Geospatial clustering of suicide mortality in Sardinia

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Abstract



The Mediterranean island of Sardinia shows the highest suicide rate in Italy among men $(23.07 \times 10^5$ per year vs the average national rate of 13.80×10^5 per year). In contrast, the suicide rate among Sardinian women is one of the lowest across all the Italian regions. The aim of this epidemiological study was to investigate the distribution of suicide mortality in Sardinia in relation with environmental and social factors using geospatial analysis. Data available from the total 377 Sardinian municipalities, including suicidal mortality and several socio-economic indicators, were retrieved and analysed. Ordinary least squares regression was used to investigate the association between suicide mortality and the selected indicators. Suicide among men reached a peak in the Southern-Eastern area of the island. Overall, the multivariable analysis showed that suicidal mortality was significantly and positively related with the altitude (0.243, P=0.001), the occupational hardship index (0.230, P=0.016), and the social services hardship index (0.149, P < 0.0001), and negatively with pro-capita income (-0.122, P=0.012). After adjusting for all covariates, the index of multiple deprivation, the environmental and the educational index respectively, remained the only significant predictors. These findings suggest that social distress is the main factor leading to suicide among Sardinia men.

Keywords Suicide · Sardinia · Social distress

Introduction

Suicide is a complex and multidetermined event, in which several variables are likely to play a causal role, intertwined with each other (Franklin et al. 2017). Suicide is the fifteenth leading cause of death in the world (WHO Global Health Observatory 2017) and the second leading cause of death in the 15–29 age group (World Health Organization 2019). In many countries suicide has become a public health problem (O'Rourke et al. 2021). For instance, suicidal deaths outweigh the combined deaths from terrorist attacks, wars and natural disasters. In Italy, according to the *Istituto Superiore di Sanità* and the Health Observatory, about 3900 people die each year from suicide, and almost 80% are men (Italiano and Istituto nazionale di statistica 2019). In both sexes,

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suicide mortality increases with advancing age: for women the increase is linear, for men the increase is exponential starting from 65 years of age (Erlangsen et al. 2003). Suicidal behaviours can be conceptualized as a complex process ranging from ideation, which can be communicated subliminally through verbal or non-verbal actions, to suicide planning, attempting, and in the worst case, successful suicide. Biological, family history, psychological, social, environmental and situational factors are the main determinants of suicidal behaviours (Fazel and Runeson 2020).

Being a tragic event that deeply impact on the collective imagination, suicide evokes human fragility and the bitter aspects of existence. It may occur in all ages and in all countries of the world with considerable variations in incidence depending on the geographical area (Fountoulakis and Gonda 2018). Suicide prediction and prevention is receiving increasing attention, however, being a multifaceted phenomenon, we are still far from understanding exhaustively the etiology and the factors playing a role in its emergence (Niedzwiedz et al. 2014). Risk factors for suicide usually include mental and physical illness, alcohol or drug abuse, chronic illness, acute emotional distress, violence, a

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sudden and major change in an individual's life, such as loss of employment, separation from a partner, or other adverse events, or, in many cases, a combination of these factors. In addition, traumatic childhood experiences, capable to influence the quality of life, may play a role in the major affective disorders (Serafini et al. 2016). While mental health problems may play a role, varying across different contexts, broader factors, such as cultural and socio-economic status, are also considered influential (World Health Organization 2012). Suicide risk is rising in some categories of frail people, especially adolescents (Geoffroy et al. 2020; Itzhaky et al. 2020), and advanced societies are implementing measures to fight the phenomenon. From the epidemiological point of view the worldwide suicide rate has been estimated around 10/100,000/year accounting for nearly 1.4% of all deaths (World Health Organization 2019). The highest rate of suicide recorded in the world is in Northern Europe and the lowest in Southern Europe with a few exceptions (World Health Organization 2019). The methods most used to take one's own life differs in resource-rich and resource-poor countries: while in the former, firearms, hanging and poisoning are most commonly used, in the latter, pesticide selfpoisoning is used more often (World Health Organization 2019). In Italy, data relating to suicide are made available by the Italian National Institute of Statistics (ISTAT) and can be downloaded from the website https://www.istat.it/it/archivio/ 14562. In 2019 the suicide rate in Italy was 6.7 / 100,000, far lower than the global world rate. However, there are considerable internal differences across the 20 Italian regions, suggesting the influence of peculiar factors depending upon geographic or environmental determinants (Giupponi et al. 2018; Martiello et al. 2019). The geographic distribution of suicide in Italy shows a clear North-South gradient with the only exception represented by the population living in the Sardinia island, which shows the highest suicide rate among men in Italy $(23.07 \times 10^5 \text{ per year})$ compared with the average national of 13.80×10^5 per year, a difference which is significantly higher by 67%. In contrast, the island has one of the lowest suicide rates among women within Italian regions, close to that of the Southern and the Central regions. Some epidemiological data, obtained from the databases mentioned earlier, indicate a remarkable concentration of the suicidal phenomenon in the internal mountainous area. This might appear surprising, as the population living in this area is famous for its healthy lifestyle (Pes et al. 2013), happiness (Fastame et al. 2021a) and longevity (Poulain et al. 2013), usually associated to wellbeing (Fastame et al. 2021b; Pes et al. 2016). On the basis of these premises, we hypothesised that factors rooted in rural economy and in traditional culture still prevailing in this specific geographic area (Pes et al. 2015), may constitute a suicidal risk factor.

The aim of this ecological analysis was to investigate the spatial distribution of suicidal mortality in Sardinia and its

relationship with some environmental and social factors using aggregated data.

Materials and methods

Study area

Sardinia extends for 24,100 km² with a population of 1,624,216 inhabitants (ISTAT n.d.). The island is characterized by a central mountainous area, surrounded by hilly and flat areas extending in all directions towards the coast. The most populated areas encompass two cities located in the extreme north and south of the island and in few smaller towns (Alghero, Olbia, Tempio Pausania, Carbonia, Iglesias, Quartu Sant'Elena) while the remaining population, largely rural, is sparsely scattered on the central uplands. Sardinia is administered by 377 local municipalities which represent the spatial units of this study.

Study design and measures

The raw data for suicide mortality were retrieved from the ISTAT which provided the number of observed deaths for each municipality, allowing the calculation of the suicidal mortality rate (MR) for the category 60–84 according to the International Classification of Diseases 10th revision (ICD–10). The calculated MR in each municipality was included in all statistical models as dependent variable.

A total of ten distinct indicators available for the 377 Sardinian municipalities, reflecting environmental and social characteristics at local level, have been retrieved from several available statistical sources, and used as potential predictors of suicide mortality in the analysis (Table 1). The altitude and population density of the residence municipality were retrieved from geographic databases (Sardegna 1934). The inbreeding coefficient α , based on marriages occurring in each Sardinian municipality over a given time interval, was used as a rough estimate of the genetic homogeneity of Sardinian population, according to the study of Lisa et al. (Lisa et al. 2015) and categorized into quartiles, as reported by the authors, and already used in previous studies (Pes et al. 2017a). Seven further indicators were retrieved from the "Sistema informativo IDMS 2011 – P.O. FESR Sardegna 2007/2013" (Sistema informativo IDMS 2011) as listed in Table 1: the average pro capita income (PCI), defined as the proportion of families in a given municipality below the absolute poverty threshold, out of the total households. According to the ISTAT, the absolute poverty threshold corresponds to the monetary value, at current prices, of goods and services considered essential for each family, based on members' age, geographical location and category of residence.

Table 1 Indicators selected to test the association of average quality of life in the Sa	ardinian municipalities
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Covariates	Definition	Reference Sardegna (1934)	
Altitude (mt.)	Altitude (mt) of the urban center of the municipality		
Population density (per sq. km)	Total inhabitants per unit (municipality) area	Sardegna (1934)	
Consanguinity (inbreeding coefficient α)	Inbreeding coefficient α	Lisa et al. 2015)	
Pro Capita Income (PCI)	Proportion of families below the absolute poverty threshold out of the total households in the municipality	Sistema informativo IDMS 2011)	
Occupational Hardship Index (OHI)	Arithmetic mean of three basic indices: the proportion of the unemployed persons, the proportion of the unemployed regis- tered in the public employment service, and the share of benefits paid to individuals with work incapacity	Sistema informativo IDMS 2011)	
Environmental Hardship Index (EHI)	A composite indicator reflecting the quality of the air and water, the territorial surface burnt by fires, and some climate variables such as temperature and rainfall	Sistema informativo IDMS 2011)	
Health Global Index (HGI)	Arithmetic mean of two elementary indices (standardized mortal- ity rate from cardiovascular disease and standardized mortality rate from cancer)	Sistema informativo IDMS 2011)	
Social Services Hardship Index (SSHI)	Composite indicator of difficulty of accessing pharmacies, banks, police stations, primary, intermediate and high schools	Sistema informativo IDMS 2011)	
Educational Index (EI)	Arithmetic mean of three basic indices: delay rate (ratio between the number of repeating students in the eighth grade and the total enrolled students in the same class), the failure rate (ratio between those who have not been admitted to the secondary school exam and the total number of students scrutinized) and rate of dismissed with the minimum grade	Sistema informativo IDMS 2011)	
Multiple Deprivation Index (MDI)	A composite score combining OHI, EHI, HGI, SSHI and EI	Sistema informativo IDMS 2011)	

Hence, a family is defined as "absolutely poor" if it incurs a monthly consumption expenditure equal to or less than this monetary value.

A synthetic Occupational Hardship Index (OHI) was calculated as the arithmetic mean of three basic indices: the proportion of the unemployed persons, the proportion of the unemployed registered in the public employment service, and the share of benefits paid to individuals with work incapacity.

An Environmental Hardship Index (EHI), as a measure of environmental marginality and disadvantage, was derived by the quality of the air and water, the territorial surface burned by fires, and a few climate variables such as temperature and rainfall.

A Health Global indicator (HGI) was calculated as the arithmetic mean of two basic indices, namely, the standardized mortality rate from cardiovascular disease and that from all cancers.

A Social Services Hardship Index (SSHI), retrieved from the above-mentioned database, was calculated to estimate the difficulty of accessing the following services: pharmacies, hospitals, banks, police stations, primary, intermediate and high schools. In cases of absence of the service in a given municipality, the distance in km from the nearest municipality with the same service was considered. The indicator assumes a value between zero (when all the services considered were present in the municipality) and one (when access to all services was maximally burdensome compared to nearby municipalities).

A synthetic Educational Index (EI), reflecting the average education level of the population in each municipality was calculated as the arithmetic mean of three basic indices, namely, the delay rate (ratio between the number of repeating students in the eighth grade and the total enrolled students attending the class), the failure rate (ratio between those who have not been admitted to the secondary school and the total number of students scrutinized) and the rate of dismissed with the minimum grade. The indicator was normalized to obtain values between zero (less disadvantaged municipalities) and one (more disadvantaged municipalities).

Finally, a composite Multiple Deprivation Index (MDI) was calculated by combining the preceding indices in accordance with the model developed by Dres of the University of Cagliari and WIMD 2008 (Sistema informativo IDMS 2011).

Statistical analysis

A multistep approach was adopted, running first an exploratory correlation analysis, and subsequently an ordinary least square (OLS) regression model to analyse the association of the selected factors. Spatial autocorrelation in the variables was explored using the global Moran's I (1950), a widely used measure of global spatial autocorrelation, which tests whether there are some relationships between location and attribute values. A significant positive statistic indicates that nearby locations of similar attribute values are more spatially clustered than randomly distributed. In contrast, a significant negative statistic denotes dissimilar values at nearby locations and indicates a more dispersed pattern.

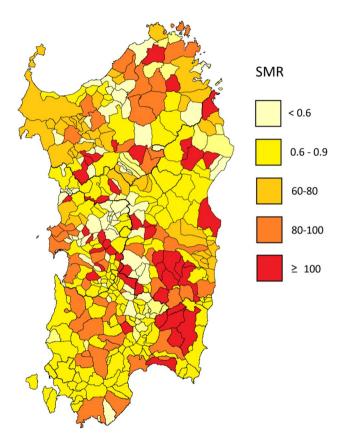


Fig. 1 Distribution of suicidal mortality rate (per 100,000) across the 377 municipalities of Sardinia

The association between the variables was performed using an Ordinary Least Squares (OLS) regression model with SPSS version 22.0 software (Chicago, IL) to compute parameter estimates, entering MR for suicidality as dependent variable, and the other variables as independent. Adjusted R² values and F-tests were used to assess the model fitting. Statistical significance was taken as p < 0.05.

Results

Exploratory analysis

The distribution of suicidal MR across the 377 municipalities of Sardinia is illustrated in Fig. 1. Overall, mortality showed a trend for clustering in the Southern-Eastern municipalities (part of Barbagia and lower Ogliastra) corresponding to an "archaic zone" where the first settlers of the island arrived in pre-Roman times (Vona 1997).

In the exploratory analysis the correlation of MR for suicide with the independent variables was tested including altitude, population density, inbreeding, average *pro capita* income, OHI, EHI, HGI, SSHI, CI. Non–parametric Spearman's correlation coefficients showed that suicidal mortality was significantly and positively related with the municipality altitude (r=0.189, P<0.01) and the Occupational Hardship Index (r=0.194, P<0.0001), and negatively related with the environmental index (r=-0.140, P=0.029) and the Index of Multiple Deprivation (r=-0.182, p<0.0001), whereas the other variables did not show correlations significantly different from zero (Table 2).

The next analysis was aimed to evaluate whether variables were affected by autocorrelation using Moran's *I* statistic. This index was calculated for the dependent variable and all ten predictors already mentioned. Results indicate that all

 Table 2
 Correlation and multivariable ordinary least square regression to evaluate the association of suicidal mortality with some potential predictors

Covariates	Spearman <i>r</i> coefficient	Standardized regression coefficient (univariable)	Standardized regression coefficient (multivariable)	Standardized coefficient after stepwise backward elimina- tion
Altitude	0.189 *	0.259 **	0.236 **	0.243 *
Population density	-0.179	-0.119 *	0.135	-
Consanguinity	0.007	0.096	0.002	-
Pro capita income	0.068	0.068	-0.127 *	-0.122 *
Occupational Hardship Index	0.194 **	0.273 **	0.223 **	0.230 **
Environmental Hardship Index	-0.140 *	-0.192	-0.042	-
Health Global Index	0.078	0.061	0.028	-
Social Services Hardship Index	0.079	0.216 **	0.148 *	0.149 **
Educational Index	-0.058	0.015	-0.009	-
Multiple Deprivation Index	-0.182 **	-0.205 **	-	-

*p<0.05; **p<0.0001

the independent variables did not display a spatial autocorrelation significantly different from a random distribution.

Ordinary least square (OLS) regression model

In the next analysis the suicidal mortality rate was the dependent variable. The ten variables considered as potential predictors were entered in the multivariate OLS regression model as independent variables. The results are illustrated in Table 2. When the variables were included together (full model), a significant positive association was detected for altitude (standardized β coefficient 0.236), Occupational Hardship Index (standardized β coefficient 0.223), and Social Services Hardship Index (standardized β coefficient 0.223), whereas a negative association was found for pro capita income (standardized β coefficient -0.127).

When all variables were entered in a stepwise backward regression model with alpha of 0.10 for backward elimination, the four variables remained significant predictors of suicidal mortality.

Discussion

The ecological analysis performed in this study confirmed that suicidal mortality in the Southern-Eastern area of Sardinia reached a peak especially among men and was significantly and positively related with altitude. Additional predictors were the occupational hardship index, the social services hardship index and a low pro-capita income that remained the only significant predictors after adjusting for all covariates. On the contrary, factors such as population density, consanguinity, environmental hardship index, health global index and educational index did not show any significant relationship in the adjusted model.

The historical and geographical features of the Sardinian suicidal mortality hot spot are unique and must be carefully considered when attempting to understand the ultimate causes of the phenomenon. The suicide mortality "spot" is located predominantly in a mountainous area, lacking an efficient road network until recently, and whose inhabitants remained isolated for centuries, resulting into considerable impact on local economy (Vona 1997). Overall, this population, compared to the general population of Sardinia, experienced a slower economic development (Pes et al. 2017b), source of social malaise, and the advent of modernity was often perceived as a sort of collapse of the traditional social order, strongly internalized. This scenario remembers in some way the anomie condition described by Durkheim, occurring when changes drive to the lack of social and moral rules, further resulting in a suicidal risk (Durkheim 1897). According to other studies reported in literature the suicide hot spot in our analysis was detected in a rural area (Hirsch 2006; Ivey-Stephenson et al. 2017). For example, the average size population of municipalities encompassing the suicide hot spot was of 1847 inhabitants compared to 2683 in the remaining part of the island. Furthermore, the population examined appeared to have a higher average age and a proportion of elderly individuals higher than the national standard (Poulain et al. 2004). Ivey-Stephenson et al. analyzed the suicide rate in three different urban contexts: large, medium and small metropolitan or rural areas. The suicide rate in the population of rural areas was always higher than in metropolitan areas (large and medium-sized). These findings remain also constant even after adjusting for age, sex, ethnicity, and the suicidal method used (Ivey-Stephenson et al. 2017). A higher prevalence of suicide in rural areas was also confirmed by Reccord et al. in an observational study (Reccord et al. 2021). High suicide rates in rural areas were also reported in numerous studies from different countries including USA (Association and of suicidology 1999), Australia (Dudley et al. 1998) and Scotland (Hawton et al. 1999).

People living in rural areas may be particularly exposed to social cultural isolation and the correlation found between suicide and social isolation was confirmed by data reported in a previous study conducted in Sardinia (Bocchetta and Traccis 2017). More specifically, the study showed that the distribution of suicides and admission to psychiatric hospitals, across municipalities for schizophrenia, bipolar disorder and depression, between 1901 and 1964 and suicides were more frequent in small municipalities located at higher altitude, in the south-eastern area of Sardinia (Bocchetta and Traccis 2017). Given this framework, it is reasonable to associate the high suicide rate in the south-eastern area of Sardinia with its geographic isolation. In fact, the definition of social isolation is not univocal as it is a multidimensional concept, in which "structural" dimensions (living alone, having few relationships) intersect with "functional" dimensions, such as the material and emotional support, conveyed by social relationships (Durkheim 1897; EpiCentro - Portale di epidemiologia per gli operatori sanitari 2012; Calati et al. 2019; Heikkinen et al. 1993a; Heikkinen et al. 1993b; Jing et al. 2021). Social isolation is increasingly associated with the individual's health. In particular, the absence or scarcity of social relationships are considered risk factors for the individual wellbeing similarly to other risk factors such as cigarette smoking, alcohol addiction and obesity (Malcolm et al. 2019).

In our study it was also observed a positive correlation trend between suicide mortality and municipality altitude. Beside the fact that altitude may contribute to isolation, especially in poor regions (for example for the paucity of infrastructures). Limited access to the public service, including healthcare, with some areas even missing the primary care. Barriers in accessing health service suggests an increased or worsening of organic diseases, especially those untreated and/or leading to chronicity and disability, may play a role in suicide ideation (O.M.S. 2014; Hurst et al. 2007). In our study, limitations to access the public service resulted a risk factor for suicide. Moreover, it has been hypothesized a possible effect of altitude on metabolic stress, resulting from a mild hypoxia, in subjects with mood disorders (Bocchetta and Traccis 2017).

In agreement with literature (Bachmann 2018) our data showed that more than 60% of the suicide victims were males. In this kind of community, the inability of job retraining and the ensuing frustration potentially experienced at a young age by males, it could be a risk factor for suicide.

Our study highlighted a correlation between suicidality and socio-economic status: the latter can be subdivided into three elements which are per capita income, occupation and education. In our study, the first two factors, as expected, showed a significant association with suicidality, respectively negative and positive, while the third was unrelated with suicide. The average income in the hot spot population was significantly lower compared to the people at national level (Poulain et al. 2013). In a previous study, conducted in the same geographical area, we found that the proportion of semiskilled and unskilled workers and uneducated shepherds and peasants (the lowest socioeconomic category) was significantly greater (79% vs. 21%, p < 0.0001) (Pes et al. 2020). Literature reports that people with a lower socioeconomic level have a double risk of suicide (Näher et al. 2019) that may be more common in individuals with unskilled than in skilled occupations (McIntosh et al. 2016). A meta-analysis including 34 studies found that suicide risk was higher among low-skilled laborers than in the general working-age population (rate ratio 1.8, 95% CI 1.5-2.3) (Milner et al. 2013). In contrast, suicide risk was lower in more skilled workers (e.g., general managers solving complex problems) than in the general working-age population (rate ratio 0.7, 95% CI 0.5- 0.9). It has been reported that unemployment and economic tension can increase the suicidal risk (Chang et al. 2013). Although the average education level in the suicide hot-spot was almost half that for their peers compared with an urban area (Pes et al. 2020) we did not find association with suicidal mortality, probably because although the level of literacy in the mountainous area is two points lower than the regional average, the schooling level is rarely a cause of social ostracism in this community.

Similarly, our spatial analysis did not detect a positive association between suicide and some variables reported in the literature as risk factors. For instance, our study did not highlight a significant spatial association of suicide mortality with the health global index that was observed in more advanced socio-cultural contexts, such as in the United States (Tondo et al. 2006). In fact, the literature highlights that the disorders most frequently associated with suicidal behaviour are chronic and highly disabling pathologies. The risk of suicide, overall, increases with organic disease, recent surgery, and chronic or terminal illness (Crump et al. 2014; Juurlink et al. 2004). Furthermore, depressive symptoms secondary to the underlying disease may also play a role (Kontaxakis et al. 1988). On the contrary, in the Sardinian hot spot population is not the average state of health of the population to act as a trigger for suicide, but rather how the acute discomfort, derived from the rapid transformation of cultural models, according to the Durkheim hypothesis (Durkheim 1897).

In the past, a robust body of literature has underlined the link between crime in general and suicidality (Harriss and Hawton 2011; Modestin and Emmenegger 1986; Stenbacka et al. 2014). In some cases, this relationship could have been reinforced by the availability of lethal metters. In countries such as the United States, which are being progressively adopting a more restrictive legislation on the use of firearms, suicidality and crime in general tend to decline (Martinez-Ales et al. 2020).

Finally, the environmental index did not show a spatial association with suicide mortality rate: first of all, probably because the environment in the mountainous part of the island is very well preserved and protected by regional laws (Lai et al. 2017) and did not undergo degradation as it often occurs in other Italian regions. Interestingly, in a study conducted in Sardinia, Bocchetta et al. (Bocchetta and Traccis 2017) reported an inverse relationship between suicide mortality and the lithium content in the tap water. It has long been known that lithium is an element with great ability to prevent suicidal ideation as it can improve mood disorders (Rybakowski 2020), and a geospatial study conducted in the Texas counties had highlighted how the levels of lithium in public water supply were negatively associated with suicide rates (Blüml et al. 2013). Similarly, an inverse spatial relationship between lithium and suicide has also been confirmed in studies conducted in Japan (Ohgami et al. 2009) and Austria (Kapusta et al. 2011). In Italy, a significant correlation between suicide rate and lithium concentration was reported by Pompili et al. among women in the period 1980-1989 (Pompili et al. 2015). The concentration of lithium in the waters of central-eastern Sardinia is very low unlike those of the rest of the island (0.006 vs 0.022 mg/L) (Abbanoa S.p.A. n.d.).

A puzzling finding of our study was that although in the suicide hot spot outlined in our study the consanguinity rate is frequent among partners, given the high isolation, however this variable was not found to be associated with suicidal mortality. While some studies have reported the association between consanguinity and depression (Rao et al. 2009), others seem to exclude any link between consanguinity of parents and mental health of children (Hosseinpour et al. 2016). However, even though in general, consanguinity can

be assumed as a marker of greater heritability of phenotypic features, the association with suicide is a still debated topic.

Our study has several limitations that need to be mentioned. The outcome variable was exclusively the mortality from suicide, as data on the incidence of suicide, much more difficult to collect, were not available. Being an ecological study based on aggregate data, the results are only association and no inference about a causal relationship between explanatory variables and outcome is possible, although it may be helpful for further exploratory research. Furthermore, we cannot rule out the existence of other potential risk factors for suicide mortality, not available in our database, such as exposure to some medications, a family history of suicide, alcohol or drugs addiction, among others. An additional limit of our study was the lack of clinical information subtracting an important interpretative key about numerical data. Nonetheless, the study confirmed that among the Italian regions Sardinia has the highest male suicidality, although with a different prevalence across municipalities, likely ascribable to a disadvantage of the rural population living in the hinterland.

The main implication of the present investigation is that occupational and social service hardship resulted to be significant predictors of suicide mortality and, especially in rural communities, they more likely important than health status or environmental hardship.

Enhancing supporting network is essential to remove the discomfort and to develop social and economic programs in the specific local setting.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval Ethics approval and consent to participate were not required, as this is an observational study based on anonymized data routinely collected by the ISTAT, which is a public Italy bodies reporting on health and socio economic determinants (according to Italian law, the study was exempted from approval by an ethics committee because all the data used were deidentified and publicly available). This study is also ethically compliant with the National Law (D.Lgs. 101/2018) and the "General Authorisation to Process Personal Data for Scientific Research Purposes" (nos. 8 and 9 of 2016, referred to in the Data Protection Authority action of December 13, 2018).

Conflict of interest The authors have no conflicts of interest relevant to this article.

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