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

Dan Chaltiel¹, Chantal Julia^{1,2}, Raphaël Chaltiel³, Julia Baudry¹, Mathilde Touvier¹, Valérie Deschamps⁴, Paule Latino-Martel¹, Léopold K. Fezeu^{1,2}, Serge Hercberg^{1,2}, Emmanuelle Kesse-Guyot¹

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

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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

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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

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

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

11 **Results:** The sample included 78% of women, aged on average 44.4 years (SD=14.6) with on average
12 6.6 (SD=2.3) dietary records. Average PNNS-GS2 was 1.5 (SD=3.4) and median follow-up was 6.6
13 years for cancers and 6.2 years for CVD and deaths. PNNS-GS2 was significantly associated with the
14 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
15 cases), and CVD ($HR_{Q5vsQ1}=0.64[0.51-0.81]$, 964 cases). More specifically, PNNS-GS2 was
16 significantly associated with colorectal and breast cancer risks but not prostate cancer risk.

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

20 Introduction

21 In almost all countries, the burden of non-communicable diseases (NCD) is a major public health
22 concern. Indeed, in 2016, according to the WHO, the mortality due to NCD was 71% worldwide, and
23 up to 88% in high-income countries such as France, where cardiovascular diseases (CVD) and cancers
24 represent the largest causes of death¹.

25 As NCDs induce a high mortality and social burden, the challenge is to develop preventive measures
26 by acting on modifiable risk factors such as dietary habits. As a matter of fact, there is growing
27 recognition of the importance of diet, among other lifestyle factors, in the development of cancer and
28 CVD².

29 “*Optimal*” diet is not absolute and most countries, which differ on culture and ethnicity, have each
30 their own definition of a favorable diet and translate them into easily understandable food-based
31 dietary guidelines (FBDG)³. However, there is a growing consensus on which food groups should be
32 promoted or limited in order to minimize the risk of NCD, and most guidelines recommend high
33 consumption of fruits, vegetables and wholegrains and low intake of meats, fats, sugary and salted
34 foods³.

35 When assessing the association between overall diet quality and health outcomes, many studies use
36 dietary quality scores, such as the Healthy Eating Index or the Mediterranean Diet Score⁴⁻⁷ but also
37 specific dietary guidelines developed in European countries such as Denmark⁸, UK⁹ and Netherland¹⁰.
38 Some of these have been recently compared in a modelling study¹¹. Indeed, considering dietary
39 exposure through scores allows to consider diet as a whole, accounting for complex synergies between
40 foods and nutrients, which is considered closer to reality as foods are not consumed in isolation¹²⁻¹⁵.

41 When a diet quality score is based on official guidelines, studying its association with health outcomes
42 also allows assessing the relevance of the guidelines regarding the prevention of these outcomes.

43 In France, FBDG were revised in March 2017¹⁶ as a core part of the 4th (2019-2023) French Nutrition
44 and Health Program (*Programme National Nutrition Santé*, “PNNS”). Recently, we developed and
45 validated the PNNS-Guidelines Score 2 (PNNS-GS2), aiming to estimate the adherence to the 2017
46 FBDG¹⁷. The PNNS-GS2 was meant to update the PNNS-GS, based on 2001 guidelines, which were
47 less specific, less plant-based and did not consider organic food.

48 Hence, the present study aimed at assessing the prospective associations between the PNNS-GS2 and
49 risk of non-accidental mortality, cardiovascular disease mortality or incidence and cancer mortality or
50 incidence in a large French prospective cohort. In particular, the role of adjustment on BMI was
51 assessed as we previously showed that the PNNS-GS2 is highly associated with the risk of overweight
52 and obesity¹⁸, which are themselves major risk factors for cancer and CVD¹⁹⁻²¹.

53 **Subjects and Methods**

54 **Study population**

55 The data were collected in the NutriNet-Santé cohort, a large observational prospective web-based
56 cohort launched in 2009 in France. Its purpose is to investigate the associations between nutrition and
57 health, as well as determinants of dietary behavior and nutritional status. The detailed design and
58 methodology have been described elsewhere²². Participants were recruited through vast multimedia
59 campaigns, amongst the adult (>18 years old) population having access to the internet. All
60 questionnaires were pilot-tested and completed online using a dedicated website ([www.etude-nutrinet-](http://www.etude-nutrinet-sante.fr)
61 [sante.fr](http://www.etude-nutrinet-sante.fr)). The NutriNet-Santé study is conducted in accordance with the Declaration of Helsinki and
62 was approved by the ethics committee of the French Institute for Health and Medical Research (IRB
63 Inserm no. 0000388FWA00005831) and by the National Commission on Informatics and Liberty
64 (CNIL no. 908450 and no. 909216). Electronic informed consent was obtained from all participants.
65 The NutriNet-Santé study is registered in ClinicalTrials.gov (NCT03335644).

66 **Dietary data**

67 Participants are asked to provide three non-consecutive 24h dietary records assigned over a 2-week
68 period at baseline then twice a year. Days are randomly attributed into two weekdays and one weekend
69 day to account for intra-individual variability in intake. All food and drink consumption throughout
70 the entire day (midnight to midnight) are recorded by participants via the dedicated online platform
71 providing a food browser (grouped by category) or a search engine. Participants declare intakes as
72 absolute units when known (in g or mL), common household measures or using food portion size from
73 validated pictures²³.

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

76 food items²⁴. Under-reporters were excluded using the published method by Black et al. with Goldberg
77 cut-offs, which is based on physical activity level (PAL) and basal metabolic rate (BMR). BMR was
78 calculated using the Schofield's equations²⁵, accounting for gender, age, height and weight. Within-
79 subject variation coefficient (day-to-day) for energy intake was calculated individually for each
80 participant based on their 24h dietary records data and within-subject coefficients of variations for
81 BMR and PAL were defined at 8.5% and 15% respectively^{26,27}. . This dietary recording protocol has
82 been tested and validated against an interview by a trained dietitian and against blood and urinary
83 biomarkers²⁸⁻³⁰.

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

90 **Computation of dietary scores**

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

96 **Case ascertainment**

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

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

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

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

117 **Covariates**

118 Using a dedicated self-administered web-based questionnaire²², participants filled in their
119 sociodemographic and lifestyle characteristics (age, sex, education, occupation, income, marital status,
120 physical activity and smoking habits). Physical activity was assessed by the International Physical
121 Activity Questionnaire (IPAQ)³³. Monthly income was estimated per consumption unit according to a
122 weighting system, where one consumption unit (cu) is attributed for the first adult in the household,
123 0.5 CU for other persons aged 14 or older, and 0.3 cu for children under 14³⁴. Baseline height and
124 weight were self-reported at enrolment using a web-based anthropometric questionnaire^{35,36}. BMI
125 (kg/m²) was then computed by dividing weight by height squared. Data from specific questionnaires
126 and medication were used to retrieve the status regarding hypertension, dyslipidaemia, menopause,
127 oral contraception and hormonal treatment for menopause.

128 **Sample selection**

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

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

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

139 **Statistical analysis**

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

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

144 Sociodemographic characteristics are presented across quintiles of PNNS-GS2.

145 We first estimated the association between PNNS-GS2 and incidence of non-accidental mortality
146 (among participants older than 35 years old), CVD and cancer, using a multivariable Cox proportional
147 hazard model with age as time-scale³⁷. For each specific outcome, participants contributed follow-up
148 time from their entry in the study until the date of disease diagnosis, date of last completed
149 questionnaire, date of death or May 2019, whichever occurred first, so that each person contributed
150 only one endpoint to the analysis. The data were thus left-truncated and right-censored.

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

155 In order to account for competing events, we used cause-specific models, as it is recommended when
156 addressing inference questions³⁸. Therefore, our models are censored on death not related to the event,
157 and on cancer on a different localization for cancer by localization.

158 Several models were used. The first model, m0, was only adjusted for sex. The model m1 was further
159 adjusted for energy intake without alcohol (continuous variable), number of completed 24h dietary
160 records (continuous variable), height (continuous variable), season of inclusion (4 modalities),
161 educational level (primary, secondary, university), monthly income (≤ 1800 €/cu, 1800 - 2700 €/cu,
162 >2700 €/cu, >2700 €/cu), occupation (farmers / self-employed, managerial staff, employees, students,

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

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

175 Log-linearity was tested graphically for PNNS-GS2 using martingale residuals. All other continuous
176 covariates have been corrected for log-linearity using restricted cubic splines with 3 nodes³⁹ using the
177 *rms* package for R^{®40}. Proportional hazard assumption was tested by performing a Grambsch-Therneau
178 test⁴¹ and validated graphically using Schoenfeld residuals. All analyses were performed in men and
179 women altogether as no significant interaction with sex was ever detected.

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

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

184 **Patient involvement**

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

189

190 **Results**

191 The working sample was composed of 78% women and 22% men, providing on average 6.6 (SD=2.3)
192 24h dietary records and 14.8 (SD=9.2) validated health questionnaires per person. Participants were
193 on average 44.4 (SD=14.6) years old. Mean PNNS-GS2 was 1.5 (SD=3.4) and median follow-up was
194 6.7 years for cancer and 6.2 years for both mortality and MCV analyses.

195 Associations of PNNS-GS2 with baseline covariates are presented in **Table 2**. Higher adherence with
196 2017 French FBDG was positively associated with age, education, income, cohabiting status and
197 physical activity, and negatively associated with baseline BMI, energy intake without alcohol, alcohol
198 consumption and smoking habit. For descriptive purpose, consumption of macronutrients and food
199 groups are presented in **Supplemental Table 1**. By design, PNNS-GS2 was positively associated with
200 higher consumption of fruits, vegetables, legumes and whole grain cereals and higher frequency of
201 organic food consumption, and negatively associated with higher consumption of red and processed
202 meat, refined cereals and sweetened and alcoholic drinks.

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

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

212 First, as association with breast cancer was unexpectedly not significant⁴², we ran a non-prespecified
213 analysis, considering the risk of cancer either before or after the menopause. Results are presented in
214 **Supplemental Table 2**. Here, PNNS-GS2 was significantly associated with a lower risk of breast
215 cancer occurring after menopause, but with a higher risk of breast cancer before menopause. This latter
216 association persisted after further adjustment for eating disorder (yes/no) or after stratification on
217 number of children, BMI class (<25 vs \geq 25), physical activity, or parental history of cancer (data not
218 shown).

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

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

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

231 **Discussion**

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

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

248 The observed association with mortality, as the risk of cardiovascular diseases, was similar to number
249 of other studies on other diet quality scores, even if all do not reflect dietary guidelines^{4,5,45-48}.

250 Concerning the risk of cancer, the strong negative association with diet quality as per the PNNS-GS2
251 was also consistent with the above-mentioned studies^{4,5,45,46}. By location, the negative association
252 between PNNS-GS2 and risk of colorectal cancer was analogous to the one reported by Park et al.,
253 which used dietary indices elaborated for the American population (HEI-2010 and AHEI-2010) in a
254 larger cohort⁴⁹. Also, a colorectal cancer specific diet quality index, namely the CDQI, recently
255 developed and based on consumption of processed meat, fiber and dairy products, have documented
256 an inverse association with risk of colorectal cancer⁵⁰. Since these food groups are directly or indirectly
257 assessed by the PNNS-GS2, this is consistent with our results. Interestingly, a previous study
258 conducted in the NutriNet-Santé cohort study, with a shorter follow-up (6.4y), did not report any
259 association with AHEI and colorectal cancer⁵¹.

260 For breast cancer, a recent meta-analysis reported that it is negatively associated with a healthy/prudent
261 diet and positively associated with a Western diet⁵². This is consistent with current knowledge between
262 dietary components of the PNNS-GS2 and breast cancer, notably regarding vegetables, saturated fat,
263 and red and processed meat⁴², alcohol⁴⁴, and dietary fibers⁵³. The meta-analysis also presented a
264 subgroup analysis concluding that this latter association is significant in post-menopausal women but
265 remains marginal in pre-menopausal women⁵². This was also consistent with a large prospective study
266 (N=96,959)⁵⁴, considering diet quality as per American guidelines (AHEI-2010 score). As we found
267 no significant association between PNNS-GS2 and global risk of breast cancer, this motivated our non-
268 prespecified supplemental analysis, which also concluded to a significant protective association in
269 post-menopausal women. However, the association of PNNS-GS2 with a higher risk of breast cancer
270 in pre-menopausal women was rather puzzling. We could find only one study, published in 2013 on
271 49,258 women, that reported a positive association between Mediterranean Diet and risk of cancer in
272 pre-menopausal women with a HR of 1.10 (CI=[1.01;1.21])⁵⁵, but this result was explained by the
273 promotion of moderate alcohol consumption, which is not promoted by the 2017 French FBDG. Since
274 other articles describe either a protective or a non-significant association, and since none of our
275 additional explorations could identify a relevant confounding factor, we attributed this finding to an
276 artifact or to residual, unidentified confounding as no mechanistic hypothesis was identified to explain

277 this finding. Still, as these results come from non-prespecified analysis, they should be taken with
278 particular caution. Interestingly, the above-mentioned previous study conducted in the NutriNet-Santé
279 cohort study did not report any association with either AHEI, Medilite or mPNNS-GS and breast
280 cancer⁵¹.

281 On the very few studies that have measured the association between diet quality and prostate cancer,
282 one has identified a significant association with HEI-2005 and AHEI-2010, but only in men screened
283 for PSA, which are obviously particularly at risk of prostate cancer⁵⁶. This association was not
284 significant in men without PSA screening. Still, since our population was predominantly female, it
285 would be interesting to replicate our study in a larger male population to benefit from a higher
286 statistical power.

287 The main difference between the 2017 French FBDG and most FBDG is the consideration of organic
288 food. Indeed, organic food consumption have already been associated to an lower risk of cancer in the
289 NutriNet-Santé cohort⁵⁷. Our results are consistent with this study regarding risk of all-sites, prostate
290 and post-menopausal breast cancer. However, no association was detected with colorectal and pre-
291 menopausal breast cancer risk in that study. We thus can hypothesize that for these specific cancers,
292 exposure to pesticides residues, which is one of the potential mechanisms for explaining the protective
293 effect of organic food consumption on cancer risk, may be of lesser importance than nutritional
294 properties of specific food groups like processed meat, fiber and dairy products. Another hypothesis
295 may rely on statistical power since our population was larger and our follow-up time longer.

296 Some limitations of our study are worth noting. First, our analyses were based on volunteers who were
297 probably particularly concerned about their health, which limited the generalizability of our results.
298 Indeed, NutriNet-Santé participants are more likely to be women, well-educated, rather young, and to
299 have healthier behaviors than the general French population⁵⁸. This selection bias could have led to a
300 lower NCD incidence and to a better diet quality than would have been estimated in the general
301 population, so we should expect that our results were underestimated, although overestimation bias
302 could not be totally ruled out. Second, residual confounding cannot be excluded in an observational
303 study, thus unmeasured behavioral factor as well as lack of precision in the measurement of covariates
304 and dietary records could have influenced the observed associations, although we accounted for a wide
305 range of potential confounders. Third, most of our data were self-declared and could therefore lack

306 precision or suffer from social desirability bias. However, dietary data were validated against urinary
307 and blood biomarkers^{29,30} and objective measurement³⁶.

308 Nevertheless, although these limitations were noted, our study found strong negative associations
309 between PNNS-GS2 and risk of non-accidental death, cancer and CVD. An important strength of this
310 work is its prospective design and its median follow-up duration of 6.7 years, which may have limited
311 reverse causality. Given the relatively large size of our population, this allowed a satisfying statistical
312 power. However, this power was restricted for studying risk of death, probably because of the selection
313 of a rather young and healthy population. Our dietary data were also highly accurate with on average
314 6.6 24h records per individual, thus accounting for daily variation. The PNNS-GS2 has been validated
315 in its construction and has proven a reliable construct in other studies^{17,18}. Finally, our health events
316 (cancer and CVD) were validated by trained physicians, and data were linked to medico-administrative
317 databases, which should limit the declaration bias.

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

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337 **Author's contributions:**

338 EKG, SH, CJ and MT were responsible for the development of the design and protocol of the study;
339 EKG and DC were responsible for the design of the research. DC performed the statistical analysis
340 and wrote the paper; EKG supervised statistical analysis and paper writing; DC, CJ, RC, JB, MT, VD,
341 PLM, LF, SH, and EK-G were involved in interpreting the results and editing the manuscript for
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Figures

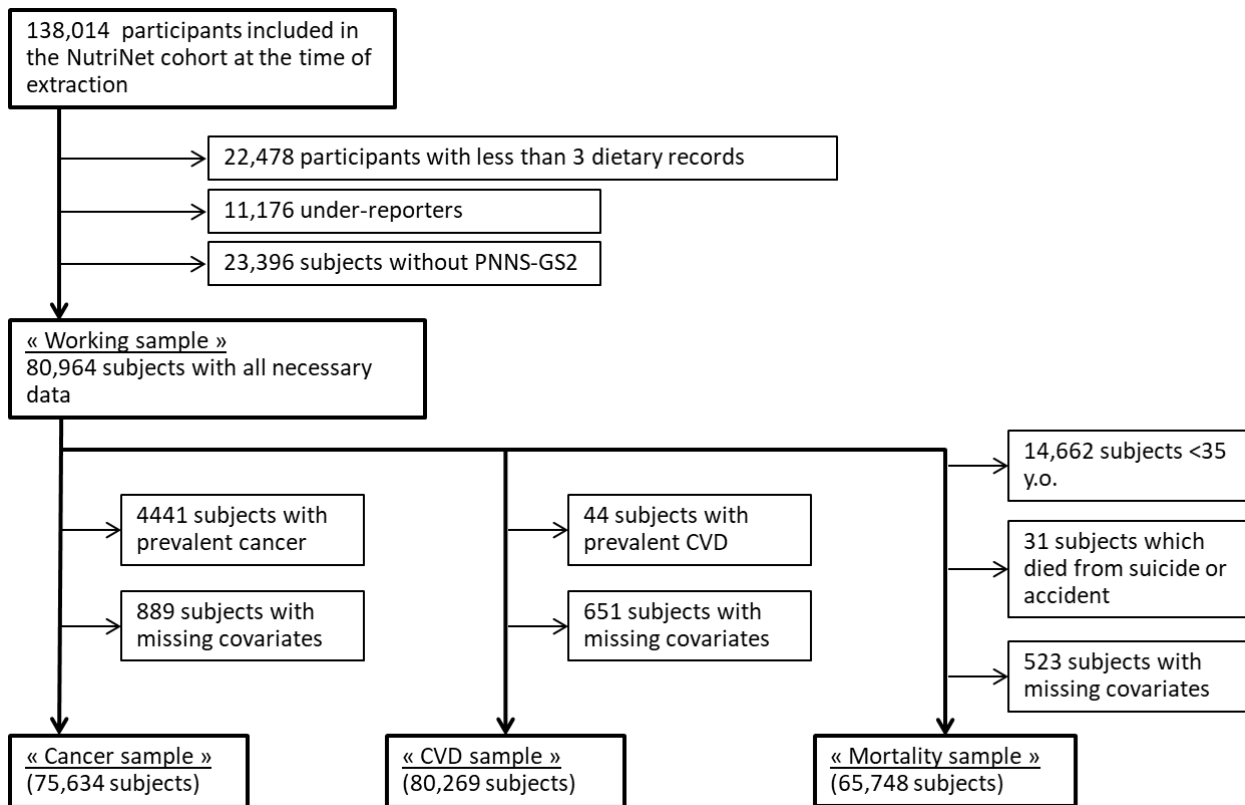


Figure 1 – Flowchart of subjects included in the present analysis of the NutriNet cohort. PNNS-GS2: Programme National Nutrition Santé – guidelines score 2, CVD: cardio-vascular diseases.

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/m ²)	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 menopausal women and oral contraception in non-menopausal 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 menopausal women and oral contraception in non-menopausal 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 menopausal women and oral contraception in non-menopausal 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 menopausal women and oral contraception in non-menopausal 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 menopausal women and oral contraception in non-menopausal 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.