

Title

Association between the nutrient profile system underpinning the Nutri-Score front-of-pack nutrition label and mortality in the SUN Project: a prospective cohort study

Author names and affiliations

Clara Gómez-Donoso^{1,2}, Miguel Ángel Martínez-González^{1,2,3,4}, Aurora Pérez-Cornago⁵, Carmen Sayón-Orea^{1,2}, J. Alfredo Martínez^{2,3,6,7}, Maira Bes-Rastrollo^{1,2,3}

¹ Department of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain

² Biomedical Research Centre Network on Physiopathology of Obesity and Nutrition (CIBERObn), Institute of Health Carlos III, Madrid, Spain

³ Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

⁴ Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, USA

⁵ Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom.

⁶ Department of Nutrition, Food Sciences and Physiology, Faculty of Pharmacy and Nutrition, University of Navarra, Pamplona, Spain.

⁷ Madrid Institute for Advanced Studies in Food (IMDEA Food), CEI UAM+CSIC, Madrid, Spain.

Corresponding author: Maira Bes Rastrollo (mbes@unav.es)

c/Irunlarrea 31008, Pamplona (Navarra), Spain; 948 425 600, ext. 6463

Abstract

Background & aims: Front-of-pack nutrition labelling is a key public health policy that can be adopted as part of a comprehensive set of measures to promote healthy diets. The Nutri-Score, a five-colour summary label based on a modified version of the British Food Standards Agency Nutrient Profiling System (FSAm-NPS), is being considered for implementation in several European countries including Spain. This study aimed to prospectively assess the association between the FSAm-NPS and mortality rate in a Spanish cohort of university graduates.

Methods: Analyses included 20,503 participants (mean [SD] age: 38 [12] years) from the SUN cohort. Dietary intake was assessed at baseline and after 10-years of follow-up with a validated semi-quantitative food-frequency questionnaire. The FSAm-NPS was calculated for each food/beverage based on their amount of energy, saturated fat, sugar, sodium, fibre, protein, fruits, vegetables, legumes, nuts, rapeseed, walnut and olive oils per 100 grams of product. The FSAm-NPS Dietary Index (DI) was computed as an energy-weighted mean of the FSAm-NPS scores of all foods and beverages consumed by each participant. Multivariable-adjusted Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause and cause-specific mortality according to baseline and updated FSAm-NPS DI scores.

Results: Over a median follow-up of 10.9 years, 407 participants died. A higher baseline FSAm-NPS DI score, reflecting consumption of foods with lower nutritional quality and hence less favourable Nutri-Score rating, was directly associated with all-cause mortality (HR $_{Q4 \text{ versus } Q1}$ = 1.82; 95% CI: 1.34 to 2.47; p-trend<0.001) and cancer mortality (HR: 2.44; 95% CI: 1.54 to 3.85; p-trend<0.001). No association was found for cardiovascular mortality.

Conclusions: The consumption of food products with a higher FSAm-NPS score (lower nutritional quality) was associated with a higher rate of all-cause and cancer mortality in a large prospective cohort of Spanish, middle-aged university graduates. These findings further support the implementation of Nutri-Score in Euro-Mediterranean countries

Keywords: Nutrient profiling system, Front-of-pack nutrition label, Non-communicable diseases, Mortality, Cohort study

31

Introduction

Globally, dietary risk factors are responsible for approximately 11 million deaths per year and 255 million DALYs (disability-adjusted life-years), which are attributable to preventable chronic diseases such as cardiovascular disease, cancer, and type 2 diabetes [1]. The continuously increasing availability and consumption of highly processed foods and beverages with low nutritional and high caloric content are key drivers of diet-related conditions [2].

Front-of-pack (FOP) nutrition labelling is one of the “best buy” policy measures that can be implemented in conjunction with educational campaigns to promote healthy eating and prevent diet-related chronic diseases [3-5]. FOP nutrition labels use nutrient profiling models to assess the nutritional quality of food products and display their healthiness in a simplified, visual form. Their purpose is to clarify nutritional information presented on-pack to help consumers make healthier food choices, and to encourage the industry to improve the nutritional composition of their products through reformulation [6].

The Nutri-Score FOP labelling scheme is a scientifically validated five-colour labelling system developed by independent French researchers [9]. It relies on a modified version of the British Food Standards Agency Nutrient Profiling System (FSAm-NPS) that was originally developed for the UK regulator for broadcast media to regulate television advertising to children [10, 11]. The algorithm allocates an overall score to a given food/beverage according to its nutrient

50 composition. Based on this overall score, Nutri-Score categorizes food products into five colours
51 reflecting their nutritional quality [9]. Each colour is also associated with a letter from A (dark
52 green) to E (dark orange) to make the labelling more accessible and understandable to consumers.

53 Several studies have shown that the underlying algorithm of the Nutri-Score is able to
54 discriminate the nutritional quality of foods in a way that is mostly consistent with current
55 nutritional recommendations [12-14]. Furthermore, the Nutri-Score format (i.e. interpretive, colour-
56 coded summary nutrition rating system) has been found to be well perceived and better understood
57 than other FOP nutrition labels such as the industry-preferred Reference Intakes label [15, 16]. It
58 has also been shown to be relatively useful in helping consumers to be aware of the nutritional
59 quality of foods and improving the nutritional quality of both intentional and actual purchases [17-
60 20]. In addition, it has been suggested that FOP labels such as Nutri-Score have the potential to help
61 decrease mortality from non-communicable diseases [21].

62 Previous prospective studies in the UK and France have reported that diets with a lower
63 nutritional quality (based on the FSA-NPS) are associated with a higher risk of developing chronic
64 diseases such as obesity, cardiovascular disease and cancer [22-32]. However, there have been no
65 studies evaluating prospective associations between potential adoption of the Nutri-Score and
66 mortality rate in the Spanish population. In this context, where olive oil is the major culinary fat,
67 and particularly given the strong evidence supporting the beneficial effects of olive oil regardless of
68 its energy and fat content [33-35], it also seems important to assess the effect of assigning olive oil
69 the highest nutritional quality. Therefore, this study aims to evaluate the association between
70 adherence to the FSAm-NPS Dietary Index (DI) and all-cause and cause-specific mortality in the
71 Seguimiento Universidad de Navarra (SUN) prospective cohort study.

72 **Methods**

73 **Study population: The SUN Study**

74 The SUN Study is a prospective, dynamic, multipurpose and permanently open cohort of
75 Spanish university graduates investigating the impact of diet and lifestyle on non-communicable

diseases. The design, objectives, and methods have been described elsewhere [36]. Briefly, since December 1999 graduates from the University of Navarra and other Spanish universities and professional are invited to participate. Information of participants is gathered through postal or web-based self-reported questionnaires at baseline and every 2 years. By July 2018, the cohort included 22,790 participants.

To ensure a minimum follow-up of two years, we only considered participants recruited before October 2015. Out of 22,467 eligible participants, we excluded 446 with a total daily energy intake below and above the 1st and 99th centiles. Among the remaining participants, 1518 were lost to follow-up (retention rate: 93%). For the present analyses, we used data from 20,503 participants of the SUN cohort.

Dietary intake assessment

Dietary intake was assessed at baseline using a semi-quantitative 136-item food-frequency questionnaire (FFQ) previously validated and repeatedly re-evaluated in Spain [37, 38]. The FFQ classifies 136 food items into general food groups: Dairy, eggs, meat and fish, vegetables, fruits, legumes and cereals, oils and fats, pastries, beverages and miscellaneous. A commonly used portion size was specified (slices, glass, teaspoons, etc.) for each of the food items, and participants were asked how often they had consumed that unit on average over the previous year. There were nine options offered to indicate frequency of consumption, ranging from never or hardly ever to more than six times a day. To estimate daily consumption for each food item, the portion size was multiplied by the frequency of consumption. Nutrient intakes were computed as the sum of the frequency of consumption (converted to daily intake) of each item multiplied by nutrient composition of a specified portion size, according to the Spanish food composition tables [39].

Adherence to the Mediterranean Diet was evaluated using the a priori 9-item Mediterranean Diet Score proposed by Trichopoulou et al. [40]. Additionally, adherence to the Spanish food pyramid was assessed according to the Spanish Society of Community Nutrition (“Sociedad Española de Nutrición Comunitaria”, SENC) food pyramid score [41] to examine the consistency of

102 Nutri-Score with national dietary guidelines. The frequency of consumption (servings/day) of ultra-
103 processed food, as defined by the NOVA food classification system [42], was also assessed.

104 **FSAm-NPD DI computation**

105 The FSAm-NPS score is a modified version of the original FSA-NPS, which was developed
106 in the UK by the Office of Communication (Ofcom) to categorize foods and drinks as ‘healthier’
107 and ‘less healthy’ in order to regulate television food advertising to children [10,11]. The FSAm-
108 NPS score included adaptations in the established cut-offs to allow for more than two categories
109 reflecting nutritional quality. Additional modifications included the scoring criteria for cheese,
110 added fats and beverages, according to recommendations from the French National Nutrition and
111 Health Program and the French High Council for Public Health [43, 44].

112 The FSAm-NPS score, which punctuates the amount of nutrients per 100 grams of product,
113 was calculated for all foods and beverages in the SUN FFQ as follows (full details shown in
114 Supplemental File 1 and previous publications [23-30]): 0 to 40 points were allocated for the
115 content of critical nutrients that should be limited (0–10 points for each: sugars [g], saturated fats
116 [g], sodium [mg], and energy [kJ]), and 0 to 15 points were allocated for the content of beneficial
117 nutrients that should be encouraged (0– 5 points for each: fibres [g], proteins [g], and the percentage
118 of fruits, vegetables, legumes, nuts , rapeseed, walnut and olive oils that compose the total product
119 [%]). The total score of the product was calculated by subtracting the “negative” (nutrients to limit)
120 points from the “positive” (nutrients to encourage) points. Thus, the final FSAm-NPS score for each
121 food/beverage was based on a discrete continuous scale that could theoretically range from –15
122 (most healthy) to +40 (least healthy). To obtain a dietary score at the individual level, the FSAm-
123 NPS Dietary Index (DI) was computed as an energy-weighted mean of the FSAm-NPS scores of all
124 foods and beverages consumed by a participant using the following equation:

$$125 \quad FSAm - NPS DI = \frac{\sum_{i=1}^n (FS_i E_i)}{\sum_{i=1}^n E_i}$$

126 FS_i represents the score of food/beverage i , E_i the energy intake from food/beverage i , and n the
127 total number of food/beverage consumed. Therefore, higher FSAm-NPS-DI scores reflected lower
128 nutritional quality in the total foods consumed.

129 **Mortality assessment**

130 Information on mortality and its cause was identified through an active follow-up. Three
131 postal addresses, email addresses and phone numbers were requested for each participant. Up to
132 five mailings were sent to complete the biennial follow-up questionnaires and, if an answer was not
133 received, participants were contacted by email or phone. In most cases, vital status was ascertained
134 by reports from next of kin, work associates, or authority postal service. Additionally, both the
135 National Statistics Institute and the Spanish National Death Index were checked on a yearly basis,
136 which allowed us to confirm the deaths and their causes. The specific cause of death was only
137 unknown for 16 out of 407 deaths (3.9%).

138 **Assessment of covariates**

139 An extensive questionnaire was completed by all participants upon enrolment. This baseline
140 questionnaire collects self-reported data on participants' sociodemographics, anthropometrics,
141 personal and family medical history, and lifestyle habits. Many self-reported measures have been
142 previously validated: anthropometric data including body mass index (BMI) [45], physical activity
143 [46], hypertension [47], and depression [48], and have been found to be sufficiently valid as to be
144 used in epidemiological studies.

145 Taking advantage of the information on physical activity and sedentary behaviours collected
146 in the SUN cohort, a 0–8-point active lifestyle score was calculated according to previously
147 published criteria [50]. This score takes into account the volume, intensity and frequency of
148 physical activity, as well as the average hours spent in sedentary activities like watching television
149 and sitting per day.

150 **Statistical analyses**

151 Inverse probability weighting was used to adjust the means or proportions of baseline
152 characteristics of participants for age and sex according to FSAm-NPS-DI quartiles.

153 Associations between FSAm-NPS DI (quartiles and per 2-point increment) and all-cause
154 mortality, cardiovascular mortality and cancer mortality were characterized fitting multivariable
155 Cox proportional hazards models with age as the underlying time variable (birth date as origin).
156 Participants contributed person-years to the model until their date of death, loss to follow-up, or
157 when the last follow-up questionnaire was completed, whichever occurred first. For cause-specific
158 mortality analyses (cancer and cardiovascular mortality), deaths due to other causes were excluded.
159 Hazard ratios (HR) and 95% confidence intervals (CI) were estimated for the second to fourth
160 quartile, considering the first quartile as the reference.

161 Cox regression models were adjusted for several potential confounders defined a priori
162 based on the existing literature [51]. Multivariable models were stratified for age and recruitment
163 period, and adjusted for other known risk factors: Model 1 was adjusted for sex, marital status
164 (married), 8-item active lifestyle score (continuous), smoking status (never, current, former,
165 missing), between-meal snacking (yes/no), following a special diet at baseline (yes/no), BMI (linear
166 and quadratic terms), total energy intake (continuous), and years of university education
167 (continuous); Model 2 was additionally adjusted for pack-years of cigarette smoking (continuous),
168 family history of cardiovascular disease (CVD, yes/no), family history of cancer (yes/no), and
169 baseline CVD, diabetes, hypertension, high blood cholesterol, cancer and depression (yes/no).
170 When participants' data on between-meal snacking or following a special diet were missing, we
171 assigned them a value of 0 (no). For continuous covariates, missing data were imputed using
172 predictor variables like age, sex, years of university education, BMI and physical activity.

173 To minimize potential measurement errors and account for long-term variations in diet, Cox
174 models were also fitted with repeated measures of diet by using updated data on food intake after 10
175 years of follow-up. The last observations were carried forward to prevent participants being
176 excluded from the analyses (i.e. dietary intake data collected in the 10-y follow-up FFQ was used

177 when available [excluding mortality cases that occurred before] and baseline data was used in the
178 case of participants that had been followed for longer than 10 years but had not completed 10-y
179 follow-up FFQ).

180 Linear trend tests were performed by assigning quartile-specific medians to each category
181 and treating the FSAm-NPS-DI as a continuous variable. We verified the proportionality of hazards
182 through examination of the interaction of the FSAm-NPS-DI with time.

183 To determine the contribution of different food groups to the between-person variance in the
184 FSAm-NPS-DI score, a series of nested least-squares linear regression models were constructed
185 after stepwise-selection regression analyses. The additional contribution of a given food group was
186 reflected in the cumulative R^2 . The FFQ items included in each food group are shown in
187 Supplemental Table 2.

188 To assess consistency of the algorithm underpinning the Nutri-Score with the Spanish
189 dietary recommendations, Pearson's correlation coefficients were calculated between the FSAm-
190 NPS-DI, the Mediterranean Diet score and the Spanish food pyramid score.

191 Nelson-Aalen estimators were plotted to show all-cause mortality rates during follow-up
192 (cumulative hazard curves) according to baseline FSAm-NPS-DI quartiles. Inverse probability
193 weighting was used to adjust the Nelson-Aalen curves for the previously mentioned confounders.
194 For simplification purposes, we merged the first and second quartiles into one group (i.e.
195 participants with FSAm-NPS-DI scores below the median) and the third and fourth quartiles into
196 another group (scores above the median). This grouping lowers random variability and provides
197 more robust estimates.

198 A priori stratified analyses were conducted according to sex (men/women), age at
199 recruitment ($>55/ \leq 55$ years), baseline BMI ($\geq 25/ < 25$ kg/m²), smoking status (ever/never smoker)
200 and ultra-processed food intake ($\geq 3/ < 3$ serving/day). To assess effect modification, we calculated
201 the P value for interaction between FSAm-NPS-DI quartiles and the abovementioned prespecified

202 variables through likelihood-ratio tests that compared the fully adjusted Cox regression model and
203 the same model with interaction product-terms (three degrees of freedom).

204 We also reran our analyses under different scenarios: using different cut-offs for plausible
205 energy intakes (predefined limits proposed by Willett [<800 or >4000 kcal/d for men and <500 or
206 >3500 kcal/d for women] [51] and 5th and 95th centiles); excluding participants with prevalent
207 conditions at baseline (CVD and/or cancer, hypertension, depression and following a special diet);
208 excluding deaths from injuries, cancer, and CVD; excluding early deaths (follow up < 2 years);
209 modifying adjustments (additionally adjusting for a ratio of monounsaturated fatty acids [MUFA] to
210 saturated fatty acids [SFA] and excluding BMI); and modifying the FSAm-NPS score for olive oil
211 from “C-yellow” (original score according to Nutri-Score algorithm) to “A-dark green” (FSAm-
212 NPS value -11 was assigned to olive oil, which corresponds to the lowest (i.e. more favourable)
213 score among food items in the SUN FFQ).

214 All P values were two-tailed, and statistical significance was set at the conventional 0.05
215 level. Analyses were performed using STATA version 14.0 (StataCorp, College Station, TX).

216 **Results**

217 Among 20,503 participants (8,016 men and 12,487 women; 38 ± 12 years [mean \pm SD age
218 at enrollment]), a total of 407 deaths during 223,574 persons-years of follow-up (median follow-up
219 time: 10.9 years) were identified. Among 407 all-cause deaths, 208 deaths were attributed to cancer
220 and 83 to CVD. The mean \pm SD age at death among deceased participants was 66 ± 16 years, and
221 the main cause of death was cancer ($n=208$).

222 Age-and sex-adjusted baseline characteristics of participants according to FSAm-NPS-DI
223 quartiles are shown in Table 1.

Table 1. Age and sex adjusted* baseline characteristics of participants across FSAm-NPS DI quartiles, SUN cohort, 1999-2015. Values are means (\pm standard deviations) unless stated otherwise.

	Quartiles of the FSAm-NPS DI score			
	Q1 (n=5126)	Q2 (n=5126)	Q3 (n=5126)	Q4 (n=5125)
FSAm-NPS DI range	-4.2 to 3.4	3.5 to 4.8	4.9 to 6.1	6.2 to 16.4
FSAm-NPS DI mean	2.2 (1.1)	4.2 (0.4)	5.5 (0.4)	7.4 (1.1)
Married (<i>N</i> (%))	2406 (46.8)	2609 (51.1)	2651 (51.8)	2557 (49.9)
Years of university education	5.0 (1.5)	5.0 (1.5)	5.1 (1.5)	5.1 (1.5)
Smoking status (<i>N</i> (%))				
Never	2775 (53.9)	2468 (48.3)	2386 (46.6)	2296 (44.8)
Current	835 (16.2)	1084 (21.2)	1224 (23.9)	1339 (26.1)
Former	1491 (29.0)	1513 (29.6)	1474 (29.0)	1443 (28.1)
Body mass index (kg/m ²)	23.5 (3.5)	23.6 (3.5)	23.5 (3.6)	23.5 (3.6)
Chronic conditions at baseline (<i>N</i> (%)):				
Cancer	175 (3.4)	168 (3.3)	181 (3.5)	164 (3.2)
Diabetes	123 (2.4)	107 (2.1)	76 (1.5)	58 (1.1)
Hypertension	1016 (19.8)	1005 (19.7)	994 (19.4)	1020 (19.9)
Hypercholesterolaemia	967 (18.8)	890 (17.4)	826 (16.1)	803 (15.7)
Cardiovascular disease	98 (1.9)	71 (1.4)	70 (1.4)	86 (1.7)
Depression	610 (11.9)	582 (11.4)	582 (11.4)	605 (11.8)
Family history of CVD (<i>N</i> (%))	714 (13.9)	725 (14.2)	668 (13.1)	743 (14.5)
Family history of cancer (<i>N</i> (%))	754 (14.7)	756 (14.8)	802 (15.7)	840 (16.4)
Physical activity (MET hours/week)	27.5 (27.4)	23.6 (21.7)	21.5 (20.7)	20.6 (20.6)
Sedentary activities:				
Television viewing (h/day)	1.5 (1.1)	1.6 (1.1)	1.7 (1.2)	1.7 (1.2)
Sitting time (h/day)	5.1 (2.1)	5.2 (2.1)	5.3 (2.0)	5.5 (2.1)
Active lifestyle score (0–8 points) ^a	4.6 (1.8)	4.3 (1.8)	4.1 (1.8)	3.9 (1.8)
Following special diets (<i>N</i> (%))	735 (14.3)	407 (8.0)	277 (5.4)	236 (4.6)
Between-meal snacking (<i>N</i> (%))	1320 (25.7)	1646 (32.2)	1831 (35.8)	2220 (43.3)
Adherence to MedDiet (0–9 points) ^b	5.3 (1.6)	4.5 (1.7)	4.0 (1.6)	3.3 (1.6)
Adherence to Spanish Dietary Guidelines SENC food pyramid score (0–140 points) ^c	90.3 (14.6)	82.7 (13.2)	77.6 (12.5)	70.8 (13.1)
Total energy intake (kcal/day)	2296 (744)	2432 (718)	2536 (730)	2737 (863)
Macronutrient intake (% energy):				
Carbohydrate	46.8 (7.7)	43.7 (6.9)	42.4 (6.6)	40.7 (7.4)
Protein	19.5 (3.7)	18.5 (2.9)	17.6 (2.7)	16.5 (3.1)
Fat:	32.3 (6.3)	36.0 (5.7)	37.8 (5.6)	40.2 (6.2)
SFAs	10.1 (2.7)	12.1 (2.5)	13.1 (2.6)	14.7 (3.3)

MUFAs	14.0 (3.6)	15.6 (3.6)	16.2 (3.4)	17.0 (3.6)
PUFAs	4.6 (1.4)	5.0 (1.4)	5.4 (1.5)	5.7 (1.7)
Total dietary fibre intake (g/day)	37.7 (17.4)	30.0 (12.4)	26.8 (10.6)	24.2 (10.7)
Alcohol intake (g/day)	4.2 (6.3)	6.1 (8.2)	7.5 (10.4)	9.6 (15.5)
Ultra-processed food intake (servings/day) ^d	2.2 (1.2)	3.1 (1.4)	3.8 (1.6)	5.3 (2.5)
Food consumption (servings/day):				
Vegetables	3.2 (2.2)	2.5 (1.5)	2.1 (1.2)	1.8 (1.1)
Fruits	3.8 (3.1)	2.6 (1.9)	2.1 (1.5)	1.7 (1.4)
Nuts	0.2 (0.4)	0.2 (0.3)	0.1 (0.2)	0.1 (0.2)
Vegetable fat	1.8 (1.4)	2.0 (1.6)	1.9 (1.6)	1.9 (1.8)
Olive oil	1.6 (1.4)	1.7 (1.5)	1.6 (1.4)	1.5 (1.5)
Animal fat	0.1 (0.2)	0.1 (0.3)	0.2 (0.3)	0.2 (0.4)
Legumes	0.5 (0.4)	0.4 (0.3)	0.4 (0.3)	0.3 (0.3)
Whole-grain bread ^e	0.4 (0.8)	0.3 (0.6)	0.2 (0.5)	0.1 (0.4)
Dairy products	1.3 (1.4)	1.7 (1.4)	1.9 (1.4)	2.1 (1.7)
Reduced-fat dairy products	1.8 (1.8)	1.5 (1.5)	1.2 (1.3)	1.1 (1.4)
Fish and shellfish	0.9 (0.7)	0.8 (0.5)	0.7 (0.4)	0.6 (0.4)
Red meat	0.5 (0.3)	0.5 (0.3)	0.6 (0.3)	0.6 (0.3)
Poultry meat	0.4 (0.4)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)
Processed meat	0.6 (0.5)	0.9 (0.5)	1.0 (0.6)	1.3 (1.0)
Fast food ^f	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.3 (0.2)
Miscellaneous food ^g	0.5 (0.7)	0.7 (0.8)	0.8 (0.8)	0.9 (1.2)
Pastries	0.5 (0.5)	0.9 (0.7)	1.2 (0.9)	2.0 (1.7)
Sugary drinks	0.2 (0.3)	0.3 (0.4)	0.4 (0.5)	0.5 (0.8)
Fermented alcoholic beverages	0.3 (0.5)	0.4 (0.7)	0.5 (0.9)	0.6 (1.0)

FSAm-NPS DI=Food Standards Agency Nutrient Profiling System (modified version) Dietary Index; MET=metabolic equivalent of task; SFAs=saturated fatty acids; MUFAs=monounsaturated fatty acids; PUFAs=polyunsaturated fatty acids.

*Adjusted through inverse probability weighting.

^a Active lifestyle score based on both physical activity and sedentary behaviours [49].

^b 9-item Mediterranean Diet Score proposed by Trichopoulou et al. [40].

^c Spanish Society of Community Nutrition (“Sociedad Española de Nutrición Comunitaria”, SENC) food pyramid score [41]

^d NOVA food classification system [42].

^e Information on other whole-grain products was unavailable in the SUN cohort FFQ.

^f Hamburgers, sausages, and pizza.

^g Croquettes, instant soups, and commercial sauces (ketchup, mayonnaise).

224 Participants with a higher FSAm-NPS DI score, reflecting a diet of lower nutritional quality,
225 were more likely to consume higher amounts of unhealthy foods and beverages (e.g. processed
226 meat, fast food, pastries, sugary drinks and alcohol) and lower amounts of healthy foods (e.g. fruits,
227 vegetables, nuts, legumes, fish and poultry meat). Consequently, they presented lower adherence to
228 the Spanish dietary guidelines and to the Mediterranean Diet Score. They also reported higher total
229 energy intake and lower levels of physical activity, and were more likely to snack between meals,
230 be current smokers and have a family history of CVD and cancer (Table 1).

231 Associations between the FSAm-NPS DI and all-cause mortality are shown in Table 2. A
232 higher FSAm-NPS DI score was directly associated with a higher rate of all-cause and cancer
233 mortality in all models. The HR for all-cause mortality in the highest versus the lowest FSAm-NPS
234 DI quartile was 1.82 (95% CI: 1.34–2.47; P-trend < 0.001) in the fully adjusted model. For cancer
235 mortality, the fully-adjusted HR in the highest versus the lowest FSAm-NPS DI quartile was 2.44
236 (95% CI: 1.54–3.85; P-trend < 0.001). Every 2 additional points in the FSAm-NPS DI score were
237 associated with a 19% relatively higher rate of all-cause mortality and 24% relatively higher rate of
238 cancer mortality. Consistently, 1-point increment in the FSAm-NPS DI score was associated with
239 higher rates of all-cause mortality (multivariable-adjusted [model b] HR, 95% CI = 1.09, 1.04–1.15)
240 and cancer mortality (multivariable-adjusted [model b] HR, 95% CI = 1.11, 1.04–1.19). No
241 significant associations were observed for cardiovascular mortality.

242 Accordingly, multivariable-adjusted Nelson-Aalen curves (Fig 1) exhibited a progressively
243 higher cumulative hazard rate of all-cause mortality across increasing baseline FSAm-NPS DI
244 quartiles.

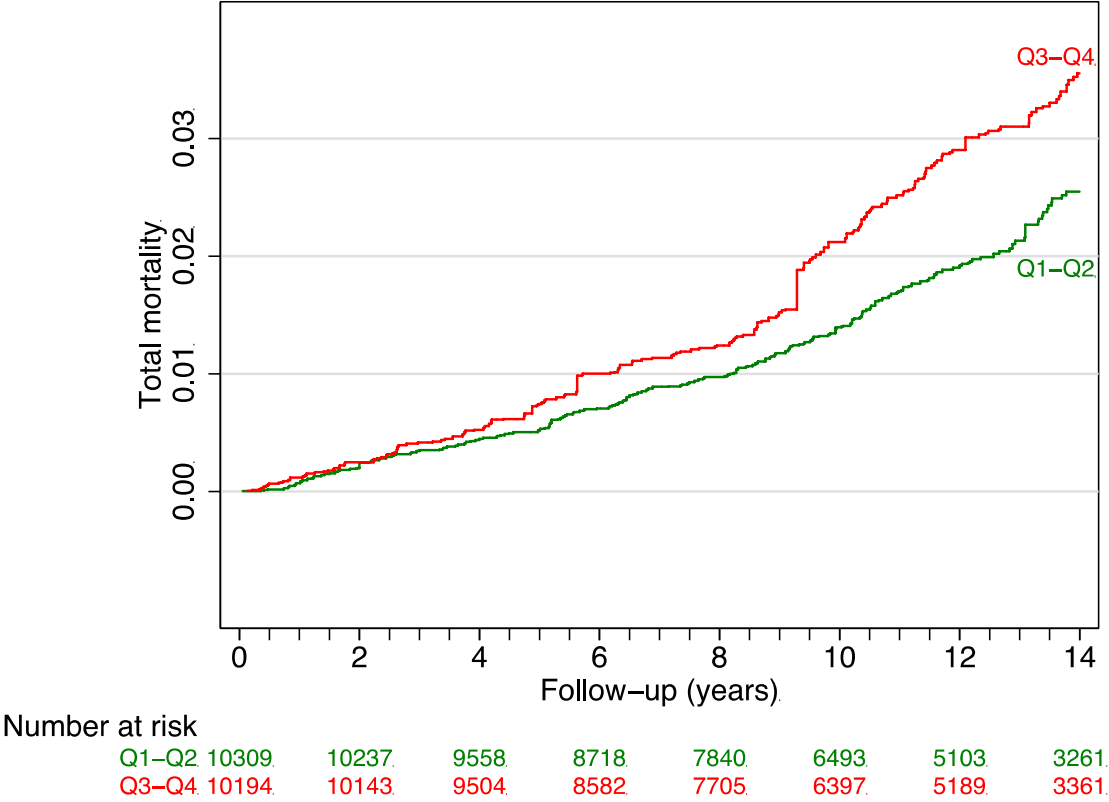


Figure 1. Nelson-Aalen estimates of all-cause mortality according to FSAm-NPS DI quartiles. Adjusted (using inverse probability weighting) for age, sex, marital status, 8-item physical activity score, smoking status, pack-years of smoking, snacking, special diet at baseline, body mass index, years of university education, total energy intake, family history of CVD, family history of cancer, baseline CVD, diabetes, hypertension, hypercholesterolaemia, cancer and depression, and recruitment period.

Table 2. Cox proportional hazard ratios (95% confidence intervals) for mortality according to quartiles of the FSAm-NPS DI.

	Quartiles (Q) of the FSAm-NPS DI score					
All-cause mortality	Q1	Q2	Q3	Q4	P-trend	Per 2-point increment
<i>N</i>	5126	5126	5126	5125		
Person years	53 399	55 446	57 255	57 474		
Deaths	104	107	93	103		
Age- and sex-adjusted	1.00 (ref)	1.53 (1.16 to 2.03)	1.56 (1.18 to 2.08)	2.11 (1.58 to 2.82)	<0.001	1.26 (1.15 to 1.38)
Multivariable adjusted ^a	1.00 (ref)	1.41 (1.06 to 1.88)	1.40 (1.05 to 1.88)	1.85 (1.37 to 2.50)	<0.001	1.19 (1.08 to 1.32)
Multivariable adjusted ^b	1.00 (ref)	1.37 (1.03 to 1.83)	1.43 (1.06 to 1.94)	1.82 (1.34 to 2.47)	<0.001	1.19 (1.08 to 1.32)
Repeated measurements of diet ^a	1.00 (ref)	1.30 (0.98 to 1.73)	1.30 (0.97 to 1.74)	1.73 (1.29 to 2.34)	<0.001	1.18 (1.07 to 1.31)
Repeated measurements of diet ^b	1.00 (ref)	1.28 (0.96 to 1.70)	1.33 (0.99 to 1.79)	1.71 (1.26 to 2.31)	<0.001	1.18 (1.06 to 1.31)
Cancer deaths						
<i>N</i>	5065	5081	5085	5073		
Person-years	52 958	55 073	56 920	57 079		
Cancer deaths	43	62	52	51		
Age- and sex-adjusted	1.00 (ref)	2.23 (1.50 to 3.32)	2.18 (1.44 to 3.32)	2.64 (1.73 to 4.05)	<0.001	1.32 (1.16 to 1.49)
Multivariable adjusted ^a	1.00 (ref)	2.11 (1.41 to 3.16)	1.95 (1.29 to 2.95)	2.49 (1.59 to 3.89)	<0.001	1.26 (1.11 to 1.43)
Multivariable adjusted ^b	1.00 (ref)	2.08 (1.37 to 3.15)	1.99 (1.30 to 3.06)	2.44 (1.54 to 3.85)	<0.001	1.24 (1.09 to 1.41)
Repeated measurements of diet ^a	1.00 (ref)	1.94 (1.30 to 2.88)	1.75 (1.16 to 2.64)	2.32 (1.50 to 3.58)	<0.001	1.25 (1.09 to 1.44)
Repeated measurements of diet ^b	1.00 (ref)	1.90 (1.27 to 2.84)	1.78 (1.16 to 2.71)	2.26 (1.45 to 3.52)	<0.001	1.24 (1.08 to 1.43)
Cardiovascular deaths						
<i>N</i>	5057	5034	5048	5040		
Person-years	52 913	54 715	56 605	56 760		
CVD deaths	35	15	15	18		

Table 2. Continued						
Age- and sex-adjusted	1.00 (ref)	0.69 (0.37 to 1.29)	0.90 (0.49 to 1.65)	1.40 (0.76 to 2.58)	0.457	1.14 (0.90 to 1.46)
Multivariable adjusted ^a	1.00 (ref)	0.50 (0.24 to 1.00)	0.65 (0.35 to 1.21)	0.98 (0.52 to 1.84)	0.745	1.09 (0.85 to 1.39)
Multivariable adjusted ^b	1.00 (ref)	0.57 (0.27 to 1.17)	0.78 (0.41 to 1.49)	1.02 (0.52 to 1.98)	0.953	1.12 (0.88 to 1.42)
Repeated measurements of diet ^a	1.00 (ref)	0.43 (0.21 to 0.89)	0.64 (0.35 to 1.18)	0.93 (0.50 to 1.75)	0.968	1.02 (0.79 to 1.31)
Repeated measurements of diet ^b	1.00 (ref)	0.49 (0.23 to 1.04)	0.76 (0.39 to 1.45)	0.96 (0.50 to 1.86)	0.801	1.03 (0.81 to 1.31)
^a Adjusted for age (underlying time variable), sex, marital status (married), 8-item physical activity score (continuous), smoking status (never, current, former), snacking (dichotomous), special diet at baseline (dichotomous), body mass index (linear and quadratic terms), total energy intake (continuous), and years of university education (continuous). Stratified by age and recruitment period. ^b Additionally adjusted for family history of cardiovascular disease (CVD) and cancer, baseline CVD, diabetes, hypertension, cancer and depression, self-reported hypercholesterolaemia at baseline, and lifelong smoking (pack-years of smoking, continuous).						

247 The main sources of variability in the FSAm-NPS DI score are shown in Table 3. Pastries
248 and processed meats were the major contributors to the FSAm-NPS DI score variability among
249 participants from the SUN cohort. The contribution made by each food group is reflected in the
250 change in cumulative R^2 .
251

Table 3. Main sources of variability in the Food Standards Agency modified Nutrient Profiling System Dietary Index (FSAm-NPS DI) and Pearson correlation coefficients (R), SUN cohort, 1999-2015.

	Pearson's r	R ²	Change in R ²
Pastries	0.63	0.39	
Processed meats	0.55	0.62	0.22
Whole-fat dairy products	0.44	0.70	0.08
Miscellaneous foods ^a	0.34	0.77	0.07
Fermented alcoholic beverages	0.19	0.80	0.03
Fruits	0.17	0.82	0.02
Vegetable fats	0.22	0.84	0.02
Sugary drinks	0.27	0.86	0.02
Vegetables	0.16	0.87	0.01
Animal fats	0.24	0.88	0.01

^a Croquettes, instant soups, and commercial sauces (ketchup, mayonnaise).

252

253 The classification of foods according to the nutrient profiling system underlying the Nutri-
254 Score was consistent with Mediterranean and national dietary recommendations. The higher the
255 FSAm-NPS DI score, the lower the adherence to the Spanish dietary guidelines (Pearson's
256 correlation coefficient [r] = -0.51) and the Mediterranean Diet Score (r = -0.45). Analyses at the
257 food level revealed that foods which consumption is recommended on a daily basis according to
258 Spanish dietary guidelines (cereals, fruits, vegetables, dairy, legumes, nuts, olive oil, poultry meat
259 and fish) were more favorably classified (e.g. 88.1% were classified as A or B) than foods which
260 consumption should be limited (processed and red meats, pastries, and added fats) (e.g. 76.9%
261 were classified as D or E).

262 None of the tests for interaction were significant (P for all > 0.1) and similar results were
263 observed in subgroup analyses (Fig 2). In addition, results remained substantially unchanged in the
264 alternative scenarios assessed in sensitivity analyses, suggesting that the direct linear association
265 between FSAm-NPS DI and mortality was robust. Remarkably, assigning an A score (i.e. the
266 highest nutritional quality) instead of a C score to olive oil strengthened the association between
267 FSAm-NPS and all-cause mortality.

Figure 2. Subgroup and sensitivity analyses for association between FSAm-NPS DI and all-cause mortality (multivariable-adjusted^b HR and 95% CI for the highest vs. lowest quartile).
See table 2 footnote^b for adjustment factors.

Discussion

In this prospective cohort study of Spanish middle-aged university graduates, a higher FSAm-NPS DI score (i.e. consuming food products with a lower nutritional quality) was associated with a higher rate of all-cause and cancer mortality. Every 2 additional points in the FSAm-NPS DI score were associated with a significant 19% higher rate of all-cause mortality and 24% higher rate of cancer mortality. There was no association with CVD mortality.

To our knowledge, this study represents the first effort to evaluate the association between the potential implementation of the Nutri-Score and all-cause mortality in the Spanish population, as assessed using the FSAm-NPS underpinning the Nutri-Score labelling system. Previous studies investigated prospective associations between FSAm-NPS DI and chronic diseases in two large French cohorts, the SU.VI.MAX (SUpplementation en VItamines et Minéraux AntioXydants) [26-29] and the NutriNet-Santé [24,30], and in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study [25]. Less-healthy food choices, as reflected by a higher FSAm-NPS DI, were associated with a higher risk of developing cancer [24-26], metabolic syndrome [27], overweight and obesity [28], and cardiovascular disease [29, 30].

Similar results were observed in a UK population-based cohort, the Whitehall II study, using the original FSA-NPS (UK Ofcom nutrient profile model) as indicator of the nutritional quality of the diet [31]. Likewise, another study of UK adults from the EPIC-Norfolk cohort found no associations between consumption of less-healthy food, defined using the FSA-NPS, and incident cardiovascular disease or cardiovascular mortality, but did find an association between the quantity of less-healthy food consumed and all-cause mortality [32]. Our study found a particularly strong association for cancer mortality across successive quartiles of the FSAm-NPS DI score. The FSAm-NPS score relies on nutritional components that are known to be involved in both cancer and

cardiometabolic disease development, such as CVD and diabetes [52], and it is in line with the World Cancer Research Fund's recommendations related to diet [53]. Furthermore, the FSAm-NPS also takes into account the energy content of food products, so a higher FSAm-NPS DI score implies a higher consumption of foods with a higher energy density and may contribute to overweight and obesity, which is an established preventable risk factor for many types of cancer [54]. The fact that no association was found for CVD mortality could be due to a lack of statistical power, as the number of observed CVD deaths in this young and highly-educated Mediterranean cohort was small.

There is currently a global societal debate concerning the need to introduce a simplified nutritional label on foods as part of a broader policy approach to improve population diets, which led to the announcement of the implementation of the Nutri-Score labelling scheme in November 2018 by Spanish authorities. The findings of the present study are consistent with those based on French and other European settings and show a positive association with mortality. Additionally, this study provides new evidence on the consistency between the nutrient profiling system underlying the Nutri-Score and both Mediterranean and Spanish dietary recommendations, thereby supporting the suitability of the adoption of Nutri-Score in Europe and specifically in Spain. Importantly, reclassifying olive oil score from "C-yellow" into "A-dark green" strengthened the association between Nutri-Score and all-cause mortality in the Spanish context, which supports the case for reassessing the way in which olive oil is integrated in the Nutri-Score computation. Such reconsideration could improve consistency with strong scientific evidence obtained from the PREDIMED (Prevention with Mediterranean Diet) trial that showed that a Mediterranean Diet supplemented with extra-virgin olive oil was associated with a reduced risk of breast cancer, cardiovascular disease and type 2 diabetes [33-35]. Many other epidemiological and experimental studies have also thoroughly supported the beneficial health effects of olive oil, which are not comparable to the effects of any other added fat [55]. Therefore, and considering that Nutri-Score aims to facilitate comparison of foods within the same category, it seems that olive oil should score

317 higher than any other oil [56]. This could be achieved by introducing a modification to the Nutri-
318 Score algorithm (FSAm-NPS) that better accounts for unsaturated fat content and bioactive
319 molecules like polyphenolic compounds that may contribute to beneficial health properties [55].

320 Nutri-Score is among the designs that appear to be most successful in improving nutrition
321 literacy, guiding consumer choice and reducing portion size [57-59]. Nonetheless, there is also
322 evidence suggesting that the Nutri-Score system may require more public education than other more
323 intuitive symbols such as the 'high in' warning labels [60]. On the other hand, there is limited
324 evidence on the impact of FOP nutrition labelling on food reformulation [61]. This is also among
325 the main purposes of FOP nutrition labelling and warrants further attention, given that a focus on
326 nutritional reformulation of critical nutrients may not necessarily be effective [62]. In this sense, it
327 is noteworthy that the association between a higher FSAm-NPS DI score and all-cause mortality
328 was particularly strong among participants with a high intake of ultra-processed foods (≥ 3
329 servings/day). In addition, in a previous study from the SUN cohort, we found that a high
330 consumption of ultra-processed foods was independently associated with a 62% relatively increased
331 hazard for all-cause mortality [63]. These findings suggest that educational campaigns and broader
332 food system policies should be implemented on top of the Nutri-Score to primarily encourage the
333 consumption of whole, unprocessed foods [64].

334 Moreover, there are important policy decisions to be made regarding the legal framework
335 used for implementation (i.e. voluntary or mandatory). Evidence to date suggests that the uptake of
336 voluntary FOP nutrition labelling is slow and insufficient [6]. A review of the voluntary Health Star
337 Rating system reported that, after four years, stars were still on less than one third of eligible
338 products in Australia, with scores skewed towards the upper end of the five-star scale [65].
339 European countries currently can only implement voluntary labelling policies according to INCO
340 (EU regulation on the provision of food information to consumers). For this reason, there is an
341 ongoing European Citizen Initiative named «PRO-NUTRISCORE» to impose a single official
342 labelling system. This is a crucial point given that previous experiences with voluntary measures to

343 self-regulate advertising have been of doubtful effectiveness. In Spain, the PAOS code (self-
344 regulation code for food advertising aimed at children in order to prevent obesity and encourage
345 healthy habits) was implemented in 2005, but evidence showed that compliance was very low in
346 2008, and even lower in 2012 [66]. This and other experiences have led some scholars to
347 characterize corporate self-regulation as a political strategy to deliberately delay or pre-empt more
348 effective public health actions [67]. Other than the legal framework, there are other essential
349 features of regulation that deserve attention and recognition to ensure an effective implementation
350 of FOP nutrition labelling [68].

351 Finally, it must be clearly pointed out that Nutri-Score, like any FOP label, is only one
352 element to consider within a comprehensive set of nutrition policies. Its implementation should be
353 accompanied by educational and communication strategies regarding its use, meaning and
354 limitations. Additionally, it should be complementary to other public health measures that go
355 beyond the individual level and aim to create an environment that helps consumers make the
356 'healthy choice' favoring the availability and affordability of healthy, minimally processed foods.
357 However, this should not divert the attention of the need to take a critical step towards the
358 improvement of diet quality by effectively adopting FOP labelling policies. Complexity arguments,
359 in line with the notion of 'nothing can be done until everything is done', have been identified as one
360 of the main framings used by food, beverage, alcohol and gambling industries to undermine
361 effective regulation of those activities that are harmful to the public's health [69].

362 Strengths of this study include its prospective and dynamic design, long follow-up, high
363 retention rate (90% overall), relatively large sample size, and the use of repeated measures of diet.
364 However, limitations should also be acknowledged. Firstly, the FFQ was not specifically designed
365 to collect data about pre-packaged food products that qualify for a Nutri-Score label, and it only
366 covers a small sample of the food products available for consumption. Participants from the SUN
367 cohort, as university graduates collaborating with a study focused on lifestyle and health, tend to be
368 more health-conscious compared to the general population. Consequently, unhealthy dietary

369 behaviours may have been underrepresented in this study. On the other hand, although the findings
370 were based on self-reported data, the fact that participants were highly motivated university
371 graduates adds validity to the information derived from their questionnaires and reduces the
372 potential misclassification bias. Moreover, inherent to the observational nature of this study,
373 residual confounding cannot be entirely ruled out even though our models included a large range of
374 potential confounding variables. Finally, the number of observed deaths was relatively small, and
375 we acknowledge that some analyses may be underpowered, especially in analyses considering only
376 smaller subgroups of cause-specific mortality.

377 In conclusion, the results of this Mediterranean prospective cohort suggest that the
378 consumption of foods with higher FSAm-NPS scores (reflecting a lower nutritional quality) is
379 associated with a higher rate of all-cause mortality and, specifically, cancer mortality. These
380 findings further support the FSAm-NPS as underlying nutrient profiling system of the Nutri-Score
381 label in the Spanish context.

382

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