Prospective association between adherence to the 2017 French dietary guidelines and risk of death, CVD and cancer in the NutriNet-Santé cohort

Dan Chaltiel, Chantal Julia, Raphaël Chaltiel, Julia Baudry, Mathilde Touvier, Valérie Deschamps, Paule Latino-Martel, Léopold K Fezeu, Serge Hercberg, Emmanuelle Kesse-Guyot

Prospective association between adherence to the 2017 French dietary guidelines and risk of death, cardiovascular diseases, and cancer in the NutriNet-Santé cohort

Dan Chaltiel[1], Chantal Julia[1,2], Raphaël Chaltiel[3], Julia Baudry[1], Mathilde Touvier[1], Valérie Deschamps[4], Paule Latino-Martel[1], Léopold K. Fezeu[1,2], Serge Hercberg[1,2], Emmanuelle Kesse-Guyot[1]

[1] Sorbonne Paris Nord University, Inserm, INRAE, Cnam, Nutritional Epidemiology Research Team (EREN), Epidemiology and Statistics Research Center – University of Paris (CRESS), 93017 Bobigny, France
[2] Public Health Department, Avicenne Hospital, AP-HP, Bobigny, France
[3] Jean Godinot Cancerology Institute, Reims, France
[4] Nutritional Surveillance and Epidemiology Team (ESEN), French Public Health Agency, Paris-13 University, Centre de recherche en épidémiologie et statistiques, COMUE Sorbonne Paris Cité, Bobigny, France

PubMed indexing: Chaltiel, Julia, Chaltiel, Baudry, Touvier, Deschamps, Latino-Martel, Fezeu, Hercberg, Kesse-Guyot

Corresponding author:
Emmanuelle KESSE-GUYOT
Equipe de Recherche en Epidémiologie Nutritionnelle (EREN)
SMBH Sorbonne Paris Nord
74 rue Marcel Cachin, 93017 Bobigny, France
Tel: +33 1 48 38 89 63
Fax: +33 1 48 38 89 31
E-mail: e.kesse@eren.smbh.univ-paris13.fr

Running head: French dietary guidelines and cancer, cardiovascular diseases and death

Words count: abstract =308, text = 3819
Number of tables: 4 + 4
Number of figures: 1

Keywords: nutrition, dietary index, adherence, guidelines, risk, cancer, cardiovascular diseases, death

Abbreviations:
NCD: Non-communicable diseases
CVD: cardiovascular diseases
PNNS: French Nutrition and Health Program (Programme National Nutrition Santé)
PNNS-GS2: PNNS Guidelines Score 2
mPNNS-GS: modified PNNS-GS
FBDG: food-based dietary guidelines

HEI: Healthy Eating Index
AHEI-2010: Alternate HEI, version 2010
MDS: Mediterranean Diet Score
CU: consumption unit
ICD-10: international classification of diseases, 10th revision
IPAQ: International Physical Activity Questionnaire
CDQI: cancer specific diet quality index

Abstract

Background: Non-communicable diseases, such as cancers and cardiovascular diseases (CVD), represent a major public health concern and diet is an important factor in their development. French dietary recommendations were updated in 2017 and an adherence score, the PNNS-GS2, has been developed and validated using a standardised procedure. This study aimed to analyze the prospective association between PNNS-GS2 and the risk of death, cancer and CVD.

Methods: Our sample consisted of French adults included in the prospective NutriNet-Santé cohort (N=67,748, N=75,634, and N=80,269 for the risk of death, cancer, and CVD respectively). PNNS-GS2 (range: -∞ to 14.25) was calculated from the 24-hour dietary records of the first 2 years of monitoring. Association between PNNS-GS2 (in quintiles, Q) and risk of death, cancer and CVD was studied using Cox models adjusted for the main confounding factors.

Results: The sample included 78% of women, aged on average 44.4 years (SD=14.6) with on average 6.6 (SD=2.3) dietary records. Average PNNS-GS2 was 1.5 (SD=3.4) and median follow-up was 6.6 years for cancers and 6.2 years for CVD and deaths. PNNS-GS2 was significantly associated with the risk of death (HR_{Q5vsQ1}[CI95%]=0.77[0.60-1.00], 828 cases), cancer (HR_{Q5vsQ1}=0.80[0.69-0.92], 2,577 cases), and CVD (HR_{Q5vsQ1}=0.64[0.51-0.81], 964 cases). More specifically, PNNS-GS2 was significantly associated with colorectal and breast cancer risks but not prostate cancer risk.

Conclusion: Our results suggest that strong adherence to the 2017 French dietary recommendations is associated with a lower risk of death, cancer or CVD. This reinforces the validity of these new recommendations and will help to promote their dissemination.

Introduction

In almost all countries, the burden of non-communicable diseases (NCD) is a major public health concern. Indeed, in 2016, according to the WHO, the mortality due to NCD was 71% worldwide, and up to 88% in high-income countries such as France, where cardiovascular diseases (CVD) and cancers represent the largest causes of death[1].

As NCDs induce a high mortality and social burden, the challenge is to develop preventive measures by acting on modifiable risk factors such as dietary habits. As a matter of fact, there is growing recognition of the importance of diet, among other lifestyle factors, in the development of cancer and CVD [2].

"*Optimal*" diet is not absolute and most countries, which differ on culture and ethnicity, have each their own definition of a favorable diet and translate them into easily understandable food-based dietary guidelines (FBDG)[3]. However, there is a growing consensus on which food groups should be promoted or limited in order to minimize the risk of NCD, and most guidelines recommend high consumption of fruits, vegetables and wholegrains and low intake of meats, fats, sugary and salted foods[3].

When assessing the association between overall diet quality and health outcomes, many studies use dietary quality scores, such as the Healthy Eating Index or the Mediterranean Diet Score[4–7] but also specific dietary guidelines developed in European countries such as Denmark[8], UK[9]and Netherland[10]. Some of these have been recently compared in a modelling study[11].Indeed, considering dietary exposure through scores allows to consider diet as a whole, accounting for complex synergies between foods and nutrients, which is considered closer to reality as foods are not consumed in isolation[12–15]. When a diet quality score is based on official guidelines, studying its association with health outcomes also allows assessing the relevance of the guidelines regarding the prevention of these outcomes.

In France, FBDG were revised in March 2017[16] as a core part of the 4th (2019-2023) French Nutrition and Health Program (*Programme National Nutrition Santé*, "PNNS"). Recently, we developed and validated the PNNS-Guidelines Score 2 (PNNS-GS2), aiming to estimate the adherence to the 2017 FBDG[17]. The PNNS-GS2 was meant to update the PNNS-GS, based on 2001 guidelines, which were less specific, less plant-based and did not consider organic food.

Hence, the present study aimed at assessing the prospective associations between the PNNS-GS2 and risk of non-accidental mortality, cardiovascular disease mortality or incidence and cancer mortality or incidence in a large French prospective cohort. In particular, the role of adjustment on BMI was assessed as we previously showed that the PNNS-GS2 is highly associated with the risk of overweight and obesity[18], which are themselves major risk factors for cancer and CVD[19–21].

Subjects and Methods

Study population

The data were collected in the NutriNet-Santé cohort, a large observational prospective web-based cohort launched in 2009 in France. Its purpose is to investigate the associations between nutrition and health, as well as determinants of dietary behavior and nutritional status. The detailed design and methodology have been described elsewhere[22]. Participants were recruited through vast multimedia campaigns, amongst the adult (>18 years old) population having access to the internet. All questionnaires were pilot-tested and completed online using 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 for Health and Medical Research (IRB Inserm no. 0000388FWA00005831) and by the National Commission on Informatics and Liberty (CNIL no. 908450 and no. 909216). Electronic informed consent was obtained from all participants. The NutriNet-Santé study is registered in ClinicalTrials.gov (NCT03335644).

Dietary data

Participants are asked to provide three non-consecutive 24h dietary records assigned over a 2-week period at baseline then twice a year. Days are randomly attributed into two weekdays and one weekend day to account for intra-individual variability in intake. All food and drink consumption throughout the entire day (midnight to midnight) are recorded by participants via the dedicated online platform providing a food browser (grouped by category) or a search engine. Participants declare intakes as absolute units when known (in g or mL), common household measures or using food portion size from validated pictures[23].

Intakes were weighted according to weekday vs. weekend day and daily energy and nutrient intakes were computed using a validated and constantly updated composition tables including more than 3,500

food items[24]. Under-reporters were excluded using the published method by Black et al. with Goldberg cut-offs, which is based on physical activity level (PAL) and basal metabolic rate (BMR). BMR was calculated using the Schofield's equations [25], accounting for gender, age, height and weight. Within-subject variation coefficient (day-to-day) for energy intake was calculated individually for each participant based on their 24h dietary records data and within-subject coefficients of variations for BMR and PAL were defined at 8.5% and 15% respectively [26,27]. . This dietary recording protocol has been tested and validated against an interview by a trained dietitian and against blood and urinary biomarkers[28–30].

Frequency of organic food consumption was assessed within 2 months after inclusion for fruits, vegetables, bread, and starchy foods (rice, pasta and legumes) using a previously described questionnaire[17,31]. Frequencies were assessed using three modalities of consumption: (1) most of the time; (2) occasionally; (3) never. Concerning starchy foods, the frequency of organic food consumption was considered twice, once for rice and pasta and once for legumes, but each item was considered null if it was not reported as consumed in the 24-hour dietary records.

Computation of dietary scores

The PNNS-GS2 is a dietary index (theoretical range = [-17;13.5]) designed to reflect the adherence to the 2017 French FBDG[16,32]. It includes 13 components, 6 of adequacy and 7 of moderation, and is penalized on energy intake in such a way that if a participant has an energy intake higher than 105% of the energy expenditure, the score is reduced by the same ratio. Its components, scorings and weights are presented in **Table 1**.

Case ascertainment

Participants self-declared health events through the health status questionnaire every three months, or at any time using a specific interface on a secured dedicated website.

For each incident disease declared, a physician from the study team contacted the participant and asked to provide any relevant medical records (e.g., diagnoses, hospital admissions, radiological reports, electrocardiograms). If necessary, the study physicians could contact the patient's physician or hospitals to collect additional information. Afterwards, a committee of physicians reviewed all medical data to validate major health events. Participants' families or doctors, based on data previously provided by the participants, were contacted when there had been no response to the study website for

more than one year. This process constituted the main source of case ascertainment in the cohort. In addition, our research team was the first in France authorized by the Council of State (No 2013-175) to link data from our general population-based cohorts to medico-administrative databases of national health insurance (SNIIRAM). This data collection has helped us to limit the potential bias from those who had not reported their health events to the study investigators.

We also used linkage to the French national cause-specific mortality registry (CépiDC) to detect deaths and potentially missed cases for deceased participants. We classified cancer and CVD cases by using the international classification of diseases, 10th revision (ICD-10). In this study, we considered all first primary cancers diagnosed between the inclusion date and 13th May, 2019 to be cases, except for basal cell skin carcinoma which we did not consider as cancer. For CVD, we focused on first incident cases of stroke (I64), myocardial infarction (I21), acute coronary syndrome (I20.0 and I21.4), and angioplasty (Z95.8).

Covariates

Using a dedicated self-administered web-based questionnaire[22], participants filled in their sociodemographic and lifestyle characteristics (age, sex, education, occupation, income, marital status, physical activity and smoking habits). Physical activity was assessed by the International Physical Activity Questionnaire (IPAQ)[33]. Monthly income was estimated per consumption unit according to a weighting system, where one consumption unit (cu) is attributed for the first adult in the household, 0.5 CU for other persons aged 14 or older, and 0.3 cu for children under 14[34]. Baseline height and weight were self-reported at enrolment using a web-based anthropometric questionnaire[35,36]. BMI (kg/m^2) was then computed by dividing weight by height squared. Data from specific questionnaires and medication were used to retrieve the status regarding hypertension, dyslipidaemia, menopause, oral contraception and hormonal treatment for menopause.

Sample selection

For the present analysis, we included all participants who filled in at least three 24 h dietary records during the first two years after inclusion (n=115,536). Data used in the present paper were based on participants included between 2009 and 2014 and followed up until May 2019 at the most. PNNS-GS2 was not computable for some participants due to missing data, mostly on organic food consumption. For mortality analysis, participants were considered at risk when they were over 35 years old and

accidental deaths were not considered as event. We also excluded all prevalent cases of the studied outcome and subjects with missing covariates.

Detailed flowchart is presented in **Figure 1**. Exclusions led to a working sample of 80,964 participants and analyses for risk of mortality, cancer and CVD were performed on 67,748, 75,634 and 80,269 participants respectively.

Statistical analysis

Analyses were hypothesis-oriented based on the relationship between PNNS-GS2 and prospective occurrence of cancer, CVD or death. To investigate unexpected results, two non-prespecified analyses were performed.

Quintiles (Q) of PNNS-GS2 were calculated for men and women separately.

Sociodemographic characteristics are presented across quintiles of PNNS-GS2.

We first estimated the association between PNNS-GS2 and incidence of non-accidental mortality (among participants older than 35 years old), CVD and cancer, using a multivariable Cox proportional hazard model with age as time-scale[37]. For each specific outcome, participants contributed follow-up time from their entry in the study until the date of disease diagnosis, date of last completed questionnaire, date of death or May 2019, whichever occurred first, so that each person contributed only one endpoint to the analysis. The data were thus left-truncated and right-censored.

In a second set of analysis, we estimated the association between PNNS-GS2 and incidence of cancer by localization (colorectal, prostate in men, and breast in women, i.e., the most frequent cancer locations in the cohort). Here, the number of events, and therefore the power, was lower, which is why the results were described in sex-specific tertiles instead of quintiles.

In order to account for competing events, we used cause-specific models, as it is recommended when addressing inference questions[38]. Therefore, our models are censored on death not related to the event, and on cancer on a different localization for cancer by localization.

Several models were used. The first model, m0, was only adjusted for sex. The model m1 was further adjusted for energy intake without alcohol (continuous variable), number of completed 24h dietary records (continuous variable), height (continuous variable), season of inclusion (4 modalities), educational level (primary, secondary, university), monthly income (≤1800 €/cu, 1800 - 2700 €/cu, >2700 €/cu, >2700 €/cu), occupation (farmers / self-employed, managerial staff, employees, students,

manual workers, intermediates professions, retired, unemployed), cohabiting status (living alone, cohabiting), baseline physical activity ([0-30[min/day, [30-60[min/ day, ≥ 60 min/ day), smoking status (nonsmokers, former smokers, smokers), menopausal status in women (yes/no), hormonal treatment for menopause in menopaused women (yes/no) and oral contraception in non-menopaused women (yes/no). The model m2 was further adjusted for ethanol intake (continuous variable). Ethanol intake is partially included in the PNNS-GS2 by design, but since it is a major risk factor, we wanted to further consider it as a confounding variable. The model m3 was further adjusted for baseline BMI (continuous variable).

For cancer analysis, models m1 and m2 were further adjusted for parental history of cancer (yes/no), and for number of children (continuous variable) for breast cancer. For CVD analysis, models m1 and m2 were further adjusted for parental history of CVD (yes/no) and an additional model m3 also included baseline hypertension (yes/no), diabetes (yes/no) and dyslipidaemia status (yes/no).

Log-linearity was tested graphically for PNNS-GS2 using martingale residuals. All other continuous covariates have been corrected for log-linearity using restricted cubic splines with 3 nodes[39] using the *rms* package for R®[40]. Proportional hazard assumption was tested by performing a Grambsch-Therneau test[41] and validated graphically using Schoenfeld residuals. All analyses were performed in men and women altogether as no significant interaction with sex was ever detected.

As a sensitivity analysis, we replicated these analyses without considering early events (<2 years after inclusion) in order to reduce the reverse causality bias.

All statistical analyses were conducted using R® (version 3.4.2) and SAS® (version 7.15) with a significance level of 5% for two-sided tests.

Patient involvement

The research hypothesis developed in this article corresponds to an important interest for the participants involved in the NutriNet-Santé cohort and for the public in general. The results of this study will be disseminated to the NutriNet-Santé participants through the cohort website, public seminars, and a press release.

Results

The working sample was composed of 78% women and 22% men, providing on average 6.6 (SD=2.3) 24h dietary records and 14.8 (SD=9.2) validated health questionnaires per person. Participants were on average 44.4 (SD=14.6) years old. Mean PNNS-GS2 was 1.5 (SD=3.4) and median follow-up was 6.7 years for cancer and 6.2 years for both mortality and MCV analyses.

Associations of PNNS-GS2 with baseline covariates are presented in **Table 2.** Higher adherence with 2017 French FBDG was positively associated with age, education, income, cohabiting status and physical activity, and negatively associated with baseline BMI, energy intake without alcohol, alcohol consumption and smoking habit. For descriptive purpose, consumption of macronutrients and food groups are presented in **Supplemental Table 1**. By design, PNNS-GS2 was positively associated with higher consumption of fruits, vegetables, legumes and whole grain cereals and higher frequency of organic food consumption, and negatively associated with higher consumption of red and processed meat, refined cereals and sweetened and alcoholic drinks.

The results of the prospective association between PNNS-GS2 and the risk of non-accidental mortality, all-sites cancer and CVD are presented in **Table 3**. After adjustment for confounding variables and regardless of the model, a higher adherence to the 2017 FBDG (measured by the PNNS-GS2) was negatively associated with the risk of death (828 cases), all cancer (2,577 cases) and CVD (964 cases).

The results of the prospective association between PNNS-GS2 and the risk of cancer by type are presented in **Table 4**. After adjustment for confounding variables, the PNNS-GS2 was significantly associated with a lower risk of colorectal cancer, but no significant association could be found for prostate cancer or for breast cancer. These results prompted us to perform two sets of non-prespecified analyses to investigate them.

First, as association with breast cancer was unexpectedly not significant[42], we ran a non-prespecified analysis, considering the risk of cancer either before or after the menopause. Results are presented in **Supplemental Table 2**. Here, PNNS-GS2 was significantly associated with a lower risk of breast cancer occurring after menopause, but with a higher risk of breast cancer before menopause. This latter association persisted after further adjustment for eating disorder (yes/no) or after stratification on number of children, BMI class (<25 vs ≥ 25), physical activity, or parental history of cancer (data not shown).

Second, to make sure that the association between PNNS-GS2 and cancer was not entirely driven by colorectal cancer, another non-prespecified analysis was run, considering all cancers except colorectal to point out the association for other location. Results are presented in **Supplemental Table 3**. PNNS-GS2 was still strongly associated with the risk of cancer, validating this result.

The results of the sensitivity analysis without considering early events are presented in **Supplemental Table 4**. Although significance was reduced for lower quintiles, the PNNS-GS2 was still significantly negatively associated with the risk of death, CVD and cancer in all models.

Schoenfeld residuals graphical analysis and Grambsch-Therneau tests showed that the multivariable global assumption was never significantly violated. Log-linearity of PNNS-GS2's hazard rate was validated graphically using Martingale residuals on the null model, which showed linear association for death, all-sites cancer and CVD study. However, this hypothesis was slightly violated for cancers by localization, hence results given for 1 point or 1 SD should be interpreted cautiously.

Discussion

In the present study, the adherence to the 2017 French FBDG assessed by the PNNS-GS2 was associated, after adjustment for confounding variables, with a significantly lower risk of non-accidental mortality (up to -18% in Q5 vs Q1), cancer incidence or mortality (up to -17% in Q5 vs Q1), and cardiovascular diseases incidence or mortality (up to -27% in Q5 vs Q1). The sensitivity analysis which did not consider early events provided similar findings. PNNS-GS2 was also significantly associated with a lower risk of colorectal cancer (up to -17% for 1 SD), but was not associated with prostate cancer or breast cancer.

Our results are consistent with the ones of a recent meta-analysis on association between dietary scores and risk of death, CVD and cancer, Schwingshackl et al.[5]. Indeed, the authors reported a pooled risk reduction of -22% for all-cause mortality, -22% for CVD incidence or mortality and -16% for cancer incidence or mortality when comparing high versus low adherence. Despites some differences, notably in the food groups considered as harmful, cut-offs and scoring, all these dietary scores (namely the Healthy Eating Index and the Alternate Healthy Eating Index, reflecting American guidelines, and the Dietary Approaches to Stop Hypertension Score, designed to reduce hypertension) promote, similarly to the PNNS-GS2, the consumption of fruits, vegetables, whole grains, nuts, and legumes, which are known to lower the risk of CVD and some types of cancer[43,44].

The observed association with mortality, as the risk of cardiovascular diseases, was similar to number of other studies on other diet quality scores, even if all do not reflect dietary guidelines[4,5,45–48].

Concerning the risk of cancer, the strong negative association with diet quality as per the PNNS-GS2 was also consistent with the above-mentioned studies[4,5,45,46]. By location, the negative association between PNNS-GS2 and risk of colorectal cancer was analogous to the one reported by Park et al., which used dietary indices elaborated for the American population (HEI-2010 and AHEI-2010) in a larger cohort[49]. Also, a colorectal cancer specific diet quality index, namely the CDQI, recently developed and based on consumption of processed meat, fiber and dairy products, have documented an inverse association with risk of colorectal cancer[50]. Since these food groups are directly or indirectly assessed by the PNNS-GS2, this is consistent with our results. Interestingly, a previous study conducted in the NutriNet-Santé cohort study, with a shorter follow-up (6.4y), did not report any association with AHEI and colorectal cancer[51].

For breast cancer, a recent meta-analysis reported that it is negatively associated with a healthy/prudent diet and positively associated with a Western diet[52]. This is consistent with current knowledge between dietary components of the PNNS-GS2 and breast cancer, notably regarding vegetables, saturated fat, and red and processed meat[42], alcohol[44], and dietary fibers[53]. The meta-analysis also presented a subgroup analysis concluding that this latter association is significant in post-menopausal women but remains marginal in pre-menopausal women[52]. This was also consistent with a large prospective study (N=96,959)[54], considering diet quality as per American guidelines (AHEI-2010 score). As we found no significant association between PNNS-GS2 and global risk of breast cancer, this motivated our non-prespecified supplemental analysis, which also concluded to a significant protective association in post-menopausal women. However, the association of PNNS-GS2 with a higher risk of breast cancer in pre-menopausal women was rather puzzling. We could find only one study, published in 2013 on 49,258 women, that reported a positive association between Mediterranean Diet and risk of cancer in pre-menopausal women with a HR of 1.10 (CI=[1.01;1.21])[55], but this result was explained by the promotion of moderate alcohol consumption, which is not promoted by the 2017 French FBDG. Since other articles describe either a protective or a non-significant association, and since none of our additional explorations could identify a relevant confounding factor, we attributed this finding to an artifact or to residual, unidentified confounding as no mechanistic hypothesis was identified to explain

this finding. Still, as these results come from non-prespecified analysis, they should be taken with particular caution. Interestingly, the above-mentioned previous study conducted in the NutriNet-Santé cohort study did not report any association with either AHEI, Medilite or mPNNS-GS and breast cancer[51].

On the very few studies that have measured the association between diet quality and prostate cancer, one has identified a significant association with HEI-2005 and AHEI-2010, but only in men screened for PSA, which are obviously particularly at risk of prostate cancer[56]. This association was not significant in men without PSA screening. Still, since our population was predominantly female, it would be interesting to replicate our study in a larger male population to benefit from a higher statistical power.

The main difference between the 2017 French FBDG and most FBDG is the consideration of organic food. Indeed, organic food consumption have already been associated to an lower risk of cancer in the NutriNet-Santé cohort[57]. Our results are consistent with this study regarding risk of all-sites, prostate and post-menopausal breast cancer. However, no association was detected with colorectal and pre-menopausal breast cancer risk in that study. We thus can hypothesize that for these specific cancers, exposure to pesticides residues, which is one of the potential mechanisms for explaining the protective effect of organic food consumption on cancer risk, may be of lesser importance than nutritional properties of specific food groups like processed meat, fiber and dairy products. Another hypothesis may rely on statistical power since our population was larger and our follow-up time longer.

Some limitations of our study are worth noting. First, our analyses were based on volunteers who were probably particularly concerned about their health, which limited the generalizability of our results. Indeed, NutriNet-Santé participants are more likely to be women, well-educated, rather young, and to have healthier behaviors than the general French population[58]. This selection bias could have led to a lower NCD incidence and to a better diet quality than would have been estimated in the general population, so we should expect that our results were underestimated, although overestimation bias could not be totally ruled out. Second, residual confounding cannot be excluded in an observational study, thus unmeasured behavioral factor as well as lack of precision in the measurement of covariates and dietary records could have influenced the observed associations, although we accounted for a wide range of potential confounders. Third, most of our data were self-declared and could therefore lack

precision or suffer from social desirability bias. However, dietary data were validated against urinary and blood biomarkers[29,30] and objective measurement[36].

Nevertheless, although these limitations were noted, our study found strong negative associations between PNNS-GS2 and risk of non-accidental death, cancer and CVD. An important strength of this work is its prospective design and its median follow-up duration of 6.7 years, which may have limited reverse causality. Given the relatively large size of our population, this allowed a satisfying statistical power. However, this power was restricted for studying risk of death, probably because of the selection of a rather young and healthy population. Our dietary data were also highly accurate with on average 6.6 24h records per individual, thus accounting for daily variation. The PNNS-GS2 has been validated in its construction and has proven a reliable construct in other studies[17,18]. Finally, our health events (cancer and CVD) were validated by trained physicians, and data were linked to medico-administrative databases, which should limit the declaration bias.

In conclusion, our findings suggest that following 2017 FBDG tend to be associated with a lower risk of death, cancer and CVD. These results reinforce the validity and relevance of the updated recommendations and should comfort the evidence supporting their dissemination.

Acknowledgments

The authors warmly thank all the volunteers of the NutriNet-Santé cohort. We also thank Cédric Agaesse, Vristi Desan and Cynthia Perlin (dietitians); Thi Hong Van Duong, Younes Esseddik (IT manager), Paul Flanzy, Régis Gatibelza, Jagatjit Mohinder and Aladi Timera (computer scientists); Julien Allegre, Nathalie Arnault, Laurent Bourhis and Fabien Szabo de Edelenyi, PhD (supervisor) (data-manager/statisticians); Fatoumata Diallo, MD, Roland Andrianasolo, MD, and Sandrine Kamdem (physicians); and Nathalie Druesne-Pecollo, PhD (operational manager) for their technical contribution to the NutriNet-Santé study.

Financial Support

The NutriNet-Santé study was supported by the following public institutions: Ministère de la Santé, Santé Publique France, Institut National de la Santé et de la Recherche Médicale (INSERM), Institut national de recherche pour l'agriculture, l'alimentation et l'environnement (INRAe), Conservatoire National des Arts et Métiers (CNAM) and Université Sorbonne Paris Nord. Researchers were

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

Disclaimer: None of the authors declare any conflicts of interest.

Author's contributions:

EKG, SH, CJ and MT were responsible for the development of the design and protocol of the study; EKG and DC were responsible for the design of the research. DC performed the statistical analysis and wrote the paper; EKG supervised statistical analysis and paper writing; DC, CJ, RC, JB, MT, VD, PLM, LF, SH, and EK-G were involved in interpreting the results and editing the manuscript for important intellectual content. All authors read and approved the final manuscript.

References

1. World Health Organization. Global Health Estimates 2016: Disease burden by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018 [Internet]. 2018 [cited 2019 Jun 19]. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

2. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Lond Engl. 2019;393:1958–72.

3. Montagnese C, Santarpia L, Buonifacio M, Nardelli A, Caldara AR, Silvestri E, et al. European food-based dietary guidelines: A comparison and update. Nutrition. 2015;31:908–15.

4. Lassale C, Gunter MJ, Romaguera D, Peelen LM, Van der Schouw YT, Beulens JWJ, et al. Diet Quality Scores and Prediction of All-Cause, Cardiovascular and Cancer Mortality in a Pan-European Cohort Study. PloS One. 2016;11:e0159025.

5. Schwingshackl L, Bogensberger B, Hoffmann G. Diet Quality as Assessed by the Healthy Eating Index, Alternate Healthy Eating Index, Dietary Approaches to Stop Hypertension Score, and Health Outcomes: An Updated Systematic Review and Meta-Analysis of Cohort Studies. J Acad Nutr Diet. 2018;118:74-100.e11.

6. Dinu M, Pagliai G, Casini A, Sofi F. Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr. 2018;72:30–43.

7. Galbete C, Kröger J, Jannasch F, Iqbal K, Schwingshackl L, Schwedhelm C, et al. Nordic diet, Mediterranean diet, and the risk of chronic diseases: the EPIC-Potsdam study. BMC Med. 2018;16:99.

8. Hansen SH, Overvad K, Hansen CP, Dahm CC. Adherence to national food-based dietary guidelines and incidence of stroke: A cohort study of Danish men and women. PloS One. 2018;13:e0206242.

9. Scheelbeek P, Green R, Papier K, Knuppel A, Alae-Carew C, Balkwill A, et al. Health impacts and environmental footprints of diets that meet the Eatwell Guide recommendations: analyses of multiple UK studies. BMJ Open. 2020;10:e037554.

10. Voortman T, Kiefte-de Jong JC, Ikram MA, Stricker BH, van Rooij FJA, Lahousse L, et al. Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. Eur J Epidemiol. 2017;32:993–1005.

11. Springmann M, Spajic L, Clark MA, Poore J, Herforth A, Webb P, et al. The healthiness and sustainability of national and global food based dietary guidelines: modelling study. BMJ. 2020;370:m2322.

12. Ocké MC. Evaluation of methodologies for assessing the overall diet: dietary quality scores and dietary pattern analysis. Proc Nutr Soc. 2013;72:191–9.

13. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3–9.

14. Jacobs DR, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. Am J Clin Nutr. 2009;89:1543S-1548S.

15. Burggraf C, Teuber R, Brosig S, Meier T. Review of a priori dietary quality indices in relation to their construction criteria. Nutr Rev. 2018;76:747–64.

16. High Council for Public Health. French Nutrition and Health Programme's dietary guidelines for adults for the period 2017-2021 [Internet]. 2017 Feb. Available from: https://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspa20170216_reperesalimentairesactua2017_en.pdf

17. Chaltiel D, Adjibade M, Deschamps V, Touvier M, Hercberg S, Julia C, et al. Programme National Nutrition Santé – guidelines score 2 (PNNS-GS2): development and validation of a diet quality score reflecting the 2017 French dietary guidelines. Br J Nutr. 2019;1–12.

18. Chaltiel D, Julia C, Adjibade M, Touvier M, Hercberg S, Kesse-Guyot E. Adherence to the 2017 French dietary guidelines and adult weight gain: A cohort study. PLOS Med. 2019;16:e1003007.

19. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer — Viewpoint of the IARC Working Group. N Engl J Med. 2016;375:794–8.

20. Hruby A, Manson JE, Qi L, Malik VS, Rimm EB, Sun Q, et al. Determinants and Consequences of Obesity. Am J Public Health. 2016;106:1656–62.

21. Bastien M, Poirier P, Lemieux I, Després J-P. Overview of Epidemiology and Contribution of Obesity to Cardiovascular Disease. Prog Cardiovasc Dis. 2014;56:369–81.

22. Hercberg S, Castetbon K, Czernichow S, Malon A, Mejean C, Kesse E, et al. The Nutrinet-Sante Study: a web-based prospective study on the relationship between nutrition and health and determinants of dietary patterns and nutritional status. BMC Public Health. 2010;10:242.

23. Le Moullec N, Deheeger M, Preziosi P, Monteiro P, Valeix P, Rolland-Cachera M-F, et al. Validation du manuel-photos utilisé pour l'enquête alimentaire de l'étude SU. VI. MAX. Cah Nutr Diététique. 1996;31:158–64.

24. Etude NutriNet-Santé. Table de Composition des Aliments de l'étude NutriNet-Santé [NutriNet-Santé Study Food Composition Database]. Economica: Paris,France; 2013.

25. Schofield WN. Predicting basal metabolic rate, new standards and review of previous work. Hum Nutr Clin Nutr. 1985;39 Suppl 1:5–41.

26. Black AE. Critical evaluation of energy intake using the Goldberg cut-off for energy intake:basal metabolic rate. A practical guide to its calculation, use and limitations. Int J Obes Relat Metab Disord J Int Assoc Study Obes. 2000;24:1119–30.

27. Goldberg GR, Black AE, Jebb SA, Cole TJ, Murgatroyd PR, Coward WA, et al. Critical evaluation of energy intake data using fundamental principles of energy physiology: 1. Derivation of cut-off limits to identify under-recording. Eur J Clin Nutr. 1991;45:569–81.

28. Touvier M, Kesse-Guyot E, Méjean C, Pollet C, Malon A, Castetbon K, et al. Comparison between an interactive web-based self-administered 24 h dietary record and an interview by a dietitian for large-scale epidemiological studies. Br J Nutr. 2011;105:1055–64.

29. Lassale C, Castetbon K, Laporte F, Camilleri GM, Deschamps V, Vernay M, et al. Validation of a Web-based, self-administered, non-consecutive-day dietary record tool against urinary biomarkers. Br J Nutr. 2015;113:953–62.

30. Lassale C, Castetbon K, Laporte F, Deschamps V, Vernay M, Camilleri GM, et al. Correlations between Fruit, Vegetables, Fish, Vitamins, and Fatty Acids Estimated by Web-Based Nonconsecutive Dietary Records and Respective Biomarkers of Nutritional Status. J Acad Nutr Diet. 2016;116:427-438.e5.

31. Baudry J, Méjean C, Péneau S, Galan P, Hercberg S, Lairon D, et al. Health and dietary traits of organic food consumers: results from the NutriNet-Santé study. Br J Nutr. 2015;114:2064–73.

32. Santé Publique France. Avis d'experts relatif à l'évolution du discours public en matière de consommation d'alcool en France organisé par Santé publique France et l'Institut national du cancer. 2017 May.

33. Hallal PC, Victora CG. Reliability and validity of the International Physical Activity Questionnaire (IPAQ). Med Sci Sports Exerc. 2004;36:556.

34. INSEE. Definition - Consumption unit | Insee [Internet]. 2016 [cited 2018 Jul 27]. Available from: https://www.insee.fr/en/metadonnees/definition/c1802

35. Touvier M, Méjean C, Kesse-Guyot E, Pollet C, Malon A, Castetbon K, et al. Comparison between web-based and paper versions of a self-administered anthropometric questionnaire. Eur J Epidemiol. 2010;25:287–96.

36. Lassale C, Péneau S, Touvier M, Julia C, Galan P, Hercberg S, et al. Validity of web-based self-reported weight and height: results of the Nutrinet-Santé study. J Med Internet Res. 2013;15:e152.

37. Lamarca R, Alonso J, Gómez G, Muñoz A. Left-truncated data with age as time scale: an alternative for survival analysis in the elderly population. J Gerontol A Biol Sci Med Sci. 1998;53:M337-343.

38. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016;133:601–9.

39. Harrell FEJ. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Springer; 2015. 598 p.

40. Harrell FE. rms: Regression modeling strategies [Internet]. 2011. (f.harrell@vanderbilt.edu). Available from: http://CRAN.R-project.org/package=rms

41. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika. 1994;81:515–26.

42. Dandamudi A, Tommie J, Nommsen-Rivers L, Couch S. Dietary Patterns and Breast Cancer Risk: A Systematic Review. Anticancer Res. 2018;38:3209–22.

43. Mozaffarian D. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity: A Comprehensive Review. Circulation. 2016;133:187–225.

44. AICR/WCRF. Diet, Nutrition, Physical activity, and the Prevention of Cancer: a global perspective. Washington, DC: American Institute for Cancer Research: American Institute for Cancer Research & World Cancer Research Fund; 2018.

45. Onvani S, Haghighatdoost F, Surkan PJ, Larijani B, Azadbakht L. Adherence to the Healthy Eating Index and Alternative Healthy Eating Index dietary patterns and mortality from all causes, cardiovascular disease and cancer: a meta-analysis of observational studies. J Hum Nutr Diet. 2017;30:216–26.

46. Wang J, Haslam D, Ruan M, Chen F, Du M, Zhang FF. Diet Quality in Association with All-Cause, Cardiovascular, and Cancer Mortality Among US Adults: NHANES 1999-2010 (OR14-04-19). Curr Dev Nutr. 2019;3.

47. Trébuchet A, Julia C, Fézeu L, Touvier M, PharmaD DC, Hercberg S, et al. Prospective association between several dietary scores and risk of cardiovascular diseases: Is the Mediterranean diet equally

associated to CVD compared to National Nutritional Scores? Am Heart J [Internet]. 2019 [cited 2019 Jul 29]; Available from: http://www.sciencedirect.com/science/article/pii/S000287031930184X

48. Aljuraiban GS, Gibson R, Oude Griep LM, Okuda N, Steffen LM, Van Horn L, et al. Perspective: The Application of A Priori Diet Quality Scores to Cardiovascular Disease Risk—A Critical Evaluation of Current Scoring Systems. Adv Nutr. 2020;11:10–24.

49. Park S-Y, Boushey CJ, Wilkens LR, Haiman CA, Le Marchand L. High-Quality Diets Associate With Reduced Risk of Colorectal Cancer: Analyses of Diet Quality Indexes in the Multiethnic Cohort. Gastroenterology. 2017;153:386-394.e2.

50. Vulcan A, Ericson U, Manjer J, Ohlsson B. A colorectal cancer diet quality index is inversely associated with colorectal cancer in the Malmö diet and cancer study. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP. 2018;

51. Lavalette C, Adjibade M, Srour B, Sellem L, Fiolet T, Hercberg S, et al. Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Santé Cohort. Cancer Res. 2018;78:4427–35.

52. Xiao Y, Xia J, Li L, Ke Y, Cheng J, Xie Y, et al. Associations between dietary patterns and the risk of breast cancer: a systematic review and meta-analysis of observational studies. Breast Cancer Res BCR [Internet]. 2019 [cited 2020 Jul 1];21. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6352362/

53. Latino-Martel P, Cottet V, Druesne-Pecollo N, Pierre FHF, Touillaud M, Touvier M, et al. Alcoholic beverages, obesity, physical activity and other nutritional factors, and cancer risk: A review of the evidence. Crit Rev Oncol Hematol. 2016;99:308–23.

54. Haridass V, Ziogas A, Neuhausen SL, Anton-Culver H, Odegaard AO. Diet Quality Scores Inversely Associated with Postmenopausal Breast Cancer Risk Are Not Associated with Premenopausal Breast Cancer Risk in the California Teachers Study. J Nutr. 2018;148:1830–7.

55. Couto E, Sandin S, Löf M, Ursin G, Adami H-O, Weiderpass E. Mediterranean Dietary Pattern and Risk of Breast Cancer. PLoS ONE [Internet]. 2013 [cited 2019 Jul 1];8. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3563544/

56. Bosire C, Stampfer MJ, Subar AF, Park Y, Kirkpatrick SI, Chiuve SE, et al. Index-based Dietary Patterns and the Risk of Prostate Cancer in the NIH-AARP Diet and Health Study. Am J Epidemiol. 2013;177:504–13.

57. Baudry J, Assmann K, Touvier M, Allès B, Seconda L, d'autres..., et al. Association of Frequency of Organic Food Consumption With Cancer Risk. JAMA Intern Med [Internet]. 2018 [cited 2018 Nov 5]; Available from: https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2707948

58. Andreeva VA, Salanave B, Castetbon K, Deschamps V, Vernay M, Kesse-Guyot E, et al. Comparison of the sociodemographic characteristics of the large NutriNet-Santé e-cohort with French Census data: the issue of volunteer bias revisited. J Epidemiol Community Health. 2015;69:893–8.

Figures

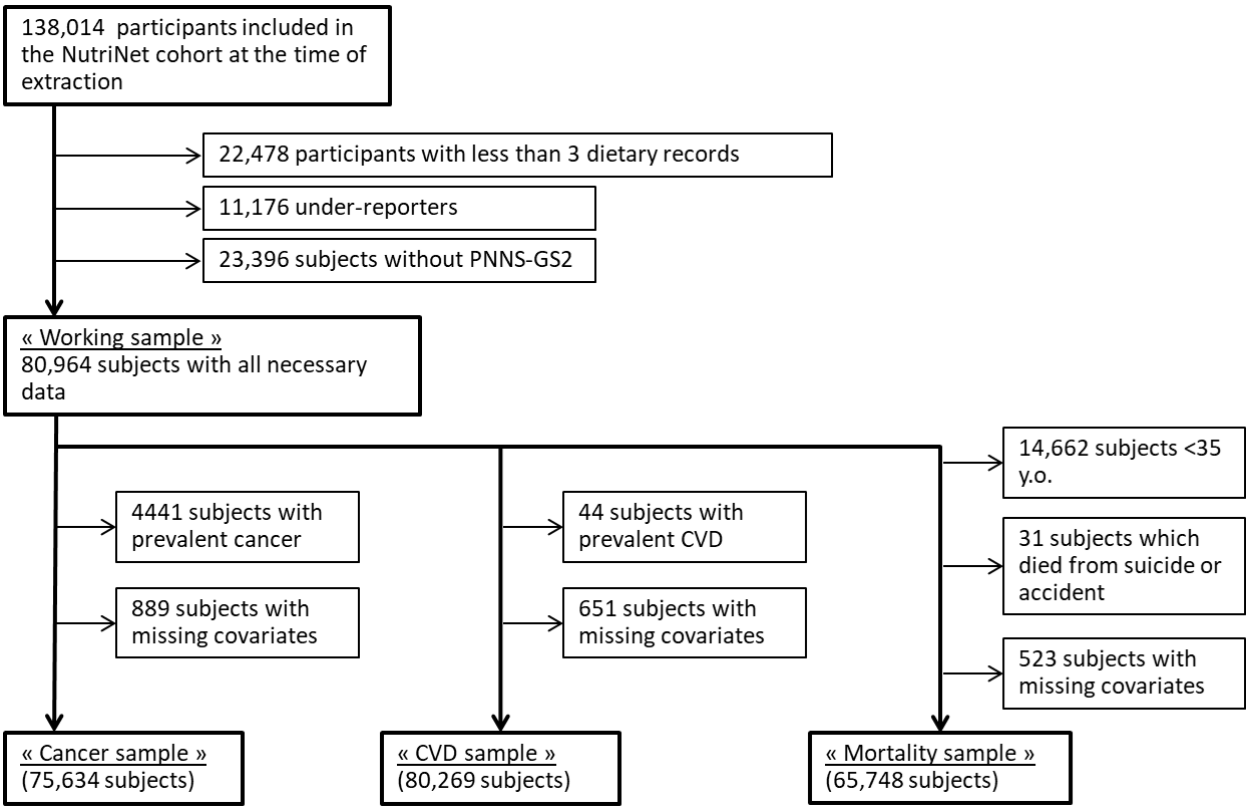

Figure 1 – Flowchart of subjects included in the present analysis of the NutriNet cohort. PNNS-GS2: Programme National Nutrition Santé – guidelines score 2, CVD: cardio-vascular diseases.

Tables

Table 1 – PNNS-GS2 components and scoring

Dietary components	Recommendation [a]	Servings per day unless otherwise is stated	Score
Fruits and vegetables (weight=3)	**At least 5 servings/day, with 1 max as juice and 1 max as dried**	≥0 - <3.5	0
		≥3.5 - < 5	0.5
		≥5 - < 7.5	1
		≥7.5	2
	Prefer organic fruits	Most of the time	0.5
		Occasionally	0.25
		Never	0
	Prefer organic vegetables	Most of the time	0.5
		Occasionally	0.25
		Never	0
Nuts (weight=1)	**A handful/day**	0	0
		]0 - < 0.5	0.5
		≥0.5 - < 1.5	1
		≥1.5	0
Legumes (weight=1)	**At least 2 servings/week**	0 /week	0
		> 0 - < 2 /week	0.5
		≥2 /week	1
	Prefer organic legumes	Most of time	0.5
		Occasionally	0.25
		Never	0
Whole-grain food (weight=2)	**Every day**	0	0
		>0 - < 1	0.5
		≥1 - < 2	1
		≥2	1.5
	Prefer organic bread	Most of the time	0.5
		Occasionally	0.25
		Never	0
	Prefer organic grains	Most of the time	0.5
		Occasionally	0.25
		Never	0
Milk and dairy products (weight=1)	**2 servings/day**	≥0 - < 0.5	0
		≥0.5 - < 1.5	0.5
		≥1.5 - < 2.5	1
		≥2.5	0
Red meat (weight=2)	**Limit consumption**	≥0 - < 500 g/week	0
		≥500 - < 750 g/week	-1
		≥750 g/week	-2
Processed meat (weight=3)	**Limit consumption**	≥0 - < 150 g/week	0
		≥150 - < 300 g/week	-1
		≥300 g/week	-2
	Prefer white ham over other processed meat [c]	Ratio <50%	0
		Ratio ≥50%	0.5
Fish and seafood (weight=2)	**2 servings/week**	≥0 - < 1.5 servings /week	0
		≥1.5 - < 2.5 servings /week	1
		≥2.5 - < 3.5 servings /week	0.5
		≥3.5 servings /week	0
	Fatty fish 1 serving/week	≥0 - < 0.5 servings/week	0
		≥0.5 - < 1.5 servings/week	1
		≥1.5 servings/week	0
Added fat (weight=2)	**Limit consumption**	>16% of EIWA [f]	0
		≤16% of EIWA	1.5
	Prefer vegetal fat over animal fat	Ratio >50%	1
		Ratio ≤50%	0
	Prefer ALA-rich [f] and olive oils over other oils	Ratio <50%	0
		Ratio ≥50%	1
Sugary foods (weight=3)	**Limit consumption**	<10 % of EIWA	0
		≥10-15[% of EIWA	-1
		≥15% of EIWA	-2

Dietary components	Recommendation [a]	Servings per day unless otherwise is stated	Score
Sweet-tasting beverages [d] (weight=3)	**Limit consumption**	0 mL/day	0
		>0 - 250< mL/day	-0.5
		≥250 - 750< mL/day	-1
		≥ 750mL mL/day	-2
Alcoholic beverages (weight=3)	**Limit consumption**	0 g/week	0.5
		>0- ≤ 100 g/week	0
		>100- ≤ 150 g/week	-1
		>150- ≤ 200 g/week	-1.5
		>200 g/week	-2
Salt (weight=3)	**Limit consumption**	<6 g/day	1
		≥6 - < 8 g/day	0
		≥8 - < 10 g/day	-0.5
		≥10 - < 12 g/day	-1
		≥12 g/day	-2

Abbreviations: EIWA = energy intake without alcohol, ALA = α-linolenic acid

[a] Principal benchmark are written in bold.

[b] Servings per day unless otherwise is stated

[c] Conditional: the 0.5 bonus point only occurs if total processed meat consumption is more than 150 g/week

[d] Sweetened beverages are specifically sweet beverages, artificially sweetened beverages and fruit juices

Table 2 – Baseline characteristics of the participants by quintile of PNNS-GS2, NutriNet-Santé study, N=80,964 [a].

	Total	Q1	Q2	Q3	Q4	Q5
PNNS-GS2 mean (sd)	1.5 (3.4)	-3.0 (1.9)	-0.2 (1.3)	1.6 (1.1)	3.3 (1)	6.0 (1.5)
PNNS-GS2 range in women		< -0.6	-0.6 – 1.3	1.3 – 2.9	2.9 – 4.7	> 12.4
PNNS-GS2 range in men		< -3.4	-3.4 – -1.3	-1.3 – 0.7	0.7 – 2.8	> 12.6
Age at inclusion (years)	44.4 (14.6)	40.4 (14)	42.8 (14.4)	44.5 (14.5)	46.1 (14.5)	48.1 (14.2)
BMI (kg/m²)	23.8 (4.5)	24.6 (5.2)	24.1 (4.7)	23.8 (4.4)	23.6 (4.2)	22.9 (3.9)
Height (cm)	166.5 (8.7)	167.6 (8.8)	166.9 (8.8)	166.4 (8.7)	166.1 (8.4)	165.7 (8.8)
Energy intake without alcohol (kcal/d)	1816 (449)	2047 (472)	1890 (448)	1790 (410)	1713 (407)	1642 (388)
Ethanol intake (g/d)	7.9 (11.5)	14.1 (16.6)	9.1 (12.0)	7.2 (9.7)	5.5 (7.4)	3.8 (5.7)
Sex						
Male	21.9%	21.9%	21.8%	22.0%	21.8%	22.0%
Female	78.1%	78.1%	78.2%	78.0%	78.2%	78.0%
Menopausal status [b]						
Postmenopausal	29.0%	18.9%	24.3%	28.6%	33.9%	39.4%
Premenopausal	71.0%	81.1%	75.7%	71.4%	66.1%	60.6%
Hormone Replacement Therapy for menopause [b]						
On HRT	23.9%	24.3%	23.7%	24.2%	24.3%	23.1%
Not on HRT	76.1%	75.7%	76.3%	75.8%	75.7%	76.9%
Pill contraception[b]						
On pill	37.0%	42.9%	39.9%	36.9%	33.6%	29.0%
Not on pill	55.3%	50.9%	53.2%	55.4%	57.5%	61.4%
Education						
Primary	1.0%	1.3%	1.1%	0.9%	1.0%	0.9%
Secondary	34.1%	36.8%	34.4%	33.8%	33.1%	32.5%
University	64.8%	61.9%	64.5%	65.3%	65.9%	66.6%
Occupational category						
Farmers / self-employed	1.9%	2.2%	2.0%	1.7%	1.8%	1.9%
Managerial staff	23.6%	21.7%	23.0%	23.6%	24.8%	24.7%
Employees	17.5%	21.4%	18.9%	17.9%	15.6%	13.9%
Students	7.3%	9.1%	8.1%	7.4%	6.4%	5.6%
Manual workers	1.1%	1.8%	1.3%	1.0%	0.8%	0.7%
Intermediates professions	17.4%	17.6%	17.8%	17.7%	17.3%	16.5%
Retired	19.5%	13.3%	17.4%	19.6%	22.1%	25.1%
Unemployed	11.7%	12.9%	11.4%	11.1%	11.2%	11.7%
Income [c]						
≤1800 €/cu [f]	45.3%	52.1%	47.6%	44.7%	42.2%	39.9%
1800 - 2700 €/cu	26.9%	25.0%	26.5%	26.9%	27.8%	28.1%
>2700 €/cu	27.8%	22.9%	26.0%	28.4%	29.9%	32.0%
>2700 €/cu	27.8%	22.9%	26.0%	28.4%	29.9%	32.0%
Physical activity						
[0-30[min/day	26.7%	32.0%	29.1%	27.3%	24.7%	20.3%
[30-60[min/ day	24.4%	23.4%	25.3%	24.5%	24.8%	24.1%
≥ 60 min/ day	48.9%	44.5%	45.5%	48.3%	50.5%	55.7%
Smoking						
Non smokers	50.2%	43.8%	49.6%	51.0%	52.1%	54.4%
Former smokers	34.3%	32.6%	33.2%	34.5%	35.3%	36.1%
Smokers	15.5%	23.6%	17.2%	14.6%	12.6%	9.5%
Living status						
Living alone	27.7%	26.5%	26.3%	26.9%	28.4%	30.3%
Cohabiting	72.3%	73.5%	73.7%	73.0%	71.5%	69.7%

[a] Values are percentages or mean (standard deviation) as appropriate. All p-values were ≤0.0001

[b] Percentages are given in women only for menopausal status, in postmenopausal women for HRT and in premenopausal women only for pill contraception

[c] cu = consumption unit

Table 3 – Prospective association between PNNS-GS2 and risk of non-accidental mortality (for participants aged 35+), all-sites cancer and cardiovascular diseases, NutriNet-Santé study [a]

	Q1	Q2	Q3	Q4	Q5	1 pt	pval[b]
Mortality							
n	13,177	13,152	13,194	13,127	13,098	65,748	
Events	160	184	150	169	165	828	
Person-years	84,399	85,650	85,424	85,199	84,704	425,377	
HR_{m0} [c]	1	0.99 [0.80-1.23]	**0.76 [0.61-0.95]**	**0.80 [0.64-0.99]**	**0.73 [0.59-0.91]**	**0.96 [0.94-0.98]**	**0.0002**
HR_{m1} [d]	1	1.06 [0.85-1.31]	0.84 [0.67-1.06]	0.88 [0.70-1.10]	0.84 [0.66-1.06]	**0.97 [0.95-1.00]**	**0.03**
HR_{m2} [e]	1	1.04 [0.83-1.29]	0.81 [0.64-1.03]	0.84 [0.66-1.06]	**0.77 [0.60-1.00]**	**0.96 [0.94-0.99]**	**0.005**
HR_{m3} [f]	1	1.06 [0.85-1.32]	0.84 [0.66-1.07]	0.87 [0.69-1.12]	0.82 [0.63-1.06]	**0.97 [0.95-1.00]**	**0.02**
Cancer							
n	15,174	15,115	15,151	15,121	15,073	75,634	
Events	452	503	559	548	515	2,577	
Person-years	89,091	90,950	92,029	92,283	92,526	456,878	
HR_{m0} [c]	1	0.95 [0.84-1.08]	0.97 [0.86-1.10]	**0.88 [0.77-0.99]**	**0.75 [0.66-0.85]**	**0.97 [0.96-0.98]**	**<0.0001**
HR_{m1} [d]	1	0.95 [0.84-1.08]	0.97 [0.85-1.10]	**0.88 [0.77-1.00]**	**0.76 [0.66-0.87]**	**0.97 [0.95-0.98]**	**< 0.0001**
HR_{m2} [e]	1	0.98 [0.86-1.11]	1.00 [0.88-1.14]	0.92 [0.80-1.06]	**0.80 [0.69-0.92]**	**0.97 [0.96-0.99]**	**<0.0001**
HR_{m3} [f]	1	0.99 [0.87-1.13]	1.02 [0.89-1.17]	0.94 [0.82-1.08]	**0.83 [0.71-0.96]**	**0.97 [0.96-0.99]**	**0.0009**
CVD							
n	16,105	16,129	15,972	16,146	15,917	80,269	
Events	187	181	183	199	214	964	
Person-years	95,637	98,443	98,638	99,882	98,869	491,469	
HR_{m0} [c]	1	**0.81 [0.66-0.99]**	**0.75 [0.61-0.91]**	**0.75 [0.61-0.91]**	**0.74 [0.60-0.90]**	**0.97 [0.95-0.99]**	**0.003**
HR_{m1} [d]	1	**0.81 [0.66-1.00]**	**0.74 [0.60-0.91]**	**0.74 [0.60-0.91]**	**0.73 [0.59-0.91]**	**0.97 [0.95-0.99]**	**0.007**
HR_{m2} [e]	1	**0.78 [0.63-0.96]**	**0.69 [0.55-0.86]**	**0.67 [0.53-0.84]**	**0.64 [0.51-0.81]**	**0.96 [0.94-0.98]**	**0.0004**
HR_{m3} [f]	1	**0.80 [0.64-0.98]**	**0.72 [0.58-0.90]**	**0.71 [0.57-0.90]**	**0.71 [0.56-0.91]**	**0.97 [0.95-0.99]**	**0.01**
HR_{m4} [g]	1	**0.80 [0.65-0.99]**	**0.73 [0.59-0.91]**	**0.73 [0.58-0.92]**	**0.73 [0.58-0.93]**	**0.97 [0.95-1.00]**	**0.03**

[a] For each model, 3 Cox regressions were fitted: one with PNNS-GS2 in quintiles, one with PNNS-GS2 for 1 point and one with PNNS-GS2 for 1 SD. Bold values are significant for alpha at 5%.

[b] p-values are drawn from a Wald test for the PNNS-SG2 in continuous, which effect is presented for 1 point

[c] m0 is the base model, adjusted only for sex (and age as time-scale).

[d] m1 is m0, further adjusted for energy intake without alcohol, number of completed 24h dietary records, height, season of inclusion, physical activity, occupation, smoking status, educational level, monthly income, cohabiting status, menopausal status in women, hormonal treatment for menopause in menopaused women and oral contraception in non-menopaused women, parental history (for cancer and CVD only) and number of children (for cancer and in women only).

[e] m2 is m1, further adjusted for ethanol intake.

[f] m3 is m2, further adjusted for baseline BMI.

[g] m4, a complementary model for CVD, is m3, further adjusted for baseline hypertension status and dyslipidaemia status.

Table 4 – Prospective association between PNNS-GS2 and risk of cancer by localization, NutriNet-Santé study [a]

	T1	T2	T3	1 pt	1 SD	p [b]
Colorectal						
n	25231	25219	25184	75634	75634	
Events	56	88	63	207	207	
Person-years	148689	152448	153143	454281	454281	
HR_{m2} [c]	1	1.18 [0.82-1.69]	0.66 [0.43-1.01]	**0.94 [0.89-0.99]**	**0.82 [0.69-0.98]**	**0.03**
Prostate/						
n	5524	5509	5509	16542	16542	
Events	98	116	94	308	308	
Person-years	33161	33442	33674	100277	100277	
HR_{m2} [c]	1	1.13 [0.85-1.52]	0.90 [0.63-1.27]	0.98 [0.94-1.02]	0.92 [0.79-1.07]	0.28
Breast						
n	19707	19710	19675	59092	59092	
events	239	244	276	759	759	
Person-years	115528	119006	119469	354004	354004	
HR_{m2} [c]	1	0.85 [0.70-1.03]	0.85 [0.69-1.04]	0.98 [0.95-1.01]	0.94 [0.86-1.02]	0.15

[a] Bold value are significant for alpha at 5%.

[b] p-values are drawn from a Wald test for the PNNS-SG2 in continuous, which effect is presented for 1 point and for 1 standard deviation. As log-linearity hypothesis of Cox model was not fully satisfying on these outcomes, results should be treated with caution.

[c] model m2 is adjusted on sex, energy intake without alcohol, ethanol intake, number of completed 24h dietary records, height, season of inclusion, physical activity, occupation, smoking status, educational level, monthly income, cohabiting status, baseline BMI, menopausal status in women, hormonal treatment for menopause in menopaused women and oral contraception in non-menopaused women, parental history of cancer and number of children (in women only).

Supplemental Tables

Supplemental Table 1 – Food group consumption by quintile of the PNNS-GS2, NutriNet-Santé study, 2009, N=80,965 [a]

	Total	Q1	Q2	Q3	Q4	Q5	Correlation [b]
Energy intake without alcohol (kcal)	1816.7 (449.2)	2047.5 (472.5)	1889.6 (447.8)	1789.7 (410.1)	1712.8 (406.8)	1642.5 (388.2)	**-0.419 [-0.425 ; -0.414]**
Proteins	17.5 (3.6)	17.5 (3.7)	17.5 (3.6)	17.6 (3.6)	17.6 (3.6)	17.2 (3.8)	-0.032 [-0.039 ; -0.025]
Carbohydrates	42.8 (6.3)	40.8 (6.2)	42.1 (5.9)	42.8 (6.0)	43.6 (6.1)	44.7 (6.6)	0.198 [0.192 ; 0.205]
Lipids	39.4 (5.9)	41.4 (5.4)	40.1 (5.5)	39.2 (5.6)	38.4 (5.9)	37.8 (6.4)	-0.198 [-0.205 ; -0.192]
Fruits (g)	201.3 (144.7)	121.1 (108.4)	166.1 (119.4)	195.1 (124.3)	228.8 (136.3)	296.1 (165.5)	**0.41 [0.404 ; 0.416]**
Vegetables (g)	221.4 (111.2)	172.7 (95.7)	200.2 (99.5)	217.9 (99.8)	238.3 (108.5)	278.2 (121.3)	**0.321 [0.315 ; 0.327]**
Fruit juices (mL)	53.5 (73.1)	55.2 (82.9)	55.9 (75.3)	54.8 (70.2)	53.4 (69.2)	48.3 (66.8)	-0.031 [-0.038 ; -0.024]
Vegetables juices (mL)	1.8 (14.3)	1.2 (12.7)	1.3 (13.3)	1.4 (11.1)	1.9 (14.5)	3.1 (18.8)	0.045 [0.038 ; 0.052]
Legumes (g)	11.8 (21.6)	7.4 (17.4)	9.0 (17.6)	10.4 (18.5)	12.5 (20.7)	19.9 (29.3)	0.198 [0.191 ; 0.204]
Potatoes and tubers (g)	45.7 (39.8)	47.5 (43.9)	45.4 (39.7)	45.4 (38.8)	45.3 (37.8)	45.0 (38.5)	-0.02 [-0.027 ; -0.013]
Whole-grain cereals (g)	34.9 (43.8)	16.8 (30.3)	26 (36.1)	31.9 (38.5)	40.6 (44.7)	59.3 (53.3)	**0.331 [0.325 ; 0.337]**
Refined cereals (g)	141.0 (68.9)	145.4 (71.6)	147.2 (70.1)	145.2 (67.5)	141.3 (66.8)	125.6 (65.8)	-0.096 [-0.102 ; -0.089]
Breakfast cereals (g)	6.7 (14.6)	4.5 (12.8)	5.8 (13.7)	6.5 (13.9)	7.5 (15.5)	9.0 (16.5)	0.109 [0.102 ; 0.116]
Milk and dairy (mL and g)	233.4 (145.9)	229.0 (153.4)	239.5 (146.5)	244.4 (146.3)	241.0 (143)	212.7 (137.8)	-0.031 [-0.038 ; -0.024]
Eggs (g)	13.9 (17.2)	12.8 (18.3)	13.6 (17.3)	13.9 (16.6)	14.3 (16.6)	14.8 (16.9)	0.038 [0.032 ; 0.045]
Fish and seafood (g)	38.6 (35.7)	32.7 (36.5)	37.2 (35.5)	39.7 (35.1)	41.5 (35.3)	41.9 (35.3)	0.086 [0.079 ; 0.093]
Meat (g)	69.4 (44.4)	83.5 (50.2)	73.8 (44.3)	70.0 (41.6)	65.4 (40.3)	54.3 (39.2)	**-0.227 [-0.233 ; -0.22]**
Processed meat/fish (g)	34 (28.1)	55.6 (33.9)	40.3 (27.8)	31.9 (23.4)	25.0 (19.5)	17.2 (15.4)	**-0.467 [-0.472 ; -0.462]**
Fatty, sweet or salty food (g)	102.6 (50.5)	105.5 (58.8)	106.7 (53)	105.5 (48.9)	101.5 (46.1)	93.8 (43.2)	-0.074 [-0.081 ; -0.067]
Non-oil fats (g)	61.6 (48.1)	56.2 (47.3)	60.5 (46.9)	63.0 (47.9)	64.5 (48.4)	63.7 (49.7)	0.052 [0.045 ; 0.059]
Non-olive oil (g)	4.5 (5.3)	5.0 (6)	4.5 (5.2)	4.4 (4.9)	4.3 (4.9)	4.5 (5.3)	-0.032 [-0.039 ; -0.025]
Olive oil (g)	4.5 (5.7)	2.8 (5)	3.8 (5.4)	4.3 (5.3)	5.0 (5.6)	6.4 (6.6)	**0.21 [0.203 ; 0.217]**
Alcoholic drinks (mL)	96.8 (135.6)	167.9 (192.6)	109.7 (141)	88.2 (113.5)	68.7 (90.8)	49.1 (73.7)	**-0.312 [-0.319 ; -0.306]**
Unsweetened drinks (mL)	1113.2 (516.5)	1029.4 (531.8)	1082.6 (515.4)	1110.9 (501.3)	1142.7 (502.6)	1201.3 (515)	0.112 [0.105 ; 0.119]
Sweetened drinks (mL)	41.5 (89.3)	77.2 (149.3)	44.8 (85.6)	34.4 (64)	28.4 (51.9)	22.7 (39.4)	**-0.223 [-0.229 ; -0.216]**

[a] Values are given per day, as mean (standard deviation), adjusted for energy intake and sex using the residual method, except for the organic score.

[b] Pearson's correlation coefficients with 95% confidence intervals. All were significantly different from 0 ($p<0.001$). Absolute values >0.2 are written in bold.

Supplemental Table 2 – Prospective association between the PNNS-GS2 and the risk of breast cancer depending on menopausal status, NutriNet-Santé study [a]

	T1	T2	T3	1 pt	1 SD	p [b]
Breast (premenopausal)						
n	14116	14077	14078	42271	42271	
Events	82	102	97	281	281	
Person-years	284405	260440	237616	782462	782462	
HR_{m2} [c]	1	1.24 [0.91-1.68]	1.32 [0.95-1.85]	**1.05 [1.00-1.10]**	**1.17 [1.01-1.35]**	**0.03**
Breast (postmenopausal)						
n	7845	7852	7838	23535	23535	
Events	184	134	159	477	477	
Person-years	89683	97372	101252	288307	288307	
HR_{m2} [c]	1	**0.72 [0.57-0.91]**	0.84 [0.65-1.07]	**0.96 [0.92-0.99]**	**0.88 [0.79-0.98]**	**0.02**

[a] Bold value are significant for alpha at 5%.

[b] p-values are drawn from a Wald test for the PNNS-SG2 in continuous, which effect is presented for 1 point and for 1 standard deviation. As log-linearity hypothesis of Cox model was not fully satisfying on these outcomes, results should be treated with caution.

[c] model m2 is adjusted on sex, energy intake without alcohol, ethanol intake, number of completed 24h dietary records, height, season of inclusion, physical activity, occupation, smoking status, educational level, monthly income, cohabiting status, baseline BMI, menopausal status in women, hormonal treatment for menopause in menopaused women and oral contraception in non-menopaused women, parental history of cancer and number of children.

Supplemental Table 3 – Prospective association between PNNS-GS2 and risk of cancer of all sites except colorectal, NutriNet-Santé study [a]

	Q1	Q2	Q3	Q4	Q5	1 pt	pval[b]
Cancer (except colorectal)							
n	15,174	15,115	15,151	15,121	15,073	75,634	
Events	420	459	501	521	469	2370	
Person-years	88,636	90,418	91,493	91,770	91,964	454,281	
HR_{m0} [c]	1	0.94 [0.82-1.07]	0.94 [0.82-1.07]	0.90 [0.79-1.03]	**0.74 [0.65-0.85]**	**0.97 [0.96-0.98]**	**<0.0001**
HR_{m1} [d]	1	0.97 [0.84-1.11]	0.98 [0.85-1.13]	0.96 [0.83-1.11]	**0.80 [0.69-0.94]**	**0.97 [0.96-0.99]**	**<0.0001**
HR_{m2} [e]	1	0.98 [0.85-1.12]	1.00 [0.87-1.15]	0.99 [0.85-1.14]	**0.83 [0.71-0.98]**	**0.98 [0.96-0.99]**	**0.0009**

[a] For each model, 3 Cox regressions were fitted: one with PNNS-GS2 in quintiles, one with PNNS-GS2 for 1 point and one with PNNS-GS2 for 1 SD. Bold values are significant for alpha at 5%.

[b] p-values are drawn from a Wald test for the PNNS-SG2 in continuous, which effect is presented for 1 point and for 1 standard deviation.

[c] m0 is the base model, adjusted only for sex (and age as time-scale).

[d] m1 is further adjusted for energy intake without alcohol, ethanol intake, number of completed 24h dietary records, height, season of inclusion, physical activity, occupation, smoking status, educational level, monthly income, cohabiting status, menopausal status in women, hormonal treatment for menopause in menopaused women and oral contraception in non-menopaused women, parental history (for cancer and CVD only) and number of children (for cancer and in women only).

[e] m2 is the principal model, further adjusted for baseline BMI.

[f] m3 is a complementary model for CVD, further adjusted for baseline hypertension status and dyslipidemia status.

Supplemental Table 4 – Prospective association between the PNNS-GS2 and the risk of non-accidental mortality (for participants aged 35+), all-sites cancer and cardiovascular diseases without considering early cases (time < 2 years), NutriNet-Santé study [a]

	Q1	Q2	Q3	Q4	Q5	1 pt	p [b]
Mortality							
n	13,177	13,152	13,194	13,127	13,098	65,748	
Events	122	136	103	126	128	615	
Person-years	84,399	85,650	85,424	85,199	84,704	425,377	
HR_{m0} [c]	1	0.94 [0.74-1.20]	**0.67 [0.51-0.87]**	**0.75 [0.59-0.97]**	**0.71 [0.55-0.91]**	**0.96 [0.93-0.98]**	**0.0004**
HR_{m1} [d]	1	0.97 [0.76-1.25]	**0.69 [0.52-0.92]**	0.78 [0.59-1.02]	**0.73 [0.55-0.99]**	**0.96 [0.93-0.99]**	**0.005**
HR_{m2} [e]	1	0.99 [0.77-1.28]	**0.72 [0.54-0.96]**	0.81 [0.61-1.08]	0.78 [0.58-1.05]	**0.96 [0.94-0.99]**	**0.017**
Cancer							
n	15,174	15,115	15,151	15,121	15,073	75,634	
Events	327	368	390	394	356	1835	
Person-years	89,091	90,950	92,029	92,283	92,526	456,878	
HR_{m0} [c]	1	0.95 [0.82-1.10]	0.92 [0.79-1.06]	**0.85 [0.73-0.98]**	**0.69 [0.60-0.81]**	**0.96 [0.94-0.97]**	**<0.0001**
HR_{m1} [d]	1	0.98 [0.84-1.15]	0.96 [0.82-1.13]	0.91 [0.77-1.07]	**0.74 [0.62-0.89]**	**0.96 [0.95-0.98]**	**<0.0001**
HR_{m2} [e]	1	1.00 [0.85-1.16]	0.98 [0.84-1.15]	0.93 [0.79-1.10]	**0.77 [0.65-0.92]**	**0.97 [0.95-0.98]**	**0.0001**
CVD							
n	16,105	16,129	15,972	16,146	15,917	80,269	
Events	135	136	145	136	161	713	
Person-years	95,637	98,443	98,638	99,882	98,869	491,469	
HR_{m0} [c]	1	0.83 [0.65-1.05]	0.80 [0.63-1.01]	**0.68 [0.54-0.87]**	**0.74 [0.59-0.93]**	**0.97 [0.95-0.99]**	**0.004**
HR_{m1} [d]	1	0.81 [0.63-1.03]	**0.74 [0.58-0.96]**	**0.63 [0.48-0.82]**	**0.66 [0.50-0.86]**	**0.96 [0.93-0.98]**	**0.001**
HR_{m2} [e]	1	0.82 [0.64-1.04]	**0.77 [0.59-0.99]**	**0.65 [0.50-0.85]**	**0.70 [0.53-0.92]**	**0.96 [0.94-0.99]**	**0.007**
HR_{m3} [f]	1	0.81 [0.64-1.04]	0.78 [0.60-1.00]	**0.66 [0.51-0.87]**	**0.71 [0.54-0.95]**	**0.97 [0.94-0.99]**	**0.013**

[a] Bold values are significant for alpha at 5%.

[b] p-values are computed using a Wald test for the PNNS-SG2 in continuous, which effect is presented for 1 point.

[c] m0 is the base model, adjusted only on sex.

[d] m1 is further adjusted on energy intake without alcohol, ethanol intake, number of completed 24h dietary records, height, season of inclusion, physical activity, occupation, smoking status, educational level, monthly income, cohabiting status, menopausal status in women, hormonal treatment for menopause in menopaused women and oral contraception in non-menopaused women, parental history (for cancer and CVD only) and number of children (for cancer and in women only).

[e] m2 is the principal model, further adjusted on BMI.

[f] m3 is a complementary model for CVD, further adjusted on baseline hypertension status and dyslipidemia status.