Mediterranean diet and risk of Sjögren's syndrome

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ABSTRACT

Objective. *Non-genetic risk factors for Sjögren's syndrome (SS) are poorly understood. Adherence to a Mediterranean diet has been associated with reduction in other autoimmune diseases. We examined the association of Mediterranean diet with SS.*

Methods. *New patients attending a single centre warranting investigation for primary SS (pSS) were recruited into the Optimising Assessment in Sjögren's Syndrome cohort established in Birmingham, UK (2014-2018). Participants were classified into pSS and non-SS sicca, considered as cases and non-cases, respectively, and asked to complete an optional food frequency questionnaire on their diet before onset of symptoms. A semi-quantitative Mediterranean diet score (MDS) was calculated (possible range=0 to 18). Using multivariate logistic regression, corrected for energy intake, body-mass index, sex, age, symptom duration, and smoking status, we examined the association of MDS with SS.*

Results. *Dietary data were available for 133/243 (55%) eligible patients (n=82 pSS and n=51 sicca). In the adjusted model, a higher total MDS (mean ± SD, 9.41±2.31 points) was associated with lower odds of pSS (OR 0.81, 95% CI 0.66-0.99; p=0.038) per one unit of MDS. Among MDS components, the strongest association was seen with fish with OR 0.44 (95% CI 0.24-0.83; p=0.01) in the comparison between <1 portion/week and 1 to 2.5 portions/week. Higher galactose, vitamin A-retinol-equivalents and vitamin C showed associations with lower odds of pSS in multivariate analysis, where the association of vitamin C was attenuated when adjusted for MDS.*

Conclusion. *When adjusted for potential confounders, adherence to the Mediterranean diet was associated with lower likelihood of having pSS.*

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease leading to severe oral and ocular dryness, fatigue, and systemic manifestations in a proportion of patients. It is characterised by poor health-related quality of life and costs to the individual, healthcare system and society (1, 2). In common with other autoimmune connective tissue diseases, there are polygenic associations, most notably in the HLA region (3, 4), but considerable non-genetic attributable risk is assumed. Indeed, a Taiwanese study found familial factors (shared genetic and environmental factors) only accounted for 54% of risk (5). However, little is known about environmental risk factors for pSS. Both viruses and hormonal factors have been thought to play a role but without definitive evidence yet of mechanism (6). Unlike in rheumatoid arthritis (RA), smoking has been associated with less severe pSS (7), although these findings need to be replicated and confounding remains a concern. Diet has been little explored with existing data examining diet in established disease rather than from the perspective of disease risk (8-10). In RA, a more widely studied autoimmune connective tissue disease, several studies report a possible protective effect of fish intake on disease occurrence (11, 12). This may point to a beneficial effect from long-chain n-3 polyunsaturated fatty acids (PUFA) found in deep sea fish. Recent studies have also suggested a protective association of plant-derived n-6 PUFA with RA (13, 14). Moderate alcohol has been reported to decrease risk of RA (15, 16). Other findings suggesting that low vitamin C and high red meat intake were associated with inflammatory arthritis (17, 18) have not been replicated (19-21).

These individual dietary components are factors in a more complex dietary habit and recent studies have explored

the role of Mediterranean diet patterns with RA risk. The Mediterranean diet is primarily a plant-based diet with high intake of fruit, vegetables, whole grains and legumes, moderate intake of fish, white meat and alcohol, and only low red meat and sugar intake (22). Higher adherence to a Mediterranean diet has been associated with a number of health benefits including a reduction in mortality, cardiovascular disease and type 2 diabetes (23, 24). Johansson and colleagues found that high adherence to a Mediterranean diet reduced the odds of RA development by 21%; an effect only seen in men and in seropositive RA (25). A reduction in risk was not seen in the Nurses Health Studies and in the Vasterbotten Intervention Program (VIP) cohort (26, 27), however all these studies used a score based on population medians that may vary from country to country.

Given the putative anti-inflammatory potential of the Mediterranean diet (28, 29), and emerging evidence of a possible protective role in other autoimmune diseases, we set out to examine the association of Mediterranean diet, using a semi-quantitative score, as a risk factor for SS.

Methods

Participants

The Optimising Assessment in Sjögren's Syndrome (OASIS) cohort has been recruiting new patients who attend the multidisciplinary Sjögren's clinic at Queen Elizabeth Hospital Birmingham, UK, since 2014. Participants are over the age of 18 and have been referred with symptoms, signs or tests warranting investigation for pSS or with a diagnosis of pSS. In this study, we evaluated participants who joined OASIS by December 2018 and who had physician diagnosis of pSS and met the 2016 ACR/EULAR classification criteria (30). Participants with sicca had signs and/or symptoms of dryness but did not have a physician diagnosis of SS or meet 2002 or 2016 classification criteria and were considered to have a probable non-inflammatory cause for their symptoms.

At enrolment into OASIS, demographic data, symptom duration and disease activity scores, including the European League Against Rheumatism (EULAR) SS Disease activity Index (ESSDAI), were collected. Tear production was assessed by Schirmer's test without anaesthetic, and unstimulated salivary flow over 5 minutes was measured. As part of the initial assessments subjects were given questionnaires that included patient reported outcomes including the EULAR Sjögren's syndrome Patient Reported Index (ESSPRI), questions on hypothetical risk factors including smoking, as well as an optional semi-quantitative European Investigation into Cancer and Nutrition (EPIC)-Norfolk food frequency questionnaire (FFQ) (31). Participants were asked to complete the FFQ with regard to their diet in the year before symptom onset. All subjects provided written informed consent and the study was approved by the Wales Research Ethics Committee 7 (WREC 7) formerly Dyfed Powys REC; 13/WA/0392.

Dietary data

FFQ data were utilised to derive food group intake in grams, using the FFQ EPIC Tool for Analysis (FETA) (31). We assessed adherence to the Mediterranean diet by calculating Mediterranean diet score (MDS) (24). The MDS was developed using weighted food intake derived from a meta-analysis of studies. It consists of 9 domains each scored 0-2, giving a total score of 0-18 and is summarised in Supplementary Table S1. Unlike the commonly used score of Trichopoulou *et al*. (32), this does not rely upon a population median which may differ between countries, meaning that a patient with similar intake might have different scores depending on whether they lived in a low or high Mediterranean diet adherent country. For olive oil the MDS allocates 0 for occasional use, 1 for frequent use and 2 for regular use. Due to limitations imposed by the FFQ structure, we assigned 0 for non-consumers, 1 for 1-3 times per week and 2 for 4-6 times per week/daily. The FETA program was also used to calculate nutrient intake (31). Subjects with 10 or more missing lines of data in part 1 of the FFQ, out of a total of 130 lines, were excluded. Participants with a calculated energy intake of less than 1000 kilo calories were also excluded.

Statistical analysis

Baseline characteristics of the pSS and sicca group were compared using an independent sample T test or chi-square test as appropriate. Association of MDS with disease group was assessed with logistic regression, corrected for total calorie intake (kcal), body-mass index (BMI), sex, age, symptom duration and smoking status. For the purposes of these analyses, smoking was classified as current, previous or never. As the Mediterranean diet consists of a number of different components, we wished to ascertain whether an observed association was a function of the diet as a whole or specific components within it. We therefore conducted additional analysis after recalculating MDS with each of the single domains removed in turn. We also conducted secondary analysis of logistic regression after classifying into anti-Ro positive and negative subgroups. Linear regression was used to correlate MDS with measures of disease activity/severity, corrected for kcal, BMI, sex, age, symptom duration and smoking status. Nutrient and food group values were compared between disease groups using independent sample T test. All analyses were performed in SPSS v. 24 (IBM, New York, USA).

Results

Baseline characteristics

At the time of analysis, optional FFQ data were available for 133/243 (55%) OASIS participants who met the criteria for either pSS or sicca as defined above. No differences were observed in baseline characteristics between participants with and without FFQ data (online supplementary Table S2). Comparing disease groups, participants with pSS (n=82) were more likely than those with sicca (n=51) to be autoantibody positive and have focal lymphocytic sialadenitis on biopsy with a focus score ≥1, to have lower salivary flow and Schirmer's test values, and higher IgG and IgA levels (Table I). No difference was seen in age, symptom duration or symptom severity as determined by ESSPRI.

Table I. Baseline characteristics of participants included in the study: retrospective analysis in the Optimising Assessment in Sjögren's Syndrome cohort (2014-2018).

	pSS (n=82)	Sicca (n=51)	*p*-values
Age at inclusion (years), mean (SD)	56.0 (14.0)	57.4 (11.0)	0.53 [t]
Symptom duration (years), median (IQR)	5.8 (2.2, 11.9)	5.4 (3.3, 10.2)	0.72 [t]
Female, n (%)	77 (93.9)	47 (92.0)	0.70 [X2]
BMI, mean (SD)	27.9 (5.7)	27.5 (5.7)	0.68 [t]
Smoking status, n (%)			
current	5 (6.1)	3 (5.9)	0.96 [X2]
previous	24 (29.3)	16 (31.4)	
non-smokers	49 (59.8)	29 (56.9)	
unspecified	4 (4.9)	3 (5.9)	
Anti-Ro(SSA) patients, n (%)	70 (85.4)	0 (0.0)	**0.001** [X2]
Anti-La(SSB) patients, n (%)	38 (46.3)	1 (2.0)	**0.001** [X2]
Rheumatoid factor (RF) patients, n (%)	42 (51.2)	4 (7.8)	**0.001** [X2]
Salivary flow(ml/5min), mean (SD)	0.5 (1.0)	0.8 (1.0)	**0.044** [t]
Schirmer's tests,			
mean (SD)			
Left	7.1 (12.5)	14.6 (14.0)	**0.003** [t]
Right	6.9 (12.0)	13.8 (13.0)	**0.003** [t]
Immunoglobulins (g/L), mean (SD)			
IgG	16.8 (8.0)	10.3 (2.4)	**0.001** [t]
IgM	1.2 (0.9)	1.1 (0.5)	0.12 [t]
IgA	2.9 (1.4)	2.3 (2.0)	**0.016** [t]
Focus score ≥1, n (%)	27/35 (77)	0/21 (0)	**<0.001** [X2]
Focus score, mean (SD)	1.8 (1.1)	N/A	N/A
ESSPRI, mean (SD)	6.1 (2.0)	5.8 (2.0)	0.40 [t]
ESSDAI, median (IQR)	4.5 (0, 5.5)	N/A	N/A
Mediterranean diet score			
Mean (SD)	9.17 (2.39)	9.80 (2.15)	0.125
0-6 points, n (%)	11 (13.4)	2 (3.9)	0.200
7-12 points, n (%)	65 (79.3)	45 (88.2)	
>12 points, n (%)	6 (7.3)	4 (7.9)	

pSS: primary Sjögren's syndrome; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; EULAR: European League Against Rheumatism; SD: standard deviation; IQR: interquartile range; N/A: not applicable.
ESSDAI not applicable for Sicca as it is SS-specific test. n=133.
[t]Independent Sample T test, significance if p**<0.05.**
[X2]Chi-square test, significance if p<0.05.

Mediterranean diet score and pSS

The MDS was normally distributed across the cohort. Mean MDS in the pSS group was 9.17 (SD 2.39) and 9.80 (SD 2.15) for sicca (Table I). In the adjusted model, a higher total MDS was associated with lower odds of pSS (OR 0.81, 95% CI 0.66–0.99; p=0.038) per one unit difference in MDS (Table II). After re-calculating MDS with one component removed, the association was attenuated with removal of the fish, dairy and vegetable domains, with the most notable change following removal of the fish domain (Table II). When classifying pSS into anti-Ro positive (n=70) and negative (n=12), a similar pattern of associations was seen with a wider 95% confidence interval (online supplementary Table III). Due to small numbers, the anti-Ro negative subgroup could not be analysed.

The MDS fish domain was inversely associated with pSS on both univariate (OR 0.60, 95% CI 0.36–0.98; p=0.041) and multivariate analysis (OR 0.44, 95% CI 0.24–0.83; p=0.01) (Table III). In the sicca group, 5 (9.8%) patients consumed less than 1 portion of fish per week (portion defined as 100 g) (24), 15 (29.4%) consumed 1–2.5 portions per week and 31 (60.8%) consumed more than 2.5 portions per week. The respective values for the pSS group were 18 (22.0%), 27 (32.9%) and 37 (45.1%). Supplements containing cod liver oil, omega 3 or fish oil were taken by 30 participants and were not associated with pSS in this cohort (multivariate OR 1.44, 95% CI 0.56–3.72; p=0.45).

The MDS vegetable domain was also inversely associated with odds of pSS on multivariate analysis (OR 0.47; 95% CI 0.24, 0.92; p=0.027).

Given the long median symptom duration we conducted a sensitivity analysis by excluding subjects with a symptom duration of greater than 8 years. In this analysis the median symptom duration was 2.9 (IQR 1.1, 4.5) and 3.8 (IQR 2.4, 5.4) years for pSS (n=44) and sicca (n=29) respectively. We found a similar negative association of MDS with pSS diagnosis (OR 0.81; 95% CI 0.64, 1.03; p=0.09) on univariate analysis and in the adjusted model (OR 0.74; 95% CI 0.55, 0.99; p=0.04). Similarly, the MDS fish domain had an OR 0.47 (95% CI 0.23, 0.97; p=0.04) on univariate analysis and 0.34 (95% CI 0.13, 0.91; p=0.03) in the adjusted model.

Mediterranean diet score and disease severity

No association was seen between MDS and tests of tear and saliva production, patient symptoms as measured by ESSPRI, systemic disease activity as measured by ESSDAI and IgG levels (Table IV). Analyses were repeated with the MDS fish domain; significant inverse associations were seen with IgG levels in the pSS group, and with unstimulated salivary flow in the sicca group.

Other nutrients

Supplementary Table S4 shows the FETA derived nutrient and food groups compared between pSS and sicca. Four nutrient groups with statistical trends (p<0.1) towards a difference between pSS and sicca were compared in univariate and multivariate models (Table V). Higher galactose, vitamin A-retinol-equivalents and vitamin C showed associations with lower odds of pSS in multivariate analysis, although vitamin C was not associated independently of MDS.

Discussion

In this study we observed that higher adherence to a Mediterranean diet was associated with a lower likelihood of developing pSS. When corrected for potential confounders, a one-unit increase in MDS was associated with

Table II. Associations between adherence to the Mediterranean diet and odds of primary Sjögren's syndrome: logistic regression analysis evaluating total MDS and MDS with one of nine components removed: the Optimising Assessment in Sjögren's Syndrome cohort (2014-2018).

	Univariate OR (95% CI)	Univariate analysis [u] *p*-value	Multivariate OR (95% CI)	Multivariate analysis [m1] *p*-value
MDS	0.89 (0.76-1.04)	0.13	0.81 (0.66-0.99)	**0.038**
MDS minus Fruit	0.88 (0.73-1.06)	0.18	0.79 (0.62-1.00)	**0.049**
MDS minus Vegetables	0.90 (0.75-1.08)	0.24	0.83 (0.67-1.04)	0.11
MDS minus Legumes	0.88 (0.75-1.04)	0.14	0.82 (0.67-1.01)	0.061
MDS minus Alcohol	0.88 (0.75-1.04)	0.13	0.80 (0.65-0.99)	**0.039**
MDS minus Meat	0.86 (0.72-1.02)	0.077	0.71 (0.55-0.91)	**0.006**
MDS minus Fish	0.92 (0.78-1.09)	0.35	0.88 (0.72-1.07)	0.12
MDS minus Olive Oil	0.85 (0.72-1.01)	0.064	0.79 (0.64-0.98)	**0.032**
MDS minus Dairy	0.93 (0.80-1.07)	0.29	0.84 (0.69-1.01)	0.070
MDS minus Cereal	0.84 (0.70-1.00)	**0.048**	0.77 (0.62-0.96)	**0.020**

MDS: Mediterranean diet score, a measure of adherence to the Mediterranean diet, developed by a systematic review of literature on the diet pattern; OR: odds ratio; CI: confidence interval. n=133.
[u]Univariate binary logistic regression analysis. Significance if $p<0.05$. ORs (95% CI) per one unit difference in each MDS variable are presented.
[m1]Multivariable binary logistic regression analysis, correcting for energy intake (kcals), Body Mass Index, sex, age, symptom duration, and smoking status. Significance if $p<0.05$.

Table III. The association of individual components of the Mediterranean diet with odds of Sjögren's syndrome: the Optimising Assessment in Sjögren's Syndrome cohort (2014-2018).

MDS domain	Univariate analysis OR (95% CI)	Univariate analysis [u] *p*-value	Multivariate analysis OR (95% CI)	Multivariate analysis [m1] *p*-value
Fish	0.60 (0.36-0.98)	0.041	0.44 (0.24-0.83)	0.011
Vegetables	0.64 (0.38-1.09)	0.10	0.47 (0.24-0.92)	0.027
Legumes	0.86 (0.49-1.51)	0.60	0.70 (0.36-1.36)	0.29
Dairy	0.82 (0.54-1.23)	0.34	0.86 (0.52-1.44)	0.57
Fruit and nuts	0.78 (0.51-1.19)	0.25	0.73 (0.44-1.21)	0.22
Alcohol	0.92 (0.29-2.95)	0.89	0.75 (0.22-2.58)	0.65
Meat	1.11 (0.73-1.70)	0.62	1.56 (0.90-2.71)	0.11
Olive oil	1.30 (0.73-2.33)	0.37	0.99 (0.52-1.89)	0.97
Cereal	1.19 (0.79-1.79)	0.40	1.11 (0.65-1.91)	0.70

MDS: literature-based Mediterranean diet score; OR: odds ratio; CI: confidence interval.
n=133. For portion size and categorisation of each domain see Supplementary Table S1.
[u]Univariate binary logistic regression analysis. Significance if $p<0.05$.
[m1]Multivariable binary logistic regression analysis correcting for energy intake (kcals), Body Mass Index, sex, age, symptom duration, and smoking status. Significance if $p<0.05$.

a 19% decrease in the odds of having pSS; a similar magnitude of reduction in odds as that seen for RA in the Swedish EIRA cohort (25). A number of MDS domains contributed to this effect and in particular fish intake. Fish intake has been suggested to reduce the risk of other autoimmune disorders such as RA. The association is often attributed to the presence of high levels of n-3 PUFA. Recent data have also posited a protective role for plant-derived n-6 PUFA in RA (13, 14) but, to our knowledge, no data specifically addresses PUFA or fish intake and risk of pSS. Although PUFA may have direct immunomodulatory roles (33, 34), it is increasingly recognised that the impact of diet upon health may be mediated by alterations in the gut microbiome (35). Adherence to a Mediterranean diet has been associated with beneficial changes in microbial diversity and metabolite production (36, 37). Likewise, the constitutive production of n-3 PUFA in mice leads to an increase in phylogenic diversity in the caecum (38).

In our study we did not identify an association of total MDS with symptoms, ESSDAI as a measure of systemic activity, immunoglobulin levels or measures of tear and saliva flow. However, it is important to note that the participants were asked to assess their diet predating current disease activity assessments and the effect of diet on disease activity would need to be explored in well-designed clinical trials.

SS is a chronic disease with a high unmet need (1). Our results require confirmation in other studies, and the implementation of dietary intervention in order to specifically reduce pSS risk would be associated with a number of challenges, in particular, the identification of those at risk. Targeting family members of pSS sufferers might be one approach given that familial factors contribute just over half of disease risk. However, the polygenic liability model suggests that the majority of cases will still be sporadic (5).

Although not the primary hypothesis being tested in this study, we also observed that galactose, vitamin A-retinol-equivalents and vitamin C showed inverse associations with odds of pSS. The active metabolite of vitamin A, retinoic acid, has long been known to have important roles within the immune system. Recent work has shown that retinoic acid influences the tolerogenic function of dendritic cells and, in a context-dependent fashion, can inhibit pro-inflammatory Th17 cell differentiation and enhance Treg responses (39). Vitamin C may also be important for immune system functioning (40).

The strengths of our study are a well-characterised participant population and use of a meta-analysis derived MDS not based upon population medians. There are a number of limitations. Firstly, the sample size is small, although given the absence of data in this area we hope that this will encourage further research. Secondly, there was a long-time on average between symptom onset and completion of questionnaires. This might have affected dietary recall and resulted in random errors, but reassuringly symptom duration was very similar between the two groups of participants and unlikely to cause substantial systematic bias. Thirdly, we only asked about diet in the year before symptom onset whereas the pattern of diet over a longer period of time may be more relevant but is difficult to assess.

Table IV. The association of the adherence to the Mediterranean diet score and fish consumption with primary Sjögren's syndrome and sicca disease severity: the Optimising Assessment in Sjögren's Syndrome cohort (2014-2018).

	Total score of the Mediterranean diet score				Fish consumption			
	pSS		Sicca		pSS		Sicca	
	β (95% CI)	*p*-value	B-coefficient	*p*-value	B-coefficient	*p*-value	B-coefficient	*p*-value
Schirmer's	0.43 (-0.60, 1.46)	0.41	-0.97 (-3.23, 1.29)	0.39	1.79 (-1.30, 4.89)	0.25	-4.11 (-11.85, 3.64)	0.29
IgG	-0.59 (-1.60, 0.42)	0.25	-0.006 (-0.37, 0.36)	0.97	-3.19 (-5.94, -0.44)	**0.024**	0. 70 (-0.58, 1.97)	0.27
Unstimulated salivary flow	-0.02 (-0.09, 0.06)	0.65	0.07 (-0.08, 0.21)	0.34	-0.006 (-0.21, 0.20)	0.96	-0.62 (-1.08, -0.17)	**0.009**
ESSPRI	0.06 (-0.21, 0.33)	0.67	-0.26 (-0.54, 0.02)	0.071	-0.45 (-1.27, 0.37)	0.28	0.04 (-1.04, 1.13)	0.93
ESSDAI	0.58 (-0.12, 1.12)	0.055	N/A	N/A	0.30 (-1.40, 2.00)	0.73	N/A	N/A
Focus score	-0.07 (-0.43, 0.30)	0.71	N/A	N/A	0.33 (-0.29, 0.95)	0.29	N/A	N/A

ESSDAI: EULAR Sjögren's Syndrome Disease Activity Index; ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index; EULAR: European League Against Rheumatism. Schirmer's test is a mean of values from right and left eye. n=133.
Linear regression analysis correcting for energy intake (kcals), Body Mass Index, sex, age, symptom duration, and smoking status. Regression coefficients were estimated per one unit difference in the Mediterranean diet score and fish domain.

Table V. Comparison of selected nutrient intakes between primary Sjögren's syndrome and sicca: the Optimising Assessment in Sjögren's Syndrome cohort (2014-2018).

Nutrient	Mean (SD)	Crude [u]		Multivariable [m1]		Further adjusted for the Mediterranean diet score [m2]	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Carotene total	4.25 mg (3.48)	0.90 (0.80-1.02)	0.106	0.87 (0.74-1.02)	0.091	0.90 (0.78-1.04)	0.161
Galactose	0.68 g (0.87)	0.96 (0.92-1.00)	0.054	0.94 (0.89-0.99)	**0.02**	0.93 (0.88-0.99)	**0.016**
Vitamin A- Retinol- equivalents	1.15 mg (0.73)	0.95 (0.91-1.00)	0.069	0.92 (0.85-0.99)	**0.02**	0.93 (0.86-1.00)	**0.04**
Vitamin C- Ascorbic Acid	119.77 mg (74.49)	0.95 (0.90-1.00)	**0.04**	0.92 (0.86-0.99)	**0.024**	0.94 (0.87-1.01)	0.099

OR: odds ratio; CI: confidence interval. n=133 (82 Sjögren's syndrome, 51 Sicca).
[u]Univariate binary logistic regression analysis. Results considered significant if $p<0.05$. ORs were estimated per 1milligram/day for total carotenoids, 100micrograms/day of galactose, 100micrograms RAE/day of vitamin A, and 10 mg/day of vitamin C.
[m1]Multivariate analysis - corrected for energy intake (kcals), Body Mass Index, sex, age, symptom duration, and smoking status.
[m2]Multivariate analysis – as for m1 but with additional correction for total Mediterranean diet score, a measure of adherence to the diet pattern.

Fourthly, we have not included healthy controls in this analysis. However, an advantage of a sicca group comparator is that the risk of reverse causation, *i.e.* onset of dryness symptoms altering diet, may be more balanced between groups. Further, symptom burden as measured by ESSPRI was similar between the two groups and published data suggests that impairment in health-related quality of life is also similar (41). Fifthly, the assessment of individual nutrient variables was not corrected for multiple testing and these results should only be considered hypothesis-generating and viewed with caution. Finally, we cannot exclude unmeasured confounding; notably we have no data on physical activity for example and have not included comorbidities.

Despite these limitations our results are of importance, given the paucity of data on diet and indeed other risk factors for SS, and we hope they will stimulate further research and larger studies. Our results were also consistent with an increasing body of evidence showing health benefits associated with adherence to a Mediterranean diet. Adoption of a Mediterranean diet is associated with high compliance and is considered affordable and sustainable (42). Were our findings to be confirmed in other studies, dietary intervention trials might be warranted.

Take home messages

- Higher adherence to the Mediterranean diet was associated with a lower likelihood of developing SS.
- Fish intake was the Mediterranean diet domain most strongly associated with lower likelihood of SS.
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References

1. MIYAMOTO ST, VALIM V, FISHER BA: Health-related quality of life and costs in Sjögren's syndrome. *Rheumatology* (Oxford) 2019 Feb 15 [Online ahead of print].
2. CAFARO G, CROIA C, ARGYROPOULOU OD *et al*.: One year in review 2019: Sjögren's syndrome. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S3-15.
3. IMGENBERG-KREUZ J, RASMUSSEN A, SIVILS K, NORDMARK G: Genetics and epigenetics in primary Sjögren's syndrome. *Rheumatology* (Oxford) 2019 Feb 15 [Online ahead of print].
4. HARRIS VM, SCOFIELD RH, SIVILS KL: Genetics in Sjögren's syndrome: where we are and where we go. *Clin Exp Rheumatol* 2019; 37 (Suppl. 118): S234-9.
5. KUO CF, GRAINGE MJ, VALDES AM *et al*.: Familial risk of Sjögren's syndrome and co-aggregation of autoimmune diseases in affected families: a nationwide population study. *Arthritis Rheumatol* 2015; 67: 1904-12.
6. VOULGARELIS M, TZIOUFAS AG: Pathogenetic mechanisms in the initiation and perpetuation of Sjögren's syndrome. *Nat Rev Rheumatol* 2010; 6: 529-37.
7. STONE DU, FIFE D, BROWN M *et al*.: Effect of tobacco smoking on the clinical, histopathological, and serological manifestations of sjögren's syndrome. *PLoS One* 2017; 12: e0170249.
8. NESVOLD MB, JENSEN JL, HOVE LH *et al*.: Dietary intake, body composition, and oral health parameters among female patients with primary Sjögren's syndrome. *Nutrients* 2018; 10: 866.
9. CERMAK JM, PAPAS AS, SULLIVAN RM, DANA MR, SULLIVAN DA: Nutrient intake in women with primary and secondary Sjögren's syndrome. *Eur J Clin Nutr* 2003; 57: 328-34.
10. HAY KD, MORTON RP, WALL CR: Quality of life and nutritional studies in Sjögren's syndrome patients with xerostomia. *N Z Dent J* 2001; 97: 128-31.
11. DI GIUSEPPE D, CRIPPA A, ORSINI N, WOLK A: Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. *Arthritis Res Ther* 2014; 16: 446.
12. ROSELL M, WESLEY AM, RYDIN K, KLARESKOG L, ALFREDSSON L: Dietary fish and fish oil and the risk of rheumatoid arthritis. *Epidemiology* 2009; 20: 896-901.
13. DE PABLO P, ROMAGUERA D, FISK HL *et al*.: High erythrocyte levels of the n-6 polyunsaturated fatty acid linoleic acid are associated with lower risk of subsequent rheumatoid arthritis in a southern European nested case-control study. *Ann Rheum Dis* 2018; 77: 981-7.
14. ZHAO JV, SCHOOLING CM: Role of linoleic acid in autoimmune disorders: a Mendelian randomisation study. *Ann Rheum Dis* 2019; 78: 711-3.
15. DI GIUSEPPE D, ALFREDSSON L, BOTTAI M, ASKLING J, WOLK A: Long term alcohol intake and risk of rheumatoid arthritis in women: a population based cohort study. *BMJ* 2012; 345: e4230.
16. JIN Z, XIANG C, CAI Q, WEI X, HE J: Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies. *Ann Rheum Dis* 2014; 73: 1962-7.
17. PATTISON DJ, SILMAN AJ, GOODSON NJ *et al*.: Vitamin C and the risk of developing inflammatory polyarthritis: prospective nested case-control study. *Ann Rheum Dis* 2004; 63: 843-7.
18. PATTISON DJ, SYMMONS DP, LUNT M *et al*.: Dietary risk factors for the development of inflammatory polyarthritis: evidence for a role of high level of red meat consumption. *Arthritis Rheum* 2004; 50: 3804-12.
19. BENITO-GARCIA E, FESKANICH D, HU FB, MANDL LA, KARLSON EW: Protein, iron, and meat consumption and risk for rheumatoid arthritis: a prospective cohort study. *Arthritis Res Ther* 2007; 9: R16.
20. COSTENBADER KH, KANG JH, KARLSON EW: Antioxidant intake and risks of rheumatoid arthritis and systemic lupus erythematosus in women. *Am J Epidemiol* 2010; 172: 205-16.
21. PEDERSEN M, STRIPP C, KLARLUND M, OLSEN SF, TJONNELAND AM, FRISCH M: Diet and risk of rheumatoid arthritis in a prospective cohort. *J Rheumatol* 2005; 32: 1249-52.
22. TRICHOPOULOU A, MARTINEZ-GONZALEZ MA, TONG TY *et al*.: Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. *BMC Medicine* 2014; 12: 112.
23. SALAS-SALVADO J, GUASCH-FERRE M, LEE CH, ESTRUCH R, CLISH CB, ROS E: Protective effects of the Mediterranean diet on type 2 Diabetes and Metabolic syndrome. *J Nutr* 2016; 146: 920s-27s.
24. SOFI F, MACCHI C, ABBATE R, GENSINI GF, CASINI A: Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score. *Public Health Nutr* 2014;17: 2769-82.
25. JOHANSSON K, ASKLING J, ALFREDSSON L, DI GIUSEPPE D: Mediterranean diet and risk of rheumatoid arthritis: a population-based case-control study. *Arthritis Res Ther* 2018; 20: 175.
26. HU Y, COSTENBADER KH, GAO X, HU FB, KARLSON EW, LU B: Mediterranean diet and incidence of rheumatoid arthritis in women. *Arthritis Care Res* 2015;6 7: 597-606.
27. SUNDSTROM B, JOHANSSON I, RANTAPAA-DAHLQVIST S: Diet and alcohol as risk factors for rheumatoid arthritis: a nested case-control study. *Rheumatol Int* 2015; 35: 533-9.
28. CASAS R, SACANELLA E, ESTRUCH R: The immune protective effect of the Mediterranean diet against chronic low-grade inflammatory diseases. *Endocr Metab Immune Disord Drug Targets* 2014; 14: 245-54.
29. GIUGLIANO D, CERIELLO A, ESPOSITO K: The effects of diet on inflammation: emphasis on the metabolic syndrome. *J Am Coll Cardiol* 2006; 48: 677-85.
30. SHIBOSKI CH, SHIBOSKI SC, SEROR R *et al*.: 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017; 76: 9-16.
31. MULLIGAN AA, LUBEN RN, BHANIANI A *et al*.: A new tool for converting food frequency questionnaire data into nutrient and food group values: FETA research methods and availability. *BMJ Open* 2014; 4: e004503.
32. TRICHOPOULOU A, COSTACOU T, BAMIA C, TRICHOPOULOS D: Adherence to a Mediterranean diet and survival in a Greek population. *New Engl J Med* 2003; 348: 2599-608.
33. CALDER PC, WILLEMSEN LEM: Immunopharmacology of fatty acids. *Eur J Pharmacol* 2016; 785: 1.
34. FISHER BA, HARBIGE LS: Effect of omega-6 lipid-rich borage oil feeding on immune function in healthy volunteers. *Biochem Soc Trans* 1997; 25: 343S.
35. GENTILE CL, WEIR TL: The gut microbiota at the intersection of diet and human health. *Science* 2018; 362: 776-80.
36. DE FILIPPIS F, PELLEGRINI N, VANNINI L *et al*.: High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* 2016; 65: 1812-21.
37. GARCIA-MANTRANA I, SELMA-ROYO M, ALCANTARA C, COLLADO MC: Shifts on gut microbiota associated to Mediterranean diet adherence and specific dietary intakes on general adult population. *Front Microbiol* 2018; 9: 890.
38. BIDU C, ESCOULA Q, BELLENGER S *et al*.: The Transplantation of omega3 PUFA-altered gut microbiota of fat-1 mice to wild-type littermates prevents obesity and associated metabolic disorders. *Diabetes* 2018; 67: 1512-23.
39. ERKELENS MN, MEBIUS RE: Retinoic acid and immune homeostasis: a balancing act. *Trends Immunol* 2017; 38: 168-80.
40. CARR AC, MAGGINI S: Vitamin C and immune function. *Nutrients* 2017; 9: 1211.
41. CHOU A, GONZALES JA, DANIELS TE, CRISWELL LA, SHIBOSKI SC, SHIBOSKI CH: Health-related quality of life and depression among participants in the Sjögren's International Collaborative Clinical Alliance registry. *RMD Open* 2017; 3: e000495.
42. GARCIA-FERNANDEZ E, RICO-CABANAS L, ROSGAARD N, ESTRUCH R, BACH-FAIG A: Mediterranean diet and cardiodiabesity: a review. *Nutrients* 2014; 6: 3474-500.