Prospective association between several dietary scores and risk of cardiovascular diseases: Is the Mediterranean diet equally associated to cardiovascular diseases compared to National Nutritional Scores?

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The authors' contributions were as follows – AT, MA, and EKG: designed the research; CJ, LF, PG, MT, SH, PG, EKG: conducted the research; AT: performed statistical analysis and drafted the manuscript; EKG: supervised statistical analysis and the writing; AT, CJ, LF, MT, DC, SH, PG, MA and EKG: contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. EKG had primary responsibility for the final content, she is the guarantor.

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Running title: Association between dietary scores and CVD

Abbreviations:

ACS: Acute Coronary Syndrome

AESA: Energy intake without alcohol

AHEI-2010: Alternative Healthy Eating Index 2010

BMI: Body Mass Index

CepiDC: Epidemiological Center on the medical causes of death

CI: Confidence interval

CU: Consumption unit

CVD: Cardiovascular diseases

HEI-2010: Healthy Eating Index 2010

HR: Hazard Ratio

ICD-10: International Chronic Diseases Classification, 10th Revision, Clinical Modification

INSERM: National Institute for Health and Medical Research

IPAQ: International Physical Activity Questionnaire

MEDI-LITE: Literature-based Adherence score to the Mediterranean Diet

MI: Myocardial infarction

mPNNS-GS: Modified and "penalised" score to the French Programme National Nutrition Santé

PT: Person-time

SNIIRAM: Medico-administrative database of the National Health Insurance

TIA: Transient ischemic attacks

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ABSTRACT

Background: Mediterranean diet has been consistently negatively associated with cardiovascular diseases (CVD) but the superiority compared to official nutritional guidelines has not been tested yet. Our objective was to prospectively investigate the association between several nutritional scores and incidence of cardiovascular diseases.

Methods and findings: A total of 94,113 participants from the NutriNet-Santé cohort were followed between 2009 and 2018. The participants have completed at least three 24h dietary records during the first two-years of follow-up to compute nutritional scores reflecting adherence to the Mediterranean diet (MEDI-LITE), American dietary guidelines (AHEI-2010) and French dietary guidelines (mPNNS-GS). Sex-specific quartiles (Q) of scores were computed. Multivariable Cox proportional hazards models were used to estimate the associations between scores and incidence of CVD, documented using Hazard Ratio (HR) and 95% confidence intervals (95%CI). Thus, 1,399 incident CVD events occurred during the follow-up (mean follow-up=5.4 years). Comparing Q4 versus Q1 quartile, HR for the MEDI-LITE and AHEI-2010 were 0.79 (95% CI: 0.67-0.93, P-trend=0.004) and 0.75 (95% CI: 0.63-0.89, P-trend=0.002) respectively. These associations remained similar when removing early cases of CVD, when analyses were restricted to participants with >6 dietary records and when considering transient ischemic attacks. In this last case, association between CVD's risk and mPNNS-GS become significant.

Conclusions: A better nutritional quality of diet is overall associated with lower risk of CVD. The future version of the PNNS-GS, based on the updated version of the French dietary guidelines, should strengthen the CVD protective effect of French recommendations.

Keywords: dietary scores, nutritional scores, cardiovascular diseases, chronic diseases.

INTRODUCTION

Cardiovascular diseases (CVD) are the first cause of death worldwide leading to one third of the overall mortality [1]. Thus, improving prevention of CVD is a challenge in public health as they are the results of multifactor conditions wherein nutrition plays a predominant role [2–4]. As a modifiable determinant, diet represents a key lever for prevention.

Dietary patterns involved in the reduction of CVD's risks have been extensively studied over the last decades [2,3,5,6]. In particular, the beneficial role of adherence to Mediterranean style diets upon cardiovascular diseases prevention is clearly documented [5–12]. Health benefits of Mediterranean diet was firstly introduced by Ancel Keys in the 1970s and then studied by many researchers in several medical fields including randomized trials. It is characterized by olive oil as primary source of fat and moderate consumption of alcohol. It also includes elevated consumption of fruit, legumes and vegetables, and for some variants, fish consumption [13].

In epidemiological studies, adherence to Mediterranean diet has been assessed by several *a priori* dietary scores. The most common Mediterranean-style dietary scores are the Mediterranean Diet Score, the modified Mediterranean Diet Score, the American Mediterranean Diet Score and the Literature-based Adherence score to the Mediterranean Diet (MEDI-LITE) [14] that differed by the presence or absence of olive oil, the definition of the components and the system for point allocation.

Besides, most of the countries develop and disseminate official nutrition recommendations elaborated to prevent a wide range of chronic diseases [3]**,** which are more or less in coherence with the Mediterranean diet. In France, the Programme National Nutrition Santé guideline score (PNNS-GS) was previously developed to reflect the official French nutritional guidelines [15]. These guidelines are mostly based on the current scientific knowledge about the relationships between diet, nutrition and chronic diseases (in 2001). For this time, it encourages the French population to consume a high proportion of fruits, vegetables and fish, to avoid a high consumption of red meats, cold meats, fats, sugar and salt.

In that context, other dietary scores have been developed to evaluate the adherence to the different recommendations in the population, and then studied in relationships with health outcomes and specifically CVD. For instance, Healthy Eating Index-2010 (HEI-2010) was developed for evaluating the adequacy between population diet and the 2010 Dietary Guidelines for Americans [16]. The Alternative Healthy Eating Index-2010 (AHEI-2010) was then proposed to better account for the association between nutrition and chronic diseases [16]. The AHEI-2010 has previously been associated with the risk of CVD in several studies conducted in a large group of countries (USA, Europe, Japan, Australia, UK, Cuba) [17].

The objective of this study was 1) to prospectively estimate the association between CVD events and the following dietary scores: MEDI-LITE, AHEI-2010 and a modified version (without physical activity) of the PNNS-GS (the mPNNS-GS), in the large prospective web-based NutriNet-Santé cohort and 2) to evaluate potential differences in the predictive value of each score on the risk of CVD.

Thus, this study focused on three specific dietary scores. Firstly, the MEDI-LITE, literature-based, has the advantages of being based on science literature data; being useful and commonly used for research and for clinical evaluation at an individual level; the literature about this score is particularly sound specifically about its relation with CVD; and, because this score uses the typical food groups of the Mediterranean diet (based on population studied by Sofi and al.), this score is useful for many populations. Thereby, this score was chosen as a reference of the study.

Concerning the score HEI, developed to evaluate the adherence of the American population to the American Dietary Guidelines: the AHEI-2010 is the most recent updated version of the HEI score that can be used in the study. The AHEI-2015 has not been used because of the time needed to consider the changes between the 2015 and the 2010 versions to compute correctly the latest data of this cohort. This score is important as it is usually used in the scientific literature. Thus, we used it for comparison purpose.

Finally, the mPNNS-GS is the only score which has been developed to evaluate the adherence to the French food-based dietary guidelines.

METHODS

Study population

The NutriNet-Santé is an observational cohort study launched in May 2009 aiming to evaluate the relationships between nutrition and health status, and to investigate the interaction of sociodemographic factors and nutritional patterns. Inclusion criteria were age above 18 years and access to the Internet. Registration and participation are conducted online using a secured web site (www.etude-NutriNet-sante.fr). The NutriNet-Santé study's aims and methods are described in details elsewhere [18]. The NutriNet-Santé study is conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of the French Institute for Health and Medical Research (IRB Inserm no. 0000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL no. 908450 and no. 909216). Electronic informed consent was obtained from all participants. The NutriNet-Santé study is registered in ClinicalTrials.gov (NCT03335644).

In the present study, we selected participants from the NutriNet-Santé cohort, followed from March 2009 to March 2018, who had completed at least three 24h dietary records during the first two years of follow-up (exposure window), had available complementary data to compute the mPNNS-GS score and had a non-zero follow-up time and with no prevalent CVD at baseline (Figure I). A total of 104,380 participants were eligible for the present study (available and valid dietary data and no under-reporters).

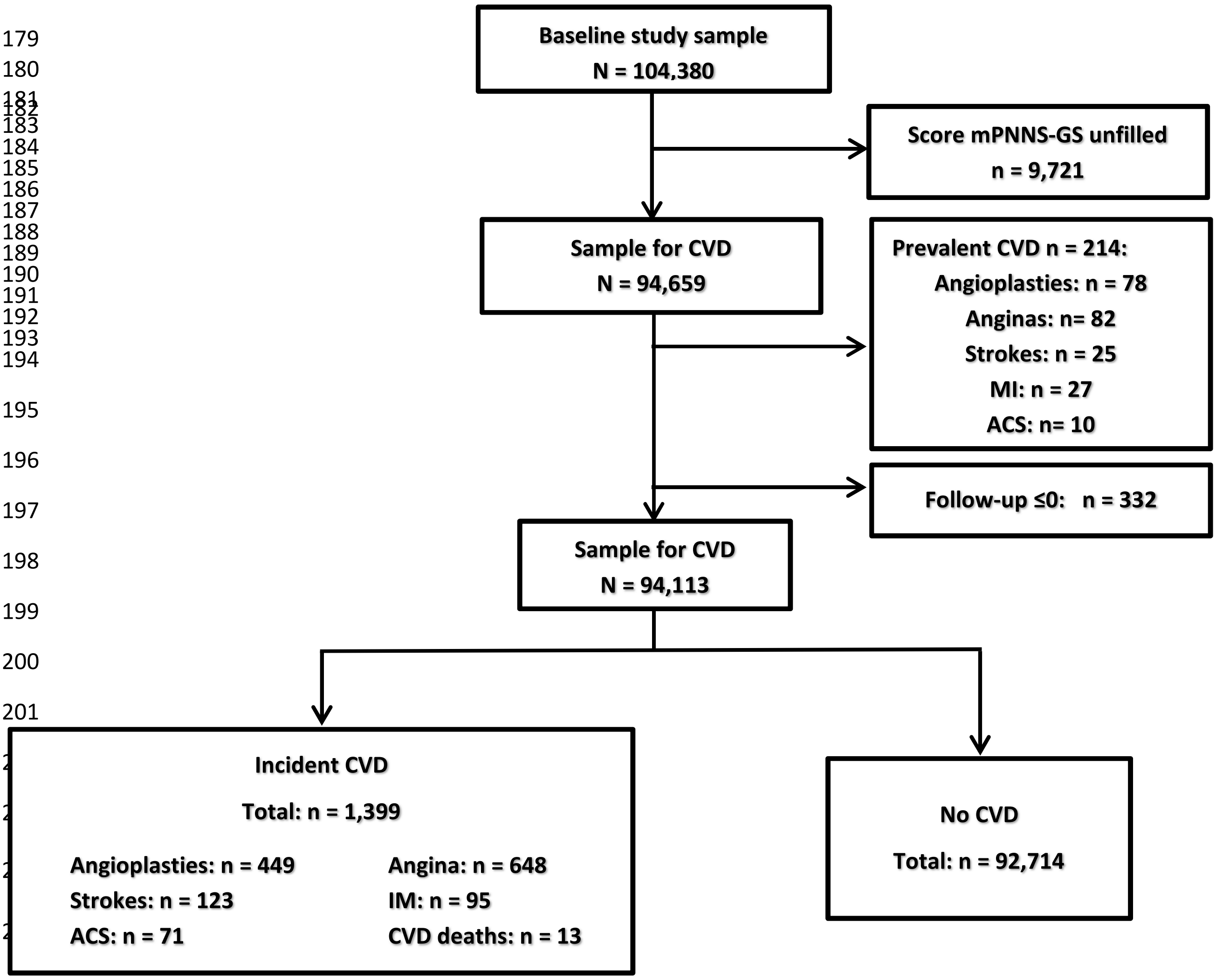

Figure I. Flow chart.

Data collection

Cases ascertainment

Participants self-declared health events at baseline and yearly after, through a health questionnaire or at any time through a specific interface on the study website. They were invited to send their medical records (diagnosis, hospitalization, radiological reports, electrocardiograms, etc.) and, if necessary, the study physicians contacted the participants' treating physician or the medical structures to collect additional information. The medical data were validated for major events (strokes, myocardial infarctions and acute coronary syndromes). Besides, data from our cohort are linked to medico-administrative databases of the National health insurance (SNIIRAM), to limit any potential misclassification. Vital status and causes of death were identified via the National death registry (CepiDC Inserm). CVD cases were classified using the International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10). The present study focused on all validated first events of stroke, myocardial infarction, acute coronary syndrome, as well as angioplasty, angina and deaths caused by CVD.

Sociodemographic, lifestyle and anthropometric data

A set of validated self-administered questionnaires was proposed at baseline to collect sociodemographic information [19], lifestyle characteristics and anthropometrics' data (18,19). In this study, we focused on age, sex, season of recruitment (spring – summer – autumn – winter), educational level (less than a high-school degree – high-school degree – after high-school degree), and baseline occupation (no employment – farmer, merchant, artisan, company director, manual workers – employees – intermediate profession – top manager), cohabiting status (yes/no), smoking status (non-smokers – former smokers – smokers), Body Mass Index (BMI, computed as weight (kg) divided by square height (m^2)), physical activity (International Physical Activity Questionnaire [IPAQ] [20]) and monthly household income (not communicated – 0 to 1,200 € monthly – 1,200 to 1,800 € monthly – 1,800 to 2,700 € monthly – more than 2,700 € monthly). The family history of CVD was also collected in the baseline questionnaire and referred to anginas, myocardial infarctions and strokes. From IPAQ, energy expenditure was categorised as low physical activity (<30 minutes of physical activity; equivalent to brisk walking / day), moderate physical activity (≥30 and <60 minutes) or high physical activity (≥60 minutes). Monthly household income was estimated per consumption unit according to a weighting system where one consumption unit (CU) is attributed for the first adult in the household, 0.5 CU for other persons aged 14 or older, and 0.3 CU for children under 14 [21].

Dietary data

Participants were invited to biannually complete three self-administrated non-consecutive validated 24h dietary records randomly distributed between week and weekend days (2 weekdays and 1 weekend day). Participants reported all foods and beverages consumed (type and quantity) at each meal (breakfast, lunch, dinner or others). Portion sizes were assessed by photographs (3 photographs of small portions, 2 intermediate and 2 extreme portions, thus reflecting 7 portions sizes [22]), or by grams or volume. Composite dishes recipes were validated by nutrition professionals. Nutrients intakes were calculated using a composition database [23]. Energy under-reporters were identified through the method proposed by Black, using the basal metabolic rate and Goldberg cut-off. Under-reporters (about 20%) were excluded [24]. The dietary scores have been computed using dietary data collected before the start of the follow-up for all participants (2009-2014). The mean of the repeated measures of diet over a two years period have been considered as usual diet.

Dietary scores

This study focused on the Literature-based Adherence score to the Mediterranean Diet (MEDI-LITE), the Alternative Healthy Eating Index-2010 (AHEI-2010) and the modified and “penalised” Programme National Nutrition Santé guideline score (mPNNS-GS).

The MEDI-LITE, ranging from 0 (less healthy) to 18 (most healthy), includes 9 components focusing on consumption of fruit, vegetables, whole grains, nuts and legumes, olive oil (positive points), dairy, red and processed meat (negative points), and alcohol (points according to consumption) [14]. Points are allocated according to a scoring system based on daily or weekly consumption.

The food-based mPNNS-GS, ranging from negative scores (less healthy) to 13.5 (most healthy), includes 12 components reflecting the consumption of fruit and vegetables, starches, whole grains, dairy products, meat and eggs, fish and seafood, alcohol, lipids level on added fat, added fat, sodium, added sugar and sweetened beverages. A penalty of participants with overconsumption was applied as follows: if total energy intake exceeds 105% of the calculated needs, the score is reduced by the same percentage by which energy needs are exceeded [15,25].

The AHEI-2010, ranging from 0 (less healthy) to 90 (most healthy), includes 10 components focusing on consumption of fruit, vegetables, nuts and legumes, whole grains, red and processed meat, long-chain fats, PUFA, sugar-sweetened beverages and fruit juice, sodium and alcohol [26]. Trans-fatty acids were not available in the composition Table and thus not considered.

The scores considered haven't been normalized by the overall caloric intake, but adjusted on the caloric intake in the model.

More details about scores computation are described in Supplemental Table I.

Statistical analyses

A total of 9,721 participants were excluded due to missing values on specific non-dietary data that prevented the calculation of the mPNNS-GS score. Then 214 participants were excluded for having declared a cardiovascular disease before the beginning of the study (78 angioplasties, 82 anginas, 25 strokes, 27 myocardial infarctions and 10 acute coronary syndromes), and 332 were excluded due to lack of follow-up (after the dietary exposure window). Therefore, the final sample included 94,113 participants.

For all covariates, less than 5% of values were missing and were replaced by multivariable imputation using the hot deck method [27]. Quartiles of each dietary score were computed by sex.

Included and excluded participants were compared using Chi^2 test or ANOVA.

Characteristics across quartiles were presented as mean and standard deviation (SD) or N (%). P-values referred to linear contrast or Chi^2 tests.

Hazard ratios (HR) and 95% confidence intervals (CI) were obtained from Cox proportional hazards model using age as time-scale to estimate the association between dietary scores and risk of CVD (overall and by subtype). Participants contributed person-time (PT) until the date of diagnostic of the first cardiovascular event, the date of death, the date of the last completed questionnaire, or March 31st 2018, whichever occurred first. For subtype analyses, other CVD cases were censored at the date of diagnosis. Associations were estimated across sex-specific quartiles (Q) of each score (with the 1st quartile as reference category) and for continuous standardized scores for comparison purpose.

Log-log (survival) versus log-time plots were used to confirm risk proportionality assumptions. Multivariable Cox proportional hazards model were adjusted for age (time-scale), sex, cohabiting status, occupation, educational level, monthly household income, smoking status, physical activity, alcohol consumption, number of 24h dietary records, season of recruitment, Body Mass Index and family history of CVD. Tests for linear trend were performed using the ordinal score on sex-specific quartiles of each score. We tested linearity of the association between CVD' risk and the three scores by the restricted cubic splines (RCS) functions using the SAS® macro written by Desquilbet and Mariotti [28], with the cut off percentiles method described by Harrell [29].

The Harrell C-index has been used to estimate the predictive values of the scores. The C-index is a measure of the probability that a patient who experiences an event was detected by the model as having a high risk of experience the event (more precisely, a higher risk than a patient who had not experienced the event). This statistic measures the discriminating capacity of the model, i.e. "is the model able to rank correctly the patients at risk or not at risk of disease?" The value of the C-statistic is informative compared to the value of 0.5 but doesn't permit to compare the scores amongst themselves as the models are not nested.

To test for robustness, sensitivity analyses were conducted. The data were rerun after 1) removing incident cases occurring during the two first years of the study, 2) adding transient ischemic attacks (TIA) events to outcome CVD and 3) removing persons completing less than 6 24h dietary records. 4) subdividing the principal outcome in three subgroups: 'softer events' only including angina, 'medium events' including acute coronary syndrome and angioplasty, and 'harder events' including myocardial infarction, stroke and CVD death.

All tests were two sided and $p < 0.05$ was considered statistically significant. SAS® version 9.4 (SAS® Institute) was used for the analyses.

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	All	Q1	Q2	Q3	Q4

Researchers were independent from funders. Funders had no role in the study design, the collection, analysis, and interpretation of data, the writing of the report, and the decision to submit the article for publication.

RESULTS

Compared to included participants, those excluded had a less healthy diet (mean mPNNS-GS: excluded=8.72 and included=9.61, p<0.0001) and were younger (mean age: excluded=43.88 and included=40.69, p<0.0001). They were also more often men, part of a lower social class, more often smokers, more physically active and completed fewer dietary records (all p<0.05).

Overall, 1,399 CVD events were recorded during a mean follow-up of 5.4 years (SD=2.5) (510,603 persons-years): 449 angioplasties, 648 anginas, 123 strokes, 95 myocardial infarctions, 71 acute coronary syndromes, 13 cardiovascular deaths. Mean number of dietary records was 6.2 (SD=2.8) per individual.

Characteristics of the participants across quartiles of MEDI-LITE are presented in Table I. In this study, there was a large proportion of women (78.6%). Compared to participants with a low MEDI-LITE (Q1), participants with a high MEDI-LITE (Q4) were older, less frequently smokers (and more former smokers), less physically active, had a lower BMI and a higher energy intake. They also exhibited more often family history of CVD (all P values < 0.005).

Table I

Baseline characteristics of the study population overall and according to sex-specific quartiles of the MEDI-LITE, NutriNet-Santé Cohort, France, 2009–2018.

	(n=94,113)	(n=21,916)	(n=23,678)	(n=24,277)	(n=24,242)	P*
	N (%) or mean± SD	N (%) or mean ± SD	N (%) or mean ± SD	N (%) or mean± SD	N (%) or mean± SD	
MEDI-LITE †	9.61 ± 2.77	5.92 ± 1.16	8.53 ± 0.50	10.47 ± 0.50	13.14 ± 1.22	
Sex						<0.0001
Men	20,174 (21.44)	4,712 (21.50)	4,810 (20.31)	5,099 (21.00)	5,553 (22.91)	
Women	73,939 (78.56)	17,204 (78.50)	18,868 (79.69)	19,178 (79.00)	18,689 (77.09)	
Age	43.88 ± 14.63	38.95 ± 13.95	42.57 ± 14.51	45.48 ± 14.43	48.01 ± 14.08	<0.0001
Season of recruitment						<0.0001
Spring	16,113 (17.12)	3,508 (16.01)	3,985 (16.83)	4,138 (17.04)	4,482 (18.49)	
Summer	51,868 (55.11)	12,740 (58.13)	13,220 (55.83)	13,349 (54.99)	12,559 (51.81)	
Autumn	11,787 (12.52)	2,247 (10.25)	2,871 (12.13)	3,208 (13.21)	3,461 (14.28)	
Winter	14,345 (15.24)	3,421 (15.61)	3,602 (15.21)	3,582 (14.75)	3,740 (15.43)	
Educational level						<0.0001
< High-school degree	17,519 (18.61)	4,787 (21.84)	4,475 (18.90)	4,336 (17.86)	3,921 (16.17)	
High-school degree	16,078 (17.08)	4,722 (21.55)	4,154 (17.54)	3,811 (15.70)	3,391 (13.99)	
After High-school degree	60,516 (64.30)	12,407 (56.61)	15,049 (63.56)	16,130 (66.44)	16,930 (69.84)	
Occupation						<0.0001
No employement	4,979 (5.29)	1,772 (8.09)	1,368 (5.78)	1,039 (4.28)	800 (3.30)	
Farmer, merchant, artisan, company director, manual workers	5,518 (5.86)	1,561 (7.12)	1,402 (5.92)	1,312 (5.40)	1,243 (5.13)	
Employes	27,235 (28.94)	8,157 (37.22)	7,227 (30.52)	6,427 (26.47)	5,424 (22.37)	
Intermediate profession	25,007 (26.57)	5,061 (23.09)	6,238 (26.35)	6,766 (27.87)	6,942 (28.64)	
Top manager	31,374 (33.34)	5,365 (24.48)	7,443 (31.43)	8,733 (35.97)	9,833 (40.56)	
Monthly household income						<0.0001
Not communicated	11,077 (11.77)	3,022 (13.79)	2,745 (11.59)	2,777 (11.44)	2,533 (10.45)	
From 0 to 1,200 € monthly	15,716 (16.70)	5,139 (23.45)	4,157 (17.56)	3,531 (14.54)	2,889 (11.92)	
From 1,200 to 1,800 € monthly	23,043 (24.48)	5,949 (27.14)	6,100 (25.76)	5,792 (23.86)	5,202 (21.46)	
From 1,800 to 2,700 € monthly	21,949 (23.32)	4,430 (20.21)	5,500 (23.23)	5,923 (24.40)	6,096 (25.15)	
More than 2,700 € monthly	22,328 (23.72)	3,376 (15.40)	5,176 (21.86)	6,254 (25.76)	7,522 (31.03)	
Couple						<0.0001
No	26,959 (28.65)	6,808 (31.06)	6,786 (28.66)	6,677 (27.50)	6,688 (27.59)	
Yes	67,154 (71.35)	15,108 (68.94)	16,892 (71.34)	17,600 (72.50)	17,554 (72.41)	
Smoking status						<0.0001
Non-smokers	47,211 (50.16)	11,016 (50.26)	11,976 (50.58)	12,125 (49.94)	12,094 (49.89)	
Former smokers	31,866 (33.86)	6,270 (28.61)	7,686 (32.46)	8,608 (35.46)	9,302 (38.37)	
Smokers	15,036 (15.98)	4,630 (21.13)	4,016 (16.96)	3,544 (14.60)	2,846 (11.74)	
Physical activity						<0.0001
Low	31,063 (33.01)	6,584 (30.04)	7447 (31.45)	8159 (33.61)	8873 (36.60)	
Moderate	40,538 (43.07)	8,975 (40.95)	10,112 (42.71)	10,601 (43.67)	10,850 (44.76)	
High	22,512 (23.92)	6,357 (29.01)	6,119 (25.84)	5,517 (22.73)	4,519 (18.64)	
Body Mass Index, kg/m²	23.84 ± 4.57	24.49 ± 5.06	24.12 ± 4.74	23.76 ± 4.45	23.05 ± 3.88	0.003
Energy intake without alcohol, kcal/d	1,809.37 ± 454.91	1,743.81 ± 481.98	1,782.98 ± 459.68	1,816.56 ± 445.13	1,887.23 ± 421.82	0.0005
Alcool intake, g/d	7.80 ± 11.52	8.04 ± 14.25	7.85 ± 11.83	7.72 ± 10.68	7.62 ± 8.96	0.2
Number of 24 h record	6.20 ± 2.84	5.36 ± 2.65	6.04 ± 2.81	6.49 ± 2.83	6.81 ± 2.84	<.0001
Family history of cardiovascular diseases						<0.0001
No	66,481 (70.64)	16,575 (75.63)	16,984 (71.73)	16,855 (69.43)	16,067 (66.28)	
Yes	27,632 (29.36)	5,341 (24.37)	6,694 (28.27)	7,422 (30.57)	8,175 (33.72)	
Family history of diabetes						0.3
No	92,509 (98.30)	21,570 (98.42)	23,231 (98.11)	23,821 (98.12)	23,887 (98.54)	
Yes	1604 (1.70)	346 (1.58)	447 (1.89)	456 (1.88)	355 (1.46)	
Family history of hypertension						<0.0001
No	85,988 (91.37)	20,296 (92.61)	21,655 (91.46)	21,967 (90.48)	22,070 (91.04)	
Yes	8,125 (8.63)	1,620 (7.39)	2,023 (8.54)	2,310 (9.52)	2,172 (8.96)	

[*] P value for the comparison between quartiles of MEDI-LITE, by tests from Mantel-Henzel Chi² for dichotomises or ordinals variables, Chi² for others categorical variables and generalized linear models with linear contrast for numeric variables.
[†] Sex-specific cut-offs for quartiles of MEDI-LITE were 8.00/10.00/12.00 for women and 8.00/10.00/12.00 for men.

By construction, a higher MEDI-LITE was associated with healthier dietary profiles: a regular use of olive oil, a major consumption of fruit, vegetables, legumes, grain group, fish and seafood, and a moderate to low consumption of meat, dairy products and alcohol.

The association between MEDI-LITE, mPNNS-GS and AHEI-2010 and risk of CVD are presented in Table II.

Table II

Multivariable[*] associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or sex-specific quartiles of MEDI-LITE[†], mPNNS-GS[‡] and AHEI-2010[§] and risk of cardiovascular disease, NutriNet-Santé Cohort, France, 2009–2018.

	Continuous score		Sex-specific quartiles				
Diseases	All	P-value[‖]	Q1	Q2	Q3	Q4	P-trend
MEDI-LITE							
N for cases / non-cases	1,399 / 92,714		273 / 21,643	339 / 23,339	368 / 23,909	419 / 23,823	
HR (95%CI)	0.92 (0.87-0.98)	0.008	1.00 (-)	0.87 (0.74-1.02)	0.77 (0.66-0.91)	0.79 (0.67-0.93)	0.004

mPNNS-GS							
N for cases / non-cases	1,399 / 92,714		236 / 24,126	285 / 22,183	387 / 23,319	491 / 23,086	
HR (95%CI)	0.95 (0.89-1.01)	0.09	1.00 (-)	0.94 (0.79-1.12)	0.91 (0.77-1.08)	0.91 (0.77-1.08)	0.3
AHEI-2010							
N for cases / non-cases	1,399 / 92,714		237 / 23,290	324 / 23,205	417 / 23,112	421 / 23,107	
HR (95%CI)	0.91 (0.85-0.97)	0.002	1.00 (-)	0.87 (0.73-1.03)	0.86 (0.73-1.02)	0.75 (0.63-0.89)	0.002

[*] Models were adjusted for age (time-scale), sex, BMI (kg/m2, continuous), physical activity (high, moderate, low), smoking status (never smokers, former smokers, smokers), numbers of dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of cardiovascular diseases (yes/no), educational level (≤ high-school degree and/ high-school degree/ 2 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual workers/employees/intermediate profession/top manager), monthly household income (not communicated / <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly), cohabiting status (yes/no) and season of recruitment (spring, summer, fall, winter).

[†] Sex-specific cut-offs for quartiles of MEDI-LITE were 8.00/10.00/12.00 for women and 8.00/10.00/12.00 for men.

[‡] Sex-specific cut-offs for quartiles of mPNNS-GS were 6.80/8.00/9.05 for women and 6.75/7.80/9.00 for men.

[§] Sex-specific cut-offs for quartiles of AHEI-2010 were 38.45/47.11/56.09 for women and 35.74/44.60/53.88 for men.

[||] P-value for the continuous score.

A higher MEDI-LITE was associated with a lower CVD's risk (HR Q4 vs.Q1=0.79 (0.67-0.93), P-trend=0.004). Similarly, the AHEI-2010 was also associated with a lower CVD' risk (HR Q4 vs.Q1=0.75 (0.63-0.89), P-trend=0.002).

The mPNNS-GS was associated with a trend to a lower CVD' risk but was not statistically significant (HR Q4 vs. Q1=0.91 (0.77-1.08), P-trend=0.31).

The associations between MEDI-LITE and subtypes of CVD are presented in Supplemental Table IV. Similar results were obtained when cases where restricted to angioplasty (HR Q4 vs. Q1=0.69 (0.52-0.92), P-trend=0.02) and angina (HR Q4 vs Q1=0.81 (0.64-1.03), P-trend=0.06). The association between MEDI-LITE and myocardial infarction (HR Q4 vs Q1=0.70 (0.35-1.39), P-trend=0.22), acute coronary syndrome (HR Q4 vs Q1=1.62 (0.76-3.42), P-trend=0.081), stroke (HR Q4 vs Q1=0.68 (0.39-1.18), P-trend=0.13) or death (HR Q4 vs Q1=0.14 (0.01-1.49), P-trend=0.16) were not significant, albeit the associations exhibited a similar trend.

The sensitivity analyses conducting by removing early cases of CVD during the first 2 years of follow-up and by removing persons who had answered less than 6 dietary records provided similar results. When considering TIA events as CVD outcome, the association between mPNNS-GS and CVD become significant (HRQ4 vs Q1=0.83 (0.72-0.95), p=0.02) (Tables III, IV, V).

Table III

Multivariable[*] associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or sex-specific quartiles of MEDI-LITE[†], mPNNS-GS[‡] and AHEI-2010[§] and cardiovascular diseases risk after removed events appeared after 2 years of follow-up, NutriNet-Santé Cohort, France, 2009–2018.

Scores	Continuous score		Sex-specific quartiles				
	All	P-value[||]	Q1	Q2	Q3	Q4	P-trend
MEDI-LITE							
N for cases / non-cases	952 / 81,954		179 / 17,997	218 / 20,538	256 / 21,556	299 / 21,863	
HR (95%CI)	0.92 (0.85-0.98)	0.01	1.00 (-)	0.83 (0.68-1.01)	0.77 (0.63-0.94)	0.79 (0.64-0.97)	0.04
mPNNS-GS							
N for cases / non-cases	952 / 81,954		151 / 20,449	210 / 19,421	264 / 20,969	327 / 21,115	
HR (95%CI)	0.93 (0.86-1.00)	0.06	1.00 (-)	1.07 (0.86-1.32)	0.96 (0.78-1.18)	0.92 (0.75-1.14)	0.20
AHEI-2010							
N for cases / non-cases	952 / 81,954		151 / 19,476	228 / 20,515	278 / 20,872	295 / 21,091	
HR (95%CI)	0.90 (0.83-0.97)	0.004	1.00 (-)	0.93 (0.75-1.15)	0.87 (0.70-1.07)	0.78 (0.63-0.97)	0.01

[*] Models were adjusted for age (time-scale), sex, BMI (kg/m2, continuous), physical activity (high, moderate, low), smoking status (never smokers, former smokers, smokers), numbers of dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of cardiovascular diseases (yes/no), educational level (≤ high-school degree and/ high-school degree/ 2 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual workers/employees/intermediate profession/top manager), monthly household income (not communicated / <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly), cohabiting status (yes/no) and season of recruitment (spring, summer, fall, winter).

[†] Sex-specific cut-offs for quartiles of MEDI-LITE were 8.00/10.00/12.00 for women and 8.00/10.00/12.00 for men.

[‡] Sex-specific cut-offs for quartiles of mPNNS-GS were 6.80/8.05/9.30 for women and 6.80/7.80/9.00 for men.

[§] Sex-specific cut-offs for quartiles of AHEI-2010 were 38.45/47.11/56.09 for women and 35.74/44.60/53.88 for men.

[||] P-value for the continuous score.

Table IV

Multivariable[*] associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or sex-specific quartiles of MEDI-LITE[†], mPNNS-GS[‡] and AHEI-2010[§] and cardiovascular disease risk, after considered TIA events in CVD outcome, NutriNet-Santé Cohort, France, 2009–2018.

Scores	Continuous score		Sex-specific quartiles				P-trend
	All	P-value[||]	Q1	Q2	Q3	Q4	
MEDI-LITE							
N for cases / non-cases	2,094 / 91,941		399/21,496	482/23,176	556/23,702	657/23,567	

HR (95%CI)	0.93 (0.89-0.98)	0.0064	1.00 (-)	0.84 (0.73-0.96)	0.79 (0.69-0.90)	0.83 (0.72-0.95)	0.01
mPNNS-GS							
N for cases / non-cases	2,094 / 91,941		377/23,966	416/22,040	573/23,110	728/22,825	
HR (95%CI)	0.93 (0.88-0.98)	0.0048	1.00 (-)	0.85 (0.74-0.98)	0.84 (0.73-0.96)	0.83 (0.72-0.95)	0.02
AHEI-2010							
N for cases / non-cases	2,094 / 91,941		352/23,163	467/23,045	624/22,874	651/22,859	
HR (95%CI)	0.92 (0.87-0.96)	0.0008	1.00 (-)	0.82 (0.71-0.95)	0.84 (0.73-0.97)	0.75 (0.65-0.86)	0.0003

* Models were adjusted for age (time-scale), sex, BMI (kg/m2, continuous), physical activity (high, moderate, low), smoking status (never smokers, former smokers, smokers), numbers of dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of cardiovascular diseases (yes/no), educational level (≤ high-school degree and/ high-school degree/ 2 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual workers/employees/intermediate profession/top manager), monthly household income (not communicated / <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly), cohabiting status (yes/no) and season of completion of recruitment (spring, summer, fall, winter).

† Sex-specific cut-offs for quartiles of MEDI-LITE were 8.00/10.00/12.00 for women and 8.00/10.00/12.00 for men.

‡ Sex-specific cut-offs for quartiles of mPNNS-GS were 6.80/8.00/9.05 for women and 6.75/7.80/9.00 for men.

§ Sex-specific cut-offs for quartiles of AHEI-2010 were 38.45/47.11/56.09 for women and 35.74/44.60/53.88 for men.

|| P-value for the continuous score.

Table V

Multivariable* associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or sex-specific quartiles of MEDI-LITE†, mPNNS-GS‡ and AHEI-2010§ and cardiovascular disease risk, after removed persons answered less than 6 dietary questionnaires, NutriNet-Santé Cohort, France, 2009–2018.

	Continuous score		Sex-specific quartiles				P-trend
Scores	All	P-value||	Q1	Q2	Q3	Q4	
MEDI-LITE							
N for cases / non-cases	1,136 / 53,668		191 / 9,550	268 / 12,919	307 / 15,061	370 / 16,138	
HR (95%CI)	0.94 (0.88-1.00)	0.056	1.00 (-)	0.860 (0.71-1.04)	0.750 (0.63-0.91)	0.780 (0.65-0.94)	0.009
mPNNS-GS							
N for cases / non-cases	1,136 / 53,668		157 / 11,447	234 / 12,303	326 / 14,430	419 / 15,488	

HR (95%CI)	0.96 (0.89-1.02)	0.204	1.00 (-)	1.070 (0.87-1.31)	1.000 (0.82-1.22)	0.980 (0.80-1.19)	0.5
AHEI-2010							
N for cases / non-cases	1,136 / 53,668		156 / 10,354	265 / 13,231	351 / 14,692	364 / 15,391	
HR (95%CI)	0.91 (0.85-0.98)	0.0078	1.00 (-)	0.930 (0.76-1.14)	0.900 (0.74-1.10)	0.780 (0.63-0.95)	0.007

[*] Models were adjusted for age (time-scale), sex, BMI (kg/m2, continuous), physical activity (high, moderate, low), smoking status (never smokers, former smokers, occasional or permanent smokers), numbers of dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of cardiovascular diseases (yes/no), educational level (≤ high-school degree and/ high-school degree/ 2 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual workers/employees/intermediate profession/top manager), monthly household income (not communicated / <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly), cohabiting status (yes/no) and season of completion of recruitment (spring, summer, fall, winter).

[†] Sex-specific cut-offs for quartiles of MEDI-LITE were 8.00/10.00/12.00 for women and 8.00/10.00/12.00 for men.

[‡] Sex-specific cut-offs for quartiles of mPNNS-GS were 6.80/8.05/9.30 for women and 6.80/7.80/9.00 for men.

[§] Sex-specific cut-offs for quartiles of AHEI-2010 were 38.95/47.55/56.41 for women and 36.37/45.04/54.19 for men.

[||] P-value for the continuous score.

Concerning 'softer events', only the AHEI-2010 was associated with a lower risk (HRQ5-Q1=0.68, 95% CI: 0.53-0.87, Ptrend=0.004).

Concerning 'medium events' (acute coronary syndrome and angioplasty), the mPNNS-GS only was associated with a lower risk (HRQ5-Q1=0.75, 95% CI: 0.57-0.98, Ptrend=0.02).

Concerning 'harder events', the results for MEDI-LITE and AHEI-2010 become insignificants.

In these analyses, cutting the outcome in this way leads to a lack of power (Supplemental Table V).

The geographical distribution of participants did not change the results (data not shown). The spline analyses of the relation between MEDI-LITE, mPNNS-GS and AHEI-2010 and CVD's risk showed that the hypothesis of linearity was reliable.

The discrimination was elevated and similar whatever the dietary score examined. The C-index values were 0.7664 (95% CI =0.7664-0.7665) for AHEI-2010, 0.7680 (95% CI =0.7679-0.7681) for mPNNS-GS, and 0.7681 (95% CI =0.7680-0.7681) for MEDI-LITE.

DISCUSSION

In this prospective study, higher MEDI-LITE, AHEI-2010, and to a lesser extent mPNNS-GS, were associated with a lower risk of developing CVD. Then, an association was specifically found between MEDI-LITE and angioplasty. These results were similar in sensitivity analyses. As regards mPNNS-GS, the association became significant when TIA were considered as cardiovascular events.

Concerning the association between the MEDI-LITE and the risk of CVD, our results are consistent with the findings previously documented in the scientific literature focusing on Mediterranean diet and CVD although other dietary scores were used. Two meta-analyses – Grosso and al. including 17 cohorts or RCTs studies [30], Sofi and al. including 14 studies [14] – reported evidence of a beneficial role of high adherence to a Mediterranean Diet on CVD's mortality (lower CVD' risk of 24%, Grosso and al.; lower CVD' risk of 8%, Sofi and al.), and in CVD's incidence (lower CVD' risk of 0.24, Grosso and al.; lower CVD' risk of 0.10, Sofi and al.). The meta-review of Martinez-Lacoba (including 9 reviews and 24 meta-analyses) also documented an association between CVD and Mediterranean Diet [31]. All these findings corroborate those of the 2014 United States Department of Agriculture report based on 55 studies reporting a favourable role of adherence to Mediterranean Diets and cardiovascular health with a lower risk of CVD ranging from 22% to 59% for the highest level of adherence. In that report, a favourable association was also documented as regards the association between Mediterranean diets and coronary heart diseases (CHD) risk [5].

A recent meta-analysis including 28 prospective cohorts analysing the association between the original AHEI and CVD or mortality has reported a reduction of 25% (95% CI = 28%-23%) comparing participants with high versus low adherence to the AHEI [17]. Besides, in Huffmann's study, the original AHEI was found negatively correlated with 10-years CHD risk among type 2 diabetes' patients, but not among patients free of type 2 diabetes [32].

Also, no significant association was found between level of the original AHEI and 10-year CVD' risk in a population with unknown diabetes status [33]. Our findings are in favour of a negative relationship between AHEI-2010 and CVD's risk.

In this study, the mPNNS-GS wasn't statistically significantly associated with CVD' risk. This could be due to a lower discriminant power of this specific score or to a lack of power as when TIA events were included, the association become significant. Indeed, in the SU.VI.MAX cohort, a strong inverse association between PNNS-GS and CVD' risk was found [34]. However, the original PNNS-GS including physical activity was used. The predominant role of physical activity in CVD aetiology [12] may at least partly explain the difference in results between these two studies.

Our findings also showed that the association between MEDI-LITE and CVD' risk was mainly driven by the association with angioplasty and to a lesser extent to other events except for angina. This may be largely due to statistical power as occurrence of angioplasty is more frequent than other cardiovascular events. In addition, we focused on first cardiovascular event, thus angioplasty is the "first-in-time" disease susceptible to occur leading to lower the number of other coronary events. Unexpectedly, in the Supplemental Table IV, a higher

MEDI-LITE score is associated with a higher risk of acute coronary syndrome, although this result was not significant. However, the negative association found can be the rely on others factors not considered in this study as regular changes in diet, work-life, social life and regular or important stress [12,35].

Then, the analyses conducted for ‘softer’, ‘medium’ and ‘harder’ cardiovascular events shown inconsistent findings. The AHEI-2010 seems to be particularly associated with ‘softer events of CVD’ (anginas), the mPNNS-GS seems to be particularly associated with ‘medium events of CVD’ and the MEDI-LITE seems to be specifically associated with overall cardiovascular diseases’ risk. Noticed that because they have been conducted post-hoc, these results should be takes with caution. These findings may reflect specific role of nutritional factors on different CVD events or, more probably, a lack of statistical power when considering specific events with low number of cases.

These results are coherent with the scientific knowledge about the role of nutritional factors in CVD’s aetiology. Indeed, a high adherence to a Mediterranean diet is marked by an important consumption of fruits, vegetables, legumes and whole grain, of fish and seafood, use of olive oil, moderate alcohol intake and low consumption of meat and dairy products [36]. In epidemiological studies, fruits, vegetables and grains consumption are associated with a lower risk of CVD, unlike meat, fat and sodium consumption, associated with a higher risk [2,6,30] thus, the combination of all these dietary characteristics may be involved in the associations.

Compared to MEDI-LITE, AHEI-2010 doesn’t include fish and seafood, dairy products and olive oil, while saturated fat, fatty acids and sugar are included. A large proportion of studies have highlighted the importance of olive oil in the Mediterranean Diet, which is considered as being the most important component in CVD prevention [2,5,7]. For instance, Estruch and al. showed that adding supplemental olive oil ration to Mediterranean diet should most help to reduce CVD's risk than reducing saturated fat consumption [7]. In addition, some dairy products may account for harmful role because of their composition [37]: In fact, replacement of saturated fatty acid with polyunsaturated fatty acid and monounsaturated fatty acid seems to lower LDL-cholesterol. But studies reported that only higher saturated fatty acid from dairy products can lower the risk of cardiovascular heart diseases. It seems that if the effect of fatty acids on LDL cholesterol is a constant, their effect on the risk of cardiovascular diseases depends of their food source. Unfortunately, these different effects of dairy products on CVD' risk could not be evaluated in this study. Thus, these disparities between MEDI-LITE and AHEI-2010 may explain the difference in magnitude of the association.

Compared to the mPNNS-GS, MEDI-LITE and AHEI-2010 are marked by a lower threshold of the quantity of fruit and vegetables consumption for reaching the maximum subscore but also promote higher consumption of fish and vegetable (olive) oil, and a lower consumption of dairy product and meat. Both MEDI-LITE and AHEI-2010 consider specially legumes while the mPNNS-GS does not. And some nutrients, or some others aspects as excessive energy intake, are taken into account in the mPNNS-GS and MEDI-LITE (instead of the AHEI-2010). But it should be noticed that the mPNNS-GS and the AHEI-2010 don't account for alcohol consumption in the energy intake for the computation of some items: as for percentage of sugar and lipids for the mPNNS-GS, and polyunsaturated fatty acids for AHEI-2010. These differences between components (food and/or nutrients), in particular a relative promotion of animal products in the mPNNS-GS, and scoring may explain that the association between mPNNS-GS and CVD was not significant.

The recent update of the French food-based dietary guidelines [38] recommending moderate consumption of meat and dairy product, and increasing consumption in non-refined cereals, nuts, fruit and legumes while avoiding sugar-rich foods, may probably be more preventive for CVD health. Specifically, updated guidelines propose a decrease in dairy products consumption from 3 to 2 serving per day and a low consumption of red meat up to 500 g/week. A new dietary score based on the 2017 French guidelines is now needed to investigate such hypothesis. This could probably strengthen the CVD protective effect of those recommendations.

Concerning the C-Index, they were superior to 0.5 for all the scores. It means that all scores provided consistent predictions of the outcome's measures. Nonetheless, the reader should notice that the C-Index doesn't use the participants' data which are unharmed of CVD events at the end of the study. In fact, it computes the probability of having a higher risk prediction when having a fewer time of survival considering that this time is lower than the followed-up time, that means that the computation depends of the duration of followed-up. Thus, the C-Index is a quite biased and truncated statistic, which should be interpreted with cautious.

Some limitations of our study be mentioned.

The event 'ischemic transient attack' hasn't been validated in this study. The occurrence of this event has only been declarative; thus, sensitive analyses might be interpreted with caution. Finding a way to better diagnose and record this type of events should strengthen future studies.

The change in diet over time has not been considered as we used a strictly prospective scheme and this should be investigated in further studies. Thus, the extrapolation of the results of the study should be make with caution. Specifically, it is possible that some participants changed their diet following a medical examination or other disease occurrence.

For example, cancers incidence has not been considered in this study, but such disease and related treatments may lead to change in diet of the patients. In our study, we assume that this phenomenon had affected a low proportion of participants, but exclusion of incident or prevalent cancer cases does not affect the findings (data not shown). Also, we considered sensitive analysis suppressing the events appeared in the first 2-years of followed-up, supposing that they could be the effect of a previous diet, even if the participant has chosen to undertake a recent change in his diet. The analysis shown that this possibility didn’t change the results of the study.

The energy intake on which was adjusted the scores in the model could be improved as suggested by Archer and al. [39]. All the models have been adjusted for energy intake, thus if a bias was introduced by this variable, it may not be differential and probably may lead to a misestimating of the amplitude of the HR. Nevertheless, this method needs to be clearly evaluated and modified as needed in futures studies to ensure that energy intake assessment will be real and reliable.

This study shown a small proportion of participants excluded for prevalent cases of CVD. A healthy effect might exist: these participants follow a healthy diet, exhibit healthier behaviours (such as lower tobacco use) and have a higher social status (higher graduate and higher income) [40,41]. Furthermore, there was a high proportion of women in this study, which may drive the findings. Although many confounding factors were accounted for in this study, residual confounding is possible. Finally, this cohort included a sample of the population which was probably more concerned by nutrition and health. Thus, generalization of these findings should be made with caution.

Some important strengths should be highlighted. Our study stems from a large and prospective cohort. The dietary exposure data were evaluated by repeated 24h records to avoid the bias introduced by memory-based dietary assessment [42]. Then, these dietary data were validated by nutrition professionals and the cases ascertainment and date of diagnosis were validated by medical staff. Also, a sensitive analysis after removing the events occurring during the first 2-years of follow-up (early cases) has been conducted to eliminate reverse causality. The findings remained unchanged.

CONCLUSION

The evidence of a beneficial impact of Mediterranean-type diet on CVD's risk seems to achieve a consensus as confirmed in the NutriNet-Santé cohort. However, other specific diets based on dietary guidelines are also important for CVD prevention. Considering our findings and previous scientific literature, the optimal score to evaluate CVD' risk may focus on fruit, vegetables and whole grain, but also alcohol intake, olive oil, meat, fish or dairy consumption, sodium and sugar intakes. Therefore, futures studies should focus on the impact of some specific components as dairy products on CVD' risk. In that context, French food-based dietary guidelines have been revised in 2017 and include some modification, in particular moderate consumption of red and processed meat and dairy products. In the next future, a new dietary score based on this will be built and validated to estimate predictive value on the risk of CVD.

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