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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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35 BMI: Body Mass Index
36 CepiDC: Epidemiological Center on the medical causes of death
37 CI: Confidence interval
38 CU: Consumption unit
39 CVD: Cardiovascular diseases
40 HEI-2010: Healthy Eating Index 2010
41 HR: Hazard Ratio
42 ICD-10: International Chronic Diseases Classification, 10th Revision, Clinical Modification
43 INSERM: National Institute for Health and Medical Research
44 IPAQ: International Physical Activity Questionnaire
45 MEDI-LITE: Literature-based Adherence score to the Mediterranean Diet
46 MI: Myocardial infarction
47 mPNNS-GS: Modified and “penalised” score to the French Programme National Nutrition Santé
48 PT: Person-time
49 SNIIRAM: Medico-administrative database of the National Health Insurance
50 TIA: Transient ischemic attacks

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79 **ABSTRACT**

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

84 **Methods and findings:** A total of 94,113 participants from the NutriNet-Santé cohort were
85 followed between 2009 and 2018. The participants have completed at least three 24h
86 dietary records during the first two-years of follow-up to compute nutritional scores
87 reflecting adherence to the Mediterranean diet (MEDI-LITE), American dietary guidelines
88 (AHEI-2010) and French dietary guidelines (mPNNS-GS). Sex-specific quartiles (Q) of scores
89 were computed. Multivariable Cox proportional hazards models were used to estimate the
90 associations between scores and incidence of CVD, documented using Hazard Ratio (HR) and
91 95% confidence intervals (95%CI). Thus, 1,399 incident CVD events occurred during the
92 follow-up (mean follow-up=5.4 years). Comparing Q4 versus Q1 quartile, HR for the MEDI-
93 LITE and AHEI-2010 were 0.79 (95% CI: 0.67-0.93, P-trend=0.004) and 0.75 (95% CI: 0.63-
94 0.89, P-trend=0.002) respectively. These associations remained similar when removing early
95 cases of CVD, when analyses were restricted to participants with >6 dietary records and
96 when considering transient ischemic attacks. In this last case, association between CVD's risk
97 and mPNNS-GS become significant.

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

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

103 **INTRODUCTION**

104 Cardiovascular diseases (CVD) are the first cause of death worldwide leading to one third of
105 the overall mortality [1]. Thus, improving prevention of CVD is a challenge in public health as
106 they are the results of multifactor conditions wherein nutrition plays a predominant role [2–
107 4]. As a modifiable determinant, diet represents a key lever for prevention.

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

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

122 Besides, most of the countries develop and disseminate official nutrition recommendations
123 elaborated to prevent a wide range of chronic diseases [3], which are more or less in
124 coherence with the Mediterranean diet. In France, the Programme National Nutrition Santé
125 guideline score (PNNS-GS) was previously developed to reflect the official French nutritional
126 guidelines [15]. These guidelines are mostly based on the current scientific knowledge about

127 the relationships between diet, nutrition and chronic diseases (in 2001). For this time, it
128 encourages the French population to consume a high proportion of fruits, vegetables and
129 fish, to avoid a high consumption of red meats, cold meats, fats, sugar and salt.

130 In that context, other dietary scores have been developed to evaluate the adherence to the
131 different recommendations in the population, and then studied in relationships with health
132 outcomes and specifically CVD. For instance, Healthy Eating Index-2010 (HEI-2010) was
133 developed for evaluating the adequacy between population diet and the 2010 Dietary
134 Guidelines for Americans [16]. The Alternative Healthy Eating Index-2010 (AHEI-2010) was
135 then proposed to better account for the association between nutrition and chronic diseases
136 [16]. The AHEI-2010 has previously been associated with the risk of CVD in several studies
137 conducted in a large group of countries (USA, Europe, Japan, Australia, UK, Cuba) [17].

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

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

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

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

158

159 **METHODS**

160 Study population

161 The NutriNet-Santé is an observational cohort study launched in May 2009 aiming to
162 evaluate the relationships between nutrition and health status, and to investigate the
163 interaction of sociodemographic factors and nutritional patterns. Inclusion criteria were age
164 above 18 years and access to the Internet. Registration and participation are conducted
165 online using a secured web site (www.etude-NutriNet-sante.fr). The NutriNet-Santé study's
166 aims and methods are described in details elsewhere [18]. The NutriNet-Santé study is
167 conducted in accordance with the Declaration of Helsinki and was approved by the ethics
168 committee of the French Institute for Health and Medical Research (IRB Inserm no.
169 0000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL
170 no. 908450 and no. 909216). Electronic informed consent was obtained from all participants.
171 The NutriNet-Santé study is registered in ClinicalTrials.gov (NCT03335644).

172 In the present study, we selected participants from the NutriNet-Santé cohort, followed
173 from March 2009 to March 2018, who had completed at least three 24h dietary records

174 during the first two years of follow-up (exposure window), had available complementary
 175 data to compute the mPNNS-GS score and had a non-zero follow-up time and with no
 176 prevalent CVD at baseline (Figure 1). A total of 104,380 participants were eligible for the
 177 present study (available and valid dietary data and no under-reporters).

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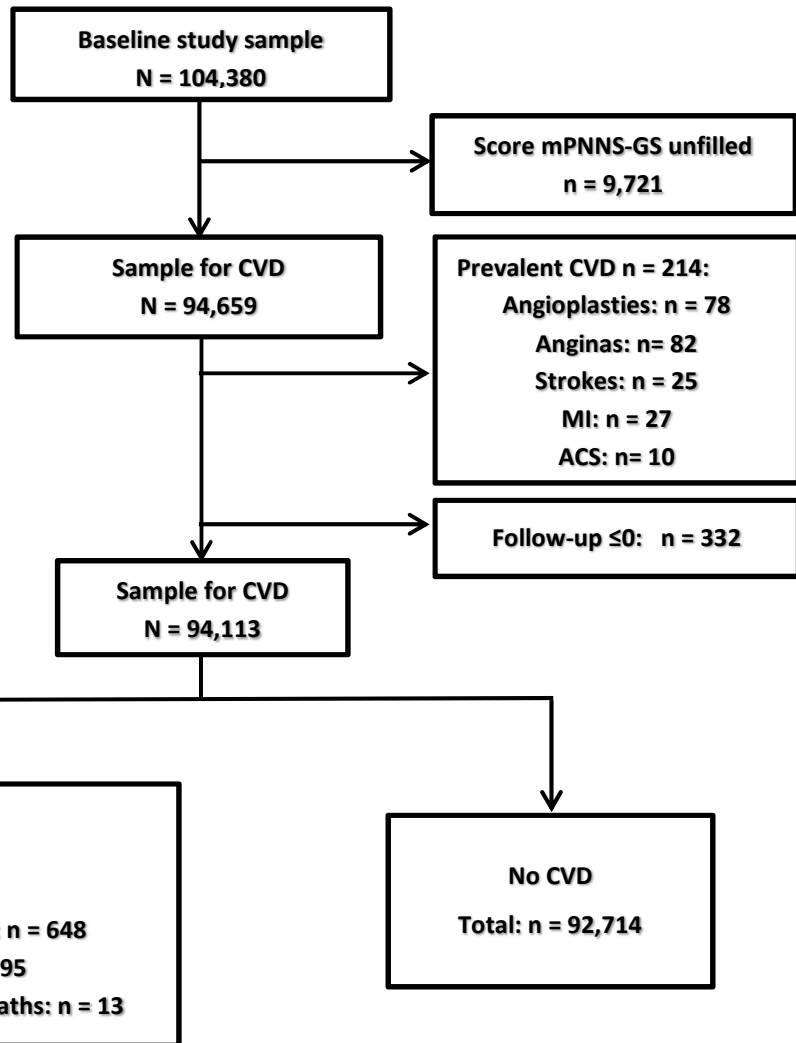


Figure 1. Flow chart.

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

212 invited to send their medical records (diagnosis, hospitalization, radiological reports,
213 electrocardiograms, etc.) and, if necessary, the study physicians contacted the participants'
214 treating physician or the medical structures to collect additional information. The medical
215 data were validated for major events (strokes, myocardial infarctions and acute coronary
216 syndromes). Besides, data from our cohort are linked to medico-administrative databases of
217 the National health insurance (SNIIRAM), to limit any potential misclassification. Vital status
218 and causes of death were identified via the National death registry (CepiDC Inserm). CVD
219 cases were classified using the International Chronic Diseases Classification, 10th Revision,
220 Clinical Modification (ICD-10). The present study focused on all validated first events of
221 stroke, myocardial infarction, acute coronary syndrome, as well as angioplasty, angina and
222 deaths caused by CVD.

223 *Sociodemographic, lifestyle and anthropometric data*

224 A set of validated self-administered questionnaires was proposed at baseline to collect
225 sociodemographic information [19], lifestyle characteristics and anthropometrics' data
226 (18,19). In this study, we focused on age, sex, season of recruitment (spring – summer –
227 autumn – winter), educational level (less than a high-school degree – high-school degree –
228 after high-school degree), and baseline occupation (no employment – farmer, merchant,
229 artisan, company director, manual workers – employees – intermediate profession – top
230 manager), cohabiting status (yes/no), smoking status (non-smokers – former smokers –
231 smokers), Body Mass Index (BMI, computed as weight (kg) divided by square height (m²)),
232 physical activity (International Physical Activity Questionnaire [IPAQ] [20]) and monthly
233 household income (not communicated – 0 to 1,200 € monthly – 1,200 to 1,800 € monthly –
234 1,800 to 2,700 € monthly – more than 2,700 € monthly). The family history of CVD was also
235 collected in the baseline questionnaire and referred to anginas, myocardial infarctions and

236 strokes. From IPAQ, energy expenditure was categorised as low physical activity (<30
237 minutes of physical activity; equivalent to brisk walking / day), moderate physical activity
238 (≥ 30 and < 60 minutes) or high physical activity (≥ 60 minutes). Monthly household income
239 was estimated per consumption unit according to a weighting system where one
240 consumption unit (CU) is attributed for the first adult in the household, 0.5 CU for other
241 persons aged 14 or older, and 0.3 CU for children under 14 [21].

242 *Dietary data*

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

255 *Dietary scores*

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

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

264 The food-based mPNNS-GS, ranging from negative scores (less healthy) to 13.5 (most
265 healthy), includes 12 components reflecting the consumption of fruit and vegetables,
266 starches, whole grains, dairy products, meat and eggs, fish and seafood, alcohol, lipids level
267 on added fat, added fat, sodium, added sugar and sweetened beverages. A penalty of
268 participants with overconsumption was applied as follows: if total energy intake exceeds
269 105% of the calculated needs, the score is reduced by the same percentage by which energy
270 needs are exceeded [15,25].

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

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

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

279

280 *Statistical analyses*

281 A total of 9,721 participants were excluded due to missing values on specific non-dietary
282 data that prevented the calculation of the mPNNS-GS score. Then 214 participants were

283 excluded for having declared a cardiovascular disease before the beginning of the study (78
284 angioplasties, 82 anginas, 25 strokes, 27 myocardial infarctions and 10 acute coronary
285 syndromes), and 332 were excluded due to lack of follow-up (after the dietary exposure
286 window). Therefore, the final sample included 94,113 participants.

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

290 Included and excluded participants were compared using Chi² test or ANOVA.

291 Characteristics across quartiles were presented as mean and standard deviation (SD) or N
292 (%). P-values referred to linear contrast or Chi² tests.

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

301 Log-log (survival) versus log-time plots were used to confirm risk proportionality
302 assumptions. Multivariable Cox proportional hazards model were adjusted for age (time-
303 scale), sex, cohabiting status, occupation, educational level, monthly household income,
304 smoking status, physical activity, alcohol consumption, number of 24h dietary records,
305 season of recruitment, Body Mass Index and family history of CVD. Tests for linear trend
306 were performed using the ordinal score on sex-specific quartiles of each score. We tested

307 linearity of the association between CVD' risk and the three scores by the restricted cubic
308 splines (RCS) functions using the SAS® macro written by Desquilbet and Mariotti [28], with
309 the cut off percentiles method described by Harrell [29].

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

317 To test for robustness, sensitivity analyses were conducted. The data were rerun after 1)
318 removing incident cases occurring during the two first years of the study, 2) adding transient
319 ischemic attacks (TIA) events to outcome CVD and 3) removing persons completing less than
320 6 24h dietary records. 4) subdividing the principal outcome in three subgroups: 'softer
321 events' only including angina, 'medium events' including acute coronary syndrome and
322 angioplasty, and 'harder events' including myocardial infarction, stroke and CVD death.

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

325 *Funding*

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327 Santé, Santé Publique France, Institut National de la Santé et de la Recherche Médicale
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329 Arts et Métiers (CNAM) and Université Paris 13. Bernard Srour was funded by the French
330 National Cancer Institute (grant number INCa_8085) and the Fondation de France.

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

334

335 **RESULTS**

336 Compared to included participants, those excluded had a less healthy diet (mean mPNNS-GS:
337 excluded=8.72 and included=9.61, $p<0.0001$) and were younger (mean age: excluded=43.88
338 and included=40.69, $p<0.0001$). They were also more often men, part of a lower social class,
339 more often smokers, more physically active and completed fewer dietary records (all
340 $p<0.05$).

341 Overall, 1,399 CVD events were recorded during a mean follow-up of 5.4 years ($SD=2.5$)
342 (510,603 persons-years): 449 angioplasties, 648 anginas, 123 strokes, 95 myocardial
343 infarctions, 71 acute coronary syndromes, 13 cardiovascular deaths. Mean number of
344 dietary records was 6.2 ($SD=2.8$) per individual.

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

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351

352 **Table I**

353 Baseline characteristics of the study population overall and according to sex-specific quartiles of the MEDI-LITE,
354 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 employment	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/m ²	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
Alcohol 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)	

355 * P value for the comparison between quartiles of MEDI-LITE, by tests from Mantel-Henzel Chi² for
 356 dichotomises or ordinals variables, Chi² for others categorical variables and generalized linear models with
 357 linear contrast for numeric variables.

358 † 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
 359 men.

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

367 The association between MEDI-LITE, mPNNS-GS and AHEI-2010 and risk of CVD are
 368 presented in [Table II](#).

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373 **Table II**

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

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Diseases	Continuous score		Sex-specific quartiles				P-trend
	All	P-value	Q1	Q2	Q3	Q4	
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

378 * Models were adjusted for age (time-scale), sex, BMI (kg/m², continuous), physical activity (high, moderate,
379 low), smoking status (never smokers, former smokers, smokers), numbers of dietary records (continuous),
380 alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of
381 cardiovascular diseases (yes/no), educational level (\leq high-school degree and/ high-school degree/ 2 years after
382 high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual
383 workers/employees/intermediate profession/top manager), monthly household income (not communicated /
384 <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly),
385 cohabiting status (yes/no) and season of recruitment (spring, summer, fall, winter).

386 † 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
387 men.

388 ‡ 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.

389 § 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
390 men.

391 || P-value for the continuous score.

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393

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

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

399 The associations between MEDI-LITE and subtypes of CVD are presented in Supplemental
400 Table IV. Similar results were obtained when cases were restricted to angioplasty (HR Q4
401 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-
402 trend=0.06). The association between MEDI-LITE and myocardial infarction (HR Q4 vs
403 Q1=0.70 (0.35-1.39), P-trend=0.22), acute coronary syndrome (HR Q4 vs Q1=1.62 (0.76-
404 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

405 vs Q1=0.14 (0.01-1.49), P-trend=0.16) were not significant, albeit the associations exhibited
406 a similar trend.

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

437

438 **Table III**

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

442 * Models were adjusted for age (time-scale), sex, BMI (kg/m², continuous), physical activity (high, moderate,
443 low), smoking status (never smokers, former smokers, smokers), numbers of dietary records (continuous),
444 alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of
445 cardiovascular diseases (yes/no), educational level (\leq high-school degree and/ high-school degree/ 2 years after
446 high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual
447 workers/employees/intermediate profession/top manager), monthly household income (not communicated /
448 <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly),
449 cohabiting status (yes/no) and season of recruitment (spring, summer, fall, winter).

450 † 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
451 men.

452 ‡ 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.

453 § 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
454 men.

455 || P-value for the continuous score.

456

457 **Table IV**

458 Multivariable* associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or
459 sex-specific quartiles of MEDI-LITE[†], mPNNS-GS[‡] and AHEI-2010[§] and cardiovascular disease risk, after
460 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

461 * Models were adjusted for age (time-scale), sex, BMI (kg/m², continuous), physical activity (high, moderate,
462 low), smoking status (never smokers, former smokers, smokers), numbers of dietary records (continuous),
463 alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family history of
464 cardiovascular diseases (yes/no), educational level (\leq high-school degree and/ high-school degree/ 2 years after
465 high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual
466 workers/employees/intermediate profession/top manager), monthly household income (not communicated /
467 <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly),
468 cohabiting status (yes/no) and season of completion of recruitment (spring, summer, fall, winter).

469 † 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
470 men.

471 ‡ 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.

472 § 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
473 men.

474 || P-value for the continuous score.

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478 **Table V**

479 Multivariable* associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or
480 sex-specific quartiles of MEDI-LITE[†], mPNNS-GS[‡] and AHEI-2010[§] and cardiovascular disease risk, after removed
481 persons answered less than 6 dietary questionnaires, 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	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

482 * Models were adjusted for age (time-scale), sex, BMI (kg/m², continuous), physical activity (high, moderate,
483 low), smoking status (never smokers, former smokers, occasional or permanent smokers), numbers of dietary
484 records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, g/d, continuous), family
485 history of cardiovascular diseases (yes/no), educational level (\leq high-school degree and/ high-school degree/ 2
486 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual
487 workers/employees/intermediate profession/top manager), monthly household income (not communicated /
488 <1,200€ monthly /from 1,200€ to 1,800€ monthly/from 1,800€ to 2,700€ monthly/>2,700€ monthly),
489 cohabiting status (yes/no) and season of completion of recruitment (spring, summer, fall, winter).

490 † 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
491 men.

492 ‡ 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.

493 § 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
494 men.

495 || P-value for the continuous score.

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

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

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

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

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509 The geographical distribution of participants did not change the results (data not shown).
510 The spline analyses of the relation between MEDI-LITE, mPNNS-GS and AHEI-2010 and CVD's
511 risk showed that the hypothesis of linearity was reliable.
512 The discrimination was elevated and similar whatever the dietary score examined. The C-
513 index values were 0.7664 (95% CI =0.7664-0.7665) for AHEI-2010, 0.7680 (95% CI =0.7679-
514 0.7681) for mPNNS-GS, and 0.7681 (95% CI =0.7680-0.7681) for MEDI-LITE.

515

516 **DISCUSSION**

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

522 Concerning the association between the MEDI-LITE and the risk of CVD, our results are
523 consistent with the findings previously documented in the scientific literature focusing on
524 Mediterranean diet and CVD although other dietary scores were used. Two meta-analyses –
525 Grosso and al. including 17 cohorts or RCTs studies [30], Sofi and al. including 14 studies [14] –
526 reported evidence of a beneficial role of high adherence to a Mediterranean Diet on CVD's
527 mortality (lower CVD' risk of 24%, Grosso and al.; lower CVD' risk of 8%, Sofi and al.), and in
528 CVD's incidence (lower CVD' risk of 0.24, Grosso and al.; lower CVD' risk of 0.10, Sofi and al.).
529 The meta-review of Martinez-Lacoba (including 9 reviews and 24 meta-analyses) also
530 documented an association between CVD and Mediterranean Diet [31]. All these findings
531 corroborate those of the 2014 United States Department of Agriculture report based on 55
532 studies reporting a favourable role of adherence to Mediterranean Diets and cardiovascular

533 health with a lower risk of CVD ranging from 22% to 59% for the highest level of adherence.
534 In that report, a favourable association was also documented as regards the association
535 between Mediterranean diets and coronary heart diseases (CHD) risk [5].
536 A recent meta-analysis including 28 prospective cohorts analysing the association between
537 the original AHEI and CVD or mortality has reported a reduction of 25% (95% CI = 28%-23%)
538 comparing participants with high versus low adherence to the AHEI [17]. Besides, in
539 Huffmann's study, the original AHEI was found negatively correlated with 10-years CHD risk
540 among type 2 diabetes' patients, but not among patients free of type 2 diabetes [32].
541 Also, no significant association was found between level of the original AHEI and 10-year
542 CVD' risk in a population with unknown diabetes status [33]. Our findings are in favour of a
543 negative relationship between AHEI-2010 and CVD's risk.
544 In this study, the mPNNS-GS wasn't statistically significantly associated with CVD' risk. This
545 could be due to a lower discriminant power of this specific score or to a lack of power as
546 when TIA events were included, the association become significant. Indeed, in the
547 SU.VI.MAX cohort, a strong inverse association between PNNS-GS and CVD' risk was found
548 [34]. However, the original PNNS-GS including physical activity was used. The predominant
549 role of physical activity in CVD aetiology [12] may at least partly explain the difference in
550 results between these two studies.
551 Our findings also showed that the association between MEDI-LITE and CVD' risk was mainly
552 driven by the association with angioplasty and to a lesser extent to other events except for
553 angina. This may be largely due to statistical power as occurrence of angioplasty is more
554 frequent than other cardiovascular events. In addition, we focused on first cardiovascular
555 event, thus angioplasty is the "first-in-time" disease susceptible to occur leading to lower the
556 number of other coronary events. Unexpectedly, in the Supplemental Table IV, a higher

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

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

569 These results are coherent with the scientific knowledge about the role of nutritional factors
570 in CVD's aetiology. Indeed, a high adherence to a Mediterranean diet is marked by an
571 important consumption of fruits, vegetables, legumes and whole grain, of fish and seafood,
572 use of olive oil, moderate alcohol intake and low consumption of meat and dairy products
573 [36]. In epidemiological studies, fruits, vegetables and grains consumption are associated
574 with a lower risk of CVD, unlike meat, fat and sodium consumption, associated with a higher
575 risk [2,6,30] thus, the combination of all these dietary characteristics may be involved in the
576 associations.

577 Compared to MEDI-LITE, AHEI-2010 doesn't include fish and seafood, dairy products and
578 olive oil, while saturated fat, fatty acids and sugar are included. A large proportion of studies
579 have highlighted the importance of olive oil in the Mediterranean Diet, which is considered
580 as being the most important component in CVD prevention [2,5,7]. For instance, Estruch and

581 al. showed that adding supplemental olive oil ration to Mediterranean diet should most help
582 to reduce CVD's risk than reducing saturated fat consumption [7]. In addition, some dairy
583 products may account for harmful role because of their composition [37]: In fact,
584 replacement of saturated fatty acid with polyunsaturated fatty acid and monounsaturated
585 fatty acid seems to lower LDL-cholesterol. But studies reported that only higher saturated
586 fatty acid from dairy products can lower the risk of cardiovascular heart diseases. It seems
587 that if the effect of fatty acids on LDL cholesterol is a constant, their effect on the risk of
588 cardiovascular diseases depends of their food source. Unfortunately, these different effects
589 of dairy products on CVD' risk could not be evaluated in this study. Thus, these disparities
590 between MEDI-LITE and AHEI-2010 may explain the difference in magnitude of the
591 association.

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

604 The recent update of the French food-based dietary guidelines [38] recommending
605 moderate consumption of meat and dairy product, and increasing consumption in non-
606 refined cereals, nuts, fruit and legumes while avoiding sugar-rich foods, may probably be
607 more preventive for CVD health. Specifically, updated guidelines propose a decrease in dairy
608 products consumption from 3 to 2 serving per day and a low consumption of red meat up to
609 500 g/week. A new dietary score based on the 2017 French guidelines is now needed to
610 investigate such hypothesis. This could probably strengthen the CVD protective effect of
611 those recommendations.

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

619 Some limitations of our study be mentioned.

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

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

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

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

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

650 Some important strengths should be highlighted. Our study stems from a large and
651 prospective cohort. The dietary exposure data were evaluated by repeated 24h records to

652 avoid the bias introduced by memory-based dietary assessment [42]. Then, these dietary
653 data were validated by nutrition professionals and the cases ascertainment and date of
654 diagnosis were validated by medical staff. Also, a sensitive analysis after removing the
655 events occurring during the first 2-years of follow-up (early cases) has been conducted to
656 eliminate reverse causality. The findings remained unchanged.

657

658 **CONCLUSION**

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

670

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