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This is an **author produced version** of a paper published in:

American Journal of Clinical Nutrition 113.5 (2021): 1301-1311

DOI: <https://doi.org/10.1093/ajcn/nqaa389>

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Five-Color Nutri-Score labelling and mortality risk in a nationwide, population-based cohort in Spain: the ENRICA cohort study

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Authorship: All authors listed fully meet the criteria for authorship

Competing interests: The authors have declared that no competing interests exist.

Funding information: FIS grants 17/1709, 19/319 and 19/665 (Instituto de Salud Carlos III, State Secretary of R+D+I, and FEDER/FSE), the CIBERESP (Instituto de Salud Carlos III).

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Data described in the manuscript, code book, and analytic code will be made available upon request pending [e.g., application and approval, payment, other].

ABBREVIATIONS:

5-CNS	5-Color Nutri-Score
5-CNS DI	5-CNS dietary index
CI	Confidence Intervals
DH-ENRICA	Dietary history from the ENRICA Study
DI	Dietary index
ENRICA	Study on Nutrition and Cardiovascular Risk in Spain
EPIC	European Prospective Investigation into Cancer and Nutrition
FSA	British Food Standards Agency
FSA-NPS	Nutrient profiling system developed by the British Food Standards Agency
FSAm-NPS	Modified version of the FSA-NPS
HR	Hazard ratio

1 **ABSTRACT**

2 **Background**

3 The 5-Color Nutri-Score (5-CNS) front-of-package labelling classifies products according to their
4 nutritional quality, so healthier choices are easier when shopping. A higher consumption of products
5 with worse score on the 5-CNS has been associated with higher risk of several adverse health
6 outcomes, but its association with long-term mortality is still uncertain.

7 **Objective**

8 We examined the association between 5-CNS-based food consumption and long-term mortality in
9 the non-institutionalized Spanish adult population.

10 **Methods**

11 Data were taken from 12,054 individuals, representative of the Spanish population aged ≥ 18 , who
12 were recruited in 2008-10 and followed up to 2017. Habitual food consumption was collected at
13 baseline with a validated computerized dietary history, conducted by trained interviewers. Based on
14 nutritional quality, foods consumed were categorized into five labels (A/Green–best quality, B, C, D,
15 E/Red–worst quality) using an established algorithm. For each individual, a 5-CNS dietary index (5-
16 CNS DI) was calculated by summing up the amount of g/day from the foods consumed by their
17 corresponding nutritional quality rate (e.g., A/Green rated 1 and E/Red rated 5) and divided by kg of
18 weight. The associations between sex-specific categories of the baseline 5-CNS DI and all-cause and
19 cause-specific mortality were analyzed using multivariate-adjusted Cox models.

20 **Results**

21 After a mean follow-up of 8.7 years, 514 deaths occurred (140 cardiovascular deaths and 144
22 cancer deaths). The all-cause mortality hazard ratio (HR) (95% confidence interval) for the highest
23 vs. the lowest quartile of baseline 5-CNS DI (g/day/kg) was 1.93 (1.34, 2.79); P-trend 0.001. The
24 association slightly higher for cardiovascular mortality and similar for cancer. Those with the highest

25 intake of foods labelled as D or E also had a higher all-cause mortality risk than those with the
26 lowest intake [HR 2.15 (1.56, 2.97); P-trend <0.001]. Further, the isocaloric replacement of food
27 products labelled as D or E with fresh foods decreases the risk of death.

28 **Conclusions**

29 A prospective association was found between the consumption of poor-quality 5-CNS-labelled
30 food products, and higher mortality in Spain. Pending further studies, these findings provide
31 additional evidence to reinforce food policies on the use of this simple labelling tool at a country
32 level.

33 **Key word:** Five-Color Nutri-Score, mortality, Spain, ENRICA Study

34

35

36 INTRODUCTION

37 Over the last 20 years, industrially processed foods have substantially replaced fresh or minimally
38 processed foods in our daily diets. In some countries, processed food accounts for up to 60% of what
39 we eat (1, 2). Processed food products are cheap and highly palatable, have a long shelf life and save
40 time when preparing meals. This makes them a convenient option in many households, especially for
41 families with a limited food budget. Most processed foods (especially ultra-processed foods) tend to
42 be energy-dense, high in unhealthy fats, refined starches, simple sugars and salt, as well as, poor in
43 proteins, dietary fiber, and micronutrients (3); moreover, they have been linked to worse health (4)
44 and increased death risk (5). In this scenario, the food industry needs to be encouraged to move away
45 from its unhealthiest ultra-processed products in favor of healthier options, while helping consumers
46 choose those healthier products.

47 Although providing an ingredient list on a food package label is a useful tool, and has become
48 good general practice, it has several drawbacks, such as the need of both time and some technical
49 knowledge to read and understand the composition of a product. Also, some ingredients like sugar
50 and salt might be listed under other names. For example, some alternative terms for sugar are corn
51 syrup, agave nectar, evaporated cane juice, dextrose, malt syrup, or molasses; and other alternative
52 labelling for sodium include monosodium glutamate or disodium phosphate.

53 A front-of-pack labelling system called 5-Color Nutri-Score (5-CNS) was developed in France to
54 translate numbers and some nutritional information (presented in the form of a table on the back of
55 the packaging) into a simple and intuitive logo placed on the front of the product. This labelling
56 system helps consumers to see and compare at a glance the nutritional value of packaged foods. This
57 synthetic information system uses a modified version of a nutrient profiling system (FSAm-NPS)
58 initially developed by the British Food Standards Agency (FSA-NPS). This scoring system (FSA-
59 NPS) provides a score for each food or drink according to their nutritional composition and the
60 adequacy of nutritional recommendations (6). The adapted French scoring system (FSAm-NPS), in

61 which the Nutri-Score labelling system using five colors is based, is similar to FSA-NPS but scores
62 fats, cheeses, and beverages differently. This nutritional quality index, FSAm-NPS, is simplified and
63 represented by letters and colors, with the letter A (green) indicating the highest nutritional quality,
64 and the letter E (red) indicating the worst nutritional quality, becoming the 5-CNS (6, 7). The 5-CNS
65 is visual and easily understood by less literate consumers, reducing social inequalities in health,
66 increasing an individual's ability to choose, and this could ultimately force the industry into
67 producing healthier options (8).

68 Some studies such as the SU.VI.MAX(cita), the NutriNet-Santé (cita), and the EPIC cohort (cita),
69 have consistently described the association of poorer health outcomes – including cardiovascular
70 disease (9, 10) and cancer (11-13) – with a higher FSAm-NPS dietary index (DI) score (representing
71 lower nutritional quality). Most recently, the FSAm-NPS DI score has also been associated with all-
72 cause and cancer mortality, but not with cardiovascular mortality (14, 15).

73 We hypothesized a positive prospective association between the Nutri-Score-based food
74 consumption when applied at the individual level, and long-term risk of death (from all causes, as
75 well as, from cardiovascular disease and cancer) examined in a representative sample of the non-
76 institutionalized adult population of Spain, where, as in many other countries, food policy decisions
77 are made at the country level. We also examined the hypothetical isocaloric substitution of those
78 foods with the worst nutritional quality level (labelled as D or E) for both fresh food as well as for
79 processed food with the highest nutritional quality level (labelled as A or B). All this would provide
80 policymakers with a wider evidence basis for using this simple framework to inform food-labelling
81 decisions at the national level.

82

83 **PARTICIPANTS AND METHODS**

84 **Study population: the ENRICA cohort**

Data were taken from the Study on Nutrition and Cardiovascular Risk in Spain (ENRICA), whose methods have been reported elsewhere (17). In brief, 12,948 individuals aged ≥ 18 years old were selected between June 2008 and October 2010 by random stratified cluster sampling to ensure a representative sample of the non-institutionalized Spanish population. First, the sample was stratified by province and municipality size. Second, the clusters were randomly selected in 2 stages: municipalities and census sections. Finally, the households within each section were selected by random telephone dialing using the telephone directory as the sampling frame. Participants in the households were selected proportionally to sex and age distribution of the Spanish population. During the telephone call, the overall objectives and procedures of the study were explained, and invited individuals provided initial consent to participate; a formal letter of invitation and detailed written information on the study characteristics were then sent to the participant's home. Collection of blood and urine samples was included for acceptance to participate, and the response rate was 51.5%. Among those not participating, the most frequent reasons were the refusal to give a blood sample (51.7%), no interest in the study (37.8%), and lack of time to participate (10.7%) (17).

When compared with Spanish participants in the European Health Interview Survey, conducted with over 20,000 individuals in 2009 (18), those in the ENRICA study had a slightly higher educational level. As in many health surveys using phone interviews, the response rate tends to be higher among those with a higher level of education.

Written informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committees of the La Paz University Hospital in Madrid and the Hospital Clinic in Barcelona (Spain).

Baseline data collection

108 Trained and certified personnel collected information in 3 sequential stages: 1) a telephone
 109 interview to obtain data on sociodemographic factors, health behaviors, self-rated health, and
 110 morbidity; 2) a first home visit to collect blood and urine samples, and 3) a second home visit to
 111 perform a physical examination, and to obtain habitual diet by using a computerized dietary history
 112 (17).

113 **Dietary assessment and computation of the 5-CNS DI and the continuous Nutri-Score dietary** 114 **indexes**

115 To ascertain the participant's habitual food consumption, we used a validated computer-based
 116 dietary history (DH-ENRICA), which consists of a structured questionnaire administered by a
 117 trained interviewer following each mealtime, from breakfast to bedtime. Participants are asked about
 118 food consumption during the week and on the weekend, as well as for seasonal variations. The
 119 interview also asks about the food groups that were not reported, and about specific foods that are
 120 difficult to report spontaneously, like alcoholic beverages or bread. Thus, the DH-ENRICA collects
 121 standardized information on 880 foods cooked in 29 different ways, as well as 184 recipes for dishes
 122 commonly eaten in Spain. A set of 129 photographs with different portion sizes of many foods helps
 123 to quantify the amount of food consumed. The software includes aids for the correct classification of
 124 some foods (e.g., fermented milk or butter and margarine) (19). Spanish standard food composition
 125 tables allowed for the calculation of the amount of energy and nutrients consumed (20, 21).

126 The 5-CNS relies on the computation of a modified version of the British FSA algorithm, with
 127 adaptations in the allocation of points for beverages, cheese, and added fats, to ensure a higher
 128 consistency of the FSA-NPS with nutritional recommendations (6, 7). Thus, the modified FSA-NPS
 129 DI (FSAm-NPS DI) was calculated based on the nutritional content of foods suitable for packaging
 130 (i.e, excluding fresh foods) consumed in the ENRICA cohort. Fresh food items were mainly fruit,
 131 vegetables, fresh meat, and fresh fish. Each non-fresh food item consumed received positive points
 132 (0-10) for total energy (kj), sugar (g), saturated fatty acids (g), and sodium content (mg). Each food

item also received negative points (0-5) according to their content of fruit/vegetables/legumes/nuts (in percentage), dietary fiber (g), and protein content (g). The percentage of fruit/vegetables/legumes/nuts was derived using standard Spanish recipes. The FSAm-NPS DI therefore uses a discrete continuous scale from +40 (least healthy food) to -15 (most healthy food). In the second step, this score that ranges from +40 to -15 points was divided into five categories to derive the 5-CNS. These five categories/colors were established to ensure a high discriminating power, while maintaining a central category in order to avoid dichotomous thinking -food as only being good or bad (6). Letters and colors were added in order to improve the readability of the labelling. Thus, the final 5-CNS labelling contains five letters (A, B, C, D, E) with corresponding colors, from dark green (letter A) indicating the highest nutritional quality, light green (letter B), orange (letter C), light red (letter D), and to dark red (letter E), being the worst nutritional quality.

For each study participant, we calculated the following four Nutri-scores DI based on the FSAm-NPS:

1. **5-CNS DI (g/day/kg)**: calculated by summing up the g consumed from each non-fresh food/beverage by its corresponding 5-CNS (ranging from A rated 1 to E rated 5) and divided by body weight (kg).
2. **Continuous Nutri-Score DI (g/day/kg)**: calculated by summing up the number of g consumed from each non-fresh food/beverage by its corresponding FSAm-NPS (ranging from +40 to -15) and divided by body weight (kg).
3. **5-CNS DI (% of energy)**: calculated by summing up the calories consumed from each non-fresh food/beverage by its corresponding 5-CNS (ranging from A rated 1 to E rated 5) and divided by total calorie intake.
4. **Continuous Nutri-Score DI (% of energy)**: calculated by summing up the number of calories consumed from each non-fresh food/beverage by its corresponding FSAm-NPS (ranging from +40 to -15) and divided by total calorie intake.

For these four overall Nutri-score DIs, a higher score represents lower nutritional quality considering diet as a whole.

Mortality ascertainment

All-cause mortality, as well as cardiovascular disease and cancer mortality from baseline in 2008-2010 to the end of follow-up on December 31, 2017, was obtained for 99.9% of the cohort. A computerized search was performed in the Spanish National Death Index that contains information on the vital status of all residents in Spain. Follow-up was censored at the date of death or at the end of follow-up, whichever occurred first.

Covariates

At baseline, data on sociodemographic, lifestyle, and morbidities were collected. Self-reported information was obtained on sex, age, educational level (no formal education, primary, and secondary or higher), and smoking status (current, former, and never smoker). Weight and height were measured at home under standardized conditions, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Physical activity was recorded using the EPIC questionnaire and a physical activity index was calculated based on a cross-tabulation of occupational, household, and recreational activities, categorizing individuals into 4 levels of activity: inactive, moderately inactive, moderately active, and active (22). Alcohol consumption, fiber intake, and total energy intake were derived from the national food composition tables. The number of medications were checked against drug packages. Hypertriglyceridemia was defined as fasting plasma triglycerides ≥ 150 mg/dL; hypercholesterolemia as fasting plasma total cholesterol level ≥ 200 mg/dL or taking lipid-lowering medications; and high blood pressure was defined as $\geq 140/90$ or taking antihypertensive medication. Finally, self-reported chronic conditions diagnosed by a

physician (chronic respiratory disease, coronary heart disease, stroke, heart failure, osteoarthritis/arthritis, cancer, depression requiring treatment, and diabetes) were also collected.

Statistical analysis

Of the 13,105 study participants, 884 without information on diet and 60 with total energy intake outside predefined limits (800 or 5,000 Kcal/day for men and 500 or 4,000 Kcal/day for women) were excluded. Furthermore, the 107 subjects with missing value in weight were not included in the main analysis where the Nutri-score is measured in g/day/kg of weight. Thus, the main analyses were conducted with 12,054 individuals (5,708 men and 6,346 women) (**Online Supplementary Figure 1**). Participants were categorized according to sex-specific quartiles for the four Nutri-score DIs: 5-CNS DI (g/day/kg), 5-CNS DI (% of energy), continuous Nutri-Score DI (g/day/kg), and continuous Nutri-Score DI (% of energy). For specific-mortality and subgroup analysis, participants were categorized according to sex-specific tertiles of the 5-CNS DI (g/day/kg).

To assess the prospective associations between the Nutri-score DIs and mortality, Cox proportional hazards models were fitted, with attained age as the underlying timescale. Hazard Ratios (HRs) and their 95% Confidence Intervals (CI) were calculated by using the lowest category of the Nutri-score DI as reference.

Linear trend across categories were tested by calculating the median in each quartile and modelled it as a continuous variable. HRs for mortality per unit increment in the Nutri-score DIs were also calculated. Schoenfeld residuals were plotted against time to detect violations of the proportional hazard assumption, and we found no obvious deviation from the assumption.

Two consecutive Cox models were built, both stratified by age at recruitment. Model 1, was adjusted for sex and age, and Model 2 was further adjusted for educational level, smoking status, BMI, physical activity, alcohol consumption, fiber intake, total energy intake, number of

206 medications, hypertriglyceridemia, hypercholesterolemia, high blood pressure, and number of self-
207 reported chronic conditions (chronic respiratory disease, coronary disease, stroke,
208 osteoarthritis/arthritis, cancer, depression requiring treatment, and diabetes). Restricted cubic spline
209 analyses—with three knots (at the 10th, 50th, and 90th percentiles), and adjusted for the same
210 potential confounders were also depicted. Isocaloric substitution models were built to assess the
211 impact of replacing foods labelled as D or E with fresh foods or with foods labelled as A or B (23).

212 We used imputation methods for missing values in covariates, which were less than 1%, with
213 stochastic regression (which adds a random error term and can more appropriately reproduce the
214 correlation between X and Y). All results were checked against models built selecting participants
215 with complete information for all variables.

216 To assess the potential for residual confounding, we also carried out subgroup analyses according
217 to major potential confounders (such as energy intake, sex, age, educational level, smoking status,
218 body mass index, physical activity, alcohol consumption, and diabetes prevalence). P for interaction
219 was obtained for each subgroup analysis from the likelihood ratio test of models with and without the
220 interaction term.

221 As BMI could be a confounder as well as a mediator, we also built models without adjusting for
222 BMI. Finally, some sensitivity analyses were conducted using the 5th and 95th centiles as limits for
223 allowable total energy intake; excluding participants with prevalent chronic conditions, and
224 excluding participants who died during the first 2 years of follow-up.

225 Analyses were carried out using STATA/SE version 16.0 (StataCorp, College Station, TX, USA).
226 Analyses were weighted by using the survey (svy) prefix command to account for the complex
227 sampling design, and the variances were also corrected to calculate appropriate 95% CI. P values
228 were two-tailed and $p < 0.05$ was considered statistically significant.

229

RESULTS

The cohort comprised of 12,054 adults (mean age: 47 ± 17 years; 52.5% females) had an average 5-CNS (g/day/kg) and continuous Nutri-Score DIs (g/day/kg) of 35.5 ± 19.6 and 55.3 ± 51.0 respectively. Those with less healthy Nutri-score DIs (highest quartiles) consumed more total energy, were younger, less educated, and less frequently obese (**Table 1 and Figure 1**).

After a mean follow-up of 8.7 years and 104,877 person-years of follow-up, 502 deaths (140 from cardiovascular disease and 144 from cancer) occurred. In all models, participants in the highest (reflecting consumption of food with lower nutritional quality and hence less favorable Nutri-Score rating) vs. lowest quartile of the Nutri-score DIs had a higher mortality risk. For the 5-CNS DI (g/day/kg) and continuous Nutri-score (g/day/kg), the fully adjusted HRs (95% CI) for all-cause mortality were, respectively, 1.93 (1.34-2.79; P-trend <0.001), and 1.72 (1.21, 2.43; P-trend <0.001) when comparing the highest to the lowest quartile (**Table 2 and Figure 2**). Also, grams from foods classified as D or E were summed up and divided by body weight in kg (g/kg), and the sex-specific quartiles were analyzed. After controlling for foods classified as A, B, or C, the corresponding HRs were 2.15 (1.56, 2.97; P-trend <0.001) (**Table 2**). Consistent results were obtained using the Nutri-score DIs based on % of energy, although the magnitude of the associations became slightly lower (**Online supplemental Table 2**).

Likewise, a higher baseline 5-CNS DI was associated with cardiovascular and cancer mortality. When comparing participants in the highest vs. the lowest tertile of 5-CNS DI (g/day/kg), the HR (95% CI) for cardiovascular mortality was 2.82 (1.47, 5.34; P-trend 0.093), and 1.94 (0.98, 3.82, P-trend 0.036) for cancer mortality (**Table 3**).

The subgroup analyses showed the consistency of the association with all-cause mortality across categories of the major potential confounders, although the magnitudes were stronger for some strata (**online supplementary Table 3**). Associations were higher especially in those over 65, more

frequently educated, non-smokers, BMI <30 kg/m², less physically active, non-drinkers, and with diabetes at baseline. The interaction between the 5-CNS DI and each of these variables was not statistically significant, apart from diabetes status (P=0.036). The HR (95% CI) of 5-CNS DI (g/day/kg), T3 (highest) vs. T1 (lowest), was 1.80 (1.26, 2.58; P-trend 0.197) for those free of diabetes, and 3.18 (1.56, 6.50; P-trend 0.050) for participants with prevalent diabetes (**online supplementary Table 3**).

Restricted cubic spline analysis of the risk of death associated with the hypothetical isocaloric replacement of foods labelled as D or E with fresh foods (i.e., fruit, vegetables and non-processed meat and fish) showed that the more energy from foods labelled as D or E is replaced with, the lower the risk of death (**Figure 3A**). Likewise, the more energy from foods labelled as D or E is replaced with those foods labelled as A or B, the lower the risk of death, but did not achieve statistical significance (**Figure 3B**).

Results were similar in the models without BMI, with a change in the HR (95% CI), from Q4 vs. Q1, 1.93 (1.34, 2.79; P-trend <0.001) to 2.11 (1.47, 3.04; P-trend 0.002). Finally, sensitivity analyses were consistent with the main results (data not shown).

DISCUSSION

In this large prospective cohort, based on a representative sample of the non-institutionalized adult population of Spain, participants with the highest Nutri-Score DIs (those consuming foods with a lower nutritional quality) were at a higher long-term risk of death from all-cause mortality, cardiovascular disease, as well as cancer mortality. The association might be especially relevant among subjects with diabetes.

The association between a higher Nutri-score DI and all-cause mortality was particularly strong among participants with a high intake of foods labelled as D or E (poorest nutritional scores).

278 Examples of foods labeled as D or E are pastries, processed meat products, margarine, mayonnaise
 279 and other creams and sauces, soft and soda drinks, some cheeses, jam or fruit confitures, and fruit
 280 juice. A lower risk of death was evident when replacing a percentage of energy from packaged foods
 281 with the poorest nutritional quality (letters D or E) with the same percentage of energy from fresh
 282 food (i.e., fruit, vegetables, non-processed meat, and fish). Nevertheless, the benefit of replacing a
 283 percentage of energy from foods labelled as D or E with foods labelled as A or B, was less apparent.
 284 Examples of foods labelled as A or B are most of the dairy products, flours and breads, nuts, canned
 285 boiled legumes, canned fish, and canned vegetables (**Online supplementary Table 4**). This finding
 286 allows us to emphasize that the choice of fresh food in the daily diet remains preferential.

287 Our results are in line with the current knowledge about the Nutri-score nutritional components,
 288 that are known to be involved in the development of both cardiovascular diseases (26) and cancer
 289 (24, 25). They also are in accordance with the World Cancer Research Fund's recommendations
 290 related to diet (27). Results based on the Nutri-score are also consistent with recent reports from the
 291 Global Burden of Disease Study and the EAT Lancet Commission, both of which stated that less
 292 sodium, sugars, and saturated fats, as well as a higher intake of dietary fiber, whole grains, fruit,
 293 vegetables, legumes, and nuts would prevent millions of deaths worldwide (28, 29).

294 Our findings are consistent with previous evidence obtained in France, (poner las citas del
 295 SU.VI.MAX y del NutriNet-Sant  ), as well as, the Whitehall II (30) and the EPIC-Norfolk (16)
 296 cohorts which have shown an association between having better quality rates in the FSA-NPS and a
 297 lower risk of all-cause and cancer mortality. In both studies, no association with mortality from
 298 cardiovascular diseases was observed. Similarly, in a study conducted in Spain among middle-aged
 299 university graduates (the SUN Project) (15), a higher baseline Nutri-score DI (FSAm-NPS DI score)
 300 was associated with all-cause and cancer mortality. However, no association was found, for
 301 cardiovascular mortality (15). Finally, a recent analysis conducted with the whole EPIC cohort (10
 302 European countries) showed that a higher Nutri-score DI was associated with a higher risk for all-

303 cause and cancer mortality, but again the association with cardiovascular disease was not found.
304 Unlike our study, these two previous studies were conducted in selected populations.

305 The fact that our study observed an association between Nutri-score DIs and cardiovascular
306 mortality might be explained by a better ranking of participants due to the approach used in our study
307 conducted with the 5-CNS DI (g/day/kg) and based on a large number of foods. Another plausible
308 explanation is that individuals with a higher cardiovascular risk at baseline also had a healthier diet
309 (reverse causation). This is the case of the participants in the EPIC study, where those with the
310 lowest FSAm-NPS DI (better dietary quality) also had a higher BMI and were more likely to have
311 prevalent cardiovascular disease or prevalent diabetes at baseline (14).

312 The Nutri-Score is based on establishing a series of limits for isolated nutrients, with negative rates
313 (such as the content of sugar, saturated fat, salt, and energy density), or positive ones (such as the
314 content of protein and fiber, in addition to the proportion of fruit and vegetables in the food
315 composition). This approach which focused on the consumption of specific “bad” nutrients, has been
316 criticized (31). For example, the association between saturated fats and heart disease is not as firmly
317 established, nor does the evidence support a major benefit of focusing on saturated fat alone, without
318 considering the overall food itself, as well as what is eaten in its place (31). Dietary saturated fats are
319 obtained from a diverse number of foods—red meat, poultry, processed meat, yoghurt, milk, cheese,
320 butter, vegetable oils, and nuts, among others—that contain many other components that could
321 modify the overall health effects (32). Likewise, added sugars and white flours are not the same as
322 carbohydrates naturally present in food (33). Therefore, it would be more appropriate to set specific
323 nutrient limits by virtue of the category to which the food belongs. For example, the WHO nutrient
324 profile indicates which products or foods, depending on their nature or characteristics, should or
325 should not be the object of advertising aimed at children (34). Moreover, some specifications should
326 be established for trans fatty acids (the unhealthiest type of fats) that are present in many baked

327 goods (such as donuts, muffins, and sweet and savory pies), snacks (crackers, popcorn), and some
328 fried food (35).

329 Another weak point of the Nutri-score algorithm is that the consumption of small amounts of
330 certain food groups is not considered. Some foods could be caloric but healthy, and are eaten in
331 small amounts, as is the case of extra-virgin olive oil, which is labelled as C while being a pivotal
332 food in the Mediterranean diet with proven beneficial cardiovascular effects (36). Reclassifying the
333 olive oil score from “C-yellow” to “A-dark green” strengthened the association between the Nutri-
334 Score and all-cause mortality in the Spanish context. This supports a reassessment of the way in
335 which olive oil is integrated in the Nutri-Score computation (15).

336 Finally, using this labelling system, the industry could adjust the proportions of these “bad” and
337 “good” ingredients to obtain a favorable score (i.e. adding fiber and lowering the fat content to
338 compensate for huge amounts of sugar), but the overall food itself continues to be unhealthy. In order
339 to avoid that, the Chilean government's labelling system, instead, establishes alerts for products with
340 a high content of sugar, saturated fats, sodium, and calories (37). This labelling system is less
341 susceptible to these misleading changes in reformulations by the food industry. Moreover, packaged
342 foods are not only characterized by their nutrient content, but also by their additive content, by
343 substances absorbed when food is in contact with packaging, as well as, by compounds formed
344 during production, processing, and storage – none of these are taken into account in the Nutri-Score
345 algorithm. Finally, to incorporate processing information in the Nutri-Score algorithm (like the
346 NOVA system (38)), could be an advantage in this regard.

347

348 **Policy implications**

The public health community and policy makers have repeatedly stated the importance of the implementation of policies based on research evidence. Our results support the use of the 5-CNS front-of-pack labelling system as a valid public health strategy to reduce disease and mortality.

The 5-CNS labelling has impacted on food choices helping consumers differentiate foods that are healthier from those that are less healthy, and better understand their nutritional content (39). Therefore, its implementation could present advantages in real shopping situations where quick choices are usually made. Our findings reinforce the use of the 5-CNS as a valid tool in public health for Spain and countries of similar culture. Moreover, the most disadvantaged groups of people are likely to benefit most from this strategy, since unhealthy choices are more frequent in lower income families. So, its use could also reduce health inequalities (8, 40). Lastly, if the consumer demands changes toward healthier options, the food industry will also respond to this new demand; thus, the 5-CNS labelling could also promote and encourage the food industry to reformulate their products in order to make them healthier.

Strengths and limitations

We acknowledged there are some limitations in the study. Firstly, diet was only measured at baseline. Therefore, we assume that the participant's diet remained in the same category during follow-up. Although, this is a conservative assumption, because we expect participant's diet to incorporate higher levels of ultra-processed and unhealthy foods due to market trends. As well, as previously discussed, the Nutri-Score only accounts for the nutrient content of foods, but ignores potentially harmful compounds such as additives (41), compounds from the packaging being in contact with food (42), as well as substances formed during production and processing (43). Nor does it take into account the possible presence of pesticides or genetically modified ingredients.

372 Lastly, owing to the observational design of this study, residual confounding cannot be entirely ruled
373 out.

374 The study also has many strengths, such as its prospective design and a long follow-up. Of note, it
375 was conducted on a large and representative sample of the non-institutionalized adult population,
376 which broadens the generalization of the results within the country. Also, a validated and detailed
377 habitual dietary assessment was performed, using a computerized dietary history that includes a
378 larger number and variety of foods than a typical food frequency questionnaire. Moreover, several
379 confounding factors were accounted for in the analysis, which highlights the study's internal validity.
380 Finally, we used a variety of sensitivity analyses that support the robustness of our findings.

381 In conclusion, we found a prospective association between the consumption of food products
382 labelled by the 5-CNS as poor quality, with higher mortality in a whole country. The main findings
383 of this investigation provide the consumer with information that lets them know their choices in the
384 supermarket will also have an impact on their health. Also, the isocaloric replacement of foods
385 labelled as D or E (poorest nutritional scores) with fresh food (such as fruit, vegetables, unprocessed
386 meat, or fish), but not with packaged products with best quality (labelled as A or B), was associated
387 with a lower mortality risk. Thus, our results strengthen the rationale to promote fresh food as a first
388 choice. Therefore, suggesting that broader food system policies should be implemented in addition to
389 the Nutri-Score, to primarily encourage the consumption of fresh, whole, and unprocessed food.

390 These findings extend previous results at a national level, and reinforce the use of 5-CNS front-of-
391 pack labelling system as a valid public health strategy, despite some inherent limitations of the
392 algorithm supporting the Nutri-score. Our findings need to be confirmed in further studies not only at
393 a national but also at international level, and the Nutri-score needs to remain open to further
394 improvements.

395

396 **FIGURE LEGEND**

Figure 1

Title

Consumption of each food group classified by the 5-Color Nutri-Score (% of energy), by age group.

Explanation

The average consumption (presented as percentages), by age groups, of foods classified as A, B, C, D or E in the 5-Color Nutri-Score (5-CNS), as well as the consumption of fresh foods to which the Nutri-Score is not applied.

397

Figure 2

Title

Risk of death associated with the continuous Nutri-score Dietary Index (% of energy)

Explanation

The average consumption (presented as percentages), by age groups, of foods classified as A, B, C, D or E in the 5-Color Nutri-Score (5-CNS), as well as the consumption of fresh foods to which the Nutri-Score is not applied.

Continuous Nutri-Score DI (% of energy) was calculated by summing up the product number of calories consumed from each food/beverage by its corresponding FSA score (ranging from +40 to -15) and divided by total calorie intake. The higher the continuous Nutri-score DI (% of energy) the more consumption of unhealthy foods. The y-axis shows the predicted hazard ratios (HRs) for total mortality (right) and the number of subjects in each range of the continuous Nutri-score DI (% of energy) (left). The x-axis shows the continuous Nutri-score DI (% energy) as a continuous score.

Lines are restricted cubic splines, showing the shape of the association between total mortality as the continuous Nutri-score DI (% of energy). The solid line represents the adjusted hazard ratio and the dashed lines indicate the lower and upper 95% CIs. The knots were located at the 10th, 50th, and 90th percentiles (corresponding to points 0.23, 0.51, and 0.82, respectively). Cox regression was adjusted as in model 2. Participants with a continuous Nutri-Score DI (% of energy) above the 99th percentile (n = 121) were excluded. Sample size n=12,040.

398

Figure 3

Title

Risk of death associated with the hypothetical isocaloric replacement of foods labelled as D or E with fresh foods (A) and with foods labelled as A or B (B)

Explanation

A Replacement with fresh foods. Hypothetical effect of the isocaloric substitution of foods with the worst nutritional quality labelled as D or E with fresh foods.

B Replacement with foods labelled as A or B. Hypothetical effect of the isocaloric substitution of foods with the worst nutritional quality labelled as D or E with foods with the highest nutritional quality labelled as A or B.

Lines are restricted cubic splines. The solid line represents the adjusted hazard ratio and the dashed lines indicate the lower and upper 95% CIs. The knots were located at the 10th, 50th, and 90th percentiles. Cox regression was adjusted as in model 2.

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Table 1 Age-standardized baseline characteristics of the cohort participants according to quartiles of the Nutri-Score Dietary Indexes: the ENRICA Study (2008-2010) (N=12,054)

	5-CNS DI (based on g/day/kg)			Continuous Nutri-Score DI (based on g/day/kg)		
	Sex-specific quartiles			Sex-specific quartiles		
Characteristics¹	Q1 (best diet quality)	Q4 (worst diet quality)	P-trend	Q1 (best diet quality)	Q4 (worst diet quality)	P-trend
n	Missing					
5-CNS DI (based on g/day/kg)	17.5±4.1	58.9±21.3		20.2±8.7	56.3±22.4	
Continuous Nutri-Score DI (based on g/day/kg)	17.4±13.7	109.0±61.4		11.2±9.4	115.7±56.4	
Packaged foods (g/d)	664.9±186.5	1407.0±419.4	<0.001	781.0±302.1	1303.4±416.5	<0.001
Labelled as A	255.7±172.9	238.3±162.3	<0.001	312.5±197.2	212.0±139.8	<0.001
Labelled as B	242.6±139.9	502.5±332.8	<0.001	310.0±250.6	418.1±249.1	<0.001
Labelled as C	73.6±60.6	165.4±117.9	<0.001	83.1±70.6	147.6±113.0	<0.001
Labelled as D	56.2±44.4	150.0±106.5	<0.001	47.2±35.8	152.4±106.8	<0.001
Labelled as E	36.9±39.0	350.7±312.7	<0.001	28.1±28.7	373.4±301.3	<0.001
Fresh fruit/vegetables intake (g/d)	499.3±263.3	384.7±203.6	<0.001	512.0±264.9	370.6±197.4	<0.001
Non-processed meat and fish intake (g/d)	340.9±220.6	315.5±252.9	<0.001	332.1±210.2	298.8±237.1	<0.001
Total energy intake (kcal/d)	1684.8±498.7	2593.0±627.3	<0.001	1739.2±528.2	2571.3±632.1	<0.001
Women (%)	51.0	50.4	0.994	51.7	51.5	0.994
Age (y)	55.3± 15.1	37.1±15.3	<0.001	55.8±15.0	37.2±15.2	<0.001
Educational level (%)			<0.001			<0.001
No formal education	30.3	33.0		30.6	32.6	
Primary	38.3	43.6		38.6	44.0	
Secondary or higher	31.4	23.5		30.8	23.5	
Smoking status (%)			0.001			<0.001
Current smoker	44.9	47.4		47.1	47.3	
Former smoker	28.2	21.3		28.1	22.1	
Never smoker	26.8	31.3		24.8	30.6	
Body mass index (%)			<0.001			<0.001

<25 kg/m ²	24.2	47.3		30.2	44.4	
≥ 25 to 30 kg/m ²	41.9	38.5		40.8	38.8	
>30 kg/m ²	33.9	14.2		28.9	16.8	
Physical activity index (%)			<0.001			<0.001
Inactive	62.7	60.6		62.9	59.9	
Moderately inactive	21.3	23.4		21.9	24.2	
Moderately active	15.7	15.9		15.0	15.8	
Active	0.3	0.2		0.2	0.1	
Alcohol consumption (g/d)	9.0±18.9	7.9±13.2	0.126	8.1±16.7	8.4±14.4	0.687
Fiber intake (g/d)	20.9±8.2	24.5±8.4	<0.001	23.0±9.0	23.0±8.0	<0.001
Number of medications (%)			<0.001			<0.001
0	61.5	66.8		61.7	67.3	
1 to 3	29.3	27.4		28.5	27.1	
>3	9.3	5.8		9.8	5.6	
Hypertriglyceridemia (%)	20.5	18.5	<0.001	20.5	18.3	<0.001
Hypercholesterolemia (%)	53.9	48.7	<0.001	52.9	49.8	<0.001
High blood pressure (%)	37.0	29.9	<0.001	34.8	29.5	<0.001
Number of chronic conditions ² (%)			<0.001			<0.001
0	61.5	66.9		65.2	67.2	
1	25.6	23.2		24.8	22.6	
≥2	9.7	9.9		10.0	10.2	

Abbreviations: DI: dietary index, 5-CNS: 5-Color Nutri-Score

Only extreme quartiles are presented. Continuous variables presented as mean ± standard error and categorical variables as percentage and number of participants. P for trend across ordered groups were obtained using a Wilcoxon-type nonparametric test.

¹ All factors, except age, were directly standardized to the age distribution of the study participants. Percentages may not sum to 100 because of rounding.

² Chronic respiratory disease, coronary disease, stroke, osteoarthritis/arthritis, cancer, depression requiring treatment, and diabetes

Table 2. All-cause mortality risk according to the Nutri-score Dietary Indexes						
5-Color Nutri-score (5-CNS) DI (based on g/day/kg)						
	Sex-specific quartiles of the 5-CNS DI					
	Q1 (best diet quality)	Q2	Q3	Q4 (worst diet quality)	P-trend	Per 10-unit increment
5-CNS DI, interquartile range	15.0–20.8	24.9–28.9	33.7–39.4	47.6–66.3		
n	3,014	3,013	3,014	3,013		
Deaths	165	136	119	82		
Person-years	26,551	25,388	25,830	27,108		
Model 1, HR (95% CI)	1 (Ref.)	1.05 (0.80, 1.37)	1.18 (0.91, 1.54)	1.62 (1.23, 2.15)	0.001	1.13 (1.06, 1.20)
Model 2, HR (95% CI)	1 (Ref.)	1.11 (0.83, 1.49)	1.29 (0.96, 1.75)	1.93 (1.34, 2.79)	<0.001	1.16 (1.09, 1.24)
	Sex-specific quartiles of g/day/kg intake from foods labelled as D or E¹					
	Q1 (lowest intake)	Q2	Q3	Q4 (highest intake)	P-trend	Per 1-g/day/kg increment
Interquartile range (g/day/kg)	0.6–1.2	1.7–2.2	3.0–3.9	5.3–8.8		
n	3,014	3,013	3,014	3,013		
Deaths	179	146	95	82		
Person-years	26,452	25,328	25,742	27,356		
Model 1, HR (95% CI)	1 (Ref.)	1.15 (0.90, 1.48)	1.05 (0.78, 1.42)	1.79 (1.35, 2.37)	<0.001	1.07 (1.03, 1.10)
Model 2, HR (95% CI)	1 (Ref.)	1.20 (0.93, 1.56)	1.21 (0.87, 1.67)	2.15 (1.56, 2.97)	<0.001	1.08 (1.05, 1.12)
Continuous Nutri-Score DI (based on g/day/kg)						
	Sex-specific quartiles of the continuous Nutri-score DI					
	Q1 (best diet quality)	Q2	Q3	Q4 (worst diet quality)	P-trend	Per 10-unit increment
Continuous Nutri-score DI, interquartile range	5.0–17.4	27.0–37.0	49.1–64.6	86.6–136.4		

n	3,014	3,013	3,014	3,013		
Deaths	189	129	108	76		
Person-years	25,748	26,052	25,835	27,243		
Model 1, HR (95% CI)	1 (Ref.)	1.01 (0.78, 1.30)	1.08 (0.82, 1.42)	1.43 (1.06, 1.93)	0.025	1.03 (1.01, 1.06)
Model 2, HR (95% CI)	1 (Ref.)	1.06 (0.81, 1.40)	1.26 (0.94, 1.68)	1.72 (1.21, 2.43)	0.002	1.05 (1.02, 1.07)

Abbreviations: CI: Confidence Intervals, DI: dietary index, HR: Hazard ratio, 5-CNS: 5-Color Nutri-score

¹Grams from foods classified as D or E were summed up and divided by body weight in kg (g/kg), and participants were classified into sex-specific quartiles. The analyses were adjusted for the g/kg from foods classified as A, B, or C.

Cox regression **Model 1** was adjusted for sex and age (continuous), and **Model 2** was further adjusted for educational level (no formal education, primary, and secondary or higher), smoking status (current, former, and never smoker), body mass index (<25, ≥25-30, and >30 kg/m²), physical activity (inactive, moderately inactive, moderately active, active), alcohol consumption (g/day), fiber intake (g/day), total energy intake (kcal/d), number of medications (0, 1 to 3, and >3), hypertriglyceridemia (yes/no), hypercholesterolemia (yes/no), high blood pressure (yes/no), and number of self-reported chronic conditions (0,1, and ≥2). All models were further stratified by age.

Table 3. Cause-specific mortality risk according to the 5-Color Nutri-Score Dietary Indexes				
	Sex-specific terciles of the 5-CNS DI (based on g/day/kg)			
	T1 (best diet quality)	T2	T3 (worst diet quality)	P-trend
Interquartile range	16.3–22.9	28.4–34.5	42.9–60.9	
Person-years	35,100	34,016	35,761	
n	4,019	4,018	4,017	
All cause-mortality				
Deaths	212	162	128	
Model 1, HR (95% CI)	1 (Ref.)	1.06 (0.85, 1.33)	1.68 (1.33, 2.12)	0.024
Model 2, HR (95% CI)	1 (Ref.)	1.22 (1.52, 2.85)	2.08 (1.52, 2.85)	0.013
Cardiovascular mortality				
Deaths	54	46	40	
Model 1, HR (95% CI)	1 (Ref.)	1.20 (0.76, 1.91)	2.28 (1.40, 3.70)	0.044
Model 2, HR (95% CI)	1 (Ref.)	1.32 (0.78, 2.22)	2.82 (1.47, 5.34)	0.093
Cancer mortality				
Deaths	60	53	31	
Model 1, HR (95% CI)	1 (Ref.)	1.32 (0.88, 1.97)	1.37 (0.84, 2.21)	0.119
Model 2, HR (95% CI)	1 (Ref.)	1.68 (1.00, 2.83)	1.94 (0.98, 3.82)	0.036
Abbreviations: CI: Confidence Intervals, DI: dietary index, HR: Hazard ratio, 5-CNS: 5-Color Nutri-Score				
Cox regression Model 1 was adjusted for sex and age (continuous), and Model 2 was further adjusted for educational level (no formal education, primary, and secondary or higher), smoking status (current, former, and never smoker), body mass index (<25, ≥25-30, and >30 kg/m ²), physical activity (inactive, moderately inactive, moderately active, active), alcohol consumption (g/day), fiber intake (g/day), total energy intake (kcal/d), number of medications (0, 1 to 3, and >3), hypertriglyceridemia (yes/no), hypercholesterolemia (yes/no), high blood pressure (yes/no), and number of self-reported chronic conditions (0,1, and ≥2). All models were further stratified by age.				

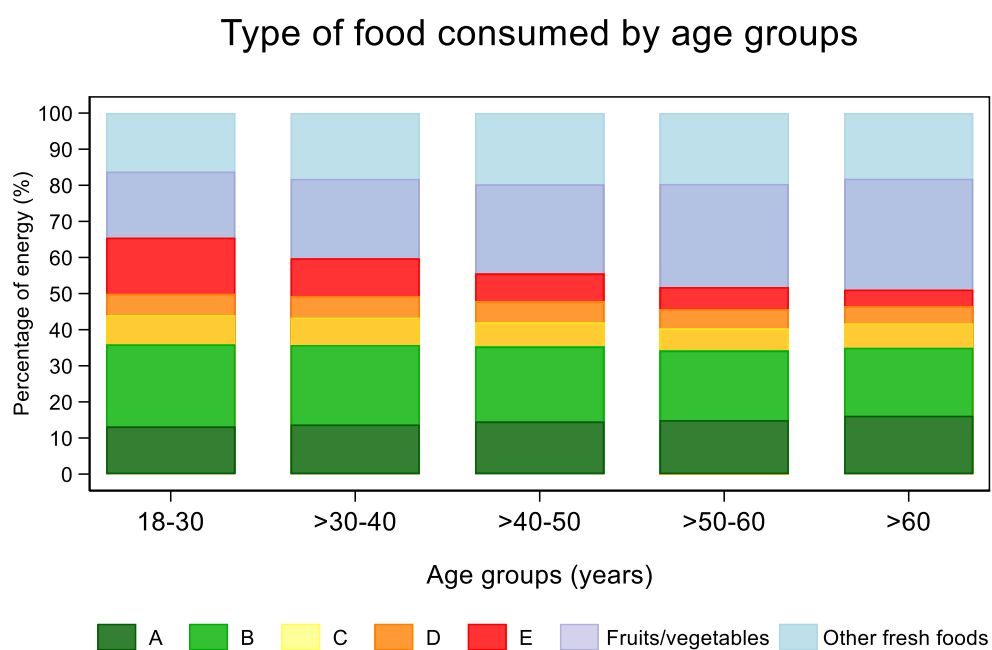
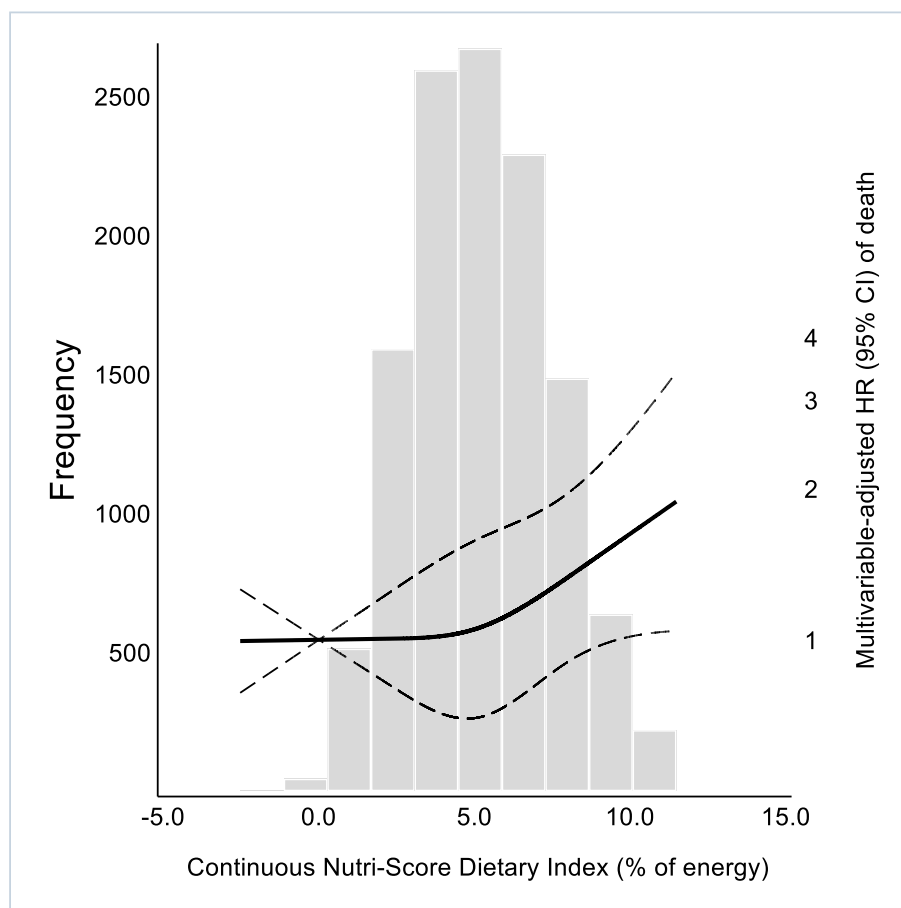
Figure 1**Figure 2**

Figure 3