

# Gastric cancer incidence and geographical variations: the influence of gender and rural and socioeconomic factors, Zaragoza (Spain)

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## Abstract

**Background** Socioeconomic status (SES) and rural factors have been shown to be associated with gastric cancer epidemiology. The aim of this study was to identify geographical variations in gastric cancer incidence in Zaragoza province (Spain) during the period 1993–2002, and their association with SES and rural factors.

**Methods** Incident cases were extracted from the population-based Zaragoza Cancer Registry. The geographical analysis unit was the census tract (CT) in Zaragoza city ( $N = 462$ ) and the municipalities for the rest of the province ( $N = 292$ ). Four indexes were applied: two deprivation and two rurality indexes, included in a Bayesian risk model discretized in quartiles. Standardized incidence ratios (SIRs) were calculated using the incidence rates in Spain. SIRs were adjusted by a Bayesian generalized linear mixed model (GLMM).

**Results** From 1993 to 2002, 1,309 cases of gastric cancer were registered in Zaragoza city and 578 in the rest of the province. High risk was observed in CTs for the peripheral areas of the city. The incidence risk in men was 2 (95 % confidence interval [CI] 1.22–2.98) times higher in the most deprived CTs compared with the least deprived CTs, but no statistically significant differences were found in women. Municipalities with higher risk were observed in the north of the province, but no significant association was found with SES. Regarding the rurality index, a positive trend was observed in women, but it was statistically significant only for the most rural quartile (2.49, 95 % CI 1.07–4.92).

**Conclusions** Geographical differences in gastric cancer incidence were detected. Although these differences could be partially explained by the deprivation index for men in Zaragoza city, deprivation index cannot explain geographical differences for women. In the rest of the province, the rurality index 1991 could explain, at least for women, geographical differences. It is still necessary to develop a deprivation index suitable for small municipalities.

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## Introduction

Instead of decreasing in recent decades, stomach cancer remains the 4th most frequent cancer worldwide. In Spain, and according to GLOBOCAN 2008 [1], stomach cancer showed an age-standardized incidence rate of 12.1 per 100,000 person-years and a mortality rate of 8.7 in males. In females, the rates were lower, with an age-standardized incidence rate of 5.3 per 100,000 person-years and a

mortality rate of 3.8. The highest incidence is found in men over 50 years of age. It has high mortality levels, especially due to its frequency of metastasis (80–90 %) [2], being the fifth most common cause of cancer death in both sexes in Spain [1]. Survival rates were low in the EURO CARE-4 study period (1995–1999) and the low rates continued to December 2003. Age-standardized 5-year relative survival was 27.8 % (95 % confidence interval [CI]: 26.4–29.3) in Spain and 24.5 % (95 % CI: 24.1–24.9) in Europe as a whole [3]. Similar results were obtained for the 2000–2002 period analysis of the EURO CARE-4 data, the age-adjusted 5-year relative survival rate being 24.9 % (95 % CI: 23.7–26.2) in Europe, although in Spain the survival rate was higher (31.8 %, 95 % CI: 25.9–39.2) [4].

Infection by *Helicobacter pylori* is considered to be the most important stomach cancer risk factor. About half of the world's population is estimated to be infected with this bacterium [5]. However, the development of gastric cancer cannot be explained just by infection with *Helicobacter pylori*, because only a small percentage of the individuals infected by the bacteria, between 2 and 5 %, ever develop a gastric cancer [6, 7]. Therefore, other risk factors must be considered. Compared with controls, more frequent intake of a high-risk diet, history of heavy smoking, heavy intake of alcohol, lower social economic status, body mass index >30, urban residence, and more frequent exposure to harmful occupational environments were observed in all age groups and both genders in young-age gastric cancer. These relationships were weaker in females compared with males of the same age, and were stronger as the age of the patients increased [8]. Other authors have explored the association between stomach cancer and salt and low amounts of fruits and vegetables in the diet, as well as smoking habits [9, 10] and the level of nitrate in drinking water [11].

Socioeconomic status (SES) has also been considered a risk factor in gastric cancer and has been explored by different indicators. Although the differences observed by social class are probably related to factors already explained, such as diet and other lifestyle factors, part of the variation cannot be attributed to already known factors [12]. Regarding occupation, higher incidence and greater mortality have been found in some kinds of jobs [13, 14]. This association remains even after adjustment by different risk factors, such as smoking status [15]. An association between the risk of stomach cancer and low income level [16] and the use of deprivation indexes was also observed [17].

Although the incidence of stomach cancer has decreased in the past few decades, this trend shows wide geographical variations [18]. The decrease in developed countries has been accompanied by a decline in the prevalence of *Helicobacter pylori* infection [1]. In spite of the importance of

this cancer in developing countries, other geographical variations related to urbanization must be considered.

Regarding the aspects previously considered, the main objective of this study was to identify geographical variations in the incidence of stomach cancer in the province of Zaragoza (Spain) during the period 1993–2002, and their association with socioeconomic and rural factors.

## Population, materials, and methods

A small-area ecological study was conducted. The population under analysis was all the residents in the province of Zaragoza (861,855 persons according to the 2001 census). The province of Zaragoza belongs to the Autonomous Community of Aragón, located in northeastern Spain.

All incident cases of stomach cancer (code C16 of the International Classification of Diseases for Oncology 3rd Edition; ICD-O-3) were obtained from the Zaragoza population-based Cancer Registry for the period 1993–2002. The number of inhabitants in 19 age groups (0–4, 5–9, ..., over 90 years) was obtained for each census tract (CT) by the National Statistics Institute (INE) from the Population and Housing Census 2001. Socioeconomic data relating to 20 indicators were provided by the INE from the Population and Housing Census 2001.

To study geographical variability, two different units of analysis were used, depending on the geographical context. In the city of Zaragoza (with 70 % of the inhabitants of the whole of Zaragoza province), the units of analysis were CTs ( $N = 462$ ), which were the smallest geographical units available. In the rest of the province, municipalities were used ( $N = 292$ ) for the analysis, because there were no available data for smaller geographical units, although 90 % of the municipalities matched the CTs exactly. The analyses were carried out separately: one for the city of Zaragoza, using CTs, and another one for the rest of the province, considering municipalities as the geographical unit of study. The analyses were also conducted stratified by gender.

Three indexes were included in the analysis to explore the relationship between stomach cancer incidence and SES and rural characteristics. The MEDEA deprivation index [19] was developed for large Spanish cities. This index was obtained by principal component analysis (PCA) and finally included five single indicators in the first principal component. While 75 % of the variability was explained using this index for the city of Zaragoza, only 31 % of the variability was explained for the rest of the province. Thus, two other indexes were included in the analysis for the rest of the Zaragoza province: the deprivation index developed by Sanchez-Cantalejo [20] and the Ocana-Riola rurality index [21]. The deprivation index

developed by Sanchez-Cantalejo [20], which was used to explore deprivation in small municipalities, consists of 3 single indicators. To explore rural facets, the Ocana-Riola index [21] was used. The single indicators were obtained from the data of the Population and Housing Census 2001 for the deprivation indexes. Regarding the rurality index, two different references were considered, using data from both the Population and Housing Census in 1991 and that in 2001 (i.e., the rurality index 1991 and the rurality index 2001). These four indexes were developed by PCA, and adequacy was measured by Bartlett’s test and the Kaiser–Meyer–Olkin index. High values for the deprivation indexes (MEDEA and Sanchez-Cantalejo) correspond to lower SES, and for the rurality indexes high values were related to higher rurality (Fig. 1).

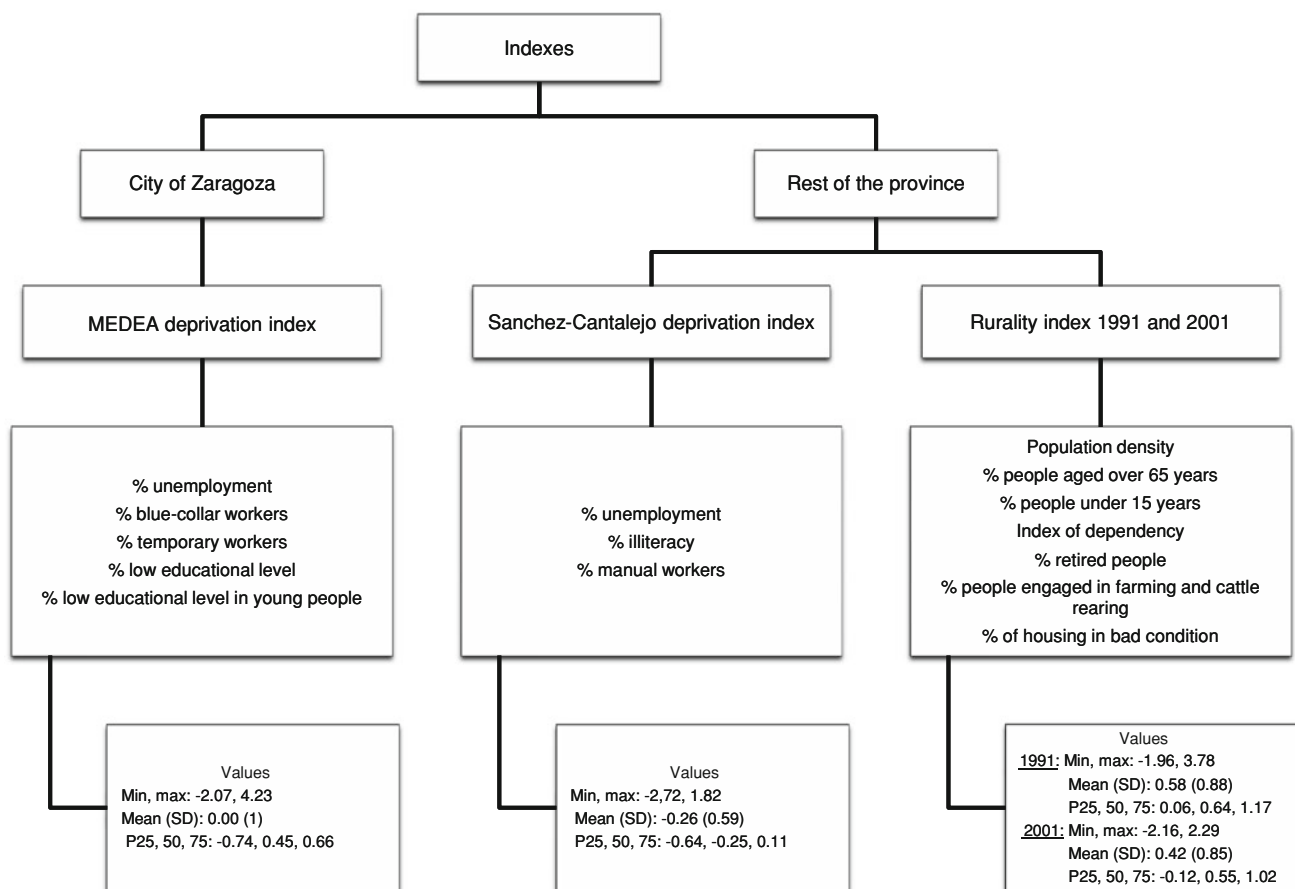
For each unit of analysis, standardized incidence ratios (SIRs) were calculated. As a reference, the rates of stomach cancer incidence in Spain (including data from the Spanish population-based cancer registries) [22] were used. To identify geographical patterns, smoothed SIRs were obtained using the Bayesian methodology proposed in the MEDEA project [23], applying a generalized linear mixed

model (GLMM) proposed by Besag et al. [24]. Posterior probabilities (PRP) of presenting a smoothed SIR greater than 1 were also calculated for each unit of analysis. The indexes included in the Bayesian-risk model were discretized in quartiles, where a relative risk (RR) of 1 was assigned to the first quartile (lowest values for deprivation or rurality). In order to compare the different models obtained, the deviance information criterion (DIC) was used, considering the best model as the one with the lowest value for DIC.

SPSS 15 software (SPSS, Chicago, IL, USA) was used to develop the PCA; R-2.2.1 and WinBUGS14 (WinBUGS14, Cambridge, UK) were used to calculate the models; and ArcView (ArcView, Redlands, CA, USA) was the software chosen to draw the maps.

### Results

During the period 1993–2002, 1,887 incident cases of gastric cancer were registered in Zaragoza province, where 1,309 (69.37 %) belonged to the city of Zaragoza (758 in men and 551 in women), yielding incidence rates of 25.58



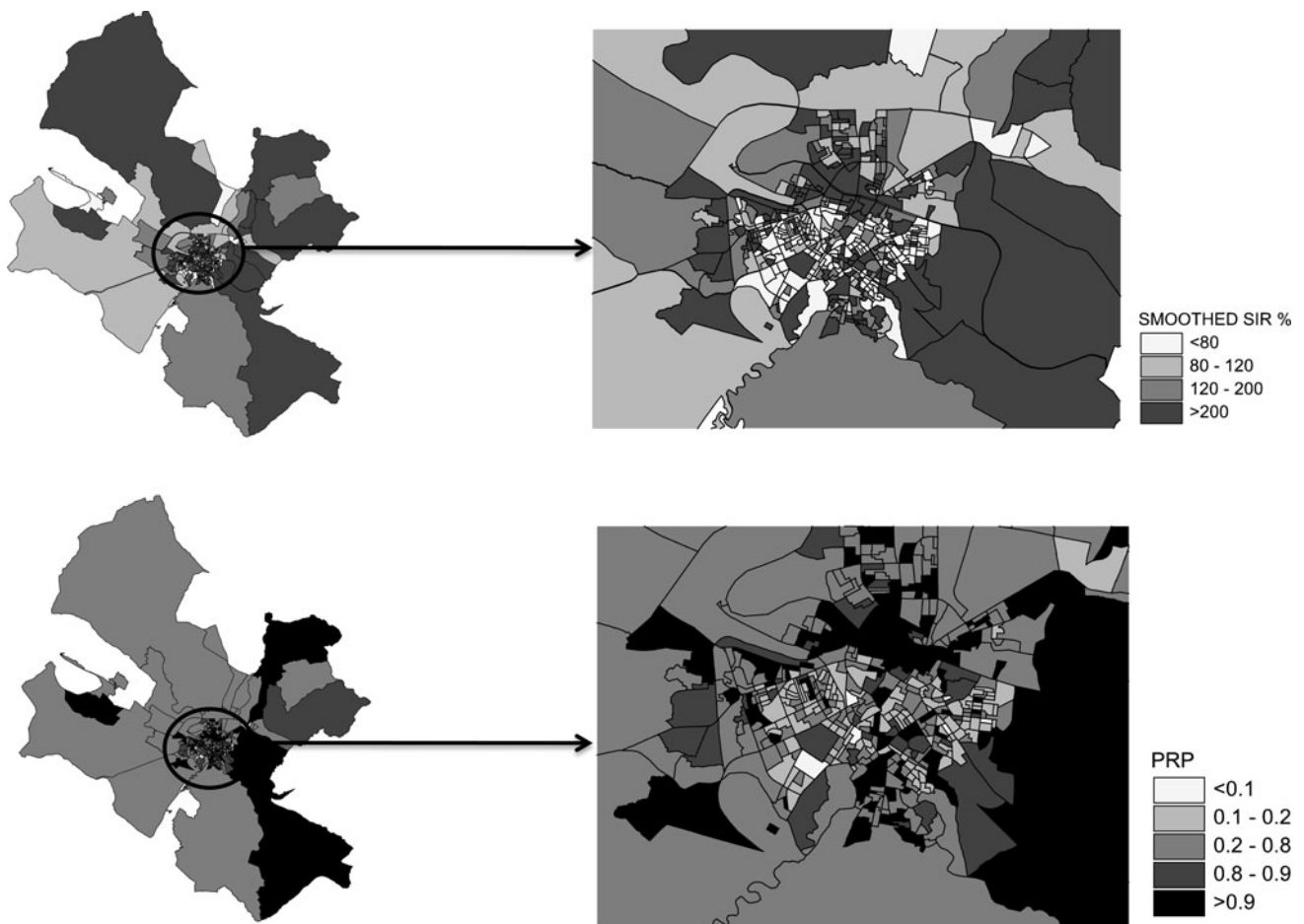
**Fig. 1** Indexes included in the Bayesian risk model: indicators and descriptive analysis. *Min* minimum, *Max* maximum, *SD* standard deviation, *P25...P75* percentile 25... percentile 75

**Table 1** Analysis units used for identifying geographical variations in stomach cancer incidence, Zaragoza 1993–2002

	City of Zaragoza		Rest of the province	
	Male	Female	Male	Female
Number with at least 1 case (% of the total) <sup>a</sup>	242 (52.4 %)	223 (48.3 %)	133 (45.6 %)	97 (33.2 %)
Mean (95 % CI) <sup>b</sup>	1.62 (1.41–1.84)	1.18 (1.01–1.36)	1.20 (0.87–1.54)	0.75 (0.51–0.98)
Median <sup>b</sup>	1	0	0	0
SD <sup>b</sup>	2.35	1.87	2.92	2.04
Q1 <sup>b</sup>	0	0	0	0
Q3 <sup>b</sup>	3	2	1	1

<sup>a</sup> Number of census tracts or municipalities where at least one case of stomach cancer was identified during the period of analysis, and the percentage with respect to the total number of geographical units

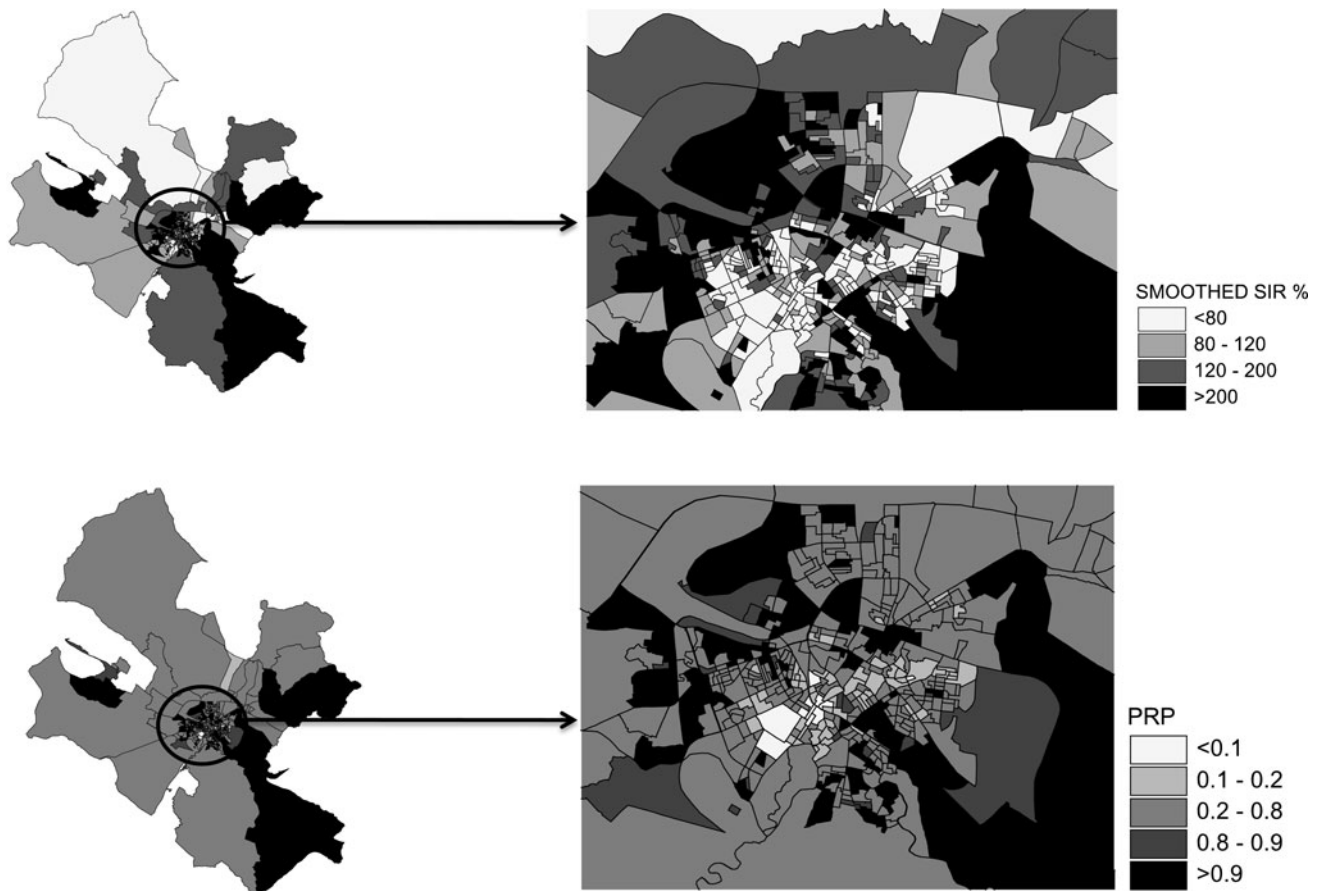
<sup>b</sup> Mean and 95 % confidence interval (95 % CI), median, standard deviation (SD), and first and third quartiles (Q1 and Q3) of stomach cancer cases by census tract



**Fig. 2** Stomach cancer smoothed standardized incidence ratios (SIRs) and posterior probabilities (PRP) in males in the city of Zaragoza, 1993–2002

cases per 100,000 men-years and 17.29 cases per 100,000 women-years. In the rest of the province, 578 cases of stomach cancer were registered (355 men and 223 women) and the incidence rates were 28.6 and 18.8, respectively. These cases were not distributed homogeneously (Table 1).

In the city of Zaragoza, in males, high risk was identified in the rural CTs to the north, east, and south-east of the city. In the center, the CTs of the Historical Quarter and the left bank of the river showed the highest risk of stomach cancer. This risk was statistically significant especially in the CTs of the left bank of the river (PRP > 0.9). In



**Fig. 3** Stomach cancer smoothed standardized incidence ratios (SIRs) and posterior probabilities (PRP) in females in the city of Zaragoza, 1993–2002

females, rural areas to the north and the east (“Las Fuentes”) presented an incidence excess. In the center of the city, high risk was detected in the CTs to the west and east. The risk was significantly higher than the average risk in Spain mainly in the east (Figs. 2, 3).

With respect to the rest of the province, in males, a large number of municipalities presented an excess of risk, with a particularly notable concentration in the north and west of the province, a distribution that could be identified with the high PRP values ( $>0.9$ ) obtained in these areas. In females, the geographical pattern was similar, with the only exception being the south-east of the province, which presented a statistically significant excess of risk, the opposite of the results observed in males (Fig. 4).

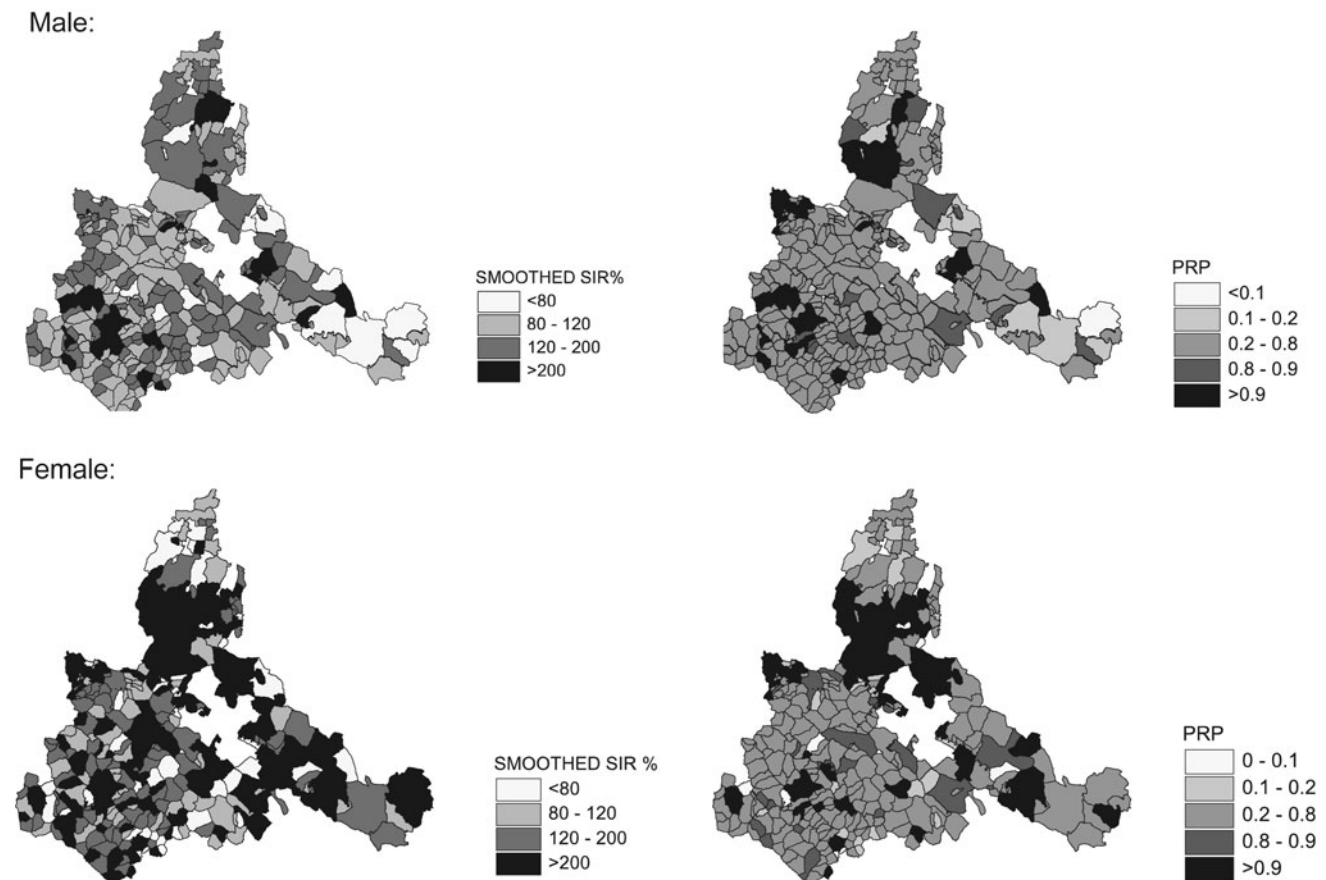
The deprivation index developed in the MEDEA project was introduced into the model. A positive trend between the incidence of gastric cancer and the values of the index was shown for males in the city of Zaragoza. Males living in the most deprived areas (quartiles  $Q_{d3}$  and  $Q_{d4}$ ) faced almost twice (1.93; 95 % CI: 1.22–2.98) the risk of developing stomach cancer compared with those in the most affluent areas. No significant differences were found in females. In the rest of Zaragoza province, in males, all

the quartiles showed an RR close to 1. Statistically significant differences were obtained in females, especially in the  $Q_{d2}$  (2.37; 95 % CI: 1.17–4.52) and  $Q_{d4}$  (2.58; 95 % CI: 1.14–5.13) with a higher risk of stomach cancer for the most deprived municipalities.

In relation to the Sanchez-Cantalejo deprivation index, it was not possible to find any statistically significant association with the incidence of stomach cancer, the negative trend found in females being especially noteworthy. Concerning the rurality indexes, the results obtained were similar for the index created for 1991 and that created for 2001. Although no association was found between the rurality indexes studied and the incidence of gastric cancer for males, a positive trend was observed for females, being statistically significant in the fourth quartile for the 1991 index (2.49; 95 % CI: 1.07–4.92) (Table 2).

## Discussion

Geographical differences in the incidence of gastric cancer were observed in the province of Zaragoza. In the city of Zaragoza, the CTs that presented a higher risk than



**Fig. 4** Stomach cancer smoothed standardized incidence ratios (SIRs) and posterior probabilities (PRP) by gender in the municipalities of the province of Zaragoza, 1993–2002

expected were similar for both genders, and were mainly located in the CTs in the east of the city. These differences could be explained, at least partially, by the MEDEA deprivation index, although the association (RR) between the MEDEA deprivation index and the risk of stomach cancer was significant only in males. The lack of significant results in females could be explained by the lower number of cases.

The distribution of the high risk of stomach cancer in the rest of the province of Zaragoza showed differences by gender. These differences could be explained, at least partially, by the MEDEA index in females. The Sanchez-Cantalejo deprivation index could not explain geographical variations among more rural areas in Zaragoza. Differences in stomach cancer risk between the less and the most deprived municipalities could be explained, at least partially, by the rurality index proposed by Ocana-Riola, using the 1991 census data.

The results obtained in this study are along the same lines as those observed for other cancers and chronic diseases where the MEDEA index was used [25, 26],

including previous work in the city of Zaragoza [27]. Our results are also concordant with other studies that used different deprivation measures [28–33]. Regarding the use of a rurality index, its application in southern Spain [34] showed a reduction in mortality rates for the most rural municipalities, with a risk of death for men 13.3 % lower in the most rural areas compared with that in more urban environments, and a risk of death for women 14.1 % lower than that in more urban environments. Similar associations between the rural characteristics of the area of residence and stomach cancer were obtained in rural areas of China [35]. A study conducted in Lithuania [36], however, showed higher mortality levels in rural areas, especially due to a slower decrease in mortality rates with respect to the urban ones. These results were associated with improvements in dietetic habits and a decrease in *Helicobacter pylori* infection. Other studies have also pointed to a higher risk of stomach cancer in rural areas [37, 38], where nutritional and occupational factors could be involved.

Despite the presence of some potential limitations of the present study, it is unlikely that the procedures we used

**Table 2** Relative risk (RR) and 95 % confidence intervals (95 % CIs) obtained with the different indexes used in the models, stratified by area and gender

	City of Zaragoza				Rest of the province			
	Male		Female		Male		Female	
	RR	95 % CI	RR	95 % CI	RR	95 % CI	RR	95 % CI
MEDEA deprivation index								
$Q_d1$	1		1		1		1	
$Q_d2$	1.50	0.97–2.25	1.38	0.84–2.15	0.99	0.61–1.52	2.37	1.17–4.52
$Q_d3$	1.94	1.20–2.98	1.58	0.94–2.48	1.19	0.71–1.83	0.99	0.44–1.98
$Q_d4$	1.93	1.22–2.98	1.33	0.78–2.08	0.96	0.56–1.53	2.58	1.14–5.13
Model information	NI:100000; DIC:1963.39		NI:100000; DIC:1043.14		NI:300000; DIC:520.93		NI: 300000; DIC:734.13	
Sanchez-Cantalejo deprivation index								
$Q_{ds-c}1$					1		1	
$Q_{ds-c}2$	NA		NA		1.13	0.64–1.83	2.25	0.85–4.88
$Q_{ds-c}3$	NA		NA		1.40	0.83–2.25	1.93	0.70–4.43
$Q_{ds-c}4$	NA		NA		0.90	0.53–1.45	1.73	0.59–4.07
Model information					NI: 300000; DIC: 577.30		NI: 300000; DIC: 898.71	
Rurality index 1991								
$Q_{r91}1$					1		1	
$Q_{r91}2$	NA		NA		0.71	0.45–1.08	1.64	0.84–2.87
$Q_{r91}3$	NA		NA		0.76	0.47–1.17	1.50	0.68–2.80
$Q_{r91}4$	NA		NA		0.71	0.42–1.10	2.49	1.07–4.92
Model information					NI: 500000; DIC: 399.43		NI: 500000; DIC: 644.78	
Rurality index 2001								
$Q_{r01}1$					1		1	
$Q_{r01}2$	NA		NA		0.74	0.46–1.11	1.66	0.82–3.02
$Q_{r01}3$	NA		NA		0.84	0.51–1.29	1.39	0.63–2.69
$Q_{r01}4$	NA		NA		0.86	0.49–1.35	2.03	0.86–3.95
Model information					NI: 300000; DIC: 423.25		NI: 300000; DIC: 609.99	

Comparison of DIC values can be conducted only within the same gender and area of analysis

NA not applicable, NI number of iterations of the model, DIC deviance information criterion,  $Q_d$  quartile of the MEDEA Project deprivation index,  $Q_{ds-c}$  quartile of Sánchez-Cantalejo deprivation index,  $Q_{r91}$  quartile of rurality index year 1991,  $Q_{r01}$  quartile of rurality index year 2001

biased the results, although the interpretation of the results must be cautious. First of all, and related to methodology, the ecological fallacy, although possible, was mitigated by the use of small geographical units [39]. There are also other limitations related to the methodology we used; for example, the moment of location of each case in a specific geographical area and the instant in which the exposure was considered. In both situations, the process could have generated some failures that were impossible to control. In this study, and regarding the moment of exposure, both data of 1991 and 2001 were used, but the utilization of previous exposures should also be considered in future research. The limitations related to the quality of data and the case locations are unlikely to have had any influence over the results. The ICD-O-3 for the codification of the cases is broadly defined and permits comparison with other registries. The location of the cases was successful in almost all of the

cases (1.08 % missing in males and 0.90 % in females). This low number of missing cases makes the existence of bias derived from this process highly unlikely.

However, other aspects useful for the evaluation of the results must be considered. The low number of stomach cancer cases in the province of Zaragoza, which meant that many municipalities did not show cases for the period of analysis, is a remarkable factor, and the results in the province must be interpreted cautiously. Another aspect of interest is the difficulty of establishing causal relationships for a disease with a long latency period, as well as the wide range of possible variables affecting its incidence in relation to SES and the area of residence.

Among the strengths of the study were the use of a well-developed methodology and the utilization of various indexes, which allowed a wide perspective on the situation of stomach cancer.

The different results obtained depending on gender and the geographical level of analysis by the various indexes used requires special attention. Concerning the MEDEA deprivation index [19], the lack of statistically significant results for females in the city of Zaragoza could be due to the low number of cases in women. Although the same pattern existed in the rest of the province, a positive association was observed in females but no such trend could be found in males. These results, which seem to contradict those obtained for the city of Zaragoza, make necessary a cautious interpretation of the index in rural areas. Similar results for the province of Zaragoza were obtained with the Sanchez-Cantalejo deprivation index [20], even though this index was developed with a focus on small municipalities. In relation to rurality indexes [21], the lack of association for males could be due to the existence of a different pattern of disease in that gender or the lack of suitability of the index.

In this sense, as well as the complexities related to gender, the area of residence must also be taken into consideration. As Senior suggested [40], there are multiple explanations for the differences between the health experiences of urban and rural areas, such as the demographic and social structure of the population, lifestyles, working conditions, or the action of specific local factors, which make an analysis of both levels of residence and a comparison of the results especially complex.

To this end, further research evaluating the different patterns of disease incidence must be conducted, both by geographical level and by gender. In the same way, other indexes should be evaluated in order to explain population differences in disease incidence. Only a deep knowledge of the causes of disease will provide a basis for future work on implementing preventive policies.

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