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**Association between adherence to the EAT-Lancet diet and risk of cancer and cardiovascular outcomes in the prospective NutriNet-Santé cohort.**

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**Running Head:** EAT-Lancet recommendations and chronic diseases

**Abbreviations:**

AHEI-2010: Alternate HEI, version 2010

BMI: Body Mass Index

CI: Confidence Interval

CU: consumption unit

CVD: cardiovascular diseases

DASH: Dietary Approaches to Stop Hypertension Score

ELD-I: EAT-Lancet Diet Index

FBDG: Food-based Dietary Guidelines

HEI: Healthy Eating Index

HR: Hazard Ratio

ICD-10: international classification of diseases, 10th revision

IPAQ: International Physical Activity Questionnaire

NCD: Non-communicable diseases

PNNS-GS2: PNNS Guidelines Score 2

Q: Quintile

SD: Standard Deviation

WHO: World Health Organization

WISH: World Index for Sustainability and Health

**Number of tables:** 3

**Number of figures:** 1

**Supplementary Material:** 10 tables

**Word count:** abstract = 295, text=4,627

## 1 **Abstract**

2 **Background:** The EAT-Lancet commission proposed, in 2019, a planetary, healthy and universal  
3 dietary. However, this diet has been rarely studied in relation to various health outcomes.

4 **Objective:** We aimed to prospectively estimate the association between the EAT-Lancet diet and  
5 cancer and cardiovascular risk.

6 **Design:** The study was conducted among participants of the NutriNet-Santé cohort (2009 – 2021).  
7 The endpoints were the incident outcomes (cancer and cardiovascular diseases (CVD) and mortality  
8 from these diseases), combined and separately. Adherence to the EAT-Lancet diet was estimated using  
9 the EAT-Lancet Diet Index (ELD-I) modelled as quintiles (Q). Multivariable Cox proportional  
10 hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs),  
11 adjusted for potential confounders and moderators.

12 **Results:** A total of 62,382 subjects were included, 2,475 cases of cancer and 786 cases of  
13 cardiovascular occurred during a median follow-up of 8.1 years. The sample was 76% female, the  
14 mean age at inclusion was 51 years (Standard Deviation (SD) = 10.2 years). The ELD-I ranged from -  
15 162 to 332 points with a mean score of 45.4 points (SD = 25.6 points). In multivariable models, no  
16 significant association between the EAT-Lancet diet and the risk of cancer and CVD combined, and  
17 separately, was observed. Alcohol consumption was an effect modifier of the association. A  
18 significant association was observed among low drinkers (HR<sub>Q5 vs Q1</sub>=0.86, (95% CI 0.73, 1.02), p-  
19 trend=0.02). A higher ELD-I was significantly associated with a lower risk of overall cancer only  
20 among females, (HR<sub>Q5 vs Q1</sub>=0.89, (95% CI 0.75, 1.05), p-trend=0.03). Both associations were largely  
21 attenuated by body mass index.

22 **Conclusion:** Contrary to our hypothesis, our results documented significant associations between  
23 adherence to the EAT-Lancet diet and incidence of cancer only in some subgroups, and no association  
24 with CVD.

25  
26 **Keywords:** nutrition, sustainable diet, healthy eating, food system, chronic diseases.

## 27 **Introduction**

28 Non-communicable disease (NCD) burden is a major global public health issue. According to the  
29 World Health Organization (WHO), in 2019, NCD were the leading cause of premature death  
30 worldwide. They accounted for more than 74 % of death worldwide and more than 88 % in high-  
31 income countries such as France (1), where cancer and cardiovascular diseases (CVD) are the leading  
32 causes of death.

33 It is now established that some modern dietary habits, rich in fat, sugar and salt have deleterious health  
34 effects and contribute to chronic disease development (2,3). It is also recognized that plant-based diets  
35 can help prevent chronic diseases (4–7). **However, these diets, which are considered healthier, are**  
36 **sometimes rich in ultra-processed foods and are not always beneficial to health** (8). In addition,  
37 compared to the current food production which has significant negative effects on the environment  
38 (6,9,10) and accounts for 26% of the anthropogenic greenhouse gas emissions (11,12), mainly from  
39 ruminants, diets rich in plant products have lower environmental impacts (10,13,14). If no drastic and  
40 rapid changes are made to the current food system, greenhouse gas emissions (15,16), disruption of  
41 biogeochemical cycles (17), loss of biodiversity, land use changes (18) and global water use (19)  
42 would push natural processes beyond global limits (20–23). In addition to food losses and wastes, the  
43 entire production system and human dietary behaviors (24) require drastic changes, as diet is one of  
44 the most powerful lever for optimizing both planetary and human health (4).

45 In that context, in 2019, the international EAT-Lancet commission, composed of 37 experts of various  
46 fields, has developed a universal planetary healthy reference diet (4). It is an evidence-based diet  
47 considering the multiple links between nutrition, health and the environment, aimed at « estimating  
48 health and environmental effects of adopting an alternative diet ». The EAT-Lancet diet provides a set  
49 of recommendations for feeding the entire world population within planetary boundaries. This diet has  
50 been designed to serve as an anchor for integrating sustainability into national dietary  
51 recommendations of culturally diverse countries. For this purpose, it is standardized on the daily  
52 energy intake and based on a cut-off structure, so that it can be adaptable to different preferences,  
53 settings and populations. Overall, the EAT-Lancet diet is a 2,500 kcal per day diet which encourages

54 the consumption of plant-based foods, such as fruit and vegetables, wholegrain products, legumes,  
55 oleaginous, and unsaturated oils. It consists of very moderate amounts of seafood, eggs and poultry  
56 and considerably limits the consumption of products rich in added fats and sugars, refined cereals, and  
57 foods of animal origin, such as beef, pork and lamb. Thus, this diet could have important health  
58 benefits, and according to the authors, could prevent approximately 10 million premature deaths per  
59 year worldwide, representing a 19% decrease in the total number of deaths among adults (4). The  
60 EAT-Lancet diet is already considered as a universal healthy reference diet, although few studies have  
61 explored its nutritional quality and its long-term health impacts. In addition, the few existing studies  
62 are rather contradictory. In particular, a modeling study analyzing national food-based dietary  
63 guidelines (FBDG) from 85 countries (25) and a Swedish prospective cohort study (26) have shown  
64 beneficial effects of EAT-Lancet diet on mortality and on the risk of certain chronic diseases.  
65 Similarly, a United Kingdom prospective study showed a decrease in diabetes with adherence to the  
66 EAT-Lancet diet pattern, although this association was largely mediated by body mass index (BMI)  
67 (27). However, a British cohort study conducted in 46,069 participants invalidated these results (28)  
68 while another questioned the validity of the EAT-Lancet guidelines (29).

69 We therefore aimed to estimate the association between the adherence to the EAT-Lancet diet and the  
70 risk of major chronic diseases (i.e. cancers and CVD) in a large prospective cohort of French adults.

## 71 **Methods**

### 72 *Study population*

73 The NutriNet-Santé study is a French web-based prospective cohort launched in 2009 and still  
74 ongoing, with the objective to study the relationships between nutrition, its determinants and health.  
75 The NutriNet-Santé study's design and methods are described elsewhere (30). Participants were  
76 recruited from the general population through a large multimedia campaign, among adult volunteers ( $\geq$   
77 18 years old) with access to the internet. Registration and follow-up are done online on a dedicated  
78 website ([www.etude-nutrinet-sante.fr](http://www.etude-nutrinet-sante.fr)). The NutriNet-Santé study is conducted in accordance with the  
79 Declaration of Helsinki and was approved by the Ethics Committee of the French Institute of Health  
80 and Medical Research (IRB Inserm Research (IRB Inserm n° 0000388FWA00005831) and by

81 National Commission on Informatics and Liberty (CNIL n° 908450 and n°909216). The NutriNet-  
82 Santé study is registered in ClinicalTrials.gov (NCT03335644). At inclusion in the study, all  
83 participants signed an electronic informed consent via the online platform. This procedure is  
84 appropriate for web-based cohorts and has been validated by the ethical and regulatory authorities  
85 mentioned above.

## 86 ***Data collection***

### 87 **Cases ascertainment**

88 Health data were self-reported by participants at baseline, and then through at least yearly health  
89 questionnaire or at any time through a dedicated interface on the study website. For each new declared  
90 event, participants were invited to provide their medical records (diagnoses, hospitalization,  
91 radiological reports, electrocardiograms). If necessary, the physicians of the research team contacted  
92 the patients' referring physicians or specialists to obtain additional information. These data were then  
93 evaluated by team's physicians to validate and code the main health events. In addition, health data  
94 were linked to medico-administrative databases of the French national health insurance (SNIIRAM) to  
95 retrieve potential additional cases. Vital status of the subjects as well as the causes of death were  
96 identified using the French national cause-specific mortality registry (CépiDC). Cancers and CVD  
97 cases were classified using the international classification of diseases, 10th revision (ICD-10) (31). All  
98 first incident cancers or death by cancer were considered as cases except for basal cell skin carcinomas  
99 (32). For CVD, we considered the first incident validated events of ischemic stroke, myocardial  
100 infarction, acute coronary syndrome, angioplasty and death due to one of these events. Other  
101 cardiovascular diseases such as ischemic transient attacks were not considered in the present work as  
102 they were not systematically validated by the physicians' team.

### 103 **Dietary data**

104 Dietary intakes were assessed at inclusion and thereafter twice a year using a series of three non-  
105 consecutive 24h dietary records, randomized over a two-week period (two weekdays and one weekend  
106 day). Participants reported all food and beverages (type and quantity) consumed during a 24-hour  
107 period: three main meals (breakfast, lunch, and dinner) as well interprandial and alcohol

108 consumptions. Portion sizes were estimated using photographs from a previously validated photo  
109 booklet (33) or in unit, grams or volumes depending on the food. Daily nutritional intakes were  
110 calculated using a French food composition table (34). Intake from composite dishes was calculated  
111 using reference recipes validated by nutrition professionals. The collection methods were validated  
112 against biomarkers of nutritional status and against conventional data collection methods (35–37).  
113 Moreover, ultra-processed food consumption was estimated according to NOVA classification (38).  
114 Under-reporters were identified with Black's method (39) using Goldberg's cut-offs (40) and basal  
115 metabolic rate, based on Schofield's equations (41) according to the sex, weight and height of the  
116 subjects at inclusion.

117 **Computation of the EAT-Lancet diet index** Adherence to the EAT-Lancet diet was estimated using  
118 the EAT-Lancet diet index (ELD-I) based on continuous scoring for each component what has been  
119 shown to better captures inter-individual variability and thus has greater discriminant power than  
120 scores instead considering discrete or even binary scoring for each component (42). This dietary score  
121 has been previously developed and described (43). The ELD-I was elaborated from NutriNet-Santé  
122 data and includes the following components: potatoes and tubers, fruits, vegetables, whole dairy,  
123 beef/lamb/pork, chicken and other poultry, eggs, fish, legumes, nuts, saturated oil, unsaturated oils and  
124 added sugar. Cut-off values, presented in **Supplementary Table 1**, were adapted on those proposed in  
125 EPIC-Oxford study (28). Slight modifications were made. The initial score used a cut-off of 500  
126 grams/d for all dairy products so as to consider that a full-fat dairies consumption more than 100  
127 grams per day is too high in a country where milk consumption is low and cheese consumption is high.  
128 Regarding grains, we chose to consider here only refined cereals which should be limited as  
129 previously authors included all cereals in the same component including whole grains (28) which are  
130 promoted in the EAT-Lancet diet and therefore should not be limited. Energy intake was standardized  
131 to 2,500 kcal and for each component the value considered corresponded to the deviation from the cut-  
132 off value. The computing of the ELD-I leads to a continuous variable (positive or negative). The higher  
133 the score, the more in line the individual's diet is with the EAT-Lancet recommendations. In the  
134 present study, the ELD-I was estimated for each participant using the mean of all 24 h dietary records



135 during the first two years after inclusion in the NutriNet-santé cohort. All mixed dishes have  
136 decomposed to weigh in the ELD-I food groups. The follow-up period considered in the study began  
137 at the end of these exposure window.

### 138 **Covariates**

139 Participants completed a set of validated self-administered questionnaires (30) at baseline, during the  
140 same period as the first 24h dietary records, to recover sociodemographic and lifestyle characteristics  
141 as well as health information. Data collected included sex, age, education level, monthly household  
142 income, occupation, and marital status. Monthly household income was calculated per consumption  
143 unit (cu) according to a weighting system, where one cu is attributed for the first adult in the  
144 household, then 0.5 cu for each person aged 14 years or older, and 0.3 cu for all children under 14  
145 years old (44). Lifestyle characteristics included physical activity calculated according to the  
146 International Physical Activity Questionnaire [IPAQ] (45), smoking status. Anthropometrics  
147 characteristics were self-reported (37,46) and body mass index (BMI) was calculated from the formula  
148 weight (kg) / height squared (m). Finally, personal and family history (history of parents and siblings)  
149 of diabetes, hypertension, cancer and cardiovascular events were collected. For females,  
150 characteristics related to reproductive life included number of biological children, age of the first  
151 period, menopausal status, and medication including oral contraception and hormonal treatment for  
152 menopause were also collected.

### 153 ***Sample selection***

154 In the present study, participants included between May 2009 to January 2021 and who had validated  
155 at least three 24 h dietary records during the first two years after inclusion into the cohort. Participants  
156 were considered at risk and therefore included when they were 35 years and older. Under-reporters  
157 were excluded from the analyses. In addition, prevalent cases and subjects who were diagnosed with  
158 one of the studied diseases during the exposure window were also excluded from the analyses.  
159 Therefore, analyses of risk of cancer and CVD combined and separately were thus performed on  
160 62,382, 63,891 and 68,247 participants, respectively (**Figure 1**). During the follow-up of 3,512 cases  
161 of cancer and CVD combined, 2,475 cancer cases and 786 cardiovascular events.

162 *Statistical analyses*

163 Baseline characteristics and daily food consumption of participants were described across sex-specific  
164 quintiles (Q) of the ELD-I using mean and standard deviation (SD) or percentage. For all covariates,  
165 less than 1 % of values were missing and were imputed by their modal values.

166 P-values referred to p-value for Mantel-Haenszel  $\chi^2$  for dichotomised or ordinals variables,  $\chi^2$  for other  
167 categorical variables and generalized linear models with linear contrast for numeric variables.

168 Linearity of the ELD-I association with the risk of cancer and CVD combined and separately were  
169 tested using fractional polynomial. Schoenfeld residuals were examined to confirm risk proportionality  
170 assumption.

171 First, we characterized the relationship between ELD-I and incidence of cancer and CVD combined ,  
172 cancers (overall and by most frequent localizations in the NutriNet-Santé cohort: colorectal, lung,  
173 prostate in males and breast in females) and CVD (overall and by subtype: coronary and  
174 cerebrovascular), generating Hazard Ratios (HRs) and 95 % confidence intervals (95% CIs), using  
175 multivariable Cox proportional hazard models with age as time-scale (47). For each specific outcome  
176 participants contributed person-time until the date of diagnosis, date of death, date of last completed  
177 questionnaire or January 21st, 2021, whichever occurred first. As recommended in the presence of  
178 competing events (48), we used cause-specific models. Then, for analyses of cancers localizations and  
179 CVD subtypes, other cases than those of the studied pathology in the model were censored at the date  
180 of diagnosis. Associations were estimated across sex-specific quintiles (with the first as reference) and  
181 for continuous score which was modeled for a 100-point increase.

182 Several models were performed. The first model was adjusted for sex and energy intake without  
183 alcohol (kcal/day, continuous variable). The second model was further adjusted for education level  
184 (less than high school degree, < 2 years after high-school degree,  $\geq$  2 years after high-school degree),  
185 occupational status (unemployed/farmer, merchant, artisan, self-employed, manual workers/  
186 employees/ intermediate profession/ managerial staff), monthly household income (refuse to declare, <  
187 1,200 €, from 1,200 to 1,800 €, from 1,800 to 2,700 €,  $\geq$  2,700€), marital status (single/ married, civil  
188 union, cohabiting/ separated, divorced, widowed). The full model without BMI was further adjusted

189 for number of completed 24h dietary records (continuous variable), height (cm, continuous variable),  
190 physical activity (not communicated, high, moderate, low), smoking status (never smoker, former  
191 smoker, current smoker), alcohol consumption (g/day, continuous variable), and family history of  
192 cancer or CVD (yes/no). The full model with BMI was further adjusted for baseline BMI (under-  
193 weight or normal ( $< 25 \text{ kg/m}^2$ ), overweight (from  $\geq 25 \text{ kg/m}^2$  to  $< 30 \text{ kg/m}^2$ ) and obese ( $\geq 30 \text{ kg/m}^2$ )).

194 For cancer analysis, model 3 was further adjusted for family history of cancer, and among females for  
195 number of biological children (continuous variable), menstruating at 12 years old (yes/no),  
196 menopausal status (premenopausal, perimenopausal, and postmenopausal status), oral contraception  
197 (yes/no), and hormonal treatment for menopause (yes/no). For CVD analysis, model 3 was further  
198 adjusted for family history of stroke (yes/no), family history of diabetes (yes/no), and baseline  
199 hypertension (yes/no) or diabetes (yes/no).

200 In order to verify whether certain characteristics such as gender or lifestyle habits such as smoking and  
201 alcohol consumption do not modify the effect of EAT-lancet diet recommendations on the occurrence  
202 of these diseases, interactions were tested. When the latter was statistically significant, a stratification  
203 on the interaction variable was performed by adding the multiplicative interaction term into the model.

204 Regarding cancer and CVD combined sample, effect modification by alcohol intake (modeled as  
205 categories using the official recommendation (49)) was also evaluated in stratified analysis as alcohol  
206 is not accounting for in the ELD-I.

207 Sensitivity analyses were also conducted. First, we tested reverse causality by excluding subjects  
208 diagnosed during the first 2 years of follow-up and subjects with less than 2 years of follow-up. Lastly,  
209 full models were additionally adjusted for hypertension and diabetes at baseline or for the proportion  
210 (in weight) of ultra-processed food in the diet.

211 All tests were two-sided and  $P < 0.05$  was considered statistically significant. Statistical analyses were  
212 conducted using R<sup>®</sup> version 4.0.4 and SAS<sup>®</sup> version 8.3 (SAS Institute).

## 213 **Results**

214 In the principal sample (i.e. investigating cancers and CVD combined), the median follow-up was 8.1  
215 years, and the mean number of dietary records was 6.3 (SD=2.9).

216 Baseline characteristics of participants are described in **Table 1**. The principal sample was composed  
217 of 75.8 % females, mean age at baseline was 51.0 years (SD=10.2). ELD-I ranged from -162 to 332  
218 points, and the average value was 45.4 points (SD=25.6). Compared to participants with low ELD-I  
219 (quintile 1), participants with high ELD-I (quintile 5) were older, had a higher education level and  
220 monthly income. They also were less frequently smokers, more physically active and had a lower  
221 BMI. As well, there were significant correlations between socio-demographic factors and the ELD-I  
222 regardless of sex, although the association with marital status was less strong in males  
223 (**Supplementary Tables 2 and 3**).

224 By construction, a higher ELD-I was associated with higher consumption of fruit, vegetables,  
225 legumes, nuts, seafoods. Conversely, a higher score was associated with lower consumption of tubers,  
226 eggs, meat, fat, fatty and/or sweetened products, sweetened soft drinks. Although not included in the  
227 ELD-I, certain healthy components, such as non-alcoholic and non-sugary beverages were associated  
228 with a higher ELD-I, whereas certain unhealthy components, such as alcoholic beverages were  
229 associated with a lower ELD-I. The dietary description is presented in **Supplementary Table 4**.

230 The associations between ELD-I and cancer and CVD combined and separately are presented in **Table**  
231 **2**. After adjustment for confounding variables, there was no statistically significant association  
232 between a higher adherence to the EAT-Lancet diet and the risk of cancer and CVD combined (HR<sub>Q5</sub>  
233 vs Q1 =0.98 (0.87,1.09), p-trend=0.19). Alcohol consumption (p for interaction=0.05) and sex (p for  
234 interaction=0.05) were effect modifiers of the association unlike smoking status (p for  
235 interaction=0.80). After stratification on alcohol consumption according to the sex-specific median  
236 value (**Table 3**), high ELD-I was negatively associated with the risk of cancer and CVD combined  
237 among low consumers of alcohol only (HR<sub>Q5 vs Q1</sub> =0.86 (0.73,1.02), p-trend=0.02). For both stratified  
238 and unstratified model on alcohol, BMI emerged as an important mediator between diet adequacy and  
239 cancer and CVD combined risk leading to attenuated associations.

240 No association between ELD-I and the risk of cancer overall (HR<sub>Q5 vs Q1</sub> =0.96 (0.84,1.10), p-  
241 trend=0.18) and by site was detected. Sex (p for interaction=0.01) was an effect modifier of the  
242 association. After sex stratification of models for cancer incidence (**Supplementary Table 5**), we  
243 found a significantly lower risk of cancer among females having higher adherence to the EAT-Lancet  
244 diet compared to those with low adherence (HR<sub>Q5 vs Q1</sub> =0.89 (0.75,1.05), p-trend=0.03). This  
245 association was not significant when BMI was considered in the adjustment (HR<sub>Q5 vs Q1</sub> =0.91  
246 (0.77,1.08), p-trend=0.07). No association was observed among males.

247 For risk of CVD (HR<sub>Q5 vs Q1</sub> =0.89 (0.71,1.12), p-trend=0.60) and by sub-types (**Table 2**), there was no  
248 significant association.

249 Sensitivity analyses conducted according the official drinking recommendation are presented in  
250 **Supplementary Table 6**. The association between ELD-I and risk of cancer and CVD combined was  
251 not statistically significant (HR<sub>Q5 vs Q1</sub> =0.95 (0.84,1.08), p-trend=0.09). When excluding early events  
252 (n=15,009) similar results in comparison to the main analyses were observed (**Supplementary Table**  
253 **7**). In addition, when considering further adjustment for high blood pressure and diabetes on the one  
254 hand (**Supplementary Table 8**), and the consumption of ultra-processed foods on the other  
255 (**Supplementary Table 9**), relationships were not significant and showed similar trend than that of the  
256 main analysis.

257 Significant associations were detected only in the highest score quintile (Q5) and all linear results  
258 (continuous ELD-I score) were nonsignificant.

## 259 **Discussion**

260 In the present study, after adjustment for multiple confounding factors, adherence to the EAT-Lancet  
261 diet was not associated with a significantly lower risk of cancer and CVD combined, except in  
262 participants with a very low alcohol consumption (<20g/day). The latter association suggests that,  
263 among heavy alcohol consumers, a high adherence to the EAT-Lancet diet does not counterbalance  
264 the harmful effect of alcohol (50–52). An association between the EAT-Lancet diet and cancer risk  
265 was also observed, in females, but was largely attenuated by BMI. Also, we did not observe a

266 significant association between adherence to the EAT-Lancet diet and breast cancer risk in females.  
267 The association found in females was, therefore, not specifically driven by breast cancer. Moreover,  
268 no significant association was observed between the ELD-I and CVD risk. These results were  
269 consistent in sensitivity analyses.

270 To the best of our knowledge, only one study has documented the relationship between cancer risk and  
271 the EAT-Lancet diet (53). However, numerous studies have investigated this relationship using other  
272 indices reflecting recommendations towards more plant-based diets, as prescribed by the EAT-Lancet  
273 diet. In the NutriNet-Santé cohort study, a score reflecting adherence to the Mediterranean diet (MEDI-  
274 Lite), which is a plant-based diet and therefore close to the ELD-I, was not associated with overall  
275 cancer risk (54), while the PNNS-GS2, reflecting the recent update of the French FBDG was  
276 associated with a 3% reduction in risk of cancer for every 1 point increase (55). The PNNS-GS2  
277 includes a higher number of components, including alcoholic beverages and processed meat (56), than  
278 the ELD-I. Another difference concerns the way total energy intake is considered in the PNNS-GS2  
279 (the PNNS-GS2 directly penalizes excessive energy intake). These three components are major risk  
280 factors for chronic diseases, in particular in Western countries (51,57), and could possibly explain  
281 the differences observed.

282 As mentioned above, only one study has specifically investigated the relationship between the EAT-  
283 Lancet diet and cancer risk. Conducted as part of the EPIC study (53), which includes more than  
284 400,000 subjects from several European countries, this study showed, using the score developed by  
285 Knuppel (28), that 10-39% of cancers could be prevented by adopting the EAT-Lancet diet over a 20-  
286 year period. The main difference between the present study and that of Laine, apart from different  
287 sample size, is the greater variety of dietary profiles observed in the EPIC study, since the latter  
288 includes participants from different cohorts recruited across ten European countries. In contrast, our  
289 study includes participants with rather healthy and plant-based dietary patterns.

290 Previous meta-analyses and as well as studies conducted in the NutriNet-Santé cohort examining the  
291 role of various dietary quality indexes on breast cancer risk did not report statistically significant  
292 associations (54,55).

293 With regard to the risk of colorectal and prostate cancers, we did not identify significant associations  
294 with adherence to the EAT-Lancet diet (56). A study conducted in the NutriNet-Santé study and  
295 considering the PNNS-GS2 documented a negative association with the risk of colorectal cancer but  
296 not with prostate cancer risk (55). Again, processed meats and alcohol are important risk factors for  
297 colorectal cancer (57,58). The non-inclusion of these typical French foods may explain this difference  
298 in results.

299 Regarding CVD, the relationships between stroke, some subtypes both ischemic and hemorrhagic, and  
300 the EAT-Lancet recommendations have been studied (28,59), however to our knowledge, only one  
301 study on coronary diseases has been conducted (60). Whether carried out in the elderly or in the  
302 general population, no association was found between a better adherence to the EAT-Lancet  
303 recommendations and the risk of stroke (28,59). This is consistent with our findings and with those  
304 observed in previous studies conducted in the NutriNet-Santé cohort using other dietary scores (61). It  
305 is noteworthy that a better adherence to the EAT-Lancet diet was associated with a 28% risk reduction  
306 of ischemic heart disease in British adults (28), as well as with a lower risk of subarachnoid  
307 hemorrhage in individuals over 50 years of age (59). Of note, hemorrhagic events were not considered  
308 in the present analyses. It would be relevant to study them to confirm or infirm this association in our  
309 study population. However, a Dutch study, which included 2,543 cases, reported a 15% reduction in  
310 coronary heart disease risk with a higher adherence to EAT-Lancet recommendations (60). Meta-  
311 analyses on the MEDI-Lite (62,63), also reported negative associations between diet quality scores  
312 and risk of all CVD while it was not the case in our study, nor in the Lazarova's study, which also did  
313 not find an association between adherence to the EAT-Lancet diet and the occurrence of all-cause  
314 stroke (64). One explanation could be the important weight given to olive oil in these scores, which  
315 has been shown to have beneficial effects on cardiovascular events when consuming moderately  
316 (62,63,65–68). Indeed, in a previous study conducted using NutriNet-Santé data, the MEDI-Lite  
317 scores were respectively associated with a 21% reduction in the risk of stroke, myocardial infarction,  
318 acute coronary syndrome, as well as angioplasty, angina combined (61). Another hypothesis could be  
319 the consideration of alcohol in these scores, although the potential benefits of moderate alcohol  
320 consumption are still debated as regards cardiovascular health (69).

321 Additionally, the relationship between the EAT-Lancet diet and premature mortality has been  
322 investigated in several simulation and observational epidemiologic studies, but has yielded conflicting  
323 results. In Sweden, highest adherence to the EAT-Lancet recommendations was associated with a 25%  
324 lower risk of all-cause mortality, a 24% lower risk of cancer mortality and a 32% lower risk of  
325 cardiovascular mortality, compared to low adherence (70). In line with these findings, Springmann et  
326 al., (25), using a modelling approach, concluded that adherence to the EAT-Lancet diet would result in  
327 a reduction in premature mortality of 34% per year. According to the same study, the EAT-Lancet diet  
328 would be more efficient than the global recommendations defined by the WHO and the Food and  
329 Agriculture Organization and the national FBDG. For the authors, this greater reduction would be  
330 mainly explained by the more stringent recommended cut-offs in the EAT-Lancet diet concerning  
331 whole grains, nuts, seeds and legumes and processed meat. In contrast, another study which sought to  
332 replicate Springmann's analysis, using equivalent data, documented that, contrary to what claimed by  
333 the authors, adherence to the EAT-Lancet diet does not appear to have a stronger effect on mortality  
334 reduction in the United States than that due to management of weight-related risk factors (29). These  
335 latter observations seemed to be corroborated by the British study, conducted in EPIC Oxford, which  
336 found no association between high adherence to the EAT-Lancet diet and total mortality (28). In  
337 addition, the relationship between adherence to the EAT-Lancet diet and other outcomes such as  
338 diabetes and obesity has also been studied. It was found that higher adherence to the EAT-Lancet diet  
339 was not associated with a lower risk of obesity, nor was it associated with a lower overall chronic  
340 disease risk (64). However, a negative association was observed between an increase in the Knuppel's  
341 EAT score and the risk of type 2 diabetes, although this association was largely mediated by BMI and  
342 waist circumference (27).

343 In the present study, significant associations were detected only in the highest quintile of ELD-I (Q5).  
344 Consideration of the continuous score did not highlight significant results, although that were narrowly  
345 for some associations such as adherence to the EAT-Lancet diet and occurrence of cancer and CVD  
346 combined among low consumers of alcohol (HR=0.82 (0.67,1.00), p-value=0.05) (**Table 3**).

347 Replication of this study in another setting with more diverse profiles or an even larger number of  
348 subjects might allow detection of associations using the continuous score. Nevertheless, this



349 observation showed that associations were visible solely in individuals with a very high ELD-I  
350 score. The first limitation of this work concerns the representativeness of the study population. Owing  
351 to the voluntary recruitment, NutriNet-Santé participants may be more health conscious and therefore  
352 exhibit healthier dietary profiles than the general population (71). Indeed, NutriNet-Santé participants  
353 are more frequently females, younger, have a higher level of education and have healthier lifestyle  
354 habits than the general French population. This may have led to a lower incidence of chronic diseases  
355 in our sample and a higher quality of diet than those of the general population. It is therefore likely  
356 that possible associations were underestimated, although an overestimation cannot be ruled out.  
357 Generalization of the results must therefore be done with caution. Nevertheless, given its large sample  
358 size, we had access to a variety of profiles and the proportion of some specific populations was  
359 acceptable (e.g., older, low-income or disadvantaged individuals). In addition, certain chronic diseases  
360 (such as type 2 diabetes) were not considered in the analyses because we chose to privilege frequent,  
361 validated pathologies and leading causes of mortality in France. We thus focused on pathologies  
362 validated by a dedicated physicians' team so as to limit information bias related to self-report and thus  
363 misclassification. The intra-individual variation could have been better accounted for by using usual  
364 dietary data, however the adjustment on the number of 24-hour records remains a robust method since  
365 we had on average 6.3 records per participant. Subjective and potentially arbitrary decisions, such as  
366 the calculation method used, were also considered in the development of the ELD-I, which was  
367 developed based on a subsample of the NutriNet-Santé study (43). Like most dietary indexes, the  
368 ELD-I can take an infinite number of intermediate values. In contrast, extreme values are less  
369 frequent, as extreme values represent very healthy or unhealthy diets. However, the use of another  
370 index based also on the EAT-Lancet diet, i.e. WISH score (World Index for Sustainability and Health)  
371 (72), revealed similar findings (**Supplementary Table 10**)).

372 The main strengths of this study rely on the prospective study design and the size of the study sample.  
373 Indeed, the large size of our population and the median follow-up of more than 8 years, may have  
374 limited reverse causality, bias that was also addressed by removing early cases. The sensitivity  
375 analysis excluding early cases led to similar findings. Besides, the number of incident cases was  
376 substantial and the statistical power satisfying. Due to the large amount of data available in NutriNet,

377 we were able to account for a wide range of confounders and to examine potential effect modification.  
378 However, some confounding factors not measured in the present work, such as stress or sleep, would  
379 be also relevant to include; and, therefore residual confounding cannot be ruled out despite extensive  
380 adjustment. Finally, we used very detailed and high-quality nutritional data, as well as validated  
381 outcomes. Furthermore, the dietary assessment method used in the NutriNet-Santé study was validated  
382 by comparison to urinary and blood biomarkers (35,36), as well as to objective measurements  
383 performed by dietitians (37).

### 384 **Conclusion**

385 In conclusion, our findings show a beneficial effect of adherence to EAT-Lancet diet  
386 recommendations, but only in some population subgroups (low alcohol consumers and females). In  
387 addition, BMI was a strong mediator. Some important dietary factors, such as processed meat or  
388 excessive energy intake, not considered in the EAT-Lancet diet, should be considered in the future.  
389 Further research, based on cohort studies using a variety of outcomes and in different country  
390 contexts, would be of high value to document in more detail the associations between long-term health  
391 and EAT-Lancet diet.

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## 400 **Authors' contributions:**

401 The authors' contributions were as follows: EKG and FB designed the study. FB performed statistical  
402 analyses and wrote the manuscript; EKG supervised statistical analysis and paper writing. All authors:  
403 contributed to the data interpretation and revised each draft for important intellectual content. All  
404 authors read and approved the final manuscript. FB and EKG had full access to all the data in the  
405 study, EKG takes responsibility for the integrity of the data and the accuracy of the data analysis, she  
406 is the guarantor. The corresponding author (EKG) attests that all listed authors meet authorship criteria  
407 and that no others meeting the criteria have been omitted.

## 408 **Transparency statement**

409 Dr Emmanuelle Kesse-Guyot (the guarantor) affirms that the manuscript is an honest, accurate, and  
410 transparent account of the study being reported; that no important aspects of the study have been  
411 omitted; and that any discrepancies from the study as planned have been explained.

## 412 **Conflict of Interest**

413 The authors declare no conflict of interest.

## 414 **Data sharing statement**

415 Analytic code will be made available upon request pending. Researchers from public institutions can  
416 submit a collaboration request including information on the institution and a brief description of the

417 project to [collaboration@etude-nutrinet-sante.fr](mailto:collaboration@etude-nutrinet-sante.fr). All requests will be reviewed by the steering  
418 committee of the NutriNet-Santé study. If the collaboration is accepted, a data access agreement will  
419 be necessary and appropriate authorizations from the competent administrative authorities may be  
420 needed. In accordance with existing regulations, no personal data will be accessible.

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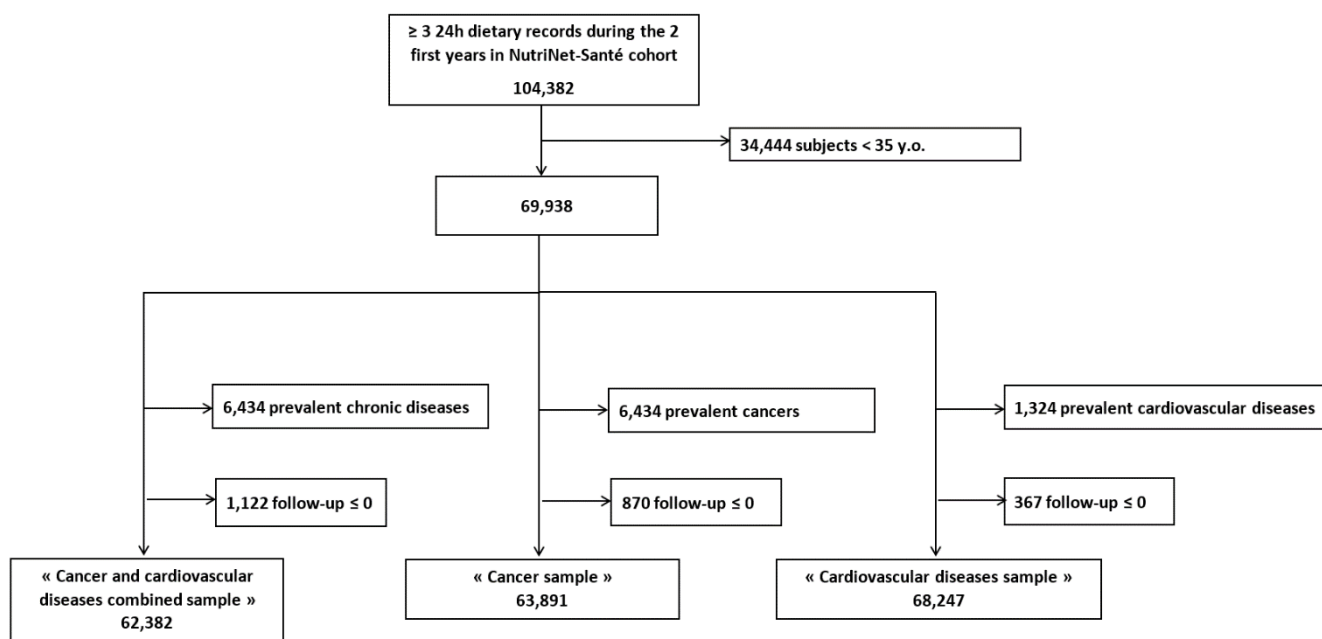
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## Figures



**Figure 1. Flow-chart of subjects included in the present analysis, NutriNet Santé study, France 2009-2021.**

## Tables

**Table 1. Description of anthropometric, socio-demographic and lifestyle characteristics at inclusion, by EAT-Lancet Diet Index sex-specific quintiles (cancer and cardiovascular disease combined sample). NutriNet Santé study, France 2009-2021 (n=62,382).**

	All	Sex-specific quintiles <sup>1</sup>					p-value <sup>2</sup>
		Q1	Q2	Q3	Q4	Q5	
<b>n</b>	62,382	12,476	12,476	12,478	12,476	12,476	
<b>EAT-Lancet Diet Index</b>							
Females	46.6 (25.8)	12.2 (16.3)	34.7 (3.7)	46.1 (3.1)	58.0 (3.9)	81.9 (17.9)	
Males	41.7 (24.8)	8.8 (15.3)	30.6 (3.5)	41.3 (2.9)	52.4 (3.7)	75.5 (18.8)	
<b>Sex (female), %</b>	75.8	75.8	75.8	75.8	75.8	75.8	
<b>Age (years old)</b>	51.0 (10.2)	48.2 (9.6)	49.8 (10.0)	51.1 (10.3)	52.2 (10.1)	53.4 (10.1)	<0.0001
<b>Education level, %</b>							<0.0001
< High-school degree	24.4	30.0	25.0	23.2	22.1	21.6	
≥ High-school degree to < 2 y after high-school degree	16.3	18.6	16.8	15.9	15.4	14.9	
≥ 2 y after high-school degree	59.3	51.4	58.2	60.9	62.5	63.5	
<b>Occupation, %</b>							<0.0001
Unemployed	0.5	0.5	0.5	0.5	0.4	0.6	
Farmer, merchant, artisan, company director, manual worker	6.7	8.8	6.9	6.2	5.6	6.0	
Employees	27.7	35.3%	29.8	25.9	24.4	23.2	
Intermediate profession	29.0	25.9	28.5	29.8	30.8	29.7	
Managerial staff	36.1	29.5	34.3	37.6	38.7	40.5	
<b>Monthly household income, %</b>							<0.0001
No communicated	10.6	11.3	10.5	10.2	10.1	11.1	
<1,200 €	13.7	20.9	14.6	12.8	10.8	9.8	
1,200 – 1,800 €	24.2	26.8	25.6	24.8	23.0	20.6	
1,800 – 2,700 €	23.6	20.5	23.4	23.7	25.3	24.8	
≥ 2,700 €	27.9	20.5	25.9	28.5	30.8	33.7	
<b>Marital status, %</b>							<0.0001
Single	9.9	9.5	9.4	9.3	10.0	11.5	
Married, civil union, cohabiting	75.9	76.7	77.9	77.5	75.3	72.2	
Separated, divorced, widowed	14.2	13.8	12.7	13.2	14.7	16.3	
<b>Smoking status, %</b>							<0.0001
Never smoker	45.6	41.7	45.2	46.1	46.9	48.1	
Former smoker	40.3	37.0	39.2	40.8	41.8	42.8	
Current smoker	14.1	21.3	15.6	13.1	11.3	9.1	
<b>Energy intake without alcohol (kcal/d)</b>	1,866 (478)	1,850 (503)	1,926 (487)	1,912 (469)	1,871 (454)	1,771 (461)	<0.0001
<b>Number of 24h records</b>	6.3 (2.9)	5.6 (2.8)	6.3 (2.9)	6.6 (2.9)	6.6 (2.9)	6.2 (2.9)	<0.0001
<b>Alcohol consumption (g/ d)</b>	8.6 (12.1)	8.7 (12.9)	9.7 (13.5)	9.3 (12.5)	8.6 (11.5)	6.5 (9.6)	<0.0001
<b>Physical activity<sup>3</sup>, %</b>							<0.0001
No communicated	13.0	15.4	13.2	12.2	11.8	12.2	
Low	31.4	27.5	28.9	31.1	32.8	36.8	
Moderate	35.3	32.2	35.0	36.3	36.9	36.0	
High	20.3	24.9	22.9	20.4	18.5	15.0	
<b>Height (cm)</b>	166.5 (8.2)	166.7 (8.2)	166.7 (8.2)	166.7 (8.2)	166.3 (8.0)	166.2 (8.1)	<0.0001
<b>Body Mass Index (kg/m<sup>2</sup>)</b>	24.4 (4.6)	25.3 (5.1)	24.7 (4.8)	24.4 (4.5)	24.1 (4.4)	23.7 (4.2)	<0.0001

Mean (standard deviation) for quantitative variables and percentages for qualitative variables.

<sup>1</sup> Sex-specific cut-offs for quintiles of EAT-Lancet diet index (ELD-I) were -161.5/27.8/40.7/51.7/65.2/323.9 for females and for -140.1/23.8/36.3/46.5/59.2/332.2 males.

<sup>2</sup> P-value for comparison between quintiles of ELD-I by test from Mantel-Haenszel  $\chi^2$  for dichotomizes or ordinals variables,  $\chi^2$  for others categorical variables and generalized linear models with linear contrast for numeric variables.

<sup>3</sup> Physical activity: low (irregular), moderate (<1h/day walking or equivalent), high (≥1h/day walking or equivalent).

**Table 2. Prospective association between the EAT-Lancet Diet Index and risk of total cancer and cardiovascular diseases combined and separately. NutriNet-Santé study, France 2009-2021.**

	Continuous score (100-point increase)		Sex-specific quintiles					p-trend <sup>2</sup>
	All	p-value <sup>1</sup>	Q1	Q2	Q3	Q4	Q5	
<b>Cancer and CVD combined</b>								
N	62,382		12,476	12,476	12,478	12,476	12,476	
Events	3,512		535	700	765	751	761	
Person-years	322,453		57,599	64,405	66,805	68,191	65,453	
HR (95% CI)								
Model 1 <sup>3</sup>	<b>0.85 [0.73, 0.98]</b>	<b>0.02</b>	1.00 [-]	1.05 [0.94, 1.18]	1.03 [0.92, 1.15]	0.94 [0.84, 1.05]	0.93 [0.83, 1.04]	<b>0.03</b>
Model 2 <sup>4</sup>	<b>0.87 [0.75, 1.00]</b>	<b>0.04</b>	1.00 [-]	1.06 [0.95, 1.19]	1.04 [0.93, 1.17]	0.95 [0.85, 1.07]	0.95 [0.85, 1.06]	<b>0.04</b>
Model 3 <sup>5</sup>	0.90 [0.78, 1.05]	0.18	1.00 [-]	1.05 [0.94, 1.18]	1.04 [0.93, 1.16]	0.96 [0.86, 1.07]	0.98 [0.87, 1.09]	0.19
Model 4 <sup>6</sup>	0.94 [0.82, 1.09]	0.44	1.00 [-]	1.06 [0.95, 1.19]	1.05 [0.94, 1.18]	0.97 [0.87, 1.09]	1.00 [0.89, 1.12]	0.42
<b>Cancers</b>								
n	63,891		12,777	12,779	12,779	12,779	12,777	
Events	2,475		379	507	538	534	517	
Person-years	335,112		59,797	66,912	69,456	70,814	68,134	
HR (95% CI)								
Model 1 <sup>3</sup>	0.86 [0.73, 1.02]	0.09	1.00 [-]	1.08 [0.95, 1.24]	1.03 [0.90, 1.18]	0.96 [0.84, 1.10]	0.92 [0.81, 1.05]	<b>0.04</b>
Model 2 <sup>4</sup>	0.87 [0.73, 1.03]	0.10	1.00 [-]	1.08 [0.95, 1.24]	1.03 [0.90, 1.18]	0.96 [0.84, 1.10]	0.93 [0.81, 1.06]	<b>0.04</b>
Model 5 <sup>7</sup>	0.92 [0.77, 1.09]	0.34	1.00 [-]	1.09 [0.95, 1.24]	1.04 [0.91, 1.19]	0.98 [0.86, 1.13]	0.96 [0.84, 1.10]	0.18
Model 6 <sup>8</sup>	0.95 [0.79, 1.13]	0.53	1.00 [-]	1.09 [0.95, 1.25]	1.05 [0.92, 1.20]	1.00 [0.87, 1.14]	0.98 [0.85, 1.12]	0.28
<b>Colorectal cancer</b>								
Events	209		35	37	50	38	49	
Person-years	335,112		59,797	66,912	69,456	70,814	68,134	
HR (95% CI)								
Model 1 <sup>3</sup>	0.74 [0.41, 1.32]	0.30	1.00 [-]	0.83 [0.52, 1.32]	0.98 [0.63, 1.51]	0.68 [0.43, 1.08]	0.84 [0.54, 1.30]	0.30
Model 2 <sup>4</sup>	0.77 [0.43, 1.37]	0.37	1.00 [-]	0.84 [0.53, 1.34]	1.00 [0.65, 1.55]	0.70 [0.44, 1.11]	0.87 [0.56, 1.35]	0.38
Model 5 <sup>7</sup>	0.80 [0.44, 1.46]	0.47	1.00 [-]	0.82 [0.52, 1.31]	0.98 [0.63, 1.53]	0.69 [0.43, 1.10]	0.89 [0.57, 1.39]	0.48
Model 6 <sup>8</sup>	0.82 [0.45, 1.50]	0.52	1.00 [-]	0.83 [0.52, 1.32]	0.99 [0.64, 1.54]	0.70 [0.44, 1.12]	0.90 [0.58, 1.41]	0.52
<b>Lung cancer</b>								
Events	125		33	20	18	31	23	
Person-years	335,112		59,797	66,912	69,456	70,814	68,134	
HR (95% CI)								
Model 1 <sup>3</sup>	0.49 [0.23, 1.03]	0.06	1.00 [-]	<b>0.48 [0.27, 0.83]</b>	<b>0.37 [0.21, 0.67]</b>	<b>0.59 [0.36, 0.97]</b>	<b>0.41 [0.24, 0.70]</b>	<b>0.01</b>
Model 2 <sup>4</sup>	0.57 [0.27, 1.20]	0.14	1.00 [-]	<b>0.50 [0.28, 0.87]</b>	<b>0.40 [0.22, 0.72]</b>	<b>0.64 [0.39, 1.05]</b>	<b>0.45 [0.26, 0.78]</b>	<b>0.03</b>
Model 5 <sup>7</sup>	0.91 [0.44, 1.90]	0.80	1.00 [-]	0.58 [0.33, 1.01]	0.49 [0.28, 0.89]	0.84 [0.51, 1.40]	0.63 [0.36, 1.09]	0.34
Model 6 <sup>8</sup>	0.90 [0.43, 1.89]	0.79	1.00 [-]	0.57 [0.33, 1.01]	0.50 [0.28, 1.89]	0.84 [0.51, 1.39]	0.62 [0.36, 1.08]	0.34
<b>Breast cancer</b>								
n	48,013		9,602	9,603	9,602	9,602	9,602	
Events	715		114	162	151	149	139	
Person-years	250,306		44,586	50,020	51,995	52,795	50,991	
HR (95% CI)								

Model 1 <sup>3</sup>	0.81 [0.60, 1.11]	0.19	1.00 [-]	1.19 [0.94, 1.52]	1.04 [0.81, 1.33]	0.98 [0.77, 1.26]	0.94 [0.73, 1.21]	0.20
Model 2 <sup>4</sup>	0.78 [0.57, 1.07]	0.12	1.00 [-]	1.18 [0.92, 1.50]	1.02 [0.80, 1.30]	0.96 [0.75, 1.23]	0.91 [0.71, 1.18]	0.13
Model 7 <sup>9</sup>	0.78 [0.57, 1.08]	0.13	1.00 [-]	1.15 [0.90, 1.46]	0.99 [0.78, 1.27]	0.94 [0.73, 1.21]	0.92 [0.71, 1.18]	0.15
Model 8 <sup>10</sup>	0.81 [0.59, 1.13]	0.21	1.00 [-]	1.16 [0.91, 1.47]	1.01 [0.79, 1.29]	0.96 [0.75, 1.23]	0.94 [0.73, 1.22]	0.22
<b>Prostate cancer</b>								
n	15,878		3,175	3,176	3,176	3,176	3,175	
Events	310		30	67	68	61	84	
Person-years	84,807		15,211	16,892	17,462	18,019	17,224	
HR (95% CI)								
Model 1 <sup>3</sup>	1.51 [0.93, 2.46]	0.10	1.00 [-]	1.69 [1.10, 2.60]	1.46 [0.95, 2.25]	1.22 [0.79, 1.89]	1.63 [1.07, 2.47]	0.29
Model 2 <sup>4</sup>	1.42 [0.87, 2.33]	0.16	1.00 [-]	1.65 [1.07, 2.55]	1.42 [0.92, 1.19]	1.18 [0.76, 1.83]	1.56 [1.03, 2.38]	0.40
Model 5 <sup>7</sup>	1.45 [0.87, 2.41]	0.15	1.00 [-]	1.64 [1.06, 2.52]	1.40 [0.91, 2.17]	1.16 [0.74, 1.80]	1.57 [1.03, 2.41]	0.39
Model 6 <sup>8</sup>	1.41 [0.85, 2.34]	0.19	1.00 [-]	1.64 [1.06, 2.52]	1.40 [0.90, 2.15]	1.15 [0.74, 1.79]	1.55 [1.01, 2.37]	0.44
<b>CVD</b>								
n	68,247		13,649	13,650	13,649	13,650	13,649	
Events	786		151	155	158	164	158	
Person-years	364,913		64,799	73,241	75,727	77,236	73,910	
HR (95% CI)								
Model 1 <sup>3</sup>	<b>0.71 [0.52, 0.96]</b>	<b>0.03</b>	1.00 [-]	<b>0.78 [0.62, 0.99]</b>	<b>0.79 [0.63, 0.99]</b>	<b>0.79 [0.63, 0.99]</b>	<b>0.78 [0.62, 0.98]</b>	0.09
Model 2 <sup>4</sup>	0.75 [0.55, 1.02]	0.07	1.00 [-]	0.80 [0.63, 1.01]	0.81 [0.64, 1.02]	0.82 [0.65, 1.03]	0.82 [0.65, 1.04]	0.19
Model 9 <sup>11</sup>	0.85 [0.62, 1.16]	0.30	1.00 [-]	0.81 [0.64, 1.03]	0.82 [0.65, 1.04]	0.85 [0.68, 1.07]	0.89 [0.71, 1.12]	0.60
Model 10 <sup>12</sup>	0.87 [0.63, 1.19]	0.38	1.00 [-]	0.81 [0.64, 1.03]	0.83 [0.66, 1.05]	0.85 [0.68, 1.07]	0.90 [0.72, 1.14]	0.69
<b>Coronary diseases<sup>13</sup></b>								
Events	667		121	118	134	148	146	
Person-years	364,913		64,799	73,241	75,727	77,236	73,910	
HR (95% CI)								
Model 1 <sup>3</sup>	<b>0.66 [0.48, 0.92]</b>	<b>0.01</b>	1.00 [-]	<b>0.76 [0.59, 0.98]</b>	<b>0.77 [0.60, 0.99]</b>	<b>0.77 [0.60, 0.98]</b>	<b>0.73 [0.57, 0.93]</b>	0.04
Model 2 <sup>4</sup>	<b>0.71 [0.51, 0.98]</b>	<b>0.04</b>	1.00 [-]	0.77 [0.60, 1.00]	0.80 [0.62, 1.02]	0.80 [0.63, 1.02]	0.76 [0.60, 0.97]	0.09
Model 9 <sup>11</sup>	0.79 [0.56, 1.11]	0.18	1.00 [-]	0.79 [0.61, 1.02]	0.81 [0.63, 1.05]	0.83 [0.65, 1.06]	0.83 [0.65, 1.07]	0.36
Model 10 <sup>12</sup>	0.81 [0.58, 1.14]	0.22	1.00 [-]	0.81 [0.62, 1.04]	0.84 [0.66, 1.08]	0.86 [0.67, 1.10]	0.85 [0.66, 1.09]	0.41
<b>Cerebrovascular diseases<sup>14</sup></b>								
Events	119		16	21	23	26	33	
Person-years	364,913		64,799	73,241	75,727	77,236	73,910	
HR (95% CI)								
Model 1 <sup>3</sup>	1.05 [0.48, 2.29]	0.91	1.00 [-]	0.97 [0.51, 1.87]	0.93 [0.49, 1.77]	0.96 [0.51, 1.79]	1.17 [0.64, 2.13]	0.57
Model 2 <sup>4</sup>	1.11 [0.50, 2.47]	0.80	1.00 [-]	0.97 [0.51, 1.87]	0.92 [0.48, 1.75]	0.96 [0.51, 1.81]	1.20 [0.65, 2.21]	0.50
Model 9 <sup>11</sup>	1.29 [0.57, 2.95]	0.54	1.00 [-]	0.96 [0.50, 1.86]	0.90 [0.47, 1.73]	0.99 [0.52, 1.87]	1.31 [0.71, 2.43]	0.31
Model 10 <sup>12</sup>	1.36 [0.59, 3.10]	0.47	1.00 [-]	0.97 [0.50, 1.87]	0.92 [0.48, 1.76]	1.01 [0.53, 1.91]	1.35 [0.73, 2.51]	0.27

Notes: 95% CI: 95% confidence interval; CVD: Cardiovascular Diseases; HR: Hazard Ratio; Q: Quintile.

<sup>1</sup> P-value of Wald test for continuous score variable.

<sup>2</sup> P trend modelling quintiles as an independent ordinal variable.

<sup>3</sup> Model 1 is Cox proportional hazard model adjusted for age (time scale), sex, and energy intake (without alcohol, kcal/day).

<sup>4</sup> Model 2 is Model 1 further adjusted for education level (<high-school degree, ≥ high-school degree to <2 y after high-school degree, ≥2 y after high-school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual workers/ employees/ intermediate profes-

sion/ managerial staff), monthly household income (not communicated, < 1,200 €, from 1,200 to 1,800 €, from 1,800 to 2,700 €, ≥ 2,700€), marital status (single/ married, civil union, cohabiting/ separated, divorced, widowed).

<sup>5</sup> Model 3 is Model 2 further adjusted for number of completed 24h dietary records, physical activity (high, moderate, low, calculated according to IPAQ recommendations), smoking status (never smoker, former smoker, current smoker), alcohol consumption (g/day), height (cm), family history of chronic disease (yes/no).

<sup>6</sup> Model 4 is Model 3 further adjusted for body mass index (kg/m<sup>2</sup>).

<sup>7</sup> Model 5 is Model 3 further adjusted for family history of cancer (yes/no).

<sup>8</sup> Model 6 is Model 5 further adjusted for body mass index (kg/m<sup>2</sup>).

<sup>9</sup> Model 7 is Model 3 further adjusted for number of biological children (continuous), menopausal status (pre, peri, post), oral contraception (yes/no), hormonal treatment for menopause (yes/no).

<sup>10</sup> Model 8 is Model 7 further adjusted for body mass index (kg/m<sup>2</sup>).

<sup>11</sup> Model 9 is Model 3 further adjusted for family history of diabetes (yes/no), family history of stroke (yes/no), baseline history of diabetes (yes/no), and history of hypertension (yes/no).

<sup>12</sup> Model 10 is Model 9 further adjusted for body mass index (kg/m<sup>2</sup>).

<sup>13</sup> Coronary diseases: Myocardial infarction, acute coronary syndrome, angioplasty.

<sup>14</sup> Cerebrovascular diseases: Ischemic stroke.

**Table 3. Prospective association between EAT-Lancet Diet Index and cancer and cardiovascular diseases combined stratified<sup>1</sup> on median alcohol consumption by sex. NutriNet-Santé Study, France, 2009-2021 (n= 62,382).**

	Continuous score (100 pt increase)		Sex-specific quintiles <sup>2</sup>					p-trend <sup>4</sup>
	All	p-value <sup>3</sup>	Q1	Q2	Q3	Q4	Q5	
<b>Low consumers<sup>5</sup></b>								
n	31,190		6,530	5,749	5,722	5,956	7,233	
Events	1,523		253	280	308	314	368	
Person-years	156,516		29,336	29,031	29,593	31,728	36,827	
HR (95% CI)								
Model 1 <sup>6</sup>	0.82 [0.67, 1.00]	0.05	1.00 [-]	1.02 [0.86, 1.21]	0.99 [0.84, 1.18]	0.91 [0.77, 1.08]	0.86 [0.73, 1.02]	<b>0.02</b>
Model 2 <sup>7</sup>	0.78 [0.71, 1.06]	0.17	1.00 [-]	1.04 [0.87, 1.23]	1.01 [0.86, 1.20]	0.94 [0.79, 1.11]	0.90 [0.76, 1.06]	0.08
<b>Heavy consumers<sup>5</sup></b>								
n	31,192		5,946	6,727	6,756	6,520	5,243	
Events	1,989		282	420	457	437	393	
Person-years	165,937		28,262	35,374	37,211	36,343	28,626	
HR (95% CI)								
Model 1 <sup>6</sup>	0.99 [0.81, 1.23]	0.95	1.00 [-]	1.09 [0.94, 1.27]	1.08 [0.93-1.26]	0.99 [0.85, 1.15]	1.08 [0.92-1.26]	0.91
Model 2 <sup>7</sup>	1.02 [0.82, 1.26]	0.85	1.00 [-]	1.09 [0.94, 1.27]	1.09 [0.94, 1.27]	1.00 [0.86-1.16]	1.10 [0.94-1.28]	0.74

Notes: HR: Hazard Ratio; 95% CI: 95% confidence interval; Q: Quintile.

<sup>1</sup> P for interaction was 0.05.

<sup>2</sup> Sex-specific cut-offs for quintiles of EAT-Lancet Diet Index were -161.5/27.8/40.7/51.7/65.2/323.9 for females and -140.1/23.8/36.3/46.5/59.2/332.2 for males.

<sup>3</sup> p-value of Wald test for continuous score variable.

<sup>4</sup> p of trend modelling quintiles as an independent ordinal variable.

<sup>5</sup> Median alcohol cut-offs values for males were < 10.67 g/day for low consumers and ≥ 10.67 g/day for heavy consumers; for females were < 3.10 g/day for low consumers and ≥ 3.10 g/day for heavy consumers.

<sup>6</sup> Model 1 is Cox proportional hazard model adjusted for age (time-scale), sex, energy intake (without alcohol, kcal/day), education level (<high-school degree, ≥ high-school degree to <2 y after high-school degree, ≥2 y after high-school degree), occupation (unemployed/farmer, merchant, artisan, company director, manual workers/ employees/ intermediate profession/ managerial staff), monthly household income (not communicated, < 1,200 €, from 1,200 to 1,800 €, from 1,800 to 2,700 €, ≥ 2,700€), marital status (single/ married, civil union, cohabiting/ separated, divorced, widowed), number of completed 24h dietary records, physical activity (high, moderate, low, calculated according to IPAQ recommendations), smoking status (never smoker, former smoker, current smoker), alcohol consumption (g/day), height (cm), family history of chronic disease (yes/no).

<sup>7</sup> Model 2 is Model 1 further adjusted for body mass index (kg/m<sup>2</sup>).