Supplemental material

Appendix 1: Identification procedure of energy under-reporting in the NutriNet-Santé cohort

Energy underreporting was identified using Black's method (1,2) based on the original method developed by Goldberg et al (3), relying on the hypothesis that energy expenditure and intake, when weight is stable, are equal. Black's equations are based on an estimate of the person's basal metabolic rate (BMR) calculated via Schofield's equations (4) and taking into account sex, age, height and weight, as well as physical activity level (PAL), number of 24h records, intra-individual variabilities of reported energy intake and BMR, and intra/inter-variabilities of PAL. In the present study, intra-individual coefficients of variations for BMR and PAL were fixed using the values proposed by Black et al., i.e. 8.5 % and 15%, respectively. For identifying under-reporters, the 1.55 value of PAL was used. It corresponds to the WHO value for "light" activity, which is the probable minimum energy requirement for a normally active but sedentary individual (not sick, disabled or frail elderly). A higher value might have exaggerated the extent of under-reporting. Some under-reporting individuals were not excluded if their reported energy intake, initially estimated abnormally low, was found to be likely in case of recent weight variation or reported practice of weight-loss restrictive diet or proactive statement of the participant that he/she ate less than usual on the day of the dietary record. In the cohort, 20.0 % of the subjects were considered as under-reporters and were excluded from the analyses.

Appendix 2: Precisions and examples of ultra-processed foods according to the NOVA classification

All food and beverage items of the NutriNet-Santé composition table were categorized by a team of three trained dieticians into one of the four food groups in NOVA, a food classification system based on the extent and purpose of industrial food processing (5–7). The whole classification was then reviewed by a committee composed of the three dietitians and five researchers, specialists in nutritional epidemiology. In case of uncertainty for a given food/beverage item, a consensus was reached among researchers based on the percentage of home-made and artisanal foods versus industrial brands reported by the participants.

The "ultra-processed foods" group of the NOVA classification is the primarily focus of this study. Examples of such products as well as examples of distinctions between ultra-processed products and products from other NOVA categories are provided below:

Examples of ultra-processed food according to the NOVA classification:

Carbonated drinks; sweet or savoury packaged snacks; ice-cream, chocolate, candies (confectionery); mass-produced packaged breads and buns; margarines and spreads; industrial cookies (biscuits), pastries, cakes, and cake mixes; breakfast 'cereals', 'cereal' and 'energy' bars; 'energy' drinks; flavoured milk drinks; cocoa drinks; sweet desserts made from fruit with added sugars, artificial flavours and texturizing agents; cooked seasoned vegetables with ready-made sauces; meat and chicken extracts and 'instant' sauces; 'health' and 'slimming' products such as powdered or 'fortified' meal and dish substitutes; ready to heat products including pre-prepared pies, pasta and pizza dishes; poultry and fish 'nuggets' and 'sticks', sausages, burgers, hot dogs, and other reconstituted meat products, and powdered and packaged 'instant' soups, noodles and desserts.

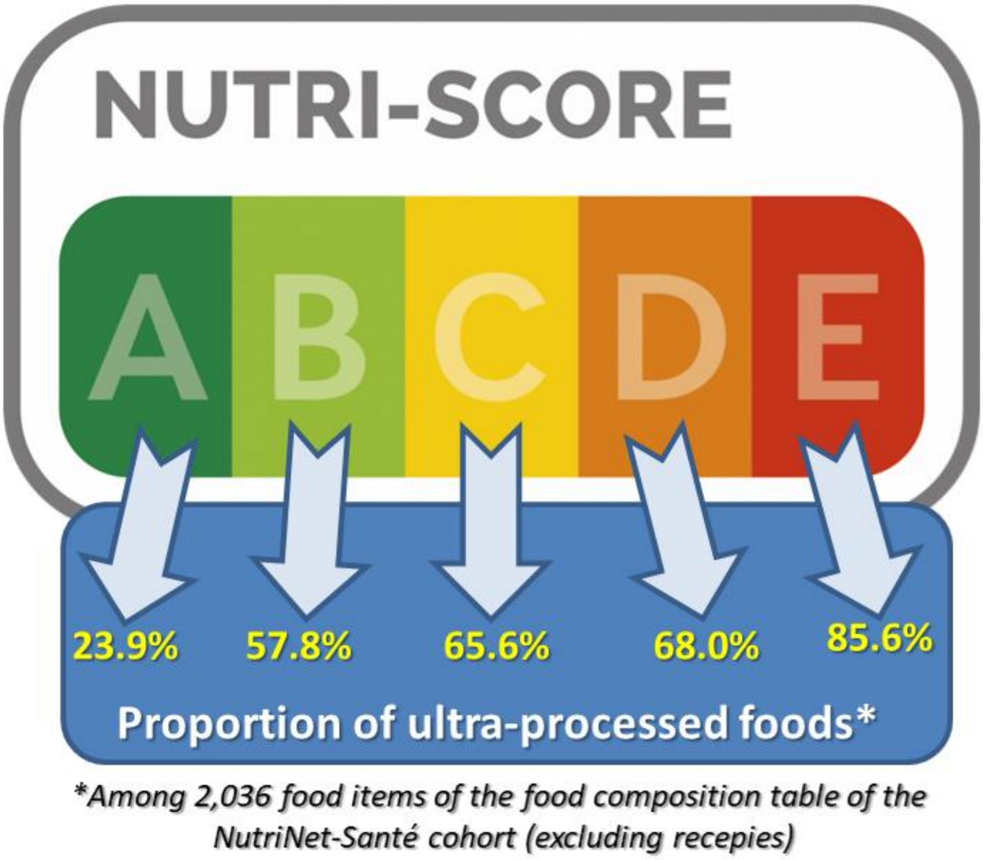
For instance, salted-only red or white meats are considered as "processed foods" whereas smoked or cured meats with added nitrites and conservatives, such as sausages and ham are classified as "ultra-processed foods".

Similarly, canned salted vegetables are considered as "processed foods" whereas industrial cooked or fried seasoned vegetables, marinated in industrial sauces with added flavourings are considered as "ultra-processed foods".

Regarding soups, canned liquid soups with added salts, herbs and spices are considered as "processed foods" while instant dry soup mixes are considered as "ultra-processed foods".

Example of list of ingredients for an industrial Chicken and Leek flavour soup considered as "ultra-processed" according to the NOVA classification: *"Dried Glucose Syrup, Potato Starch, Flavourings, Salt, Leek Powder (3.6%), Dried Leek (3.5%), Onion Powder, Dried Carrot, Palm Oil, Dried Chicken (0.7%), Garlic Powder, Dried Parsley, Colour [Curcumin (contains MILK)], Ground Black Pepper, MILK Protein, Stabilisers (Dipotassium Phosphate, Trisodium Citrate)"*.

Appendix 3: Categorization of the ultra-processed food items of the NutriNet-Santé cohort according to their nutritional quality scored by the Foods Standard Agency Nutritent Profilng system (FSAm-NPS)



The Nutri-Score was selected by the French, the Spanish and the Belgian Ministries of Health as the official front-of-pack nutrition label to be implemented in these countries, an initiative officially commended by the WHO-Europe (8). It uses a modified version of the British Food Standards Agency Nutrient Profiling System (FSAm-NPS) to categorize food products into 5 colours reflecting their nutritional quality (from A-green: best nutritional quality to E-red lower nutritional quality). It takes into account the content per 100g of energy, saturated fatty acids, sugar, sodium, dietary fibres, proteins and fruit/vegetables (9): The FSAm-NPS score was calculated for all foods and beverages in the NutriNet-Santé food composition database as follows: points (0–10) are allocated for the content per 100 g in total sugars (g), saturated fatty acids (g), sodium (mg), and energy (kJ) (i.e., nutrients that should be consumed in limited amounts) and can be balanced by opposite points (0–5) allocated for dietary fibres (g), proteins (g), and fruits/vegetables/legumes/nuts (percent) (i.e., nutrients/components that should be promoted). The grids for point attribution are displayed below. The percentage of fruits/vegetables/legumes/nuts was derived using standard recipes. The FSAm-NPS score for each food/beverage is based on a unique discrete continuous scale ranging theoretically from −15 (most healthy) to +40 (least healthy).

1) FSAm-NPS score computation at food/beverage level

Points are allocated according to the nutrient content for 100g of foods or beverages.
Points are allocated for 'Negative' nutrients (A points) and can be balanced according to 'Positive' nutrients (C points).

A points

Total A points = (points for energy) + (points for saturated fat) + (points for total sugar) + (points for sodium)

Points	Energy (kJ)	Saturated Fat (g)	Total Sugars (g)	Sodium (mg)
0	≤ 335	≤ 1	≤ 4.5	≤ 90
1	> 335	> 1	> 4.5	> 90
2	> 670	> 2	> 9	> 180
3	> 1005	> 3	> 13.5	> 270
4	> 1340	> 4	> 18	> 360
5	> 1675	> 5	> 22.5	> 450
6	> 2010	> 6	> 27	> 540
7	> 2345	> 7	> 31	> 630
8	> 2680	> 8	> 36	> 720
9	> 3015	> 9	> 40	> 810
10	> 3350	> 10	> 45	> 900

C points

Total C points = (points for fruits/vegetables/legumes/nuts) + (points for fibres) + (points for proteins)

Points	Fruits/vegetables/legumes/nuts	Fibre (g) *	Protein (g)
0	≤ 40	≤ 0.7	≤ 1.6
1	> 40	> 0.7	> 1.6
2	> 60	> 1.4	> 3.2
3	-	> 2.1	> 4.8
4	-	> 2.8	> 6.4
5	> 80	> 3.5	> 8.0

* FSAm-NPS score allocates different thresholds for fibres, depending on the measurement method used. We used NSP cut-offs to compute fibres score.

For 100g of a given food, the percentage of fruits/vegetables/legumes/nuts is obtained by summing up the amount (in grams) of all fruits, legumes and vegetables (including oleaginous fruits, dried fruits and olives) contained in this food.

Overall score computation

- If Total A points <11, then FSAm-NPS score =Total A points – Total C points
- If Total A points ≥11,
    - If points for fruits/vegetables/legumes/nuts =5, then FSAm-NPS score =Total A points – Total C points
    - Else if points for fruits/vegetables/legumes/nuts <5, then FSAm-NPS score = Total A points – (points for fibre + points for fruits/vegetables/legumes/nuts).

Exceptions were made for cheese, added fat, and drinks to better rank them according to their nutrient profile, consistently with nutritional recommendations:

Score computation for cheese

For cheese, the score takes in account the protein content, whether the A score reaches 11 or not, i.e.: FSAm-NPS score =Total A points – Total C points

Score computation for added fat

For added fat, the grid for point attribution is based on the percentage of saturated fat among total lipids (instead of saturated fat (g)) and has a six-point homogenous ascending step, as shown thereafter:

Points	**Saturated Fat/Lipids (%)**
0	< 10
1	< 16
2	< 22
3	< 28
4	< 34
5	< 40
6	< 46
7	< 52
8	< 58
9	< 64
10	≥ 64

Points attribution for the other nutrients follows the grid displayed in "A points" and "C points" above.

Score computation for drinks

For drinks, the grids for point attribution regarding energy, sugars and fruits/vegetables/ legumes/nuts (%) were modified.

Points	**Energy (kJ)**	**Sugars (g)**	**Fruits/vegetables/legumes/nuts (%)**
0	≤ 0	≤ 0	< 40
1	≤ 30	≤ 1.5	
2	≤ 60	≤ 3	> 40
3	≤ 90	≤ 4.5	
4	≤ 120	≤ 6	> 60
5	≤ 150	≤ 7.5	
6	≤ 180	≤ 9	
7	≤ 210	≤ 10.5	
8	≤ 240	≤ 12	
9	≤ 270	≤ 13.5	
10	> 270	> 13.5	> 80

Points attribution for the other nutrients follows the grid displayed in "A points" and "C points" above.

Given the modification of the grid for fruit and vegetables for beverages, the threshold in the final computation to take into account protein content is set at 10 points:

- If Total A points <11, then FSAm-NPS score =Total A points – Total C points
  - If Total A points ≥11,
    - If points for fruits/vegetables/legumes/nuts =10, then FSAm-NPS score =Total A points – Total C points
    - Else if points for fruits/vegetables/legumes/nuts <10, then FSAm-NPS score = Total A points – (points for fibre + points for fruits/vegetables/legumes/nuts).

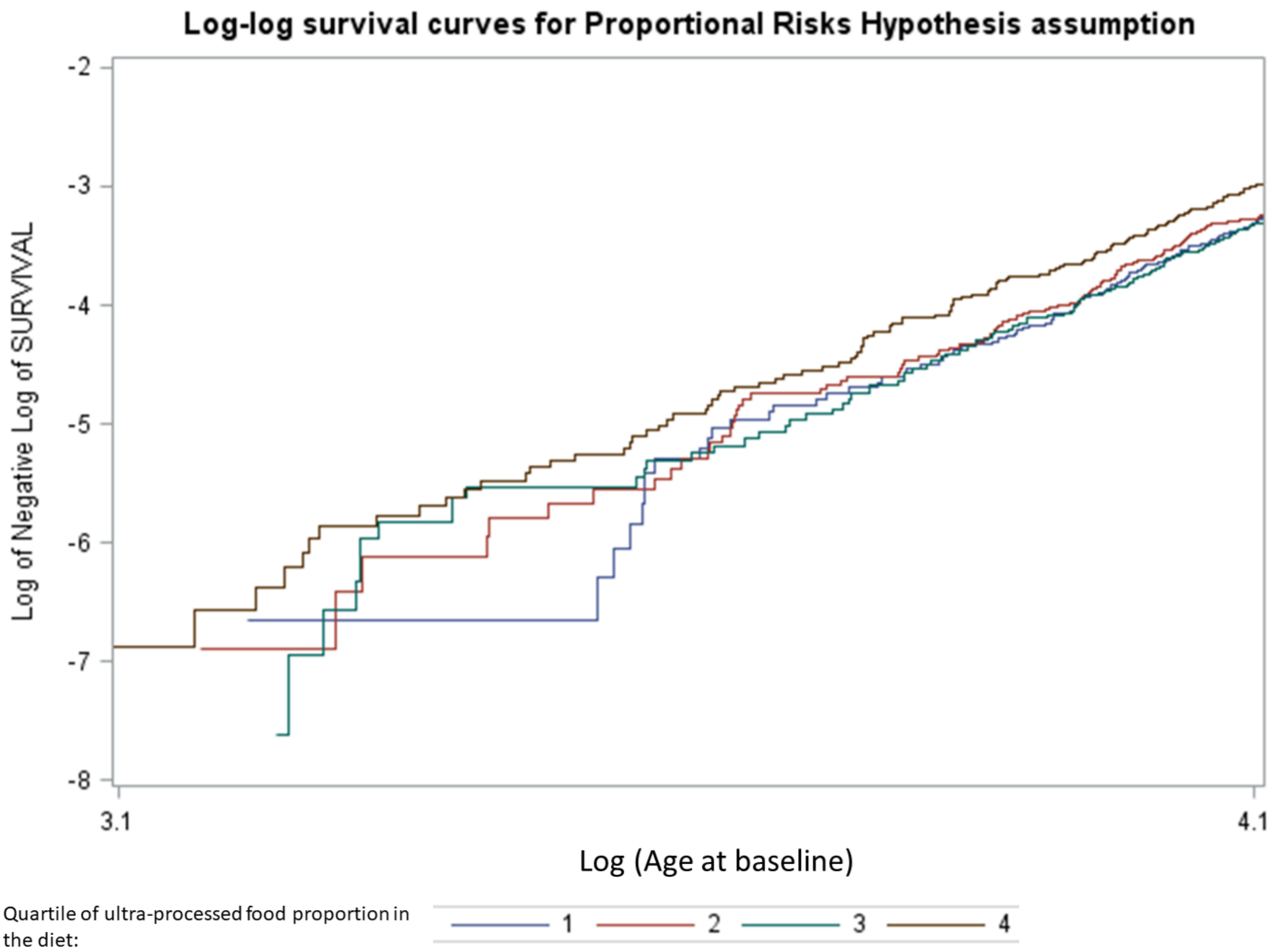
Milk and vegetable milk are not concerned by this exception. Their scores are computed using the overall score computation system.

FSAm-NPS score and Attribution of Nutri-Score colours

Foods (points)	**Beverages (points)**	**Colour**	
Min to -1	Water	Dark green	*Highest nutritional quality*
0 to 2	Min to 1	Light green	
3 to 10	2 to 5	Yellow	
11 to 18	6 to 9	Light orange	
19 to max	10 to max	Dark orange	*Lowest nutritional quality*

Santé Publique France 2017, Nutri-Score Logo

Appendix 4: Cox models assumption testing: Results of proportional risk assumption testing (log(-log) survival vs. log(time) plots)

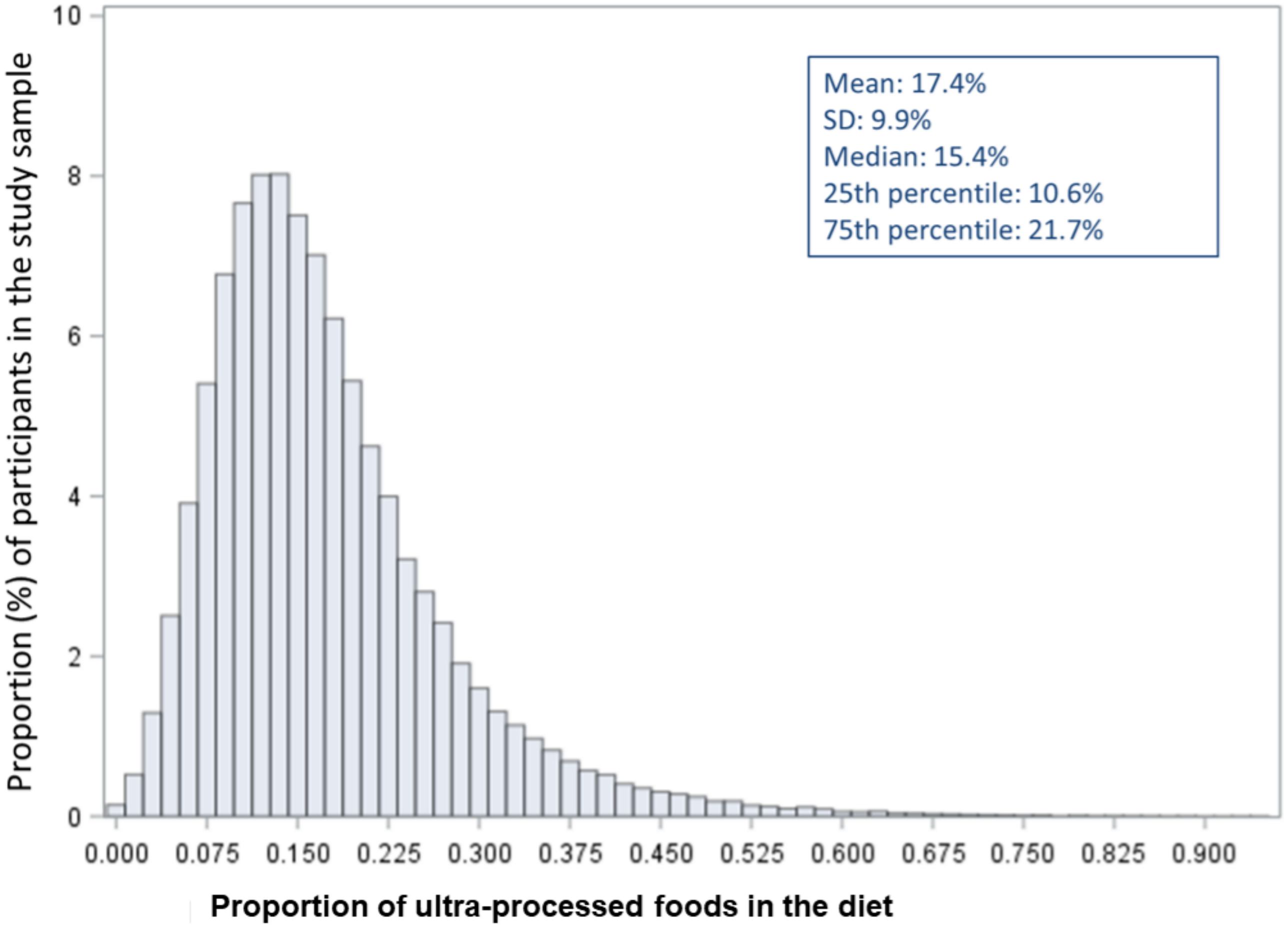


Appendix 5: Method for deriving dietary patterns by principal component analysis and corresponding factor loadings

Dietary patterns were produced from principal-components analysis based on 20 predefined food groups, using the SAS ‘‘Proc Factor’’ procedure (SAS Institute Inc., Cary, North Carolina). This factor analysis forms linear combinations of the original food groups, thereby grouping together correlated variables. Coefficients defining these linear combinations are called factor loadings. A positive factor loading means that the food group is positively associated with the factor, whereas a negative loading reflects an inverse association with the factor. For interpreting the data, we considered foods with a loading coefficient under -0.25 or over 0.25. We rotated factors by orthogonal transformation using the SAS ‘‘Varimax’’ option to maximize the independence (orthogonality) of retained factors and obtain a simpler structure for easier interpretation. In determining the number of factors to retain, we considered eigenvalues greater than 1.25, the scree test (with values being retained at the break point between components with large eigenvalues and those with small eigenvalues on the scree plot), and the interpretability of the factors. For each subject, we calculated the factor score for each pattern by summing observed consumption from all food groups, weighted by the food group factor loadings. The factor score measures the conformity of an individual’s diet to the given pattern. Labeling was descriptive, based on foods most strongly associated with the dietary patterns. The healthy pattern (explaining 10.6% of the variance) was characterized by higher intakes of fruit, vegetables, soups and broths, unsweetened soft drinks and whole grains and lower sweetened soft drinks intake. The Western pattern (explaining 7.0% of the variance) was characterized by higher intakes of fat and sauces, alcohol, meat and starchy foods.

	Factor loadings	
	Healthy Pattern	Western Pattern
Alcoholic drinks	-.099552	0.284771
Breakfast cereals	0.079447	-.181769
Cakes and biscuits	-.197629	0.003444
Dairy products	0.066066	-.013702
Eggs	0.078582	0.043744
Fats and sauces	0.012600	0.544911
Fish and seafood	0.204373	0.100759
Fruit	0.354075	0.052298
Meat	-.188274	0.318483
Pasta and rice	-.212857	0.341941
Potatoes and tubers	-.029615	0.402694
Poultry	-.030137	0.064064
Processed meat	-.228028	0.207877
Pulses	0.192815	0.026104
Soups and broths	0.264233	0.227787
Sugar andconfectionery	-.088870	0.120660
Sweetened soft drinks	-.288870	-.007506
Unsweetened soft drinks	0.258563	0.152704
Vegetables	0.471255	0.231818
Whole grains	0.380881	-.043132

Appendix 6: Distribution of the main exposure (proportion of ultra-processed food in the diet) in the study sample (N=105,159), NutriNet-Santé, France



Appendix 7: Associations between ultra-processed food intake and overall cardiovascular diseases, in different strata of the population from multivariable Cox proportional hazard models [a], NutriNet-Santé cohort, France, 2009 – 2018 (n=105,159)

	Overall cardiovascular diseases			
	Cases/non-cases	HR* (95% CI)	P-value	P-value for interaction[Ț]
Sex				
Men	701/21211	1.12 (1.02 to 1.23)	0.02	0.9
Women	708/82539	1.13 (1.03 to 1.24)	0.01	
Age				
Younger adults (≤45 years old)	182/59224	1.15 (1.00 to 1.32)	0.004	0.2
Older adults (>45 years old)	1227/44526	1.10 (1.02 to 1.19)	0.01	
Lipid intake				
Low intakes (≤78.87 g/d)	664/51905	1.11 (1.01 to 1.23)	0.02	0.4
High intakes (>78.87 g/d)	745/51045	1.13 (1.03 to 1.24)	0.01	
Dietary pattern[b]				
Healthy dietary pattern	870/51710	1.11 (1.01 to 1.22)	0.03	0.4
Less healthy pattern	539/52040	1.12 (1.02 to 1.24)	0.02	
BMI				
Normal weight (BMI<25kg/m2)	755/74434	1.11 (1.01 to 1.22)	0.03	0.8
Overweight/obese (BMI≥25kg/m2)	654/29316	1.14 (1.03 to 1.25)	0.008	
Physical activity level[c]				
Moderate to high	974/67395	1.10 (1.01 to 1.20)	0.02	0.9
Low	257/21893	1.17 (1.02 to 1.34)	0.03	

CI: confidence interval, HR: Hazard ratio

*HR for an absolute increment of 10 in the percentage of ultra-processed foods in the diet

[a]Models are adjusted for age (timescale), sex (except when stratified by sex), energy intake, number of 24h-dietary records, smoking status, educational level, physical activity (except when stratified by physical activity level), BMI, alcohol intake, and family history of CVD.

[b]Stratification by the median of the Healthy dietary component derived from Principal Component Analysis

[c]Classes determined according to IPAQ guidelines

[Ț]P-value for the interaction test between ultra-processed food intake and respectively: sex, physical activity (categorical variables), age, lipid intake, dietary pattern, and BMI (continuous variables)

Appendix 8: Associations between the quantity (g/d) of each food group (a. ultraprocessed and b. non ultra-processed, for an increase of 100g of the quantity consumed in g/day) and the risks of overall cardiovascular (n=1,409 cases), coronary heart (n=665 cases) and cerebrovascular (n=829 cases) diseases, from multivariable Cox proportional hazard models[a], NutriNet-Santé cohort, France, 2009 – 2018 (n=105,159)

a. **Food groups in their ultra-processed form**

	Overall cardiovascular diseases		**Coronary heart diseases[b]**		**Cerebrovascular diseases[c]**	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Beverages	1.06 (1.02 to 1.10)	0.004	1.04 (0.98 to 1.10)	0.1	1.06 (1.01 to 1.12)	0.01
Dairy products	1.01 (0.92 to 1.11)	0.8	1.03 (0.90 to 1.18)	0.7	0.98 (0.86 to 1.11)	0.7
Fats and sauces	1.40 (0.95 to 2.07)	0.09	1.73 (1.01 to 2.94)	0.04	1.26 (0.74 to 2.13)	0.4
Fruits and vegetables	1.00 (0.95 to 1.05)	0.9	0.99 (0.92 to 1.07)	0.8	1.00 (0.93 to 1.07)	0.9
Meat, fish and egg	1.19 (0.99 to 1.42)	0.06	1.28 (1.00 to 1.64)	0.05	1.08 (0.85 to 1.38)	0.5
Starchy foods and breakfast cereals	0.95 (0.79 to 1.13)	0.5	0.89 (0.69 to 1.16)	0.4	0.97 (0.77 to 1.23)	0.8
Sugary products	1.07 (0.97 to 1.17)	0.2	1.00 (0.87 to 1.14)	0.9	1.12 (1.00 to 1.27)	0.05
Salty snacks	1.65 (0.97 to 2.82)	0.06	1.29 (0.56 to 2.92)	0.5	2.03 (1.04 to 3.94)	0.04

b. **Food groups in their non-ultra-processed form**

	Overall cardiovascular diseases		**Coronary heart diseases[b]**		**Cerebrovascular diseases[c]**	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Beverages	0.99 (0.98 to 1.01)	0.4	0.99 (0.98 to 1.01)	0.4	1.00 (0.98 to 1.01)	0.9
Dairy products	1.00 (0.96 to 1.03)	0.7	0.99 (0.94 to 1.04)	0.6	1.00 (0.96 to 1.05)	0.9
Fats and sauces	0.91 (0.66 to 1.24)	0.5	1.02 (0.65 to 1.60)	0.9	0.78 (0.51 to 1.18)	0.2
Fruits and vegetables	0.98 (0.95 to 1.00)	0.05	0.98 (0.94 to 1.01)	0.2	0.97 (0.94 to 1.01)	0.1
Meat, fish and egg	1.00 (0.91 to 1.09)	0.9	1.03 (0.90 to 1.17)	0.7	0.97 (0.86 to 1.10)	0.6
Starchy foods and breakfast cereals	0.98 (0.92 to 1.05)	0.6	0.98 (0.89 to 1.07)	0.6	0.98 (0.90 to 1.07)	0.7
Sugary products	1.07 (0.93 to 1.24)	0.3	0.98 (0.80 to 1.21)	0.9	1.11 (0.92 to 1.33)	0.3
Salty snacks	2.27 (1.28 to 4.00)	0.005	2.94 (1.31 to 6.63)	0.009	1.78 (0.83 to 3.80)	0.1

CI: confidence interval, HR: Hazard ratio

Proportions of the ultra-processed forms of each food group were: 7.7% for beverages, 61.8% for dairy products, 36.3% for fats and sauces, 15.3% for fruits and vegetables, 21.7% for meat, fish and egg, 18.0% for starchy foods and breakfast cereals, 78.5% for sugary products and 56.8% for salty snacks.

[a] Adjusted for age (timescale), sex, energy intake, number of 24h-dietary records, smoking status, educational level, physical activity, BMI, alcohol intake, and family history of CVD.

[b]Coronary heart diseases include myocardial infarctions, angioplasty and acute coronary syndromes

[c]Cerebrovascular diseases include strokes and transitory ischemic attacks

Appendix 9: Associations between ultra-processed food intake and overall cardiovascular diseases, coronary heart diseases and cerebrovascular diseases from multivariable Cox proportional hazard models [a], after sensitivity analyses, NutriNet-Santé cohort, France, 2009 – 2018 (n=105,159)

	Overall cardiovascular diseases			**Coronary heart diseases[b]**			**Cerebrovascular diseases[c]**		
	Cases/non-cases	HR* (95% CI)	P-value	Cases/non-cases	HR* (95% CI)	P-value	Cases/non-cases	HR* (95% CI)	P-value
Model 1 + Western dietary pattern[d]	1409/103750	1.12 (1.05 to 1.20)	0.0009	665/104494	1.12 (1.02 to 1.24)	0.02	829/104330	1.11 (1.01 to 1.21)	0.02
Model 1 + fruit and vegetable consumption	1409/103750	1.10 (1.03 to 1.18)	0.006	665/104494	1.11 (1.00 to 1.23)	0.04	829/104330	1.09 (0.99 to 1.19)	0.07
Model 1 + total dietary fiber intake	1409/103750	1.11 (1.04 to 1.19)	0.002	665/104494	1.12 (1.01 to 1.23)	0.03	829/104330	1.10 (1.01 to 1.20)	0.03
Model 1 + number of pack-years	1409/103750	1.12 (1.05 to 1.20)	0.0008	665/104494	1.12 (1.02 to 1.24)	0.02	829/104330	1.11 (1.01 to 1.21)	0.02
Model 1 + season of inclusion in the cohort	1409/103750	1.12 (1.05 to 1.20)	0.0008	665/104494	1.12 (1.02 to 1.24)	0.02	829/104330	1.11 (1.01 to 1.21)	0.02
Model 1 + region of residence	1409/103750	1.12 (1.05 to 1.20)	0.0008	665/104494	1.13 (1.02 to 1.24)	0.02	829/104330	1.11 (1.01 to 1.21)	0.02
Model 1 unadjusted for BMI and energy intake	1409/103750	1.13 (1.05 to 1.21)	0.0004	665/104494	1.13 (1.03 to 1.25)	0.01	829/104330	1.11 (1.02 to 1.21)	0.01
Model 1 by multiple imputation[e]	1409/103750[¥]	1.16 (1.08 to 1.24)	<.0001	665/104494[¥]	1.15 (1.04 to 1.27)	0.007	829/104330[¥]	1.15 (1.05 to 1.26)	0.002
Model 1 by complete case analysis[f]	1154/83839	1.13 (1.05 to 1.21)	0.002	557/84436	1.11 (1.00 to 1.24)	0.05	668/84325	1.14 (1.03 to 1.25)	0.01
Model 1 excluding CVD cases diagnosed during the first two years of follow-up	1087/103750	1.14 (1.05 to 1.23)	0.0008	496/104494	1.17 (1.05 to 1.31)	0.006	658/104330	1.10 (1.00 to 1.22)	0.05

CI: confidence interval, HR: Hazard ratio

*HR for an absolute increment of 10 in the percentage of ultra-processed foods in the diet

[a]Model 1 is adjusted for age (timescale), sex, energy intake, number of 24h-dietary records, smoking status, educational level, physical activity, BMI, alcohol intake, and family history of CVD.

[b]Coronary heart diseases include myocardial infarctions, angioplasty and acute coronary syndromes

[c]Cerebrovascular diseases include strokes and transitory ischemic attacks

[d]Obtained by a Principal Component Analysis

[e]Multiple imputation for missing data using the MICE method (10) by fully conditional specification (FCS, 20 imputed datasets) for the outcome (11) ([¥]50 to 70 additional cases by imputed dataset) and for the following covariates: level of education, physical activity level and BMI. Results were combined across imputation based on Rubin's combination rules (12,13) using the SAS PROC MIANALYZE procedure (14).

[f]N=84993

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