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Rural-urban gradients and all-cause, cardiovascular and cancer mortality in Spain using individual data

Ana Ayuso-Álvarez [a,b], Cristina Ortiz [a], Teresa López-Cuadrado [a,c], Carmen Rodríguez-Blázquez [a], Pablo Fernández-Navarro [a,d], Javier González-Palacios [d], Javier Damián [a], Iñaki Galán [a,c,*]

[a] National Centre for Epidemiology, Institute of Health Carlos III, Madrid, Spain
[b] Sociology Department, Faculty of Economic and Business Sciences, Autonomous University of Madrid, Spain
[c] Department of Preventive Medicine and Public Health, Autonomous University of Madrid/IdiPAZ, Madrid, Spain
[d] Bioinformatics and Data Management Group (BIODAMA), National Centre for Epidemiology, Carlos III Institute of Health, Madrid, Spain

1. Introduction

The rich literature reporting on rural-urban health status disparities remains inconclusive (Allan et al., 2017; Smith et al., 2008; Teckle et al., 2012). Some studies find worse health indicators amongst people living in urban areas than in rural areas (Allan et al., 2017, 2019; House et al., 2000; Levin, 2003; O'Reilly et al., 2007; Riva et al., 2009; Senior et al., 2000; Teckle et al., 2012), whereas others report the opposite (Bremberg, 2020; Cosby et al., 2019; Cross et al., 2021; Lankila et al., 2012; Subedi et al., 2019; Van Hooijdonk et al., 2008; Zimmer et al., 2007). Further, recent published works indicate that the worst health indicators are more likely to be present in the two geographical opposite poles, i.e., large cities and remote rural areas (Barnett et al., 2001). Similar rural-urban variability is also observed in northern Europe and North America. Studies carried out in Sweden (Bremberg, 2020), Finland (Bremberg, 2020; Lankila et al., 2012), Norway (Bremberg, 2020), The Netherlands (van Hooijdonk et al., 2008), USA (Cosby et al., 2019; Cross et al., 2021), and Canada (Subedi et al., 2019) described worse health indicators in urban than in rural areas, whereas in Great Britain the reverse was observed (Allan et al., 2017, 2019; O'Reilly et al., 2007; Riva et al., 2009; Teckle et al., 2012), and in Denmark no differences were found (Bremberg, 2020).

Spanish studies also report conflicting results. Voigt et al. (2019) observed higher all-cause mortality in urban than rural areas. Similarly, Moreno-Lostao et al. (2019) showed that men, but not women, in large urban areas, were at higher risk for cardiovascular mortality than their rural counterparts, whereas the risk was higher in women residing in small urban cities.

Several hypotheses have been pointed out as possible explanations for these inconsistencies (Allan et al., 2017, 2019; Teckle et al., 2012). 1) The lack of a standard categorization of urban and rural areas; 2) the different sociodemographic and economic characteristics of the territories that impact dissimilarities amongst countries and even amid regions within the same country; 3) differences in study designs (ecological vs. individual) and in the degree of adjustment for potentially confounding factors. All this makes it difficult to compare results across studies.

1.1. Urban-rural territory classification

In the last decade of the 20th century, the postmodern economy, the digital society, and the new economic and social relations in the context of globalization have brought about substantial regional transformations, especially affecting the rural environment, and forcing a redefinition of its characteristics. In Spain, these changes have generated two divergent realities. First, an ongoing and substantial depopulation of the interior of the country (except the country's capital, Madrid) - known now as the "empty Spain"- with a deep displacement effect. Second, an increasing population densification and growth in the country's periphery like coastal areas, certain privileged mountain enclaves, or peri-urban areas and county service centers (Camarero et al., 2009; Molinero Hernando, F., 2019). As a result, Spanish rural areas currently occupy 90% of the territory but are home to only 20% of the population (LDSMR, 2007; Molinero Hernando, F., 2019).

The same depopulation process responsible for the "empty Spain" is also taking place in the rest of Europe, except in Ireland and France (Camarero et al., 2009), and it has been the target of numerous rural development and recovery studies and interventions. In recent years, however, the heterogeneity of urban and rural areas, the processes of rapid and continuous change they are subjected to, their

* Corresponding author. National Centre for Epidemiology, Instituto de Salud Carlos III, Monforte de Lemos 5, 28029, Madrid, Spain.
E-mail address: igalan@isciii.es (I. Galán).

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interdependence and dynamism, and the trend towards a greater degree of urbanization has led to abandoning the concept of an urban-rural dichotomy in favor of an urban-rural continuum (Levin, 2003).

Although initiatives to organize the degree of urbanization into standardized categories are being developed (Dijkstra et al., 2020), currently, there are no universally accepted definitions for *urban* and *rural* areas. For example, in the UK there are an estimated 30 distinct related definitions (Allan et al., 2017). Thus, because researchers make reasonable approximations to fit their study's objectives, the observed variations could be artifacts of such definitions and decisions.

The combination of population size, population density, and accessibility to services are among the most commonly used criteria to categorize geographical areas as either urban or rural. Whereas the Organisation for Economic Co-operation and Development (OECD) defines an area with a density <150 inhabitants/km^2 as rural, Eurostat's threshold is a density <100 inhabitants/km^2 (Spanish Ministry of Environment, Rural and Marine Affairs, 2009). The Spanish National Institute of Statistics uses population size as criteria, considering population centers with >10,000 inhabitants as urban, and those with 10, 000 inhabitants or below as rural. Rural areas, in turn, are divided into mid-size rural (2,000–10,000 inhabitants) and small rural (<2,000 inhabitants). The Law on the Sustainable Development of the Rural Environment (LDSMR 45/2007 for its Spanish acronym), on December 13th' 2007, dictated that both population size and density be used to characterize the rural environment, as they each describe different characteristics of the territory. And more recently, several authors include accessibility as a key indicator for rurality (Subedi et al., 2019; Teckle et al., 2012; Voigt et al., 2019).

Each one of these criteria (size, density and geographic accessibility) allows the characterization of the different territories. Size is related to functional diversity, attractiveness and growth capacity, interrelations with the environment and its capacity to be an "urban node." Density is a key factor in rural development policy and funding allocation. For example, the European Union sets a minimum of 8 inhabitants/km^2 as the eligibility threshold for regional development funds (Molinero Hernando, F., 2019). Geographical accessibility is an indicator of social cohesion and social welfare, it denotes the ability to access certain services and goods, it is part of welfare policies, and it is framed in the context of equal opportunities. Consequently, geographical accessibility becomes a key factor of inclusion and social justice (Farrington & Farrington, 2005; Fundación Matrix and Research and Sustainable Development, 2019).

1.2. Methodological differences across study designs

In this field, the vast majority of studies follow an ecological design in which official mortality statistics are analyzed for different levels of geographic aggregation while adjusting for various socioeconomic components (Bremberg, 2020; Cosby et al., 2019; Cross et al., 2021; Gartner et al., 2011; Moreno-Lostao et al., 2019; Senior et al., 2000; Subedi et al., 2019; van Hooijdonk et al., 2008). However, this design fails to control for individual health characteristics that may significantly impact urban-rural variations. Whereas ecological studies control for age and socioeconomic position by calculating these variables for the corresponding level of aggregation, health behaviors and other relevant individual characteristics are usually measured at the individual-level. For instance, estimates predict that adjusting statistical models for tobacco and alcohol consumption would reduce the variation of unadjusted estimates by 30% (House et al., 2000).

To our knowledge, longitudinal studies, either based on following an original cohort or based on a cross-sectional health survey data linked to mortality outcomes, are scarce. However, most report a higher mortality risk with higher degree of urbanization (Allan et al., 2019; House et al., 2000; O'Reilly et al., 2007; Teckle et al., 2012) except for a study performed in China (Zimmer et al., 2007).

1.3. Causes of health status differentials across geographical areas

Both compositional and contextual perspectives have been used to explain health status disparities across geographical areas (Allan et al., 2019; Senior et al., 2000).

The compositional perspective is based on the different distribution of the individual-level variables associated with health status such as age, sex, marital status, socioeconomic status, and health-related behaviors. Rural Spain is characterized by an aging, masculinized, and less educated population than urban Spain. Usually, controlling for these variables greatly reduces urban-rural disparities (Allan et al., 2019; Senior et al., 2000).

In contrast, the contextual perspective posits that the source of variation is inherent to the exposure to environmental, physical, and social determinants of the area of residence. Factors such as air pollution (Khomenko et al., 2021), scarcity of green areas (Rojas-Rueda et al., 2019), noise pollution (Cai et al., 2021), crime and violence rates (Lorenc et al., 2012), and overcrowding (Alirol et al., 2011; Ecob & Jones, 1998) could explain observed urban-rural disparities in health status. Nevertheless, the combination of both theories explains a substantial portion of these differences, but not all (Allan et al., 2017). With this in mind, other studies analyzed factors that had so far been practically ignored, such as health services structure (Teckle et al., 2012). For residents of rural municipalities, especially if very remote, accessing certain health services may prove difficult, which would explain part of the inequalities in health indicators (Allan et al., 2019; O'Reilly et al., 2007; Teckle et al., 2012).

1.4. What is this study's contribution to the State-of-the-Field?

Most studies to date are based on Anglo-Saxon and northern European country data, where the socioeconomic and demographic characteristics that typify the urbanization process are very different from those found in Spain, and very likely in other Southern European countries as well. Further, there is scant research based on longitudinal individual level data. This is especially true when it comes to population-based cohorts including individuals of a wide age range. In our study, we will be able to adjust for the main confounding variables related to sociodemographic and economic characteristics, lifestyles, health status and health services use.

Cardiovascular diseases and cancer are the first and second causes of death in Spain, showing great differences in the rural-urban continuum. In 2019, the crude death rate for cardiovascular diseases ranged between 325 per 100,000 population in municipalities with fewer than 10,000 inhabitants and 239 in those with a population of more than 100,000 and municipalities in provincial capital cities (Spanish National Institute of Statistics, 2019). Regarding tumors, the figures ranged between 274 per 100,000 in small municipalities and 248 in those over 100,000 inhabitants and municipalities in provincial capital cities (Spanish National Institute of Statistics, 2019). These differences could be associated to compositional variables but also to contextual factors. Both social and built neighborhood environments are essential determinants of health and have direct implications in the entire cancer development continuum as well as cardiovascular risk factors (Bikomeye et al., 2021).

The two main objectives of this work are, first, to evaluate whether there are rural-urban disparities in cardiovascular-, cancer-, and all-cause mortality in Spain, net of compositional and contextual characteristics; and, if so, to assess whether these differences are homogeneous by sex, age, and educational level. The identification of rural-urban disparities would be the first step in the design, development, and implementation of relevant health interventions.

2. Methodology

2.1. Study design and population

This is a longitudinal study based on data from the Spanish National Health Survey 2011–2012 (ENSE 2012, for its Spanish acronym) and the European Health Survey in Spain 2014 (EESE 2014, for its Spanish acronym). These data were then linked to mortality data up to December 2020 (*Linking Mortality to the Spanish Health Surveys, MESES* study, for its Spanish acronym). Sample designs and questionnaires for both surveys are standardized (Spanish Ministry of Health and Spanish National Institute of Statistics, 2011; Spanish Ministry of Health and Spanish National Institute of Statistics, 2014). The sampling design is multistage, where first a sample of municipalities is selected within each province, then a sample of census tracts is drawn, from which households are sampled. Finally, an adult ≥15 years of age from each household selected is randomly chosen to participate. Data on sociodemographic and economic variables, health status, social determinants, lifestyles, use of health services are collected during the face-to-face interviews. The surveys were conducted at the participant's home with the help of a computer (Computer-Assisted Personal Interviewing, CAPI). The response rate was 71% of the selected households. The total sample includes data on 43,849 individuals from 4191 census tracts.

2.2. Variables

2.2.1. Mortality

All-cause, cardiovascular (ICD10: I00–I99) and neoplasm (ICD10: C00-D48) mortality data for the period 2011–2020 were obtained from the mortality registry of the Spanish National Institute of Statistics and, linked to the ENSE-2012 and EESE-2014 datasets through the national identification document number.

2.2.2. Classification of place of residence

The municipalities were classified as either urban or rural according to the criteria dictated by the December 13th, Law 45/2007 on Sustainable Development and Rural Environment (LDSMR 45/2007, December 13th, for its Spanish acronym). This law defines as rural any municipality with a population under 30,000 residents and a density under 100 residents per km^2). In addition to population size and density, a geographic accessibility indicator was included. This indicator was built using the Bing™ Maps REST Services Application Programming Interface (API), created by Microsoft to calculate driving distances (https://docs.microsoft.com/en-us/bingmaps/rest-services/), and the RCurl and Risonio software packages. Using the coordinates of the municipal centroids, we calculated the distance and driving time from any rural municipality to its nearest urban municipality of at least 30,000 inhabitants. A rural municipality is considered "accessible" when the driving time required to reach an urban municipality (>30,000 inhabitants) is under 45 min and in turn, "non-accessible" when travelling time is 45 min or more (Reig Martinez, E et al., 2016).

The category Urban I designated large cities >500,000 inhabitants; Urban II referred to mid-size cities >50,000–500,000 inhabitants regardless of population density, as well as province capital cities regardless of population size or density. Urban III consisted of small cities ≥30,000–50,000 inhabitants regardless of density as well as those <30,000 inhabitants but with a density >100 inhabitants/km^2. The category of Rural I denotes accessible municipalities ≥2,000–30,000 inhabitants with a density <100 inhabitants/km^2. Rural II stands for non-accessible municipalities ≥2000–30,000 inhabitants, with a density <100 inhabitants/km2. Rural III designates accessible municipalities <2000 inhabitants, with a density <100 inhabitants/km2. Finally, Rural IV refers to non-accessible municipalities <2000 inhabitants, with a density <100 inhabitants/km^2.

2.2.3. Covariates

The following variables from the ENSE-2012 and EESE-2014 data were included as covariates:

Socioeconomic and demographic data: sex, age (15–24; 25–34; 35–44; 45–54; 55–64; 65–74; >74), marital status, educational level, autonomous region of residence, per capita family income (low, medium, or high), and socioeconomic deprivation index.

Based on census tract data we calculated the socioeconomic deprivation index, as developed by the Spanish Society of Epidemiology for the entire country at the census tract level. It comprises 6 indicators: manual worker population, casual wage-earning population, unemployment level, individuals 16 and over and between 16 and 29 years of age with primary education or less, and main dwellings without Internet access (Duque et al., 2020). The score is grouped into quartiles from lowest to highest socioeconomic deprivation.

Lifestyle: tobacco consumption (never smoker, ex-smoker, smoker ≤14 cigarettes, smoker >14 cigarettes); sedentary leisure time (no exercise or leisure time spent almost completely sedentary vs. other); adherence to the Mediterranean diet (0–10: worst-best diet quality). Diet quality was assessed using an index adapted from the Mediterranean Diet Adherence Screener (MEDAS for its Spanish acronym) (Schröder et al., 2011). Average daily alcohol consumption: alcohol consumption was estimated based on the frequency of habitual consumption of 6 types of alcoholic beverages for each day of the week. Participants were categorized as follows: no consumption, low-risk consumption (≤20 g/day in men and ≤10 g/day in women), and high-risk consumption (>20 g/day in men and >10 g/day in women). Binge drinking was defined as the consumption in one seating, i.e., within 4–6 h, of 6 or more alcoholic drinks for men and 5 or more for women, in the past month.

Health status variables: body mass index (BMI) in kg/m^2 from self-reported weight and height (underweight, normal weight, overweight, and obese), perception of health status (very good, good, fair, poor, very poor).

Use of health services in the last 12 months: hospital admissions in the past 12 months (yes/no), emergency room visits in the past 12 months (yes/no), and day hospital visits in the past 12 months (yes/no).

2.3. Statistical analysis

Our sample included 43,189 respondents with valid information for all study variables out of the 43,849 respondents in the ENSE-2012 and EESE-2014 surveys. Subjects contributed follow-up time from their assigned baseline interview until death or the administrative censoring date, December 31, 2020. As our main outcome variable is time-to-event, which in our case event is death, we used the Cox model, as it is the standard analytical method to model time-to-event data (or survival). Thus, hazard ratios (HR) were calculated using fixed-covariate proportional hazard models, assessing the proportional hazards assumption with the Schoenfeld residuals test. Four sequential models were developed: Model 1: Unadjusted model; Model 2: Adjusting only for sociodemographic variables (sex, age groups, marital status, educational level, region of residence, per capita family income, socioeconomic deprivation index); Model 3: model 2 plus adjustment for lifestyle and health status variables (tobacco consumption; sedentary leisure time; adherence to the mediterranean diet, average daily alcohol consumption, binge drinking, body mass index, self-perceived health); and Model 4: model 3 plus adjustment for use of health services (hospital admissions, emergency room visits, and day-hospital visits).

Possible interactions in the association between type of municipality (rural-urban) and mortality were evaluated according to sex, age (≤65 years and >65 years) and educational level (first-level secondary school or lower and second-level secondary school and higher).

Estimates were weighted by sampling weights to restore proportionality. All analyses were performed with Stata v.17 (StataCorp, College Station, Texas, U.S.), using the survey data module to incorporate the complex sampling design characteristics of the surveys.

2.3.1. Ethical considerations

This study was approved by the Research Ethics Committee of the Institute of Health Carlos III, Nº: CEI PI 28_2019.

3. Results

3.1. Sample characteristics

Table 1 shows the distribution of the socioeconomic and demographic characteristics of the population across the urban/rural spectrum. Slightly more women reside in large cities and older populations are observed in the more rural areas. Cities include individuals with higher income and educational levels, and they comprise the census tracts with lower deprivation indices compared to rural areas. These relationships gradually reverse as the degree of urbanization decreases, reaching far less favorable situations in the smaller, non-accessible rural areas. An unequal distribution of the population among the autonomous regions is also observed. Whereas the large cities are concentrated in just 5 autonomous regions, another 5 regions are home to 73.5% of the residents of small and non-accessible rural municipalities.

Table 2 describes lifestyles and health status according to the urban-rural categories. We observe that the rural environment, made up of small municipalities, presents higher prevalence of high-risk alcohol

Table 1

Sociodemographic characteristics of the sample, according to type of municipality of residence. Spanish population ≥15 years of age.

		Urban I N = 5393	Urban II N = 16621	Urban III N = 12940	Rural I N = 3526	Rural II N = 1429	Rural III N = 2013	Rural IV N = 1276	
	N[a]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	p-value
Sex, %									0.006
Men	19877	46.7	48.6	49.6	48.8	48.9	51.0	51.7	
Women	23312	53.3	51.4	50.4	51.2	51.1	49.0	48.3	
Age, mean (SD)	43289	48.0 (16.9)	47.0 (18.6)	46.3 (18.1)	48.6 (19.6)	49.2 (20.3)	52.8 (22.5)	55.5 (23.0)	<0.001
Marital Status, %									<0.001
Married	11672	35.7	30.8	29.8	27.7	27.9	26.4	29.5	
Single	22982	50.9	56.8	59.1	60.2	60.3	60.9	54.9	
Widowed	5630	8.1	7.1	6.5	8.3	8.4	9.2	12.4	
Separated/Divorced	2905	5.3	5.3	4.6	3.8	3.4	3.5	3.2	
Education Level, %									<0.001
≤Primary	13647	18.4	23.7	26.5	38.0	45.6	40.3	46.8	
Secondary, 1st stage	11141	22.3	27.7	30.2	33.6	27.7	29.4	29.2	
Secondary, 2nd stage	11134	30.6	29.9	28.8	20.0	19.6	21.0	18.2	
University	7267	28.6	18.6	14.5	8.3	7.1	9.3	5.7	
Income Level, %									<0.001
Low (tertile 1)	12048	19.2	25.5	26.0	35.7	38.0	29.7	33.6	
Medium (tertile 2)	12246	25.7	29.0	29.3	31.6	30.6	24.3	28.6	
High (tertile 3)	9284	29.3	22.7	21.0	14.5	10.1	15.6	13.2	
No Answerr	9611	25.7	22.8	23.7	18.3	21.3	30.4	24.6	
Deprivation index, %									<0.001
Low (cuartil 1)	10793	52.3	30.2	19.7	2.2	3.2	7.5	0.9	
Medium-Low (quartile 2)	10805	21.8	25.9	28.8	12.7	12.4	19.9	5.6	
Medium-High (quartile 3)	10809	16.1	24.1	27.1	30.4	26.9	28.9	28.4	
High (quartile 4)	10782	9.8	19.8	24.4	54.7	57.5	43.7	65.1	
Autonomous Region, %									<0.001
Andalusia	5066	16.1	17.7	15.9	31.7	33.3	9.1	6.1	
Aragon	1882	8.9	0.5	0.9	4.2	3.7	4.9	15.2	
Principality of Asturias	1664	0	3.8	1.3	3.0	7.7	0.9	2.5	
Balearic Islands	1531	0	2.9	3.5	1.7	2.8	1.0	0	
Canary Islands	2102	0	6.6	5.5	2.7	6.1	0	2.1	
Cantabria	1550	0	1.4	1.9	1.5	0	1.4	1.4	
Castile and León	2575	0	0.6	3.6	6.2	6.1	24.1	21.9	
Castile-La Mancha	2143	0	3.1	4.3	11.8	13.3	10.3	15.3	
Catalonia	4572	21.6	13.9	20.0	3.7	3.9	16.3	5.8	
Valencian Region	3432	10.2	8.6	15.8	8.6	3.4	5.3	5.1	
Extremadura	1762	0	1.8	1.8	4.6	11.9	5.7	9.3	
Galicia	2505	0	5.9	7.3	12.0	5.0	7.2	11.8	
Madrid Region	4316	43.1	13.5	5.1	1.3	0	1.0	0	
Murcia Region	1812	0	4.6	3.4	4.2	0.3	0	0	
Navarra Region	1583	0	1.1	1.7	1.9	0.4	5.9	1.6	
Basque Country	2435	0	6.1	7.5	0.4	0	4.4	1.6	
La Rioja	1378	0.9	0.6	0.6	2.8	2.6	2.2	0.7	
Ceuta	351	0	0.4	0	0	0	0	0.2	
Melilla	530	0	0.4	0	0	0	0	0.2	

Urban I (large cities), Urban II (mid-size cities), Urban III (small cities), Rural I (large and accessible), Rural II (large and non-accessible), Rural III (small and accessible) and Rural IV (small and non-accessible).

P-value for homogeneity of sampling-weighted percentages among type of municipality categories, computed through chi squared tests (for categorical variables) or analysis of variance (for continuous variables).

[a] Unweighted sample N.

[b] % or weighted mean, SD Standard Deviation.

Table 2
Sample characteristics related to lifestyles, health status, and use of health services, according to type of municipality of residence. Spanish population ≥15 years of age.

		Urban I N = 5393	Urban II N = 16621	Urban III N = 12940	Rural I N = 3526	Rural II N = 1429	Rural III N = 2013	Rural IV N = 1276	
	N[a]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	%/mean[b]	p-value
Tobacco Consumption, %									0.002
Non smoker	22381	51.5	51.2	50.4	52.2	51.8	51.3	53.5	
Past smoker	10147	24.6	22.4	22.3	21.2	20.1	24.6	23.7	
1-14 cig/day	6490	14.7	15.8	17.5	16.3	16.5	14.6	13.4	
>14 cig/day	4171	9.2	10.5	10.1	10.4	11.5	9.5	9.4	
Alcohol Consumption, %									<0.001
Non drinkers	25583	56.3	60.1	57.3	61.7	61.2	56.0	57.2	
Low-Risk Consumption	13705	35.0	32.0	33.6	29.9	29.9	31.0	29.2	
High-Risk Consumption	3901	8.7	7.9	9.0	8.4	8.9	13.0	13.6	
Binge drinking, %									0.038
No	40331	92.9	93.6	93.5	92.3	91.7	90.9	91.2	
Yes	2858	7.1	6.4	6.5	7.7	8.3	9.1	8.8	
Leisure time Sedentarism, %									<0.001
No	25555	61.5	60.1	59.6	54.5	54.8	58.8	54.3	
Yes	17634	38.5	39.9	40.4	45.5	45.2	41.2	45.7	
Mediterranean Diet, mean (SD)	43189	5.66 (1.41)	5.59 (1.43)	5.52 (1.48)	5.52 (1.50)	5.52 (1.54)	5.66 (1.41)	5.54 (1.46)	0.034
Body Mass Index, %									<0.001
Underweight	798	3.1	2.3	2.0	1.6	1.7	2.8	1.1	
Normal weight	17563	46.7	44.5	43.2	37.3	36.8	36.2	30.7	
Overweight	14993	31.1	34.1	33.5	35.2	33.5	36.0	36.7	
Obesity	6946	14.1	14.7	15.9	18.79	20.6	16.1	19.5	
No answer	2889	4.9	4.4	5.5	7.2	7.4	8.8	11.9	
Self-Perceived Health, %									<0.001
Very Good	7838	22.1	21.1	22.5	19.5	17.9	18.9	16.1	
Good	21373	51.6	50.7	50.1	47.8	47.0	48.3	48.3	
Fair	9815	18.7	20.4	19.6	23.0	24.5	22.6	25.2	
Poor	3199	5.8	6.2	5.8	7.3	8.5	7.8	6.3	
Very Poor	964	1.8	1.7	2.0	2.3	2.6	1.8	2.6	
Hospital Admissions, %									0,200
No	39366	91.9	91.3	92.3	92.9	92.2	91.5	92.1	
Yes	3823	8.1	8.7	7.7	7.6	7.8	8.5	7.9	
ER Visits, %									<0.001
No	31552	74.4	71.6	72.2	72.4	72.4	78.3	79.4	
Yes	11637	25.6	28.4	27.8	25.6	27.5	21.7	20.6	
Day Hospital Visits, %									0.165
No	39990	93.3	93.0	92.8	92.0	92.0	94.5	91.2	
Yes	3199	6.7	7.0	7.2	7.9	8.0	5.5	8.8	
Deaths, %									<0.001
No	38848	91.5	93.2	93.2	91.4	91.8	89.4	85.9	
Yes	4341	8.5	6.8	6.7	8.6	8.2	10.6	14.1	

Urban I (large cities), Urban II (mid-size cities), Urban III (small cities), Rural I (large and accessible), Rural II (large and non-accessible), Rural III (small and accessible) and Rural IV (small and non-accessible).
P-value for homogeneity of sampling-weighted percentages among type of municipality categories, computed through chi squared tests (for categorical variables) or analysis of variance (for continuous variables).
[a] Unweighted sample N.
[b] % or weighted mean, SD Standard Deviation.

consumption, binge drinking, sedentary leisure time, and excess weight.

Table 2 also shows that rural residents report worse perceived health than urban residents. In addition, residents of smaller rural municipalities had lower numbers of emergency room visits and higher mortality rates.

3.2. All-cause mortality

The median follow-up time was 6.4 years, during which 4,341 deaths were recorded. Table 3 describes the association between rural-urban municipality type and all-cause mortality. In the unadjusted model (model 1) and with Urban I as the reference category, the HRs for mortality show a J-shaped association, i.e., hazards are lower for Urban II and III but they increase for Rural III reaching a maximum for Rural IV (HR = 1.68; 95%CI:1.37–2.05). When model 2 adjusts for the socioeconomic and demographic variables, this J-shaped relationship dissolves, showing a lower mortality risk in all types of municipalities compared to Urban I. In the next two models, when lifestyle factors are also controlled for (model 3) and use of health services is further taken into account (model 4) the estimates remain practically the same. Model 4, the fully adjusted model, shows that Rural II and III dwellers enjoy the lowest mortality risks: HR = 0.67 (95%CI: 0.54–0.84) and HR = 0.72 (95%CI: 0.58–0.88), respectively. Finally, we tested for interactions of this association by sex, age or level of education (Table 1S of supplementary material) with no clear differences.

3.3. Cardiovascular and cancer mortality

As seen above, analyses for cardiovascular mortality (Table 4) also show a J-shaped unadjusted relationship (model 1), which again

Table 3
Rural-Urban Association with all-cause mortality. Spanish population ≥15 years of age.

	Model 1			Model 2			Model 3			Model 4		
Type of Municipality	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Urban I	Ref			Ref			ref			ref		
Urban II	0.80	0.71–0.90	<0.001	0.81	0.71–0.92	0.002	0.82	0.72–0.94	0.004	0.83	0.73–0.95	0.008
Urban III	0.79	0.70–0.90	<0.001	0.82	0.71–0.95	0.006	0.83	0.72–0.96	0.010	0.84	0.73–0.97	0.020
Rural I	1.02	0.87–1.20	0.785	0.78	0.65–0.94	0.008	0.77	0.64–0.93	0.005	0.77	0.64–0.93	0.006
Rural II	0.99	0.80–1.22	0.892	0.64	0.51–0.80	<0.001	0.68	0.55–0.85	0.001	0.67	0.54–0.84	0.001
Rural III	1.28	1.07–1.52	0.007	0.69	0.57–0.85	<0.001	0.70	0.57–0.87	0.001	0.72	0.58–0.88	0.002
Rural IV	1.68	1.37–2.05	<0.001	0.74	0.58–0.94	0.012	0.77	0.61–0.98	0.031	0.80	0.63–1.01	0.061

HR: Hazard Ratio.
Model 1: Unadjusted.
Model 2: Adjusted for socioeconomic and demographic variables (sex, age groups, marital status, educational level, autonomous region of residence, per capita family income, socioeconomic deprivation index).
Model 3: Model 2 + adjusted for lifestyles and health status (tobacco consumption; sedentary leisure time; adherence to the Mediterranean diet, average daily alcohol consumption, binge drinking, body mass index, self-perceived health).
Model 4: Model 3 + adjusted for use of health services (hospital admissions, emergency room visits, and day hospital visits).
Urban I (large cities), Urban II (mid-size cities), Urban III (small cities), Rural I (large and accessible), Rural II (large and non-accessible), Rural III (small and accessible) and Rural IV (small and non-accessible).

Table 4
Rural-Urban association with cardiovascular mortality. Spanish population ≥15 years of age.

	Model 1			Model 2			Model 3			Model 4		
Type of Municipality	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Urban I	Ref			ref			ref			ref		
Urban II	0.84	0.68–1.03	0.093	0.94	0.75–1.19	0.612	0.97	0.77–1.23	0.806	0.97	0.76–1.23	0.788
Urban III	0.84	0.68–1.05	0.126	0.98	0.77–1.25	0.872	0.99	0.78–1.26	0.955	1.00	0.79–1.28	0.978
Rural I	1.34	1.03–1.75	0.031	1.13	0.83–1.55	0.424	1.15	0.85–1.57	0.368	1.18	0.86–1.61	0.300
Rural II	0.95	0.66–1.37	0.784	0.69	0.47–1.03	0.068	0.73	0.49–1.08	0.113	0.72	0.49–1.07	0.107
Rural III	1.48	1.10–1.99	0.010	0.98	0.69–1.37	0.886	0.99	0.70–1.40	0.932	0.99	0.70–1.41	0.962
Rural IV	1.90	1.35–2.66	<0.001	0.97	0.66–1.43	0.874	0.99	0.67–1.45	0.954	1.01	0.69–1.49	0.955

HR: Hazard Ratio.
Model 1: Unadjusted.
Model 2: Adjusted for socioeconomic and demographic variables (sex, age groups, marital status, educational level, autonomous region of residence, per capita family income, socioeconomic deprivation index).
Model 3: Model 2 + adjusted for lifestyles and health status (tobacco consumption; sedentary leisure time; adherence to the Mediterranean diet, average daily alcohol consumption, binge drinking, body mass index, self-perceived health).
Model 4: Model 3 + adjusted for use of health services (hospital admissions, emergency room visits, and day hospital visits).
Urban I (large cities), Urban II (mid-size cities), Urban III (small cities), Rural I (large and accessible), Rural II (large and non-accessible), Rural III (small and accessible) and Rural IV (small and non-accessible).

disappears when the socioeconomic and demographic covariates are introduced (model 2). Results from the fully adjusted analyses (model 4) are compatible with an absence of association.

Finally, the rural-urban gradient for cancer mortality (Table 5) is quite similar to that observed with overall mortality. Unadjusted results (model 1) show an increased risk for Rural IV residents, although this crude effect is substantially impacted by adjustment for relevant covariates. The accessible rural municipalities, regardless of population size

Table 5
Rural-Urban association with cancer mortality. Spanish population ≥15 years of age.

	Model 1			Model 2			Model 3			Model 4		
Type of Municipality	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value	HR	95%CI	p-value
Urban I	Ref			ref			ref			ref		
Urban II	0.81	0.65–1.00	0.051	0.72	0.56–0.92	0.008	0.73	0.57–0.93	0.011	0.73	0.57–0.93	0.012
Urban III	0.84	0.67–1.05	0.123	0.74	0.57–0.96	0.025	0.76	0.58–0.99	0.038	0.77	0.59–1.00	0.048
Rural I	0.80	0.60–1.08	0.143	0.55	0.39–0.76	<0.001	0.55	0.40–0.77	<0.001	0.56	0.40–0,78	0.001
Rural II	0.99	0.67–1.46	0.955	0.61	0.40–0,92	0.017	0.64	0.43–0.97	0.036	0.65	0.43–0.98	0.042
Rural III	0.99	0.70–1,40	0.952	0.48	0.33–0,71	<0.001	0.49	0.33–0.73	<0.001	0.51	0.34–0.75	0.001
Rural IV	1.66	1.20–2.29	0.002	0.70	0.48–1.02	0.060	0.74	0.51–1.07	0.109	0.77	0.53–1.12	0.171

HR: Hazard Ratio.
Model 1: Unadjusted.
Model 2: Adjusted for socioeconomic and demographic variables (sex, age groups, marital status, educational level, autonomous region of residence, per capita family income, socioeconomic deprivation index).
Model 3: Model 2 + adjusted for lifestyles and health status (tobacco consumption; sedentary leisure time; adherence to the Mediterranean diet, average daily alcohol consumption, binge drinking, body mass index, self-perceived health).
Model 4: Model 3 + adjusted for use of health services (hospital admissions, emergency room visits, and day hospital visits).
Urban I (large cities), Urban II (mid-size cities), Urban III (small cities), Rural I (large and accessible), Rural II (large and non-accessible), Rural III (small and accessible) and Rural IV (small and non-accessible).

(Rural I and III), show clear mortality benefits compared to large cities: 0.56 (95%CI: 0.40–0.78), and 0.51 (95%CI: 0.34–0.75), respectively.

4. Discussion

Our results show that the risks of all-cause and cancer mortality are greater in large cities (Urban I) than in other municipalities, with no clear urban-rural gradient. However, we found no urban-rural disparities in cardiovascular mortality.

4.1. All-cause mortality

A proper comparison of these results with other studies presents a challenge because of methodological differences in study design and in the definition and classification of urban-rural municipalities. Comparing to the most methodologically similar studies -longitudinal studies using individual-level data and adjusting for socioeconomic and demographic factors (Allan et al., 2019; Voigt et al., 2019) and health variables (House et al., 2000; Teckle et al., 2012; Zimmer et al., 2007)- the ones from Scotland (Teckle et al., 2012), England and Wales (Allan et al., 2019), and the USA (House et al., 2000) report a higher mortality risk among urban dwellers than among their rural counterparts. Meanwhile, a study conducted in Andalusia (Spain) found no differences (Voigt et al., 2019); and, in contrast, a study carried out in China observed higher mortality in rural than in urban areas (Zimmer et al., 2007). However, besides the difficulty in comparing studies across such different countries, none of these studies includes the category of large cities, the Urban I category used here, which could mask any differences if variability were present as was the case in our work.

The sequential adjustment by blocks of variables allowed us to identify risk changes associated with compositional differences. Socioeconomic and demographic variables had the greatest impact, especially for rural outcomes. This is not surprising given that rural areas present older, mostly male residents with low socioeconomic level populations. However, in contrast with previous studies (House et al., 2000) adjusting for lifestyle variables hardly had any impact. Research performed in the USA (Miller et al., 1987; Smith et al., 2008) and Scotland (Teckle et al., 2012) similarly concluded that urban-rural mortality inequalities are mostly due to changes in the municipalities demographic structure. Longitudinal studies have also shown that up to 30% of the health disparities associated with geographical areas in England (Riva et al., 2011) and up to 50% in Wales (Connolly et al., 2007), could be explained by selective population movements in search of the goods and services provided elsewhere.

Compared to Spanish urban areas, rural areas exhibit similar levels of smoking and leisure-time sedentarism, higher prevalence of high-risk alcohol consumption, while reporting a more balanced diet. This distribution would explain the small impact of adjusting for lifestyle variables on the risk estimates (Galán et al., 2021). Similarly, no changes were observed when the model included the use of health services. The Spanish National Health System (an universal coverage system organized following a territorially decentralized primary care structure) offers good access to health services, and continues expanding to reduce the number of municipalities lacking accessible health care points (Urbanos-Garrido, 2016). Currently, about 90% of the Spanish population resides in areas that enjoy optimal or favorable hospital accessibility (Fundación Matrix, 2019).

Seeing as compositional factors do not fully explain the rural-urban inequalities in mortality risk, it may be argued that contextual factors that characterize large urban areas may partially explain such disparities. For instance, air pollution, with its highest concentrations found in large cities and with consistent evidence of its impact on mortality (Khomenko et al., 2021; Liu et al., 2019). Also, extremes temperatures, in the form of heat and cold waves, are known to affect Spanish metropolitan areas more than rural municipalities, as illustrated in recent research in the Madrid region (López-Bueno, Navas-Martín, Díaz, et al., 2021; 2021b). The traffic-related noise pollution has also been linked to premature mortality in large cities (Cai et al., 2021). In fact, in Spain about 90% of premature mortality is registered in urban areas (European Environment Agency, 2021). Other factors, such as a green area deficit (Rojas-Rueda et al., 2019), higher crime and violence rates (Lorenc et al., 2012), and greater overcrowding rates (Alirol et al., 2011; Ecob & Jones, 1998), may help explain the higher mortality risk observed in large urban areas.

The classification method used in the study, with categories that describe the rural-urban gradient from a sociodemographic and geographic perspective, allows for a more detailed description of mortality risk than in past studies. An important finding of this study is that the mortality risk of mid-size cities and rural areas do not substantially differ. One could argue that these mid-size cities attract population with better health status and more resources as they provide all the urban services and amenities while maintaining a better quality of life than that of a large city (Gonzalez et al., 2011; Organisation of consumers and users, 2021) and without exposure to its harmful risk factors (Mueller et al., 2018; O'Reilly et al., 2007). Despite the lack of a strong relationship between the size of the municipality and its quality of life indicators, none of the large Spanish cities are among the top 50 municipalities regarding quality of life (Gonzalez et al., 2011).

4.2. Cardiovascular and cancer mortality

A somewhat unexpected result, based on previous literature, was the lack of an association between type of municipality and cardiovascular mortality. A longitudinal study in Canada that analyzed the association of urban-rural residence with different causes of mortality, after adjusting for compositional factors, observed that cardiovascular and cancer mortality rates were higher in remote rural areas than in cities. The authors explained these differences in terms of accessibility to care, i.e., rural areas having limited health care resources and scarce basic health care coverage (Subedi et al., 2019). In addition, two studies based on the analysis of routine statistics analyzed mortality by major cause categories. The first one, carried out in England and Wales, found no differences in cancer or cardiovascular mortality (Gartner et al., 2011), but a second study, performed in the Netherlands, observed results similar to ours (van Hooijdonk et al., 2008).

Considering that cardiovascular and cancer mortality share modifiable risk factors (included in our analysis), as well as unadjusted factors such as environmental pollution, the observed urban-rural disparities could be explained by inequalities in health care access and disease management. For example, in the case of cancer, differences in screening programs, early detection, or lower treatment adherence have been reported in rural populations in the USA (Loccoh et al., 2022; Yabroff et al., 2020). These differences may well lead to decreased survival for rural residents (Afshar et al., 2019; Carriere et al., 2018). Although in Spain we do not have data on cancer survival inequalities by urban-rural residence, a recent article reports that participation in screening programs do not differ substantially by size of the municipality (Molina-Barceló, A et al., 2021).

Unlike for cancer patients, cardiovascular mortality, due to coronary heart disease or stroke, for instance, is closely related to the speed with which specialized health care is received. Although we do not have information for Spain as a whole, regional research provides evidence that living in rural areas of the Catalonian region increases the risk of cardiovascular mortality (CabréVila et al., 2018). Results in the same direction have been observed in Norway (Mathiesen et al., 2018) and in Ireland, where, despite similar cardiac event incidence across rural-urban areas, residents in urban areas enjoyed greater survival rates (Masterson et al., 2015). These findings indicate that management of, and access to, specialized health services plays a great role in rural-urban disparities in cardiovascular mortality. Thus, it is likely that the greater mortality risk related to exposure to harmful environmental factors in large cities is offset by better access to emergency care for acute events. This would explain why, unlike cancer mortality, no differences in cardiovascular mortality were found in our study.

4.3. Strengths and limitations

The main strengths of our study are its design, a population-based cohort representative of all the regions of Spain, and its large sample size. The sample includes participants from the early age of 15 years, which allows for age-relevant analyses. Another strength is the linking of the individual-level data to mortality records via national identification document number, thus reducing classification errors. A median follow-up time of almost 6.5 years allowed for the evaluation of medium-term rural-urban residence effect on cardiovascular and cancer mortality. Regarding the categorization of rural vs. urban areas, we consider that basing the definition of rural and urban municipalities on three criteria (population size, population density, and accessibility to urban services) is a noteworthy contribution to the field. We believe the combination of these three criteria better reflect the heterogeneity of the rural-urban reality and allow us to evaluate health-related disparities in the urban-rural continuum. Finally, the analyses were adjusted for the main confounding factors related to mortality outcomes, i.e., socioeconomic and demographic factors, individual lifestyle, health status, and the use of health services.

The major limitation of this study is the information bias inherent in self-reported health data not validated with objective measures of health. In addition, due to data limitations our analyses do not include information on potentially relevant environmental contextual factors, travel distance to health services, or changes in municipality of residence.

5. Conclusions

Based on our results, residents of Spanish large cities are at a higher risk of overall and cancer mortality than individuals residing outside large urban areas, with no clear rural-urban gradient. Further studies should examine whether this risk is homogeneous across large cities, as well as within each city, while identifying the contextual factors associated with these differences.

Understanding mortality inequalities in different type of geographical areas requires the use of standardized definitions, the incorporation of new compositional and contextual factors, and the development of more specific analytical designs and instruments. However, the elimination of these disparities requires reducing rural-urban imbalances in terms of social, cultural, economic, and environmental sustainability. To this end, further research is needed to identify the specific factors that "promote and damage health" in each of the rural-urban spectrum. This information would inform the design, implementation, and evaluation of relevant health interventions aimed at making rural and urban areas healthier, more inclusive, sustainable, and resilient. This is an important aim in terms of both public health and social justice.

Ethical statement

Hereby, I consciously assure that for the manuscript the following is fulfilled:

1) This material is the authors' own original work, which has not been previously published elsewhere.
2) The paper is not currently being considered for publication elsewhere.
3) The paper reflects the authors' own research and analysis in a truthful and complete manner.
4) The paper properly credits the meaningful contributions of co-authors.
5) The results are appropriately placed in the context of prior and existing research.
6) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

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CRediT authorship contribution statement

Ana Ayuso-Álvarez: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Cristina Ortiz:** Methodology, Data curation, Writing – review & editing. **Teresa López-Cuadrado:** Methodology, Writing – review & editing. **Carmen Rodríguez-Blázquez:** Validation, Writing – review & editing. **Pablo Fernández-Navarro:** Methodology, Validation, Software, Writing – review & editing. **Javier González-Palacios:** Software, Methodology. **Javier Damián:** Methodology, Writing – review & editing. **Iñaki Galán:** Conceptualization, Methodology, Formal analysis, Validation, Writing – review & editing, Supervision.

Declaration of competing interest

None.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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