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Antidepressant sales and regional variations of suicide mortality in Germany

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ABSTRACT

Suicides account for over one million deaths per year worldwide with depression among the most important risk factors. Epidemiological research into the relationship between antidepressant utilization and suicide mortality has shown heterogeneous and contradictory results. Different methodological approaches and limitations could at least partially explain varying results. This is the first study assessing the association of suicide mortality and antidepressant sales across Germany using complex statistical approaches in order to control for possible confounding factors including spatial dependency of data. German suicide counts were analyzed on a district level ($n = 402$) utilizing ecological Poisson regressions within a hierarchical Bayesian framework. Due to significant spatial effects between adjacent districts spatial models were calculated in addition to a baseline non-spatial model. Models were adjusted for several confounders including socioeconomic variables, quality of psychosocial care, and depression prevalence. Separate analyses were performed for Eastern and Western Germany and for different classes of antidepressants (SSRIs and TCAs). Overall antidepressant sales were significantly negatively associated with suicide mortality in the non-spatial baseline model, while after adjusting for spatially structured and unstructured effects the association turned out to be insignificant. In sub-analyses, analogue results were found for SSRIs and TCAs separately. Suicide risk shows a distinct heterogeneous pattern with a pronounced relative risk in Southeast Germany. In conclusion, the results reflect the heterogeneous findings of previous studies on the association between suicide mortality and antidepressant sales and point to the complexity of this hypothesized link. Furthermore, the findings support tailored suicide preventive efforts within high risk areas.

1. Introduction

Suicide is a major public health issue accounting for over one million deaths per year making it the tenth leading cause of death worldwide (Turecki and Brent, 2015). Suicidal behavior is highly complex with multiple risk factors. Among these factors, the presence of psychiatric disorders in general and major depressive disorder in particular increase the risk for committing suicide (Harris and Barraclough, 1997; Hawton et al., 2013; Turecki and Brent, 2015). The correct diagnosis and adequate treatment of depressive disorders are therefore key elements in suicide prevention strategies (Mann et al., 2005; Turecki and Brent, 2015; Zalsman et al., 2016).

In many Western countries suicide rates have declined markedly over the last decades (Värnik, 2012), while prescription rates of antidepressant medication have consistently increased (Gusmão et al., 2013). Since antidepressants are one of the most effective treatment options for depressive disorders, studies suggested that the decline in suicide rates could at least partially be explained by more extensive use of antidepressant medication and general

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improvements in mental health systems (Isacsson, 2000; Isacsson et al., 2010b). Recently, this relationship between antidepressant medication sales and suicide rates has become the focus of an increasing body of research (Cheung et al., 2015; Gusmão et al., 2013; Isacsson et al., 2010a). The practical challenges of conducting randomized controlled trials on the suicide preventive effects of antidepressants (Meyer et al., 2010) and therefore the absence of direct evidence from clinical trials resulted in ecological population-based research designs to investigate the suicide-antidepressant medication hypothesis (Gusmão et al., 2013; Kamat et al., 2014). Given the significance of suicidal behavior for public health and the necessity for enhanced prevention strategies these ecological studies are of key relevance, despite well-known methodological issues including the inability to prove causality and ecological fallacy (Piantadosi et al., 1988).

Previous studies have predominantly found an inverse correlation between antidepressant sales and suicide rates (Barak and Aizenberg, 2006; Bramness et al., 2007; Gibbons et al., 2005, 2007; Gusmão et al., 2013; Hall et al., 2003; Isacsson et al., 2009, 2010a; Kapusta et al., 2009; Ludwig et al., 2009; Nakagawa et al., 2007). Respective data was reported from more than 30 countries worldwide suggesting a possible anti-suicidal effect of increasing antidepressant sales (Korkeila et al., 2007). These results have been interpreted differently, with some researchers hypothesizing a causal relationship while others proposed a more cautious approach taking antidepressant sales as an indirect measure of improved depression recognition and overall psychosocial care development (Bramness et al., 2007; Kamat et al., 2014). However, these results have not been unanimous as some studies could not find a significant association between antidepressant sales and suicide rates (Barbui et al., 1999; Guaiana et al., 2005; Reseland et al., 2006; Zahl et al., 2010). One recent study even found a small, albeit statistically significant positive association between antidepressant prescriptions and suicide rates in a large sample of 20 OECD countries (Kamat et al., 2014). Different methodological approaches could at least partially explain varying results. Concerns have been raised repeatedly about the lack of possible confounding variables and statistical limitations of past studies (Gusmão et al., 2013; Moustgaard et al., 2014).

Most ecological studies used a longitudinal research design for assessing the correlation between these two variables using aggregated data on a less detailed country level (e.g., Gusmão et al., 2013; Kamat et al., 2014; Korkeila et al., 2007). Only a few studies also investigated regional variations in antidepressant sales and their association with suicide mortality on a county or district level. Following the pivotal study of Gibbons et al. (2005) using a mixed cross-sectional and longitudinal design in the US, similar studies were conducted in Norway (Bramness et al., 2007), Slovenia (Jagodič et al., 2013), and Finland (Moustgaard et al., 2014). However, there has been no study investigating the association of antidepressant sales and suicide mortality in Germany at district level. Of similar importance, with a few exceptions (Helbich et al., 2015; Kawaguchi and Koike, 2016), previous analyses of regional variations of suicide rates have not accounted for possible spatial dependence between adjacent districts, which can provoke a serious model estimation bias (Elliott and Wartenberg, 2004). Germany is known to show considerable regional differences regarding mental health care provision and psychiatric medication prescribing practices (Fritze, 2014; Melchior et al., 2014) thus allowing for analysis of regional suicide mortality. On a national level, using longitudinal data from 1986 to 2009, a significant inverse association between antidepressant utilization and suicide rates was reported (Gusmão et al., 2013).

Based on the above identified research gaps, the primary aim of this study was to test the complex association between antidepressant sales and suicide mortality in Germany for the period 2010 to 2013. Regional variations of these variables were assessed using Bayesian spatial regressions while controlling for a wide range of regional-based confounders. Also, the prevalence of depression was considered in order to control for the possibility of variations of depression rates across districts being responsible for variable suicide mortality. Since there is evidence for a differential effect of different classes of antidepressants on suicide rates, separate analyses for SSRIs and tricyclic antidepressants (TCAs) were conducted (Gibbons et al., 2005). The secondary objective was to estimate and map the suicide mortality risk across Germany. Such risk maps are of crucial importance for public health decision-makers to identify high-risk areas and to develop strategies for areas of priority in the existing National Suicide Prevention Program (Schmidtke and Fiedler, 2002).

2. Material and methods

2.1. Study area

The influence of antidepressant sales on regional variations of suicide mortality in Germany were analyzed on a district level. Districts represent an intermediate level of administration between the German states and municipalities. They correspond to the European NUTS 3 classification (Nomenclature of Territorial Units for Statistics) and are roughly equivalent to counties in the United States. Germany is divided into 402 districts consisting of 295 rural districts and 107 urban districts.

2.2. Data

Suicide and antidepressant sales data were obtained for each district. Suicide data based on ICD-10 codes X60 – X84 was provided by the Statistical State Office of the Free State of Saxony/Research Data Centres of the German Federation or the Federal States for the years 2010–2013. Data were obtained as suicide numbers per district per year and the average suicides between 2010 and 2013 were computed to prevent random annual fluctuations observed in time series.

Data on antidepressant sales (pills per 100,000 persons) on a district level were obtained from IMS Health, Inc, for the years 2010–2013. This variable refers to over the counter sales of all licensed pharmacies in Germany and therefore can be considered to be representative of the total antidepressant sales in the districts. Antidepressants of the Anatomical Therapeutic Chemical Classification System (ATC) class N06A4 (selective serotonin reuptake inhibitors - SSRIs) and N06A9 (tricyclic antidepressants - TCAs) were included.

As potential confounders, the following variables were collected: District-level data on population (average of years: 2010–2013), population density, gross domestic product (GDP) per capita in 1000 €, unemployment, general practitioner density per 100,000 persons, and psychiatrist density per 100,000 persons (all for the year 2011) were obtained from the German Federal Statistical Office. Data on psychotherapists per 100,000 persons (year: 2011) and the prevalence of depressive disorders based on ambulatory care claims data (year: 2011) were retrieved from the Central Research Institute of Ambulatory Health Care in Germany.

Informed consent and institutional review board approval were not required because this was a retrospective analysis of aggregate data.

2.3. Statistics

Besides descriptive statistics, Spearman rank correlations were

calculated to test for multicollinearity between the confounders and to investigate the bivariate associations between the raw standardized mortality ratios, i.e. the ratio between observed and expected numbers of suicides, for each district and the variable of interest (i.e., antidepressant sales). We obtained the expected suicides by multiplying the total national suicide mortality rate by the population of the respective district. As exploratory test, the Moran's I statistic was assessed to quantify the degree of spatial dependence in the suicide counts while adjusting for the population at risk (Schabenberger and Gotway, 2005). Following Helbich et al. (2013), Queen contiguity (i.e., sharing a common boundary) is utilized to specify adjacency.

Multivariate associations between the counts of suicides and antidepressant sales were estimated through ecological Poisson regressions within a hierarchical Bayesian framework (Rue et al., 2009). The non-spatial baseline model solely considered the aforementioned covariates and the number of expected suicides cases within each area as an offset (model 1). Independent and identically distributed priors following a Normal distribution were assigned to each covariate. However, due to spatial effects between adjacent districts the observed suicides are spatially correlated and not independently distributed across space (Helbich et al., 2015). Therefore, model 1 was extended towards a spatial model (model 2; BYM) as proposed by Besag et al. (1991). Briefly, BYM models consider the variability in a district as a combination of two area-specific random effects, namely a spatially structured effect and an unstructured effect. The former is specified as an intrinsic conditionally autoregressive prior assuming spatial dependence between adjacent districts (queen contiguity) while the unstructured effect accounts for non-spatial differences between the districts. Both effects are set-up with minimally informative priors. Besides the country-wide models, separate models were also calculated for Eastern (including Berlin) and Western Germany. To obtain estimates of the variables' posterior distributions, the computations are carried out through the Integrated Nested Laplace Approximation (Rue et al., 2009). To evaluate the model qualitythe deviance information criterion (DIC; Spiegelhalter et al., 2002) was used with lower DIC values indicating a better model fit.

3. Results

Descriptive characteristics of the 402 German districts are given in Table 1. The average number of suicides per district is 25.3 (SD = 26.5) resulting in an average suicide rate per 100,000 persons of 12.97. The mean number of antidepressant pills sold per 100,000 persons across the German districts is 120.4 (SD = 29.3). The raw standardized mortality ratios (SMR) for suicides from 2010 to 2013 and the sold antidepressant on a district level in Germany are shown in Fig. 1

Spearman rank correlation tests showed no significant association between the raw SMR and overall antidepressant sales ($p = 0.242$). Separate analyses for SSRIs and TCAs found no correlation between SSRIs and suicide mortality ($p = 0.954$) and a significant negative association for TCAs ($\rho = -0.16$, $p = 0.001$). Further significant associations were found with prevalence of depression ($\rho = 0.15$, $p = 0.002$), population density ($\rho = -0.13$, $p = 0.009$), psychiatrist density ($\rho = 0.14$, $p = 0.006$), and general practitioners density ($\rho = 0.30$, $p < 0.001$). Antidepressant sales were in turn significantly correlated with prevalence of depression ($\rho = 0.37$, $p < 0.001$), general practitioner density ($\rho = 0.18$, $p < 0.001$), and unemployment ($\rho = -0.26$, $p < 0.001$). No indication was found for high correlation between the confounders.

A significant residual autocorrelation of the raw SMR was observed (Moran's I: 0.329, $p < 0.001$) referring to a significant spatial pattern indicating the need for a spatially explicit model. As described above, two ecological regression models with different complexity were estimated. Besides the fact that the non-spatial model faced problems due to significant residual autocorrelation ($p < 0.017$), also the DIC score of 2224 favored model 2 having both a structured and unstructured effect, compared to the DIC of model 1 of 2286. data and its results can be considered to be more robust.

Table 1
Descriptive statistics.

	Mean ± SD	Min; Max
Average suicides per year	25.2 ± 26.5	4.2; 349.3
Antidepressant sales per 100,000	120.4 ± 29.3	10.1; 234.4
Depression prevalence in %	11.8 ± 1.8	7.6; 20.0
General Practitioners per 100,000	64.4 ± 7.6	46.1; 96.6
Psychiatrists per 100,000	5.3 ± 3.1	0; 19.3
Psychotherapists per 100,000	21.7 ± 17.2	1.7; 129.8
Population density per km^2	514 ± 665.8	37.1; 4468.3
GDP per capita in 1000€	28.34 ± 11.28	13.74; 86.87
Unemployment rate in %	6.6 ± 3.2	1.4; 16.7

The (residual) relative risk (RR) for each variable is represented through its posterior mean as well as the 95% credible intervals. While posterior means higher or lower than 1 refer to the direction of the effect, a variable is considered to be significant when the 95% credible intervals (CI) do not include a value of 1. Table 2 shows the results for models 1 and 2. In model 1, antidepressant sales are inversely associated with suicide mortality. Psychotherapists per 100,000 persons and population density show a negative association with suicide mortality, while depression prevalence, unemployment rate, and density of general practitioners are positively associated with suicide mortality. In the slightly better performing model 2, there is no significant association between antidepressant sales and suicide mortality. Only general practitioners per 100,000 persons, population density, and unemployment rate are associated with suicide mortality in this model.

Next, separate analyses for SSRIs and TCAs were conducted. The detailed results for the multivariate regression models are shown in Table 3. As in the overall models, SSRIs and TCAs were both shown to be negatively associated with suicide mortality in the baseline non-spatial model, while no significant associations were found in the slightly better performing spatial model.

In the stratified analyses for Eastern (including Berlin) and Western Germany, there were no significant associations between antidepressant sales (all antidepressants as well as SSRIs and TCAs separately) and suicide mortality in any of the spatial and non-spatial models (detailed results on request).

Finally, Fig. 2 visualizes the district specific RR of suicide compared to the country-wide risk resulting from model 2. Areas having a posterior probability exceeding 1 are facing a pronounced risk while areas below 1 have a reduced suicide mortality risk after considering the confounders.

4. Discussion

Our results show markedly regional differences in antidepressant sales and suicide mortality across the 402 districts of Germany. Suicide rates range from 3.7 to 23.0 per 100,000 persons, varying by factor 4. Even more striking are the regional differences in antidepressant sales, which vary by factor 23 (range: 10.1 to 234.4 pills per 100,000 persons/year). Both variables show a significant positive correlation with depression prevalence and the density of general practitioners. These findings are in line with studies from the US showing that GPs prescribe the majority of antidepressants (Mark et al., 2009). Depression prevalence is known to feature considerable regional variations caused by a complex interplay of

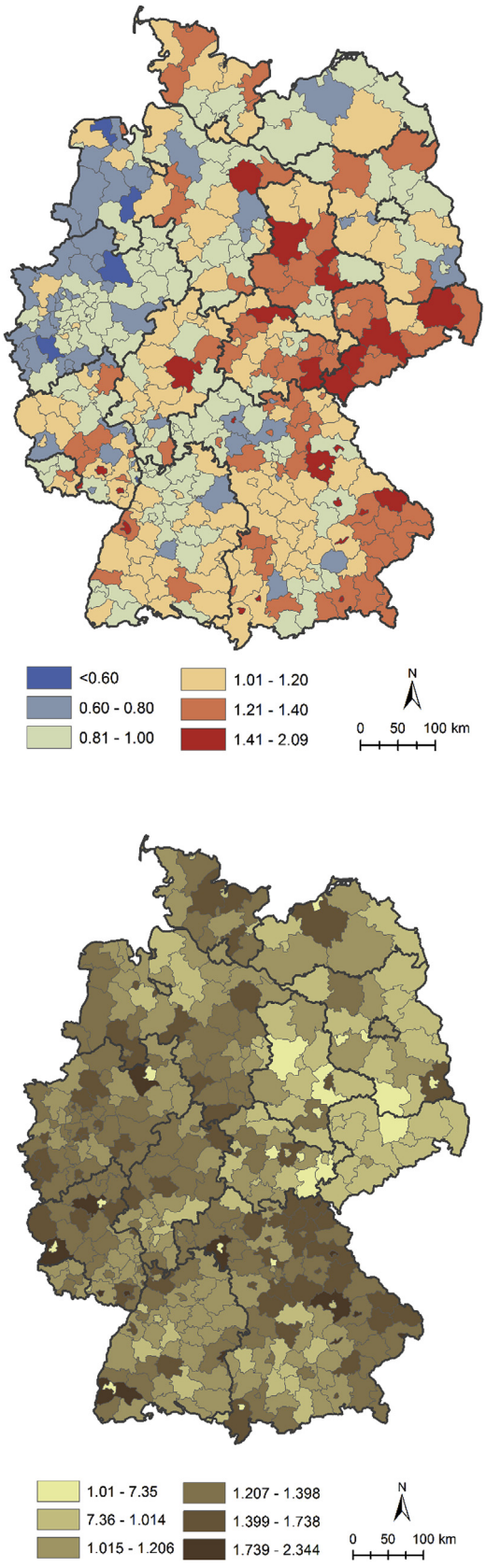

Fig. 1. Raw standardized mortality ratios (upper panel) and antidepressant sales (lower panel).

factors. These include regional differences in known risk factors for depression such as various socioeconomic characteristics as well as differences in service provision and health care utilization (Melchior et al., 2014; Moriarty et al., 2009; Strine et al., 2009). Areas with higher depression prevalence were found to show increased antidepressant sales. Nevertheless, in line with research on risk factors for suicide (e.g. Harris and Barraclough, 1997), higher depression prevalence was also associated with higher suicide mortality calling for further improvements in psychosocial healthcare provision and depression treatment. Specifically, our results show a distinct pattern of increased suicide mortality in the Southeast region of Germany highlighting the need for special suicide preventive efforts in this area.

The analyses of the relationship between antidepressant sales and suicide mortality led to heterogeneous results. In bivariate testing, no significant correlation between antidepressant sales and suicide mortality was found in our sample. In multivariate regression models, a more differentiated picture emerged. In the baseline non-spatial Poisson regression model, higher overall antidepressant sales were associated with lower suicide mortality in Germany This finding is in line with the majority of previously conducted ecological studies on the same subject (Bramness et al., 2007; Gibbons et al., 2005; Gusmão et al., 2013; Korkeila et al., 2007). The ecological design of these studies does not allow inferences of causality, so the interpretation of the underlying mechanisms of the observed negative association between antidepressant sales and suicide mortality remains on the level of hypotheses. Considering the accumulating evidence from randomized controlled trials (RCTs), observational studies, and large pharmaco-epidemiological studies it seems reasonable to propose a direct relationship between higher rates of antidepressant medication utilization and lower suicide rates (Isacsson et al., 2010a; Ludwig et al., 2009; Turecki and Brent, 2015; Zalsman et al., 2016). However, antidepressant sales could also be considered as a more indirect measure of the quality of psychosocial care and depression recognition and treatment (Bramness et al., 2007; Kapusta et al., 2009). In our study, we controlled for some pertinent indicators for psychosocial care, such as the density of general practitioners, psychiatrists, and psychotherapists. The finding that antidepressant sales remain negatively associated with suicide mortality even after adjusting for these possible confounders in the baseline multivariate regression model indicates an independent effect of antidepressants on suicide mortality. Previous studies have also pointed to varying rates of depression across regions as a possible alternative explanation for the observed associations between antidepressant sales and suicide mortality (Gibbons et al., 2005). Again, the negative association between antidepressant sales and suicide mortality remained significant even after adjusting for depression prevalence as a possible confounding factor.

In a second step, our investigation expands on these routine statistical procedures by taking into account significant spatial autocorrelation of the underlying data. Thereby, the quality of the regression model could be slightly improved to better fit the original data. In these spatial models, antidepressant sales were not significantly associated with suicide mortality anymore. To the best of our knowledge, this is the first study to use this methodology to assess the impact of antidepressant sales on suicide mortality. Our results therefore point toward the complexity of the hypothesized link between antidepressant sales and suicide mortality. While the majority of existing studies support the hypothesis that higher antidepressant sales are associated with lower suicide mortality, there are an increasing number of investigations that question these results. Several studies could not find a general association between antidepressant sales and suicide rates (Barbui et al., 1999; Guaiana et al., 2005; Moustgaard et al., 2014; Reseland et al., 2006;

Table 2
Relative risk for suicide mortality of the base non-spatial model (model 1) and the BYM model 2 for all antidepressant sales.[a]

	Model 1		Model 2	
	RR	95% CI	RR	95% CI
Antidepressant sales per 100,000	0.981*	0.973; 0.989	0.992	0.983; 1.002
Depression prevalence in %	1.224*	1.049; 1.428	1.165	0.974; 1.393
General practitioners per 100,000	1.114*	1.073; 1.156	1.053*	1.007; 1.101
Psychiatrists per 100,000	1.073	0.951; 1.211	1.061	0.929; 1.211
Psychotherapists per 100,000	0.974*	0.955; 0.993	0.988	0.966; 1.010
Population density per km^2	0.925*	0.894; 0.958	0.928*	0.890; 0.968
GDP per capita in 1000€	1.010	0.988; 1.032	1.005	0.981; 1.029
Unemployment rate in %	1.093*	1.004; 1.188	1.244*	1.106; 1.402
Intercept	0.497	0.381; 0.648	0.601	0.443; 0.817
	(DIC: 2286)		**(DIC: 2224)**	

* Statistically significant at $p < 0.05$.
[a] For a better differentiability of the results, all variables were divided by 10, while population density was divided by 1000.

Table 3
Relative risk for suicide mortality of the base non-spatial model (model 1) and the BYM model 2; separate analyses for SSRIs and tricyclics.[a]

	SSRI				Tricyclics			
	Model 1		Model 2		Model 1		Model 2	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
SSRI sales per 100,000	0.980*	0.969; 0.992	0.990	0.977; 1.003				
Tricyclics sales per 100,000					0.945*	0.926; 0.964	0.982	0.957; 1.007
Depression prevalence in %	1.188*	1.017; 1.386	1.162	0.971; 1.390	1.209*	1.039; 1.406	1.146	0.961; 1.365
General practitioners per 100,000	1.118*	1.077; 1.160	1.052*	1.006; 1.100	1.103*	1.062; 1.145	1.052*	1.006; 1.100
Psychiatrists per 100,000	1.079	0.955; 1.218	1.063	0.930; 1.215	1.046	0.927; 1.180	1.051	0.921; 1.200
Psychotherapists per 100,000	0.976*	0.957; 0.995	0.988	0.966; 1.010	0.978	0.959; 0.997	0.989	0.967; 1.011
Population density per km^2	0.926*	0.895; 0.958	0.928*	0.890; 0.968	0.921*	0.890; 0.953	0.928*	0.890; 0.968
GDP per capita in 1000€	1.011	0.989; 1.033	1.005	0.981; 1.029	1.008	0.987; 1.030	1.004	0.980; 1.028
Unemployment rate in %	1.095*	1.005; 1.192	1.244*	1.104; 1.402	1.128*	1.039; 1.224	1.257*	1.119; 1.414
Intercept	0.466	0.359; 0.606	0.597	0.440; 0.812	0.517	0.397; 0.675	0.596	0.440; 0.810
	(DIC: 2297)		**(DIC: 2224)**		**(DIC: 2277)**		**(DIC: 2225)**	

* Statistically significant at $p < 0.05$.
[a] For a better differentiability of the results, all variables were divided by 10, while population density was divided by 1000.

Zahl et al., 2010). A large study using data from 20 OECD countries (including Germany) even showed a small, but statistically significant positive association between antidepressant prescriptions and suicide rates over the years 1995–2008 (Kamat et al., 2014). Possible explanations for these heterogeneous results include varying data quality, diverse definitions of antidepressant utilization, and different methodological approaches (Moustgaard et al., 2014). As supported by our analyses, the use of aspatial and spatial regressions leads to small, but statistically significant differences in results, therefore highlighting the susceptibility of the association for differences in statistical approaches. This needs to be taken into account when interpreting the heterogeneous findings of our study. Nevertheless, as shown by the lower DIC values, we believe that the advanced BYM model considering spatial effects used in our study is the best fitting model for the underlying data and therefore constitutes a considerable methodological improvement (Elliott and Wartenberg, 2004). Notably, these considerations primarily concern cross-sectional approaches as applied in the present study.

Previous studies also reported a differential effect of different classes of antidepressants on suicide rates (Gibbons et al., 2005; Nakagawa et al., 2007). In many Western countries, the rise of modern antidepressants such as SSRIs has been linked with an observed decline in suicide rates (Gusmão et al., 2013; Ludwig et al., 2009; Kapusta et al., 2009). A higher proportion of prescription of modern antidepressants such as SSRIs as opposed to TCAs was proposed to serve as a proxy for a better quality of mental health care (Gibbons et al., 2005). TCAs are also known to possess higher toxicity than SSRIs which has been linked to increased risk of fatal self-poisoning (Hawton et al., 2010). We could not find evidence for significant differences between these classes of antidepressants in their association with suicide mortality in our study as the separate analyses for SSRIs and TCAs provided uniform results. In order to interpret this finding it should be taken into account that most previous studies reporting a differential association of SSRIs and TCAs used a longitudinal research design spanning a time-period when there was an important shift in the pharmacological treatment of depression from older TCAs to newer antidepressants such as SSRIs (Gusmão et al., 2013; Ludwig et al., 2009; Kapusta et al., 2009). In the observed time-period of the present study (2010–2013) this process has already been completed and pharmacoepidemiologic studies for Germany have shown stable sales of TCAs during that time (Fritze, 2014).

5. Strengths and limitations

This is the first small-area study analyzing the association between antidepressant sales and suicide mortality on a district level in Germany. We were able to control for a wide range of potential confounders including depression prevalence, indicators for psychosocial care, and socioeconomic parameters. The use of geospatial statistical approaches further improves the quality of the applied regression models. Nevertheless, our study has several limitations. The analyses in this study comprised aggregated data across all age groups and for both sexes. Suicide mortality in most Western countries including Germany are known to be significantly

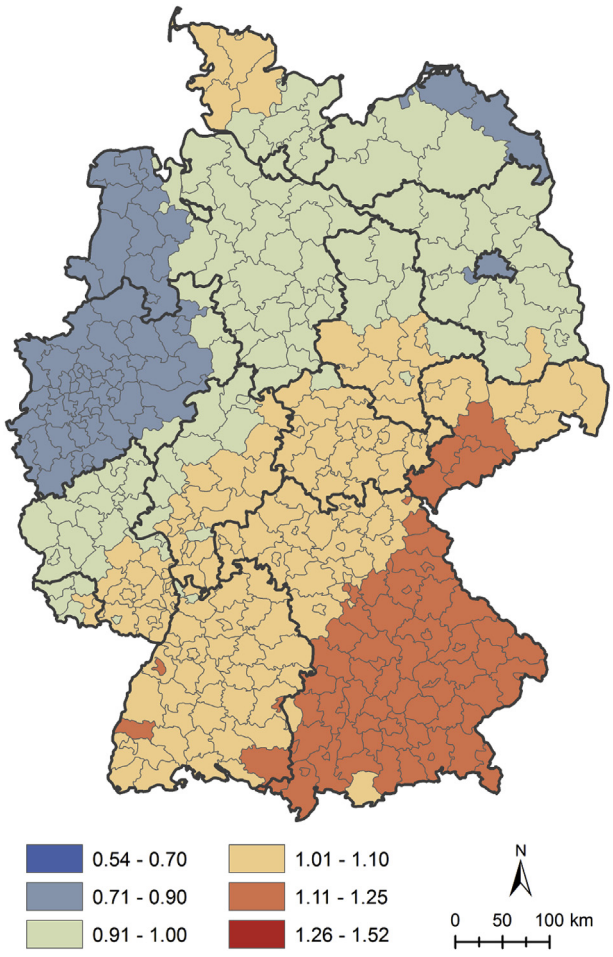

Fig. 2. Smoothed relative risk of suicide compared to the Germany-wide risk.

higher in men than in women, while antidepressant medication use is more common among women (Bramesfeld et al., 2010; Hawton, 2000). Additionally, it has been suggested that the impact of antidepressant use on suicidal behavior varies across the lifespan (Barbui et al., 2009; Hall et al., 2003; Kalmar et al., 2008). Due to the small absolute number of suicide cases in many of the less populated German districts it was not feasible to include further separate analyses for different age groups and sex.

Further, the ecological, purely cross-sectional design and the aggregated nature of our data do not allow for causal inferences and necessitate cautious interpretation. Issues of data availability for longer time-periods and the low absolute numbers of suicides on the small-area level of analysis necessitated the aggregation of suicide data over the available time-period. Further studies combining longitudinal data analyses covering longer time periods with geospatial statistical approaches in mixed space-time models are needed to further clarify the complex relationship between antidepressant sales and suicide mortality. Finally, data on depression prevalence only comprises patients utilizing services with public health insurance, leaving out privately insured patients. Even though the large majority of German citizen have public health insurance (about 90%), a possible confounding due to the uneven distribution of privately insured patients across the districts cannot be ruled out (Sundmacher and Ozegowski, 2016).

In conclusion, our results reflect the heterogeneous findings of previous studies of the association between antidepressant sales and suicide mortality. In the non-spatial model, antidepressants were inversely associated with suicide mortality even after controlling for important co-variates such as depression prevalence. After adjusting for autospatial correlation, no significant association was found between antidepressant sales and suicide mortality in this large German-wide analysis. No differences between SSRIs and TCAs could be observed. Further, a homogenous pattern of increased suicide mortality is observable in the south-east region of Germany, a fact worth being considered in the ongoing National Suicide Prevention Program of Germany.

Declaration of interest

PLP has been involved in a clinical trial with Lundbeck. He received funding from the DFG, the BfArM, the VW and Baden-Wuerttemberg Foundation. He declares no conflict of interest with regard to this publication. NDK reports to have received research funding from Shire and Lundbeck in the past 5 years. He declares no conflict of interest with regard to this publication. JFM reports that during the last 5 years received research funding from the EU, DFG (German Research Foundation), BMG (Federal Ministry of Health), BMBF (Federal Ministry of Education and Research), BMFSFJ (Federal Ministry of Family, Senior Citizens, Women and Youth), German armed forces, several state ministries of social affairs, State Foundation Baden-Württemberg, Volkswagen Foundation, European Academy, Pontifical Gregorian University, RAZ, CJD, Caritas, Diocese of Rottenburg-Stuttgart. Moreover, he received travel grants, honoraria and sponsoring for conferences and medical educational purposes from DFG, AACAP, NIMH/NIH, EU, Pro Helvetia, Janssen-Cilag (J&J), Shire, several universities, professional associations, political foundations, and German federal and state ministries. JFM holds no stocks of pharmaceutical companies. He is majority owner of the 3Li institute. He declares no conflict of interest with regard to this publication.

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Author contributions

NDK, PLP, JMF, MH, and VB were involved in the study design. MM, RT, SH, PLP, JMF, and NDK were involved in data collection and processing. MM, RT, BV, UL, NDK, and VB contributed to literature searches. MH, VB, and NDK were involved in data analysis and statistics. All authors contributed to data interpretation. VB wrote the first draft of the manuscript. All authors contributed to the writing of the final version of the manuscript and approved of its submission in the present form.

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