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## **Inflammatory potential of the diet and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study**

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**This study is listed on the ISRCTN registry with the study ID ISRCTN12136108.**

Short running head: Inflammatory potential of diet and gastric cancer.

Abbreviations used:

CGC: Cardia gastric cancer

CI: Confidence interval

CRP: C-reactive protein

DII: Dietary Inflammatory Index

EPIC: European Prospective Investigation into Cancer and Nutrition

FFQ: Food-frequency questionnaire

GC: Gastric cancer

GEJ: Gastro-esophageal junction

24hDR: 24-hour Dietary recall

HR: Hazard ratio

IARC: International Agency for Research on Cancer

ICD-O: International Classification of Diseases for Oncology

ISD: Inflammatory Score of the Diet

LR: Likelihood ratio

NCC: Non-cardia cancer

OR: Odds ratio

SD: Standard deviation

## 1 ABSTRACT

2

3 **Background:** Chronic inflammation plays a critical role in the pathogenesis of the two major types of  
4 gastric cancer. Several foods, nutrients, and non-nutrient food components seem to be involved in the  
5 regulation of chronic inflammation.

6 **Objective:** To assess the association between the inflammatory potential of the diet and the risk of  
7 gastric carcinoma, overall and for the two major subsites: cardia cancers and non-cardia cancers.

8 **Design:** A total 476160 subjects (30% males, 70% females) from the European Investigation into  
9 Cancer and Nutrition (EPIC) study were followed for 14 years, during which 913 incident cases of  
10 gastric carcinoma were identified, including 236 located in the cardia, 341 in the distal part of the  
11 stomach (non-cardia), and 336 with overlapping or unknown tumor site. The dietary inflammatory  
12 potential was assessed by means of an inflammatory score of the diet (ISD), calculated using 28  
13 dietary components and their corresponding inflammatory scores. The association between the ISD  
14 and gastric cancer risk was estimated by hazard ratios (HR) and 95%-confidence intervals (CI)  
15 calculated by multivariate Cox regression models adjusted for confounders.

16 **Results:** The inflammatory potential of diet was associated with an increased risk of gastric cancer.  
17 The HR (95% CI) for each increase in one standard deviation of the ISD were 1.25 (1.12, 1.39) for all  
18 gastric cancers, 1.30 (1.06, 1.59) for cardia cancers, and 1.07 (0.89, 1.28) for non-cardia cancers. The  
19 corresponding values for the highest compared to the lowest quartiles of the ISD were 1.66 (1.26,  
20 2.20), 1.94 (1.14, 3.30), and 1.07 (0.70, 1.70) respectively.

21 **Conclusions:** Our results suggest that low-grade chronic inflammation induced by the diet **may be**  
22 **associated with gastric cancer risk.** This pattern seems to be more consistent for gastric carcinomas  
23 located in the cardia than for those located in the distal stomach.

24

25 **Keywords:** gastric cancer, nutrition, chronic inflammation, inflammatory score of the diet,  
26 prospective studies.

27

## 28 INTRODUCTION

29 Gastric cancer (GC) is the fifth most common cancer and the third cause of death from cancer  
30 worldwide (1). Although often considered as a single entity, GC can be classified into two  
31 topographical subsites: cardia gastric cancers (CGC) arising at the area closest to the esophagus, and  
32 those arising in the distal parts of the stomach (non-cardia cancers, NCC). These two subsites of GC  
33 display different epidemiology features; while incidence of NCC has been declining over the past  
34 decades in almost all countries, the rates of CGC have remained stable or rose in several Western  
35 countries (2).

36 Chronic inflammation is known to play an important role in carcinogenesis (3) and several lines of  
37 evidence suggest that inflammation plays a critical role in the pathogenesis of the two major types of  
38 GC. The carcinomas arising in the distal stomach seem to be the consequence of a multistep process  
39 starting from chronic inflammatory gastritis associated with persistent *H. pylori* infection, which may  
40 evolve towards chronic atrophy gastritis, and subsequent changes in the gastric mucosa which appear  
41 to be precursor conditions of NCC (4). The pathogenesis of CGC is less well established, but some of  
42 its risk factors are similar to esophageal adenocarcinoma, including obesity (5) and probably gastro-  
43 esophageal reflux (6), two conditions associated chronic inflammation. Further evidence of the  
44 potential role of inflammation on gastric carcinogenesis comes from its association with  
45 polymorphisms in inflammation-related genes such as *IL1RN*, *IL1B*, and *TNF- $\alpha$*  (4,7).

46 Diet may play a role in the regulation of chronic inflammation; several foods and food components  
47 have an impact on blood concentrations of inflammatory markers, including cytokines, chemokines,  
48 acute-phase proteins, soluble adhesion molecules and cytokine receptors (8). Different  
49 epidemiological studies have assessed the association between the inflammatory potential of diet,  
50 measured by means of the dietary inflammatory index (DII), an index combining the intake of dietary  
51 constituents and its association with well-known inflammatory markers (9), and gastro-intestinal  
52 tumors (10-17). So far, only one hospital-based case-control study has addressed the association of  
53 dietary inflammation with GC (17); the risk of GC more than doubled when comparing the highest



54 versus the lowest quartile of the DII. The sample size was relatively small (230 cases) and stratified  
55 analyses according to anatomical site of the tumors were not performed.

56 In this paper we calculated an index to reflect the inflammatory potential of the diet (inflammatory  
57 score of the diet, ISD) and assessed its association with the risk of GC in a large prospective cohort  
58 from ten European countries. In addition we considered the potential role of dietary inflammation  
59 separately for the two major anatomical subsites of gastric carcinoma (CGC and NCC), as well as for  
60 the two main histological types (intestinal and diffuse).

61

## 62 **METHODS**

### 63 **Study setting and population**

64 The European Investigation into Cancer and Nutrition (EPIC) is a large prospective cohort study  
65 designed to investigate the relationships between diet, lifestyle, environmental factors and cancer.  
66 Recruitment procedures and data collection of the EPIC study have been described elsewhere (18). In  
67 summary, 521324 subjects, mostly aged 30 to 70 years, were recruited between 1992 and 2000 in 23  
68 centers from ten European countries (France, Italy, Spain, United Kingdom, the Netherlands, Greece,  
69 Germany, Sweden, Denmark, and Norway). Written informed consent was provided by all  
70 participants. The ethical review boards from the International Agency for Research on Cancer (IARC)  
71 and from all local centers approved the study. Prior to analysis, the following exclusions were made:  
72 participants with a prevalent cancer at baseline (25184), with missing follow-up information (4148),  
73 lacking lifestyle or dietary information (6259), and those in the highest and lowest 1% of the  
74 distribution for the ratio of energy intake to estimated energy requirement (9573). Therefore, our final  
75 study population included 476160 participants (142241 men and 333919 women) (**Supplemental**  
76 **Figure 1**).

77

### 78 **Follow-up and ascertainment of gastric cancer**

79 Follow-up for incident cancer cases and assessment of vital status was provided through record  
80 linkage with population cancer registries and national or regional mortality registries in most of the

81 participating countries. In France, Germany and Greece an active follow-up used a combination of  
82 approaches, including cancer and pathology registries, health insurance records, and active follow-up  
83 contacting participants or their next-of-kin. Cases were defined as malignant, primary incident GCs.

84 During the follow-up, a total of 1049 subjects were newly diagnosed with a malignant primary  
85 cancer of the stomach (topographical code C16) according to the International Classification of  
86 Diseases for Oncology, Third Edition (ICD-O-3). Among them 45 could not be classified with respect  
87 to their morphology, 31 were mesenchymal or other non-epithelial tumors, and 48 were lymphomas;  
88 moreover there were 12 endocrine carcinomas; therefore the cases in the present study were 913 GCs  
89 (epithelial tumors of the stomach excluding endocrine tumors), among which the vast majority (877)  
90 were adenocarcinoma. The GC cases with code C16.0 were classified as CGC and those with codes  
91 C16.1-C16.6 as NCC; the remaining cases had an overlapping tumor (C16.8) or could not be  
92 classified according to their localization (C16.9). Furthermore, the GCs were classified according the  
93 two main histologic types of the Lauren classification (intestinal and diffuse) based upon the  
94 morphology codes of the ICD-O (19,20).

95

#### 96 **Diet, lifestyle and anthropometric information**

97 A lifestyle questionnaire, anthropometric measurements using standardized procedures, and a  
98 blood sample were collected at recruitment. The questionnaire included information on medical  
99 history, socio-demographic characteristics, the highest school level reached, detailed history of  
100 smoking habits, and a four-level index of physical activity. The usual diet over the previous twelve  
101 months was assessed at baseline by means of country-specific validated questionnaires. In most  
102 countries, extensive quantitative food frequency questionnaires (FFQ) or semi-quantitative FFQ were  
103 used, though some used diet-history questionnaires or a combination of diet record and FFQ. In  
104 addition, highly standardized 24-hour dietary recall (24hDR) measurements were obtained from  
105 representative subsamples (5%-12%) of each EPIC cohort. These data were used to correct for  
106 systematic differences between the dietary questionnaires and to minimize measurement error (21).  
107 Food consumption data was used to calculate energy, macro and micronutrients and other dietary

108 components using country-specific food composition databases, which had been standardized across  
109 countries (22).

110

### 111 **The Inflammatory Score of the Diet (ISD)**

112 We calculated the ISD to reflect the inflammatory potential of the diet taking the DII as the starting  
113 point (11). The DII comprises 45 food items (including macro and micronutrients, other dietary  
114 components and foods) that have been assigned an inflammatory weight after a literature review  
115 according to the pro- or anti-inflammatory effect of the food. The weight reflects the association of  
116 each food item with well-known inflammatory markers (IL-1 $\beta$ , IL-4, IL-6, IL-10, TNF- $\alpha$  and CRP).  
117 To calculate the ISD in the present study we used the weights as reported (9) for a set of 28 food items  
118 available in the EPIC databases for all centers (**Supplemental Table 1**). In order to calculate the  
119 subject's ISD each individual's food item's intake was standardized using the mean and standard  
120 deviation of our study population. These z-scores were converted to percentile scores to avoid the  
121 right skewness of data, and then centered on 0 by doubling each percentile score and subtracting 1.  
122 The centered percentile values were then multiplied by its respective inflammatory effect score  
123 (weight) to obtain the food item-specific ISD, which are summed to produce the overall ISD for each  
124 participant.

125 The procedure to calculate the ISD is similar to the DII (9), but there are slight differences. First,  
126 we did not use the weight for total fat to compute the ISD because the three components of dietary fat  
127 (saturated, mono-unsaturated, and poly-unsaturated fats) are also included; therefore, using a weight  
128 (inflammatory effect score) for total fat would overestimate the inflammatory potential of the diet.  
129 Second, we used a different weight for alcohol owing to its dose-dependent effect. In the original  
130 database (9) alcohol is considered to be anti-inflammatory (it has a negative weight); however, the  
131 negative relationship with inflammatory markers has been showed only among moderate consumers  
132 (less than 30-40 g/day) (23,24) and therefore, for subjects with intake >40 g/day the weight for  
133 alcohol was set to 0. Finally, a major difference with respect to the DII was that to calculate the  
134 subject's ISD, each individual's food item's intake was standardized using the mean and standard

135 deviation of our study population, while the DII used the mean and standard deviation of a regional  
136 worldwide database taken as a ‘referent’ population. However, the purpose of our study was not to  
137 compare the inflammatory potential of diet across populations, but to assess whether the inflammatory  
138 potential of the diet was associated with cancer risk. Therefore, we gave priority to internal validity  
139 and we used the mean and standard deviation from our own population to standardize the intakes of  
140 the ISD components.

141 By the way the ISD is calculated, positive values indicate a more pro-inflammatory diet and  
142 negative values correspond to a more anti-inflammatory diet. However, it should be noted that the  
143 weights used to calculate the score do not have units: they are only an indicator of the inflammatory  
144 potential of particular dietary component. Therefore, the value of the ISD for an individual is not an  
145 absolute measure of the inflammatory effect of the subject’s diet, but a ‘relative’ index that allows  
146 categorizing individuals’ diets on a continuum from maximally anti-inflammatory to maximally pro-  
147 inflammatory.

148

#### 149 **Statistical analysis**

150 Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox proportional  
151 hazards models to assess the association between GC and the inflammatory potential of diet measured  
152 by the ISD. Entry time was defined as age at recruitment, and exit time was age at diagnosis (cases),  
153 death, or end of follow-up, whichever occurred first. Subjects with a diagnosis of stomach cancer  
154 other than gastric carcinoma were censored at the time of diagnosis. All models were stratified by  
155 center and age at recruitment and adjusted for sex and total energy intake. Furthermore the  
156 multivariate models were adjusted for the following potential confounders: education (none/primary  
157 not completed, primary, technical/professional school, secondary school, longer education including  
158 university); smoking status and intensity (never smoker; current, 1-15 cigarettes/day; current, 16-25  
159 cigarettes/day; current, >25 cigarettes/day; former, quit ≤10 years; former, quit 11-20 years; former,  
160 quit >20 years; other smokers, including occasional smokers, exclusive smokers of cigar and/or pipe,  
161 and smokers with unknown status and/or unknown amount smoked); body mass index (BMI, kg/m<sup>2</sup>

162 <25, 25.00-29.99,  $\geq 30$ ); alcohol consumption and intake (by quartiles) of red meat, processed meat,  
163 citrus fruit, and non-citrus fresh fruit. The model for CGC did not include the intake of red or  
164 processed meat, while the model for NCC did not include BMI. The selection of confounders was  
165 done *a priori*, based upon the known risk factors of gastric cancer (both CGC and NCC) available in  
166 our dataset, and associated with the inflammatory potential of the diet. Some confounders are dietary  
167 factors and can be source of components included in the ISD; therefore, the intakes of energy, alcohol,  
168 red and processed meat, and citrus and non-citrus fresh fruit were included into the multivariate model  
169 as the residuals of a linear regression of each dietary variable on the ISD.

170 The ISD was analyzed both as a categorical classified by quartiles (with first quartile as the  
171 reference category) and as a continuous variable, divided by its standard deviation. Trend tests across  
172 quartiles of the ISD were calculated by entering the categorical variable into the model as a  
173 continuous term. The nonlinearity of the effect of ISD on GC risk was assessed by adding a quadratic  
174 term to the model with the ISD as continuous variable and comparing the likelihood of the models  
175 with and without the quadratic term by means of the likelihood ratio (LR) test. A significant *p*-value  
176 of this test would be interpreted as departure from linearity; although this is not a formal proof of  
177 linearity, a non-significant *p*-value was interpreted as an indication of a linear effect of the ISD on GC  
178 risk. The LR test was also used to evaluate the significance of the interaction of ISD with other  
179 variables of interest. The homogeneity of the risks of ISD for CGC and NCC, as well as for intestinal  
180 and diffuse types, was assessed by means of the Wald statistic. The heterogeneity of HRs for the ISD  
181 across countries was explored using a meta-analytic random-effects model. A chi-squared test based  
182 upon the scaled Schoenfeld residuals was used to ensure that the assumptions of proportional hazards  
183 were met. A sensitivity analysis was conducted to evaluate possible reverse causality by excluding  
184 subjects with two or less years of follow-up.

185

### 186 *Calibration of intakes*

187 A linear regression calibration approach was used to improve the comparability of dietary data across  
188 centers and to minimize measurement error using data from the subsample of subjects 24hDR (25).

189 Sex- and country-specific calibration models were applied to obtain individual predicted values of  
190 dietary exposures; the 24hDR measurements were regressed on dietary intake from the questionnaire,  
191 including in the model total energy intake, age at recruitment, center, education, smoking, BMI and  
192 physical activity. Afterward, these models were used to obtain predicted values on intake for all  
193 participants. For zero consumption values reported in the main dietary questionnaire a zero was  
194 directly imputed as the corrected value, and negative values occasionally arising after regression were  
195 set to zero as well. The predicted values (calibrated intake) of each food component were used to  
196 calculate the ISD. A bootstrap sampling procedure was used to compute the mean and standard  
197 deviation of the predicted (calibrated) intake of each food component of the ISD in our population. A  
198 total of 400 repetitions were used to ensure the stability of the estimates (25).

199

## 200 RESULTS

201 During an average follow-up of 14 years, a total of 913 incident cases of GC (56% males, 44%  
202 females) were identified among the 476160 subjects of the cohort. A total of 236 tumors were CGC,  
203 341 NCC, and 336 had overlapping or unknown tumor site; regarding the histology 645 were  
204 intestinal, 222 diffuse, and for 46 could not be classified according the Lauren classification. Overall  
205 the inflammatory potential of the diet in the whole cohort, as measured by the ISD, had a mean value  
206 of 0.38 with a standard deviation of 1.70. The range of the ISD was from -6.44 to 5.67; the median  
207 and 25<sup>th</sup> and 75<sup>th</sup> percentiles were 0.53, -0.75, and 1.65 respectively.

208 The distribution of subjects and the ISD according to the main characteristics of the population are  
209 presented in the **Table 1**. The women had a more pro-inflammatory diet than men, and the  
210 inflammatory potential of the diet increased with age. The ISD increased with BMI, current smokers  
211 had a remarkably higher ISD than never or former smokers, while no a clear pattern was shown for  
212 the ISD with respect of education. The ISD was also positively associated with the intake of red and  
213 processed meat, and inversely associated with the intake of citrus and other fresh fruit and with  
214 alcohol consumption. Although the absolute differences were often small (in the ISD scale), all of  
215 them were statistically significant owing to the large sample size.

216 A more complete picture of the relationship between the ISD and the usual diet of the EPIC  
217 population is shown in **Supplemental Table 2**. As expected from the weight (inflammatory effect  
218 score) of the dietary components of the ISD, there was a strong inverse correlation between the index  
219 and the intake of legumes, vegetables, fruits (all kinds), condiments and sauces, fruit juices, coffee  
220 and tea, and to a lesser extent, cereal products and alcoholic beverages; this means that all these food  
221 groups tend to confer anti-inflammatory capacity to the diet. On the contrary, a strong positive  
222 correlation was evident for meat and meat products (including red and processed meat), foods based  
223 on fats and oils, and sugar and confectionery; according to this, diets rich in these foods tend to have a  
224 higher inflammatory potential.

225 The association of the inflammatory potential of the diet with GC, overall and according to the  
226 location of the tumor and the histological type, is presented in the **Table 2**. There was an increasing  
227 risk of GC with higher values of the ISD, evident both for the categorized and the continuous variable.  
228 Part of the effect of the ISD can be explained by the other risk factors of GC, but an independent  
229 association with the ISD remains after adjusting for the relevant confounders. For GC, a significant  
230 HR was observed for each quartile of the ISD as compared with the lowest, with a significant trend.  
231 For the highest quartile there was a 66% increased risk of GC (HR 1.66, 95% CI 1.26, 2.20), and the  
232 risk of GC significantly increased by 25% (HR 1.25, CI 1.12, 1.39) for each SD increase in the score.

233 This association with the ISD seemed to be more consistent for tumors located in the cardia than  
234 for those located in the distal stomach. The adjusted HRs for one SD increase in the ISD were 1.30  
235 (1.06, 1.59) and 1.07 (0.89, 1.28) for the CGC and the NCC respectively. Despite the apparently  
236 different effect of ISD by anatomical site, no heterogeneity of the association was observed, with non-  
237 significant Wald test comparing the HRs of CGC *versus* NCC ( $p$ -value 0.08). **It is worth noting that,**  
238 **contrary to CGC, the significant HR for NCC in the basic model became no-significant in the**  
239 **multivariate model. Stepwise analysis (results not shown) showed that only the inclusion of smoking**  
240 **and/or education significantly reduced the magnitude of the HR, while the dietary factors had a**  
241 **negligible effect on the HR and its statistical significance. Tumors located at the border between the**  
242 **cardia and the distal stomach (overlapping) or those whose localization was unknown had an HR of**  
243 **1.43 (1.18, 1.73). These tumors could be either CGC or NCC and therefore the specific HR for this**

244 **category is not easily interpretable.** Regarding histology, the HRs for the intestinal and diffuse types  
245 were, respectively, 1.18 (1.03, 1.34) and 1.33 (1.06, 1.67), with no significant heterogeneity ( $p$ -value  
246 0.31 for the Wald test).

247 The LR tests assessing departure from linearity were no statistically significant (for all GC as well  
248 as for CGC and NCC) and therefore we assumed that the effects of ISD on risk can be reasonably well  
249 represented by means of a linear dose-response relationship. Using this feature the increase (or  
250 decrease) in risk for any given value of the ISD it can be estimated (**Supplemental Figure 2**). For  
251 instance, taking the median of the ISD as the reference (representing medium inflammatory potential  
252 of the diet in our population), the subjects with an ISD corresponding to the 10<sup>th</sup> percentile (assumed  
253 to have a high anti-inflammatory diet) had a significant decrease in risk of GC of 27% (HR 0.73, CI  
254 0.62, 0.85), and those with ISD corresponding to the 90<sup>th</sup> percentile (assumed to have a high pro-  
255 inflammatory diet) had a significant increased risk of 29% (HR 1.29, CI 1.13, 1.46). The  
256 corresponding HR (95% CI) for CGC were 0.69 (0.51, 0.92) and 1.35 (1.07, 1.70), and 0.91 (0.70,  
257 1.19) and 1.07 (0.87, 1.33) for NCC.

258 No significant differences in the association of GC, CGC or NCC with the ISD were observed  
259 between men and women, according to age or by educational level (**Table 3**). Since tobacco smoking,  
260 BMI and physical activity may contribute to low-grade chronic inflammation, we also explored  
261 whether the effect of the inflammatory potential of the diet on the risk of GC was modified by  
262 smoking status and different levels of BMI and physical activity (**Table 3**). Although the association  
263 seemed to be more marked for smokers and subjects with normal weight, mainly for CGC, no  
264 significant interactions were observed between the ISD and smoking status, BMI or physical activity  
265 level, either in all GCs or in tumors from the cardia or non-cardia regions.

266 The association between the ISD (for one SD increase of the ISD) and GC by country was  
267 assessed by means of a meta-analytic approach (**Figure 1**). All countries but Italy had HRs above the  
268 unity, although statistically significant estimates were observed only for UK, Sweden and Denmark  
269 (the countries with the largest number of cases). However these effects can be considered  
270 homogenous since the test of heterogeneity between countries according to a random effects model  
271 was not statistically significant. No heterogeneity was evident for CGC or NCC, although the patterns



272 were less consistent, mainly for CGCs, owing to the small number of cases (detailed results in  
273 **Supplemental Table 3**).

274 Finally, in order to assess the potential effect of reverse causality produced by a modification of  
275 the diet induced by a pre-existing (not clinically evident) condition, we excluded the subjects with  
276 follow-up below 2 years, which excluded 77 GC cases. In these analyses the adjusted HR (95%-CI)  
277 for each SD increase in the score was 1.22 (1.09, 1.37) for all GC, as compared with the 1.25 (1.12,  
278 1.39) in the whole data set (**Table 2**). The corresponding estimates for the CGC and NCC were 1.29  
279 (1.04, 1.60) and 1.05 (0.87, 1.27).

280

## 281 **DISCUSSION**

282 We have observed that the inflammatory potential of the diet, as measured by the ISD is associated  
283 with higher risk of GC in a population of European adults. Each increase of one SD of the score  
284 significantly increased the GC risk by 25%; subjects eating a diet with the highest ISD (4<sup>th</sup> quartile)  
285 have a 66% increase in GC risk as compared with those in the lowest quartile. This pattern seems to  
286 be more consistent for tumors located in the cardia than for those located in the distal stomach, while  
287 no differences were seen between the two major histological types (intestinal and diffuse).

288 As far as we know this is the first prospective study on the association between GC risk and  
289 inflammatory potential of the diet. Our results are consistent with those reported in an Italian hospital-  
290 based study with 230 GC cases and 547 matched controls (17). The adjusted odds ratio (OR)  
291 comparing the highest to the lowest quartile of the DII was 2.35 (95% CI 1.32, 4.20), while in our  
292 population the adjusted HR was 1.66 (1.26, 2.20). This study did not provide results according to  
293 anatomical tumor site of GC or by histological types. Although the results from both studies cannot be  
294 directly compared as they are based upon different indexes, the DII and the ISD are actually close to  
295 each other (see **Methods**). **In our population the Pearson's correlation coefficient between the ISD  
296 and the DII was 0.91, with  $p$ -value <0.001.** A population-based case-control study addressed the  
297 relationship of DII and the risk of esophageal cancer in Sweden (16) reported separate results for 255  
298 adenocarcinoma of the gastro-esophageal junction (GEJ) compared with 806 controls. The adjusted

299 OR (95% CI) comparing the fourth versus the first quartile of the DII was 2.04 (1.24, 3.36), similar to  
300 our estimate for the CGC (1.94, 95% CI 1.14, 3.30). The definition of GEJ has led to controversies and  
301 they have been alternatively considered as esophageal or gastric tumors, but in many instances they  
302 are still classified within the CGCs (26).

303 A role of inflammation in the pathogenesis of GCs has a strong biological plausibility (4-7), and  
304 several dietary components have potential to modulate chronic inflammation (27). In previous studies  
305 we have shown a potential role in the GC risk of foods and nutrients that are in turn determinants of  
306 the inflammatory potential of the diet measured by the ISD. For instance an increased risk of GC was  
307 found to be associated with higher intake of red and processed meat, especially for NCC (28), while  
308 lower risks were associated with higher consumption of fruit and vegetables, mainly for CGC (29),  
309 cereal fiber (30) and dietary flavonoids (31). A reduced GC risk was also observed with higher  
310 plasmatic levels of vitamin C (32) as well as with higher circulating levels of some carotenoids,  
311 retinol, and  $\alpha$ -tocopherol (33).

312 The inflammatory potential of the diet seems to have an independent effect on GC risk, not  
313 explained by other factors. The multivariate model included a list of potential confounders selected *a*  
314 *priori*, based upon the known risk factors of CGC and NCC, and found to be associated with the  
315 inflammatory potential of the diet in our population. Particular consideration was given to dietary  
316 factors as potential confounders; some of them (alcohol consumption, energy intake) are components  
317 of the ISD, while other (intake of red and processed meat, intake citrus and non-citrus fresh fruit) are  
318 major sources of dietary included in the calculation of the ISD. On one side, including simultaneously  
319 the ISD and the above mentioned factors in a model could produce overadjustment or collinearity; on  
320 the other hand, these dietary factors may be true causes of GC and excluding them from the model  
321 could result in effect estimates affected by residual confounding. We try to avoid these unwanted  
322 effects by introducing into the multivariate model the residuals of a linear regression on the ISD of  
323 each dietary variable (intakes of alcohol, energy, red and processed meat, and citrus and non-citrus  
324 fresh fruit) Therefore the HR of the ISD accounts for all the inflammatory potential of the diet,  
325 whereas the HRs for each dietary factor account for their potential effect on GC by mechanisms other  
326 than inflammation.

327 Among the strengths of our study are the prospective design and its high statistical power, owing  
328 to a large number of cases, an accurate case-ascertainment, and the ability to carry out specific  
329 analyses according to histology and tumor localization of GC. The latter is particularly relevant since  
330 there is growing evidence that CGC and NCC have different pathological and epidemiological  
331 features. One of the most prominent is the differential role of *H. pylori*: chronic infection with *H.*  
332 *pylori* is acknowledged as a cause of NCC (34), but no clear association with CGC. Moreover, recent  
333 studies have shown that eventually all cases of NCC have been previously infected by *H. pylori*,  
334 suggesting that it is a necessary cause of this cancer (35). Therefore, it is unlikely that the association  
335 between the ISD and NCC risk has been confounded by lack of adjustment by *H. pylori* infection.  
336 However, since the inflammatory process associated to *H. pylori* infection may be related with some  
337 features of the bacterium such as virulence factors (36), detailed information on *H. pylori* infection  
338 would have been useful to assess its potential modifying effect of the inflammatory potential of diet.  
339 Although we have no data to assess this hypothesis, it could be that the inflammatory pathway leading  
340 to cancer in the distal part of the stomach is mostly driven by changes in the gastric mucosa induced  
341 by *H. pylori* infection, and other factors related to chronic inflammation (i.e. diet) do not add too  
342 much to already established process, while in the cardia, dietary factors (and maybe obesity) are more  
343 relevant regarding the chronic inflammation associated with carcinogenesis.

344 A limitation of our study is that the estimation of the inflammatory potential of diet is based upon  
345 the self-reported information on usual diet, gathered by means of methods relying on the subject's  
346 memory. Although we used validated tools (37) the potential for error measurement can never be  
347 ruled out. In order to minimize the potential for measurement error in the usual diet subjects with  
348 implausible diets (those in the highest and lowest 1% of the distribution of the ratio between energy  
349 intake and estimated energy requirement) were excluded; in addition a linear regression calibration  
350 approach using data from 24hDR data was applied (25) and calibrated dietary intake was used to  
351 calculate the ISD. On the other hand, since dietary information was collected on healthy individuals at  
352 the beginning of the study, measurement errors would be expected to be non-differential. It is likely  
353 that some measurement error may persist; however, its effect would most likely dilute the true  
354 association. Finally, **we lack information on the usual consumption of anti-inflammatory drugs or**

355 supplements, nor was information collected on foods preserved by salting or sodium intake; all these  
356 factors could have affected both the inflammatory potential and GC risk.

357 In summary, our results suggest that a diet with higher inflammatory potential is associated with  
358 increased risk of GC; such association seems to be more consistent for gastric carcinomas located in  
359 the cardia than for those located in the distal stomach. This effect seems to be independent of other  
360 risk factors of GC and other conditions related to chronic inflammation such as smoking, adiposity or  
361 low levels of physical activity. They also suggest that beyond the potential effects of specific dietary  
362 components, diet may play a role in gastric carcinogenesis as an overall modulator of low-grade  
363 chronic inflammation. Further research including biomarkers of inflammation together with the  
364 inflammatory potential of the diet would help to better understand the mechanisms underlying the role  
365 of diet-related inflammation and gastric carcinogenesis.

366

367 **Conflict of Interest Statement:** None of the authors declared a conflict of interest.

368

369 **Authors' Contribution:** AA designed and conducted the research, contributed to the data analysis,

370 wrote the manuscript and had primary responsibility for the final content of the manuscript. PJ

371 designed and conducted the research, contributed to the data analysis, and had primary responsibility

372 for the final content of the manuscript. VC and CB performed the statistical analysis. ER is the overall

373 coordinator of the EPIC study. All authors contributed to recruitment, data collection and acquisition,

374 biological sample collection, and follow-up and/or management of the EPIC cohort and to the

375 interpretation of the present findings and approval of the final version of the manuscript for

376 publication.

377

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**Table 1** Main characteristics, number of events, and Inflammatory Score of the Diet (ISD) in the EPIC population.

	N	(%)	Gastric cancer	(CGC / NCC)	ISD Median (p25, p75)	Mean (95% CI) <sup>1</sup>
<b>Sex</b>						
Men	142241	(29.9%)	509	(157 / 166)	-0.46 (-1.56, 0.61)	-0.30 (-0.31, -0.29)
Women	333919	(70.1%)	404	(79 / 175)	0.94 (-0.24, 1.93)	0.68 (0.67, 0.68)
<b>Age at recruitment (years)</b>						
< 40	56146	(11.8%)	25	(1 / 13)	-0.43 (-1.98, 1.18)	-0.48 (-0.49, -0.47)
40 to <50	145768	(30.6%)	124	(32 / 50)	0.59 (-0.71, 1.73)	0.41 (0.41, 0.42)
50 to <60	181378	(38.1%)	388	(104 / 140)	0.59 (-0.56, 1.64)	0.51 (0.51, 0.52)
≥ 60	92868	(19.5%)	376	(99 / 138)	0.70 (-0.46, 1.75)	0.60 (0.59, 0.61)
<b>Educational level</b>						
None/primary not completed	20926	(4.4%)	55	(5 / 29)	0.43 (-1.04, 1.76)	0.14 (0.12, 0.16)
Primary	121856	(25.6%)	390	(77 / 166)	1.25 (0.09, 2.25)	1.10 (1.09, 1.10)
Technical/professional	105864	(22.2%)	218	(75 / 69)	0.60 (-0.68, 1.78)	0.48 (0.47, 0.49)
Secondary	97204	(20.4%)	94	(27 / 23)	0.60 (-0.49, 1.53)	0.34 (0.34, 0.35)
Longer (inc. university)	113379	(23.8%)	121	(38 / 47)	-0.32 (-1.51, 0.82)	-0.29 (-0.30, -0.28)
Unknown	16931	(3.6%)	35	(14 / 7)	0.01 (-1.30, 1.11)	-0.32 (-0.34, -0.30)
<b>Smoking status</b>						
Never	233096	(49.0%)	337	(60 / 151)	0.43 (-0.83, 1.48)	0.12 (0.12, 0.13)
Former	126822	(26.6%)	264	(81 / 81)	0.20 (-1.07, 1.43)	0.22 (0.21, 0.23)
Current	106564	(22.4%)	299	(91 / 105)	1.06 (-0.20, 2.18)	1.09 (1.08, 1.10)
Pipe/cigar/occasional/other <sup>2</sup>	9678	(2.0%)	13	(4 / 4)	1.40 (0.28, 2.24)	1.02 (0.99, 1.05)
<b>BMI (kg/m<sup>2</sup>)</b>						
< 25.0	246060	(51.7%)	343	(81 / 120)	0.44 (-0.84, 1.53)	0.18 (0.18, 0.19)
25.0-29.9	166134	(34.9%)	397	(122 / 149)	0.53 (-0.73, 1.72)	0.55 (0.54, 0.56)
≥ 30.0	63966	(13.4%)	173	(33 / 72)	0.87 (-0.44, 1.93)	0.71 (0.70, 0.72)
<b>Alcohol consumption</b>						

non consumer	60724	(12.8%)	128	(17 / 51)	1.35 (0.27, 2.22)	0.85 (0.83, 0.86)
< 45.0 g/day	390277	(82.0%)	697	(194 / 261)	0.43 (-0.84, 1.57)	0.30 (0.29, 0.30)
45.0 - 59.9 g/day	12905	(2.7%)	39	(14 / 14)	-0.20 (-1.23, 0.87)	0.44 (0.41, 0.46)
≥ 60.0 g/day	12254	(2.6%)	49	(11 / 15)	-0.13 (-1.23, 0.95)	0.74 (0.72, 0.77)
Red meat (g/day, quartiles)						
< 16.11	119108	(25.0%)	167	(35 / 69)	0.22 (-1.48, 1.58)	-0.22 (-0.23, -0.21)
16.11-34.86	118974	(25.0%)	223	(49 / 96)	0.79 (-0.45, 1.85)	0.47 (0.46, 0.48)
34.87-63.10	119038	(25.0%)	244	(60 / 95)	0.73 (-0.43, 1.78)	0.62 (0.61, 0.63)
≥ 63.11	119040	(25.0%)	279	(92 / 81)	0.32 (-0.77, 1.34)	0.66 (0.65, 0.67)
Processed meat (g/day, quartiles)						
< 10.51	119040	(25.0%)	155	(35 / 51)	0.15 (-1.47, 1.48)	-0.24 (-0.25, -0.23)
10.51-24.25	119040	(25.0%)	211	(63 / 76)	0.72 (-0.47, 1.80)	0.40 (0.39, 0.41)
24.26-43.85	119063	(25.0%)	240	(53 / 93)	0.73 (-0.40, 1.77)	0.62 (0.61, 0.63)
≥ 43.86	119017	(25.0%)	307	(85 / 121)	0.39 (-0.75, 1.52)	0.76 (0.75, 0.77)
Citrus fruit (g/day, quartiles)						
< 8.23	121096	(25.4%)	268	(90 / 71)	0.99 (-0.22, 2.05)	0.81 (0.80, 0.82)
8.23-31.32	117206	(24.6%)	219	(61 / 83)	0.63 (-0.56, 1.71)	0.55 (0.54, 0.56)
31.33-70.52	119116	(25.0%)	185	(46 / 68)	0.46 (-0.75, 1.55)	0.28 (0.27, 0.29)
≥ 70.53	118742	(24.9%)	241	(39 / 119)	-0.06 (-1.36, 1.22)	-0.11 (-0.12, -0.10)
Other fresh fruit (g/day, quartiles)						
< 64.46	119126	(25.0%)	231	(75 / 72)	1.08 (-0.03, 2.09)	0.98 (0.97, 0.99)
64.46-133.05	118954	(25.0%)	245	(68 / 87)	0.70 (-0.56, 1.77)	0.54 (0.54, 0.55)
133.06-226.10	119040	(25.0%)	221	(56 / 91)	0.36 (-0.87, 1.48)	0.19 (0.18, 0.20)
≥ 226.11	119040	(25.0%)	216	(37 / 91)	-0.13 (-1.40, 1.11)	-0.18 (-0.19, -0.17)

<sup>1</sup> Age, sex, and energy-adjusted means (95% CI) obtained from a linear regression model; the *p*-values comparing these means are always <0.001; for categorized variables with a categories are based upon quantitative values (age, BMI, alcohol consumption, and all other dietary variables) this value corresponds to the *p*-trend.

<sup>2</sup> Includes occasional smokers, exclusive smokers of cigar and/or pipe, and smokers with unknown status and/or unknown amount smoked.

Abbreviations: CGC: cardia gastric cancer; NCC: non-cardia cancer.

**Table 2** Adjusted hazard ratios (HRs) and 95% CI of gastric cancer (by tumor subsite and histologic type) according to the Inflammatory Score of the Diet (ISD) in the EPIC population.

		HR (95% CI)				<i>p</i> -trend	ISD continuous <sup>1</sup>
		Quartile 1	Quartile 2	Quartile 3	Quartile 4		HR (95% CI)
Gastric cancer							
	Basic model <sup>2</sup>	Referent	1.36 (1.11, 1.67)	1.77 (1.42, 2.20)	2.17 (1.70, 2.77)	<0.001	1.38 (1.26, 1.52)
	Multivariate model <sup>3</sup>	Referent	1.25 (1.02, 1.55)	1.50 (1.19, 1.89)	1.66 (1.26, 2.20)	<0.001	1.25 (1.12, 1.39)
Cardia gastric cancer							
	Basic model <sup>2</sup>	Referent	1.47 (0.99, 2.18)	2.03 (1.34, 3.07)	2.82 (1.79, 4.43)	<0.001	1.51 (1.28, 1.80)
	Multivariate model <sup>4</sup>	Referent	1.32 (0.88, 1.98)	1.64 (1.06, 2.55)	1.94 (1.14, 3.30)	0.011	1.30 (1.06, 1.59)
Non-cardia cancer							
	Basic model <sup>2</sup>	Referent	1.23 (0.88, 1.72)	1.66 (1.16, 2.36)	1.52 (1.01, 2.28)	0.02	1.21 (1.04, 1.42)
	Multivariate model <sup>5</sup>	Referent	1.17 (0.83, 1.65)	1.39 (0.96, 2.02)	1.07 (0.70, 1.70)	0.55	1.07 (0.89, 1.28)
Overlapping/unknown site							
	Basic model <sup>2</sup>	Referent	1.41 (1.00, 2.00)	1.61 (1.10, 2.35)	2.44 (1.62, 3.68)	<0.001	1.45 (1.24, 1.70)
	Multivariate model <sup>3</sup>	Referent	1.31 (0.92, 1.87)	1.46 (0.98, 2.17)	2.35 (1.46, 3.77)	0.001	1.43 (1.18, 1.73)
GC, intestinal type							
	Basic model <sup>2</sup>	Referent	1.36 (1.06, 1.75)	1.81 (1.40, 2.35)	2.25 (1.69, 3.01)	<0.001	1.35 (1.21, 1.51)
	Multivariate model <sup>3</sup>	Referent	1.26 (0.98, 1.62)	1.53 (1.16, 2.01)	1.65 (1.18, 2.31)	0.002	1.18 (1.03, 1.34)
GC, diffuse type							
	Basic model <sup>2</sup>	Referent	1.33 (0.89, 1.99)	1.59 (1.02, 2.47)	1.71 (1.04, 2.82)	0.029	1.41 (1.16, 1.70)
	Multivariate model <sup>3</sup>	Referent	1.18 (0.78, 1.78)	1.28 (0.81, 2.04)	1.30 (0.73, 2.31)	0.34	1.33 (1.06, 1.67)

<sup>1</sup>Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

<sup>2</sup>Stratified by age and center, and adjusted for sex and energy intake.

<sup>3</sup>Multivariate model: basic model and further adjusted by: educational level, tobacco smoking, BMI, alcohol consumption, and intake of red meat, processed meat, citrus fruit, and other fresh fruit (all the dietary variables expressed as residuals with respect to ISD).

<sup>4</sup>Multivariate model for cardia gastric cancers: model (3) excluding intake of red meat and processed meat.

<sup>5</sup>Multivariate model for non-cardia cancers: model (3) excluding BMI.

**Table 3** Association between the Inflammatory Score of the Diet (ISD) and gastric cancer risk by age, sex, education and non-dietary variables associated with chronic inflammation.

		HR (95% CI) <sup>1</sup>		
		Gastric cancer (GC) <sup>2</sup>	Cardia (CGC) <sup>3</sup>	Non-cardia (NCC) <sup>4</sup>
Sex	Men	1.22 (1.05, 1.41)	1.21 (0.95, 1.56)	1.12 (0.87, 1.46)
	Women	1.31 (1.09, 1.57)	1.53 (1.04, 2.25)	1.05 (0.80, 1.40)
<i>p</i> -value for interaction		0.54	0.16	0.8
Age at recruitment	<50 years	1.18 (0.88, 1.59)	1.37 (0.78, 2.39)	1.13 (0.74, 1.73)
	50 to <60 years	1.26 (1.06, 1.48)	1.46 (1.08, 1.98)	1.08 (0.82, 1.43)
	≥ 60 years	1.28 (1.08, 1.51)	1.17 (0.86, 1.60)	1.05 (0.79, 1.41)
<i>p</i> -value for interaction		0.57	0.43	0.28
Educational level	None / Primary	1.22 (1.03, 1.45)	1.34 (0.91, 1.96)	0.91 (0.70, 1.18)
	Technical/professional	1.22 (0.98, 1.52)	1.10 (0.77, 1.58)	1.33 (0.89, 2.00)
	Secondary	1.39 (0.95, 2.04)	1.52 (0.75, 3.08)	1.28 (0.62, 2.63)
	Longer (inc. university)	1.18 (0.89, 1.57)	1.32 (0.83, 2.09)	1.15 (0.69, 1.91)
<i>p</i> -value for interaction		0.45	0.84	0.15
Smoking status	Never	1.02 (0.84, 1.25)	1.06 (0.70, 1.62)	0.99 (0.74, 1.33)
	Former	1.40 (1.15, 1.71)	1.47 (1.04, 2.09)	0.97 (0.68, 1.38)
	Current	1.35 (1.11, 1.64)	1.41 (1.01, 1.97)	1.24 (0.89, 1.74)
<i>p</i> -value for interaction		0.82	0.68	0.81
BMI (kg/m <sup>2</sup> )	< 25.0	1.47 (1.23, 1.77)	1.55 (1.10, 2.18)	1.13 (0.83, 1.55)
	25.0-29.9	1.15 (0.97, 1.36)	1.26 (0.94, 1.68)	1.03 (0.78, 1.37)
	≥ 30.0	1.07 (0.82, 1.39)	0.95 (0.54, 1.67)	1.09 (0.70, 1.69)
<i>p</i> -value for interaction		0.14	0.32	0.28
Physical activity	Inactive	1.38 (1.09, 1.73)	1.11 (0.71, 1.73)	1.22 (0.83, 1.78)
	Moderately inactive	1.25 (1.00, 1.56)	1.53 (0.99, 2.34)	1.14 (0.77, 1.68)
	Moderately active	1.29 (1.01, 1.66)	2.15 (1.36, 3.41)	0.80 (0.54, 1.21)
	Active	1.12 (0.89, 1.42)	1.08 (0.73, 1.61)	1.06 (0.72, 1.57)
<i>p</i> -value for interaction		0.41	0.54	0.71

<sup>1</sup>Hazard ratio (HR) per each increase in one standard deviation (SD) of the ISD.

<sup>2</sup>Stratified by age and center, and adjusted for sex and energy intake, educational level, tobacco smoking, BMI, alcohol consumption, and intake of red meat, processed meat, citrus fruit, and other fresh fruit (all the dietary variables expressed as residuals with respect to the ISD).

<sup>3</sup>As model for GC excluding red and processed meat intake.

<sup>4</sup>As model for GC excluding BMI.

The *p*-value for interaction is based upon the Likelihood ratio (LR) test

## Legends for figures

**Figure 1** Association between the Inflammatory Score of the Diet (ISD) and gastric cancer in EPIC by country.

### Footnote:

HR (95% CI): Hazard ratio for each increase of one standard deviation of the ISD, estimated from a Cox model stratified by age and center, and adjusted for sex, energy intake, educational level, tobacco smoking, BMI, alcohol consumption, and intake of red meat, processed meat, citrus fruit, and other fresh fruit (all the dietary variables as residuals with respect to the ISD).

RE Model: summary estimate from a random effects meta-analysis

Heterogeneity test:  $Q_{(9 \text{ df})} = 7.35$ ,  $p$ -value 0.60