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A Mediterranean lifestyle reduces the risk of cardiovascular disease in the "Seguimiento Universidad de Navarra" (SUN) cohort

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Abstract *Background and aims:* A healthy lifestyle is essential to prevent cardiovascular disease (CVD). However, beyond dietary habits, there is a scarcity of studies comprehensively assessing the typical traditional Mediterranean lifestyle with a multi-dimensional index. We assessed the association between the Mediterranean lifestyle (measured with the MEDLIFE index including diet, physical activity, and other lifestyle factors) and the incidence of CVD.
Methods and results: The "Seguimiento Universidad de Navarra" (SUN) project is a prospective, dynamic and multipurpose cohort of Spanish university graduates. We calculated a MEDLIFE score, composed of 28 items on food consumption, dietary habits, physical activity, rest, social habits, and conviviality, for 18,631 participants by assigning 1 point for each typical Mediterranean lifestyle factor achieved, for a theoretically possible final score ranging from 0 to 28 points. During an average follow-up of 11.5 years, 172 CVD cases (myocardial infarction, stroke or cardiovascular death) were observed. An inverse association between the MEDLIFE score and the risk of primary cardiovascular events was observed, with multivariable-adjusted hazard ratio (HR) = 0.50; (95% confidence interval, 0.31–0.81) for the highest MEDLIFE scores (14–23 points) compared to the lowest scores (0–9 points), p (trend) = 0.004.
Conclusion: A higher level of adherence to the Mediterranean lifestyle was significantly associated with a lower risk of CVD in a Spanish cohort. Public health strategies should promote the Mediterranean lifestyle to preserve cardiovascular health.

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Introduction

Cardiovascular disease (CVD) is the number one cause of death globally. 85% of all deaths caused by CVD are due to cardiac attacks and cardiovascular incidents, meanwhile a third of these deaths occur prematurely in people under the age of 70 years [1]. CVD has a multifactorial etiology, highly influenced by external factors, including dietary habits and other lifestyles. Furthermore, these unhealthy dietary habits have been linked with one third of global causes of mortality [2].

In this context, prevention is key and must be the top priority when addressing CVD. Targeting the behaviors that determine the development of CVD risk factors has proven to be an effective approach for health promotion [3–5]. Several benefits have been directly attributed to the Mediterranean diet, including mortality reduction and a lower CVD incidence [6,7]. The Mediterranean diet is a traditional dietary pattern of the Mediterranean region characterized by olive oil as the main source of fat, a high consumption of plant-derived foods (i.e., fruits, nuts, vegetables, legumes, cereals, and seeds), frequent consumption of fish, moderate wine consumption with meals, and low consumption of meat (mainly poultry), dairy products and sweets [8,9]. In addition, the Mediterranean lifestyle promotes social interactions, local and biodiverse agriculture, and conserves other healthy cultural habits, which have been suggested to further reduce CVD risk to a greater extent than dietary intake alone [5,10].

Most of the studies supporting current recommendations for CVD prevention have assessed single effects of diet, physical activity or other lifestyle habits, considered in isolation [6,7]. Other studies have combined classic risk factors (i.e., tobacco, body mass index (BMI), alcohol, diet, and physical activity) without considering other lifestyle factors [2,5,11]. In this context, evidence on the combined effect of all the elements of a traditional healthy Mediterranean lifestyle, measured according to the recommendations issued by the Fundación Dieta Mediterranea, and its association with CVD risk is needed.

The main purpose of this study was to analyze the effect of a multidimensional index capturing the Mediterranean lifestyle recommendations in a comprehensive manner, as defined by the Mediterranean Diet Foundation, on the incidence of hard CVD events. We evaluated the association between the validated Mediterranean lifestyle (MEDLIFE) index [12] and a composite of hard clinical cardiovascular events, including fatal or non-fatal myocardial infarction, fatal or non-fatal stroke and other cardiac deaths.

Methods

Study population

The Seguimiento Universidad de Navarra (SUN) project is a prospective, dynamic and multipurpose cohort comprised of almost 23,000 Spanish college graduates that began in 1999 with permanently open enrollment. Participants' informed consent was given upon completion of the baseline questionnaire and participation consists of biennial mailed or web-based follow-up questionnaires. The SUN project has been approved by the IRB of the University of Navarra and registered at clinicaltrials.gov (NCT02669602). According to the principles of the Declaration of Helsinki, we informed the potential candidates of their right to refuse to participate in the SUN project or to withdraw their consent to participate at any time without reprisal. Further explanation of this study's objective, design, and methods has been published previously [9].

We excluded those participants who were only recently recruited for the cohort, because they would not be materially able to complete the first 2-year follow-up assessment. Our criteria, taking into account the expected delay in receiving the first 2-year follow-up assessment was to exclude those participants who were recruited less than 2 years and 9 months before the closing of the data base (n = 341) because they would not have had sufficient time as to return the first (2-year) follow-up questionnaire. The mean follow-up time was 11.5 years (SD: 4.5) and the maximum follow-up time was 20 years. We also excluded those lost to follow-up after the initial questionnaire (n = 1888; retention = 91.2%), those with a total energy intake outside of predetermined levels (800–4000 kcal/d men, 500–3500 kcal/d women) [13] (n = 1945) and those with prevalent CVD at baseline (n = 301) (Fig. 1). After exclusions 18,419 participants were included in the final analysis (11,152 females and 7267 males).

Main exposure variable

a. Dietary and lifestyle data collection:

The information collected in the SUN cohort baseline questionnaire contains 554 items. These questions provide information on sociodemographics, lifestyle factors, anthropometrical measures, eating habits, medical history, physical activity habits and frequency of these activities, sports and sedentary activities in their free time [9]. Food intake was collected at baseline with a 136 item semi-quantitative food frequency questionnaire (FFQ) previously administrated and validated in a Spanish population [14,15].

b. The Mediterranean lifestyle (MEDLIFE) index:

The previously reported MEDLIFE index, based on the Mediterranean diet pyramid, is a valid instrument for evaluating adherence to the Mediterranean lifestyle in middle-aged adults [12,16,37]. MEDLIFE was designed as an independent and potentially easy to use tool, which includes the intake of specific foods as well as other traditional Mediterranean lifestyle habits (i.e. preference for water, light wine consumption, minimal snacking, short regular naps, an adequate night's sleep and socializing, among others). With a possible total score of 28 points, it is divided into three groups deduced from the Mediterranean pyramid. Every item provides the same score, 0 or 1 point, for a final categorical range between

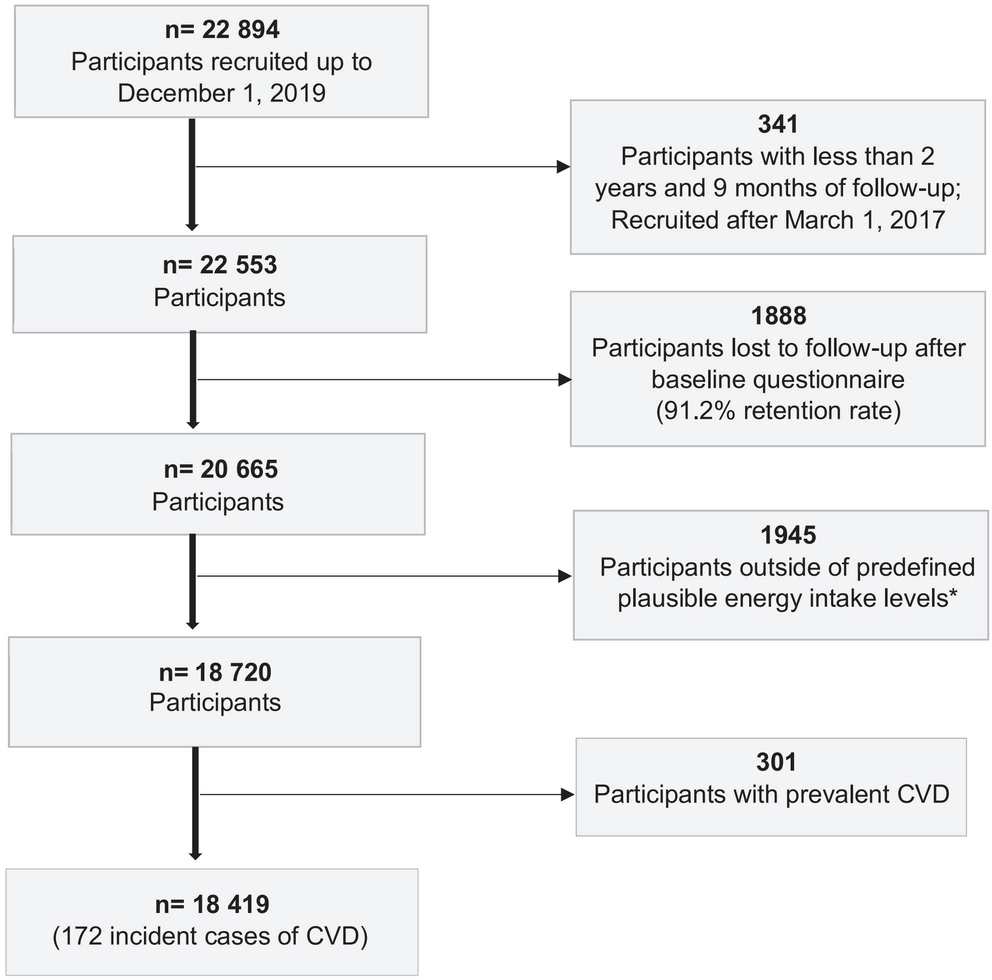

Figure 1 Flowchart depicting the selection of participants in the SUN project (1999–2019) included in the present analyses. CVD: cardiovascular disease [13].

0 (worst) to 28 (best). The first group has fifteen items that gather food intake frequencies. The second group consists of seven items that collect Mediterranean dietary habits. The third group is comprised of six items on physical activity, rest, social habits, and conviviality (Table 1) [12]. The MEDLIFE index has been modified for the SUN cohort in 13 items to best adapt the available data provided by the baseline questionnaire (Table S1).

Outcome assessment: incidence of cardiovascular disease

The primary outcome of the study was incident CVD. CVD events included myocardial infarction, stroke, and CVD death, which were defined according to the following criteria: myocardial infarction was diagnosed using universal criteria [17], whereas non-fatal stroke was defined as a sudden onset focal-neurological deficit with a vascular mechanism that lasted more than 24 h. We requested the participants' clinical records or information from their families in the event that any of these diagnoses were reported in any of the follow-up questionnaires. All reported cases were evaluated and confirmed by an expert medical team that did not have prior knowledge of the participants' lifestyle information. Confirmed events where classified according to the International Classification of Diseases (ICD-10).

Deaths were confirmed by death certificates and medical records sent by next of kin or computerized record linkage to the Spanish National Statistics Institute (www.ine.es). We consider that with both sources of information all deaths were obtained. The date and cause of death were recorded and encoded using ICD-10.

Co-variables evaluation

The baseline questionnaire with a total of 554 items gathered sociodemographic information, dietary intake, lifestyle habits, anthropometric measurements, medical history, and physical activity. Energy intake was calculated using the dietary intake collected with a validated self-administered semi-quantitative 136-item FFQ and distributed into tertiles [18,19]. Anthropometric measurements were previously validated in a cohort subgroup [20]. BMI was calculated by dividing weight by height squared (kg/m^2) and distributed

Table 1 Description of the Mediterranean Lifestyle (MEDLIFE) index modified for the SUN cohort.

Score items	Components (serving size)	Criteria for 1 point
Block 1: Mediterranean food consumption		
1. Sweets	Cookies, chocolate cookies, pastries, donuts, homemade baked goods, store-bought baked goods (50 g), muffins (25–50 g), tea biscuits (90 g), chocolates (30 g), churros (100 g), turrón (35 g)	≤2 servings/wk
2. Red meat	Beef, pork, lamb (100–150 g)	<2 servings/wk
3. Processed meat	Sausage, soft spicy sausage, bacon (50 g), cured ham (60 g), cooked ham (30 g), hamburger (150 g), liver, organ meats (100–150 g), pâté (25 g)	≤1 serving/wk
4. Eggs	Eggs (1 unit)	2-4 servings/wk
5. Legumes	Lentils, beans, chickpeas, peas (60 g uncooked)	≥2 servings/wk
6. White meat	Chicken/turkey with skin, chicken/turkey without skin, rabbit (100–150 g)	2 servings/wk
7. Fish/seafood	White fish, fatty fish, codfish, salted or smoked fish, shrimp, octopus, calamari (100–150 g), oysters and shellfish (6 units)	≥2 servings/wk
8. Potatoes	Baked or boiled potatoes (150 g)	≤3 servings/wk
9. Low-fat dairy products	Skim milk, low-fat milk (200 cc), low fat yogurt (125 g), fresh soft cheese (50 g)	2 servings/d
10. Nuts and olives	Almonds, peanuts, hazelnuts, walnuts (50 g), olives (10 units)	1-2 servings/d
11. Sofrito	Olive oil, pepper, other vegetables (250 g), tomato (150 g)	>2/4 ingredients above the median
12. Fruit	Orange, banana, apple, pear, kiwi, mango, avocado, peach, apricot, nectarine (1 unit), clementine (2 units), strawberry (6 units), cherries, plums, figs, grapes (1 dessert plate), watermelon, melon (200–250 g), dates and dried fruits (150 g)	3-6 servings/d
13. Vegetables	Spinach, cauliflower, broccoli, lettuce, carrot, squash, green beans, eggplant, zucchini, cucumber, pepper, asparagus, gazpacho, garden salad, other vegetables (250 g), tomato (150 g) *(excludes potatoes)*	≥2 servings/d
14. Olive oil	Olive oil (1Tbsp)	≥3 servings/d
15. Cereals	White bread, whole-grain bread (3 slices), white rice, pasta (60 g uncooked), pizza (200 g), breakfast cereal (30 g)	3-6 servings/d
Block 2: Mediterranean dietary habits		
16. Water and coffee	Tap water, bottled water (200 cc), coffee, decaffeinated coffee (50 cc)	≥6 servings/d
17. Wine	Red/white wine (1 glass 100 cc)	women: ≤ 0.5 serving/d men: ≤ 1 serving/d
18. Limit salt at meals	Do you limit salt at meals?	Yes
19. Preference for whole grain products	Do you try to consume a lot of fiber? + fiber from cereals	Yes, > 6 g/d fiber from cereals
20. Snacks	Potato chips (150 g)	<1 serving/wk
21. Limit snacking between meals	Do you tend to snack in between meals?	No
22. Limit sugar in beverages (including sugar-sweetened beverages)	Do you add sugar to some beverages? + sugar-sweetened beverages + bottled juice (200 cc)	No,< 1/wk, < 1/wk
Block 3: Physical activity, rest, social habits, and conviviality		
23. Physical activity	Brisk walking, jogging, running, climbing stairs, bicycling, stationary cycling, swimming, dance, aerobic exercise, martial arts, gymnastics, gardening, tennis, soccer, skiing, ice skating, team sports, and other physical activities or sports	>300 min/wk
24. Nap	Napping throughout the week	Yes, but ≤30 min/d
25. Hours of sleep	Sleeping throughout the week	6–8 h/d
26. Watching TV	Watching TV/videos throughout the week	≤2 h/d
27. Socializing with friends	Socializing throughout the week	>1 h/d
28. Collective sports	Playing soccer, tennis, squash, basketball or other team sports	≥1 h/wk

Abbreviations: min: minutes, h: hours, d: day, wk: week, cc: cubic centimeter, g: grams, Tbsp: tablespoons, TV: television.

into tertiles. Alcohol was incorporated as tertiles of frequency of consumption of beer and distilled beverages. Participants with hypercholesterolemia, hypertension, diabetes, CVD, or cancer were identified if they had a previous diagnosis or treatment with antihypertensive, antidiabetic, or lipid-lowering medications, respectively.

Statistical analysis

To analyze CVD risk according to MEDLIFE adherence, we divided adherence to the MEDLFE index into three categories (low scores from 0 to 9 points, medium scores from 10 to 13 points, and high scores from 14 to 23 points), maintaining a balanced distribution of participants in each category of total MEDLIFE scores. For each participant, follow-up was calculated from the date the baseline questionnaire was returned to the date of CVD events, the last follow-up questionnaire was received, or date of death, whichever came first.

We used Nelson-Aalen curves to describe the incidence of CVD across three categories of MEDLIFE and applied the inverse probability weighting method to control for possible confounding.

We estimated hazard ratios (HR) and their 95% confidence intervals (CI) using Cox regression models, with age as the underlying time variable, for the two higher adherence categories compared to the lowest category as the reference. Linear trends were analyzed by assigning the median of each category of MEDLIFE adherence and including it as a continuous variable in the multivariable models. HRs and 95% CIs for the 28 items and 3 blocks of MEDLIFE were assessed individually, adjusting for all confounding variables and the remaining items or blocks, respectively. The reference category for each item was the absence of the given MEDLIFE item (0 points).

Multivariable adjusted models were stratified by age (decades of age) and calendar year entering the cohort and adjusted for the following confounding factors: sex (male/female), BMI (kg/m^2), total energy intake (kcal/d), special diets (yes/no), alcohol intake, excluding wine (g/d), smoking cigarettes (pack-years), university education (years), family history of cardiovascular disease, prevalent hypercholesterolemia, hypertension, diabetes and cancer (yes/no). A sensitivity analysis was conducted for the exclusion of BMI as a confounding factor and exclusion of participants with family history of CVD, prevalent hypercholesterolemia, hypertension, diabetes or cancer at baseline.

All p values presented are two-tailed; $p < 0.05$ was considered statistically significant. Analyses were performed using STATA 12.0.

Results

Our study population of 18,419 participants was 39.5% male with a mean age (SD) of 38.1 (±12.1). After a mean follow up of 11.5 year (SD: 4.5), a total of 172 (0.9%) incident cases of CVD were confirmed and adjudicated; myocardial infarction (n = 83), stroke (n = 62), CVD death (n = 28). Participants with higher scores exhibited greater total energy intake and greater physical activity. However, they also exhibited a higher frequency of family history of cardiovascular disease, prevalence of hypertension, diabetes and cancer. Other baseline characteristics of participants according to the MEDLIFE categories are presented in Table 2.

The MEDLIFE score showed a significant inverse association with the risk of primary cardiovascular events with multivariable-adjusted hazard ratio [HR] = 0.50 (95% CI: 0.31–0.81) for the highest versus the lowest category (p for trend 0.004). When stratified by the type of cardiovascular events, only myocardial infarction showed a statistically significant decreased risk (HR = 0.48; 95% CI, 0.25–0.92) for the comparison between extreme categories (p for trend 0.025). Furthermore, each additional five point increment in the total MEDLIFE score was significantly associated with a 27% lower risk of incident CVD (HR: 0.73; 95% CI: 0.55–0.96) (Table 3). A sensitivity analysis with the exclusion of BMI as a possible confounder (HR = 0.49; 95% CI: 0.30–0.80) and the exclusion of participants with family history of CVD, prevalent hypercholesterolemia, hypertension, diabetes or cancer at baseline (total n = 12,107) (HR = 0.40; 95% CI: 0.18 to 0.89) further supported the robustness of our findings.

Fig. 2 shows Nelson-Aalen curves for the risk of CVD events according to low scores (0–9 points), medium scores (10–13 points), and high scores (14–23 points) adjusted with inverse probability weighting. The 3 categories of MEDLIFE exhibited a clearly divergent pattern during the follow-up period, showing a strong inverse association: the higher the adherence to MEDLIFE, the lower the risk of CVD.

Fig. 3 shows the multivariable HRs and 95% CI for each block of the MEDLIFE index in association with incident

Table 2 Baseline characteristics of participants according to MEDLIFE scores in the SUN cohort, 1999–2017.

Characteristic	Low score (0–9 pts.)	Medium score (10–13 pts.)	High score (14–23 pts.)
N	2928	9548	5943
Women (%)	57.92	58.36	65.35
Age (years)	36.9 (11.7)	38.3 (12.2)	38.3 (12.2)
BMI (kg/m^2)	23.6 (3.7)	23.7 (3.5)	23.3 (3.3)
Alcohol consumption (g/d)	5.9 (11.1)	6.9 (10.5)	6.5 (8.8)
Total energy intake (kcal/d)	2253 (605)	2319 (613)	2431 (619)
Following special diets (%)	4.37	6.88	12.17
Physical activity (METs-h/week)	12.4 (16.2)	20.1 (21.3)	29.0 (25.9)
Smoking (pack-year)	5.9 (11.0)	5.4 (9.8)	5.0 (9.3)
Years of university	5.0 (1.5)	5.1 (1.5)	5.0 (1.5)
Family history of CVD (%)	13.1	13.5	14.4
Hypercholesterolemia (%)	15.4	18.1	17.6
Hypertension (%)	9.2	10.1	10.5
Diabetes (%)	1.40	1.74	2.17
Cancer (%)	2.15	2.51	2.68

Continuous variables are expressed as mean and standard deviation and categorical variables as percentage, unless otherwise stated.
Abbreviations: BMI: body mass index, CVD: cardiovascular disease, h: hour, kcal: kilocalories, kg: kilograms, m: meter, METs: metabolic equivalent of tasks.

Table 3 Cox proportional hazard ratios (HR) and 95% confidence intervals (CI) for cardiovascular disease according to MEDLIFE scores in the SUN cohort.

All-cause CVD:	Categories of adherence to MEDLIFE			For each 5-point increment	p for trend
	Low score (0–9 pts)	Medium score (10–13 pts)	High score (14–23 pts)		
N	2928	9547	5943	18,418	
Cases	33	100	39	172	
Person-years	34,806	111,577	65,548	211,930	
Crude HR (95% CI)	1 Ref.	0.71 (0.48–1.06)	0.49 (0.31–0.79)	0.73 (0.56–0.95)	0.003
Age and sex adjusted HR (95% CI)	1 Ref.	0.71 (0.48–1.06)	0.50 (0.31–0.80)	0.74 (0.57–0.97)	0.003
Multivariable adjusted HR (95% CI)[a]	1 Ref.	0.73 (0.48–1.10)	0.50 (0.31–0.81)	0.73 (0.55–0.96)	0.004
Fatal or non-fatal myocardial infarction:					
Cases	21	43	19	83	
Multivariable adjusted HR (95% CI)[a]	1 Ref.	0.51 (0.30–0.90)	0.48 (0.25–0.92)	0.78 (0.53–1.17)	0.025
Fatal or non-fatal stroke:					
Cases	7	39	16	62	
Multivariable adjusted HR (95% CI)[a]	1 Ref.	1.33 (0.58–3.05)	0.87 (0.34–2.20)	0.78 (0.49–1.23)	0.593
All Deaths from CVD:					
Cases	5	19	4	28	
Multivariable adjusted HR (95% CI)[a]	1 Ref.	0.81 (0.28–2.39)	0.30 (0.07–1.31)	0.59 (0.27–1.27)	0.106

[a] Adjusted for sex, BMI, total energy intake, special diets, alcohol intake (excluding wine), smoking cigarette pack-years, years of university, family history of cardiovascular disease, prevalent hypercholesterolemia, hypertension, diabetes, and cancer. Stratified by age group and year of recruitment. Age was used as the underlying time variable in all models.

CVD. For the first block assessing Mediterranean food consumption the HR was 0.91 (95% CI: 0.83–0.99). For the second block assessing Mediterranean dietary habits the HR was 0.99 (95% CI: 0.87–1.13) and for the third block including physical activity, rest, social habits and conviviality, the HR was 0.87 (95% CI: 0.74–1.01). Preference for whole grain products and napping for less than 30 min/day were statistically significant factors that showed an association with a decreased risk of CVD after adjusting for possible confounders and the remaining components of the MEDLIFE index (Fig. 3).

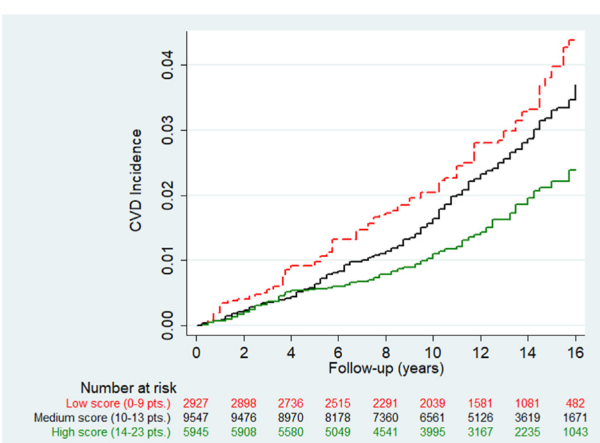

Figure 2 Nelson-Aalen curves adjusted with inverse probability weighting for cumulative CVD incidence according to MEDLIFE scores in the SUN cohort. Adjusted for age, year of recruitment, sex, BMI, total energy intake, special diets, alcohol intake (excluding wine), smoking cigarette pack-years, years of university, family history of cardiovascular disease, prevalent hypercholesterolemia, prevalent hypertension, prevalent diabetes and prevalent cancer.

Discussion

In this Mediterranean population of Spanish university graduates, greater adherence to the Mediterranean lifestyle, unique in its food and dietary habits, physical activity, rest and social habits, was associated with a 50% decrease in CVD risk when compared with individuals with low adherence to the Mediterranean lifestyle. These findings are consistent with existing guidelines for the primary prevention of cardiovascular risk and with previous studies, which support the adoption of a healthy lifestyle, such as the Mediterranean lifestyle, in order to decrease CVD. Numerous studies have confirmed the cardiovascular benefits of interventions directed towards each of these factors, but the combination of a wide array of factors defining the traditional Mediterranean lifestyle in a single multidimensional index is a novel aspect of our study.

Some studies evaluating the concomitant effect of different lifestyle factors [21,6], observed that the decrease in the relative risk of CVD was greater than the sum of the effect of each of these factors separately, suggesting a synergistic effect produced by all these lifestyle factors [22,10,23,24]. Unlike other lifestyle studies, in this study we use a validated Mediterranean lifestyle index. The MEDLIFE index defines the Mediterranean lifestyle comprised of unique items in a single multidimensional index that better reflects an overall way of life, with a total of 28 points divided into three blocks, which specifically evaluates adherence to the recommendations that appear in the Mediterranean Diet Foundation's pyramid [25].

In contrast with other previous indexes that combine a small number of beneficial items [26,27,5,23], we did not include smoking, BMI, hypertension or biochemical parameters (glucose, lipids), focusing exclusively on the

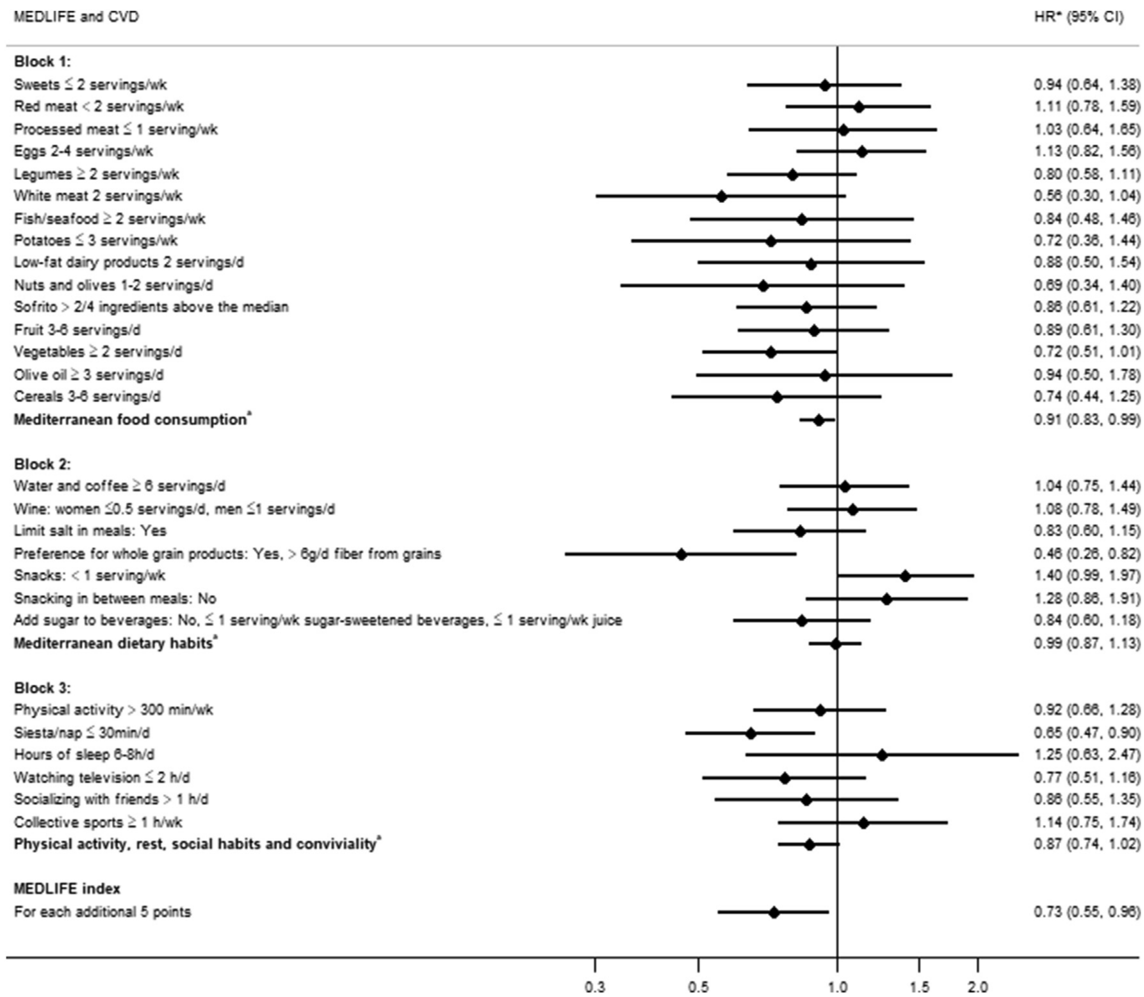

Figure 3 Hazard ratios (HR) and confidence intervals (95% CI) for each of the items and three blocks that define the MEDLIFE index on incident CVD. *Adjusted for sex, BMI, total energy intake, special diets, alcohol intake (excluding wine), smoking cigarette pack-years, years of university, family history of cardiovascular disease, prevalent hypercholesterolemia, prevalent hypertension, prevalent diabetes, prevalent cancer and the remaining MEDLIFE items or blocks, respectively. Age was the underlying time variable and the model was stratified by age group and year of recruitment. The reference category for each item was the absence of the given MEDLIFE item (0 points). [a]Mediterranean food consumption is comprised of block 1 items, Mediterranean dietary habits is comprised of block 2 items, physical activity, rest, social habits, and conviviality is comprised of block 3 items of the MEDLIFE index.

Mediterranean lifestyle defined by a previously issued set of recommendations from an independent body, the Mediterranean Diet Foundation. Despite these omissions, the risk of CVD was significantly reduced among those with higher MEDLIFE adherence in our study population.

Both by frequency and quantity of the food consumed and way of cooking that characterizes the Mediterranean diet, this dietary pattern has amply been proven to have a high nutritional value and beneficial effects for the prevention of different health conditions, including a decrease in CVD incidence, some types of cancer and other chronic diseases [11,28,29]. The cardiovascular health benefits induced by the Mediterranean diet can be attributed to lipid-lowering effects, protection against oxidative stress, and reductions in inflammation and platelet aggregation [30]. The crucial role of physical activity in the prevention of CVD is also well known [31].

The MEDLIFE index combines the classical recommendations with other factors that are not usually included in the cardiovascular risk indexes, such as hours of sleep, time spent watching television, socializing with friends, practicing group sports, or napping. Diet and physical activity are the most frequently recommended lifestyle habits, however our study suggests that other lifestyle factors are also important and must be considered jointly in order to prevent CVD [32].

When the different components of MEDLIFE were analyzed individually, we observed whole-grain food consumption was inversely associated with the risk of CVD [23,30,31]. Evidence suggests whole-grain foods might attenuate the postprandial blood glucose response and may moderate glycemic profiles [32,33,34]. Taking a short nap, less than 30 min, most days of the week was also associated with a lower CVD risk possibly due to the stress-relieving effect of short naps [35], whereas no association was found for avoiding snacks between meals or limiting snacks to less than once a week. In our study the Mediterranean lifestyle showed a clear inverse association with cardiovascular disease, therefore the Mediterranean lifestyle could serve as an additional recommendation, including counseling on an active lifestyle, daily short naps, decreasing television time and increasing time socializing with friends, to the classical preventive measures.

Although each association observed for the MEDLIFE items were not statistically significant, the combined effect of several factors was significant. Previous studies on combined indexes, though they might be less extensive, have shown similar results on cardiovascular risk and mortality [17,18]. Therefore, it is safe to conclude that incorporating individually beneficial lifestyle habits at the same time provides greater benefit. The findings of the present study highlight the combined impact of various healthy lifestyle habits. Even if we did not consider classic cardiovascular risk factors such as blood pressure, cholesterol, triglycerides or glucose, promoting adherence to a greater number of these habits was associated with a decreased risk of cardiovascular events.

Achieving greater adherence to this lifestyle (which means increasing the final MEDLIFE score) is an easy message to transmit to the general population and provides greater autonomy and self-control of their health without depending on other health factors. We believe that it is a simple and accessible population strategy for promoting cardiovascular health [19].

Among the limitations of this study, we must point out that the information is reported by the patient, although all questionnaires: the FFQ questionnaire, the physical activity questionnaire and the outcome event questionnaire have been previously validated [14,33]. As in any study, there could be some degree of measurement errors if some participants overestimated or underestimated their health habits, but in the event that there were any important misclassification, it could be expected to be more likely non-differential, which would shift the estimates towards the null. In addition, the primarily young study population with a high educational level and few risk factors is not generalizable to the general population. The power of the study limited the interpretation of the specific analyses using only myocardial infarction, stroke and CVD deaths, each as a separate outcome.

Adherence to MEDLIFE may provide a more clinically significant preventive effect among the highest risk category. In the other adherence groups, fewer events were observed possibly hindering the statistical power and therefore increasing the likelihood of a type 2 error and limiting statistically significance. The selection of items and the scoring criteria could be debatable; however, MEDLIFE is based on previous recommendations proposed by the Mediterranean Diet Foundation [25] and on the existing evidence on lifestyle factors in the Mediterranean region to establish cut-off points.

Among the strengths of the study we should highlight its prospective design, with a long follow-up period, the large sample size and the high retention rate. On the other hand, the only inclusion criterion in this cohort requires being a university graduate, which reduces the likelihood of confounding by educational level, improves the retention rate and improves the reliability of the self-reported information. All of the preceding characteristics help improve the internal validity of the study. In addition, a significant number of variables have been previously validated, the outcomes were blindly verified and confirmed with the medical records, reducing the potential misclassification of the outcome, and the models were adjusted for a large number of covariates to control for possible confounding.

The Mediterranean diet has proven effective in preventing cardiovascular risk in both the Mediterranean and non-Mediterranean populations [27] and is a current recommendation for the American population [34,35]. In this regard, and taking into account the results of the present study, we believe that other populations should encourage the incorporation of other Mediterranean lifestyle factors in combination with diet to improve CVD incidence [27,36].

Conclusions

A high level of adherence to the Mediterranean lifestyle was significantly associated with a lower risk of CVD. The joint effect of the different factors that make up the Mediterranean lifestyle has shown a possible synergistic effect at lowering cardiovascular risk. Public health strategies should be aimed at promoting the Mediterranean lifestyle to preserve cardiovascular health. Further studies are needed to evaluate the use of MEDLIFE index in different populations as a primordial prevention strategy to reduce CVD.

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Declaration of competing interest

The authors declare that there is no conflict of interest.

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Appendix A. Supplementary data

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