# Nutritional quality of diet characterized by the Nutri-Score profiling system and cardiovascular disease risk: a prospective study in 7 European countries

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## Summary

**Background** Nutri-Score is a scientifically validated 5-color front-of-pack nutrition label reflecting the nutrient profile of foods. It has been implemented in several European countries on a voluntary basis, pending the revision of the

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European labeling regulation. Hence, scientific evidence is needed regarding the ability of the nutrient profile underlying the Nutri-Score (uNS-NPS, 2023-updated version) to characterize healthier foods. Our objective was therefore to study the prospective association between the nutritional quality of diet characterized by the uNS-NPS and the risk of cardiovascular diseases in a large European population.

**Methods** Our analyses included 345,533 participants from the European Prospective Investigation into Cancer and Nutrition study (EPIC, 1992–2010, 7 European countries). Food intakes were assessed at baseline using country-specific dietary questionnaires. The uNS-NPS was calculated as a continuous scale for each food, based on its 100 g content of energy, sugars, saturated fatty acids, salt, fibre, and protein and percentage content of fruit, vegetables, and pulses. A dietary index was derived at the individual level (uNS-NPS DI: energy-weighted mean of uNS-NPS scores of all foods consumed by a participant). Cardiovascular events during follow-up were retrieved using country-specific methods (self-report, registry data). Multi-adjusted Cox models were computed.

**Findings** Overall, 16,214 first cardiovascular events were reported (median follow-up: 12.3 years; 4,103,133 person-years). The consumption of foods with a higher uNS-NPS score (reflecting a lower overall nutritional quality of diet) was associated with higher risks of total cardiovascular events (Hazards Ratio (HR) for an increment of 1 standard deviation: 1.03 (95% Confidence Interval 1.01–1.05)), especially myocardial infarction (HR = 1.03 (1.01–1.07)), and stroke (HR = 1.04 (1.01–1.07)).

**Interpretation** In this large prospective study among European adults, a higher risk of cardiovascular diseases (total and several subtypes) was observed in individuals consuming a diet with a lower nutritional value, as graded by the uNS-NPS score. This brings new evidence on the relevance of the updated nutrient profile underlying the Nutri-Score to characterize foods with a healthier nutrient profile.

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**Keywords:** Food labelling; Cardiovascular disease risk; Nutrient profile; Nutrition; Prospective study; Europe

### Research in context

#### Evidence before this study

Nutri-Score is a scientifically-validated label based on a nutrient profiling system (NPS) attributing points according to the 100 g content in terms of energy, sugars, saturated fatty acids, sodium, fibre and protein, and of fruits, vegetables and legumes. Studies published in English or French until June 26, 2024 regarding the associations between diet nutritional quality assessed using the Nutri-Score underlying algorithm (in its subsequent versions since 2013) and the risk of cardiovascular diseases (not cardiovascular mortality) were retrieved from a search using the terms "(FSA-NPS or FSAm-NPS or uNS-NPS or Nutri-Score) AND cardiovascular diseases". Two prospective studies conducted by our group in two French cohorts were identified. They used a dietary index based on the initial version of the Nutri-Score algorithm (FSA-NPS) and showed associations between a higher FSA-NPS dietary index (lower diet nutritional value) and a higher risk of cardiovascular diseases. These studies were meta-analyzed in 2024, resulting in a pooled HR associated with a 2-unit increase of 1.08 (95% CI: 1.00, 1.18; $I^2$: 70%). Hence the available evidence is focused on French populations and did not consider the recent 2023-update in the Nutri-Score algorithm.

#### Added value of this study

This study was the first conducted on the risk of cardiovascular diseases in a large multinational European population, including 345,533 participants from the European Prospective Investigation into Cancer and Nutrition cohort study (1992–2010) in 7 European countries and using the 2023-updated version of the Nutri-Score algorithm (uNS-NPS). The results showed that the consumption of foods with a higher uNS-NPS score (reflecting a lower nutritional value) was associated to a higher risk of cardiovascular diseases and particularly of myocardial infarction and stroke. This brings new evidence on the relevance of the updated nutrient profile underlying the Nutri-Score to characterize foods with a healthier nutrient profile in a multi-cultural European context with diverse dietary patterns.

#### Implications of all the available evidence

All the available evidence points to the usefulness and importance of the Nutri-Score and its profiling system as a public health tool to guide consumers in their food choices for chronic disease prevention. This should be considered in the ongoing discussions regarding a mandatory and harmonized front-of-pack labelling scheme within the European Union's Farm-to-Fork strategy.

## Introduction

Cardiovascular diseases are the leading cause of death in Western Europe, with an estimated 1.4 million deaths in 2019 (i.e. 33.5% of all deaths in that region).[1] Among the well-established risk factors for cardiovascular diseases, dietary factors rank second and are estimated to be responsible for 30% of cardiovascular disease deaths.[1] Importantly, unhealthy diet is modifiable and could therefore be targeted by public health prevention strategies.

Official food-based dietary guidelines have been developed in European countries to provide benchmarks of recommended food groups and nutrient intakes and to prevent diet-related chronic diseases. Yet, complementary information at the point of purchase is needed to help consumers limit their consumption of foods with less favourable nutritional quality. To this end, front-of-pack nutrition labels have been suggested as a quick and easy-to-use summary of the mandatory back-of-pack nutrition facts. Front-of-pack nutrition labels also have the potential to push food manufacturers to improve the nutritional profile of their products.[2]

The Nutri-Score label has been developed to reflect the overall nutritional quality of food products with 5 colours and letters (from A-dark green to E-dark orange).[3] The computation of the Nutri-Score is based on a nutrient profiling system (NPS), originally designed by the United Kingdom (UK) Food Standards Agency (FSA-NPS)[4] and modified for labelling purposes (FSAm-NPS).[5] In 2022–2023, the computation algorithm was modified, following propositions from the Nutri-Score international scientific committee, to improve consistency with dietary guidelines.[6,7] This new version of the algorithm will be called uNS-NPS throughout the manuscript.

The Nutri-Score is one of the most scientifically validated candidate of front-of-pack nutrition labels in the European region,[8] which has led the public health authorities in France, Belgium, Germany, Spain, the Netherlands, Switzerland and Luxembourg to officially endorse the Nutri-Score. Yet, the European Union (EU)'s current regulation on Consumer information imposes that front-of-pack nutritional labels remain optional, leaving the choice to the food manufacturers to affix it on their products or not. However, within the EU's Farm-to-Fork strategy, a revision of the current regulation is on the agenda for the coming years, with the purpose to select a unique and harmonized mandatory front-of-pack nutrition label at the EU level.

According to the theoretical framework set by the World Health Organization, one major step towards the validation of a front-of-pack nutrition label is the validation of its nutrient profiling system, notably through prospective studies of the associations between the nutritional quality of diet, derived from the nutrient profile of the food products consumed, and several health outcomes.[9] In this context, previous studies have shown that the consumption of food products with a higher FSAm-NPS score (indicating a lower nutritional quality) was associated with several unfavourable health outcomes, including weight gain,[10,11] metabolic syndrome,[12] and mortality.[13–16] Additionally, three studies also showed associations with unfavourable outcomes for cardiovascular diseases[17,18] (meta-analysed in[19]) and associated risk factors,[20] but these studies were restricted to French and older Spanish populations with a limited number of events. Hence, it is important to provide evidence from a large pan-European population.

Therefore, considering the updated version of the nutrient profile underlying Nutri-Score, which was officially adopted in 2023 (uNS-NPS), this study aims to provide new evidence on the association between nutritional quality of diet according to the uNS-NPS and cardiovascular disease risk within the large European population in the European Prospective Investigation into Cancer and Nutrition (EPIC) study.

## Methods

### Study population

EPIC is a pan-European multi-centre prospective cohort study that enrolled over 520,000 volunteers between 1992 and 2000 (aged 25–70 years at baseline), from 23 centres in 10 European countries using a joint protocol (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the UK). Its objectives are to investigate metabolic, dietary, lifestyle, and environmental factors associated with the risk of cancer and other non-communicable diseases. The study complied with the Declaration of Helsinki and was approved by the local ethics committees and by the Internal Review Board of the International Agency for Research on Cancer. All participants gave their written informed consent. Details regarding EPIC have been published elsewhere.[21–23]

### Baseline data collection

At baseline recruitment, EPIC participants completed questionnaires that collected standardized data on sociodemographic characteristics (e.g., age, self-reported binary gender, and educational level), lifestyle factors (e.g., smoking and physical activity) and personal and family history of diseases. Height and weight were measured with standardized procedures in all centres, except in Oxford, Norway, and France (self-reported). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$.

### Dietary data collection

Usual dietary intakes were assessed at baseline using country-specific, validated dietary questionnaires.[21] These questionnaires included (i) self- or interviewer-administered semi-quantitative food frequency questionnaires (FFQs), with estimations of individual average portions or standard portions, and (ii) diet history questionnaires that combined FFQ and 7-day dietary records. The diversity of dietary habits across countries was taken into account in these questionnaires and reflected in the EPIC food composition database (including more than 10,000 items).

### uNS-NPS dietary index computation

Every food and beverage item in the EPIC food composition database was attributed a uNS-NPS score. Details of the uNS-NPS score computation are available in Supplementary Methods and have been published elsewhere.[24] Briefly, points are allocated based on the composition per 100 g of food (fresh, non-mixed foods and composite dishes) or 100 mL of beverage following specific grids: 'A points' for 4 components that should be limited: sugars (g), saturated fatty acids (g), salt (g), and energy (kJ); and 'C points' for 3 components that should be promoted: dietary fibre (g), protein (g) and specific ingredients (%), that is, fruits, vegetables, and pulses. The latter percentage content was derived using standard recipes for composite dishes. The sum of 'C points' is then subtracted from the sum of 'A points' to derive the uNS-NPS score. The uNS-NPS is therefore on a discrete continuous scale, theoretically ranging from −17 to +55 points, with higher uNS-NPS scores reflecting lower relative nutritional quality.

To characterize the nutritional quality of an individual's diet according to the food-level uNS-NPS score, a dietary index (uNS-NPS DI, individual-level score) was computed. The uNS-NPS DI was calculated as the sum of the uNS-NPS score for each food/beverage consumed, weighted by the amount of energy consumed from this product (energy content per 100 g multiplied by the daily intake estimated from the baseline dietary questionnaires), and divided by the total amount of energy intake. The following equation was used,[25] where $uNS_i$ is the score of food/beverage i, $E_i$ is the energy intake from food/beverage i, and $n$ is the number of foods/beverages consumed:

$$\text{uNS-NPS DI} = \frac{\sum_{i=1}^{n} (\text{uNS}_i \text{E}_i)}{\sum_{i=1}^{n} \text{E}_i}$$

By design, a higher uNS-NPS DI reflects an overall lower nutritional quality of the diet.

### Cardiovascular event ascertainment

Data on cardiovascular events during follow-up were retrieved from self-reported questionnaires and/or linkage with several registries of morbidity and/or mortality, depending on the centres/countries. EPIC centres were asked to ascertain and validate the first cardiovascular events. Cardiovascular events were either coronary heart disease events (ICD-10 codes I20–I25), including mainly myocardial infarction (I21, I22), or cerebrovascular events (I60–I69, F01), including mainly stroke (I60–I64). The events were validated via medical records, hospital notes, contact with medical professionals, death certificates, or verbal autopsy, either for all suspected events (Denmark, Germany, Italy, Spain) or for a subset of events (Sweden, the Netherlands, UK).[22] The end of follow-up for cardiovascular events ranged from 2003 to 2010, depending on the centres/countries. Participants experiencing a first cardiovascular event (fatal or non-fatal) during the follow-up period qualified as valid first incident cardiovascular event for our analyses.

### Statistical analyses

From the initial EPIC sample (n = 521,323), we excluded participants from Greece, France, and Norway due to unavailable data. Further exclusion criteria included lack of follow-up data, absence of baseline lifestyle questionnaires or dietary data, and energy intake-to-requirement ratios within the highest and lowest percentile. Participants reporting a cardiovascular event (myocardial infarction or stroke) prior to their inclusion in the EPIC study were no longer eligible for a first cardiovascular event and therefore neither included in our analyses. In addition, participants experiencing a cardiovascular event within the first two years of follow-up were excluded (as done previously).[26–29] This was to limit the potential for reverse causality bias, given that participants at higher risk for cardiovascular at baseline might report a healthier diet due to recent changes of behaviours induced by a pre-disease state before baseline assessment (flowchart provided in Supplementary Figure S1).

The associations between the uNS-NPS DI (assessed from baseline dietary data) and cardiovascular events (diagnosed during the follow-up period) were examined using time-to-event Cox proportional hazards regression models with age as the underlying time scale. We confirmed that the assumption of proportional hazards, that is, that the ratio of hazards comparing individuals is constant over time, was satisfied through examination of the Schoenfeld residuals, showing no specific pattern (Supplementary Figure S2). Cardiovascular events were considered overall and by subtype, using cause-specific models for coronary heart disease events (overall and MI) and cerebrovascular events (overall and stroke). Participants contributed with person-time to the analyses from their age at inclusion until their age at first cardiovascular event (fatal or non-fatal; coronary heart disease or cerebrovascular event, respectively, in cause-specific analyses), death, loss of follow-up (information no longer available regarding the health status), or end of the centre-specific follow-up period, whichever occurred first. In cause-specific models, participants may contribute to both a first coronary heart disease event and a first cerebrovascular event but they contributed only to one first cardiovascular event in the overall model. In the myocardial infarction and stroke cause-specific models, participants who had a coronary heart disease other than myocardial infarction or a cerebrovascular event other than stroke were censored at the date of that event. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed from multivariable Cox models stratified by age at recruitment (1-year intervals) and study centre[30] to account for differences in centres (and therefore countries) characteristics. Models included the following baseline confounders and cardiovascular risk factors: age (timescale), gender, educational level, total physical activity, smoking status and intensity, intakes of alcohol and energy, BMI, height and personal history of high blood pressure, high cholesterol, and diabetes. The uNS-NPS DI was analysed as a continuous variable using an increment of 1 standard deviation (SD; 2.4 points of score). The linearity assumption of the associations was explored using restricted cubic splines with 3 knots (5th, 50th and 95th percentiles).[31]

Missing data on covariates at baseline were handled with the Multiple Imputation by Chained Equations (MICE) method,[32] using linear or logistic regression and full conditional specification (10 imputed datasets): physical activity—n = 31,277 (9.0%), educational level—n = 12,399 (3.6%), smoking status and intensity—n = 2663 (0.8%), BMI—n = 2918 (0.8%), personal history of high blood pressure—n = 9398 (2.7%), personal history of high cholesterol—n = 51,745 (15.0%), and personal history of diabetes—n = 2596 (0.7%).

Tests for interactions were performed between the uNS-NPS DI and the following variables using the Wald test: gender, physical activity (active, moderately active, moderately inactive, inactive), smoking status (never, former, current smokers), BMI (</≥ 25 $kg/m^2$), alcohol intake (</≥ gender-specific median value).

Sensitivity analyses were performed: (a) without adjustment; (b) using the previous version of the algorithm underlying the Nutri-Score (FSAm-NPS); (c) without excluding cases diagnosed within the first 2 years of follow-up; (d) without adjustment for cardiovascular risk factors (BMI and personal history of high blood pressure, high cholesterol and diabetes); (e) excluding participants with prevalent cardiovascular risk factors (high blood pressure, high cholesterol or diabetes) at baseline; (f) without multiple imputation, that is, instead, imputing missing data on height and weight with centre-, age- and gender-specific average values and introducing a "missing" class for missing data on categorical covariates; (g) restricting to participants aged ≥45 years; (h) with additional adjustment for the proportion of ultra-processed food intake[29,33] in the diet (%); (i) with additional adjustment for country; (j) using inverse probability weighting[34,35] to account for differences between the characteristics of participants reaching a complete follow-up by centre (end of follow-up for each centre, date of cardiovascular event or date of death) and those who did not (details in Supplementary Table S5). Analyses were also conducted separately by country.

All tests were two-sided. SAS version 9.4 (SAS Institute) was used for the analyses.

### Role of the funding source

The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

## Results

Applying all exclusion criteria (see flowchart in Supplementary Figure S1) resulted in an analytical sample of 345,533 participants.

Baseline characteristics of the participants (63.3% women, mean age: 51.1 [standard deviation (SD): 10.5] years) are shown in Table 1 (unadjusted cross-sectional description). Participants with a higher uNS-NPS DI score (reflecting a lower nutritional value of the overall diet) were more likely to be smokers and physically inactive but also more likely to have a lower BMI and a lower prevalence of high blood pressure, high cholesterol, and diabetes. Consistent with the uNS-NPS DI score computation, they displayed unhealthier dietary intakes (higher intakes of energy, sugar, total fats, processed meat, sweet beverages, and ultra-processed foods; lower intakes of dietary fibre, fruit, vegetables, and fish). The distribution of the uNS-NPS DI scores (mean 8.1 [SD: 2.4]) overall and by gender, age, and country is available in Supplementary Figure S3. uNS-NPS DI scores were lower in participants from Spain (median: 5.5 (interquartile range: 4.0–7.1)), intermediate in those from Italy (7.6 (6.5–8.8)), and higher in participants from Denmark (8.3 (6.8–9.7)), The Netherlands (8.5 (7.3–9.7)), the UK (8.4 (6.6–10.3)), Sweden (8.6 (7.1–10.1)), and Germany (8.8 (7.5–10.0)).

During a median follow-up of 12.3 years (4,103,133 person-years overall, with follow-up by country shown in Supplementary Table S1), 16,214 first cardiovascular events occurred, comprising 11,009 coronary heart disease events (6565 myocardial infarction) and 6669 cerebrovascular events (6245 strokes). Fig. 1 displays the associations between the uNS-NPS DI and the risk of cardiovascular events. A higher uNS-NPS DI score was associated with higher risk of cardiovascular diseases ($HR_{1\text{-SD increment}}$ = 1.03 (95% CI 1.01–1.05)), myocardial infarction (HR = 1.03 (1.01–1.07)), cerebrovascular diseases (HR = 1.04 (1.01–1.07)) and stroke (HR = 1.04 (1.01–1.07)), while there was no clear association with overall coronary heart disease events (HR = 1.01 (0.99–1.03)). In restricted cubic spline analyses (Fig. 2), no formal evidence of non-linearity was observed for the outcomes except for myocardial infarction (P-interaction = 0.04). There seemed to be a potential threshold

| | All (N = 345,533) | Gender-specific quintiles of the uNS-NPS DI score[a] | | | | |
|---|---|---|---|---|---|---|
| | | Q1 (N = 69,146) | Q2 (N = 69,095) | Q3 (N = 69,114) | Q4 (N = 69,099) | Q5 (N = 69,079) |
| | N (%[b]) | N (%[c]) | N (%[c]) | N (%[c]) | N (%[c]) | N (%[c]) |
| **uNS-NPS DI Score** | 8.1 (2.4) | 4.7 (1.3) | 6.9 (0.5) | 8.1 (0.5) | 9.3 (0.5) | 11.4 (1.3) |
| **Age (years)**—mean (SD) | 51.1 (10.5) | 51.1 (9.8) | 51.1 (10.0) | 50.9 (10.4) | 50.9 (10.7) | 51.3 (11.6) |
| **Gender** | | | | | | |
| Men | 126,687 (36.7) | 25,361 (20.0) | 25,324 (20.0) | 25,345 (20.0) | 25,335 (20.0) | 25,322 (20.0) |
| Women | 218,846 (63.3) | 43,785 (20.0) | 43,771 (20.0) | 43,769 (20.0) | 43,764 (20.0) | 43,757 (20.0) |
| **Country** | | | | | | |
| Italy | 45,000 (13.0) | 8324 (18.5) | 12,888 (28.6) | 11,033 (24.5) | 8101 (18) | 4654 (10.3) |
| Spain | 40,026 (11.6) | 24,347 (60.8) | 7638 (19.1) | 3893 (9.7) | 2415 (6.0) | 1733 (4.3) |
| United Kingdom | 72,599 (21.0) | 13,908 (19.2) | 12,199 (16.8) | 12,173 (16.8) | 13,304 (18.3) | 21,015 (29.0) |
| The Netherlands | 36,777 (10.6) | 3160 (8.6) | 7299 (19.9) | 9254 (25.2) | 9773 (26.6) | 7291 (19.8) |
| Germany | 50,407 (14.6) | 4740 (9.4) | 8532 (16.9) | 11,431 (22.7) | 13,460 (26.7) | 12,244 (24.3) |
| Sweden | 47,922 (13.9) | 6138 (12.8) | 9548 (19.9) | 9860 (20.6) | 10,364 (21.6) | 12,012 (25.1) |
| Denmark | 52,802 (15.3) | 8529 (16.2) | 10,991 (20.8) | 11,470 (21.7) | 11,682 (22.1) | 10,130 (19.2) |
| **Educational level**[d] | | | | | | |
| None | 14,767 (4.3) | 8737 (59.2) | 2822 (19.1) | 1486 (10.1) | 1003 (6.8) | 719 (4.9) |
| Primary school | 95,675 (27.7) | 20,294 (21.2) | 19,147 (20.0) | 18,614 (19.5) | 18,275 (19.1) | 19,345 (20.2) |
| Technical/professional school | 91,285 (26.4) | 13,741 (15.1) | 17,048 (18.7) | 18,894 (20.7) | 20,227 (22.2) | 21,375 (23.4) |
| Secondary school | 51,145 (14.8) | 8803 (17.2) | 11,273 (22.0) | 11,248 (22.0) | 10,660 (20.8) | 9161 (17.9) |
| Longer education (incl. University degree) | 80,262 (23.2) | 15,045 (18.7) | 16,739 (20.9) | 16,837 (21.0) | 16,766 (20.9) | 14,875 (18.5) |
| **Physical activity**[e] | | | | | | |
| Inactive | 56,759 (16.4) | 10,082 (17.8) | 10,956 (19.3) | 11,535 (20.3) | 12,002 (21.2) | 12,184 (21.5) |
| Moderately inactive | 90,390 (26.2) | 17,053 (18.9) | 17,368 (19.2) | 17,753 (19.6) | 18,304 (20.3) | 19,912 (22.0) |
| Moderately active | 132,181 (38.3) | 29,788 (22.5) | 26,230 (19.8) | 25,420 (19.2) | 25,389 (19.2) | 25,354 (19.2) |
| Active | 34,926 (10.1) | 6893 (19.7) | 6613 (18.9) | 7090 (20.3) | 7175 (20.5) | 7155 (20.5) |
| **Smoking status and intensity**[f] | | | | | | |
| Never | 153,900 (44.5) | 34,118 (22.2) | 30,579 (19.9) | 30,148 (19.6) | 29,926 (19.5) | 29,129 (18.9) |
| Current, 1–15 cigarettes/day | 42,660 (12.4) | 6925 (16.2) | 8234 (19.3) | 8638 (20.3) | 9206 (21.6) | 9657 (22.6) |
| Current, 16–25 cigarettes/day | 22,915 (6.6) | 3297 (14.4) | 4105 (17.9) | 4483 (19.6) | 5059 (22.1) | 5971 (26.1) |
| Current, 26+ cigarettes/day | 5734 (1.7) | 951 (16.6) | 1016 (17.7) | 1054 (18.4) | 1192 (20.8) | 1521 (26.5) |
| Current, pipe/cigar/occasional | 17,763 (5.1) | 4218 (23.8) | 4031 (22.7) | 3677 (20.7) | 3160 (17.8) | 2677 (15.1) |
| Former, quit ≤10 years | 34,815 (10.1) | 7421 (21.3) | 7074 (20.3) | 7006 (20.1) | 6742 (19.4) | 6572 (18.9) |
| Former, quit 11–20 years | 30,334 (8.8) | 5884 (19.4) | 6544 (21.6) | 6323 (20.8) | 6071 (20) | 5512 (18.2) |
| Former, quit >20 years | 29,259 (8.5) | 5160 (17.6) | 6049 (20.7) | 6113 (20.9) | 6029 (20.6) | 5908 (20.2) |
| Current/Former, missing intensity | 5490 (1.6) | 786 (14.3) | 1006 (18.3) | 1185 (21.6) | 1233 (22.5) | 1280 (23.3) |
| **BMI (kg/m$^2$)**—mean (SD) | 25.7 (4.2) | 26.5 (4.4) | 25.9 (4.1) | 25.7 (4.1) | 25.5 (4.1) | 25.2 (4.2) |
| **Personal history of diseases** | | | | | | |
| High blood pressure (yes) | 63,889 (18.5) | 14,039 (22.0) | 13,316 (20.8) | 13,075 (20.5) | 12,463 (19.5) | 10,996 (17.2) |
| High cholesterol (yes) | 44,482 (12.9) | 12,305 (27.7) | 9759 (21.9) | 8756 (19.7) | 7638 (17.2) | 6024 (13.5) |
| Diabetes (yes) | 8246 (2.4) | 3289 (39.9) | 1879 (22.8) | 1346 (16.3) | 999 (12.1) | 733 (8.9) |
| **Dietary intakes**—mean (SD) | | | | | | |
| Alcohol (g/d) | 12.7 (17.7) | 12.5 (19.1) | 12.8 (17.6) | 13.1 (17.4) | 13.1 (17.4) | 12.1 (16.9) |
| Energy (kcal/d) | 2099 (627) | 1912 (599) | 2014 (596) | 2089 (602) | 2170 (614) | 2308 (650) |
| Carbohydrates (g/d) | 234.2 (75.8) | 217.7 (71.2) | 228.4 (73.0) | 233.6 (74.1) | 239.2 (75.2) | 252 (80.7) |
| Sugar (g/d) | 106.8 (45.5) | 95.1 (39.5) | 98.6 (39.0) | 103.2 (41.1) | 110.3 (44.6) | 126.5 (54.5) |
| Proteins (g/d) | 86.5 (27.7) | 87.8 (29.7) | 86.8 (28.1) | 86.8 (27.4) | 86.5 (26.9) | 84.7 (26.4) |
| Total fats (g/d) | 80.6 (29.5) | 66.7 (27.1) | 73.6 (25.7) | 79.4 (26.1) | 86 (27.4) | 97 (31.4) |
| Dietary fibre (g/d) | 23.1 (8.0) | 26.3 (9.3) | 23.8 (7.9) | 22.8 (7.4) | 21.9 (7.1) | 20.5 (6.9) |
| Vegetables (g/d) | 185.1 (123.4) | 251 (158.5) | 191.9 (119.6) | 171.8 (106.1) | 158.9 (98.6) | 152 (97.0) |
| Fruits, nuts and seeds (g/d) | 232.4 (184.2) | 337.8 (244.3) | 256.8 (181.5) | 218.9 (156.4) | 189.7 (137.6) | 158.9 (120.2) |
| Dairy products (g/d) | 344.5 (247) | 351.7 (273.6) | 367.2 (262.5) | 354.4 (246.6) | 336.3 (230.6) | 312.8 (213.6) |
| Fish and shellfish (g/d) | 32.6 (31.1) | 45.2 (41.1) | 32.6 (29.5) | 29.7 (26.9) | 28.1 (26.0) | 27.4 (25.5) |
| Red meat (g/d) | 43.1 (36.4) | 37 (35.6) | 42.4 (35.9) | 45.1 (36.4) | 46.6 (37.0) | 44.1 (36.3) |

(Table 1 continues on next page)

| | All (N = 345,533) | Gender-specific quintiles of the uNS-NPS DI score[a] | | | | |
|---|---|---|---|---|---|---|
| | | Q1 (N = 69,146) | Q2 (N = 69,095) | Q3 (N = 69,114) | Q4 (N = 69,099) | Q5 (N = 69,079) |
| | N (%[b]) | N (%[c]) | N (%[c]) | N (%[c]) | N (%[c]) | N (%[c]) |
| (Continued from previous page) | | | | | | |
| Processed meat (g/d) | 33.2 (32.5) | 20.2 (20.8) | 27.0 (24.0) | 33.0 (28.1) | 39.7 (33.7) | 46.0 (43.9) |
| Sweet beverages (g/d) | 154.8 (218.4) | 106.5 (185.7) | 138.0 (202.3) | 158.9 (215.1) | 178.4 (229.1) | 192.0 (244.2) |
| Ultraprocessed foods (%)[g] | 32.8 (14.7) | 21.9 (13.8) | 28.4 (13.0) | 32.6 (12.4) | 36.9 (11.8) | 44.3 (12.0) |

Frequencies are presented, unless otherwise specified. Abbreviations: BMI, body mass index; DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; uNS-NPS, Nutrient Profiling System underlying the Nutri-Score; SD, standard deviation. [a]Cut-offs for gender-specific quintiles of the uNS-NPS DI were, for women: 5.90/7.28/8.43/9.78, for men: 6.53/7.95/9.09/10.41. A higher uNS-NPS DI indicates a lower nutritional quality of the foods consumed. [b]Column percentages. [c]Row percentages. [d]N = 333,134. [e]N = 314,256; Cambridge index based on occupational physical activity and other physical exercise, including cycling. [f]N = 342,870. [g]N = 330,213.

*Table 1:* **Baseline characteristics of the participants overall and by gender-specific quintiles of the uNS-NPS DI score, EPIC cohort study.**

effect for myocardial infarction, with associations observed only for the highest values of the uNS-NPS DI score. In terms of absolute risk reduction, participants with the lowest uNS-NPS DI scores (highest diet nutritional quality), had 126 cases per 100,000 person-years less than participants with the highest uNS-NPS DI scores (364 vs. 490 cardiovascular events per 100,000 person-years in the first vs. fifth gender-specific quintile of the uNS-NPS DI). Hence, 790 people would have to adopt a healthier diet in order to avoid 1 cardiovascular event (number needed to treat).

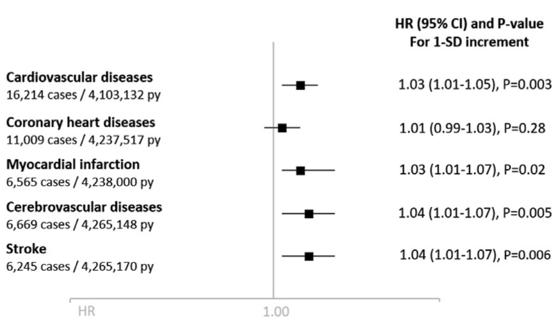


*Fig. 1:* **Associations between the uNS-NPS DI and cardiovascular diseases, multivariable Cox proportional hazards regression models [a], EPIC cohort study, 1992–2010.** The models used age as the time scale and were stratified by age (1-y interval) and study centre and adjusted for gender, body mass index, educational level (longer education, including university degree; technical/professional school; secondary school; primary school; none), total physical activity (Cambridge index based on occupational physical activity and other physical exercise, including cycling; gender-specific categories: active; moderately active; moderately inactive; inactive), smoking status, duration and intensity (current, 1–15 cigarettes/d; current, 16–25 cigarettes/d; current, ≥26 cigarettes/d; current, pipe/cigar/occasional; current/former, missing intensity; former, quit ≤10 y; former, quit 11–20 y; former, quit >20 y; never smoker), alcohol and energy intakes (continuous), and personal history of high blood pressure, high cholesterol and diabetes. A higher uNS-NPS DI indicates a lower nutritional quality of the foods consumed. The SD for the uNS-NPS DI was 2.4. Abbreviations: CI, confidence interval; DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; uNS-NPS, Nutrient Profiling System underlying the Nutri-Score; HR, hazard ratio; py, person-years; SD, standard deviation.

There was no interaction between the uNS-NPS DI and gender, physical activity or alcohol intake with respect to outcome status (Supplementary Tables S2 and S3). Per journal style we show results separately for men and women in Supplementary Table S2. Although in the same direction for both genders, associations were statistically significant in men but not in women. This could result from a lower proportion of events and therefore a lower power in women since there was no indication of statistical heterogeneity (all P for interaction with gender >0.10). However, interactions were detected with BMI for cerebrovascular events (P-interaction = 0.06) and stroke (P-interaction = 0.02) but not for cardiovascular, coronary heart diseases and MI; and with smoking status for overall cardiovascular (P-interaction = 0.008), coronary heart diseases (P-interaction = 0.004) and myocardial infarction (P-interaction = 0.007) but not for cerebrovascular events or stroke (Supplementary Table S2). Associations with cerebrovascular events and stroke were more apparent in overweight or obese participants (BMI ≥25 $kg/m^2$): HR = 1.07 (1.03–1.11) and 1.07 (1.03–1.12), respectively, while associations with cardiovascular, coronary heart diseases and myocardial infarction were more pronounced in current smokers: HR = 1.09 (1.05–1.12), 1.09 (1.05–1.13) and 1.11 (1.06–1.17), respectively (Supplementary Table S2).

Analyses by country suggested stronger exposure-outcome associations in countries with higher uNS-NPS DI scores, larger variability in uNS-NPS DI scores, and higher number of cardiovascular events (Denmark, Sweden, UK) (Supplementary Table S4).

Sensitivity analyses (a-c, f-j) provided similar results overall (Supplementary Table S5). Analyses without adjustment for cardiovascular risk factors (d) were no longer significant, except for an inverse association observed with the risk of coronary heart diseases. Analyses excluding participants with prevalent cardiovascular risk factors at baseline (e) were weakened. The association with myocardial infarction remained

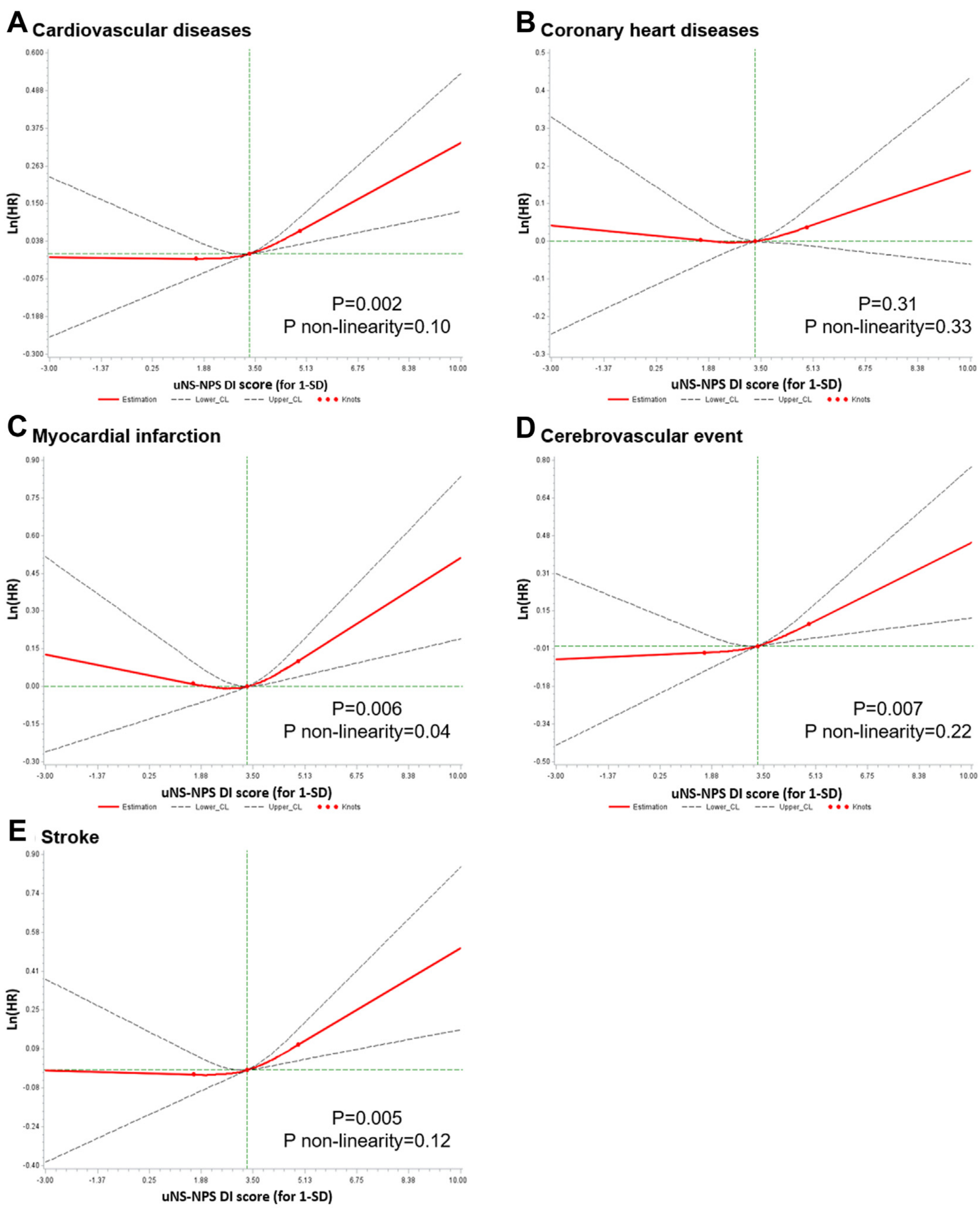


***Fig. 2:*** **Associations between the uNS-NPS DI and Cardiovascular diseases (A), Coronary heart diseases (B), Myocardial infarction (C), Cerebrovascular diseases (D), and Stroke (E), non-linear modelling using restricted cubic splines, EPIC cohort study, 1992–2010.** A higher uNS-NPS DI indicates a lower nutritional quality of the foods consumed. The Cox proportional hazards model used age as the time scale and was stratified by age (1-y interval) and study centre and adjusted for gender, body mass index (continuous), height (continuous), educational level (longer education, including university degree; technical/professional school; secondary school; primary school; none), total physical activity (gender-specific categories: active; moderately active; moderately inactive; inactive), smoking status, duration and intensity (current, 1–15 cigarettes/d; current, 16–25 cigarettes/d; current, ≥26 cigarettes/d; current, pipe/cigar/occasional; current/former, missing intensity; former, quit ≤10 y; former, quit 11–20 y; former, quit >20 y; never smoker), alcohol and energy intakes (continuous), and personal history of high blood pressure, high cholesterol and diabetes. Abbreviations: DI, Dietary Index; EPIC, European Prospective Investigation into Cancer and Nutrition; uNS-NPS, Nutrient Profiling System underlying the Nutri-Score; HR, hazards ratio. The 3 knots were set at the 5th, 50th (reference value), and 95th percentiles, as described in Desquilbet and Mariotti,[31] of the uNS-NPS DI distribution. The dashed lines are 95% confidence intervals.

statistically significant (HR = 1.05 (1.01–1.09)) while the other associations were borderline significant (HR = 1.02 (1.00–1.05) for cardiovascular diseases, and 1.03 (0.99–1.07) for cerebrovascular diseases and for stroke). Associations with cerebrovascular diseases and stroke remained statistically significant after additional adjustment for the proportion of ultra-processed food intake in the diet (g).

## Discussion

This study aimed to investigate the association between the uNS-NPS scores of foods consumed (that is, the 2023-updated algorithm behind the Nutri-Score) and cardiovascular disease risk, utilizing data from 7 European countries. Our results suggested that diets with a higher uNS-NPS DI score (corresponding to foods with less favourable Nutri-Score and reflecting a lower nutritional quality) were associated with a higher risk of overall cardiovascular diseases, particularly of myocardial infarction and stroke.

Previous studies on this subject were based on the former version of the nutrient profile underlying Nutri-Score (called FSA-NPS or FSAm-NPS). In the French cohorts SU.VI.MAX (181 cardiovascular events)[17] and NutriNet-Santé (509 cardiovascular events),[18] higher FSAm-NPS DI scores (lower overall nutritional quality of the diet) were also associated with higher cardiovascular risks, specifically for coronary heart diseases in NutriNet-Santé (262 events). These two studies were meta-analyzed recently, resulting in a pooled HR associated with a 2-unit increase of 1.08 (95% CI: 1.00, 1.18; $I^2$: 70%).[19] In the EPIC-Norfolk cohort,[36] the FSA-NPS (original version of the nutritional profile) was used to categorize foods as *healthier* or *less healthy*, applying a binary cut-off set by the UK's communications regulator (Ofcom). The authors did not find associations between the consumption of *less healthy* foods and cardiovascular diseases incidence (4965 events) or mortality (1524 events). Similarly, in the Whitehall II cohort,[37] no association was observed between the variety of *healthier* food products consumed (categorized according to the FSA-NPS and the Ofcom's cut-off) and the incidence of coronary heart diseases (318 events). The reason for the different findings may relate to the use of the uNS-NPS on a continuous scale at the food-level in our study (vs. 2-category *healthier/less healthy*), most likely resulting in a more refined discrimination of the nutritional quality of food products and a better ranking of participants according to their diets.

Focusing on cardiovascular mortality as the outcome, we previously reported a small association between a higher FSAm-NPS DI score and a higher mortality rate from diseases of the circulatory system in the EPIC cohort (13,246 events).[15] In Italy and Spain associations were reported between the FSAm-NPS DI score and cardiovascular mortality in the Moli-sani (792 events) and ENRICA (140 events) cohort studies,[14,16] while no association was observed in the SUN cohort (83 events).[13] Finally, a study conducted in Australia,[38] which defined diet quality with the Health Star Rating (HSR) system (another variation of the original FSA-NPS), also observed that a higher quality of the foods consumed was associated with lower rates of cardiovascular mortality.

Regarding intermediate cardiovascular risk factors, in the Spanish PREDIMED-plus study, an increase in the FSAm-NPS DI score after 1 year of follow-up was associated with an increase in plasma glucose and triglyceride concentrations as well as with an increase in diastolic blood pressure, BMI, and waist circumference.[20] In the Italian Moli-sani study,[16] cross-sectional associations were observed between the FSAm-NPS DI and higher diastolic blood pressure and concentrations of biomarkers related to glucose (insulin, C-peptide) or lipid (apolipoprotein B100) metabolism, renal function (cystatin-C) or inflammation (C reactive protein), but also lower concentrations of blood glucose, HDL-cholesterol, triglycerides or lipoprotein (a). In addition, a cross-sectional study in the UK (Airwave Health Monitoring Study, N = 5848)[39] used the UK nutrient profile (NP) model (based on the original FSA-NPS) and showed that the NP score was consistent with a score reflecting adherence to the Public Health England's dietary policy for optimal health and prevention of cardiovascular diseases. In this cross-sectional study, a higher NP score (reflecting a higher nutritional quality of the foods consumed) was associated with lower HbA1c and total cholesterol concentrations but also with higher BMI. This cross-sectional association between a higher dietary quality and a higher BMI, when assessed simultaneously, is not unusual and was also observed in our study, as participants with the lowest uNS-NPS DI scores tended to have higher BMI and prevalence of cardiovascular risk factors in unadjusted cross-sectional comparison from Table 1. Although this observation could relate to differences in diet quality and BMI levels across countries, or underreporting of dietary intakes in individuals with higher BMI or cardiovascular risk factors,[40] it may also reflect improved diet quality in individuals at higher risk of cardiovascular diseases, following medical advice. Indeed, since we collected the current usual diet of participants at baseline, we cannot say if that diet had recently changed (prior to study baseline), either due to underlying health conditions or medical advices. Hence, for some participants reporting that they already have metabolic disturbances at baseline (overweight/obesity, high blood cholesterol, diabetes), the current diet reported at baseline may no longer reflect the past diet leading to their metabolic condition. This results in a situation where participants with existing metabolic conditions and higher risks of cardiovascular diseases report the healthiest diets (as illustrated in Table 1), potentially leading to some reverse causality bias. Thus, inference of associations cannot be drawn from Table 1 because of major reverse causality and confounding bias. In contrast, our prospective models carefully accounted for various potential confounding factors, including BMI and metabolic disturbances to account for differences in risk, behaviours and treatments between individuals with and without cardiovascular risk factors. In these models, despite the cross-sectional pattern of associations at baseline between a higher proportion of metabolic risk factors and a higher diet quality that would tend to drive associations in the reverse direction, significant associations were observed between a lower diet quality (higher uNS-NPS DI) and higher cardiovascular diseases risk. Sensitivity analyses were run without adjustment for- or excluding individuals with-prevalent metabolic disturbances. The first one led to non-significant results and an inverse association with the risk of coronary heart diseases, which tends to support our hypothesis of reverse causality bias, and the second one led to weakened associations (association with myocardial infarction remained statistically significant while the three others were only borderline significant), likely due to a selection bias towards very healthy participants (which is not methodologically recommended)[41] and a loss of statistical power.

Our analyses suggested some interactions of BMI and smoking status in the association between the uNS-NPS DI scores and cardiovascular outcomes, with stronger associations in overweight or obese participants for cerebrovascular events and stroke and stronger associations in current smokers for cardiovascular diseases, coronary heart diseases, and myocardial infarction. Because overweight and smoking are strong risk factors for cardiovascular events, such results could be due to a higher incidence, hence a higher statistical power, in the overweight and smoker categories. The findings could also indicate a synergistic effect between a lower diet quality and these cardiovascular risk factors.

RCS analyses only indicated a non-linear exposure-outcome association for myocardial infarction. A potential threshold effect was observed, meaning that an increased risk of myocardial infarction would only occur above a certain level of the uNS-NPS DI score.

In a recent study based on the Open Food Facts database of 129,950 food products on the French market, we showed that only 5.3% of ultra-processed foods were ranked NutriScore 'A' (lowest values of the uNS-NPS).[42] Overall, these foods present a lower nutritional quality on average than minimally processed foods. Thus, unsurprisingly, additional adjustment for the proportion of ultra-processed foods led to some attenuation of the studied relationships of uNS-NPS DI with cardiovascular diseases and myocardial infarction (overadjustement). However, associations with cerebrovascular diseases and stroke remained significant, illustrating the fact that food (ultra)processing and nutritional profile are two complementary dimensions that also have independent effects on human health.[43]

The uNS-NPS was created based on the existing scientific data regarding the associations between the nutritional factors included in the score and different health outcomes.[44] For each component of the uNS-NPS, there is abundant scientific literature and high level of evidence with respect to mechanistic and epidemiological data regarding the protective (e.g., dietary fibre, fruits and vegetables) or deleterious (e.g., sodium, sugar) effects on health outcomes, including cardiometabolic health. The uNS-NPS score is, therefore, consistent with current knowledge on the nutritional risk factors and dietary target priorities for cardiovascular health[45,46] as well as with the constitution of a healthy diet according to the *Global Burden of Disease* and World Health Organization.[1,47,48] Such consistency is reflected in the distribution of the uNS-NPS DI scores across countries in our data, with countries traditionally following a Mediterranean dietary pattern (Spain and Italy) exhibiting the lowest uNS-NPS DI scores (highest nutritional quality of the diet on average). As a perspective, other analyses are ongoing in the EPIC cohort to explore how the uNS-NPS DI relate to biomarkers in the potential mechanistic pathways between nutrition and health.

Our study had several strengths, including its prospective design with a long follow-up period, the large number of cardiovascular events, and the multinational European context with various dietary habits and phenotypes that were extensively characterized within the framework of the EPIC study. Some limitations should, however, be acknowledged. The data collection via questionnaires may have induced some misclassification from imprecision in the reporting of exposure and covariates. In particular, dietary intakes were assessed through FFQs in most centres, a method that provides a good estimation of usual dietary intakes but with more limited discrimination of the nutritional quality of individual food products (compared to, for example, repeated 24-h dietary records, as were used in the SU.VI.MAX and NutriNet-Santé cohorts).[17,18] Because of the prospective design, any measurement error was likely non-differential with regard to case/non-case status, but it could still have resulted in some underestimation or overestimation of the associations. The assessment of dietary intakes was only performed once at baseline and we were unable to consider potential changes in food consumption over time. Nevertheless, baseline estimations are considered to reflect dietary habits throughout middle-age adulthood,[49] which is likely to influence the onset of chronic diseases later in life. In addition, information regarding cardiovascular risk factors was not available after baseline, which prevented the investigation of mediation effects. The definition of cardiovascular events differed between EPIC centres, with some centres only considering myocardial infarction as coronary heart disease event. Hence, this may have resulted in a higher incidence rate of myocardial infarction as the first coronary heart disease event in these centres but not necessarily in bias in the exposure-outcome association. Exhaustive information regarding medical care or treatment for hypertension, hypercholesterolemia or diabetes during the entire follow-up was not available and therefore could not be accounted for. Because the baseline status regarding these risk factors was defined based on self-declaration by the participants, it is likely that they receive some kind of related medical treatment or care. Diet quality constitutes a recognized risk factor for cardiovascular diseases[1] and studies showed that diet quality was associated to cardiovascular risk including recurrent cardiovascular diseases in populations with prevalent cardiovascular diseases or diabetes regardless of their treatment.[50] Hence, diet can still play a role in the development of cardiovascular diseases in addition to treatment. In addition, EPIC participants were volunteers from Western Europe (ethnicity not documented), involved in a long-term cohort study investigating the association between nutrition and health. Thus, participants probably had more health-conscious behaviours and less unhealthy dietary behaviours compared to the general population and caution is needed when extrapolating the results to other populations worldwide, or minority ethnic groups in Western Europe. Finally, this study was conducted using an observational design, meaning that a certain degree of residual and unmeasured confounding is expected. Yet, major confounders were carefully considered in our analyses via adjustment, interaction testing or exclusions. Also, the large number of sensitivity analyses confirmed the robustness of our results.

This study adds to the current literature on the health relevance of grading the nutritional quality of foods, specifically using the 2023-updated version of the nutrient profile underlying Nutri-Score, by providing new evidence on cardiovascular disease risk at a multi-country European scale. Assessing the relevance of the nutrient profile is only one aspect of the validation of a labelling system and other studies have focused on the graphical design of the Nutri-Score, evaluating the perception and understanding, the impact on food choices, and on nutritional quality of purchases.[51] Overall, the available evidence supports the usefulness and importance of the Nutri-Score and its profiling system as tools to guide consumers in their food choices. In 2022, the Organisation for Economic Co-operation and Development (OECD) estimated that, based on all published data, transferring the Nutri-Score to all OECD countries would result in a reduction of around 1.6 million cardiovascular disease cases by 2050.[52] Beyond front-of-pack nutrition labelling, Nutri-Score and its underlying nutrient profile are already planned to be used in other settings (e.g., unpacked food products and collective catering) and can also be used for other public health nutrition policies (e.g., regulation of advertisement and taxation).[8]

To conclude, in this large cohort study from 7 European countries, the consumption of foods with a less favourable uNS-NPS score was associated with a higher risk of cardiovascular diseases in general and myocardial infarction and stroke in particular. This adds support to the relevance of the Nutri-Score grading system (using the 2023-updated version) to characterize the nutritional and health value of food products in a multi-country and multi-cultural European population with diverse dietary patterns, and it should be considered in the ongoing discussions regarding a mandatory and harmonized front-of-pack labelling within the EU's Farm-to-Fork strategy.

#### Contributors
The authors' contributions were as follows—MDT, IH, CJ, SH and MT conceptualised the study and defined the analytical strategy; MDT, NA and MT performed statistical analyses and provided preliminary interpretation of findings; MDT and writing group (IH, NA, CJ, SH, BSa, MF, BSr, EKG, LKF, CB, CC, BH, EW, MGMP, NM, HF, PF, MJG, MT) drafted the manuscript; CB, CC, BH, AT, KENP, VK, RK, MS, GM, VP, SP, FR, WMMV, JB, YTvdS, GS, AA, EMM, JMH, CMI, UE, ES, AS, VO, TYNT, AKH, EKA, JD, ER and MJG played a key role in the acquisition of the data, and were active in searching for funding to continue the study. All authors critically helped in the interpretation of results, revised the manuscript and provided relevant intellectual input. They all read and approved the final manuscript. MDT and MT had primary responsibility for the final content, they are the guarantors. The corresponding author (MDT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

#### Data sharing statement
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.

#### Declaration of interests
Guri Skeie reports a leadership role in the National Nutrition Council (Norwegian Directorate of Health). John Danesh reports grants and activities unrelated to the present work: grants from Merck Sharp & Dohme Corporation, Novartis and Astra Zeneca for work outside of the present manuscript; leadership roles in Cambridge University Hospital NHS Foundation Trust (Honorary Consultant), UK Biobank (Steering Committee), MRC International Advisory Group, MRC High Throughput Science 'Omics Panel, and Scientific Advisory Committee for Sanofi (Member), Wellcome Sanger Institute (Faculty Member), Novartis (Advisor). All other authors declare no competing interests.

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IARC disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101006.

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