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Adherence to the Mediterranean dietary pattern and incidence of anorexia and bulimia nervosa in women: the SUN cohort

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List of Abbreviations:

AN: Anorexia nervosa

BN: Bulimia nervosa

ED: Eating disorder

HR: Hazard ratio

MDP: Mediterranean dietary pattern

MUFA: Monounsaturated fatty acids

PUFA: Polyunsaturated fatty acids

SFA: Saturated fatty acids

Highlights

- No study assessed the role of dietary pattern on the incidence of eating disorders
- Mediterranean diet was associated with a lower risk of anorexia and bulimia nervosa
- Cereals and olive oil consumptions were associated with a lower risk
- Diet may have a protective role against the incident risk of eating disorders

Abstract

Objective: No study has assessed the association between dietary pattern and incidence of eating disorders. This study aimed to assess the association between the adherence to the Mediterranean dietary pattern (MDP) and the incident risk of anorexia (AN) and bulimia nervosa (BN).

Research Methods & Procedures: We conducted a prospective cohort study on 11800 women from the SUN Project. Participants were classified as having incident AN or BN if they were free of AN or BN at baseline and reported a physician-made diagnosis of AN or BN during follow-up. Nutritional status, lifestyle and behavioural variables were investigated and used as covariates. A validated 136-item food frequency questionnaire and the Trichopoulou score were used to assess adherence to MDP.

Results: After a median follow-up of 9.4 years, 100 new cases of AN and BN were identified. The multivariate HR (95%CI) of AN and BN for the 2 upper categories of adherence to the MDP were 0.39 (0.20-0.75) and 0.32 (0.14-0.70) (P_{trend}=0.021). Inverse dose-response relationships were found for the consumption of cereals and olive oil and marginally for the polyunsaturated fatty acids intake. To address reverse causation, multivariable linear regressions were run by means of a cross-sectional approach between the adherence to the MDP and the risk of AN and BN at baseline. No difference in adherence was found between participants with and without eating disorders.

Conclusion: Our results suggest a potential inverse association between MDP and the risk of AN and BN. Additional longitudinal studies and trials are needed.

Keywords: Epidemiology; Cohort study; Mediterranean diet; Anorexia nervosa; Bulimia nervosa; Eating disorder.

Introduction

Eating disorders (EDs) are severe chronic mental health disorders characterized by abnormal eating, dysfunctional relationships with food, and a preoccupation about body weight and shape [1]. Among these, anorexia nervosa (AN) is a serious psychiatric illness characterized by an inability to maintain an adequate, healthy body weight, while bulimia nervosa (BN) is characterized by recurrent episodes of binge eating in combination with some form of unhealthy compensatory behaviour [1].

It is well recognized that EDs have a multifactorial aetiology. A wide array of potential causes including genetic vulnerability, sociocultural factors, family and educational factors may contribute to the development of EDs [2-4]. In particular, it has been argued that AN and BN share some of these risk and liability factors because these disorders are often cross-transmitted in families and share many behavioural traits [5, 6]. Moreover, in the last years, there has been a considerable interest in the role of serotonin in the aetiology of EDs [7]. Several lines of evidence suggest disturbances of serotonin pathways as playing a role in the pathogenesis and pathophysiology of AN and BN [5-8]. Serotonin pathways are known to contribute to the modulation of a range of behaviours and psychiatric symptoms commonly seen in individuals with AN and BN (e.g. harm avoidance, behavioural inhibition, obsessionality, anxiety, fear, depression, as well as physiological traits such as satiety for food consumption) [7, 9-12]. Moreover, several studies show disturbances of serotonin activity in individuals who were ill or recovered from AN and BN [5, 7, 10, 12].

An emerging field of research in nutritional epidemiology is the assessment of several links between nutritional quality and mental health [13]. In particular, previous cohort studies and trials, albeit with controversial results, suggest an inverse relationship between Mediterranean dietary pattern (MDP) and risk for depression [13-15]. One of the proposed mechanisms to explain this inverse relationship is the potential interaction of some typical nutrients of MDP with the serotoninergic transmission, including metabolism, release, uptake, and receptor function [13, 16]. In the light of this, it is plausible to think that a dietary pattern like MDP may protect against EDs like AN and BN. Recently, a cross-sectional study showed an inverse association between MDP and binge eating behaviour, suggesting a potential protective role of MDP against EDs [17]. However, to date, no previous study has assessed the role of an overall healthy dietary pattern on the incidence of AN and BN.

Therefore, in this study, we evaluated the relationship between adherence to the MDP and risk of AN and BN. A secondary aim was to assess the role of each component of the MDP with regard to AN and BN incidence.

Material and methods

Study population

The Seguimiento Universidad de Navarra/University of Navarra Follow-up (SUN) Project is a multipurpose Spanish cohort composed of former students of the University of Navarra, Spanish registered professionals, and other university graduates. Baseline information with regard to dietary habits, lifestyles, and health conditions is gathered by mailed questionnaires. After the baseline evaluation, information is updated every two years with a follow-up questionnaire. The recruitment of participants started on December 21, 1999, and is permanently ongoing. The overall follow-up rate approaches 90% [18]. Before December 1, 2013, 21677 participants had completed their baseline questionnaire. From them, we excluded men (8445), participants who had no follow-up questionnaires (1130), participants with diagnosis of AN and BN at baseline (62) and subjects who reported extremely low or high values of energy intake (<1st percentile or >99th percentile) (240). Some individuals met more than 1 of these exclusion criteria. Finally, 11800 women who answered at least 1 follow-up questionnaire were included in the study (**Figure 1**). This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Human Research Ethical Committee at the University of Navarra (091/2008). Voluntary completion of the first questionnaire was considered to imply informed consent; this handling of consent was approved by the ethics committee.

Exposure assessment

Dietary intake was assessed during baseline using a semi-quantitative food frequency questionnaire (136 food items) previously validated in Spain [19]. A trained dietitian updated the nutrient databank by means of the latest available information included in food composition tables for Spain. Adherence to the MDP was evaluated using Trichopoulou score [20]. Briefly, for each of the 6 protective components (MUFA/SFA ratio, legumes, cereal, fruit and nuts, vegetables, or fish), a participant received 1 point if his or her intake was over the sample median. The participant received 1 point if the intake was below the median for the 2 non protective components (whole-fat dairy products and meat and meat products). For ethanol, 1 point was assigned only for moderate amounts of intake (5–25 g/d for women). This score, which ranges from 0 (minimal adherence) to 9 (maximal adherence), was categorized into 3 groups (0-1, 2-5, and 6-9 points). This categorization was used to ensure an adequate distribution of the sample.

Covariates assessment

The baseline questionnaire gathered information with regard to socio-demographic characteristics (e.g. sex, age, marital status, and employment status), anthropometric variables (e.g. weight and

height), lifestyle and health-related habits (e.g. smoking status, physical activity, and following a special diet). Physical activity was assessed through a validated physical activity questionnaire with data about 17 activities [21]. Leisure-time activities were computed by assigning an activity metabolic equivalent score to each activity multiplied by the time spent in each activity, and summing up all activities. The prevalence and history of CVD, cancer, type 2 diabetes mellitus and depression was ascertained at baseline. Energy intake also was calculated through the information collected from the semi-quantitative food-frequency questionnaire administered at baseline. Self-perception of body image was assessed using the Figure Rating Scale [22]. Self-perception of competitiveness, anxiety, and psychological dependence levels among participants were ascertained using Likert scales as it was previously used in other studies [15].

Outcome assessment

We defined participants as having incident AN or BN when they were free of AN or BN at baseline and positively responded, in any of the follow-up questionnaires, to the following question: "Have you ever been diagnosed with anorexia or bulimia nervosa by a medical doctor?". Subsequently, we sent a letter to every participant who positively responded asking for a confirmation of their responses. Of these, 24 letters were sent back with a confirmation of the diagnosis, whereas the majority of subjects (55%), despite of numerous remainders, did not provide any answer.

Statistical analysis

Some continuous variables had non-Gaussian distributions, and all are reported as 25^{th}, 50^{th} and 75^{th} percentiles. Discrete variables are reported as percentages. Cox proportional-hazards regression models were fitted to assess the relationship between the adherence to the MDP and the incidence of AN and BN. Hazard ratios (HRs) and their 95%CIs were calculated considering the lowest category as the reference category. We also assessed the association between each of the components of the MDP scale, olive oil consumption, polyunsaturated fatty acids (PUFA) intake and the incidence of AN and BN. We included these components, categorized into tertiles (the first tertile was used as the reference category), in a Cox regression model. To control for potential confounding factors, the results were adjusted for age (continuous), BMI (kg/m^2, continuous), following a special diet (yes or no), figure rating scale (continuous), self-perception of competitiveness, anxiety, and psychological dependence levels (continuous), presence of depression at baseline (yes or no), and stratified for energy intake (deciles) and year of recruitment. We also tested the association of marital status, education, smoking (non-smoker, ex-smoker, current smoker), physical activity during leisure time (METs h/week, continuous), and number of work hours per week (<35, 35-45, >45) and presence of several diseases at baseline (CVD, diabetes and

cancer), but they were removed from the model because were not significantly associated (data not shown). Tests of linear trend across increasing categories of adherence were conducted by assigning the medians to each category and treating it as a continuous variable. The proportional hazard assumption made by Cox regression was checked using Schoenfeld residuals. Multivariable fractional polynomials were used to test whether the multivariable relationship between continuous variables and the outcome was linear. Sensitivity analyses were performed by changing several parameters: 1) excluding participants with CVD, diabetes and cancer at baseline, 2) excluding participants with long follow-up (≥10 years); 3) excluding early cases (diagnosed during the two years of follow-up); 4) excluding participants older than 30 and 40 years; 5) including only as incident cases of AN or BN those participants with available confirmation diagnosis; 6) excluding subjects who did not confirm the diagnosis; and HRs were estimated comparing categories of the MDP in the fully adjusted model. To address reverse causation, because being a person with AN or BN at baseline may determine changes in baseline adherence to the MDP, multivariable linear regression was run by means of a cross-sectional approach at baseline. The β coefficients and their 95%CIs were calculated, with prevalence of AN and BN at or before inception designated as the exposure and baseline adherence to the MDP as the outcome. All P-values were two-tailed and $P<0.05$ was considered significant.

Results

We recorded 100 incident cases of AN and BN during a median follow-up time of 9.4 years. The main characteristics of the participants in accordance with categories of adherence to the MDP are presented in **Table 1**.

The association between the MDP and the risk of AN and BN is shown in **Table 2**. A lower risk was found for the upper categories of adherence to the MDP with reductions in AN and BN risk higher than 60% in the multivariable model (HR 0.32; 95%CI 0.14-0.70 for the third category). Moreover, a significant dose–response relationship was found (P_{trend}=0.021).

Table 3 shows the adjusted HRs in the sensitivity analyses after modifying some of our assumptions. When the analysis was restricted to those participants with <10 years of follow-up, we did not observe any substantial change in the HR for the upper category of adherence to the MDP. However, the trend was only marginally significant. Similar results were obtained when we excluded participants with history for chronic diseases. Moreover, to avoid a possible reverse causation bias (that is, participants with subclinical AN or BN at baseline and could change their diet as a consequence of pre-existing AN or BN), we repeated the analysis with the exclusion of those cases of AN and BN reported in the first 2 years of follow-up (n=38). The HRs (95%CIs) for the second and the third categories of adherence to the MDP were only slightly attenuated: 0.50 (0.23-1.12) and 0.39 (0.14-1.06), respectively. However, the dose-response relationship was no more significant. In addition, as young subjects had a higher risk for EDs, we restricted the analysis to participants who were maximum 30 and 40 years old at baseline. In both cases, we observed a significant lower risk in the upper categories of adherence to the MDP compared to the lowest. Finally, we repeated the analyses excluding subjects who did not confirm the diagnosis and considering only those participants with available confirmatory diagnosis of AN and BN. In both cases, we observed a reduced risk in the upper categories, although in the second case they lost their statistical significance.

Table 4 shows the associations between the components of the MDP with AN and BN risk. We observed an inverse linear trend between cereals consumption and risk of AN and BN, with a reduction in the risk of 40% for those in the upper tertile compared to the lowest one. It should be noted, however, that the HR was not statistically significant. We found an inverse association between olive oil consumption, PUFAs intake and the risk for AN and BN. The multivariate HRs (95%CIs) of AN and BN for successive tertiles of consumption of olive oil were 1 (reference), 0.57 (0.36-0.90), and 0.47 (0.29-0.76), with a dose-response relationship statistically significant

(P_{trend}=0.005), while for successive tertiles of PUFAs intake were 1 (reference), 0.87 (0.52-1.43), and 0.53 (0.27-1.05), with a dose-response relationship marginally significant (P_{trend}=0.059).

Finally, to ensure the direction of the association between the adherence to the MDP and the risk for AN and BN, a cross-sectional analysis was performed to assess the association between suffering AN or BN at or before baseline and the 9-point score of adherence to the MDP. No difference in adherence was found between participants with and without diagnosis of AN or BN at baseline (age adjusted β=0.2, P=0.317; multivariable-adjusted β=0.17, P=0.4).

Discussion

An inverse association between adherence to the MDP and the risk of self-reported AN and BN has been found in this longitudinal analysis of the SUN cohort. To the best of our knowledge, this is the first study that reports a protective role of MDP against EDs like AN and BN. In a previous cross-sectional study, an inverse relationship between MDP and binge eating behaviour was observed [17]. This study reinforced the hypothesis that MDP could be a healthy dietary pattern for preventing EDs. In fact, we observed a reduction in the risk of AN and BN in the highest category of adherence to the MDP compared to the lowest category. When we repeated the analyses considering only those participants with available confirmatory diagnosis of AN and BN, the results were in the same direction, although they lost their statistical significance. Moreover, the inverse significant trend was marginally lost after changing some of our assumptions. We believe that this may be caused by the reduction of incident cases that, in turn, lead to a reduction of statistical power. Therefore, our findings need a careful interpretation, but encourage further studies to investigate the role of diet in the prevention of EDs.

The specific mechanisms by which a better adherence to the MDP could prevent the occurrence of AN and BN is not well known. Several lines of evidence suggest disturbances of serotonin pathways as playing a role in the pathogenesis and pathophysiology of AN and BN [5]. One of the most likely mechanisms that could be used to explain the inverse relationship between adherence to the MDP and the risk of AN and BN is through the role that some nutrients typical of the MDP might have on serotonin pathways. However, it is important to emphasize that brain neurotransmitter pathways do not work in isolation. Neurotransmitter systems have complex interactions and, therefore, it is likely that multiple systems are involved.

Within the Mediterranean diet pyramid, cereals, especially whole cereals, are at the basis of the pyramid and should be included in every main meal [23]. In our cohort, an inverse trend between cereals consumption and incident risk for AN and BN was found, although it should be noted that the HRs for the second and third tertile were not statistically significant. Previous studies reported that a high consumption of carbohydrate and a moderate intake of protein can enhance brain serotonin release [24, 25]. In particular, carbohydrate consumption causes an insulin mediated fall in plasma levels of the large neutral amino acids which compete with tryptophan for uptake into the brain. Tryptophan is the precursor of serotonin and enhances serotonin release and also increases the saturation of tryptophan hydroxylase [26, 27], the enzyme responsible for serotonin synthesis. Therefore, a greater uptake of tryptophan leads to a higher brain serotonin synthesis and release [28]. On the other hand, dietary proteins tend to block these effects by contributing large amounts of

the large neutral amino acids to the blood stream. This would explain why we found no association between protein foods and the risk of AN and BN. However, it should be emphasized that proteins can have different effects on the plasma tryptophan to large neutral amino acids ratio as a function of their amino acid composition [28]. It has been demonstrated that the consumption of proteins rich in tryptophan and poor in large neutral amino acids (e.g. whey protein rich in α-lactalbumin) greatly increased the plasma ratio of plasma tryptophan to large neutral amino acids ratio compared to other proteins (e.g. casein) characterized by smaller amounts of tryptophan [29-31]. In addition, cereals consumption determines a higher ghrelin suppression and satiety that may lead, in turn, to a reduction of binge eating behaviours.

Lower incident cases of AN and BN were observed in the upper tertile of olive oil consumption compared to the lowest one. This finding agrees with previous studies suggesting a protective role of olive oil on EDs and other mental illnesses (e.g. depression) [17]. Olive oil increases the δ-9 desaturase enzyme activity and maintains, in this manner, the physiochemical properties of neuronal membranes [32]. Moreover, several studies suggested a beneficial effect of MUFA intake from olive oil that may improve the binding of serotonin to its receptors [33]. Nevertheless, we did not observe any significant association between MUFA/SFA ratio and incidence of AN and BN. However, we found an inverse association between PUFAs intake and the risk for AN and BN. A higher intake of n-3 PUFAs can improve serotonin synthesis and signalling through two main neurophysical mechanisms [34-36]. n-3 PUFAs, in particular EPA and DHA, reduce the production of pro-inflammatory eicosanoids derived from arachidonic acid (n-6 PUFA) by competing with this latter for incorporation into cell membrane phospholipids and reducing its cellular and plasma levels [37]. DHA and EPA also inhibit the release of pro-inflammatory cytokines [38] such as interleukin-1b, interleukin-2, interleukin-6, interferon-g, and TNFα, which depend on eicosanoid release [39], and are demonstrated to reduce the serotonin precursor availability. Moreover, n-3 PUFAs play an important role in maintaining membrane integrity and fluidity, which is crucial for neurotransmitter binding [34, 36]. In particular, a higher presence of n-3 PUFAs rather than n-6 PUFAs increases the membrane fluidity, with consequent higher receptor binding of serotonin to its 5-HT_2 receptor [40]. On the contrary, an increased n-6 to n-3 ratio has been proven to increase the amount of 5-HT_2 receptors in the frontal cortex [36, 41]. In the light of this, it appears important to keep a low dietary n-6 to n-3 ratio. In this sense, we observed that a higher adherence to the MDP provided a lower n-6 to n-3 ratio, accordingly with previous studies [42, 43].

Despite of the effects of single food and nutrients, we believe that the role of the overall dietary pattern may be more important. It is plausible that the synergistic combination of a sufficient intake

of tryptophan together with PUFA and other natural unsaturated fatty acids, large amounts of natural folates, B vitamins and antioxidants in the overall MDP may exert a fair degree of protection against AN and BN.

The possibility of reverse causality could be an alternative explanation for our results. Participants with an undiagnosed or subclinical ED at the beginning of our study might have changed their food habits, which would lead them to decrease their consumption of supposedly healthy food items. To exclude this hypothesis, we adjusted our analysis for some psychological characteristics of our participants, such as competitiveness, anxiety and psychological dependence levels, figure rating scale and depression as participants with AN and BN may have personality traits associated with a worse mental health, such as a lower self-control and willpower, dysperception of own body imagine and anxious and depressive symptoms. We acknowledge, however, the possibility of residual confounding even after adjusting for those characteristics. Moreover, in the sensitivity analysis we excluded participants that reported a diagnosis of AN or BN in the first two years of follow-up finding similar results, although they lost their statistical significance probably due to a lack of enough statistical power.

Further limitation is the exclusion of men from our study. Even though it is well recognized that being women is a risk factor for developing EDs, cases of AN and BN has been reported also in men. However, we decided to exclude men because we registered a very low number of incident cases. Moreover, we used a self-reported diagnosis of AN or BN as outcome, and when we tried to have a confirmation of the diagnosis, only twenty-four subjects confirmed the diagnosis, whereas the majority of subjects (55%) did not answer probably due to an unacceptability bias. We acknowledge that these limitations may have affected the correct assessment of the outcome, and, therefore, our results need a confirmation by further studies. We also acknowledge the limitation of the non-differentiation of AN and BN, and the lack of information about the subtypes of AN and BN did not allow to establish the impact of MDP on different subtypes of AN and BN. Additionally, some potential residual confounders, particularly those related to familiar and social living context, such as family history of EDs, family and social traumas, and social network of participants, have not been collected in the SUN cohort. The lack of control for these potential confounders demands caution in the interpretation of our findings. Moreover, as in any observational study, potential residual confounding could not be ruled out.

Conclusion

In summary, the results of our analysis suggest the possibility that a MDP is inversely associated with AN and BN incidences. However, we acknowledge that our results must be confirmed by additional prospective studies with better control for other potential confounders and also by clinical trials with a more rigorous and objective assessment of the outcome.

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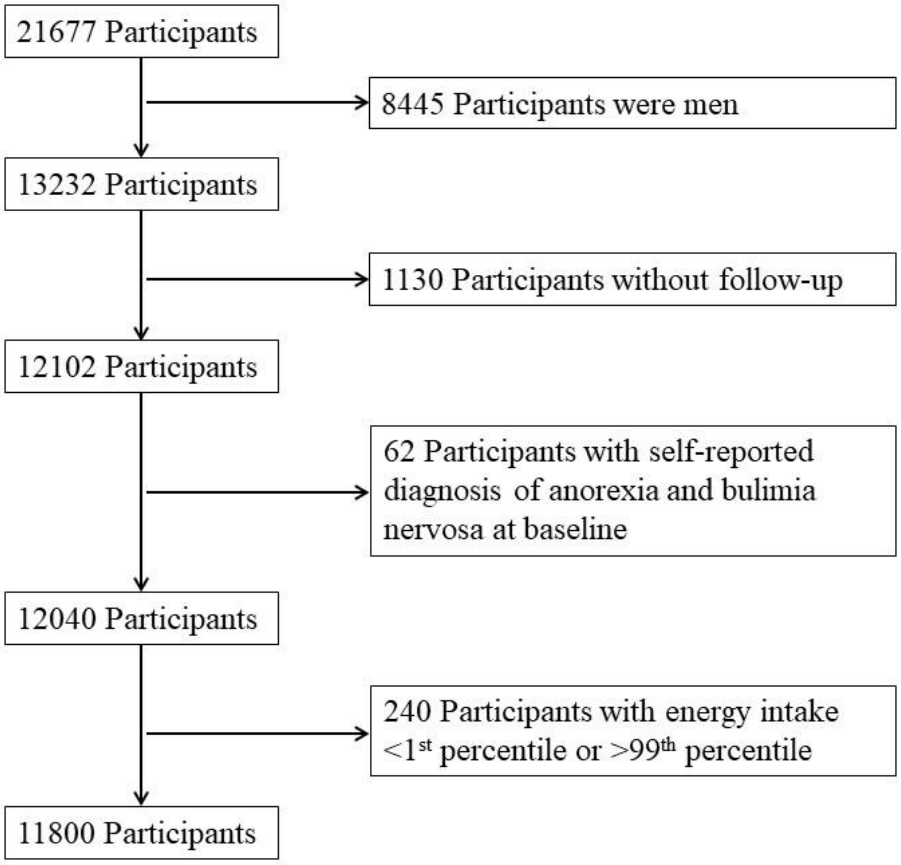
Figure 1.



Title: Flow-chart for the Seguimiento Universidad de Navarra (SUN) cohort study.

455 **Table 1:** Baseline characteristics of the participants according to the category of adherence to the
456 Mediterranean dietary pattern

				Categories of adherence to the Mediterranean dietary pattern								
	Total (N=11800)			0-1 (N=545)			2-5 (N=8483)			6-9 (N=2772)		
	P50	P25	P75	P50	P25	P75	P50	P25	P75	P50	P25	P75
Age (years)	33	27	43	31	25	38	32	26	41	36	28	46
BMI (kg/m^2)	21.6	20.1	23.6	21.3	19.8	23.2	21.6	20.1	23.5	21.7	20.2	23.8
Body image score	4	3	4	4	3	4	4	3	4	4	3	4
Competitiveness score	7	6	8	7	6	8	7	6	8	7	6	8
Anxiety score	6	5	8	7	5	8	6	5	8	6	5	8
Psychological dependence score	3	1	6	3	2	6	3	2	6	3	1	6
Physical activity (MET h/wk)	14.1	5.0	27.4	9.8	3.6	22.3	13.2	4.4	26.4	17.6	7.5	32.0
Alcohol intake (g/day)	1.2	0	3.8	0.8	0	2.1	1.2	0	3.0	2.1	0	6.7
Vegetables consumption (g/day)	509	355	730	311	221	400	471	329	667	703	557	921
Fruit consumption (g/day)	316	188	514	169	94	243	279	171	459	447	345	681
Fish consumption (g/day)	88	58	131	56	41	73	78	53	120	120	95	159
Legumes consumption (g/day)	21	13	26	13	8	17	17	12	26	25	21	30
Milk and dairy products consumption (g/day)	395	279	622	589	439	692	414	285	630	337	243	536
Meat and meat products consumption (g/day)	169	122	222	202	174	247	175	126	227	146	106	195
MUFA/SFA ratio	1.3	1.1	1.5	1.1	1.0	1.2	1.2	1.1	1.4	1.4	1.3	1.7
Olive oil consumption (g/day)	15	10	27	10	6	15	14	9	27	26	12	30
PUFA intake (g/day)	13.1	9.6	17.6	12.4	8.9	17.1	12.8	9.4	17.4	14.1	10.5	18.5
n-6/n-3 PUFAs ratio	6.5	4.6	8.6	7.7	6.0	9.6	6.8	4.9	9.0	5.5	4.0	7.2
		%			%			%			%	
Presence of CVD, diabetes or cancer		8.1			9.9			7.6			9.1	
Depression		5.1			4.6			5.2			4.8	
Following a special diet		8.3			5.9			8.1			9.3	
Marital status (Married)		43.2			40.7			42.2			46.6	
Education												
Graduated		79.4			76.0			79.0			81.1	
Master/doctoral		14.3			15.5			14.4			13.7	
Smoking status												
Past smoker		25.3			19.6			24.3			29.4	
Current smoker		23.3			22.3			23.6			22.6	

457 Values are expressed as median and interquartile range or percentages.

458 Abbreviations: P50, 50th percentile/median; P25, 25th percentile; P75, 75th percentile

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Table 2: Association between Mediterranean dietary pattern and risk of Anorexia and Bulimia nervosa

	Categories of adherence to the Mediterranean diet			P value
	0-1	**2-5**	**6-9**	**for trend**
N. of cases / person-years	10/5025	71/81088	19/25146	
Crude model				
HR (95% CI)	1 (reference)	0.46 (0.23-0.88)	0.40 (0.19-0.87)	0.065
Multivariable model				
HR (95% CI)	1 (reference)	0.39 (0.20-0.75)	0.32 (0.14-0.70)	0.021

Crude model: unadjusted model.

Multivariable model: adjusted for age, BMI, following a special diet, figure rating scale, self-perception of competitiveness, anxiety, and psychological dependence levels, presence of depression at baseline, and stratified for energy intake and year of recruitment.

Table 3: Sensitivity analyses (Adjusted* Hazard ratios (HR) and 95% confidence intervals)

		Categories of adherence to the Mediterranean diet			P value for
	N. of cases per person-years	**0-1**	**2-5**	**6-9**	**trend**
Overall	100/111259	1 (reference)	0.39 (0.20-0.75)	0.32 (0.14-0.70)	0.021
Excluding participants with CVD, diabetes or cancer at baseline	92/102388	1 (reference)	0.46 (0.22-0.94)	0.37 (0.16-0.87)	0.055
Excluding cases diagnosed during the first 2 years of follow-up	62/111170	1 (reference)	0.50 (0.23-1.12)	0.39 (0.14-1.06)	0.102
Excluding participants with ≥10 years of follow-up	83/95799	1 (reference)	0.47 (0.21-1.02)	0.35 (0.14-0.90)	0.055
Excluding subjects older than 30 years	47/45808	1 (reference)	0.23 (0.10-0.54)	0.21 (0.07-0.61)	0.02
Excluding subjects older than 40 years	77/78695	1 (reference)	0.34 (0.17-0.67)	0.36 (0.16-0.80)	0.082
Including only confirmed incident cases of eating disorder	24/110854	1 (reference)	0.33 (0.10-1.11)	0.45 (0.10-2.16)	0.57
Excluding subjects who did not confirm the diagnosis	79/111143	1 (reference)	0.36 (0.18-0.72)	0.34 (0.14-0.81)	0.07

* Adjusted for age, BMI, following a special diet, figure rating scale, self-perception of competitiveness, anxiety, and psychological dependence levels, presence of depression at baseline, and stratified for energy intake and year of recruitment.

477 **Table 4:** Incident risk of Anorexia and Bulimia nervosa associated with consumption of each component of the Mediterranean dietary pattern

		HR (95% CI) for Anorexia and Bulimia nervosa in the 2 upper tertiles of each food group or nutrient compared with the lowest tertile			
		T1	**T2**	**T3**	**P trend**
Meat and meat products	Median (g/day)	103	169	249	
	HR	1 (reference)	1.18 (0.75-1.85)	0.71 (0.41-1.25)	0.221
Legumes	Median (g/day)	12	21	34	
	HR	1 (reference)	0.62 (0.38-1.01)	0.75 (0.46-1.21)	0.29
Alcohol	Median (g/day)	0	1.2	5.6	
	HR	1 (reference)	0.85 (0.53-1.36)	0.91 (0.56-1.47)	0.816
Cereals	Median (g/day)	43	85	170	
	HR	1 (reference)	1.03 (0.65-1.61)	0.60 (0.35-1.03)	0.047
Fish	Median (g/day)	49	89	155	
	HR	1 (reference)	1.41 (0.89-2.24)	1.04 (0.63-1.72)	0.972
Vegetables	Median (g/day)	293	511	858	
	HR	1 (reference)	0.70 (0.42-1.16)	0.70 (0.42-1.16)	0.212
Fruit and Nuts	Median (g/day)	143	317	624	
	HR	1 (reference)	1.05 (0.64-1.73)	1.26 (0.74-2.17)	0.381
Dairy products	Median (g/day)	236	395	684	
	HR	1 (reference)	1.11 (0.66-1.85)	1.32 (0.80-2.18)	0.251
MUFA/SFA ratio	Median (g/day)	1.0	1.2	1.6	
	HR	1 (reference)	0.39 (0.22-0.67)	0.85 (0.55-1.30)	0.71
Olive oil	Median (g/day)	8	15	30	
	HR	1 (reference)	0.57 (0.36-0.90)	0.47 (0.29-0.76)	0.005
Polyunsaturated fatty acids	Median (g/day)	8.5	13.0	20.0	
	HR	1 (reference)	0.87 (0.52-1.43)	0.53 (0.27-1.05)	0.059

478 Multivariable models: adjusted for age, BMI, following a special diet, figure rating scale, self-perception of competitiveness, anxiety, and
479 psychological dependence levels, presence of depression at baseline, and stratified for energy intake and year of recruitment.
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