High adherence to the Western, Prudent, and Mediterranean dietary patterns and risk of gastric adenocarcinoma: MCC-Spain study. Adela Castelló, Nerea Fernández de Larrea, Vicente Martín, Verónica Dávila-Batista, Elena Boldo, Marcela Guevara, Víctor Moreno, Gemma Castaño-Vinyals, Inés Gómez-Acebo, Guillermo Fernández-Tardón, Rosana Peiró, Rocío Olmedo-Requena, Rocio Capelo, Carmen Navarro, Silvino Pacho-Valbuena, Beatriz Pérez-Gómez, Manolis Kogevinas, Marina Pollán, Nuria Aragonés, On behalf of the MCC-Spain researchers

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ABSTRACT

Background: The influence of dietary habits in the development of gastric adenocarcinoma is not clear. The objective of the present study was to explore the association of three previously identified dietary patterns with gastric adenocarcinoma by sex, age, cancer site and morphology.

Methods: MCC-Spain is a multicase-control study that included 295 incident cases of gastric adenocarcinoma and 3040 controls. The association of the Western, Prudent and Mediterranean dietary patterns- derived in another Spanish case-control study- with gastric adenocarcinoma was assessed using multivariable logistic regression models with random province-specific intercepts and considering a possible interaction with sex and age. Risk according to tumour

site (cardia; non-cardia) and morphology (intestinal/diffuse) was evaluated using multinomial regression models.

Results: A high adherence to the Western pattern increased gastric adenocarcinoma risk (Odds $Ratio_{fourth\_vs.\_first\_quartile}$ (95%Confidence interval):2.09 (1.31;3.33)) even at low levels (Odds $Ratio_{second\_vs.\_first\_quartile}$ (95%Confidence interval):1.63 (1.05;2.52)). High adherences to the Mediterranean dietary pattern could prevent gastric adenocarcinoma (Odds $Ratio_{fourth\_vs.\_first\_quartile}$ (95%Confidence interval):0.53 (0.34;0.82)). Although no significant heterogeneity of effects was observed, the harmful effect of the Western pattern was stronger among older participants and for non-cardia adenocarcinomas, while the protective effect of the Mediterranean pattern was only observed among younger participants and for non-cardia tumours.

Conclusion: Decreasing the consumption of fatty and sugary products, and red and processed meat in favour of an increase in the intake of fruits, vegetables, legumes, olive oil, nuts and fish might prevent gastric adenocarcinoma.

Keywords: **"**Diet, Mediterranean"; "Diet, Western"; "Stomach Neoplasms"; "Adenocarcinoma"; "prevention and control"; "Principal Component Analysis"; population attributable fraction.

INTRODUCTION

Despite the fact that age-standardized incidence rates of gastric cancer (GC) have decreased globally during the last decades, this tumour continues to be the fifth most diagnosed worldwide and the absolute number of new cases has raised from nearly 1.2 million in 2005 to more than 1.3 million in 2015 [1]. Also, due to its poor survival rates, it ranks third in mortality worldwide [1]. Therefore, in the following years, cancer prevention efforts should be as important as related delivery of care.

Even though the global burden of GC that is attributable to *Helicobacter pylori* (*H. pylori*) is estimated to be around 89% [2], some authors suggest that diet might also play an important role [3-6]. However, the last report on updated evidence on Food, Nutrition, Physical Activity, and the Prevention of GC published in 2016 by the World Cancer Research Fund and the American Institute of Cancer Research (WCRF/AICR) concludes that there is only strong evidence for a detrimental effect of a high consumption of alcohol, salt preserved foods and processed meat in GC risk and suggests a possible protective effect of citrus fruits for some types of GC tumours [5].

In the last decades some authors argued that the lack of conclusive associations between diet and some diseases might be due to the fact that the effect of foods and nutrients are usually explored individually [7-9], and suggest that dietary pattern analysis would be more adequate since it allows the exploration of the effect of food and nutrient interactions in disease [7-9]. Although two recent reviews [10, 11] confirm the potential preventive effect of a diet labelled as "Prudent/Healthy" and the detrimental effect of the so called "Western/Unhealthy", the WCRF/AICR does not consider the evidence sufficient to include the effect of these diets as conclusively related to GC [5].

A recent Spanish study on female breast cancer (BC) –EpiGEICAM- identified three data-driven dietary patterns [12]: A Western pattern associated with increased risk, a Prudent

pattern not associated with BC, and a protective Mediterranean pattern. The EpiGEICAM study presents the novelty of being able to identify, with data-driven statistical methods and over a single population, two patterns that are commonly interchanged in the related literature (Prudent and Mediterranean). According to this study, these two patterns represent two diets with different characteristics that might be determinant in their association with disease risk [12]. We believe that the application of these patterns in different populations and the exploration of their association with tumours other than BC are of great scientific interest. In fact, these patterns have already been applied over an independent sample and the reproducibility of the results obtained in EpiGEICAM has been assessed for breast [13] and prostate cancer [14].

The objective of the present study is to assess the reproducibility of the associations found between a high adherence to the Western, Prudent and Mediterranean dietary patterns and BC risk in our country, with gastric adenocarcinoma (GAC) by sex, age, cancer site and morphology.

METHODS

The multicase-control study MCC-Spain [15] was conducted with the objective of identifying environmental, demographic, anthropometric, lifestyle and genetic factors related to five common cancers: breast, prostate, colorectal, gastric and chronic lymphocytic leukaemia. Cases were recruited in 23 hospitals from 12 Spanish provinces (Asturias, Barcelona, Cantabria, Gerona, Granada, Guipúzcoa, Huelva, León, Madrid, Murcia, Navarra and Valencia). A single set of population-based controls frequency matched by age and sex with the overall distribution of cases in each province was randomly selected from the list of residents assigned to selected primary care health centres located within the catchment area of each of the collaborating hospitals. Controls were contacted by phone, and those who agreed to

participate attended a personal interview. For the specific case of GC, MCC-Spain recruited 459 histologically confirmed cases and 3440 population controls between September 2008 and December 2013 in 10 of the 12 participating provinces (all except Gerona and Guipúzcoa). The detailed selection process of GC cases and controls has been previously described elsewhere [15, 16]. Briefly, participants able to answer the questionnaire, who lived in the study area for at least 6 months before the diagnosis and were 20-85 years old were invited to participate. Cases were identified, as soon as possible after their diagnosis, through active search that included periodical visits to the collaborating hospital departments. Histologically confirmed incident cases of GC (codes C16: Malignant neoplasm of stomach; D00.2:Carcinoma in situ of stomach; and C15.5: Malignant neoplasm of lower third of oesophagus; of the 10th revision of the International Statistical Classification of Diseases ICD-10) with no prior history of the disease, and diagnosed within the recruitment period, were included. Tumours were classified according to their location in cardia and non-cardia and by tumour morphology following Lauren´s classification into intestinal or diffuse [17, 18]. Classification into cardia and non-cardia gastric cancer cases was done according to the information available in the medical records. Cardia cases included tumours described as located in the "oesophagogastric junction" or in the "cardia". Non-cardia cases included those located distal to the oesophagogastric junction (fundus, body, antrum and pylorus). Controls were randomly selected from general practitioner lists in the same areas. The response rate was 57% among cases and 53% among controls.

The protocol of MCC-Spain was approved by each of the Ethics Committees of the participating institutions. The specific study reported here was approved by the Instituto de Salud Carlos III Ethics Committee. All participants were informed about the study objectives and signed an informed consent.

A structured computerized epidemiological questionnaire was administered by trained personnel in a face-to-face interview to collect information on socio-demographic factors, lifestyle and personal/family medical history among other. Missing values on key variables and specific questions on additional study objectives were completed through subsequent telephone contact. Height and weight at different ages were self-reported and diet was assessed with a 154-items semi-quantitative food frequency questionnaire (FFQ), which was based on a validated instrument in Spain [19], modified to include regional products. Dietary information referred to the previous year before diagnosis in cases and before interview in controls.

All participants were asked for donation of blood samples, which were processed, aliquoted and stored at -80ºC in the first 48 hours. Only 235 (61%) of cases and 1900 (64%) controls donated a blood sample. From these participants, an aliquot of serum was sent on dry ice to the German Cancer Research Centre (DKFZ), Heidelberg, Germany, for the *H. pylori* multiplex serology assay [20].

In the present work, three dietary patterns identified in a previous Spanish case-control study (EpiGEICAM) that explored the association between dietary patterns and female BC risk [12] are examined: A Western dietary pattern positively associated with BC risk that is characterized by high intakes of high-fat dairy products, processed meat, refined grains, sweets, caloric drinks, convenience food and sauces and by low intakes of low-fat dairy products and whole grains; A Prudent pattern with no relationship with BC that represented high intakes of low-fat dairy products, vegetables, fruits, whole grains and juices; and a Mediterranean pattern that seemed to be protective and denoted a high intake of fish, vegetables, legumes, boiled potatoes, fruits, olives and vegetable oil - represented by 72% of olive oil consumption, 23% of olives intake and the remaining 5% coming from sunflower, corn or soybean oil consumption among controls-, and a low intake of juices. The three dietary patterns were identified in the EpiGEICAM study by grouping all the items of the FFQ used into 26 inter-correlated food

groups. Afterwards, principal component analysis without rotation of the variance-covariance matrix was applied over these 26 food groups [21] obtaining a set of weights (pattern loadings in **Table 1**) that represents the correlation between food consumption and the component/pattern scores and can be used to reproduce such patterns in other samples as explained in detail elsewhere [22, 23]. To apply these patterns to the MCC-Spain sample, we grouped 146 of the 154 items of the FFQ (excluding non-caloric and alcoholic beverages) into the same 26 food groups described in EpiGEICAM (**Table 1**) and calculated the scores for the level of adherence to the Western, Prudent and Mediterranean dietary patterns of the MCC-Spain participants as a linear combination of the weights of each food group and pattern published in the EpiGEICAM study (**Table 1**) [12] and consumption reported by the MCC-Spain participants in the current study for each food group.

After describing the sample with basic descriptive statistics, adjusted associations between adherence to each dietary pattern and GAC risk were evaluated using logistic regression models with random province-specific intercepts. As fixed-effects terms, sex, age, education, body mass index (BMI), family history of gastric cancer, physical activity (metabolic equivalents (METs)) during the 10 years before diagnosis/interview, smoking status, *H. pylori* seropositivity, and caloric and alcohol intake were considered as potential confounders. Scores of adherence were analysed both, as categorical (grouping the scores of adherence into quartiles of their distribution among controls) and continuous (1-standard deviation increase taking into account the dispersion among controls) variables.

Since including data on *H. pylori* seropositivity implied losing a big part of the sample (36% of the participants with complete data on the variables included in the analyses), an initial sensitivity analysis was carried out to choose the best modelling strategy (see **Table S1** from Online Resource 1). The results from five models were compared: Model 1 included only the province of residence as a random effect; Model 2 was adjusted for all the potential confounders

except *H. pylori* seropositivity; to estimate the effect of reducing the sample size when including *H. pylori* data independently from its confounding effect, Model 3 included the same set of potential confounders than Model 2 but analyses were restricted to those individuals with information on *H. pylori* infection; Model 4 was adjusted by all potential confounders, including *H. pylori* infection status to assess the possible confounding effect of this variable and Model 5 included the same set of potential confounders than Model 2 but was restricted to *H. pylori* positive participants (89% of those with *H. pylori* data) to check the associations in this specific group. The direction of the associations found were similar for all the analyses and the conclusions of the study did not differ among modelling strategies except for the power of the study to detect statistically significant estimations. Differences found between models with and without *H. pylori* information were caused by a loss of power when including in the models only individuals with blood samples and not by a confounding effect of this variable as it is shown by the different results found for Models 2 and 3 in contrast with the very similar results obtained from Models 3 and 4. Taking this into account and, in order to keep the maximum statistical power for further estimations, we decided to select the modelling strategy from Model 2 for all the analyses included in Tables 3-4.

Heterogeneity of the effects of each dietary pattern by sex and age group (defined by the median age among cases to ensure equal distribution of individuals among groups: ≤68 and >68 years old) was tested including in the models an interaction term between these two variables and the score of adherence to each of the three dietary patterns under study.

Multinomial logistic regression models were used to evaluate the association of the adherence to the Western, Prudent and Mediterranean dietary patterns with GAC by location (cardia and non-cardia) and morphology (intestinal and diffuse). All these models were adjusted for sex, age, education, BMI, family history of gastric cancer, physical activity (METs) during

the 10 years before diagnosis/interview, smoking status, caloric and alcohol intake and province of residence.

Finally, assuming a causal relation between adherence to each of the patterns and GC for all analyses, the population attributable fraction (PAF%) was calculated using Levin's formula [24] modified by Hanley J.A. [25] to accommodate exposures with more than one category. The PAF% describes the proportion of gastric cancer in this population that hypothetically would not have occurred if all participants were in the optimal quartile of adherence to the dietary patterns (first quartile for Western and Prudent dietary patterns and fourth quartile for the Mediterranean). Confidence intervals for the PAF were computed using bootstrap with 500 iterations.

Analyses were performed using STATA/MP (version 14.1, 2015, StataCorp LP) and statistical significance was set at 2-sided $p < 0.05$.

RESULTS

Initially, 3440 controls and 459 cases of GC were recruited. Among them, 3040 (88%) controls and 354 (77%) cases reported data on diet. Cases that provided dietary information later than 6 months after diagnosis were excluded (n=40). Tumours other than adenocarcinomas (n=19) were also excluded from the analyses. Therefore 295 GAC cases and 3040 controls aged 23 to 85 years were included in the present study.

Compared to controls, GAC cases showed a higher adherence to the three dietary patterns and reported higher energy and alcohol intake than controls in the univariable analyses. The proportion of males was higher among GAC cases that were also older and reported lower levels of physical activity and formal education (**Table 2)**.

Table 3 summarizes the adjusted ORs for the association between GAC incidence and the scores of adherence to Western, Prudent and Mediterranean dietary patterns, for the whole sample and stratified by sex and age. A higher adherence to the Western pattern was associated with higher odds of GAC even for moderate adherence, going from a 63% increased risk for participants in the second quartile of adherence ($OR_{\text{second vs. first quartile}}$ (95%CI): 1.63 (1.05;2.52)), to more than a 2-fold increased risk for participants in the third and fourth quartiles of adherence ($OR_{\text{third vs. first quartile}}$ (95%CI): 2.23 (1.45;3.43) and $OR_{\text{fourth vs. first quartile}}$ (95%CI): 2.09 (1.31;3.33)). Risks were very similar by sex (p-interaction=0.799) and age (p-interaction=0.398) groups, but data suggest that the deleterious effect of moderate adherences to the Western dietary pattern might be stronger for older (>68: $OR_{\text{second vs. first quartile}}$ (95%CI): 1.88 (1.04;3.41) and $OR_{\text{third vs. first quartile}}$ (95%CI): 2.74 (1.54;4.88)) than for younger (≤68: $OR_{\text{second vs. first quartile}}$ (95%CI): 1.39 (0.74;2.72) and $OR_{\text{third vs. first quartile}}$ (95%CI): 1.83 (0.99;3.37)) individuals. While no clear effect was observed between GAC and the adherence to the Prudent dietary pattern, a high adherence to the Mediterranean dietary pattern seems to have a considerable protective effect against this tumour with a significant linear trend. Participants in the highest category of adherence to the Mediterranean dietary pattern compared to those in the lowest category had an odds ratio of developing GAC of 0.53 (95% CI 0.34;0.82). Even if heterogeneity of the effects was not statistically significant ($p\text{-interaction}_{sex}$=0.314 and $p\text{-interaction}_{age}$=0.684), our data suggest that this effect might be stronger among males ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 0.51 (0.31;0.83)) than among females ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 0.59 (0.27;1.30)) and among younger ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 0.46 (0.26;0.81)) than among older ($OR_{\text{fourth vs. first quartile}}$ (95%CI): 0.60 (0.33;1.08)) participants. In concordance with these results and assuming a causal relation between the adherence to these dietary patterns and GAC risk, the estimations indicate that 45% (95%CI: 24%;66%) of GAC cases could have been prevented if all the participants had been in the lowest category of adherence to the Western

pattern and that 34% (95%CI: 15%;54%) of GAC cases could have been prevented if all the participants had the highest adherence to the Mediterranean pattern. Such PAFs% were very similar for males and females and for younger and older participants. The positive trend found for the Western dietary pattern and the inverse trend found for the Mediterranean dietary pattern in the overall analyses was also observed by tumour location and morphology (**Table 4**). However, dose-response trends were only statistically significant for Non-Cardia tumours, for both the Western pattern (Cardia: $OR_{1SD\text{-}increase}$ (95%CI)= 1.29(0.93;1.77); Non-Cardia: $OR_{1SD\text{-}increase}$(95%CI)= 1.35 (1.12;1.63); p-heterogeneity=0.800) and the Mediterranean pattern (Cardia: $OR_{1SD\text{-}increase}$(95%CI)= 0.91(0.67;1.24); Non-Cardia: $OR_{1SD\text{-}increase}$(95%CI)= 0.78 (0.66;0.93); p-heterogeneity=0.395). No clear differences were observed regarding tumour morphology. The associations between Western and Mediterranean patterns were very similar in both Intestinal and Diffuse tumours.

DISCUSSION

The associations observed for BC in EpiGEICAM, were also found for GAC in the MCC-Spain study. Our results suggest that a high adherence to the Western dietary pattern might increase the risk of developing GAC even for low adherences, and that high adherences to the Mediterranean dietary pattern could prevent GAC. It is also highlighted that the Prudent pattern, in spite of sharing some characteristics with the Mediterranean diet, has no clear effect on GAC risk. Our data also point out to a possible stronger effect of the Western pattern among older participants and for non-cardia tumours and a bigger influence of the Mediterranean pattern on males, younger participants and for non-cardia tumours, even though tests of heterogeneity were not statistically significant.

Most of the studies exploring the association between data-driven dietary patterns and GC risk, identify two types of dietary patterns: A Western/Unhealthy pattern and a

Healthy/Prudent pattern. The first one usually loads high in red and processed meat, sweets, soft drinks, high fat dairy, fast food and sauces and is positively associated with GC risk [26-28]. Some studies collect these foods in two different patterns (Western and Traditional/Mixed) with at least one of them positively associated with GC [29-32] while others report a null effect of the Western pattern on GC risk [33, 34]. The Mediterranean/Healthy pattern usually loads high in fruits and vegetables, fish, legumes and vegetable oil and appears to be protective in most cases [26, 27, 29-32] with few exceptions for studies including only tumours in the cardia [28] or patterns that only contain fruits and vegetables [33], in concordance with the absence of an association we found for the Prudent pattern. Only 3 of these studies explored differences by tumour location [26, 27] or morphology [26, 31]. While some authors show similar strength of the associations for cardia and non-cardia tumours [26] others claim a stronger effect of the Western and Mediterranean/Healthy dietary patterns among non-cardia tumours in females and among cardia tumours in males [27]. Unfortunately, the sample size of the present study did not allow the exploration of a possible interaction between dietary patterns and sex by tumour location. Regarding the tumour morphology, while Bastos et al [26] state that the effect of the Western pattern is only observed among intestinal adenocarcinomas, Kim et al [31] found a stronger effect of the healthy pattern for female diffuse adenocarcinomas. However, none of the authors provide assessment of the statistical significance of the differences declared. In our case, we believe that the greater sample size of the Non-Cardia and Intestinal tumour subtypes might be behind the greater significance of the associations found for these subgroups.

Some biological mechanisms support the plausibility of the associations found. The Western pattern includes a high consumption of red and processed meat, which contribute to the generation of N-Nitroso compounds that are suspected mutagens and carcinogens [35]. Additionally, cooking and processing meat at high temperatures might also contribute to the production of polycyclic aromatic hydrocarbons that are well known carcinogens [36]. The iron

present in these types of meat might also induce free radicals, which cause DNA double strand breaks and oncogene activation [37]. In addition, the saturated fats that can be found in fast food, sauces and desserts, also included in the Western diet, can induce expression of certain inflammatory mediators associated with carcinogenesis [38]. Regarding the Mediterranean pattern, the high content of antioxidants in fruits and vegetables might be partly behind the protective effect of the Mediterranean diet. Antioxidants quench free radicals, reduce oxidative damage to DNA and intervene in various cancer-related biological pathways such as carcinogen bio-activation, cell-signalling, cell cycle regulation, angiogenesis, and inflammation [39, 40]. Additionally, allium vegetables, particularly garlic, can reduce the severity of *H. pylori* associated gastritis and bioactive constituents in fruit might protect against *H. pylori*-induced damage, particularly inflammation, which is implicated in the development of gastric cancers [41]. Moreover, Omega-3 polyunsaturated fatty acids, present in fish and nuts, may have preventive effects by influencing multiple targets implicated in various stages of cancer development, including cell proliferation, cell survival, angiogenesis, inflammation, and metastasis [42].

Our results should be interpreted in the context of the study's limitations. Recall bias is always a concern in case-control studies, especially when evaluating the effect of self-reported dietary information. Anticipating the existence of this bias, some questions about general dietary habits were included in the questionnaire and used to adjust the responses to the FFQ [43]. In order to minimize even more the effect of this possible bias, only cases that responded to the questionnaire within the 6 months following the diagnosis were included. On the other hand, the response rate was 57% for cases and 53% for controls, which may appear to be low and might arise some concerns about selection bias. Participating controls might have better lifestyles resulting in an overestimation of the effects. However, no effect was found for the

prudent pattern that includes consumption of products widely known as "Healthy". We believe it is unlikely that the effect of this bias is selective and affects only some associations. Furthermore, although the literature does not reflect agreement on a minimum acceptable response rate, there is general consensus that a 50% response rate might be adequate [44]. In addition, the strength of the associations found, their consistency across sex, age and subtypes, their consistency with the results from EpiGEICAM [12] (Western pattern increased the risk of BC in EpiGEICAM and GAC in MCC-Spain, the Prudent pattern had no effect over these two tumours and the Mediterranean pattern appeared to be protective against both BC (EpiGEICAM) and GAC (MCC-Spain)) and from other GC studies, as well as their biological plausibility deem it unlikely that our findings are a result of recall or selection bias. Finally, results were not adjusted by data on *H. pylori* infection, the main explanatory cause of non-cardia GC. However, the sensitivity analyses carried out (**Table S1** from Online Resource 1) showed no important differences in the estimation of the effects when taking this factor into account, thus supporting that the reported associations between diet and GAC are independent of *H. pylori* infection.

One of the strengths of the current research is the recruitment of histologically confirmed incident cases of GC and population-based controls. Additionally, the reproducibility [23] and applicability [22] of the data-driven dietary patterns found in the EpiGEICAM study [12] were methodologically tested in two recent studies [22, 23]. These studies concluded that similar patterns can be found in independent samples [23] and that scores of adherence to data-driven dietary patterns can be calculated following the exact same rules over different populations, resulting in different levels of adherence but still being valid [22]. Furthermore, the sample size allowed the evaluation of potential interactions of diet with sex and age and the exploration of the associations by tumour location and morphology. Finally, the inclusion of cases and controls recruited from 10 provinces from the North, South, Centre,

West and East of the country ensured the representation of the different diets coexisting within Spain. The dietary variability of the participants allowed the differentiation of the effect of two very similar patterns on GAC risk. Prudent and Mediterranean dietary patterns are commonly interchanged in the literature of data-driven dietary patterns, but they showed different effects on GAC in our study, adding novel information about the association of the so called "healthy" dietary habits and GAC. In addition, if our result of a lack of protective effect of the Prudent pattern on GAC risk is confirmed, the effect sizes estimated for the Mediterranean pattern in studies that have not differentiated it from the Prudent pattern could be underestimations of the true protective role of the Mediterranean diet.

CONCLUSION

A high consumption of fruits, vegetables and whole grains together with a restriction of dietary fat is not enough to prevent GAC. The risk of this tumour might be reduced in the general population by providing dietary recommendations based on a decrease of the consumption of high-fat dairy products, red and processed meat, refined grains, sweets, caloric drinks, convenience food and sauces in favour of an increase in the intake of fruits, vegetables, legumes, olive oil, nuts and fish.

ONLINE RESOURCE 1:

Table S1. Sensitivity analysis to choose the most adequate model to explore the association between gastric adenocarcinoma incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.

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CONFLICT OF INTEREST STATEMENT:

The authors do not have conflicts of interest in connection with the paper.

ETHICAL STATEMENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

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Table 1: Composition of food groups based on the food frequency questionnaire of the MCC-Spain study and component loadings for each pattern identified in the previous study [12].

FOOD GROUP	FOOD[a]	W[b]	P[b]	M[b]
HIGH-FAT DAIRY	Whole-fat milk, condensed milk, whole-fat yogurt, semi-cured, cured, or creamy cheese, blue cheese, custard, milk shake, ice-cream, double cream.	0.60	-0.11	0.20
LOW-FAT DAIRY	Semi-skimmed and skimmed milk, soy milk, skimmed yogurt, curd, cottage or fresh white cheese.	-0.49	0.60	-0.01
EGGS	Eggs.	0.19	0.08	0.16
WHITE MEAT	Chicken, rabbit and duck.	0.08	0.17	0.18
RED MEAT	Pork, beef, lamb, liver (beef, pork or chicken), entrails, hamburgers (pork or beef) and meatballs (pork or beef).	0.27	0.09	0.22
PROCESSED MEAT	Sausages, serrano ham and other cold meat, bacon, pâté, foie-gras.	0.36	0.10	0.26
WHITE FISH	Fresh or frozen white fish (hake, sea bass, sea bream), ½·salted fish and ½·smoked fish.	0.01	0.24	0.34
OILY FISH	Fresh or frozen blue fish (tuna, swordfish, sardines, anchovies, salmon), canned fish, ½·salted fish and ½·smoked fish.	0.05	0.24	0.44

SEAFOOD/SHELLFISH	Clams, mussels, oysters, squid, cuttlefish, octopus, prawn, crab, shrimp and similar products.	0.17	0.27	0.35
LEAFY VEGETABLES	Spinach, chard, lettuce and other leafy vegetables.	-0.11	0.34	0.40
FRUITING VEGETABLES	Tomato, eggplant, zucchini, cucumber, pepper, artichoke and avocado.	0.00	0.36	0.45
ROOT VEGETABLES	Carrot, pumpkin and radish.	0.05	0.35	0.44
OTHER VEGETABLES	Cooked cabbage, cauliflower or broccoli, onion, green beans, asparagus, mushrooms, corn, garlic, gazpacho, vegetable soup and other vegetables.	-0.04	0.40	0.42
LEGUMES	Peas, lentils, chickpeas, beans and broad beans.	0.21	0.15	0.34
POTATOES	Roasted or boiled potatoes and sweet potatoes.	0.17	0.25	0.40
FRUITS	Orange, grapefruit, mandarin, banana, apple, pear, grapes, kiwi, strawberries, cherries, peach, figs, melon or watermelon, prunes, mango and papaya and other fresh or dried fruits.	-0.07	0.31	0.31
NUTS	Almonds, peanuts, pine nuts, hazelnut	0.18	0.22	0.29
REFINED GRAINS	White-flour bread, rice, pasta	0.37	0.15	0.23
WHOLE GRAINS	Whole-grain bread and breakfast cereals	-0.43	0.47	-0.06

OLIVES AND VEGETABLE OIL	Olives, added olive oil to salads, bread and dishes, other vegetable oils (sunflower, corn, and soybean).	0.12	0.19	0.34
OTHER EDIBLE FATS	Margarine, butter and lard.	0.22	0.02	0.11
SWEETS	Chocolate and other sweets, cocoa powder, plain cookies, chocolate cookies, pastries (croissant, donut, cake, pie or similar)	0.35	0.18	0.05
SUGARY	Jam, honey, sugar and fruit in sugar syrup.	0.24	0.05	0.00
JUICES	Tomato juice, freshly squeezed orange juice, juice (other than freshly squeezed)	0.25	0.67	-0.39
CALORIC DRINKS	Sugar-sweetened soft drinks and nut milk.	0.74	0.21	-0.25
CONVENIENCE FOOD AND SAUCES	Croquette, fish sticks, dumplings, kebab, fried potatoes, crisps, pizza, instant soup, mayonnaise, tomato sauce, hot sauce, ketchup and other sauces.	0.47	0.12	0.24

[a] Log-transformed centred intake in grams.

[b] W: Western; P: Prudent; M: Mediterranean

Table 2. Description of scores of adherence to Western, Prudent and Mediterranean dietary patterns and other baseline characteristics for gastric adenocarcinoma cases and controls.

	Controls n=3040	Cases n=295	p
Age (years) mean(SD[a])	63.93 (11.43)	65.89 (12.63)	0.005
Sex n(%[b])			<0.001
Male	1692 (56%)	207 (70%)	
Female	1348 (44%)	88 (30%)	
Education n(%[b])			<0.001
No formal Education	545 (18%)	82 (28%)	
Primary School	1027 (34%)	113 (38%)	
Secondary School	852 (28%)	69 (23%)	
University or more	616 (20%)	31 (11%)	
Western mean(SD[a])	-0.34 (3.49)	0.84 (3.48)	<0.001
Prudent mean(SD[a])	-0.10 (3.30)	0.36 (3.35)	0.022
Mediterranean mean(SD[a])	0.05 (2.88)	0.41 (2.54)	0.043
Energy (kcal/day) mean(SD[a])	1912.50 (571.94)	2095.19 (651.32)	<0.001
Alcohol(g/day) median(IQR)	7.57 (0.00;24.72)	12.92 (1.41;40.42)	<0.001
BMI[a] (kg/m2) mean(SD[a])	26.70 (4.33)	27.15 (3.87)	0.094
Physical activity			<0.001
0 METs[a]/week	1189 (39%)	147 (50%)	
0.1-8 METs[a]/week	410 (13%)	33 (11%)	
8.1-15.9METs[a]/week	355 (12%)	15 (5%)	

>=16 METs[a]/week	1048 (34%)	100 (34%)	
Unknown	38 (1%)	0 (0%)	
Smoking n(%[b])			0.703
Never Smoker	1332 (44%)	123 (42%)	
Former Smoker	1092 (36%)	104 (35%)	
Current Smoker	604 (20%)	67 (23%)	
Unknown	12 (0%)	1 (0%)	
Family history of GC n(%[b])			<0.001
No	2707 (89%)	231 (78%)	
2nd Degree	139 (5%)	14 (5%)	
One of 1st degree	182 (6%)	43 (15%)	
More than one of 1st degree	12 (0%)	7 (2%)	

[a] SD: Standard Deviation; BMI: Body mass index; GC: Gastric cancer; METS: Metabolic equivalent.

Table 3. Association between gastric adenocarcinoma incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns and attributable fractions by sex and age.

[b] Percentages might not add up 100 because of rounding.	ALL (n=3092)		MALE (n=1783)		FEMALE (n=1309)			≤68 years (n=1925)		>68 years (n=1167)		
	Co/Ca[a]	OR(95%CI)[b]	Co/Ca[a]	OR(95%CI) [c]	Co/Ca[a]	OR(95%CI) [c]	p-int[a]	Co/Ca[a]	OR(95%CI) [d]	Co/Ca[a]	OR(95%CI) [d]	p-int[a]
WESTERN												
Q1[a]	675/39	1	325/25	1	350/14	1		367/16	1	312/22	1	
Q2[a]	721/61	1.63 (1.05;2.52)	379/40	1.52 (0.88;2.62)	342/21	1.83 (0.90;3.74)		437/28	1.39 (0.74;2.62)	276/32	1.88 (1.04;3.41)	
Q3[a]	720/82	2.23 (1.45;3.43)	412/58	2.10 (1.24;3.55)	308/24	2.51 (1.24;5.07)		465/40	1.83 (0.99;3.37)	247/42	2.74 (1.54;4.88)	
Q4[a]	705/89	2.09 (1.31;3.33)	471/73	2.09 (1.21;3.58)	234/16	1.96 (0.89;4.31)		499/61	2.01 (1.09;3.73)	204/32	2.13 (1.13;4.00)	
p-trend		0.001		0.005		0.043			0.015		0.007	
1SD-increase		1.31 (1.11;1.55)		1.30 (1.08;1.57)		1.35 (1.04;1.76)	0.799		1.34 (1.09;1.64)		1.32 (1.06;1.64)	0.398
PAF%[e]		45%(24%;66%)		42%(16%;68%)		48%(20%;76%)			42%(15%;68%)		48%(18%;77%)	
PRUDENT												
Q1[a]	687/64	1	456/54	1	231/10	1		406/27	1	282/36	1	
Q2[a]	706/58	0.90 (0.61;1.33)	403/47	0.94 (0.61;1.46)	303/11	0.81 (0.33;1.97)		416/41	1.42 (0.84;2.40)	281/17	0.47 (0.25;0.87)	
Q3[a]	722/66	1.10 (0.74;1.63)	388/42	0.94 (0.59;1.48)	334/24	1.63 (0.75;3.56)		464/32	1.05 (0.60;1.83)	248/35	1.17 (0.69;2.00)	
Q4[a]	706/83	1.40 (0.93;2.11)	340/53	1.28 (0.81;2.05)	366/30	1.80 (0.83;3.90)		482/45	1.33 (0.77;2.32)	228/40	1.55 (0.90;2.67)	
p-trend		0.065		0.337		0.032			0.565		0.023	

1SD-increase		1.16 (0.99;1.37)		1.12 (0.94;1.34)		1.33 (0.98;1.81)	0.913		1.10 (0.89;1.36)		1.24 (1.00;1.54)	0.491
PAF%[e]		10%(-14%;34%)		-3%(-28%;23%)		33%(-11%;77%)			-2%(-32%;29%)		28%(-13%;69%)	
MEDITERRANEAN												
Q1[a]	697/60	1	385/44	1	312/16	1		446/31	1	252/27	1	
Q2[a]	713/73	0.98 (0.67;1.44)	364/48	0.94 (0.59;1.50)	349/25	1.09 (0.56;2.12)		454/37	0.85 (0.51;1.42)	249/35	1.19 (0.68;2.09)	
Q3[a]	711/70	0.76 (0.51;1.13)	393/49	0.71 (0.44;1.14)	318/21	0.88 (0.44;1.76)		449/43	0.83 (0.50;1.39)	258/28	0.65 (0.36;1.18)	
Q4[a]	700/68	0.53 (0.34;0.82)	445/55	0.51 (0.31;0.83)	255/13	0.59 (0.27;1.30)		419/34	0.46 (0.26;0.81)	280/38	0.60 (0.33;1.08)	
p-trend		0.002		0.003		0.146			0.010		0.023	
1SD-increase		0.82 (0.71;0.96)		0.80 (0.67;0.95)		0.89 (0.67;1.19)	0.314		0.80 (0.65;0.98)		0.84 (0.69;1.04)	0.684
PAF%[e]		34%(15%;54%)		36%(14%;57%)		33%(-2%;68%)			37%(16%;58%)		31%(-3%;66%)	

[a] Co: Controls; Ca: Cases; Q1, Q2, Q3 and Q4: First, Second, Third and Fourth quartiles; p-int=p-value for the interaction.

[b] Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, caloric intake and alcohol intake as fixed effects and province of residence as a random effect.

[c] Same as [b] including an interaction term with sex.

[d] Same as [b] including an interaction term with age.

[e] PAF= Population attributable fraction. Proportion of gastric cancer cases that could be prevented if all participants were in the most beneficial category of adherence to each pattern (Q1 for Western and Prudent and Q4 for Mediterranean)

$$PAF = \frac{PF_{Q1} \cdot \left(OR_{Q1} - 1\right) + PF_{Q2} \cdot \left(OR_{Q2} - 1\right) + PF_{Q3} \cdot \left(OR_{Q3} - 1\right) + PF_{Q4} \cdot \left(OR_{Q4} - 1\right)}{1 + [PF_{Q1} \cdot \left(OR_{Q1} - 1\right) + PF_{Q2} \cdot \left(OR_{Q2} - 1\right) + PF_{Q3} \cdot \left(OR_{Q3} - 1\right) + PF_{Q4} \cdot \left(OR_{Q4} - 1\right)]} \bullet 100$$

PF=Proportion of population in the specific exposure category

OR= Odds ratio for the especific exposure category

Table 4. Adjusted odds ratios for the association between gastric adenocarcinoma incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns by tumour site (cardias, no cardias) and morphology (intestinal and diffuse)

		Cardia (n=65)		Non-Cardia (n=199)			Intestinal (n=106)		Diffuse (n=66)		
	Controls (n=2821)	Cases	OR[b](95%CI)	Cases	OR[b](95%CI)	p-het	Cases	OR[b](95%CI)	Cases	OR[b](95%CI)	p-het
WESTERN											
Q1[a]	675	2	1[c]	35	1		20	1	9	1	
Q2[a]	721	15		44	1.38 (0.86;2.23)		28	1.80 (0.96;3.36)	12	1.26 (0.52;3.07)	
Q3[a]	720	26	2.69 (1.40;5.17)	55	1.83 (1.14;2.94)		24	1.80 (0.93;3.50)	19	1.96 (0.84;4.57)	
Q4[a]	705	22	1.40 (0.66;2.99)	65	2.01 (1.21;3.35)		34	2.74 (1.38;5.45)	26	2.10 (0.86;5.10)	
p-trend			0.340		0.004			0.007		0.063	
1SD-increase			1.29 (0.93;1.77)		1.35 (1.12;1.63)	0.800		1.39 (1.08;1.79)		1.40 (1.02;1.91)	0.977
PAF%[d]			40%(5%;75%)		27%(4%;50%)			15%(-3%;34%)		31%(-14%;77%)	
PRUDENT											
Q1[a]	687	16	1	46	1		30	1	11	1	
Q2[a]	706	14	0.89 (0.42;1.88)	44	0.94 (0.60;1.46)		15	0.48 (0.25;0.94)	15	1.25 (0.56;2.80)	

Q3[a]	722	13	0.93 (0.43;2.04)	51	1.14 (0.73;1.78)		28	1.08 (0.60;1.93)	16	1.32 (0.58;2.97)	
Q4[a]	706	22	1.58 (0.73;3.40)	58	1.32 (0.82;2.12)		33	1.55 (0.83;2.87)	24	1.74 (0.76;3.99)	
p-trend			0.243		0.175			0.053		0.193	
1SD-increase			1.21 (0.90;1.63)		1.13 (0.94;1.36)	0.684		1.27 (0.98;1.65)		1.35 (0.97;1.89)	0.785
PAF%[d]			-2%(-18%;13%)		2%(-19%;24%)			-16%(-31%;-1%)		15%(-34%;64%)	
MEDITERRANEAN											
Q1[a]	697	10	1	49	1		22	1	11	1	
Q2[a]	713	19	1.64 (0.73;3.70)	54	0.86 (0.56;1.32)		22	0.82 (0.43;1.55)	20	1.46 (0.67;3.16)	
Q3[a]	711	20	1.44 (0.63;3.32)	46	0.59 (0.37;0.93)		33	0.94 (0.51;1.75)	17	1.06 (0.47;2.41)	
Q4[a]	700	16	0.74 (0.30;1.86)	50	0.47 (0.29;0.77)		29	0.57 (0.29;1.12)	18	0.90 (0.38;2.15)	
p-trend			0.318		0.001			0.146		0.536	
1SD-increase			0.91 (0.67;1.24)		0.78 (0.66;0.93)	0.395		0.81 (0.63;1.03)		0.92 (0.68;1.26)	0.405
PAF%[d]			22%(-3%;46%)		21%(2%;41%)			12%(-4%;28%)		14%(-20%;47%)	

[a] Ca: Cases; Q1, Q2, Q3 and Q4: First, Second, Third and Fourth quartiles; p-het=p-value for the heterogeneity of effects.

[b] Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, caloric intake, alcohol intake and province of residence.

[c] Categories corresponding to first and second quartile were summed up and used as a reference for the exploration of the association between the adherence to the Western pattern and the risk of gastric adenocarcinoma in the cardia.

[d] PAF= Population attributable fraction. Proportion of gastric cancer cases that could be prevented if all participants were in the most beneficial category of adherence to each pattern (Q1 for Western and Prudent and Q4 for Mediterranean)

$$PAF = \frac{PF_{Q1}\cdot\left(OR_{Q1}-1\right)+PF_{Q2}\cdot\left(OR_{Q2}-1\right)+PF_{Q3}\cdot\left(OR_{Q3}-1\right)+PF_{Q4}\cdot\left(OR_{Q4}-1\right)}{1+[PF_{Q1}\cdot\left(OR_{Q1}-1\right)+PF_{Q2}\cdot\left(OR_{Q2}-1\right)+PF_{Q3}\cdot\left(OR_{Q3}-1\right)+PF_{Q4}\cdot\left(OR_{Q4}-1\right)]}\bullet 100$$

PF=Proportion of population in the specific exposure category

OR= Odds ratio for the especific exposure category

SUPPLEMENTARY MATERIAL

High Adherence to the Western, Prudent and Mediterranean Dietary Patterns and Risk of Gastric Adenocarcinoma. Gastric Cancer. Adela Castelló, Nerea Fernández de Larrea, Vicente Martín, Verónica Dávila-Batista, Elena Boldo, Marcela Guevara, Víctor Moreno, Gemma Castaño-Vinyals, Inés Gómez-Acebo, Guillermo Fernandez-Tardon, Rosana Peiró, Rocío Olmedo-Requena, Rocio Capelo, Carmen Navarro, Silvino Pacho-Valbuena, Beatriz Pérez-Gómez, Manolis Kogevinas, Marina Pollán, Nuria Aragonés on behalf of MCC-Spain researchers

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Table S1. Sensitivity analysis to choose the most adequate model to explore the association between gastric adenocarcinoma incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.

	MODEL 1		MODEL 2		MODEL 3		MODEL 4		MODEL 5	
	n=3335		n=3092		n=1979		n=1979		n=1760	
	Co/Ca[a]	OR[b](95%CI)	Co/Ca[a]	OR[c](95%CI)	Co/Ca[a]	OR[d](95%CI)	Co/Ca[a]	OR[e](95%CI)	Co/Ca[a]	OR[f](95%CI)
WESTERN										
Q1[a]	760/42	1	675/39	1	448/22	1	448/22	1	405/22	1
Q2[a]	760/65	1.66 (1.11;2.49)	721/61	1.63 (1.05;2.52)	459/37	1.67 (0.95;2.94)	459/37	1.68 (0.96;2.94)	405/34	1.55 (0.87;2.75)
Q3[a]	760/88	2.45 (1.66;3.62)	720/82	2.23 (1.45;3.43)	472/50	1.93 (1.11;3.36)	472/50	1.93 (1.11;3.37)	424/45	1.74 (0.99;3.07)
Q4[a]	760/100	2.83 (1.93;4.15)	705/89	2.09 (1.31;3.33)	435/56	1.78 (0.98;3.25)	435/56	1.80 (0.99;3.29)	372/53	1.76 (0.95;3.25)
p-trend		0.000		0.001		0.074		0.068		0.082
1SD-increase		1.51 (1.33;1.71)		1.31 (1.11;1.55)		1.21 (0.98;1.50)		1.22 (0.99;1.50)		1.21 (0.97;1.51)

(Continued on the next page)

Table S1 (cont). Sensitivity analysis to choose the most adequate model to explore the association between gastric adenocarcinoma incidence and scores of adherence to Western, Prudent and Mediterranean dietary patterns.

	MODEL 1		MODEL 2		MODEL 3		MODEL 4		MODEL 5	
	n=3335		n=3092		n=1979		n=1979		n=1760	
	Co/Ca[a]	OR[b](95%CI)	Co/Ca[a]	OR[c](95%CI)	Co/Ca[a]	OR[d](95%CI)	Co/Ca[a]	OR[e](95%CI)	Co/Ca[a]	OR[f](95%CI)
PRUDENT										
Q1[a]	760/68	1	687/64	1	447/38	1	447/38	1	400/38	1
Q2[a]	760/63	0.85 (0.59;1.22)	706/58	0.90 (0.61;1.33)	447/35	0.95 (0.57;1.56)	447/35	0.95 (0.57;1.56)	395/34	0.90 (0.54;1.49)
Q3[a]	760/73	1.03 (0.73;1.46)	722/66	1.10 (0.74;1.63)	456/39	1.08 (0.65;1.78)	456/39	1.07 (0.65;1.77)	408/36	0.94 (0.56;1.58)
Q4[a]	760/91	1.32 (0.94;1.85)	706/83	1.40 (0.93;2.11)	464/53	1.33 (0.80;2.21)	464/53	1.34 (0.81;2.24)	403/46	1.15 (0.68;1.94)
p-trend		0.051		0.065		0.228		0.212		0.572
1SD-increase		1.16 (1.02;1.32)		1.16 (0.99;1.37)		1.08 (0.89;1.32)		1.08 (0.89;1.32)		1.02 (0.84;1.24)
MEDITERRANEAN										
Q1[a]	760/65	1	697/60	1	424/32	1	424/32	1	371/30	1
Q2[a]	760/76	1.05 (0.74;1.50)	713/73	0.98 (0.67;1.44)	445/47	1.24 (0.75;2.05)	445/47	1.24 (0.75;2.05)	391/45	1.28 (0.76;2.15)
Q3[a]	760/77	1.00 (0.70;1.42)	711/70	0.76 (0.51;1.13)	465/45	0.88 (0.53;1.49)	465/45	0.88 (0.52;1.48)	413/41	0.82 (0.48;1.42)
Q4[a]	760/77	0.93 (0.65;1.33)	700/68	0.53 (0.34;0.82)	480/41	0.58 (0.33;1.03)	480/41	0.58 (0.33;1.03)	431/38	0.58 (0.32;1.05)
p-trend		0.615		0.002		0.020		0.020		0.017
1SD-increase		1.05 (0.92;1.20)		0.82 (0.71;0.96)		0.84 (0.69;1.03)		0.84 (0.69;1.03)		0.83 (0.68;1.02)

[a] Co: Controls; Ca: Cases; Q1, Q2, Q3 and Q4: First, Second, Third and Fourth quartiles; SD: Standard Deviation; p-int=p-value for the interaction.

[b] Model 1: Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by province of residence as a random effect.

[c] Model 2: Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, caloric intake and alcohol intake as fixed effects and province of residence as a random effect.

[d] Model 3: Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, caloric intake and alcohol intake

as fixed effects and province of residence as a random effect resulting from a model restricted to the individuals that had data on *H. pylori* infection.

[e] Model 4: Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, *H. pylori* infection, caloric intake and alcohol intake as fixed effects and province of residence as a random effect.

[f] Model 5: Odds ratio of gastric adenocarcinoma associated with the adherence to the Western, Prudent and Mediterranean dietary patterns adjusted by sex, age, education, BMI, family history of gastric cancer, physical activity (METs), smoking status, caloric intake and alcohol intake as fixed effects and province of residence as a random effect resulting from a model restricted to seropositive individuals against *H. pylori* infection.