



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

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### Abstract

Non-communicable diseases, such as cancers and 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 *Programme National Nutrition Santé* Guidelines Score (PNNS-GS2), has been developed and validated using a standardised procedure. The present study aimed to analyse the prospective association between PNNS-GS2 and the risk of death, cancer and CVD. Our sample consisted of French adults included in the prospective NutriNet-Santé cohort ( $n$  67 748, 75 634 and 80 269 for the risk of death, cancer and CVD, respectively). PNNS-GS2 (range:  $-\infty$  to 14.25) was calculated from the 24-h dietary records of the first 2 years of monitoring. Association between PNNS-GS2 (in quintiles, Q) and the risk of death, cancer and CVD was studied using Cox models adjusted for the main confounding factors. 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 (hazard ratio (HR)<sub>Q5vsQ1</sub>: 0.77 (95% CI 0.60, 1.00), 828 cases), cancer (HR<sub>Q5vsQ1</sub> = 0.80 (95% CI 0.69, 0.92), 2577 cases) and CVD (HR<sub>Q5vsQ1</sub> 0.64 (95% CI 0.51, 0.81), 964 cases). More specifically, PNNS-GS2 was significantly associated with colorectal and breast cancer risks but not prostate cancer risk. 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.

**Key words:** Nutrition: Dietary index: Dietary guidelines: Risk: Cancer: CVD: Death

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 CVD and cancers represent the largest causes of death<sup>(1)</sup>.

As NCD 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 life-style factors, in the development of cancer and CVD<sup>(2)</sup>.

'Optimal' diet is not absolute and most countries, which differ on culture and ethnicity, have each their own definition of a

favourable diet and translate them into easily understandable food-based dietary guidelines (FBDG)<sup>(3)</sup>. However, there is a growing consensus on which food groups should be promoted or limited in order to minimise 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<sup>(3)</sup>.

When assessing the association between overall diet quality and health outcomes, many studies use dietary quality scores, such as the Healthy Eating Index (HEI) or the Mediterranean Diet Score<sup>(4–7)</sup> but also specific dietary guidelines developed in European countries such as Denmark<sup>(8)</sup>, UK<sup>(9)</sup> and the Netherlands<sup>(10)</sup>. Some of these have been

**Abbreviations:** AHEI, Alternate Healthy Eating Index; FBDG, food-based dietary guidelines; HEI, Healthy Eating Index; NCD, non-communicable diseases; PNNS-GS2, *Programme National Nutrition Santé* Guidelines Score 2; Q, quintiles.

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recently compared in a modelling study<sup>(11)</sup>. 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<sup>(12–15)</sup>. 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 on 16 March 2017 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<sup>(16)</sup>. 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, CVD 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<sup>(17)</sup>, which are themselves major risk factors for cancer and CVD<sup>(18–20)</sup>.

## 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 behaviour and nutritional status. The detailed design and methodology have been described elsewhere<sup>(21)</sup>. Participants were recruited through vast multimedia campaigns, among 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](http://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 24-h 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<sup>(22)</sup>.

Intakes were weighted according to weekday *v.* weekend day, and daily energy and nutrient intakes were computed using a validated and constantly updated composition tables including more than 3500 food items<sup>(23)</sup>. Under-reporters were excluded using the published method by Black *et al.* with Goldberg cut-offs, which is based on physical activity level and basal metabolic rate (BMR). BMR was calculated using the Schofield's equations<sup>(24)</sup>, accounting for sex, age, height and weight. Within-subject coefficient of variation (day-to-day) for energy intake was calculated individually for each participant based on their 24-h dietary records data, and within-subject coefficients of variations for BMR and physical activity level were defined at 8.5 and 15 %, respectively<sup>(25,26)</sup>. This dietary recording protocol has been tested and validated against an interview by a trained dietitian and against blood and urinary biomarkers<sup>(27–29)</sup>.

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<sup>(16,30)</sup>. Frequencies were assessed using three modalities of consumption: (1) most of the time, (2) occasionally and (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-h 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<sup>(31,32)</sup>. It includes thirteen components, six of adequacy and seven of moderation, and is penalised 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 3 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 1 year. This process constituted the main source of case ascertainment in the cohort. In addition, our research team was the first in France authorised 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



**Table 1.** PNNS-GS2 components and scoring

Dietary components	Recommendation*	Criteria†	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	
Prefer organic vegetables	Never	0		
	Most of the time	0.5		
	Occasionally	0.25		
Nuts (weight = 1)	A handful/day	Never	0	
		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‡	Ratio <50 %	0
Fish and seafood (weight = 2)	2 servings/week	Ratio ≥50 %	0.5	
		≥0–<1.5 servings /week	0	
		≥1.5–<2.5 servings /week	1	
		≥2.5–<3.5 servings /week	0.5	
	Fatty fish 1 serving/week	≥3.5 servings /week	0	
		≥0–<0.5 servings/week	0	
		≥0.5–<1.5 servings/week	1	
Added fat (weight = 2)	Limit consumption	≥1.5 servings/week	0	
		>16 % of EIWA	0	
	Prefer vegetal fat over animal fat	≤16 % of EIWA	1.5	
		Ratio >50 %	1	
		Ratio ≤50 %	0	
Sugary foods (weight = 3)	Limit consumption	Prefer ALA-rich and olive oils over other oils	Ratio <50 %	0
		Ratio ≥50 %	1	
		<10 % of EIWA	0	
		≥10–15 % of EIWA	–1	
Sweet-tasting beverages§ (weight = 3)	Limit consumption	≥15 % of EIWA	–2	
		0 ml/d	0	
		>0–250 <ml/d	–0.5	
		≥250–750 <ml/d	–1	
Alcoholic beverages (weight = 3)	Limit consumption	≥750 ml ml/d	–2	
		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	

**Table 1.** (Continued)

Dietary components	Recommendation*	Criteria†	Score
Salt (weight = 3)	Limit consumption	<6 g/d	1
		≥6–<8 g/d	0
		≥8–<10 g/d	–0.5
		≥10–<12 g/d	–1
		≥12 g/d	–2

EIWA, energy intake without alcohol; ALA,  $\alpha$ -linolenic acid

\* Principal benchmark are written in bold.

† Servings per day unless otherwise is stated.

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

§ Sweetened beverages are specifically sweet beverages, artificially sweetened beverages and fruit juices.

(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 using the international classification of diseases, 10th revision. In the present study, we considered all first primary cancers diagnosed between the inclusion date and 13 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<sup>(21)</sup>, participants filled in their socio-demographic 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<sup>(33)</sup>. Monthly income was estimated per consumption unit according to a weighting system, where one consumption unit is attributed for the first adult in the household, 0.5 consumption unit for other persons aged 14 years or older and 0.3 consumption unit for children under 14<sup>(34)</sup>. Baseline height and weight were self-reported at enrolment using a web-based anthropometric questionnaire<sup>(35,36)</sup>. BMI (kg/m<sup>2</sup>) 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 2 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 flow chart is presented in Fig. 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.

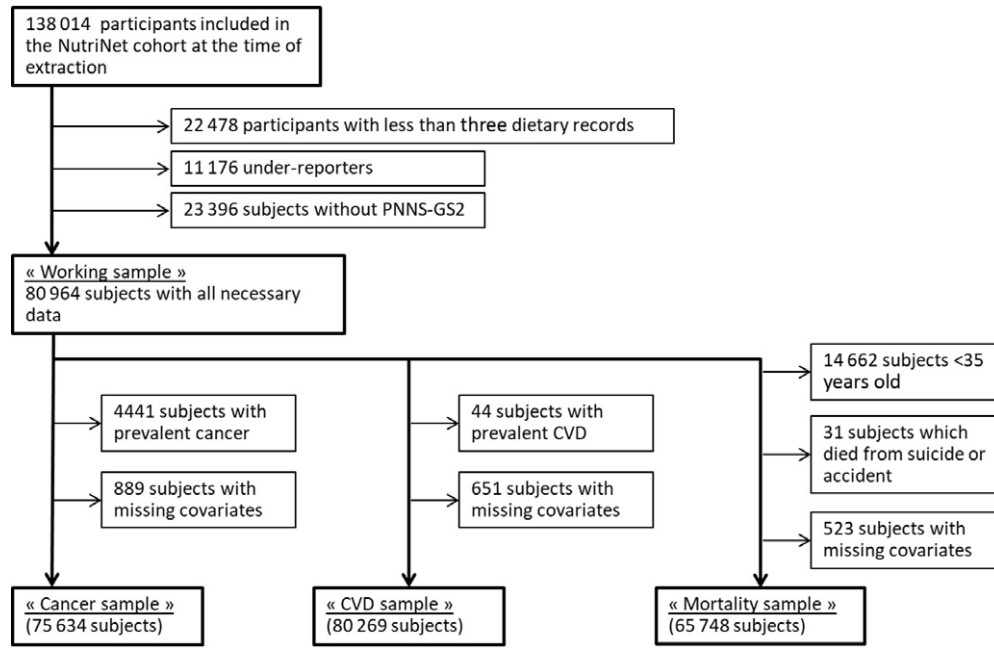
Socio-demographic characteristics are presented across quintiles of PNNS-GS2.

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 timescale<sup>(37)</sup>. 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 localisation (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<sup>(38)</sup>. Therefore, our models are censored on death not related to the event, and on cancer on a different localisation for cancer by localisation.

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 24-h dietary records (continuous variable), height (continuous variable), season of inclusion (four modalities), educational level (primary, secondary, university), monthly income ( $\leq$ 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,



**Fig. 1.** Flow chart of subjects included in the present analysis of the NutriNet cohort. PNNS-GS2, Programme National Nutrition Santé – guidelines score 2; CVD, cardiovascular diseases.

cohabiting), baseline physical activity (0–30 min/d, 30–60 min/d, ≥60 min/d), smoking status (non-smokers, former smokers, smokers), menopausal status in women (yes/no), hormonal treatment for menopause in menopausal women (yes/no) and oral contraception in non-menopausal 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 three nodes<sup>(39)</sup> using the *rms* package for R<sup>®</sup><sup>(40)</sup>. Proportional hazard assumption was tested by performing a Grambsch–Therneau test<sup>(41)</sup> 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<sup>®</sup> (version 3.4.2) and SAS<sup>®</sup> (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 the present 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) 24-h 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 CVD 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 online Supplementary Table S1. 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

**Table 2.** Baseline characteristics of the participants by quintile of PNNS-GS2, NutriNet-Santé study, *n* =80 964\* (Mean values and standard deviations)

	Total	Q1	Q2	Q3	Q4	Q5
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
PNNS-GS2	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 <sup>2</sup> )	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†						
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†						
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†						
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						
≤1800 €/cu	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/d	26.7 %	32.0 %	29.1 %	27.3 %	24.7 %	20.3 %
30-60 min/d	24.4 %	23.4 %	25.3 %	24.5 %	24.8 %	24.1 %
≥60 min/d	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

Cu, consumption unit.

\* All *P*-values were ≤ 0.0001.

† Percentages are given in women only for menopausal status, in postmenopausal women for HRT and in premenopausal women only for pill contraception.

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 (2577 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<sup>(42)</sup>, we ran a non-prespecified analysis, considering the risk of cancer either before or after the menopause. Results are presented in online Supplementary Table S2. 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

**Table 3.** Prospective association between PNNS-GS2 and risk of non-accidental mortality (for participants aged 35+ years), all-sites cancer and CVD, NutriNet-Santé study\* (HR and 95%CI)

	Q1	Q2 HR (95%CI)	Q3 HR (95%CI)	Q4 HR (95%CI)	Q5 HR (95%CI)	1 pt HR (95%CI)	P†
<b>Mortality</b>							
<i>n</i>	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 <sub>m0</sub> ‡	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 <sub>m1</sub> §	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 <sub>m2</sub>	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 <sub>m3</sub> ¶	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
<b>Cancer</b>							
<i>n</i>	15 174	15 115	15 151	15 121	15 073	75 634	
Events	452	503	559	548	515	2577	
Person-years	89 091	90 950	92 029	92 283	92 526	456 878	
HR <sub>m0</sub> ‡	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 <sub>m1</sub> §	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 <sub>m2</sub>	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 <sub>m3</sub> ¶	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
<b>CVD</b>							
<i>n</i>	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 <sub>m0</sub> ‡	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 <sub>m1</sub> §	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 <sub>m2</sub>	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 <sub>m3</sub> ¶	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 <sub>m4</sub> **	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

\* For each model, 2 Cox regressions were fitted: one with PNNS-GS2 in quintiles and one with PNNS-GS2 for 1 point.

† P-values are drawn from a Wald test for the PNNS-SG2 in continuous, which effect is presented for 1 point.

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

§ m1 is m0, further adjusted for energy intake without alcohol, number of completed 24-h 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).

|| m2 is m1, further adjusted for ethanol intake.

¶ m3 is m2, further adjusted for baseline BMI.

\*\* 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 localisation, NutriNet-Santé study\* (HR and 95%CI)

	T1	T2 HR (95%CI)	T3 HR (95%CI)	1 pt HR (95%CI)	1 sd HR (95%CI)	P†
<b>Colorectal</b>						
<i>n</i>	25 231	25 219	25 184	75 634	75 634	
Events	56	88	63	207	207	
Person-years	148 689	152 448	153 143	454 281	454 281	
HR <sub>m2</sub> ‡	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
<b>Prostate/</b>						
<i>n</i>	5524	5509	5509	16 542	16 542	
Events	98	116	94	308	308	
Person-years	33 161	33 442	33 674	100 277	100 277	
HR <sub>m2</sub> ‡	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
<b>Breast</b>						
<i>n</i>	19 707	19 710	19 675	59 092	59 092	
Events	239	244	276	759	759	
Person-years	115 528	119 006	119 469	354 004	354 004	
HR <sub>m2</sub> ‡	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

\* For each model, 3 Cox regressions were fitted: one with PNNS-GS2 in quintiles and, one with PNNS-GS2 for 1 point and one with PNNS-GS2 for 1 sd.

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

‡ Model m2 is adjusted on sex, energy intake without alcohol, ethanol intake, number of completed 24-h 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).

further adjustment for eating disorder (yes/no) or after stratification on number of children, BMI class (<25 *v.* ≥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 online Supplementary Table S3. 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 online Supplementary Table S4. 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 localisation; 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 *v.* Q1), cancer incidence or mortality (up to –17% in Q5 *v.* Q1) and CVD incidence or mortality (up to –27% in Q5 *v.* 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 one of a recent meta-analysis on association between dietary scores and the risk of death, CVD and cancer, Schwingshackl *et al.*<sup>(5)</sup>. 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 *v.* low adherence. Despite some differences, notably in the food groups considered as harmful, cut-offs and scoring, all these dietary scores (namely the HEI and the Alternate Healthy Eating Index (AHEI), 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<sup>(43,44)</sup>.

The observed association with mortality, as the risk of CVD, was similar to number of other studies on other diet quality scores, even if all do not reflect dietary guidelines<sup>(4,5,45–48)</sup>.

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<sup>(4,5,45,46)</sup>. 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<sup>(49)</sup>. Also, a colorectal cancer-specific diet quality index, namely the CDQI, has been recently developed. It is based on consumption of processed meat, fibre and dairy products, and the princeps study have documented an inverse association with risk of colorectal cancer<sup>(50)</sup>. 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 (6–4 years), did not report any association with AHEI and colorectal cancer<sup>(51)</sup>.

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<sup>(52)</sup>. 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<sup>(42)</sup>, alcohol<sup>(44)</sup> and dietary fibres<sup>(53)</sup>. The meta-analysis also presented a subgroup analysis concluding that this latter association is significant in postmenopausal women but remains marginal in premenopausal women<sup>(52)</sup>. This was also consistent with a large prospective study (*n* 96 959)<sup>(54)</sup>, 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 postmenopausal 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 premenopausal women with a hazard ratio of 1.10 (95% CI (1.01, 1.21))<sup>(55)</sup>, 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<sup>(51)</sup>.

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 prostate specific antigen (PSA), which are obviously particularly at risk of prostate cancer<sup>(56)</sup>. 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 has already been associated with a lower risk of cancer in the NutriNet-Santé cohort<sup>(57)</sup>. Our results are





consistent with the present study regarding risk of all-sites, prostate and postmenopausal breast cancers. However, no association was detected with colorectal and premenopausal breast cancer risk in that study. We thus can hypothesise 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, fibre 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 generalisability of our results. Indeed, NutriNet-Santé participants are more likely to be women, well-educated, rather young and to have healthier behaviours than the general French population<sup>(58)</sup>. 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 behavioural 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<sup>(28,29)</sup> and objective measurement<sup>(36)</sup>.

Nevertheless, although these limitations were noted, our study found strong negative associations between PNNS-GS2 and the 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 the 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 24-h 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<sup>(16,17)</sup>. 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.

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E. K.-G., S. H., C. J. and M. T. were responsible for the development of the design and protocol of the study; E. K.-G. and D. C. were responsible for the design of the research. D. C. performed the statistical analysis and wrote the paper; E. K.-G. supervised the statistical analysis and paper writing; D. C., C. J., R. C., J. B., M. T., V. D., P. L. M., L. F., S. H. and E. K.-G. were involved in interpreting the results and editing the manuscript for important intellectual content. All authors read and approved the final manuscript.

None of the authors declare any conflicts of interest.

### Supplementary material

For supplementary material referred to in this article, please visit <https://doi.org/10.1017/S0007114521001367>

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