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Original article

Joint association of the Mediterranean diet and smoking with all-cause mortality in the Seguimiento Universidad de Navarra (SUN) cohort

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ABSTRACT

Objectives: Although low-quality diets and smoking are independently associated with higher mortality risk, a joint analysis of both risk factors in relation to mortality has not been sufficiently studied. The aim of this study was to explore the effect modification between level of adherence to a Mediterranean dietary pattern (MedDiet) and smoking status on all-cause, cancer, and cardiovascular mortality.

Methods: We conducted a prospective analysis to assess the association between diet and smoking status in the SUN (Seguimiento Universidad de Navarra) cohort study. Deaths were confirmed by review of the National Death Index. Participants were classified into six categories according to the MedDiet (adherence/non-adherence) and their exposure to smoking (never/former/current smoker). Multivariate-adjusted Cox regression models were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for mortality. During a mean follow-up of 11.5 y (SD 4.5), we observed 18 948 participants (mean age 38.4 y; SD 12.4) and 431 deaths (51.3% cancer deaths).

Results: A higher risk for death was found among smokers with a low adherence to the MedDiet (HR, 2.20; 95% CI, 1.45–3.34) compared with never smokers with high adherence to the MedDiet. The *P* value for supra-multiplicative effect modification was not statistically significant, meaning that the effect of both factors is multiplicative. A higher risk for premature death from cancer was found in smokers and in those non-adherent with the MedDiet.

Conclusion: Smoking and poor adherence to the MedDiet exerted a multiplicative effect in increasing all-cause mortality and cancer-related mortality in a Spanish population of university graduates.

Introduction

A suboptimal diet was globally responsible for 11 million deaths in 2017, more than any other risk factor [1]. Smoking is also one of the leading lifestyle risk factors [2] and it is globally responsible for >8 million deaths per year. Life expectancy is reduced in both current smokers and individuals following a low-quality diet [3,4]. Both suboptimal diet and tobacco are associated with the most prevalent non-communicable chronic diseases, including cardiovascular disease (CVD) and cancer, and they significantly decrease the quality of life.

It is well-known that smokers usually present a poorer diet than non-smokers [4–9]. In fact, dietary habits of smokers are characterized by higher intakes of total energy, saturated fats, cholesterol, and alcohol and by lower intakes of antioxidant vitamins and dietary fiber [5,9–11]. However, a better understanding of the

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complex effect modification between diet with tobacco consumption and premature mortality is still needed [5,12–14]. To our knowledge, the effect modification between smoking and diet quality in relation to mortality has not yet been studied sufficiently.

In this study and based on the principle that the Mediterranean diet (MedDiet) is a healthy dietary pattern supported by strong scientific evidence [15–18], we hypothesized that the effect of smoking on premature mortality was modified by the level of adherence to the MedDiet. The aim of the study was to assess the association between smoking, MedDiet, and the effect modification of both lifestyle factors in relation with total, cardiovascular, and cancer deaths in the Spanish SUN (Seguimiento Universidad de Navarra) cohort study.

Methodology

Design and study population

Methods and design of the SUN project have been previously described [18]. Briefly, the SUN study is a multipurpose Spanish cohort, continually open for recruitment, and the only inclusion criteria requires participants to be university graduates and to be willing to provide their answers to periodic questionnaires inquiring about diet and health conditions. The study was approved by the Institutional Review Board of the University of Navarra and registered at clinicaltrials.gov (NCT02669602). After receiving information on the study and providing their informed consent, all participants answered a self-administered baseline questionnaire. Additionally, participants biennially received follow-up questionnaires, in which they provided information on their dietary habits, other lifestyleshabits such as tobacco consumption, and reported new-onset medically diagnosed diseases.

Figure 1 shows the selection of the analytical sample. From December 1999 to March 2017, baseline questionnaires were completed by 22 552 individuals. For the present analysis, we excluded 173 participants who had missing data on smoking, 2118 with total energy intake out of predefined limits (<800 or >4000 kcal/d in men and <500 or >3500 kcal/d in women), and 1313 with insufficient follow-up time (in this cohort, we systematically removed participants with follow-up time <2 y and 9 month, to allow for completion of the 2-y follow-up questionnaire). We included 18 948 individuals (overall retention 93.5%). However, given that, in addition to our main sources of information (see below), the National Death Index was also consulted at least once a year, we can consider that the retention proportion approaches 100% for mortality in this cohort.

Dietary and smoking assessment

A validated semiquantitative 136-item food frequency questionnaire (FFQ) was used to assess the habitual diet of the participants [19–21] . Participants were asked how often on average over the previous year they had consumed each food item according to a commonly used portion size. Nutrient intakes were computed as the sum of the frequency of consumption multiplied by nutrient composition of a specified portion size. Nutrient intake was estimated from Spanish food composition tables [20,22,23].

The 10-point Trichopoulou's Mediterranean Diet Score was used to measure the level of adherence to the MedDiet. This index is based on nine nutritional components of the MedDiet [20,24]. One point was assigned to participants whose consumption was at or above the sex-specific median of each component within the MedDiet (vegetables, pulses, fruit and nuts, grains, fish, and the ratio monounsaturated fatty acid/saturated fatty acid) or below the sex-specific median in those items less consumed in the traditional MedDiet (meats and dairy products). For alcohol, men consuming 10 to 50 g/d and women consuming 5 to 25 g/d were assigned 1 point. Thus, this MedDiet score ranged from 0 to 9 points, with the higher score implying a higher adherence to the MedDiet. In the present study, the variable was then categorized into non-adherence to the MedDiet (≤4 points) and adherence to the MedDiet (>4 points).

Smoking status was collected by the following question: "Have you smoked 100 cigarettes or more in your lifetime?", categorized as never, former or current smoker. Ever smokers were asked about the average number of cigarettes per day consumed during the following age ranges: <15, 15 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59 and >60 y. Those who indicated that they were former smokers were also asked how long it had been since they had quit smoking (<=10, and >10 y).

Covariates assessment

The baseline questionnaire also included questions about sociodemographic characteristics (sex, age, civil status, and college degree), height, weight, and physical activity level. Finally, baseline questionnaire also collected information about family history of premature CVD and each participant's medically diagnosed conditions such as hypertension, hypercholesterolemia, diabetes mellitus, CVD, cancer, and depression.

Outcomes assessment

The primary outcome was all-cause mortality, and the secondary outcomes were cancer and cardiovascular death. Participants were followed up with biennial questionnaires sent through postal mail or email. Additionally, we collected information from family members, work colleagues, and the postal system about potentially deceased participants. Finally, at least once a year the National Death Index was checked to inform vital status and identify causes of death, if unknown. The International Classification of Diseases, 10th version was used to code all causes of death based on the data provided by the National Death Index.

Statistical analysis

Categorical variables are described as percentages (%) and continuous variables as mean ± SD. To avoid confounding related to the distribution of age and sex, we applied the inverse probability weighting method to adjust for age and sex in the description of baseline variables (Table 1). Baseline characteristics of included and excluded participants were evaluated using the Student's *t* test with Welch correction (if variances were not equal) to compare means and the Pearson's χ^2 test to compare proportions.

A joint analysis was conducted to assess the potential interaction (effect modification) between adherence to the MedDiet (≤4 and >4 points) and smoking (never smokers, former smokers, and current smokers) in relation to all-cause mortality. We ran Cox regression analyses to estimate the hazard ratios (HR) of mortality and 95% confidence intervals (CIs). High adherence to the MedDiet and never smokers with were used as the category of reference. In all Cox regression models, age was used as the underlying time variable, and the model was stratified by both calendar date of recruitment and deciles of age. In multivariable model 1, we adjusted for sex, marital status (single, married, other), body mass index (kg/m^2), leisure time physical activity (metabolic equivalent h/wk, quartiles), and total energy intake (kcal/d). In model 2, we additionally adjusted for family history of CVD and prevalent diseases at baseline including diabetes, hypercholesterolemia, hypertension, CVD, cancer, and depression. To assess the potential supra-multiplicative interaction (effect modification) between the MedDiet and smoking status we conducted a likelihood test (2 degrees of freedom) comparing two models, with and without the product term for the MedDiet (2 categories) and smoking (3 categories). An additional joint analysis separately assessed mortality risk among former smokers who quit smoking ≤10 y versus those >10 y since their enrollment in the study.

The proportional hazards assumption was assessed based on Schoenfeld residuals and visual inspection of log–log plots. We identified slight violations for prevalent CVD and prevalent cancer in multivariable model 2 for the analysis of total mortality. We used the "strata" option from Stata to fit stratified Cox regression models according to these two variables.

Based on the method of Fine and Gray [25], we conducted competing-risk regression analyses to assess the association between MedDiet and smoking with cancer, cardiovascular, and other-cause mortality deaths, thus considering other causes of death. We adjusted for the same variables previously used in the main analysis for all-cause mortality.

To assess the robustness of our results, we conducted several sensitivity analyses, always with the outcome of all-cause mortality: excluding participants <40 y of age at recruitment or during follow-up; using the Mediterranean Diet Adherence Score to measure the adherence to the MedDiet instead of the Trichopoulou Mediterranean Diet Score [24]; using percentiles 1 and 99 to select participants with extreme values of total energy intake instead of the previously mentioned predefined limits; excluding participants who died in the first 3 y of follow-up; excluding participants with ≥30 missing items in the FFQ; and excluding participants who referred to have lost ≥5 kg during the 5 y before being recruited for the study.

All statistical analyses were conducted with Stata version 16 (StataCorp, College Station, TX, USA). *P* values were two-tailed and $P < 0.05$ was considered significant.

Results

Supplementary Table 1 shows the baseline characteristics of included and excluded participants in this study. No substantial differences between both groups was observed except that participants excluded were slightly younger and the percentage of men was lower. Table 1 shows the participants' baseline characteristics according to their baseline adherence to the MedDiet and smoking status. Supplementary Table 2 shows the baseline characteristics of participants according to adherence to the MedDiet and

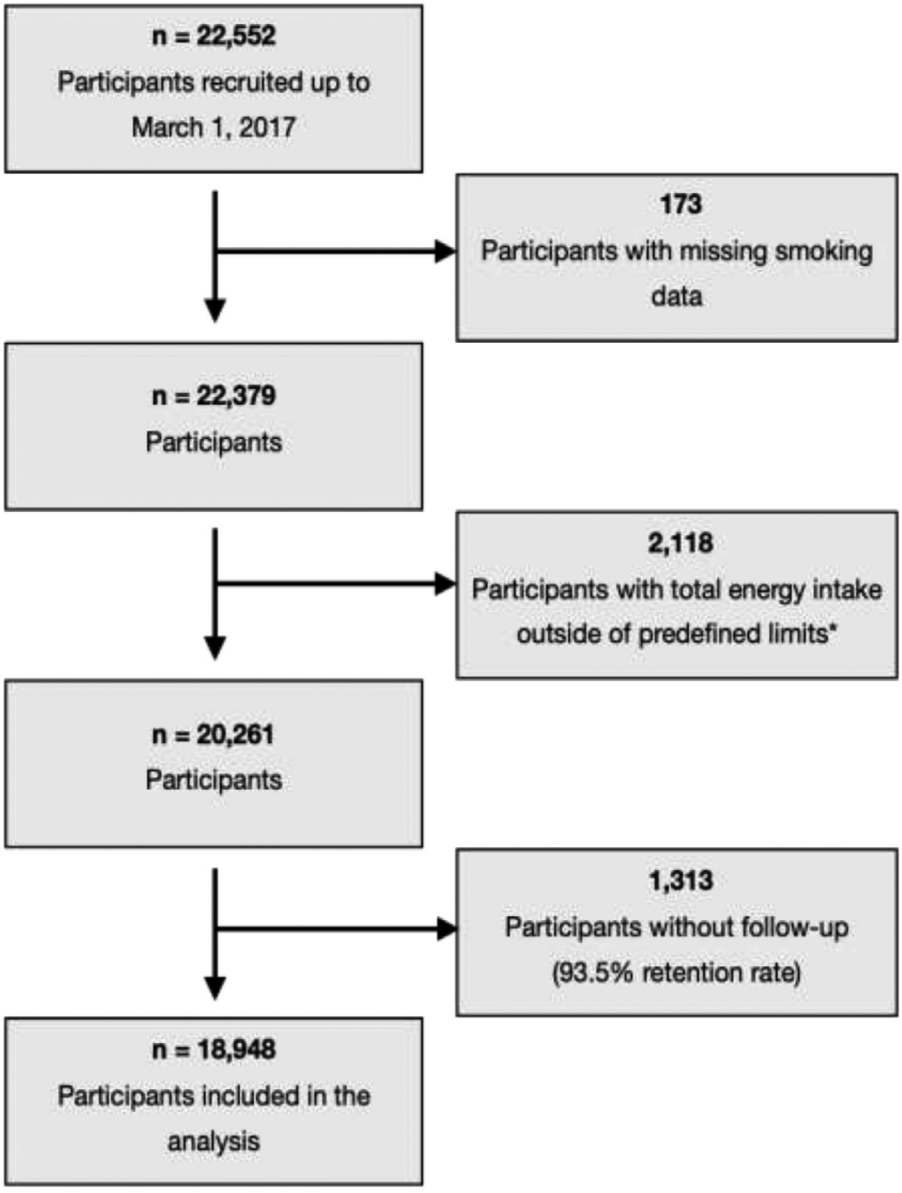

Fig. 1. Flowchart of the eligible participants in the SUN cohort 1999–2017. *<800 kcal/d or >4000 kcal/d in men and <500 kcal/d or >3500 kcal/d in women. Willett W. *Nutritional Epidemiology*. Third edit. New York, NY: Oxford University Press; 2012. Doi:10.1093/acprof:oso/9780199754038.001.0001.

smoking status separately. Among former smokers, a lower percentage of women was found, they were slightly older, and more likely to be married and to have hypertension. Furthermore, participants with adherence to the MedDiet and former smokers presented a higher percentage of former smokers over 10 y, a higher prevalence of family history of CVD, and a higher percentage of hypertension.

Of 18 948 participants, 431 died during a mean of 11.5 y (4.5) of follow-up. The mean age of participants at baseline was 38.4 y and 59.9% were women. Cancer was the leading cause of early mortality with 221 deaths (51.3%), CVD was reported as the cause of 81 deaths (18.8%), and 129 participants died due to other causes (29.9%).

The combined analysis according to the joint exposure to adherence to the MedDiet (≤4 and >4 points in Trichopoulou score) and to smoking status (never, former, and current smoker) is shown in Table 2. The results from multivariable model 2 showed a higher risk for not following the MedDiet (current smokers: HR, 2.20; 95% CI, 1.45–3.34) than following the MedDiet (current smokers: HR, 1.91; 95% CI, 1.26–2.90) compared with participants with high adherence levels to the MedDiet and never smokers (Fig. 2). Nevertheless, the *P* value for supra-multiplicative effect modification between adherence to the MedDiet and tobacco status with total death was not statistically significant ($P = 0.293$). A significant association was also observed for participants with a high MedDiet adherence and former smokers and with low adherence to the MedDiet and former smokers compared to those with high MedDiet adherence and never smokers.

A stronger association was observed among participants with low adherence to the MedDiet and current smokers than those with high MedDiet adherence and current smokers in the competing-risk regression analyses for cancer death. The HR from multivariable model 2 was 2.48 for participants with low MedDiet

Table 1
Age and sex-adjusted baseline characteristics* of participants of the SUN cohort according to smoking status and to Mediterranean diet adherence (1999–2017).

	Smoking status and adherence to MedDiet at baseline					
	Adherence to MedDiet† and never smokers	Adherence to MedDiet and formers	Adherence to MedDiet and smokers	Not adherence to MedDiet and never smokers	Not adherence to MedDiet and formers	Not adherence to MedDiet and smokers
n	3753	2812	1868	5315	2643	2557
Civil status, %						
Single	47.1	35.7	46.4	46.2	37.7	42.9
Married	47.6	58.5	46.4	48.4	56.8	49.4
Other	5.2	5.9	7.2	5.4	5.5	7.7
Postgraduate studies, %	19.7	16.7	14.7	20.1	18.2	17.1
Smoking pack-years (pack-year)	-	10.5 (10.5)	10.9 (12.5)	-	10.5 (11.2)	11.3 (12.1)
Quit smoking, %						
<=10 y	-	45.3	-	-	63.4	-
>10 y	-	52.8	-	-	34.8	-
BMI (kg/m^2)	23.4 (3.4)	23.9 (3.7)	23.6 (3.7)	23.6 (3.8)	23.8 (3.6)	23.6 (3.5)
MedDiet score (0–9 pt)‡	5.9 (1.0)	5.9 (1.0)	5.9 (1.0)	2.9 (1.0)	3.0 (1.0)	3.0 (1.0)
MEDAs	7.1 (1.6)	7.2 (1.6)	6.8 (1.7)	5.3 (1.6)	5.3 (1.6)	5.2 (1.6)
Alcohol (g/d)§	5.8 (8.1)	9.1 (11.1)	10 (11.4)	3.8 (6.7)	6.6 (11.3)	7.9 (12.8)
Total energy intake (kcal/d)	24780 (600)	24029 (597)	2459 (594)	2231 (627)	2207 (607)	2247 (646)
Physical activity (MET-h/w)	26.3 (26.6)	24.4 (24.7)	20.9 (21.2)	19.9 (20.6)	19.3 (20.9)	17.2 (20.0)
Family history of CVD, %	13.8	14.7	14.5	13.2	14.6	13.5
Disease prevalence, %						
HTN	11.2	13.2	11.0	12.9	11.4	9.2
Hypercholesterolemia	6.3	8.6	8.7	5.7	6.9	7.1
CVD	4.2	5.6	4.4	4.6	4.6	4.9
Diabetes mellitus	2.1	2.7	1.9	2.1	2.0	1.4
Cancer	2.4	2.9	2.1	3.1	2.8	2.1
Depression	9.5	12.9	14.1	11.2	12.7	13.5

BMI, body mass index; CVD, cardiovascular disease; HTN, hypertension; MEDAs, Mediterranean Diet Adherence score; MedDiet, Mediterranean diet; MET, metabolic equivalent.
*Means ± SD are shown unless otherwise stated.
†The cut-off point for adherence or non-adherence to the MedDiet was 4.
‡Trichopoulou Mediterranean score including alcohol (nine items).
§Alcohol includes beer and distilled alcohol beverage.

adherence and smokers compared with those with high MedDiet adherence and never smokers (Table 2). No significant associations were observed for cardiovascular or other-cause (non-cancer and non-cardiovascular) deaths.

Supplementary Table 3 shows the association of adherence or non-adherence to the MedDiet and smoking status on premature death, considering the time elapsed since former smokers quit smoking (<=10 y or >10 y). The results from multivariable model 2 suggested a higher risk for all-cause death in former smokers who quit smoking within the past 10 y and who did not follow the MedDiet (HR, 1.90; 95% CI, 1.20–2.99) compared with non-smokers following the MedDiet. A non-significant lower risk was observed for former smokers who quit smoking >10 y ago and were not following the MedDiet (HR, 1.30; 95% CI, 0.85–1.99) compared with never smokers with a high level of adherence to the MedDiet.

Supplementary Table 4 shows the sensitivity analyses of the joint analysis between adherence to the MedDiet and smoking status on all-cause mortality. All analyses showed that the strongest association with all-cause mortality was found among current smokers with low adherence to the MedDiet.

Discussion

Results from this large prospective cohort study suggested that low adherence to the MedDiet may exacerbate the negative health effects of smoking, indicating synergistic multiplicative adverse effects, but with no evidence of any supra-multiplicative effect modification. We observed a stronger risk for death among current smokers with low adherence to the MedDiet than among never smokers with high MedDiet adherence and among current smokers with high adherence to the MedDiet. This adverse effect was higher for the risk for cancer deaths. Additionally, former smokers also had a higher risk for dying prematurely than those who had never smoked, regardless of their adherence to the MedDiet, highlighting that not smoking is always the best choice.

Knopps et al. [26] and Prinelli et al. [27], in their studies about the MedDiet, lifestyle habits, and premature mortality in an elderly European population and an Italian population, respectively, found that adherence to the MedDiet (excluding alcohol), moderate alcohol consumption, high physical activity levels and non-smoking were associated with a lower all-cause mortality after 10 and 20 y of follow-up. Moreover, Knopps et al. [26] also found that these elderly individuals had a lower mortality rate for cancer and CVD. Additionally, Tanaka et al. [28] showed that Japanese women who never smoked or who had a higher quality diet, exhibited lower cancer mortality. These studies, however, did not explore the potential effect modification between diet and smoking on mortality risk.

This increased risk for premature mortality related to non-adherence to the MedDiet and smoking could be due to the fact that a low-quality diet can also activate the inflammatory pathways, oxidative stress, and hormonal changes related to cancer diseases [29,30], meanwhile inhaling smoke derived from tobacco combustion alters cellular DNA and increases inflammation and oxidative stress [29,31].

Surprisingly, we observed a higher risk for all-cause and cancer-related deaths among participants with high adherence to the MedDiet and former smokers than among those with low

Table 2
Cox proportional HRs and 95% CIs for all-cause mortality according to smoking status and adherence to MedDiet.

	Smoking status and adherence of MedDiet at baseline					
	Adherence to MedDiet* and never smokers	Adherence to MedDiet and formers	Adherence to MedDiet and smokers	Not adherence to MedDiet and never smokers	Not adherence to MedDiet and formers	Not adherence to MedDiet and smokers
Total deaths						
Cases/person-y	49/41 373	122/31 855	50/21 096	69/62 562	89/31 094	52/30 573
Crude (95% CI)	1 (Ref.)	1.74 (1.24–2.43)	1.97 (1.32–2.93)	1.44 (0.99–2.10)	1.74 (1.22–2.48)	2.29 (1.54–3.41)
Multivariable Model 1† (95% CI)	1 (Ref.)	1.63 (1.16–2.29)	1.83 (1.23–2.74)	1.34 (0.91–1.95)	1.51 (1.05–2.17)	2.01 (1.34–3.01)
Multivariable Model 2‡ (95% CI)	1 (Ref.)	1.61 (1.13–2.29)	1.91 (1.26–2.90)	1.39 (0.93– 2.07)	1.52 (1.05– 2.22)	2.20 (1.45–3.34)
Cancer deaths§						
Cases/person-y	26/41 373	63/31 855	30/21 096	31/62 562	37/31 094	34/30 573
Crude HZ (95% CI)	1 (Ref.)	1.74 (1.11–2.74)	2.13 (1.26–3.60)	1.24 (0.74–2.10)	1.36 (0.82–2.10)	2.60 (1.56–4.30)
Multivariable Model 1† (95% CI)	1 (Ref.)	1.75 (1.11–2.76)	2.07 (1.22–3.551	1.21 (0.71–2.08)	1.31 (0.78–2.19)	2.45 (1.46–4.41)
Multivariable Model 2‡ (95% CI)	1 (Ref.)	1.66 (1.05–2.63)	2.01 (1.18–3.40)	1.21 (0.70–2.08)	1.28 (0.77–2.15)	2.48 (1.48–4.17)
Cardiovascular deaths§						
Cases/person-y	8/41 373	31/31 855	5/21 096	9/62 562	21/31 094	7/30 573
Crude HR (95% CI)	1 (Ref.)	2.43 (1.11–5.35)	1.14 (0.37–3.51)	1.15 (0.45–2.93)	2.24 (0.99–5.05)	1.89 (0.70–5.09)
Multivariable Model 1† (95% CI)	1 (Ref.)	2.10 (0.95–4.64)	1.00 (0.32–3.08)	0.91 (0.36–2.35)	1.71 (0.75–3.87)	1.52 (0.58–4.00)
Multivariable Model 2‡ (95% CI)	1 (Ref.)	1.89 (0.82–4.34)	0.89 (0.27–2.96)	0.92 (0.34–2.49)	1.64 (0.70–3.85)	1.66 (0.60–4.56)
Other cause deaths§						
Cases/person-y	15/41 373	28/31 855	15/21 096	29/62 562	31/31 094	11/30 573
Crude HZ (95% CI)	1 (Ref.)	1.17 (0.63–2.20)	1.97 (0.99–3.92)	1.87 (1.00–3.49)	1.84 (1.00–3.38)	1.48 (0.67–3.25)
Multivariable Model 1† (95% CI)	1 (Ref.)	1.07 (0.57–2.04)	1.89 (0.95–3.73)	1.77 (0.94–3.33)	1.59 (0.86–2.94)	1.32 (0.59–2.93)
Multivariable Model 2‡ (95% CI)	1 (Ref.)	1.03 (0.54–1.96)	1.87 (0.94–3.72)	1.86 (0.99–3.50)	1.57 (0.84–2.92)	1.41 (0.64–3.15)

BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; HTN, hypertension; MedDiet, Mediterranean diet.
*The cut-off point for adherence or non-adherence to the MedDiet was 4.
†Adjusted for sex, civil status, BMI, physical activity, and total energy intake.
‡Additionally adjusted for family history of CVD, prevalence of diabetes, HTN, hypercholesterolemia, CVD, and cancer.
§Competing-risk regression analyses.

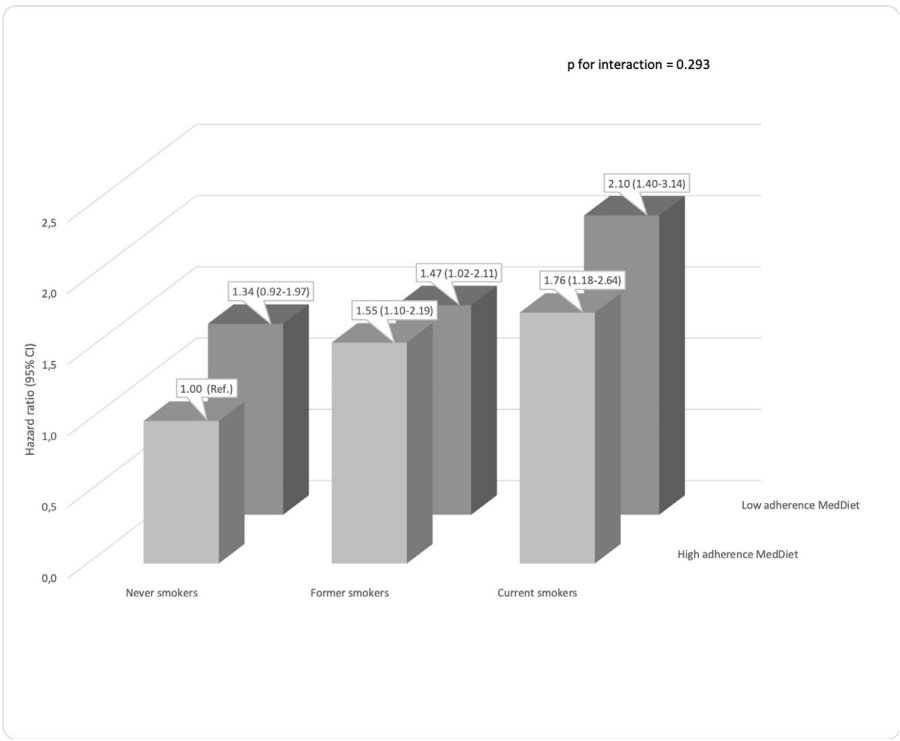

Fig. 2. Joint analysis of smoking and MedDiet and all-cause death risk. Hazard ratios and 95% confidence intervals.

adherence and former smokers compared with participants with high adherence to the MedDiet and non-smokers. In the latter, the associations were weaker or non-significant. A change in diet behavior after smoking cessation could be an explanation; however, further studies are needed to explore this question on a deeper level. In any case, the present study also showed that former smokers, regardless of adherence or non-adherence to the MedDiet, had a higher risk for premature death than non-smokers. This could be explained by the fact that smoking cessation is usually accompanied by weight gain [32,33] of around 2.9 kg at 3 mo and 4.67 kg after 12 mo of abstinence [34]. As shown in the literature, this weight gain during the process of quitting could be explained by increases in energy intake and reduced energy expenditure to cope with nicotine withdrawal [30,35], and the removal of nicotine's effects on the central nervous system, which could also increase weight [32,33].

The systematic review by Farley et al. [34] shows that pharmacologic interventions for smoking cessation are not found to be effective in preventing weight gain. However, behavioral interventions are showing promising results. Specifically, interventions tailored to the individual needs, including weight management education with both feedback on personal goals and a personal energy prescription have shown reduced weight gain at 1 y of smoking cessation, but the estimate of effect was very imprecise covering both substantial benefit and a clinically irrelevant benefit [34,36]. In accordance with this line of thought, smoking cessation interventions should also address the adherence to high-quality diets, such as the MedDiet, to prevent smoking cessation-related weight gain. These interventions would not only reduce the risk for dying prematurely but would also increase the effectiveness of smoking cessation interventions, as weight gain is one of the reasons for relapsing [35]. Moreover, the detrimental effect of weight gain after smoking cessation could be mitigated by a higher adherence to the MedDiet [37–39].

This study had several strengths. It explored the effect modification between the MedDiet and smoking status on mortality risk in a large sample size with long follow-up, and this assessment of effect modification represents a novelty. Additionally, the retention rate was relatively high for a young cohort and the statistical analysis was adjusted for the main confounding factors. Moreover, sensitivity analyses supported the robustness of our findings. Nevertheless, three main limitations in this study need to be acknowledged. First, the external validity of the results might be limited by the fact that all participants in the SUN cohort are university-educated and are not representative of the general population. However, this limitation improves the internal validity of the study because the retention rate is higher, the probability of information bias is lower, and it limits the data to be confounded by educational level. Second, the results were based on self-reported data. This may have led some participants to indicate that they were non-smokers even if they were smokers. Moreover, the methods and tools for the collection of diet as FFQ of the SUN cohort have been validated [19–21]. Finally, some of our analyses can be underpowered because the number of deaths, especially regarding cardiovascular deaths, was—fortunately for our participants—small and the statistical power might be limited. An important reason for this low number of accrued deaths is that this was a young cohort and deaths, particularly cardiovascular deaths, are usually observed in older people. However, it also represents a strength related to the novelty of the young average age of participants in the SUN cohort. Only seldom mortality data have been assessed in such a young cohort.

Conclusion

The present data suggested that no supra-multiplicative effect modification between MedDiet and smoking was observed, although the joint exposure to poor adherence to a MedDiet and smoking exhibited a multiplicative association with a higher risk for all-cause and cancer related mortality in a Spanish population. However, due to the low incidence of cardiovascular death, further research is necessary to better assess the risk for dying from this cause. These data highlight the need to develop policies that promote the acquisition of healthy habits, especially for the two major public health problems of unhealthy diets and smoking. Additionally, to design, implement, and evaluate the effectiveness of a smoking cessation intervention where the smokers also are personally counseled on the MedDiet represents a priority for public health.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.nut.2022.111761.

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