Association between nutritional profiles of foods underlying Nutri-Score front-of-pack labels and mortality: EPIC cohort study in 10 European countries

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ABSTRACT

OBJECTIVE

To determine if the Food Standards Agency nutrient profiling system (FSAm-NPS), which grades the nutritional quality of food products and is used to derive the Nutri-Score front-of-packet label to guide consumers towards healthier food choices, is associated with mortality.

DESIGN

Population based cohort study.

SETTING

European Prospective Investigation into Cancer and Nutrition (EPIC) cohort from 23 centres in 10 European countries.

PARTICIPANTS

521 324 adults; at recruitment, country specific and validated dietary questionnaires were used to assess their usual dietary intakes. A FSAm-NPS score was calculated for each food item per 100 g content of energy, sugars, saturated fatty acids, sodium, fibre, and protein, and of fruit, vegetables, legumes, and nuts. The FSAm-NPS dietary index was calculated for each participant as an energy weighted mean of the FSAm-NPS score of all foods consumed. The higher the score the lower the overall nutritional quality of the diet.

MAIN OUTCOME MEASURE

Associations between the FSAm-NPS dietary index score and mortality, assessed using multivariable adjusted Cox proportional hazards regression models.

RESULTS

After exclusions, 501 594 adults (median follow-up 17.2 years, 8 162 730 person years) were included in the analyses. Those with a higher FSAm-NPS dietary index score (highest versus lowest fifth) showed an increased risk of all cause mortality (n=53 112 events from non-external causes; hazard ratio 1.07, 95% confidence interval 1.03 to 1.10, P<0.001 for trend) and mortality from cancer (1.08, 1.03 to 1.13, P<0.001 for trend) and diseases of the circulatory system (1.04, 0.98 to 1.11, P=0.06 for trend), respiratory (1.39, 1.22 to 1.59, P<0.001), and digestive (1.22, 1.12 to 1.32, P<0.001) diseases.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Helping consumers make healthier food choices is a major challenge for the prevention of non-communicable diseases and related deaths.

The Food Standards Agency nutrient profiling system (FSAm-NPS), which grades the nutritional quality of food products based on 100 g content of energy, sugars, saturated fatty acids, sodium, fibre and protein, and of fruit, vegetables, legumes, and nuts, underlies the Nutri-Score.

Nutri-Score is a simple nutrition label selected by several countries in Europe and considered at the European Union level as a candidate for enabling uniform food labelling systems.

FSAm-NPS defined nutritional quality of foods has been studied in relation to health but not to mortality in French cohorts, and recently to cancer risk in the large multinational European Prospective Investigation into Cancer and Nutrition (EPIC) cohort; evidence in an international setting for other health outcomes and especially mortality is still needed.

WHAT THIS STUDY ADDS

This study used data from EPIC, a large cohort comprising 501 594 adults from 10 European countries (53 112 deaths), with diverse profiles and dietary patterns and showed that the consumption of foods with higher FSAm-NPS scores (lower nutritional quality) was associated with increased all cause and cause specific mortality.

These results add support to the relevance of using the FSAm-NPS (and the derived Nutri-Score) to characterise healthier food choices as a basis for public health nutritional policies in Europe.

This is an important consideration ongoing and future debates at the EU level on making food labelling systems uniform on the front of food product packaging.

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These results add support to the relevance of using the FSAm-NPS (and the derived Nutri-Score) to characterise healthier food choices as a basis for public health nutritional policies in Europe.

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1.02 to 1.45, P=0.03 for trend) systems. The age standardised absolute rates for all cause mortality per 10 000 persons over 10 years were 760 (men=1237; women=563) for those in the highest fifth of the FSAm-NPS dietary index score and 661 (men=1008; women=518) for those in the lowest fifth.

CONCLUSIONS
In this large multinational European cohort, consuming foods with a higher FSAm-NPS score (lower nutritional quality) was associated with a higher mortality for all causes and for cancer and diseases of the circulatory, respiratory, and digestive systems, supporting the relevance of FSAm-NPS to characterise healthier food choices in the context of public health policies (eg, the Nutri-Score) for European populations. This is important considering ongoing discussions about the potential implementation of a unique nutrition labelling system at the European Union level.

Introduction
Poor nutrition is a major well known risk factor for non-communicable diseases, with an estimated 11 million deaths from such diseases attributed to unhealthy diets worldwide in 2017. Although it is well established that less sugars, saturated fats, salt, and energy and more dietary fibres or fruit and vegetables should be consumed for better health, putting these recommendations into practice remains an important challenge. Helping consumers make healthier food choices could therefore serve as one of the key strategies to prevent mortality from non-communicable diseases. A front-of-pack label providing user friendly information on the nutritional quality of food products has been identified as a possible solution to this problem. Such labels have the potential to help consumers choose food products with a better nutritional quality at the point of purchase, and, simultaneously, to incentivise food manufacturers to improve the nutritional quality of products, thus contributing to a healthier food environment. The Nutri-Score labelling system, which uses five colours, is considered promising in a broad international context. Nutri-Score classifies food products into five categories according to nutritional quality (from category A, indicating higher nutritional quality, to category E, indicating lower nutritional quality) assessed using the Food Standards Agency nutrient profiling system (FSAm-NPS), an adapted version of a nutrient profiling system (FSA-NPS) initially developed by the British Food Standards Agency. This scoring system was developed to prevent a large range of nutrition related non-communicable diseases, by allocating a score to a given food or beverage per 100 g content of energy, saturated fatty acids, sugars, sodium, dietary fibre, and protein, and of fruit, vegetables, legumes, and nuts. 

In 2017, public health authorities in France officially adopted Nutri-Score after a series of studies showed the validity, scientific relevance, and potential public health benefits of the FSAm-NPS and of the Nutri-Score label as a tool for public health nutrition policies (reviewed in ). Subsequently, Belgium, Spain, Germany, the Netherlands, Switzerland, and Luxembourg adopted Nutri-Score. Medical professionals and academic societies in Europe have also recognised the importance and potential public health impact of Nutri-Score as a tool that can be recommended to the general public and patients to guide them towards food choices of higher nutritional quality.

Under current European Union labelling regulations, member states cannot legally enforce the inclusion of a front-of-pack nutrition label such as Nutri-Score, which leaves the choice to food manufacturers. The stakes are therefore high for standardised nutritional labelling systems at the EU level, using a unique mandatory front-of-pack nutrition label. Similar discussions are ongoing in America and Australia. Since most of the original studies assessing the validity of the FSAm-NPS underlying Nutri-Score were performed in France, it is important that the validity of the model is extended to international settings to provide relevant scientific evidence for ongoing discussions in the EU and beyond.

Part of the validity assessment of FSAm-NPS is to study the association between the nutritional quality of food products graded by the scoring system and health outcomes. Such studies, done in the French SU.VI.MAX and NutriNet-Santé cohorts, showed that on average consumption of more food products with lower FSAm-NPS scores (representing higher nutritional quality) was associated with more favourable outcomes for weight gain, asthma symptoms, metabolic syndrome, cardiovascular diseases, and cancer. Recently, we showed that similar observations could be made for cancer risk in a large multinational European cohort, the European Prospective Investigation into Cancer and Nutrition (EPIC) study. In the current study we investigated the association between the FSAm-NPS scores of food products consumed and mortality in this large and diverse European population.

Methods
Study population: EPIC cohort
This study was conducted within the framework of the EPIC cohort study (https://epic.iarc.fr/), which enrolled more than 500 000 volunteers (aged 25-70 years) from 23 centres in 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, and the United Kingdom) between 1992 and 2000. This cohort study investigates metabolic, dietary, lifestyle, and environmental factors associated with the development of cancer and other non-communicable diseases in Europe. All participants gave written informed consent. Details of the study design, recruitment, and data collection are published elsewhere.

Baseline data collection
Information on the participants was obtained during enrolment from questionnaires that covered sociodemographic characteristics, lifestyle factors,
personal and family history of diseases, and, for women, menstrual and reproductive history. Anthropometric measurements, such as height and weight, were performed in all centres at baseline using standard procedures; except in France, the UK, and Norway, where self-reported data were collected. Updated data on weight during follow-up were obtained for a subsample of participants involved in the European Prospective Investigation into Cancer and Nutrition-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating Out of Home and Obesity (EPIC-PANACEA) study.19

Dietary intake assessment
To assess the usual dietary intakes of participants, we used country specific and validated dietary questionnaires at recruitment. Depending on the study centres, these questionnaires were either self-administered or interviewer administered semi-quantitative food frequency questionnaires, with an estimation of individual average portions or with the same standard portion assigned to all participants, or diet history questionnaires, some combining a food frequency questionnaire and seven day dietary records.28 The EPIC food composition database comprises more than 10,000 food and beverage items reflecting the types of food consumed in each country.29 A subset of the EPIC cohort (random samples of 5–12% of participants from each EPIC centre) also completed one computer assisted 24 hour dietary recall (EPIC-SOFT computer program), as part of a calibration study.31

FSAm-NPS dietary index computation
The FSAm-NPS is a modified version of the original nutrient profiling system (FSA-NPS), with slight adaptations to the allocation of points for specific foods (beverages, cheese, and added fats) recommended by the French High Council for Public Health to ensure a proper discrimination of the nutritional quality of products within these groups and a high consistency of the FSAm-NPS score with nutritional recommendations.16 Details on how the FSAm-NPS score is calculated are published elsewhere8 12 14 35 (also see supplementary methods).

For each food or beverage in the EPIC food composition database we calculated the FSAm-NPS score (food level score) based on its composition for each 100 g of content: we allocated A points (ie, nutrients that should be consumed in limited amounts) for total sugars (g), saturated fatty acids (g), sodium (mg), and energy (kJ) and C points (ie, nutrients or components that should be promoted) for dietary fibre (g) and protein (g) and for fruit, vegetables, legumes, and nuts (%). The percentage content of fruit, vegetables, legumes, and nuts was derived using standard recipes. A points (range 0–10 for each of the four items) and C points (range 0–5 for each of the three items) are allocated following specific grids for each item (see supplementary methods) and summed. To obtain the FSAm-NPS score the sum of C points is then subtracted from the sum of A points (see supplementary methods). The FSAm-NPS score for each food or beverage is based on a unique discrete continuous scale ranging theoretically from −15 points (highest nutritional quality) to 40 points (lowest nutritional quality). Cut-offs are then applied to the FSAm-NPS score to derive the Nutri-Score. The supplementary methods provide examples of the FSAm-NPS score calculation, Nutri-Score cut-offs, and food products classified according to Nutri-Score.

In a second step, we calculated a FSAm-NPS dietary index to characterise the nutritional quality of an individual’s diet. The FSAm-NPS dietary index (individual level score) was obtained as the sum of FSAm-NPS score for each food or beverage consumed, multiplied by the amount of energy provided by this product (energy content per 100 g multiplied by the estimated daily intake assessed using the baseline dietary questionnaires), divided by the total amount of energy intake (fig 1).32 A higher FSAm-NPS dietary index score reflects an overall lower nutritional quality of foods consumed.

Follow-up for vital status
We obtained data on vital status and cause of death through linkage to mortality registries combined with data collected during follow-up of the cohort. The end of follow-up or closure dates of the study period varied between 2012 and 2015 depending on the country. The cause of death was coded using ICD-10 (international classification of diseases, 10th revision).43 In this study, in addition to mortality from all causes we considered mortality due to specific causes: cancer (C00–D48), diseases of the circulatory system (I00–I99), diseases of the respiratory system (J00–J99), and diseases of the digestive system (K00–K93), and, as a negative control, mortality due to external causes (injury, poisoning, and other consequences of external causes: S00–T98, and external causes of morbidity and mortality: V01–T98). Mortality from all non-external causes (main exposure) was defined as mortality from all causes except external causes of death.

Statistical analyses
Of the 521 324 participants, we excluded those with missing lifestyle or dietary information (n=6902), along with those with an extreme ratio of energy intake to energy requirement (highest and lowest centiles, n=10 241), participants with no follow-up (n=2516), and those with missing date of death (n=71). A total of 54 951 deaths were recorded during follow-up, 1839 of which were due to external causes (see flowchart in supplementary figure 1).

We calculated age standardised absolute rates as the number of cases per 10 000 persons over 10 years in the highest and lowest fifths of the FSAm-NPS dietary index.

We considered the FSAm-NPS dietary index as a continuous variable (increment of 1 standard deviation—ie, 2.1 points of score) and as sex specific fifths. Tests for linear trends were performed assigning
the median for each fifth of FSAm-NPS dietary index. Restricted cubic spline modelling was used to explore
non-linear associations. Cox proportional hazards regression models were computed to analyse the
associations between the FSAm-NPS dietary index score and all cause and cause specific mortality. Examination of the Schoenfeld residuals confirmed that the assumptions of proportionality were satisfied
(see supplementary figure 2). Participants contributed person time to the model until date of death, date
of emigration or loss to follow-up, or end of follow-up, whichever occurred first. For analyses of cause
specific mortality, participants who died from another cause than the one under study were included and
censored at the date of the competing death event. Similarly, for analyses on mortality from non-
external causes, we included participants who died from external causes in the model and censored them at date of death. Competing risks were also tested using Fine and Gray models. Hazard ratios
and corresponding 95% confidence intervals were derived from multivariable Cox regression models
using age as the underlying time variable. Models derived from multivariable Cox regression models
were computed to analyse the associations between the FSAm-NPS dietary index score and all cause and cause specific mortality. This index reflects food consumed, regardless of cultural context. Owing

Fig 1 | Equation to calculate the Food Standards Agency nutrient profiling system
(FSAm-NPS) dietary index

\[
FSAm-NPS \text{ dietary index } = \frac{\sum_i (FSe_i)}{\sum_i E_i}
\]

\[
FSe = \text{ score of food or beverage } i
\]

\[
E = \text{ energy intake from food or beverage } i
\]

\[
n = \text{ number of foods or beverages consumed}
\]

(MICE method) by fully conditional specification (10
imputed datasets). We also conducted a complete case
approach (ie, excluding participants with missing data
on covariates).

We considered BMI as a confounding factor in the
analyses and therefore it was adjusted for in the
multivariable models. As BMI could also be considered
as an intermediate mediating factor, however, we
performed sensitivity analyses without adjustment for
BMI, and analyses of mediation through variation in
BMI were also implemented using a method proposed
previously.

To test the robustness of the associations, we carried
out several sensitivity analyses: we removed energy
intake from the models (assessing a potential collider bias), we included coffee and soft drink intakes in the
models (assuming if these two dietary factors recently
found to be strongly associated with mortality in EPIC would entirely explain the associations), we
excluded from the analyses participants with a history
of cancer, cardiovascular diseases, and diabetes
(assessing a potential bias from modified dietary
behaviours after these major health events, such as
indications to follow a healthier diet), and we excluded
from the analyses those participants who died during
the first five years of follow-up (allowing a longer delay
between baseline dietary assessment and mortality
event). To assess the potential for residual confounding
we also carried out subgroup analyses according
to major potential confounders (sex, BMI, physical
activity, educational level, smoking status, alcohol
intake, energy intake). Potential residual confounding from unmeasured confounders was assessed using E
values.

All tests were two sided and we considered P<0.05
to be statistically significant. SAS version 9.4 (SAS
Institute) and R version 3.6.2 were used for the
analyses.

Patient and public involvement
The research question developed in this article
corresponds to concerns of the participants involved
in the EPIC cohort, and of the public in general. The
results of the present study will be disseminated
through institutional websites and the media.

Results
A total of 501594 adults (70.8% women, median
age 51.6 years) were included in this study (see
supplementary figure 1). After a median follow-up of
17.2 years (8162730 person years), 54951 deaths
occurred, 23143 of which were from cancer, 13246
from diseases of the circulatory system, 2857 from
diseases of the respiratory system, 1561 from diseases
of the digestive system, and 1839 from external causes.

Table 1 shows the baseline characteristics of the
participants overall and according to sex specific fifths
of the FSAm-NPS dietary index. This index reflects
the overall nutritional quality of an individual’s diet
based on the intrinsic nutritional quality of each
food consumed, regardless of cultural context. Owing
| Country               | Median (interquartile range) | Educational level†† | Physical activity†† | Smoking status‡‡ |
|----------------------|-------------------------------|---------------------|--------------------|------------------|
| France               | 27920 (14.0)                  | None or primary school | Inactive           | Non-smoker       |
| Italy                | 45700 (9.1)                   | Technical, professional, or secondary school | Moderately inactive | Former smoker    |
| Spain                | 40619 (8.1)                   | University degree    | Moderately active  | Current smoker   |
| UK                   | 80461 (16.0)                  | None or primary school | Active             | Non-smoker       |
| Netherlands          | 38195 (7.6)                   | Technical, professional, or secondary school | Inactive           | Former smoker    |
| Greece               | 26651 (5.3)                   | University degree    | Moderately inactive| Former smoker    |
| Germany              | 52010 (10.4)                  | University degree    | Moderately active  | Current smoker   |
| Denmark              | 55818 (11.1)                  | University degree    | Active             | Non-smoker       |
| Norway               | 36439 (7.26)                  | University degree    | Inactive           | Former smoker    |

### Dietary Intake

#### Nutrient Intake (Median (interquartile range))

- **Educational level**
  - None or primary school: 21030 (20.3)
  - Technical, professional, or secondary school: 22405 (20.0)
  - University degree: 23402 (20.0)

- **Physical activity**
  - Inactive: 20030 (19.7)
  - Moderately inactive: 21435 (19.8)
  - Moderately active: 22990 (19.5)
  - Active: 23995 (19.3)

- **Smoking status**
  - Non-smoker: 24929 (48.8)
  - Former smoker: 134382 (26.8)
  - Current smoker: 111938 (22.4)

### Nutritional Quality

- **Country**
  - France: 52 (18.2%)
  - Italy: 45 (15.6%)
  - Spain: 40 (15.6%)
  - UK: 72 (25.8%)
  - Netherlands: 36 (12.8%)
  - Greece: 43 (14.9%)
  - Germany: 45 (15.6%)
  - Denmark: 41 (14.3%)
  - Norway: 36 (12.8%)
  - Sweden: 52 (18.2%)
  - Norway: 36 (12.8%)
  - Italy: 45 (15.6%)
  - UK: 72 (25.8%)
  - Netherlands: 36 (12.8%)
  - Greece: 43 (14.9%)

- **Current smoker**
  - Non-smoker: 24929 (48.8)
  - Former smoker: 134382 (26.8)
  - Current smoker: 111938 (22.4)

### Nutritional Quality Scores

- **Fifth (lowest nutritional quality)**
  - France: 27920 (14.0)
  - Italy: 45700 (9.1)
  - Spain: 40619 (8.1)
  - UK: 80461 (16.0)
  - Netherlands: 38195 (7.6)
  - Greece: 26651 (5.3)
  - Germany: 52010 (10.4)
  - Denmark: 55818 (11.1)
  - Norway: 36439 (7.26)
  - Sweden: 52 (18.2%)
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| Characteristics | Country      | Median (interquartile range) | Physical activity†† | Smoking status‡‡ |
|-----------------|--------------|-----------------------------|---------------------|------------------|
| Age at recruitment (years) | France | 51.6 (45.3-58.4) | Inactive | Non-smoker |
| Educational level** | Italy | 45 (18.0%): 134 (44.3%) | Moderate inactive | Former smoker |
| Physical activity** | Spain | 40 (15.6%): 134 (44.3%) | Active | Non-smoker |
| Smoking status** | UK | 72 (25.8%): 134 (44.3%) | Inactive | Former smoker |

*Column percentages.
††Missing for 91 (18.2%).
‡‡Missing for 90 (18.0%).
**Missing for 3833 (1.7%).
††Missing for 34 (0.6%).
‡‡Missing for 10345 (2.1%)
§§Missing for 78 (0.15%).
¶¶Missing for 39 (0.7%).
to the diverse dietary patterns of the 10 countries participating in the EPIC cohort, FSAm-NPS dietary index scores were lower, indicating diets of overall higher nutritional quality in Spain (median 4.06), Greece (4.49), Norway (4.92), and Italy (5.34), and higher in the UK (6.01), Sweden (6.19), the Netherlands (6.22), Denmark (6.25), Germany (6.73), and France (7.25).

Participants with higher FSAm-NPS dietary index scores were more likely to have less healthy dietary intakes (lower intakes of dietary fibres, fruit and vegetables, and fish and higher intakes of red and processed meat) and higher energy intakes. Nonetheless, a broad range of energy intakes was observed within each fifth. Participants with higher FSAm-NPS dietary index scores were also more likely to smoke, to be less physically active, and to have a higher alcohol intake and higher level of education, and a history of cancer. In contrast, a higher proportion of existing cardiovascular diseases or diabetes and a higher BMI was observed in participants with lower FSAm-NPS dietary index scores, which might reflect a change in diet required for management of disease in these participants.

Table 2 shows the associations between the FSAm-NPS dietary index and mortality. A higher score (lower nutritional quality diet) was associated with higher mortality overall (highest fifth versus lowest fifth: hazard ratio 1.06, 95% confidence interval 1.03 to 1.09, P<0.001 for trend, P=0.001 for non-trend). Mortality from external causes was not associated with these participants. Participants with higher FSAm-NPS dietary index scores were also more likely to smoke, to be less physically active, and to have a higher alcohol intake and higher level of education, and a history of cancer. In contrast, a higher proportion of existing cardiovascular diseases or diabetes and a higher BMI was observed in participants with lower FSAm-NPS dietary index scores, which might reflect a change in diet required for management of disease in these participants.

Some evidence of non-linearity was observed for all cause mortality and mortality from cancer and diseases of the circulatory system. Such non-linearity was mainly observed for low FSAm-NPS dietary index scores, whereas for higher scores the association had a linear shape (see supplementary figure 4). Similar results were observed across all sensitivity analyses (see supplementary table 1).

Overall, subgroup analyses showed the robustness of the results across categories of major potential confounders (fig 2): associations with all cause mortality were consistent across strata for men and women, non-smokers and smokers, and according to energy or alcohol intakes and education levels (although strengthened in highly educated participants); associations were stronger in non-obese participants and in those who were less physically active.

Mediation analyses suggested a limited mediation effect from variation in BMI during follow-up in the association between FSAm-NPS dietary index score and mortality (see supplementary table 2). Removing BMI from the models did not change the results of the main models (see supplementary table 1).

Finally, E values suggested that residual confounding due to potential unmeasured confounding factors is likely to be moderate (see supplementary table 3).

Discussion
This study was conducted in a large population from 10 European countries participating in the EPIC cohort to assess the relevance of the FSAm-NPS dietary index score (high values representing low nutritional quality of food products) to characterise healthier food choices in a European context. We found that a higher consumption of food products with higher FSAm-NPS scores (ie, higher FSAm-NPS dietary index scores at the individual level) was positively associated with mortality from all causes and from cancer and diseases of the circulatory, respiratory, and digestive systems.

Comparison with other studies
This work builds on previous analyses conducted on cancer incidence in the EPIC cohort\(^\text{35}\) to investigate the association between the FSAm-NPS dietary index and health outcomes in a large European population, and it complements the analyses conducted in the French SUVI.MAX and NutriNet-Santé cohorts.\(^\text{27-34}\) These studies consistently reported poorer health outcomes (weight gain, \(^\text{29}\) metabolic syndrome, \(^\text{10}\) cancer, \(^\text{33-35}\) cardiovascular diseases, \(^\text{31}\) asthma symptoms\(^\text{27}\)) associated with higher FSAm-NPS dietary index scores.

Previous studies in the UK have also investigated the association between the FSA-NPS score (the original score before modifications were made and it was renamed FSAm-NPS) and mortality, applying to the FSA-NPS a cut-off to categorise food products as healthier or less healthy (Ofcom threshold used for advertising regulation\(^\text{9}\)). The results of these studies were consistent with ours, showing a lower all cause and cancer related mortality associated with intake of...
Table 2 | Associations between fifths of Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index score and all cause and cause specific mortality, from multivariable Cox proportional hazards regression models, in participants of European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, 1992-2015. Values are hazard ratios (95% confidence intervals) unless stated otherwise

| Mortality | Continuous (per 1 SD increment) | P value | First (highest nutritional quality) | Second | Third | Fourth | Fifth (lowest nutritional quality) | P for trend | P for non-trend |
|-----------|---------------------------------|---------|-------------------------------------|--------|-------|--------|------------------------------------|------------|----------------|
| All causes |                                 |         |                                     |        |       |        |                                    |            |                |
| No/person years | 54 951/8 162 730 | 10 887/1 605 206 | 99 34/1 585 846 | 10 275/1 626 056 | 11 098/1 662 098 | 12 757/1 683 523 |
| Sex adjusted model | 1.04 (1.03 to 1.05) | <0.001 | 0.97 (0.94 to 1.00) | 0.98 (0.95 to 1.01) | 1.01 (0.98 to 1.04) | 1.10 (1.07 to 1.14) | <0.001 | <0.001 |
| Main model | 1.02 (1.01 to 1.03) | <0.001 | 1.00 (ref) | 0.98 (0.96 to 1.01) | 0.99 (0.96 to 1.02) | 1.01 (0.98 to 1.04) | 1.06 (1.03 to 1.09) | <0.001 | <0.001 |
| Cause specific | | | | | | | | |
| Non-external | | | | | | | | |
| No/person years | 53 112/8 162 730 | 10 515/1 605 206 | 96 05/1 585 846 | 99 22/1 626 056 | 10 728/1 662 098 | 12 342/1 683 523 |
| Sex adjusted model | 1.04 (1.03 to 1.05) | <0.001 | 0.97 (0.94 to 1.00) | 0.98 (0.95 to 1.01) | 1.01 (0.98 to 1.04) | 1.10 (1.07 to 1.14) | <0.001 | <0.001 |
| Main model | 1.03 (1.02 to 1.04) | <0.001 | 1.00 (ref) | 0.99 (0.96 to 1.02) | 0.99 (0.96 to 1.02) | 1.01 (0.98 to 1.04) | 1.07 (1.03 to 1.1) | <0.001 | <0.001 |
| Cancer | | | | | | | | |
| No/person years | 1839/7 783 132 | 372/1 568 430 | 329/1 538 426 | 353/1 556 361 | 370/1 562 787 | 415/1 557 129 |
| Sex adjusted model | 1.03 (0.98 to 1.09) | 0.23 | 0.95 (0.81 to 1.10) | 1.00 (0.86 to 1.17) | 1.00 (0.86 to 1.17) | 1.08 (0.92 to 1.27) | 0.21 | 0.54 |
| Main model | 1.00 (0.95 to 1.05) | 0.93 | 1.00 (ref) | 0.94 (0.81 to 1.18) | 0.98 (0.84 to 1.15) | 0.99 (0.84 to 1.16) | 0.98 | 0.93 |
| Circulatory diseases | | | | | | | | |
| No/person years | 23 143/7 783 132 | 4550/1 568 430 | 4288/1 538 426 | 4482/1 556 361 | 4700/1 562 787 | 5123/1 557 129 |
| Sex adjusted model | 1.06 (1.04 to 1.07) | <0.001 | 1.00 (ref) | 1.00 (0.96 to 1.04) | 1.04 (0.99 to 1.08) | 1.07 (1.03 to 1.12) | 1.16 (1.11 to 1.21) | <0.001 | <0.001 |
| Main model | 1.03 (1.01 to 1.04) | <0.001 | 1.00 (ref) | 0.99 (0.95 to 1.04) | 1.02 (0.98 to 1.07) | 1.03 (0.99 to 1.08) | 1.08 (1.03 to 1.13) | <0.001 | <0.001 |
| Respiratory diseases | | | | | | | | |
| No/person years | 13 246/7 783 132 | 2973/1 568 430 | 2432/1 538 426 | 2377/1 556 361 | 2526/1 562 787 | 2938/1 557 129 |
| Sex adjusted model | 1.02 (1.00 to 1.04) | 0.04 | 1.00 (ref) | 0.91 (0.86 to 0.96) | 0.92 (0.87 to 0.97) | 0.95 (0.90 to 1.01) | 1.03 (0.97 to 1.09) | 0.11 | <0.001 |
| Main model | 1.02 (1.00 to 1.04) | 0.03 | 1.00 (ref) | 0.96 (0.91 to 1.01) | 0.96 (0.91 to 1.02) | 1.00 (0.94 to 1.06) | 1.04 (0.98 to 1.11) | 0.06 | 0.02 |
| Digestive diseases | | | | | | | | |
| No/person years | 2857/7 783 132 | 508/1 568 430 | 501/1 538 426 | 507/1 556 361 | 591/1 562 787 | 750/1 557 129 |
| Sex adjusted model | 1.16 (1.12 to 1.21) | <0.001 | 1.00 (ref) | 1.12 (0.98 to 1.27) | 1.15 (1.01 to 1.31) | 1.30 (1.14 to 1.47) | 1.56 (1.37 to 1.76) | <0.001 | <0.001 |
| Main model | 1.11 (1.06 to 1.15) | <0.001 | 1.00 (ref) | 1.15 (1.01 to 1.31) | 1.16 (1.01 to 1.32) | 1.27 (1.11 to 1.45) | 1.39 (1.22 to 1.59) | <0.001 | <0.001 |
| *Cut-offs for sex specific fifths of the FSAm-NPS dietary index were 4.14, 5.35, 6.43, and 7.68 for women and 4.32, 5.55, 6.63, and 7.88 for men. A higher score indicates a lower nutritional quality of foods consumed. |
| †Sex adjusted model was stratified for age (one year interval) and study centre and adjusted for age (time scale) sex, body mass index, height, educational level (longer education, including university degree, technical or professional school, secondary school, primary school, missing), combined total physical activity (sex specific categories: active, moderately active, moderately inactive, inactive, missing), smoking status and intensity of smoking (current, 1-15 cigarettes daily, 16-25 cigarettes daily, ≥26 cigarettes daily, pipe, cigar, occasional, current or former, missing, former, quit 11-19 years, quit ≥20 years, non-smoker, missing), baseline alcohol intake, baseline energy intake, and history of cancer (yes, no), cardiovascular diseases (yes, no), diabetes (yes, no, missing). |

a wide variety of healthier food items in the Whitehall II cohort and a higher all cause mortality associated with a higher consumption of less healthy food items in EPIC-Norfolk (highest versus lowest fifth: hazard ratio 1.11, 95% confidence interval 1.02 to 1.20). In both studies no association was observed with mortality from cardiovascular diseases, whereas in our study we found a borderline statistically significant association. This might be related to the larger sample size in our study or to a better ranking of participants using the continuous FSAm-NPS, which allows for a more refined discrimination of the nutritional quality of food products likely resulting in a better ranking of participants according to the overall nutritional quality of their diets.

The approach used in our study, in which a dietary index at the individual level is derived from the nutrient profile of the foods consumed and is studied in relation to health outcomes, was also implemented with different nutrient profiling systems in two other studies. In the Nurses’ Health Study and the Health Professionals Follow-up Study, the Overall Nutritional

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### Table: Associations between Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index score and all cause mortality, subgroup analyses from multivariable Cox proportional hazards regression models in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, 1992-2015.

| Study                                | No with event/ No without event | Hazard ratio (95% CI) per 1 SD increment | Hazard ratio (95% CI) per 1 SD increment |
|--------------------------------------|---------------------------------|------------------------------------------|------------------------------------------|
| **Sex**                              |                                 |                                          |                                          |
| Men                                  | 23 425/122 904                  | **1.03 (1.01 to 1.04)**                  | **1.02 (1.01 to 1.04)**                  |
| Women                                | 29 687/325 578                  |                                          |                                          |
| **Weight status**                    |                                 |                                          |                                          |
| Normal                               | 22 817/243 240                  | **1.03 (1.02 to 1.05)**                  | **1.02 (1.01 to 1.04)**                  |
| Overweight                           | 20 745/149 781                  | **1.04 (1.02 to 1.05)**                  |                                          |
| Obese                                | 9 550/55 461                    | **1.01 (1.00 to 1.03)**                  |                                          |
| **Physical activity**                |                                 |                                          |                                          |
| Inactive                             | 6 371/78 982                    | **1.05 (1.02 to 1.08)**                  | **1.01 (0.97 to 1.05)**                  |
| Moderately inactive                  | 20 751/151 663                  | **1.04 (1.02 to 1.05)**                  |                                          |
| Moderately active                    | 22 228/173 776                  | **1.01 (1.00 to 1.03)**                  |                                          |
| Active                               | 3 762/44 061                    | **1.01 (0.97 to 1.05)**                  |                                          |
| **Smoking status**                   |                                 |                                          |                                          |
| Non-smoker                           | 20 137/231 012                  | **1.02 (1.00 to 1.04)**                  | **1.03 (1.01 to 1.05)**                  |
| Smoker                               | 16 447/97 413                   |                                          |                                          |
| **Energy intake**                    |                                 |                                          |                                          |
| < median: 1992 kcal/day              | 28 145/222 802                  | **1.03 (1.01 to 1.04)**                  | **1.03 (1.01 to 1.04)**                  |
| ≥ median: 1992 kcal/day              | 24 967/225 680                  | **1.03 (1.01 to 1.04)**                  |                                          |
| **Alcohol Intake**                   |                                 |                                          |                                          |
| < median: 5.29 g/day                 | 28 350/222 667                  | **1.02 (1.01 to 1.03)**                  | **1.03 (1.02 to 1.05)**                  |
| ≥ median: 5.29 g/day                 | 24 762/225 815                  | **1.03 (1.02 to 1.05)**                  |                                          |
| **Educational level**                |                                 |                                          |                                          |
| None or primary school               | 22 538/130 071                  | **1.02 (1.01 to 1.04)**                  | **1.03 (1.01 to 1.04)**                  |
| Secondary or technical or professional school | 20 301/201 402 | **1.02 (1.01 to 1.04)**                  | **1.02 (1.01 to 1.04)**                  |
| Longer education including university degree | 10 273/117 009 | **1.04 (1.02 to 1.07)**                  |                                          |

**Fig 2** | Associations between Food Standards Agency nutrient profiling system (FSAm-NPS) dietary index score and all cause mortality, subgroup analyses from multivariable Cox proportional hazards regression models in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, 1992-2015. A higher score indicates a lower nutritional quality of consumed foods. The main model was stratified for age (one year interval) and study centre and adjusted for sex, body mass index, height, educational level (longer education, including university degree, technical or professional school, secondary school, primary school, missing), combined total physical activity (sex specific categories: active, moderately active, moderately inactive, inactive, missing), smoking status and intensity of smoking (current, 1-15 cigarettes daily, 16-25 cigarettes daily, ≥26 cigarettes daily, pipe, cigar, or occasional; current or former, missing; former, quit ≤10 years, quit 11-19 years, quit ≥20 years; non-smoker; missing), baseline alcohol intake, baseline energy intake, and history of cancer (yes, no, missing), and diabetes (yes, no, missing). P for interaction, obtained for each subgroup analysis from the likelihood ratio test of models with and without the interaction term, were: sex, P=0.04; weight status, P=0.22; physical activity, P=0.23; smoking status, P<0.001; energy intake, P=0.05; alcohol intake, P=0.07; educational level, P=0.27.

Quality Index translated into the ONQI-f score at the individual level was associated with lower mortality.53 In the Rotterdam Study, the Nutrient-Rich Food 9.3 score at the individual level was inversely associated with all cause mortality but not with mortality from cardiovascular diseases.54 These scores nonetheless differ by the number and types of nutritional items considered. The FSAm-NPS was designed to be easily computable by industrial and public stakeholders in a transparent manner to serve as a basis for tools of public health nutritional policies (such as the Nutri-Score label). Hence the FSAm-NPS consists of a unique scale applicable to all food products (raw or manufactured) and to all countries (as was done in the present study) and intentionally focuses on seven items only (energy, saturated fatty acids, sodium, sugars, dietary fibre, and protein, and fruit, vegetables, legumes, and nuts). These items are generally found in the nutritional information on food labels and were selected based on an association with non-communicable diseases or because they reflect the nutritional value of foods, in line with dietary guidelines.8 42 In contrast, the Overall Nutritional Quality Index is based on 30 items and the Nutrient-Rich Food 9.3 is based on 12 items, both including not only macronutrients, vitamins, and minerals but also polyphenols (Overall Nutritional Quality Index) and reference values of intake (Nutrient-Rich Food 9.3) that might differ across countries.

The FSAm-NPS is also consistent with recent reports from the Global Burden of Disease Study and the EAT-Lancet Commission, both of which estimated that about 11 million deaths worldwide could be prevented with healthier diets, including, notably, less sodium, sugars, and saturated fats and more dietary fibre and whole grains, fruit, vegetables, legumes, and nuts.55 Our results showed a strong association of the FSAm-
NPS dietary index score with mortality from respiratory diseases. Beyond the well established impact of nutrition on cancer and cardiometabolic risks, a mounting evidence also supports a substantial impact of nutrition on respiratory health through several pathways involving oxidative stress and inflammation, epigenetics, and the gut microbiome. Notably, dietary fibres (involved in anti-inflammatory responses) and fruit and vegetables (sources of antioxidants), as part of a healthy diet, have been suggested to play a beneficial role in respiratory health, whereas components such as saturated fats and red or processed meat (involved in pro-inflammatory responses), or, more generally, a Western diet, would have detrimental effects. The FSAm-NPS dietary index score has also been associated with asthma symptoms in the NutriNet-Santé cohort study. Similar strong associations with mortality from respiratory diseases (compared with mortality from other causes) have been observed in previous studies of saturated fatty acid and vegetables and red meat intakes. These results are consistent with the items in the FSAm-NPS dietary index.

Non-linearity and associations between FSAm-NPS dietary index and BMI
In our study, evidence of non-linearity was observed for associations with all cause mortality and mortality from cancer and diseases of the circulatory system at low values of FSAm-NPS dietary index scores. Such values reflect healthy food choices that might have been adopted by individuals with a greater risk of disease (and thus high underlying risks of mortality). Hence, individuals consuming diets of the highest nutritional quality (lowest FSAm-NPS dietary index scores) would be the ones with higher mortality rates, thus blurring the association overall. Evidence of this can be seen in table 1 where participants in the lowest fifth of the FSAm-NPS dietary index have a higher baseline BMI (cross sectional analyses) and were more likely to have prevalent cardiovascular disease or prevalent diabetes at baseline (probably partly related to their past diet). This might also help to explain why weaker (although statistically significant) associations were observed for mortality from circulatory diseases or why we observed stronger results in non-obese participants at baseline, because mechanisms leading to premature death have to some extent already played out for obese individuals. Finally, our analyses showed little mediation effect of variation in BMI in the association between the FSAm-NPS dietary index score and mortality. This suggests that the overall nutritional quality of a diet might have an impact on mortality beyond weight gain.

Associations between FSAm-NPS dietary index and educational level
The positive cross sectional association between the FSAm-NPS dietary index score and educational level might seem counterintuitive but has also been observed in studies conducted in the independent SUIV.MAX and NutriNet-Santé cohorts. Several hypotheses can explain this finding. In EPIC, countries with a higher proportion of participants with lower mean educational level (eg, Greece, Spain, Italy) also had the lowest FSAm-NPS dietary index scores (reflecting trends towards a Mediterranean or healthier diet in countries of southern Europe). At least in these countries, people with lower education might be more likely to consume traditional diets that could include food of better nutritional quality. This trend could also be related to an age or generation effect. Younger people tend to have a higher educational level but also to have a higher consumption of “junk food,” leading to higher FSAm-NPS dietary index scores (diets of lower nutritional quality). Associations were statistically significant for all categories of educational level but slightly strengthened in highly educated participants. The latter finding might be related to more contrasted FSAm-NPS dietary index scores in the category of participants with longer education. Another hypothesis is that participants with longer education might be less exposed to risk factors linked to occupation or environment than those of a lower socioeconomic position.

Strengths and limitations of this study
Strengths of our study pertain to its prospective design and long follow-up of many participants from different European countries with various phenotypes, and for whom collected data have been standardised. This provided an opportunity to study the nutritional quality of food choices in relation to mortality in a broad European context of diverse dietary patterns. Additionally, a large array of lifestyle data was available which allowed adjustment for major potential confounding factors in our main model and the performance of in-depth sensitivity analyses. Our study also has some limitations. Firstly, owing to the observational design, potential residual confounding or unmeasured confounding (from genetic or environmental factors that could not be taken into account) cannot be ruled out. In addition, as we collected data using questionnaires, we cannot exclude misclassification bias from imprecise dietary data and covariates. Because data were collected before the studied outcome (prospective design), any misclassification resulting from measurement errors is likely to have been non-differential—that is, independent of death status. Nonetheless, this might have resulted in biased estimates of effect (underestimation or overestimation). In particular, the tools used to estimate an individual’s usual diet are subject to imprecision and inaccuracy (such as misreporting bias, inherent in assessments of usual dietary intakes) and therefore could have resulted in some misclassification of the nutritional quality of foods consumed by participants. Indeed, most EPIC centres used a food frequency questionnaire to assess dietary intakes, which, despite allowing for a good estimation of usual dietary intakes, still limits discrimination between the nutritional quality of individual food products (compared with, for example, repeated 24 hour dietary records, as used...
in the SU.VI.MAX and NutriNet-Santé cohorts, where larger effect estimates were observed for associations between FSAm-NPS dietary index scores and health outcomes.\(^{31-34,63}\) In the subsample from the EPIC calibration study (n=34 367), good concordance was shown between the FSAm-NPS dietary index score calculated from the diet questionnaires (mainly food frequency questionnaires) and the calibrated 24 hour dietary recall (68% of participants were classified in either the same or the adjacent fifth, only 3% were classified in extreme opposite fifths, data not tabulated). However, only one day of 24 hour recall was available for participants in the calibration study. Therefore, although the diet questionnaires available for the whole EPIC cohort might have some limitations about the level of detail available for each food item, the questionnaires still provide a better overview of the usual diet of participants compared with the single 24 hour recall. In addition, we only assessed dietary intakes at baseline. Although changes in food consumption might have occurred during follow-up, it is hypothesised that the baseline estimation usually reflects general eating behaviour throughout middle age.\(^{69}\) Also, EPIC participants were volunteers involved in a long term cohort study investigating the association between nutrition and health and likely had more health conscious behaviours and less unhealthy dietary behaviours than the general population. This might have resulted in weaker observed associations (hence a smaller effect size) owing to smaller differences between high and low FSAm-NPS dietary index scores. Additionally, EPIC participants were recruited from 10 countries in western Europe and so caution is warranted in extrapolating the results to other populations or ethnicities worldwide. Finally, the order of magnitude for the association between the FSAm-NPS dietary index score and mortality found in our study was relatively modest but still in line with the one traditionally observed in nutritional epidemiology, and it was similar to the one observed in the study on cancer incidence in EPIC.\(^{18}\) From a public health perspective, the opportunity to prevent 7% of premature deaths globally through healthier food choices might nonetheless be of great interest.

Potential sources of bias in our study warrant caution in the interpretation of the findings. Despite the low hazard ratios, several things allow for some confidence in our results and are in favour of an association supporting possible causality, beyond residual confounding: the robustness of associations across sensitivity analyses, including across categories of major potential confounders; null results obtained for associations between FSAm-NPS dietary index scores and mortality from external causes, which are unrelated to diet (negative control); E values that suggest moderate potential unmeasured confounding;\(^{49,50}\) consistency of the results with previous studies on the association between the FSAm-NPS dietary index score and health outcomes in independent cohorts;\(^{27,29-34}\) and consistency of the results with mechanistic hypotheses, supporting biological plausibility.

Conclusions and policy implications
In this large cohort study involving 10 European countries, a diet composed on average of more food products with higher FSAm-NPS scores, which reflected poorer nutritional profiles, was associated with higher all cause and cause specific mortality. Overall, that a higher FSAm-NPS dietary index score, obtained for varied dietary patterns in different countries representing a diverse European population, leads to higher mortality rates, suggests that the FSAm-NPS is a relevant tool to characterise more or less healthy food products, no matter the food category or the specificities of the national dietary patterns.

This study adds to the current body of evidence for the FSAm-NPS score and for Nutri-Score, a nutrition label derived from the FSAm-NPS: studies linking the FSAm-NPS dietary index to health outcomes, including one study in the EPIC cohort,\(^{27,29-35}\) and studies on the perception and understanding of Nutri-Score and its actual impact on food choices.\(^{24-26,28,70}\) Together, these results back up the relevance of using the FSAm-NPS to grade the nutritional quality of food products in the framework of public health nutritional measures such as the Nutri-Score label, a tool aimed at the general public and patients to help them to choose food products of a higher nutritional quality. This is important considering ongoing and future debates at the EU level about making food labelling systems uniform on the front of food product packaging.

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Ethical approval: This study was approved by the Local ethics committees and the internal review board of the International Agency for Research on Cancer.

Data sharing: Information on submitting an application for access to EPIC data or biospecimens is available at https://epic.iarc.fr/access/index.php.

The lead authors (the manuscript’s guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study as planned and presented; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and presented are not due to the decisions, policy, or views of IARC/WHO. The lead authors (the manuscript’s guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study as planned and presented; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and presented are not due to the decisions, policy, or views of IARC/WHO.

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