

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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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

ABSTRACT

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

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

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

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

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

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

INTRODUCTION

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

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

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

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

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

METHODS

Study setting and population

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

Follow-up and ascertainment of gastric cancer

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

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

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

Diet, lifestyle and anthropometric information

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

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

The Inflammatory Score of the Diet (ISD)

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

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

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

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

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (CI) were estimated using Cox proportional hazards models to assess the association between GC and the inflammatory potential of diet measured by the ISD. Entry time was defined as age at recruitment, and exit time was age at diagnosis (cases), death, or end of follow-up, whichever occurred first. Subjects with a diagnosis of stomach cancer other than gastric carcinoma were censored at the time of diagnosis. All models were stratified by center and age at recruitment and adjusted for sex and total energy intake. Furthermore the multivariate models were adjusted for the following potential confounders: education (none/primary not completed, primary, technical/professional school, secondary school, longer education including university); smoking status and intensity (never smoker; current, 1-15 cigarettes/day; current, 16-25 cigarettes/day; current, >25 cigarettes/day; former, quit ≤10 years; former, quit 11-20 years; former, quit >20 years; other smokers, including occasional smokers, exclusive smokers of cigar and/or pipe, and smokers with unknown status and/or unknown amount smoked); body mass index (BMI, kg/m²

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

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

Calibration of intakes

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

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

RESULTS

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

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

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

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

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

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

The LR tests assessing departure from linearity were not statistically significant (for all GC as well as for CGC and NCC) and therefore we assumed that the effects of ISD on risk can be reasonably well represented by means of a linear dose-response relationship. Using this feature the increase (or decrease) in risk for any given value of the ISD it can be estimated (**Supplemental Figure 2**). For instance, taking the median of the ISD as the reference (representing medium inflammatory potential of the diet in our population), the subjects with an ISD corresponding to the 10th percentile (assumed to have a high anti-inflammatory diet) had a significant decrease in risk of GC of 27% (HR 0.73, CI 0.62, 0.85), and those with ISD corresponding to the 90th percentile (assumed to have a high pro-inflammatory diet) had a significant increased risk of 29% (HR 1.29, CI 1.13, 1.46). The 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, 1.19) and 1.07 (0.87, 1.33) for NCC.

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

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

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

Finally, in order to assess the potential effect of reverse causality produced by a modification of the diet induced by a pre-existing (not clinically evident) condition, we excluded the subjects with follow-up below 2 years, which excluded 77 GC cases. In these analyses the adjusted HR (95%-CI) 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, 1.39) in the whole data set (**Table 2**). The corresponding estimates for the CGC and NCC were 1.29 (1.04, 1.60) and 1.05 (0.87, 1.27).

DISCUSSION

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

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

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

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

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

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

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

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

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

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Authors' Contribution: AA designed and conducted the research, contributed to the data analysis, wrote the manuscript and had primary responsibility for the final content of the manuscript. PJ designed and conducted the research, contributed to the data analysis, and had primary responsibility for the final content of the manuscript. VC and CB performed the statistical analysis. ER is the overall coordinator of the EPIC study. All authors contributed to recruitment, data collection and acquisition, biological sample collection, and follow-up and/or management of the EPIC cohort and to the interpretation of the present findings and approval of the final version of the manuscript for publication.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359-86.
2. Colquhoun A, Arnold M, Ferlay J, Goodman KJ, Forman D, Soerjomataram I. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. *Gut* 2015;64:1881-8.
3. Schottenfeld D, Beebe-Dimmer J. Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA Cancer J Clin* 2006;56:69-83.
4. González CA, Agudo A. Carcinogenesis, prevention and early detection of gastric cancer: where we are and where we should go. *Int J Cancer* 2012;130:745-53.
5. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group.. Body Fatness and Cancer--Viewpoint of the IARC Working Group. *N Engl J Med* 2016;375:794-8.
6. Derakhshan MH, Malekzadeh R, Watabe H, Yazdanbod A, Fyfe V, Kazemi A, Rakhshani N, Didevar R, Sotoudeh M, Zolfeghari AA, et al. Combination of gastric atrophy, reflux symptoms and histological subtype indicates two distinct aetiologies of gastric cardia cancer. *Gut* 2008;57(3):298-305.
7. Persson C, Canedo P, Machado JC, El-Omar EM, Forman D. Polymorphisms in inflammatory response genes and their association with gastric cancer: A HuGE systematic review and meta-analyses. *Am J Epidemiol* 2011;173:259-70.
8. Minihane AM, Vinoy S, Russell WR, Baka A, Roche HM, Tuohy KM, Teeling JL, Blaak EE, Fenech M, Vauzour D, et al. Low-grade inflammation, diet composition and health: current research evidence and its translation. *Br J Nutr* 2015;114:999-1012.
9. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR. Designing and developing a literature-derived, population-based dietary inflammatory index. *Public Health Nutr* 2014;17:1689-96.
10. Shivappa N, Prizment AE, Blair CK, Jacobs DR Jr, Steck SE, Hébert JR. Dietary inflammatory index and risk of colorectal cancer in the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev* 2014;23:2383-92.

11. Tabung FK, Steck SE, Ma Y, Liese AD, Zhang J, Caan B, Hou L, Johnson KC, Mossavar-Rahmani Y, Shivappa N, et al. The association between dietary inflammatory index and risk of colorectal cancer among postmenopausal women: results from the Women's Health Initiative. *Cancer Causes Control* 2015;26:399-408.
12. Wirth MD, Shivappa N, Steck SE, Hurley TG, Hébert JR. The dietary inflammatory index is associated with colorectal cancer in the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Br J Nutr* 2015;113:1819-27.
13. Harmon BE, Wirth MD, Boushey CJ, Wilkens LR, Draluck E, Shivappa N, Steck SE, Hofseth L, Haiman CA, Le Marchand L, et al. The Dietary Inflammatory Index Is Associated with Colorectal Cancer Risk in the Multiethnic Cohort. *J Nutr* 2017;147:430-438.
14. Shivappa N, Hébert JR, Rashidkhani B. Dietary Inflammatory Index and Risk of Esophageal Squamous Cell Cancer in a Case-Control Study from Iran. *Nutr Cancer* 2015;67:1253-9.
15. Shivappa N, Zucchetto A, Serraino D, Rossi M, La Vecchia C, Hébert JR. Dietary inflammatory index and risk of esophageal squamous cell cancer in a case-control study from Italy. *Cancer Causes Control* 2015;26:1439-47.
16. Lu Y, Shivappa N, Lin Y, Lagergren J, Hébert JR. Diet-related inflammation and oesophageal cancer by histological type: a nationwide case-control study in Sweden. *Eur J Nutr* 2016;55:1683-94.
17. Shivappa N, Hébert JR, Ferraroni M, La Vecchia C, Rossi M. Association between Dietary Inflammatory Index and Gastric Cancer Risk in an Italian Case-Control Study. *Nutr Cancer* 2016;68:1262-8.
18. Riboli E, Hunt KJ, Slimani N, Ferrari P, Norat T, Fahey M, Charrondière UR, Hémon B, Casagrande C, Vignat J, et al. European Prospective Investigation into Cancer and Nutrition (EPIC): study populations and data collection. *Public Health Nutr* 2002;5(6B):1113-24.
19. Henson DE, Dittus C, Younes M, Nguyen H, Albores-Saavedra J. Differential trends in the intestinal and diffuse types of gastric carcinoma in the United States, 1973-2000: increase in the signet ring cell type. *Arch Pathol Lab Med* 2004;128:765-70.
20. Hu B, El Hajj N, Sittler S, Lammert N, Barnes R, Meloni-Ehrig A. Gastric cancer: Classification, histology and application of molecular pathology. *J Gastrointest Oncol* 2012;3:251-61.

21. Slimani N, Kaaks R, Ferrari P, Casagrande C, Clavel-Chapelon F, Lotze G, Kroke A, Trichopoulos D, Trichopoulou A, Lauria C, et al. European Prospective Investigation into Cancer and Nutrition (EPIC) calibration study: rationale, design and population characteristics. *Public Health Nutr* 2002;5(6B):1125-45.
22. Slimani N, Deharveng G, Unwin I, Southgate DA, Vignat J, Skeie G, Salvini S, Parpinel M, Møller A, Ireland J, et al. The EPIC nutrient database project (ENDB): a first attempt to standardize nutrient databases across the 10 European countries participating in the EPIC study. *Eur J Clin Nutr* 2007;61:1037-56.
23. Sierksma A, van der Gaag MS, Kluft C, Hendriks HF. Moderate alcohol consumption reduces plasma C-reactive protein and fibrinogen levels; a randomized, diet-controlled intervention study. *Eur J Clin Nutr* 2002;56:1130-6.
24. Avellone G, Di Garbo V, Campisi D, De Simone R, Raneli G, Scaglione R, Licata G. Effects of moderate Sicilian red wine consumption on inflammatory biomarkers of atherosclerosis. *Eur J Clin Nutr* 2006;60:41-7.
25. Ferrari P, Day NE, Boshuizen HC, Roddam A, Hoffmann K, Thiébaud A, Pera G, Overvad K, Lund E, Trichopoulou A, et al. The evaluation of the diet/disease relation in the EPIC study: considerations for the calibration and the disease models. *Int J Epidemiol* 2008;37:368-78.
26. Buas MF, Vaughan TL. Epidemiology and risk factors for gastroesophageal junction tumors: understanding the rising incidence of this disease. *Semin Radiat Oncol* 2013;23:3-9.
27. Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, Folkerts G, Friedmann PS, Frost GS, Guarner F, et al. Inflammatory disease processes and interactions with nutrition. *Br J Nutr* 2009;101 Suppl 1:S1-45.
28. González CA, Jakszyn P, Pera G, Agudo A, Bingham S, Palli D, Ferrari P, Boeing H, del Giudice G, Plebani M, et al. Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006;98:345-54.
29. Gonzalez CA, Lujan-Barroso L, Bueno-de-Mesquita HB, Jenab M, Duell EJ, Agudo A, Tjønneland A, Boutron-Ruault MC, Clavel-Chapelon F, Touillaud M, et al. Fruit and vegetable intake and the risk of gastric adenocarcinoma: a reanalysis of the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST) study after a longer follow-up. *Int J Cancer* 2012;131:2910-9.

30. Mendez MA, Pera G, Agudo A, Bueno-de-Mesquita HB, Palli D, Boeing H, Carneiro F, Berrino F, Sacerdote C, Tumino R, et al. Cereal fiber intake may reduce risk of gastric adenocarcinomas: the EPIC-EURGAST study. *Int J Cancer* 2007;121:1618-23.
31. Zamora-Ros R, Agudo A, Luján-Barroso L, Romieu I, Ferrari P, Knaze V, Bueno-de-Mesquita HB, Leenders M, Travis RC, Navarro C, et al. Dietary flavonoid and lignan intake and gastric adenocarcinoma risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Am J Clin Nutr* 2012;96:1398-408.
32. Jenab M, Riboli E, Ferrari P, Sabate J, Slimani N, Norat T, Friesen M, Tjønneland A, Olsen A, Overvad K, et al. Plasma and dietary vitamin C levels and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Carcinogenesis* 2006;27:2250-7.
33. Jenab M, Riboli E, Ferrari P, Friesen M, Sabate J, Norat T, Slimani N, Tjønneland A, Olsen A, Overvad K, et al. Plasma and dietary carotenoid, retinol and tocopherol levels and the risk of gastric adenocarcinomas in the European prospective investigation into cancer and nutrition. *Br J Cancer* 2006;95:406-15.
34. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Freeman C, Galichet L, Coglian V; WHO International Agency for Research on Cancer Monograph Working Group. A review of humancarcinogens--Part B: biological agents. *Lancet Oncol* 2009;10:321-2.
35. González CA, Megraud F, Buissonniere A, Lujan Barroso L, Agudo A, Duell EJ, Boutron-Ruault MC, Clavel-Chapelon F, Palli D, Krogh V, et al. *Helicobacter pylori* infection assessed by ELISA and by immunoblot and noncardia gastric cancer risk in a prospective study: the Eurgast-EPIC project. *Ann Oncol* 2012;23:1320-4.
36. Qadri Q, Rasool R, Gulzar GM, Naqash S, Shah ZA. *H. pylori* infection, inflammation and gastric cancer. *J Gastrointest Cancer* 2014;45:126-32.
37. Kaaks R, Slimani N, Riboli E. Pilot phase studies on the accuracy of dietary intake measurements in the EPIC project: overall evaluation of results. *European Prospective Investigation into Cancer and Nutrition. Int J Epidemiol* 1997;26 Suppl 1:S26-36.

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

| | N | (%) | Gastric cancer | (CGC / NCC) | Median (p25, p75) | ISD Mean (95% CI) ¹ |
|--|--------|---------|-------------------|----------------|---------------------|-----------------------------------|
| Sex | | | | | | |
| 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) |
| Age at recruitment (years) | | | | | | |
| < 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) |
| Educational level | | | | | | |
| 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) |
| Smoking status | | | | | | |
| 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 ² | 9678 | (2.0%) | 13 | (4 / 4) | 1.40 (0.28, 2.24) | 1.02 (0.99, 1.05) |
| BMI (kg/m ²) | | | | | | |
| < 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) |
| Alcohol consumption | | | | | | |

| | | | | | | |
|--------------------------------------|--------|---------|-----|-------------|---------------------|----------------------|
| 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) |

¹ 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.

² 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 ¹ |
|---------------------------------|-------------|-------------------|-------------------|-------------------|-----------------|-----------------------------|
| | Quartile 1 | Quartile 2 | Quartile 3 | Quartile 4 | | HR (95% CI) |
| Gastric cancer | | | | | | |
| Basic model ² | 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 ³ | 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 ² | 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 ⁴ | 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 ² | 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 ⁵ | 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 ² | 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 ³ | 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 ² | 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 ³ | 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 ² | 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 ³ | 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) |

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

²Stratified by age and center, and adjusted for sex and energy intake.

³Multivariate 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).

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

⁵Multivariate 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) ¹ | | |
|---------------------------------|--------------------------|----------------------------------|---------------------------|-------------------------------|
| | | Gastric cancer (GC) ² | Cardia (CGC) ³ | Non-cardia (NCC) ⁴ |
| 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 ²) | < 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 |

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

²Stratified 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).

³As model for GC excluding red and processed meat intake.

⁴As 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