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Trabajo Original

Epidemiología y dietética

Association between overall quality of macronutrients and incidence of overweight and obesity in the SUN *(Seguimiento Universidad de Navarra)* cohort

Asociación entre la calidad global de macronutrientes y la incidencia de sobrepeso y obesidad en la cohorte SUN (Seguimiento Universidad de Navarra)

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Abstract

Introduction: no previous large prospective studies have assessed the global quality of macronutrients in association with the risk of overweight/obesity.

Objective: to prospectively assess the association of an overall macronutrient quality index (MQI) with weight change and the incidence of overweight/obesity in the Seguimiento Universidad de Navarra (SUN) cohort.

Methods: the diet of 9,344 Spanish university graduates free of overweight/obesity (mean age: 36.5 [SD, 11.1]) was assessed through a validated 136-item food frequency questionnaire. The MQI was calculated as the sum of the Carbohydrate Quality Index, the Fat Quality Index, and the Healthy Plate Protein Quality Index. Participants were classified into groups (G) according to MQI. Incident overweight/obesity was defined if follow-up questionnaires indicated BMI was ≥ 25 kg/m^2. Multiple linear regression models and Cox proportional hazard models were used to assess the average yearly weight change and the risk of overweight/obesity over follow-up time.

Results: 2,465 cases of incident overweight/obesity were identified (median follow-up: 10.7 years). Increasing MQI was significantly associated with lower annual weight gain (g): β coefficient: -99.0, (95 % CI: -173.6 to -24.5) in the G4 vs G1, p for trend = 0.007. In the fully adjusted model the incidences of overweight/obesity in G4 and G1 were 21.7 % (431 cases) and 29.3 % (954 cases), respectively. The adjusted HR was 0.87 (95 % CI, 0.77-0.98, *p* for trend = 0.036). When we used repeated analyses updating the MQI after 10 years of follow-up, results remained similar.

Conclusions: a significant inverse association between a multidimensional MQI and the risk of overweight/obesity was found in this Mediterranean cohort of adults.

Keywords:

Macronutrient quality. SUN cohort. Weight change. Overweight. Obesity.

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Ethical standards disclosure: voluntary completion of baseline questionnaire was considered to imply informed consent. The study was conducted according to the Declaration of Helsinki, and all procedures involving human subjects were approved by the Institutional Review board of the University of Navarra. The cohort is registered at clinicaltrials.gov as NCT02669602.

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Resumen

Introducción: ningún estudio prospectivo previo de gran tamaño ha evaluado la asociación entre la calidad global de los macronutrientes y el riesgo de sobrepeso/obesidad.

Objetivo: evaluar la asociación del índice global de calidad de macronutrientes (MQI) con el cambio de peso y la incidencia de sobrepeso/obesidad en la cohorte Seguimiento Universidad de Navarra (SUN).

Métodos: la dieta se evalúo en 9344 graduados universitarios españoles mediante un cuestionario validado de frecuencia de consumo. El MQI se calculó como la suma del índice de calidad de carbohidratos, el índice de calidad de grasas y el índice de calidad de proteínas del plato saludable. Los participantes se clasificaron en cuartiles según el MQI. Se definió la incidencia de sobrepeso/obesidad durante el seguimiento si el IMC era ≥ 25 kg/m^2. Se utilizaron modelos de regresión lineal múltiple y de riesgo proporcional de Cox para evaluar el cambio de peso anualizado y el riesgo de sobrepeso/obesidad durante el seguimiento.

Resultados: 2465 casos incidentes de sobrepeso/obesidad (mediana de seguimiento: 10,7 años). El aumento del MQI se asoció significativamente con un menor aumento de peso anual (g): coeficiente ß: -99,0 (IC 95 %: -173,6 a -24,5) en Q4 *vs.* Q1 (*p* tendencia lineal = 0,007). En el modelo más ajustado, la incidencia de sobrepeso/obesidad en Q4 y Q1 fue del 21,7 % (431 casos) y del 29,3 % (954 casos), respectivamente. El HR ajustado fue 0,87 (IC 95 %, 0,77-0,98, *p* tendencia lineal = 0,036).

Conclusiones: se encontró una asociación inversa significativa entre el MQI multidimensional y el riesgo de sobrepeso/obesidad en esta cohorte mediterránea de adultos.

Palabras clave:

Calidad de macronutrientes. Cohorte SUN. Cambio de peso. Sobrepeso. Obesidad.

INTRODUCTION

Obesity is considered to be a pandemic disease and a major public health problem among adults worldwide because it is associated with much morbidity and mortality derived from most non-communicable diseases (NCDs). Obesity rates have increased dramatically over the last few decades. If trends continue, around two billion adults globally will be obese by 2035 (1). Overweight and obesity increase the risk of cardiovascular diseases (CVD), diabetes, cancers and other health problems (2) and are associated with increased health care costs (3). Its etiology is complex and multifactorial and involves genetic components. However, dietary factors, low physical activity and sedentary lifestyle play important roles in body composition (1).

Thus, identifying dietary patterns, isolated dietary components or foods and macronutrient distribution related to obesity prevention has become a major priority for public health.

The Dietary Guidelines for Americans (DGA) 2020-2025 reflect with moderate evidence that dietary patterns emphasizing vegetables, fruits, and whole grains; seafood and legumes; moderate in dairy products and alcohol; low in sugar-sweetened foods and beverages, and refined grains and lower in meats (including red and processed meats), are associated with favorable outcomes related to the risk of obesity or body weight. Specifically, dietary pattern components associated with these favorable outcomes include lower intakes of saturated fats, cholesterol, and sodium, and higher intakes of unsaturated fats (4).

Notwithstanding, the acceptable macronutrient distribution ranges (AMDR) associated with lower chronic disease risk and adequate micronutrient intake, are: 45-65 %, 20-35 % and 10-35 % of total energy intake (TEI) for carbohydrates, fats and proteins, respectively (5). However, evidence on the relationship between macronutrient distributions aside from the AMDR, and risk of overweight/obesity in adults is scarce and the results are inconsistent or report no significant association (6).

Previous research has classified dietary patterns based on macronutrient proportion into three main types of diets: low carbohydrate, moderate macronutrients and low fat (7).

Nevertheless, the role of macronutrient in obesity remains controversial (8). There is an emerging scientific interest to assess whether the "quality" of macronutrients could be more important than their "quantity" to prevent obesity (9-11).

Diet quality indices have been previously used to assess their association with general obesity or abdominal obesity (12,13). However, diet quality indices based solely on nutrients are less common. Although an adequate balance of macronutrients is a common dimension included in the construction of diet quality indices, specific indices based on the quality dimension of macronutrients are scarce (13,14).

In this context, several *a priori dietary* indices have been developed to evaluate the quality of macronutrients individually (15,16) or globally (16).

Our team has previously investigated the specific role of fat and carbohydrates (17-19) on the risk of obesity. However, no previous large prospective studies have simultaneously assessed the global quality of macronutrients, through a priori and multidimensional dietary index (MQI), in association with risk of overweight/obesity. Thus, we aimed to longitudinally evaluate the association between MQI and average yearly weight change and risk of overweight/obesity, in the "Seguimiento Universidad de Navarra (SUN)" Project.

MATERIAL AND METHODS

DESIGN

The SUN Project (www.proyectosun.es) is a multipurpose, dynamic prospective cohort that began in 1999. The participants of this cohort are all Spanish university graduates of the University of Navarra and other Spanish universities. Its main objective is to evaluate the impact of lifestyle and diet, in particular the Mediterranean Diet (MedDiet), on NCDs such as diabetes, obesity, cancer and CVD. Self-administered questionnaires, at baseline and every 2 years, by mail or web-based, collected information on sociodemographic characteristics, anthropometric measures, lifestyle variables, family and personal medical history, diet and health- related habits. The overall retention rate is greater than 90% in the SUN cohort. Additional details on this cohort have been described elsewhere.

SUBJECTS

In the SUN cohort, 23,133 participants were included until May 2022, excluding 234 who did not answer the baseline questionnaire before August 31st, 2019 to ensure a minimum follow-up of 2 years; 6,744 participants with a baseline BMI ≥ 25; 1,616 participants with an energy intake outside of the predefined limits established by Willett (men < 800 or > 4,000 kcal/d and women < 500 or > 3500 kcal/d), 3,277 women who were pregnant at the time of enrollment into the cohort or during the follow-up; 562 with prevalent diabetes, CVD, or cancer; 1,319 participants who had no follow-up; and finally 37 participants without information on variables of interest. Thus, our study included a total of 9,344 participants.

The SUN project was conducted according to the principles expressed in the Declaration of Helsinki. Informed consent for their participation in the cohort is implied when an answer to the first questionnaire (Q0) is received and potential candidates are informed of their right to leave the study at any time without consequences. This project was approved by the University of Navarra Institutional Review Committee (approval code 010830) and this cohort was registered at Clinicaltrials.gov as NCT02669602.

DIETARY ASSESSMENT

Dietary variables were assessed at baseline and after 10 years of follow-up through a self-administered 136-item semi-quantitative food frequency questionnaire (FFQ). This FFQ has been previously validated in Spain (22,23) with typical portion sizes specified for each item and with nine categories from "never or almost never" to "≥ 6 times/day". Participants report their frequency of consumption, on average, during the previous year.

Finally, the calculation of dietary intake was performed by a team of trained nutritionists using the Spanish Food Composition Tables (24,25).

Adherence to the MedDiet was measured through the use of two dietary indices: the MDS developed by Trichopolou et al. (26) and the MEDAS with ranges of 0 to 9 points and of 0 and 14 points respectively (27). On the other hand, adherence to the Provegetarian food pattern was calculated according to the score proposed by Martínez-González, et al. (28). In all cases, higher scores indicated greater adherence to each dietary pattern.

EXPOSURE ASSESSMENT: MACRONUTRIENT QUALITY INDEX

The MQI (16) was established based on three sub-indexes: the Carbohydrate Quality Index (CQI), the Fat Quality Index (FQI), and the Healthy Plate Protein Source Quality index (HPPQI) as follows: MQI = CQI + FQI + HPPQI.

This CQI (19) is based on four equally weighted domains: glycemic index (GI), total fiber intake (g/d), ratio of carbohydrates from solid/total (solids + liquids), ratio of carbohydrates from whole grain /total cereals (whole grain + refined). Participants were categorized into quintiles for each of the four components of the CQI. A value (range 1 to 5) was given according to each quintile (only for the GI were the values upside down) and finally, the four values for each participant were added to obtain the CQI.

The FQI (19) was calculated using the following ratio: [monounsaturated fatty acids (MFA) + polyunsaturated fatty acids (PFA)]/ [saturated fatty acids (SFA) + trans fatty acids (TFA)].

Finally, the HPPQI (16) was calculated based on the following ratio HPPQI = (seafood + poultry + legumes + nuts) / (red and processed meat + cheese); according to the Harvard Healthy Eating Plate (29), food groups placed in the numerator and denominator reflect healthy and unhealthy sources of protein, respectively.

To calculate the MQI, participants were classified into quintiles for each sub-index (CQI, FQI, and HPPQI), assigning values from 1 (low quality) to 5 (high quality). All sub-indices were added yielding a MQI score from 3 (low macronutrient quality) to 15 (high macronutrient quality). Finally, Participants were categorized into the following 4 groups to create 4 reasonably equal groups according the MQI: very lowest adherence (MQI from 3 to 7), lowest adherence (MQI from 8 to 9), medium adherence (MQI from 10 to 11) and highest adherence (MQI from 12 to 15).

OUTCOME ASSESSMENT

Self-reported weight was collected at baseline and in all follow-up questionnaires. BMI was calculated from the weight and height reported at baseline and throughout follow-up.

Reliability and validity of participants' self-reported bodyweights had been previously evaluated in a subsample of the cohort (30). Self-reported body weights showed a high correlation with directly measured body weights (*r*: 0.991; 95 % CI: 0.986-0.994). The mean relative error in self-reported weight was 1.45 %.

In this study, incident overweight or obesity was defined as when participants had a baseline BMI < 25 kg/m^2 in Q0 and a BMI ≥ 25 kg/m^2 in any of the successive follow-up questionnaires.

ASSESSMENT OF OTHER VARIABLES

Information of non-dietary variables was also collected at baseline. Physical activity and hypertension have been previously validated in subsamples of this cohort (31). The prevalence and history of several NCDs was ascertained at baseline and updated until the exit of the cohort or until death was reported.

STATISTICAL ANALYSES

We describe the baseline characteristics of participants adjusted for age and sex using the inverse probability weighting method according to groups of the MQI. Proportions and means and standard deviations (SDs) were used to describe categorical and quantitative variables, respectively.

Multiple linear regressions models and Cox proportional hazard models were used to assess the association between MQI and average yearly weight change (in g) and risk of overweight/obesity, respectively, over follow-up time, across groups of adherence to MQI.

We calculated hazard ratios (HRs) and their 95 % CIs. The follow-up time for each participant was defined as the interval between the date of returning the Q0 to the date of the first report of a body weight corresponding to overweight/obesity or the date of the last questionnaire. In all models, age was the underlying time variable.

We performed a crude model and three multivariable model adjusting for well-known potential confounders. In Model 1 we adjusted for sex, year of recruitment (5 categories), and age in deciles. Model 2 was additionally adjusted for baseline BMI (continuous, kg/m^2), smoking habit (continuous, packs/year), physical activity (continuous, MET-h/s), hours spent sitting (continuous, h/d), alcohol consumption (never, < 5 g/d women/< 10 g/d men, 5-25 g/d women or 10-50 g/d men, and > 25 g/d women/> 50 g/d men) and marital status (single, married, widowed and other) and finally Model 3 was additionally adjusted for total energy (continuous, kcal/d), snacking between meals (yes/no), family history of obesity (yes/no), university years (continuous), fast food consumption (continuous, g/d), and special diet follow-up (yes/no). In all analyses, we used the lowest group as the reference category.

We used MQI as a continuous variable, assigning medians to each group, to assess the significance of the linear trend tests.

To evaluate a more realistic assessment of long-term diet during follow-up, we repeated the main analyses with dietary variables included in FFQ-10 after 10 years of follow-up, using updated data and cumulative average MQI.

We assessed the combined effect of adherence to the MedDiet, evaluated through Mediterranean Diet Score (MDS) and Mediterranean Diet Adherence Screener (MEDAS), and the Provegetarian food pattern, with the MQI. For this purpose, we categorized each dietary index by the median, interpreted as "low adherence" and "high adherence", and the MQI in tertiles (T1, T2 and T3). In all analyses, the reference category was the Q1 in MQI and the lowest adherence of MDS, MEDAS or Provegetarian diet.

Finally, the following sensitivity analyses were also performed to assess the robustness of our findings: modifying the energy limits outside the established limits (5th and 95th percentile), modifying the energy limits outside the established limits (1th and 99th percentile), additional adjustment for weight gain ≥ 3 kg in the 5 years before entering the cohort, exclusion of participants who did not answer more than 30 items of the FFQ and finally excluding participants who followed a special diet at baseline.

These analyses were performed using STATA version 15. Any *p*-values < 0.05 were considered statistically significant.

RESULTS

A total of 9344 participants were followed for an average time of 16.0 years (99 719 person-years). During this time, 2465 cases of overweight/obesity were found. Table I represents the age and sex adjusted baseline characteristics of the participants according to MQI groups. The mean score in MQI was 9 (range from 3 to 15), the mean of age was 36.5 years (SD, 11.1) and 64.7 % of participants were women. On average, participants in the highest group of the MQI (range 12 to 15) tended to be single, non-smokers, physically more active, avoided snacks between meals, followed a special diet, used supplementation, and had higher adherence to the MedDiet. On the other hand, participants with lower adherence in the MQI (range 3 to 7) were more likely to be married, current smokers, never consume alcohol, and spent more time sitting.

Table I. Baseline sociodemographic characteristics adjusted for age and sex according to the Macronutrient Quality Index (MQI) groups of participants in the SUN cohort (*n* = 9,344)[1,2]

	G1	G2	G3	G4
n (frequency)	3251	2245	1870	1978
MQI (range)	3-7	8-9	10-11	12-15
MQI (median)	6	9	10	13
Marital status (%)				
Single	45.8	45.1	46.1	48.9
Married	49.3	48.6	48.9	44.6
Widowed	0.9	0.8	1.1	0.7
Others	4.0	5.5	4.0	5.8

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Tabla I (Cont.). Baseline sociodemographic characteristics adjusted for age and sex according to the Macronutrient Quality Index (MQI) groups of participants in the SUN cohort (n = 9,344)[1,2]

	G1	G2	G3	G4
Years at university	5.1 (1.6)	5.1 (1.6)	5.1 (1.5)	5.0 (1.5)
Smoking (%)				
Never	50.6	50.8	52.2	55.9
Current	23.6	23.5	21.6	16.2
Former	25.8	25.8	26.2	27.9
Cumulative smoking habit (packs-year)	5.5 (8.9)	5.2 (8.4)	4.9 (8.3)	4.4 (7.5)
Alcohol intake (g/d)				
Never	20.3	18.1	18.0	19.0
< 5 g/d women/< 10 g/d men	46.0	48.4	47.9	50.8
5-25 g/d women/10-50 g/d men	32.1	32.0	32.3	28.8
> 25 g/d women/> 50 g/d men	1.6	1.6	1.7	1.3
Physical activity (MET s-h/week)	20.7 (22.4)	22.0 (22.5)	24.5 (26.6)	28.7 (28.1)
BMI, baseline (kg/m²)	22.0 (1.9)	22.1 (1.8)	22.0 (1.9)	21.9 (1.9)
Time spent sitting (h/d)	5.3 (2.1)	5.2 (2.0)	5.2 (2.1)	5.1 (2.0)
Prevalent hypertension (%)	6.3	6.0	6.6	6.7
Prevalent dyslipemia (%)	3.3	3.3	3.6	3.5
Prevalent depression (%)	11.2	10.7	12.0	11.0
Snacking (%)	32.9	31.6	28.8	27.0
Special diet (%)	4.7	5.4	6.7	11.2
Vitamin supplement use (%)	18.0	17.9	21.3	23.6
Adherence MDS (0-9)	3.0 (1.4)	4.0 (1.5)	4.9 (1.5)	5.9 (1.4)
Adherence MEDAS (0-14)	4.9 (1.5)	5.8 (1.5)	6.5 (1.5)	7.7 (1.6)

%: percentage; G: group; BMI: body mass index; MQI: macronutrient quality index. [1]Adjusted by the inverse probability weighting method. [2]Values are expressed as averages ± SD or percentages.

As expected, participants who were in Q4 (best MQI) had a higher consumption of vegetables, fruits, pulse, whole and refined grains, fish, white meat, low-fat dairy products, nuts and olive and a lower consumption of red meats, dairy products and fast-food (Table II). Regarding baseline energy and nutrient intakes, the participants in Q4 (best MQI) reported a higher intake of energy from carbohydrates and had a higher intake of fiber, while participants in Q1 (worst MQI) had a diet with a higher intake of energy from fats, saturated fatty acids, trans fatty acids and cholesterol.

On the other hand, absolute average yearly weight change (g/y) decreased across groups of MQI. Thus, participants with the highest MQI showed a lower weight gain = +336.1 g/y, whereas those with the lowest MQI showed the highest weight change = +514.6 g/y. We found a significant inverse association between the MQI at baseline and weight change in the full multivariable adjusted model. The β coefficient for the fourth group versus the first group was -99.0, 95 % CI: -173.6 to -24.5), p for trend = 0.007 (Table III).

A total of 2,465 cases of incident overweight/obesity were identified, of which 954 were in Q1, 618 in Q2, 462 in Q3, and 431 in Q4. Table IV shows the results of Cox regression analyses carried out to assess the association between MQI and the incidence of overweight and obesity. In general, an inverse association between MQI and the risk of overweight/ obesity was observed in both the crude model and the 3 multivariate models. Point estimates also decreased across the MQI groups. Statistical significance was observed in the Q4 vs Q1 across all models, also showing significant p for trends in both the age- and sex-adjusted model and the 3 adjusted models. Thus, in the more adjusted model, the incidence of overweight/obesity was lower in Q4 with 431 cases (22 %) compared to 954 incident cases (29 %) in Q1. In model 3, the HR and 95 % CI in each category were: 0.99 (0.89-1.10), 0.96 (0.85-1.08) and

Table II. Basal food intake and basal energy and nutrient intake according to the groups of the Macronutrient Quality Index (MQI) (*n* = 9344)

		G1	G2	G3
n (frequency)	3251	2245	1870	1978
MQI (range)	3-7	8-9	10-11	12-15
MQI (median)	6	9	10	13
Food (g/d)				
Vegetables	395.3 (228.4)	505.5 (297.0)	579.5 (363.3)	721.8 (426.1)
Fruits	202.3 (173.9)	273.5 (226.8)	322.5 (251.5)	423.2 (293.5)
Pulse	18.7 (11.1)	22.3 (15.6)	26.1 (23.0)	28.7 (23.9)
Whole grains	3.7 (14.4)	9.3 (26.2)	15.2 (32.7)	31.6 (44.8)
Refined grains	101.0 (72.2)	103.2 (72.3)	105.4 (75.2)	111.7 (72.5)
Fish	73.2 (40.9)	93.0 (50.5)	105.5 (57.0)	123.2 (67.0)
Red meat	95.2 (48.6)	81.0 (44.2)	67.8 (40.5)	49.8 (34.9)
White meat	39.5 (32.1)	47.8 (32.6)	50.6 (41.8)	53.0 (38.5)
Dairy products	286.1 (239.2)	209.9 (190.1)	158.1 (158.9)	111.5 (126.3)
Low- fat dairy products	187.9 (241.4)	213.6 (240.1)	235.7 (238.8)	258.7 (262.3)
Eggs	25.0 (17.2)	24.2 (16.1)	22.7 (13.9)	20.6 (13.4)
Nuts	4.6 (6.3)	6.3 (8.6)	8.5 (11.4)	15.2 (20.1)
Olive oil	14.5 (11.9)	18.4 (15.3)	20.8 (15.4)	24.0 (16.5)
Fast food	25.9 (21.7)	23.0 (20.0)	21.2 (20.5)	16.4 (18.3)
Alcohol	6.2 (8.8)	6.0 (8.7)	5.9 (8.5)	5.5 (8.1)
Energy and nutrients				
Energy (kcal/d)	2360 (611)	2377 (610)	2374 (635)	2370 (603)
Carbohydrates (% E)	42.2 (7.11)	43.6 (6.9)	44.7 (7.2)	46.5 (7.6)
Fiber (g/d)	17.7 (6.4)	21.7 (8.0)	25.0 (9.6)	31.2 (11.1)
Proteins (% E)	18.2 (3.2)	18.1 (3.1)	17.9 (3.5)	17.9 (3.4)
Fats (% E)	37.7 (6.0)	36.5 (6.3)	35.5 (6.7)	33.9 (7.0)
MUFA (% E)	15.9 (3.1)	15.8 (3.7)	15.8 (4.1)	15.5 (4.2)
PFA (% E)	4.9 (1.4)	5.3 (1.5)	5.4 (1.8)	5.3 (1.6)
SFA (% E)	14.6 (3.0)	12.8 (2.4)	11.5 (2.4)	9.6 (2.4)
TFA (% E)	0.5 (0.2)	0.4 (0.2)	0.3 (0.1)	0.2 (0.1)
PFA-n3 (g/d)	2.3 (1.0)	2.5 (1.2)	2.7 (1.3)	2.9 (1.3)
PFA-n6 (g/d)	18.8 (12.5)	18.8 (12.2)	18.0 (12.0)	16.3 (11.2)
Cholesterol (mg/d)	445.0 (198.9)	431.5 (154.3)	401.8 (143.8)	359.4 (137.9)

MQI: macronutrient quality index; %E: percentage of total energy consumed; MUFA: monounsaturated fatty acids; PFA: polyunsaturated fatty acids; SFA: saturated fatty acids; TFA: trans fatty acids; PFA-n3: omega 3 fatty acids; PFA-n6: omega 6 fatty acids.

0.87 (0.77-0.98) for Q2, Q3 and Q4, respectively, compared to Q1, *p* for trend = 0.036.

Spearman's correlation coefficients (r) for the MQI and its components at baseline were calculated. The highest correlation coefficients at baseline were observed between MQI and FQI or CQI, both (r = 0.65), while the lowest correlation was between MQI and HPPQI (r = 0.27).

In order to have a more up-to-date dietary approach, the main analysis was re-analyzed, with repeated measures of diet evaluated with two different methods: updated diet and cumulative diet average (Table V). In both analyses the results are very similar to those obtained when evaluating the diet at baseline. Thus, for model 3 using the updated diet method, the HR and 95 % CI were as follows: 0.96 (0.87-1.06), 0.97 (0.85-1.10) and 0.86 (0.75-0.98) for Q2, Q3 and Q4, respectively, *p* for trend: 0·035. On the other hand, when using the cumulative diet method, these values were 0.99 (0.89-1.10), 0.98 (0.87-1.10) and 0.87 (0.77-0.98) for Q2, Q3 y Q4, respectively, *p* for trend: 0.033. As for the other models, only the highest group presented significance.

Figure 1A, 1B and 1C represent the HRs for the incidence of overweight/obesity according to the combined analysis of MQI and MDS, MEDAS and Provegetarian diet, respectively. For each analysis, participants were categorized into 6 groups according to the MQI and the adherence of each dietary pattern. In all cases, the reference category included the participants with

Table III. Annual weight change (g) in participants without overweight/obesity according to the groups of the MQI· Beta regression coefficients and 95 % confidence intervals (CI)

			G1		G2		G3		*p* for trend
n (frequency)	3251		2245		1870		1978		
Weight change (g/year)	514.6		385.6		408.4		336.1		
	Coef β	**95 % CI**	**Coef β**	**95 % CI**	**Coef β**	**95 % CI**	**Coef β**	**95 % CI**	
Crude model	0 (Ref·)		*-129.1*	*-198.9; -60.2*	*-106.3*	*-179.1; -33.4*	*-178.5*	*-250.1; -107.0*	*< 0.001*
Model 1	0 (Ref·)		*-107.2*	*-176.2; -38.2*	-66.3	-139.7; 7.4	*-117.3*	*-190.1; -43.8*	*0.001*
Model 2	0 (Ref·)		*-108.8*	*-177.4; -40.2*	-58.7	-131.9; 14.5	*-96.7*	*-170.3; -23.1*	*0.008*
Model 3	0 (Ref·)		*-106.5*	*-175.0; -38.1*	-59.5	-132.8; 13.8	*-99.0*	*-173.6; -24.5*	*0.007*

Ref: reference value; MQI: macronutrient quality index; G: groups. Model 1: adjusted for sex, year of recruitment (5 categories) and age deciles (in addition to using age as the underlying time variable). Model 2: was additionally adjusted for BMI (continuous, kg/m²), smoking habit (continuous, packs/year), physical activity (continuous, MET-h/s), hours spent sitting (continuous, h/d), alcohol consumption (never, < 5 g/d women/< 10 g/d men, 5-25 g/d women or 10-50 g/d men, and > 25 g/d women/> 50 g/d men) and marital status (single, married, widowed and other). Model 3 additionally adjusted for total energy, snacking between meals (yes/no), family history of obesity (yes/no), years at university (continuous), fast food consumption (continuous, g/d) and special diet follow-up (yes/no).

Table IV. Incidence of overweight or obesity (BMI ≥ 25 kg/m²) in participants without overweight/obesity at the beginning of the study in relation to the groups of the MQI· Hazard ratios and 95 % confidence intervals

		G1	G2	G3	*p* for trend
Subjects (n)	3251	2245	1870	1978	
Overweight/obesity cases (n)	954	618	462	431	
Person-years	35119	24358	19641	20600	
Overweight/obesity rate/1000 persons years	2.7	2.5	2.4	2.1	
Age-and sex-adjusted	1.00 (Ref)	0.97 (0·87-1·07)	0.92 (0.83-1.04)	*0.83 (0.74-0.93)†*	*0.002*
Model 1	1.00 (Ref)	0.97 (0·87-1·07)	0.92 (0.82-1.03)	*0.82 (0.73-0.93)‡*	*0.001*
Model 2	1.00 (Ref)	0.99 (0·89-1·10)	0.96 (0.86-1.08)	*0.88 (0.78-0.99)**	*0.048*
Model 3	1.00 (Ref)	0.99 (0·89-1·10)	0.96 (0.85-1.08)	*0.87 (0.77-0.98)†*	*0.036*

*Model 1: adjusted for sex, year of recruitment (5 categories) and age deciles (in addition to using age as the underlying time variable). Model 2: was additionally adjusted for BMI (continuous, kg/m²), smoking habit (continuous, packs/year), physical activity (continuous, MET-h/s), hours spent sitting (continuous, h/d), alcohol consumption (never, < 5 g/d women/< 10 g/d men, 5-25 g/d women or 10-50 g/d men, and > 25 g/d women/> 50 g/d men) and marital status (single, married, widowed and other). Model 3 additionally adjusted for total energy, snacking between meals (yes/no), family history of obesity (yes/no), years of university (continuous), fast food consumption (continuous, g/d) and special diet follow-up (yes/no). *p < 0.01. †p < 0.05. ‡p < 0.001.*

the worst MQI and the worst adherence of each dietary pattern (Mediterranean or Provegetarian). The figures show that the lowest risk of developing overweight/obesity was observed in those participants with better MQI (T3) and greater adherence to the Mediterranean or Provegetarian patterns. Thus, for the analysis with MDS, MEDAS or Provegetarian diet, the subjects with the best score in both dietary patterns had a 12 %, 19 % and 15 % lower risk respectively, compared to those with the worst score in both scores. The HR (95 % CI) for participants with higher adherence to the MedDiet measured by MDS or MEDAs (≥ median) and higher MQI (T3) were, respectively 0.88 (0.78-0.99) and 0.81 (0.72-0.92). Similarly, participants with higher adherence to the Provegetarian (≥ median) and higher MQI (T3) had a HR (95 % CI) of 0.85 (0.75-0.97).

Multiple sensitivity analyses were performed to check the robustness of the main findings (Table VI). In general, an inverse association between MQI and the incidence of overweight/ obesity was observed in the different scenarios that were considered, except when excluding participant with 30 or more missing values in the FFQ.

Table V. Analysis of repeated measures after 10 years of follow-up· Hazard ratios and 95 % confidence intervals for the association between MQI and the incidence of overweight/obesity in the SUN cohort

Updated diet		**G1**	**G2**	**G3**	***p* for trend**
Incidence of overweight/obesity	682	907	452	424	
Person/ years	25589	35211	18661	20258	
Age-and sex-adjusted	1.00 (Ref)	0.97 (0.87-1.07)	0.92 (0.83-1.04)	*0.83 (0.74-0.93)**	*0.016*
Model 1	1.00 (Ref)	0.98 (0.89-1.09)	0.95 (0.84-1.08)	*0.84 (0.74-0.95)**	*0.007*
Model 2	1.00 (Ref)	0.96 (0.87-1.07)	0.97 (0.86-1.10)	*0.87 (0.76-0.99)**	*0.043*
Model 3	1.00 (Ref)	0.96 (0.87-1.06)	0.97 (0.85-1.10)	*0.86 (0.75-0.98)**	*0.035*
Cumulative diet average		**G1**	**G2**	**G3**	***p* for trend**
Incidence of overweight/obesity	953	624	469	419	
Age-and sex-adjusted	35477	24576	19431	20234	
Crude model	1.00 (Ref·)	0.93 (0.84-1.03)	0.88 (0.78-0.98)	*0.74 (0.66-0.84)**	*< 0.000*
Model 1	1.00 (Ref·)	0.99 (0.89-1.09)	0.96 (0.86-1.07)	*0.83 (0.73-0.93)**	*0.003*
Model 2	1.00 (Ref·)	1.00 (0.90-1.10)	0.98 (0.87-1.10)	*0.87 (0.77-0.99)**	*0.042*
Model 3	1.00 (Ref·)	0.99 (0.89-1.10)	0.98 (0.87-1.10)	*0.87 (0.77-0.98)**	*0.033*

*Ref: reference value; MQI: macronutrient quality index; G: group. Model 1: adjusted for sex, year of recruitment (5 categories) and age deciles. Model 2: was additionally adjusted for BMI (continuous, kg/m²), smoking habit (continuous, packs/year), physical activity (continuous, MET-h/s), hours spent sitting (continuous, h/d), alcohol consumption (never, < 5 g/d women/< 10 g/d men, 5-25 g/d women or 10-50 g/d men, and > 25 g/d women/> 50 g/d men) and marital status (single, married, widowed and other). Model 3 additionally adjusted for total energy, snacking between meals (yes/no), family history of obesity (yes/no), years of university (continuous), fast food consumption (continuous, g/d) and special diet follow-up (yes/no). *p < 0.05.*

Table VI. Hazard ratio and confidence intervals at 95 % or the association between the Macronutrient Quality Index and the incidence of overweight and obesity of the SUN cohort. Group 4 *vs* group 1

	n	**Events**	**G4 *vs* G1**	***p* for trend**
Main analyses	9344	2465	*0.87 (0.77-0.98)**	*0.036*
Sensitivity analyses				
Exclusion participants with energy intake < 5th percentile and > 95th percentile	9311	2412	*0.87 (0.77-0.98)**	*0.046*
Exclusion participants with energy intake < 1th percentile and > 99th percentile	10144	2622	*0.87 (0.77-0.98)**	*0.014*
Additional adjustment for weight gain ≥ 3 kg in the 5 y before to entering the cohort	9344	2465	*0.87 (0.77-0.98)**	*0.036*
Excluding participant with 30 or more missing values in FFQ	8991	2373	0.88 (0.78-1.00)	0.058
Excluding participants with special diet at baseline	8729	2243	*0.83 (0.73-0.95)**	*0.008*

Adjusted for sex, year of recruitment (5 categories), age deciles, BMI (continuous, kg/m²), smoking habit (continuous, packs/year), physical activity (continuous, MET-h/s), hours spent sitting (continuous, h/d), alcohol consumption (never, < 5 g/d women/< 10 g/d men, 5-25 g/d women or 10-50 g/d men, and > 25 g/d women/> 50 g/d men) and marital status (single, married, widowed and other), total energy, snacking between meals (yes/no), family history of obesity (yes/no), years of university (continuous), fast food consumption (continuous, g/d) and special diet follow-up (yes/no).

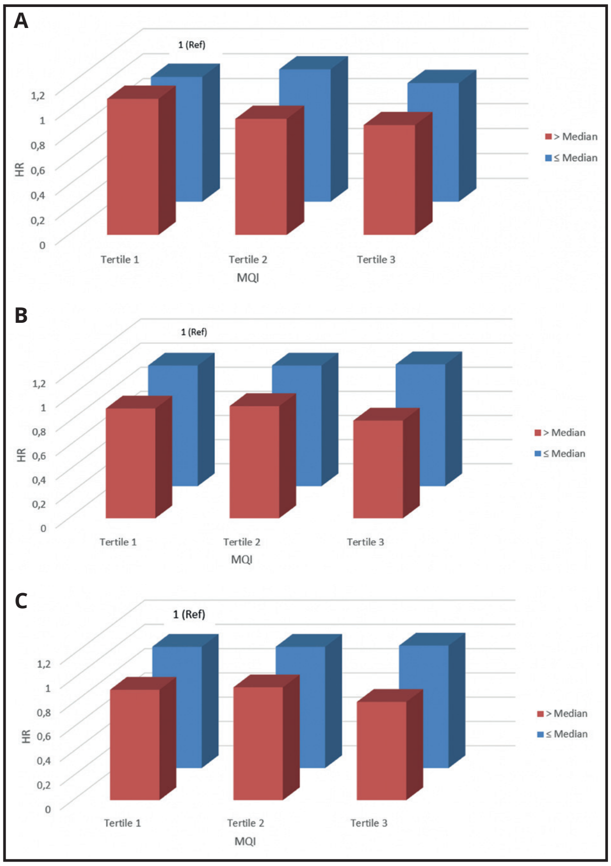

Figure 1.

A. Combined analysis between Adherence to Mediterranean Diet Score and MQI, and the incidence of overweight/obesity among participants in the SUN cohort. B. Combined analysis between adherence to MEDAS and MQI and incidence of overweight/obesity in participants in the SUN cohort. C. Combined analysis between adherence to the Provegetarian Diet Score and MQI and the incidence of overweight/obesity in participants in the SUN cohort (Ref: reference value; MQI: macronutrient quality index; T: tertile. Model stratified by year of recruitment [five categories] and age deciles, and adjusted for sex, BMI [continuous, kg/m²], smoking habit [straight, packs/year], physical activity [continuous, MET-h/s], hours spent sitting [continuous, h/d], alcohol consumption [never, < 5 g/d women/< 10 g/d men, 5-25 g/d women or 10-50 g/d men, and > 25 g/d women/> 50 g/d men], marital status [single, married, widowed and other], total energy, snacking between meals [yes/no], family history of obesity [yes/no], years of university [continuous], fast food consumption [continuous, g/d], and exceptional diet follow-up [yes/no]).

DISCUSSION

To the best of our knowledge, no previous study has assessed the association between the overall quality of macronutrients, as measured by the MQI, and the incidence of overweight/obesity in a large Mediterranean population. The most important finding was the significant decrease in the risk of overweight/obesity among participants with the best MQI.

Participants in the highest MQI had a higher consumption of vegetables, fruits, legumes, whole grains, fish, white meats, skimmed dairy products, nuts and olive oil, and lower of red and processed meat, fast-food and alcohol. These food groups provide vitamins, minerals, protein, fiber, healthy fats, low calories, and low GI that help prevent overweight and obesity (4,32).

Participants with the best MQI were more likely to meet fiber, SFA, TFA and cholesterol recommendations. In absolute terms, the TEI and percentage of each macronutrient was quite similar across groups, suggesting that the quality is more important than the quantity when assessing the risk of obesity in adults.

Most studies have used individual components or dietary carbohydrates, mainly a load of GI, dietary fiber, or whole grains, instead of a clearly defined multidimensional index to evaluate its effects on the risk of overweight and obesity. In fact, the International Carbohydrate Quality Consortium summarize and disseminate the science around dietary carbohydrate and health with a focus on carbohydrate quality, especially on dietary fiber, GI and whole grains (33). On the other hand, a high consumption of carbohydrates with starch and sugar content is associated with a higher incidence of overweight and obesity and mortality risk. However, there are several previous studies that have used the CQI as a tool to determine dietary carbohydrate quality, and have evaluated its association with several obesity indicators and its role on body fat deposition in different studies. Thus, better overall carbohydrate quality, as assessed by the CQI, has been associated with a lower risk of overweight/obesity (19), favorable changes in visceral and overall adiposity distribution as well as overall and abdominal obesity (18,34).

On the other hand, the ideal proportion of energy derived from fat in the diet and its relation to body weight is not clear (35). The participants with the best MQI had a lower percentage of total dietary fats, MUFA, SFA, TFA and cholesterol, but a higher PUFA percentage from a higher consumption of fish and nuts. Nonetheless, in all four groups the mean TEI from fats was near or even higher than the AMDR (20-35 % TEI), range associated with a reduced risk of inadequate nutrient intakes (5).

Studies on the influence of dietary fat subtypes on obesity began several years ago (36). A systematic literature review in 2012 suggested that the proportion of macronutrients in the diet was not important in predicting changes in weight or waist circumference (37); meanwhile, more recently, the PREDIMED trial concluded that increasing the intake of unsaturated fatty acids at the expense of SFA, proteins, and carbohydrates had beneficial effects on body weight and obesity. This study also recommended high-quality fat diets like the MedDiet, instead of restricting total fat intake (38).

It is reasonable to promote the replacement of SFA with MUFA and PUFA and avoidance of consumption of industrial TFA, to reduce the risk of chronic disease (39). In fact, a scoping review concluded that although most dietary guidelines recommended total fat intakes of 30-35 % of TEI, the replacement of SFA with PUFA and MUFA, and avoidance of industrial TFA, was recommended. Moreover, it was suggested that future guidelines should give recommendations on dietary fat intake and fat quality (40).

In our study, the percentage of energy from sources of protein was very similar across the four categories of MQI, in spite of the differences in consumption. Thus, participants with the higher MQI consumed more fish, white meat and low-fat dairy products, but less red and processed meat and eggs. These results suggest than the quality could be more important than the quantity of macronutrients to prevent weight gain.

High-protein intake is commonly recommended to help people manage body weight, weight loss or muscle gain (41). However, the relationship between protein intake and cardiometabolic health is complex and influenced by concomitant changes in body weight and overall diet composition. A high-protein, low-carbohydrate and reduced-energy diet has been associated with increased cardiometabolic disease risk, presumably mediated by the changes in the hormonal milieu after high-protein intake (41). Thus, in 2020 a research concluded that as far as the health effects of different diets are concerned, the macronutrient composition, the GI, the sources of nutrients (e.g. plant or animal), the food matrix, and other dietary variables could be important (42).

In addition to analyzing the effect of macronutrients, it is crucial to consider the dietary pattern, as opposed to individual nutrients.

We also found that a higher MQI and adherence to MedDiet was associated with a lower risk of overweight/obesity. In line with this finding, the MedDiet, one of the most studied and well-known high-quality dietary patterns worldwide, has been associated with a wide range of benefits for health. A recent narrative review confirmed that there is strong evidence for its benefits on cardiovascular health, including a reduction in the incidence of cardiovascular outcomes as well as risk factors. In fact, suggestive evidence with moderate effects have shown that the MedDiet is not associated with obesity and does not increase weight gain. Moreover, benefits on weight loss are stronger with energy-restricted MedDiet interventions (43).

Among 6 prospective cohort studies, higher adherence to the MedDiet was associated with a lower risk of overweight and/or obesity. The MedDiet was significantly associated with less weight gain during 5 years of follow-up among 4 cohort studies (44).

On the other hand, the Provegetarian diet has been associated with a lower risk of becoming overweight/obese (45). This association is most likely attributable to a high intake of fruits and vegetables, very low intake of processed meat, with low energy density, but rich in micronutrients and phytochemicals.

Some limitations should be considered. First, the participants are university graduates so our sample may not represent the general Spanish population. However, the generalization of the findings must be based on biological mechanisms and both the level of education and the homogeneity add validity to the results and reduce the likelihood of misclassification bias while increasing internal validity. Second, the FFQ was self-reported and may have a certain degree of measurement bias, but is considered the gold standard in large cohorts and our FFQ has been validated previously (22,23). Third, the MQI was derived from the FFQ and it has not been validated, but it has already been used in previously published studies to evaluate its association with CVD incidence (46), and its three sub-indexes have also been used in previous investigations. Fourth, even though the analyses were adjusted for potential confounders, a certain degree of residual confounding could remain. However, we adjusted for well-known risk-factors of weight gain. Fifth, self-reported outcomes were used, but have been previously validated in this SUN cohort. Finally, a causal association cannot be properly established because of the observational study design.

The strengths of our study include the large sample size, the high retention rate, its prospective design, the large follow-up period and adjustments for many potential confounding factors, a sufficient number of overweight/obesity cases, the use of previously validated questionnaires, the use of repeated measures, and sensitivity analyses.

In this Mediterranean cohort, we found a significant inverse relationship between a higher macronutrient quality, as measured by the MQI, and incidence of overweight/obesity. Furthermore, participants who had greater adherence to the MedDiet and Provegetarian patterns, and presented the highest MQI had a lower incidence of being overweight and obese.

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