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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

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Abstract

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

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

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

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

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

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

Introduction

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

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

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

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

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

Methods

Study population

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

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

Data collection

Cases ascertainment

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

Dietary data

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

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

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

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

Covariates

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

Sample selection

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

Statistical analyses

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

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

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

For risk of CVD (HR_{Q5 vs Q1} =0.89 (0.71,1.12), p-trend=0.60) and by sub-types (**Table 2**), there was no significant association.

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

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

Discussion

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

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

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

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

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

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

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

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

In the present study, significant associations were detected only in the highest quintile of ELD-I (Q5). Consideration of the continuous score did not highlight significant results, although that were narrowly for some associations such as adherence to the EAT-Lancet diet and occurrence of cancer and CVD combined among low consumers of alcohol (HR=0.82 (0.67,1.00), p-value=0.05) (**Table 3**). Replication of this study in another setting with more diverse profiles or an even larger number of subjects might allow detection of associations using the continuous score. Nevertheless, this

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

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

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

Conclusion

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

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Authors' contributions:

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

Transparency statement

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

Conflict of Interest

The authors declare no conflict of interest.

Data sharing statement

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

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

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Figures

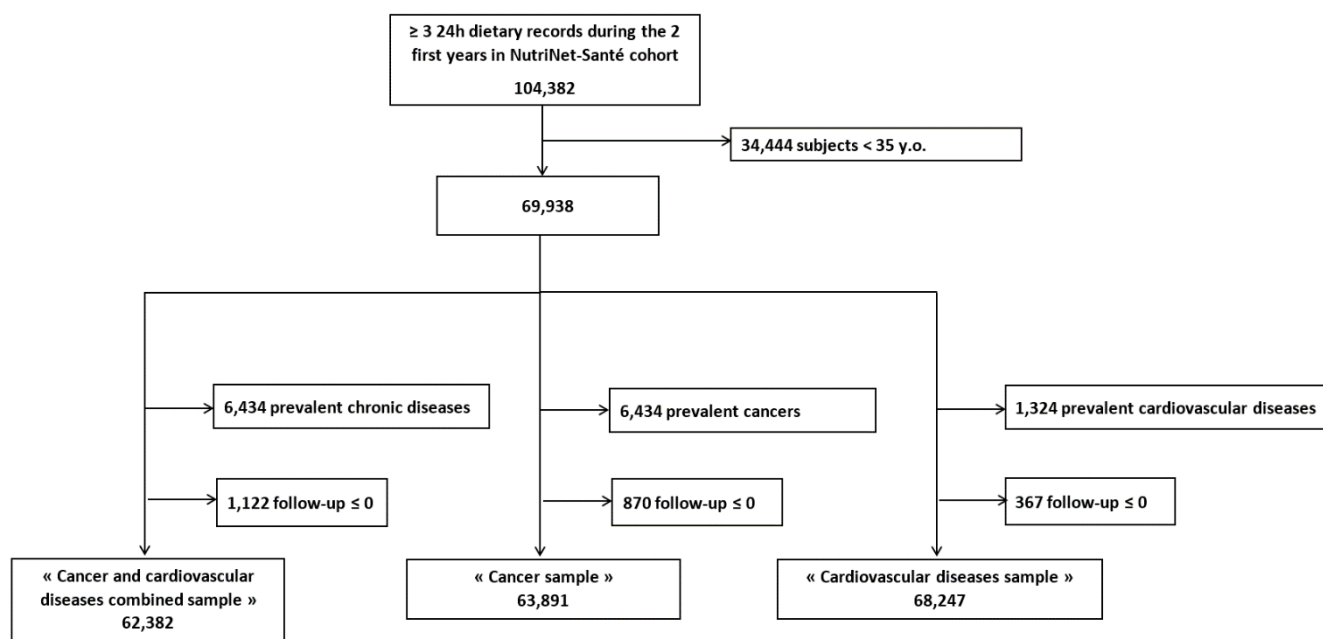


Figure 1. Flow-chart of subjects included in the present analysis, NutriNet Santé study, France 2009-2021.

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 ¹					p-value ²
		Q1	Q2	Q3	Q4	Q5	
n	62,382	12,476	12,476	12,478	12,476	12,476	
EAT-Lancet Diet Index							
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)	
Sex (female), %	75.8	75.8	75.8	75.8	75.8	75.8	
Age (years old)	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
Education level, %							<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	
Occupation, %							<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	
Monthly household income, %							<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	
Marital status, %							<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	
Smoking status, %							<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	
Energy intake without alcohol (kcal/d)	1,866 (478)	1,850 (503)	1,926 (487)	1,912 (469)	1,871 (454)	1,771 (461)	<0.0001
Number of 24h records	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
Alcohol consumption (g/ d)	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
Physical activity ³, %							<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	
Height (cm)	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
Body Mass Index (kg/m²)	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.

¹ 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.

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

³ 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					
	All	p-value ¹	Q1	Q2	Q3	Q4	Q5	p-trend ²
Cancer and CVD combined								
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 ³	0.85 [0.73, 0.98]	0.02	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]	0.03
Model 2 ⁴	0.87 [0.75, 1.00]	0.04	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]	0.04
Model 3 ⁵	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 ⁶	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
Cancers								
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 ³	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]	0.04
Model 2 ⁴	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]	0.04
Model 5 ⁷	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 ⁸	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
Colorectal cancer								
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 ³	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 ⁴	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 ⁷	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 ⁸	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
Lung cancer								
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 ³	0.49 [0.23, 1.03]	0.06	1.00 [-]	0.48 [0.27, 0.83]	0.37 [0.21, 0.67]	0.59 [0.36, 0.97]	0.41 [0.24, 0.70]	0.01
Model 2 ⁴	0.57 [0.27, 1.20]	0.14	1.00 [-]	0.50 [0.28, 0.87]	0.40 [0.22, 0.72]	0.64 [0.39, 1.05]	0.45 [0.26, 0.78]	0.03
Model 5 ⁷	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 ⁸	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
Breast cancer								
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 ³	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 ⁴	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 ⁹	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 ¹⁰	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
Prostate cancer								
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 ³	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 ⁴	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 ⁷	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 ⁸	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
CVD								
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 ³	0.71 [0.52, 0.96]	0.03	1.00 [-]	0.78 [0.62, 0.99]	0.79 [0.63, 0.99]	0.79 [0.63, 0.99]	0.78 [0.62, 0.98]	0.09
Model 2 ⁴	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 ¹¹	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 ¹²	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
Coronary diseases¹³								
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 ³	0.66 [0.48, 0.92]	0.01	1.00 [-]	0.76 [0.59, 0.98]	0.77 [0.60, 0.99]	0.77 [0.60, 0.98]	0.73 [0.57, 0.93]	0.04
Model 2 ⁴	0.71 [0.51, 0.98]	0.04	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 ¹¹	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 ¹²	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
Cerebrovascular diseases¹⁴								
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 ³	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 ⁴	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 ¹¹	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 ¹²	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.

¹ P-value of Wald test for continuous score variable.

² P trend modelling quintiles as an independent ordinal variable.

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

⁴ 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 €, \geq 2,700€), marital status (single/ married, civil union, cohabiting/ separated, divorced, widowed).

⁵ 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).

⁶ Model 4 is Model 3 further adjusted for body mass index (kg/m²).

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

⁸ Model 6 is Model 5 further adjusted for body mass index (kg/m²).

⁹ 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).

¹⁰ Model 8 is Model 7 further adjusted for body mass index (kg/m²).

¹¹ 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).

¹² Model 10 is Model 9 further adjusted for body mass index (kg/m²).

¹³ Coronary diseases: Myocardial infarction, acute coronary syndrome, angioplasty.

¹⁴ Cerebrovascular diseases: Ischemic stroke.

Table 3. Prospective association between EAT-Lancet Diet Index and cancer and cardiovascular diseases combined stratified¹ on median alcohol consumption by sex. NutriNet-Santé Study, France, 2009-2021 (n= 62,382).

	Continuous score (100 pt increase)		Sex-specific quintiles ²					p-trend ⁴
	All	p-value ³	Q1	Q2	Q3	Q4	Q5	
Low consumers ⁵								
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 ⁶	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]	0.02
Model 2 ⁷	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
Heavy consumers ⁵								
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 ⁶	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 ⁷	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.

¹ P for interaction was 0.05.

² 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.

³ p-value of Wald test for continuous score variable.

⁴ p of trend modelling quintiles as an independent ordinal variable.

⁵ 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.

⁶ 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).

⁷ Model 2 is Model 1 further adjusted for body mass index (kg/m²).