# Analysis of the relationship between socioeconomic factors and stomach cancer incidence in Slovenia

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**Received August 30, 2005**

An unequal population distribution of well-known major risk factors explains much of the variation in the incidence of stomach cancer worldwide. The aim of this study was to determine whether geographical variation of the stomach cancer incidence rate between Slovenia's municipalities during years 1995–2001 could partially be explained by variations in the socioeconomic status as an indirect stomach cancer risk factor. A composite measure of each region's socioeconomic status, labelled as deprivation index, was created from basic socioeconomic characteristics of each municipality using factor analysis. Municipalities' standardized incidence ratios for all stomach cancers and non-cardia stomach cancer were calculated. A fully Bayesian spatial model with a conditionally autoregressive prior was applied using Markov chain Monte Carlo techniques and WinBUGS software. Spatially smoothed maps of stomach cancer incidence rates by 192 Slovenian municipalities show a clear west-to-east gradient. This pattern resembles the geographical variation of socioeconomic indices, but these indices are not significant predictors of stomach cancer incidence. Geographical variation of stomach cancer incidence in Slovenia could be partially explained by the heterogeneous socioeconomic characteristics of its municipalities. It is possible that the socioeconomic status indices used in our study were not enough powerful predictors of stomach cancer risk. Some further methodological research is needed to explain why this association was not statistically evident with the current modeling approach.

*Key words: non-cardia stomach cancer, incidence, deprivation index, Bayesian small-area mapping*

Stomach was the leading cancer site in Slovenia prior to the mid-1960's. Since then, like in many other countries, the incidence started to decline [1, 2], and became stable in the mid-1980's. Stomach is currently the sixth most common cancer site in both sexes. With crude incidence rate around 25/100,000, stomach cancer accounts for approximately 5% of all new cancer cases [1]. Cancer localized to the stomach cardia accounts for approximately 10% of all stomach malignancies in Slovenia. This percentage increased slightly over recent years, but less rapidly than in some highly developed countries [3, 4].

A marked geographic variation in the incidence of Slovenian stomach cancer was first described in the Atlas of cancer incidence in Slovenia 1978–87 [5] and remained when mapping this cancer in the following time period [6]. All these maps show an obvious west-east gradient (with more cases in eastern part of the country). The west-east gradient persisted after standardization for age or stratification by gender.

A non-uniform distribution of well-known major risk factors (i.e. diet, Helicobacter pylori infection and smoking) typically accounts for much of the variations in the incidence of stomach cancer worldwide [2, 3]. Many important stomach cancer risk factors positively correlate with poor living environment and low socioeconomic status, particular during childhood [7, 8]. International studies [7] have consistently found higher stomach cancer incidence in lower socioeconomic classes. However, the incidence of cancer localized solely on stomach cardia has not been shown to be associated with socioeconomic status because the major risk factors for this disease entity are obesity and gastroesophageal reflux [4, 9, 10].

The aim of the present study was to determine whether geographical variation of the stomach cancer incidence rate among Slovenia's municipalities could partially be explained by variation in the socioeconomic status (SES) as an indirect stomach cancer risk factor.

## Material and methods

*Existing data sets*. Source of cancer incidence data is the population-based Cancer Registry of Slovenia. Stomach cancer incidence data including gender, age at diagnosis, place of residence, and cancer subsite (cardia and non-cardia) for the seven-year period 1995–2001 were collected. This time period was chosen because reliable data on cancer cases after 2001 was not available and because the pre-1995 data was not comparable to the data from 1995–2001 as the definition of background population changed in 1995.

The geographical units used in the analysis were the basic Slovenian administrative areas called municipalities. There were 192 municipalities in the study period with an average size of 106 $km^2$ and average population of 10,304. The information on the number of inhabitants stratified by gender and five-year age groups was obtained from the Statistical Office of the Republic of Slovenia.

There is no official SES index in Slovenia. The only appropriate SES information available for the chosen period and geographical unites is the Development Deficiency Index (DDI) provided by the governmental Institute of Macroeconomic Analyses and Development [11]. The DDI classifies all municipalities into five categories. The first four categories are for underdeveloped municipalities that are priority areas for regional development incentives. The DDI from 1999 was used to represent the municipalities' SES in our analysis.

*Derived data sets*. Expected numbers of cases for each single municipality were calculated using the method of indirect standardization [12]. The 2002 age specific rates for the country as a whole were used as a standard.

Additional SES indices were calculated. Data on characteristics most likely relevant to SES were gathered from the Statistical Office of the Republic of Slovenia for each single municipality including:
- number of unemployed persons per 100 inhabitants;
- average earning per capita;
- number of graduate students per 100 inhabitants in age group 20–24;
- number of inhabitants having more than secondary school per 100 inhabitants;
- number of inhabitants having at least primary school per 100 inhabitants;
- natural increase per 1000 inhabitants;
- number of households owing its own bathroom per 100 households;
- number of households with central heating per 100 households;
- number of families living with both parents per 100 families;
- number of members of an average households.

A composite measure, labeled as deprivation index (DI), was created for each municipality using factor analysis [13]. In addition, factor model was used to divide DI into its economic-educational component (DI_E), which resumes employment, income, education and housing characteristics and social component (DI_S) that resumes family and demographical characteristics.

*Modeling*. We assume that observed number of new cancers ($O_i$) in each single municipality i (i = 1,..., 192) follows a Poisson distribution with mean $\mu_i = E_i\theta_i$, where $E_i$ is the expected number of new cases in a particular municipality derived from indirect standardization and $\theta_i$ is the area-specific relative risk. The maximum likelihood estimate of $\theta_i$ is $\theta_i = O_i/E_i$, which is usually termed as standardized incidence ratio (SIR). This expression serves as Model 0. The variance of $\theta_i$ is proportional to $E_i^{-1}$ and so for areas with small populations there will be high sample variability.

Model 0 can be extended to a set of explanatory variables $x_1$, $x_1$, ..., $x_j$ in a Poisson regression model [12] for disease rates:

$$\log \mu_i = \log E_i + \sum_{j=1}^{J} \beta_j x_{ij} \qquad \text{[Model 1]}$$

where $\beta_j$ represents regression coefficient for the jth explanatory variable. This model assumes that once all the explanatory variables are in the model, the resulting map of $SIR_i$ will depict the true excess risk. However in many situations the variation not explained by the fixed effects might exceed the expected value from the Poisson model leading to overdispersion. CLAYTON and KALDOR [14] developed a random-effect Poisson regression model to handle overdispersion:

$$\log \mu_i = \log E_i + \sum_{j=1}^{J} \beta_j x_{ij} + H_i, \qquad \text{[Model 2]}$$

where $H_i$ represents the heterogeneous random effects which do not depend on geographical location. BESAG et al [15] proposed an expansion of the Model 2:

$$\log \mu_i = \log E_i + \sum_{j=1}^{J} \beta_j x_{ij} + H_i + S_i. \qquad \text{[Model 3]}$$

This model has two types of random effects: unstructured component that is geographically independent ($H_i$) and an autocorrelated component ($S_i$), which reflects local spatial structure by incorporating the influence of neighboring geographical units.

Bayesian methods are commonly used to conduct analyses of spatial hierarchical models. Prior distributions are assigned to random effects and hyperprior distributions are assigned to the parameters of the prior distributions, thus creating a multilevel hierarchical Bayesian model. In the present study, a conditional autoregressive (CAR) prior distribution is assigned to the spatial components $S_i$ [16]. In CAR distribution the estimation of the risk in any area depends on risk of its neighboring areas and the variability $\tau_s$ by which size the extent of spatial smoothing is controlled. The heterogeneity components $H_i$ are given independent normal distribution with mean zero and variance $\tau_h$. As suggested by BERNARDINELLI et al [17] gamma distribution (0.5, 0.0005) is assigned to $\tau_s$ and $\tau_h$. The results have not been affected by the hiperprior choice.

The posterior distribution is the target outcome of the described models. It characterizes the estimate of $SIR_i$, taking into account the initial SIR at region i, the explanatory variables, and the SIRs of nearby areas. The procedure is called statistical smoothing as the extreme SIRs are smoothed towards the average SIR of the nearby regions. The posterior distribution was approximated using the Gibbs sampler in WinBUGS software [18]. Two independent Markov chains were run for 20,000 iterations; the first 10,000 iterations were discarded as "burn-in" samples. Convergence was confirmed by observing Brooks-Gelman-Rubin statistic [19]. The deviance information criterion (DIC) as provided by WinBUGS was used as a goodness of fit and complexity measure for model selection – models with smaller DIC are preferred [20].

## Results

From 1995–2001, 3452 new cases of stomach cancer were registered. Cardia was the primary site in 341 cases; in the remaining 3111 cases, other parts of stomach were affected.

Figure 1 shows the standardized incidence ratios for all stomach cancers (Fig. 1a) and non-cardia stomach cancers (Fig. 1b) in the 192 municipalities. Many white or black patches can be observed irregularly throughout the map. The extreme values appear mostly in the municipalities with small population size. The SIR of municipalities with a small population has high variance so extreme values at these sites do not necessarily indicate that these municipalities have extremely high/low risk of disease. Despite this problem, a spatial west-to-east gradient (more cancers on eastern part) can be observed on both maps. The gradient is more obvious in the non-cardia map. Both the differences in the risk at the local level and the Poisson variation contribute to the unequal distribution of cancer rates.

The indirect stomach cancer risk factor (particularly for non-cardia stomach cancer) is SES. The geographical distribution of four SES indices used in this study is shown in Figure 2. Not surprisingly both composite SES measures, DDI and DI, indicate lower socioeconomic status of municipalities in the eastern part of Slovenia. Even though constructed by different methodology, DDI and DI are highly correlated (Pearson correlation coefficient is 0.80; $p<0.001$), moreover they both significantly correlate with SIR of all stomach cancers and non-cardia stomach cancers with similar Poisson regression coefficients of 0.10 and 0.11 for all stomach cancer and 0.11 and 0.12 respectively for non-cardia stomach cancer. By construction the DI parts DI_E and DI_S are uncorrelated. Regarding the correlation with stomach cancer incidence DI_ E is similar to DDI and DI, while the socio-demographic part DI_S in a simple Poisson regression does not correlate significantly with all stomach cancer SIR or with non-cardia stomach cancer SIR.

To illuminate true spatial patterns and reduce the effect of random variation, hierarchical Bayesian spatial models were applied to the raw SIR data (Models 2 and 3). Table 1 presents the variables that are included in the each model. Model 0, Model 1a–1d have no random effects and are included for comparative purposes. By evaluating the DIC statistics, the models that include random effects proved to be more efficient. The model that yields best DIC has both heterogeneity and spatial random effects (Model 3). Figure 3 shows the maps of all stomach cancer SIR estimates from Models 2 (Fig. 3a) and 3 (Fig. 3b). Both maps show a considerable amount of smoothing compared to the raw SIR map (Fig. 1a). A very clear west-east spatial pattern of SIR emerges when the spatial random effects are included in the model (Model 3). The visual impression of this map is very similar to that on maps of DDI, DI and DI_E but on the contrary, quite different from the DI_S map pattern (Fig. 2). On the basis of results presented in this and previous paragraph DI_S was not considered as a possible predictor of stomach cancer incidence in the further analysis.

DDI, DI and DI_E were successively included to the all stomach cancers and non-cardia stomach cancers models (Models 2a–2c, 3a–3c) but did not improve DIC compared to

**Table 1. The composition of various applied models and the values of deviance information criterion (DIC) for all stomach cancers and non-cardia stomach cancers**

| MODEL | Random effects | | Fixed effects (SES indicators) | | | | All stomach cancers | Non-cardia stomach cancers |
|---|---|---|---|---|---|---|---|---|
| | H | S | DDI | DI | DI_E | DI_S | DIC | DIC |
| 0 | OUT | OUT | OUT | OUT | OUT | OUT | 1197,7 | 1179,3 |
| 1a | OUT | OUT | IN | OUT | OUT | OUT | 1152,8 | 1129,5 |
| 1b | OUT | OUT | OUT | IN | OUT | OUT | 1163,1 | 1142,8 |
| 1c | OUT | OUT | OUT | OUT | IN | OUT | 1181,9 | 1166,1 |
| 1d | OUT | OUT | OUT | OUT | OUT | IN | 1198,3 | 1179,3 |
| 2 | IN | OUT | OUT | OUT | OUT | OUT | 1097,9 | 1069,1 |
| 2a | IN | OUT | IN | OUT | OUT | OUT | 1090,9 | 1062,3 |
| 2b | IN | OUT | OUT | IN | OUT | OUT | 1091,7 | 1064,5 |
| 2c | IN | OUT | OUT | OUT | IN | OUT | 1098,9 | 1069,8 |
| 3 | IN | IN | OUT | OUT | OUT | OUT | 1079,6 | 1053,3 |
| 3a | IN | IN | IN | OUT | OUT | OUT | 1081,1 | 1055,7 |
| 3b | IN | IN | OUT | IN | OUT | OUT | 1084,0 | 1055,1 |
| 3c | IN | IN | OUT | OUT | IN | OUT | 1081,9 | 1055,4 |

SES – socioeconomic status, H – heterogeneous random effects, S – spatial random effects, DDI – development deficiency index, DI – deprivation index, DI_E – economico-educational component of DI, DI_S – socio-demographical component of DI.

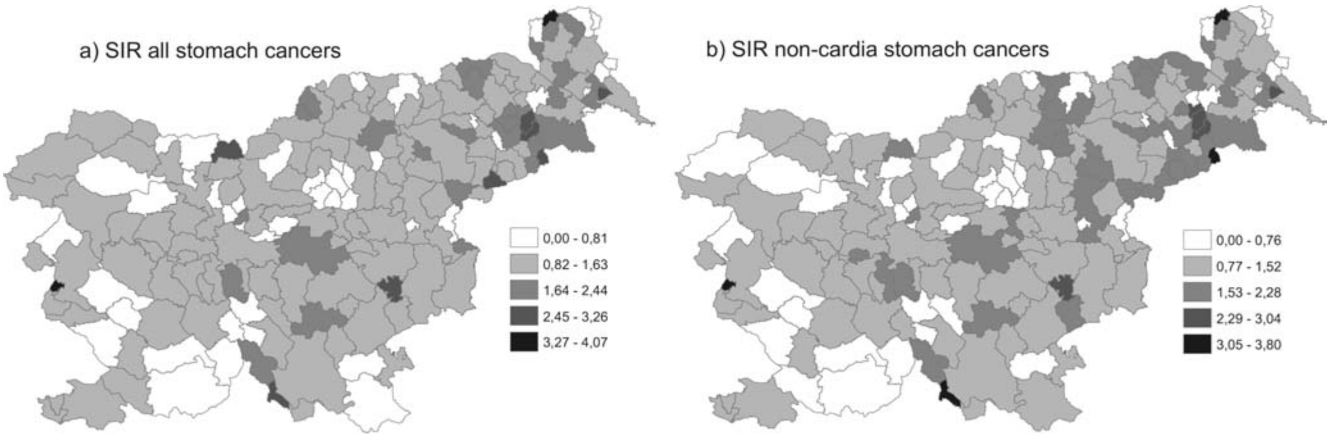


**Figure 1. Standardized incidence ratios (SIR) of a) all stomach cancers and b) non-cardia stomach cancers by municipalities – Slovenia 1995–2001.**

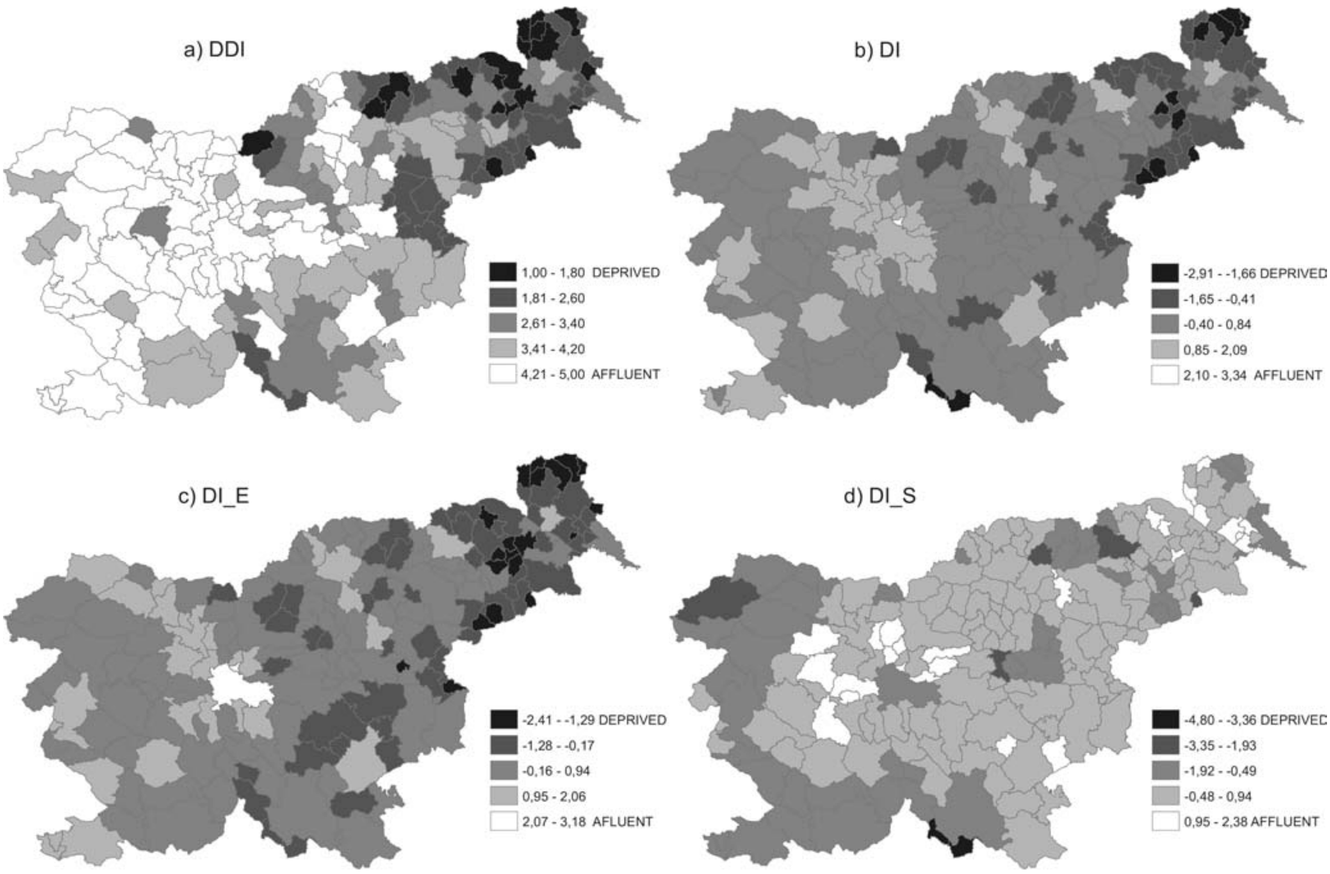


**Figure 2. Geographical distribution of two socioeconomic indices in Slovenia: a) development deficiency index (DDI), b) deprivation index (DI), c) economic-educational part of DI (DI_E), d) social part of DI (DI_S).**

Model 3. A difference in SIR estimates due to adding DDI and DI covariates (Fig. 4a and 4b) to Model 3 (Fig. 3b) for all stomach cancers cannot be detected even by careful comparison. The 95% confidence intervals of DDI, DI and DI_E posterior medians include zero what suggests that these SES variables are not a significant predictor of all stomach cancer incidence.

The same conclusion can be made when considering non-cardia stomach cancer incidence. The effects of smoothing on non-cardia stomach cancer SIR as estimated by

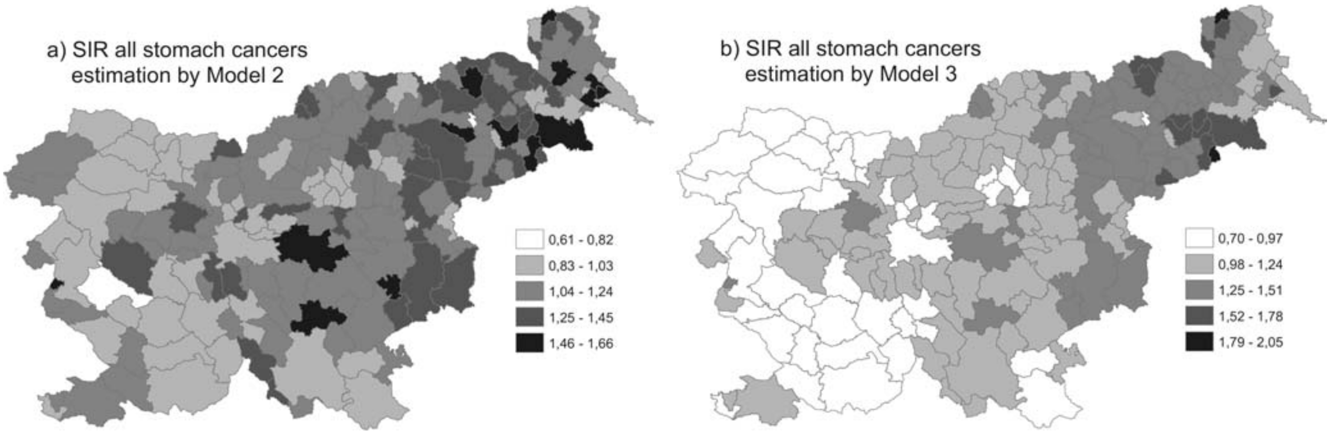


**Figure 3. Bayesian estimates of standardized incidence ratios (SIR) of all stomach cancer by municipalities – Slovenia 1995–2001: a) heterogeneous random effects in the model (Model 2), b) heterogeneous and spatial random effects in the model (Model 3).**

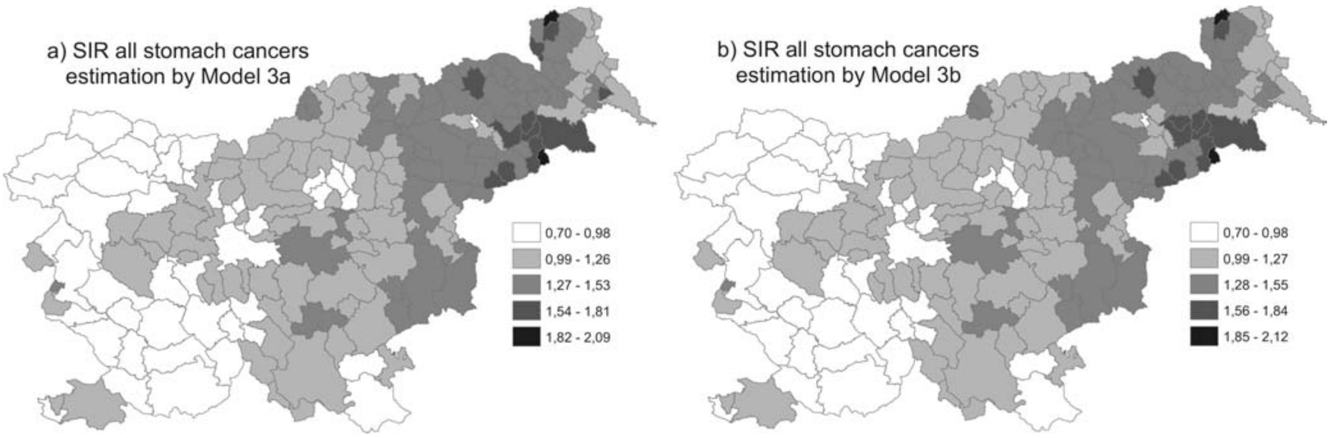


**Figure 4. Bayesian estimates of standardized incidence ratios (SIR) of all stomach cancer by municipalities – Slovenia 1995–2001: a) heterogeneous random effects, spatial random effects and development deficiency index (DDI) in the model (Model 3a), b) heterogeneous random effects, spatial random effects and deprivation index (DI) in the model (Model 3b).**

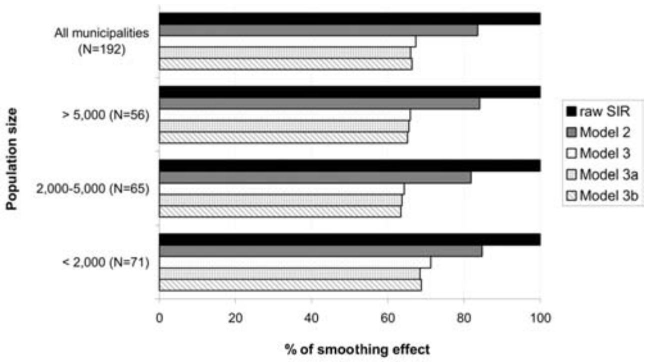


**Figure 5. The effects of smoothing on non-cardia stomach cancer standardized incidence ratios (SIR) as estimated by Models 2, 3, 3a and 3b for municipalities grouped according to their population size. The smoothing effects are calculated as the average percentage change of the SIR estimates regarding non-estimated SIR.**

Models 2, 3, 3a and 3b for three groups of municipalities (grouping made while taking into account the municipalities population size, as on average more smoothing is expected in smaller populations) is presented on Figure 5. It is obvious that all smoothing, regardless of the population size, results in the allowance for random effects, the SES fixed effects do not contribute to additional smoothing of SIR values.

## Discussion

The presentation and analysis of maps of disease incidence data is established as a basic tool for the assessment of regional public health [21]. The ecological analysis in the present study focuses on the geographical distribution of disease in relation to explanatory covariates at an aggregated spatial level. The causal relationship provided by ecological regression has been generally considered very low, but it has been shown that when appropriate statistical models are employed, the typical biases of ecological studies can greatly be improved. The key point is the inclusion of the terms for spatial correlation in the model [22]. The availability of powerful software packages like WinBUGS enables modeling of spatial referenced data within the Bayesian framework [21]. Full Bayesian hierarchical models with an autocorrelated spatial component were used to check the reasons for typical west-east geographical distribution of stomach cancer incidence in Slovenia (more cases on east).

Our analysis does not support the hypothesis of SES being important predictor of stomach cancer risk. There are two types of explanations for this unexpected result. The first are the possible biases in input data or applied methodology. The second possibility is that the SES regional differences in Slovenia were simply too small to contribute to increased/decreased diseases risk. Slovenia was part of the socialistic system of ex-Yugoslavia until 1991. The society differentiation due to the quick turn to market economy had only been observed for a short time before the data used in this study were collected. It is unlikely that only recent change in economical situation would contribute to the stomach cancer incidence variation observed between years 1995 and 2001 because carcinogenesis usually requires a very long induction period [23]. However, as early as the 1980's, POMPE-KIRN and FERLIGOJ observed that some cancer types in Slovenia (including stomach cancer) arise more commonly in eastern part of the country. They attempted to explain this with, among other factors, smaller average income, lower education and higher population percentage engaged in agriculture of those areas [24–27]. Thus we have reasons to believe that a sufficient SES gradient exists among Slovenian's municipalities already for a longer period and that it can contribute to the increased risk of certain diseases. It seems more likely that the explanation for the unexpected outcome of the present analysis lies in the area of data gathering and methodology.

It is unlikely that there is differential registration or improper allocation of cancer cases in Slovenia. Notification of cancer has been compulsory in Slovenia since the foundation of population-based Cancer Registry in 1950 [1]. The data series meet all the international quality standards [28], the coding system was fixed during the target period, and the information on the place of residence at diagnosis was collected at the point level. All this allows an adequate allocation of cancer cases to the chosen geographical units and a clear distinction between cardia and non-cardia stomach cancers.

On the contrary, there are some difficulties in obtaining data on the stomach cancer risk factors. At municipality level, no data such as diet or prevalence of infection with Helicobacter pylori are available in Slovenia. Socioeconomic status has been shown in several studies as a convenient indirect measure of non-cardia stomach cancer risk [2, 4, 7, 10], so we decided to use this indicator to explore the backgroung of geographic variability of stomach cancer rates in Slovenia. No direct SES variable on individual level, such as social class in UK [29, 30], or at area (household) level, such as SES by neighborhoods in US [31] is registered in Slovenia, not even in Census [32]. The governmental Development Deficiency Index, used for the incentive allocation, was not proved to have any influence on health status so far. To examine its potential applicability to public health issues and on the other hand, to provide a similar but more flexible tool, we decided, as in many similar studies [33], to create a new composite SES measure on the basis of available data.

The construction of the deprivation index rests on the assumption that some life circumstances are preferable to others, such as being employed rather than unemployed. The selection of appropriate characteristics based upon indices in common use like CARSTAIRS [34], JARMAN [35] and TOWNSEND [36]. Resembling the indices mentioned our additional composite measure use employment, income, education, housing, family and demographical characteristics. These factors cover individual level (first 6 variables) as well as household level (last 4 variables) information. For the purpose of determining the most meaningful characteristics it was divided into economic-educational component and social component. According to our analysis, the second component seems to have no critical influence on stomach cancer incidence in Slovenia. Bad socioeconomic circumstances in the childhood positively correlate with stomach cancer rate [8, 37, 38]. No variable representing childhood SES was included into our combined index. The lack of childhood SES indicator could be one weakness of the applied deprivation index as a predictor of stomach cancer.

Bayesian hierarchical models with an autocorrelated spatial component have been successfully applied in many studies examining cancer incidence/mortality rate patterns among small geographical areas [39, 40]. Our analysis supports the implementation of this spatial model in for our data as an efficient reduction of random variability can be achieved by using the described methodology. However, in the presence of spatial random effects, the explanatory SES variable is not a significant predictor of SIR. It is difficult to understand why SES is uninformative in this analysis, especially as it turns informative in a simple Poisson regression. As discussed in previous paragraphs, it is not very likely that SES has no influence on stomach cancer incidence in Slovenia and a simple visual comparison of SIR and SES maps suggests that SES should explain some SIR variability. A detailed statistical analysis considering this issue has been performed. We believe this unexpected result can be explained by the collinearity between the fixed-effect covariates and the CAR random effects. Further methodological research will be performed to improve the current modeling approach.

In conclusion, our results give some support to the hypothesis that SES is an indirect risk factor for stomach cancer in Slovenia and that the observed geographical variation of stomach cancer SIR could be partially explained by the heterogeneous socioeconomic characteristics of Slovenian municipalities. However it is possible that the SES indices used in our study were not enough powerful predictors of stomach cancer risk. Additional statistical methodological research is needed to understand the influence of collinearity between SES and the CAR random effects that we also suspect has influenced our results.

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