89)	0.981	11.30	0.004	82.3	
Control diet							
Paleolithic diet	1	0.40 (−0.31 to 1.11)	0.272	0.00	–	–	0.173
Other diets	6	−0.31 (−0.93 to, 0.30)	0.319	17.04	0.004	70.7	
Overall	7	−0.17 (−0.69 to 0.35)	0.529	18.90	0.004	68.2	–

CI, confidence interval; CRP, C-reactive protein; WMD, weighted mean difference; MetS, metabolic syndrome

olive oil on inflammatory markers [101], but there are a few studies to evaluate the effect of rapeseed oil on inflammation with contradictory results [102–104]. In fact, we are not aware of any study comparing the Mediterranean diet with the ND with regard to their effect on inflammatory markers. Of note, a number of investigations on the Mediterranean diet have been conducted in other parts of the world, not just Mediterranean countries, so there might be a clear distinction between the diet of participants who are assigned to the Mediterranean diet and those in the control group when studies are conducted in non-Mediterranean countries [105]. The ND has been only studied in Northern European countries including Finland, Denmark, Sweden, and Iceland from where this diet originated; therefore, the dietary changes in the intervention and control groups might not be distinct.

The results of the present study must be interpreted in the context of some limitations. The study duration was short in the majority of the included studies. Since studies with a longer duration [80,81] showed more reduction in circulating CRP levels (>6 mo: −0.9 mg/L) compared with trials of short duration (<3 mo: -0.17 mg/L; 3–6 mo: 0.25 mg/L), long-term interventions might be more effective. In addition, although we conducted a subgroup analysis based on several factors, the heterogeneity among studies was not resolved. Therefore, there might be other factors that may have led to between-study variability and we could not assess these in the present study. The assessment of the overall quality of the current meta-analysis showed a moderate confidence. Therefore, future studies are needed to confirm our results.

Conclusions

The results of our meta-analysis showed that the ND pattern might not significantly affect serum CRP, TNF-α, and IL-6 levels. Further studies are needed with larger sample sizes and adequate durations to assess the effect of the ND on body inflammation. Studies on other inflammatory markers and in populations other than Nordic countries are recommended.

Supplementary materials

Supplementary data related to this article can be found at https://doi.org/10.1016/j.nut.2018.06.020.

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