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A R T I C L E I N F O

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A B S T R A C T

Purpose: To investigate the hypothesis that a Mediterranean diet is associated with a lower risk of having dry eye disease (DED) in the general population.
Methods: DED was assessed using the Women's Health Study (WHS) dry eye questionnaire in 58,993 participants from the Dutch Lifelines Cohort with complete available dietary data (20–94 years, 60% female). Level of adherence to a traditional Mediterranean diet was assessed using the modified Mediterranean Diet Score (mMDS). High-sensitivity C-reactive Protein (hsCRP) was included as a marker of whole-body inflammation. Logistic regressions were used to examine the relationship between WHS-defined DED and mMDS, corrected for age, sex, BMI, education, income, and 48 potentially confounding comorbidities. The association between mMDS and hsCRP, and hsCRP and DED, was further explored in separate regressions.
Results: Of all participants, 9.1% had DED. In contrast to the hypothesis, higher mMDS levels were associated with greater odds of DED, corrected for demographics, smoking status, BMI, and comorbidities (OR 1.034, 95% CI: 1.015 to 1.055, $P = 0.001$). Moreover, there was a highly significant relationship between increasing mMDS and lower circulating hsCRP levels; however, there was no significant relationship between hsCRP and DED.
Conclusions: Stronger adherence to a Mediterranean diet does not appear to be associated with lower odds of having DED in the general population. Furthermore, there was no association between hsCRP and DED in this study. However, the previously described link between a Mediterranean diet and lower hsCRP was confirmed in this large population-based study.

1. Introduction

Dry eye disease (DED) is a highly prevalent, multifactorial condition hallmarked by tear film instability, hyperosmolarity, ocular surface damage, and a loss of ocular surface homeostasis [1,2]. Common symptoms include foreign body sensation, visual disturbances, ocular

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dryness and irritation [3], which can result in reduced quality of life [4,5], reduced quality of sleep [6], and large financial and humanistic burdens [7,8]. As there is currently no cure for DED, the importance of hypothesis-driven epidemiological studies for discovering modifiable risk factors was stressed in a recent consensus report [2]. To this end, our group recently investigated the relationship between dietary factors such as alcohol [9], caffeine [10], and habitual water intake [11] and DED in the large Dutch population-based Lifelines Cohort [12]. However, much is still unknown regarding the relationship between dietary patterns and DED in the general population.

The impact of diet on health and disease has garnered increasing scientific attention over the last decades [13], with a growing focus on the role of diet and nutrition in the etiology of non-communicable diseases [14,15]. The Mediterranean diet, a dietary pattern similar to the traditional diet in the rural Mediterranean Basin, has been tied to longevity [16,17] and appears to be protective for overall health [18]. Although the Mediterranean lifestyle includes non-nutritional aspects that may promote health [19,20], the hallmarks of the traditional Mediterranean diet are high consumption of vegetables, fruits and nuts, legumes, and unprocessed cereals, and more sparing consumption of meats and dairy products, in conjunction with moderate alcohol intake, mainly from wine [18]. The nutritional makeup of the diet, especially its ratio of omega-6 to omega-3 essential fatty acids, low saturated fatty acid content, and high amounts of oleic acid, dietary fiber, antioxidants, and polyphenols, are thought to have antioxidant, anti-inflammatory, and antithrombotic properties [20]. Moreover, a greater adherence to a Mediterranean diet has been linked to lower circulating levels of C-reactive protein (CRP) and other inflammatory markers [21–24].

The pathophysiology of the initiation and perpetuation of DED is complex and multifaceted [25]. However, local inflammation of the ocular surface plays a key role in the vicious cycle of dry eye, which includes oxidative stress, epithelial cell damage, and increased tear film osmolarity [25,26]. Several different treatment strategies can be used to target different aspects of the vicious circle to manage DED [27]. In addition to other treatments, strategies such as environmental modification and dietary supplementation with omega-3 fatty acids are frequently used in DED management due to their anti-inflammatory effects [28]; however, the effects of a targeted omega-3 intervention were called into question by the recent DREAM study [29]. Despite its established anti-inflammatory effects, only a few studies have explored the relationship between a Mediterranean diet and DED, and these studies have included very specific groups of subjects: patients with metabolic syndrome, Sjögren syndrome, and veterans [30–33].

The aim of this study was to investigate the hypothesis that a greater adherence to a Mediterranean diet is tied to a decreased likelihood of having DED in the general population. For this purpose, we analyzed data on DED and diet, as well as CRP, in the Dutch population-based Lifelines Cohort from the Northern Netherlands.

2. Methods

2.1. Lifelines cohort and participants

Lifelines is a multi-disciplinary, prospective, population-based cohort study examining the health and health-related behaviors of 167,729 persons living in the north of the Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical, and psychological factors, which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics [34]. Participants, almost exclusively of European ancestry, were included via general practitioners or self-enrollment between 2006 and 2013 and will be followed for at least 30 years. The cohort is described in detail elsewhere [12,35]. The study protocol was approved by the medical ethics committee of the University Medical Center Groningen (number 2007/152) and carried out in accordance with the Declaration of Helsinki, and all participants provided written informed consent.

Participants attended 1A, the first general assessment, for completion of questionnaires and physical tests between 2007 and 2013. On average 1.5 years (1B) and 2.5 years (1C) later, follow-up questionnaires were sent out. Between 2014 and 2017, the second general assessment, 2A, was conducted. While the dry eye assessment (see below) was only assessed at 2A, information related to the risk factors and confounding factors were collected at both 2A and earlier timepoints (1A-C).

2.2. Assessment of dry eye

This study used the Women's Health Study (WHS) dry eye questionnaire [36] to assess dry eye status. The questionnaire has been validated against a standardized clinical exam and has a similar sensitivity and specificity as a 16-item instrument [36]. The WHS questionnaire is the most used dry eye questionnaire in population-based studies [2], and consists of three questions: [1] "How often do your eyes feel dry (not wet enough)?" [2] "How often do your eyes feel irritated?" and [3] "Have you ever received a diagnosis of dry eye?" Possible answers are: "Never," "Sometimes," "Often," and "Constantly" for question [1] and [2] and "Yes," "No," and "I don't know" for question [3]. The main outcome, 'WHS-defined DED,' is defined as either answering "Yes" to having a diagnosis of dry eye or having both dryness and irritation symptoms either "often" or "constantly" [36,37]. A secondary outcome measure, 'symptomatic dry eye,' was defined as both dryness and irritation at least "sometimes," or either symptom at least "often".

2.3. Assessment of dietary intake and Mediterranean Diet Score

The habitual food intake and dietary pattern were calculated based on a specially designed flower-petal food frequency questionnaires developed by Wageningen University and Research [38]. At 1A, a 110-item questionnaire (the heart) was given to all participants to assess total macronutrient intake and diet regime. At each following assessments (1B, 1C, and 2A), one of three supplementary questionnaires (the flower petals) assessing micronutrients and specific food items was administered. Combined, the questionnaires account for ≥96% of absolute intake and ≥93% of inter-person variability for each nutrient [38].

The level of adherence to a traditional Mediterranean diet was assessed using the modified Mediterranean Diet Score (mMDS) by Trichopoulou et al. [16,17]. This score, with variations, is the most widely used tool to assess adherence to a Mediterranean diet [39]. The original MDS [16] was modified in 2005 to be valid across Europe [17], and it was this variant that is used in the current study. The mMDS assesses dietary intake across nine different categories and provides points based on the sex-specific median values withing each category to yield a score from 0 to 9. However, as the Dutch diet is noted to deviate from a traditional Mediterranean diet [17], a secondary Mediterranean diet score using pre-defined cut-offs was also used to assessed absolute adherence to a Mediterranean diet (aMDS) [40]. The components of both scores are shown in Supplemental Table 1.

2.4. Assessment of possible confounding factors

At 1A, participants were asked about the presence or absence of diseases across all major organ systems. At later visits, participants disclosed the occurrence of new conditions since last visit. At 2A, an additional targeted ocular questionnaire was distributed. Dichotomous variables for the occurrence of all these conditions were created, and of these were 48 found to be associated with WHS-defined DED, and deemed to be possibly confounding comorbidities, as described in a past work [41]. Physical activity was assessed using a specialized questionnaire, and minutes per week of moderate-to-vigorous physical activity (MVPA minutes) were used as a measure of habitual physical activity, in accordance with recent recommendations [42].

2.5. Assessment of circulating high-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hsCRP) was measured in blood samples collected at visit 1A. Further details on sample collection, handling, and standardization are described in previous studies [43,44].

2.6. Statistics

Study characteristics were assessed using descriptive statistics. Multivariable logistic regression models were used to investigate the relationship between WHS-defined DED (dependent variable, dichotomous) and mMDS (independent variable, scale 0–9). The analyses were adjusted for: age and sex (Model 1), relevant demographic variables (age, sex, education level [low, middle, high], and net monthly household income [<2000, 2000–3000, >3000 euros/month]), body mass index (BMI), physical activity levels (MVPA minutes), and smoking status (never, current, past history of smoking) (Model 2), and all factors in Model 2 plus 48 comorbidities associated with WHS-defined DED [41] (Model 3) (see Supplemental Table 3A). Additionally, a subsequent logistic regression was conducted, assessing the relative effect of all nine components individually that constitute the mMDS, in base units 10 or 20 g/day. To assess any sex-specific effect on the association between mMDS and WHS-defined DED, we tested the interaction term [sex*mMDS] in logistic regression models. Additionally, the interaction term [age*mMDS] was also tested. Subsequently, to mitigate the possible effects of reverse causality due to patients diagnosed with DED who might have changed their behavior after the diagnosis, we assessed the relationship between mMDS and symptomatic dry eye, after excluding those ever diagnosed with DED. Moreover, as the Dutch diet deviates from a Mediterranean diet, a secondary absolute MDS (aMDS) was also checked in logistic regressions for a relationship with WHS-defined DED. Finally, linear regression was used to assess the relationship between mMDS (dependent variable) and hsCRP (independent variable; natural logarithmic transformed due to significant right-skewedness) and logistic regression was used to assess untransformed hsCRP and WHS-defined DED. A P-value lower than 0.05 was regarded as statistically significant in all analyses. All analyses were conducted using SPSS software, version 25.0 (SPSS Inc.).

3. Results

The mean age of the 58,993 participants included in this study was 50.9 years old, range 20–94. Nearly all (98.7%) identified as white "Western or Eastern Europeans" and 60% were female. WHS-defined DED was present in 9.1% of the participants and mean mMDS was 4.3. Table 1 presents more details on the included population. Supplemental Table 2 provides an overview of population characteristics for each mMDS value.

Table 2 shows the relationship between mMDS and WHS-defined DED. Going against the initial hypothesis, increasing mMDS levels were associated with a greater risk of having WHS-defined DED in all three models. When fully adjusted for confounding factors, Model 3, the odds ratio (OR) of having WHS-defined DED per increasing mMDS level was 1.034 (95% CI 1.015–1.055, P = 0.001). Results were similar in males and females and the interaction term [mMDS*sex] was not significant in any of the models. Fig. 1 shows the crude prevalence of WHS-defined DED for each of the mMDS levels, stratified by sex.

When assessing the individual intake of each of the nine items making up the mMDS, increasing vegetable and legume intake was tied to a greater risk of having WHS-defined DED, while greater consumption of meat and poultry and higher alcohol intake was tied to decreased risk of DED in Model 3 (Table 3).

Moreover, when the association between symptomatic dry eye and mMDS was studied separately, after exclusion of those with a diagnosis of DED, higher mMDS levels were tied to greater odds of having symptomatic dry eye in all three models. When fully adjusted for confounding factors, the OR of having symptomatic dry eye per level increase in mMDS was 1.033 (95% CI 1.019–1.047, P < 0.001).

The results of the secondary analyses using the aMDS are shown in Table 4. Similar to the main analysis, no reduced risk of dry eye was found in those with higher aMDS. When fully adjusted for confounding factors, no significant relationship was observed (OR 1.021, 95% CI 0.997–1.045, P = 0.085). No significant interaction effect of sex was seen in any of the models.

Table 1
Demographics of the study population.

	All (N = 58,993)	Males (N = 23,389)	Females (N = 35,604)
Age, years, mean (standard deviation [sd])	50.9 (12.0)	51.7 (12.0)	50.3 (11.9)
Ethnicity – White, European, %	98.7	98.9	98.5
Income			
<2000 €/month, %	27.1	21.5	30.9
2000-3000 €/month, %	29.9	33.6	27.5
>3000 €/month, %	33.5	38.0	30.6
Chose not to answer, %	9.5	6.9	11.0
Smoker			
Current, %	14.6	16.0	13.7
Former, %	33.5	36.11	31.7
Never, %	48.1	47.9	54.6
Dry Eye			
Women's Health Study dry eye disease, %	9.10	5.02	11.79
Highly symptomatic dry eye, %	1.88	0.87	2.54
Clinical diagnosis of dry eye, %	8.52	4.69	11.06
Symptomatic dry eye, %	29.97	22.24	35.04
Comorbidities[a]			
Number of comorbidities, mean (sd)	2.9 (2.1)	2.4 (1.8)	3.3 (2.2)
Presence of ≥1 comorbidity, %	89.4	85.5	92.0
Physical Activity			
Moderate to vigorous physical activity, min/week, mean (sd)	500 (643)	594 (780)	440 (527)
Dietary intake			
Meat/poultry intake, g/day, mean (sd)	67.9 (42.9)	77.1 (47.1)	61.8 (38.7)
Dairy intake, g/day, mean (sd)	334.4 (205.6)	351.9 (224.2)	322.8 (191.6)
Cereal intake, g/day, mean (sd)	195.3 (110.4)	226.8 (126.6)	174.6 (92.8)
Fruit and nut intake, g/day, mean (sd)	137.6 (111.8)	134.6 (115.4)	139.6 (109.3)
Fish intake, g/day, mean (sd)	15.2 (17.0)	15.8 (17.3)	14.8 (16.8)
Legume intake, g/day, mean (sd)	8.5 (14.9)	10.4 (17.9)	7.3 (12.4)
Vegetable intake, g/day, mean (sd)	145.0 (87.3)	134.6 (83.4)	151.9 (89.1)
Mono- and polyunsaturated to saturated lipids, ratio	1.61	1.66	1.58
Ethanol, g/day, mean (sd)	6.58 (8.41)	9.60 (10.1)	4.59 (6.37)
Mediterranean Diet Score			
Modified Mediterranean Diet Score, mMDS, mean (sd)	4.33 (1.66)	4.35 (1.65)	4.31 (1.67)
Absolute Mediterranean Diet Score, aMDS, mean (sd)	3.64 (1.40)	3.52 (1.43)	3.72 (1.38)
High-sensitivity C-Reactive Protein			
C-Reactive Protein, mg/ml, mean (sd)[b]	2.48 (4.59)	2.00 (4.41)	2.79 (4.55)

[a] Contact lens wear, hypertension (measured), macular degeneration, glaucoma/ocular hypertension, eye surgery (any), allergic conjunctivitis, Bell's palsy, keratoconus, laser refractive surgery, irritable bowel syndrome, fibromyalgia, osteoarthritis, spinal disc herniation, repetitive strain injury, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, atherosclerosis, cardiac arrhythmia, liver cirrhosis, chronic cystitis, urinary incontinence, spasticity, migraine, chronic fatigue syndrome, depression, burnout, autism, gastric ulcer, Crohn's disease, asthma, acne, psoriasis, eczema, rosacea, hay fever, allergy (any), anemia, diabetes mellitus, osteoporosis, thyroid disease (any), Graves' disease, carpal tunnel syndrome, obstructive sleep apnea, lichen planus, sarcoidosis, chronic back pain, sinusitis.

[b] $N_{All} = 28{,}123$; $N_{Males} = 11{,}028$; $N_{Females} = 17{,}095$.

Table 2
Relationship between Women's Health Study-defined dry eye disease and Mediterranean Diet Score.

	Model 1[a] (N = 58,993)		Model 2[b] (N = 52,451)		Model 3[c] (N = 51,756)	
Modified Mediterranean Diet Score (mMDS)	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
mMDS, 0–9-unit scale	**1.051 (1.033–1.069)**	**<0.001**	**1.042 (1.022–1.061)**	**<0.001**	**1.034 (1.015–1.055)**	**0.001**

OR: odds ratio of having dry eye per modified Mediterranean Diet Score (mMDS) unit; CI: confidence interval.
[a] Model 1: Corrected for age and sex.
[b] Model 2: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, and net monthly household income.
[c] Model 3: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye.

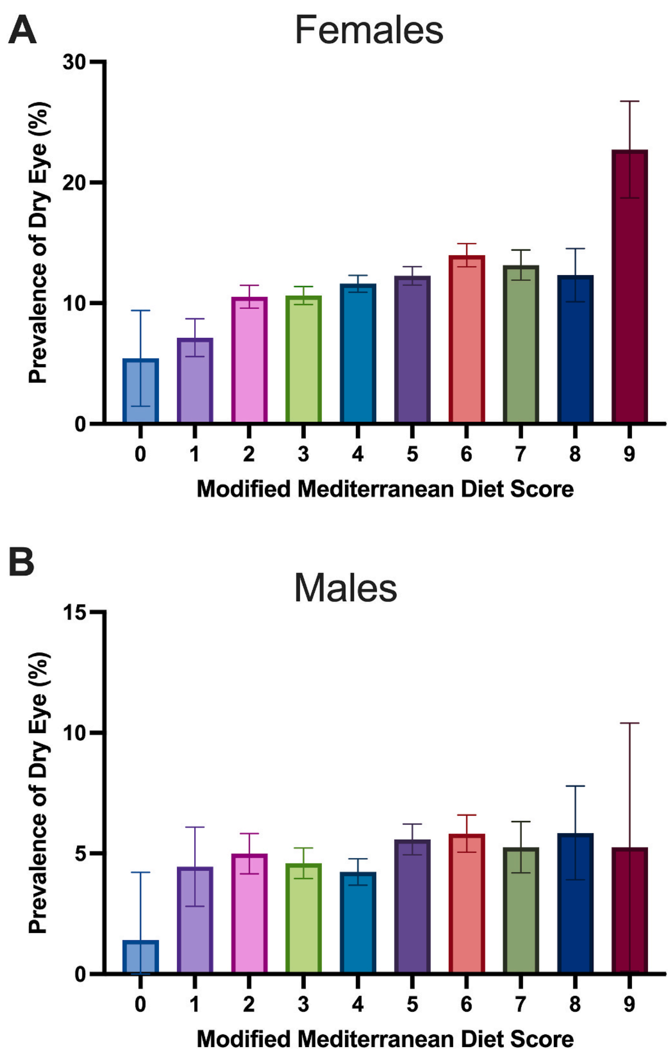

Fig. 1. Unadjusted prevalence of Women's Health Study-defined dry eye disease for each Mediterranean Diet Score, stratified by sex
Fig. 1. Unadjusted prevalence of WHS-defined dry eye with different mMDS values in A) females, n = 35,604 (0: 129, 1: 1,039, 2: 4,095, 3: 6,503, 4: 8,060, 5: 7,072, 6: 4,947, 7: 2,789, 8: 860, 9: 110), and B) males, n = 23,389 (0: 71, 1: 607, 2: 2,603, 3: 4,183, 4: 5,153, 5: 4,914, 6: 3,525, 7: 1,693, 8: 564, 9: 76). Error bars indicate 95% confidence intervals.

Lastly, greater mMDS values were associated with lower circulating hsCRP levels, even when correcting age, sex, education, income, BMI, physical activity, smoking status, and 35 potentially confounding medical conditions and comorbidities associated with both hsCRP and mMDS (see Supplemental Table 3B) (β per mMDS point −0.065, 95% CI -0.085 to −0.045, P < 0.001) (Table 5). However, there was no significant association between hsCRP and WHS-defined DED in any of the analyses (Table 6). Fig. 2 shows the crude mean hsCRP per each mMDS values, as well as in those with WHS-defined DED compared to those without, stratified by sex.

4. Discussion

In this large Dutch cohort, a greater adherence to a Mediterranean diet was not associated with a reduced risk of DED. In fact, higher mMDS values were tied to greater odds of having WHS-defined DED, also when corrected for demographics, smoking status, BMI, and 48 comorbidities associated with DED. This went against our initial hypothesis that a greater adherence to a Mediterranean diet would be protective for DED. The same relationship was found when assessing symptomatic dry eye after excluding those with a clinical diagnosis of DED, to reduce the effects of a potential reverse causality. Also when using a secondary Mediterranean diet score with pre-defined absolute cut-offs, there was no reduced risk of DED with more Mediterranean dietary patterns. Lastly, this study found a strong relationship between increasing adherence to a Mediterranean diet and lower circulating hsCRP levels, but no relationship between hsCRP and DED.

The current study, conducted in a Northern-European population, is the first large epidemiological study assessing the relationship between a Mediterranean diet and DED in the general population. The observed relationship is in-line with the findings of a smaller, cross-sectional study of male veterans, where a greater adherence to a Mediterranean diet was linked to greater odds of having dry eye syndrome [30]. In the same study, they further found a significant relationship between adherence to a Mediterranean diet and worse tear film breakup values, meibum quality, and conjunctival staining [30]. The authors proposed that harmful effects of alcohol might have counteracted the beneficial effects of other nutrients, or that people with dry eye might improve their diet to alleviate their condition. However, based on the results of the current study and recent findings [9], higher alcohol intake does not appear to be linked to more DED, and is thus not likely to be the driving factor behind the association. Furthermore, in the current study, a Mediterranean diet remained associated with more symptomatic dry eye even after excluding those diagnosed with DED, reducing the likelihood that reverse causality was a major driver.

Partially opposing the findings of the current study, a recent study of a small subsample from the PREDIMED-PLUS trial with metabolic syndrome found improvement in ocular surface measures after an intervention with a Mediterranean diet supplemented with extra virgin olive oil and nuts [31]. However, over half of the subjects also received a 30% caloric restriction, exercise recommendation, and weight loss goals and there was no control group not receiving a Mediterranean diet intervention [31]. Thus, the effects of a Mediterranean diet intervention could not be isolated from that of caloric restriction, physical activity, and weight goal interventions, as well as increased care associated with participation in an interventional study. The association between greater physical activity and lower odds of DED has been found in previous literature [45,46], and in the Lifelines population [47]. In the current study, the associations between dry eye and Mediterranean diet measures were similar both before and after correction for physical activity measures.

Table 3
Relationship between Women's Health Study-defined dry eye disease and each sub-item of the Mediterranean Diet Score.

Modified Mediterranean Diet Score (mMDS) components	Model 1[a] (N = 58,993)		Model 2[b] (N = 52,451)		Model 3[c] (N = 51,756)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Foods where below median intake adds 1 point to mMDS						
Meat and poultry, base unit 20 g/day	**0.962 (0.947–0.978)**	**<0.001**	**0.971 (0.954–0.989)**	**0.001**	**0.981 (0.963–0.999)**	**0.035**
Dairy, base unit 20 g/day	**0.997 (0.993–1.000)**	**0.033**	**0.996 (0.993–1.000)**	**0.041**	0.997 (0.994–1.001)	0.15
Foods where above median intake adds 1 point to mMDS						
Cereals, base unit 20 g/day	0.998 (0.991–1.005)	0.51	0.994 (0.986–1.002)	0.13	0.996 (0.988–1.004)	0.35
Fruits and nuts, base unit 20 g/day	1.005 (0.999–1.011)	0.094	1.003 (0.997–1.009)	0.33	1.003 (0.996–1.009)	0.40
Fish, base unit 20 g/day	1.021 (0.987–1.056)	0.23	1.022 (0.986–1.060)	0.24	1.000 (0.963–1.039)	0.98
Legumes, base unit 20 g/day	**1.049 (1.011–1.089)**	**0.011**	**1.054 (1.013–1.097)**	**0.009**	**1.046 (1.004–1.090)**	**0.032**
Vegetables, base unit 20 g/day	**1.023 (1.016–1.030)**	**<0.001**	**1.022 (1.014–1.029)**	**<0.001**	**1.013 (1.005–1.021)**	**0.002**
Mono- and polyunsaturated to saturated fats-ratio	1.016 (0.960–1.075)	0.58	1.021 (0.960–1.087)	0.51	1.040 (0.975–1.109)	0.23
Alcohol, intake between 5 and 25g/day for females and 10–50g/day for males adds 1 point to the mMDS						
Ethanol, base unit 10 g/day	**0.936 (0.898–0.975)**	**0.001**	**0.937 (0.896–0.980)**	**0.004**	**0.953 (0.910–0.998)**	**0.040**

OR: odds ratio of having dry eye per each base unit of increased intake in multivariable regression including all sub-items; CI: confidence interval.
[a] Model 1: Corrected for age and sex.
[b] Model 2: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, and net monthly household income.
[c] Model 3: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye.

Table 4
Relationship between Women's Health Study-defined dry eye disease and the absolute Mediterranean Diet Score.

Absolute Mediterranean Diet Score (aMDS)	Model 1[a] (N = 59,002)		Model 2[b] (N = 52,459)		Model 3[c] (N = 51,763)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
aMDS, 0–9-unit scale	**1.043 (1.022–1.066)**	**<0.001**	**1.030 (1.006–1.053)**	**0.012**	1.021 (0.997–1.045)	0.085

OR: odds ratio of having dry eye per absolute Mediterranean Diet Score (aMDS) unit; CI: confidence interval.
[a] Model 1: Corrected for age and sex.
[b] Model 2: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, and net monthly household income.
[c] Model 3: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye.

Table 5
Relationship between high-sensitivity C-reactive protein and modified Mediterranean Diet Score eye.

modified Mediterranean Diet Score (mMDS) values	0 (n = 81)	1 (n = 859)	2 (n = 4,079)	3 (n = 5,714)	4 (n = 6,452)	5 (n = 5,079)	6 (n = 3,451)	7 (n = 1,869)	8 (n = 607)	9 (n = 66)
Proportion with hsCRP values > 5 mg/l (%)	19.8%	15.7%	13.5%	13.7%	12.3%	12.0%	9.68%	8.40%	6.26%	9.09%

Linear regression model, natural log-transformed hsCRP	β per mMDS level (95% CI)	P-value
Model 1[a]	**−0.104 (−0.121 to −0.086)**	**<0.001**
Model 2[b]	**−0.065 (−0.086 to −0.045)**	**<0.001**
Model 3[c]	**−0.065 (−0.085 to −0.045)**	**<0.001**

[a] Model 1: Corrected for age and sex, n = 28,253.
[b] Model 2: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, and net monthly household income, n = 24,602.
[c] Model 3: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, net monthly household income, and 35 comorbidities associated with hsCRP and mMDS, n = 24,561.

Table 6
Relationship between high-sensitivity C-reactive protein and Women's Health Study-defined dry eye.

High-sensitivity C-reactive protein (hsCRP)	Model 1[a] (N = 37,127)		Model 2[b] (N = 31,349)		Model 3[c] (N = 30,923)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Plasma hsCRP, mg/l	1.006 (0.999–1.013)	0.12	1.007 (1.000–1.014)	0.07	1.005 (0.997–1.013)	0.18
Plasma hsCRP > 5 mg/l	1.033 (0.929–1.148)	0.55	1.092 (0.969–1.231)	0.15	1.085 (0.957–1.230)	0.20

[a] Model 1: Corrected for age and sex.
[b] Model 2: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, and net monthly household income.
[c] Model 3: Corrected for age, sex, physical activity level, body mass index, smoking status, education level, net monthly household income, and 48 comorbidities associated with dry eye.

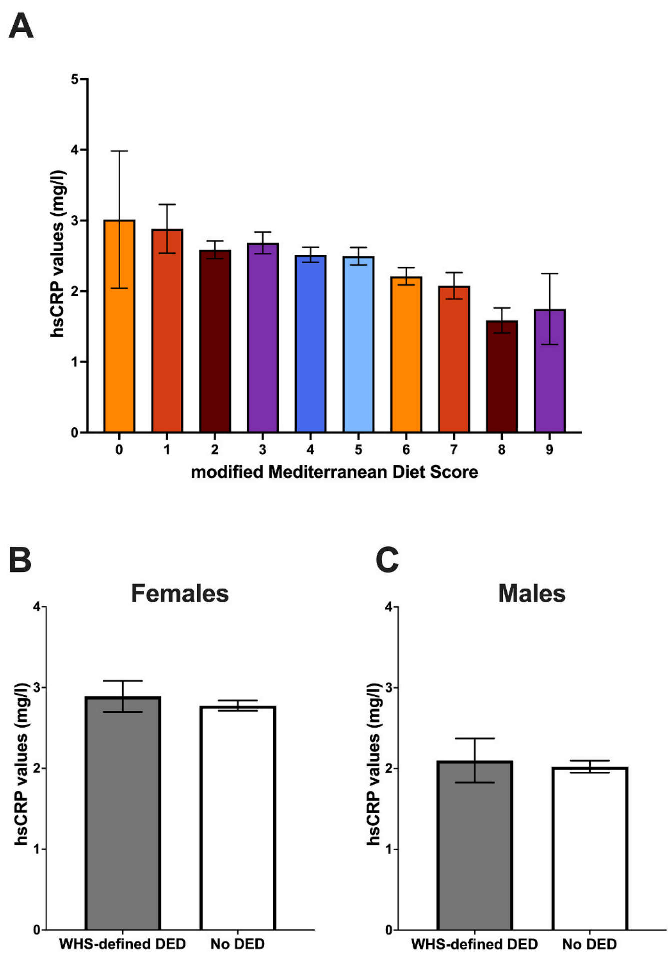

Fig. 2. High-sensitivity C-reactive protein (CRP) values in each modified Mediterranean Diet Score and for Women's Health Study-defined dry eye disease

Fig. 2, Panel A) shows the mean high-sensitivity C-reactive protein (hsCRP) values in mg/l within each modified Mediterranean Diet Score group (n = 28,257). Panels B) and C) show the mean hsCRP values in those with and without Women's Health Study-defined dry eye disease in females (n = 22,137, unpaired *t*-test: p-value >0.10) and males (n = 14,990, unpaired *t*-test: p-value >0.10), respectively. Error bars indicate 95% confidence interval.

The standard Dutch diet is quite different from the traditional Mediterranean diet, as noted in the original EPIC elderly trial [17]. Although the mMDS was modified to be valid across Europe, it is possible that the use of the sex-specific median cut-off for each domain of the mMDS could have skewed the results in the current study. However, the results were consistent also with the aMDS, which uses absolute cut-offs for intake of several key food items. Thus, the results appear to be consistent even when accounting for the lower overall adherence to a Mediterranean lifestyle seen in the Netherlands. Furthermore, surprisingly, a 2011 paper reported that university students from Amsterdam (the capital of the Netherlands) had a greater adherence to a Mediterranean diet than university students from Thessaloniki, in Greece, indicating that social and cultural factors are likely just as important as geographical for dietary patterns [48].

The findings of the current study went against the initial hypothesis that there would be an inverse relationship between mMDS and WHS-defined DED. The Mediterranean diet is thought to be anti-inflammatory and tied to lower levels of pro-inflammatory markers in the blood [22,49–51]. This was also found in the current study with higher mMDS strongly tied to lower hsCRP levels. However, no significant association was found between hsCRP and likelihood of having WHS-defined DED. This is in line with the findings of Crane et al. from 2013, who observed no link between circulating CRP levels and tear function parameters or ocular symptoms in 233 male veterans [52]. Moreover, the current results are further supported by the findings of Yoon et al., who did not find elevated levels of the inflammatory markers IL-6 and TNF-α in the blood of subjects with non-Sjögren dry eye, despite finding elevated levels of the same markers in the tear fluid [53]. However, in subjects with Sjögren syndrome, blood CRP levels are known to be elevated compared to non-Sjögren DED [54]. Furthermore, a 2021 study on participants with primary Sjögren syndrome found adherence to a Mediterranean diet to be tied to lower overall disease activity, but saw no link between Mediterranean diet and dry eye symptoms [33], in line with the findings in our study. Overall, although local ocular surface inflammation is a major driver of the vicious circle of DED, there appears to be no clear link between circulating CRP levels and dry eye symptoms in the general population, which may explain why the findings went against the initial hypothesis. However, no direct measure of ocular surface inflammation was included on the current study.

The use of long-chain fatty acids in dry eye management has been heavily debated in the last few years and recent studies have reached differing conclusions [55,56]. In the current study, there was no significant association between a higher ratio of mono- or polyunsaturated fatty acids to saturated fatty acids and decreased prevalence of DED. However, not all unsaturated fatty acids are created equal. The impact of the ratio of omega-6 to omega-3 fatty acids, and omega-6 fatty acids' role in inflammation remains controversial [57,58]. Despite the lack of clear evidence for adverse effects of higher omega-6 blood levels [57], it is possible that elevated levels may be pro-inflammatory. Furthermore, within the Western diet, nearly all omega-3 consumed comes in the form of alpha-linoleic acid, while very little is in the form of eicosapentaenoic acid (EPA) or docosahexaenoic (DHA) [59]. However, further subdivision of the mono- and polyunsaturated fatty acids consumed was not assessed in the current study. Interestingly, a recent study found no significant association between dry eye signs and levels of any individual fatty acid in plasma, but found that a profile with low polyunsaturated fatty acids, high monounsaturated fatty acids, and low saturated fat levels were tied to greater chance of having dry eye signs in a population of 740 people over the age of 65 [60].

There are several limitations to this study. Due to the cross-sectional nature, it is not possible to determine the causality of the observed association. However, potential reverse causality was addressed through the exclusion of those with a clinical diagnosis of DED and the association remained significant between mMDS and symptomatic dry eye. Moreover, the inclusion of hsCRP measurements showed the robustness of the phenotype and further reduced the likelihood that reverse causality was the main driver of the observed relationship. A further limitation of the study was the use of self-reported food frequency questionnaires, which could lead to recall bias; however, the strong negative link between hsCRP and mMDS indicated that overall, there did not appear to be a trend that participants with inflammatory conditions overreported intake of presumed beneficial food items. Additionally, the absence of clinical tests for DED prevented the assessment of associations with signs of dry eye. For instance, the direct measurement of inflammatory markers in the tear film could have offered clues as to the local effects of the diet on the ocular surface inflammation. Future prospective studies assessing the efficacy of a Mediterranean diet intervention may benefit from including these markers. However, the WHS-dry eye questionnaire employed is the most widely used item for epidemiological dry eye research and has been validated and shown to yield a strong phenotype for these purposes [2,36]. Lastly, this study was conducted in a Dutch population of nearly exclusively people identifying as white, Western Europeans. This might reduce the generalizability of the findings to other regions and ethnicities.

Strengths of the current study includes leveraging an unprecedented sample size with a subsequent substantial increase in power over past studies assessing the relationship between adherence to a Mediterranean diet and DED. Moreover, the current study was performed in a sample drawn from, and broadly representative of, the general population in the Northern Netherlands [61], reducing the effects of selection bias. Moreover, the use of the validated WHS-questionnaire improves the repeatability and robustness of the DED phenotype. Furthermore, with an over ten-fold increase in sample size over previous studies, the current study was able to confirm the link between a Mediterranean diet and lower circulating levels of CRP in a large general-population, indicated by smaller past studies [21]. This observation further validates the Mediterranean Diet assessment tool used and indicates that it is likely that a potential protective effect of the diet on DED would have been picked up on in the current study had it been present.

5. Conclusion

Based on the results of this large, population-based, cross-sectional study, a greater adherence to the Mediterranean Diet does not appear to be associated with lower odds of having DED. Contrarily, higher Mediterranean Diet Scores were tied to somewhat increased odds of having DED. The current study found no evidence for a population-wide association between levels of the inflammatory marker CRP and likelihood of having DED, despite finding a strong link between a Mediterranean Diet and lower CRP levels. In conclusion, there appears to be no large population-wide protective effect against DED of adherence to a Mediterranean Diet in the general population, despite its known anti-inflammatory effects.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtos.2023.09.013.

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