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TITLE: Geographical variations in the risk of adverse birth outcomes in Spain.

RUNNING TITLE: Risk maps of adverse birth outcomes in Spain

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ABSTRACT

Objectives: To describe the spatial risk-patterns of prematurity and low birthweight in Spain.

Methods: Descriptive spatial analysis of births registered in the Spanish Vital Statistics during 2004-2008 using municipalities as the observation unit. A geographic information system database was created. Besag-York-Mollié autoregressive spatial models were adjusted using the Integrated Nested Laplace approximation to calculate relative risks and posterior probabilities of having very and moderate preterm or low weight newborns. Results were represented in maps to assess geographic risk-patterns.

Results: Spatial analysis shows geographical variations in the risk of adverse reproductive outcomes in Spain highlighting three main high-risk zones, namely, municipalities in Asturias, Madrid City and Murcia. The specific risk-patterns identified en each zone suggests some differences regarding the potential underlying risk factors and specific areas for future research.

Conclusions: A differential exposure during pregnancy to some risks potentially related to industry or agriculture and other contextual factors could underlie an unequal vulnerability to adverse reproductive outcomes in some Spanish regions.

Keywords: adverse birth outcomes; spatial distribution; geographic variation; maps; low birth weight; preterm birth.

INTRODUCTION

Poor prenatal development is an important predictor of differences in survival and morbidity among newborns and these differences may persist throughout life resulting in a wide range of physical and cognitive disabilities and chronic health problems. Epidemiological studies on reproductive health have focused largely on individual-level risk factors. However, researchers increasingly point out to social and environmental factors as major contributors to the risk of adverse reproductive outcomes. In the last years studies using spatial statistical methods and geo-visualization techniques have provided relevant epidemiological information on geographical disparities in health related to contextual factors (Sohel, Vahter et al. 2010; Ugarte, Goicoa et al. 2010; Westercamp, Moses et al. 2010; Pedigo, Aldrich et al. 2011). However, in the realm of reproductive health research studies using this approach are still very scarce (Crosse, Alder et al. 1997; English, Kharrazi et al. 2003; Cromley and Cromley 2009; Bloch 2011; Kirby, Liu et al. 2011). We carried out a spatial analysis to explore geographical patterns in the distribution of risk of prematurity and low birthweight in Spain.

METHODS

A database with all live births registered in the period 2004-2008 was obtained from the Spanish Vital Statistics registry. This database included information about gestational age and weight of the newborns and about mother's municipality of residence. The birth rate was calculated as a weighted average across each of the years under study and was represented in a municipality map of Spain. Annual birth rates were calculated as the ratio between the numbers of births observed in each period divided by the population size at the end of the period. We classified births according to the following adverse reproductive outcomes: Very preterm birth (VPTB: <33 weeks of gestation); Moderate

Preterm Birth (MPTB: 33-36 weeks of gestation); Very low birthweight (VLBW: <1500 grams); Moderate Low Birth Weight (MLBW: 1500-2500 grams). Data on singleton births were aggregated to a municipal level for the 8098 municipalities of the Spanish territory. Assuming that the observed number of VPTB, MPTB, VLBW and MLBW cases in each municipality followed a Poisson distribution, smoothed Relative Risk (RR) and Posterior Probabilities (PP) of such RR>1 were calculated for each outcome and municipality by fitting Besag-York-Mollié autoregressive spatial models (BYM) (Clayton and Kaldor 1987; Besag, York et al. 1991) using the Integrated Nested Laplace approximation (INLA) (Rue, Martino et al. 2009).

The BYM for a given outcome was formulated as follows:

$$O_i \sim Po(E_i \lambda_i) \qquad i = 1...8098$$
$$\log(\lambda_i) = \alpha + h_i + b_i$$

$$h_i \sim Normal(\mu, \tau_h)$$
$$b_i \sim Car.Normal(\eta_i, \tau_b)$$

$$\tau_h \sim Gamma(\alpha, \varphi)$$
$$\tau_h \sim Gamma(\gamma, \delta)$$

Where: λ_i represents the relative risk in municipality i.

O_i represents the number of observed cases of the outcome in area i.

E_i represents the expected number of cases of the outcome in area i.

h_i represents a random effect capturing spatially unstructured heterogeneity.

b_i represents a random effect capturing spatially structured heterogeneity

τ_h and τ_b are the hyperparameters representing prior variance components associated with the two random effects.

So that, the expected value of the spatial random effect for each municipality is an average of such effect in the contiguous municipalities. Given the irregularity in the size and shape of Spanish municipalities, the adjacency matrix was calculated defining neighbors as those sharing a boundary.

The expected number of cases for each municipality and outcome of interest was calculated as:

$$Expected_i = National\ Raw\ Rate\ of\ Outcome \times \frac{Number\ Live\ Births\ Municipality_i^*}{} \quad i = 1...8098$$

Where the national rate was defined as:

$$National\ Raw\ Rate\ of\ Outcome = \frac{Number\ of\ Cases\ of\ Outcome}{Number\ of\ Live\ Births^*} \times 1000$$

*With complete information about the outcome of interest.

RRs and PPs were depicted in Spanish municipal maps. The smoothed maps of RRs enable homogeneous areas to be delimited and PP maps allow determining which municipalities appear to have significantly RR>1. The convention was followed and regions were identified as having a high probability of excess risk when PP≥0.8 (Richardson, Thomson et al. 2004). Both, RR and PP were represented in choropleth maps of Spanish municipalities using Geographical Information Systems (GIS) and a modified version of the Spanish Vital Statistics cartography of 2004. April the 4th 2011 version of INLA with the option of Gaussian estimation of the parameters and the standard central composite design (ccd) approach was used as the integration strategy (Rue, Martino et al. 2009).

RESULTS AND DISCUSSION

During the period 2004-2008, 2,319,555 singleton live births were registered in the 8098 municipalities of the Spanish territory. Figure 1 shows the spatial distribution of the average birth rate during the whole period. The mean birth rate was 10.50 births per 1000 inhabitants. However, this estimation is a result of an average of birth rates distributed very unequally among the Spanish territory. While most of the municipalities of Madrid, provinces from south, east coast and north-east of Spain show high birth rates, the majority of municipalities from north-centre and north-west Spain seem to have birth rates considerably below the national average.

Data on gestational age and birthweight were missing for 15.17% and 4.71% of births respectively. These data were assumed to be missing at random and the rates for each municipality were estimated using the available information. In Figures 1 and 2, maps show homogeneous areas in terms of risk (smoothed RRs) of prematurity and low birthweight and identify specific regions with a significantly high risk (PP) for each one of these four outcomes. On the Map 1 it can be identified a big area in the middle of Spain and also some isolated zones in the rest of the country with RR of VPTB between 1.10-1.30. However, as the Map 2 shows, only Madrid City and some municipalities in Toledo, Avila and Murcia and in isolated points of Tenerife and Grand Canaria had a significantly high risk (PP>0.9) of VPTB. Maps 3 and 4 show high RR and high PP of MPTB focusing mainly in several localities of the South, especially concentrated again in Murcia region. Regarding the distribution of the risk of low birthweight, Map 5 and 6 identified an excess RR of VLBW between 1.10-1.30 with PP>0.9 in Madrid City and but also in a specific point in Asturias. Finally, Maps 7 and 8 show an excess risk of MLBW, Madrid City and surroundings as well as in some localities in Asturias and in

very isolated areas in the North and in the South of Spain without including Murcia region.

This study provides new data about geographical differences in the risk of prematurity and low birthweight in Spain. Overall, our results highlight three main high-risk zones of these adverse birth outcomes, namely, municipalities in Asturias, Madrid City and Murcia. A concentration of high risk areas of MPTB was found in the south of Spain. Dissimilarities in the patterns identified may suggest some differences regarding potential underlying risk factors.

Localities in Asturias showed high risk of very or moderate low birthweight but no high risk of prematurity. Inversely, localities in Murcia showed high risk of very or moderate prematurity but no high risk of low birthweight. Previous studies have suggested a differential distribution of preterm and low birthweight across regions, pointing towards deprivation as one of the main risk factors (English, Kharrazi et al. 2003; Bloch 2011; Kirby, Liu et al. 2011). However, it has been shown that local factors other than socioeconomic may be important when identifying risks factors for prematurity and low birth weight (Crosse, Alder et al. 1997; Walsh, Bendel et al. 2010). On the other hand, some studies have suggested a possible association between residential proximity to industries and adverse birth outcomes (Morgan, Vrijheid et al. 2004; Ahern, Mullett et al. 2011; Castello, Rio et al. 2013). In this sense, it could be useful to consider the remarkable disparity between Asturias and Murcia in terms of industrial activity to assess the significance of the differences found and potential risk factors associated. Asturias is a region strongly dedicated to coal mining and iron and steel industry. By contrast, Murcia hosts the largest concentration of greenhouses in Europe, most of the population been involved in agricultural activities.

Regarding Madrid City, the risk for VPTB seemed concomitant with a high risk of low birthweight but no risk of MPTB was identified. We explored this differential distribution of prematurity and birth weight across some regions and we observed that 48% of VPTB cases had a birth weight over 1500 with a median gestational age of 32 weeks (upper limit of VPTB category) and that 58% of moderate preterm births weighted more than 2500 grams and had a median gestational age of 36 (upper limit of MPTB category). These last data suggest severe prematurity as the main problem in this Spanish area being very or moderate low birthweight partially a consequence. This, along with the high risk of moderate prematurity or moderate low birth weight found in some other places deserves further analysis.

These results must be interpreted considering some limitations. A recent study was carried out to validate the reliability of the gestational age and birthweight data of the Spanish Vital Statistics registry (Rio, Castello et al. 2010). However, missing data could be distorting our results if most cases correspond to smaller or more premature babies. To check this possibility we calculated the distribution of weight among babies with missing data for gestational age and only 4.5% were low birthweight babies (0.4% VLBW). Among babies with missing data for birthweight only 3.5% were low preterm babies (0.7% VPTB). In consequence, missing-at-random appears to be a reasonable assumption.

CONCLUSION

This exploratory study strongly suggests that a differential exposure during pregnancy to some risks potentially related to industry or agriculture and other contextual factors could underlie an unequal vulnerability to adverse reproductive outcomes in some Spanish regions. A further ecological study to explore the association between the

results found in this study and various environmental and socio-demographic factors is required.

REFERENCES

Ahern, M., M. Mullett, et al. (2011). "Residence in coal-mining areas and low-birth-weight outcomes." Matern Child Health J **15**(7): 974-979.

Besag, J., J. York, et al. (1991). "Bayesian image restoration, with two applications in spatial statistics." Annals of the Institute of Statistical Mathematics(43): 1-59.

Bloch, J. R. (2011). "Using geographical information systems to explore disparities in preterm birth rates among foreign-born and U.S.-born Black mothers." J Obstet Gynecol Neonatal Nurs **40**(5): 544-554.

Castello, A., I. Rio, et al. (2013). "Adverse birth outcomes in the vicinity of industrial installations in Spain 2004-2008." Environ Sci Pollut Res Int.

Clayton, D. and J. Kaldor (1987). "Empirical Bayes estimates of age-standardized relative risks for use in disease mapping." Biometrics **43**(3): 671-681.

Cromley, R. G. and E. K. Cromley (2009). "Choropleth map legend design for visualizing community health disparities." Int J Health Geogr **8**: 52.

Crosse, E. A., R. J. Alder, et al. (1997). "Small area variation in low birthweight: looking beyond socioeconomic predictors." Can J Public Health **88**(1): 57-61.

English, P. B., M. Kharrazi, et al. (2003). "Changes in the spatial pattern of low birth weight in a southern California county: the role of individual and neighborhood level factors." Soc Sci Med **56**(10): 2073-2088.

Kirby, R. S., J. Liu, et al. (2011). "Spatio-temporal Patterning of Small Area Low Birth Weight Incidence and Its Correlates: A Latent Spatial Structure Approach." Spat Spatiotemporal Epidemiol **2**(4): 265-271.

Morgan, O. W., M. Vrijheid, et al. (2004). "Risk of low birth weight near EUROHAZCON hazardous waste landfill sites in England." Arch Environ Health **59**(3): 149-151.

Pedigo, A., T. Aldrich, et al. (2011). "Neighborhood disparities in stroke and myocardial infarction mortality: a GIS and spatial scan statistics approach." BMC Public Health **11**: 644.

Richardson, S., A. Thomson, et al. (2004). "Interpreting posterior relative risk estimates in disease-mapping studies." Environ Health Perspect **112**(9): 1016-1025.

Rio, I., A. Castello, et al. (2010). "Quality of data used to calculate reproductive and perinatal health indicators in native and migrant populations." Gac Sanit **24**(2): 172-177.

Rue, H., S. Martino, et al. (2009). "Approximate Bayesian Inference for Latent Gaussian Models Using Integrated Nested Laplace Approximations (with discussion)." Journal of the Royal Statistical Society, Series B **61**: 319-392.

Sohel, N., M. Vahter, et al. (2010). "Spatial patterns of fetal loss and infant death in an arsenic-affected area in Bangladesh." Int J Health Geogr **9**: 53.

Ugarte, M. D., T. Goicoa, et al. (2010). "Age-specific spatio-temporal patterns of female breast cancer mortality in Spain (1975-2005)." Ann Epidemiol **20**(12): 906-916.

Walsh, D., N. Bendel, et al. (2010). "It's not 'just deprivation': why do equally deprived UK cities experience different health outcomes?" Public Health **124**(9): 487-495.

Westercamp, N., S. Moses, et al. (2010). "Spatial distribution and cluster analysis of sexual risk behaviors reported by young men in Kisumu, Kenya." Int J Health Geogr **9**: 24.

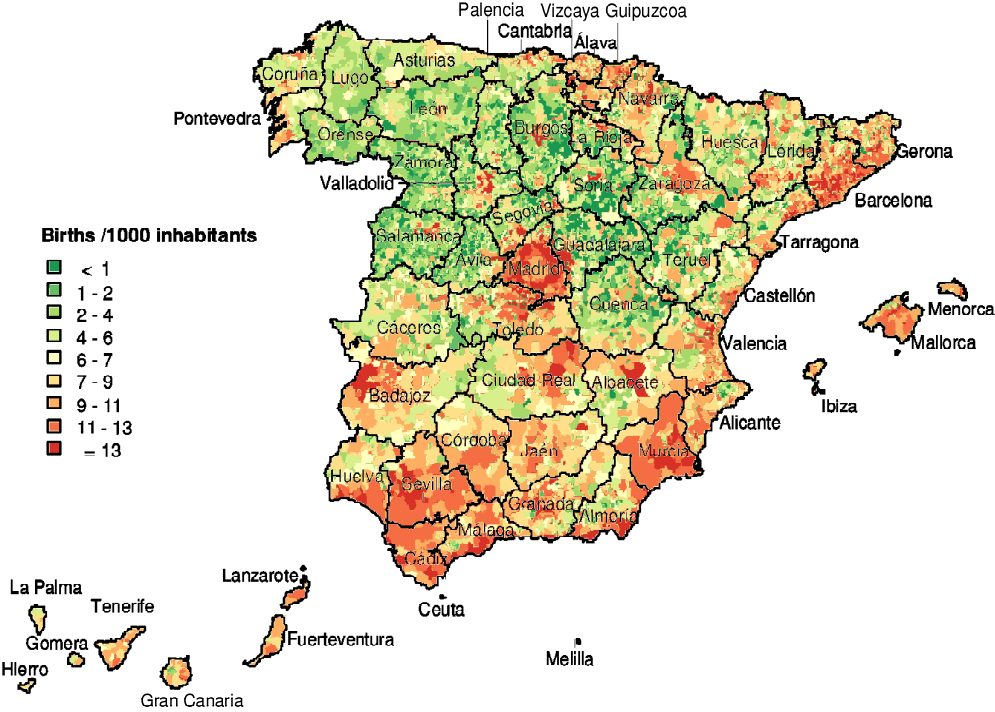**Figure 1.** Distribution of average birth rate in Spanish municipalities

Figure 2. Geographical distribution of smoothed Relative Risk (RR) and Posterior Probability (PP) of very (VPTB) and moderate (MPTB) preterm birth in Spain.
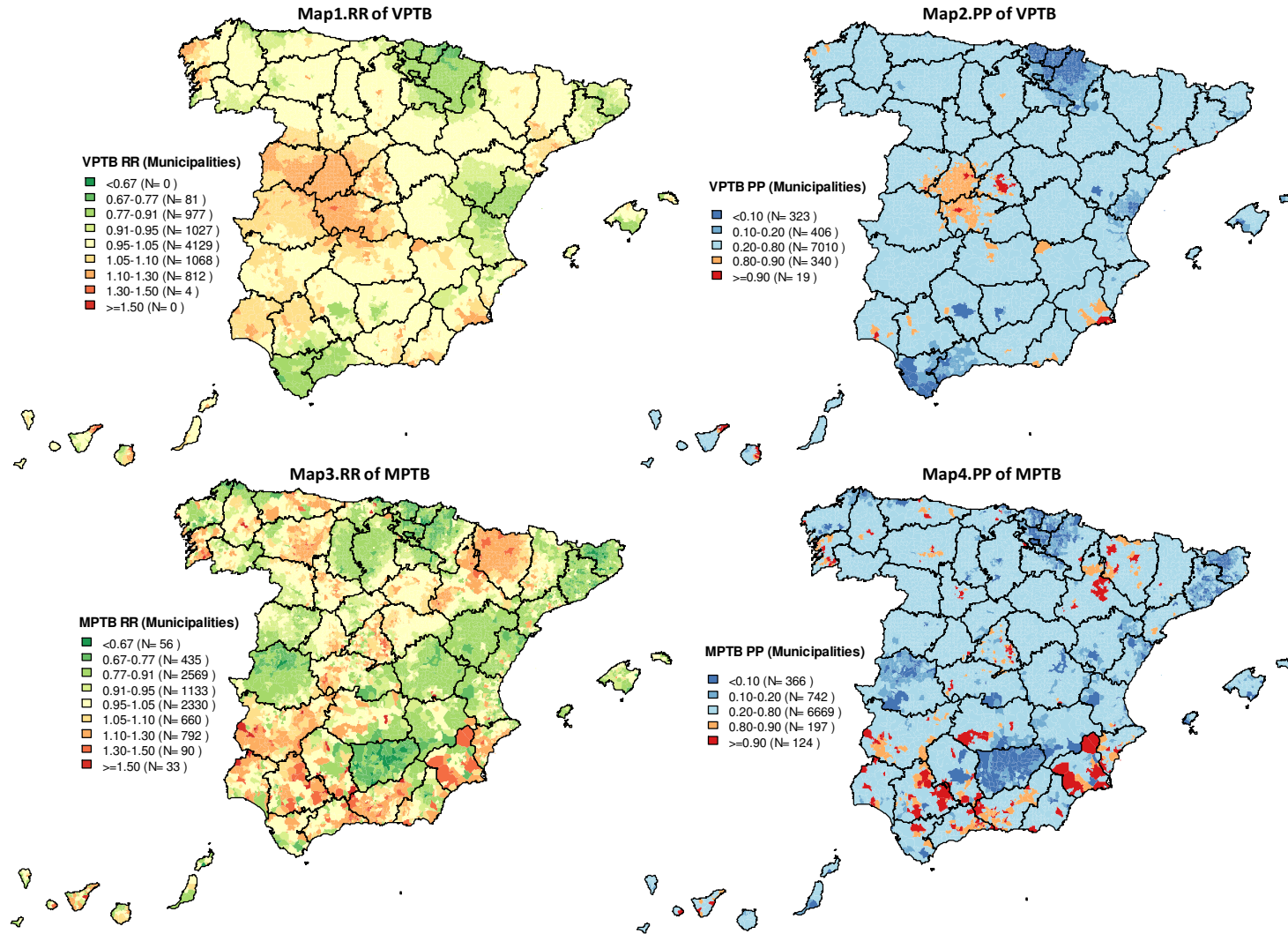
Figure 3. Geographical distribution of smoothed Relative Risk (RR) and Posterior Probability (PP) of very (VLBW) and moderate (MLBW) low birthweight in Spain.

13