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Covid-19

Mediterranean diet and the risk of COVID-19 in the 'Seguimiento Universidad de Navarra' cohort

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SUMMARY

Background & aims: A potential protection against COVID-19 by a high-quality dietary pattern is to be expected given the biological plausibility supporting the beneficial effects of an adequate dietary intake on the immune system. However, knowledge on the relationship between long-term maintained healthy dietary patterns, such as the Mediterranean diet, and the risk of SARS-CoV-2 infection is still sparse. We longitudinally assessed this association in a well-known Mediterranean cohort.

Methods: We assessed 9,677 participants from the SUN Project, a prospective cohort of middle-aged university graduates in Spain. We inquired about a positive result in a COVID-19 diagnostic test during the months of February to December 2020. After excluding health professionals (HP), 5,194 participants were included in the statistical analyses (mean age: 52.6, SD: 12.4; 55.2% women). Food habits were assessed at baseline using a previously validated semiquantitative 136-item food frequency questionnaire. Adherence to the Mediterranean diet (cumulative average of 2 repeated measurements 10 years apart) was assessed using the 0-to-9 Mediterranean Diet Score (MDS). We used multivariable logistic regression models to estimate odds ratios and 95% confidence intervals for incident COVID-19 according to the MDS.

Results: Among 5,194 non-HP participants, 122 reported to have received a positive COVID-19 diagnostic test. Participants with intermediate adherence to the Mediterranean diet ($3 < \text{MDS} \leq 6$) had a significantly lower odds of developing COVID-19 (multivariable-adjusted OR = 0.50, 95% CI: 0.34–0.73), and those with the highest adherence (MDS > 6) exhibited the lowest risk (multivariable-adjusted OR = 0.36, 95% CI: 0.16–0.84, p for trend < 0.001) as compared with participants with MDS ≤ 3. This inverse association remained robust within subgroups and in sensitivity analyses. Notwithstanding, no significant associations were observed for health professionals (p for interaction = 0.06).

Conclusion: In conclusion, better adherence to the Mediterranean diet may be associated with a lower risk of COVID-19. Our results are applicable only to persons who are not health professionals.

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1. Introduction

In December 2019, an outbreak of pneumonia of unknown origin in the city of Wuhan (China) led to the isolation of a new coronavirus, 2019-nCoV or SARS-CoV-2 [1]. A few months later, on March 2020, the coronavirus disease, COVID-19, was officially declared a pandemic by the World Health Organization. With data updated to March 2021, it has caused more than 125 million cases and 2.8 million deaths throughout 223 countries [2].

Although there are already more than 100,000 articles Indexed in PubMed about COVID-19, there is still no clear treatment protocol and many options are being tested and studied [3]. Today, the main focus of action is prevention. On the one hand, different countries have taken non-pharmacological measures to reduce the

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spread of the virus, such as the use of masks, border closures, quarantines, limitation of social gatherings, or even home confinement, with great socio-economic repercussions. On the other hand, the first vaccines are being currently applied in order to meet ambitious goals. However, to achieve herd immunity, at the current vaccination rate, it will still take quite a few months or years, depending on the region, since the vaccination rate is being very uneven among different parts of the world [4].

In this context, research on different risk factors, which may increase or reduce the probability of contracting the disease is essential. Some of the best described factors are obesity or diabetes [5,6], both of which may underlie an important role for nutrition. Other important risk factors include hypertension, cancer, asthma or cardiovascular disease [7,8].

Just because of its widely demonstrated beneficial role on these risk factors [9], it would be worth recommending a high-quality dietary pattern such as the Mediterranean diet. However, some authors already have pointed out that there is a strong rationale for expecting a protective effect of the Mediterranean diet on COVID-19 [10–14].

Despite these expectations, to our knowledge, there are still no epidemiological studies that support this hypothesis. Demonstrating this relationship could contribute a new tool to help in the fight against the virus, for which no efforts are small.

With this study we aimed to evaluate the association between a better adherence to the Mediterranean diet and the incidence of COVID-19 among participants of a well-known Mediterranean cohort, the SUN ("Seguimiento Universidad de Navarra") project.

2. Materials & methods

2.1. Study sample

The SUN Project is a prospective and multipurpose cohort study designed to evaluate different aspects of the dietary pattern and lifestyles, relating them to health outcomes. By the end of 2020 it already had nearly 23,000 participants, who are evaluated every 2 years through self-administered questionnaires. It is a dynamic cohort, so, although the recruitment started in 1999, it is permanently open. Participants are university graduates from all over Spain. The methods and many specific details of the SUN cohort have already been described [15].

In addition to the biennial questionnaires, during February to December 2020, a specific questionnaire on COVID-19 was sent to all participants. In this questionnaire they were asked whether or not they had undergone a diagnostic test for COVID-19. If this was the case, they were asked for the date and the result of the test. It also inquired about a medical diagnosis of the disease.

2.2. Outcome measurement

For the incidence of COVID-19, all those who reported a positive result in a SARS-CoV-2 diagnostic test were counted. We used this criterion because it is more specific than the clinical diagnosis. We only took into account the additional cases with medical diagnosis but without confirmation by a specific diagnostic test (probable cases) for sensitivity analyses.

2.3. Dietary assessment

The adherence to the Mediterranean diet was assessed using the Mediterranean Diet Score (MDS) proposed by Trichopoulou which has been most widely used to assess adherence to the Mediterranean diet [16]. This MDS takes into account 9 components of the diet, 1 point corresponds to moderate ethanol intake (5–25 g/d for women and 10–50 g/d for men), and another point to the monounsaturated-to-saturated fatty acids ratio, the point is given to those with a monounsaturated/saturated ratio at or above the sex-specific median. The other 7 points correspond to the consumption of food groups: 1 point is given to those who have a consumption equal or higher than the sex-specific median consumption on each beneficial food groups (cereals, fruits and nuts, vegetables, legumes and fish), or below the sex-specific median for two food groups that are not typical of the Mediterranean diet (meat and dairy products). The final punctuation ranges from 0 to 9.

Data for creating this Index were taken from a previously validated semi-quantitative Food Frequency Questionnaire (FFQ) [17]. It consists in 136 items with consumption grouped in nine categories from "never or almost never" to "$\geq$ 6 times a day". This questionnaire is assessed at baseline and at 10 years of follow-up. Ethanol and fatty acids values were calculated by using data from updated Food Composition Tables [18].

2.4. Other covariates

At baseline, standardized questionnaires were used for gathering information on demographic characteristics (age, sex, years of university education, profession and marital status), lifestyle habits (smoking status and physical activity) and anthropometric and clinical data (weight, height and comorbidities).

This information is updated with different follow-up questionnaires. The diagnosis of new diseases and weight are updated in each of these follow-up questionnaires. Other variables, however, are updated less frequently, such as marital status (questionnaire at 14-year follow-up) or height (questionnaire at 10 years). For each of them we used the most recent available information.

2.5. Statistical analysis

First, we proceeded to the description of the different variables with different statistical parameters. For categorical variables we calculated the percentage of participants included in each group and for numerical variables we calculated the mean and standard deviation or the median and the interquartile range if the distribution of the variable did not follow a normal distribution.

Secondly, to evaluate the possible effect of the adherence to the Mediterranean diet on the incidence of COVID-19, logistic regression models with successive degrees of adjustment were used to calculate Odds Ratios (OR) for COVID-19, for the 2 upper categories of the MDS (4–6 and 7 to 9) using the lowest category ($\leq$ 3) as reference. We also estimated the association using the MDS as a continuous variable and assessing the effect for every 2 points. These ORs are expressed with their 95% confidence intervals. This analysis was repeated adjusting for the potential confounding variables. We excluded from the analysis participants below the percentile 1 or above the percentile 99 of total energy intake. In addition, we adjusted all models for total energy intake (as a continuous independent variable).

All analyses were carried out both excluding and including health professionals (HP): doctors, nurses and pharmacists. Analyses were also repeated after stratifying by different subgroups (sex, age, smoking status and body mass index).

Finally, some sensitivity analyses were performed including probable cases (those with clinical diagnosis of COVID-19 and without a positive test), those who were tested during the second wave of the pandemic (after August 2020) or those with comorbidities.

We calculated the p for trend by estimating group-specific medians and treating the resulting variable as continuous.

STATA software (version 16) was used for data analysis.

3. Results

By the end of 2020 the COVID-19 questionnaire of the SUN cohort had been answered by 9,677 participants. However, 74 of them did not coincide with a participant in the SUN Project database, so the final number of subjects initially included in this study was 9,603. After excluding participants with total energy intake beyond percentiles 1st and 99th the study sample included 9,413 participants. Given the immense strength of the COVID-19 pandemic burden in Spain during 2020 and that the most relevant exposures for health professionals are related to their work in clinical care and not so much to nutritional factors, our main analyses focused on those participants who were not health professionals. A priori, a stratified analysis, with a breakdown of the sample into health professionals and not health professionals was established. This decision was based on consideration of the highly relevant differences in exposures between both types of participants in our cohort.

Baseline characteristics of the population included in the study are shown in Table 1. It is a middle-aged population (mean age = 52.6 years), with a higher proportion of women, mostly married. Near half of participants were health professionals (44.8%), a very similar proportion of the total population of the SUN cohort. Regarding lifestyles, half of the participants had never smoked. A description of the most important conditions and chronic diseases potentially related to the risk of COVID-19 is also shown in Table 1.

There were no significant differences in these characteristics when HP were excluded. We observed 369 (3.9%) cases of COVID-19 for all our study population, but only 122 (2.3%) of them were among non-health professionals.

Table 2 describes the different components included in the MDS, both for the total population and for different degrees of adherence to the Mediterranean diet. The lower part of the table is referred to non-health professionals (our main analytical sample).

Figure 1 shows the apparent inverse association between the MDS and the risk of COVID-19.

In logistic regression models (Table 3), for each 2 additional points in the MDS the risk of COVID-19 was reduced in a 5% (OR = 0.95, 95% CI: 0.84–1.07) after adjusting for sex, age, years of university studies, being a health professional, marital status (4 categories), smoking (3 categories), total ethanol intake, body mass index, leisure-time physical activity, total energy intake, period of entering the cohort and comorbidities; however, this result was not statistically significant. Among non-health professionals the reduction in the risk was significantly higher, with a 26% relative reduction (OR = 0.74, 95% CI: 0.60–0.93) and a highly significant inverse linear trend. When we assessed the interaction between these two variables, adherence to the Mediterranean diet (continuous) and being a health professional, we found only a marginally significant p for interaction (p = 0.06). The results were also statistically significant for the inverse linear trend when we only excluded medical doctors and nurses (but not other health professionals).

The magnitude of the effect was also analyzed comparing a high adherence to the Mediterranean diet with a low adherence. A stronger effect was observed for the adherence to Mediterranean diet measured as a categorical instead of a quantitative variable, with strong risk reductions (>50% relative reductions) for the upper versus the lowest category when health professionals were excluded.

When analyses were stratified by sex, no relevant modification of effect was observed. Similar conclusions were obtained after stratifying by age categories, smoking status or BMI. Within the subgroups of current smokers and obese participants (BMI $\geq$ 30 kg/m^2) no cases of COVID-19 were observed if the adherence to de Mediterranean diet was in the best category (Table 4).

Finally, some sensitivity analyses were carried out (Table 5). First, participants with a clinical diagnosis of COVID-19 and no positive test (i.e., probable cases) were also included, obtaining only a very small change in the association. Secondly, those who were tested during the second wave (after August 2020) were also excluded, since many more tests were carried out in this period, detecting more asymptomatic cases. An additional analysis was

Table 1
Baseline characteristics of the SUN cohort participants who answered the COVID-19 specific questionnaire.

	All (N = 9,413)	Excluding HP (N = 5,194)
Demographic characteristics		
Age (years), mean (SD)	52.6 (12.0)	52.6 (12.4)
Sex (female) (%)	62.3	55.2
Years of university education, median (IQR)	5 (4–5)	5 (4–5)
Marital status (%)		
Single	27.8	30.6
Married	63.3	61.5
Divorced	4.5	3.9
Others	4.4	4
>10 years in the cohort (%)	88.1	88.9
Health professionals (%)	44.8	–
Lifestyle habits		
Smoking status (%)		
Current smoker	20.4	21.5
Former smoker	28.4	27.7
Physical activity (METS/week), median (IQR)	14 (5–27)	13 (5–27)
Anthropometric and clinical data		
Total energy intake (kcal/d), mean (SD)	2,446 (705)	2,440 (718)
Adherence to the MDS (0 to 9 score), mean (SD)	4.3 (1.8)	4.1 (1.8)
Alcohol intake (g/d), median (IQR)	4 (1–9)	4 (1–10)
BMI (kg/m^2), mean (SD)	24.3 (3.9)	24.4 (3.9)
Type 2-diabetes mellitus (%)	3.1	3.2
Hypertension (%)	18.9	20.4
Cardiovascular disease (%)	4.8	4.6
Cancer (%)	6.4	6
Pulmonary disease (%)	6.4	6.2

HP: health professionals. IQR: Interquartile Range. METS: Metabolic Equivalent Task. MDS: Mediterranean Diet Score. BMI: Body Mass Index.

Table 2
Description of the different items of the Trichopoulou Index for the total study sample and for different degrees of adherence to the Mediterranean diet.

All participants (N = 9,413)	Total	MedDiet adherence (median)		
		Low (MDS ≤ 3) (N = 3,276)	Middle (3 < MDS ≤ 6) (N = 5,036)	High (MDS > 6) (N = 1,101)
Food groups (g/day)				
Cereals	94	77	101	126
Fruits and nuts	309	206	353	504
Vegetables	490	364	548	704
Legumes	21	17	21	25
Fish	89	67	101	128
Meat	169	184	165	134
Dairy products	127	198	106	64
Alcohol	3.6	2.2	4.3	7.4
Fatty acids ratio				
MUFA/SFA	1.28	1.14	1.34	1.56
Excluding HP (N = 5,194)		Low (MDS ≤ 3) (N = 1,965)	Middle (3 < MDS ≤ 6) (N = 2,694)	High (MDS > 6) (N = 535)
Food groups (g/day)				
Cereals	94	77	103	125
Fruits and nuts	289	196	344	478
Vegetables	471	357	537	680
Legumes	21	16	21	25
Fish	895	66	99	127
Meat	168	183	165	137
Dairy products	137	202	112	67
Alcohol	3.9	2.7	4.6	7.5
Fatty acids ratio				
MUFA/SFA	1.26	1.13	1.34	1.56
Excluding HP Participant characteristics	(N = 5,194)	Low (MDS ≤ 3) (N = 1,965)	Middle (3 < MDS ≤ 6) (N = 2,694)	High (MDS > 6) (N = 535)
Age(years), mean (SD)	52.6 (12.4)	50.1 (10.8)	53.4 (12.7)	57.7 (13.8)
Sex (female) (%)	55.2	56.2	55.5	50.1
Total energy intake (kcal/d), mean (SD)	2,440 (718)	2,293 (675)	2,506 (730)	2,649 (711)
BMI (kg/m^2), mean (SD)	24.4 (3.9)	24.3 (4.0)	24.4 (3.8)	24.4 (3.7)
Phys. activity (METS/wk), mean (SD)	19.2 (20.0)	16.8 (17.5)	20.0 (20.1)	24.0 (22.7)
Current smoker (%)	21.5	23.6	20.2	20.2
Former smoker (%)	27.7	21.0	31.0	35.7
Married (%)	61.5	58.6	62.8	65.2
Type 2-diabetes mellitus (%)	3.2	2.4	3.6	4.3
Hypertension (%)	20.4	17.3	21.6	26.0
Cardiovascular disease (%)	4.6	4.3	4.7	5.2
Cancer (%)	6.0	4.5	6.4	9.3
Pulmonary disease (%)	6.2	6.9	6.1	4.5
Any history of chronic disease (%)	32.4	29.2	33.5	38.9

HP: health professionals. MedDiet: Mediterranean diet. MDS: Mediterranean Diet Score. MUFA: monounsaturated fatty acids. SFA: saturated fatty acids.

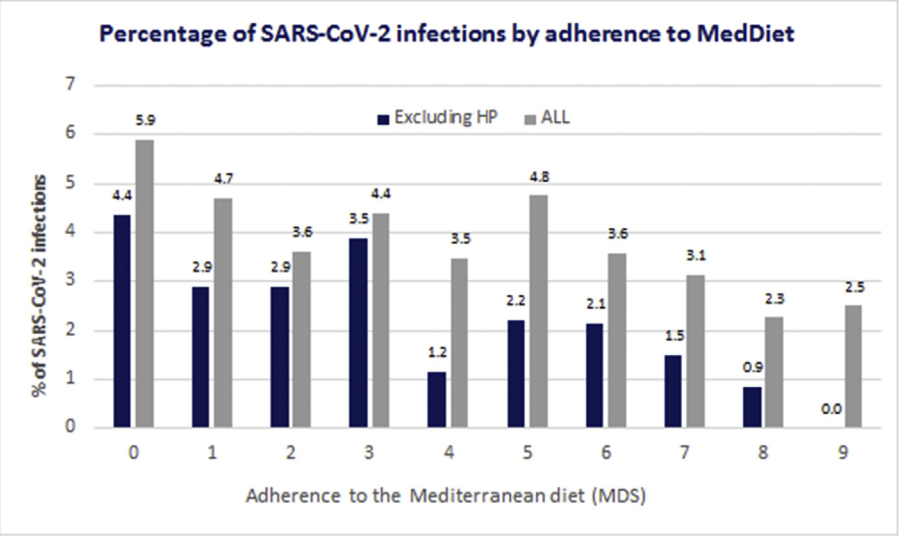

Fig. 1. Percentage of participants with SARS-CoV-2 infection by adherence to the Mediterranean diet. The SUN project, Spain 2020. HP: Health professionals. MDS: Mediterranean Diet Score (Trichopoulou).

Table 3
Odds ratios (OR) and 95% confidence intervals (CI) of incident COVID-19 according to adherence to the Mediterranean diet (Mediterranean Diet Score, MDS proposed by Trichopoulou).

All participants OR (95% CI) (N = 9,413)	Low (MDS ≤ 3) (N = 3,276)	Middle (3 < MDS ≤ 6) (N = 5,036)	High (MDS > 6) (N = 1,101)	p for trend	For +2 additional points in MDS
Cases	139	198	32		
% of infections	4.24	3.93	2.91		
Crude model	1 (ref.)	0.91 (0.73–1.14)	0.66 (0.45–0.98)	0.070	0.90 (0.80–1.01)
Sex-, age-adjusted	1 (ref.)	0.98 (0.79–1.23)	0.81 (0.54–1.21)	0.471	0.96 (0.85–1.09)
Multivariable adjusted[a]	1 (ref.)	0.96 (0.76–1.20)	0.77 (0.51–1.17)	0.321	0.95 (0.84–1.07)
Excluding only doctors and nurses OR (95% CI) (N = 5,801)	**Low (MDS ≤ 3) (N = 2,142)**	**Middle (3 < MDS ≤ 6) (N = 3,054)**	**High (MDS > 6) (N = 605)**	**p for trend**	**For + 2 additional points in MDS**
Cases	70	76	9		
% of infections	3.27	2.49	1.49		
Crude model	1 (ref.)	0.74 (0.53–1.03)	0.43 (0.21–0.88)	0.010	0.85 (0.71–1.02)
Sex-, age-adjusted	1 (ref.)	0.76 (0.55–1.07)	0.47 (0.23–0.96)	0.023	0.88 (0.73–1.05)
Multivariable adjusted[a]	1 (ref.)	0.71 (0.50–1.00)	0.41 (0.20–0.87)	0.007	0.84 (0.69–1.01)
Excluding all health professionals OR (95% CI) (N = 5,194)	**Low (MDS ≤ 3) (N = 1,965)**	**Middle (3 < MDS ≤ 6) (N = 2,694)**	**High (MDS > 6) (N = 535)**	**p for trend**	**For + 2 additional points in MDS**
Cases	67	48	7		
% of infections	3.41	1.78	1.31		
Crude model	1 (ref.)	0.50 (0.34–0.72)	0.36 (0.16–0.73)	<0.001	0.74 (0.60–0.90)
Sex-, age-adjusted	1 (ref.)	0.52 (0.36–0.77)	0.40 (0.18–0.89)	<0.001	0.77 (0.63–0.95)
Multivariable adjusted[a]	1 (ref.)	0.50 (0.34–0.73)	0.36 (0.16–0.84)	<0.001	0.74 (0.60–0.93)

OR: Odds Ratio. MDS: Mediterranean Diet Score.
All models are adjusted for total energy intake. Participants beyond percentiles 1st and 99th of total energy intake were excluded. P value for interaction (health professionals * MDS (continuous), 1 df, p = 0.064).
[a] Adjusted for sex, age, years of university studies, being a health professional, marital status, smoking, BMI, leisure-time, physical activity, total alcohol intake, year of entering the cohort and previous diagnosis of chronic diseases (diabetes, hypertension, cardiovascular disease, cancer or pulmonary disease).

Table 4
Subgroup analysis among non-health professionals. Multivariable adjusted odds ratios and 95% Confidence Interval (CI) of incident COVID-19 according to adherence to the Mediterranean diet (Mediterranean Diet Score, MDS proposed by Trichopoulou). Comparison of extreme categories, linear trend test) in different subgroups and test for interaction.

Non-health professionals	Cases/total	Multivariable-adjusted[a] OR (95% CI) for MDS > 6 vs MDS ≤ 3	p for linear trend	p for interaction
Main analysis	**122/5,194**	**0.36 (0.16–0.84)**	**<0.001**	
Stratified by sex				0.258
Men	56/2,326	0.56 (0.18–1.75)	0.154	
Women	66/2,868	0.26 (0.08–0.90)	<0.001	
Stratified by age (y)				0.373
≤45	43/1,520	0.44 (0.11–1.69)	0.015	
>45 to 60	57/2,250	0.36 (0.08–1.60)	0.052	
>60	66/2,868	0.30 (0.06–1.49)	0.033	
Stratified by smoking status				0.844
Never smokers	64/2,606	0.41 (0.13–1.29)	0.003	
Current smokers	25/1,117	0[b]	0.070	
Former smokers	33/1,438	0.57 (0.16–2.04)	0.177	
Stratified by BMI (kg/m^2)		0.367		0.249
≤25	78/3,219	0.36 (0.13–1.01)	0.002	
25 to <30	31/1,561	0.56 (0.12–2.67)	0.233	
≥30	13/414	0[b]	0.050	

OR: Odds Ratio. MDS: Mediterranean Diet Score. BMI: body mass index.
All models are adjusted for total energy intake. Participants beyond percentiles 1st and 99th of total energy intake were excluded. P value for interaction (health professionals * MDS (continuous), 1 df, p = 0.064).
[a] Adjusted for sex, age, years of university studies, being a health professional, marital status, smoking, BMI, leisure-time physical activity, total alcohol intake, year of entering the cohort and previous diagnosis of chronic diseases (diabetes, hypertension, cardiovascular disease, cancer or pulmonary disease).
[b] No cases of COVID-19 were observed within these subgroups when the MDS was >6.

carried out excluding participants with comorbidities. Finally, instead of excluding participants who were beyond percentiles 1–99 of total energy intake, we set alternative limits for allowable total energy intake (400–3500 kcal/d in women and 800–4000 kcal/d in men, as recommended in some instances of nutritional epidemiology) and rerun the analysis. In all these alternative scenarios, the inverse linear trend remained significant. More importantly, regardless of the subgroup used or the alternatives imposed in the sensitivity analyses, the lowest absolute risks were always present in the best category of adherence to the Mediterranean diet.

4. Discussion

A beneficial effect of the Mediterranean diet on the incidence of COVID-19 was apparent in the SUN cohort when considering non-health professionals.

Table 5
Sensitivity analyses among non-health professionals. Multivariable-adjusted Odds Ratios (OR) and 95% Confidence Interval (CI) of COVID-19 according to adherence to the Mediterranean diet (comparison of extreme categories of the Mediterranean Diet Score, MDS, proposed by Trichopoulou) under alternative scenarios.

Non-health professionals	Cases/total	Multivariable-adjusted[a] OR (95% CI) for MDS > 6 vs MDS ≤ 3	p for linear trend
Main analysis	122/5,194	0.36 (0.16–0.84)	< 0.001
Sensitivity analyses			
Including probable cases with clinical diagnosis of COVID-19 but without positive test	193/5,194	0.37 (0.19–0.76)	0.001
Excluding participants who were tested during the second wave (after August 2020)	77/4,751	0.50 (0.19–1.29)	0.023
Excluding participants with chronic conditions	87/3,511	0.25 (0.08–0.76)	<0.001
Applying alternative limits for allowable total energy intake (400–3500 kcal/d in women and 800–4000 kcal/d in men)	113/4,867	0.41 (0.18–0.96)	0.001

[a] Adjusted for sex, age, years of university studies, being a health professional, marital status, smoking, BMI, leisure-time physical activity, total alcohol intake, year of entering the cohort and previous diagnosis of chronic diseases (diabetes, hypertension, cardiovascular disease, cancer or pulmonary disease).

This effect, moreover, became stronger when comparing more extreme adherence groups; however, the results were not significant unless health professionals were excluded. The reason to exclude this group is that the circumstances in which they have lived the COVID-19 pandemic have been totally different from the rest of the studied sample. This sector has had a much higher exposure to the virus and the main factors related to exposure are far from their nutritional habits, because they are related to the conditions of providing clinical care in circumstances that have been extremely adverse in Spain during the first wave of the pandemic. In fact, Spain has been one of the countries with the highest number of cases of COVID-19 among health professionals and there are studies that stratify belonging to this group as an exposure factor comparable to having had contact with the disease [19]. In addition, especially during the first months of the pandemic, virus detection tests were prioritized for this group [19]. Nevertheless, the councils of health professionals expressed severe complaints against the government for the negligent attention of demands for masks, individual protection equipments and provision of sufficient testing.

With regards to the biological mechanisms that could explain the protective effect of the Mediterranean diet, there are different plausible explanations. It seems that the main factor determining the evolution of the disease is the immune response [20]. An adequate immune response favors the asymptomatic course of the infection, while the opposite leads to a cytokine storm that produces the most severe forms of the disease. This would be favored by the pro-inflammatory and oxidative state typical of obesity or diabetes, being the Mediterranean diet an anti-inflammatory element in this context.

Adequate intake of all micronutrients seems important for a balanced and appropriate immune response [21,22]. Specifically, there are already several published reports that have linked vitamin D deficiency with different harmful outcomes of COVID-19, and they speculate as well on the potential benefits of supplementation, pending of the results of sufficiently powered randomized trials [23,24]. The possible benefit of vitamin D supplementation is not definitively established [25]. Other supplementations under testing are vitamin C and Zn, but no significant benefit has been attained so far [26]. Perhaps, although the beneficial effect of these micronutrients is true, their individual effect is not enough. This would reinforce the idea of the importance of evaluating an overall dietary pattern. In this context, the Mediterranean diet has been shown to cover the needs of all these micronutrients [27].

Other nutrients found in the Mediterranean diet, including polyphenols and phytochemicals, or a greater proportion of monosaturated and polyunsaturated fatty acids (specially omega-3 found in fish and nuts) rather than saturated fatty acids have shown beneficial immune-enhancing and anti-inflammatory effects [28].

Other possible mechanisms would be mediated by the lower glycemic index of this dietary pattern [30], since it has been shown that high glucose levels are predictors of morbidity and mortality regardless whether or not diabetes is present [6]. Low cholesterol levels may also play a role, since SARS-CoV, the closest relative of SARS-CoV-2, uses cholesterol to facilitate viral budding following S–protein binding to cellular ACE2 receptors, allowing spread to neighboring cells. Cholesterol depletion in ACE2-expressing cells results in a marked reduction in viral S–protein binding [29].

All these proposed mechanisms of action lead us to expect that the Mediterranean diet would have a beneficial effect on the evolution of COVID-19, favoring an asymptomatic course and avoiding complications or decreasing the viral load. Thus, it would also have been interesting to study the severity of disease and the eventual clinical outcomes in addition to the incidence of infection. However, unfortunately, information on the clinical course after infection is not available for participants in the SUN cohort, and the restriction to only infected participants will render the data sparse and underpowered as to provide stable estimates of effect. The potential favorable effect of adherence to the Mediterranean diet on the prognosis of infected patients can be better assessed in clinical settings than in a population-based cohort. The available information in the SUN cohort cannot accurately specify what type of test was used to confirm the diagnosis of the disease in each patient and we admit that this fact can be seen as another limitation of our study. Nevertheless, it can be safely assumed that the test used was a polymerase–chain reaction (PCR) test in almost one hundred per cent of cases, given that PCR was the diagnostic test used in Spain during the months when we conducted this study (mainly, the first wave).

Given that we assessed the incidence of COVID-19 as an outcome in a situation of high early symptomatic detection by PCR test (the most sensitive test), it would be difficult to obtain an inaccurate result when including only medically-diagnosed cases which were also confirmed by specific testing. In any case, we addressed the potential limitations derived from the potential use of other testing procedures in the second wave with suboptimal performance by conducting a sensitivity analysis after excluding participants tested in the "second wave", in which the work of screening and detection of asymptomatic cases was enhanced. This ancillary also showed a beneficial effect of the Mediterranean diet.

Nevertheless, one of the main limitations of our study is not having measured several other exposures of the participants, depending on how rigorous they have been in complying with non-pharmacologic preventive measures (masks, physical distancing, hand washing, ventilation) as well as the type of test for virus detection and the reason for testing (presence of symptoms, screening, etc.). These limitations have led us to propose as an approximation the exclusion of health professionals. When they were excluded we obtained significant results that support the

potential beneficial role of the Mediterranean diet that could become another tool in the fight against SARS-CoV-2.

5. Conclusions

To our knowledge, this is the first longitudinal epidemiological study to relate a dietary pattern to COVID-19. Our results indicate that higher adherence to the Mediterranean Diet may be associated with a lower subsequent risk of COVID-19. We found significant results with a risk reduction of more than 60% for the categories of higher adherence to the Mediterranean Diet. This inverse association remained robust within subgroups and in sensitivity analyses. However, our results are not applicable to health professionals, a population group that has been more exposed to the virus. In fact, one of the main limitations of our study is not having data on the different exposures of the participants, depending on how rigorous they have been in complying with other nonpharmacological preventive measures.

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Author contributions

Perez-Araluce R: Conceptualization, Methodology, Formal analysis, Writing - Original Draft; Martinez-Gonzalez MA: Conceptualization, Methodology, Formal analysis, Writing - Review & Editing, Supervision; Fernández-Lázaro CI: Methodology, Writing - Review & Editing; Bes-Rastrollo M: Writing - Review & Editing; Gea A: Writing - Review & Editing; Carlos S: Conceptualization, Writing - Review & Editing, Supervision.

Conflict of interest

All authors declare no conflict of interest.

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