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Abstract

Background/Objectives: Nutritional recommendations are widely disseminated, but assessment of their predictive value for risk of chronic diseases and mortality is essential for ensuring their validity**.** We evaluated, in a large population-based study, the association between the French Programme National Nutrition Santé (PNNS) Guideline Score (GS) (maximum score of 15 points), an a priori-based score, and the incidences of cancer, cardiovascular disease (CVD) and overall mortality.

Subjects/Methods: Subjects included in the present analysis (n=5 823) were participants in the Supplémentation en Vitamines et Minéraux AntioXydants study (SU.VI.MAX), with available data for estimating the PNNS-GS. Hazards ratios (HR) and 95% confidence intervals (95% CI) for outcomes (cancer, CVD and death) were estimated across quartiles of PNNS-GS using Cox proportional hazards models.

Results: A total of 734 major events were recorded during an average 11.6-year follow-up (maximum 13 years): 423 cancers, 193 ischemic diseases and 118 deaths. In the fully-adjusted model, a significant reduction in CVD risk between the first and fourth PNNS-GS quartiles (HR=0.65, 95% CI= 0.41, 1.00, P for trend=0.04) was observed. No significant overall association with risk of cancer or death was detected.

Conclusions: These observations support the role of nutritional guidelines in prevention of CVD.

Keywords: nutritional guidelines, dietary index, cancer, mortality, cardiovascular diseases

Introduction

In the past few decades, associations between nutritional factors and chronic diseases, especially cardiovascular diseases (CVD) and cancer, have been widely investigated. A posteriori and a priori methods which take into account overall diet have emerged to overcome the limitations of the nutrient or single food approach based on correlations and interactions between dietary pattern components (Moeller *et al.*, 2007). Although a posteriori methods enable to empirically deriving dietary patterns, a priori scores are often based on nutritional guidelines or diet quality (Moeller *et al.*, 2007).

A major issue lies in assessing the predictive value of adherence to nutritional guidelines for primary prevention of chronic disease risk, since guidelines are theoretically designed for this purpose. Some studies have investigated the potential effect of adherence to dietary guidelines, including or not physical activity, on the incidence of chronic diseases, cancer, CVD and overall mortality, as recently reviewed (Waijers *et al.*, 2007).

Initial and subsequent a priori scores based on Dietary Guidelines for Americans (DGA), were shown to be only weakly or not at all associated with CVD and cancer occurrence (Waijers *et al.*, 2007). This may be partly due to variations in construction of dietary scores and disparities in sample size and follow-up duration for some studies. Despite the absence of a significant association with chronic disease risk, better adherence to dietary scores has been consistently associated with lower mortality (Kaluza *et al.*, 2009; Kant *et al.*, 2009).

We had previously developed a score (FSIPO) based on the nine public health goals of the French Nutrition and Health Program (Estaquio *et al.*, 2008). In the SU.VI.MAX cohort, this score was associated with a significant 36% reduction in the risk of chronic diseases and death among men, but no significant association was observed among women. Such arguments concerning nutritional guidelines should be more convincing and comprehensive, mainly in terms of public health messages.

Recently, we developed another a priori score, the PNNS Guidelines Score (PNNS-GS), based on the individual French national nutritional guidelines (Estaquio *et al.*, 2009), aimed to describe the level of dietary adherence to these guidelines.

The purpose of the present work was to evaluate the prospective associations between PNNS-GS quartiles and risk of chronic diseases and mortality during a maximum 13-year follow-up.

Materials and methods

Population

The design and rationale of the SU.VI.MAX study (Supplémentation en Vitamines et Minéraux Antioxydants) have been extensively detailed previously (Hercberg *et al.*, 1998).

The SU.VI.MAX study was initially designed as a randomized, double-blind, placebo-controlled, primary prevention trial to test the potential efficacy of daily supplementation with antioxidant vitamins and minerals at nutritional doses on the incidence of cancers, cardiovascular diseases and overall mortality. Eligible subjects, 7 713 women aged 35–60 years and 5 028 men aged 45–60 years at baseline, were included in 1994-1995 and initially followed up for 7.5 y. After stopping supplementation, the follow-up was extended to 13 years. The SU.VI.MAX study was approved by the Ethical Committee for Studies with Human Subjects of the Paris-Cochin Hospital (CCPPRB n°706) and the "Commission Nationale Informatique et Liberté" (CNIL n°334641), which ensures that medical information be kept confidential and anonymous.

Data assessment

Sociodemographic data and lifestyle, including gender, date of birth and tobacco status, were collected using a self-administrated questionnaire at baseline.

Subjects were asked to provide a 24-h record every 2 months for a total of 6 records per year covering all days of the week and all seasons. To facilitate coding food portions, participants were assisted by an instruction manual which included validated photographs of more than

250 typical foods represented in three different portion sizes. Subjects could also choose from two intermediate or two extreme portions, for a total of seven different possible portion sizes (Le Moullec et al., 1996). As previously detailed (Touvier *et al.*, 2010), dietary records that reported <100 kcal/d or>6000 kcal/d were excluded and further subjects who had >2/3 of their records that reported <800 kcal/d in men and <500 kcal/d in women were excluded. Dietary nutrient intakes were calculated using a food composition table which included more than 900 foods (Hercberg S (coordinator), 2005). Specific information on weekly consumption of seafood was collected by a self-administrated questionnaire at baseline. In addition, alcohol intake (grams of alcohol per day) was estimated using a short validated semi-quantitative dietary questionnaire (Lasfargues *et al.*, 1990).

A French validated self-administered version of the Modifiable Activity Questionnaire (MAQ) was used in 1998 to assess physical activity (Vuillemin *et al.*, 2000). Type, frequency and duration of activity, each performed at least 10 times for 10 minutes each session during leisure time over the past 12 months, were collected. Using published compendiums (Ainsworth *et al.*, 2000), metabolic equivalent tasks (MET) were assigned to each leisure activity reported and summary scores were computed, including the average MET-h per week of physical activity. For subjects with missing data for the MAQ, we used data from other sources and imputations as previously reported (Estaquio *et al.*, 2009).

At the first clinical examination during the follow-up (1995-1996), weight was measured using an electronic scale (Seca, Germany), with subjects wearing indoor clothes and no shoes. Height was measured under the same conditions with a wall-mounted stadiometer.

Cases ascertainment

Information about health was self-reported via a monthly questionnaire. Other sources of information regarding outcome included yearly visits. In case of no contact with a participant for a long period, or failure to show up for the yearly visit, an investigation was launched to determine the reasons. In case of a suspected event, investigations were conducted to obtain relevant medical data (clinical, biochemical, histological and radiological reports) from participants, physicians and/or hospitals. All events were then reviewed and validated by an independent expert committee, unaware of the supplementation group assignment. Causes of death were confirmed using information provided by physicians or family members. Vital status of all subjects and causes of death were verified using the national death registry. Health events were classified using the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) (WHO, 2003). Major outcomes included cardiovascular events (ICD-10-CM codes I20-I24) and cancer of any kind (ICD-10-CM codes C00-C97, D00-D09, D37-D48), except for basal cell carcinoma of the skin (ICD-10-CM codes C44 and M809-M811) and all-cause mortality. First, we considered as outcome the occurrence of a major chronic disease event defined as a combination of CVD, cancer or death, whichever came first. Secondly, we also studied each health event separately. Subjects contributed person-time up to the date of the health outcome (n=635), the date of the last completed questionnaire or contact (n=1 145) or September 1st 2007 (n=4 043), whichever occurred first. CVD was not accounted for in cancer analysis, and vice-versa.

PNNS-GS computation

PNNS-GS computation, including food grouping, serving sizes, scoring, cut-off and penalties, was previously described in detail (Estaquio *et al.*, 2009). Briefly, the score included 13 components for a total of 15 points maximum. Eight components referred to food groups, including recommended servings, and four components were related to overall limitation. The final component dealt with adherence to the physical activity recommendation. Scoring and cut-off values are presented in table 1. Each component's subscore were summed for a theoretical maximum total of 15 points.

A penalty for overconsumption was assigned to individuals with energy intakes higher than needs. Schofield's basal metabolic rate was estimated using age, height and weight. Basal metabolic rate and physical activity level were used to estimate energy expenditures (Schofield, 1985). If energy intake was greater than 5% compared to calculated energy needs, an identical fraction was deducted from the score (Estaquio *et al.*, 2009).

Inclusion criteria

In the present analysis, we selected men and women aged 45-60 y at baseline who provided at least three 24-h records during the first 2 years of follow-up and other data needed for PNNS-GS computation, and who had no missing co-variables for the present analyses (Fig. 1). We excluded subjects who developed health outcomes during the first two years of follow-up.

Statistical analysis

Means of food and nutrient intake were calculated from at least three 24-h dietary records during the first two years of follow-up. Body mass index (BMI) was calculated as the ratio of weight to squared height (kg/m^2).

Descriptive results are reported as mean ± standard deviation or percent across quartiles of PNNS-GS. Reported P-values referred to the Kruskal-Wallis test or chi^2 test as appropriate.

Hazard ratio (HR) of disease risk or death and 95% confidence intervals (CI) across quartiles of PNNS-GS (using the 1^{st} quartile as reference) were estimated using Cox proportional hazards models (Cox, 1972).

Graphic methods (log–log (survival) versus log–time plots) were used to check for proportional hazards assumptions for this study. An interaction between PNNS-GS quartiles and gender, intervention group, tobacco status and BMI (<25, 35-30, >30 kg/m^2) on the risk of chronic diseases or mortality was tested.

Models were controlled for age (continuous), smoking status (never, former, current), education level (primary school, secondary school, high school or equivalent), total energy intake from diet (continuous), BMI (continuous) and daily supplementation (placebo or intervention group) to account for the study design.

Analyses among smokers and former smokers were further adjusted on frequency (1-5, 6-10, 10-15, 16-20, 21-30, >30 cigarettes per day) and duration of tobacco use (1-5, 6-10, 11-15, 16-20, 21-30, >30 years). Among former smokers, time since quitting was also accounted for 1-5, 6-10, 11-15, 16-20, 21-30, >30 years).

Significance tests were 2-sided, with a type I error set at <0.05. All analyses were performed using SAS software (SAS Institute, version 9).

Results

The present analyses included 5 823 subjects (2 437 men and 3 386 women) from the 12 741 subjects initially participating in the SU.VI.MAX study (Fig. 1).

At baseline, men and women were aged 51.9 ± 4.7 and 47.0 ± 6.5 years, respectively.

During the follow-up period (mean=11.6 years, corresponding to 66 168 person-years), 734 major chronic disease endpoints were recorded among 635 subjects: 423 cancers (201 in men and 222 in women), 193 cardiovascular diseases (154 in men and 39 in women) and 118 deaths (70 in men and 48 in women).

Characteristics of the population are presented across PNNS-GS quartiles (Table 2). Subjects were more often women, older, higher educated and non-smokers with increasing PNNS-GS quartiles. Additionally, they showed lower energy intake, higher energy from proteins and carbohydrates and lower energy from lipids with increasing PNNS-GS quartile overall.

After adjustment for age and gender (Table 3), a decrease in risk of CVD across the quartiles of PNNS-GS was observed. In the fully adjusted multivariate model, the hazard risk for CVD of participants in the upper quartile of PNNS-GS compared to those in the lower was 0.65 (95%CI=0.42, 1.00, P for trend=0.04). Other outcomes were not associated with the PNNS-GS quartiles.

No significant interactions were found between gender or supplementation group and PNNS-GS on the risk of chronic diseases or death (P>0.30).

However, a significant interaction (P=0.03) was observed between tobacco status and PNNS-GS quartiles on the risk of cancer. All other interactions were non-significant. Analyses were therefore separately performed in never-smokers, former smokers and current smokers. No association of PNNS-GS with the risk of cancer was observed among never-smokers (HR Q4 versus Q1=0.84, 95%CI =0.55, 1.30) or former smokers (HR Q4 versus Q1=1.19, 95%CI=0.74, 1.91). However, in the subgroup of smokers, a higher toward risk of cancer was observed in subjects in the fourth PNNS-GS quartile compared to the first (HR=2.50, CI95%=1.10, 5.68, P for trend=0.02).

Discussion

In our study, a 35% reduction in the risk of cardiovascular diseases was observed among subjects showing better compliance with French nutritional guidelines. A non-statistically significant trend towards an increase in risk of cancer was observed among smokers only, with a statistically significant interaction between PNNS-GS and smoking status. No relationship was observed in terms of overall mortality and cancer incidence.

We should mention several strengths and limitations of our study. First, the generalization of our findings is subject to caution. Indeed, our subjects were volunteers participating in a nutritional intervention study (Hercberg *et al.*, 2004) who generally had a higher education level and occupational status, along with a healthier diet, than the general population. Furthermore, selection may have led to an overselected sample, as subjects displaying complete data for PNNS-GS computation may have been particularly compliant and health-conscious. Such a limitation might have led to homogeneity in our population. However, we had previously reported variability in PNNS-GS in the SU.VI.MAX study (Estaquio *et al.*, 2009). Second, the absence of an association between PNNS-GS and cancer risk and mortality may have been partly due to a lack of power due to the small sample size, the rather young age of the population or too short a follow-up period, which did not enable detecting an association with such long times process as cancer development or death. Other possible explanations are related to the inclusion process of motivated subjects, who may present overall "healthy" behavior in addition to the cohort effect, leading to a lower incidence of death and/or cancer. Finally, information on frequency, duration and time since stopping of smoking were ordinal, a possible residual confounding from smoking cannot entirely been removed especially in the highest categories.

Development of an a priori score for assessing diet via a holistic approach is of crucial importance for taking into account dietary factors when examining the relationship between nutrition and health. Nutritional guideline-based scores are also useful tools for monitoring compliance with nutritional guidelines and evaluating dietary guidelines for disease prevention. Nonetheless, development of a priori indices present some limitations which were recently extensively discussed (Moeller *et al.*, 2007; Waijers *et al.*, 2007). Briefly, not all components of the diet are accounted for, and scoring, cut-off criteria and selection of components are subjective decisions. In addition, the a priori method did not account for the full range of consumption, as components are dichotomized or ordinal. However, as shown in the literature, several of them have proven to be predictive of later disease and mortality, underlying the validity of nutritional recommendations currently disseminated in populations.

Despite the fact that it is only rarely accounted for in the literature (Estaquio *et al.*, 2008; Harnack *et al.*, 2002), physical activity may be of particular interest, as a healthy diet and physical activity may act synergistically to enhance chronic disease prevention. However, findings remained stable by removing physical activity of the PNNS-GS (data not shown).

When assessed in the same population, the FSIPO was shown to be associated with a 36% lower risk of "major chronic diseases" (including cancer, CVD and death) among men only.

Therefore, use of FSIPO or PNNS-GS may lead to different conclusions, probably due to their varying conceptions. First, both FSIPO and PNNS-GS shared some characteristics (fruits and vegetables, physical activity, alcohol), but differed regarding scoring criteria and definitions of indicators. For example, for fruit and vegetables, public health objectives considered that a "low consumer" ate <3.5 servings/day", while the nutritional advice used as a reference in the PNNS-GS defined it as "at least 5 servings/ day". In addition, fruits and vegetables weighed higher in the FSIPO than in the PNNS-GS. Second, since the FSIPO was developed with a view toward public health objectives, cardiovascular risk factors such as hypertension, hypercholesterolemia and body mass were accounted for. Although no statistically significant interaction between gender and PNNS-GS was observed on the risk chronic diseases, we nonetheless performed these analyses in men and women separately (data not shown). Regarding composite variable, no association was found with PNNS-GS whatever the gender. This finding strengthens the above-cited hypothesis. Thus, we hypothesize that the association between chronic diseases and FSIPO was mainly influenced by a stronger reduction in risk of CVD.

Few studies have reported a significant predictive value for nutritional guideline-based scores in the risk of overall mortality (Huijbregts *et al.*, 1997; Kaluza *et al.*, 2009; Seymour *et al.*, 2003). In our study, the absence of an association may have been due to too short a follow-up (mean=11.6 y) among middle-aged subjects.

In agreement with our results, other studies detected an association between adherence to nutritional guidelines (for Americans), assessed using the original HEI, and risk of CVD. Among subjects with a high level of HEI, a significant reduction in CVD risk of 28% in men (McCullough *et al.*, 2000a) and of 14% in women (McCullough *et al.*, 2000b) was observed, but no association was observed for cancer risk in either gender. Subsequent analysis based on an alternate version of the HEI was more accurate than the original HEI at predicting CVD risk but again, no association was observed with cancer risk (McCullough *et al.*, 2002; McCullough *et al.*, 2006).

Like most of the studies, we did not found an association with risk of overall cancers (Kaluza *et al.*, 2009; McCullough *et al.*, 2000a; McCullough *et al.*, 2000b; McCullough *et al.*, 2006; Seymour *et al.*, 2003). In contrast, one study on a large cohort (Reedy *et al.*, 2008) observed lower risk of colorectal cancer among men with higher scores (HEI, alternate HEI, RFS), but this was true for women only with higher HEI-2005. Another study carried out among postmenopausal women showed a significant protective effect of an increased Dietary Guidelines Index Score upon cancer risk (Harnack *et al.*, 2002), particularly for cancers of the colon, bronchus and lung, breast and uterus.

The lack of an association between dietary scores and cancer risk in many studies may be partly related to the fact that cancers are studied overall due to the lack of power when considering site-specific cancers, whereas some nutritional factors may be protective for some sites only. Finally, since certain factors seemed to play particular important role in cancer prevention (American Institute for Cancer Research / World Cancer Research Fund, 2007), the components of scores related to these factors should be carefully considered. Indeed, some food groups such as alcohol, processed meat, fruit and vegetables may weigh more strongly in terms of with cancer risk.

An increase in risk was observed among the small subgroup of smokers with the highest PNNS-GS compared to the lowest. Usually, smoking has been frequently associated with a cluster of unhealthy behavior (Kesse-Guyot *et al.*, 2009; McNaughton *et al.*, 2007). No study reported an interaction between the nutritional score and smoking in terms of risk of cancer. Nevertheless, vegetable and fruit consumption was recently related to an increase in risk of colorectal cancer among smokers, while a protective effect was observed among never and former smokers (van Duijnhoven *et al.*, 2009). One observational study (Touvier *et al.*, 2005) and a recent meta-analysis of randomized clinical trials (Druesne-Pecollo *et al.*, 2009) reported association between beta-carotene supplementation and several types of cancers among smokers. Mechanisms based on in vitro studies might explain the harmful effects of beta-carotene in smokers. Beta-carotene may act as a pro-oxidant at high doses, affecting cell proliferation or apoptosis in cells exposed to smoke condensate, or it may increase DNA oxidative damage (Druesne-Pecollo *et al.*, 2009).

In conclusion, better adherence to French nutritional guidelines was associated with a lower incidence of CVD after a maximum 13-year follow-up period in middle-aged adults. These findings partially argue for the benefits of nutritional guidelines, and similar investigations should be reproduced in other varied populations. Complementary investigations in high-risk subgroups are also needed.

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Table 1 Components and scoring for calculation of the PNNS-GS, according to PNNS recommendation scores

	Recommendation	**Scoring criteria**	**Score**
Fruits and vegetables	≥5 servings/d	0 to <3.5 servings/d	0
		3.5 to <5 servings/d	0.5
		5 to <7.5 servings/d	1
		≥7.5 servings/d	2
Bread, cereals, potatoes and legumes	At each meal according to appetite	0 to <1 servings/d	0
		1 to <3 servings/d	0.5
		3 to <6 servings/d	1
		≥6 servings/d	0.5
Whole grain food	Preferentially choose whole grains and whole grain breads	0 to <0.33 servings/d[1]	0
		0.33 to <0.66 servings/d[1]	0.5
		≥0.66 servings/d[1]	1
Milk and dairy products (yogurt, cheese, etc.)	3 servings/d (individuals aged≥ 55 years: 3-4 servings/d)	0 to <1 servings/d	0
		1 to <2.5 servings/d	0.5
		2.5 to 3.5 servings/d (participants aged ≥55y: 2.5 to 4.5 servings/d)	1
		>3.5 (participants aged ≥55y: >4.5 servings/d)	0
Meat and poultry, seafood and eggs	1-2 servings/d	0 servings/d	0
		>0 to <1 servings/d	0.5
		1 to 2 servings/d	1
		>2 servings/d	0
Seafood	≥2 servings/wk	<2 servings/wk	0
		≥2 servings/wk	1
Total added fats[2]	Limit consumption	Lipids from animal and vegetable added fats >16%EI[3]/d	0
		Lipids from animal and vegetable added fats ≤16%EI[3]/d	1
Vegetable added fats	Favor fats of vegetable origin	No consumption of vegetable oil or ratio vegetable oil/total added fats ≤0.5	0
		No consumption of added fats or ratio vegetable oil/total added fats >0.5	1
Sweetened foods[2]	Limit consumption	Added sugars from sweetened foods ≥15% EI[3]/d	-0.5

		Added sugars from sweetened foods [10 – 15[% EI[3]/d	0
		Added sugars from sweetened foods < 10% EI[3]/d	1
Water and soda[4]	Drink water as desired;	< 1 L of water and > 250 mL of soda/d	0
	Limit sweetened beverages	≥ 1 L of water and > 250 mL of soda/d	0.50
	to ≤1 one glass/d	< 1 L of water and ≤ 250 mL of soda/d	0.75
		≥ 1 L of water and ≤ 250 mL of soda/d	1
Alcohol[5]	≤2 glasses of wine/d for	>20 g ethanol/d for women and >30 g ethanol/d for men	0
	women and ≤3 glasses of	Ethanol ≤20 g/d for women and ≤30 g/d for men	0.8
	wine/d for men	Abstainers and irregular consumers (<1 glass of wine/wk)	1
Salt	Limit consumption	>12 g/d	-0.5
		>10 to 12 g/d	0
		>8 to 10 g/d	0.5
		>6 to 8 g/d	1
		≤ 6 g/d	1.5
Physical activity	At least the equivalent of 30	0 to <30 min/d	0
	min of brisk walking/d	30 to <60 min/d	1
		≥ 60 min/d	1.5

[1] As a proportion of 24-h dietary records during which whole-grain consumption was reported

[2] Established according to the French RDA

[3] EI: total energy intake without alcohol

[4] Water included water, tea, coffee, herbal tea, milk, and diet beverages

[5] Pregnant women are advised to abstain from all alcohol consumption during the entire pregnancy

Table 2 Baseline characteristic (mean ± SD or %) of the population across PNNS-GS quartiles, SU.VI.MAX Study, 1994-2007

	Q1	**Q2**	**Q3**	**Q4**	**P[1]**
PNNS-GS range	≤6.52	>6.52-≤7.75	>7.75-≤9	>9	
N	1456	1470	1447	1450	
Male (%)	49.04	42.72	39.32	36.28	<.0001
Age	48.24 ± 6.16	48.74 ± 6.16	49.09 ± 6.32	50.04 ± 6.47	<.0001
BMI	23.98 ± 3.85	24.22 ± 3.82	24.18 ± 3.66	23.90 ± 3.39	0.21
Education					
Primary	22.05	20.2	20.53	18.69	0.02
Secondary	38.94	39.8	37.11	39.17	
High	39.01	40.0	42.36	42.14	
Smoking status					
Non-smokers	43.27	47.69	49.76	50.14	<.0001
Former smokers	38.53	37.48	38.91	41.24	
Smokers	18.20	14.83	11.33	8.62	
Intervention group (%)	50.55	51.29	50.73	49.52	0.53
Physical activity[2]					
[0-30[min/d	82.90	66.33	52.45	27.24	<.0001
[30-60[min/d	10.71	17.76	25.16	30.28	
≥60 min/d	6.39	15.92	22.39	42.48	
Energy intake (total) (Kcal/d)	2 440.4 ± 646.4	2 073.3 ± 573.7	2 003.0 ± 532.2	1 922.9 ± 520.2	<.0001
Energy intake (without alcohol) (Kcal/d)	2 259.0 ± 595.3	1 944.2 ± 525.9	1 893.5 ± 490.8	1 831.0 ± 481.5	<.0001

Proteins (%)[3]	17.52 ± 2.91	17.89 ± 2.96	17.92 ± 2.74	18.19 ± 2.77	<.0001
Carbohydrates (%)[3]	41.27 ± 6.35	41.12 ± 6.26	41.85 ± 5.91	42.91 ± 5.82	<.0001
Lipids (%)[3]	41.20 ± 5.02	40.97 ± 5.11	40.21 ± 5.05	38.89 ± 5.24	<.0001
Point for each component (theoretical range), mean ± sd					
Fruits and vegetables [0-2]	0.68 ± 0.59	0.77 ± 0.57	0.93 ± 0.59	1.21 ± 0.64	<.0001
Bread, cereals, potatoes and legumes [0-1]	0.76 ± 0.27	0.74 ± 0.27	0.75 ± 0.27	0.75 ± 0.27	0.14
Whole grain food [0-1]	0.11 ± 0.27	0.14 ± 0.30	0.20 ± 0.35	0.33 ± 0.42	<.0001
Milk and dairy products [0-1]	0.35 ± 0.40	0.46 ± 0.40	0.52 ± 0.40	0.62 ± 0.41	<.0001
Meat and poultry, seafood and eggs [0-1]	0.52 ± 0.47	0.67 ± 0.43	0.74 ± 0.40	0.83 ± 0.33	<.0001
Seafood [0-1]	0.20 ± 0.40	0.28 ± 0.45	0.42 ± 0.49	0.65 ± 0.48	<.0001
Sweetened foods [0-1]	0.70 ± 0.49	0.81 ± 0.41	0.88 ± 0.33	0.94 ± 0.24	<.0001
Total added fats [0-1]	0.65 ± 0.48	0.71 ± 0.45	0.76 ± 0.43	0.83 ± 0.37	<.0001
Vegetable added fats [0-1]	0.41 ± 0.49	0.60 ± 0.49	0.72 ± 0.45	0.86 ± 0.35	<.0001
Water and soda [0-1]	0.86 ± 0.16	0.84 ± 0.13	0.91 ± 0.13	0.89 ± 0.12	<.0001
Alcohol [0-1]	0.60 ± 0.42	0.71 ± 0.36	0.78 ± 0.30	0.85 ± 0.22	<.0001
Salt [-0.5-1.5]	-0.10 ± 0.53	0.18 ± 0.63	0.26 ± 0.63	0.42 ± 0.64	<.0001
Physical activity [0-1.5]	0.20 ± 0.46	0.42 ± 0.60	0.59 ± 0.64	0.94 ± 0.61	<.0001

[1] P Values based on Kruskal-Wallis test or chi-squared test

[2] Physical activity: as equivalent of 30 min of brisk walking/d

[3] Values are percentage of total daily energy intake (without alcohol)

Table 3 Hazards ratio (95% CI) of major chronic diseases and PNNS-GS quartiles during the period 1994-2007

	Q1	Q2	Q3	Q4	P[1]
Composite variable [2]					
Number of cases	150	161	162	162	
Age and gender-adjusted	1	1.06	1.03	0.97	0.74
HR		(0.84,1.32)	(0.83,1.29)	(0.77,1.21)	
Fully adjusted HR[3]	1	1.05	1.03	0.97	0.77
		(0.84,1.32)	(0.82,1.30)	(0.77,1.24)	
Cancer [4]					
Number of cases	96	101	113	113	
Age and gender-adjusted	1	1.01	1.09	1.01	0.81
HR		(0.76,1.33)	(0.83,1.43)	(0.77,1.34)	
Fully adjusted HR[3]	1	1.05	1.15	1.07	0.54
		(0.79,1.41)	(0.86,1.53)	(0.80,1.44)	
Cardiovascular diseases					
Number of cases	56	53	45	39	
Age and gender-adjusted	1	0.98	0.82	0.68	0.04
HR		(0.68,1.43)	(0.55,1.21)	(0.45,1.03)	
Fully adjusted HR[3]	1	0.93	0.78	0.65	0.04
		(0.63,1.36)	(0.52,1.17)	(0.42,1.00)	
Death					
Number of cases	26	33	27	32	
Age and gender-adjusted	1	1.24	0.99	1.11	0.95
HR		(0.73,2.10)	(0.57,1.74)	(0.64,1.93)	

Fully adjusted HR[3]	1	1.24 (0.73,2.10)	0.99 (0.57,1.74)	1.11 (0.64,1.93)	0.95

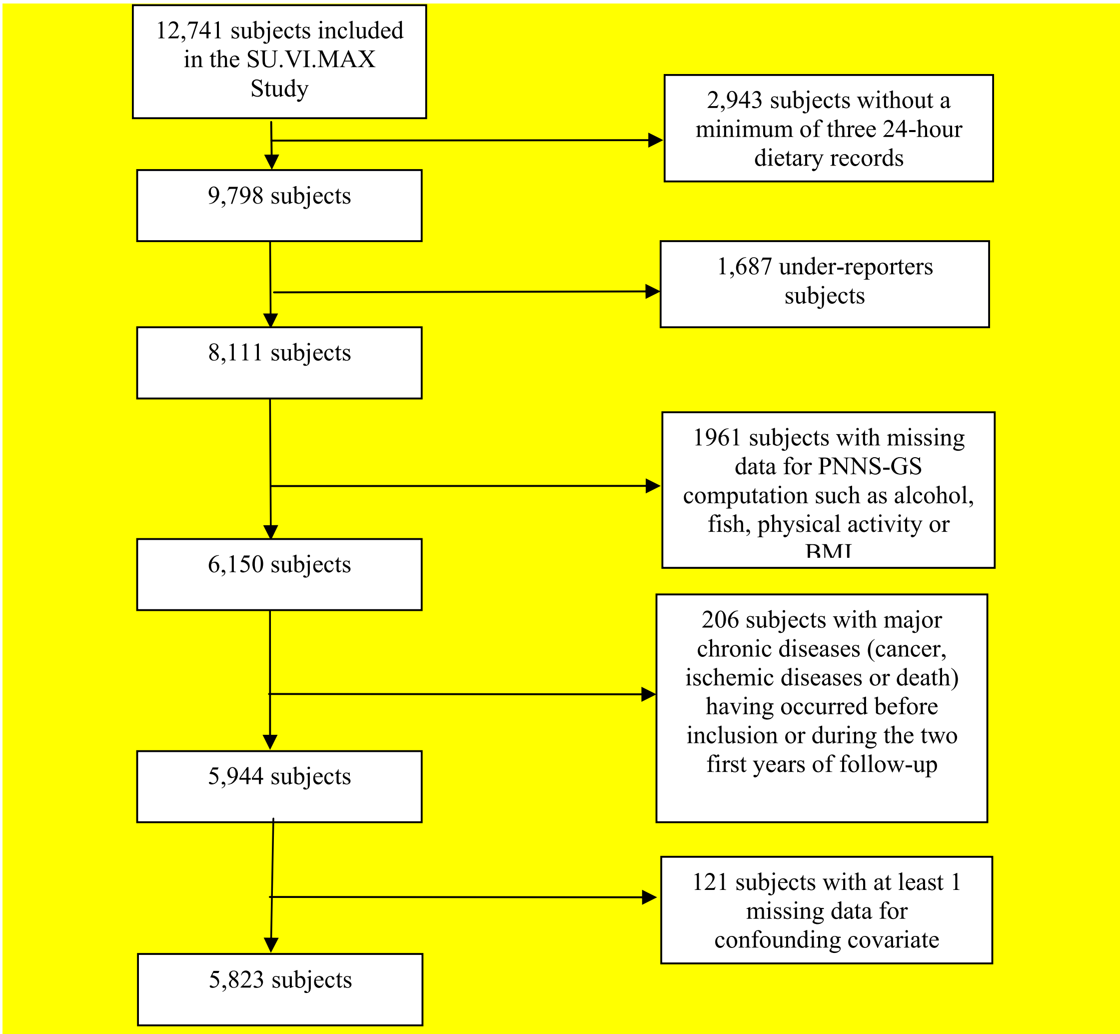
[1] Test for trend across quartiles

[2] Cancer, cardiovascular diseases or death

[3] Controlled for gender, age (continuous), BMI (continuous), smoking (never, past, current), total energy intake (continuous), education (primary school, secondary school, high school or equivalent), supplementation group (active versus placebo).

[4] Cancer included all sites of cancer except basal cell carcinoma of the skin

Figure 1 Flow chart of subjects included in the present analysis, SU.VI.MAX Study 1994-2007.


12,741 subjects included in the SU.VI.MAX Study
2,943 subjects without a minimum of three 24-hour dietary records
9,798 subjects
1,687 under-reporters subjects
8,111 subjects
1961 subjects with missing data for PNNS-GS computation such as alcohol, fish, physical activity or BMI
6,150 subjects
206 subjects with major chronic diseases (cancer, ischemic diseases or death) having occurred before inclusion or during the two first years of follow-up
5,944 subjects
121 subjects with at least 1 missing data for confounding covariate
5,823 subjects