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1	Prospective association between several dietary scores and risk of
2	cardiovascular diseases: is the Mediterranean diet equally associated to CVD
3	compared to National Nutritional Scores?
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13	The authors' contributions were as follows – AT, MA, and EKG: designed the research; CJ, LF, PG, MT,
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30	Running title: Association between dietary scores and CVD
31	Abbreviations:
32	ACS: Acute Coronary Syndrome
33	AESA: Energy intake without alcohol
34	AHEI-2010: Alternative Healthy Eating Index 2010

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, 10 th Revision, Clinical Modification
43	INSERM: National Institute for Health and Medical Research
43	IPAQ: International Physical Activity Questionnaire
45	MEDI LITE: Literature based Adherence score to the Mediterranean Diet
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
51 52 53 54	Conflict of interest statement : The authors declare that they have no conflict of interest.
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79 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 84 followed between 2009 and 2018. The participants have completed at least three 24h 85 dietary records during the first two-years of follow-up to compute nutritional scores 86 reflecting adherence to the Mediterranean diet (MEDI-LITE), American dietary guidelines 87 (AHEI-2010) and French dietary guidelines (mPNNS-GS). Sex-specific quartiles (Q) of scores 88 were computed. Multivariable Cox proportional hazards models were used to estimate the 89 90 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 91 follow-up (mean follow-up=5.4 years). Comparing Q4 versus Q1 quartile, HR for the MEDI-92 LITE and AHEI-2010 were 0.79 (95% CI: 0.67-0.93, P-trend=0.004) and 0.75 (95% CI: 0.63-93 0.89, P-trend=0.002) respectively. These associations remained similar when removing early 94 cases of CVD, when analyses were restricted to participants with >6 dietary records and 95 96 when considering transient ischemic attacks. In this last case, association between CVD's risk 97 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.

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

102

103 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.

108 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 109 style diets upon cardiovascular diseases prevention is clearly documented [5–12]. Health 110 benefits of Mediterranean diet was firstly introduced by Ancel Keys in the 1970s and then 111 studied by many researchers in several medical fields including randomized trials. It is 112 characterized by olive oil as primary source of fat and moderate consumption of alcohol. It 113 114 also includes elevated consumption of fruit, legumes and vegetables, and for some variants, 115 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 130 different recommendations in the population, and then studied in relationships with health 131 outcomes and specifically CVD. For instance, Healthy Eating Index-2010 (HEI-2010) was 132 developed for evaluating the adequacy between population diet and the 2010 Dietary 133 Guidelines for Americans [16]. The Alternative Healthy Eating Index-2010 (AHEI-2010) was 134 then proposed to better account for the association between nutrition and chronic diseases 135 [16]. The AHEI-2010 has previously been associated with the risk of CVD in several studies 136 conducted in a large group of countries (USA, Europe, Japan, Australia, UK, Cuba) [17]. 137

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 webbased 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, literaturebased, 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.

158

159 METHODS

160 Study population

161 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 162 interaction of sociodemographic factors and nutritional patterns. Inclusion criteria were age 163 above 18 years and access to the Internet. Registration and participation are conducted 164 online using a secured web site (www.etude-NutriNet-sante.fr). The NutriNet-Santé study's 165 aims and methods are described in details elsewhere [18]. The NutriNet-Santé study is 166 conducted in accordance with the Declaration of Helsinki and was approved by the ethics 167 committee of the French Institute for Health and Medical Research (IRB Inserm no. 168 0000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL 169 no. 908450 and no. 909216). Electronic informed consent was obtained from all participants. 170 171 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 (<u>Figure I</u>). A total of 104,380 participants were eligible for the present study (available and valid dietary data and no under-reporters).



208 Data collection

209 Cases ascertainment

210 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, electrocardiograms, etc.) and, if necessary, the study physicians contacted the participants' 213 treating physician or the medical structures to collect additional information. The medical 214 data were validated for major events (strokes, myocardial infarctions and acute coronary 215 syndromes). Besides, data from our cohort are linked to medico-administrative databases of 216 217 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 218 cases were classified using the International Chronic Diseases Classification, 10th Revision, 219 Clinical Modification (ICD-10). The present study focused on all validated first events of 220 stroke, myocardial infarction, acute coronary syndrome, as well as angioplasty, angina and 221 deaths caused by CVD. 222

223 Sociodemographic, lifestyle and anthropometric data

A set of validated self-administered questionnaires was proposed at baseline to collect 224 sociodemographic information [19], lifestyle characteristics and anthropometrics' data 225 (18,19). In this study, we focused on age, sex, season of recruitment (spring - summer -226 autumn – winter), educational level (less than a high-school degree – high-school degree – 227 after high-school degree), and baseline occupation (no employment – farmer, merchant, 228 artisan, company director, manual workers – employees – intermediate profession – top 229 230 manager), cohabiting status (yes/no), smoking status (non-smokers - former smokers smokers), Body Mass Index (BMI, computed as weight (kg) divided by square height (m²)), 231 physical activity (International Physical Activity Questionnaire [IPAQ] [20]) and monthly 232 233 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 234 collected in the baseline questionnaire and referred to anginas, myocardial infarctions and 235

strokes. From IPAQ, energy expenditure was categorised as low physical activity (<30 minutes of physical activity; equivalent to brisk walking / day), moderate physical activity (\geq 30 and <60 minutes) or high physical activity (\geq 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].

242 Dietary data

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

255 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.

278 More details about scores computation are described in <u>Supplemental Table I</u>.

279

280 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.

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.

Hazard ratios (HR) and 95% confidence intervals (CI) were obtained from Cox proportional 293 294 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 295 date of diagnostic of the first cardiovascular event, the date of death, the date of the last 296 completed questionnaire, or March 31st 2018, whichever occurred first. For subtype 297 analyses, other CVD cases were censored at the date of diagnosis. Associations were 298 estimated across sex-specific quartiles (Q) of each score (with the 1st quartile as reference 299 category) and for continuous standardized scores for comparison purpose. 300

Log-log (survival) versus log-time plots were used to confirm risk proportionality assumptions. Multivariable Cox proportional hazards model were adjusted for age (timescale), 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 Cindex 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.

325 Funding

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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.

334

335 **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 <u>Table I</u>. 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).

350

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(%) or meantN(%) or meantN(%) <th></th> <th>(n=94,113)</th> <th>(n=21,916)</th> <th>(n=23,678)</th> <th>(n=24,277)</th> <th>(n=24,242)</th> <th>Ρ*</th>		(n=94,113)	(n=21,916)	(n=23,678)	(n=24,277)	(n=24,242)	Ρ*
SD N (%) orman 1.5 SD SD SD SD SD Ker -		N (%) or mean±		N (%) or mean ±	N (%) or mean±	N (%) or mean±	
MEDILITE ' Shif 2.77 Sp2 ± 1.16 8.53 ± 0.50 10.47 ± 0.30 13.14 ± 1.22 Men 20.174 (21.44) 4.712 (21.50) 4.810 (20.31) 5.099 (21.00) 5.53 (22.91)		SD	N (%) or mean ± SD	SD	SD	SD	
sex 0.0001 5,533 (22.91) 0.0001 Women 73,393 (78.26) 17,204 (78.50) 18,888 (76.69) 19,178 (79.00) 18,689 (77.09) Age 438 ± 14.63 83.85 ± 1.33 33.95 ± 1.35 43.51 ± 4.43 48.01 ± 1.44.3 0.0001 Sommer 15,188 (55.11) 12,740 (15.81) 3,282 ± 1.63 3,349 (54.99) 1.2559 (51.81) Auturn 11,787 (12.52) 2,471 (12.15,01) 3,820 (15.21) 3,582 (14.75) 3,740 (15.30) Winter 14,345 (15.24) 3,421 (15.61) 3,602 (15.71) 3,381 (17.60) 3,921 (16.17) High-school degree 16,078 (7.08) 4,722 (12.80) 4,536 (17.70) 3,391 (15.70) 3,391 (15.70) 3,391 (15.70) 3,391 (15.70) 3,391 (15.70) 3,392 (15.70) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (17.90) 4,350 (13.90)		9.61 ± 2.77	5.92 ± 1.16	8.53 ± 0.50	10.47 ± 0.50	13.14 ± 1.22	<0.0001
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Page 93.89 1 PA.39 94.39 1 PA.39 94.39 1 PA.39 94.39 1 PA.39 94.39 1 PA.39 94.30 1 PA.33 94.30 1 PA.33 <td>Ago</td> <td>/3,939 (/8.50) /2 99 ± 17 62</td> <td>17,204 (78.50) 29 05 ± 12 05</td> <td>18,808 (79.09)</td> <td>19,178 (79.00)</td> <td>18,089 (77.09)</td> <td><0.0001</td>	Ago	/3,939 (/8.50) /2 99 ± 17 62	17,204 (78.50) 29 05 ± 12 05	18,808 (79.09)	19,178 (79.00)	18,089 (77.09)	<0.0001
Sexon Direct function 16,113 (17.12) 3,508 (16.01) 3,985 (16.83) 1,318 (17.04) 4,482 (18.49) Symmer 51,866 (55.11) 12,740 (58.13) 13,220 (55.83) 13,349 (54.99) 12,555 (51.81) 3,740 (15.43) Minter 14,345 (15.24) 3,212 (15.51) 3,502 (14.75) 3,582 (14.75) 3,571 (14.28) 0,0001 Summer 14,345 (15.24) 3,471 (15.43) 3,211 (15.70) 3,391 (16.17) 4,0001 High-school degree 16,078 (17.08) 4,722 (12.54) 4,475 (12.80) 1,338 (17.64) 3,921 (16.17) 1,039 (4.28) 800 (3.30) No employment 4,979 (5.29) 1,772 (8.09) 1,368 (5.78) 1,039 (4.28) 800 (3.30) 5,000 (3.30) Farmer, merchant, antian, company director, manual 5,138 (5.86) 1,561 (7.12) 1,402 (5.92) 1,312 (5.40) 1,243 (5.13) 1,410 (3.99) Note minouncited 2,723 (28.94) 8,157 (37.22) 7,227 (30.52) 6,427 (26.47) 5,424 (22.37) 1,110 (10.10) Intermediate profession 2,304 (26.24) 5,391 (14.34) 8,733 (35.97) 9,383 (40.55)	Age	43.88 ± 14.03	38.95 ± 13.95	42.57 ± 14.51	45.48 ± 14.43	48.01 ± 14.08	<0.0001
spmm 10,11 (1/12) 3,300 (10.01) 4,350 (17.40) 4,452 (12.43) 4,452 (12.43) Summer 5,186 (55.11) 12,240 (58.13) 13,220 (55.83) 13,349 (54.99) 12,356 (15.11) Autumn 11,787 (12.52) 2,247 (10.25) 2,471 (12.13) 3,208 (13.21) 3,528 (14.75) 3,401 (15.43) Cituational level - - - - - - - High-school degree 16,078 (17.08) 4,727 (21.84) 4,475 (18.90) 4,336 (17.86) 3,921 (16.17) High-school degree 16,078 (17.08) 1,2407 (56.61) 15,049 (63.56) 16,130 (66.44) 16,930 (98.40) Cocupation - - - - - - No employment 4,979 (5.29) 1,772 (8.09) 1,368 (5.78) 1,039 (4.28) 800 (3.30) - Intermediate profession 2,5007 (26.57) 5,061 (21.20) 6,426 (25.65) 6,766 (27.87) 6,942 (23.27) - Intermediate profession 1,5716 (17.07) 3,022 (13.79) 2,745 (11.59) 2,731 (14.54) 2,5	Season of recruitment	16 112 (17 12)	2 509 (16 01)	2 095 (16 92)	4 120 (17 04)	4 492 (19 40)	<0.0001
summer 54,865 (53.11) 12,40 (35.13) 13,240 (35.83) 13,349 (34.93) 12,359 (31.821) 34,250 (31.821)	Spring	10,113 (17.12)	3,508 (10.01)	3,985 (10.83)	4,138 (17.04)	4,482 (18.49)	
Autum 11/37 (12:52) 2.47 (10:25) 2.47 (10:25) 5.268 (12:52) 5.268 (12:52) 5.268 (12:52) 5.268 (12:52) 5.268 (12:52) 5.268 (12:52) 5.268 (12:52) 5.258 (14:75) 5.740 (15:43) 5.000 (12:52) 5.358 (14:75) 5.740 (15:43) 5.000 (12:52) 5.358 (14:75) 3.740 (15:43) 5.000 (12:52) 5.358 (14:75) 3.740 (15:43) 5.000 (12:52) 5.358 (14:75) 3.740 (15:43) 5.000 (13:30) Vilgh-school degree 16,730 (16:40) 12,407 (56:61) 15,049 (63:56) 16,130 (66:44) 16,930 (69:84) 0.0001 Starmer, merchant, artism, company director, manal workers 5,518 (55.80) 1,561 (7.12) 1,402 (5.92) 1,312 (54.01) 1,243 (51.31) - 4,243 (22:37) intermediate profession 5,502 (25:7) 5,051 (12:30) 6,238 (26:35) 6,766 (27:87) 6,942 (28:64) - 4,0001 Intermediate profession 2,507 (12:7) 5,518 (13:7) 5,312 (13:43) 8,733 (35:97) 9,833 (40:56) - 0,0001 Not communicated 11,077 (11:77) 3,022 (13:79) 2,745 (11:59) 2,777 (11:41) 2,533 (14:44) <td>Summer</td> <td>51,808 (55.11) 11,707 (12,52)</td> <td>12,740 (58.13)</td> <td>13,220 (55.83)</td> <td>13,349 (54.99)</td> <td>12,559 (51.81)</td> <td></td>	Summer	51,808 (55.11) 11,707 (12,52)	12,740 (58.13)	13,220 (55.83)	13,349 (54.99)	12,559 (51.81)	
write 14,349 (13,24) 3,421 (13,64) 5,002 (13,74) 5,322 (14,75) 5,740 (13,74) Coupation 16,078 (17,08) 4,727 (12,15) 4,154 (17,54) 3,331 (13,90) 4,336 (17,80) 3,331 (13,90) After High-school degree 60,516 (64,30) 12,407 (56,61) 15,049 (63,356) 16,130 (66,44) 16,930 (69,84) Occupation No employment 4,979 (5,29) 1,772 (8,09) 1,368 (5,78) 1,039 (4,28) 800 (3,30) Farmer, merchant, artisn, company director, manual 5,518 (5,86) 1,551 (7,12) 1,402 (5,92) 1,312 (5,40) 1,243 (5,13) Monthy household income 5,518 (3,334) 5,355 (24,48) 7,443 (31,43) 8,733 (35,77) 5,424 (22,37) Not communicated 1,077 (11,77) 3,022 (13,79) 2,727 (11,44) 2,533 (10,45) 1,540 (15,70) From 0 12,00 € monthy 15,716 (17,67) 5,192 (12,59) 5,717 (11,44) 2,538 (10,45) 5,920 (21,46) From 0 12,00 € monthy 2,304 (24,48) 5,949 (27,14) 6,100 (25,76) 5,792 (23,86) 5,202 (21,46) Monthy household income 1,209 (40,82) </td <td>Autumn</td> <td>11,787 (12.52)</td> <td>2,247 (10.25)</td> <td>2,871 (12.13)</td> <td>3,208 (13.21)</td> <td>3,401 (14.28)</td> <td></td>	Autumn	11,787 (12.52)	2,247 (10.25)	2,871 (12.13)	3,208 (13.21)	3,401 (14.28)	
Control level 7,519 (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) Affer High-school degree 16,078 (17.08) 12,407 (55.61) 15,049 (63.56) 15,100 (65.44) 15,303 (65.44) 15,303 (65.43) No employment 4,975 (15.92) 1,772 (8.09) 1,368 (5.78) 1,039 (4.28) 800 (3.30) Farmer, merchant, artisan, company director, manual 5,518 (5.86) 1,551 (7.12) 1,402 (5.92) 1,312 (5.40) 2,248 (22.237) Intermediate profession 25,007 (25.75) 5,056 (12.30) 6,238 (25.23) 6,766 (27.87) 6,942 (28.64) Nonthly household income 10,771 (11.77) 3,022 (13.79) 2,745 (11.59) 2,777 (11.44) 2,538 (10.65) From 1,200 to 1,200 to monthly 15,716 (15.70) 5,139 (23.45) 4,157 (17.56) 3,531 (14.54) 2,889 (11.92) From 1,200 to 2,700 to 21,949 (23.22) 4,300 (22.1) 5,500 (23.23) 5,923 (24.40) 6,066 (25.15) More than 2,700 to monthy <td></td> <td>14,345 (15.24)</td> <td>3,421 (15.01)</td> <td>3,002 (15.21)</td> <td>3,582 (14.75)</td> <td>3,740 (15.43)</td> <td>-0.0001</td>		14,345 (15.24)	3,421 (15.01)	3,002 (15.21)	3,582 (14.75)	3,740 (15.43)	-0.0001
Ampschool degree 17,39 (12.8.1) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 4,76 (12.8.9) 1,712 (10.1.7) 5,921 (10.1.7) 5,931 (13.9.9) 4,70 (12.8.9) 1,712 (10.1.7) 5,012 (12.5.9) 1,712 (10.1.7) 5,012 (12.5.9) 1,712 (10.1.7) 1,029 (12.8.9) 1,312 (5.40) 1,243 (5.13)	Educational level	17 510 (10 61)	4 707 (24 04)	4 475 (10 00)	4 226 (17 06)	2 0 2 1 (1 C 1 7)	<0.0001
High school degree 10,198 (17,08) 3,722 (21,25) 4,154 (17,454) 3,511 (15,70) 3,591 (13,39) Occupation	< High-school degree	17,519 (18.61)	4,787 (21.84)	4,475 (18.90)	4,336 (17.86)	3,921 (10.17)	
Atter high-school agerge bb, bb [bb, ab] 15, 30 [bb, ab] 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 5, 518 (5, 86) 1, 561 (7, 12) 1, 402 (5, 22) 1, 312 (5, 40) 1, 243 (5, 13) workers Employes 27, 225 (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) Monthly household income 10,077 (11,77) 3, 022 (13, 79) 2, 745 (11,59) 2, 777 (11,44) 2, 533 (10,45) 5, 200 (21, 46) From 1, 200 to 1, 800 to 2, 700 € 11, 904 (23, 32) 4, 430 (20, 21) 5, 500 (23, 23) 5, 923 (24, 40) 6, 096 (25, 15) 5, 000 (21, 46) More than 2, 700 € monthly 23, 242 (23, 72) 3, 376 (15, 40) 5, 176 (21, 86) 6, 677 (27, 50) 6, 588 (27, 99) 4, 530 (23, 99) Montha 2, 700 € 19, 99 (28, 55)	High-school degree	16,078 (17.08)	4,722 (21.55)	4,154 (17.54)	3,811 (15.70)	3,391 (13.99)	
Occupation 4,979 (5.29) 1,772 (8.09) 1,368 (5.78) 1,039 (4.28) 800 (3.00) Farmer, merchant, artisan, company director, manual 5,518 (5.86) 1,561 (7.12) 1,402 (5.92) 1,312 (5.40) 1,243 (5.13) company director, manual 5,518 (5.86) 1,561 (7.12) 1,402 (5.92) 6,227 (26.47) 5,424 (22.37) 6,942 (26.64) Top manager 31,374 (33.34) 5,365 (24.40) 7,433 (31.43) 8,733 (35.97) 9,833 (40.56) Monthly houshold income 5,176 (16.70) 5,133 (23.45) 4,157 (17.56) 3,531 (14.54) 2,889 (11.92) From 1,200 to 1,800 € 23,043 (24.48) 5,949 (27.14) 6,100 (25.76) 5,923 (24.40) 6,960 (25.15) More than 2,700 € monthly 21,949 (23.32) 4,430 (20.21) 5,500 (23.23) 5,923 (24.40) 6,960 (25.15) More than 2,700 € monthly 22,328 (23.72) 3,376 (15.40) 5,176 (21.86) 6,772 (72.50) 6,688 (27.59) Yes 6,7154 (71.35) 15,108 (68.94) 1,680 (72.50) 17,554 (72.4) 1,000 (23.33) Smoking status 4,7211 (50.16) <td< td=""><td>After High-school degree</td><td>60,516 (64.30)</td><td>12,407 (56.61)</td><td>15,049 (63.56)</td><td>16,130 (66.44)</td><td>16,930 (69.84)</td><td></td></td<>	After High-school degree	60,516 (64.30)	12,407 (56.61)	15,049 (63.56)	16,130 (66.44)	16,930 (69.84)	
No employement 4,97 (5.29) 1,77 (8.09) 1,368 (5.78) 1,039 (4.28) 800 (3.30) Farmer, mechant, artisa, 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) 6,942 (28.64) Top manager 31,374 (33.34) 5,365 (24.48) 7,433 (31.43) 8,733 (35.97) 9,833 (40.56) Not communicated 11,077 (11.77) 3,022 (13.79) 2,745 (11.59) 2,777 (11.44) 2,583 (10.45) From 0 1,200 to 1,800 € 23,043 (24.48) 5,949 (27.14) 6,100 (25.76) 5,792 (23.86) 5,020 (21.46) More than ,700 € monthly 22,328 (23.72) 3,376 (15.40) 5,176 (21.86) 6,577 (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) Yes 67,154 (71.35) 15,108 (68.94) 16,892 (71.34) 17,600 (72.50) 17,554 (72.41) Smokers 47,211 (50.16) 11,016 (50.26) 11,976 (50.58)<	Occupation	4 070 (5 20)	4 772 (0.00)	4 200 (5 70)	4 020 (4 20)	000 (2.20)	<0.0001
Partner, metroand, 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) 6,494 (22.37) 6,942 (26.47) Intermediate profession 2,007 (26.57) 5,061 (23.09) 6,238 (26.35) 6,766 (27.7) 6,942 (26.47) 6,942 (26.47) Top manager 31,374 (33.34) 5,356 (24.48) 7,443 (31.43) 8,733 (35.97) 9,833 (40.56) Monthly houshold income 5,138 (23.45) 4,157 (17.56) 3,531 (14.54) 2,889 (11.92) From 1,200 € monthly 15,716 (16.70) 5,138 (23.45) 4,157 (17.56) 3,518 (44.80) 5,020 (21.32) 5,020 (21.46) From 1,800 to 2,700 € 21,949 (23.22) 4,430 (20.21) 5,500 (23.23) 5,923 (24.40) 6,066 (25.15) More than 2,700 € monthly 21,949 (23.22) 1,510 (80.21) 1,682 (71.34) 1,700 (72.50) 6,688 (72.90) Smoking stus 5,715 (17.35) 15,108 (63.94) 1,010 (50.26) 1,976 (50.58) 1,2125 (49.94) 2,094 (48.89) <	No employement	4,979 (5.29)	1,772 (8.09)	1,368 (5.78)	1,039 (4.28)	800 (3.30)	
company director, manual workers 1,581 (5.86) 1,591 (7.12) 1,402 (5.92) 1,512 (5.40) 1,243 (5.13) Employes 27,235 (28.94) 8,157 (37.22) 7,227 (30.52) 6,427 (26.47) 6,542 (22.37) 6,942 (23.35) Intermediate profession 25,007 (26.57) 5,061 (23.09) 6,238 (26.35) 6,766 (27.87) 6,942 (23.35) 7,237 (11.44) 2,533 (10.45) Not communicated 11,077 (11.77) 3,022 (13.79) 2,745 (11.59) 2,777 (11.44) 2,533 (10.45) From 1,200 to 1,800 € 23,043 (24.48) 5,949 (27.14) 6,100 (25.76) 5,792 (23.86) 5,202 (21.46) Monthly 23,043 (24.48) 5,949 (27.14) 6,100 (25.76) 5,792 (23.86) 5,202 (21.46) More than 2,700 € monthly 23,328 (23.72) 3,376 (15.40) 5,176 (21.86) 6,254 (25.76) 7,522 (31.03) 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) 16,692 (34.61) 16,000 (25.76) 7,522 (31.03) Smoking status 30,366 (33.86)	Farmer, merchant, artisan,		1 5 6 1 (7 1 2)	1 402 (5 02)	1 212 (5 40)	1 242 (5 12)	
workers start <	company director, manual	5,518 (5.86)	1,561 (7.12)	1,402 (5.92)	1,312 (5.40)	1,243 (5.13)	
Lintgruediate profession 27,235 (26.34) 6,137 (37.22) 7,227 (30.32) 6,727 (26.37) 5,642 (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	workers Employee	27 225 (28 04)	0 157 (27 22)	7 227 (20 52)	C 427 (2C 47)		
Intermediate protestion 25,007 (26.57) 5,007 (25.37) 5,036 (22.49) 6,766 (27.87) 6,942 (28.64) Top manager 31,374 (33.44 5,365 (24.48) 7,443 (31.43) 8,733 (35.97) 9,833 (40.56) Monthly household income	Employes	27,235 (28.94)	8,157 (37.22)	7,227 (30.52)	0,427 (20.47)	5,424 (22.37)	
Top manager 1,5,1,4 (3.5.34) 5,363 (24-46) 7,443 (31.45) 6,735 (35.97) 9,635 (40.56) Nonthly household income		25,007 (20.57)	5,061 (23.09)	0,238 (20.33)	0,700 (27.87)	0,942 (28.04)	
Not communicated 11,077 (11.77) 3,022 (13.79) 2,745 (11.59) 2,777 (11.44) 2,533 (10.45) From 1,200 to 1,800 € 3,043 (24.48) 5,949 (27.14) 6,100 (25.76) 5,792 (23.86) 5,202 (21.46) · From 1,200 to 1,800 € 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) 6,677 (27.50) 6,688 (27.59) · No 26,959 (28.65) 6,808 (31.06) 6,786 (28.66) 6,677 (27.50) 6,688 (27.59) · <td>Nonthly household income</td> <td>31,374 (33.34)</td> <td>5,305 (24.48)</td> <td>7,443 (31.43)</td> <td>8,733 (33.97)</td> <td>9,833 (40.50)</td> <td>-0 0001</td>	Nonthly household income	31,374 (33.34)	5,305 (24.48)	7,443 (31.43)	8,733 (33.97)	9,833 (40.50)	-0 0001
Not communicated 11,07 (11.7) 5,022 (13.73) 2,74 (11.39) 2,74 (11.44) 2,383 (10.43) From 0.1,200 to 1,200 € 15,716 (16.70) 5,139 (23.45) 4,157 (17.56) 3,511 (14.54) 2,889 (11.92) From 1,200 to 1,800 € 23,043 (24.48) 5,949 (27.14) 6,100 (25.76) 5,792 (23.86) 6,096 (25.15) More than 2,700 € 21,949 (23.32) 4,430 (20.21) 5,500 (23.23) 5,923 (24.40) 6,096 (25.15) More than 2,700 € 6,715 (71.53) 15,108 (68.94) 16,892 (71.34) 17,600 (72.50) 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 5,036 (13.68) 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) 4,030 (40.76) High 22,512 (23.92) 6,357 (29.01) 6,119 (25.84) 5,517 (22.73) 4,519 (18.60) Moderate 40,538 (43.07) 8,975 (40.95) 10,112 (42.71) 10,601 (43	Not communicated	11 077 (11 77)	2 022 (12 70)	2 745 (11 50)	2 777 (11 44)	2 522 (10 45)	<0.0001
From 1,200 to 2,700 € 5,33 (24.43) 5,949 (27.14) 6,100 (25.76) 5,792 (23.86) 5,202 (21.46) From 1,200 to 2,700 € 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 No 26,959 (28.65) 6,808 (31.06) 6,786 (28.266) 6,677 (27.50) 17,554 (72.41) Smoking status Non-smokers 47,211 (50.16) 11,016 (50.26) 11,976 (50.58) 12,125 (49.94) 12,094 (49.89) Former smokers 15,036 (15.98) 4,630 (21.13) 4,016 (16.96) 3,544 (14.60) 2,846 (11.74) Moderate 40,538 (43.07) 8,975 (40.95) 10,112 (42.71) 10,601 (43.67) 10,850 (44.76) High <	From 0 to 1 200 6 monthly	11,077 (11.77)	5,022 (13.79) F 120 (22.4F)	2,745 (11.59)	2,777 (11.44)	2,533 (10.45)	
Initial 200 (b) 1,000 cf 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) 6,257 (27.50) 6,688 (27.59) No 26,959 (28.65) 6,808 (31.06) 6,786 (28.66) 6,677 (27.50) 6,688 (27.59) Yes 6,7154 (71.35) 15,108 (68.94) 16,892 (71.34) 17,600 (72.50) 17,554 (72.41) Smoking status 7 5,366 (33.86) 6,270 (28.61) 7,686 (32.46) 8,608 (35.46) 9,302 (38.37) Smokers 31,663 (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 22,121 (23.92) 6,357 (29.01) 6,119 (25.81) 5,517 (22.73) 4,519 (18.64) Low 31,063 (33.01) 6,584 (30.04) 7447 (31.45) 8159 (33.61)	From 1 200 to 1 200 £	15,710 (10.70)	5,139 (23.45)	4,157 (17.50)	3,531 (14.54)	2,889 (11.92)	
Industry From 1,800 to 2,700 € 21,949 (23.32) 4,430 (20.21) 5,500 (23.23) 5,923 (24.40) 6,096 (25.15) More than 2,700 € 21,949 (23.32) 3,376 (15.40) 5,176 (21.86) 6,254 (25.76) 7,522 (31.03) Couple 7 7 7 7 7 6,688 (27.59) 7 Yes 67,154 (71.35) 15,108 (68.94) 16,892 (71.34) 17,600 (72.50) 17,554 (72.41) 7 Smoking status 7 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 (15.96) 3,544 (14.60) 2,044 (49.89) Physical activity 7 10,033 (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 2,2512 (23.92) 6,357 (29.01) 6,119 (28.34) 2,316 ± 4.45 </td <td>FIOIN 1,200 to 1,800 €</td> <td>23,043 (24.48)</td> <td>5,949 (27.14)</td> <td>6,100 (25.76)</td> <td>5,792 (23.86)</td> <td>5,202 (21.46)</td> <td></td>	FIOIN 1,200 to 1,800 €	23,043 (24.48)	5,949 (27.14)	6,100 (25.76)	5,792 (23.86)	5,202 (21.46)	
Initial Lybor (2), 100 c 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) <0.0001	Erom 1 800 to 2 700 \pounds						
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	monthly	21,949 (23.32)	4,430 (20.21)	5,500 (23.23)	5,923 (24.40)	6,096 (25.15)	
Non-chain 2, No C monthly 22, 22 (2.5.72) 5, 370 (2.5.82) 5, 370 (2.5.80)	More than 2 700 £ monthly	22 228 (22 22)	3 376 (15 40)	5 176 (21 86)	6 254 (25 76)	7 522 (31 03)	
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 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 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 (29.01) 6,119 (25.84) 5,17 (22.73) 4,519 (18.64)	Couple	22,320 (23.72)	5,570 (15.40)	5,170 (21.00)	0,234 (23.70)	7,522 (51.05)	<0 0001
No 20,55 (26.85) 5,50 (26.85) 6,60 (26.85) 6,60 (26.85) 6,60 (26.85) 7,750 (27.84) 7,750 (27.84) 7,7554 (72.41) Smoking status - -	No	26 959 (28 65)	6 808 (31 06)	6 786 (28 66)	6 677 (27 50)	6 688 (27 59)	0.0001
No.s No.s <th< td=""><td>Ves</td><td>67 154 (71 35)</td><td>15 108 (68 94)</td><td>16 892 (71 34)</td><td>17 600 (72 50)</td><td>17 554 (72 41)</td><td></td></th<>	Ves	67 154 (71 35)	15 108 (68 94)	16 892 (71 34)	17 600 (72 50)	17 554 (72 41)	
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	Smoking status	07,104 (71.00)	13,100 (00.34)	10,032 (71.34)	17,000 (72.50)	17,334 (72.41)	<0 0001
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	Non-smokers	47 211 (50 16)	11 016 (50 26)	11 976 (50 58)	12 125 (49 94)	12 094 (49 89)	\0.0001
Sinder sincles 31,050 (35.00) 0,210 (25.01) 7,050 (25.00) 3,540 (14.60) 3,540 (14.60) 2,846 (11.74) Smokers 15,036 (15.98) 4,630 (21.13) 4,016 (16.96) 3,544 (14.60) 2,846 (11.74) Physical activity	Former smokers	31 866 (33 86)	6 270 (28 61)	7 686 (32 46)	2,123 (4 3.54) 8 608 (35 46)	9 302 (38 37)	
biolocity 1,000 (15.50) 4,000 (11.15) 4,010 (10.50) 5,544 (14.00) 2,000 (11.14) Physical activity (10001) (10001) (10001) (10001) (10001) Moderate 40,538 (43.07) 8,975 (40.95) 10,112 (42.71) 10,601 (43.67) 10,850 (44.76) (10001) High 22,512 (23.92) 6,357 (29.01) 6,119 (25.84) 5,517 (22.73) 4,519 (18.64) (10005) 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 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	Smokers	15 036 (15 98)	4 630 (21 13)	1,000 (32.40) 1,016 (16.96)	3 544 (14 60)	2 846 (11 74)	
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	Physical activity	15,050 (15.58)	4,030 (21.13)	4,010 (10.90)	5,544 (14.00)	2,040 (11.74)	<0 0001
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		31 063 (33 01)	6 584 (30 04)	7447 (31 45)	8159 (33 61)	8873 (36 60)	\0.0001
High22,512 (23.92)6,357 (29.01)6,119 (25.84)5,517 (22.73)4,519 (18.64)Body Mass Index, kg/m223.84 ± 4.5724.49 ± 5.0624.12 ± 4.7423.76 ± 4.4523.05 ± 3.880.003Energy intake without alcohol, kcal/d1,809.37 ± 454.911,743.81 ± 481.981,782.98 ± 459.681,816.56 ± 445.131,887.23 ± 421.820.0005Alcool intake, g/d7.80 ± 11.528.04 ± 14.257.85 ± 11.837.72 ± 10.687.62 ± 8.960.2Number of 24 h record6.20 ± 2.845.36 ± 2.656.04 ± 2.816.49 ± 2.836.81 ± 2.84<.0001	Moderate	A0 538 (A3 07)	8 975 (<i>1</i> 0 95)	10 112 (12 71)	10 601 (43 67)	10 850 (44 76)	
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 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	High	40,550 (45.07) 22 512 (23 92)	6 357 (29 01)	6 119 (25 84)	5 517 (22 73)	10,000 (44.70) 1 519 (18 61)	
body Muss mack, kg/m 23.84 ± 4.97 24.45 ± 5.00 24.11 ± 4.74 25.70 ± 4.45 25.00 ± 1.60 0.0005 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	Body Mass Index kg/m ²	22,312 (23.32)	24 49 + 5 06	2/112 (23.04)	23 76 + 4 45	23 05 + 3 88	0 003
Linergy 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	Epergy intake without alcohol	23.04 ± 4.37	24.45 ± 5.00	24.12 ± 4.74	25.70 ± 4.45	25.05 ± 5.00	0.005
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	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
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	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
Family history of cardiovascular diseases <0.0001	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
diseases <0.0001	Family history of cardiovascular	0.20 2 2.0 1	5.50 - 2.05	0.01 2 2.01	0.15 2 2.05	0.01 2 2.01	
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	diseases						<0.0001
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 No 85 988 (91 37) 20 296 (92 61) 21 655 (91 46) 21 967 (90 48) 22 070 (91 04)	No	66,481 (70,64)	16.575 (75.63)	16.984 (71.73)	16.855 (69.43)	16.067 (66.28)	
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	Yes	27 632 (29 36)	5 341 (24 37)	6 694 (28 27)	7 422 (30 57)	8 175 (33 72)	
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 <	Family history of diabetes	_,,002 (20.00)	0,011(21.07)	2,00 (20.27)	., 122 (00.07)	5,2,5 (55.72)	0.3
Yes 1604 (1.70) 346 (1.58) 447 (1.89) 456 (1.88) 355 (1.46) Family history of hypertension <0.0001	No	92,509 (98 30)	21,570 (98 42)	23,231 (98 11)	23.821 (98.12)	23,887 (98 54)	0.0
Family history of hypertension S540 (1.50) S440 (1.50) S550 (1.60) S550 (1.40) No 85 988 (91 37) 20 296 (92 61) 21 655 (91 46) 21 967 (90 48) 22 070 (91 04)	Yes	1604 (1 70)	346 (1.58)	447 (1 89)	456 (1 88)	355 (1 46)	
No 85 988 (91 37) 20 296 (92 61) 21 655 (91 46) 21 967 (90 48) 22 070 (91 04)	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)	Yes	8,125 (8.63)	1,620 (7.39)	2,023 (8.54)	2,310 (9.52)	2,172 (8.96)	

355 356 357	* P value dichotor linear co	e for the comparis mises or ordinals v ontrast for numeri	on between qu variables, Chi ² c variables.	uartiles of M for others ca	EDI-LITE, by tests tegorical variable	from Mantel-Henzel (s and generalized line	Chi ² for ear models with	
358 359 360	† _{Sex-sp} men.	ecific cut-offs for	quartiles of M	EDI-LITE wer	e 8.00/10.00/12.0	0 for women and 8.00	0/10.00/12.00 f	ōor
361								
362								
363								
364	By con	struction, a hig	gher MEDI-L	ITE was as	sociated with I	nealthier dietary p	profiles: a reg	gular
365	use of	olive oil, a m	ajor consun	nption of f	ruit, vegetable	es, legumes, grain	n group, fish	and
366	seafoo	d, and a mode	rate to low o	consumptio	on of meat, dai	ry products and al	lcohol.	
367	The as	ssociation bet	ween MED	I-LITE, mP	NNS-GS and	AHEI-2010 and r	risk of CVD	are
368	presen	ted in <u>Table II</u> .						
369								
370								
371								
372								
373	Table II							
374	Multiva	riable [*] associat	ions (hazard	ratios (HR) and 95% con	fidence intervals (95% CI)) betv	veen
375	continu	ous or sex-spe	ecific quartil	es of MEI	DI-LITE [†] , mPNN	S-GS [‡] and AHEI-2	010 [§] and ris	k of
376	cardiov	ascular disease,	NutriNet-Sar	ité Cohort,	France, 2009–20	18.		
377								
	<u>.</u>	Continuous	score	-	Sex-sp	ecific quartiles		
Disea	ses	All	P-value	Q1	Q2	Q3	Q4	P-trend
MEDI	-LITE							

N for cases / 1,399 / 92,714 273 / 21,643 339 / 23,339 368 / 23,909 419 / 23,823 non-cases 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 cardiovascular diseases (yes/no), educational level (< high-school degree and/ high-school degree/ 2 years after 381 382 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).

¹ 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.

391 P-value for the continuous score.

392

393

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

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

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 <u>Supplemental</u>

400 Table IV. Similar results were obtained when cases where 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

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, <u>∨</u>). Table III Multivariable^{*} associations (hazard ratios (HR) and 95% confidence intervals (95% CI)) between continuous or

449 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.

	Continuous	score	Sex-specific quartiles				
Scores	All	P-value	Q1	Q2	Q3	Q4	P-trend
MEDI-LITE							
N for cases /	952 / 81,954		179 / 17,997	218 / 20,538	256 / 21,556	299 / 21,863	
non-cases							
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 /	952 / 81,954		151 / 20,449	210 / 19,421	264 / 20,969	327 / 21,115	
non-cases							
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 /	952 / 81,954		151 / 19,476	228 / 20,515	278 / 20,872	295 / 21,091	
non-cases							
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 (< high-school degree and/ high-school degree/ 2 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual 446 447 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), 448 449 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.

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.

\$ 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.

455 P-value for the continuous score.

456

457 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.

	Continuous	score		Sex-s	specific quartiles		- Dtrond
Scores	All	P-value	Q1	Q2	Q3	Q4	P-trenu
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 (< high-school degree and/ high-school degree/ 2 years after high school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual 465 466 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), cohabiting status (yes/no) and season of completion of recruitment (spring, summer, fall, winter). 468 469 [†] 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. 475 476 477 Table V 478 479 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.

	Continuous	score	Sex-specific quartiles				P-trend
Scores	All	P-value	Q1	Q2	Q3	Q4	
MEDI-LITE							
N for cases /	1,136 / 53,668		191 / 9,550	268 / 12,919	307 / 15,061	370 / 16,138	
non-cases 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			156 / 10 254	265 / 12 224		264 / 15 201	
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 (tir	me-scale), sex, B	MI (kg/m2, continu	ous), physical activ	vity (high, moderate,	<u>-</u>
483 lo	ow), smoking status (ne	ever smoker	rs, former smoke	rs, occasional or pe	ermanent smokers)	, numbers of dietary	
484 re	ecords (continuous), al	cohol intake	e (g/d, continuou	s), energy intake (w	vithout alcohol, g/d	, continuous), family	
485 h	istory of cardiovascula	r diseases (y	ves/no), educatio	nal level (≤ high-scl	nool degree and/ h	igh-school degree/ 2	
486 y	ears after high school d	armediate n	upation (unemple rofession/ton m	byed/farmer, mercr	ousebold income (any director, manual	
488 <	1.200€ monthly /fron	n 1.200€ to	o 1.800€ month	ulv/from 1.800€ to	2.700€ monthly/	>2.700€ monthly).	
489 c	ohabiting status (yes/n	o) and sease	on of completion	of recruitment (spr	ing, summer, fall, w	vinter).	
490 [†]	Sex-specific cut-offs for	r quartiles o	f MEDI-LITE were	8.00/10.00/12.00	for women and 8.0	0/10.00/12.00 for	
491 m	ien.						
492 [‡]	Sex-specific cut-offs for	r quartiles o	f mPNNS-GS wer	e 6.80/8.05/9.30 fo	r women and 6.80/	7.80/9.00 for men.	
493 §	Sex-specific cut-offs for	r quartiles o	f AHEI-2010 were	2 38.95/47.55/56.41	L for women and 36	5.37/45.04/54.19 for	
494 m	ien.						
495	P-value for the continu	ous score.					
496							
497							
498							
499							
500 C	concerning 'softer	events', c	only the AHEI	2010 was asso	ciated with a lo	ower risk (HRQ5-	
501 C	01=0.68, 95% CI: 0.5	53-0.87 <i>,</i> P	trend=0.004).				
502 C	concerning 'mediur	n events'	(acute coron	ary syndrome a	ind angioplasty)	, the mPNNS-GS	
503 O	nly was associated	with a low	ver risk (HRQ5	-Q1=0.75, 95% (Cl: 0.57-0.98, Ptr	end=0.02).	
504 C	Concerning 'harder	events', th	ne results for N	/IEDI-LITE and AI	HEI-2010 becom	e insignificants.	
505 li	n these analyses, c	utting the	outcome in t	this way leads to	o a lack of pow	er (<u>Supplemental</u>	
506 <u>T</u>	able V).						
507							
508							

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

risk showed that the hypothesis of linearity was reliable.

The discrimination was elevated and similar whatever the dietary score examined. The Cindex 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.

515

516 **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 522 consistent with the findings previously documented in the scientific literature focusing on 523 Mediterranean diet and CVD although other dietary scores were used. Two meta-analyses – 524 Grosso and al. including 17 cohorts or RCTs studies [30], Sofi and al. including 14 studies [14] -525 reported evidence of a beneficial role of high adherence to a Mediterranean Diet on CVD's 526 527 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.). 528 The meta-review of Martinez-Lacoba (including 9 reviews and 24 meta-analyses) also 529 530 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 55 531 studies reporting a favourable role of adherence to Mediterranean Diets and cardiovascular 532

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 <u>Supplemental Table IV</u>, 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].

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

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

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

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

604 The recent update of the French food-based dietary guidelines [38] recommending moderate consumption of meat and dairy product, and increasing consumption in non-605 606 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 607 products consumption from 3 to 2 serving per day and a low consumption of red meat up to 608 609 500 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 610 those recommendations. 611

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.

619 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 628 related treatments may lead to change in diet of the patients. In our study, we assume that 629 this phenomenon had affected a low proportion of participants, but exclusion of incident or 630 prevalent cancer cases does not affect the findings (data not shown). Also, we considered 631 sensitive analysis suppressing the events appeared in the first 2-years of followed-up, 632 supposing that they could be the effect of a previous diet, even if the participant has chosen 633 to undertake a recent change in his diet. The analysis shown that this possibility didn't 634 change the results of the study. 635

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 642 healthy effect might exist: these participants follow a healthy diet, exhibit healthier 643 behaviours (such as lower tobacco use) and have a higher social status (higher graduate and 644 higher income) [40,41]. Furthermore, there was a high proportion of women in this study, 645 646 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 647 population which was probably more concerned by nutrition and health. Thus, 648 649 generalization of these findings should be made with caution.

50 Some important strengths should be highlighted. Our study stems from a large and 51 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.

657

658 CONCLUSION

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

670

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