Consumption of ultra-processed foods associated with weight gain and obesity in adults: a multi-national cohort study

Reynalda Cordova, MSc[1,2]; Nathalie Kliemann, PhD[1]; Inge Huybrechts, PhD[1]; Fernanda Rauber, PhD[3,4]; Eszter P. Vamos, PhD[5]; Renata Bertazzi Levy, PhD[3,4]; Karl-Heinz Wagner, PhD[2]; Vivian Viallon, PhD[1]; Corinne Casagrande, Ms[1]; Geneviève Nicolas, MSc[1]; Christina C. Dahm, PhD[6;]; Jie Zhang, MPH[6]; Jytte Halkjær, PhD[7]; Anne Tjønneland, PhD[7,8]; Marie-Christine Boutron-Ruault, MD[9,10]; Francesca Romana Mancini, PhD[9,10]; Nasser Laouali, PhD[9,10]; Verena Katzke, PhD[11]; Bernard Srour, PhD[11]; Franziska Jannasch, PhD[12,13,14]; Matthias B. Schulze, PhD[12,15]; Giovanna Masala, MD[16]; Sara Grioni, BSc[17]; Salvatore Panico, MD[18]; Yvonne T. van der Schouw, PhD[19]; Jeroen W.G. Derksen, PhD[19]; Charlotta Rylander, PhD[20]; Guri Skeie, PhD[20]; Paula Jakszyn, PhD[21,22]; Miguel Rodriguez-Barranco, PhD[23,24,25];José María Huerta, PhD[26,27]; Aurelio Barricarte, PhD[25,28,29]; Lousie Brunkwall, MSc[30]; Stina Ramne, MSc[30]; Stina Bodén, MSc[31]; Aurora Perez-Cornago, PhD[32]; Alicia K. Heath, PhD[5]; Paolo Vineis, PhD[5]; Elisabete Weiderpass, PhD[1,]; Carlos Augusto Monteiro, PhD[3,4]; Marc J. Gunter, PhD[1]; Christopher Millett, PhD[5]; Heinz Freisling, PhD[1]

[1] Section of Nutrition and Metabolism, International Agency for Research on Cancer (IARC-WHO), Lyon, France

[2] Department of Nutritional Sciences, University of Vienna, Vienna, Austria

[3] Center for Epidemiological Research in Nutrition and Health, University of São Paulo, São Paulo, Brazil

[4] Department of Nutrition, School of Public Health, University of São Paulo, São Paulo, Brazil

[5] Public Health Policy Evaluation Unit, School of Public Health, Imperial College London, UK

[6] Department of Public Health, Aarhus University, Denmark

[7] Danish Cancer Society Research Center, Copenhagen

[8] Department of Public Health, University of Copenhagen, Copenhagen

[9] French National Institute of Health and Medical Research (INSERM), Centre for Research in Epidemiology and Population Health (CESP), UVSQ, Université Paris-Saclay, Université Paris-Sud, France

[10] Institut Gustave Roussy, F-94805 Villejuif, France

[11] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

[12] Department of Molecular Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke, Nuthetal, Germany

[13] German Center for Diabetes Research (DZD), München-Neuherberg, Germany

[14] NutriAct - Competence Cluster Nutrition Research Berlin-Potsdam, Nuthetal, Germany

[15] Institute of Nutritional Science, University of Potsdam, Nuthetal, Germany

[16] Molecular and Lifestyle Epidemiology Branch, Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for cancer research, prevention and clinical network ISPRO, Florence, Italy

[17] Epidemiology and Prevention Unit Fondazione IRCCS Istituto Nazionale dei Tumori di Milano

Via Venezian, 120133 Milano-Italy

[18] Dipartimento di Medicina Clinica E Chirurgia Federico II University, Naples, Italy

[19] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

[20] Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

[21] Unit of Nutrition and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology, Barcelona, Spain

[22] Blanquerna School of Health Sciences, Ramon Llull University, Barcelona, Spain

[23] Escuela Andaluza de Salud Pública (EASP), Granada, Spain

[24] Instituto de Investigación Biosanitaria ibs.GRANADA, Granada, Spain

[25] Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

[26] Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

[27] CIBER Epidemiología y Salud Pública (CIBERESP), Murcia, Spain

[28] Navarra Public Health Institute, Pamplona, Spain.

[29] Navarra Institute for Health Research (IdiSNA) Pamplona, Spain

[30] Department of Clinical Sciences, Lund University, Malmö, Sweden

[31] Department of Radiation Sciences, Oncology, Umeå University, Umeå, Sweden

[32] Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK

Address for correspondence and reprints

Dr. Heinz Freisling

International Agency for Research on Cancer (IARC-WHO), Lyon, France

150 Course Albert Thomas, 69372 Lyon Cedex 08, France

Phone : +33 47 273 84 85

Email : freislingh@iarc.fr

Competing Interests

The authors declare no competing financial interests

Abstract

Background: There is a worldwide shift towards increased consumption of ultra-processed foods (UPF) with concurrent rising prevalence of obesity. We examined the relationship between the consumption of UPF and weight gain and risk of obesity.

Methods: This prospective cohort included 348 748 men and women aged 25-70 years. Participants were recruited between 1992 and 2000 from 9 European countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Two body weight measures were available, at baseline and after a median follow-up time of 5 years. Foods and drinks were assessed at baseline by dietary questionnaires and classified according to their degree of processing using NOVA classification. Multilevel mixed linear regression was used to estimate the association between UPF consumption and body weight change (kg/5 years). To estimate the relative risk of becoming overweight or obese after 5 years we used Poisson regression stratified according to baseline body mass index (BMI).

Results: After multivariable adjustment, higher UPF consumption (per 1 SD increment) was positively associated with weight gain (0·12 kg/5 years, 95% CI 0·09 to 0·15). Comparing highest vs. lowest quintile of UPF consumption was associated with a 15% greater risk (95% CI 1·11, 1·19) of becoming overweight or obese in normal weight participants, and with a 16% greater risk (95% CI 1·09, 1·23) of becoming obese in participants who were overweight at baseline.

Conclusions: These results are supportive of public health campaigns to substitute UPF for less processed alternatives for obesity prevention and weight management.

Keywords

Ultra-processed foods, Obesity, NOVA, Weight gain, Europe, Adults

Introduction

In 2016, more than 39% of the world population was affected by overweight or obesity (body mass index, BMI ≥ 25 kg/m^2) and it is projected that the prevalence of obesity will increase further in the years to come [1]. Obesity is defined as a state of excess body fatness and is the consequence of a sustained positive energy balance [2]. Dietary factors are among the many factors that can contribute towards an energy imbalance. Several characteristics of foods and drinks are known to influence the amount consumed, including energy density and portion size [2]. Continued efforts are needed to identify additional modifiable factors for the prevention of weight gain and obesity [3].

Globally, the consumption of industrially processed foods, so-called ultra-processed foods (UPFs), increased in the last few decades [4] representing nowadays 50%–60% of daily energy intake in some high-income countries [5–7]. In contrast to fresh or minimally processed foods, UPFs tend to have a higher energy density [8], and they can trigger a higher eating rate/energy intake rate [9]. These properties may result in energy overconsumption and weight gain when consuming a diet with a large proportion of UPFs [8,9].

UPFs are defined by the NOVA food system classification as products formulated mostly or entirely from food constituents, not found in home cooking, and culinary ingredients such as fat, sugar, and salt [10]. During manufacturing they undergo physical and chemical processes, such as extruding, prefrying, or hydrogenation [11]. Typically, UPFs are mass-produced packaged breads, sugared breakfast cereals, buns, biscuits, sweet or savoury packaged snacks, instant soups and noodles, processed meat as well as certain industrially pre-prepared meals [12]. These foods provide for many people, particularly in urban areas or for those with extensive or unusual working hours, easily accessible and affordable sources of energy[13] .

Several cross-sectional and four prospective cohort studies, using NOVA, suggested positive associations between a higher consumption of UPFs and excess body weight [14–19]. In a meta-analysis of 13 cross-sectional and one prospective observational study, average positive associations between UPF consumption and overweight or obesity were reported [14] . However, there was evidence for publication bias and heterogeneity across studies was substantial ($I^2 \geq 85\%$), which hampers the possibility to draw robust conclusions. Different study designs and different level of adjustment for confounders may at least partly explain the large heterogeneity in previous studies. Further evaluation whether UPFs promote energy overconsumption and weight gain in diverse populations is therefore warranted.

We investigated relationships between UPF consumption and weight change among adults in a multi-national setting, which allowed assessment of potential heterogeneity across study populations with different underlying dietary habits, while applying a uniform adjustment for confounders. We also investigated associations with risk of developing overweight or obesity.

Material & Methods

Study population

The EPIC study is an ongoing prospective cohort study across 23 centers in 10 European countries: Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom (UK). From 1992 to 2000 a total of 521 448 men and women were recruited. In France, Norway, Utrecht (Netherlands) and Naples (Italy), only women were recruited. Individuals were selected from the general population with a few exceptions. In France, state-school employees were recruited. The Utrecht and Florence (Italy) centers included women invited for a local population-based breast cancer screening program. Some centers in Italy and Spain included members of local blood donor associations. In Oxford (United Kingdom), one-half of the cohort was recruited from lacto-ovo vegetarians and vegans. The rationale and design of EPIC has been described in detail elsewhere [20,21]. The EPIC study was approved by the Ethical Review Boards of the IARC and the Institutional Review Board of each participating EPIC center.

For this study, selected centers were combined within countries depending on their follow-up times and/or weight measurement methods, resulting in 16 centers from 23 originally. We excluded pregnant women, participants with missing dietary or lifestyle information, missing data on weight and height or with unreliable anthropometric values at baseline (n=23 713). We further excluded 122 154 individuals with missing weight at follow-up and 2 288 individuals with outlying anthropometry at follow-up: weight change < -5 or > 5 kg/year and BMI at follow up < 16 kg/m².

More details on follow-up exclusions are given in Supplementary Material (Supplementary Material Fig. S1) and have been described previously [22] . After excluding Greece (not providing data for this study) and one participant from Bilthoven, who withdrew participation in EPIC, a sample of 348 748 participants was available for analyses.

Anthropometric measures and weight change

Two body weight measures were available for each participant: at baseline and after a median follow-up time of 5 years [min.: 2 years for Heidelberg (Germany), max.:11 years for Varese (Italy)]. All centers used standardized procedures to measure weight and height at baseline, except, in France, Norway, and Oxford, where subjects self-reported their weight. Follow-up weight was self-reported, except for Cambridge (UK) and Doetinchem (The Netherlands) where it was measured [22]. The accuracy of self-reported anthropometric measures at baseline and at follow-up was improved with prediction equations derived from subjects with both measured and self-reported weight at baseline [23].

The main outcome of our study was weight change in kg per 5 years, calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years. With these two available time points of weight assessment, we could not assess whether weight change was non-linear over time, but an overall gain or loss of weight during this period was captured. This is in line with findings that weight change in humans is quite constant throughout a period of energy imbalance [24].

Dietary assessment and estimation of UPF consumption

In the EPIC study, usual food intake in the previous 12 months was assessed at baseline using country-specific validated dietary questionnaires [20]. In brief, three types of dietary assessment methods were applied to examine the consumed food over the previous 12 months; a) quantitative dietary questionnaires in northern Italy, Ragusa in Italy, The Netherlands, Germany, Spain and France, b) semi-quantitative food-frequency questionnaires in Denmark, Norway, Naples in Italy, and Umeå in Sweden, and c) a combination of semi-quantitative food-frequency questionnaires and 7- and 14-day records in Malmö (Sweden) and the UK, respectively. The food items reported in each dietary questionnaire were classified in respective harmonized food groups common across questionnaires. In addition, the frequency of consumption, the portion size consumed on each occasion, and the applied standard portion sizes were stored in a central database at IARC, from which the total quantity of each food was estimated as grams per day [20].

To estimate UPF consumption, the NOVA food classification system was incorporated into the EPIC database containing more than 11 000 food items. Generic or multi-ingredient foods were decomposed into ingredients and were then classified according to the NOVA classification. NOVA classifies each food item (or ingredient) into one of four groups: 1) unprocessed or minimally processed foods (e.g., fresh, dry or frozen fruits or vegetables, grains, flours and pasta); 2) processed culinary ingredients (e.g., table sugar, oils, salt); 3) processed foods (e.g., cheese, simple breads, fruits in syrup, canned fish); and group 4) ultra-processed foods (e.g., soft drinks, sweet or savory packaged snacks, processed meat, and pre-prepared frozen or shelf-stable dishes) [12]. Our exposure of interest in this analysis was the NOVA group 4, which includes UPFs without alcoholic drinks. The list of food subgroups included in NOVA group 4 is given in Supplementary Material (Supplementary Table S1).

Since dietary assessment was conducted in the nineties, three scenarios, labelled as lower, middle, and upper bound, were considered when classifying food items and ingredients according to NOVA to account for potential transition of food processing over time. The middle-bound scenario represents the most likely applicable scenario regarding the past 25 years in the different countries of interest and was used in the main analysis. In case a given food or ingredient could have been also less processed compared to the middle-bound scenario, it was assigned into a less processed NOVA group and included in the lower-bound scenario. The same applied to foods or ingredients that could have been more processed, resulting in being classified into the upper-bound. This means that, depending on the foods an individual consumed, the proportion of UPFs in the diet was lower or higher and the ranking of individuals within the study population in terms of UPF consumption was altered accordingly.

Assessment of covariates

Data on socio-demographic, lifestyle and other factors, including education level, physical activity, alcohol intake and smoking history were collected at baseline through validated questionnaires [20].

Statistical analyses

Habitual consumption of energy-adjusted UPFs was modelled both on a continuous scale per 1 standard deviation (SD)/day increment (corresponding to ~ 250 g/day) and by categories, where energy-adjusted UPF consumption was divided into quintiles and the lowest consumption quintile was used as reference category. We used the residual method for energy adjustment, where we generated standardized residuals by regressing the consumption of UPFs (g/day) on total energy intake and center. These standardized residuals of UPF consumption are uncorrelated with total energy intake and account for residual variation of estimated food consumption across centers that are due to different dietary assessment instruments used. We corrected for energy intake to reduce measurement error in dietary intake estimates. Although this is an efficient approach to improve the validity of the energy-adjusted dietary intake [25], energy intake as such cannot be used as an exposure (or mediator) [26]. Therefore, we argue that despite including energy intake (a potential mediator of the association between UPF consumption and weight gain) in our regression model, we still observe the total ‘effect’ of UPF consumption on weight gain.

Multilevel mixed linear regression was used, with center as random effect and UPF consumption and confounders as fixed effects, to estimate the association with body weight change (kg/5 years). Three models were fit. Model 1 was adjusted for age, sex, and body mass index (BMI) (continuous, kg/m^2) at baseline. Model 2 was further adjusted for educational level (none, primary school, secondary school/technical school, longer education, missing), levels of physical activity (inactive, moderately inactive, moderately active, active, missing), smoking status at baseline (never, former, current, missing), alcohol consumption (continuous, g/day), and an indicator for energy mis-reporting using Goldberg cut-offs [27]. Model 3 was additionally adjusted for Mediterranean diet, representing healthy dietary habits, using the modified relative Mediterranean Diet Score (mrMDS) [28].

Participants with missing values for physical activity (n= 5 493, 1·6%), education (n= 4 882, 1·4%) and smoking status (n= 6 476, 1·9%) at baseline were classified in a separate category and included in the models. Model assumptions and fit were checked visually by plotting the residuals against each of the categorical covariates.

Heterogeneity across countries/centers was evaluated by using generalized linear models (with adjustments as model 3 above) and pooling results by random effects meta-analysis. We also estimated 95% prediction intervals to not only estimate the average association across countries/centers, but also to appreciate associations within an individual country/center [29].

To assess shape and linearity of associations between consumption of UPFs and weight gain, a three-knot restricted cubic splines model was used in combination with a Wald-type test. Knots were placed at percentiles 10, 50, and 90.

We tested *a priori* for effect modification by age (categorised as younger than median age ≤51 and >51 years), sex, and BMI categories at baseline (<25, 25-30, ≥ 30 kg/m²). This was done by including interaction terms between each potential effect modifier and the predictor variable UPF (g/day) in the models. *P* values for interaction were calculated using a Likelihood-ratio test.

Food intake was classified into the four NOVA groups, consequently they sum up to a constant and represent compositional data. Therefore, we performed substitution analyses [30]. For example, excluding NOVA group 1, while holding the consumption of the other 3 groups constant, represents the substitution of 1 unit of unprocessed food by 1 unit of UPFs. We repeated the analysis substituting NOVA group 4 for NOVA group 1 (minimally processed foods), expecting an inverse association with weight gain.

We performed a range of sensitivity analyses to assess robustness of our findings and address potential biases (Supplementary Table S2). For example, adjustment for NOVA 4 soft drinks subgroup in our main model, which are known to induce weight gain. Also, associations between UPF consumption and weight gain was additionally tested by using %g/day and %kcal/day instead of g/day as well as using the crude UPF variable without energy adjustment (Supplementary Table S2).

We used a modified Poisson regression approach [31] to estimate the relative risk (RR) and 95% confidence intervals (CI) of becoming overweight in participants with an initial normal weight BMI (< 25 kg/m^2) or obese with an initial BMI marking overweight (≥ 25 kg/m^2 < 30) according to the consumption of UPF. RRs were adjusted as described in model 3 above. Furthermore, quintiles of the consumption of UPFs were calculated separately in normal weight and overweight participants at baseline.

All statistical analyses were performed with STATA 16.1 (College Station, Texas, USA).

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all of the data in the study and had final responsibility for the decision to submit for publication.

Results

Characteristics of the study population

Table 1 shows the main characteristics of the study population at baseline by quintiles of UPF consumption. Participants in the highest quintile had greater weight gain, were younger, and consumed more sugar/confectionary, and cakes and biscuits. Furthermore, participants in the highest quintile consumed more soft drinks and less alcohol compared to those in the lowest quintile.

Consumption of UPFs and 5-year changes in body weight

Between baseline and the second weight assessment on average five years later, the mean weight increase in the study population was 2·1 kg with large variation between participants (SD 5·0 kg). Body weight changes (kg) over an average of 5 years according to energy-adjusted baseline UPF consumption are shown in Table 2. After controlling for confounding, higher consumption of UPFs was associated with greater weight gain (0·120 kg per 1 SD increment/5 years, 95% CI 0·087 to 0·152). Associations remained nearly unchanged after further adjustment for the Mediterranean diet (Table 2). Analyses by quintiles of UPF consumption confirmed these findings, and participants in the highest quintile gained more weight (0·357 kg/5 years, 95% CI 0·272 to 0·442) as compared to participants in the lowest quintile (Table 2).

In our meta-analytical approach, we found consistent associations across countries/centers with some expected heterogeneity (Figure 1). This heterogeneity can at least partly be explained by differences in UPF consumption (Supplementary Table S3), length of follow-up, and other differences in study populations or methods used. Despite this heterogeneity in associations, the estimated overall prediction intervals (0·0001 to 0·201 kg/5 years) showed that higher UPF consumption was detrimental in at least 95% of the individual study settings.

Evaluating the shape of the association with a restricted cubic spline model, showed a linear dose-response relationship between higher consumption of UPFs and weight gain (Figure 2). For example, weight gain associated with UPF consumption corresponding to the ninetieth percentile was equal to 0·32 kg/5 years (95% CI 0·22 to 0·42).

In substitution models, replacing minimally processed foods by an equal amount of UPFs yielded results close to our main results. Furthermore, replacing UPFs by an equal amount of minimally processed foods was inversely associated with weight gain (-0·280 kg/1 SD replacement, 95% CI -0·445 to -0·115) (Supplementary Table S4).

Similar positive associations with weight gain were observed by sex, age groups, and among participants with normal weight and overweight, while among participants with obesity the association with weight gain was attenuated (Supplementary Table S5).

Sensitivity analysis

The main findings were robust to a range of sensitivity analyses. However, associations with weight gain were attenuated by about one third after adjusting for the NOVA 4 soft drink subgroup. Using the proportion of UPFs in the diet in %g/day or %kcal/day were similar to our main analysis. The results of all sensitivity analyses are shown in the Supplementary Material (Supplementary Table S2).

Consumption of UPFs and risk of overweight and obesity

Adjusted relative risks (95% CI) of becoming overweight or obese after 5 years according to consumption of UPFs and baseline BMI are shown in Table 3. At baseline 191 255 participants were normal weight while 103 259 were overweight. Participants with normal weight in the highest vs. lowest quintile of UPF consumption (g/day) had 15% higher risk (95% CI 1·11 to1·19) of becoming overweight or obese (P trend <0·001) during the follow-up period. Similarly, overweight participants at baseline had a 16% higher risk (95% CI 1·09 to1·23) of becoming obese (P trend <0·001) comparing the highest vs. lowest quintile of UPF consumption.

Discussion

In this large prospective study among adults from 9 European countries, we found that higher consumption of UPFs was associated with significantly higher 5-year body weight gain in a dose-response manner. We further found a 15% higher risk of becoming overweight or obese for normal weight participants at baseline in the highest quintile of UPF consumption compared to the lowest. These findings were robust to sensitivity analyses and largely consistent across countries characterized by heterogeneous study populations in terms of distribution of sex, age, and lifestyle behaviours. Given that virtually the whole population is exposed to UPF to some degree, even the small effect sizes observed in our study could be of concern regarding future population obesity prevalence.

Our findings are congruent with a Spanish prospective cohort study, which assessed UPF consumption by servings per day over a median follow-up of 8·9 years and showed a 26% higher risk of developing overweight or obesity for participants in the highest quartile compared to the lowest quartile of UPF consumption [18]. Similarly, Beslay et al. showed a positive association between the proportion of UPFs in the diet and gain in BMI in participants from the French prospective population-based NutriNet-Santé cohort [15]. In the same study, higher consumption of UPFs was associated with higher risk of overweight and obesity, 11% and 9%

respectively for a 10% increment of UPFs [15]. Furthermore, Canhada et al., evaluated in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) cohort the association between UPF consumption and weight gain, increase in waist circumference, as well as the incidence of overweight and obesity. Participants were followed for an average of 3·8 years and those who were in the highest quartile of UPF consumption (percent energy intake) had a 27% greater risk of experiencing larger weight gain than those in the lowest quartile. Similarly, there was a 20% higher risk to develop overweight for participants in the highest quartile who had normal weight at baseline compared to the lowest quartile [16] . These results are in line with ours, as were previous cross-sectional studies [19,32]. Consistently, an inpatient randomized controlled trial showed that an UPF diet caused elevated *ad libitum* energy intake of ~500 kilocalorie per day and weight gain of + 1·1 kg after 14 days compared to an unprocessed diet [9].

The mechanism by which UPFs may influence energy intake and weight gain are incompletely understood. UPF are widely available and convenient to consume or prepare. While this is not necessarily problematic, UPFs tend to have a high energy density (calories per weight or volume) [33] and can be consumed at a higher energy intake rate (calories per time unit) [9]. The latter is because UPFs are usually less solid and lower in volume compared to unprocessed foods [33]. Either of these characteristics of UPFs – high energy density and eating rate – can promote overconsumption and weight gain [2,9].

An emerging hypothesis with comparably limited evidence to date relates to the accumulation of advanced glycation endproducts (AGEs) in foods that undergo prolonged dry heat processing to improve aroma and colour such as crackers, biscuits and cereal products, or industrial food preservation such as canned meats [34]. In our study population, we found that dietary intake of AGEs was 1 SD higher in the 5th compared to the 1st quintile of UPF consumption. There is suggestive evidence from animal models that higher dietary intake of AGEs can lead to insulin resistance and weight gain [35–38]. A systematic review of randomized clinical trials reported that the consumption of a low-AGE diet compared to a high-AGE diet was associated with improved insulin sensitivity and reduced body weight, waist circumference, and BMI in overweight and obese men and women [39]. Furthermore, higher AGEs exposure could lead to a hypothalamic inflammatory state, which can compromise the signalling of two key hormones in energy homeostasis, i.e. insulin and leptin. In line with this hypothesis, we found in a previous investigation in the same cohort that higher exposure to dietary AGEs was associated with greater weight gain [40].

We acknowledge that the NOVA group 4 (i.e. UPF) consists of very heterogeneous foods representing virtually all major food groups. Non-exhaustive examples include breakfast cereals, fruit drinks, meat products, milk drinks, instant soups, pastries, and soft drinks. Although UPFs have on average a higher energy-density compared to minimally processed foods [33], they are not equally high in their energy-density or intake rate and may thus contribute differentially to energy overconsumption. To explore this further, we adjusted our main model for soft drink consumption. A high consumption of soft drinks is a well-established risk factor for weight gain and obesity [41]. After accounting for soft drink consumption, the positive association between UPF consumption and weight change was attenuated by about one third but remained statistically significant with a difference in body weight gain of +0.075 kg (95% CI 0.024-0.126) over 5 years (Supplementary Table 2). This suggests that part of the associations between UPF consumption and weight gain are driven by soft drink consumption, but other foods (or their properties) in the UPFs category also contribute. Soft drink consumption is likely also correlated with other components of UPFs and could thus be regarded as a mediator of observed associations. Although the NOVA group 4 also contains foods that can be very valuable in various contexts (e.g. ready-to-eat meals for elderly people), it nevertheless appears that the overall share of UPFs in a dietary pattern is still a useful indicator to study population health outcomes.

Strengths and limitations

The results of our study should be interpreted with the following limitations in mind. First, the dietary questionnaires were not specifically designed to assess UPF consumption. However, three scenarios were considered when classifying food items and ingredients according to NOVA to evaluate the impact of possible exposure misclassification. Second, only self-reported weight at follow-up was available in most centers. To mitigate this possible source of bias, we applied a prediction equation to improve self-reported weight estimates [23]. Furthermore, in the EPIC-Norfolk study (UK Cambridge center of EPIC) a high correlation between self-reported and measured weight data has been shown (r=0·97 in men and r=0·98 women) [42]. Likewise the Norway center of EPIC showed that self-reported weight and height provide a valid classification of BMI in their cohort of middle-aged Norwegian women, which means that ranking of participants according to self-reported weight was adequate [43]. Third, we were not able to accurately measure changes in body composition (e.g. using dual-energy X ray absorptiometry, DXA); therefore, we had to make the reasonable assumption that encountered weight changes are largely due to changes in body fat mass and not in lean body mass or height. This is supported by a study in a subsample of PREDIMED-Plus (n=1485), where higher UPF consumption was associated with greater fat accumulation as measured with dual-energy X-ray absorptiometry (DXA) [44]. Fourth, we were not able to account for potential changes in diet during follow-up; yet dimensions of change in weight appear to be more pronounced and more robust if changes in diet can be accounted for [45]. In order to minimise measurement error bias, an inherent limitation of studies using self-reported dietary data, we adjusted for total energy intake and for plausibility of dietary energy reporting; the latter has been shown in the EPIC-Potsdam sub-study to improve expected associations between intakes of energy-dense foods and BMI [46]. Apart of energy adjustment, energy intake is less reliable as exposure [26], which means that our findings can still be interpreted as the total association between UPF and weight gain and obesity risk.

Strengths of our study include its prospective design with a long follow-up, the heterogeneous study population, and the large sample size, which allowed assessment of associations in population sub-groups, and potential real differences in associations across 9 European countries. We also controlled for a Mediterranean diet score [28], which has been previously shown to be inversely associated with weight gain [47], suggesting that associations between UPF consumption and weight change are independent of healthy dietary habits.

Conclusion

In conclusion, this prospective study of adults from 9 European countries representing populations with heterogeneous diets provides further evidence that a higher proportion of UPFs in the diet is associated with greater weight gain and a greater risk to develop overweight or obesity.

Author Contributions

Freisling and Cordova had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Freisling, Gunter, Monteiro, Millett

Acquisition, analysis, or interpretation of data: Cordova; Kliemann, Huybrechts; Rauber; Vamos; Levy; Wagner; Viallon; Casagrande; Nicolas; Dahm; Zhang; Halkjær; Tjønneland; Boutron-Ruault; Mancini; Laouali; Katzke; Srour; Jannasch; Schulze; Masala; Grioni; Panico; T. van der Schouw; Derksen; Rylander; Skeie; Jakszyn; Rodriguez-Barranco; Huerta; Barricarte; Brunkwall; Ramne; Bodén; Perez-Cornago; Heath; Vineis; Weiderpass; Monteiro; Gunter; Millett; Freisling

Drafting of the manuscript: Cordova, Freisling

Critical revision of the manuscript for important intellectual content:

Cordova, Kliemann, Huybrechts; Rauber; Vamos; Levy; Wagner; Viallon; Casagrande; Nicolas; Dahm; Zhang; Halkjær; Tjønneland; Boutron-Ruault; Mancini; Laouali; Katzke; Srour; Jannasch; Schulze; Masala; Grioni; Panico; T. van der Schouw; Derksen; Rylander; Skeie; Jakszyn; Rodriguez-Barranco; Huerta; Barricarte; Brunkwall; Ramne; Bodén; Perez-Cornago; Heath; Vineis; Weiderpass; Monteiro; Gunter; Millett; Freisling

Statistical analysis: Cordova, Freisling, Viallon

Administrative, technical, or material support: Huybrechts, Rauber, Vamos, Bertazzi Levy, Wagner, Casagrande, Nicolas, Gunter

Supervision: Huybrechts, Rauber, Vamos, Bertazzi Levy, Wagner, Viallon, Monteiro, Gunter, Millett, Freisling

Conflict of interest statement

None of the authors declared a conflict of interest.

Acknowledgements

The authors would like to thank the EPIC study participants and staff for their valuable contribution to this research. The authors would also like to especially thank Mr. Bertrand Hemon for preparing the EPIC databases.

Funding

Reynalda Cordova is a recipient of a DOC Fellowship of the Austrian Academy of Sciences at the Institute of Nutritional Sciences, University of Vienna.

This work was partially financially supported by the Fondation de France (FDF, grant no. 00081166, HF, RC).

Fernanda Rauber is a beneficiary of a postdoctoral fellowship from the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), grant numbers 2016/14302-7.

The national cohorts are supported by the following funders: Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Education Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro-AIRC-Italy and National Research Council (Italy); Dutch Ministry of Public Health,Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland),World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS-ISCIII), the Regional Governments of Andalucía, Asturias, Basque Country, Murcia, Navarra, and the Catalan Institute of Oncology (Barceloan), Spain); Cancer Research UK (14136 to EPIC-Norfolk; C570/A16491 and C8221/A19170 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk, MR/M012190/1 to EPIC-Oxford) (UK).

The Public Health Policy Evaluation Unit is grateful for support from the NIHR School of Public Health Research. Swedish Cancer Society, Swedish Research Council and County Council of Västerbotten, Sweden.

Data sharing

Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval. For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at: http://epic.iarc.fr/access/index.php.

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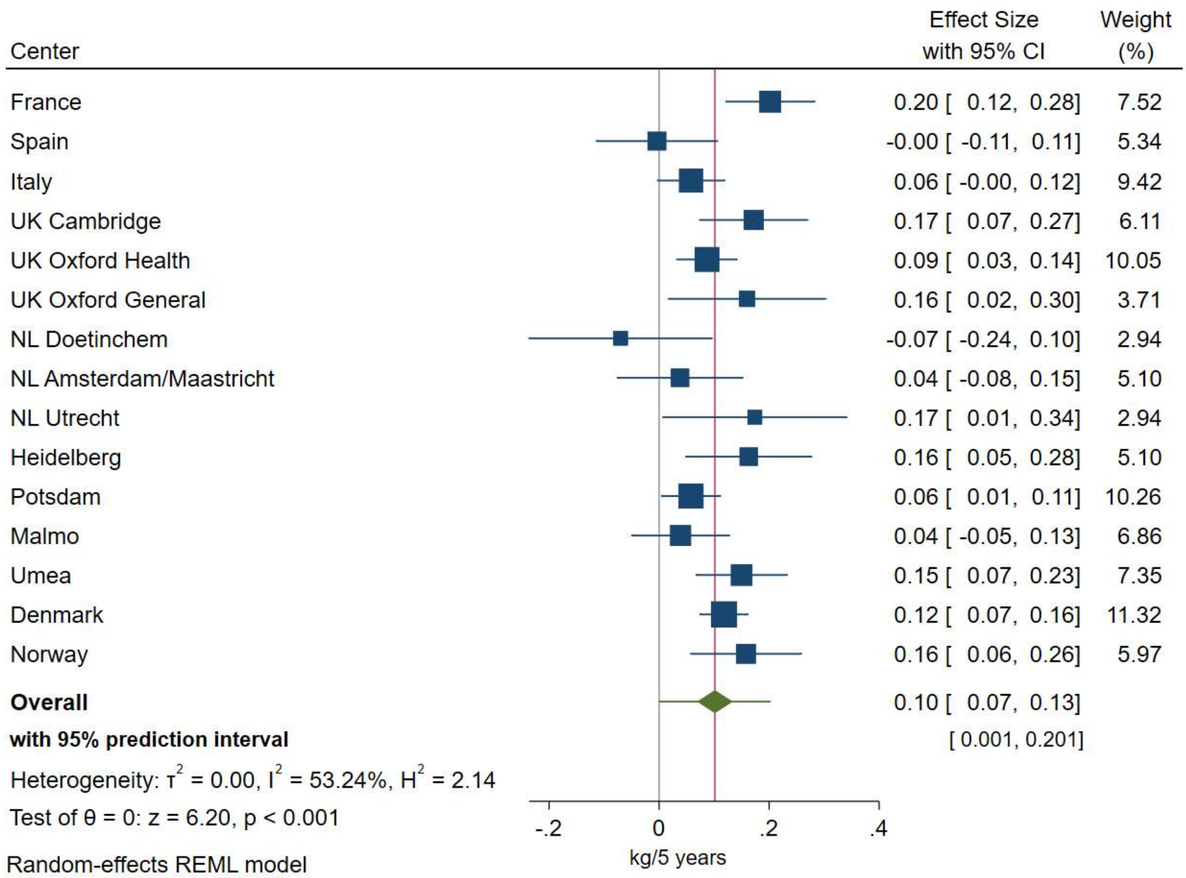

Figure 1 Random effects meta-analysis and 95% prediction intervals of associations between UPF[a] consumption (per 1 SD/day) and weight gain in 348 748 men and women.

Center-specific results were estimated using generalized linear models adjusted for age, sex, body mass index (BMI) at baseline, educational level, levels of physical activity, alcohol intake at baseline, smoking status at baseline, and plausibility of dietary energy reporting and modified relative Mediterranean diet score.

[a] Energy-adjusted baseline ultra-processed food (UPF) consumption (g/day) using residual methods. Standardized residuals were computed by a linear regression of baseline UPF (g/day) regressed on energy and center. Overall mean 5-year weight gain corresponded to 2.1 kg (SD 5.0) and positive beta values indicate more weight gain (kg) over the same period. Study centers were based on the general adult population, with some exceptions. In France, Norway, Utrecht, and Naples only women were recruited. Furthermore, in France, state-school employees were recruited. The Utrecht and Florence (Italy) centers included women invited for a local population-based breast cancer screening program. Some centers in Italy and Spain included members of local blood donor associations. Oxford Health recruited among subjects who did not eat meat, including lacto-ovo vegetarians, fish eaters and vegans.

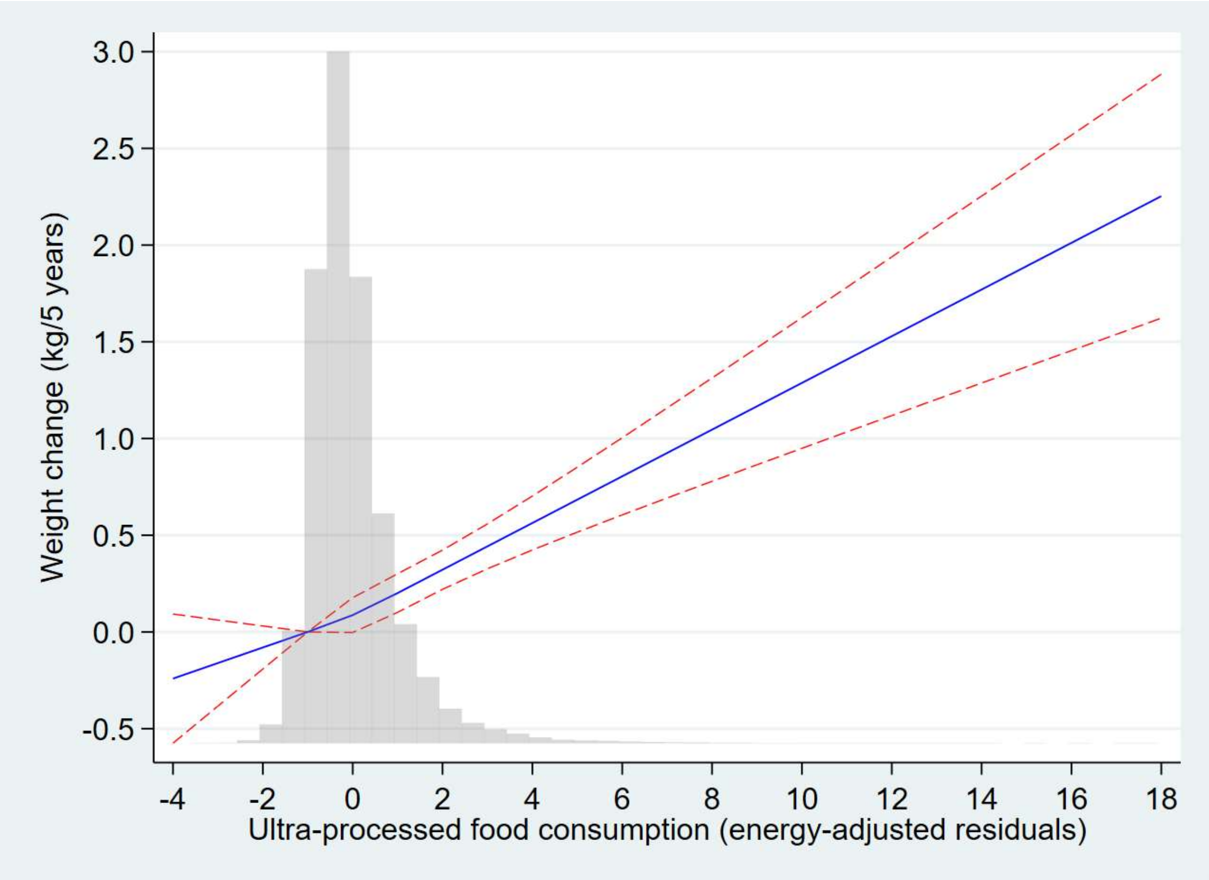

Figure 2 Three knot splines for the association between UPF[a] consumption (per 1 SD/day) and weight gain.

Multilevel linear mixed models with random effect on the intercept and slope according to center. Overall mean 5-year weight gain corresponded to 2.1 kg (SD 5.0) and positive beta values indicate more weight gain (kg) over the same period.

[a]Energy-adjusted baseline ultra-processed food (UPF) consumption (g/day) using residual methods. Standardized residuals were computed by a linear regression of baseline UPFs (g/day) regressed on energy and center. Main model (model3) adjusted for age, sex, BMI at baseline, educational level, levels of physical activity, alcohol intake at baseline, smoking status at baseline, and plausibility of dietary energy reporting and modified relative Mediterranean diet score.

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Correspondence:
Dr. Heinz Freisling

International Agency for Research on Cancer (IARC-WHO),

150 Course Albert Thomas, 69372 Lyon Cedex 08, France

Email : freislingh@iarc.fr

Figure S1 Flow chart of participants exclusion criteria for the present study

EPIC cohort
n=521,448

↓ *PANACEA baseline exclusion (n=*23,713*) (1)*

PANACEA baseline dataset
n=497,735

↓ *No follow-up weight available (n=*122,154*) (2)*

PANACEA follow-up dataset
n=375,581

↓ *Extreme anthropometry at follow-up (n=2,288) (3)*

PANACEA follow-up dataset
n=373,293

↓ *Exclusion of Greece (not participating in this study) and one participant from Bilthoven, who withdrew participation in EPIC (n=24,545) (4)*

PANACEA follow-up dataset used in the present study
n=348,748

(1) PANACEA baseline exclusions:
   1. Length of follow-up equals to 0 (n=1,517)
   2. No dietary data available (n= 6,611)
   3. Those in the lowest and highest 1% of the ratio of reported total energy intake / energy requirement (EI/ER) (n=10,209)
   4. No lifestyle information (n=64)
   5. Pregnant women (n=623)
   6. Unreliable anthropometry [height <130 cm (n=16), BMI <16.0 kg.m^{-2} (n=302), waist circumference <40 cm (n=0) or waist circumference >160 cm (n=16), waist circumference <60 cm if BMI >25 kg.m^{-2} (n=42)]
   7. Missing information on weight (n=4,079)
   8. Missing information on height (n=234)

(2) Reasons for missing data on follow-up assessment of body weight:
   1. Death before the follow-up body weight assessment (n=8,226)
   2. Not yet approached for follow-up body weight assessment (n=23,957)
   3. (E)migrated (n=3,991)
   4. Non-respondents to the invitation to participate in the second follow-up assessment of body weight (n=85,967)
   5. Follow-up time missing (n=13)

(3) Extreme anthropometry at follow-up:
   1. Weight change < -5 kg/year or > 5 kg/year (n=1,926)
   2. BMI at follow-up <16 kg/m^2 (n=140)
   3. Missing BMI at follow-up (n=222)

(4) Not participating:
   1. Greece (n=24,544)
   2. Participant from Bilthoven (n=1)

Table S1 Descriptive table of food items included in NOVA group 4 in g/day

Food subgroups	Mean (g/day)	SD (g/day)
Ultra-processed breads	43	67
Pastries, buns, and cakes	23	30
Biscuits	14	19
Breakfast cereals	5	10
Ice cream, ice pops and frozen yogurts	7	12
Industrial desserts	2	11
Packaged salty snacks	2	5
Potato products	8	16
Pizza and focaccia (dough)	6	11
Pasta (filled)	3	7
Instant and canned soups	9	21
Dairy substitute products	3	31
Processed cheese	3	6
Sauces, dressing and gravies also powder, dehydrated, condensed form	11	13
Vegetable spread and products	0	2
Soft drinks	46	116
Dairy desserts and drinks (ultra-processed versions)	45	70
Fruit drinks, iced tea and other sweetened beverages	40	116
Beverages dry weight	1	4
Alcoholic distilled drinks and other alcoholic drinks	9	22
Artificial sweeteners	0	2
Sweet snacks	12	19
Processed meat (beef, pork and fish)	36	33
Meat alternatives	1	3
Nutrition powders and drinks	0	1
Margarine	13	17
Ready meals	6	13
Alcohol-free versions of alcoholic beverages	3	30
Vegetables and legumes in ultra-processed medium	3	12
Rice-based dishes	0	0

Table S2 Difference in body weight gain (kg) over 5 years per 1 standard deviation (SD)/day increase according to baseline ultra-processed food[a] consumption in men and women after different sensitivity tests

Models	N (%)	Beta	Lower 95%	Upper 95%
Model 3	348 748 (100)	0·118	0·085	0·151
Model S1	348 748 (100)	0·062	0·023	0·100
Model S2	348 748 (100)	0·098	0·051	0·145
Model S3	348 748 (100)	0·123	0·087	0·158
Model S4	348 748 (100)	0·096	0·051	0·140
Model S5	334 114 (96)	0·118	0·084	0·152
Model S6	348 748 (100)	0·112	0·087	0·158
Model S7	348 748 (100)	0·118	0·085	0·151
Model S8	150 334 (43)	0·110	0·082	0·137
Model S9	238 828 (68)	0·133	0·095	0·171
Model S10	348 748 (100)	0·078	0·038	0·117
Model S11	276 377 (79)	0·109	0·070	0·148
Model S12	348 748 (100)	0·132	0·096	0·168
Model S13	348 748 (100)	0·075	0·024	0·126

[a] Energy-adjusted baseline ultra-processed food consumption (g/day) using the residual method (1 standard deviation, SD=250g). Standardized residuals were computed by a linear regression of baseline ultra-processed foods (g/day) regressed on energy and center.
Main model 3: adjusted for age, sex, BMI at baseline, educational level, levels of physical activity, alcohol intake at baseline, smoking status at baseline, and plausibility of dietary energy intake reporting and for modified relative Mediterranean diet score.
Model S1 using residuals of the middle-bound scenario variable in % g/day as predictor variable.
Model S2 using the standardized middle-bound scenario variable in % kcal /day as predictor variable.
Model S3 using residuals of the lower-bound scenario variable in g/day as predictor.
Model S4 using residuals of the upper-bound scenario variable in g/day as predictor.
Model S5 excluding subjects with missing values in any of the covariates.
Model S6 using smoking at follow-up instead of smoking status at baseline.
Model S7 adjusting for chronic conditions at recruitment using an indicator for missing values.
Model S8 excluding centers with less than 5 years of weight follow-up.
ModelS9 excluding over-and under reporter of energy intake reports.
Model S10 Model 3 (main model) additional adjusted for weight change at follow-up.
Model S11 Model 3 (main model) adjusted for weight and height instead of baseline BMI.
Model S12 Model 3(main model) with crude ultra-processed food variable (g/day) without adjustment for energy intake.
1

Table S3 Ultra-processed food consumption (g/day) by NOVA 4 group subgroups and by countries

	France		Italy		Spain		United Kingdom		The Netherlands		Germany		Sweden		Denmark		Norway	
Ultra-processed breads	9	±32	0	±0	4	±10	84	±59	0	±0	6	±11	2	±4	143	±65	128	±59
Pastries, buns, and cakes	26	±26	24	±33	25	±40	18	±24	20	±18	44	±45	25	±24	13	±15	9	±8
Biscuits	14	±16	25	±24	16	±27	14	±17	18	±16	10	±17	18	±19	7	±10	10	±13
Breakfast cereals	3	±8	0	±0	1	±8	13	±14	3	±7	2	±4	6	±10	8	±13	3	±4
Ice cream, ice pops and frozen yogurts	5	±6	17	±20	2	±8	10	±15	8	±8	6	±9	10	±16	4	±6	8	±10
Industrial desserts	0	±0	1	±3	0	±0	0	±1	2	±2	2	±2	12	±32	0	±0	0	±0
Packaged salty snacks	0	±0	0	±0	1	±3	6	±9	0	±0	3	±8	2	±4	3	±4	2	±2
Potato products	0	±0	0	±0	0	±0	25	±24	22	±26	10	±11	10	±16	2	±4	0	±0
Pizza and focaccia (dough)	7	±7	0	±0	1	±3	7	±9	9	±14	11	±14	7	±13	0	±0	17	±15
Pasta (filled)	1	±1	15	±16	0	±2	8	±11	0	±0	3	±4	0	±3	0	±0	0	±0
Instant and canned soups	4	±4	12	±28	4	±20	22	±30	22	±24	11	±17	13	±30	0	±0	1	±1
Dairy substitute products	0	±0	0	±0	0	±8	18	±79	0	±0	0	±0	1	±6	0	±0	0	±0
Processed cheese	2	±5	6	±8	3	±7	0	±0	9	±11	2	±4	1	±4	2	±6	3	±4
Sauces, dressing and gravies also powder, dehydrated, condensed form	6	±6	1	±1	5	±5	17	±14	19	±16	19	±18	6	±9	17	±14	2	±3
Vegetable spread and products	0	±0	0	±0	1	±2	0	±0	1	±2	0	±2	1	±3	0	±0	0	±0
Soft drinks	0	±0	37	±99	30	±94	66	±143	91	±123	64	±171	39	±81	51	±118	83	±122

Dairy desserts and drinks (Ultra Processed versions)	61	±82	26	±50	21	±44	48	±47	76	±84	75	±100	16	±42	34	±65	29	±30
Fruit drinks, iced tea and other sweetened beverages	9	±45	20	±39	1	±4	57	±145	28	±40	86	±121	57	±124	88	±206	1	±3
Beverages dry weight	0	±0	0	±0	1	±3	4	±8	1	±2	1	±2	0	±2	0	±0	0	±0
Alcoholic distilled drinks and other alcoholic drinks	14	±25	5	±14	5	±17	7	±15	20	±44	4	±9	12	±21	10	±18	1	±2
Artificial sweeteners	2	±5	0	±0	0	±1	0	±0	0	±0	0	±2	0	±0	0	±0	0	±0
Sweet snacks	10	±17	5	±9	3	±11	15	±25	15	±17	12	±19	11	±16	23	±24	7	±9
Processed meat (beef, pork and fish)	24	±19	14	±13	28	±30	24	±24	34	±27	59	±41	59	±38	30	±21	67	±32
Meat alternatives	0	±0	0	±0	0	±0	4	±8	1	±4	0	±1	0	±1	0	±0	0	±0
Nutrition powders and drinks	0	±0	0	±0	0	±0	0	±0	0	±0	0	±0	0	±2	0	±0	0	±0
Margarine	3	±5	0	±1	2	±5	15	±16	16	±13	11	±13	38	±23	18	±15	14	±12
Ready meal	13	±15	0	±0	0	±1	4	±8	2	±5	0	±0	1	±5	22	±22	1	±1
Alcohol-free versions of alcoholic beverages	2	±23	0	±0	5	±37	0	±0	9	±49	11	±63	0	±1	0	±0	0	±0
Vegetables and legumes in ultra-processed medium	0	±0	0	±0	0	±0	20	±25	0	±0	0	±0	1	±6	0	±0	0	±0
Rice-based dishes	0	±0	0	±0	0	±0	0	±0	0	±0	0	±0	0	±0	0	±0	0	±0

Data are expressed as arithmetic mean ± standard deviation (SD) if not stated otherwise.

Table S4 Difference in body weight gain (kg) over 5 years according to baseline ultra-processed foods[a] consumption (g/day) in 348 748 men and women using substitution analyses

		Substitution Model 1 (ultra-processed food)	Substitution Model 2 (minimally/unprocessed foods)
Beta (95%CI) per 1 SD/day		0·093 (0·055, 0·131)	-0·280 (-0·445, -0·115)
Quintiles of ultra-processed food consumption			
	UPF (g/day) mean intake ± standard deviation (SD)		
Lowest	176 (±102)	Reference	Reference
Q2	221 (±117)	-0·006 (-0·088, 0·076)	-0·081 (-0·172, 0·009)
Q3	270 (±129)	0·098 (-0·002, 0·198)	-0·108 (-0·246, 0·030)
Q4	364 (±133)	0·177 (0·091, 0·264)	-0·142 (-0·294, 0·010)
Q5	686 (±303)	0·294 (0·201, 0·387)	-0·266 (-0·492, -0·041)
P trend (linear)		<0·001	0·027

[a] Energy-adjusted baseline ultra-processed food consumption (UPF) (g/day) using the residual method (1 standard deviation, SD=250g). Standardized residuals were computed by a linear regression of baseline ultra-processed foods (g/day) regressed on energy intake and center. Main model (Model 3) adjusted for age, sex, and BMI at baseline, for educational level, levels of physical activity, alcohol intake at baseline, smoking status at baseline, and plausibility of dietary energy reporting and modified relative Mediterranean diet score. Substitution Model 1: Exclusion of NOVA group 1, while keeping the intake of the other NOVA groups (2, 3,4 plus the total of all NOVA groups) constant. Representing the substitution of 1 SD of minimally/unprocessed foods by 1 SD ultra-processed foods. Substitution Model 2: Exclusion of NOVA group 4, while keeping the intake of the other NOVA groups (1, 2, 3, plus the total of all NOVA groups) constant. Representing the substitution of 1 SD of ultra-processed foods by 1 SD of minimally/unprocessed foods.

Table S5 Difference in body weight gain (kg) over 5 years according to baseline ultra-processed food[a] consumption (g/day) in different subgroups

Subgroups	N	Beta (95%CI) per 1 SD /day	interaction p-value
Sex			< 0·001
female	255 441	0·132 (0·109, 0·155)	
male	93 307	0·087 (0·049, 0·125)	
Age			< 0·001
under/equal 52 years	178 236	0·157 (0·117, 0·197)	
over 52 years	170 512	0·131 (0·085, 0·177)	
BMI			< 0·001
<25	191 255	0·151 (0·114, 0·189)	
25-30	116 744	0·092 (0·044, 0·141)	
≥30	40 749	0·025 (-0·058, 0·109)	

Multilevel linear mixed models with random effect on the intercept and slope according to center. Overall mean 5- year weight gain corresponded to 2·1 kg (SD 5·0) and positive beta values indicate more weight gain (kg) over the same period.
[a] Energy-adjusted baseline ultra-processed food consumption (g/day) using the residual method (1 standard deviation, SD=250g). Standardized residuals were computed by a linear regression of baseline ultra-processed foods (g/day) regressed on energy intake and center.
Main model (Model 3) adjusted for age, sex, and BMI at baseline, for educational level, levels of physical activity, alcohol intake at baseline, smoking status at baseline, and plausibility of dietary energy intake reporting and modified relative Mediterranean diet score.