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Titre en français : **Transformation des aliments et risque de pathologies chroniques dans la cohorte NutriNet-Santé**

Titre en anglais : **Food processing and risk of non-communicable diseases : findings from the NutriNet-Santé cohort**

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABREVIATIONS

ACS	Acute Coronary Syndrome
AHA	American Heart Association
BMI	Body Mass Index
BMR	Basal Metabolic Rate
CCA	Complete Case Analysis
CépiDC	*Certification électronique des causes de décès*
CI	Confidence Interval
CNIL	*Commission Nationale de l'Informatique et des Libertés*
ECHA	European Chemicals Agency
EFSA	European Food Safety Agency
ENNS	*Etude Nationale Nutrition Santé*
EPIC	European Prospective Investigation into Cancer and Nutrition
FCRN	Food Climate Research Network
FCS	Fully Conditional Specification
ICD	International Chronic Diseases Classification
IDF	International Diabetes Federation
IFIC	International Food Information Council Foundation
IFPRI	International Food Policy Research Institute
IPAQ	International Physical Activity Questionnaire
MICE	Myocardial Infarction
MICE	Multiple Imputation by Chained Equations

NIH	National Institute of Health
PAL	Physical Activity Level
RCS	Restricted Cubic Spline
RCT	Randomized Controlled Trial
SNIIRAM	*Système national d'information inter-régimes de l'assurance maladie*
T2D	Type-2 Diabetes
TIA	Transitory Ischemic Attack
UNC	University of North Carolina
UPF	Ultra-Processed Food

PUBLICATIONS, COMMUNICATIONS AND ACHIEVEMENTS

I. Original scientific articles

A- Articles that are part of this thesis

1. **Srour, B**. ✉, Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Andrianasolo, RM., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M., 2019. Ultra-processed food intake and risk of cardiovascular disease: a prospective cohort study (NutriNet-Santé). **Bmj-British Medical Journal**, BMJ 2019;365:l1451. https://doi.org/10.1136/bmj.l1451 **(IF=23.5, 4/155 of Medicine journals)**

2. **Srour, B**.*✉, Fiolet, T.*, Sellem, L., Kesse-Guyot, E., Alles, B., Mejean, C., Deschasaux, M., Fassier, P., Latino-Martel, P., Beslay, M., Hercberg, S., Lavalette, C., Monteiro, C.A., Julia, C., Touvier, M., 2018**.** Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. **Bmj-British Medical Journal** 360, k322 *(*equally contributed)*. https://doi.org/10.1136/bmj.k322 **(top 1% publications of its academic field) (IF=23.5, 4/155 of Medicine journals)**

3. **Srour, B**. ✉, Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Debras, C., Druesne-Pecollo, N., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M. Ultra-processed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective Cohort *(under review)*

4. **Srour, B.*** ✉, Beslay, M.*, Mejean, C., Alles, B., Fiolet, T., Debras, C., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, CA., Kesse-Guyot, E., Touvier, M.≠, Julia, C.≠ Consumption of ultra-processed foods and the risk of overweight and obesity, and weight trajectories in the French cohort NutriNet-santé *(* and ≠: equal contributions) (in preparation)*

B- Other articles in the scope of ultra-processed foods

1. **Srour, B.** ✉, Touvier, M., Julia, C. Letter: Evidence for the Full Potential of Daily Food Choices to Minimize Premature Mortality- Reply. **JAMA Internal Medicine** 179 (8): 1149–50. https://doi.org/10.1001/jamainternmed.2019.2208 **(IF=19.98, 5/155 of Medicine journals)**

2. Adjibade, M., Julia, C., Allès, B., Touvier, M., Lemogne, C., **Srour, B.**, Hercberg, S., Galan, P., Assmann, K.E., Kesse-Guyot, E., 2019. Prospective association between ultra-processed food consumption and incident depressive symptoms in the French NutriNet-Santé cohort. **BMC Med.** https://doi.org/10.1186/s12916-019-1312-y **(IF=9.08, 10/155 of Medicine journals)**

3. Schnabel, L., Kesse-Guyot, E., Alles, B., Touvier, M., **Srour, B.,** Hercberg, S., Buscail, C., Julia, C., 2019. Association Between Ultraprocessed Food Consumption and Risk of Mortality Among Middle-aged Adults in France. **JAMA internal medicine**. https://doi.org/10.1001/jamainternmed.2018.7289 **(IF=19.98, 5/155 of Medicine journals)**

C- Articles that are not directly part of this thesis

1. Chazelas, E., **Srour, B**. ✉, Desmetz, E., Kesse-Guyot, E., Julia, C., Deschamps, V., Druesne-Pecollo, N., Galan, P., Hercberg, S., Latino-Martel, P., Deschasaux, M., Touvier, M. Sugary drink consumption and cancer risk: results from NutriNet-Santé prospective cohort. **Bmj-British Medical Journal**, BMJ 366, l2408. https://doi.org/10.1136/bmj.l2408 **(IF=23.5, 4/155 of Medicine journals)**

2. **Srour, B.** ✉, Plancoulaine, S., Andreeva, V.A., Fassier, P., Julia, C., Galan, P., Hercberg, S., Deschasaux, M., Latino-Martel, P., Touvier, M., 2018**.** Circadian nutritional behaviours and cancer risk: New insights from the NutriNet-sante prospective cohort study. **International Journal of Cancer** 143, 2369–2379. https://doi.org/10.1002/ijc.31584 **(IF=7.3, 23/223 of Oncology journals)**

3. **Srour, B**.*, Kane-Diallo, A.*, Sellem, L., Deschasaux, M., Latino-Martel, P., Hercberg, S., Galan, P., Fassier, P., Gueraud, F., Pierre, F.H., Kesse-Guyot, E., Alles, B., Touvier, M., 2018. Association between a pro plant-based dietary score and cancer risk in the prospective NutriNet-sante cohort. **International Journal of Cancer** 143, 2168–2176 *(*equally contributed)*. https://doi.org/10.1002/ijc.31593 **(IF=7.3, 23/223 of Oncology journals)**

4. Lavalette, C., Adjibade, M., **Srour, B.** ✉**,** Sellem, L., Fiolet, T., Hercberg, S., Latino-Martel, P., Fassier, P., Deschasaux, M., Kesse-Guyot, E., Touvier, M., 2018. Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Sante Cohort. **Cancer Research** 78, 4427–4435. https://doi.org/10.1158/0008-5472.CAN-18-0155 **(IF=9.1, 17/223 of Oncology journals)**

5. Sellem, L., **Srour, B.** ✉, Gueraud, F., Pierre, F., Kesse-Guyot, E., Fiolet, T., Lavalette, C., Egnell, M., Latino-Martel, P., Fassier, P., Hercberg, S., Galan, P., Deschasaux, M., Touvier, M., 2018. Saturated, mono- and polyunsaturated fatty acid intake and cancer risk: results from the French prospective cohort NutriNet-Sante. **European journal of nutrition.** https://doi.org/10.1007/s00394-018-1682-5 **(IF=4.4, 14/83 of Nutrition journals)**

6. Lécuyer, L., Dalle, C., Lyan, B., Demidem, A., Rossary, A., Vasson, M.-P., Petera, M., Lagree, M., Ferreira, T., Centeno, D., Galan, P., Hercberg, S., Deschasaux, M., Partula, V., **Srour, B.**, Latino-Martel, P., Kesse-Guyot, E., Druesne-Pecollo, N., Durand, S., Pujos-Guillot, E., Touvier, M., 2019. Plasma metabolomic signatures associated with long-term breast cancer risk in the SU.VI.MAX prospective cohort. **Cancer Epidemiol. Biomark. Prev.** Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. https://doi.org/10.1158/1055-9965.EPI-19-0154

7. Deschasaux, M., Huybrechts, I., Murphy, N., Julia, C., Hercberg, S., **Srour, B.**, Kesse-Guyot, E., Latino-Martel, P., Biessy, C., Casagrande, C., Jenab, M., Ward, H., Weiderpass, E., Dahm, C.C., Overvad, K., Kyro, C., Olsen, A., Affret, A., Boutron-Ruault, M.-C., Mahamat-Saleh, Y., Kaaks, R., Kuehn, T., Boeing, H., Schwingshackl, L., Bamia, C., Peppa, E., Trichopoulou, A., Masala, G., Krogh, V., Panico, S., Tumino, R., Sacerdote, C., Buen-de-Mesquita, B., Peeters, P.H., Hjartaker, A., Rylander, C., Skeie, G., Ramon Quiros, J., Jakszyn, P., Salamanca-Fernandez, E., Maria Huerta, J., Ardanaz, E., Amiano, P., Ericson, U., Sonestedt, E., Huseinovic, E., Johansson, I., Khaw, K.-T., Wareham, N., Bradbury, K.E., Perez-Cornago, A., Tsilidis, K.K., Ferrari, P., Riboli, E., Gunter, M.J., Touvier, M., 2018. Nutritional quality of food as represented by the FSAm-NPS nutrient profiling system underlying the Nutri-Score label and cancer risk in Europe: Results from the EPIC prospective cohort study. **Plos Medicine** 15, e1002651. https://doi.org/10.1371/journal.pmed.1002651

8. Deschasaux, M., Souberbielle, J.-C., Partula, V., Lecuyer, L., Gonzalez, R., **Srour, B.,** Guinot, C., Malvy, D., Latino-Martel, P., Druesne-Pecollo, N., Galan, P., Hercberg, S., Kesse-Guyot, E., Fassier, P., Ezzedine, K., Touvier, M., 2016. What Do People Know and Believe about Vitamin D? **Nutrients** 8, 718. https://doi.org/10.3390/nu8110718

9. Diallo, A., Deschasaux, M., Partula, V., Latino-Martel, P., **Srour, B**., Hercberg, S., Galan, P., Fassier, P., Gueraud, F., Pierre, F.H., Touvier, M., 2016. Dietary iron intake and breast cancer risk: modulation by an antioxidant supplementation. **Oncotarget** 7, 78994–79002. https://doi.org/10.18632/oncotarget.12592

10. Fassier, P., **Srour, B.,** Raynard, B., Zelek, L., Cohen, P., Bachmann, P., Touillaud, M., Druesne-Pecollo, N., Bellenchombre, L., Cousson-Gelie, F., Cottet, V., Feliu, F., Mas, S., Deschasaux, M., Galan, P., Hercberg, S., Latino-Martel, P., Touvier, M., 2018. Fasting and weight-loss restrictive diet practices among 2,700 cancer survivors: results from the NutriNet-Sante cohort. **International Journal of Cancer** 143, 2687–2697. https://doi.org/10.1002/ijc.31646

11. Merle, B.M.J., Moreau, G., Ozguler, A., **Srour, B.,** Cougnard-Gregoire, A., Goldberg, M., Zins, M., Delcourt, C., 2018. Unhealthy behaviours and risk of visual impairment: The CONSTANCES population-based cohort. **Scientific Reports** 8, 6569. https://doi.org/10.1038/s41598-018-24822-0

12. Lecuyer, L., Bala, A.V., Deschasaux, M., Bouchemal, N., Triba, M.N., Vasson, M.-P., Rossary, A., Demidem, A., Galan, P., Hercberg, S., Partula, V., Le Moyec, L., **Srour, B.,** Fiolet, T., Latino-Martel, P., Kesse-Guyot, E., Savarin, P., Touvier, M., 2018. NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer. **International Journal of Epidemiology** 47, 484–494. https://doi.org/10.1093/ije/dyx271

13. Fassier, P., Zelek, L., Bachmann, P., Touillaud, M., Druesne-Pecollo, N., Partula, V., Hercberg, S., Galan, P., Cohen, P., Hoarau, H., Latino-Martel, P., **Srour, B.,** Gonzalez, R., Deschasaux, M., Touvier, M., 2017. Sociodemographic and economic factors are

associated with weight gain between before and after cancer diagnosis: results from the prospective population-based NutriNet-Sante cohort. **Oncotarget** 8, 54640–54653. https://doi.org/10.18632/oncotarget.17676

14. Fassier, P., Zelek, L., Partula, V., **Srour, B.**, Bachmann, P., Touillaud, M., Druesne-Pecollo, N., Galan, P., Cohen, P., Hoarau, H., Latino-Martel, P., Menai, M., Oppert, J.-M., Hercberg, S., Deschasaux, M., Touvier, M., 2016. Variations of physical activity and sedentary behavior between before and after cancer diagnosis: Results from the prospective population-based NutriNet-Sante cohort. **Medicine** 95, e4629. https://doi.org/10.1097/MD.0000000000004629

✉ = corresponding author

II. Communications at scientific conferences

A- Invited conferences as presenting author

Evidence-based seminar on raw food in animals of University of Helsinki, Helsinki, September 2019

1. **Srour, B.,** Touvier M. **Ultra-processed foods and risk of chronic diseases.** Evidence-based seminar on raw food in animals, Helsinki, September 2019.
2. **Srour, B.,** Touvier M. **Fatty acids and cancer risk: Findings from NutriNet-Santé and SU.VI.MAX cohorts.** Evidence-based seminar on raw food in animals, Helsinki, September 2019.

Processed foods: how and why we need to identify them, Clermont-Ferrand, September 2019

3. **Srour, B.,** Touvier M. **Food processing in link to human health.** Université d'été de Nutrition du CRNH Auvergne, Clermont-Ferrand, September 2019.

Transdisciplinary Seminar of Galilée Doctoral School (ED146), Paris, May 2019

4. **Srour, B.,** Touvier, M. **NutriNet-Santé: an innovative tool - Big data, and epidemiology.** Transdisciplinary Seminar of Galilée Doctoral School (ED146), Paris, May 2019.

The nutrition of the future, Seminar of the University of Créteil (IUT Vitry-Créteil), Paris, March 2019

5. **Srour, B.,** Julia, C., Kesse-Guyot, E., Allès, B., Deschasaux, M., Latino-Martel, P., Monteiro, CA., Hercberg, S., Galan, P., Méjean, C., Fiolet, T., Schnabel, L., Buscail, C, Touvier, M. **Ultra-processed foods and risk of chronic diseases.** The nutrition of the future, Seminar of the University of Créteil, Paris, March 2019.

Health and Big Data - The joint Seminar on Big Data of CNRS, Polytechnique, PSL, MinesParisTech and TelecomParisTech, Paris, February 2019

6. **Srour, B.,** Hercberg, S., Touvier, M. **NutriNet-Santé: an innovative tool - Big data, and epidemiology.** The joint Seminar on Big Data of CNRS, Polytechnique, PSL, MinesParisTech and TelecomParisTech, Paris, February 2019.

"Benefits of Homemade Food" - Paris Institute of technology for life, food and environmental sciences (AgroParisTech), Paris, January 2019

7. **Srour, B.,** Julia, C., Kesse-Guyot, E., Allès, B., Deschasaux, M., Latino-Martel, P., Monteiro, CA., Hercberg, S., Galan, P., Méjean, C., Fiolet, T., Schnabel, L., Buscail, C., Touvier, M. **Ultra-processed foods and risk of chronic diseases.** "Benefits of Homemade Food" - Paris Institute of technology for life, food and environmental sciences (AgroParisTech), January 2019.

Congress of the French Nutrition Society, Nice 2018 *(published in Nutrition Clinique et Métabolisme)*

8. Dalle, C.*, Lecuyer, L.*, Pétéra M., Centeno, D., Lyan, B., Durand, S., Pujos-Guillot, E., Micheau, P., Morand, C., **Srour B**., Galan, P., Hercberg, S., Partula, V., Deschasaux, M., Latino-Martel, P., Kesse-Guyot, E., Touvier, M.#, Manach, C.#. *(* and #: equal contributions)*. **Metabolomics applied to nutritional epidemiology to identify biomarkers of food intake in the Metabo-Brest Cancer project.** Congress of the French Nutrition Society, 30 November 2018, Nice.

12th International Congress of Nutrition and Dietetics (Nutricion Practica), Madrid, April 2018

9. **Srour, B**.*, Fiolet, T.*, Sellem, L., Kesse-Guyot, E., Alles, B., Mejean, C., Deschasaux, M., Fassier, P., Latino-Martel, P., Beslay, M., Hercberg, S., Lavalette, C., Monteiro, C.A., Julia, C., Touvier, M., 2018. **Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort.** *(*equally contributed).* 12th International Congress of Nutrition and Dietetics (Nutricion Practica), Madrid, April 2018.

Training for French MDs undergoing a diploma in Nutrition, Paris, June 2018

10. **Srour, B**., Julia, C., Touvier, M., 2018**. Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort.** Training for French MDs undergoing a diploma in Nutrition, Paris, June 2018.

B- Oral communications as presenting author

The 12th European Public Health Conference, Marseille, November 2019

1. **Srour, B.***, Beslay, M.*, Mejean, C., Alles, B., Fiolet, T., Debras, C., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, CA., Kesse-Guyot, E., Touvier, M.≠, Julia, C.≠ **Consumption of ultra-processed foods and the risk of overweight and obesity, and weight trajectories in the French cohort NutriNet-santé** *(* and ≠: equal contributions)* Congress of the European Public Health Association, November 2019, Marseille. (**Top 5 abstracts of the congress)**
2. **Srour, B**., Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Andrianasolo, RM., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M., 2019. **Ultra-processed food intake and risk of cardiovascular disease: a prospective cohort study (NutriNet-Santé).** Congress of the European Public Health Association, November 2019, Marseille.
3. **Srour, B**. Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Debras, C., Druesne-Pecollo, N., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M. **Ultra-processed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective Cohort** (oral pitch). Congress of the European Public Health Association, November 2019, Marseille.

Congress of the French Nutritional Society, Nice 2018 *(published in Nutrition Clinique et Métabolisme)*

4. **Srour, B**., Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Andrianasolo, RM., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M., 2019. **Ultra-processed food intake and risk of cardiovascular disease: a prospective cohort study (NutriNet-Santé).** Congress of the French Nutrition Society, 30 November 2018, Nice.

IUNS 21st International Congress of Nutrition (ICN), Buenos Aires, October 2017 *(published in Annals of Nutrition and Metabolism 71)*

5. Lecuyer, L., Victor, B.A., Vasson, M.-P., **Srour, B.**, Galan, P., Hercberg, S., Fassier, P., Savarin, P., Touvier, M., 2017. **NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer.** IUNS 21st International Congress of Nutrition (ICN), Buenos Aires, October 2017.
6. Fassier, P., **Srour, B.**, Zelek, L., Touillaud, M., Bachman, P., Cohen, P., Raynard, B., Lecuyer, L., Latino-Martel, P., Touvier, M., 2017**. Fasting and restrictive diet to lose weight among cancer survivors: profiles, sources of nutritional information, knowledges and opinions: results from the NutriNet-Sante cohort.** IUNS 21st International Congress of Nutrition (ICN), Buenos Aires, October 2017.
7. Fassier, P., Egnell, M., Vasson, M.-P., Galan, P., Lecuyer, **Srour, B.**, L., Latino-Martel, P., Hercberg, S., Deschasaux, M., Touvier, M., 2017. **Quantitative assessment of dietary supplement intake in 77 000 French adults: impact on nutritional inadequacy, excessive intake, and extent.** IUNS 21st International Congress of Nutrition (ICN), Buenos Aires, October 2017.

Congress of the French Nutrition Society, Nantes 2017

8. **Srour, B.**, Plancoulaine, S., Andreeva, V.A., Fassier, P., Julia, C., Galan, P., Hercberg, S., Deschasaux, M., Latino-Martel, P., Touvier, M., 2018. **Circadian nutritional behaviours and cancer risk: New insights from the NutriNet-sante prospective cohort study.** Congress of the French Nutrition Society, 15 December 2017, Nantes.

Fall seminar of the French Network for Nutrition and Cancer Research (Réseau NACRe), Paris, November 2017

9. **Srour, B**.*, Fiolet, T.*, Sellem, L., Kesse-Guyot, E., Alles, B., Mejean, C., Deschasaux, M., Fassier, P., Latino-Martel, P., Beslay, M., Hercberg, S., Lavalette, C., Monteiro, C.A., Julia, C., Touvier, M., 2018. **Consumption of ultra-processed foods and cancer risk: results from NutriNet-Sante prospective cohort.** *(*equally contributed).* Fall seminar of the French Network for Nutrition and Cancer Research (Réseau NACRe), Paris, November 2017

Annual seminar of the French Network for Nutrition and Cancer Research (Réseau NACRe), Paris, March 2017

10. **Srour, B.**, Plancoulaine, S., Andreeva, V.A., Fassier, P., Julia, C., Galan, P., Hercberg, S., Deschasaux, M., Latino-Martel, P., Touvier, M., **Circadian nutritional behaviours and cancer risk: New insights from the NutriNet-sante prospective cohort study.** Annual seminar of the French Network for Nutrition and Cancer Research (Réseau NACRe), Paris, March 2017

C- Poster communications

The 13th European Nutrition Conference (FENS), Dublin, October 2019

1. **Srour, B.***, Beslay, M.*, Mejean, C., Alles, B., Fiolet, T., Debras, C., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, CA., Kesse-Guyot, E., Touvier, M.≠, Julia, C.≠ **Consumption of ultra-processed foods and the risk of overweight and obesity, and weight trajectories in the French cohort NutriNet-santé** *(* and ≠: equal contributions).* **The 13th European Nutrition Conference (FENS), Dublin, October 2019**
2. **Srour, B**. Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Debras, C., Druesne-Pecollo, N., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M. **Ultra-processed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective Cohort. The 13th European Nutrition Conference (FENS), Dublin, October 2019**

Seminar of Galilée Doctoral School (ED146), Villetaneuse, June 2018

3. **Srour, B.**, Plancoulaine, S., Andreeva, V.A., Fassier, P., Julia, C., Galan, P., Hercberg, S., Deschasaux, M., Latino-Martel, P., Touvier, M., **Circadian nutritional behaviours and cancer risk: New insights from the NutriNet-sante prospective cohort study.** Seminar of Galilée Doctoral School (ED146), Villetaneuse, June 2018

Congress of the French Nutrition Society, Nantes, December 2017

4. **Srour, B.,** Lavalette, C., Adjibade, M., Sellem, L., Fiolet, T., Hercberg, S., Latino-Martel, P., Fassier, P., Deschasaux, M., Kesse-Guyot, E., Touvier, M., 2018. **Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Sante Cohort.** Congress of the French Nutrition Society, Nantes 2017
5. **Srour, B.**, Sellem, L., Gueraud, F., Pierre, F., Kesse-Guyot, E., Fiolet, T., Lavalette, C., Egnell, M., Latino-Martel, P., Fassier, P., Hercberg, S., Galan, P., Deschasaux, M., Touvier, M., 2018. **Saturated, mono- and polyunsaturated fatty acid intake and**

cancer risk: results from the French prospective cohort NutriNet-Sante. Congress of the French Nutrition Society, Nantes 2017

6. **Srour, B.,** Fassier P., Hercberg, S., Touvier, M. **Everybody plays with public health - Results of a gameshow dedicated to public health and nutrition on France2 TV-Channel.** Congress of the French Nutrition Society, Nantes 2017

Fall seminar of the French Network for Nutrition and Cancer Research (Réseau NACRe), Paris, November 2017

7. **Srour, B.,** Lavalette, C., Adjibade, M., Sellem, L., Fiolet, T., Hercberg, S., Latino-Martel, P., Fassier, P., Deschasaux, M., Kesse-Guyot, E., Touvier, M., 2018. **Cancer-Specific and General Nutritional Scores and Cancer Risk: Results from the Prospective NutriNet-Sante Cohort.** Fall seminar of the French Network for Nutrition and Cancer Research (Réseau NACRe), Paris, November 2017

IUNS 21st International Congress of Nutrition (ICN), Buenos Aires, October 2017 *(published in Annals of Nutrition and Metabolism 71)*

8. **Srour, B.,** Plancoulaine, S., Andreeva, V., Fassier, P., Lecuyer, L., Galan, P., Deschasaux, M., Latino-Martel, P., Touvier, M., 2017. **Nutrition and cancer in primary prevention: new insights from circadian regulation.** Annals of Nutrition and Metabolism 71, 919–919. IUNS 21st International Congress of Nutrition (ICN), Buenos Aires, October 2017

III. Articles targeting the general public

1. **Srour, B.,** Touvier, M., Hercberg, S. Les aliments ultra-transformés sont aussi associés à un risque accru de maladies cardiovasculaires. **The Conversation, July 4th 2019.** [http://theconversation.com/les-aliments-ultra-transformes-sont-aussi-associes-a-un-risque-accru-de-maladies-cardiovasculaires-119038]
2. **Srour, B.,** Touvier, M., Hercberg, S. La consommation d'aliments ultra-transformés est-elle liée à un risque de cancer ? **The Conversation, March 14th 2018.** [https://theconversation.com/les-aliments-ultra-transformes-sont-aussi-associes-a-un-risque-accru-de-maladies-cardiovasculaires-119038]

IV. Other activities conducted during the PhD

- More than **50 media interviews** (BBC, Le Figaro, Rai Uno, France Inter, Radio Canada, Medscape, Reuters…)
- **Expert** for the French National Institute of Cancer (INCa), 2018-2019: **"Nutrition and cancer tertiary prevention"**
- **Co-supervision** of pre-graduate internships of 5 students (Eloi Chazelas, Elisa Desmetz, Juliane Ladvie, Thibault Fiolet, Laury Sellem, Céline Lavalette)
- **Reviewer** for international peer-reviewed journals (e.g. BMJ, Int J Cancer, Eur J Epidemiol)
- **Guest-Editor** for a special issue on Food Processing and Health, Nutrients
- **Chairman** for the annual seminar of the French Network of Nutrition and Cancer 2019
- **Visiting Lecturer** in the Masters Programme of Nutrition and Public Health - University of Paris 13 (Dyslipidemia, Methods in Epidemiology, Food processing and Health)
- **Teaching assistant**, Biology **|** University of Paris 13 – Faculty of Medicine and Biology (50 hours)

'Have confidence in America's food industry, it deserves it'

-Fredrick John Stare (1910-2002), American nutritionist-

STATE OF KNOWLEDGE

I. The burden of non-communicable diseases

Non-communicable diseases (NCD) are the number one cause of mortality worldwide. According to the Global Burden of Diseases (GBD), 73.4% of the 57 million deaths which occurred in 2017, were linked to NCDs (1). Among these NCDs in 2017, cardiovascular diseases (CVD) were responsible of 17.8 million deaths (accounting for 43% of all NCD deaths and 32% of all global deaths); cancers for 9.6 million deaths (accounting for 23% of all NCD deaths and 17% of all global deaths); and diabetes for 1.4 million deaths (3.3% of all NCD deaths and 2.4% of all global deaths) (1). In 2016, the risk from dying from a NCD was 18% (higher in men than in women), decreased from 22% in 2000 (2).

Economically, the output loss linked to NCDs over the period 2011-2030 could be estimated at nearly US$ 47 trillion, according to a report by the World Economic Forum and the Harvard School of Public Health (3).

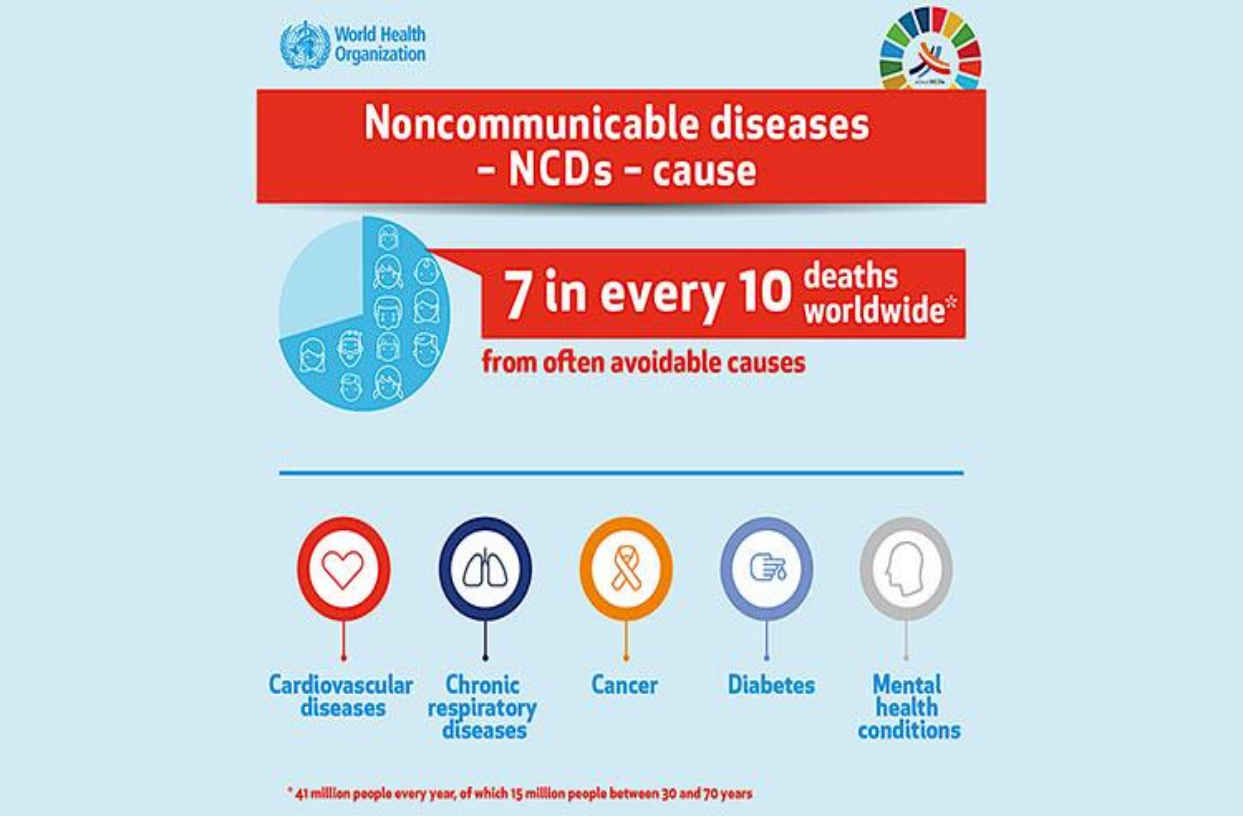

Figure 1 - Impact of NCDs on mortality according to the World Health Organization (WHO) (2)

II. Modifiable risk factors

NCDs have a long latency period along with a complex etiology, and they are multifactorial (i.e. they have multiple risk factors). According to the Centers for Disease Control (CDC), a risk factor is "an aspect of personal behavior or lifestyle, an environmental exposure, or a hereditary characteristic that is associated with an increase in the occurrence of a particular disease, injury, or other health condition" (4). Risk factors can be non-modifiable (e.g. age, sex, race, family history and genetics) or modifiable. A modifiable risk factor is a behavioral or lifestyle risk factor, than can be reduced or controlled by intervention (a personal or a public intervention), thereby reducing or increasing the probability or the severity of a disease (4).

Low-cost solutions exist for governments and other stakeholders to reduce the common modifiable risk factors (5). Monitoring progress and trends of NCDs and their risk is important for guiding policy and priorities. In order to address the growing burden of NCDs, the WHO selected in 2011 a package of 16 "best buy" interventions that are affordable and feasible (figure 2) (6). Implementing all 16 "best buys" in all countries between 2018 and 2025 would avoid 9.6 million premature deaths, thus moving countries appreciably towards the NCD mortality reduction targets (6). On the other hand, and on the level of the individual, the WHO has prioritized physical inactivity, tobacco use, alcohol consumption and unhealthy diets, based on which actions and interventions can be planned in order to reduce the human and economic burden of NCDs (6).

Beyond mortality, NCDs also contribute in reducing the number of disability free years. Interventions targeting modifiable risk factors can therefore have promising impacts on disability-adjusted life years (DALYs)[*] (7). For instance, 67.95% of DALYs linked to stroke are attributable to behavioral risk factors, 67.42% for lung cancer, 81.81% for ischemic heart disease, 44.75% for diabetes, and 51.39% for colorectal cancer (figure 3) (8).

Among modifiable risk factors, unbalanced diet is responsible of 1 in 5 deaths globally according to the latest report of the GBD in 195 countries (7).

[*] The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death.
DALYs are calculated by taking the sum of these two components: DALY = Years of Life Lost (YLL) + Years Lived with Disability (YLD)

Risk factor / disease	Interventions
Tobacco use	• Tax increases • Smoke-free indoor workplaces and public places • Health information and warnings • Bans on tobacco advertising, promotion and sponsorship
Harmful alcohol use	• Tax increases • Restricted access to retailed alcohol • Bans on alcohol advertising
Unhealthy diet and physical inactivity	• Reduced salt intake in food • Replacement of trans fat with polyunsaturated fat • Public awareness through mass media on diet and physical activity
Cardiovascular disease (CVD) and diabetes	• Counselling and multi-drug therapy for people with a high risk of developing heart attacks and strokes (including those with established CVD) • Treatment of heart attacks with aspirin
Cancer	• Hepatitis B immunization to prevent liver cancer (already scaled up) • Screening and treatment of pre-cancerous lesions to prevent cervical cancer

Figure 2 - NCD's "best-buys" according to the WHO (6)

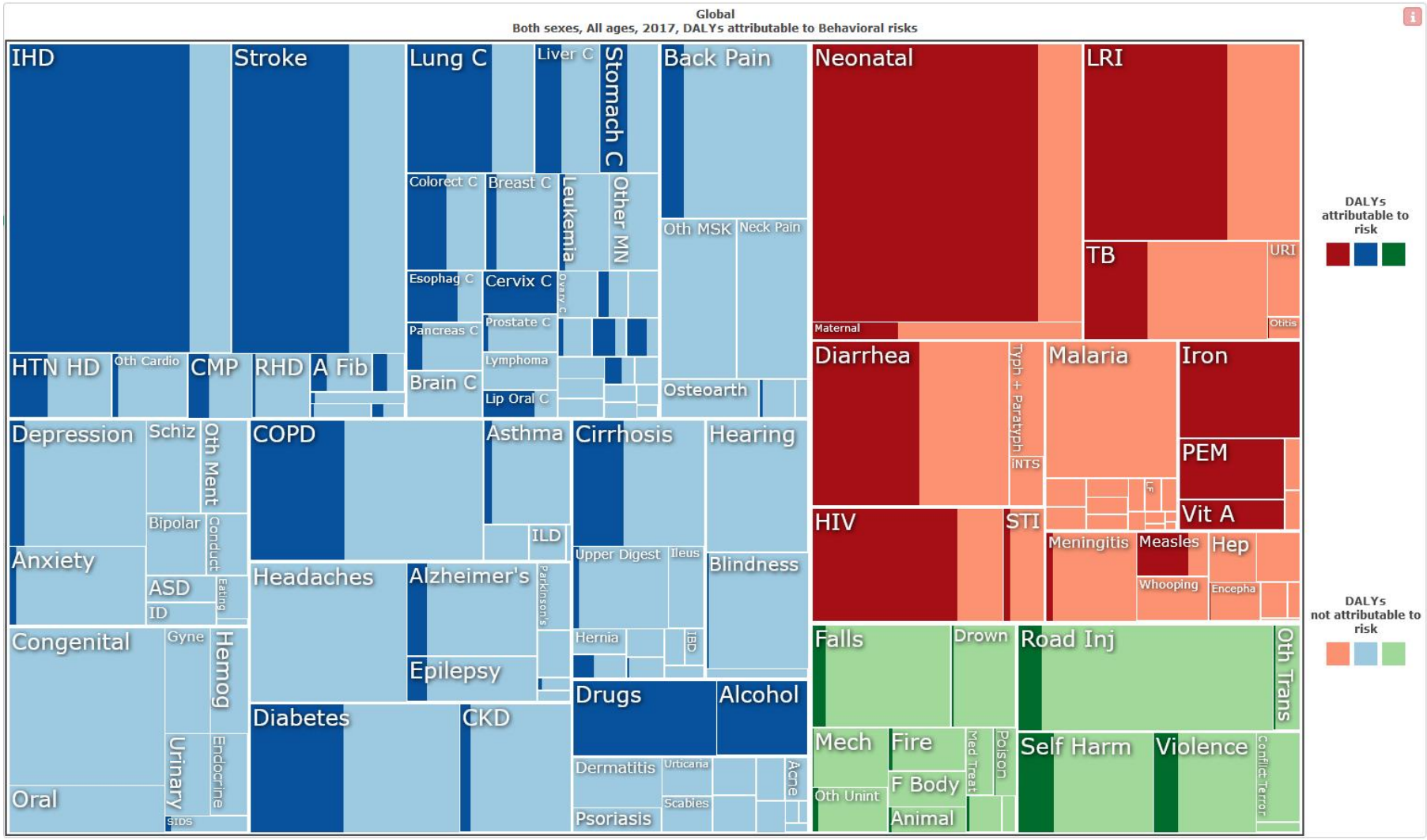

Figure 3 - DALYs attributable to behavioral risks according to the Global Burden of Diseases health data (8)

III. Preventing non-communicable diseases using diet: what is already known?

On 1st of April 2016, the General Assembly of the United Nations (UN) proclaimed the UN Decade of Action on Nutrition, 2016-2025. The UN Decade of Action on Nutrition is an unprecedented opportunity for achieving nutrition impact at a large scale, with a collective vision of a healthier and more sustainable future (9). As stated above, among the modifiable risk factors of NCDs, diet plays an important role in the prevention of NCDs (6). In 2017, 11 million deaths and 255 million DALYs were attributable to dietary risk factors (7). High intake of sodium, low intake of whole grains, and low intake of fruits were the leading dietary risk factors for deaths and DALYs globally and in many countries (7).

According to the Food and Agriculture Organization (FAO), nearly one in three people has at least one form of malnutrition and this will reach one in two by 2025 (10), based on current trends (11). Malnutrition includes not only nutritional disorders caused by deficient intake of energy or nutrients, such as stunting, wasting, and micronutrient deficiencies, but it also includes excessive and imbalanced intake, leading to overweight, obesity, and diet related NCDs. Both categories of malnutrition are caused by unhealthy, poor quality diets, and they can be linked (12). In Western countries the latter category is more frequent than the first one. Researchers in chronic disease epidemiology, prevention, and treatment have produced in the last three decades an enormous body of evidence on healthy eating from studies that discuss multiple aspects of the diet, starting from molecular biology of nutrients to population-level interventions, including the study of trending behaviors (13). Translating the results of these studies into practical advice and recommendations on healthy eating to prevent and control chronic diseases remains a big challenge.

Besides, even though a lot has been done to control the rising trends of chronic disease incidence, several aspects of the diet, especially those not directly linked to nutrients intake, remain to be fully explained. High levels of scientific concordance have been established for macro and micro-nutrients (e.g. saturated fats, sodium, sugar, dietary fiber), as well as food groups (e.g. fruit and vegetables, red meat, whole grain). This has resulted in nutritional public health recommendations, such as the implementation of front-of-pack nutritional labels, as it is the case for the French Nutri-Score system (14). On the other hand, scientific knowledge remains limited for other aspects of the diet. For instance, there is a lack in epidemiological

literature as regards to chronic simultaneous exposure to a large range of food additives on human health, as well as to the health effect of several food processing technologies and the potentially generated compounds. Further experimental, mechanistic and epidemiological studies and public independent research are needed in order to elucidate these aspects and reach a scientific consensus sufficiently enough to lead to public health policies and regulations.

There are different levels of evidence on NCDs prevention by diet between cancer, cardiovascular disease and diabetes. The summary of the findings of the studies is generally performed though collective expertise by disease-specific national or international organizations specialized in appraising and combining the findings of the studies (epidemiological and experimental results), aiming to establish different levels of evidence. When such structures do not exist for a specific disease, meta-analyses and systematic reviews remain the main key to summarize the existing literature and translate it into practical advice, and later on to recommendations by the national and the international health authorities.

A- Cancer

With regards to diet in cancer prevention, since 1997, the World Cancer Research Fund (WCRF) along with American Institute for Cancer Research (AICR) continuously lists and analyses the literature through the "Continuous Update Project" (CUP) to provide comprehensive analyses of the research on diet, nutrition, physical activity and cancer (15). The CUP is an ongoing review and captures new research from around the world as it is published. The findings from the CUP help to identify priority areas for future cancer prevention and survival research, and to provide recommendations targeting both the general population and cancer survivors. To sum up, a package of eight nutrition and physical activity recommendations reflecting healthy lifestyle choices, "together, can make an enormous impact on people's likelihood of developing cancer and other non-communicable diseases over their lifetimes" as stated by Martin Wiseman, Medical and Scientific Adviser at the WCRF (15):

- Having a health weight
- Being physically active
- Eating whole grains, vegetable, fruit and beans
- Limiting “fast foods” (and other processed foods high in fats, starches or sodium)
- Limiting red and processed meat
- Limiting the consumption of sugar sweetened drinks (because of their effect on obesity)
- Limiting alcohol consumption
- Not relying on supplements and aiming to meet nutritional needs through diet alone.

The levels of evidence range from convincing to limited in both ways of risk change. Main foods and food groups responsible for convincing to probable evidence in increasing cancer risk are red *(probable evidence)* and processed meat (colon rectum cancer) *(convincing evidence)*, foods preserved by salting (gastric cancer) *(probable evidence)*, mate (esophagus cancer) *(probable evidence)*, Cantonese style salted fish (nasopharyngeal cancer) *(probable evidence)*, and alcoholic drinks (head and neck, liver, colorectal, postmenopausal breast and esophagus *(convincing evidence)*, as well as stomach and premenopausal breast cancers *(probable evidence)*) (16,17). As for probable evidence in decreasing cancer risk, the main foods and food groups are whole grains (colon rectum cancer), foods containing dietary fiber (colon rectum cancer), dairy products (colon rectum cancer), and coffee (liver and endometrium cancers).

Glycemic load is associated with an increased risk of endometrium cancer with a probable weight of evidence. In addition, adult height is associated with increased risks of colorectal, breast and ovary cancers with a convincing level of evidence and endometrium, prostate, kidney and pancreatic cancers with a probable level of evidence. Adult body fatness is associated with increased risks of several cancer locations with convincing to probable levels of evidence. As for physical activity, it is associated with a decreased risk of colorectal cancer *(convincing evidence)* and endometrium and breast cancer *(probable evidence).*

In France, the National Cancer Institute (INCa) published in 2015 a report based on an expertise work group, emphasizing these findings (18). Unfavorable dietary habits led to 16,930 new cancer cases in 2015, representing 5.4% of all new cancer cases; low intake of fruit and dietary fiber being the largest contributor to this burden (19).

On the international level, the International Agency for Research on Cancer (IARC) is also an important contributor to scientific expertise in establishing evidence levels for deleterious nutritional and non-nutritional factors.

Details about convincing, probable and limited evidence for nutrition and physical activity are provided in the full WCRF matrix, in figure 4 (15).

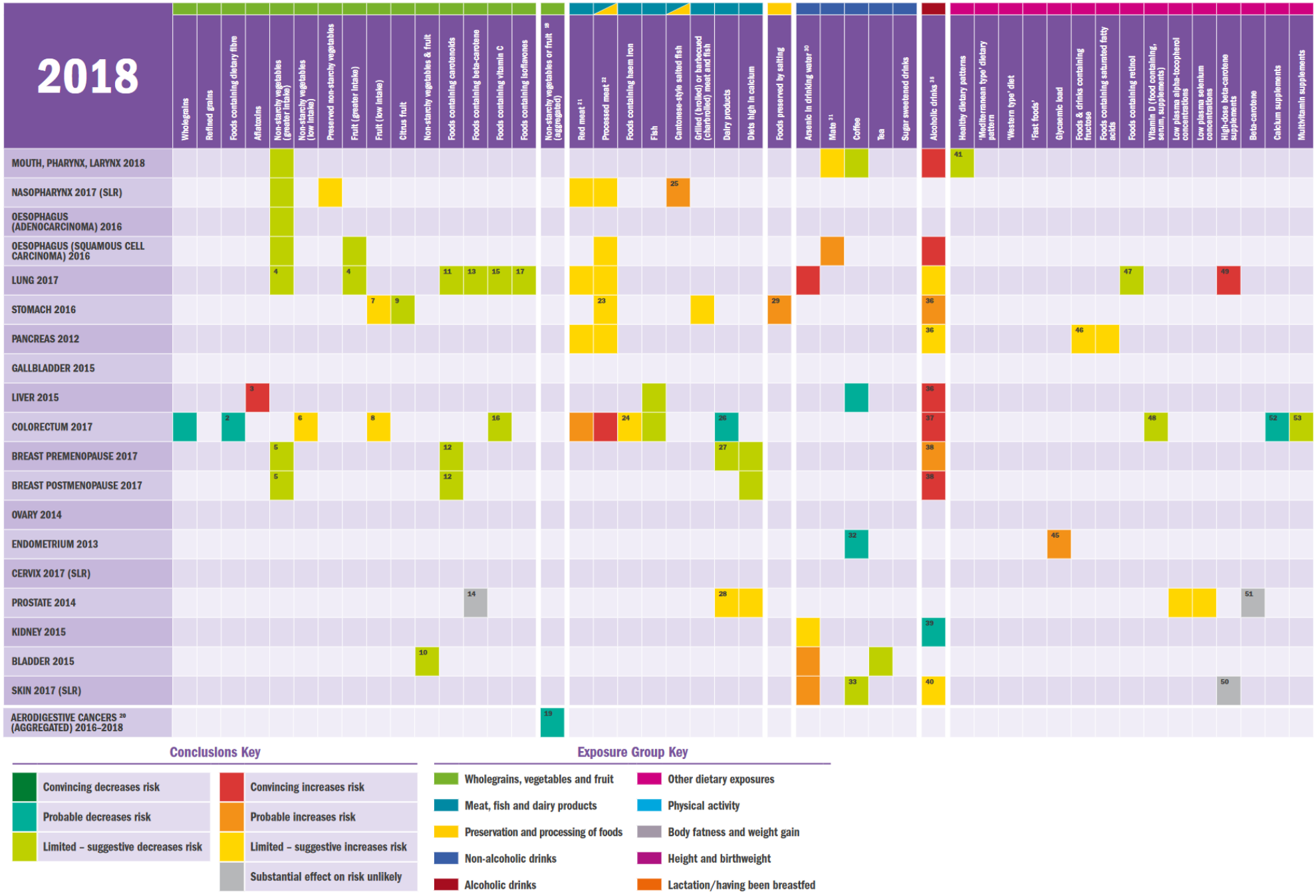

Figure 4 - Summary of the 2018 conclusions of the WCRF/AICR CUP on nutritional factors in cancer prevention, available at wcrf.org/matrix

B- Cardiovascular diseases

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for the delivery of quality cardiovascular care. The ACC and AHA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts. They classify nutritional factors based on class of recommendations, and level of evidence as stated in the figure below (20).

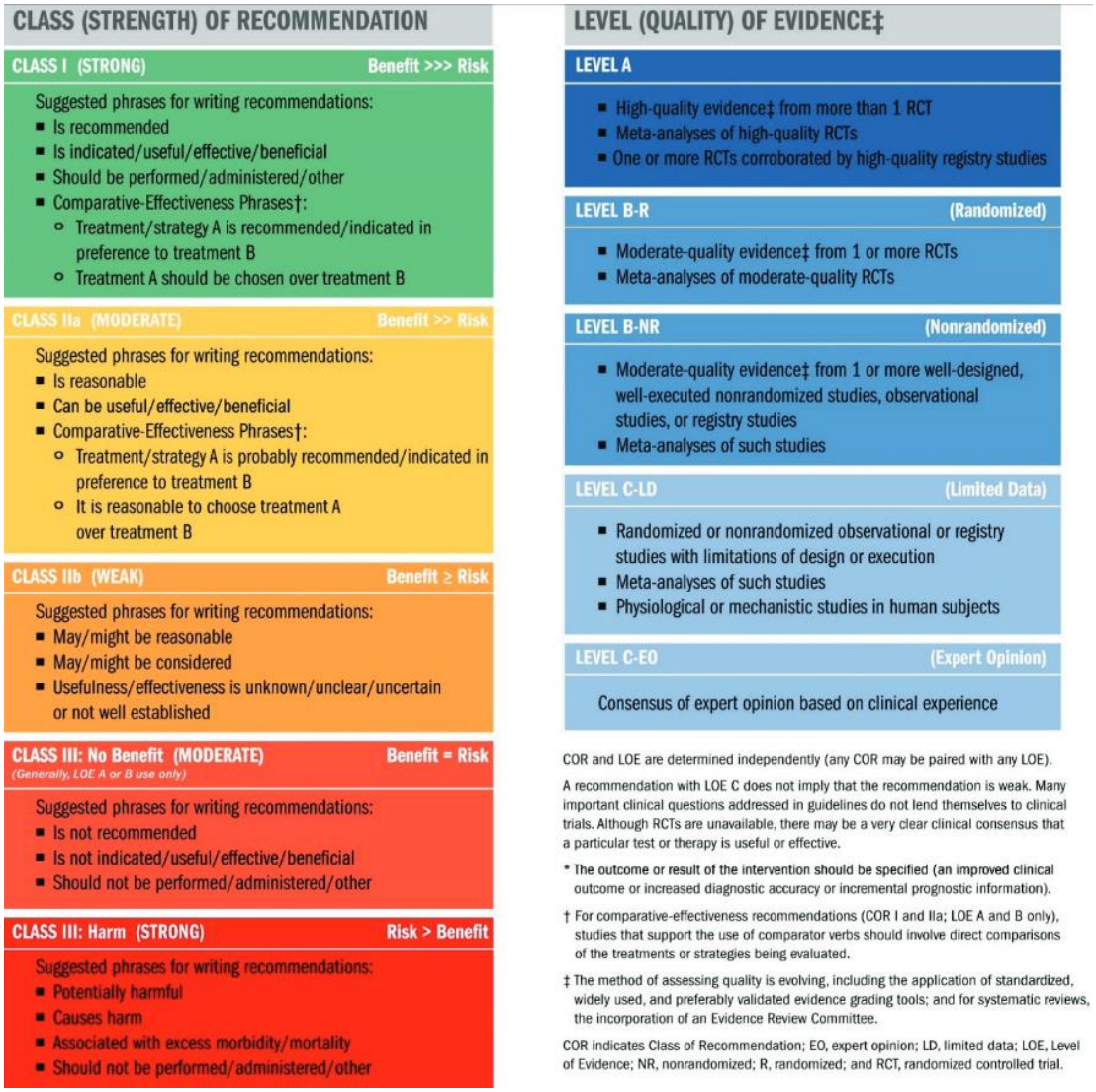

Figure 5 - Classes of recommendation and quality of evidence classification of the AHA/ACC (20)

As stated by the latest report of the AHA, the cardiovascular nutrition literature is limited by the paucity of large-scale prospective randomized controlled trials (RCTs) with atherosclerotic cardiovascular diseases outcomes (20). Although RCTs focused on hard endpoints are limited, multiple observational studies have focused on the association of CVD mortality with dietary patterns—specifically, sugar, low-calorie sweeteners, high-carbohydrate diets, low-carbohydrate diets, refined grains, trans fat, saturated fat, sodium, red meat, and processed red meat(e.g., bacon, salami, ham, hot dogs, sausage).

Strong benefits were found for diets emphasizing intakes of vegetable, fruits, legumes, nuts, whole grains and fish, while strong harms were established for intakes of trans-fats, through moderate levels of evidence. Moderate benefits with moderate levels of evidence were also established for unsaturated fats and diets containing low sodium intakes and lower consumptions of sugar, processed meat and sugary drinks (figure 6).

COR	LOE	Recommendations
I	B-R	1. A diet emphasizing intake of vegetables, fruits, legumes, nuts, whole grains, and fish is recommended to decrease ASCVD risk factors (S3.1-1–S3.1-11).
IIa	B-NR	2. Replacement of saturated fat with dietary monounsaturated and polyunsaturated fats can be beneficial to reduce ASCVD risk (S3.1-12, S3.1-13).
IIa	B-NR	3. A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease ASCVD risk (S3.1-9, S3.1-14–S3.1-16).
IIa	B-NR	4. As a part of a healthy diet, it is reasonable to minimize the intake of processed meats, refined carbohydrates, and sweetened beverages to reduce ASCVD risk (S3.1-17–S3.1-24).
III: Harm	B-NR	5. As a part of a healthy diet, the intake of *trans* fats should be avoided to reduce ASCVD risk (S3.1-12, S3.1-17, S3.1-25–S3.1-27).

Figure 6 – Nutritional recommendations for CVD prevention as stated by the AHA/ACC report in 2019 (20)

There is uncertainty to insufficient levels of evidence for dairy products, poultry, eggs, butter, unprocessed meat, 100% fruit juices and non-caloric sweeteners, as described by a comprehensive review published in 2016 by Prof. D. Mozaffarian from Tufts University in Boston (21).

C- Type 2 diabetes (T2D)

Concerning T2D risk, the International Diabetes Federation (IDF) produces a series of consensus statements related to the care, management, and prevention of diabetes (22). It also provides recommendations for a healthy diet for the general population (22). Other reviews and position papers have also summarized the findings of existing studies about the link between several food groups and T2D risk, and categorized the findings based on their certainty levels (23,24). To sum up, strong consensus in T2D prevention exists (in addition to weight management and energy balance) for recommending the consumptions of vegetable, fruit, nuts, legumes whole grains, yoghurt, and an overall Mediterranean diet, and avoiding red and processed meat, refined grains and sugars (especially sugary drinks), as well as foods rich in sodium and trans fat (indirect association via their cardiovascular impact). Uncertainty in guidelines concerns the consumption of overall dairy products (strong evidence only for yoghurt and low-fat dairy products), fish, and oils (except for evidence for potential benefits of olive oils within a Mediterranean diet).

D- Overweight and obesity

The WCRF includes in its cancer risk matrix a dedicated line for dietary risk factors associated with weight gain (15), since weight gain is itself a metabolic risk factor for several cancers (esophagus, pancreas, liver, colon rectum, postmenopausal breast, endometrium, kidney, gallbladder, mouth, pharynx and larynx, stomach, ovary and advanced prostate cancers) (15). Foods containing dietary fiber as well as a Mediterranean diet are associated with a probable decrease of weight gain risk, as well as whole grains, with limited to suggested evidence. Sugar sweetened drinks are found to increase weight gain risk with a strong level of evidence, as well as ‘fast-foods’ and a Western-type diet. Refined grains are suggested to increase weight gain risk (figure 7).

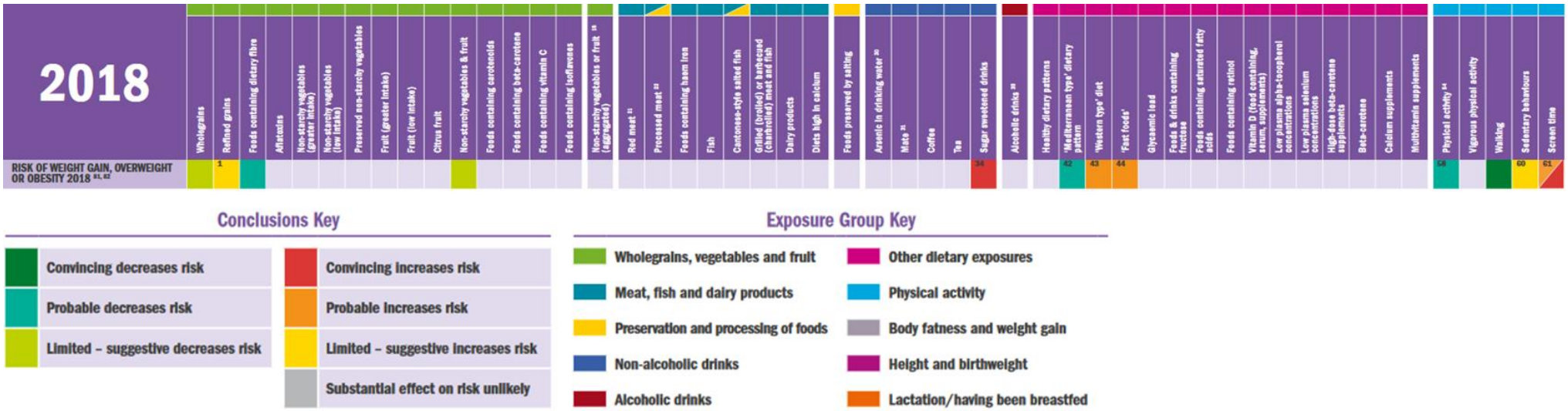

Figure 7 - Summary of the 2018 conclusions of the WCRF/AICR CUP on nutritional factors in weight gain prevention, available at wcrf.org/matrix

Overall, so far, the link between diet and health mostly relied on classical food group classifications which did not account for the mode of production or for the degree and type of food processing. In consequence, until very recently, official nutritional recommendations worldwide did not take into account those dimensions of the diet. However, the foods and drinks consumed contain other bioactive compounds than nutrients that may interact with human health and NCD risk, such as food additives, pesticide residues, compounds created during the transformation/process, or even materials coming from packaging. This PhD program aimed at starting exploring the "process dimension" in relationship with chronic disease risk.

IV. Food processing

The FAO defines food processing as *"Food processing and preparation activities cover three main fields: (1) the preservation of foods by (a) modern methods such as refrigeration, canning and irradiation, and (b) traditional methods such as drying, salting, smoking and fermentation; (2) the development of protein - rich foods; (3) food additives."*(25)

Since the beginning of mankind, humans have created and used many tools to process their food. These tools were developed slowly and gradually over hundreds of thousands of years, starting from gatherer-hunter to pastoral-migrant to peasant-agricultural ways of life. Humans began to build towns and cities and needed to provide their residences with food, usually supplied from the surrounding countryside. These foods were almost all fresh or preserved with simple manual tools as sun drying, salting, pickling or smoking. More sophisticated processes were used for wheat bread, which was prepared using mills to process flour which was afterwards mixed by water, as the Romans did and later on the Arabs and the Europeans (26). In the early 1800s, during the Industrial Revolution especially in Europe and the US, the first industrial processes were invented, using steam and coal machines, and helped the large-scale production of culinary ingredients, such as fats, oils, sugars, flour and salt (27). Nearly one century later, other mechanical process techniques to ensure food preservation were developed such as roller milling, pressure rendering and extrusion, as well as chemical techniques such as hydrogenation and hydroxylation with the use of flavors and of preservatives and additives such as bleaches and dyes. These techniques led to a large manufacturing of mass-produced cheap breads and buns, breakfast cereals, candies, cookies, soft drinks, meat, fish, cheese and dairy products, which were sold in very affordable prices (28,29). Starting the 1950s, rates of CVD started to rapidly increase in the US, and this was attributed to increased consumptions of saturated fat and to decreased physical activity levels (30,31). In the meantime, the United Nations started recommending the reduction of consumptions of saturated fats, sugar and salt and to increase dietary fiber consumption (32). With the beginning of the economic globalization in the 1980s, a drastic shift between artisanal food and processed mass-produced food began to rise in middle to low-income countries, and these highly processed products started to intensively take place on supermarket shelves internationally (33).

A- Existing definitions and state of knowledge

Starting the 2000s, research teams and international health organizations started developing classifications in order to categorize foods based on their level of processing. A systematic literature review performed by Moubarac and colleagues from the University of Sao Paulo (34) identified and evaluated 5 food classification systems based on food processing, all are briefly described in the following paragraphs. In the framework of this thesis, epidemiological studies were based on the NOVA classification, presented in detail below.

1. The NOVA classification

NOVA is a food classification developed by the team of Pr. Carlos Monteiro, from the Centre of Epidemiological Studies in Health of Nutrition at the School of Public Health, University of Sao Paulo (35–38). It categorizes foods according to the extent and purpose of food processing, into four clearly distinct groups, with an extensive scientific literature published to specify which foods belong in each group. NOVA includes in food processing physical, biological, and chemical processes that occur between the separation of foods from nature and before their consumption of their use in the preparation of meals or dishes. The authors define industrial food processing as 'the methods and techniques used by food manufacturers and associated industries to make unprocessed or "raw" foods less perishable, easier to prepare, consume or digest, or more palatable and enjoyable, or else to transform them into products'. The up-to-date NOVA version used in the framework of this thesis (39), classifies foods into four groups:

a- Unprocessed and minimally processed foods

Unprocessed foods can be of plant or animal origin, available shortly after collection (e.g. leaves, roots, fruits, nuts, seeds, meat, eggs, milk…). Minimally processed foods are obtained from unprocessed foods by simple processes without introducing any substance, but might involve the removal on non-edible parts, cleaning/washing, peeling, grinding, grating, squeezing, flaking, skinning, boning, portioning, drying, skimming, freezing, pasteurization, sealing, wrapping, gas packing and even fermenting when the process does not generate alcohol.

Examples include: vegetables and fruits (fresh, frozen, vacuum-packed, dried), cereals and rice, beans (fresh, dried or frozen), fresh or dried unsalted nuts, 100% fruit juices, fresh, dried

and frozen meats/poultry/fish/seafood, milk (fresh, pasteurized, skimmed, low-fat, fermented), eggs, teas and infusions, coffee and mineral water.

b- Processed culinary ingredients

This category includes food products extracted and purified usually by industrial manufacturers, or directly obtained from nature such as salt. The ingredients are obtained by pressing, milling or pulverizing. The products of this category have the specificity of not being consumed alone, but in addition to other foods.

Examples include: plant oils and animal fats, sugars and simple syrups, unmodified starches and flours, uncooked 'raw' pastas (prepared with flour, water and salt).

c- Ready-to-consume processed foods

The foods are prepared by adding processed culinary ingredients (oil, sugar, salt…) to unprocessed or minimally processed foods in order to make them more palatable, and more durable. The foods in this category are directly derived from whole foods, and can be of home-made, artisanal or industrial origin, but contain only culinary ingredients of frequent domestic use. Processes include canning, bottling, seasoning, cooking, smoking, curing and preservation by salting, salt-pickling, or in simple syrup.

Examples include: canned or bottled vegetables and legumes (preserved with added salt, including or not oils, herbs, or spices), peeled, sliced or crushed fruits preserved with added sugar or syrup, fish preserved with oils, salts, water and spices, salted nuts, un-reconstituted processed meat, fish and poultry preserved with salt, smoked fish.

d- Ready-to-eat ultra-processed foods (36)

These foods are made mostly or entirely from substances derived from foods. They might contain or not whole foods. These products are convenient, highly or ultra-palatable, and often mass-produced. They tend to imitate the appearance and flavors of foods and some of them are no longer really foods, they are better thought of as formulations. They often contain ingredients not available in retail stores, in particular food additives.

Ingredients that are characteristic of ultra-processed foods can be divided into food substances of no or rare culinary use and classes of additives whose function is to make the final product palatable or often hyper-palatable ('cosmetic additives'). Food substances of no or rare culinary

use, and used only in the manufacture of ultra-processed foods, are usually obtained through industrial 'cracking' techniques, and several include varieties of sugars (fructose, high-fructose corn syrup, 'fruit juice concentrates', invert sugar, maltodextrin, dextrose, lactose), modified oils (hydrogenated or interesterified oils) and protein sources (hydrolyzed proteins, soya protein isolate, gluten, casein, whey protein and 'mechanically separated meat'). Cosmetic additives, also used only in the manufacture of ultra-processed foods, are flavors, flavor enhancers, colors, emulsifiers, emulsifying salts, sweeteners, thickeners, and anti-foaming, bulking, carbonating, foaming, gelling and glazing agents. These classes of additives disguise undesirable sensory properties created by ingredients, processes or packaging used in the manufacture of ultra-processed foods, or else give the final product sensory properties especially attractive to see, taste, smell and/or touch (figure 8).

Ultra-processed foods are often packaged in attractive plastic packaging materials, inside which they can be kept for relatively long periods until their expiry dates. They are mostly of industrial origins, but can as well be obtained by artisanal processes (e.g. artisanal sausages with added nitrites). Processes include hydrolysis, hydrogenation, extruding, molding, reshaping, pre-processing by frying, high temperature heating.

Examples include: Poultry and fish nuggets and sticks and other reconstituted meat products transformed with addition of preservatives other than salt (e.g. nitrites); instant noodles and dehydrated soups; sodas; chocolate, chewing gums and candies (confectionery); margarines; instant desserts; most breakfast 'cereals', 'energy' bars; 'energy' drinks; flavoured milk drinks; sweet desserts made from fruit with added sugars, artificial flavours and texturizing agents; cooked seasoned vegetables with ready-made sauces or vegetable patties (meat substitutes) including food additives; health' and 'slimming' products such as powdered or 'fortified' meal and dish substitutes.

The NOVA classification is workable and internationally transposable (34). It has been applied in several countries to food expenditure data and dietary surveys, such as Brazil (40), Chile (41), Mexico (42), Canada (43), the US (44), Taiwan (45), New Zealand (46), Belgium (47), the UK (48), Spain (49), and France (50).

Figure 8 - Unprocessed and processed foods *versus* ultra-processed foods, adapted by Pr. Carlos Monteiro

2. Other classifications

2.1.The IARC classification

In 2009, the IARC proposed a methodology based on data from the European Prospective Investigation into Cancer and Nutrition (EPIC) (51). Foods were categorized into three main groups: non-processed foods, modestly/moderately processed foods, and highly-processed foods (table 1).

Table 1 - Food processing classification of IARC-EPIC (51), adapted by Moubarac *et al.* (34)

Food groups and definition	Examples
1 Non-processed	
Foods consumed raw without any further processing, preparation, except washing, cutting, squeezing	Raw fruits; non-processed nuts; fresh raw vegetables; fresh grated vegetables; raw crustaceans/ mollusks; fresh juices; fresh and not enriched farmer's milk; whole fresh cream; raw meat; raw egg white; honey.
2 Modestly or moderately processed	
2.1 Industrial and commercial foods involving relatively modest processing and consumed with no further cooking	2.1 Dried or semi-dried fruits; nuts and seeds; raw, vacuum packed or controlled atmosphere foods (e.g. salads); frozen or vacuum-packed raw meat; extra virgin olive oil; fruits, vegetables canned in water, brine, own juice; green and chamomile tea.
2.2 Foods processed at home and prepared/cooked from raw foods or moderately processed foods	2.2 Fresh vacuum-packed or frozen cooked potato (including homemade French fries); fresh fruit, compote, boiled; cooked fruit; fresh or frozen cooked vegetables; dried boiled legumes, boiled grain; whole-meal boiled rice; fresh or vacuum-packed cooked meat, fish, offal; whole cooked egg.
3 Processed	
Foods industrially prepared involving high degree of processing such as drying, flaking, hydrogenation, heat treatment, use of industrial ingredients and industrial deep frying. It also includes foods from bakeries and catering outlets requiring no or minimal domestic preparation apart from heating and cooking. This category is subdivided into processed staple/basic foods and highly processed foods, with examples given.	3.1 Processed staple/basic Bread; pasta; rice; milk; butter; vegetable oils. 3.2 Highly processed Cakes; biscuits; breakfast cereals; crisp bread; confectionery; processed meat; fish; yoghurt; cheese; cream.

This classification has initiated the exploratory investigation of food consumption based on the degree of food processing in a large cohort with consumption data from 10 European countries (51). However, it was criticized for being partially coherent regarding the definitions of the degree of processing. For example, while drying technology is supposed to lead corresponding foods into the 'highly processed' groups according to the definition, dried fruits were classified into the 'modestly processed' group.

2.2.The IFIC classification

The International Food Information Council Foundation, along with the American Society of Nutrition have devised a classification for food processing mainly based on the complexity of the used food processes as well as the physical, chemical, and sensory changes in food products caused by processing (52). The categories are: minimally processed, foods processed for preservation, mixtures of combined ingredients, ready-to-eat processed foods, and prepared food/means (table 2).

Table 2 - The US food processing classification (52), adapted by Moubarac *et al.* (34)

Food groups and definition	Examples
1 Minimally processed	
Foods that require little processing or production, which retain most of their inherent properties.	Washed and packaged fruits and vegetables; bagged salads; roasted and ground nuts, coffee beans; homemade soups.
2 Foods processed for preservation	
Foods processed to help preserve and enhance nutrients and freshness of foods at their peak.	Canned tuna, beans and tomatoes; frozen fruits and vegetables; pureed and jarred baby foods; soups made from other canned vegetables or broth.
3 Mixtures of combined ingredients	
Foods containing sweeteners, spices, oils, colors, flavors, and preservatives used for promotion of safety, taste, visual appeal. Group further divided into 'packaged mixes and jarred sauces' and 'mixtures probably home prepared' (no details or examples given of foods in these sub-categories).	Some packaged foods, such as instant potato mix, rice, cake mix, jarred tomato sauce, spice mixes, dressings and sauces, and gelatin.
4 Ready-to-eat processed	
Foods needing minimal or no preparation. Group subdivided into 'packaged ready-to-eat foods' and 'mixtures possibly store prepared' (no details or examples given of foods fitting in these sub-categories).	Breakfast cereal; flavored oatmeal; crackers; jams and jellies; nut butters; ice cream; yogurt; garlic bread; granola bars; cookies; fruit chews; rotisserie chicken; luncheon meats; honey-baked ham; cheese spreads; fruit drinks; carbonated beverages.
5 Prepared foods/meals	
Foods packaged for freshness and ease of preparation	Prepared deli foods and frozen meals; entrées; pot pies and pizzas.

This classification was criticized for being partially specific when categorizing into foods processed for preservation, and prepared foods/meals, partially clear especially the group 'mixtures' (bread and garlic bread are in two different categories). In addition, this classification has no mention of unprocessed foods (i.e. grains, legumes, milk).

2.3.The Mexican classification

This classification was developed in 2007 by researchers from the National Institute of Public Health in Mexico (53), and its rationale was distinguishing between industrialized and local food and products, and between modern and traditional foods and products, as well as a temporality criterion. It is based on three categories: 'industrialized modern foods', 'industrialized traditional foods' (products part of the Mexican diet since before the 20th century) and 'non-industrialized foods' (table 3). Although very interesting in introducing the

anthropological and temporal dimension of food processing, the limitations of this classification that were pointed out by the scientific community were its lack of specificity regarding the defined methods of industrial and artisanal-domestic processing and its lack of generalizability to other countries.

Table 3 - The Mexican food processing classification (53), adapted by Moubarac *et al.* (34)

Food groups and definition	Examples
1 Modern industrialized	
Foods that have been incorporated into the Mexican diet. They can be found as a single product or mixed with other ingredients, impossible to separate.	Powdered milk, non-fat milk, 1 % milk; breakfast cereals; whole wheat bread; salty wheat bread; sausages; packaged sweet breads; oil and modified oils; granulated and liquid sugar; sweetened drinks; instant coffee; baby formulas; compotes; supplements.
2 Industrialized traditional	
Foods that have been part of the traditional Mexican food culture according to customs and traditions since before the 20th century and that nowadays are being produced at a large scale in an industrial way.	Corn flour for tortillas or *atoles*; whole cow milk.
3 Non-industrialized	
3.1 Modern preparations outside the home	3.1 Modern preparations outside the home
Preparations, ingredients not typical of Mexican food.	Burgers; sandwiches; pizza; milkshakes.
3.2 Traditional preparations outside the home	3.2 Traditional preparations outside the home
Preparations with ingredients often impossible to separate. Prepared locally or at home, and that have been part of the traditional food culture of Mexico.	Beans or stews with beans; *tacos; atoles; tamales*; fresh water; artisanal sweetened drinks; *gordassolas o rellenas*; broths; salsas; fish; meat stews; fried fish; vegetable or legume pies; *pozole; chilaquiles*; soups; salads; *carnitas*.
3.3 Locally made traditional foods	3.3 Locally made traditional foods
Typical Mexican cuisine. Home-made or artisanal on a small and very small scale.	Corn tortillas; salty and sweet bread (*bolillo*); animal fats such as pig skin or lard; home-made sugar and drinks.
3.4 Not processed	3.4 Not processed
Raw foods not processed except by collection, selection, cleaning.	Fruits; vegetables; legumes; cereals; tubers; red and white meats; fish; eggs.

2.4.The IFPRI classification

This classification, developed by a researcher from the International Food Policy Research Institute (54) identifies three categories: ‘unprocessed foods’, ‘primary of partially processed foods’ and ‘highly processed foods’. One limit that has been underlined for this classification was that it might lack specificity regarding ‘highly processed foods’, as this category might include home-made culinary recipes as well industrial ‘convenience-foods’ (table 4).

Table 4 - The Guatemalan food processing classification (54), adapted by Moubarac *et al.* (34)

Food groups and definition	Examples
1 Unprocessed	
Not defined	Staple foods like corn and other grains; roots and tubers; beans; vegetables; fruits; meat; fish; eggs; dairy including fresh, dried milk, cream.
2 Primary or partially processed	
Not defined	Corn products, including tortillas; dairy products like evaporated milk, cheese; yogurt; animal fats including lard and butter.
3 Highly processed	
Foods that have undergone secondary processing into readily edible form, likely to contain high levels of added sugars, fats or salt.	Pastries; cookies; crackers; sausage and prepared meats; ice cream; frozen desserts; breakfast cereals; confectionery (sweets, chocolate); fat spreads and shortening; pasta products; soft drinks; prepared meals like dried soup; formula and complementary foods.

2.5.The University of North Carolina (UNC) classification

This classification described in 2015 by Poti and colleagues (55) is based on the 4-category NOVA classification but modified to adapt category definitions and example foods for the complexity of the US food supply and enhanced detail of dietary recall or purchase data. The final classification includes 7 categories. The ultra-processed category has been split into two groups based on whether the food product is normally consumed alone (stand-alone (category VII)) or as an ingredient, especially for dressings and sauces (details and examples are provided in table 5 as adapted by Bleiwess-Sande and colleagues (56)). According to the latter article (56), and to a systematic review by Crino and colleagues (57), the agreement levels between the NOVA and the UNC classifications ranged between 80 and 81%.

Table 5 - The UNC (by Poti and colleagues) food processing classification (55), adapted by Bleiwess-Sande *et al.* (56)

	Category I	Category II	Category III	Category IV	Category V	Category VI	Category VII
UNC	Unprocessed & minimally processed: Single-ingredient foods with no or very slight modifications that do not change inherent properties of the food as found in its natural form.	Processed basic ingredients: single isolated food components obtained by extraction or purification using physical or chemical processes that change inherent properties of the food.	Processed for basic preservation or precooking: single minimally processed foods modified by physical or chemical processes for the purpose of preservation or precooking but remaining as single foods.	Moderately processed for flavor: single minimally or moderately processed foods with addition of flavor additives for the purpose of enhancing flavor	Moderately processed grain products: grain products made from whole-grain flour with water, salt, and/or yeast.	Highly processed ingredients: multi-ingredient industrially formulated mixtures processed to the extent that they are no longer recognizable as their original plant/animal source.	Highly processed stand-alone: multi-ingredient industrially formulated mixtures processed to the extent that they are no longer recognizable as their original plant/animal source.
	Examples: Plain milk; fresh, frozen or dried plain fruit or vegetables; eggs, unseasoned meat; whole grain flour and pasta; brown rice; honey, herbs and spices.	Unsweetened fruit juice not from concentrate; whole grain pasta; oil, unsalted butter, sugar, salt.	Unsweetened fruit juice from concentrate; unsweetened/unflavored canned fruit, vegetables, legumes; plain peanut butter, refined grain pasta, white rice; plain yogurt.	Sweetened fruit juice, flavored milk; frozen French fries; salted peanut butter; smoked or cure meats; cheese, flavored yogurt, salted butter.	Whole grain breads, tortillas or crackers with no added sugar or fat.	Tomato sauce, salsa, mayonnaise, salad dressing, ketchup.	Soda, fruit drinks; formed lunchmeats; breads made with refined flours; pastries; ice-cream, processed cheese; candy.

2.6.The SIGA classification

This classification has been developed in 2017, mainly for commercial purposes. It is based on the NOVA classification, but includes as well, and on the same level, the nutritional aspects of food products. It distinguishes ultra-processed foods based on both their nutritional value (sugar, salt, and fat contents) and their food processing degree, considering the number of food additives as a marker of this ultra-processing (figure 9). This approach is quite confusing as it combines different aspects of the diet, for which the levels of evidence and scientific knowledge are not equivalent, and establishes recommendations targeting the consumers without having any scientific validation. Scientific literature using this classification is inexistent to our knowledge, and the detailed classification algorithm is kept confidential, with a possibility of commercial use by food choice mobile applications, food industrials and distributors. It is therefore impossible to conduct studies in the framework of cohorts or food surveys using this classification.

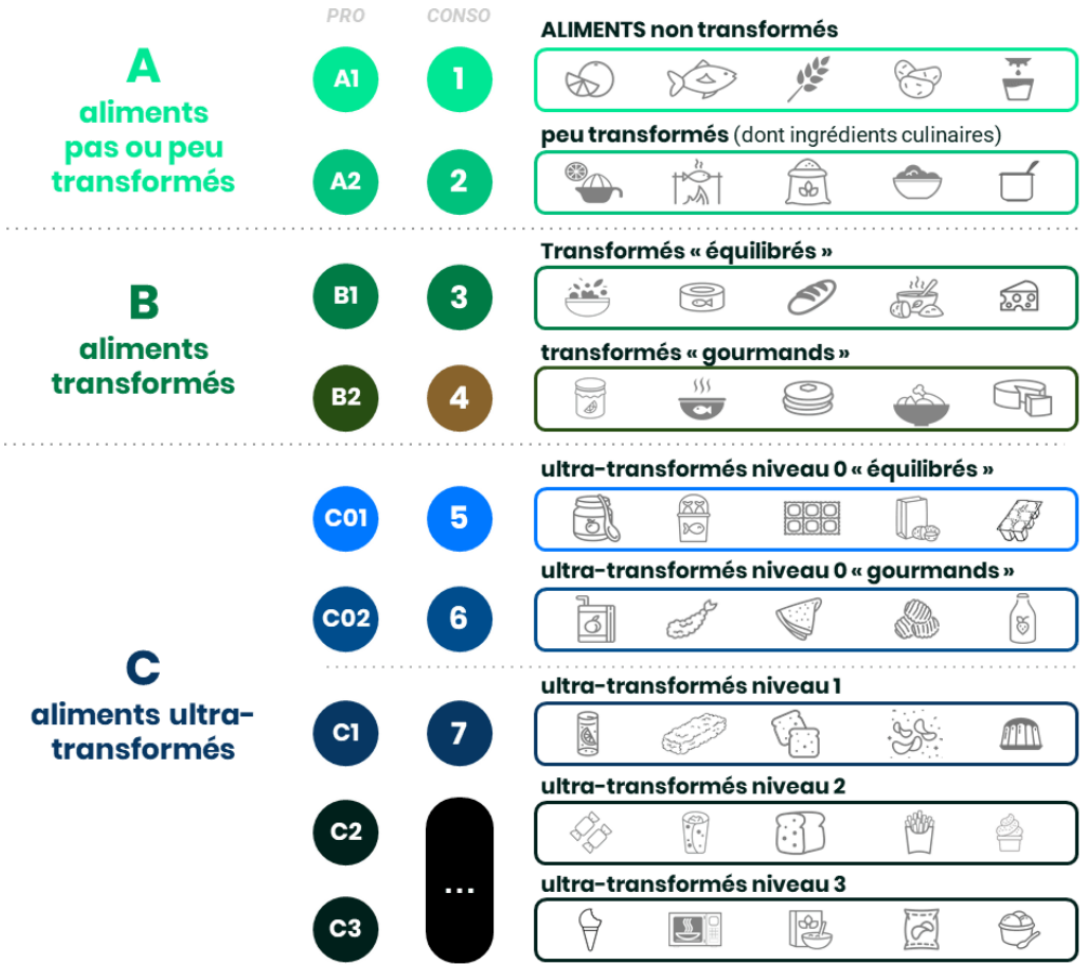

Figure 9- The Siga classification, available on siga.care (Siga ©)

These classifications are somehow similar to the NOVA classification. However, they have been rarely used in application to large-scale dietary consumption data (51), and they are often less detailed and might contain inconsistencies between the definition and the application to specific food items. In addition, some of them might not be generalizable to other countries, such as the Mexican classification (53).

Most importantly, the reliability of these classifications depends on the level of detail available in dietary consumption data. When used in the framework of food frequency questionnaires (FFQ) or in dietary records or recalls with limited food items selection, these classifications might lead to uncertainty and high discrepancies between assigned raters. The aspects are discussed further in the discussion section.

In case of detailed food composition databases, the risks of misclassification and subjective inter-rater disagreement are probably lower. The NutriNet-Santé food composition database is based on more than 3,500 generic food items, with a possible sub-selection of commercial brands. In the framework of this thesis, we have decided to use the NOVA classification applied to NutriNet-Santé's food composition database, to investigate the associations between highly processed foods and human health, through an epidemiological exploratory approach.

V. Consumption of ultra-processed foods in Western countries

In the last two decades, ultra-processed food products represented between 16 and 58% of total daily energy intake in the US, Canada, Taiwan, Europe, and Latin American countries, according to surveys assessing food intakes (40–45,47,58,59) (figure 10). These contributions have drastically increased compared with the last century (45,60–65). For instance, in Sweden, the household spending on ultra-processed food has increased by 142% between 1960 and 2010 (66). This is partially due to a very high availability of these products on supermarket shelves. In New Zealand, a study estimated that approximately 83% of food products found in supermarkets were ultra-processed (46).

In France, a recent study (unpublished data) based on the *Etude Nationale Nutrition Santé* national representative survey (ENNS) coordinated by the French Public Health Agency (67),

in collaboration with researchers from the University of Sao-Paulo, evaluated the contribution of ultra-processed foods to daily energy intake in France to 33%.

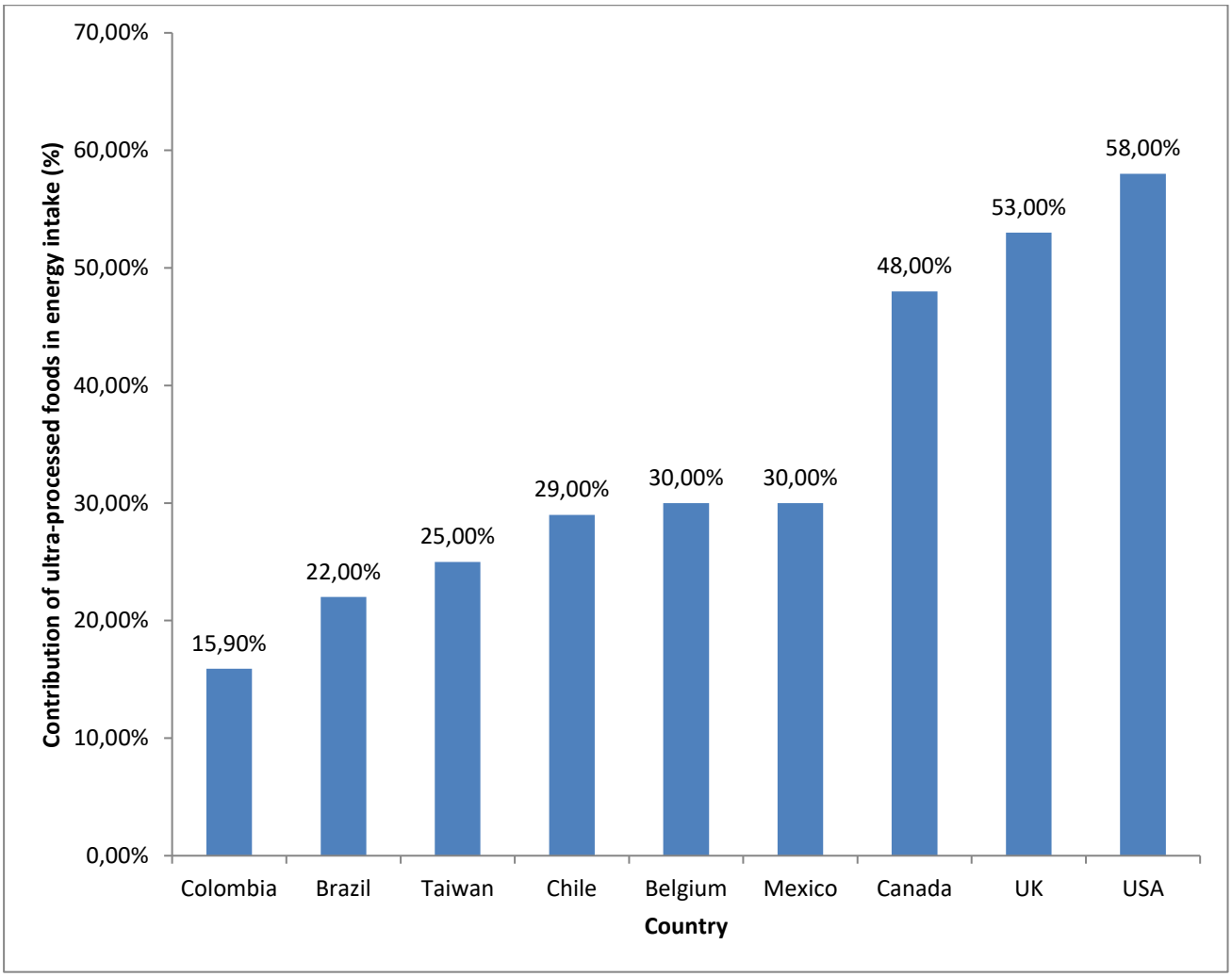

Figure 10 - Contributions of ultra-processed foods to energy intakes in several countries (41–45,47,58,59,68), based on dietary intake nationally representative surveys

VI. Possible interactions with human health

Several characteristics of ultra-processed food could influence disease etiology. All these hypotheses of mechanisms are developed in the discussion, but briefly:

These products are convenient to eat and require no or a short time of preparation. Most of them are very practical to consume during busy schedules, or in the absence of kitchen utensils and culinary ingredients. They usually have a relatively low microbiological risk, due to sterilization and chemical and thermal processing, which provides them a relatively longer shelf-life than unprocessed or processed foods; even though recent studies have revealed that thermal processing of food might contribute to a strong reduction of gut microbial diversity and might differentially drive microbial alterations (69). On the other hands, these foods might contain antioxidants and polyphenols and other components, having beneficial health impacts. For instance, bixin (e160b) has shown reduction of postprandial inflammatory and oxidative stress responses to high-calorie meals in a human randomized-controlled trial (70). Furthermore, ascorbic acid (e300) might contribute as a food additive to total ascorbic acid intake, as suggested by the European Food Safety Agency (EFSA) combined exposure assessment (71). Also, some food additives such as extracts of rosemary (e392) could also be of interest as many of their components are phenolic acids. Sodium alginate (e401) has been suggested to improve liver steatosis, insulin resistance, chronic inflammation, and oxidative stress, preventing the development of liver tumorigenesis among obese and diabetic mice (72). Finally, some industrial processes (used for instance in tomato sauces preparation) might be beneficial as they may lead to enhanced bioaccessibility of antioxidants (73).

Conversely, ultra-processed foods often have a lower nutritional quality in average, with higher content of total fat, saturated fat, added sugar, energy density and salt, along with a lower fiber and vitamin density (40,41,43,44,46,51,55,59,68,74), many of these nutritional features being directly related to cardiometabolic health (21,24) and cancer (15). They were also suggested to have an impact on satiety control and glycemic responses (75). Moreover, food processing may affect nutrient availability in the small intestine by altering the properties of the plant/animal food cells (76). Beyond strictly nutritional aspects, several compounds of ultra-processed foods that are neoformed during process may also play a role in cardiovascular and metabolic health, as well as carcinogenesis. For instance, contaminants such as acrylamide, heterocyclic amines, polycyclic aromatic hydrocarbons, and acrolein are present in heat-treated processed food

products (77) and might have carcinogenic properties (78), increase CVD risk (79,80) and insulin resistance (81,82). Furthermore, the packaging of ultra-processed foods may contain some materials in contact with food, such as bisphenol A, which might increase the risk of CVD (83), cancer (84), T2D (85) and obesity (86). Last, ultra-processed foods often contain food additives. While most of them are probably safe, adverse carcinogenic, cardiometabolic and diabetogenic effects have been suggested for some of them, such as nitrites (87–90), titanium dioxide (91,92), glutamates (93), emulsifiers (94), sulfites (95), carrageenan (96) and certain sweeteners (97–99) in studies performed on animal models or (in rare cases) in human populations.

Therefore, the associations between the consumption of ultra-processed foods and chronic disease risk need to be explored, especially in the context of the actual increasing trends in the consumption of these food products and their suspected health interactions.

VII. Ultra-processed foods and risk of chronic diseases: insights from nutritional epidemiology

Nutritional epidemiology deals with dietary-related (nutritional and non-nutritional) exposures and their roles in the occurrence of diseases and impaired health conditions (100). The assessment of these exposures is made possible using several collection tools validated against blood and urinary biomarkers, such as food frequency questionnaires or 24h dietary records, allowing the computation of estimates of dietary intakes of foods groups, macro and micronutrients, and other compounds of the diet. The link between these exposures and health end points is the core activity of nutritional epidemiology, especially in the framework of observational studies (100). Very recently, using these tools, researchers in nutritional epidemiology started exploring the associations between the consumption of processed foods and the risk of chronic diseases. These investigations face many challenges: large scale cohorts are needed with relatively long follow-ups, a large series of lifestyle, medical and socio-economic factors, biological and clinical data, as well as dietary assessment, which should be detailed enough to allow computing information about the consumption of foods in different levels of processing. During the last decade, the development of food processing classifications has allowed researchers to estimate the consumption of foods depending on their processing level, and in case of prospective cohorts, to investigate the links between the consumption of

processed foods and the risk chronic diseases and mortality. The scientific community is currently very active on this topic and the literature evolved rapidly since the beginning of this thesis.

So far and except for the NutriNet-Santé results presented in this thesis, some observational studies were recently published on the relationship between ultra-processed food categorized according to the NOVA classification and disease risk:

Cross-sectional and ecological studies linked the intake of ultra-processed foods to overweight, obesity (64–66,101,102) and metabolic syndrome (103), as well as higher odds of gastrointestinal disorders (104).

In prospective cohort studies, ultra-processed food consumption was associated with higher risks of dyslipidemia (48) and waist circumference change (105) in children, frailty in older adults (106), higher incidences of overweight and obesity (107), hypertension (108), depressive symptoms (109,110) and mortality (111–113). These observational studies constitute a first solid body of evidence in the exploration of the heath end points linked to the consumption of ultra-processed foods. The other classifications of foods according to their degree of processing were never used in prospective etiological studies to our knowledge.

However, no prospective study had previously investigated the link between ultra-processed food intake and cancer, cardiovascular disease and type 2 diabetes risks.

A first RCT on ultra-processed foods was published this year by Hall and colleagues (114). It included subjects admitted to the National Institute of Health Clinical Center and allocated them either to an ultra-processed or unprocessed diet for 2 weeks, immediately followed by the alternate diet for 2 weeks. Results showed that the ultra-processed diet led to an increased energy intake (508 ± 106 kcal/d during the ultra-processed diet), which was highly correlated with weight gain (0.8 ± 0.3 kg; P= .01) *vs* a weight loss of 1.1 ± 0.3 kg during the unprocessed diet, which might increase the risk of metabolic morbidity.

OBJECTIVES

In a large population of adults from the French prospective NutriNet-Santé cohort, this PhD thesis aimed to investigate the associations between the consumption of ultra-processed foods, defined using the NOVA classification and:

- The risk of cancer (overall and by specific site)
- The risk of cardiovascular diseases (coronary heart diseases and cerebrovascular diseases)
- The risk of type 2 diabetes
- The risk of overweight and obesity, and weight trajectories

For each of these analyses, a secondary objective was to investigate whether the associations were only driven by the overall poorer nutritional quality of ultra-processed foods.

MATERIAL AND METHODS

I. The NutriNet-Santé cohort

The NutriNet-Santé study (115) was the first web-based prospective cohort worldwide on such a large scale (>165 000 participants so far). Its main objectives are to study the relationships between diet (nutrients, foods, nutritional profiles, nutritional status, physical activity, alcohol, dietary behaviors, non-nutritional dietary exposures) and health (in particular various health events such as the incidence of cardiovascular diseases, cancers, diabetes, obesity, mortality, dermatological/rheumatologic diseases...) as well as the determinants of food consumption and nutritional status (e.g. social, economic, and cultural determinants, dietary perceptions and preferences, etc.). It was launched in May 2009 in France. Recruitment of participants from the general population through extensive media campaigns is still ongoing. Only two inclusion criteria apply: participants should be over the age of 18 and have Internet access. All the questionnaires are completed online via a dedicated and secured website (www.etude-nutrinet-sante.fr) using an online platform linked to the participant's email address, and are available via a computer, a smartphone or a tablet. Participants ("Nutrinautes") can change their email address, phone number, or postal address at any time on the NutriNet-Santé website. Newsletters and alerts about new questionnaires are sent by email. In case of an "undelivered email" problem, participants are contacted by telephone and then by regular mail. A website for researchers and healthcare professionals is also available, where all questionnaires are listed, as well as the detailed study design and protocol (https://info.etude-nutrinet-sante.fr/). Among included participants, approximately 77% are women, with an average age of 41.9 ± 14.7 years. The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines and was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm n°0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL n°908450/n°909216). The study is registered at clinicaltrials.gov as NCT03335644. Electronic informed consent is obtained from each participant.

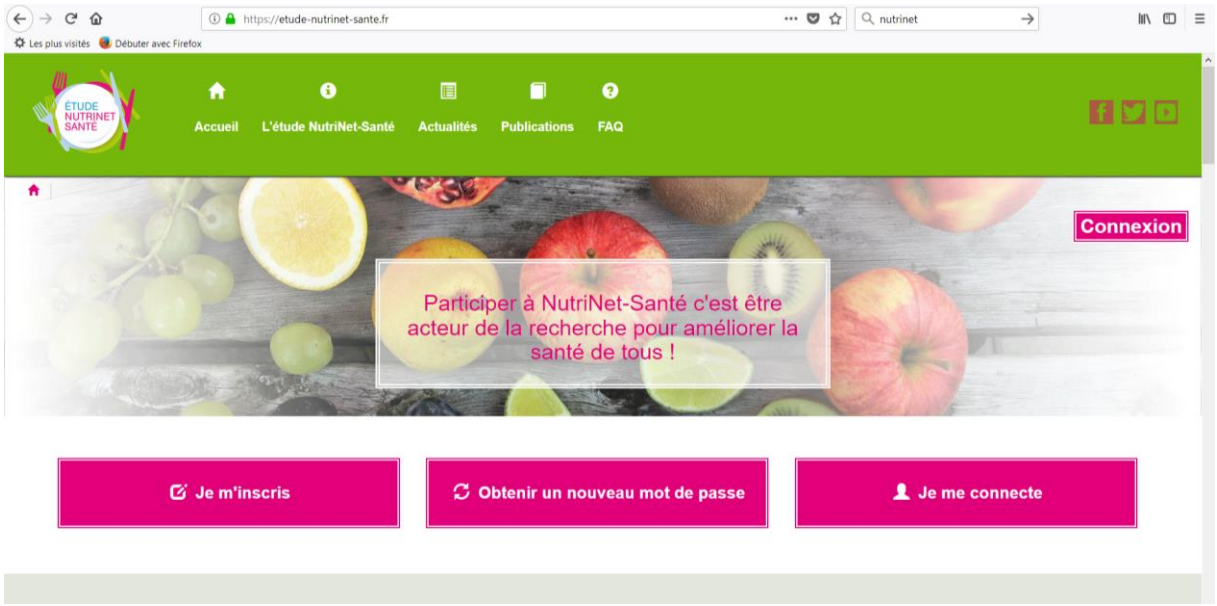

Figure 11 - Homepage of the NutriNet-Santé website (https://etude-nutrinet-sante.fr/), 2009-2019

II. Data collection

A- Sociodemographic, anthropometric and lifestyle data

At baseline, participants completed a set of five questionnaires related to socio-demographic and lifestyle characteristics (called "baseline kit") (e.g. sex, date of birth, occupation, educational level, smoking status, number of children, marital status, alcohol consumption, etc.) (116), anthropometry (117,118) (e.g. height, weight, perceived silhouette scale, waist circumference, practice of restrictive diets), dietary intakes (see below), health status (e.g. personal and family history of diseases, medication, as well as a feminine health questionnaire containing information about pregnancy, menstruation, contraception, and menopausal status) and physical activity (validated 7-day International Physical Activity Questionnaire [IPAQ]) (119) (high, moderate or low as computed based on MET-hours from different levels of physical activities and sedentary behaviors). Anthropometric data were validated against traditional collection tools (paper-based versions) (117) and measured values (118).

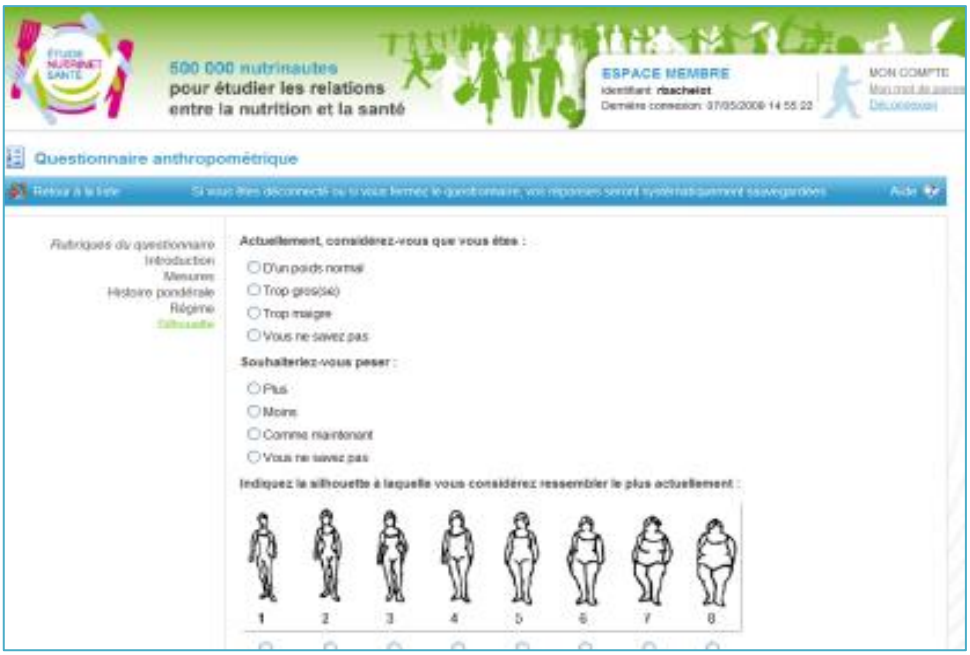

Figure 12 - Screen capture of the anthropometric questionnaire, NutriNet-Santé, 2009-2019

B- Biological data

Participants in the NutriNet-Santé study were invited, on a voluntary basis, for a visit in one of the local centers specifically set up for biological sampling and clinical examination, including bio-impedance measurements, in each region (83 hospital centers). These biological and clinical data were collected for 19 772 participants of the cohort. During the visit, blood samples were collected after at least a 6h-fast period and centralized and analyzed at a single laboratory (IRSA, Tours, France). Total serum cholesterol (cholesterol oxidase C8000, Abbott), HDL-cholesterol (High Density Protein – cholesterol) (direct accelerator C8000, Abbott), serum triglycerides (glycerol kinase C8000, Abbott) and fasting blood glucose were measured (hexokinase on C8000 automat, Abbott, Suresnes, France).

C- Dietary data

Participants were invited to complete a series of three non-consecutive validated web-based 24h-dietary records at baseline and every 6 months (to vary the season of completion), randomly assigned over a 2-week period (two weekdays and one weekend day) (120–122). The NutriNet-Santé web-based self-administered 24h-dietary records have been tested and validated against an interview by a trained dietitian (120), and against blood and urinary biomarkers

(121,122). Participants used the dedicated web interface to declare all foods and beverages consumed during a 24h-period, from midnight until midnight, for each of the three main meals (breakfast, lunch, dinner) and any other eating occasion. Portion sizes were estimated using previously validated photographs or usual containers (123).

Figure 13 - Portion size estimation using validated photographies within the dietary questionnaire, NutriNet-Santé, 2009-2019

Mean daily alcohol, micro- and macro-nutrient and energy intake were calculated using the NutriNet-Santé food composition database, which contains more than 3,500 different items (124). Amounts consumed from composite dishes were estimated using French recipes validated by nutrition professionals. Sodium intake was assessed via a specific module included in the 24 hour records, taking into account native sodium in foods, salt added during the cooking, and salt added on the plate. It has been validated against sodium urinary excretion biomarkers (121).

In order to avoid modification of dietary behaviors, no individual data or advice is transmitted to the participants (only general information on scientific results from the study).

Mean dietary intakes from all the 24h-dietary records available during the first two years of each participant's follow-up (up to 15 records) were averaged and considered as baseline usual dietary intakes in the prospective analyses for cancer, cardiovascular and diabetes risks. Weight change is a shorter time end-point than chronic diseases, thus a smaller gap between the exposure and follow-up was retained and dietary intakes from the baseline kit (2 or 3 records) were averaged and considered as baseline in the analyses of overweight, obesity and weight change.

D- Energy underreporting

Energy underreporting was identified using Black's method (125,126) based on the original method developed by Goldberg *et al.* (127), 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 (128) 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.

III. Application of the NOVA classification on NutriNet-Santé's food composition table

All food and beverage items of the NutriNet-Santé composition table were categorized into one of the four food groups in NOVA (unprocessed/minimally processed foods, culinary ingredients, processed foods, ultra-processed foods) (38,50). The whole classification was then reviewed by a committee composed of three dieticians 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.

This study primarily focused on the "ultra-processed foods" NOVA group. Home-made and artisanal food preparations were identified and decomposed using standardized recipes, and the NOVA classification was applied to their ingredients.

The NOVA categorization has been described in detail in section IV of the state of knowledge. Examples of distinction between processed and ultra-processed foods are provided below:
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 flavorings 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 flavor soup considered as "ultra-processed" according to the NOVA classification: *"Dried Glucose Syrup, Potato Starch, Flavorings, Salt, Leek Powder (3.6%), Dried Leek (3.5%), Onion Powder, Dried Carrot, Palm Oil, Dried Chicken (0.7%), Garlic Powder, Dried Parsley, Color [Curcumin (contains MILK)], Ground Black Pepper, MILK Protein, Stabilizers (Dipotassium Phosphate, Trisodium Citrate)"*.

IV. Case ascertainment

Participants were asked to declare major health events through the yearly health questionnaire, through a specific check-up questionnaire every three months, or at any time through a specific interface on the study website. They were also asked to declare all medications and treatments they used via the check-up and yearly questionnaires. Following this declaration, participants having declared an incident cancer or cardiovascular disease were invited to send their medical records (diagnosis, hospitalization, radiological reports, electrocardiograms, etc.) and, if necessary, the study physicians contacted the participants' physicians or the medical structures to collect additional information. Then, medical data were reviewed by a specific committee of physicians of the team for the validation of major health events. An investigation was also conducted by the physicians of the NutriNet-Santé study by contacting the participant's family and/or his/her physician in case of no connection to the study website for more than one year. This system constitutes the main source of case ascertainment in the cohort. Besides, the EREN team was the first in France to obtain the authorization by Decree in the Council of State (n°2013-175) to link data from our general population-based cohorts to medico-administrative

databases of the National health insurance (SNIIRAM database), providing detailed information about the reimbursement of medication and medical consultations, limiting potential bias due to participants with cancer or CVD who might have not reported their disease to the study investigators. A very low proportion of participants (1.7%) emigrated to other countries and were not covered by the SNIIRAM database. Last, an additional and exhaustive linkage to the French National cause-specific mortality registry was used to detect death and potentially missed CVD and cancer cases for deceased participants (CépiDC, which includes both dates and causes of death, and is accessible for all French citizens, without specific authorization or identification number). Pathologies were classified using the International Chronic Diseases Classification, 10th Revision, Clinical Modification (ICD-10). The present study focused on all first primary cancers (except for basal cell skin carcinoma) diagnosed between the inclusion date and 1 January 2017, as well as all first cases of incident stroke, transitory ischemic attack (TIA), myocardial infarction (MI), acute coronary syndrome (ACS) and angioplasty occurring between the inclusion and January 2018. T2D cases were ascertained using a multi-source approach, i.e. T2D declaration during follow-up along with declaration of the use of T2D medication (or a reimbursement of T2D medication detected from SNIIRAM), or hyperglycemia in the biological data along with one T2D medication use.

In regards to the overweight/obesity and weight change analyses, at inclusion and each year of the follow-up, participants are invited to self-report information on height and weight. Web-based self-reported anthropometrics have been demonstrated to be valid against a traditional paper and pencil anthropometrics questionnaire (117) and measured valued, using notably Kappa statistics and percent agreement (i.e., concordance) (129). BMI was calculated as the ratio of weight in kilograms to the square of height in meters (kg/m^2). Overweight (including obesity) was defined by the World Health Organization as BMI ≥ 25 kg/m^2, and obesity as BMI ≥ 30 kg/m^2 (130).

V. General statistical methodology

For each studied disease, participants having this specific prevalent pathology at baseline were excluded. For each subject, the proportion (%) of ultra-processed foods in the total weight of food/beverages consumed (g/d) was calculated. It was determined by making a weight ratio rather than an energy ratio in order to take into account processed food that do not provide energy (e.g. artificially sweetened beverages) and non-nutritional issues related to food processing (e.g. neoformed contaminants, food additives and alterations to the structure of raw foods). Sensitivity analyses were performed by weighting the ultra-processed variable by the energy (%Kcal/day) instead of weight, and by replacing the proportion variable by the absolute amount of ultra-processed food consumption (g/day). For all covariates except physical activity, ≤5% of values were missing and were imputed to the modal value (for categorical variables) or to the median (for continuous variables). For physical activity, the proportion of missing values was higher (14%) since the answers of all IPAQ questions were needed to calculate the score. To avoid massive imputation for a non-negligible number of subjects or exclusion of subjects with missing data and risk of selection bias, we included a missing class into the models for this variable (main analysis). However, complete case analysis (CCA) and/or multiple imputation were also tested in sensitivity analyses: multiple imputation for missing data was performed using the MICE method (131) by fully conditional specification (FCS, 20 imputed datasets) for the outcome (132) and for the following covariates: level of education (5.0% missing data), physical activity level (13.9% missing data) and BMI (0.6% missing data) (except for overweight/obesity and weight change analyses). Results were combined across imputations based on Rubin's combination rules (133,134) using the SAS PROC MIANALYZE procedure (135).

Differences in baseline characteristics of participants between quartiles of the proportion of ultra-processed food in the diet with sex-specific cut-offs (computed with the PROC RANK BY SEX procedure in SAS®) were examined using ANOVA or $\chi 2$ tests wherever appropriate. The choice of sex-specific cut-offs was based on the fact that women generally tend to have a healthier diet and lower food amounts than men, which has allowed us to ensure equivalent sex-ratios between quartiles. In order to provide some information on the nutritional quality of ultra-processed foods, we have calculated their proportion across the different categories of the Nutri-Score (14). This score, calculated based on a modified version of the Food Standard Agency Nutrient Profiling system (136) has been endorsed by the French and Belgian Ministries of

Health as the official nutrient profiling system in these countries (details about its calculation are provided in Appendix 3 of the full-text article on the associations between ultra-processed food consumption and CVD risk).

A- Multivariable analyses: multi-adjusted Cox proportional hazard models

Cox proportional hazards models with age as the primary time-scale were used to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as quartiles with sex-specific cut-offs) and incidence of overall cancer and cancer specific sites (breast, prostate, colorectal), overall CVD, cerebrovascular diseases (stroke and TIA) and coronary heart diseases (MI, ACS and angioplasty), type 2 diabetes, overweight (including obesity) and obesity. Methods like survival analyses are well adapted to assess instantaneous risks over the follow-up period in cohort studies by estimating hazard functions in different groups. Among these methods, the Cox proportional hazards model, a model mainly based on the proportional risk hypothesis, assuming that the ratios of hazard functions between groups (commonly called Hazard Ratio) remain constant during follow-up was used: this assumption has been tested and verified (see below). Hazard ratios are helpful as well to assess other events simultaneously (death and lost to-follow-up participants) that happen before the endpoint using the censoring method, while taking into account the delay of the event. Furthermore, we used left-truncated cox models to take into account delayed entries, as the inclusion in the cohort is still ongoing.

In these models, other incident cancers than the one studied were censored at the date of diagnosis (i.e. a cause-specific approach: they were considered as non-cases for the disease of interest and they contributed person-year until the date of diagnosis of their cancer). Similarly for CVD, other incident cardiovascular outcomes than the one studied were censored at the date of diagnosis. Log-log (survival) vs. log-time plots or Schoenfeld residuals were generated in order to confirm risk proportionality assumptions. Hazard ratios (HR) and 95% confidence intervals (CI) were computed. In continuous models, HR corresponded to the ratio of instantaneous risks for an absolute increment of 10 in the percentage of ultra-processed foods in the diet (i.e. a 0.1 absolute increase in the proportion of ultra-processed foods in the diet). In models based on quartiles of the percentage of ultra-processed food in the diet, P-values for linear trends were obtained by coding quartiles of ultra-processed food as an ordinal variable (1/2/3/4). The assumption of linearity between ultra-processed food consumption and disease

risk was verified using restricted cubic spline (RCS) functions using the SAS® macro written by Desquilbet and Mariotti (137). The date of event for cases was defined as the date of declaration/diagnosis of their pathology for cancer, CVD and T2D. For overweight and obesity analyses, date of event for cases was defined as the middle date between the anthropometric questionnaire in which the participant's self-reported weight corresponding to overweight or obesity and the date of the immediate previous anthropometric questionnaire (138). For non-cases, in all analyses, the date of end of follow up was calculated with the date of death, the date of loss to follow-up, or date of data extraction, whichever occurred first.

Confounding bias is the main limit of observational studies, and the main obstacle to establishing causal links. Multi-adjusted regression models allows accounting for confounding factors, by computing the associations in every category of the confounding factor, and then combining the associations into one estimate.

We proceeded with an adjustment strategy based on known confounding factors in the scientific literature, in addition to age as timescale: sociodemographic and lifestyle factors, anthropometrics, medical history (based on the pathology) and women health (for breast cancer analyses, including contraception, menopause and number of children). In order to account for the nutritional quality of diet, we performed adjustments for nutritional factors (suspicious deleterious/beneficial nutrients or food groups, energy intake, overall dietary patterns derived by principal component analysis (see below)). Other adjustment factors were also used depending on the analysis, such as factors depending on the cohort (number of dietary records, season of inclusion), metabolic comorbidities and corresponding treatments, region of residence, etc. All adjustments are specified in the footnotes to results' tables.

B- Principal components analysis for dietary patterns

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.

C- Stratified analyses

The association between ultra-processed food consumption and chronic disease risk was also investigated separately in different strata of the population; for instance men/women, younger adults (<45y)/older adults (≥45y), participants with a high lipid intake (>median)/those with a lower one, participants with a BMI<25 Kg/m2/those with a BMI≥25 Kg/m2, smokers/non-smokers, participants exhibiting a healthy dietary pattern/those exhibiting a less healthy one, and participants who tended to be sedentary (the low class of IPAQ)/those who tended to be more physically active.

D- Sensitivity analyses

Sensitivity analyses were performed in order to test the robustness of the models. To account for the risk of reverse causality, cases having occurred during at least the first two years of follow-up were excluded. Participants responding to more dietary records are more likely to be interested and cautious about their nutritional behaviors. We have tested this hypothesis by excluding participants having less than 6 dietary records. Models without adjustment for BMI and energy intake were also tested to explore the variation of the association. Sensitivity analyses may vary from one investigated outcome to another according to the relevance of each further exploration in the context of each study. All sensitivity analyses are presented in detail below.

The association between the consumption of ultra-processed food in specific food groups was also tested (either by testing the proportion of the consumption of this specific group in its ultra-processed form, or by using the absolute amount of consumption of ultra-processed food in the specific group) to disentangle the part of the association 'due' to the processed form of the group from the part 'due' to nutritional quality of the food group itself.

Secondary analyses were also performed to test the associations between the proportions in the diet of unprocessed/minimally processed foods with chronic diseases risk, using multi-adjusted Cox models.

E- Mixed models for weight gain analyses

We measured the associations between the proportion of ultra-processed food in the diet (as continuous and sex-specific quartiles) and BMI over time using mixed models for repeated measures (PROC MIXED in the SAS statistical software), with ultra-processed food as fixed effect, and intercept and time as random effects. Models were adjusted for age, sex, educational level, smoking status, marital status, physical activity level, energy intake, alcohol intake, and number of dietary records. Additional adjustments for sugar, fiber, sodium, and saturated fatty acids intakes were performed, as well as adjustments for dietary patterns (see above) and consumptions of fruit, vegetables, and sugary drinks (convincingly linked to weight gain risk according to the WCRF (15)).

All tests were two-sided, and $P<0.05$ was considered statistically significant. SAS version 9.4 (SAS Institute) was used for the analyses.

RESULTS

Chapter I: Consumption of ultra-processed food and cancer risk

Scientific publication:

Srour, B.*, Fiolet, T.*, Sellem, L., Kesse-Guyot, E., Alles, B., Mejean, C., Deschasaux, M., Fassier, P., Latino-Martel, P., Beslay, M., Hercberg, S., Lavalette, C., Monteiro, C.A., Julia, C., Touvier, M., 2018**.** Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort. **Bmj-British Medical Journal** 360, k322 *(*equally contributed)*. https://doi.org/10.1136/bmj.k322
(Among top 1% publications of its academic field) (IF=23.5, 4/155 of Medicine journals)

The full-text of this publication is available in Appendix A.

Descriptive analyses

After exclusion of prevalent cancer cases and participants having less than two dietary records, a total of 104,980 participants with 22,821 (21.7%) men and 82,159 (78.3%) women were included in the present study.

Mean age of participants was 42.8y (SD=14.8) years (range: 18.0-72.8y). Mean number of dietary records per subject over their first two years of follow-up was 5.4 (SD=2.9); the minimum was 2, but it only represented 7.2% of the participants (n=7558/104,980). After the launching of the study by the end of May 2009, half of the records were filled between June and November and the other half between December and May. Main baseline characteristics of participants according to quartiles of the proportion of ultra-processed foods in the diet are described in Table 6. Compared to the first quartile, participants among the highest quartile of ultra-processed food intake tended to be younger, current smokers, less educated, with less family history of cancer and a lower physical activity level. Furthermore, they had higher intakes of energy, lipids, carbohydrates and sodium, lower alcohol intake, higher consumptions of red and processed meat and sugary drinks, along with lower consumptions of yoghurt, nuts, whole grains and fruit and vegetables. Although there was a higher proportion of women than men in this cohort, the contribution of ultra-processed foods to the overall diet was very similar between men and women (18.74% for men and 18.71% for women, p=0.7).

Table 6 - Baseline characteristics of the study population according to sex-specific quartiles of ultra-processed food consumption (n=104,980), NutriNet-Santé cohort, France, 2009-2019[a]

		Quartiles of ultra-processed food consumption[b]				
	All participants	**Quartile 1 (n=26,244)**	**Quartile 2 (n=26,245)**	**Quartile 3 (n=26,246)**	**Quartile 4 (n=26,245)**	**P-trend [c]**
Age, years	42.8 ± 14.8	47.9 ± 13.5	45.0 ± 14.0	42.0 ± 14.4	36.5 ± 13.6	<.0001
Sex, n (%)						
Female	82,159 (78.3)	20,539 (78.3)	20,540 (78.3)	20,541 (78.3)	205,42 (78.3)	
Male	22,821 (21.7)	5,705 (21.7)	5,706 (21.7)	5,707 (21.7)	5,708 (21.7)	
Height, cm	166.8 ± 8.1	166.3 ± 8.0	166.7 ± 8.0	167.0 ± 8.1	167.3 ± 8.2	<.0001
Body mass index, kg/m²	23.8 ± 4.6	23.8 ± 4.3	23.8 ± 4.4	23.8 ± 4.5	23.8 ± 5.0	0.9
Family history of cancer, yes[d]	35,668 (34.0)	10,542 (40.2)	9,624 (36.7)	8,625 (32.9)	6,877 (26.2)	<.0001
Higher education, n (%)						0.01
No	19357 (18.4)	5,154 (19.6)	4,961 (18.9)	4,637 (17.7)	4,605 (17.6)	
Yes <2 years	18076 (17.2)	3,938 (15.0)	1,091 (15.6)	4,426 (16.9)	5,621 (21.4)	
Yes ≥2 years	67,547 (64.3)	17,152 (65.4)	17,193 (65.5)	17,183 (65.5)	16,019 (61.0)	
Smoking status, n (%)						<.0001
Current	17,763 (16.9)	4,127 (15.7)	4,065 (15.5)	4,266 (16.3)	5,305 (20.2)	
Never/former	87,217 (83.1)	22,117 (84.3)	22,180 (84.5)	21,980 (83.8)	20,940 (79.8)	
IPAQ Physical activity level, n (%)[e]						<.0001
High	29,603 (28.2)	8,753 (33.4)	7,762 (29.6)	6,983 (26.6)	6,105 (23.3)	
Moderate	38,874 (37.0)	9,620 (36.7)	9,953 (37.9)	9,814 (37.4)	9,487 (36.2)	
Low	21,888 (20.9)	4,407 (13.8)	4,407 (16.8)	5,839 (22.3)	6,490 (24.7)	
Energy intake without alcohol, kcal/d	1,879.0 ± 473.7	1,810.6 ± 454.1	1,881.1 ± 457.7	1,908.5 ± 472.3	1,915.8 ± 501.8	<.0001
Alcohol intake, g/d	7.8 ± 11.9	9.3 ± 13.3	8.5 ± 11.9	7.5 ± 11.3	5.9 ± 10.5	<.0001
Total Lipid intake, g/d	80.5 ± 25.5	76.0 ± 24.3	80.3 ± 24.4	82.1 ± 25.3	83.4 ± 27.3	<.0001
Carbohydrate intake, g/d	195.4 ± 57.9	184.6 ± 57.8	193.9 ± 55.3	199.3 ± 56.6	203.6 ± 60.2	<.0001

Sodium intake, mg/d	2.7 ± 0.9	2.6 ± 0.9	2.7 ± 0.9	2.8 ± 0.9	2.7 ± 0.9	<.0001
Dietary fiber, g/d	19.5 ± 7.2	21.0 ± 7.7	20.1 ± 6.9	19.3 ± 6.8	17.4 ± 6.9	<.0001
Whole grains, g/d	34.4 ± 46.1	42.6 ± 52.2	36.6 ± 45.8	32.6 ± 43.6	25.7 ± 40.1	< .0001
Yoghurt, g/d	58.3 ± 68.9	66.4 ± 74.0	60.5 ± 66.4	56.8 ± 66.2	49.3 ± 67.5	< .0001
Sugary drinks, g/d	47.3 ± 105.0	12.0 ± 35.9	23.3 ± 46.7	39.6 ± 65.3	114.3 ± 173.2	< .0001
Red and processed meat, g/d	73.0 ± 51.0	67.0 ± 48.6	72.2 ± 48.1	74.8 ± 50.0	78.1 ± 56.1	< .0001
Nuts, g/d	4.8 ± 10.8	6.1 ± 13.2	5.1 ± 10.7	4.5 ± 9.6	3.4 ± 8.9	< .0001
Fruit and vegetables, g/d	408.2 ± 221.6	506.7 ± 248.5	435.8 ± 202.2	387.3 ± 192.6	302.8 ± 186.6	< .0001
Number of children	1.3 ± 1.2	1.6 ± 1.2	1.4 ± 1.2	1.3 ± 1.2	1.0 ± 1.2	<.0001
Menopausal status, n (%)[f]						<.0001
Premenopausal	57,408 (69.9)	11,797 (57.4)	13,497 (65.7)	14,961 (72.8)	17,153 (83.5)	
Perimenopausal	4,282 (5.2)	1,471 (7.16)	1,148 (5.6)	997 (4.9)	666 (3.2)	
Postmenopausal	20,469 (24.9)	7,271 (35.4)	5,895 (28.7)	4,582 (22.3)	2,721 (13.3)	
Use of hormonal treatment for menopause, yes n (%)[f]	4,324 (5.3)	1,602 (7.8)	1,242 (6.1)	932 (4.5)	548 (2.7)	<.0001
Oral contraception, yes n (%)[f]	23,073 (22.0)	3,779 (14.4)	4,990 (19.0)	6,209 (23.7)	8,095 (30.8)	<.0001
Ultra-processed food (%)	18.7 ± 10.1	8.5 ± 2.5	14.3 ± 1.4	19.8 ± 1.9	32.3 ± 9.8	-

[a]Values are means ± SDs or n (%). For all covariates except physical activity, a very low proportion of values were missing (0-5%), the latter were replaced by the modal value among the population study: '≥2y of higher education' for educational level, 0 for the number of biological children, 22.9 kg/m2 for BMI, 166 cm for height and non-smoker for smoking status.

[b]Sex specific quartiles of the proportion of ultra-processed food intake in the total quantity of food consumed. Sex-specific cut-offs for quartiles of ultra-processed proportions were 11.8%, 16.8% and 23.3% in men and 11.8%, 16.8% and 23.4% in women.

[c] P_{value} for the comparison between sex-specific quartiles of ultra-processed food consumption, by Fisher test or x^2 test where appropriate.

[d]Among first-degree relatives

[e] Available for 90,365 subjects. Subjects were categorized into the "high", "moderate" and "low" categories according to IPAQ guidelines(119)

[f]Among women

The distribution of the proportion of ultra-processed food in the diet in the study population is presented in figure 14.

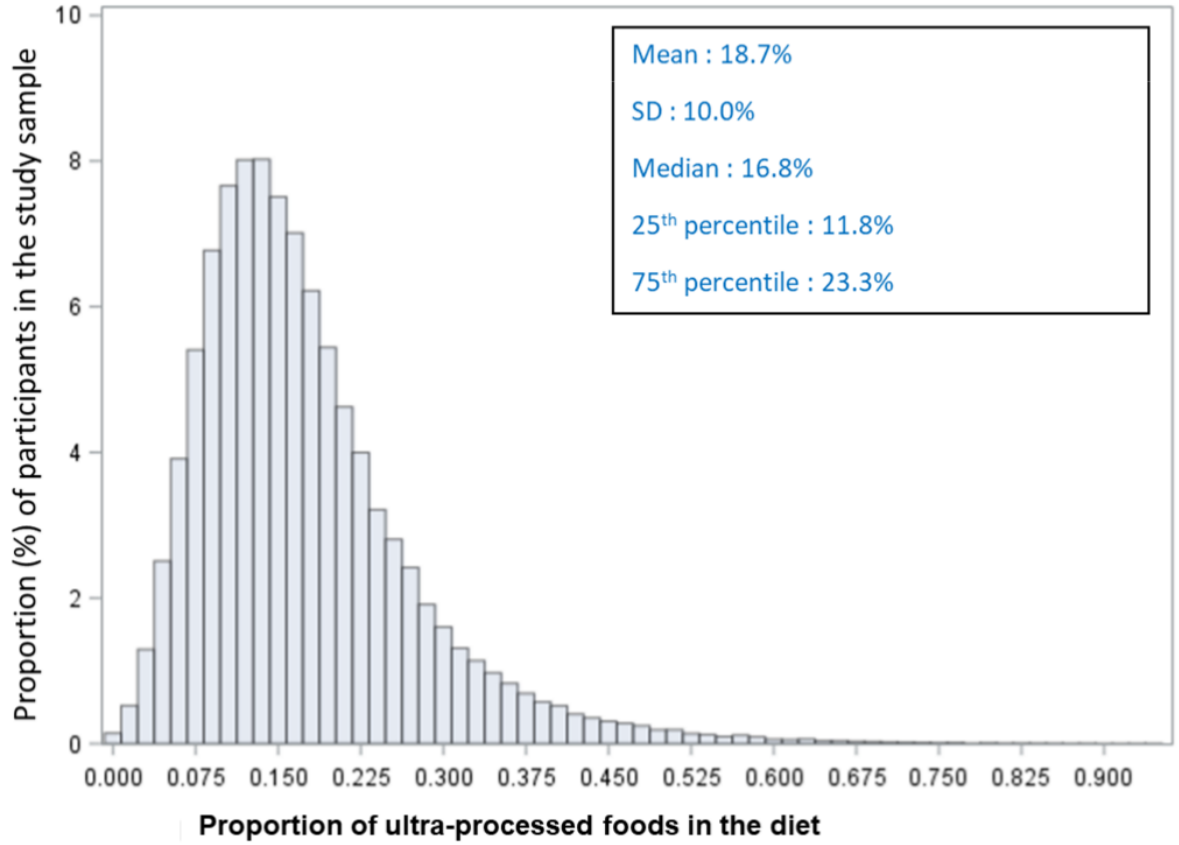

Figure 14 - Distribution of the variable "proportion of ultra-processed food in the diet" in the study sample, NutriNet-Santé, 2009-2019 (139)

Main food groups contributing to ultra-processed food intake were sugary products (26%, e.g. confectionaries, ice-cream, pastries, sweetened dairy desserts) and beverages (20%, e.g. sodas, sugary and artificially sweetened non-carbonated beverages), followed by starchy foods and breakfast cereals (16%, e.g., pre-packaged bread, industrial dough, ready-to-eat industrial pasta or potato plates, breakfast cereals) and ultra-processed fruits and vegetables (15%, e.g. instant powder dehydrated vegetable soups and broths, vegetable nuggets, fruit-based sweetened desserts) (figure 15).

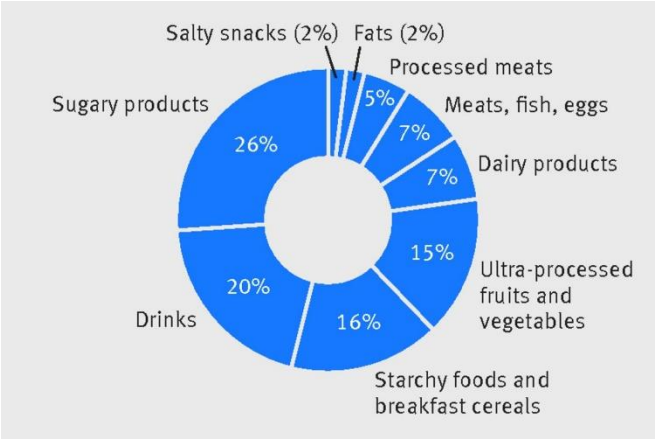

Figure 15 - Relative contribution of each food group to ultra-processed food consumption in diet (139)

Ultra-processed foods and beverages were usually products with a lower nutritional quality: in fact, ultra-processed foods in the NutriNet-Santé food composition database represented more than 85% of the products in the "E" category of the Nutri-Score five-colour labelling system (i.e., the category of lowest nutritional quality) *vs.* less than 24% in the "A" category (i.e., the category of highest nutritional quality) (figure 16).

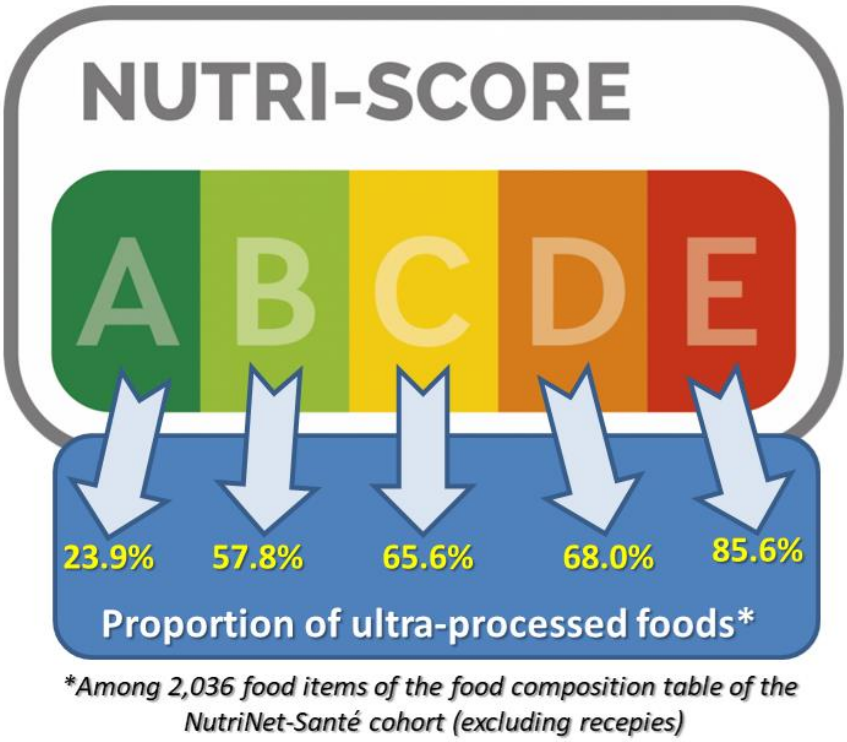

Figure 16 - Categorization of the ultra-processed food items of the NutriNet-Santé cohort according to their nutritional quality scored by the Foods Standard Agency Nutritent Profilng system (140)

Main results - Cox models

During follow-up (426,362 person-years, median follow-up time=5y), 2,228 first incident cancer cases were diagnosed and validated, among which 739 breast cancers (n=264 pre-menopausal and n=475 post-menopausal), 281 prostate cancers and 153 cases of colorectal cancers. Associations between the proportion of ultra-processed foods in the diet and overall, breast, prostate and colorectal cancer risks are shown in Table 7. In model 1, we adjusted for age (timescale), sex, energy intake without alcohol, number of 24h-dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, and family history of cancers. Breast cancer models were additionally adjusted for menopausal status, hormonal treatment for menopause, oral contraception and number of children. Ultra-processed food intake was associated with increased risks of overall cancer ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$ =1.12 (1.06 to 1.18), P<.0001) and breast cancer (HR=1.11 (1.02 to 1.22), P=0.02). The later association was more specifically observed for post-menopausal breast cancer (P=0.04) but not for pre-menopausal breast cancer (P=0.2). The association with overall cancer risk was statistically significant in all strata of the population investigated, after adjustment for model 1 covariates: in men ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$ =1.12 (1.02 to 1.24), P=0.02, 663 cases and 22158 non-cases), in women (HR= 1.13 (1.06 to 1.20), P<0.0001, 1565 cases and 80594 non-cases), in younger adults (<40 years old, HR= 1.21 (1.09 to 1.35), P=0.0006, 287 cases and 48627 non-cases), in older adults (≥40 years old, HR= 1.09 (1.03 to 1.16), P=0.03, 1941 cases and 54485 non-cases), in smokers (including adjustment for pack-years of cigarette smoked, HR =1.18 (1.04 to 1.33), P=0.01, 255 cases and 15355 non-cases), in non-smokers (HR=1.11 (1.05 to 1.17), P=0.0002, 1943 cases and 85219 non-cases), in subjects with low-to-moderate levels of physical activity (HR=1.07 (1.00 to 1.15), P=0.04, 1216 cases and 59546 non-cases), and in those with a high level of physical activity (HR=1.19 (1.09 to 1.30), P<0.0001, 744 cases and 28859 non-cases).

More specifically, ultra-processed fats and sauces ($HR_{\text{for an absolute increment of 10g in the consumption of the specific food group}}$=1.07 (1.03 to 1.12), P=0.002), sugary products (HR=1.01 (1.00 to 1.02), P=0.03), and beverages (HR=1.00 (1.00 to 1.01), P=0.005) were associated with increased overall cancer risk and ultra-processed sugary products were associated with breast cancer risk (HR=1.02 (1.01 to 1.02), P=0.006).

Further adjustment for several indicators of the nutritional quality of the diet (lipid, sodium and salt intakes – model 2; Western pattern – model 3; or both – model 4) did not modify these

findings. The Pearson correlation coefficient between the proportion of ultra-processed food in the diet and the Western-type dietary pattern was low (0.06).

No association was statistically significant for prostate and colorectal cancers. However, a borderline non-significant trend of increased colorectal cancer risk associated with ultra-processed food intake was observed ($HR_{Q4 \text{ versus } Q1}$=1.23 (1.08 to 1.40), P-trend=0.07 in Model 4).

Sensitivity analyses

Sensitivity analyses (adjusted for model 1 covariates, data not tabulated) excluding cancer cases diagnosed during the first two years of follow-up provided similar results ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$=1.10 (1.03 to 1.17), P =0.005 for overall cancer risk, n=1367 cases and 102502 non-cases included; HR=1.15 (1.03 to 1.29), P =0.02 for breast cancer risk, n=441 cases and 80940 non-cases included). Similarly, results were unchanged when non-validated cancer cancers were excluded ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$=1.11 (1.05 to 1.17), P=0.0003 for overall cancer risk, n=1967 cases and 102752 non-cases included; HR=1.12 (1.02 to 1.23), P=0.02 for breast cancer risk, n=677 cases and 81274 non-cases included).

Similar results were observed when i) we included only participants with at least six 24h records on the one hand (overall cancer risk: $HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$= 1.13 (1.06 to 1.21)), P =0.0003, n = 1494 cases and 47 920 non-cases included) and ii) we re-included participants with only one 24h record on the other hand (overall cancer risk: $HR_{\text{for a 10-point increment in the proportion of ultra-processed foods in the diet}}$=1.11 (1.06 to 1.16)), P=0.0001, n = 2383 cases and 122 196 non-cases included).

Similar findings were found when the proportion of ultra-processed food in the diet was coded as sex-specific quintiles instead of sex-specific quartiles (overall cancer risk: $HR_{Q5 \text{ versus } Q1}$= 1.25 (1.08 to 1.47), P-trend=0.0003 and breast cancer risk: $HR_{Q5 \text{ versus } Q1}$= 1.25 (0.96 to 1.63), P-trend=0.03).

Further adjustment for the following variables, in addition to model 1 covariates, did not modify the results: dietary supplement use (yes/no) at baseline ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$=1.12 (1.06 to 1.17), P<0.0001 for overall cancer and 1.11 (1.02 to 1.22), P=0.02 for breast cancer), prevalent depression at baseline (HR=1.11 (1.06 to 1.17), P<0.0001 for overall cancer and 1.11 (1.01 to 1.22), P=0.02 for breast cancer), healthy dietary pattern (HR

=1.11 (1.05 to 1.17), P<0.0001 for overall cancer and 1.10 (1.00 to 1.21), P=0.04 for breast cancer), overall fruit and vegetable consumption in g/d (HR= 1.10 (1.04 to 1.16), P=0.0009 for overall cancer and 1.11 (1.01 to 1.22), P=0.03 for breast cancer), number of smoked cigarettes in pack-years (HR = 1.13 (1.07 to 1.19), P<0.0001 for overall cancer and 1.13 (1.03 to 1.24), P=0.009 for breast cancer), and season of inclusion in the cohort (HR = 1.12 (1.06 to 1.18), P<0.0001 for overall cancer and 1.12 (1.02 to 1.22), P=0.02 for breast cancer).

Besides, we have tested other methods to deal with missing data, such as multiple imputation (132) and complete case analysis (i.e. exclusion of participants with at least one missing data for a covariate). The results were very similar: for the multiple imputation analysis: $HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$=1.11 (1.06 to 1.17), P<0.0001, 2228 cases and 102752 non-cases for overall cancer, HR=1.11 (1.01 to 1.21), P=0.02, 739 cases and 81420 non-cases for breast cancer; and for the complete case analysis: HR =1.11 (1.05 to 1.18), P=0.0003, 1813 cases and 82824 non-cases for overall cancer, HR=1.14 (1.03 to 1.26), P=0.01, 579 cases and 64642 non-cases for breast cancer.

As a secondary analysis, and consistently with our findings, the consumption of "minimally/unprocessed foods" was associated with lower risks of overall and breast cancers ($HR_{\text{for an absolute increment of 10 in the percentage of unprocessed foods in the diet}}$=0.91 (0.87 to 0.95), P<.0001, 2228 cases and 102752 non-cases for overall cancer, HR=0.42 (0.19 to 0.91), P=0.03, 739 cases and 81420 non-cases for breast cancer), in multi-adjusted analyses adjusted for model 1 covariates.

Table 7 - Associations between ultra-processed food intake and overall, prostate, colorectal and breast cancer risk, from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2019 (n=104,980)[a]

	Proportion of ultra-processed food intake in the diet						
	Continuous[b]		Sex-specific quartiles[c]				
			Q1	Q2	Q3	Q4	
	HR (95% CI)	*P*-trend	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	*P*-trend
All cancers							
N for cases/non-cases	2228/102752		712/25532	607/25638	541/25705	368/25877	
Model 1	1.12 (1.06 to 1.18)	<.0001	1	0.99 (0.89 to 1.11)	1.10 (0.99 to 1.24)	1.21 (1.06 to 1.38)	0.002
Model 2	1.12 (1.07 to 1.18)	<.0001	1	1.00 (0.90 to 1.11)	1.11 (0.99 to 1.25)	1.23 (1.08 to 1.40)	0.001
Model 3	1.12 (1.06 to 1.18)	<.0001	1	0.99 (0.89 to 1.11)	1.01 (0.98 to 1.23)	1.21 (1.06 to 1.38)	0.002
Model 4	1.13 (1.07 to 1.18)	<.0001	1	1.00 (0.90 to 1.11)	1.11 (0.99 to 1.24)	1.23 (1.08 to 1.40)	0.001
Prostate cancer							
N for cases/non-cases	281/22540		96/5609	96/5609	59/5647	30/5675	
Model 1	0.98 (0.83 to 1.16)	0.8	1	1.18 (0.89 to 1.57)	0.95 (0.69 to 1.32)	0.93 (0.61 to 1.40)	0.6
Model 2	0.98 (0.83 to 1.16)	0.8	1	1.18 (0.89 to 1.57)	0.95 (0.69 to 1.32)	0.93 (0.61 to 1.40)	0.6
Model 3	0.98 (0.83 to 1.15)	0.8	1	1.18 (0.89 to 1.56)	0.95 (0.68 to 1.31)	0.92 (0.61 to 1.39)	0.6
Model 4	0.98 (0.83 to 1.16)	0.8	1	1.18 (0.89 to 1.57)	0.95 (0.68 to 1.32)	0.93 (0.61 to 1.40)	0.6
Colorectal cancer							
N for cases/non-cases	153/104827		48/26196	43/26202	36/26210	26/26219	
Model 1	1.13 (0.92 to 1.38)	0.2	1	1.10 (0.72 to 1.66)	1.17 (0.76 to 1.81)	1.49 (0.92 to 2.43)	0.1
Model 2	1.16 (0.95 to 1.42)	0.1	1	1.12 (0.74 to 1.70)	1.22 (0.79 to 1.90)	1.59 (0.97 to 2.60)	0.07
Model 3	1.13 (0.92 to 1.38)	0.2	1	1.09 (0.92 to 1.38)	1.16 (0.75 to 1.80)	1.48 (0.91 to 2.41)	0.1
Model 4	1.16 (0.95 to 1.42)	0.1	1	1.12 (0.74 to 1.70)	1.22 (0.79 to 1.89)	1.23 (1.08 to 1.40)	0.07

Breast cancer							
N for cases/non-cases	739/81420		247/20292	202/20338	179/20361	111/20429	
Model 1	1.11 (1.02 to 1.22)	0.02	1	0.97 (0.81 to 1.17)	1.10 (0.90 to 1.34)	1.14 (0.91 to 1.44)	0.2
Model 2	1.11 (1.01 to 1.21)	0.03	1	0.96 (0.80 to 1.16)	1.09 (0.89 to 1.32)	1.12 (0.89 to 1.42)	0.2
Model 3	1.11 (1.02 to 1.22)	0.02	1	0.97 (0.80 to 1.17)	1.09 (0.90 to 1.33)	1.14 (0.91 to 1.44)	0.2
Model 4	1.11 (1.01 to 1.21)	0.03	1	0.96 (0.80 to 1.16)	1.08 (0.89 to 1.32)	1.13 (0.89 to 1.42)	0.2
Pre-menopausal breast cancer							
N for cases/non-cases	264/57151		90/14263	70/14284	55/14299	49/14305	
Model 1	1.09 (0.95 to 1.25)	0.2	1	0.91 (0.67 to 1.25)	0.92 (0.65 to 1.29)	1.30 (0.90 to 1.86)	0.3
Model 2	1.07 (0.93 to 1.23)	0.4	1	0.90 (0.66 to 1.24)	0.90 (0.64 to 1.27)	1.25 (0.87 to 1.80)	0.4
Model 3	1.09 (0.95 to 1.26)	0.2	1	0.91 (0.67 to 1.25)	0.92 (0.66 to 1.30)	1.30 (0.91 to 1.88)	0.3
Model 4	1.08 (0.94 to 1.24)	0.3	1	0.91 (0.66 to 1.24)	0.91 (0.64 to 1.28)	1.27 (0.88 to 1.83)	0.4
Post-menopausal breast cancer							
N for cases/non-cases	475/29191		107/7309	128/7289	123/7294	117/7299	
Model 1	1.13 (1.01 to 1.27)	0.04	1	1.23 (0.95 to 1.60)	1.28 (0.98 to 1.66)	1.39 (1.07 to 1.82)	0.02
Model 2	1.13 (1.00 to 1.27)	0.05	1	1.23 (0.95 to 1.60)	1.27 (0.98 to 1.65)	1.39 (1.05 to 1.81)	0.02
Model 3	1.13 (1.00 to 1.27)	0.04	1	1.23 (0.95 to 1.59)	1.27 (0.98 to 1.65)	1.38 (1.06 to 1.81)	0.02
Model 4	1.13 (1.00 to 1.27)	0.05	1	1.23 (0.95 to 1.59)	1.27 (0.97 to 1.65)	1.38 (1.05 to 1.81)	0.02

[a] Model 1 is a multi-adjusted Cox proportional hazard model adjusted for age (timescale), sex, energy intake without alcohol, number of 24h-dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, and family history of cancers. Breast cancer models were additionally adjusted for menopausal status, hormonal treatment for menopause, oral contraception and number of children.

Model 2 = Model 1 + lipid intake, sodium intake, carbohydrate intake

Model 3 = Model 1 + Western dietary pattern (derived by factor analysis)

Model 4 = Model 1 + lipid intake, sodium intake, carbohydrate intake, Western dietary pattern (derived by factor analysis). Pearson correlation coefficients with the Western dietary pattern were 0.5 for dietary lipids, 0.6 for sodium and 0.40 for carbohydrates.

[b] HR for an increase of 10% of the proportion of ultra-processed food intake in the diet

[c] Sex-specific cut-offs for quartiles of ultra-processed proportions were 11.8% ; 16.8% and 23.3% in men and 11.8% ; 16.8% and 23.4% in women.

In premenopausal women : Cut-offs for quartiles of ultra-processed proportions were 12.8% ; 18.1% and 25.0%. In postmenopausal women : Cut-offs for quartiles of ultra-processed proportions were 10.1% ; 14.3% and 19.5%.

Chapter II: Consumption of ultra-processed food and cardiovascular disease risk

Scientific publication:

Srour, B., Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Andrianasolo, RM., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M., 2019. Ultra-processed food intake and risk of cardiovascular disease: a prospective cohort study (NutriNet-Santé). **Bmj-British Medical Journal**, BMJ 2019;365:l1451. https://doi.org/10.1136/bmj.l1451 **(IF=23.5, 4/155 of Medicine journals)**

The full-text of this publication is available in Appendix B.

Descriptive analyses

After excluding participants with prevalent CVD at baseline and those having less than two dietary records, a total of 105,159 participants with 21912 (20.8%) men and 83247 (79.2%) women were included in this analysis. Mean baseline age of participants was 42.7y (SD=14.5) years (range: 18.0-72.8y)).

Mean number of dietary records per subject over their first two years of follow-up was 5.7 (SD=3.0); the minimum was 2, but it represented only 7.6% (7992 among 105159 participants) of the participants. This study sample was very similar to the sample of study of ultra-processed food and cancer risk (explained above), with main differences being related to inclusion/exclusion of prevalent cancer/CVD cases. For readability reasons, the common characteristic of both samples will not be repeated. However, the detailed description of specific study samples is available in each corresponding manuscripts (appendixes 2 and 3).

High consumers of ultra-processed foods had lower prevalence of metabolic diseases. The mean contribution of ultra-processed foods to the overall diet (in weight) was 17.6% in men and 17.3% in women.

Main results - Cox models

During follow-up (518,208 person-years, median follow-up time=5.2y, interquartile range=2.6-7.3y), 1,409 first incident CVD events occurred, among which 106 MI, 485 angioplasties, 74 ACS, 155 strokes and 674 TIA. Associations between the proportion of ultra-processed foods in the diet and overall cardiovascular diseases, coronary heart diseases and cerebrovascular diseases are shown in Table 8.

In model 1 (adjusted for age (time-scale), sex, BMI, physical activity level, smoking status, number of 24h-dietary records, alcohol intake, energy intake, family history of CVD and educational level), ultra-processed food intake was associated with increased risks of overall CVD ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$ =1.12 (1.05 to 1.20), P=0.0008, median follow-up: 5.2y, 518,208 person-years). Ultra-processed food intake was also associated with increased risks of coronary heart diseases (HR=1.13 (1.02 to 1.24), P=0.02, median follow-up: 5.2y, 520,319 person-years) and cerebrovascular diseases (HR=1.11 (1.01 to 1.21), P=0.02, median follow-up: 5.2y, 520,023 person-years). Both linearity and proportional risk assumptions were met. Statistically significant associations were observed for angioplasty (485 cases and 104,674 non-cases, HR = 1.16 (1.03 to 1.30), p=0.01) and TIA (674

cases and 104,485 non-cases, HR = 1.13 (1.03 to 1.24), p=0.01). Results were similar for overall CVD when TIA cases were not considered as CVDs (HR=1.12 (1.02 to 1.23), P=0.02, 754 cases and 104,405 non-cases), or when stable angina cases were considered as CVD (HR=1.12 (1.06 to 1.19), P=0.0002, 1601 cases and 103,120 non-cases).

The association with overall CVD risk was statistically significant in all strata of the population investigated, according to:

- Sex: in men (HR=1.12 (1.02 to 1.23), P=0.02, 701 cases and 21,211 non-cases) and in women (HR=1.13 (1.03 to 1.24), P=0.01, 708 cases and 82,539 non-cases)
- Age: in younger adults (aged 45 years old and below) (HR=1.15 (1.00 to 1.32), P=0.004, 182 cases and 59,224 non-cases) and in older adults (above 45 years old) (HR=1.10 (1.02 to 1.19), P=0.01, 1227 cases and 44,526 non-cases)
- Lipid intakes: in individuals having low lipid intakes (≤78.9 g/d) (HR=1.11 (1.01 to 1.23), P=0.02, 664 cases and 51,905 non-cases) and in those having higher intakes (HR=1.13 (1.03 to 1.24), P=0.01, 745 cases and 51,045 non-cases)
- BMI: in individuals having a normal weight (HR=1.11 (1.01 to 1.22), P=0.03, 755 cases and 74434 non-cases) and in obese and overweight participants (HR=1.14 (1.03 to 1.25), P=0.008, 654 cases and 29,316 non-cases)
- Physical activity level: in individuals having moderate to high physical activity levels (HR=1.10 (1.01 to 1.20), P=0.02, 974 cases and 67395 non-cases) and those having lower physical activity levels (HR=1.17 (1.02 to 1.34), P=0.03, 257 cases and 21,893 non-cases)

Table 8 - Associations between ultra-processed food intake and overall cardiovascular diseases, coronary heart diseases and cerebrovascular diseases from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2019 (n=105,159)[a]

Proportion of ultra-processed food intake in the diet (%)							
	Quartiles[b]					Continuous[c]	
	Q1	Q2	Q3	Q4			
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-value
All cardiovascular diseases							
N for cases/non-cases	446/25950	410/26008	330/25996	223/25796		1409/103750	
Model 0	1	1.06 (0.93 to 1.22)	1.08 (0.93 to 1.24)	1.25 (1.06 to 1.47)	0.01	1.13 (1.06 to 1.21)	0.0002
Model 1	1	1.04 (0.91 to 1.19)	1.07 (0.93 to 1.23)	1.23 (1.04 to 1.45)	0.02	1.12 (1.05 to 1.20)	0.0008
Model 2	1	1.05 (0.92 to 1.20)	1.08 (0.93 to 1.25)	1.25 (1.05 to 1.47)	0.02	1.13 (1.05 to 1.20)	0.0005
Model 3	1	1.03 (0.90 to 1.18)	1.05 (0.91 to 1.22)	1.20 (1.01 to 1.42)	0.05	1.11 (1.03 to 1.19)	0.003
Model 4	1	1.03 (0.90 to 1.18)	1.06 (0.90 to 1.23)	1.21 (1.02 to 1.45)	0.05	1.12 (1.04 to 1.20)	0.002
Model 5	1	1.05 (0.92 to 1.20)	1.08 (0.93 to 1.24)	1.26 (1.07 to 1.48)	0.01	1.13 (1.06 to 1.21)	0.0003
Model 6	1	1.04 (0.91 to 1.19)	1.06 (0.92 to 1.23)	1.23 (1.04 to 1.45)	0.03	1.12 (1.05 to 1.20)	0.001
Coronary heart diseases[d]							
N for cases/non-cases	208/26188	194/26224	166/26160	97/25922		665/104494	
Model 0	1	1.08 (0.89 to 1.31)	1.19 (0.97 to 1.46)	1.23 (0.96 to 1.57)	0.04	1.15 (1.04 to 1.26)	0.006
Model 1	1	1.07 (0.87 to 1.30)	1.19 (0.97 to 1.46)	1.20 (0.93 to 1.53)	0.07	1.13 (1.02 to 1.24)	0.02
Model 2	1	1.07 (0.87 to 1.30)	1.20 (0.97 to 1.47)	1.22 (0.95 to 1.56)	0.05	1.14 (1.03 to 1.26)	0.01
Model 3	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.44)	1.16 (0.90 to 1.49)	0.1	1.11 (1.00 to 1.23)	0.04
Model 4	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.46)	1.18 (0.91 to 1.53)	0.1	1.12 (1.01 to 1.24)	0.03
Model 5	1	1.07 (0.88 to 1.31)	1.20 (0.97 to 1.47)	1.22 (0.96 to 1.57)	0.05	1.14 (1.03 to 1.26)	0.009
Model 6	1	1.06 (0.87 to 1.29)	1.18 (0.96 to 1.45)	1.18 (0.93 to 1.52)	0.08	1.12 (1.02 to 1.24)	0.02

Cerebrovascular diseases[e]							
N for cases/non-cases	267/26129	238/26180	188/26138	136/25883		829/104330	
Model 0	1	1.03 (0.87 to 1.23)	1.01 (0.84 to 1.22)	1.24 (1.00 to 1.53)	0.1	1.11 (1.02 to 1.21)	0.02
Model 1	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.24 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02
Model 2	1	1.02 (0.86 to 1.22)	1.01 (0.84 to 1.22)	1.25 (1.01 to 1.55)	0.1	1.12 (1.02 to 1.22)	0.02
Model 3	1	1.00 (0.84 to 1.20)	0.99 (0.81 to 1.19)	1.21 (0.98 to 1.51)	0.2	1.10 (1.00 to 1.20)	0.04
Model 4	1	1.01 (0.84 to 1.21)	1.00 (0.82 to 1.21)	1.23 (0.98 to 1.54)	0.2	1.11 (1.01 to 1.22)	0.03
Model 5	1	1.02 (0.85 to 1.21)	1.00 (0.83 to 1.21)	1.26 (1.01 to 1.55)	0.1	1.11 (1.02 to 1.22)	0.01
Model 6	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.23 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02

CI: confidence interval, HR: Hazard ratio

Mean follow-up times for overall CVD, coronary heart diseases and cerebrovascular diseases were all equal to 5.2y. Person-years were respectively 518208, 520319, and 520023.

[a] Model 0 is an age (timescale) and sex-adjusted Cox proportional hazard model.

Model 1 is a multi-adjusted Cox proportional hazard model 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.

Model 2 = Model 1 + saturated fatty acid intake, sodium intake, sugar intake

Model 3 = Model 1 + Healthy dietary pattern (derived by factor analysis)

Model 4 = Model 1 + intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces

Model 5 = Model 1 without adjustment for BMI.

Model 6 = Model 1 + baseline prevalent type 2 diabetes, dyslipidaemia, hypertension and hypertriglyceridemia (yes/no) as well as treatments for these conditions (yes/no).

[b]Sex-specific cut-offs for quartiles of ultra-processed proportions were 0.108, 0.156 and 0.220 in men and 0.106, 0.154 and 0.218 in women.

[c]HR for an absolute increment of 10 in the percentage of ultra-processed foods in the diet

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

[e]Cerebrovascular diseases include strokes and transitory ischemic attacks

More specifically, ultra-processed beverages were associated with increased overall CVD risk ($HR_{\text{for an increase of 100 g/day}}$=1.06 (1.02 to 1.10), P=0.004), ultra-processed fats and sauces ($HR_{\text{for an increase of 100 g/day}}$=1.73 (1.01 to 2.94), P=0.04) and meats ($HR_{\text{for an increase of 100 g/day}}$=1.28 (1.00 to 1.64), P=0.05) were associated with increased coronary heart diseases risk, and ultra-processed beverages ($HR_{\text{for an increase of 100 g/day}}$=1.06 (1.01 to 1.12), P=0.01), sugary products ($HR_{\text{for an increase of 100 g/day}}$=1.12 (1.01 to 1.27), P=0.05) and salty snacks ($HR_{\text{for an increase of 100 g/day}}$=2.03 (1.04 to 3.94), P=0.04) were associated with increased cerebrovascular diseases risk (Appendix 8-a). In contrast, there was no strong evidence for an association between these food groups in their non-ultra-processed form and CVD risk (except for salty snacks, but with broad confidence intervals due to relatively limited consumption in our study population).

Sensitivity analyses

Further adjustment for several indicators of the nutritional quality of the diet (saturated fatty acids, sodium and sugar intakes – model 2; Healthy dietary pattern – model 3, intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces - model 4, Table 8) did not modify these findings. Further adjustment for baseline type 2-diabetes, dyslipidemia, hypertension and hypertriglyceridemia as well as treatments for these conditions did not modify the findings (model 6, Table 8).

In further sensitivity analyses, adjustments were performed for additional nutritional factors (dietary fiber, fruit and vegetable intakes, healthy and western type dietary patterns) as well as other potential confounders (i.e. number of pack-years for smoking, season of inclusion in the cohort, region of residence); hazard ratios remained almost unchanged. Unadjustment for BMI and energy was also tested and did not affect the associations ($HR_{\text{for an absolute increment of 10 in the percentage of ultra-processed foods in the diet}}$=1.13 (1.05 to 1.21), P=0.0004 for overall CVD). Other methods to deal with missing data were tested: using multiple imputation with the MICE method, the associations remained stable (HR=1.16 (1.08 to 1.24), P<.0001 for overall cardiovascular diseases, HR=1.15 (1.04 to 1.27), P=0.007 for coronary heart diseases and HR=1.15 (1.05 to 1.26), P=0.002 for cerebrovascular diseases) in multi-adjusted analyses adjusted for model 1 covariates. On the other hand, the associations remained significant after accounting for reverse causality risk by excluding CVD cases diagnosed during the first two years of follow-up: HR=1.14 (1.05 to 1.23), P=0.0008, 1,087 cases and 103,750 non cases, as well as during the first three (HR=1.14 (1.05 to 1.25), P=0.002, 879 cases and 103750 non cases), four (HR=1.14 (1.03 to 1.25), P=0.01, 663 cases and 103750 non cases) and five years (1.13 (1.00 to 1.28), P=0.04, 441 cases and 103,750 non cases).

As a secondary analysis, associations between the proportions of the unprocessed/minimally processed group of the NOVA classification in the diet and CVD risk were also tested. Consistently with our findings, the consumption of "unprocessed/minimally foods" was associated with lower risks of overall cardiovascular, coronary and cerebrovascular diseases ($HR_{\text{for an absolute increment of 10 in the percentage of unprocessed or minimally processed foods in the diet}}$ =0.91 (0.86 to 0.97), P=0.003 for overall CVD, HR=0.91 (0.84 to 0.99), P=0.04 for coronary heart diseases and HR=0.91 (0.84 to 0.98), P=0.02 for cerebrovascular diseases), in multi-adjusted analyses adjusted for model 1 covariates.

Consistently with this finding, a similar association was found between the consumption of unprocessed or minimally processed foods and mortality risk: $HR_{\text{for an absolute increment of 10 in the percentage of unprocessed or minimally processed foods in the diet}}$ =0.91 (0.84 to 0.94), P=0.03. A major number of deaths were caused by cancer and CVD.

This result was a published along with a letter to the editor, in the JAMA Internal Medicine:

Scientific publication:

Srour, B., Touvier, M., Julia, C. 2019. Letter: Evidence for the Full Potential of Daily Food Choices to Minimize Premature Mortality- Reply. **JAMA internal medicine** 179 (8): 1149–50. https://doi.org/10.1001/jamainternmed.2019.2208 **(IF=19.98, 5/155 of Medicine journals)**. **(IF=19.98, 5/155 of Medicine journals)**

The full-text of this letter is available in Appendix D.

Chapter III: Consumption of ultra-processed food consumption and type-2 diabetes risk

Scientific publication:

Srour, B., Fezeu, LK., Kesse-Guyot, E., Alles, B., Mejean, C., Debras, C., Druesne-Pecollo, N., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, C.A., Julia, C., Touvier, M. Ultra-processed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective Cohort *(under review)*

The full-text of this article is available in Appendix C.

Descriptive analyses

After excluding participants with prevalent T2D at baseline, and those having less than two dietary records, a total of 104,707 participants with 21,800 (20.8%) men and 82,907 (79.2%) women were included in the present study. Mean baseline age of participants was 42.7y (SD=14.5) years.

Main baseline characteristics of participants according to quartiles of the proportion of ultra-processed food in the diet are very similar to those of the cancer and CVD analyses.

Main results - Cox models

During follow-up (582,252 person-years, median follow-up time=6.0y, 25^{th} – 75^{th} percentile=2.8-8.4y), 821 incident cases of T2D occurred. The proportional hazard assumptions of the Cox models were met, as well as the linearity assumptions between ultra-processed food intake and T2D risk.

In model 1, we adjusted for adjusted for age (timescale), sex, educational level, BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, and family history of T2D. Ultra-processed food intake was associated with an increased risk of T2D ($HR_{\text{for an absolute increment of 10 in the percentage of UPF in the diet}}$ =1.15 (1.06 to 1.25), P=0.0009. Adjusting for sugar, sodium, fiber and saturated fatty acid intakes or for intakes of red and processed meat, sugary drinks, fruits and vegetables, nuts, whole grains and yoghurt did not change the findings (table 9). The associations also remained significant after further adjustments for metabolic comorbidities (hypertension, dyslipidemia) (table 9). The absolute amount of ultra-processed food consumption in g/d was consistently associated with T2D risk: $HR_{\text{for a 100g/day increase in UPF consumption}}$= 1.05 (1.02 to 1.09), P=0.001.

Although HRs were in the same direction, this association was significant in women only, but statistical power was reduced for men (>79% women in this population study): in women (HR=1.13 (1.08 to 1.34), P=0.0004, 519 cases and 82,388 non-cases) and in men (HR=1.03 (0.88 to 1.20), P=0.7, 302 cases and 21,498 non-cases). Results were significant in every stratum, when the models were stratified on age: among younger adults (aged 45 years old and below) (HR=1.19 (1.03 to 1.27), P=0.02, 144 cases and 59103 non-cases) and older adults (above 45 years old) (HR=1.13 (1.02 to 1.24), P=0.02, 677 cases and 44,783 non-cases); and on sugar intake (below and above the median intake: 89.61 g/day): in individuals having low sugar intakes (HR=1.13 (1.02 to 1.27), P=0.02, 509 cases and 51,838 non-cases) and in those having higher intakes (HR=1.22 (1.08 to 1.38), P=0.001, 312 cases and 52048 non-cases).

Table 9 - Associations between ultra-processed food (UPF) intake and type 2-diabetes from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2019 (n=104,707)[a]

Proportion of ultra-processed food intake in the diet (%)							
	Sex-specific quartiles[b]					Continuous[c]	
	Q1	Q2	Q3	Q4			
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-value
Type 2-Diabetes							
N for cases/non-cases	226/25950	225/25952	211/25966	159/26018		821/103886	
Model 1	1	1.02 (0.85 to 1.23)	1.10 (0.91 to 1.33)	1.30 (1.06 to 1.61)	0.01	1.15 (1.06 to 1.25)	0.0009
Model 2	1	1.04 (0.87 to 1.26)	1.14 (0.94 to 1.38)	1.42 (1.15 to 1.76)	0.02	1.20 (1.10 to 1.30)	<0.0001
Model 3	1	1.00 (0.83 to 1.21)	1.09 (0.89 to 1.32)	1.26 (1.01 to 1.57)	0.04	1.15 (1.04 to 1.26)	0.004
Model 4	1	1.03 (0.85 to 1.24)	1.11 (0.92 to 1.34)	1.24 (1.00 to 1.53)	0.04	1.13 (1.04 to 1.22)	0.005

CI: confidence interval, HR: Hazard ratio

Median follow-up times 6.0y, 582,252 person-years

[a] Model 1 was a multi-adjusted Cox proportional hazard model adjusted for age (timescale), sex, educational level, BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, and family history of T2D.

Model 2 = Model 1 + saturated fatty acid intake, sodium intake, sugar intake, dietary fiber intake

Model 3 = Model 1 + intakes of red and processed meat, sugary drinks, fruits and vegetables, whole grains, nuts and yoghurt.

Model 4 = Model 1 + baseline prevalent dyslipidaemia and hypertension (yes/no), and treatments for these conditions (yes/no).

[b] Cut-offs for quartiles were 0.108, 0.156 and 0.219 for men and 0.106, 0.153 and 0.215 for women.

[c] HR for an absolute increment of 10 in the percentage of UPF in the diet

Sensitivity analyses

The findings remained robust throughout all sensitivity models: after excluding the cases of T2D having occurred during the first two years of follow-up (HR=1.16 (1.05 to 1.28), P=0.004, 544 cases and 103,886 non-cases), unadjusting for BMI (HR=1.20 (1.11 to 1.31), P<.0001), adjusting for Healthy and Western patterns, for number of smoked pack-years, the season of inclusion in the cohort (hazard ratios remained similar). Excluding participants with less than six dietary records did not affect the significant associations (HR=1.16 (1.05 to 1.29), P=0.004, 589 cases and 51,342 non-cases); neither did the exclusion of prevalent cases of hypertension and dyslipidemia at baseline (HR=1.16 (1.04 to 1.29), P=0.008, 428 cases and 90,555 non-cases). Dealing with missing data by using multiple imputations via the MICE method (132) showed similar hazard ratios.

More specifically, the proportions of ultra-processed foods in the following food groups were associated with increased T2D risk: beverages ($HR_{\text{for an absolute increment of 10 in the percentage of beverages consumed in their ultra-processed form}}$ =1.16 (1.10 to 1.22), P<0.0001), sugary products ($HR_{\text{for an absolute increment of 10 in the percentage of sugary products consumed in their ultra-processed form}}$ =1.04 (1.01 to 1.07), P =0.02), fats/sauces ($HR_{\text{for an absolute increment of 10 in the percentage of fats and sauces consumed in their ultra-processed form}}$ =1.06 (1.03 to 1.10), P<0.0001), and dairy products ($HR_{\text{for an absolute increment of 10 in the percentage of dairy products consumed in their ultra-processed form}}$ =1.05 (1.01 to 1.08), P=0.005). The consumption of fruit & vegetables; meat, fish & eggs; starchy foods and salty snacks in their ultra-processed form was not associated with T2D risk (P=0.4; 0.2; 0.1 and 0.2 respectively). These analyses were adjusted for model 1 covariates as well as the consumption amount of the specific food group (in g/d).

In secondary analyses, and in line with these findings, the consumption of unprocessed or minimally processed foods was inversely associated with T2D risk: $HR_{\text{for an absolute increment of 10 in the percentage of unprocessed/minimally processed foods in the diet}}$ =0.91 (0.84 to 0.98), P=0.01.

Chapter IV: Consumption of ultra-processed food, weight trajectories, and overweight and obesity risks

Scientific publication:

Srour, B.*, Beslay, M.*, Mejean, C., Alles, B., Fiolet, T., Debras, C., Chazelas, E., Deschasaux, M., Hercberg, S., Galan, P., Monteiro, CA., Kesse-Guyot, E., Touvier, M.≠, Julia, C.≠ Consumption of ultra-processed foods and the risk of overweight and obesity, and weight trajectories in the French cohort NutriNet-santé *(* and ≠: equal contributions) (in preparation)*

Descriptive analyses

For the current study, baseline was considered as the average of dietary records filled at the inclusion of participants in NutriNet-Santé. This chapter is based on three analyses: weight trajectories, overweight and obesity. The corresponding samples were obtained as explained in the flowchart below (figure 17).

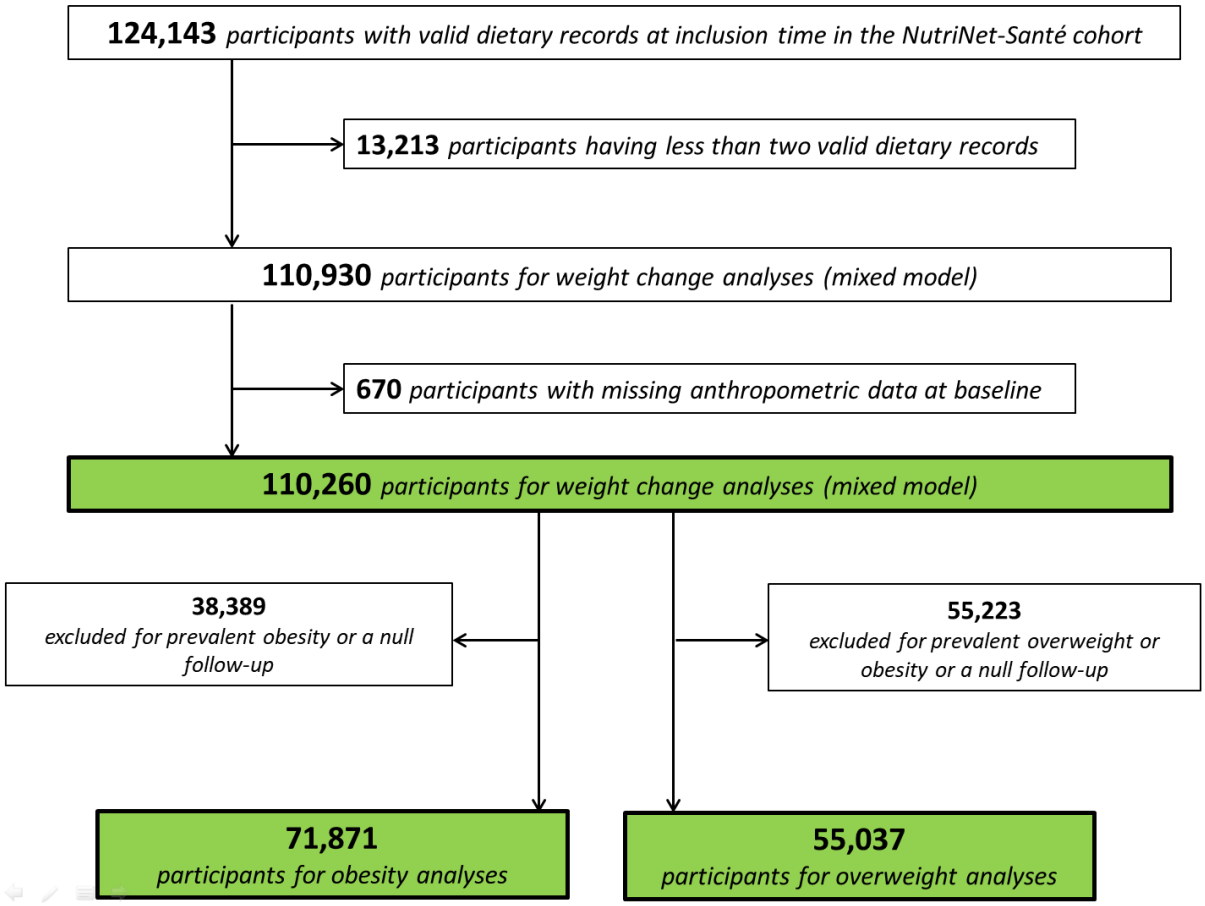

Figure 17 - Flowchart for study sample (UPF-weight change, overweight and obesity), NutriNet-Santé cohort, 2009-2019

Characteristics of the study population according to quartiles of the proportion of ultra-processed food in the diet are very similar to those of the other analyses and will not be repeated for readability purposes.

Weight trajectories - Mixed models

Results of the prospective associations between ultra-processed food consumption and BMI change on a sample of 110,260 participants are shown in table 10. Participants in the fourth quartile of ultra-processed food consumption had higher BMI at baseline (β coefficients for Q4 >0) compared to those in the 1st quartile (reference in the model). After adjustment for age, sex, marital status, educational level, physical activity level, smoking status, alcohol consumption, energy intake, and number of dietary records (model 1), participants in the first quartile of ultra-processed food consumption (reference category) had a significant increase in BMI over time (β coefficients for time significantly >0). However, participants in quartiles 2, 3 and 4 had a significantly higher increase in BMI over time compared to Q1 (β coefficients for interactions terms between time and quartile >0), the magnitude of BMI increase being the highest for Q4 ($\beta_{Q4*time}$=0.04 (0.04 to 0.05), p<0.0001). The findings remained similar after further adjustments for intakes of sugar, sodium, saturated fatty acids, and dietary fiber (model 2), for Healthy and Western dietary patterns (model 3), and for consumptions of fruit and vegetables and sugary drinks (model 4).

Table 10 - Associations between sex-specific quartiles of ultra-processed food consumption in the diet and weight change, NutriNet-Santé cohort, France, 2009-2019 (n=110,260)

	Model 1[a]		Model 2		Model 3		Model 4	
	β[b] (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Quartile 2 (BMI difference at baseline with the reference – Q1)	0.11 (0.04 to 0.19)	0.0026	0.02 (-0.05 to 0.09)	0.6	-0.00 (-0.07 to 0.07)	0.9	0.04 (-0.03 to 0.12)	0.2
Quartile 3 (BMI difference at baseline with the reference – Q1)	0.24 (0.16 to 0.31)	<0.0001	0.11 (0.03 to 0.18)	0.004	0.05 (-0.02 to 0.13)	0.1	0.13 (0.06 to 0.21)	0.0003
Quartile 4 (BMI difference at baseline with the reference – Q1)	0.60 (0.52 to 0.67)	<0.0001	0.42 (0.34 to 0.51)	<0.0001	0.30 (0.23 to 0.38)	<0.0001	0.43 (0.35 to 0.52)	<0.0001
Time (weight gain / year in the reference – Q1)	0.03 (0.03 to 0.04)	<0.0001	0.03 (0.03 to 0.04)	<0.0001	0.03 (0.03 to 0.04)	<0.0001	0.03 (0.03 to 0.04)	<0.0001
Time*quartile 2 (additional BMI gain / year compared to Q1)	0.01 (0.003 to 0.01)	0.001	0.01 (0.004 to 0.02)	0.001	0.01 (0.003 to 0.02)	0.001	0.01 (0.003 to 0.02)	0.002
Time*quartile 3 (additional BMI gain / year compared to Q1)	0.02 (0.01 to 0.02)	<0.0001	0.01 (0.01 to 0.02)	<0.0001	0.02 (0.01 to 0.02)	<0.0001	0.02 (0.01 to 0.02)	<0.0001
Time*quartile 4 (additional BMI gain / year compared to Q1)	0.04 (0.04 to 0.05)	<0.0001	0.04 (0.04 to 0.05)	<0.0001	0.04 (0.04 to 0.05)	<0.0001	0.04 (0.04 to 0.05)	<0.0001

Q1: Quartile 1, CI: confidence intervals

Quartiles of the proportion of UPF intake in the total quantity of food consumed. Cut-offs for quartiles were 0.102, 0.155 and 0.225 for men and 0.099, 0.152 and 0.221 for women.

[a] Model 1 is a mixed model for repeated measure, with intercept and time as random, adjusted for age, sex, marital status (living alone or not), educational level, physical activity level, smoking status, alcohol consumption, energy intake, and number of dietary records

Model 2 = Model 1 + intakes of sugar, sodium, saturated fatty acids and dietary fiber

Model 3 = Model 1 + Healthy and Western dietary patterns

Model 4 = Model 1 + consumptions of fruit and vegetables and sugary drinks

[b] Estimates β of parameters is interpreted as a variation of BMI in percentage.

BMI change over time by sex-specific quartiles of ultra-processed food proportion in diet is shown in figure 18. The mean BMI for each year and each quartile of dietary index is presented along with the 95% confidence interval of the mean. Graphically, and consistently with the mixed models findings, participants in the fourth quartile of ultra-processed food consumption had higher BMI at baseline. While an increase of BMI was observed in all quartiles, the BMI gain appeared to be higher for participants in quartiles 2 and 3 and particularly in the fourth quartile, compared to individuals from quartile 1.

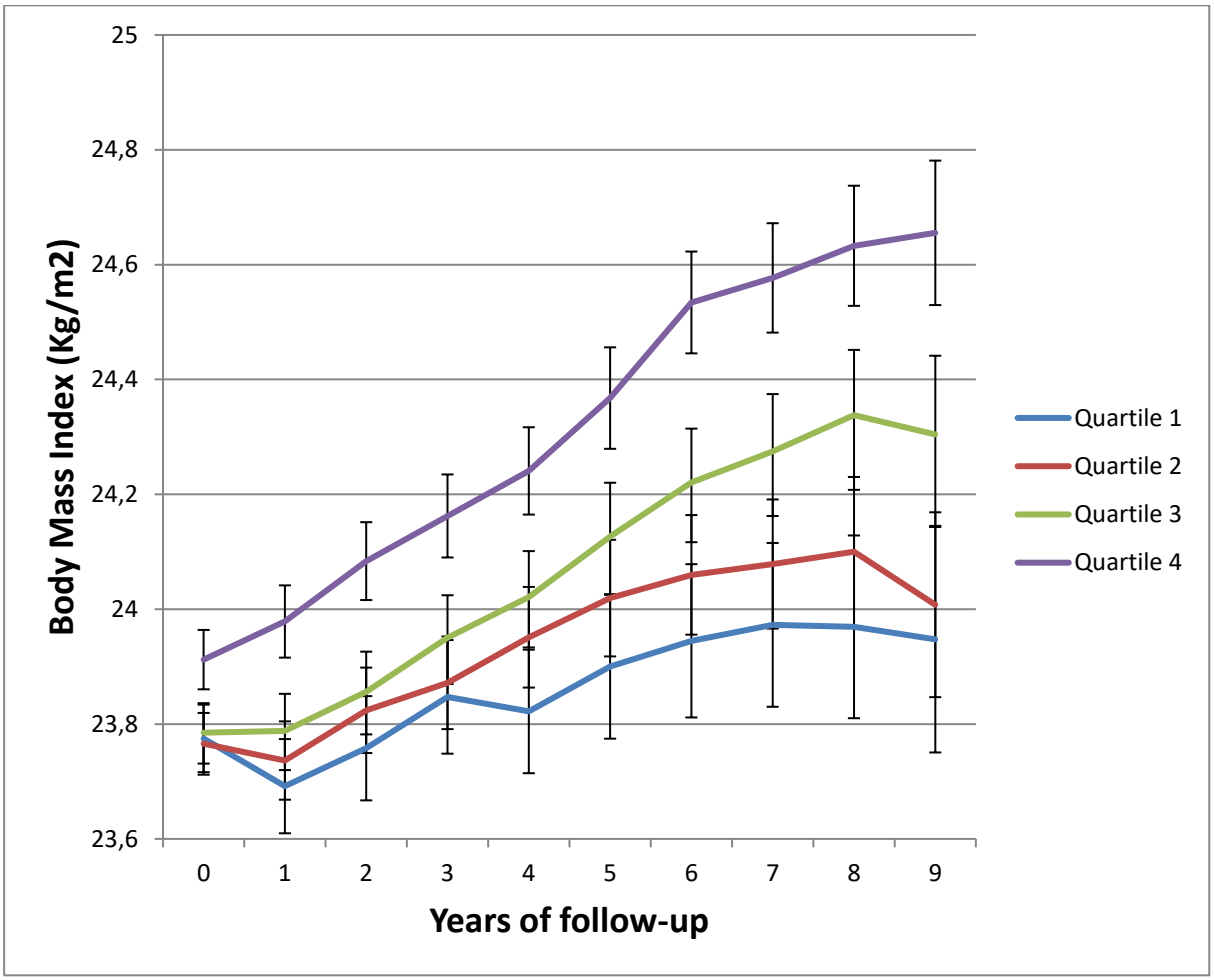

Figure 18 - Weight trajectories over time in the four quartiles of ultra-processed food consumption, NutriNet-Santé, 2009-2019

Overweight risk - Cox models

Analyses related to overweight incidence were performed on a sample of 55,037 participants. During follow-up (260,304 person-years, median follow-up time=4.1 years), 7063 incident cases of overweight occurred. The proportional hazard assumptions of the Cox models were met.

After adjustment for age (timescale), sex, BMI at baseline, marital status (living alone or not), educational level, physical activity level, smoking status, alcohol consumption, energy intake, and number of dietary records (model 1), participants with a higher proportion of ultra-processed foods in their diet had a higher risk of overweight ($HR_{\text{for an absolute increment of 10 in the percentage of UPF in the diet}}$ =1.11 (1.08 to 1.14), P<0.0001). These trends were significant starting the second quartile of UPF intake and were the strongest in the fourth quartile: $HR_{Q4 \text{ vs. } Q1}$ = 1.26 (1.18 to 1.35), p-trend <0.0001 (table 11
). These associations remained significant after unadjustment for BMI at baseline (model 2), and after further adjustments for sodium, sugar, saturated fatty acids, and dietary fiber intakes (model 3), Healthy and Western dietary patterns derived from PCA analysis (model 4) and consumption of fruit and vegetables and of sugary drinks (two factors associated with weight change according to the WCRF) (model 5).

Obesity risk - Cox models

Analyses related to obesity incidence were performed on a sample of 71,871 participants. During follow-up (365,344 person-years, median follow-up time=5.0 years), 3,066 incident cases of obesity occurred. The proportional hazard assumptions of the Cox models were met.

After adjustment for model 1 covariates, participants with a higher proportion of ultra-processed foods in their diet had a higher risk of obesity ($HR_{\text{for an absolute increment of 10 in the percentage of UPF in the diet}}$ =1.09 (1.05 to 1.13), P<0.0001). These trends were statistically significant starting the third quartile and were the strongest in the fourth quartile: $HR_{Q4 \text{ vs. } Q1}$ = 1.15 (1.04 to 1.28), p-trend=0.005 (table 11) and remained stable across all models with further adjustments.

Table 11 - Associations between ultra-processed food (UPF) intake and risks of overweight and obesity from multi-adjusted Cox proportional hazard models, NutriNet-Santé cohort, 2009 – 2019[a]

	Proportion of ultra-processed food in the diet[b]						
Overweight	**Q1**	**Q2**	**Q3**	**Q4**		**Continuous[c]**	
	HR	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**	**HR (95% CI)**	**P value**
N cases/non-cases	1666 / 12092	1706 / 12054	1830 / 11930	1861 / 11898		7063 / 47974	
Model 1	1	1.06 (1.00 to 1.14)	1.19 (1.11 to 1.28)	1.26 (1.18 to 1.35)	<.0001	1.11 (1.08 to 1.14)	<.0001
Model 2	1	1.07 (1.00 to 1.14)	1.19 (1.12 to 1.28)	1.30 (1.21 to 1.39)	<.0001	1.11 (1.08 to 1.14)	<.0001
Model 3	1	1.06 (0.99 to 1.13)	1.18 (1.10 to 1.26)	1.24 (1.16 to 1.33)	<.0001	1.10 (1.08 to 1.13)	<.0001
Model 4	1	1.05 (0.98 to 1.13)	1.17 (1.09 to 1.25)	1.22 (1.14 to 1.31)	<.0001	1.10 (1.07 to 1.13)	<.0001
Model 5	1	1.05 (0.98 to 1.13)	1.17 (1.09 to 1.25)	1.22 (1.13 to 1.31)	<.0001	1.10 (1.07 to 1.13)	<.0001
Obesity	**Q1**	**Q2**	**Q3**	**Q4**		**Continuous**	
	HR	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**p-trend**	**HR (95% CI)**	**P value**
N cases/non-cases	687 / 17280	723 / 17245	803 / 17166	853 / 17114		3066 / 68805	
Model 1	1	1.05 (0.94 to 1.16)	1.10 (1.00 to 1.22)	1.15 (1.04 to 1.28)	0.005	1.09 (1.05 to 1.13)	<.0001
Model 2	1	1.09 (0.98 to 1.21)	1.26 (1.13 to 1.39)	1.41 (1.27 to 1.57)	<.0001	1.19 (1.15 to 1.23)	<.0001
Model 3	1	1.05 (0.95 to 1.17)	1.11 (1.00 to 1.23)	1.16 (1.05 to 1.30)	0.003	1.10 (1.06 to 1.14)	<.0001
Model 4	1	1.06 (0.95 to 1.18)	1.12 (1.01 to 1.24)	1.20 (1.08 to 1.33)	0.0006	1.11 (1.07 to 1.15)	<.0001
Model 5	1	1.05 (0.95 to 1.17)	1.11 (1.00 to 1.23)	1.15 (1.03 to 1.28)	0.009	1.10 (1.05 to 1.14)	<.0001

CI: confidence interval, HR: Hazard ratio, N = 55307 for overweight analyses and 71871 for obesity analyses

[a] Model 1 was a multi-adjusted Cox proportional hazard model adjusted for age (timescale), sex, educational level, marital status, baseline BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records and energy intake

Model 2 = Model 1 unadjusted for baseline BMI

Model 3 = Model 1 + intakes of sodium, sugar, saturated fatty acids, and dietary fiber.

Model 4 = Model 1 + Healthy and Western dietary patterns

Model 5 = Model 1 + consumptions of fruit and vegetables, and sugary drinks

[b] Cut-offs for quartiles were 0.099, 0.149 and 0.215 for men and 0.096, 0.145 and 0.211 for women in the overweight analyses; and 0.098, 0.148 and 0.212 for men and 0.096, 0.145 and 0.211 for women in the obesity analyses

[c] HR for an absolute increment of 10 in the percentage of UPF in the diet

For readability purposes, having two distinct outcomes, the results for stratified and sensitivity analyses of this chapter were tabulated (table 12).
The associations with overweight and obesity risk were statistically significant in all strata of the population investigated (age groups, subgroups according to sugar and SFAs intakes, smoking status) except in men, probably due to a weaker statistical power (table 12).

Sensitivity analyses

Results of sensitivity analyses are presented table 12. The findings remained robust throughout all sensitivity models: after excluding the cases of overweight and obesity occurring during the first two years of follow-up, adjusting for the season of inclusion in the cohort or for the time spent sitting down. Replacing the ultra-processed variable by a variable computed as the proportion of ultra-processed food weighted by energy (rather than the amount) did not change the findings; neither did the replacement by the amount of ultra-processed food consumption in g/day. Dealing with missing data by using multiple imputations via the MICE method (132) showed similar results, so did complete case analysis.

More specifically, ultra-processed beverages, dairy products, fats and sauces, and meat, fish and egg, were associated with increased overweight and obesity risks, while ultra-processed starchy foods and breakfast cereals were associated with an increased risk of overweight (table 13). In contrast, there was no evidence for a positive association between these food groups in their non-ultra-processed form and increased overweight and obesity risks ($p>0.05$), except for meat, fish and eggs: $HR_{\text{for a 100g increase in non-ultra-processed meat, fish and eggs consumption}} = 1.16$ (1.12 to 1.20), $P<.0001$ for overweight, and HR=1.17 (1.11 to 1.22), $P<.0001$ for obesity (data not tabulated).

In secondary analyses, and in line with these findings, the consumption of unprocessed or minimally processed foods was inversely associated with overweight risk ($HR_{\text{for an absolute increment of 10 in the percentage of unprocessed/minimally processed foods in the diet}} =0.95$ (0.92 to 0.97), $P<0.0001$), but

statistical significance was not reached in obesity analyses (HR for an absolute increment of 10 in the percentage of unprocessed/minimally processed foods in the diet =0.97 (0.94 to 1.00), P=0.1).

Table 12 - Associations between ultra-processed food (UPF) intake and risks of overweight and obesity from multi-adjusted Cox proportional hazard models after sensitivity and stratified analyses, NutriNet-Santé cohort, France, 2009 – 2019[a]

	Overweight risk			Obesity risk		
	N cases/non-cases	**HR[*] (95% CI)**	**P-value**	**N cases/non-cases**	**HR[*] (95% CI)**	**P-value**
After excluding cases of the first two years of follow-up	3397 / 47974	1.12 (1.08 to 1.16)	<.0001	1543 / 68805	1.13 (1.07 to 1.18)	<.0001
UPF proportion weighted by energy	7063 / 47974	1.06 (1.04 to 1.08)	<.0001	3066 / 68805	1.03 (1.00 to 1.05)	0.03
Amount of UPF (g/day in the diet) (for an increment of 100 g)	7063 / 47974	1.04 (1.03 to 1.03)	<.0001	3066 / 68805	1.05 (1.03 to 1.06)	<.0001
Further adjustment for time spent sitting down or being sedentary	6440 / 44040	1.10 (1.08 to 1.13)	<.0001	2759 / 63096	1.08 (1.04 to 1.12)	<.0001
Further adjustment for season of inclusion	7063 / 47974	1.10 (1.07 to 1.13)	<.0001	3066 / 68805	1.08 (1.04 to 1.12)	<.0001
In men	1612 / 8494	1.08 (1.02 to 1.13)	0.003	638 /15228	1.02 (0.94 to 1.10)	0.5
In women	5451 / 39480	1.12 (1.09 to 1.15)	<.0001	2428 / 53577	1.10 (1.06 to 1.14)	<.0001
In younger adults (<=45 yo)	3689 / 27004	1.13 (1.09 to 1.16)	<.0001	1441 / 35488	1.09 (1.03 to 1.14)	0.0004
In older adults (> 45 yo)	3374 / 20970	1.07 (1.02 to 1.11)	0.0009	1625 / 33317	1.09 (1.03 to 1.14)	0.001
In participants having lower sugar intakes (≤ 89.9 g)	3693 / 23825	1.07 (1.03 to 1.11)	0.0002	1735 / 34201	1.07 (1.02 to 1.13)	0.002
In participants having higher sugar intakes (> 89.9 g)	3370 / 24149	1.14 (1.11 to 1.18)	<.0001	1331 / 34604	1.09 (1.04 to 1.15)	0.0003
In participants having lower SFA intakes (≤ 31.2 g)	3405 / 24114	1.10 (1.07 to 1.14)	<.0001	1536 / 34400	1.06 (1.01 to 1.12)	0.007
In participants having higher SFA intakes (> 31.2 g)	3658 / 23860	1.10 (1.07 to 1.14)	<.0001	1530 / 34405	1.09 (1.04 to 1.15)	0.0003
In smokers and former smokers	3607 / 22037	1.11 (1.07 to 1.15)	<.0001	1677 / 33223	1.06 (1.01 to 1.11)	0.01
In non-smokers	3456 / 25937	1.11 (1.07 to 1.15)	<.0001	1389 / 35582	1.11 (1.06 to 1.17)	<.0001
Multiple imputation using MICE	7063 / 47974	1.11 (1.08 to 1.13)	<.0001	3066 / 68805	1.08 (1.05 to 1.12)	<.0001
Complete case analysis	5664 / 39360	1.10 (1.07 to 1.14)	<.0001	2460 / 56261	1.10 (1.06 to 1.14)	<.0001

CI: confidence interval, HR: Hazard ratio, SFA: saturated fatty acids, YO: years-old, N = 55307 for overweight analyses and 71871 for obesity analyses

[*] HR for an absolute increment of 10 in the percentage of ultra-processed food in the diet, except when stated otherwise

[a] Models were adjusted for age (timescale), sex (except when stratified), educational level, marital status, baseline BMI, physical activity, smoking status (except when stratified), alcohol intake, number of 24h-dietary records and energy intake

[b] Multiple imputation for missing data using the MICE method (131) by fully conditional specification (FCS, 20 imputed datasets) for level of education and physical activity level. Results were combined across imputation based on Rubin's combination rules (133,134) using the SAS PROC MIANALYZE procedure (135).

Table 13 - Associations between the quantity (g/d) of each food group in their ultra-processed form, for an increase of 100g of the quantity consumed in g/day, and the risks of overweight (7063 cases) and obesity (3066 cases), NutriNet-Santé cohort, France, 2009-2019[a]

Food groups in their ultra-processed form	Overweight risk		Obesity risk	
	HR* (95% CI)	p-value	HR* (95% CI)	p-value
Beverages	1.04 (1.03 to 1.15)	<0.0001	1.06 (1.05 to 1.08)	<0.0001
Dairy products	1.09 (1.05 to 1.12)	<0.0001	1.08 (1.02 to 1.13)	0.004
Fats and sauces	1.23 (1.12 to 1.50)	0.0004	1.26 (1.03 to 1.54)	0.02
Fruits and vegetables	0.98 (0.96 to 1.01)	0.1	1.00 (0.97 to 1.03)	0.9
Meat, fish and egg	1.30 (1.22 to 1.38)	<0.0001	1.16 (1.06 to 1.27)	0.002
Starchy foods and breakfast cereals	1.07 (1.01 to 1.13)	0.03	1.07 (0.98 to 1.17)	0.1
Sugary products	1.00 (1.00 to 1.01)	0.2	1.00 (0.99 to 1.00)	0.3
Salty snacks	1.01 (0.84 to 1.23)	0.8	1.12 (0.83 to 1.51)	0.5

CI: confidence interval, HR: Hazard ratio, N = 55307 for overweight analyses and 71871 for obesity analyses
*HR for an absolute increment of 100 g/day in the consumption of the food group in its ultra-processed or non-ultra-processed form
[a] Models were adjusted for age (timescale), sex, educational level, marital status, baseline BMI, physical activity, smoking status (except when stratified), alcohol intake, number of 24h-dietary records and energy intake

DISCUSSION

I. Summary of principal findings

In the framework of my PhD thesis, **4 prospective studies** based on samples from the French **NutriNet-Santé** cohort have found linear associations between the **consumption of ultra-processed food** and **weight gain**, as well as risks of several **non-communicable diseases.**

For an **absolute increment of 10** in the percentage of **ultra-processed foods** in the diet, the corresponding risk increases were

12% for overall cancer

11% for breast cancer

13% for post-menopausal breast cancer

12% for cardiovascular diseases

13% for coronary heart diseases

11% for cerebrovascular diseases

15% for type-2 diabetes

11% for overweight

9% for obesity

In addition, I showed that the consumption of unprocessed or minimally processed foods was associated with a decreased risk of mortality (141). In addition, I have participated in investigations showing an association between the consumption of ultra-processed foods and mortality (112), and depressive symptoms (110). These results remained statistically significant and robust after multiple sensitivity analyses, including further adjustments to better account for confusion, stratified analyses, sample-restriction analyses, and multiple methods to deal with missing data. Overall, the nutritional quality of ultra-processed foods was lower than the one of less minimally or unprocessed foods, with 85% of the products scored “E” with the Nutri-Score being ultra-processed according to the Nova classification in the NutriNet-Santé

food composition database. However, nutritional quality of ultra-processed foods and of the overall diet of participants consuming these foods did not seem to fully explain the observed associations, since adjusting for these factors did not substantially modify the findings. Thus, the mechanisms underlying these associations probably rely on other factors, beyond purely nutritional aspects (nutrients and vitamins) and might involve other pathways and components of the diet.

II. Comparison and discussion in the light of epidemiological literature

To our knowledge, these studies were the first and only prospective studies so far having investigated associations between the consumption of ultra-processed foods, using the NOVA classification, and the risks of cancer, cardiovascular diseases, and type 2-diabetes. The EREN team is involved in a research project to replicate these findings in the EPIC cohort. The other classifications of foods according to their degree of processing were never used in etiological studies to our knowledge.

In regards to overweight and obesity risk, several cross-sectional studies exploring associations between ultra-processed food consumption and BMI, and odds of overweight and obesity have been published (66,142,143). On the other hand, two ecological studies suggest that increased purchases and house availability of ultra-processed foods are associated with higher BMI and higher obesity prevalence (144,145). However, only one prospective Spanish study (107) based on a sample of 8,451 adults from the SUN (University of Navarra graduates) cohort, showed increased risks of overweight and obesity linked to higher ultra-processed food consumptions ($HR_{Q4\ vs.\ Q1}$ = 1.26 (1.10 to 1.45), p-trend=0.001) consistently with our findings. This study combined overweight and obesity in a same outcome, thus, direct comparison is not straightforward with our findings, even though the magnitudes of the association of both studies are similar ($HR_{Q4\ vs.\ Q1}$ =1.26 for overweight and obesity for the Spanish study, versus 1.26 for overweight risk in our study and 1.15 for obesity risk), and the confidence intervals overlap.

In regards to weight and anthropometric change, a Brazilian longitudinal study (146) showed a positive association, in a sample of 1,035 adolescents (mean age 15.7 years old), between a ultra-processed food consumption and change in BMI using mixed models, and concluded, consistently with our findings, that higher ultra-processed food consumers (participants in Q4) had higher BMI at baseline and a greater BMI increase compared to lower consumers (individuals in Q1). Another longitudinal Brazilian study (105) explored, in children, the

association between ultra-processed food consumption at pre-school age and change in waist circumference and waist-to-height ratio between 4 and 8 years old, and concluded to an association between an increased consumption of ultra-processed and an increase in the variation of waist circumference. However, this study did not use mixed models to explore the repeated measures, but a Z-score, and did not explore the change in BMI.

Of note, in a recent randomized controlled trial (114), Hall et al. included subjects admitted to the NIH clinical center, and allocated them either to an ultra-processed or unprocessed diet for 2 weeks immediately followed by the alternate diet for 2 weeks. They showed that the ultra-processed diet led to an increased energy intake (+508±106 kcal/d during the ultra-processed diet), which was highly correlated with weight gain (0.8±0.3 kg (p=0.01)), versus a weight loss of 1.1±0.3 kg during the unprocessed diet.

The four large-scale prospective studies based on data from the NutriNet-Santé in the framework of this thesis add a significant body of evidence to the existing prospective literature on the associations between ultra-processed foods and chronic disease. Table 14 sums up all prospective studies, including ours, having investigated these associations.

Table 14 - Available prospective studies investigating associations between ultra-processed food consumption using the NOVA classification and the risk of weight change or chronic diseases

Author, year	Country (sample size)	Cohort, population type	Health outcome	Number of cases	β or Hazard Ratio or Odds Ratio (95% CI)	Adjustments
Rauber, 2015 (147)	Brazil (n=345)	Sao Leopoldo, children	Lipid profiles	N/A	β for 1% increase in energy intake from UPF = 0.43 (0.008-0.853) for total cholesterol, and 0.369 (0.005-0.733) for LDL	Sex, group of intervention, birth weight, family income, maternal schooling, BMI-for-age z-scores, total energy intake at 7-8 years.
Mendonça, 2016 (107)	Spain (n=8,451)	SUN, university graduates adults	Overweight or obesity	1,939	$HR_{Q4\ vs\ Q1}$=1.26 (1.10-1.45)	Age, sex, marital status, educational status, baseline BMI, physical activity, television watching, siesta sleep, smoking status, snacking between meals, and following a special diet.
Mendonça, 2017 (108)	Spain (n=14,790)	SUN, university graduates adults	Hypertension	1,702	$HR_{T3\ vs\ T1}$=1.21 (1.06-1.37)	Age, sex, physical activity, hours of television watching, BMI, smoking status, use of analgesics, dieting a baseline, family history of hypertension and dyslipidemia, alcohol and total energy intake, intakes of olive oil, and fruit and vegetable.

Sandoval-Insausti, 2019 (106)	Spain (n=1,822)	Seniors-ENRICA, senior adults	Frailty	132	OR $_{Q4\ vs\ Q1}$=2.57 (1.41–4.70)	Age, sex, level of education, marital status, tobacco consumption, former-drinker status, chronic respiratory disease, coronary disease, stroke, osteoarthritis/arthritis, cancer, depression requiring treatment, and number of medications used.
Gómez-Donoso, 2019 (109)	Spain (n=14,907)	SUN, university graduates adults	Depression	774	HR $_{Q4\ vs\ Q1}$=1.33 (1.07–1.64)	Age, sex, marital status, living alone, educational status, baseline BMI, total energy intake, physical activity, working hours per week, health-related career, smoking status, years of education, adherence to Trichopoulo's MeDiet score, baseline self-perception of competitiveness, anxiety, and dependence levels.
Costa, 2019 (105)	Brazil (n=307)	Sao Leopoldo, children	BMI change, BMI change, waist circumference change, waist-to-height ratio change, glucose metabolism	N/A	β for 1% increase in energy intake from UPF = 0.07 (0.01-0.13) for WC, NS for others	Sex, group status in the early phase, pre-pregnancy BMI, birth weight, breastfeeding, family income, maternal schooling and total screen duration.

Rico-Campa, 2019 (111)	Spain (n=19,899)	SUN, university graduates adults	Mortality	335	HR $_{Q4\ vs\ Q1}$=1.62 (1.13–2.33)	Age, sex, marital status, physical activity, smoking status, snacking, special diet at baseline, body mass index, total energy intake, alcohol consumption, family history of cardiovascular disease, diabetes at baseline, hypertension at baseline, self-reported hypercholesterolemia at baseline, CVD at baseline, cancer at baseline, depression at baseline, education level, lifelong smoking, sedentary index, and television viewing
Kim, 2019 (113)	USA (n=11,898)	NHANES III, adults	Mortality	2,451	HR $_{Q4\ vs\ Q1}$=1.31(1.09-1.58), NS for cardiovascular mortality	Age, sex, race/ethnicity, total energy intake, poverty level, education level, smoking status, physical activity, and alcohol intake.

Srour and Fiolet, 2018 (139)	France (n=104,980)	NutriNet-Santé, adults	Cancer	2,228 overall, 281 prostate, 153 colorectal, 739 breast cancers	HR $_{\text{for an increase of 10\% of UPF proportion}}$ =1.13 (1.07-1.18) for overall cancer, HR $_{\text{for an increase of 10\% of UPF proportion}}$ =1.11 (1.01 to 1.21) for breast cancer. NS for prostate and colorectal cancer	Age, sex, energy intake without alcohol, number of 24 hour dietary records, smoking status, educational level, physical activity, height, body mass index, alcohol intake, family history of cancers, intakes of lipids, sodium, and carbohydrates, Western dietary pattern (derived by factor analysis). Breast cancer models were additionally adjusted for menopausal status, hormonal treatment for menopause, oral contraception, and number of children.
Schnabel, 2019 (112)	France (n=44,551)	NutriNet-Santé, middle-aged adults	Mortality	602	HR $_{\text{for an increase of 10\% of UPF proportion}}$ = 1.14 (1.04-1.27)	Age, sex, income level, education level, marital status, residence, BMI, physical activity level, smoking status, energy intake, alcohol intake, season of food records, first-degree family history of cancer or cardiovascular diseases, number of food records.

Adjibade, 2019 (110)	France (n=26,730)	NutriNet-Santé, adults	Depression	2,221	HR $_{\text{for an increase of 10\% of UPF proportion}}$ =1.22 (1.16-1.29)	Age, sex, marital status, educational level, occupational categories, household income per consumption unit, residential area, number of 24-h dietary records, inclusion month, energy intake without alcohol, alcohol intake, smoking status, physical activity, intakes of lipids, sodium, and carbohydrates, Healthy pattern, Western Pattern.
Srour, 2019 (140)	France (n=105,159)	NutriNet-Santé, adults	Cardiovascular diseases	1,409 cardiovascular, 665 coronary heart, and 829 cerebrovascular diseases	HR $_{\text{for an increase of 10\% of UPF proportion}}$ =1.13 (1.15-1.20) for cardiovascular disease, HR $_{\text{for an increase of 10\% of UPF proportion}}$ =1.14 (1.03 to 1.26) for coronary heart disease, HR $_{\text{for an increase of 10\% of UPF proportion}}$ =1.12 (1.02 to 1.22) for cerebrovascular disease.	Age, sex, energy intake, number of 24 hour dietary records, smoking status, educational level, physical activity, body mass index, alcohol intake, family history of cardiovascular disease, saturated fatty acid intake, sodium intake, sugar intake.

Srour, under review	France (n=104,707)	NutriNet-Santé, adults	Type 2-diabetes	821	$HR_{\text{for an increase of 10\% of UPF proportion}}$ =1.20 (1.10-1.30)	Age, sex, educational level, BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, family history of T2D, saturated fatty acid intake, sodium intake, sugar intake, dietary fiber intake
Srour and Beslay, article in preparation	France (n=110,260)	NutriNet-Santé, adults	Overweight, obesity and weight gain	7,063 overweight and 3,066 obesity cases	$HR_{\text{for an increase of 10\% of UPF proportion}}$ =1.10 (1.08-1.13) for overweight, $HR_{\text{for an increase of 10\% of UPF proportion}}$ =1.10 (1.06 to 1.14) for obesity. $\beta_{Q4 \text{ vs } Q1}$=0.04(0.04-0.05) for weight change	Age, sex, educational level, marital status, baseline BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, intakes of sodium, sugar, saturated fatty acids, and dietary fiber.

III. Synthetic discussion of the findings in the context of potential mechanistic pathways

A- Nutritional quality of ultra-processed foods

1. Cancer

Several hypotheses could be put forward to explain our findings. The first one relates to the generally poorer nutritional quality of diets rich in ultra-processed foods. Indeed, diets that include a higher proportion of processed food products tended to be richer in energy, sodium, fat and sugar and poorer in dietary fiber and various micronutrients in several studies conducted in various countries (40,41,43,44,46,55,59,68,74). Ultra-processed foods have also been associated with a higher glycemic response and a lower satiety effect (75). Although not being the unique determinant, excessive energy, fat, and sugar intakes contribute to weight gain and obesity risk, the latter being recognized as a major risk factor for the following cancers: post-menopausal breast, stomach, liver, colorectal, esophagus, pancreas, kidney, gallbladder, endometrium, ovary, liver, prostate (advanced) and hematological malignancies (107). For instance, body fatness in post-menopausal women is estimated to contribute to 17% of the breast cancer burden (148). Besides, most of ultra-processed foods, such as dehydrated soups, processed meats, biscuits and sauces, have a high salt content. Salt-preserved foods are associated with increased gastric cancer risk (107). Conversely dietary fiber intake decreases colorectal cancer risk with a convincing level of evidence (16,107) and may also reduce breast cancer risk (15). In addition, sugary drinks, among which several are ultra-processed (in particular sodas), might be associated with increased cancer risks, as suggested in a study that we published recently in the NutriNet-Santé cohort (149). However, the association between ultra-processed food intake and cancer risk observed in this study were statistically significant despite adjustment for BMI, and remained significant after further adjustment for a Western-type dietary pattern and/or energy, fat, sugar and salt content of the diet. This suggests that other bioactive compounds contained in ultra-processed food may contribute to explain the observed relationships.

2. Cardiometabolic outcomes

Several of nutritional characteristics of ultra-processed foods are known risk factors for: i) cardiometabolic health (21) and ii) T2D risks (24) with different levels of consensus. Sweetened beverages might also delay or slow down the internal satiety signal, leading to excessive caloric ingestion (150). In addition, several food groups that are mainly ultra-processed and are largely consumed in Western-type diets have been associated with increased risks of cardiometabolic outcomes with a high concordance, i.e. sugar-sweetened beverages and processed meats (21) and are associated with increased risks of T2D (24), and weight gain (151).

Among other determinants, excessive energy, fat, and sugar intakes contribute to weight gain and overweight and obesity risk, the latter being recognized as a major risk factor for CVDs and T2D (24,152). On the other hand, several ultra-processed foods and beverages (i.e. confectionery snacks, sugar-sweetened beverages, cakes, sports drinks, breakfast cereals) may contain relatively high levels of glucose-derived advanced glycation end-products (Glu-AGE) (153), which could over time lead to and/or accelerate vascular disease (154). In addition, high consumers of ultra-processed food in our study sample had lower consumptions of fruits and vegetables, known to beneficial to cardiometabolic health with a high level of evidence, so is adherence to a healthy pattern (21).

More generally, part of the association between ultra-processed food intake and cardiometabolic risk probably went through the simultaneous lower consumption of non-ultra-processed foods. Both effects cannot be disentangled since by construction, people having an overall higher share of ultra-processed foods in their diets also had a lower overall proportion of non-ultra-processed foods (Person correlation coefficient between the proportions of minimally processed and ultra-processed foods in the diet=-0.8). However, this did not explain the whole association.

Indeed, several ultra-processed food groups were associated with increased CVD, overweight and obesity risks while the non-ultra-processed form of these food groups were not.

Besides, the associations observed in this study between ultra-processed food intake and the risk of cardiometabolic outcomes were statistically significant even after adjustment for baseline BMI, and remained significant after further adjustments for Healthy-type and Western-type dietary patterns, energy, fat, sugar, salt, dietary fiber content of the diet, as well as consumption of sugary products, salty snacks, fats and sauces, red and processed meat, beverages, and fruit and vegetables. This suggests that, as for cancer, the nutritional composition of ultra-processed foods was not the only factor driving the associations observed

and that other bioactive compounds specifically contained in ultra-processed food may as well contribute to the observed relationships.

B- Food additives

1. Cancer

While maximum authorized levels normally protect the consumers against adverse effects of each individual substance in a given food product (155), impact on human health of the cumulative intake across all ingested foods and potential cocktail/interaction effects remain largely unknown. More than 330 different additives are authorized for an adjunction to food products in Europe (156). For some of them, experimental studies on animal or cellular models have suggested carcinogenic properties that deserve further investigation in humans (87,92,157–160). For instance, this is the case for titanium dioxide (TiO2) (e171), a common food additive that contains nanoscale particles and that is used as a whitening agent or in packaging in contact with food or beverages to provide a better texture and anti-microbial properties. Experimental studies, mainly conducted in rodent models, suggested that this additive could initiate or promote the development of colon preneoplastic lesions, as well as chronic intestinal inflammation, thus, TiO2 was evaluated as "possibly carcinogenic to humans" (Group 2B) by the World Health Organization - International Agency for Research on Cancer (WHO-IARC) (92). Nonnutritive sweeteners such as acesulfame potassium, sucralose and aspartame (e950/e955/e951) have been linked with hematopoietic neoplasia and gut microbiota alteration in experimental studies on rodents (161–164). Carboxymethylcellulose (e466) has been associated with changes in microbiota composition, intestinal inflammation and metabolic syndrome (in-vivo) (165–168), pro-inflammation (in-vivo, ex-vivo) (169–172) and promotion of tumor development (in-vivo) (173). Sulfite ammonia caramel (e150d), present in almost every cola, might carry 4-methylimidazole (4-MEI) was defined as possibly carcinogenic to humans by the IARC) (174,175). Moreover, sodium nitrites and nitrates (e250/e252) have been associated in prospective cohorts with all-cause mortality (nitrates/nitrites from processed meat) (176), and gastric and pancreatic cancers (90,177).

2. Cardiometabolic outcomes

Ultra-processed foods are often characterized by the presence of several food additives, among which some substance might interact with cardiometabolic health. High oral doses of sulfites (among which potassium metabisulphite, e224), which can be found in some ready-to-consume sauces containing vinegar, caused damage on rat hearts (95); doses of monosodium glutamate (MSG) (e621) (highly present especially in sauces and ready-to-eat soups and noodles) at dose levels of 4 mg/g body weight and above in mice increased the oxidative stress via lipid peroxidation and thereby, may initiate atherosclerosis and other coronary heart diseases (93). Moreover, MSG has suspected obesogenic properties with epidemiological evidence positively correlating its consumption to increased body mass index and higher prevalence of metabolic syndrome (178). In addition, emulsifiers, often found in ultra-processed foods, and in particular carboxymethylcellulose and polysorbate-80 (e433), have shown potential roles in inducing low-grade inflammation and obesity/metabolic syndrome in mice (94). Carrageenan (e407), used as a food additive for its thickening properties, may lead to glucose intolerance, insulin resistance and inhibition of insulin signaling in vivo in mouse liver and human HepG2 cells (96,179). Furthermore, an experimental study among humans suggests a link between lecithins (e322) and coronary artery disease through the production of a proatherosclerotic metabolite, trimethylamine-N-oxide (TMAO) (180).

Several food additives commonly used in food processing have Phosphorus as their main component, adding to the contribution of phosphoric acid (e338) in sodas. In the EPIC-France cohort (E3N), high phosphorus intakes were associated with increased T2D risk (181).
Non-caloric artificial sweeteners might as well play a role in these associations: long-term consumption of acesulfam-K (e950) might accelerate atherosclerosis in cellular models (182) while sucralose (e955) was reported to increase glucose and insulin levels in obese women, alter metabolic response to a glucose load and slow down insulin clearance from plasma in a randomized control trial (183). Artificially sweetened beverages were associated with increased risks of stroke and dementia (184). Moreover, a meta-analysis of randomized controlled trials and prospective cohort studies observed that non-nutritive sweeteners consumption (acesulfam-K, aspartame, sucralose) was associated with a higher incidence of T2D and weight gain (99), consistently with a meta-analysis of prospective studies showing an association between the consumption of artificially sweetened beverages and T2D risk (even though publication bias could not be ruled out) (185).

C- Contact materials and processing aids

Ultra-processed foods, often packaged in plastic materials, might be contaminated by the migration of contact materials, especially since they have long expiry dates, among which Bisphenol-A (BPA), “a substance of very high concern” as stated by the European Chemicals Agency (ECHA) (84). The exposure to BPA, an endocrine disruptor, as well as high BPA serum concentrations have been associated with increased T2D risk in recent meta-analyses (83,85) and found to be associated with an increased risk of hypertension and coronary artery disease (83). Moreover, There is increasing evidence for involvement in the development of several non-communicable diseases, including cancer (186) linked to endocrine disruptors. Of note, BPA was forbidden for use in food packaging in 2015 in France (thus posterior to the launching of the NutriNet-Santé cohort). BPA is being replaced by other components such as Bisphenol-S (BPS). However, a recent study has revealed that this component, also having endocrine disruption properties, was on average about 250 times more absorbed orally than for BPA, in pigs (187).

In addition, phthalates used in industrial plastic packaging (PVC) might contaminate the foods. They were detected in high doses in poultry, cooking oils and cream-based dairy products. Phthalates are classified as endocrine-disrupting chemicals and have been linked to adverse health effects particularly in relation to early life exposures (188).

High-pressure processing is a safe process that can be used to inactivate microorganisms and stabilize their growth during storage in meat and meat products. Pressure levels higher than 400 MPa are generally necessary to achieve efficient microbial inactivation, depending on the product microbiota and on the meat product itself. Such pressure levels may induce significant changes in the quality attributes of meat and meat products as high pressure has been shown to induce protein denaturation and acceleration of lipid oxidation during subsequent storage (189), which might alter the meat properties, and interact with its digestibility and safety when consumed.

In addition, potatoes used for packaged chips might undergo anti-sprouting treatments using agents like chlorpropham. According to the ECHA, this substance is suspected of causing cancer and may cause damage to organs through prolonged or repeated exposure (190). Even though potatoes are rinsed after being in contact with this treatment, chlorpropham residuals might be found in chips.

D- Neoformed compounds

Ultra-processed foods that went through processes such as high-temperature heating might contain neoformed compounds: among these contaminants, acrylamide (found mainly in fried potatoes, biscuits, cakes, bread or coffee) and acrolein (found in grilled sausages and caramel candies metabolites) were associated with insulin resistance (81,82). In addition, a recent meta-analysis underlined a modest association between dietary acrylamide and both kidney and endometrial cancer risks, in non-smokers (78). In addition, the EFSA judged that proofs from animal studies were sufficient to classify acrylamide as genotoxic (77). Acrylamide was associated with higher odds of CVDs in the NHANES study (79) while acrolein exposure was associated with platelet activation and suppression of circulating angiogenic cell levels, as well as increased CVD risk in the Louisville Healthy Heart Study (80). On the other hand, urinary biomarkers of polycyclic aromatic hydrocarbons were positively associated with diabetes in the NHANES study (191).

Furthermore, high levels of furans were observed in sample of industrial breakfast cereals, canned food and coffee. Even though this substance might be detected in cooked/baked home-made food (toasted bread for instance) especially in foods rich in carbohydrates, it is likely that industrial processes lead to higher levels of furan (192). Hepatotoxic and genotoxic properties for this substance were suspected by the EFSA (193).

IV. Methodological discussion

A- Methodological aspects related to the observational design

Observational studies focusing on nutrition and physical activity have a number of strengths and limitations compared with interventional studies. Observational studies tend to be less expensive than intervention trials, though cost differences depend on the intensity and frequency of data collection. They allow the simultaneous investigation of associations between health end points and different nutrition and physical activity factors, including those that could not be tested in long-term experimental studies in humans, due to suspicions of deleterious associations with health, like ultra-processed foods. Their sample size and follow-up duration allows investigating interactions among dietary and physical activity exposures and interactions of these exposures with genetic factors, while capturing exposures as they are in daily life (194). However, observational studies have higher risks of confounding bias, due to unmeasured

factors. Thus, a causal link could not be established from a single observational study. The gold-standard in epidemiology to establish causality is RCTs. These interventional studies are less subject to confounding bias, however, they have several limits, such as not capturing the exposure or the behavior (the intervention factor) as it is in the daily life, a high cost, and a complicated feasibility due to ethical, practical and logistical reasons. For instance, in nutritional epidemiology, for obvious ethical reasons (and for logistic and methodological considerations), no RCT can be performed on a long term to investigate the effect of an intervention based on a voluntary "administration" of a putative deleterious factor (here ultra-processed food) to one arm versus placebo (e.g. unprocessed or minimally processed foods), to monitor chronic disease risk (especially cancer and cardiometabolic hard endpoints). Thus, large-scale observational cohort studies replicated in different countries and settings, in association with short term RCT and mechanistic in vivo / in vitro experimental studies will altogether constitute the body of evidence that will be taken into account to explore the possible impacts of UPF on health, an potentially to establish causality.

One short-term randomized controlled trial published so far showed a strong effect of an ultra-processed diet on weight gain and energy intake (114). This kind of trials would not be ethically or logistically feasible to investigate longer term associations with hard adverse health endpoints such as cancer, cardiovascular diseases, T2D, or mortality, but provides useful insights into potential mechanisms underlying associations observed in long-term epidemiological cohorts.

B- Potential confounding bias

All observational studies are subject to potential confounding bias. Such bias implies a factor that is related to both the exposure variable and the investigated outcome, without being a mediating factor of the association. While such bias can be reduced by the adjustment for variables that have been identified as confounding factors in the literature, unmeasured factors cannot be adjusted for. Furthermore, the impact of statistical of adjustment is limited to the degree of detail and accuracy of the measured variables. Thus, the possibility of residual confounding cannot be excluded and should be taken into account when interpreting the findings of this thesis. For instance, treatments for each metabolic disorder were considered as binary variables, and the duration of the treatment and the compliance were not accounted for. No detailed information about the type and dose of contraception or menopausal treatment was used in this study, since these potential confounding factors were coded as binary variables.

Other potential confounders were missing, such as professional stress or genetic factors, even though we tried using proxies to account for these conditions, such as baseline depression or family history of chronic diseases.

In order to limit residual confounding, a large number of potential confounders have been taken into account and several sensitivity analyses (testing further adjustments and/or stratifications) showed the high stability of the results.

C- Potential selection bias

As it is usually the case in volunteer-based cohorts, participants to the NutriNet-Santé cohort were more often women, with higher socio-professional and educational levels as compared to the general French population (195). They were also less likely to smoke (196), to be overweight/obese (28.2% in men and 29.4% in women in NutriNet-Santé vs. 54% in men and 44% in women in the French population) (197), and to be affected by type 2 diabetes (baseline prevalence in the cohort = 1.6% versus 6% in the French population (198)). Participants of the NutriNet-Santé cohort also had healthier dietary intakes than the French population: higher intakes of fruits, vegetables and fish, and lower intakes of red meat and added fats (196). This may have resulted in a lower incidence of chronic diseases compared with national estimates:

- 786 cancer cases per 100,000 person-years in our cohort *vs* 972 cases in France (199)
- 495 CVD cases per 100,000 person-years in our cohort *vs* 500 in France (200), although these figures are not strictly comparable because unlike in our cohort, no national data is available for non-hospitalized CVDs in France
- 186 T2D cases per 100,000 person-years in our cohort *vs* 289 per 100,000 in the France (201)

This may have resulted as well in an underrepresentation of high ultra-processed food consumers, leading to a lower contrast between extreme categories.

All these points most probably resulted in an underestimation of the strength of the associations. However, the possibility that selection bias may have led to an overestimation of some associations cannot be totally ruled out.

To date, no nationally representative data has been published regarding the proportion of ultra-processed food in the diet in the French population, thus comparison with our population study is not straightforward. The nationally representative INCA3 study conducted by the French

Food safety Agency in 2016 (202) was not based on the NOVA classification. However, the authors provided a list of all food groups that they considered as "transformed" (sweet pastries, biscuits, dairy desserts, ice cream, fruit purée and fruit in syrup, fruit and vegetable juices, soups and broths, sandwiches, pizzas and salted pastries, as well as mixed dishes composed of egg, meat, fish, vegetable and/or starchy foods). More than half of the "transformed" foods consumed outside catering establishments by adults aged 18-79 were manufactured industrially (about one-third were homemade, while the rest was handcrafted, e.g. caterer). Preliminary results that we obtained in the *Etude Nationale Nutrition Santé* representative survey (ENNS) (67) show that about 30% of the calories consumed by the French population come from ultra-processed food. This proportion is very similar to that in our sample (34%).

D- Potential classification bias

Nutrition and physical activity patterns are among the most difficult epidemiologic factors to measure (194). However, the nutritional data that were used in the studies included in this thesis were obtained with repeated 24-hour dietary records. In comparison with food frequency questionnaires, this method permits a much more precise assessment of the consumed quantities, with a higher level of detail (>3,500 food items in our study, compared to 100-200 items generally listed in FFQs) (203). Furthermore, it was particularly adapted for analyses on food processing, compared to a food frequency questionnaire, due to the differences of processing categories within the same FFQ item.

Besides, misclassification in the NOVA 'ultra-processed food' category cannot be ruled out. It has been reported that the disagreement rate for the NOVA classification between two assigners was 8.1%, based on a sample of 135 food items (57), among which very generic items (drinking milk products, other dairy, spreadable oils and fats…). However, the NutriNet-Santé food composition database includes approximately 3,500 food items, and is therefore much more detailed.

Even though NOVA had the lowest agreement levels with other classifications, it is unlikely that etiological findings based on each or another framework would be largely different (57). Moreover, no association between the number of processing categories described by a framework and the simplicity of assigning a food product into its category has been found (34,55,57). In addition to inter-rater reliability among three different classifications (IFIC, NOVA and UNC), Bleiwess-Sande and colleagues explored the ability of nutrient

concentration to predict processing category (56). Compared with minimally processed foods, higher sodium was a significant predictor of processed foods (in addition to ultra-processed food), which is expected since minimally processed are produced using minimally processed foods prepared with culinary ingredients (including salt). Nevertheless, this approach is questionable as the main objective of categorizing food products based on their processing levels is to isolate the non-nutritional aspect of foods linked to processes, by separating the nutritional value of the products from the other aspects.

Moreover, a committee of eight persons (three dieticians and five researchers in nutritional epidemiology) participated in or supervised the assignments in our team, therefore minimizing the misclassification risk. In addition, the committee that performed/reviewed the classification tried to avoid any unidirectional and systematic bias. Any remaining classification mistake would have led to a non-differential measurement error (i.e. identically in future cases and non-cases). This non-differential information bias in epidemiology generally leads to an under-estimation of the observed associations, although an overestimation cannot be excluded.

Ultra-processed foods as defined by the NOVA classification represent a broad and diverse spectrum of food products. This may be seen as a limitation, since with this approach, it is difficult to isolate the potential effect a specific process or food additive, but in the contrary, this exploratory approach allowed us to consider potential synergistic effects of various characteristics of ultra-processed foods. In this study, some associations were observed for several different ultra-processed food groups (beverages, fats and sauces, meat, fish and eggs, sugary products, salty snacks). The effects of ultra-processed foods on human health may go through complex mechanisms involving synergic effects of many compounds and characteristics of ultra-processed foods. A chronic exposure to multiple factors, including cocktails of food additives, neoformed compounds and contact materials may play a role in the studied association. An indicator such as the overall proportion of ultra-processed foods in the diet allows distinguishing individuals with a high/low exposure to these cocktail interactions. Subdividing this category into two or three sub-categories as suggested by some other frameworks might lead to an underestimation of the potential synergistic effects of these various factors. The fact that the associations were stronger when considering the overall ultra-processed food proportion in the diet, rather than the associations in specific food groups argue in favor of these potential cocktail effects.

E- Case ascertainment, statistical power and length of follow-up

The exhaustiveness of case detection cannot be guaranteed. However, a multi-source strategy for case ascertainment (combining validation of health events declared by participants (for cancer and CVD), deep investigation by the study physicians from participants, their families, and their physicians, disease and medication information using medico-administrative databases from the health insurance for all participants who provided their identification number, exhaustive national death and causes of death registry, and biological measures (for T2D)), allowed us to maximize cases detection.

Anthropometric data were self-reported, which represents a limitation due to potential measurement errors and social desirability bias. However, web-based self-reported weight and height data from the NutriNet-Santé study can be considered as valid enough to be used when studying associations of nutritional factors with anthropometrics and health outcomes (Kappa-coefficients for BMI between self-reported and clinically measured data=0.89 in a published validation study) (118).

Furthermore, statistical power was somehow limited for specific types of cancer and CVD, which may have impaired our ability to detect hypothesized associations.

The length of follow-up was relatively limited in time, since the cohort was launched in 2009. Thus, it allowed us to study mostly mid-term associations between ultra-processed food consumption and chronic diseases risk, while having recent data on dietary behaviors, covering therefore the consumption of "contemporary" ultra-processed foods on the market. Still, a classic assumption in nutritional epidemiology is that the measured exposure at baseline (especially since we averaged a two-year period of exposure) actually reflects more generally the usual eating habits of the individual not only at the moment of the study but also several years prior to his/her inclusion in the cohort and several years after. Thus, we assume that our study provided insights into the associations between "chronic" consumption of ultra-processed foods and chronic diseases risk. However, it will be important in the future to re-assess these associations in the cohort, in order to investigate longer-term associations.

F- Methodological strengths of the studies

Strengths of this study pertained to its prospective design, along with a detailed and up-to-date dietary intake assessment, including contemporarily available ultra-processed food products. Repeated 24h-dietary records, including about 3,500 different food items, are more accurate

than food frequency questionnaires with aggregated food groups, and household purchasing data (204), and they are more adapted for the application of food classifications such as the NOVA classification. Participants had 6 dietary records in average (up to 15) and a very low proportion (<8%) of the sample had two dietary records. Compared to food frequency questionnaires and dietary recalls, memory-related bias ("recall bias") is probably generally of smaller magnitude in 24-hour dietary records.

Social desirability bias is important to consider when interpreting nutritional data obtained from all types of nutritional assessment. Examples for such bias are underreporting of overall energy intake and fat intake, over reporting of the consumption of fruits and vegetables and inaccurate reporting of anthropometrics. The NutriNet-Santé platform is a web-based tool where the participant fills these details in his computer or mobile device without having to undergo a face-to-face interview with a dietitian, limiting social desirability bias, as suggested in our previous e-epidemiology methodological publications (120).

Moreover, in order to avoid modification of dietary behaviors, no individual data or advice was transmitted to the participants (only general information on scientific results from the study). Furthermore, the ultra-processed food topic is very recent in France for the general public, thus substantial media-driven dietary modifications regarding this specific aspect are of low probability in the time-frame considered in this study. Besides, models which focused on the individuals whose proportion of ultra-processed foods in the diet varied by less than $\left|0.1\right|$ between the beginning and the end of their follow-up provided similar results.

In addition to the large sample size (>100 000 participants), a large number of adjustment factors was used to account for confounding bias. The sources of these variables result from the richness of the NutriNet-Santé questionnaires, collecting information about lifestyle, medical, and environmental factors.

A multi-source strategy was used for case ascertainment: our research team was the first in France to obtain the authorization by Decree in the Council of State (n°2013-175) to link data from our general population-based cohorts to medico-administrative databases (for diseases, hospitalization, and prescription medication) and to the French National cause-specific mortality registry in order to improve the exhaustiveness of the cases.

Moreover, these prospective studies were among the first worldwide to investigate associations between food processing and chronic diseases using the NOVA classification. A weight ratio

(in % g/day) was used to calculate the proportion of ultra-processed foods in the diet rather than an energy ratio in order to take into account ultra-processed food that do not provide energy (e.g. artificially sweetened beverages) and non-nutritional issues related to food processing (e.g. neoformed contaminants, food additives and alterations to the structure of raw foods). This indicator has the advantage to be as much as possible de-correlated from nutritional quality, using weight and not energy. However, there is no ideal weighting method since the densities of different types of ultra-processed foods are quite different (e.g., salty snacks vs. beverages). Nonetheless, sensitivity analyses were tested using an energy ratio and results were unchanged.

The evidence that ultra-processed food is associated with a lower diet quality and increased risks of obesity and many chronic non-communicable diseases, is more and more robust. This has been shown in a recent report published by the FAO (205).

V. Perspectives for future research

A- Replication of the findings in large-scale independent cohorts

In order to add arguments helping to establish a causal link for the associations between highly processed foods and human health, these analyses need to be replicated in other independent large-scale cohort studies. For instance, a research program has been launched in the framework of the EPIC cohort, to study the associations between food processing using the NOVA classification and cancer, metabolic diseases as well as inflammatory bowel diseases. The limitation of this study will be the use of the FFQ (lower level of detail) and somehow ancient dietary data based on food products which are, for the many of them, different in the markets nowadays. However, long follow-up duration and outstanding statistical power will constitute important strengths.

B- Investigation of other outcomes in association with ultra-processed foods

It would be interesting to re-perform these analyses in the NutriNet-Santé cohort after several years, in order to investigate the associations on a longer term, while having a stronger statistical power that would sufficient to detect significant associations for specific cancer locations that could not be properly investigated here for instance.

In addition, it will be interesting to explore the associations between food processing and other diseases for which mechanistic hypotheses exist, such as Crohn disease, inflammatory dermatological pathologies (e.g. psoriasis), rheumatologic outcomes, migraine, respiratory diseases, dental health, hypertension, etc. All these research works are envisioned in the framework of the NutriNet-Santé cohort. The associations with woman reproductive health (age at menopause for instance) is also planned for the future, to explore the hypothesis of endocrine disruptors potentially migrating from contact materials, or associated with some food additives. The psychological and sociological determinants of ultra-processed food consumption are also an important topic to investigate, in order to identify specific populations that can be targeted by specific recommendations: an investigation of the consumption of ultra-processed foods in the representative survey Esteban (206) will be performed. A study exploring the consumption of ultra-processed foods among vegetarians is also ongoing.

Besides impacting upon health, it is argued that ultra-processed foods undermine social and environmental sustainability (35,37), in particular through the loss of traditional food cultures and smallholder farmers' livelihoods, and the unsustainable forms of intensive agriculture, as stated recently by a report of the Food Climate Research Network (FCRN) (207). They illustrate, in figure 19 how ultra-processed food might be seen as a proxy indicator for several issues related to health, society and environment. Exploring these aspects should be interesting in the framework of multidisciplinary research projects. In particular, the industrial processes and food additives authorized in organic agriculture versus conventional agriculture are not the same. This will be investigated in the near future in the framework of the Bionutrinet project.

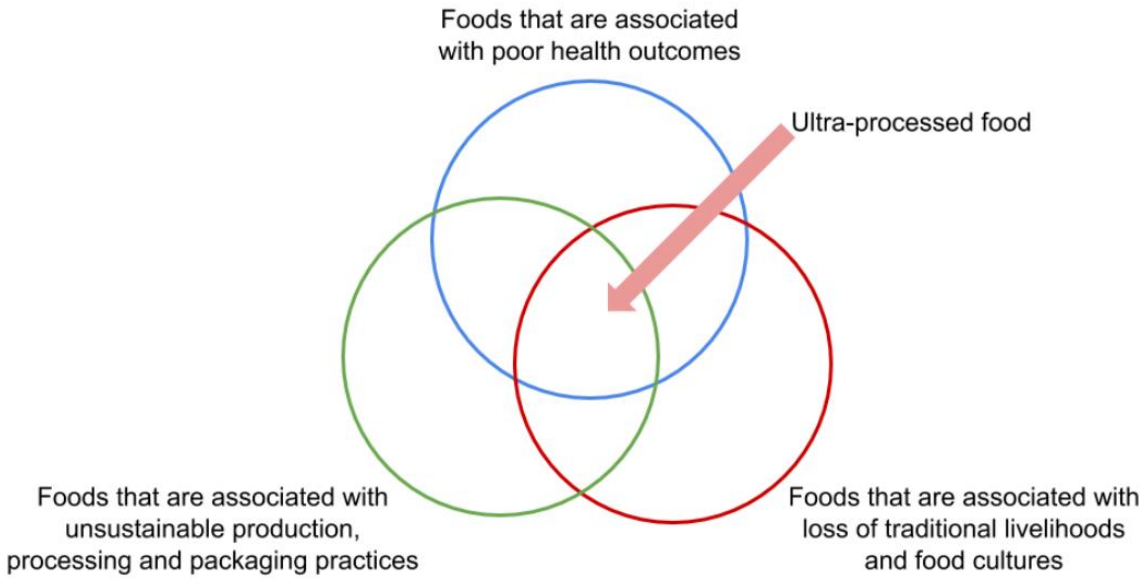

Figure 19 - Illustration of the position of ultra-processed food in the heart of health, social and environmental issues, FCRN, 2019 (207)

C- Towards a deeper exploration of the different food processes

In order to investigate the consequences of the differences in food classifications based on each framework on etiological findings, it would be interested to compare these etiological findings obtained using the NOVA classification with the same analyses using other frameworks (57). In this context, applying other existing classifications on the NutriNet-Santé food composition database has been submitted as a new project in the framework of a European JPI Healthy Diet For Healthy Life Metadis application in 2019.

The NOVA classification, as it was conceived, includes aspects of food processing (specific processes used to categorize foods) and food formulation (modified starches, hydrogenated oils, food additives). However, as used in the framework of this thesis and other prospective studies, NOVA considers in priority the formulation of food products (food additives in particular). The transformation processes and techniques are therefore somehow neglected and it remains impossible to investigate the associations between specific techniques of process and health outcomes. Ultra-processed products as defined in these studies are more ultra-formulated products than ultra-processed, since this category does not distinguish between the different industrial processes used to produce these foods and beverages. To go further into this research field, EREN is a part of an ongoing INRA-funded research project "Innov", aiming to develop, in close collaboration with food processing Experts (Dr Isabelle Souchon and colleagues, ADP Team, GMPA-INRA) an index of food processing quantifying the distance of the final food product from the original raw materials, distinguishing approximately 80 primary processing operations (e.g. freezing, mixing, frying), independently of the food additive content of the products. This index is currently undergoing validation and should be published in 2020. Beyond its use as a food processing index, this newly developed index will allow further investigations to explore the links between single processes, clusters of processes and human health, which will help identify the involved processes in the observed associations between highly processed foods and health.

D- Launching of a new research programme on food additives

While most additives allowed in the Europe are likely to be neutral for health and some may even be beneficial (e.g. antioxidants, some polyphenols, etc.), recent animal and cell-based studies have suggested detrimental effects of several such compounds, as stated in the discussion. No epidemiological study has ever assessed individual-level exposure to a wide range of food additives and its association with health. However, human diet is complex and humans are exposed simultaneously to a large number of food additives, coming from multiple sources. Even when individual additives are neutral to health in isolated exposures, and authorized doses, the effect of chronic exposure to these substances is not well known, nor is the synergistic 'cocktail' effect linked to the exposure to a large panel of food additives, coming from food groups among which many are consumed simultaneously (nitrites in processed meats with sulfites from wine, glutamates from sauces along with artificial sweeteners from diet

beverages, etc…). The main reason behind the absence of such studies is the lack of appropriate dietary assessment tools in nutritional epidemiological studies performed so far. Indeed, most dietary surveys and cohorts collect data about the generic consumed food item (chocolate cookies for example), which might be sufficient when studying nutritional factors, by averaging the nutrients (sugar, fat, salt…). However, the situation is drastically different for food additives as there are very important discrepancies in food additives within one food item (e.g. chocolate cookies) between the different brands (figure 20).

Figure 20 - Discrepancies between food additives used in five different industrial chocolate cookies on the French market (photo source: Open Food Facts)

Unlike other studies, NutriNet-Santé's dietary questionnaires collect precise and repeated data on foods and beverages usually consumed, including names and brands of industrial products, which represents a major breakthrough in this field and an important condition to accurately assess the chronic exposure to food additives. This research programme (currently starting with the matching of NutriNet-Santé database with various food additive composition databases such as Open Food Facts, Oqali and GNPD), will combine epidemiological studies and in-vitro/in-vivo experiments, with collaborations and partnerships with several research groups (208). This project will shed light on individual exposure to food additive 'cocktails' in relation to obesity, cancer, cardiovascular diseases and mortality, while exploring underlying mechanisms with its mechanistic work-packages. NutriNet-Santé benefits from a unique positioning worldwide to conduct this research program. The project will also include assessment of additive exposure, in the Esteban nationally representative survey, as well as replication of some analyses in the European EPIC cohort (authorization recently obtained).

E- Mechanistic studies

1. Mechanistic epidemiology

In order to understand the mechanisms underlying the associations found by these observational studies (between ultra-processed foods, food additives, processes and health), it is important to conduct mechanistic studies essentially based on biomarkers in biological fluids for instance. These biomarkers can be exposure biomarkers, allowing measuring the exposure to specific compounds coming from food, or effect biomarkers, helping to understand how these compounds interact with the human body. Metabolomics techniques provide interesting insights in this field, especially using untargeted approaches, to isolate metabolites that can be correlated to the intake of specific substances or compounds coming from food, by correlating these measures with dietary surveys. On the other hand, studying gut microbiota is an interesting approach to understand how the consumption of ultra-processed alters the composition of the microbiome and at what time this step interferes during the development of cancer and chronic diseases.

On the other hand, classical plasma biomarkers of inflammation and oxidative stress might be studied as mediating factors of the associations between food processing and health. This is possible thanks to the biobank of the NutriNet-Santé cohort, where we dispose of plasma sample for almost 20,000 participants. Stool collection is intended for microbiota analyses. Specific measurements techniques followed by adapted statistical models and mediation analyses will be performed.

2. In vitro / in vivo experimental approaches

Cytotoxicity, genotoxicity and oxidative stress of additive mixtures will be studied in cellular models. In addition, a combined multiple approach (metabolomics and metabolic flux, molecular biology…) will be used to study the influence of additive mixtures and processes on the proliferation and progression of tumors and cancer cells.

The effects of chronic oral exposure to additive mixtures or specific processes on intestinal permeability and inflammatory status will also be investigated in animal models.

F- Research on other potentially involved compounds

Other research perspectives are ongoing in our team to fully understand the mechanisms underlying the associations between ultra-processed foods and human health. A food composition database for acrylamide is currently being developed and matched to the 3,500 food items of the NutriNet-Santé food items. On the other hand, composition values of trans-fats in food items of the NutriNet-Santé food database are also being implemented. Trans-fats can be found in many foods – including fried foods like doughnuts, and baked goods including cakes, pie crusts, biscuits, frozen pizza, cookies, crackers, and stick margarines and other spreads, as well as all the products containing hydrogenated oils; and they were linked to increased risks of heart disease (209) and type 2-diabetes (210) and potentially cancer (211).

A questionnaire about food packaging is scheduled for the participants of the NutriNet-Santé cohort in order to explore which food packaging is privileged while purchasing food products, helping to evaluate the exposure to compounds coming from plastic packages as well as exposures to packaging inks, and eventually investigate their associations with health outcomes.

Besides, EREN's computer scientists are currently developing a module to scan the bar codes of food products directly within the dietary assessment tools, with an embedded link with the Open Food Facts database, containing extended information on food composition but also food packaging.

Another questionnaire about kitchen utensils and food containers has been developed as well and will be soon administered, in order to collect information about cooking and domestic packing practices.

On the other hand, a research project investigating the impact of thermal processing on gut microbiome diversity is ongoing (ADP team).

VI. Public health and policy implications

The published articles presented in this thesis had an important impact in the scientific community. My PhD supervisor and I were invited to present these findings in several scientific, academic, and public conferences. The study on ultra-processed food and cancer risk, published in 2018 in the BMJ, was ranked top 1% of articles of the same academic field in 2018 according to Web of Science. The two articles published in the BMJ were widely disseminated by national and international press, along with associated press releases disseminated by the journal (Altmetric scores in the top 5% of all research outputs scored by Altmetric worldwide). The wide scientific and public dissemination of these findings prompted a Parliamentary inquiry on industrial food in France in mid-2018. Along with other studies conducted using the NutriNet-Santé data, and published in high impact journals (associations with mortality (112), depressive symptoms (79), and prevalence of gastro-intestinal disorders (104)), these studies (139,140) have contributed to an evolution in public health recommendations. Indeed, even if it remains unclear to date which specific processes, compounds or ultra-processed food subtypes play a more important role, evidence is accumulating for an association between increased overall proportion of ultra-processed food in the diet and increased risks of several chronic diseases. Thus, several countries such as France or Brazil have started to officially recommend privileging the consumption of unprocessed and minimally processed foods, and limiting the consumption of ultra-processed foods in the name of the precautionary principle (212–214). The French National Nutritional Programme (PNNS) (212) has fixed an objective of reducing by 20% the consumption of ultra-processed foods in France, by the end of 2021.

Consumers should be well-informed about these findings and exploratory projects, whilst further research about food additives and processes is ongoing. In the meantime, industrials should be encouraged to improve the quality of their products, and not only by limiting the use of sugar, salt and fat, but by reducing the use of unnecessary additives. Even though the NOVA classification was not conceived to be a public health decisional tool used by the consumer, several platforms and nutritional mobile/PC applications now show the NOVA classification of industrial food products, following the public dissemination of our studies, to help consumers make better choices and avoid ‘cosmetic’ food additives (beyond nutritional quality which is fully captured by the Nutri-Score).

This is the case of Open Food Facts, a non-profit project developed by thousands of volunteers from around the world. While other food applications already propose a unique nutritional logo or a nutritional score combining different aspects of the diet with an arbitrary weighting (nutritional factors, food additives, processing, organic agriculture, fair-trade…), this approach is not scientifically relevant for the moment as the evidence for these aspects are not equivalent. Consumers need to be encouraged to prioritize at first the nutritional aspects of the food products while making purchasing choices, by privileging products with a better Nutri-Score ranking, as strong evidence is established for the nutritional quality. Scientific proofs for other aspects are still limited: Further public research, conducted and funded independently for industrial lobbies, is needed to understand the mechanisms and factors underlying these associations. The findings from these expected projects might contribute, in the future, to amendments in the regulations of authorized food additives and processes. These steps might provide the needed missing elements to create a single indicator that accounts simultaneously for the nutritional quality of food products, as well as food additives and formulation, transformation processes and techniques, and even pesticides if the research in this field comes to conclusive findings. This single indicator (score or logo) is not possible to establish in the current state of scientific knowledge.

CONCLUSION

The studies conducted in the framework of this PhD thesis, highlighted robust significant associations between the consumption of ultra-processed foods, as defined by the NOVA classification, and increased risks of overall and breast cancers, cardiovascular, cerebrovascular, and coronary heart diseases, type 2-diabetes, overweight, obesity and weight gain. Using a large sample (>100,000 participants) from the NutriNet-Santé cohort, these analyses accounted for a large number of confounders, in particular lifestyle, socio-demographic, anthropometric, medical, behavioral, and nutritional factors. These associations remained significant throughout all the sensitivity and stratified analyses.

These results add a large body of evidence to the field of food processing in relation to health outcomes, in a context of drastic changes of food consumptions in Western countries and worldwide, with increasing availability of ultra-processed foods and beverages on supermarket shelves. Besides, some industrials are going towards massive reformulations of their products, in order to reduce the amounts of salt, sugar and unhealthy fats, but these innovations are often accompanied by the introduction of a wide range of food additives and new transformation processes. The impacts of these 'revolutionary' techniques on human health are not established and deserve further investigation.

Ultra-processed foods have in average a lower nutritional quality. However, this did not fully explain the associations observed. Other hypotheses were suggested as they can plausibly underlie the associations with chronic diseases: some food additives, especially though a cocktail exposure effect, neoformed compounds, or contact materials via plastic packaging for instance.

These findings need to be confirmed by other large-scale population-based studies in different populations and settings. Besides, the concept of food processing is complex, as the possible processes and the authorized additives are multiple. Further studies are needed to investigate the relative impact of nutritional composition, and other bioactive compounds and processes in this relationship. In this perspective, our research team is currently launching several research projects, investigating the role of food additives (208), neoformed compounds, and trans-fatty acids in these associations, and developing other food processing classifications.

Even if it remains unclear to date which specific processes, compounds or ultra-processed food subtypes play a more important role, evidence is accumulating for an association between an increased overall proportion of ultra-processed food in the diet and increased risks of several chronic diseases. It is therefore important to inform the consumers about these associations, and to implement actions targeting product reformulation (e.g. improving nutritional quality and reducing the use of unnecessary additives) and communication to limit the proportion of ultra-processed foods in the diet and promote the consumption of unprocessed/minimally processed foods instead. Several countries such as France or Brazil have already introduced these aspects in their official nutritional recommendations (212–214).

On a personal level, this PhD thesis has provided me with a solid scientific background in the field of food processing applied to nutritional epidemiology, several biostatistical tools and techniques, and scientific communication skills. In addition, it was a very enriching and enlightening experience for me to work on a 'hot' public health topic especially that I had the opportunity to see the short-term impact of my research on nutritional public health.
I will be pursuing my academic research career in epidemiology with a two-year postdoctoral fellowship at the German Cancer Research Center (DKFZ) in Heidelberg, where I will be investigating the role of several biomarkers (in particular using proteomics) in the development of metabolic diseases, ageing, and life expectancy.

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APPENDIXES

Appendix A - Ultra-processed food and cancer risk (BMJ 2018)

Consumption of ultra-processed foods and cancer risk: results from NutriNet-Santé prospective cohort

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ABSTRACT

OBJECTIVE

To assess the prospective associations between consumption of ultra-processed food and risk of cancer.

DESIGN

Population based cohort study.

SETTING AND PARTICIPANTS

104 980 participants aged at least 18 years (median age 42.8 years) from the French NutriNet-Santé cohort (2009-17). Dietary intakes were collected using repeated 24 hour dietary records, designed to register participants' usual consumption for 3300 different food items. These were categorised according to their degree of processing by the NOVA classification.

MAIN OUTCOME MEASURES

Associations between ultra-processed food intake and risk of overall, breast, prostate, and colorectal cancer assessed by multivariable Cox proportional hazard models adjusted for known risk factors.

RESULTS

Ultra-processed food intake was associated with higher overall cancer risk (n=2228 cases; hazard ratio for a 10% increment in the proportion of ultra-processed food in the diet 1.12 (95% confidence interval 1.06 to 1.18); P for trend<0.001) and breast cancer risk (n=739 cases; hazard ratio 1.11 (1.02 to 1.22); P for trend=0.02). These results remained statistically significant after adjustment for several markers of the nutritional quality of the diet (lipid, sodium, and carbohydrate intakes and/or a Western pattern derived by principal component analysis).

CONCLUSIONS

In this large prospective study, a 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of greater than 10% in risks of overall and breast cancer. Further studies are needed to better understand the relative effect of the various dimensions of processing (nutritional composition, food additives, contact materials, and neoformed contaminants) in these associations.

STUDY REGISTRATION

Clinicaltrials.gov NCT03335644.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Ultra-processed foods are often characterised by lower nutritional quality and the presence of additives, substances from packaging in contact with food, and compounds formed during production, processing, and storage

A few studies have observed ultra-processed food intake to be associated with a higher incidence of dyslipidaemia in Brazilian children and higher risks of overweight, obesity, and hypertension in Spanish university students

Although epidemiological data relating to cancer risk are lacking, mechanistic studies suggest potential carcinogenic effects of several components commonly found in ultra-processed foods

WHAT THIS STUDY ADDS

This study assessed the associations between ultra-processed food consumption and risk of cancer in a large prospective cohort

A 10% increase in the proportion of ultra-processed foods in the diet was associated with a significant increase of more than 10% in the risks of overall and breast cancer

If confirmed in other populations and settings, these results suggest that the rapidly increasing consumption of ultra-processed foods may drive an increasing burden of cancer in the next decades

Introduction

Cancer represents a major worldwide burden, with 14.1 million new cases diagnosed in 2012.[1] According to the World Cancer Research Fund/American Institute for Cancer Research, about a third of the most common neoplasms could be avoided by changing lifestyle and dietary habits in developed countries.[2] Therefore, reaching a balanced and diversified diet (along with avoidance of tobacco use and reduction in alcohol intake) should be considered one of the most important modifiable risk factors in the primary prevention of cancer.[3]

At the same time, during the past decades, diets in many countries have shifted towards a dramatic increase in consumption of ultra-processed foods.[4-8] After undergoing multiple physical, biological, and/or chemical processes, these food products are conceived to be microbiologically safe, convenient, highly palatable, and affordable.[9 10] Several surveys (in Europe, the US, Canada, New Zealand, and Brazil) assessing individual food intake, household food expenses, or supermarket sales have suggested that ultra-processed food products contribute to between 25% and 50% of total daily energy intake.[10-18]

This dietary trend may be concerning and deserves investigation. Several characteristics of ultra-processed foods may be involved in causing disease, particularly cancer. Firstly, ultra-processed foods often have a higher content of total fat, saturated fat, and added sugar and salt, along with a lower fibre and vitamin density.[10-17 19] Beyond nutritional composition, neoformed contaminants, some of which have carcinogenic properties (such as acrylamide, heterocyclic amines, and polycyclic aromatic

hydrocarbons), are present in heat treated processed food products as a result of the Maillard reaction.[20] Secondly, the packaging of ultra-processed foods may contain some materials in contact with food for which carcinogenic and endocrine disruptor properties have been postulated, such as bisphenol A.[21] Finally, ultra-processed foods contain authorised,[22] but controversial, food additives such as sodium nitrite in processed meat or titanium dioxide (TiO_2, white food pigment), for which carcinogenicity has been suggested in animal or cellular models.[23 24]

Studying potential effects on health of ultra-processed foods is a very recent field of research, facilitated by the development of the NOVA classification of products according to their degree of food processing.[9] Nevertheless, epidemiological evidence linking intake of ultra-processed food to risk of disease is still very scarce and mostly based on cross sectional and ecological studies.[25-27] The few studies performed observed that ultra-processed food intake was associated with a higher incidence of dyslipidaemia in Brazilian children and higher risks of overweight, obesity, and hypertension in a prospective cohort of Spanish university students.[28-30]

To our knowledge, this prospective study was the first to evaluate the association between the consumption of ultra-processed food products and the incidence of cancer, based on a large cohort study with detailed and up to date assessment of dietary intake.

Methods

Study population

The NutriNet-Santé study is an ongoing web based cohort launched in 2009 in France with the objective of studying the associations between nutrition and health, as well as the determinants of dietary behaviours and nutritional status. This cohort has been previously described in detail.[31] Briefly, participants aged over 18 years with access to the internet have been continuously recruited from among the general population since May 2009 by means of vast multimedia campaigns. All questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr). Participants are followed using an online platform connected to their email address. They can change their email address, phone number, or postal address at any time on the NutriNet-Santé website. Newsletters and alerts about new questionnaires are sent by email. In case of an "undelivered email" problem, participants are contacted by telephone and then by regular mail. The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines, and electronic informed consent is obtained from each participant.

Data collection

At inclusion, participants completed a set of five questionnaires related to sociodemographic and lifestyle characteristics (for example, date of birth, sex, occupation, educational level, smoking status, number of children),[32] anthropometry (height, weight), dietary intakes (see below),[33 34] physical activity (validated seven day International Physical Activity Questionnaire (IPAQ)),[35] and health status (personal and family history of diseases, drug use including use of hormonal treatment for menopause and oral contraceptives, and menopausal status).

Participants were invited to complete a series of three non-consecutive, validated, web based 24 hour dietary records every six months (to vary the season of completion), randomly assigned over a two week period (two weekdays and one weekend day).[36-38] To be included in the nutrition component of the NutriNet-Santé cohort, only two dietary records were mandatory. We did not exclude participants if they did not complete all optional questionnaires. We averaged mean dietary intakes from all the 24 hour dietary records available during the first two years of each participant's follow-up and considered these as baseline usual dietary intakes in this prospective analysis. The NutriNet-Santé web based, self administered 24 hour dietary records have been tested and validated against an interview by a trained dietitian and against blood and urinary biomarkers.[36 37] Participants used the dedicated web interface to declare all food and drinks consumed during a 24 hour period for each of the three main meals (breakfast, lunch, dinner) and any other eating occasion. Portion sizes were estimated using previously validated photographs or usual containers.[39] We identified dietary under-reporting on the basis of the method proposed by Black, using the basal metabolic rate and Goldberg cut-off, and excluded under-reporters of energy intake.[40] We calculated mean daily alcohol, micronutrient and macronutrient, and energy intake by using the NutriNet-Santé food composition database, which contains more than 3300 different items.[41] We estimated amounts consumed from composite dishes by using French recipes validated by nutrition professionals. Sodium intake was assessed via a specific module included in the 24 hour records, taking into account native sodium in foods, salt added during the cooking, and salt added on the plate. It has been validated against sodium urinary excretion biomarkers.[37]

Degree of food processing

We categorised all food and drink items of the NutriNet-Santé composition table into one of the four food groups in NOVA, a food classification system based on the extent and purpose of industrial food processing.[9 42 43] This study primarily focused on the "ultra-processed foods" NOVA group. This group includes mass produced packaged breads and buns; sweet or savoury packaged snacks; industrialised confectionery and desserts; sodas and sweetened drinks; meat balls, poultry and fish nuggets, and other reconstituted meat products transformed with addition of preservatives other than salt (for example, nitrites); instant noodles and soups; frozen or shelf stable ready meals; and other food products made mostly or entirely from sugar, oils and fats, and other substances not commonly used in culinary preparations such as hydrogenated oils, modified starches, and protein isolates. Industrial processes

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notably include hydrogenation, hydrolysis, extruding, moulding, reshaping, and pre-processing by frying. Flavouring agents, colours, emulsifiers, humectants, non-sugar sweeteners, and other cosmetic additives are often added to these products to imitate sensorial properties of unprocessed or minimally processed foods and their culinary preparations or to disguise undesirable qualities of the final product.

The ultra-processed food group is defined by opposition to the other NOVA groups: "unprocessed or minimally processed foods" (fresh, dried, ground, chilled, frozen, pasteurised, or fermented staple foods such as fruits, vegetables, pulses, rice, pasta, eggs, meat, fish, or milk), "processed culinary ingredients" (salt, vegetable oils, butter, sugar, and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations), and "processed foods" (canned vegetables with added salt, sugar coated dried fruits, meat products preserved only by salting, cheeses, freshly made unpackaged breads, and other products manufactured with the addition of salt, sugar, or other substances of the "processed culinary ingredients" group). As previously described,[44] we identified homemade and artisanal food preparations, decomposed them using standardised recipes, and applied the NOVA classification to their ingredients. Precision and examples are shown in appendix 1.

Case ascertainment

Participants self declared health events through the yearly health status questionnaire, through a specific check-up questionnaire for health events (every three months), or at any time through a specific interface on the study website. For each incident cancer declared, a physician from the study team contacted participants and asked them to provide any relevant medical records. If necessary, the study physicians contacted the patient's physician and/or hospitals to collect additional information. Afterwards, an expert committee of physicians reviewed all medical data. Our research team was the first in France to obtain the authorisation by decree in the Council of State (No 2013-175) to link data from our cohorts to medico-administrative databases of the national health insurance system (SNIIRAM databases). We therefore completed declared health events with the information from these databases, thereby limiting any potential bias due to participants with cancer who may not report their disease to the study investigators. Lastly, we used an additional linkage to the French national cause specific mortality registry (CépiDC) to detect deaths and potentially missed cases of cancer for deceased participants. We classified cancer cases by using the international classification of diseases, 10th revision (ICD-10). In this study, we considered all first primary cancers diagnosed between the inclusion date and 1 January 2017 to be cases, except for basal cell skin carcinoma, which we did not consider as cancer.

We obtained medical records for more than 90% of cancer cases. Because of the high validity of self reports (95% of self reported cancers for which a medical record was obtained were confirmed by our physicians), we included as cases all participants who self reported incident cancers, unless they were identified as non-case participants by a pathology report, in which case we classified them as non-cases.

Statistical analysis

Up to 1 January 2017, we included 104 980 participants without cancer at baseline who provided at least two valid 24 hour dietary records during their two first years of follow-up. The flowchart is in appendix 2. For each participant, we calculated the proportion (percentage g/day) of ultra-processed foods in the total diet. We determined the proportion of ultra-processed foods in the diet by calculating a weight ratio rather than an energy ratio to take into account processed foods that do not provide any energy (in particular artificially sweetened drinks) and non-nutritional factors related to food processing (for example, neoformed contaminants, food additives, and alterations to the structure of raw foods). For all covariates except physical activity, less than 5% of values were missing and were imputed to the modal value (for categorical variables) or to the median (for continuous variables). Corresponding values are provided in the footnote to table 1. The proportion of missing values was higher for physical activity (14%), as the answers to all IPAQ questions were needed to calculate the score. To avoid massive imputation for a non-negligible number of participants or exclusion of those with missing data and risk of selection bias, we included a missing class into the models for this variable. We examined differences in participants' baseline characteristics between sex specific quarters of the proportion of ultra-processed food in the diet by using analysis of variance or χ^2 tests wherever appropriate. We used Cox proportional hazards models with age as the primary timescale to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as sex specific quarters) and incidence of overall, breast, prostate, and colorectal cancer. In these models, cancers at other locations than the one studied were censored at the date of diagnosis (that is, we considered them to be non-cases for the cancer of interest and they contributed person years until the date of diagnosis of their cancer). We estimated hazard ratios and 95% confidence intervals with the lowest quarter as the reference category. We generated log-log (survival) versus log-time plots to confirm risk proportionality assumptions. We tested for linear trend by using the ordinal score on sex specific quarters of ultra-processed food. Participants contributed person time until the date of diagnosis of cancer, the date of last completed questionnaire, the date of death, or 1 January 2017, whichever occurred first. Breast cancer analyses were additionally stratified by menopausal status. For these, women contributed person time to the "premenopause model" until their age at menopause and to the "postmenopause model" from their age at menopause. We determined

Table 1 | Baseline characteristics of study population according to sex specific quarters of ultra-processed food consumption (n=104 980), NutriNet-Santé cohort, France, 2009-17*. Values are numbers (percentages) unless stated otherwise

Characteristics	All participants	Quarters of ultra-processed food consumption†				P for trend‡
		1 (n=26 244)	2 (n=26 245)	3 (n=26 246)	4 (n=26 245)	
Mean (SD) age, years	42.8 (14.8)	47.9 (13.5)	45.0 (14.0)	42.0 (14.4)	36.5 (13.6)	<0.001
Female sex	82 159 (78.3)	20 539 (78.3)	20 540 (78.3)	20 541 (78.3)	20 542 (78.3)	–
Mean (SD) height, cm	166.8 (8.1)	166.3 (8.0)	166.7 (8.0)	167.0 (8.1)	167.3 (8.2)	<0.001
Mean (SD) body mass index	23.8 (4.6)	23.8 (4.3)	23.8 (4.4)	23.8 (4.5)	23.8 (5.0)	0.9
Family history of cancer§	35 668 (34.0)	10 542 (40.2)	9624 (36.7)	8625 (32.9)	6877 (26.2)	<0.001
Higher education:						
No	19 357 (18.4)	5154 (19.6)	4961 (18.9)	4637 (17.7)	4605 (17.6)	0.01
Yes, <2 years	18 076 (17.2)	3938 (15.0)	4091 (15.6)	4426 (16.9)	5621 (21.4)	
Yes, ≥2 years	67 547 (64.3)	17 152 (65.4)	17 193 (65.5)	17 183 (65.5)	16 019 (61.0)	
Smoking status:						
Current	17 763 (16.9)	4127 (15.7)	4065 (15.5)	4266 (16.3)	5305 (20.2)	<0.001
Never/former	87 217 (83.1)	22 117 (84.3)	22 180 (84.5)	21 980 (83.8)	20 940 (79.8)	
IPAQ physical activity level:¶						
High	29 603 (28.2)	8753 (33.4)	7762 (29.6)	6983 (26.6)	6105 (23.3)	<0.001
Moderate	38 874 (37.0)	9620 (36.7)	9953 (37.9)	9814 (37.4)	9487 (36.2)	
Low	21 888 (20.9)	4407 (16.8)	5152 (19.6)	5839 (22.3)	6490 (24.7)	
Mean (SD) energy intake without alcohol, kcal/d	1879.0 (473.7)	1810.6 (454.1)	1881.1 (457.7)	1908.5 (472.3)	1915.8 (501.8)	<0.001
Mean (SD) alcohol intake, g/d	7.8 (11.9)	9.3 (13.3)	8.5 (11.9)	7.5 (11.3)	5.9 (10.5)	<0.001
Mean (SD) total lipid intake, g/d	80.5 (25.5)	76.0 (24.3)	80.3 (24.4)	82.1 (25.3)	83.4 (27.3)	<0.001
Mean (SD) carbohydrate intake, g/d	195.4 (57.9)	184.6 (57.8)	193.9 (55.3)	199.3 (56.6)	203.6 (60.2)	<0.001
Mean (SD) sodium intake, mg/d	2700.1 (893.1)	2589.3 (881.6)	2731.8 (871.0)	2761.9 (884.1)	2717.7 (925.0)	<0.001
Mean (SD) No of children	1.3 (1.2)	1.6 (1.2)	1.4 (1.2)	1.3 (1.2)	1.0 (1.2)	<0.001
Menopausal status:**						
Premenopausal	57 408 (69.9)	11 797 (57.4)	13 497 (65.7)	14 961 (72.8)	17 153 (83.5)	<0.001
Perimenopausal	4282 (5.2)	1471 (7.2)	1148 (5.6)	997 (4.9)	666 (3.2)	
Postmenopausal	20 469 (24.9)	7271 (35.4)	5895 (28.7)	4582 (22.3)	2721 (13.3)	
Use of hormonal treatment for menopause**	4324 (5.3)	1602 (7.8)	1242 (6.1)	932 (4.5)	548 (2.7)	<0.001
Oral contraception**	23 073 (22.0)	3779 (14.4)	4990 (19.0)	6209 (23.7)	8095 (30.8)	<0.001
Mean (SD) ultra-processed food, %	18.7 (10.1)	8.5 (2.5)	14.3 (1.4)	19.8 (1.9)	32.3 (9.8)	–

IPAQ=International Physical Activity Questionnaire.
*For all covariates except physical activity, a very low proportion of values were missing (0-5%); these were replaced by modal value in study population: "≥2 years of higher education" for educational level, 0 for No of biological children, 22.9 for body mass index, 166 cm for height, and non-smoker for smoking status.
†Sex specific quarters of proportion of ultra-processed food intake in total quantity of food consumed; sex specific cut-offs for quarters of ultra-processed proportions were 11.8%, 16.8%, and 23.3% in men and 11.8%, 16.8%, and 23.4% in women.
‡P value for comparison between sex specific quarters of ultra-processed food consumption, by Fisher test or x^2 test where appropriate.
§Among first degree relatives.
¶Available for 90 365 participants; participants were categorised into "high," "moderate," and "low" categories according to IPAQ guidelines.[35]
**Among women.

age at menopause by using the yearly health status questionnaires completed during follow-up.

Models were adjusted for age (timescale), sex, body mass index (kg/m^2, continuous), height (cm, continuous), physical activity (high, moderate, low, calculated according to IPAQ recommendations[35]), smoking status (never or former smokers, current smokers), number of 24 hour dietary records (continuous), alcohol intake (g/d, continuous), energy intake (without alcohol, kcal/d, continuous), family history of cancer (yes/no), and educational level (less than high school degree, less than two years after high school degree, two or more years after high school degree). For breast cancer analyses, we made additional adjustments for the number of biological children (continuous), menopausal status at baseline (menopausal/perimenopausal/non-menopausal), hormonal treatment for menopause at baseline (for postmenopausal analyses, yes/no), and oral contraception use at baseline (for premenopausal analyses, yes/no) (model 1=main model). To test for the potential influence of the nutritional quality of the diet in the relation between intake of ultra-processed food and risk of cancer, this model was additionally adjusted for lipid, sodium, and carbohydrate intakes (model 2), for a Western dietary pattern derived from principal component analysis (model 3) (details in appendix 3), or for all these nutritional factors together (model 4). In addition, we did mediation analyses according to the method proposed by Lange et al to evaluate the direct and indirect effect of the relation between the exposure and the outcome through the following nutritional mediators: intakes of sodium, total lipids, saturated, mono-unsaturated and poly-unsaturated fatty acids, carbohydrates, and a Western-type dietary pattern.[45] The methods are described in appendix 4.

We did sensitivity analyses based on model 1 by excluding cases of cancer diagnosed during the first two years of each participant's follow-up to avoid reverse causality bias, testing sex specific fifths of the proportion of ultra-processed foods in the diet instead of sex specific quarters, and testing further adjustments for prevalent depression at baseline (yes/no), dietary supplement use at baseline (yes/no), healthy dietary pattern (continuous, details in appendix 3), number of cigarettes smoked in pack years (continuous), overall fruit and vegetable consumption (continuous), and

season of inclusion in the cohort (spring/summer/autumn/winter). We also investigated the association between ultra-processed food and overall cancer risk separately in different strata of the population: men, women, younger adults (under 40 years), older adults (40 years or over), smokers, non-smokers, participants with a high level of physical activity, and those with a low to moderate level of physical activity. We also tested models after restriction of the study population to the participants with at least six 24 hour dietary records during the first two years of follow-up. Similarly, we tested models including all participants with at least one 24 hour dietary record during the first two years of follow-up. We also tested associations between the quantity (g/d) of each ultra-processed food group and risk of cancer.

Secondary analyses tested the associations between the proportion in the diet of each of the three other NOVA categories of food processing (continuous) and risk of cancer, using multivariate Cox models adjusted for model 1 covariates. All tests were two sided, with P<0.05 considered to be statistically significant. We used SAS version 9.4 for the analyses.

Patient involvement

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

Results

A total of 104 980 participants (22 821 (21.7%) men and 82 159 (78.3%) women) were included in the study. The mean age of participants was 42.8 (SD 14.8, range 18.0-72.8) years. The mean number of dietary records per participant over their first two years of follow-up was 5.4 (SD 2.9); the minimum was 2, but it represented only 7.2% (7558/104 980) of the participants. After the launching of the study by the end of May 2009, half of the records were filled between June and November and the other half between December and May. Table 1 shows the main baseline characteristics of participants according to quarters of the proportion of ultra-processed foods in the diet. Compared with the lowest quarter, participants in the highest quarter of ultra-processed food intake tended to be younger, current smokers, and less educated, with less family history of cancer and a lower physical activity level. Furthermore, they had higher intakes of energy, lipids, carbohydrates, and sodium, along with lower alcohol intake. Although there was a higher proportion of women than men in this cohort, the contribution of ultra-processed foods to the overall diet was very similar between men and women (18.74% for men and 18.71% for women; P=0.7). The distribution of the proportion of ultra-processed food in the diet in the study population is shown in appendix 5. Main food groups contributing to ultra-processed food intake were sugary products (26%) and drinks (20%),

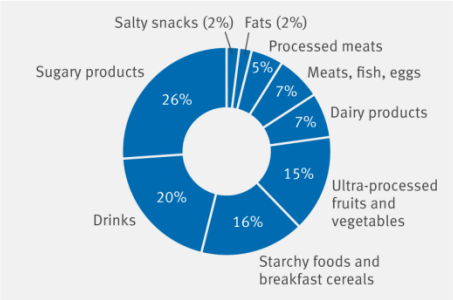

Fig 1 | Relative contribution of each food group to ultra-processed food consumption in diet

followed by starchy foods and breakfast cereals (16%) and ultra-processed fruits and vegetables (15%) (fig 1).

During follow-up (426 362 person years, median follow-up time five years), 2228 first incident cases of cancer were diagnosed and validated, among which were 739 breast cancers (264 premenopausal, 475 postmenopausal), 281 prostate cancers, and 153 colorectal cancers. Among these 2228 cases, 108 (4.8%) were identified during mortality follow-up with the national CépiDC database. The dropout rate in the NutriNet-Santé cohort was 6.7%. Table 2 shows associations between the proportion of ultra-processed foods in the diet and risks of overall, breast, prostate, and colorectal cancer. Figure 2 shows the corresponding cumulative incidence curves. In model 1, ultra-processed food intake was associated with increased risks of overall cancer (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.12 (95% confidence interval 1.06 to 1.18), P<0.001) and breast cancer (1.11 (1.02 to 1.22), P=0.02). The latter association was more specifically observed for postmenopausal breast cancer (P=0.04) but not for premenopausal breast cancer (P=0.2). The association with overall cancer risk was statistically significant in all strata of the population investigated, after adjustment for model 1 covariates: in men (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.12 (1.02 to 1.24), P=0.02, 663 cases and 22 158 non-cases), in women (1.13 (1.06 to 1.20), P<0.001, 1565 cases and 80 594 non-cases), in younger adults (<40 years old 1.21 (1.09 to 1.35), P<0.001, 287 cases and 48 627 non-cases), in older adults (≥40 years old, 1.09 (1.03 to 1.16), P=0.03, 1941 cases and 54 485 non-cases), in smokers (including adjustment for pack years of cigarettes smoked 1.18 (1.04 to 1.33), P=0.01, 255 cases and 15 355 non-cases), in non-smokers (1.11 (1.05 to 1.17), P<0.001, 1943 cases and 85 219 non-cases), in participants with low to moderate levels of physical activity (1.07 (1.00 to 1.15), P=0.04, 1216 cases and 59 546 non-cases), and in those with a high level of physical activity (1.19 (1.09 to 1.30), P<0.001, 744 cases and 28 859 non-cases).

More specifically, ultra-processed fats and sauces (P=0.002) and sugary products (P=0.03) and drinks

Table 2 | Associations between ultra-processed food intake and risk of overall, prostate, colorectal, and breast cancer, from multivariable Cox proportional hazard models*, NutriNet-Santé cohort, France, 2009-17 (n=104 980)

	Proportion of ultra-processed food intake in the diet						
			Sex specific quarters‡				
	Continuous†		1	2	3	4	
	HR (95% CI)	P for trend	HR	HR (95% CI)	HR (95% CI)	P for trend HR (95% CI)	
All cancers							
No of cases/non-cases	2228/102 752		712/25 532	607/25 638	541/25 705	368/25 877	
Model 1	1.12 (1.06 to 1.18)	<0.001	1	0.99 (0.89 to 1.11)	1.10 (0.99 to 1.24)	1.21 (1.06 to 1.38)	0.002
Model 2	1.12 (1.07 to 1.18)	<0.001	1	1.00 (0.90 to 1.11)	1.11 (0.99 to 1.25)	1.23 (1.08 to 1.40)	0.001
Model 3	1.12 (1.06 to 1.18)	<0.001	1	0.99 (0.89 to 1.11)	1.01 (0.98 to 1.23)	1.21 (1.06 to 1.38)	0.002
Model 4	1.13 (1.07 to 1.18)	<0.001	1	1.00 (0.90 to 1.11)	1.11 (0.99 to 1.24)	1.23 (1.08 to 1.40)	0.001
Prostate cancer							
No of cases/non-cases	281/22 540		96/5609	96/5609	59/5647	30/5675	
Model 1	0.98 (0.83 to 1.16)	0.8	1	1.18 (0.89 to 1.57)	0.95 (0.69 to 1.32)	0.93 (0.61 to 1.40)	0.6
Model 2	0.98 (0.83 to 1.16)	0.8	1	1.18 (0.89 to 1.57)	0.95 (0.69 to 1.32)	0.93 (0.61 to 1.40)	0.6
Model 3	0.98 (0.83 to 1.15)	0.8	1	1.18 (0.89 to 1.56)	0.95 (0.68 to 1.31)	0.92 (0.61 to 1.39)	0.6
Model 4	0.98 (0.83 to 1.16)	0.8	1	1.18 (0.89 to 1.57)	0.95 (0.68 to 1.32)	0.93 (0.61 to 1.40)	0.6
Colorectal cancer							
No of cases/non-cases	153/104 827		48/26 196	43/26 202	36/26 210	26/26 219	
Model 1	1.13 (0.92 to 1.38)	0.2	1	1.10 (0.72 to 1.66)	1.17 (0.76 to 1.81)	1.49 (0.92 to 2.43)	0.1
Model 2	1.16 (0.95 to 1.42)	0.1	1	1.12 (0.74 to 1.70)	1.22 (0.79 to 1.90)	1.59 (0.97 to 2.60)	0.07
Model 3	1.13 (0.92 to 1.38)	0.2	1	1.09 (0.92 to 1.38)	1.16 (0.75 to 1.80)	1.48 (0.91 to 2.41)	0.1
Model 4	1.16 (0.95 to 1.42)	0.1	1	1.12 (0.74 to 1.70)	1.22 (0.79 to 1.89)	1.23 (1.08 to 1.40)	0.07
Breast cancer							
No of cases/non-cases	739/81 420		247/20 292	202/20 338	179/20 361	111/20 429	
Model 1	1.11 (1.02 to 1.22)	0.02	1	0.97 (0.81 to 1.17)	1.10 (0.90 to 1.34)	1.14 (0.91 to 1.44)	0.2
Model 2	1.11 (1.01 to 1.21)	0.03	1	0.96 (0.80 to 1.16)	1.09 (0.89 to 1.32)	1.12 (0.89 to 1.42)	0.2
Model 3	1.11 (1.02 to 1.22)	0.02	1	0.97 (0.80 to 1.17)	1.09 (0.90 to 1.33)	1.14 (0.91 to 1.44)	0.2
Model 4	1.11 (1.01 to 1.21)	0.03	1	0.96 (0.80 to 1.16)	1.08 (0.89 to 1.32)	1.13 (0.89 to 1.42)	0.2
Premenopausal breast cancer							
No of cases/non-cases	264/57 151		90/14 263	70/14 284	55/14 299	49/14 305	
Model 1	1.09 (0.95 to 1.25)	0.2	1	0.91 (0.67 to 1.25)	0.92 (0.65 to 1.29)	1.30 (0.90 to 1.86)	0.3
Model 2	1.07 (0.93 to 1.23)	0.4	1	0.90 (0.66 to 1.24)	0.90 (0.64 to 1.27)	1.25 (0.87 to 1.80)	0.4
Model 3	1.09 (0.95 to 1.26)	0.2	1	0.91 (0.67 to 1.25)	0.92 (0.66 to 1.30)	1.30 (0.91 to 1.88)	0.3
Model 4	1.08 (0.94 to 1.24)	0.3	1	0.91 (0.66 to 1.24)	0.91 (0.64 to 1.28)	1.27 (0.88 to 1.83)	0.4
Postmenopausal breast cancer							
No of cases/non-cases	475/29 191		107/7309	128/7289	123/7294	117/7299	
Model 1	1.13 (1.01 to 1.27)	0.04	1	1.23 (0.95 to 1.60)	1.28 (0.98 to 1.66)	1.39 (1.07 to 1.82)	0.02
Model 2	1.13 (1.00 to 1.27)	0.05	1	1.23 (0.95 to 1.60)	1.27 (0.98 to 1.65)	1.39 (1.05 to 1.81)	0.02
Model 3	1.13 (1.00 to 1.27)	0.04	1	1.23 (0.95 to 1.59)	1.27 (0.98 to 1.65)	1.38 (1.06 to 1.81)	0.02
Model 4	1.13 (1.00 to 1.27)	0.05	1	1.23 (0.95 to 1.59)	1.27 (0.97 to 1.65)	1.38 (1.05 to 1.81)	0.02

HR=hazard ratio.
*Model 1=multivariable Cox proportional hazard model adjusted for age (timescale), sex, energy intake without alcohol, number of 24 hour dietary records, smoking status, educational level, physical activity, height, body mass index, alcohol intake, and family history of cancers; breast cancer models were additionally adjusted for menopausal status, hormonal treatment for menopause, oral contraception, and number of children. Model 2=model 1 plus intakes of lipids, sodium, and carbohydrates. Model 3=model 1 plus Western dietary pattern (derived by factor analysis). Model 4=model 1 plus intakes of lipids, sodium, and carbohydrates and Western dietary pattern (derived by factor analysis). Pearson correlation coefficients with Western dietary pattern were 0.5 for dietary lipids, 0.6 for sodium, and 0.40 for carbohydrates.
†Hazard ratio for increase of 10% in proportion of ultra-processed food intake in diet.
‡Sex specific cut-offs for quarters of ultra-processed proportions were 11.8%, 16.8%, and 23.3% in men and 11.8%, 16.8%, and 23.4% in women. In premenopausal women, cut-offs were 12.8%, 18.1%, and 25.0%. In postmenopausal women, cut-offs were 10.1%, 14.3%, and 19.5%.

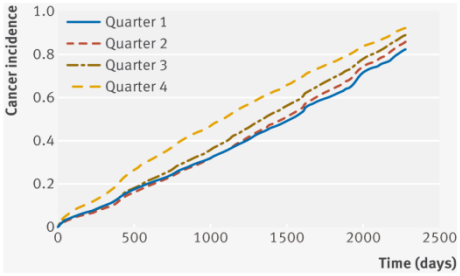

Fig 2 | Cumulative cancer incidence (overall cancer risk) according to quarters of proportion of ultra-processed food in diet

(P=0.005) were associated with an increased risk of overall cancer, and ultra-processed sugary products were associated with risk of breast cancer (P=0.006) (appendix 6).

Further adjustment for several indicators of the nutritional quality of the diet (lipid, sodium, and salt intakes—model 2; Western pattern—model 3; or both—model 4) did not modify these findings. The Pearson correlation coefficient between the proportion of ultra-processed food in the diet and the Western dietary pattern was low (0.06). Consistently, analyses performed according to the method proposed by Lange et al to assess a potential mediation of the relation between ultra-processed food and risk of cancer

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by these nutritional factors showed no statistically significant mediation effect of any of the factors tested.[45] The mediated effects ranged between 0% and 2%, with all P>0.05 (appendix 4).

No association was statistically significant for prostate and colorectal cancers. However, we observed a borderline non-significant trend of increased risk of colorectal cancer associated with ultra-processed food intake (hazard ratio for quarter 4 versus quarter 1: 1.23 (1.08 to 1.40), P for trend=0.07) in model 4.

Sensitivity analyses (adjusted for model 1 covariates, data not tabulated) excluding cancer cases diagnosed during the first two years of follow-up provided similar results (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.10 (1.03 to 1.17), P=0.005 for overall cancer risk, 1367 cases and 102 502 non-cases included; 1.15 (1.03 to 1.29), P=0.02 for breast cancer risk, 441 cases and 80 940 non-cases included). Similarly, results were unchanged when we excluded non-validated cancer cancers (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.11 (1.05 to 1.17), P<0.001 for overall cancer risk, 1967 cases and 102 752 non-cases included; 1.12 (1.02 to 1.23), P=0.02 for breast cancer risk, 677 cases and 81 274 non-cases included).

We obtained similar results when we included only participants with at least six 24 hour records (overall cancer risk: hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.13 (1.06 to 1.21), P<0.001, 1494 cases and 47 920 non-cases included) and when we re-included participants with only one 24 hour record (overall cancer risk: 1.11 (1.06 to 1.16), P<0.001, 2383 cases and 122 196 non-cases included).

Findings were also similar when we coded the proportion of ultra-processed food in the diet as sex specific fifths instead of quarters (overall cancer risk: hazard ratio for highest versus lowest fifth 1.25 (1.08 to 1.47), P for trend<0.001; breast cancer risk: 1.25 (0.96 to 1.63), P for trend=0.03).

Further adjustment for the following variables, in addition to model 1 covariates, did not modify the results: dietary supplement use at baseline (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.12 (1.06 to 1.17), P<0.001 for overall cancer; 1.11 (1.02 to 1.22), P=0.02 for breast cancer), prevalent depression at baseline (1.11 (1.06 to 1.17), P<0.001 for overall cancer; 1.11 (1.01 to 1.22), P=0.02 for breast cancer), healthy dietary pattern (1.11 (1.05 to 1.17), P<0.001 for overall cancer; 1.10 (1.00 to 1.21), P=0.04 for breast cancer), overall fruit and vegetable consumption in g/d (1.10 (1.04 to 1.16), P<0.001 for overall cancer; 1.11 (1.01 to 1.22), P=0.03 for breast cancer), number of smoked cigarettes in pack years (1.13 (1.07 to 1.19), P<0.001 for overall cancer; 1.13 (1.03 to 1.24), P=0.009 for breast cancer), and season of inclusion in the cohort (1.12 (1.06 to 1.18), P<0.001 for overall cancer; 1.12 (1.02 to 1.22), P=0.02 for breast cancer).

We also tested other methods for handling missing data, such as multiple imputation and complete case analysis (that is, exclusion of participants with missing data for at least one covariate).[46] The results were very similar for the multiple imputation analysis (hazard ratio for a 10 point increment in the proportion of ultra-processed foods in the diet 1.11 (1.06 to 1.17), P<0.001, 2228 cases and 10 2752 non-cases for overall cancer; 1.11 (1.01 to 1.21), P=0.02, 739 cases and 81 420 non-cases for breast cancer) and for the complete case analysis (1.11 (1.05 to 1.18), P<0.001, 1813 cases and 82 824 non-cases for overall cancer; 1.14 (1.03 to 1.26), P=0.01, 579 cases and 64 642 non-cases for breast cancer).

As a secondary analysis, we also tested associations between the proportions of the three other NOVA degrees of food processing and risk of cancer. We found no significant associations between the proportions of "processed culinary ingredients" or "processed foods" with risk of cancer at any location (all P>0.05). However, and consistent with our findings, the consumption of "minimally/unprocessed foods" was associated with lower risks of overall and breast cancers (hazard ratio for a 10 point increment in the proportion of unprocessed foods in the diet 0.91 (0.87 to 0.95), P<0.001, 2228 cases and 102 752 non-cases for overall cancer; 0.42 (0.19 to 0.91), P=0.03, 739 cases and 81 420 non-cases for breast cancer), in multivariable analyses adjusted for model 1 covariates.

Discussion

In this large prospective cohort, a 10% increase in the proportion of ultra-processed foods in the diet was associated with significant increases of 12% in the risk of overall cancer and 11% in the risk of breast cancer. A few studies have previously suggested that ultra-processed foods contribute to increasing the risk of cardiometabolic disorders—such as obesity,[29] hypertension,[30] and dyslipidaemia[28]—but no previous prospective epidemiological study has evaluated the association between food processing and risk cancer.

Interpretation and comparison with other studies

No estimate is available of the proportion of ultra-processed food in the diet at the national level in France. However, in the nationally representative INCA3 study conducted by the French Food safety Agency in 2016,[4] "transformed" foods included sweet pastries, biscuits, dairy desserts, ice cream, fruit purée and fruit in syrup, fruit and vegetable juices, soups and broths, sandwiches, pizzas, and salted pastries, as well as mixed dishes composed of egg, meat, fish, vegetable, and/or starchy foods (cereals, legumes, or potatoes). More than half of the "transformed" foods consumed outside catering establishments by adults aged 18-79 were manufactured industrially, about a third were homemade, and the rest was handcrafted (for example, by caterers). These figures illustrate the important share of processed, and especially industrially processed, foods in the diet of French adults.

Several hypotheses could be put forward to explain our findings. The first one relates to the generally poorer nutritional quality of diets rich in ultra-processed foods. Diets that include a higher proportion of processed food products tended to be richer in energy, sodium, fat, and sugar and poorer in fibres and various micronutrients in several studies conducted in various countries.[10-17 19] Ultra-processed foods have also been associated with a higher glycaemic response and a lower satiety effect.[47] Although not the unique determinant, excessive energy, fat, and sugar intakes contribute to weight gain and risk of obesity, with obesity recognised as a major risk factor for post-menopausal breast, stomach, liver, colorectal, oesophagus, pancreas, kidney, gallbladder, endometrium, ovary, liver, and (advanced) prostate cancers and haematological malignancies.[29] For instance, body fatness in post-menopausal women is estimated to contribute 17% of the breast cancer burden.[2] Furthermore, most ultra-processed foods, such as dehydrated soups, processed meats, biscuits, and sauces, have a high salt content. Foods preserved with salt are associated with an increased risk of gastric cancer.[29] Conversely, dietary fibre intake decreases the risk of colorectal cancer, with a convincing level of evidence,[3 29] and may also reduce the risk of breast cancer.[3] However, the associations between ultra-processed food intake and risk of cancer observed in this study were statistically significant despite adjustment for body mass index and remained significant after further adjustment for a Western-type dietary pattern and/or the energy, fat, sugar, and salt content of the diet. Mediation analyses did not support a strong effect of the "nutritional quality" component in this association, suggesting that other bioactive compounds contained in ultra-processed food may contribute to explain the observed associations.

A second hypothesis concerns the wide range of additives contained in ultra-processed foods. Although maximum authorised levels normally protect the consumers against adverse effects of each individual substance in a given food product,[48] the effect on health of the cumulative intake across all ingested foods and potential cocktail/interaction effects remain largely unknown. More than 250 different additives are authorised for addition to food products in Europe and the US.[22 49] For some of them, experimental studies in animal or cellular models have suggested carcinogenic properties that deserve further investigation in humans.[23 24 50-53] One example is titanium dioxide (TiO_2), a common food additive that contains nanoscale particles and that is used as a whitening agent or in packaging in contact with food or drinks to provide a better texture and antimicrobial properties. Experimental studies, mainly conducted in rodent models, suggest that this additive could initiate or promote the development of pre-neoplastic lesions in the colon, as well as chronic intestinal inflammation. The World Health Organization and the International Agency for Research on Cancer evaluated TiO_2 as "possibly carcinogenic to humans" (group 2B).[24] The effects of intense artificial sweeteners such as aspartame on human metabolism and on the composition and functioning of gut microbiota are also controversial.[53] Although previous experimental studies in animals confirmed the safety of aspartame, their relevance to human health outcomes has been questioned, particularly regarding potential long term carcinogenicity.[51] Another concern is the formation of carcinogenic nitrosamines in meats containing sodium nitrite when meat is charred or overcooked. These N-nitroso compounds may be involved in causing colorectal cancer.[23 52]

Thirdly, food processing and particularly heat treatments produce neoformed contaminants (for example, acrylamide) in ultra-processed products such as fried potatoes, biscuits, bread, or coffee. A recent meta-analysis found a modest association between dietary acrylamide and risk of both kidney and endometrial cancer in non-smokers.[54] In addition, the European Food Safety Agency judged that evidence from animal studies was sufficient to classify acrylamide as genotoxic.[20]

Lastly, bisphenol A is another contaminant suspected of migrating from plastic packaging of ultra-processed foods. Its endocrine disruptor properties led the European Chemicals Agency to judge it as "a substance of very high concern."[55] Increasing evidence suggests involvement in the development of several non-communicable diseases, including cancer linked to endocrinal disruptors.[21]

Strengths and limitations of study

Strengths of this study pertain to its prospective design and large sample size, along with a detailed and up to date assessment of dietary intake. Repeated 24 hour dietary records (including 3300 different food items) are more accurate than either food frequency questionnaires with aggregated food groups or household purchasing data. However, some limitations should be acknowledged. Firstly, as is generally the case in volunteer based cohorts, participants in the NutriNet-Santé cohort were more often women, with health conscious behaviours and higher socio-professional and educational levels than the general French population.[56] This might limit the generalisability of the findings and may have resulted in a lower incidence of cancer compared with national estimates (age and sex standardised incidence rate per 100 000 people per year: 786 cases in our cohort versus 972 cases in France[57]) and an overall lower exposure to ultra-processed foods, with less contrast between extreme categories. These points would tend to lead to underestimation of the strength of the associations. However, the possibility that selection bias may have led to an overestimation of some associations cannot be totally excluded. Secondly, some misclassification in the NOVA "ultra-processed food" category cannot be ruled out. Thirdly, despite a multi-source strategy for case ascertainment (combining validation of health events declared by participants, medico-administrative databases from the health insurance,

and national death registry), exhaustive detection of cancer cases cannot be guaranteed. Furthermore, statistical power was limited for some cancer locations (such as colorectal cancer), which may have impaired our ability to detect hypothesised associations. Next, the length of follow-up was relatively limited, as the cohort was launched in 2009. It allowed us to study mostly mid-term associations between consumption of ultra-processed food and risk of cancer. As is usually the case in nutritional epidemiology, we made the assumption that the measured exposure at baseline (especially as we averaged a two year period of exposure) actually reflects more generally the usual eating habits of the individual during adulthood, including several years before his or her entry into the cohort. However, as some carcinogenic processes may take several decades, it will be important in the future to reassess the associations between ultra-processed food and cancer risk in the cohort, to investigate longer term effects. This will be one of the perspectives of our work for the upcoming five to 10 years. Lastly, although we included a large range of confounding factors in the analyses, the hypothesis of residual confounding resulting from unmeasured behavioural factors and/or imprecision in the measure of included covariates cannot be entirely excluded owing to the observational design of this study. For instance, oral contraception was a binary variable in breast cancer models, as the precise doses, type, and duration of contraceptive use across reproductive life were not available. Randomised controlled trials have long been considered the only gold standard for elimination of confounding bias, but they do not capture consumption as it is in daily life. Moreover, a trial to investigate exposure for which a deleterious effect is suspected would not be ethically feasible. Our large observational cohort was therefore particularly adapted to provide insights in this field.

Conclusions and policy implications

To our knowledge, this study was the first to investigate and highlight an increase in the risk of overall—and more specifically breast—cancer associated with ultra-processed food intake. These results should be confirmed by other large scale, population based observational studies in different populations and settings. Further studies are also needed to better understand the relative effect of nutritional composition, food additives, contact materials, and neoformed contaminants in this relation. Rapidly increasing consumption of ultra-processed foods may drive an increasing burden of cancer and other non-communicable diseases. Thus, policy actions targeting product reformulation, taxation, and marketing restrictions on ultra-processed products and promotion of fresh or minimally processed foods may contribute to primary cancer prevention.[6 9] Several countries have already introduced this aspect in their official nutritional recommendations in the name of the precautionary principle.[58 59]

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Transparency statement: MT (the guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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Appendix 1-6

Supplemental material

Appendix 1: 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 [1-3]. 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.

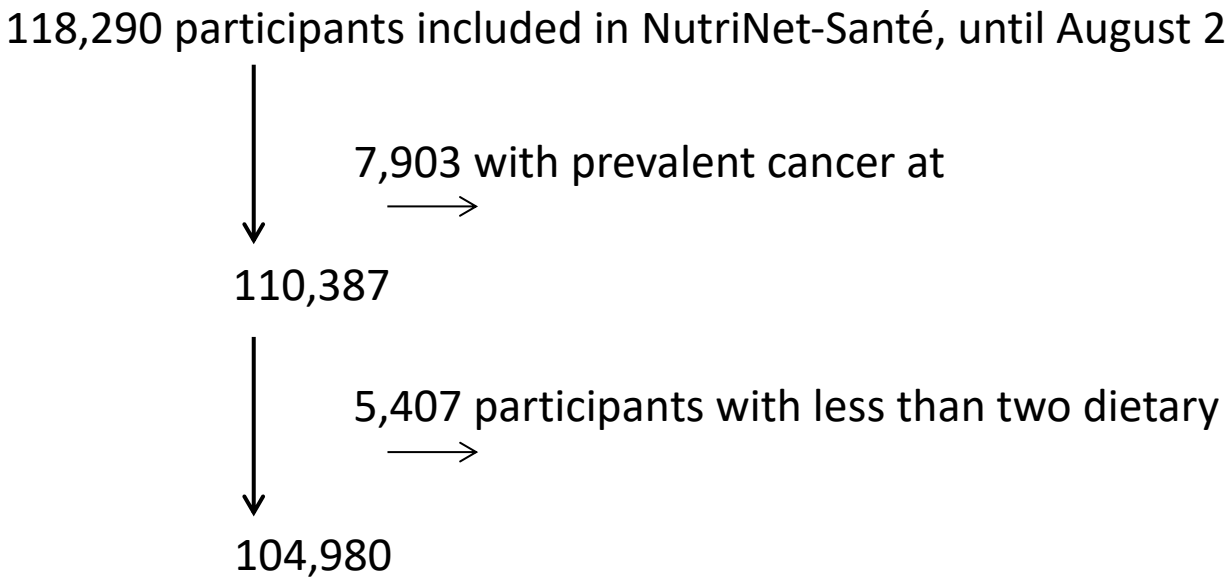
For instance, fruit compotes with only added sugar are considered as "processed foods", while flavoured fruit desserts with added sugar, texturizing agents and colorants are considered as "ultra-processed foods".

Regarding meats, 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".

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 2: Flow chart



Appendix 3: 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 4: Methodology and results of the mediation analysis

Mediation analyses were carried out according to the method proposed by Lange et al.[4] in order to evaluate the direct and indirect "effects" in the relationship between the exposure and the outcome, through nutritional mediators. Under the assumption of a causal relationship between quartiles of the proportion of ultra-processed food in the diet (=Exposure, quoted "A") and cancer risk (=Outcome, quoted "Y"), the aim was to estimate how much of this effect was mediated through various factors reflecting the nutritional quality of the diet. The latter factors (dietary intakes of sodium, total lipid, fatty acids, and carbohydrates, and Western-type dietary pattern) were considered as potential Mediators (quoted "M") in each model. The following covariates were considered as potential confounders (quoted "C"): age, sex, BMI, height, physical activity, smoking status, number of 24h-dietary records, alcohol intake, energy intake, family history of cancer, and educational level. To evaluate the direct effect and the indirect effect mediated by each nutritional factor, we applied a mediation analysis in the counterfactual framework. The mediation analyses were implemented according to the following steps for a categorical exposure:

(1) Construction of a new data set by repeating each observation in the original data set. This new variable A* corresponds to the value of the exposure relative to the indirect path. Each observation was repeated four times such that A* got to take all possible values of exposure (quartiles of ultra-processed).

(2) Fitting of a multinomial logistic regression applied to the new data set to estimate the association between ultra-processed food and cancer, conditioned on baseline confounders, and computing predicted values, first using the original variable A and then the new variable A*.

(3) Weighting (W) each observation calculated according to the following formula through applying the fitted models from steps 2 et 3 to the new dataset:

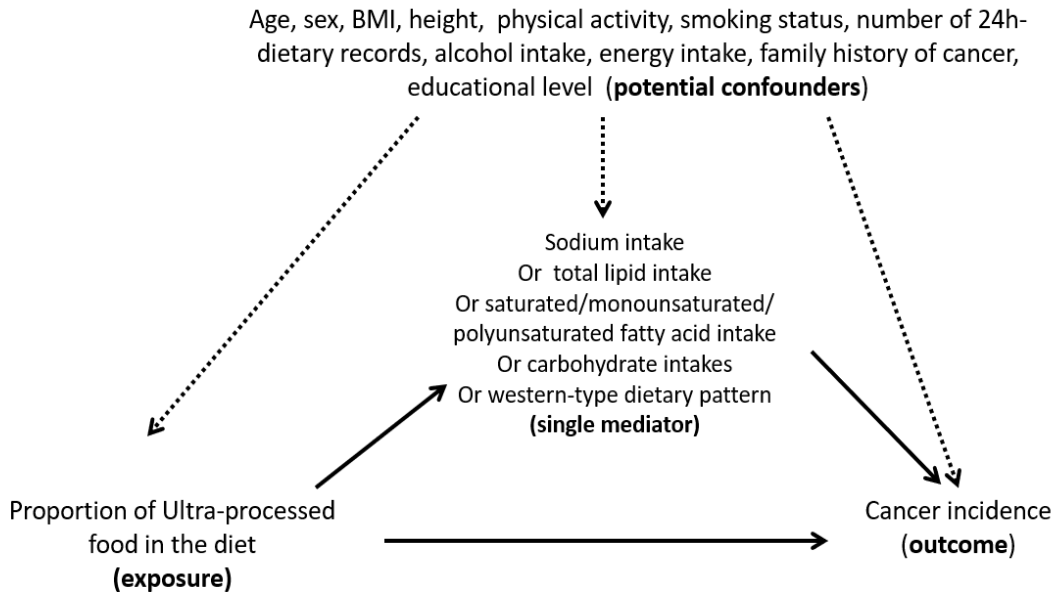
$$W_i = \frac{1}{P(A = A_i \,|C = C_i)} \frac{P(M = M_i|A = A_i^*, C = C_i)}{P(M = M_i|A = A_i, C = C_i)}$$

with A, the exposure, M, the mediator, C, the set of baseline confounders

(4) Fitting of a weighted Cox Marginal Structural Model (MSM) for direct and indirect effects controlling for baseline confounders, as the outcome corresponds to a survival time. The "Covsandwich" statement in SAS software allows getting robust standard errors.

(5) To evaluate how much of the total effect was due to the mediator effect, we calculated the 'proportion explained' by each single mediator as ($HR_{total\ effect}$ - $HR_{direct\ effect}$) / ($HR_{total\ effect} - 1$) where $HR_{total\ effect}$ and $HR_{direct\ effect}$ were respectively, the Hazard Ratios for total effect and for direct effect.

The figure below shows a conceptual model of the association between the proportion of ultra-processed foods in the diet and cancer risk, taking into account nutritional factors as potential single mediators:



Conceptual model of the association between ultra-processed food consumption and change in cancer risk taking into account nutritional factors as potential single mediator

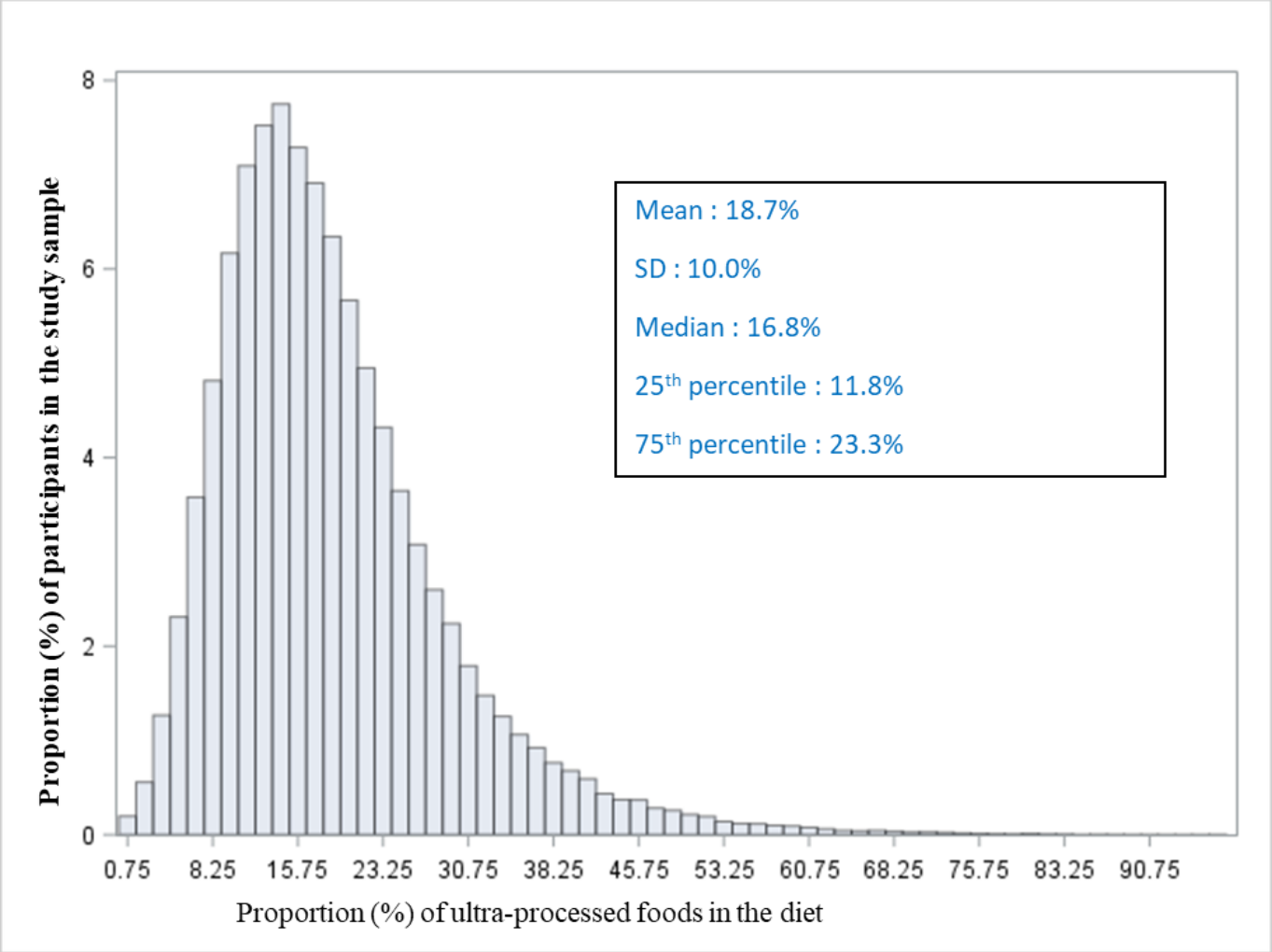
The table below shows the results of mediation analyses testing for a potential mediation by total lipid, carbohydrate, sodium, SFA, PUFA and MUFA intakes, and the Western dietary pattern of the association between ultra-processed food intake and cancer risk.

Table 15 – Hazard Ratios of direct, indirect and total effects and proportion of total effects mediated by several nutritional factors in the prospective associations between ultra-processed food and overall cancer risk, N=104980, NutriNet-Santé cohort, France, 2009-2017

	Tested nutritional mediators of the association between ultra-processed foods and overall cancer risk													
	Total lipids		Sodium		Carbohydrates		Western pattern		SFAs		PUFAs		MUFAs	
Effect	HR	p-value	HR	p-value	HR	p-value	HR	p-value	HR	p-value	HR	p-value	HR	p-value
Indirect effect	1.000	0.799	1.003	0.889	1.000	0.900	1.005	0.910	1.000	0.900	1.000	0.900	1.000	0.900
Direct effect	1.302	<0.0001	1.263	<0.0001	1.217	<0.0001	1.317	<0.0001	1.166	0.001	1.319	<0.0001	1.328	<0.0001
Total effect	1.302		1.267		1.217		1.324		1.166		1.319		1.328	
Proportion of the total effect mediated by the nutritional factor	0.00%		1.42%		0.00%		2.04%		0.00%		0.00%		0.00%	

SFAs: saturated fatty acids, PUFAs: poly-unsaturated fatty acids, MUFAs: mono-unsaturated fatty acids, HR: Hazard Ratio

Appendix 5: Distribution of the main exposure (proportion of ultra-processed food in the diet) in the study sample (N=104 980), NutriNet-Santé, France



Appendix 6: Associations between the quantity (g/d) of each ultra-processed food group and overall and breast cancer risks, from multivariable Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2017 (n=104,980)

	Continuous		
	HR[a,b]	95%CI	P-value
All cancers			
N for cases/non cases	2228/102752		
Starchy foods	1.01	(0.99-1.02)	0.4
Fruits and vegetables	1.00	(0.99-1.01)	0.2
Dairy products	1.01	(1.00-1.02)	0.05
Fats	1.07	(1.03-1.12)	0.002
Salty snacks	0.98	(0.93-1.02)	0.3
Meat, fish, eggs	1.01	(0.99-1.03)	0.4
Processed meat	0.99	(0.97-1.01)	0.5
Sugary products	1.01	(1.00-1.02)	0.03
Beverages	1.00	(1.00-1.01)	0.005
Breast Cancer			
N for cases/non cases	739/81420		
Starchy foods	1.00	(0.98-1.03)	0.7
Fruits and vegetables	1.01	(0.99-1.02)	0.3
Dairy products	1.01	(0.99-1.02)	0.3
Fats	1.06	(0.97-1.14)	0.2
Salty snacks	1.02	(0.95-1.10)	0.6
Meat, fish, eggs	1.01	(0.97-1.04)	0.8
Processed meat	0.98	(0.94-1.02)	0.4
Sugary products	1.02	(1.01-1.03)	0.006
Beverages	1.00	(0.99-1.01)	0.2

CI, confidence interval, HR, Hazard ratio

[a] adjusted for age (timescale), sex, energy intake without alcohol, number of 24h-dietary records, smoking status, educational level, physical activity, height, BMI, alcohol intake, and family history of cancers. Breast cancer models were additionally adjusted for menopausal status, hormonal treatment for menopause, oral contraception and number of children.

[b]HR for an increase of 10g of the quantity (in g/d) of each ultra-processed food group

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RESEARCH

Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé)

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ABSTRACT

OBJECTIVE

To assess the prospective associations between consumption of ultra-processed foods and risk of cardiovascular diseases.

DESIGN

Population based cohort study.

SETTING

NutriNet-Santé cohort, France 2009-18.

PARTICIPANTS

105 159 participants aged at least 18 years. Dietary intakes were collected using repeated 24 hour dietary records (5.7 for each participant on average), designed to register participants' usual consumption of 3300 food items. These foods were categorised using the NOVA classification according to degree of processing.

MAIN OUTCOME MEASURES

Associations between intake of ultra-processed food and overall risk of cardiovascular, coronary heart, and cerebrovascular diseases assessed by multivariable Cox proportional hazard models adjusted for known risk factors.

RESULTS

During a median follow-up of 5.2 years, intake of ultra-processed food was associated with a higher risk of overall cardiovascular disease (1409 cases; hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.12 (95% confidence interval 1.05 to 1.20); P<0.001, 518 208 person years, incidence rates in high consumers of ultra-processed foods (fourth quarter) 277 per 100 000 person years, and in low consumers (first quarter) 242 per 100 000 person years), coronary heart disease risk (665 cases; hazard ratio 1.13 (1.02 to 1.24); P=0.02, 520 319 person years, incidence rates 124 and 109 per 100 000 person years, in the high and low consumers, respectively), and cerebrovascular disease risk (829 cases; hazard ratio 1.11 (1.01 to 1.21); P=0.02, 520 023 person years, incidence rates 163 and 144 per 100 000 person years, in high and low consumers, respectively). These results remained statistically significant after adjustment for several markers of the nutritional quality of the diet (saturated fatty acids, sodium and sugar intakes, dietary fibre, or a healthy dietary pattern derived by principal component analysis) and after a large range of sensitivity analyses.

CONCLUSIONS

In this large observational prospective study, higher consumption of ultra-processed foods was associated with higher risks of cardiovascular, coronary heart, and cerebrovascular diseases. These results need to be confirmed in other populations and settings, and causality remains to be established. Various factors in processing, such as nutritional composition of the final product, additives, contact materials, and neoformed contaminants might play a role in these associations, and further studies are needed to understand better the relative contributions. Meanwhile, public health authorities in several countries have recently started to promote unprocessed or minimally processed foods and to recommend limiting the consumption of ultra-processed foods.

STUDY REGISTRATION

ClinicalTrials.gov NCT03335644.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The consumption of ultra-processed foods has increased during the past decades in many countries

Epidemiological studies have found associations between intake of ultra-processed food and a higher incidence of dyslipidaemia in children and higher risks of overweight, obesity, and hypertension, as well as higher risks of overall and breast cancers in the French NutriNet-Santé prospective cohort.

Some mechanistic studies suggest cardiometabolic effects for several components commonly found in ultra-processed foods; however, epidemiological evidence is lacking

WHAT THIS STUDY ADDS

In this large prospective cohort (n=105 159), an absolute increment of 10 in the percentage of ultra-processed foods in the diet was associated with a >10% increase in the rates of overall cardiovascular, coronary heart, and cerebrovascular diseases

Further studies are needed to investigate the relative impact of nutritional composition, food additives, contact materials, and neoformed contaminants in this relation

Considering other studies that have shown associations between consumption of ultra-processed foods and other non-communicable diseases, the proportion of ultra-processed food in the diet should be limited and the consumption of unprocessed or minimally processed foods should be promoted instead

Introduction

Cardiovascular disease (CVD) is the main cause of death worldwide, representing one third of all deaths globally.[1] Among modifiable risk and preventive factors in the development and prevention of CVD, the role of diet is crucial.[2] Dietary factors make the largest contribution to CVD mortality at the population level across Europe: 56% of CVD deaths in men and 48% in women were attributable to dietary factors in 2015.[3] In addition to tobacco avoidance, reaching a

balanced diversified diet (regular consumption of fruit, vegetables, fish, and whole grain foods, along with a restriction of sodium, saturated fats, and refined carbohydrates), avoiding excessive alcohol intake, and engaging in regular physical activity are recognised as key factors in the primary and secondary preventions of CVD, according to the World Health Organization and European and American guidelines.[1 4 5]

During the past decades the consumption of ultra-processed foods worldwide has increased substantially.[6-11] According to nationwide food surveys assessing intakes, household expenses, or supermarket sales in European countries, the US, Canada, New Zealand, and Latin American countries, ultra-processed products represent between 25% and 60% of total daily energy intake.[12-23] These trends are triggering the recent interest in researchers to investigate the links between ultra-processed foods and health outcomes. Ultra-processed foods are formulations of many ingredients, several of exclusive industrial use, that result from a sequence of physical and chemical processes applied to foods and their constituents. These foods are thought to be microbiologically safe, convenient, and highly palatable.[24] They often have a higher content of total fat, saturated fat, added sugar, energy density, and salt, along with a lower fibre and vitamin density,[12-20 25] many of these nutritional features being directly related to cardiometabolic health.[2] It is also suggested that these foods might affect satiety control and glycaemic responses.[26] Moreover, food processing might affect nutrient availability in the small intestine by altering the properties of the plant and animal cells in food.[27] Beyond nutritional composition, several compounds of ultra-processed foods that are neoformed during processing could also play a role in cardiovascular health. According to a recent study, acrylamide, a contaminant present in heat treated processed food products (industrially or not) as a result of the Maillard reaction, might be associated with an increased risk of CVD.[28] In addition, acrolein, a compound formed during the heating of fat and that can be found in caramel candies, might be associated with an increased risk of CVD.[29] Furthermore, the packaging of ultra-processed foods might contain materials in contact with food, such as bisphenol A, which could, according to a meta-analysis of observational studies, increase the risk of cardiometabolic disorders,[30] even though prospective cohort studies are still limited. Finally, ultra-processed foods generally contain additives. Although most of them are probably safe, adverse cardiometabolic effects have been suggested for some, such as glutamates,[31] emulsifiers,[32] sulfites,[33] and carrageenan[34] in studies performed on animal models.

NOVA, a classification of foods and drinks based on levels of processing developed by researchers from the University of São Paulo,[24] has enabled research to be carried out on the relation between food processing and health. Some cross sectional and ecological studies have linked the intake of ultra-processed foods of the NOVA classification to overweight, obesity, metabolic syndrome, and functional gastrointestinal disorders.[10 11 35-39] Consumption of ultra-processed food has also been associated with a higher risk of dyslipidaemia in a prospective study conducted on Brazilian children,[40] and higher incidences of overweight, obesity,[41] and hypertension [42] in a cohort of Spanish university students, as well as a higher risk of overall cancer and breast cancer in the French NutriNet-Santé cohort.[43]

We assessed the association between the consumption of ultra-processed foods and the risk of CVD, using up-to-date information on dietary intake.

Methods

Study population

The NutriNet-Santé study is an ongoing web based cohort launched in 2009 in France with the objective of studying the associations between nutrition and health as well as the determinants of dietary behaviours and nutritional status. Details about this cohort have been described previously.[44] Briefly, participants aged 18 years or older with access to the internet have been continuously recruited among the general population since May 2009 using multimedia campaigns. Questionnaires are completed online using a dedicated website (www.etude-nutrinet-sante.fr). Participants are followed using an online platform linked to their email address. Electronic informed consent is obtained from each participant.

Data collection

At baseline, participants completed a set of five questionnaires related to sociodemographic and lifestyle characteristics[45] (for example, sex, date of birth, occupation, educational level, smoking status, number of children), anthropometry[46 47] (height, weight), dietary intakes, physical activity (validated seven day International Physical Activity Questionnaire),[48] and health status (for example, personal and family history of diseases, drug treatment).

Participants were also invited to complete a series of three non-consecutive validated web based 24 hour dietary records at baseline and every six months (to vary the season of completion), randomly assigned over a two week period (two weekdays and one weekend day).[49-51] To be included in the nutrition component of the NutriNet-Santé cohort, it was mandatory to have two dietary records during the overall baseline period. In this prospective analysis, we averaged the mean dietary intakes from the 24 hour dietary records available during the first two years of each participant's follow-up (≤15 records) and considered these as baseline usual dietary intakes. The web based self administered 24 hour dietary records have been tested and validated against both an interview by a trained dietitian[49] and blood and urinary biomarkers.[50 51] Participants used the dedicated web interface to record all foods and beverages consumed during a 24 hour period for each of the three main meals (breakfast, lunch, and dinner) and any other eating occasion. We used previously validated photographs or usual containers

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to estimate portion sizes.[52] Dietary underreporting was identified with the method proposed by Black, using the basal metabolic rate and Goldberg cut-off, in order to screen participants with abnormally low energy intakes, and energy under-reporters (20.0% of the cohort) were excluded[53] (see supplementary appendix 1 for details about energy underreporting in the cohort). We calculated mean daily intakes of alcohol, micronutrients, macronutrients, and energy using the NutriNet-Santé food composition database, which contains more than 3300 different items.[54] Amounts consumed from composite dishes were estimated using French recipes validated by nutrition professionals. Sodium intake was assessed through a specific module included in the 24 hour records, taking into account native sodium in foods, salt added during cooking, and salt added on the plate. This method has been validated against sodium urinary excretion biomarkers.[51]

To avoid any modification of dietary behaviours, no individual data were transmitted to the participants, or advice given. We only provided general information on scientific results from the study.

Extent and purpose of food processing

Three trained dieticians categorised the food and beverage items of the NutriNet-Santé composition table into one of the four food groups in NOVA, based on the extent and purpose of industrial food processing.[24 55 56] A committee of specialists in nutritional epidemiology—three dietitians and five researchers—then reviewed the classification. When uncertainty existed about a food or beverage item, researchers reached a consensus based on the percentage of homemade and artisanal foods versus industrial brands of processed and ultra-processed foods reported by the participants. This study primarily focused on the NOVA group of ultra-processed foods. This group includes mass produced packaged breads and buns, sweet or savoury packaged snacks, industrialised confectionery and desserts, sodas and sweetened beverages, meatballs, poultry and fish nuggets, and other reconstituted meat products transformed with the addition of preservatives other than salt (eg, nitrites), instant noodles and soups, frozen or shelf stable ready meals, and other food products made mostly or entirely from sugar, oils, and fats, and other substances not commonly used in culinary preparations, such as hydrogenated oils, modified starches, and protein isolates. Industrial processes notably include hydrogenation, hydrolysis, extrusion, moulding, reshaping, and pre-processing by frying. Flavouring agents, colours, emulsifiers, humectants, non-sugar sweeteners, and other cosmetic additives are often added to these products to imitate sensorial properties of unprocessed or minimally processed foods and their culinary preparations, or to disguise undesirable qualities of the final product. In the ultra-processed group we also included food and beverages that did not fit in the three NOVA groups for unprocessed or minimally processed foods: (fresh, dried, grounded, chilled, frozen, pasteurised, or fermented staple foods such as fruit, vegetables, pulses, rice, pasta, eggs, meat, fish, or milk), processed culinary ingredients (salt, vegetable oils, butter, sugar, and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations), and processed foods (canned vegetables with added salt, sugar-coated dried fruit, meat products only preserved by salting, cheeses and freshly made unpackaged breads, and other products manufactured with the addition of salt, sugar, or other substances of the "processed culinary ingredients" group). As previously described,[57] we used standardised recipes to identify and disaggregate homemade and artisanal food preparations, and we applied the NOVA classification to the ingredients. Supplementary appendix 2 presents the details about the NOVA classification along with some examples.

Case ascertainment

Participants were asked to report major health events through the yearly health questionnaire, a check-up questionnaire every three months, or at any time through a specific interface on the study website. We then invited participants to provide their medical records (eg, diagnoses, hospital admissions, radiological reports, electrocardiograms) and, if necessary, the study doctors contacted the participants' doctors or medical facilities (clinic, hospital, or laboratory) to collect additional information. A committee of study doctors then reviewed the medical data to validate any major health events. Participants' families or doctors were contacted when there had been no response to the study website for more than one year. This process constituted the main source of case ascertainment in the cohort. Our research team was 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 (SNIIRAM). Thus, for participants who provided their social security number (n=50 240), we linked their data to medico-administrative databases of SNIIRAM, limiting potential bias from those who had not reported their CVD to the study investigators. A low proportion of participants (1.7%) emigrated and were not covered by SNIIRAM. Lastly, to identify deaths and potentially missed CVD cases for deceased participants we linked data to CépiDC, the French national cause specific mortality registry, which includes dates and causes of death. This registry is accessible to all French citizens, without specific authorisation or identification number. We classified CVD cases using ICD-CM codes (international classification of diseases-clinical modification, 10th revision). The present study focused on first incident cases of stroke (I64), transient ischaemic attack (G45.8 and G45.9), myocardial infarction (I21), acute coronary syndrome (I20.0 and I21.4), and angioplasty (Z95.8) occurring between inclusion and January 2018.

Statistical analysis

Up to 11 January 2018, 105 159 participants without CVD at baseline and who provided at least two valid 24 hour dietary records during their first two years of follow-up were included (fig 1). For each participant, we calculated the proportion (%) of ultra-processed foods in the total weight of food and beverages consumed (g/day). We determined this by creating a weight ratio rather than energy ratio to account for processed food that does not provide energy (eg, artificially sweetened beverages) and non-nutritional factors related to food processing (eg, neoformed contaminants, additives, and alterations to the structure of raw foods). A sensitivity analysis was also performed by weighting the ultra-processed variable by the energy (%Kcal/day) instead of weight. For all covariates except physical activity, 5% or less of values were missing and were imputed to the modal value (for categorical variables) or median (for continuous variables). For physical activity, the proportion of missing values was higher (14%) because we needed answers to all the questions in the International Physical Activity Questionnaire to calculate the score. To avoid massive imputation for a non-negligible number of participants or exclusion of those with missing data and risk of selection bias, we included a missing class into the models for this variable (main analysis). However, we also tested complete case analysis and multiple imputation in sensitivity analyses: multiple imputation for missing data was performed using the MICE method[58] by fully conditional specification (20 imputed datasets) for the outcome[59] and for several covariates: level of education (5.0% missing data), physical activity level (13.9% missing data), and body mass index (0.6% missing data). Results were combined across imputations based on Rubin's combination rules[60 61] using the SAS PROC MIANALYZE procedure.[62]

To examine differences in baseline characteristics of participants between quarters of the percentage of ultra-processed food in the diet with sex specific cut-offs (computed with PROC RANK BY SEX procedure in SAS), we used analysis of variance (ANOVA) or χ^2 tests when appropriate. We chose sex specific cut-offs because women generally having a healthier diet and consume lower food amounts than men, and this allowed us to ensure equivalent sex ratios between quarters. To provide some information on the nutritional quality of ultra-processed foods, we calculated the proportion across the different categories of the Nutri-score. This score is calculated based on a modified version of the Food Standard Agency Nutrient Profiling system, and it has been endorsed by the French, Spanish, and Belgian ministries of health as the official nutrient profiling system in these countries (see supplementary appendix 3 for details about its calculation).

We used Cox proportional hazards models with age as the primary timescale to evaluate the association between the proportion of ultra-processed foods in the diet (coded as a continuous variable or as quarters with sex specific cut-offs) and incidence of overall CVD, cerebrovascular diseases (stroke and transient ischaemic attack), and coronary heart diseases (myocardial infarction, acute coronary syndrome, and angioplasty). In these models, we censored CVDs other than the one studied at the date of diagnosis (ie, they were considered as non-cases for the disease of interest and contributed person years until the date of diagnosis of CVD). We generated log-log (survival) versus log-time plots to confirm risk proportionality assumptions (see supplementary appendix 4). Hazard ratios and 95% confidence intervals were computed. In continuous models, hazard ratios corresponded to the ratio of instantaneous risks for an absolute increment of 10 in the percentage of ultra-processed foods in the diet (ie, a 0.1 absolute increase in the proportion of ultra-processed foods in the diet). In models based on quarters of the percentage of ultra-processed food in the diet, we obtained P values for linear trends by coding quarters of ultra-processed food as an ordinal variable (1, 2, 3, or 4). We verified the assumption of linearity between consumption of ultra-processed food and risk of CVD using restricted cubic spline functions with the SAS macro written by Desquilbet and Mariotti.[63] Participants contributed person time until the date of CVD diagnosis, date of last completed questionnaire, date of death, or 11 January 2018, whichever occurred first.

Models were adjusted for age (timescale) and sex (model 0), in addition to body mass index (BMI, continuous), physical activity (high, moderate, low, calculated according to International Physical Activity Questionnaire recommendations[48]), smoking status (never, former, and current smokers), number of 24 hour dietary records (continuous), alcohol intake (g/day, continuous), energy intake (kcal/day, continuous), family history of CVD (yes or no), and educational level (less than high school degree, <2 years after high school degree, ≥2 years after high school degree) (model 1). To test for the potential influence of the nutritional quality of the diet in the association between intake of ultra-processed food and risk of CVD, we additionally adjusted this model for saturated fatty acids and sodium and sugar intakes (model 2), or for a healthy dietary pattern derived from principal component analysis (model 3) (see

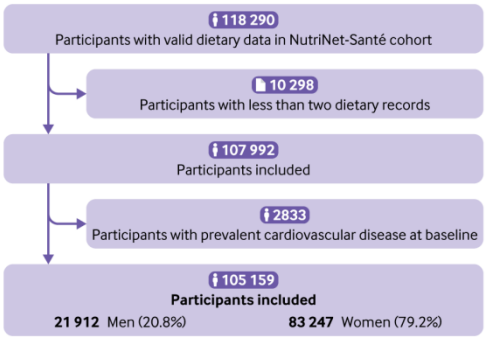

Fig 1 | Flowchart for study sample, NutriNet-Santé cohort, France, 2009-18

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supplementary appendix 5 for details), or for intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces (model 4). We also tested a model without adjustment for BMI (model 5) to account for the potential mediating role of BMI in the association. In model 6, we performed further adjustments (based on model 1) for baseline prevalent type 2 diabetes, dyslipidaemia, hypertension, and hypertriglyceridemia (yes or no) as well as treatments for these conditions (yes or no).

We also investigated the association between consumption of ultra-processed food and overall risk of CVD separately in stratums of the population: men and women, younger adults (<45 years) and older adults (≥45 years), participants with a high lipid intake (more than the median) and those with a lower lipid intake, participants with a BMI less than 25 and those with a BMI of 25 or more, participants following a healthy dietary pattern and those following a less healthy one (discriminated by the median of the healthy dietary pattern obtained by the principal component analysis), and participants who tended to be sedentary (the low class of International Physical Activity Questionnaire) and those who tended to be more physically active.

Sensitivity analyses were performed based on model 1 by excluding CVD cases diagnosed during the first two, three, four, and five years of each participant's follow-up to avoid reverse causality bias, by no adjustment for BMI and energy intake, and by testing further adjustments for a Western dietary pattern (continuous), number of smoked cigarettes in pack years (continuous), overall consumption of fruit and vegetables (continuous), dietary fibre intake (continuous), region of residence (Ile-de-France (Paris area) and east, centre east, west, north, southwest, Mediterranean region, or French overseas territories and departments), and season of inclusion in the cohort (spring, summer, autumn, or winter). Models were also tested after restriction of the population study to the participants with six or fewer, or more than six, 24 hour dietary records during the first two years of follow-up. We tested the associations between the quantity (g/day) (rather than the proportion) of intake of ultra-processed food and risk of CVD; as well as the associations between the quantity (g/day) of each ultra-processed food group and risk of CVD; we similarly tested the associations between the quantity (g/day) of non-ultra-processed foods in each group and risk of CVD to check that the associations were not driven by the consumption of specific food groups by themselves. A supplementary analysis was also performed by focusing on participants for whom the proportion of ultra-processed foods in the diet varied varied by less than |0.1| (that is, the absolute (non-negative) value of the difference) between the beginning and end of their follow-up. In the main model we included transient ischaemic attack (corresponding to a brief episode of neurological dysfunction, which has the same underlying mechanism as ischaemic stroke), but we performed a sensitivity analysis by excluding this CVD event. In this study we included angina pectoris events as acute coronary syndrome (ICD code I20), but not stable anginas (considered as soft events occurring only during effort or intense physical activity, which usually do not require hospital admission and might have other causes than coronary obstruction, such as anaemia, abnormal heart rhythms, and heart failure). However, we also tested sensitivity analyses including stable angina events.

Finally, we performed secondary analyses to test the associations between the proportions of unprocessed or minimally processed foods in the diet (continuous) with risk of CVD, using multivariate Cox models adjusted for model 1 covariates.

All tests were two sided, and we considered $P<0.05$ to be statistically significant. SAS version 9.4 (SAS Institute) was used for the analyses.

Patient and public involvement

The research question developed in this article corresponds to a strong concern of the participants involved in the NutriNet-Santé cohort, and of 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

A total of 105 159 participants (21 912 (20.8%) men and 83 247 (79.2%) women) were included in the present study. The mean baseline age of participants was 42.7 (SD 14.5) years (range 18.0-72.8 years). The mean number of dietary records for each participant over their first two years of follow-up was 5.7 (SD 3.0); the minimum was 2, but this applied to only 7.6% (7992 among 105159 participants) of the participants. Table 1 shows the main baseline characteristics of participants according to quarters of the proportion of ultra-processed foods in the diet. Compared with the first quarter (low consumption), participants among the highest quarters of ultra-processed food intake tended to be younger, be current smokers, be less highly educated, have less family history of CVD, and have lower physical activity levels. Furthermore, they had higher BMI, higher intakes of energy, lipids, carbohydrates, and sodium, lower intakes of alcohol, fruit, vegetables, and dietary fibre, and a lower prevalence of metabolic diseases. The mean contribution of ultra-processed foods to the overall diet (in weight) was 17.6% in men and 17.3% in women. Supplementary appendix 6 presents the distribution of the proportion of ultra-processed food in the diet in the study population. Main food groups contributing to ultra-processed food intake were sugary products (28%, for example, confectionaries, ice cream, pastries, sweetened dairy desserts) followed by ultra-processed fruit and vegetables (18%, for example, instant powder dehydrated vegetable soups and broths, vegetable nuggets, fruit based sweetened desserts), beverages (16%, for example, sodas, sugary and artificially sweetened non-carbonated beverages), starchy foods and breakfast cereals (12%, for example, pre-packaged bread, industrial dough, ready-to-eat

industrial pasta or potato based dishes, breakfast cereals), and processed meat and fish (11%, for example, nuggets, fish fingers, sausages, processed ham) (fig 2). Ultra-processed foods and beverages were usually products with a lower nutritional quality: ultra-processed foods in the NutriNet-Santé food composition database represented more than 85% of the products in the "E" category of the Nutri-score five colour labelling system (the category of lowest nutritional quality) versus less than 24% in the "A" category (the category of highest nutritional quality) (see supplementary appendix 3).

Main associations between ultra-processed food intake and CVD risk

During follow-up (518 208 person years, median follow-up time 5.2 years, interquartile range 2.6-7.3 years), 1409 first incident CVD events occurred, including 106 myocardial infarctions, 485 angioplasties, 74 acute coronary syndromes, 155 strokes, and 674 transient ischaemic events. Table 2 shows the associations between the proportion of ultra-processed foods in the diet and overall cardiovascular, coronary heart, and cerebrovascular diseases. Absolute incidence rates for CVD in the whole population were 253 per 100 000 person years: age and sex corrected absolute rates were 242 per 100 000 person years in the first quarter (low consumers) of the proportion of ultra-processed food intake in the diet, 254 in the second quarter, 252 in the third quarter, and 277 in the fourth quarter (high consumers); with respective rates for coronary heart disease of 109, 116, 125, and 124 per 100 000 person years, and for cerebrovascular diseases of 144, 148, 143, and 163 per 100 000 person years.

In model 1 (adjusted for age (timescale), sex, BMI, physical activity level, smoking status, number of 24 hour dietary records, alcohol intake, energy intake, family history of CVD, and educational level), during a median follow-up of 5.2 years, intake of ultra-processed food was associated with increased risks of

Table 1 | Baseline characteristics of study population according to quarters of ultra-processed food consumption with sex specific cut-offs (n=105 159), NutriNet-Santé cohort, France, 2009-18.* Values are numbers (percentages) unless stated otherwise

		Quarters of ultra-processed food consumption†				
Characteristics	All participants	First (n=26 396) (low intake)	Second (n=26 418)	Third (n=26 326)	Fourth (n=26 019) (high intake)	P value‡
Mean (SD) age (years)	42.7 (14.5)	47.6 (13.6)	44.8 (14.1)	41.8 (14.4)	36.4 (13.5)	<0.001
Sex:						
Women	83 247 (79.2)	20 890 (79.1)	20 905 (79.1)	20 845 (79.2)	20 607 (79.2)	
Men	21 912 (20.8)	5506 (20.9)	5513 (20.9)	5481 (20.8)	5412 (20.8)	
Mean (SD) body mass index	23.6 (4.4)	23.6 (4.2)	23.6 (4.2)	23.6 (4.4)	23.8 (4.8)	<0.001
Family history of CVD§	28 000 (26.6)	8431 (31.9)	7548 (28.6)	6655 (25.3)	5366 (20.6)	<0.001
Educational level:						<0.001
<High school degree	18 152 (17.3)	4797 (18.2)	4596 (17.4)	4380 (16.6)	4379 (16.8)	
<2 years after high school	17 971 (17.1)	3896 (14.8)	4006 (15.2)	4527 (17.2)	5542 (21.3)	
≥2 years after high school	69 036 (65.6)	17 703 (67.1)	17 816 (67.4)	17 419 (66.2)	16 098 (61.9)	
Smoking status:						<0.001
Current	17 946 (17.1)	4039 (15.3)	4077 (15.4)	4346 (16.5)	5484 (21.1)	
Former	34 421 (32.7)	10 022 (38.0)	9131 (34.6)	8321 (31.6)	6947 (26.7)	
Never	52 792 (50.2)	12 335 (46.7)	13 210 (50.0)	13 659 (51.9)	13 588 (52.2)	
Physical activity level¶:						<0.001
High	29 443 (28.0)	8776 (33.2)	7555 (28.6)	7146 (27.1)	5966 (22.9)	
Moderate	38 926 (37.0)	9695 (36.7)	10 167 (38.5)	9817 (37.3)	9247 (35.5)	
Low	22 150 (21.1)	4468 (16.9)	5302 (20.1)	5804 (22.0)	6576 (25.3)	
Mean (SD) intakes:						
Energy (kJ/day)	7949.9 (1959.2)	7679.5 (1871.0)	7970.0 (1877.2)	8076.6 (1953.7)	8075.3 (2100.4)	<0.001
Alcohol (g/day)	7.8 (11.8)	9.0 (13.1)	8.5 (11.9)	7.5 (11.1)	5.9 (10.7)	<0.001
Total lipid (g/day)	81.6 (25.3)	77.2 (24.1)	81.4 (24.0)	83.3 (25.0)	84.4 (27.3)	<0.001
Carbohydrate (g/day)	198.1 (57.5)	188.6 (57.4)	197.4 (54.6)	201.9 (56.3)	204.7 (60.2)	<0.001
Sodium (mg/day)	2717.2 (885.6)	2601.1 (867.6)	2749.9 (862.6)	2782.7 (876.9)	2735.3 (923.7)	<0.001
Fruit and vegetables (g/day)	407.1 (221.6)	505.2 (249.9)	434.1 (201.1)	385.2 (192.3)	302.3 (186.5)	<0.001
Total dietary fibre (g/day)	19.5 (7.2)	21.0 (7.7)	20.1 (6.9)	19.3 (6.8)	17.4 (6.9)	<0.001
Ultra-processed food (%)	17.4 (9.9)	7.5 (2.3)	13.0 (1.4)	18.3 (1.8)	30.8 (9.1)	-
Prevalent morbidity:						
Type 2 diabetes	1384 (1.3)	462 (1.7)	366 (1.4)	320 (1.2)	236 (0.9)	<0.001
Hypertension	8279 (7.9)	2613 (9.9)	2277 (8.6)	1993 (7.6)	1396 (5.4)	<0.001
Dyslipidemia	8038 (7.6)	2391 (9.1)	2193 (8.3)	1984 (7.5)	1470 (5.6)	<0.001
Hypertriglyceridemia	1441 (1.4)	384 (1.4)	380 (1.4)	355 (1.3)	322 (1.2)	0.1

IPAQ=International Physical Activity Questionnaire.
*For all covariates except physical activity, a low proportion of values were missing (0-5%); the latter were replaced by the modal value among the population study: ≥2 years of higher education for educational level and 22.9 for body mass index.
†Quarters of proportion of ultra-processed food intake in total quantity of food consumed. Sex specific cut-offs for quarters of ultra-processed proportions were 0.108, 0.156, and 0.220 in men and 0.106, 0.154, and 0.218 in women.
‡Analysis of variance or χ^2 test where appropriate.
§Among first degree relatives.
¶Available for 90 519 participants. They were categorised into the high, moderate, and low categories according to IPAQ guidelines.[48]

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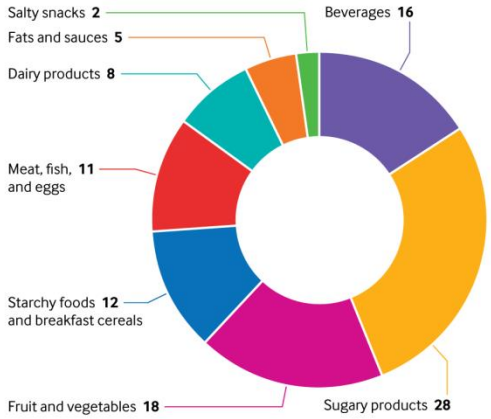

Fig 2 | Relative contribution (%) of each food group to consumption of ultra-processed food in diet

overall CVD (hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.12 (95% confidence interval 1.05 to 1.20); P<0.001, 518 208 person years). Intake of ultra-processed food was also associated with increased risks of coronary heart diseases (hazard ratio 1.13 (1.02 to 1.24); P=0.02, 520 319 person years) and cerebrovascular diseases (1.11 (1.01 to 1.21); P=0.02, 520 023 person years). The linearity assumptions between intake of ultra-processed food and risks of overall cardiovascular, coronary heart, and cerebrovascular diseases were confirmed by the restricted cubic spline (respective P values for non-linear associations 0.4, 0.7, and 0.3) (fig 3). Supplementary appendix 4 presents the log-log (survival) versus log-time plots, showing the verification of the proportional hazards assumption. Statistically significant associations were observed for angioplasty (485 cases and 104 674 non-cases, hazard ratio 1.16 (95% confidence interval 1.03 to 1.30); P=0.01) and transient ischaemic attack (674 cases and 104 485 non-cases, 1.13 (1.03 to 1.24); P=0.01). Results were similar for overall CVD when cases of transient ischaemic attack were not considered as CVD (754 cases and 104 405 non-cases, 1.12 (1.02 to 1.23); P=0.02), or when cases of stable angina were considered as CVD (1601 cases and 103 120 non-cases 1.12 (1.06 to 1.19); P<0.001).

Sensitivity analyses

Stratified analyses

The association with risk of overall CVD was statistically significant in all stratums of the population investigated, according to sex, age, lipid intakes, healthy dietary pattern, BMI, and physical activity level (see supplementary appendix 7).

Associations by ultra-processed food groups

Ultra-processed beverages were associated with increased risks of overall CVD (hazard ratio for an increase of 100 g/day=1.06 (95% confidence interval 1.02 to 1.10); P<0.001), ultra-processed fats and sauces (1.73 (1.01 to 2.94); P=0.04) and meats (1.28 (1.00 to 1.64); P=0.05) were associated with an increased risk of coronary heart diseases, and ultra-processed beverages (1.06 (1.01 to 1.12); P=0.01), sugary products (1.12 (1.01 to 1.27); P=0.05), and salty snacks (2.03 (1.04 to 3.94); P=0.04) were associated with an increased risk of cerebrovascular diseases (see supplementary appendix 8a). In contrast, no strong evidence was found for an association between these food groups in their non-ultra-processed form and CVD risk (except for salty snacks, but with broad confidence intervals owing to relatively limited consumption in our study population) (see supplementary appendix 8b).

Further adjustments and sensitivity analyses

Further adjustment for several indicators of the nutritional quality of the diet (saturated fatty acids, sodium and sugar intakes, model 2; healthy dietary pattern, model 3; intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces, model 4, table 2) did not modify these findings. Further adjustment for baseline type 2 diabetes, dyslipidaemia, hypertension, and hypertriglyceridaemia, as well as treatments for these conditions, did not modify the findings (model 6, table 2). The incidence rate for participants with six or fewer records was 209 cases per 100 000 person years (mean age 40.6 years), compared with 344 per 100 000 person years in those with more than six records (mean age 46.6 years); however, similar results were observed in both groups of participants: respectively, hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.13 (95% confidence interval 1.03 to 1.24); P<0.001, and hazard ratio 1.11 (95% confidence interval 1.01 to 1.23); P=0.03.

In further sensitivity analyses (see supplementary appendix 9), adjustments for additional nutritional factors (dietary fibre, intake of fruit and vegetables, healthy dietary pattern) as well as other potential confounders (ie, number of smoked cigarettes in pack years, season of inclusion in the cohort, region of residence) did not change the results. Not adjusting for BMI and energy did not affect the associations. We tested other methods to deal with missing data: using multiple imputation with the MICE method, in multivariable analyses adjusted for model 1 covariates the associations remained stable (hazard ratio for overall CVDs 1.16 (95% confidence interval 1.08 to 1.24); P<0.001, for coronary heart diseases 1.15 (1.04 to 1.27); P<0.001, and for cerebrovascular diseases 1.15 (1.05 to 1.26); P<0.001). Complete case analyses also showed similar results (see supplementary appendix 9). Results were also similar when analyses included only cases and censored participants with linked medico-administrative data (1.13 (1.06 to 1.1); P<0.001 for CVD risk). The associations were similar when we used the amount of ultra-processed food intake (g/day), rather than the proportion (hazard ratio for a 100 g/day increase of ultra-processed food in the diet 1.04 (95% confidence interval 1.02 to 1.07);

P=0.001 for CVD risk). However, the associations remained significant after the exclusion of CVD cases with a diagnosis during the first two years of follow-up: hazard ratio 1.14 (95% confidence interval 1.05 to 1.23); P<0.001, 1087 cases and 103 750 non-cases (see supplementary appendix 9), as well as during the first three years (1.44 (1.05 to 1.25); P<0.001, 879 cases and 103 750 non cases), four years (1.44 (1.03 to 1.25); P=0.01, 663 cases and 103 750 non-cases), and five years (1.13 (1.00 to 1.28); P=0.04, 441 cases and 103 750 non-cases). The results also remained stable when the ultra-processed variable was weighted by the energy (% Kcal/day instead of % g/day): hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet weighted by energy 1.06 (95% confidence interval 1.01 to 1.12); P=0.01, for overall CVD risk, in multivariable analyses adjusted for model 1 covariates.

Sensitivity analysis focusing on the 85 232 participants for whom the proportion of ultra-processed foods in the diet varied by less than |0.1| between the beginning and end of their follow-up, provided similar results (1029 CVD cases and 84 203 non-cases, hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet 1.09 (1.00 to 1.19); P<0.001).

Secondary analyses

As a secondary analysis, we also tested the associations between the proportions of the unprocessed or minimally processed group of the NOVA classification in the diet and risk of CVD. Consistently with our findings, the consumption of unprocessed or minimally processed foods was associated with lower risks of overall cardiovascular, coronary, and cerebrovascular diseases (hazard ratio for an absolute increment of 10 in the percentage of unprocessed or minimally processed foods in the diet 0.91 (0.86 to 0.97); P<0.001 for overall CVD, hazard ratio 0.91 (95% confidence interval 0.84 to 0.99); P=0.04 for coronary heart diseases and 0.91 (0.84 to 0.98); P=0.02 for cerebrovascular diseases), in multivariable analyses adjusted for model 1 covariates.

Discussion

In this large prospective cohort, an absolute increment of 10 in the percentage of ultra-processed foods in

Table 2 | Associations between intake of ultra-processed food and overall cardiovascular, coronary heart, and cerebrovascular diseases from multivariable* Cox proportional hazard models, in NutriNet-Santé cohort, France, 2009-18 (n=105 159). Values are hazard ratios (95% confidence intervals) unless stated otherwise

Models by disease type	Quarters of ultra-processed food consumption†				P trend	Continuous‡	P value
	First (low intake)	Second	Third	Four (high intake)			
All cardiovascular diseases							
No of cases/non-cases	446/25 950	410/26 008	330/25 996	223/25 796		1409/103 750	
Model 0	1	1.06 (0.93 to 1.22)	1.08 (0.93 to 1.24)	1.25 (1.06 to 1.47)	0.01	1.13 (1.06 to 1.21)	<0.001
Model 1	1	1.04 (0.91 to 1.19)	1.07 (0.93 to 1.23)	1.23 (1.04 to 1.45)	0.02	1.12 (1.05 to 1.20)	<0.001
Model 2	1	.05 (0.92 to 1.20)	1.08 (0.93 to 1.25)	1.25 (1.05 to 1.47)	0.02	1.13 (1.05 to 1.20)	<0.001
Model 3	1	1.03 (0.90 to 1.18)	1.05 (0.91 to 1.22)	1.20 (1.01 to 1.42)	0.05	1.11 (1.03 to 1.19)	0.003
Model 4	1	1.03 (0.90 to 1.18)	1.06 (0.90 to 1.23)	1.21 (1.02 to 1.45)	0.05	1.12 (1.04 to 1.20)	0.002
Model 5	1	1.05 (0.92 to 1.20)	1.08 (0.93 to 1.24)	1.26 (1.07 to 1.48)	0.01	1.13 (1.06 to 1.21)	<0.001
Model 6	1	1.04 (0.91 to 1.19)	1.06 (0.92 to 1.23)	1.23 (1.04 to 1.45)	0.03	1.12 (1.05 to 1.20)	0.001
Coronary heart diseases§							
No of cases/non-cases	208/26 188	194/26 224	166/26 160	97/25 922		665/104 494	
Model 0	1	1.08 (0.89 to 1.31)	1.19 (0.97 to 1.46)	1.23 (0.96 to 1.57)	0.04	1.15 (1.04 to 1.26)	0.006
Model 1	1	1.07 (0.87 to 1.30)	1.19 (0.97 to 1.46)	1 20 (0.93 to 1.53)	0.07	1.13 (1.02 to 1.24)	0.02
Model 2	1	1.07 (0.87 to 1.30)	1.20 (0.97 to 1.47)	1.22 (0.95 to 1.56)	0.05	1.14 (1.03 to 1.26)	0.01
Model 3	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.44)	1.16 (0.90 to 1.49)	0.1	1.11 (1.00 to 1.23)	0.04
Model 4	1	1.05 (0.86 to 1.28)	1.17 (0.95 to 1.46)	1.18 (0.91 to 1.53)	0.1	1.12 (1.01 to 1.24)	0.03
Model 5	1	1.07 (0.88 to 1.31)	1.20 (0.97 to 1.47)	1.22 (0.96 to 1.57)	0.05	1.14 (1.03 to 1.26)	0.009
Model 6	1	1.06 (0.87 to 1.29)	1.18 (0.96 to 1.45)	1.18 (0.93 to 1.52)	0.08	1.12 (1.02 to 1.24)	0.02
Cerebrovascular diseases¶							
No of cases/non-cases	267/26 129	238/26 180	188/26 138	136/25 883		829/104 330	
Model 0	1	1.03 (0.87 to 1.23)	1.01 (0.84 to 1.22)	1.24 (1.00 to 1.53)	0.1	1.11 (1.02 to 1.21)	0.02
Model 1	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.24 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02
Model 2	1	1.02 (0.86 to 1.22)	1.01 (0.84 to 1.22)	1.25 (1.01 to 1.55)	0.1	1.12 (1.02 to 1.22)	0.02
Model 3	1	1.00 (0.84 to 1.20)	0.99 (0.81 to 1.19)	1.21 (0.98 to 1.51)	0.2	1.10 (1.00 to 1.20)	0.04
Model 4	1	1.01 (0.84 to 1.21)	1.00 (0.82 to 1.21)	1.23 (0.98 to 1.54)	0.2	1.11 (1.01 to 1.22)	0.03
Model 5	1	1.02 (0.85 to 1.21)	1.00 (0.83 to 1.21)	1.26 (1.01 to 1.55)	0.1	1.11 (1.02 to 1.22)	0.01
Model 6	1	1.01 (0.85 to 1.21)	0.99 (0.82 to 1.20)	1.23 (1.00 to 1.53)	0.1	1.11 (1.01 to 1.21)	0.02

Mean follow-up times for overall cardiovascular, coronary heart, and cerebrovascular diseases were all equal to 5.2 years. Person years were, respectively, 518 208, 520 319, and 520 023.
*Model 0 is an age (timescale) and sex-adjusted Cox proportional hazard model.
Model 1 is a multivariable Cox proportional hazard model adjusted for age (timescale), sex, energy intake, number of 24 hour dietary records, smoking status, educational level, physical activity, body mass index, alcohol intake, and family history of cardiovascular disease. Model 2=model 1+saturated fatty acid intake, sodium intake, sugar intake. Model 3=model 1+healthy dietary pattern (derived by factor analysis). Model 4=model 1+intakes of sugary products, red and processed meat, salty snacks, beverages, and fats and sauces. Model 5=model 1 without adjustment for body mass index. Model 6=model 1+baseline prevalent type 2 diabetes, dyslipidemia, hypertension, and hypertriglyceridemia (yes or no) as well as treatments for these conditions (yes or no).
†Sex specific cut-offs for quarters of ultra-processed proportions were 0.108, 0.156, and 0.220 in men and 0.106, 0.154, and 0.218 in women.
‡Hazard ratio for an absolute increment of 10 in percentage of ultra-processed foods in diet.
§Includes myocardial infarctions, angioplasties, and acute coronary syndromes.
¶Includes strokes and transient ischaemic attacks.

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the diet was associated with a 12%, 13%, and 11% statistically significant increase in the rates of overall cardiovascular, coronary heart, and cerebrovascular disease, respectively. Although consumption of ultra-processed food has been associated with increased risks of cancer in the NutriNet-Santé cohort,[43] and with cardiometabolic disorders, such as obesity,[41] hypertension,[42] and dyslipidaemia,[40] no prospective epidemiological study had evaluated the association between the proportion of processed food in the diet and risk of CVD.

Interpretation and comparison with other studies

Several hypotheses could explain our findings. Firstly, ultra-processed foods generally have a poorer nutritional quality than unprocessed or processed foods, as they tend to be richer in sodium, energy, fat, and sugar, and poorer in fibres[12-19 25]; they are also associated with a higher glycaemic response.[26] Several of these nutritional compounds are known risk factors for cardiometabolic health, with a high level of evidence for high sodium, saturated fat, and added sugars, and low dietary fibre, and a "general concordance" for high glycaemic index or load.[2] In addition, several food groups that are mainly ultra-processed and are largely consumed in Western type diets have been associated with increased risks of cardiometabolic outcomes with a "high concordance"—that is, sugar sweetened beverages and processed meats.[2] Sugar sweetened beverages might delay the trigger of the internal satiety signal, leading to excessive caloric ingestion.[64] Among other determinants, excessive intakes of energy, fat, and sugar contribute to weight gain and the risk of overweight or obesity, the latter being recognised as a major risk factor for CVDs.[65] However, several ultra-processed foods and beverages (confectionery snacks, sugar sweetened beverages, cakes, sports drinks, breakfast cereals) might contain relatively high levels of glucose-derived advanced glycation end products,[66] which over time could lead to or accelerate vascular disease.[67] In addition, high consumers of ultra-processed food in our study sample had lower intakes of fruit and vegetables; high intakes of which, along with adherence to a healthy dietary pattern, are known to be beneficial to cardiometabolic health (a high level of evidence).[2] More generally, part of the association between intake of ultra-processed food and risk of CVD may partly come from the simultaneous lower consumption of non-ultra-processed foods. It is difficult to distinguish between both effects because, by construction, people who had an overall higher share of ultra-processed foods in their diet also had a lower overall proportion of non-ultra-processed foods (Pearson correlation coefficient between the proportions of minimally processed and ultra-processed foods in the diet −0.8). This did not, however, explain the whole association. Indeed, several ultra-processed food groups were associated with an increased risk of CVD, but not the non-ultra-processed form of these food groups. Besides, the associations observed in this study between intake of ultra-processed food and risk of CVD were statistically significant even after adjustment for BMI, and they remained significant after further adjustment for healthy and Western dietary patterns, energy, fat, sugar, salt, and fibre content of the diet, as well as consumption of sugary products, salty snacks, fats and sauces, red and processed meat, beverages, fruit, and vegetables. This suggests that the nutritional composition of ultra-processed foods was not the only factor driving the associations observed and that other bioactive compounds specifically contained in ultra-processed food could be contributing to the observed relations.

A second interpretation concerns the wide range of additives in ultra-processed foods. Although maximum authorised levels normally protect consumers against adverse effects of individual substances in certain

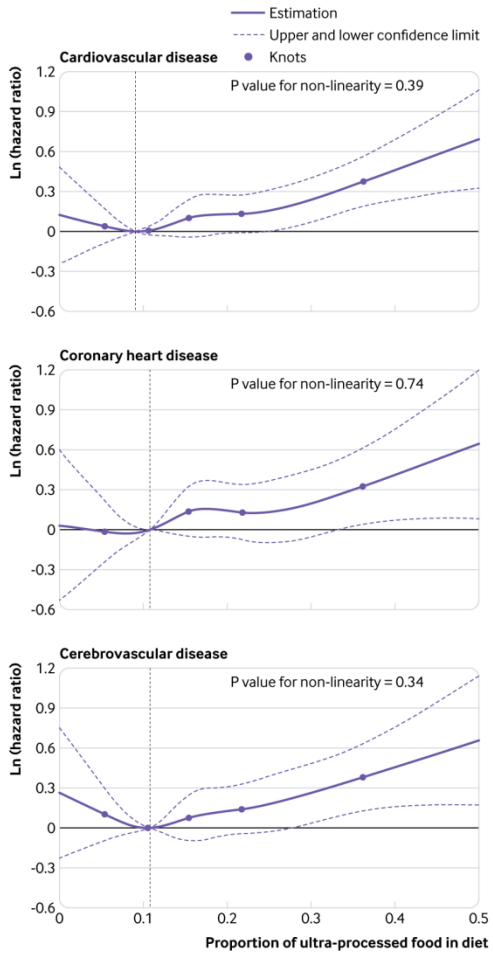

Fig 3 | Spline plot for linearity assumption of association between proportion of ultra-processed food in diet and risks of overall cardiovascular, coronary heart, and cerebrovascular diseases. Restricted cubic spline SAS macro developed by Desquilbet and Mariotti[63]

food products,[68] the health impact of the cumulative intake across all ingested foods and potential cocktail or interaction effects remain largely unknown. For some of the roughly 350 different authorised additives in Europe, several adverse effects for cardiovascular health have been suggested in experimental studies on animal or cellular models. For example, high oral doses of sulphites, which can be found in some ready-to-consume sauces containing vinegar, caused damage to rat hearts[33]; doses of monosodium glutamate (high levels present especially in sauces and ready-to-eat soups and noodles) at doses of 4 mg/g body weight or more in mice increased the oxidative stress through lipid peroxidation and thereby might initiate atherosclerosis and other coronary heart diseases.[31] Moreover, monosodium glutamate has suspected obesogenic properties, with epidemiological evidence positively correlating its consumption to increased body mass index and higher prevalence of metabolic syndrome.[69] In addition, emulsifiers, often found in ultra-processed foods, and particularly carboxymethylcellulose and polysorbate-80, have shown potential roles in inducing low grade inflammation and obesity or metabolic syndrome in mice.[32] Carrageenan, used as a food additive for its thickening properties, might lead to glucose intolerance, insulin resistance, and inhibition of insulin signalling, as shown in a study on cell and animal models.[34] Non-caloric artificial sweeteners could play a role in these associations: long term consumption of acesulfame K might accelerate atherosclerosis in cellular models,[70] whereas in a randomised control trial, sucralose was found to increase glucose and insulin levels in obese women, alter metabolic response to a glucose load, and slow down insulin clearance from plasma.[71]

Food processing, and particularly heat treatments, also produce neoformed contaminants, such as acrylamide in fried potatoes, biscuits, bread, or coffee, and acrolein in grilled sausages and caramel candies. Acrylamide was associated with higher odds of CVDs in the NHANES (National Health and Nutrition Examination Survey) study,[28] whereas in the Louisville Healthy Heart Study exposure to acrolein was associated with platelet activation and suppression of circulating angiogenic cell levels, as well as increased risks of CVD.[29]

Finally, ultra-processed foods might be contaminated by contact materials (those suspected of migrating from packaging), among which is bisphenol A in some plastic packaging, judged as "a substance of very high concern" by the European Chemicals Agency,[72] and which in a recent meta-analysis was found to be associated with an increased risk of cardiometabolic outcomes (in particular hypertension and coronary artery disease).[30]

In this observational study, to avoid modification of dietary behaviours, the participants received no individual data or advice (only general information on scientific results from the study). Moreover, the topic of ultra-processed food is relatively new to French people, thus substantial media driven dietary modifications on this specific aspect are of low probability in the timeframe considered in this study. Besides, models that focused on participants whose proportion of ultra-processed foods in the diet varied by less than |0.1| provided similar results between the beginning and end of their follow-up.

Strengths and limitations of this study

Strengths of this study relate to its prospective design, along with a detailed and up-to-date assessment of dietary intake. Repeated 24 hour dietary records (including 3300 different food items) are more accurate than food frequency questionnaires with aggregated food groups, or than household purchasing data.[73] However, the study has several limitations. Firstly, residual confounding from unmeasured behavioural factors or imprecision in the measure of included covariates cannot be excluded owing to the observational design of this study. For example, in model 6, we considered treatments for each metabolic disorder as binary variables, since the duration of treatment and compliance were not measured. To limit residual confounding, we accounted for many potential confounders, and several sensitivity analyses (testing further adjustments or stratifications) showed the high stability of the results. Causality of the associations cannot be established from this single study. Although randomised controlled trials are considered ideal for eliminating confounding bias, they would not be ethically feasible for studying exposures with a suspected deleterious effect. Besides, they do not capture consumption as it is in daily life. Our large observational cohort was therefore particularly adapted to provide such insights. Secondly, some misclassification in the NOVA category of ultra-processed food cannot be ruled out, although the committee that performed or reviewed the classifications tried to avoid any unidirectional and systematic bias. Any remaining misclassification could have led to a non-differential measurement error (identically in future cases and non-cases), most probably leading to an underestimation of the observed associations, although an overestimation cannot be excluded. Moreover, ultra-processed foods represent a broad and diverse spectrum of food products. In this study, some associations were observed for several different ultra-processed food groups (beverages, fats and sauces, meat, fish and eggs, sugary products, and salty snacks). Most importantly, the effects of ultra-processed foods on human health might go through complex mechanisms involving synergic effects of many compounds and characteristics of ultra-processed foods. Chronic exposure to multiple factors, including cocktails of commonly used food additives (eg, glutamate salts in sauces, artificial sweeteners in beverages, preservatives in ready-to-eat meals), neoformed compounds, and contact materials could play a role in the studied association. These mechanisms can hardly be distinguished based on food groups as they should be considered globally. Creating an indicator for the proportion of ultra-processed foods

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in the diet allows those with a high or low exposure to these multiple interactions to be distinguished. The fact that the associations were stronger when the overall ultra-processed food proportion in the diet was considered rather than the associations in specific food groups, argue in favour of these potential cocktail effects. Thirdly, a multi-source strategy for case ascertainment (combining validation of health events self reported by participants, thorough investigation by study doctors of participants, their families, and their doctors, medico-administrative databases from the health insurance for all participants who provided their identification number, and the exhaustive national death and causes of death registry), allowed us to maximise cases detection, but complete ascertainment cannot be guaranteed. Furthermore, statistical power was somehow limited for specific types of CVD, which could have affected our ability to detect hypothesised associations. Fourthly, the length of follow-up was relatively limited, as the cohort was launched in 2009. Thus, it allowed us to study mostly mid-term associations between consumption of ultra-processed food and risk of CVD, while having recent data on dietary behaviours, covering the consumption of "contemporary" ultra-processed foods on the market. Still, a classic assumption in nutritional epidemiology is that the measured exposure at baseline (especially since we averaged a two year period of exposure) actually reflects more generally the usual eating habits of people not only at the moment of the study but also several years before and several years after their inclusion in the cohort. Thus, we assume that our study provided insights into the associations between long term consumption of ultra-processed foods and risk of CVD. To investigate longer term associations, it will be important in the future to reassess the associations between intake of ultra-processed food and risk of CVD in the cohort.

Fifthly, we used a weight ratio (in % g/day) to calculate the proportion of ultra-processed foods in the diet rather than an energy ratio to account for ultra-processed food that does not provide energy (eg, artificially sweetened beverages) and non-nutritional factors related to food processing (eg, neoformed contaminants, food additives, and alterations to the structure of raw foods). However, because the densities of different types of ultra-processed foods differ (eg, salty snacks vs. beverages), no ideal weighting method exists. Nonetheless, sensitivity analyses were carried out using an energy ratio, and results were unchanged. Sixthly, the effect sizes observed in this study are consistent with those usually observed in large nutritional epidemiological cohorts.[74 75] Even though the hazard ratios might seem relatively limited for nutritional exposures, the potential public health impact of these associations could be important because the consumption of the studied factors (ultra-processed foods) is common and widespread in the general population. Lastly, as is usually the case in volunteer based cohorts, participants in the NutriNet-Santé cohort were younger, more often women, and had higher socio-professional and educational levels than the general French population.[76] They were also less likely to smoke,[77] to be overweight or obese (28.2% of men and 29.4% of women in NutriNet-Santé *v* 54% and 44% in French population),[78] and to have type 2 diabetes (baseline prevalence in cohort 1.6% *v* 6% in French population[79]). Participants in the NutriNet-Santé cohort also had healthier dietary intakes than the French population: higher intakes of fruit, vegetables, and fish, and lower intakes of red meat and added fats.[77] This could have resulted in a lower incidence of CVDs compared with national estimates (age and sex standardised incidence rate per 100 000 population yearly: 495 cases in our cohort (253 before standardisation) *v* 500 in France,[80] although these figures are not strictly comparable because, unlike in our cohort, no national data are available in France for patients with CVD who were not admitted to hospital) and an underrepresentation of consumers of high ultra-processed food, leading to a lower contrast between extreme categories.[80] These points most probably resulted in an underestimation of the strength of the associations. However, the possibility that selection bias might have led to an overestimation of some associations cannot be ruled out. To date, no nationally representative data are available on the proportion of ultra-processed food in the diet in the French population, thus comparison with our population study is not straightforward. The nationally representative INCA3 study conducted by the French Food safety Agency in 2016[81] was not based on the NOVA classification. However, the authors provided a list of all food groups that they considered as "transformed" (sweet pastries, biscuits, dairy desserts, ice cream, fruit purée and fruit in syrup, fruit and vegetable juices, soups and broths, sandwiches, pizzas, and salted pastries, as well as mixed dishes composed of egg, meat, fish, vegetable, or starchy foods). More than half of the "transformed" foods consumed outside catering establishments by adults aged between 18 and 79 years were manufactured (about one third were homemade, with the remainder handcrafted, such as by a caterer).

Conclusions and policy implications

In this large prospective cohort we identified an increase in the risk of CVDs associated with the proportion of ultra-processed food in the diet. These findings need to be confirmed by other large scale population based studies in different populations and settings. Besides, the concept of food processing is complex, as the possible processes and the authorised additives are multiple. Further studies are needed to investigate the relative impact of nutritional composition, food additives, contact materials, and neoformed contaminants in this association. Our research team is currently launching a large scale programme on chronic exposure to food additives (single substances and multi-exposure "cocktails") and health.[82] The NutriNet-Santé cohort is in an excellent position to conduct such an investigation

as the participants record all commercial names and brands of industrial products consumed in dietary records, which is crucial for an accurate evaluation of exposure at the individual level, as a result of the high variability in additive composition between brands for a similar type of product. Further investigations are also planned in the future, related to contact materials (eg, containers used for microwave heating of ready-made meals) and some neoformed compounds. If causality is established, increasing trends of ultra-processed food intake in developed countries could contribute to the increase in burden from CVD. Even if it remains unclear what specific processes, compounds, or ultra-processed food subtypes play a more important role, evidence is accumulating for an association between increased overall proportion of ultra-processed food in the diet and increased risks of several chronic diseases.[37 40-43] It is therefore important to inform consumers about these associations and to implement actions targeting product reformulation (eg, improving nutritional quality and reducing the use of unnecessary additives), taxation, and communication to limit the proportion of ultra-processed foods in the diet and promote the consumption of unprocessed or minimally processed foods instead.[7 24] For precautionary reasons, several countries, such as France and Brazil, have already introduced these recommendations in their official nutritional guidelines.[83 84]

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Ethical approval: The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines and was approved by the institutional review board of the French Institute for Health and Medical Research (IRB Inserm 0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL 908450/909216).

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Data sharing: No additional data available.

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Supplementary information: appendices 1-9

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.

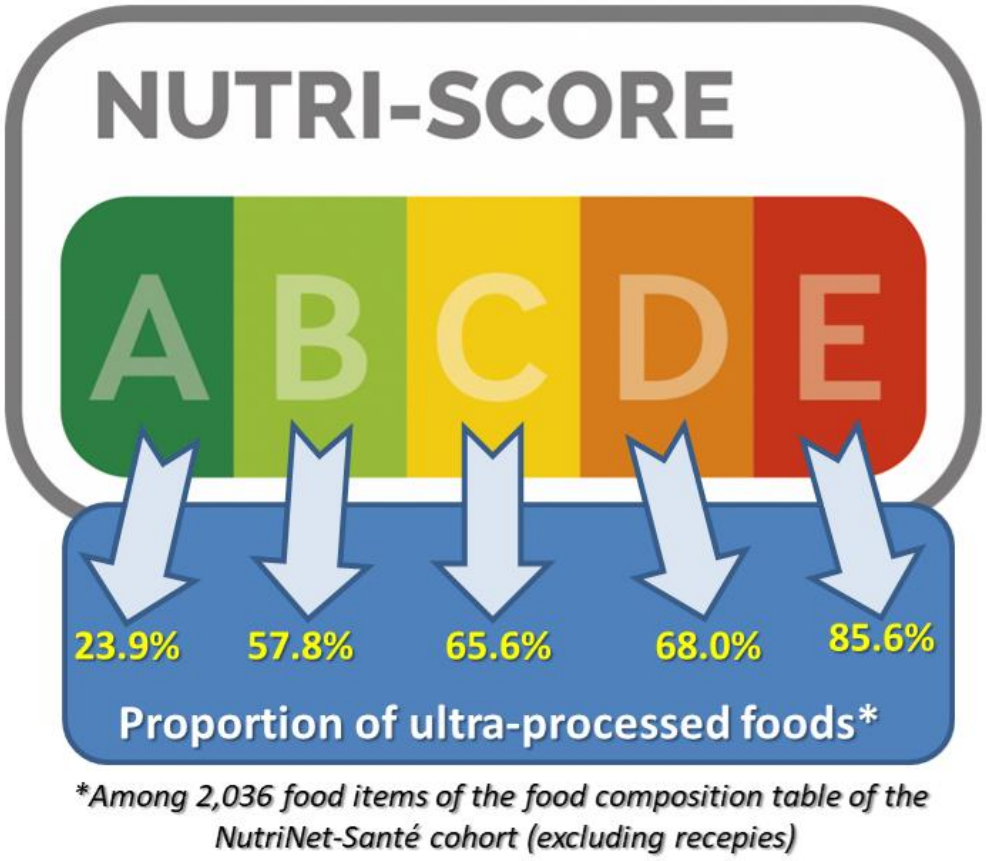
For instance, salted-only red or white meats are considered as "processed foods" whereas smoked or cured meats with added nitrites and conservatives, such as sausages and ham are classified as "ultra-processed foods".

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).

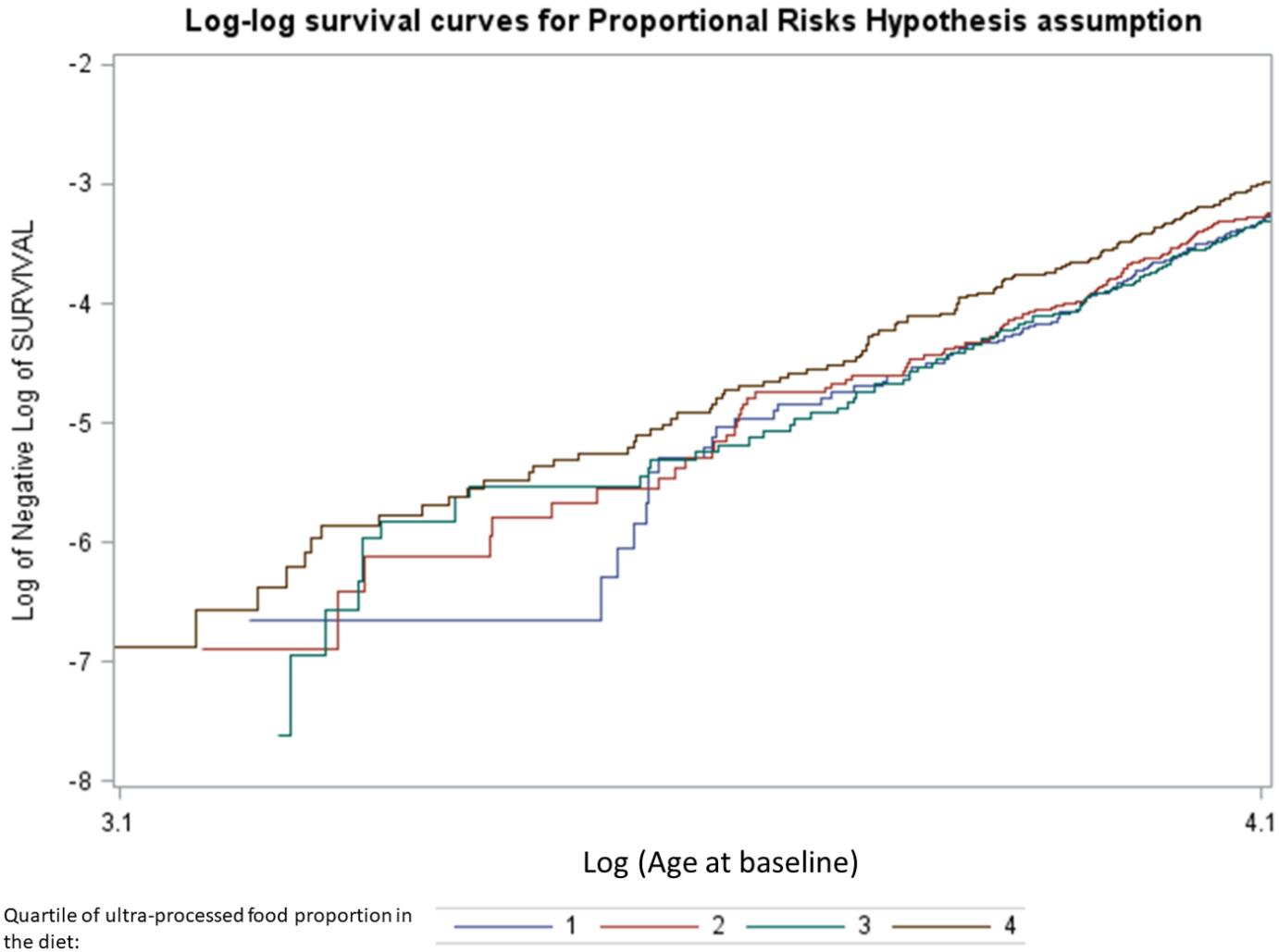
Milk and vegetable milk are not concerned by this exception. Their scores are computed using the overall score computation system.

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)

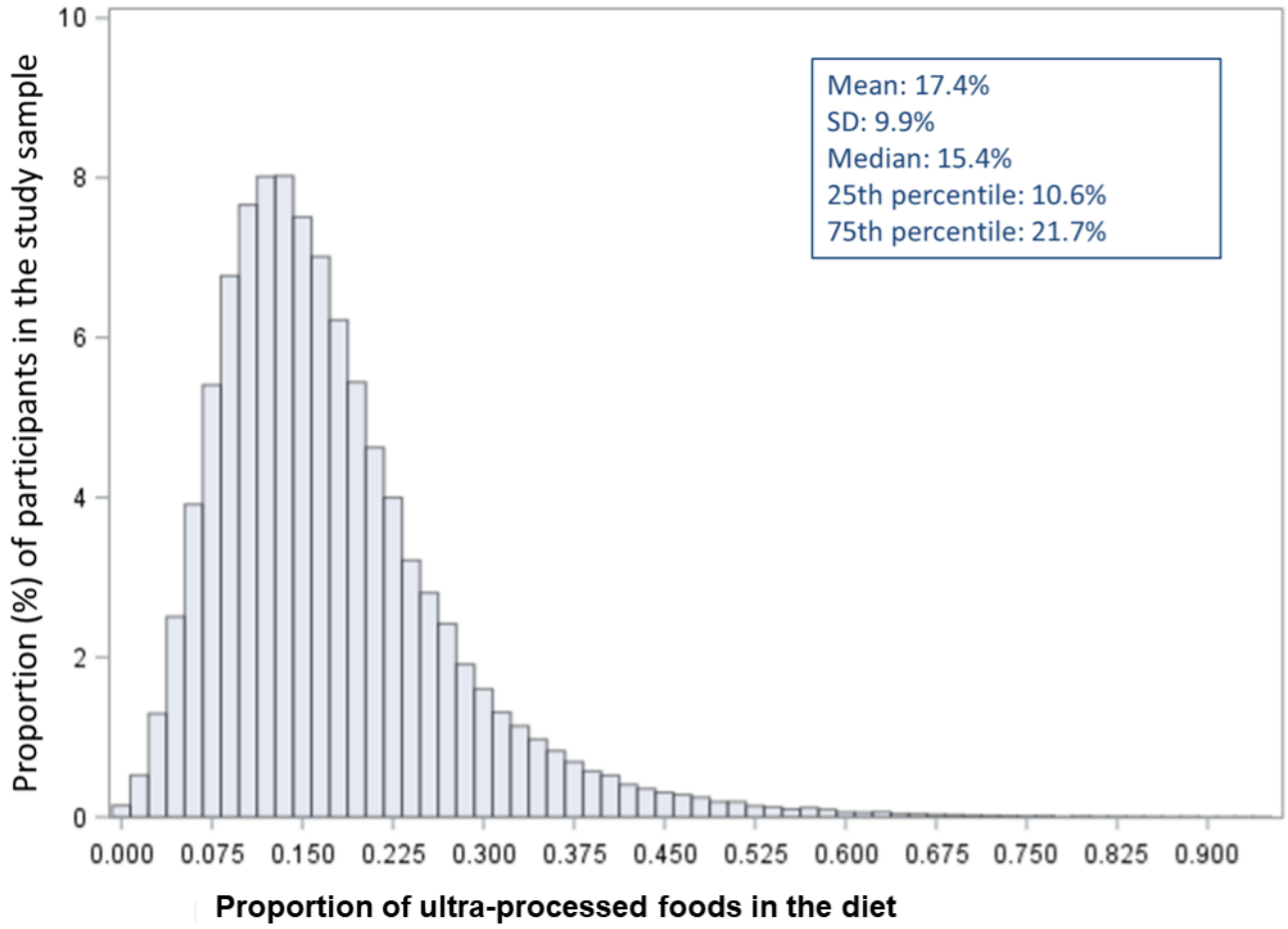


Appendix 5: Method for deriving dietary patterns by principal component analysis and corresponding factor loadings

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[T]
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

[T]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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Appendix C - Ultra-processed food and type 2-diabetes risk (under review)

Ultra-processed food consumption and risk of type 2 diabetes among participants of the NutriNet-Santé prospective Cohort

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ABSTRACT

IMPORTANCE:

Ultra-processed foods (UPF) are widespread in Western diets. Their consumption has been associated in recent prospective studies with increased risks of all-cause mortality and chronic diseases such as cancer, cardiovascular diseases, hypertension, and dyslipidemia, however, data regarding diabetes is lacking.

OBJECTIVE:

The objective of this prospective study was to assess the associations between consumption of UPF and risk of type 2 diabetes (T2D).

DESIGN:

Population based prospective cohort.

SETTING AND PARTICIPANTS:

Overall, 104,707 participants aged at least 18 years (median: 41.5 years) from the French NutriNet-Santé cohort (2009-2019) were included. Dietary intakes were collected using repeated 24 hour dietary records (5.7/participant on average), designed to register participants' usual consumption for >3500 different food items. These were categorized according to their degree of processing by the NOVA classification.

MAIN OUTCOMES AND MEASURES:

Associations between UPF consumption and risk of T2D were assessed using multivariable Cox proportional hazard models adjusted for known risk factors (sociodemographic, anthropometric, lifestyle, medical history and nutritional factors).

RESULTS:

UPF consumption was associated with a higher risk of T2D (adjusted Hazard Ratio for an absolute increment of 10 in the percentage of UPF in the diet = 1.15 (95% confidence interval 1.06 to 1.25); P=0.0009, median follow-up: 6.0y, 582252 person-years, 821 incident cases). These results remained statistically significant after adjustment for other metabolic comorbidities and for several markers of the nutritional quality of the diet.

CONCLUSIONS AND RELEVANCE:

In this large observational prospective study, a higher proportion of UPF in the diet was associated with a higher risk of T2D. Various dimensions of processing such as nutritional composition of the final product, modification of the food matrix, certain food additives, contact materials, and neoformed contaminants might play a role in these associations and further epidemiological and mechanistic studies are needed to better understand their relative contribution. Moreover, the observational design of the study does not allow establishing a causal link. These results need to be confirmed in other populations and settings. Meanwhile, public health authorities in several countries have recently started to recommend privileging unprocessed/minimally processed foods and limiting UPF consumption.

KEY POINTS:

Question: What are the associations between the consumption of ultra-processed foods and type 2 diabetes (T2D) risk?

Findings: This observational prospective study showed that an increase in the consumption of ultra-processed foods was associated with an increased T2D risk.

Meaning: A higher proportion of ultra-processed foods in the diet was associated with a higher risk of T2D. Various dimensions of food processing might play a role in these associations. These results need to be confirmed in other populations. Public health authorities in several countries recently started to recommend privileging unprocessed/minimally processed foods and limiting ultra-processed food consumption.

INTRODUCTION

Diabetes mellitus is a major public health problem worldwide, affecting 425 million people globally in 2017– an increase of 274 million since 2000, with an estimated projection of 629 million cases by 2045[1]. Death rates are higher in type 2 diabetes (T2D) patients[2], and more than 70% of them die of cardiovascular causes[3]. It is therefore urgent to control the disease by intervening on T2D modifiable risk factors. These include diet, physical activity, and weight. According to the 2018 Global Burden of Diseases, 34.9% of disability adjusted life years (DALYs) of diabetes mellitus are attributable to dietary factors[4], such as high intakes of sugar, red meat and meat products, and low intakes of vegetables, fruits, whole grains, legumes, nuts, and yoghurt[5,6].

Ultra-processed foods (UPF) (i.e. foods undergoing multiple physical, biological, and/or chemical processes, among which mostly of exclusive industrial use, and generally containing various food additives[7]) are widespread worldwide and especially in Western diets[8–13]: these products represent between 25 and 60% of total daily energy intake in European countries, the US, Canada, New Zealand, and Latin American countries, according to surveys assessing intakes, supermarket sales, or household expenses[14–26]. During the last decade, the interest of scientists to explore this topic has increased, since several characteristics of these products, beyond their nutritional quality (i.e. their higher content in saturated fat, sugar, energy, and salt, and lower content in fiber and vitamins on average[14–22,27]), are hypothesized to convey adverse health effects. Indeed, UPF usually go through a series of physical and chemical processes such as extruding, molding, pre-frying, hydrogenation[7], which may lead to the production of new compounds with potential cardiometabolic disruption properties such as acrylamide and acroleine. They also typically contain food substances of no or rare culinary use (e.g. some varieties of refined sugars, hydrogenated oils) and various types of additives (e.g. emulsifiers, sweeteners, thickening agents, colorants)[7], aiming to make the final product highly palatable and visually attractive, with adverse cardiometabolic effects postulated for some of them, such as carrageenan[28], carboxymethyl cellulose[29] and certain sweeteners[30]. Finally, UPF often have longer shelf-lives compared to non-UPF, particularly due to the use of preservatives. Thus, they stay in their packaging for several weeks or months which might contain materials in contact with food, such as bisphenol A, associated with an increased risk of T2D in a recent meta-analysis of observational studies[31].
Recently, we showed in the NutriNet-Santé cohort that UPF consumption (based on the NOVA classification[32]) was associated with increased risks of cancer[33], mortality[34], depressive symptoms[35], inflammatory bowel syndrome[36], and cardiovascular diseases[37]. Other prospective studies in various countries have also observed, using the NOVA classification, associations with mortality risk[38], depression[39], dyslipidaemia in children[40], overweight/obesity[41], and hypertension[42]. In a recent 2-week randomised controlled trial, UPF appeared to influence short-term behavioural and cardiometabolic health parameters such as satiety control and weight gain[43]. However, to our knowledge, no large scale prospective epidemiological study has been published so far regarding UPF consumption and incidence of T2D.

Thus our objective was to explore the associations between the consumption of UPF and the risk of T2D, in a cohort of French adults using detailed dietary intake data.

MATERIAL AND METHODS

Study population

The NutriNet-Santé study is an ongoing web-based cohort launched in 2009 in France aiming to study the associations between nutrition and health[44]. Participants aged 18 years or above with access to the Internet are continuously recruited since May 2009 among the general population using multimedia campaigns. Questionnaires are completed by participants using a dedicated website (etude-nutrinet-sante.fr), via an online platform. The NutriNet-Santé study is conducted according to the Declaration of Helsinki guidelines and was approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm n°0000388FWA00005831) and the "Commission Nationale de l'Informatique et des Libertés" (CNIL n°908450/n°909216). The study is registered at clinicaltrials.gov as NCT03335644. Electronic informed consent is obtained from each participant.

Data collection

At baseline, participants completed a set of five questionnaires related to socio-demographic and lifestyle characteristics[45] (e.g. sex, date of birth, occupation, educational level, smoking status, number of children), anthropometry[46,47] (e.g. height, weight), dietary intakes (see below), physical activity (7-day International Physical Activity Questionnaire [IPAQ])[48], and health status. Participants were also invited to complete a series of three non-consecutive validated web-based 24h-dietary records at baseline and every 6 months (to vary the season of completion), randomly assigned over a 2-week period (two weekdays and one weekend day)[49–51]. Mean dietary intakes from all the 24h-dietary records available during the first two years of each participant's follow-up were averaged and considered as baseline usual dietary intakes in this prospective analysis. The NutriNet-Santé web-based self-administered 24h-dietary records have been tested and validated against an interview by a trained dietitian[49], and against blood and urinary biomarkers[50,51]. Participants used the dedicated web interface to declare all foods and beverages consumed during a 24h-period for each of the three main meals (breakfast, lunch, dinner) and any other eating occasion, with an accurate estimation of portion sizes[52]. Dietary underreporting was identified on the basis of the method proposed by Black, using the basal metabolic rate and Goldberg cut-off, and under-energy reporters (20.0% of the participants of the cohort) were excluded[53]. Mean daily alcohol, micro- and macro-nutrient and energy intake were calculated using the NutriNet-Santé food composition database, which contains more than 3,500 different items (plus the possibility to enter new items in an open field)[54]. In addition, biological and clinical data were collected for 19,772 participants of the cohort, including measures for fasting glycaemia.

Extent and purpose of food processing

All food and beverage items of the NutriNet-Santé composition table were categorized into one of the four food groups in NOVA (unprocessed/minimally processed foods, culinary ingredients, processed foods, ultra-processed foods)[55], a food classification system based on the extent and purpose of industrial food processing[32,56,57]. This study primarily focused on the "ultra-processed foods" NOVA group. Products in this group undergo industrial processes notably include hydrogenation, hydrolysis, extruding, moulding, reshaping, and pre-processing by frying. Flavouring agents, colours, emulsifiers, humectants, non-sugar sweeteners and other cosmetic additives are often added to these products to imitate sensorial properties of unprocessed or minimally processed foods and their culinary preparations. The UPF group is defined by opposition to the other NOVA groups: "unprocessed or minimally processed foods" (fresh, dried, grounded, chilled, frozen, pasteurized or fermented staple foods such as fruits, vegetables, pulses, rice, pasta, eggs, meat, fish or milk), "processed culinary ingredients" (salt, vegetable oils, butter, sugar and other substances extracted from foods and used in kitchens to transform unprocessed or minimally processed foods into culinary preparations) and "processed foods" (canned vegetables with added salt, sugar-coated dry fruits, meat products only preserved by salting, cheeses and freshly made unpackaged breads, and other products manufactured with the addition of salt, sugar or other substances of the "processed culinary ingredients" group). As previously described[55], home-made and artisanal food preparations were identified and decomposed using standardized recipes, and the NOVA classification was applied to their ingredients. Precisions and examples are presented in Appendix 1.

Case ascertainment

Participants were asked to declare major health events though the yearly health questionnaire, through a specific health check-up questionnaire every three months, or at any time through a specific interface on the study website. They were also asked to declare all medications and treatments they use via the check-up and yearly questionnaires. Besides, our research team was the first in France to obtain the authorization by Decree in the Council of State (n°2013-175) to link data from our general population-based cohorts to medico-administrative databases of the National health insurance (SNIIRAM database). Thus, data from the NutriNet-Santé cohort are linked every year to medico-administrative databases of the SNIIRAM, providing detailed information about the reimbursement of medication and medical consultations. T2D cases were ascertained using a multi-source approach, i.e. T2D declaration during follow-up along with declaration of the use of T2D medication (or a reimbursement of T2D medication detected from SNIIRAM), or hyperglycaemia in the biological data along with one T2D medication use.

Statistical analyses

Up to January 9th 2019, 104,707 participants without T2D at baseline and who provided at least 2 valid 24h-dietary records during their first 2 years of follow-up were included. For each subject, the proportion (%) of UPF in the total weight of food/beverages consumed (g/j) was calculated. It was determined by making a

weight ratio rather than an energy ratio in order to take into account UPF that do not provide energy (e.g. artificially sweetened beverages). The associations between the proportion of UPF among specific food groups and T2D risk was also tested, as well as the association between the amount of UPF consumption (in g/day) and T2D risk. For all covariates except physical activity, ≤5% of values were missing and were imputed to the modal value (for categorical variables) or to the median (for continuous variables); for physical activity (13.9% missing), a missing class was included into the models. Multiple imputation for missing data was also tested in sensitivity analyses using the MICE method[58]. Differences in baseline characteristics of participants among sex-specific quartiles of the proportion of UPF in the diet were examined using ANOVA or $\chi 2$ tests wherever appropriate.

Cox proportional hazards models with age as the primary time-scale were used to evaluate the association between the proportion of UPF in the diet (coded as a continuous variable for a 10-point increment or as sex-specific quartiles) and incidence of T2D. The distribution of the ultra-processed variable in the sample is described in Appendix 2. Hazard ratios (HR) and 95% confidence intervals (CI) were computed. Schoenfeld residuals were generated in order to confirm risk proportionality assumptions (Appendix 3-a). The assumption of linearity between UPF consumption and T2D risk was verified using restricted cubic spline (RCS) functions[59] (Appendix 3-b). Participants contributed person-time until the date of T2D diagnosis, the date of last completed questionnaire, the date of death, or January 9th 2019, whichever occurred first.

Models were adjusted for age (time-scale), sex, educational level (<high-school degree, <2 years after high-school degree, ≥2 years after high-school degree), BMI (kg/m², continuous), physical activity (high, moderate, low), smoking status (never, former and current smokers), alcohol intake (g/d, continuous), number of 24h-dietary records (continuous), energy intake without alcohol (kcal/d, continuous), family history of diabetes (yes/no) (Main analysis: Model 1). To test for the potential influence of the nutritional quality of the diet in the relationship between UPF intake and T2D risk, this model was additionally adjusted for saturated fatty acids (SFA), sodium, sugar and fiber intakes (Model 2), and for intakes of several food groups which consumptions are associated with T2D risk with consistent evidence[5]: red and processed meat, sugary drinks, fruits and vegetables, nuts, whole grains and yoghurt (Model 3). In model 4, further adjustments (based on Model 1) for baseline prevalent dyslipidemia and hypertension (yes/no) as well as treatments for these conditions (yes/no) were performed. The associations between the absolute amounts (g/day) of UPF as well as the proportion of unprocessed/minimally processed foods in the diet and T2D risk were also assessed. A series of sensitivity analyses (e.g. further adjustments, stratifications, analyses accounting for reverse causality) was performed in order to assess the robustness of the findings (Appendix 4). All tests were two-sided, and $P<0.05$ was considered statistically significant. SAS® version 9.4 (SAS Institute) was used for the analyses.

RESULTS

A total of 104,707 participants with 21,800 (20.8%) men and 82,907 (79.2%) women were included in the present study. Mean baseline age of participants was 42.7y (SD=14.5) years. Main baseline characteristics of participants according to quartiles of the proportion of UPF in the diet are described in Table 1. Compared to the first quartile, participants among the highest quartile of UPF consumption tended to be younger, current smokers, less highly educated, with a lower physical activity level. Furthermore, they had higher intakes of energy, lipids, carbohydrates and sodium, along with lower alcohol, and dietary fiber intakes.

The mean contribution of UPF to the overall diet (in weight) was 17.3%. Main ultra-processed food groups consumed were sugary products (28%) followed by ultra-processed fruits and vegetables (18%), beverages (16%), starchy foods and breakfast cereals (11%), and processed meat and fish (11%).

During follow-up (582,252 person-years, median follow-up time=6.0y, 25^{th} – 75^{th} percentile=2.8-8.4y), 821 incident cases of T2D occurred. The proportional hazard assumptions of the Cox models were met (p-value for correlation between Schoenfeld residuals and time = 0.6), as well as the linearity assumptions between UPF intake and T2D risk (p-values for non-linear associations = 0.6) (Appendix 3). Absolute incidence rates for T2D in the whole population were 132 per 100,000 person years: age and sex corrected absolute rates were 113, 125, 143 and 166 per 100,000 person years in the first quarter (lowest consumers), second, third and fourth quarter (highest consumers) of the proportion of UPF intake in the diet respectively.

In model 1, UPF intake was associated with an increased risk of T2D ($HR_{\text{for an absolute increment of 10 in the percentage of UPF in the diet}}$ =1.15 (1.06 to 1.25), P=0.0009. Adjusting for sugar, sodium, fiber and saturated fatty acid intakes or for intakes of red and processed meat, sugary drinks, fruits and vegetables, nuts, whole grains and yoghurt did not change the findings (Table 2). The associations also remained significant after further adjustments for metabolic comorbidities (hypertension, dyslipidemia) (Table 2). Although HRs were in the same direction, this association was significant in women only, but statistical power was reduced for men (>79% women in this cohort) (Appendix 4-b).

The absolute amount of UPF consumption in g/d was consistently associated with T2D risk: $HR_{\text{for a 100g/day increase in UPF consumption}}$= 1.05 (1.02 to 1.09), P=0.001 (data not tabulated). In line with these findings, the consumption of unprocessed or minimally processed foods was inversely associated with T2D risk: $HR_{\text{for an absolute increment of 10 in the percentage of unprocessed/minimally processed foods in the diet}}$ =0.91 (0.84 to 0.98), P=0.01 (model 1 covariates).

Results for sensitivity analyses are presented in appendix 4-b. The findings remained robust throughout all sensitivity models.

More specifically, the proportions of UPF in the following food groups were associated with increased T2D risk: beverages, sugary products, fats/sauces, and dairy products (Appendix 4-c).

DISCUSSION

In this large prospective cohort, the consumption of UPF was associated with an increased T2D risk. To our knowledge, while UPF consumption was previously found to be associated with increased risks of cancer[33], cardiovascular diseases[37], all-cause mortality[34,38], depressive symptoms[35,39], and with metabolic disorders - such as obesity[41], hypertension[42], and dyslipidemia[40], no prior prospective epidemiological study had evaluated their association with T2D risk.

Several mechanistic hypotheses can be postulated to explain these findings. UPF usually have a lower nutritional quality[37], as they are on average richer in sodium, energy, fat, sugar and poorer in fiber[14–22,27] and often exhibit a higher glycemic index[60]. Several of these factors are associated with T2D risks with different levels of consensus[5]. Many food groups, that are mostly ultra-processed (such as processed meat, and sweetened beverages) are recognized T2D risk factors[5]. Sweetened beverages might also delay or slow down the internal satiety signal, leading to excessive caloric ingestion[61]. Consistently, in a recent randomized trial[43], Hall *et al*. included subjects admitted to the NIH clinical center, and allocated them either to an ultra-processed or unprocessed diet for 2 weeks immediately followed by the alternate diet for 2 weeks. They showed that the ultra-processed diet led to an increased energy intake (+508±106 kcal/d during the ultra-processed diet), which was highly correlated with weight gain (0.8±0.3 kg (p=0.01)), versus a weight loss of 1.1±0.3 kg during the unprocessed diet. Of note, energy balance and overweight are both associated with T2D risk[5]. This could not have entirely explained the associations observed, as our models were adjusted for BMI. Moreover, high consumers of UPF in our population had lower consumptions of whole grains, fruits and vegetables, which are recommended in the prevention of T2D, consistent with our finding of lower T2D risk in higher consumer of minimally/unprocessed foods. However, the association between UPF consumption and the risk of T2D remained significant in our models after further adjustment for a wide range of dietary factors including intakes of energy, salt, sugar, saturated fats and dietary fiber as well as for the consumption of red and processed meat, sugary drinks, fruits and vegetables, nuts, whole grains, and yoghurt, as well as a posteriori-extracted “Western” and “Healthy” dietary patterns did not substantially modified our findings. Thus, these factors do not fully explain the observed associations. Furthermore, the ultra-processed indicator we used was developed in order to be as much as possible de-correlated from nutritional quality, using weight and not energy.

Beyond nutritional values, UPF are often characterized by the presence of several food additives. Even though maximum authorized levels, based on current scientific evidence, normally protect consumers against adverse effects of each individual substance in a given food product[62], long-term health impact of the cumulative intake across all ingested foods in humans and potential cocktail/interaction effects remain largely unknown. For instance, carrageenan, a thickening and stabilizing agent, used in several dairy desserts, might contribute in the development of diabetes, by impairing glucose tolerance, increasing insulin resistance and inhibiting insulin signaling in vivo in mouse liver and human HepG2 cells[28,63]. Two

emulsifying agents, carboxymethyl cellulose and polysorbate-80, used in the recipes of various UPF may reduce gut microbial diversity, stimulating intestinal inflammation, obesity, and diabetes by inducing low-grade inflammation in mice[29]. Several food additives commonly used in food processing have Phosphorus as their main component, adding to the contribution of phosphoric acid in sodas. In the EPIC-France cohort (E3N), high phosphorus intakes were associated with increased T2D risk[64]. Moreover, a meta-analysis of randomized controlled trials and prospective cohort studies observed that non-nutritive sweeteners consumption (acesulfam-K, aspartame, sucralose) was associated with a higher incidence of T2D[30], consistently with a meta-analysis of prospective studies showing an association between the consumption of artificially sweetened beverages and T2D risk (even though publication bias could not be ruled out)[65].

UPF, often packaged in plastic materials, might be contaminated by the migration of contact materials, among which Bisphenol-A (BPA), "a substance of very high concern" as stated by the European Chemicals Agency (ECHA)[66]. The exposure to BPA, an endocrine disruptor, as well as high BPA serum concentrations have been associated with increased T2D risk in recent meta-analyses[31,67]. Of note, BPA was forbidden for use in food packaging in 2015 in France, after the dietary data collection in this study.

Last, UPF that went through processes such as high-temperature heating might contain neo-formed compounds: among these contaminants, acrylamide[68] and acrolein[69] metabolites were associated with insulin resistance, and urinary biomarkers of polycyclic aromatic hydrocarbons were positively associated with diabetes in the NHANES study[70].

This study has some limitations. Even though we used a multi-source approach to ascertain T2D cases, exhaustiveness of diabetes case ascertainment could not be guaranteed. Second, causation could not be established from this single observational study and residual confounding cannot be entirely ruled out. However, several mechanistic hypotheses support the biological plausibility of these findings, and the results remained unchanged after a series of sensitivity analyses adjusting for many lifestyle and dietary confounders. These findings are in line with previous observational studies showing associations between UPF and cardiometabolic outcomes[34,37,38,40–42]. Only one short-term randomized controlled trial published so far showed a strong effect of an ultra-processed diet on weight gain and energy intake[43]. This kind of trials would not be ethically or logistically feasible to investigate longer term associations with hard adverse health endpoints such as cancer, cardiovascular diseases, T2D, or mortality, but provides useful insights into potential mechanisms underlying associations observed in long-term epidemiological cohorts. Third, misclassification bias in the NOVA classification cannot be ruled out; however, this would have led to a non-differential measurement error, occurring both in cases and non-cases, and potentially biasing towards the null hypothesis. Fourth, the ultra-processed category is broad and covers diverse products; this approach was not designed to focus on a specific category of foods or to isolate a particular process or additive. However, it allowed us to explore overall exposure to UPF and to observe associations with T2D resulting from cumulative intakes and potential cocktails effects of their ingredients. Fifth, as compared to the general French population, participants to this study were younger, more often women, with higher educational

levels[71] and healthier dietary habits[72]. This might have underestimated the associations due to a narrower range of UPF intake. Furthermore, T2D incidence was lower (186 cases per 100,000 person-years in our sample after standardization *vs* 289 per 100,000 in the French population[73]), thereby limiting statistical power, especially for some stratified analyses (e.g. in men). However, this is the first large-scale prospective study to explore the associations between UPF and T2D risk, using a multi-source case ascertainment strategy along with a detailed dietary intake assessment using repeated 24h-dietary records with more than 3500 food items.

CONCLUSIONS

These results suggest an association between UPF consumption and T2D risk. They need to be confirmed in large scale prospective cohorts in other settings, and underlying mechanisms need to be explored in ad-hoc designed epidemiological and experimental studies. Beyond nutritional factors, non-nutritional dimensions of the diet might be driving these associations, such as some additives and contact materials. In particular, the exploration of the relationships between exposure to cocktails of food additive and chronic disease risk in the NutriNet-Santé cohort represents a key perspective of this work[74]. Even if a causal link between UPF and chronic diseases cannot be established, the accumulation of consistent data leads public health authorities in several countries such as France[75] or Brazil[76] to officially recommend privileging the consumption of unprocessed/minimally processed foods, and limiting the consumption of UPF in the name of the precautionary principle.

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Contributorship statement and guarantor

The authors' contributions were as follows – BS, CJ, EKG, BA and MT: designed the research; SH, PG, MT: conducted the research; BS: performed statistical analysis; BS: drafted the manuscript; MT: supervised the writing; BS, LF, EKG, BA, CD, NDP, EC, MD, SH, PG, CAM, CJ, and MT: contributed to the data interpretation and revised each draft for important intellectual content. All authors read and approved the final manuscript. MT had primary responsibility for the final content, she is the guarantor. The corresponding author (BS) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

No additional data available.

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TABLE 1 Baseline characteristics of the study population according to sex-specific quartiles of ultra-processed food (UPF) consumption (n=104,707), NutriNet-Santé cohort, France, 2009-2019 [a]

	All participants	Quartile 1 (n=26,176)	Quartile 2 (n=26,177)	Quartile 3 (n=26,177)	Quartile 4 (n=26,177)	P-value[c]
Age, years	42.7 (14.5)	47.5 (13.7)	44.8 (14.2)	41.9 (14.4)	36.4 (13.5)	<0.0001
Sex, n (%)						
Women	82,907 (79.2)	20,726 (79.2)	20,727 (79.2)	20,727 (79.2)	20,727 (79.2)	
Men	21,800 (20.8)	5,450 (20.8)	5,450 (20.8)	5,450 (20.8)	5,450 (20.8)	
Body mass index, kg/m²	23.6 (4.3)	23.5 (4.1)	23.6 (4.2)	23.6 (4.3)	23.7 (4.7)	0.0007
Educational level, n (%)						
< High school degree	17,952 (17.1)	4,732 (18.1)	4,516 (17.2)	4,353 (16.6)	4,351 (16.6)	
< 2 years after high school	17,882 (17.1)	3,859 (14.7)	3,946 (15.1)	4,480 (17.1)	5,597 (21.4)	
≥ 2 years after high school	68,873 (65.8)	17,585 (67.2)	17,715 (67.7)	17,344 (66.3)	1,6629 (62.0)	< 0.0001
Smoking status, n (%)						
Current	17,892 (17.1)	4,025 (15.4)	4,043 (15.4)	4,310 (16.5)	5,514 (21.1)	
Former	34,217 (32.7)	9,906 (37.8)	9,065 (34.6)	8,272 (31.6)	6,974 (26.6)	
Never	52,598 (50.2)	12,245 (46.8)	13,069 (49.9)	13,595 (51.9)	13,689 (52.3)	< 0.0001
IPAQ Physical activity level, n (%)[d]						
High	29,382 (28.1)	8,745 (33.4)	7,530 (28.8)	7,096 (27.1)	6011 (23.0)	
Moderate	38,788 (37.0)	9,613 (36.7)	10,059 (38.4)	9,782 (37.4)	9,334 (35.7)	
Low	21,976 (21.0)	4,398 (16.8)	5,204 (19.9)	5,769 (22.0)	6605 (25.2)	< 0.0001
Energy intake without alcohol, kcal/d	1,847.1 (450.9)	1,773.6 (427.9)	1,846.5 (428.8)	1,879.2 (450.4)	1,889.2 (484.8)	< 0.0001
Alcohol intake, g/d	7.8 (11.8)	9.0 (13.0)	8.5 (11.9)	7.5 (11.0)	5.9 (10.7)	< 0.0001
UPF (%)	17.3 (9.8)	7.4 (2.3)	12.9 (1.3)	18.2 (1.8)	30.5 (9.1)	
UPF, g/d	415.5 (227.5)	208.8 (82.3)	339.8 (88.9)	447.7 (117.5)	665.7 (257.8)	
Sodium intake, mg/d	2,711.3 (879.9)	2,593.0 (860.1)	2,743.6 (858.5)	2,780.1 (876.3)	2,728.4 (912.3)	< 0.0001
Saturated Fatty Acids, g/d	33.2 (12.1)	30.4 (11.4)	33.1 (11.5)	34.4 (12.1)	34.9 (12.9)	< 0.0001
Fiber, g/d	19.5 (7.2)	21.0 (7.7)	20.1 (6.9)	19.3 (6.8)	17.4 (6.9)	< 0.0001
Sugar, g/d	92.9 (33.1)	86.8 (32.4)	91.6 (30.2)	94.6 (31.7)	98.8 (36.6)	< 0.0001
Whole grains, g/d	34.4 (46.1)	42.6 (52.2)	36.6 (45.8)	32.6 (43.6)	25.7 (40.1)	< 0.0001
Yoghurt, g/d	58.3 (68.9)	66.4 (74.0)	60.5 (66.4)	56.8 (66.2)	49.3 (67.5)	< 0.0001
Sugary drinks, g/d	47.3 (105.0)	12.0 (35.9)	23.3 (46.7)	39.6 (65.3)	114.3 (173.2)	< 0.0001
Red and processed meat, g/d	73.0 (51.0)	67.0 (48.6)	72.2 (48.1)	74.8 (50.0)	78.1 (56.1)	< 0.0001
Nuts, g/d	4.8 (10.8)	6.1 (13.2)	5.1 (10.7)	4.5 (9.6)	3.4 (8.9)	< 0.0001
Fruits and vegetables, g/d	408.2 (221.6)	506.7 (248.5)	435.8 (202.2)	387.3 (192.6)	302.8 (186.6)	< 0.0001

[a] Values are means (SDs) or n (%). For all covariates except physical activity, a very low proportion of values were missing (0-5%), the latter were replaced by the modal value among the population study: '≥2y of higher education' for educational level and 22.8 kg/m² for BMI.
[b] Quartiles of the proportion of UPF intake in the total quantity of food consumed. Cut-offs for quartiles were 0.108, 0.156 and 0.219 for men and 0.106, 0.153 and 0.215 for women.
[c] P-value for the comparison across quartiles of UPF consumption, by Anova or χ^2 test where appropriate.
[d] Available for 90,146 subjects. Subjects were categorized into the "high", "moderate" and "low" categories according to IPAQ guidelines[48].

TABLE 2 Associations between ultra-processed food (UPF) intake and type 2-diabetes from multivariable Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2019 (n=104,707)[a]

	Proportion of UPF intake in the diet (%)						
	Sex-specific quartiles[b]					Continuous[c]	
	Q1	Q2	Q3	Q4			
	HR	HR (95% CI)	HR (95% CI)	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-value
Type 2-Diabetes							
N for cases/non-cases	226/25950	225/25952	211/25966	159/26018		821/103886	
Model 1	1	1.02 (0.85 to 1.23)	1.10 (0.91 to 1.33)	1.30 (1.06 to 1.61)	0.01	1.15 (1.06 to 1.25)	0.0009
Model 2	1	1.04 (0.87 to 1.26)	1.14 (0.94 to 1.38)	1.42 (1.15 to 1.76)	0.02	1.20 (1.10 to 1.30)	<0.0001
Model 3	1	1.00 (0.83 to 1.21)	1.09 (0.89 to 1.32)	1.26 (1.01 to 1.57)	0.04	1.15 (1.04 to 1.26)	0.004
Model 4	1	1.03 (0.85 to 1.24)	1.11 (0.92 to 1.34)	1.24 (1.00 to 1.53)	0.04	1.13 (1.04 to 1.22)	0.005

CI: confidence interval, HR: Hazard ratio
Median follow-up times 6.0y, 582,252 person-years
[a] Model 1 was a multivariable Cox proportional hazard model adjusted for age (timescale), sex, educational level, BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, and family history of T2D.
Model 2 = Model 1 + saturated fatty acid intake, sodium intake, sugar intake, dietary fiber intake
Model 3 = Model 1 + intakes of red and processed meat, sugary drinks, fruits and vegetables, whole grains, nuts and yoghurt.
Model 4 = Model 1 + baseline prevalent dyslipidaemia and hypertension (yes/no), and treatments for these conditions (yes/no).
[b] Cut-offs for quartiles were 0.108, 0.156 and 0.219 for men and 0.106, 0.153 and 0.215 for women.
[c] HR for an absolute increment of 10 in the percentage of UPF in the diet

Appendix 1: 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 [1–3]. 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 typical ultra-processed food according to the NOVA classification:

Poultry and fish nuggets and sticks and other reconstituted meat products transformed with addition of preservatives other than salt (e.g nitrites); instant noodles and dehydrated soups; carbonated drinks; sweet or savoury packaged snacks; chocolate, candies (confectionery); margarines and spreads; industrial pastries and instant desserts; breakfast 'cereals', 'energy' bars; 'energy' drinks; flavoured milk drinks; sweet desserts made from fruit with added sugars, artificial flavours and texturizing agents; cooked seasoned vegetables with ready-made sauces; vegetable patties (meat substitutes) containing food additives; 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.

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".

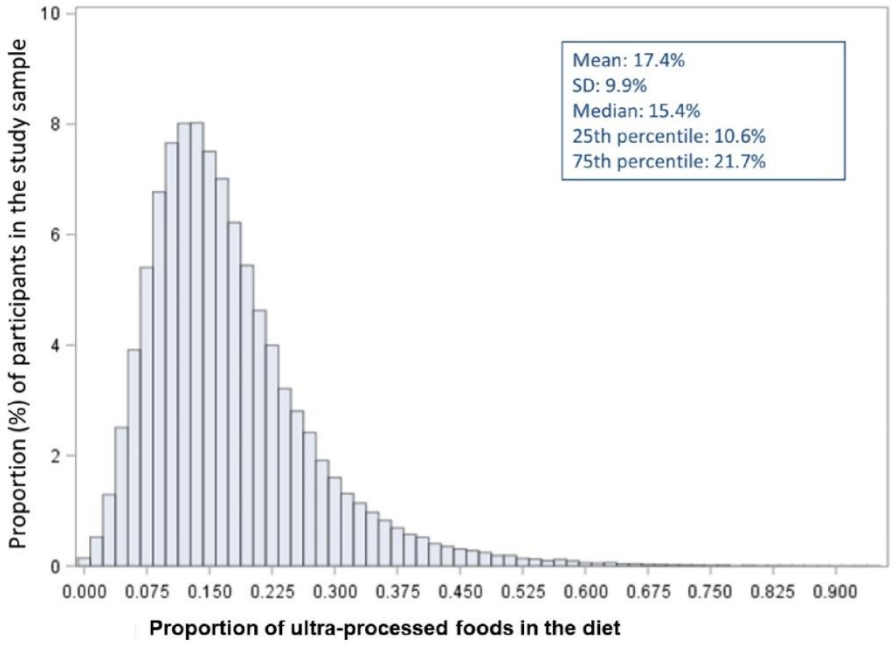
Similarly, canned salted vegetables are considered as "processed foods" whereas industrial cooked or fried seasoned vegetables, marinated in industrial sauces with added flavourings are considered as "ultra-processed foods".

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".

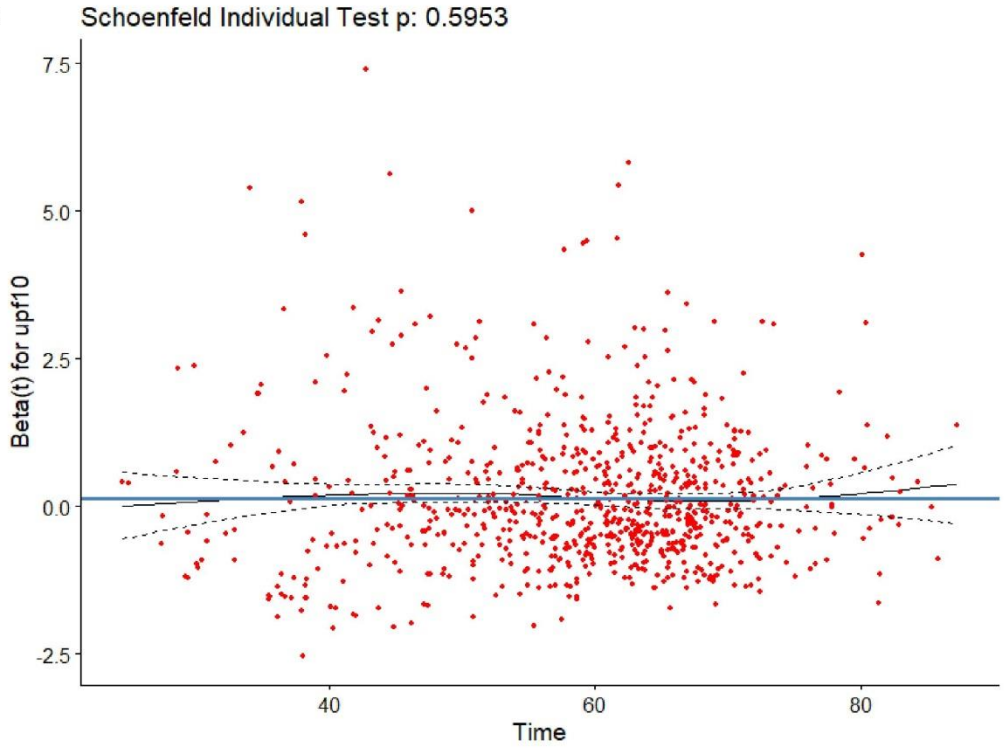
Example of list of ingredients for an industrial Chicken and Leek flavour soup considered as "ultra-processed" according to the NOVA classification: *"Dried Glucose Syrup, Potato Starch, Flavourings, Salt, Leek Powder (3.6%), Dried Leek (3.5%), Onion Powder, Dried Carrot, Palm Oil, Dried Chicken (0.7%),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

1

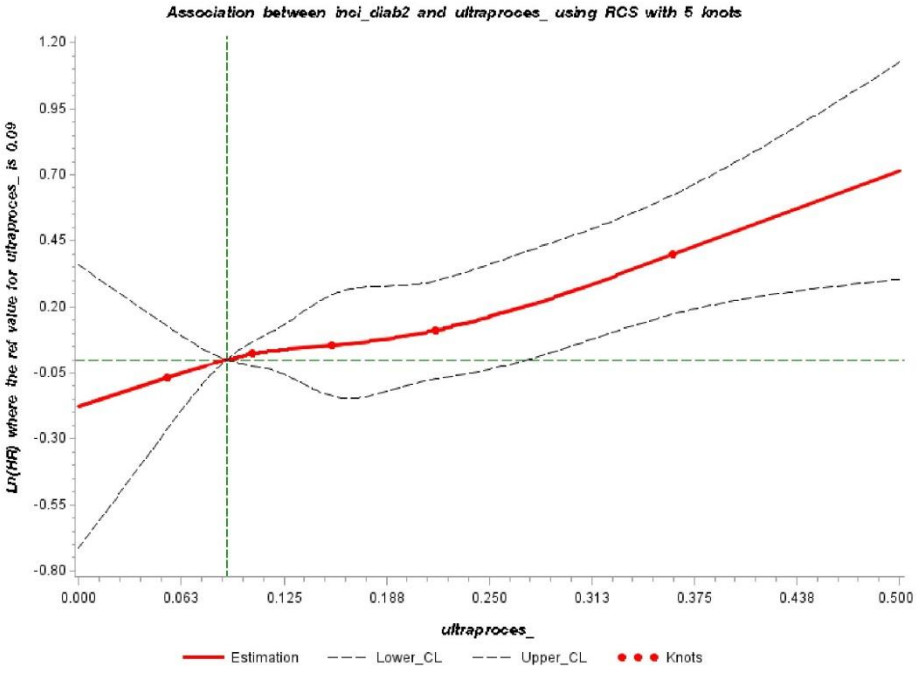
Appendix 2: Distribution of the main exposure (proportion of ultra-processed food in the diet) in the study sample (N=104,707), NutriNet-Santé, France



Appendix 3-a: Cox model proportional risk assumption testing (Schoenfeld residuals)



Appendix 3-b: Spline plot for the linearity assumption of the association between the proportion of ultra-processed food in the diet and the risk of Type-2 Diabetes using Restricted cubic spline (RCS) SAS Macro® developed by Desquilbet and Mariotti[4]



p-value for non-linearity = 0.77

Appendix 4: Sensitivity analyses

Methods

Sensitivity analyses were performed based on Model 1 by excluding T2D cases having occurred during the first two years of each participant's follow-up to avoid reverse causality bias, unadjusting for BMI, and testing further adjustments for "Healthy" and "Western" dietary patterns obtained by Principal Component Analysis (details in Appendix 4-a) (continuous), number of smoked cigarettes in pack-years (continuous), and the season of inclusion in the cohort (spring/ summer/ autumn/ winter). Models were also tested after restriction of the population study to the participants with ≥6 24h-dietary records during the first two years of follow-up, and after the exclusion of prevalent cases of hypertension and dyslipidemia. In the main analyses, for all covariates except physical activity, ≤5% of values were missing and were imputed to the modal value (for categorical variables) or to the median (for continuous variables). For physical activity, to avoid massive imputation for a non-negligible number of subjects or exclusion of subjects with missing data and risk of selection bias, we included a missing class into the models for this variable. However, multiple imputation for missing data was also tested using the MICE method[5] by fully conditional specification (FCS, 20 imputed datasets) for the outcome[6] and for the following covariates: level of education (5.0% missing data), physical activity level (13.9% missing data) and BMI (0.6% missing data). Results were combined across imputations based on Rubin's combination rules[7,8] using the SAS PROC MIANALYZE procedure[9]. A supplementary analysis was also performed by using the Fine and Gray model[10] to account for competing risks due to death during follow-up. The association between ultra-processed food and overall T2D risk was also investigated separately in different strata of the population: men/women, adults aged <45y / ≥45y, participants with higher sugar intakes (>median)/those with a lower one. All these sensitivity analyses are presented in Appendix 4.b. Finally, we have tested the associations between the proportion of ultra-processed foods in each specific food group and T2D risk (Appendix 4.c).

	Factor loadings	
	Healthy Pattern	Western Pattern
Alcoholic drinks	-.09	**0.28**
Breakfast cereals	0.07	-.18
Cakes and biscuits	-.19	0.00
Dairy products	0.06	-.01
Eggs	0.07	0.04
Fats and sauces	0.01	**0.54**
Fish and seafood	0.20	0.10
Fruit	**0.35**	0.05
Meat	-.18	**0.31**
Pasta and rice	-.21	**0.34**
Potatoes and tubers	-.02	**0.40**
Poultry	-.03	0.06
Processed meat	-.22	0.20
Pulses	0.19	0.02
Soups and broths	**0.26**	0.22
Sugar andconfectionery	-.08	0.12
Sweetened soft drinks	**-.28**	-.00
Unsweetened soft drinks	**0.25**	0.15
Vegetables	**0.47**	0.23
Whole grains	**0.38**	-.04

66

Appendix 4-b: Associations between ultra-processed food intake and Type 2-diabetes risk from multivariable Cox proportional hazard models, after sensitivity analyses, NutriNet-Santé cohort, France, 2009 – 2019 (n=104,707)

	Cases/non-cases	HR* (95% CI)	P-value
Model 1[a] excluding T2D of the first two years of follow-up	544/103886	1.16 (1.05 to 1.28)	0.004
Model 1 unadjusted for BMI	821/103886	1.20 (1.11 to 1.31)	<.0001
Model 1 + Healthy and Western dietary patterns[b]	821/103886	1.13 (1.04 to 1.24)	0.004
Model 1 + number of pack-years	821/103886	1.15 (1.06 to 1.25)	0.0009
Model 1 + season of inclusion in the cohort	821/103886	1.15 (1.06 to 1.25)	0.0007
Model 1 with multiple imputation[c]	821/103886[¥]	1.18 (1.09 to 1.28)	<.0001
Model 1 excluding participants with less than 6 dietary records	589/51342	1.16 (1.05 to 1.29)	0.004
Model 1 excluding prevalent cases of hypertension and dyslipidemia	428/90555	1.16 (1.04 to 1.29)	0.008
Model 1 using Fine and Gray model accounting for competing risks of death**	821 *(340 competing deaths)*	1.15 (1.05 to 1.25)	0.001
Model 1 among men	302/21498	1.03 (0.88 to 1.20)	0.7
Model 1 among women	519/82388	1.13 (1.08 to 1.34)	0.0004
Model 1 among younger participants (<45 years old)	144/59103	1.19 (1.03 to 1.37)	0.02
Model 1 among older participants (≥45 years old)	677/44783	1.13 (1.02 to 1.24)	0.02
Model 1 among participants with lower sugar intakes (≤89.61 g/d)	509/51838	1.13 (1.02 to 1.27)	0.02
Model 1 among participants with higher sugar intakes (>89.61 g/d)	312/52048	1.22 (1.08 to 1.38)	0.001

CI: confidence interval, HR: Hazard ratio for an absolute increment of 10 in the percentage of ultra-processed foods in the diet (except for Fine and Gray Model for which subdistribution Hazard Ratios sHR are computed[10])

[a] Model 1 is adjusted for age (timescale), sex (except when stratified for sex), educational level, BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, and family history of T2D.

[b] Obtained by a Principal Component Analysis (Appendix 3)

[c] Multiple imputation for missing data using the MICE method[5] by fully conditional specification (FCS, 20 imputed datasets) for the outcome[6] ([¥]62 to 97 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[7,8] using the SAS PROC MIANALYZE procedure[9].

Appendix 4-c: Associations between the proportion of ultra-processed food in each individual food group and Type 2-diabetes risk from multivariable Cox proportional hazard models, NutriNet-Santé cohort, France, 2009 – 2019 (n=104,707)

	Cases/Non-cases	HR* (95% CI)	p-value
Ultra-processed beverages	821/103886	1.16 (1.10 to 1.22)	<.0001
Ultra-processed dairy products	821/103886	1.05 (1.01 to 1.08)	0.005
Ultra-processed fats and sauces	821/103886	1.06 (1.03 to 1.10)	<.0001
Ultra-processed fruits and vegetables	821/103886	0.98 (0.94 to 1.02)	0.4
Ultra-processed meat, fish and eggs	821/103886	1.03 (0.98 to 1.08)	0.2
Ultra-processed starchy foods and cereals	821/103886	1.04 (0.99 to 1.09)	0.1
Ultra-processed sugary products	821/103886	1.04 (1.01 to 1.07)	0.02
Ultra-processed salty snacks	821/103886	0.99 (0.96 to 1.01)	0.2

CI: confidence interval, HR: Hazard ratio
*HR for an absolute increment of 10 in the percentage of the food group consumed in its ultra-processed form
Models are adjusted for age (timescale), sex, educational level, BMI, physical activity, smoking status, alcohol intake, number of 24h-dietary records, energy intake, family history of T2D, sugar intake, and the consumption amount of the specific food group (in g/d)

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102

Appendix D - Unprocessed food and mortality risk (JAMA Int Med 2019)

Letters

COMMENT & RESPONSE

In Reply We thank McCarthy and May for their letter regarding our Original Investigation.[1] Consistent with the US dietary guidelines,[2] the French[3] nutritional recommendations also promote the consumption of unprocessed and minimally processed foods. As McCarthy and May point out in their response, on average, the nutritional quality of ultraprocessed food is lower than that of minimally or unprocessed food: the food often contains more salt, added sugar, and saturated fatty acids, and fewer dietary fibers and vitamins.

In France, and more recently in Belgium and Spain, a 5-colored front-of-pack nutritional labeling system, Nutri-Score, has been officially adopted by health authorities to inform consumers of the overall nutritional quality of food products.[4] In the NutriNet-Santé food composition database, ultraprocessed foods represent more than 85% of the products in the E category of the Nutri-Score (the category of lowest nutritional quality) vs less than 24% in the A category (the category of highest nutritional quality). We have previously published that in contrast with ultraprocessed foods, which are associated with an increased risk of overall cancer and breast cancer in the NutriNet-Santé cohort, the consumption of minimally or unprocessed foods was associated with a decreased overall cancer risk (for a 10-point increment in the proportion of unprocessed foods in the diet: hazard ratio [HR], 0.91 [95% CI, 0.87-0.95]).[5] As suggested by McCarthy and May, we have now tested the same association for mortality risk, as we did for ultraprocessed foods.[1] As expected, the findings suggested a protective association for minimally processed foods (age-adjusted and sex-adjusted HR, 0.91 [95% CI, 0.84-0.99]; $P = .03$).

In a recent randomized trial,[6] Hall and colleagues included subjects admitted to the National Institutes of Health Clinical Center and allocated them either to an ultraprocessed or unprocessed diet for 2 weeks, immediately followed by the alternate diet for 2 weeks. Results showed that the ultraprocessed diet led to an increased energy intake (508 ± 106 kcal/d during the ultraprocessed diet), which was highly correlated with weight gain (0.8 ± 0.3 kg; $P = .01$) vs a weight loss of 1.1 ± 0.3 kg during the unprocessed diet, which might increase the risk of metabolic morbidity. Thus, public health nutritional recommendations should indeed combine both the promotion of minimally processed products and the limitation of ultraprocessed foods, as stated in the recently updated edition of the French recommendations.[3]

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Conflict of Interest Disclosures: None reported.

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ABSTRACT - Food processing and risk of non-communicable diseases

During the past decades, diets in many countries have shifted towards an important increase in the degree of food processing and formulation. Several characteristics of ultra-processed foods have led the scientific community to wonder about their potential impact on long-term human health. Ultra-processed foods have in average, a lower nutritional quality than unprocessed or minimally processed foods (higher content of saturated fat, added sugar and salt, along with a lower fiber and vitamin density). They often contain food additives, neoformed compounds created during processes, and are often packaged in materials in contact with food from which contaminants may migrate to the food matrix. We investigated within the prospective French cohort NutriNet-Santé, the associations between the consumption of ultra-processed food and risks of cancer, cardiovascular disease, type 2-diabetes, overweight, obesity, and weight trajectories. More than 100,000 adult participants were included. Dietary intakes were collected using repeated 24 hour dietary records, designed to register participants' usual consumption of more than 3,500 food items. These foods were categorized using the NOVA classification according to their degree of processing. Participants were followed, and the occurrence of chronic diseases was ascertained using a multi-source strategy including a linkage to medico-administrative databases.

The analyses highlighted robust significant associations between the consumption of ultra-processed foods, and increased risks of overall and breast cancers, cardiovascular, cerebrovascular, and coronary heart diseases, type 2-diabetes, overweight, obesity and weight gain. These analyses accounted for a large number of lifestyle, socio-demographic, anthropometric, medical, behavioral, and nutritional factors. The associations remained significant throughout all the sensitivity and stratified analyses. Beyond nutritional aspects, various factors in processing and reformulation might play a role in these associations, and further studies are needed to better understand their relative contributions and to establish a causal link. Meanwhile, public health authorities in several countries have recently started to promote unprocessed or minimally processed foods and to recommend limiting the consumption of ultra-processed foods.

Keywords: processing degree, food processing, ultra-processed foods, prospective studies, chronic diseases, cancer, cardiovascular diseases, diabetes, weight gain, obesity, overweight, nutritional epidemiology, NutriNet-Santé cohort

RESUME - Transformation des aliments et risque de pathologies chroniques

Au cours des dernières décennies, les régimes alimentaires de nombreux pays ont connu une augmentation importante du degré de transformation et de formulation des produits. Plusieurs caractéristiques des aliments ultra-transformés ont incité les chercheurs à investiguer l'impact potentiel de leur consommation sur la santé. Les aliments ultra-transformés ont en moyenne une moins bonne qualité nutritionnelle, comparée à celle des aliments non transformés, se caractérisant souvent par une teneur plus élevée en graisses saturées, en sucres ajoutés et en sel, ainsi que par une teneur plus faible en fibres et vitamines. Ces aliments contiennent souvent des additifs alimentaires, des composés néoformés, et sont en général conditionnés dans des matériaux d'emballage contenant des substances susceptibles de migrer vers la matrice alimentaire. Nous avons investigué, au sein de la cohorte française NutriNet-Santé, les associations entre la consommation d'aliments ultra-transformés et les risques de cancer, de maladies cardiovasculaires, de diabète de type 2, de surpoids, d'obésité et de trajectoires pondérales. Plus de 100 000 adultes ont été inclus. Les apports alimentaires et nutritionnels ont été collectés à l'aide d'enregistrements alimentaires de 24h répétés, conçus pour enregistrer la consommation habituelle des participants de plus de 3 500 produits alimentaires. Ces aliments ont été classés selon la classification NOVA en fonction de leur degré de transformation. La survenue de maladies chroniques et de variation pondérale pendant le suivi a été observée grâce à une stratégie multi-source incluant un couplage avec les bases de données médico-administratives.
Ces travaux ont mis en évidence des associations significatives et robustes entre la consommation d'aliments ultra-transformés et l'augmentation des risques de cancer au global, cancer du sein, de maladies cardiovasculaires, cérébrovasculaires et coronariennes, de diabète de type 2, de surpoids, d'obésité et de prise de poids. Ces analyses ont pris en compte un grand nombre de facteurs sociodémographiques, anthropométriques, de mode de vie, médicaux, comportementaux et nutritionnels. Les associations significatives ont persisté après de multiples analyses de stratification et de sensibilité. Au-delà de la qualité nutritionnelle, divers aspects de la transformation et de la reformulation pourraient jouer un rôle dans ces associations, et des études complémentaires sont nécessaires pour mieux comprendre les contributions de ces aspects, les mécanismes sous-jacents, et établir un lien de causalité. Les autorités de santé publique dans plusieurs pays recommandent depuis récemment de privilégier les aliments peu ou pas transformés, et de limiter la consommation des aliments ultra-transformés.

Mots clés: Degré de transformation des aliments, process alimentaires, aliments ultra-transformés, études prospectives, maladies chroniques, cancer, maladies cardiovasculaires, diabète, prise de poids, obésité, surpoids, épidémiologie nutritionnelle, cohorte NutriNet-Santé.

Discipline: Epidémiologie-Santé Publique

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