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Short-Term Effects of Traffic Noise on Suicides and Emergency Hospital Admissions due to Anxiety and Depression in Madrid (Spain).

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Abstract:

Studies show a relationship between some mental illnesses and suicides and different environmental variables such as air pollution, characterized by stress at the neuropsychological level. Despite the fact that traffic noise is also a powerful neurological stressor, studies that relate traffic noise to these mental disorders are practically non-existent.

The objective is to analyze the short-term impact that chemical air pollution, traffic noise and thermal extremes have on emergency hospital admissions due to anxiety, dementia and suicides in the city of Madrid.

This ecological, longitudinal study uses generalized linear models with Poisson link to analyze the short-term impact of the average daily concentrations of chemical pollutants (NO_2 , PM_{10} , $\text{PM}_{2.5}$, O_3), noise pollution indicators (Leq_{day} , $\text{Leq}_{\text{night}}$ and $\text{Leq}_{24\text{h}}$) and temperatures during heat waves (T_{heat}) and cold waves (T_{cold}) on daily admissions to emergency services in the city of Madrid from 2010-2013 due to anxiety (ICD-10: F32), depression (ICD-10: F40-F42) and suicide (ICD-10: X60-X84).

The results show no association between any of the chemical pollutants considered and the dependent variables studied. On the contrary, the values of Leq_{day} are associated with the three variables analyzed in lag 0 for the cases of anxiety and depression and in lag 1 for suicides, with RR: 1.20 (IC95% 1.14 1.26), RR: 1.11 (IC95% 1.06 1.16) and RR: 1.17 (IC95% 1.05 1.30), respectively, for increases of 1dB(A) in the values of Leq_{day} . An association was also found between T_{cold} and admissions for anxiety in lag 9 with RR: 1.62 (IC95% 1.18 2.22) for increases of 1°C in the values of T_{cold} .

Traffic noise can be considered an important risk factor related to the illnesses and anxiety and depression and for suicides in the city of Madrid, although new studies are needed to support the findings shown here.

1. Introduction

In the last decade numerous studies have shown the relationship between psychiatric disorders such as anxiety, depression and suicide and different environmental factors (Khan et al., 2019; Seltenrich et al., 2018), such as temperature (Kim et al., 2016), hours of daylight (Coimbra et al., 2016) and air pollution (Kim et al., 2010; Szyszkowicz et al., 2010, Biermann et al., 2009, Bakian et al., 2015, Lin et al., 2016, Ng et al., 2016; Kim et al., 2018). The primary explanation for the biological mechanism that links the association between environmental factors and suicides is that 90 percent of those who commit suicide have a prior history of psychiatric disorders such as anxiety, depression or personality disorders (Hawton and van Heerigen, 2009). There is a known association between levels of air pollution and the increase in hospital admissions due to depressive episodes and neuropsychiatric disorders (Szyszkowicz M, 2007; Lim et al., 2012). Through the mechanism of neuroinflammation (Bakian et al., 2015; Ng et al., 2016, Khan et al., 2019; Seltenrich et al., 2018), air pollution could be the neuropsychological stressor that would cause this worsening in symptoms and finally, suicide (Kim et al., 2010; Chen and Samet, 2018). On the other hand, one of the principal stressors in a city is traffic noise (Recio et al., 2016). In short-term longitudinal studies it has been shown that traffic noise affects hospital admissions for neurodegenerative diseases such as dementia (Linares et al., 2017), Parkinson (Linares et al., 2018) and multiple sclerosis (Carmona et al., 2018). An association has also been found between exposure to traffic noise and mental illnesses (Clark and Paunovic 2018), and the use of medications for depression and anxiety (Schreckenberget al., 2010; Welch et al., 2013). These stress mechanisms that affect the central nervous system are similar to those related to air pollution (Thomson et al., 2019), and seem to be the cause behind these associations (Carmona et al., 2018).

According to the WHO (WHO, 2017) depression is the principal worldwide cause of disability and affects more than 300 million people around the world. Spain is the fourth European country in terms of the number of cases of depression, affecting more than 2 million people, with a prevalence of depression and anxiety at 0.6 percent. According to the WHO, 800,000 people commit suicide every year (WHO, 2017). Spain is the sixth country in the EU in terms of the number of suicides per year, with around 3,600 cases. Suicide is also the primary cause of preventable death, with 10 daily deaths, a death rate of 7.51 deaths per 100,000 inhabitants (Eurostat, 2017). Specifically, Madrid is one of the communities in Spain with the lowest suicide rate at 2.8 suicides per 100,000 inhabitants (INE, 2019).

Despite that there are studies that show the link between admissions due to depression and anxiety and noise pollution independently, according to the above mentioned reference, there are few that analyze the combined impact, and those that do refer to mental illnesses in general, both in adults (Pun et al., 2019) and in young people (Dzhambov et al., 2018). To our knowledge there is no study that analyzes the short-term impact of both variables together, nor have we found any study that links traffic noise to suicides in the short term in the literature.

The objective of this study is to analyze and quantify the short-term impact of different environmental factors such as thermal extremes, air pollution and noise pollution on daily emergency hospital admissions due to anxiety, depression and suicide in the city of Madrid during 2010-2013.

2. Material and methods

The period of analysis is that between January 1, 2010 and December 31, 2013. The geographic area of the study is the municipality of Madrid.

2.1 Dependent and independent variables.

- *Dependent variables used were:*

Number of daily emergency admissions for anxiety (ICD-10: F32).

Number of daily emergency admissions for depression (ICD-10: F40-42).

Data were provided by the National Statistics Institute.

Daily number of suicides (ICD-10: X60-X84).

Data provided by the Statistical System of Criminality (SEC) of the Ministry of Interior.

- *Independent variables used:*

Air pollution variables: Average daily concentrations of PM_{10} , $PM_{2.5}$, NO_2 and O_3 in ($\mu g/m^3$) collected at stations in the city of Madrid. The average daily value was used from the total of the 24 stations of the Network of Remote Stations for Air Pollution Surveillance and Control of the city hall of Madrid.

Noise pollution variables: We worked with the equivalent level measured between 7 am and 11pm L_{eqday} , nighttime equivalent level 12 am to 8 am $L_{eqnight}$ and the daily equivalent level L_{eq24h} measured between 0 and 24 hours. Data correspond to the 24 stations that make up the Noise Pollution Surveillance Network of the city hall of Madrid. Data were provided by the city hall of Madrid.

Meteorological variables: Maximum daily temperatures were used (T_{\max}) as well as minimum daily temperatures (T_{\min}) registered in the observatory of reference in the city of Madrid. The data were provided by the State Meteorological Agency (AEMET).

- Transformation of variables

Prior studies carried out on emergency hospital admissions for all causes (Tobías et al., 2001) both neurological illnesses (Linares et al., 2017; Linares et al., 2018; Carmona et al., 2018) and the variables considered here have shown a functional relationship with the average daily concentrations of PM_{10} , $PM_{2.5}$ y NO_2 that is non-linear. The same occurs with values of Leq_{day} , Leq_{night} and Leq_{24h} . However, the relationship with O_3 is quadratic. That is to say, there is a value of the daily average ozone concentration ($O_{3\text{umbral}}$) above which the impact on health should be considered (Díaz et al., 2018). For Madrid this value is established at a daily average concentration of ozone of $60 \mu\text{g}/\text{m}^3$.

Thus, we created a new variable O_{3h} defined in the following way (Díaz et al., 2018):

$$O_{3h} = 0 \quad \text{if } O_3 < 60 \mu\text{g}/\text{m}^3$$

$$O_{3h} = O_3 - 60 \quad \text{if } O_3 > 60 \mu\text{g}/\text{m}^3$$

On the other hand, temperature can also influence the dependent variables considered here (Kim et al., 2016). In order to consider the possible effect of thermal extremes the existence of heat and cold waves was included.

Heat waves are characterized by the existence of a maximum daily threshold temperature ($T_{\text{threshold}}$) above which mortality due to heat increases in a statistically significant way (Díaz et al., 2015). This threshold $T_{\text{threshold}}$ for the case of the city of Madrid corresponds to a maximum daily temperature of 36°C (López-Bueno et al., 2019) based on these values we

define a new variable for the temperature of a heat wave T_{heat} in the following way (Díaz et al., 2015):

$$\begin{aligned} T_{\text{heat}} &= 0 && \text{if } T_{\text{max}} < 36^{\circ}\text{C} \\ T_{\text{heat}} &= T_{\text{max}} - 36 && \text{Si } T_{\text{max}} > 36^{\circ}\text{C} \end{aligned}$$

In the same way, for cold there exists a minimum daily temperature below which daily mortality increases in a statistically significant way. For the case of Madrid this minimum daily temperature is -2°C . Therefore, in the case of cold a new temperature for cold waves is defined in the following way: (Carmona et al., 2016):

$$\begin{aligned} T_{\text{cold}} &= -2 - T_{\text{min}} && \text{if } T_{\text{min}} < -2^{\circ}\text{C} \\ T_{\text{cold}} &= 0 && \text{if } T_{\text{min}} > -2^{\circ}\text{C} \end{aligned}$$

1.1 Methodology of analysis:

We carried out an ecological longitudinal study of time series to relate the dependent variables with the independent variables using log linear models (GLM) with link Poisson.

In this analysis, in addition to the independent variables already described we included other variables to control for trend, seasonality, day of the week and the autoregressive character of the series. Seasonalities were taken into account through sine and cosine functions of annual, semestral, quadrimestral and trimestral periodicities. Days of the week were included as dummy variables. The trend was considered with the inclusion of a counter n_1 that is equal to 1 on January 1' 2010, 2 on January 2, 2010... $n_1 = 1461$ on December 31, 2013.

Also, given that the effect of the independent variables on the dependent variables could occur over time, we created lags of up five days for $PM_{2.5}$, PM_{10} , NO_2 , Leq_{day} , Leq_{night} and Leq_{24h} ; eight in the case of O_3 ; five for T_{heat} and fourteen for T_{cold} (Linares et al., 2017, Linares et al., 2018; Carmona et al., 2018).

We used a backwards step modeling process, eliminating those variables that were not significant at the $p < 0.005$ level.

Poisson modeling allowed us to obtain relative risks (RR) associated with each independent variable that was statistically significant for increases of $10 \mu\text{g}/\text{m}^3$ in the pollution variables, 1 dB(A) for the values of Leq and 1°C for temperature variables. Attributable risk (AR) was calculated based on RR and using the Coste and Spira equation (Coste & Spira 1991)

$$AR = (RR-1) * 100 / RR.$$

The statistical software programs used were SPSS Statistics v.22 (IBM Company) and STATA/SE14.1 (StataCorp LP).

3. Results

Table 1 shows the descriptive statistics for the independent and dependent variables. In the analyzed period there were 528 suicides. The population of the city of Madrid for the period 2010-2013 was 3,218,500 inhabitants, with an annual suicide rate of 4.1 suicides per 100,000 inhabitants. There were 3,874 emergency hospital admissions for depression, the annual rate is 30.1 admissions per 100,000 inhabitants, and there were 1,996 emergency hospital admissions for anxiety, the annual rate is 15.5 admissions per 100,000 inhabitants.

Related to the compliance with the WHO guidance values (WHO, 2006), only 35 days (2.4%) exceed the threshold level of $50 \mu\text{g}/\text{m}^3$ daily average for the concentrations of PM_{10} and 29

(2.0%) for the guidance level of $25 \mu\text{g}/\text{m}^3$ daily average for the concentrations of $\text{PM}_{2.5}$. The WHO guidance values in the case of NO_2 set an annual average of $40 \mu\text{g}/\text{m}^3$ for concentrations that should not be exceeded. In our case the years 2010 and 2011 exceed this threshold, but the years 2012 and 2013 do not. The guidance values that the WHO establishes for tropospheric ozone are eight-hour values, and as such cannot be compared with the average daily concentrations that we worked with in this study. However, prior studies carried out in Madrid have established the average daily concentration of ozone at $60 \mu\text{g}/\text{m}^3$, above which ozone has an impact on mortality (Díaz et al., 2018). This value is exceeded on 28.8 percent of days. During the study period there were 37 days (2.5%) of heat wave in Madrid and 17 (1.2%) with cold waves. In terms of L_{eqday} levels, the threshold set by the WHO (WHO, 2018) of 65 dB(A) was only exceeded on one day, while the threshold for L_{eqnight} of 55 dB(A) was exceeded on 87.7 percent of nights.

Table 2 shows the RR and AR obtained based on the Poisson modeling process. It should be noted that the variable L_{eqday} is the only environmental variable that appears to be related to the three dependent variables that are the focus of this study. This association was established the same day in the case of anxiety and depression (Figure 1) and in lag 1 in the case of suicides. Only in the case of emergency admissions for anxiety is there also a mid-term association (lag 9) with temperature in the case of cold waves (T_{cold}).

From a quantitative perspective, the values of RR and AR are of the same order of magnitude for increases of 1dB(A) on levels of L_{eqday} in terms of their impact on the dependent variables. For increases of 1°C in T_{cold} , values of RR and AR for admissions for anxiety are greater than those of L_{eqday} , even though these differences are not statistically significant.

4. Discussion

The results obtained related to Leq_{day} and both admissions for depression and anxiety as well as for suicide show behavior that is different than that of air pollution, with a robust association among the three variables.

In prior studies carried out in Madrid that related traffic noise to emergency hospital admissions due to neurodegenerative diseases due to Parkinson (Linares et al., 2018) and dementia (Linares et al., 2017) and multiple sclerosis (Carmona et al., 2018), there was an association found with noise pollution, but not with the variables related to air pollution. This confirms what has been found in other studies that show how noise has a greater impact on health than does air pollution (Recio et al., 2017).

It should be mentioned that despite the fact that values of Leq_{day} are nearly entirely lower than what is recommended by the WHO (WHO, 2018), and practically the opposite happens with Leq_{night} , it is Leq_{day} that related to the dependent variables analyzed, probably because during the night, inside of buildings with closed windows the exposure to noise is not represented by the values of Leq_{night} measured in open air stations. This supports other studies on the impact of noise on neurodegenerative diseases in Madrid that also showed that Leq_{day} was associated with these hospital admissions (Linares et al., 2017; Linares et al., 2018; Carmona et al., 2018).

Research carried out related to the biological mechanism through which air pollution affects suicides appears to indicate the possible existence of abnormalities in the stress response in the hypothalamic-pituitary-adrenocortical axis (HPA) and in the neurotransmission of serotonin (Thomson EM, 2019) as principal factors. In depressed people, the hyperactivity of the HPA axis increases instability in personality disorders and in the risk of suicide (Chen and Samet 2018). A deficient serotonergic function and an altered HPA axis response contribute to increases in aggression and impulsivity (Mann JJ, 2003).

Noise functions in precisely the same way. Noise is processed as a stress factor at two levels: 1) it has a psychological impact that begins with the arrival of the sound signal to the thalamic hearing structures and culminates with the excitation of the hypothalamus, and 2) it operates at an organic level that starts with the allostatic response from the hypothalamus and, in certain circumstances, ends with one or several adverse physiological effects. In mammals, the primary mechanism that manages the physiological response to psychosocial stress is the hypothalamic-pituitary-adrenocortical axis (HPA) in coordination with the sympathetic-adrenal-medullary (SAM) system. The initial response to acute stress originates in the SAM axis with the release of catecholamine, while the HPA prolongs the physiological defensive response (Recio et al., 2016).

Cognitive impairment is a major contributor to suicide diathesis in the elderly (Mann JJ 2003), thus the effects on behavioral variables should be considered prior to the impact on suicides as occurs in the present study, which shows an immediate effect of Leq_{day} on hospital admissions for anxiety and depression (lag 0) while the effect on suicides is delayed in time (lag 1).

From a quantitative point of view, the values of RR found for increases of 1dB in the value of Leq_{day} for the three variables analyzed are of the same order as those found for emergency hospital admissions for cases of multiple sclerosis RR: 1.21 (95% CI: 1.16, 1.26) (Carmona et al., 2018), Parkinson RR 1.07 (95% CI: 1.04–1.09) (Linares et al., 2018) or dementia RR: 1.15 (95% CI: 1.11–1.20) (Linares et al., 2017). In all of these cases, the effect of Leq_{day} is also for lag 0.

There are some studies that link air pollution to suicides both in the case of NO_2 (Bakian et al., 2015; Ng et al., 2016; Lin et al., 2016;), as well as O_3 (Biermann et al., 2009; Yang et al., 2011; Kim et al., 2015) and especially in the cases of PM_{10} and $PM_{2.5}$ (Kim et al., 2010; Yang et al., 2011; Lin et al., 2016; Kim et al., 2015; Bakian et al., 2015). However, in our study in the case of Madrid there was no association between these pollutants and suicides. In the case

of NO₂ this association did appear in the initial models, but disappeared after controlling for the day of the week.

Other studies have also found similar results in terms of the lack of association between suicides and urban air pollution; these studies have controlled for multiple seasonal factors (Fernández-Niño JF et al., 2018; Astudillo-García CL et al., 2019).

From our point of view, there are various factors that could explain the lack of association between suicides and air pollution that was found in this study. On one hand, there is the low suicide rate in the city of Madrid, with 4.1 suicides per 100,000 inhabitants, which is much less than 26.9 in South Korea, 18.5 in Japan or 16 in Taiwan (WHO, 2017), location in which the most robust associations have been found between suicides and air pollution.

The daily levels of suicides in Madrid are similar to those in other studies that also failed to find an association (Fernández-Niño JF et al., 2018; Astudillo-García CL et al., 2019). Furthermore, in addition to the low number of cases in the dependent variable, Table 1 shows that low levels of pollution in Madrid, with the exception of NO₂, are lower even than those that appeared in the studies that failed to find an association (Fernández-Niño JF et al., 2018; Astudillo-García CL et al., 2019).

Our data source did not allow for separating suicides by sex or by age group, which could also hide possible existing associations, given that the older population has a greater risk of suicide (Hawton and van Heerigen, 2009) and that suicides are more numerous in men than in women (Eurostats, 2017). Thus, for example, in the study carried out in Belgium by Casas et al (Casas et al., 2017) an association was found between PM₁₀ and those over age 85 in a sample of 20,000 people who committed suicide.

These same causes could be behind the lack of association found between air pollution and hospital admissions due to anxiety and depression. Although it would seem that the

association between PM and symptoms of anxiety and depression in children and adolescents (Chen and Samet 2017) there is a more robust association between air pollution and mood disorders and even hospital admissions of adults both in the short (Mehta et al., 2015) and long term (Gao et al., 2017).

As shown in Table 2, the low temperatures of cold waves (T_{cold}) is the only environmental variable among all those considered besides Leqday that is related to emergency hospital admissions for anxiety. The robustness of the statistical association found seems to indicate that the association is not of a spurious nature. A relationship between poor mental health and experiencing energy poverty has also been found in the literature (Marmot Review Team, 2011). The evidence base typically focuses on anxiety, stress and depression associated with living in poor housing conditions, balancing bills, heating needs and debt (Thomson et al., 2017). Gilbertson et al. also found that cold, draught, and condensation are associated with anxiety (Gilbertson et al., 2012) as is the cost of energy (Kaye et al., 2012). **In this sense, the risk of suffering energy poverty in Madrid city is 23% (Sánchez-Guevara et al., 2018). This risk can reach up to 45% in single-family homes of women over 65. In those homes, where women provide the mainstay, the risk of suffering energy poverty increases between 35 and 120% with respect to the city average. This risk is mainly due to the impossibility of keeping the house heated, that is, in relation to the cold in winter, which could translate into a problem at the mental health, as observed in our study (Linares & Díaz, 2019).**

Both suicides and mood disorders of anxiety and depression are influenced by factors such as age and sex, as mentioned previously. But there are also other factors of influence, such as socioeconomic level or neighborhood physical and social characteristics that are also related to these behavioral disorders (Generaal et al., 2019). Obviously, these circumstances were not considered in this ecological, longitudinal study with aggregated data. **In particular, we cannot control for factors, such as individual socioeconomic data and neighborhoods near the**

hospital. Lifestyles and comorbidities influence also in the effect of noise and air pollution on hospital admissions. These factors may also act as confounders or effect modifiers. Some of these factors could have been controlled by adjusting confounders, in particular by introducing the deprivation index. However, it is likely that there was still some residual confounding (Barceló et al., 2016). It should be noted that we did not consider other risk factors which are present in these types of diseases, such as the existence of comorbidities which can alter the admission diagnosis (Baumgart et al., 2015). These limitations preclude extrapolating results at the individual level.

In previous studies conducted in Madrid, the value of daylight hours was available; this variable not considered here was statistically significantly related to temperature with positive correlation coefficient (Bischofberger & Díaz, 2000). The results point to less hours of light (winter season) are related to lower temperature. Therefore, the effect of the few hours of light could be related to Tcold. In this sense, the association found at lag 9 for Tcold and anxiety could also show this effect.

On the other hand, we used data that were averaged from various measurement stations, and therefore, these measurements do not represent individual exposure. Another bias may be found in the heterogeneity of air pollutant and noise measurement stations; given that the majorities are urban stations there are also some background stations. Despite this, the applied methodology is common in this type of study (Samet et al., 2000). These biases are minimized by the inclusion of control variables in the models, such as trend, seasonality and the autoregressive character of the series. Finally, as occurs in all of the studies that analyze the effect of air pollution on existing health variables, there is a problem of misalignment (Gotway & Young 2002; Gelfand AE, 2010; Barceló et al., 2016).

The results obtained in this study clearly show that traffic noise is a variable that is related to hospital admissions for personality disorders such as anxiety and depression and suicide in the

city of Madrid. The existence of other studies in which daytime traffic noise is related to emergency hospital admissions for different neurodegenerative diseases supports the association found here. Carrying out similar studies in other cities with higher suicide rates should corroborate the results that have been found in this study.

DISCLAIMER

The authors declare they have no actual or potential competing financial interests. This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health.

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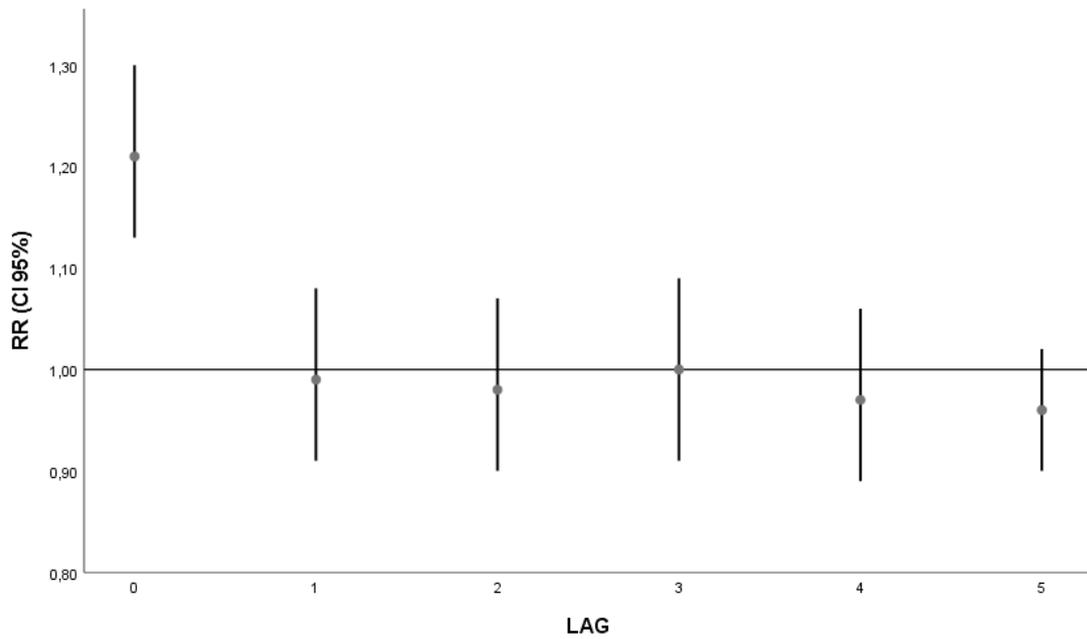


Figure 1a. Relative risks corresponding to increases of 1dB(A) in Leq_{dia} for different lags for hospital admissions for anxiety.

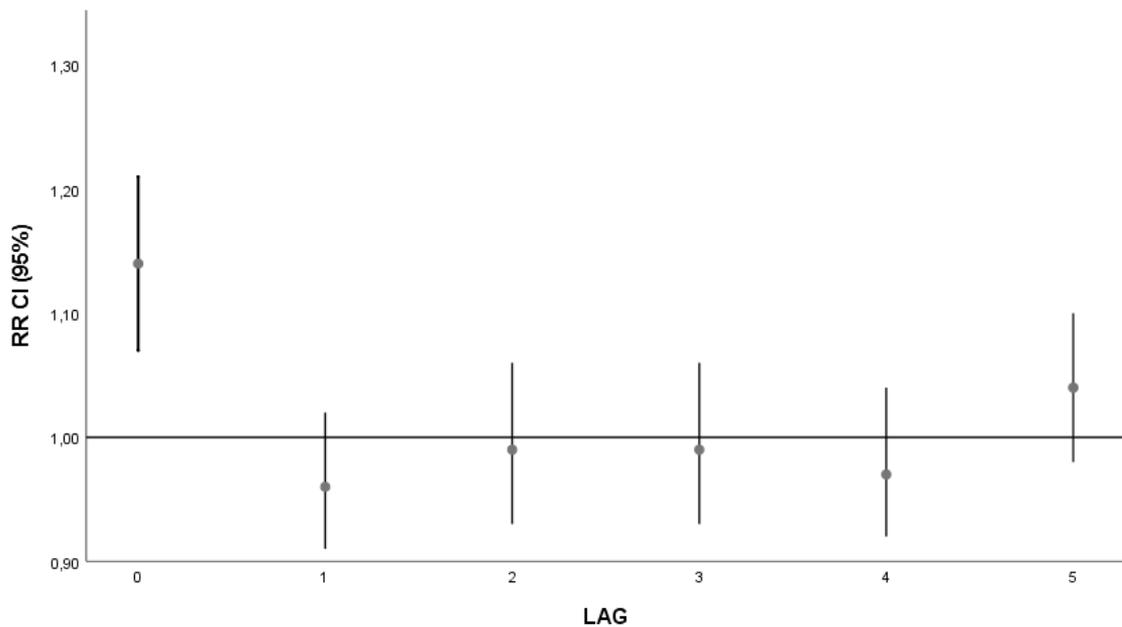


Figure 1b. Relative risks corresponding to increases de 1dB(A) in Leq_{dia} for different lags for hospital admissions for depression.

Variable	n	Mean	Std. Dev.	Min	Max
Maximum Temperature (°C)	1461	20.3	9.3	0.1	40.6
Minimum Temperature (°C)	1461	10.3	6.8	-3.8	25.7
NO ₂ (µg/m ³)	1461	40.5	17.0	8.0	108.9
PM ₁₀ (µg/m ³)	1461	21.9	12.5	4.6	152.2
PM _{2.5} (µg/m ³)	1461	11.5	5.3	3.6	51.5
O ₃ (µg/m ³)	1461	45.9	21.6	4.0	111.6
Leq24h (dB)	1461	60.0	0.8	57.0	62.9
Leq Day (dB)	1461	61.9	1.1	58.0	65.1
Leq Night (dB)	1461	56.2	1.1	52.5	65.2
Anxiety (CIE-10: F32)	1461	1.37	1.2	0	7.0
Depression (CIE-10: F40-F42)	1461	2.62	1.9	0	10.0
Suicide (CIE-10: X60-X84)	1461	0.36	0.6	0	4.0

Table 1. Descriptive statistics of all the variables used (2010-2013).

SUICIDE	RR	IC (95%)	AR (%)	IC (95%)
Leq Day (dB) Lag 1	1.17	1.05 - 1.30	14.5%	4.8% – 23.0%
ANXIETY				
LeqDay (dB) Lag 0	1.20	1.14 – 1.26	16.7%	12.8% - 20.6%
Tcold (°C) Lag 9	1.62	1.18 – 2.22	38.3%	15.2% - 54.9%
DEPRESSION				
LeqDay (dB) Lag 0	1.11	1.06 – 1.16	9.9%	5.7% - 13.8%

Table 2: Relative Risks (RR) and Attributable Risks (AR) for the variables suicide, anxiety and depression. *The risk is calculated for an increment of 1dB in Leqday and 1° Centigrade in Tcold*

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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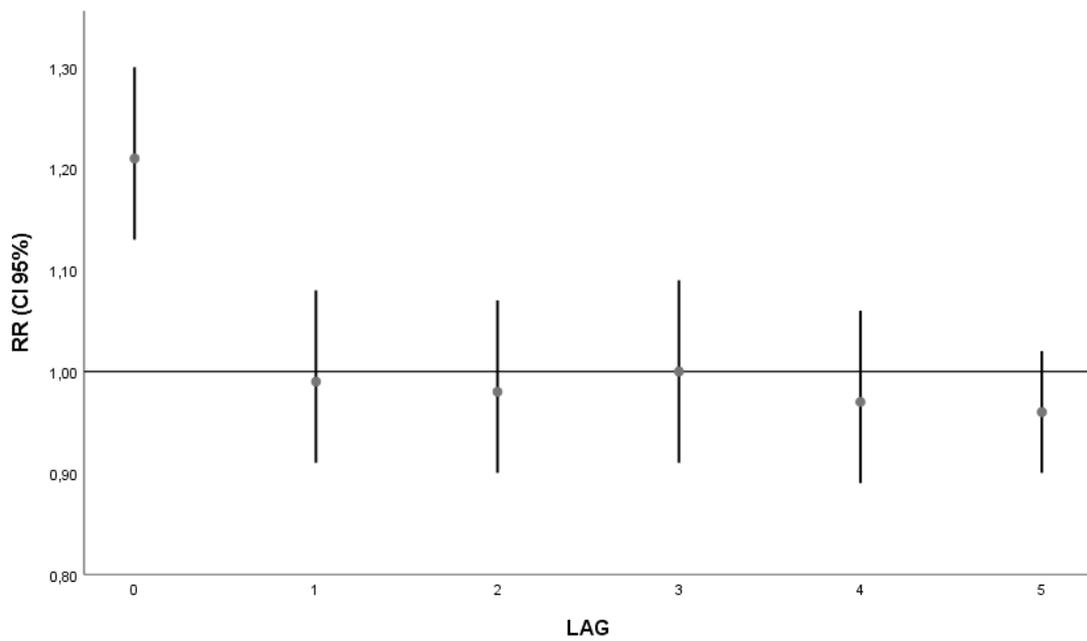


Figure 1a. Relative risks corresponding to increases of 1dB(A) in Leq_{dia} for different lags for hospital admissions for anxiety.

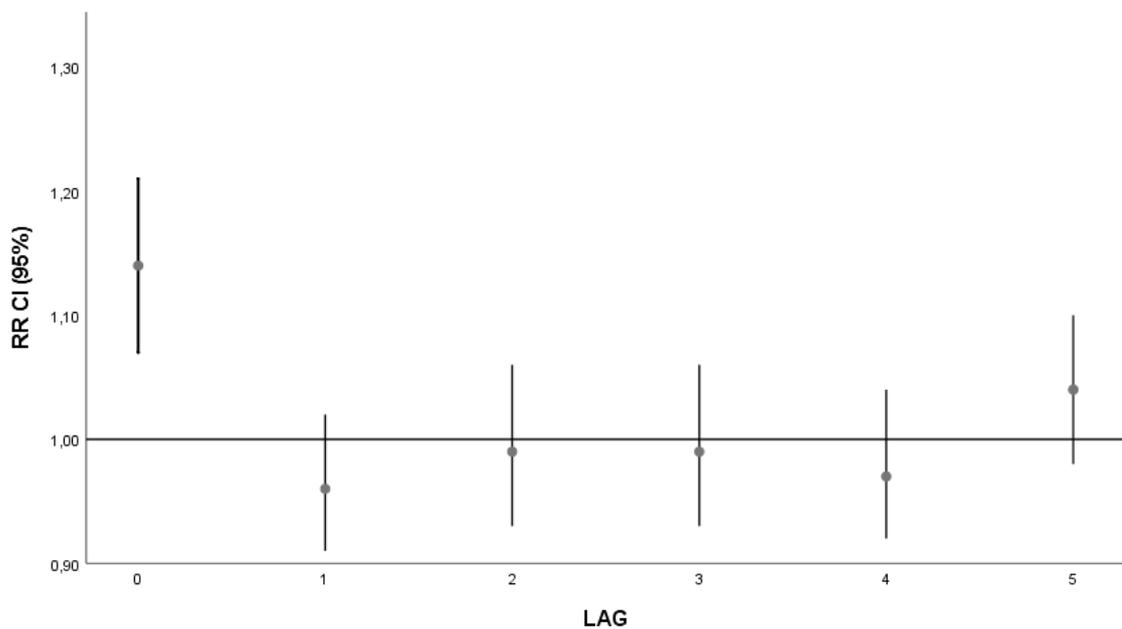


Figure 1b. Relative risks corresponding to increases de 1dB(A) in Leq_{dia} for different lags for hospital admissions for depression.

Graphical abstract

Highlights

- The results show no association between chemical pollutants and the dependent variables.
- Leq_{day} are associated in lag 0 for the cases of anxiety and depression.
- Leq_{day} are associated in lag 1 for suicides.
- An association was also found between T_{cold} and admissions for anxiety in lag 9.

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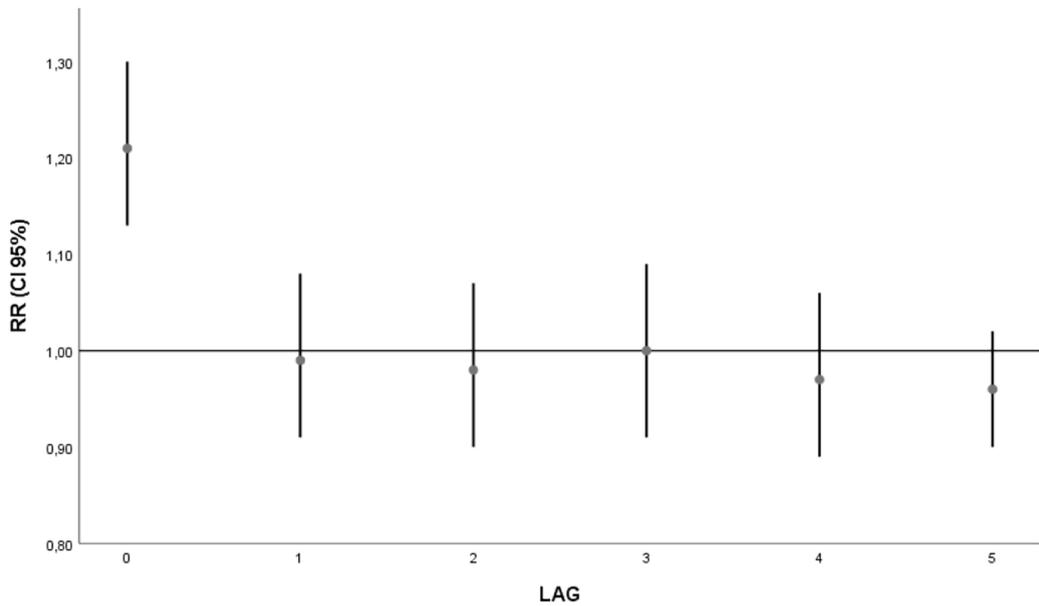
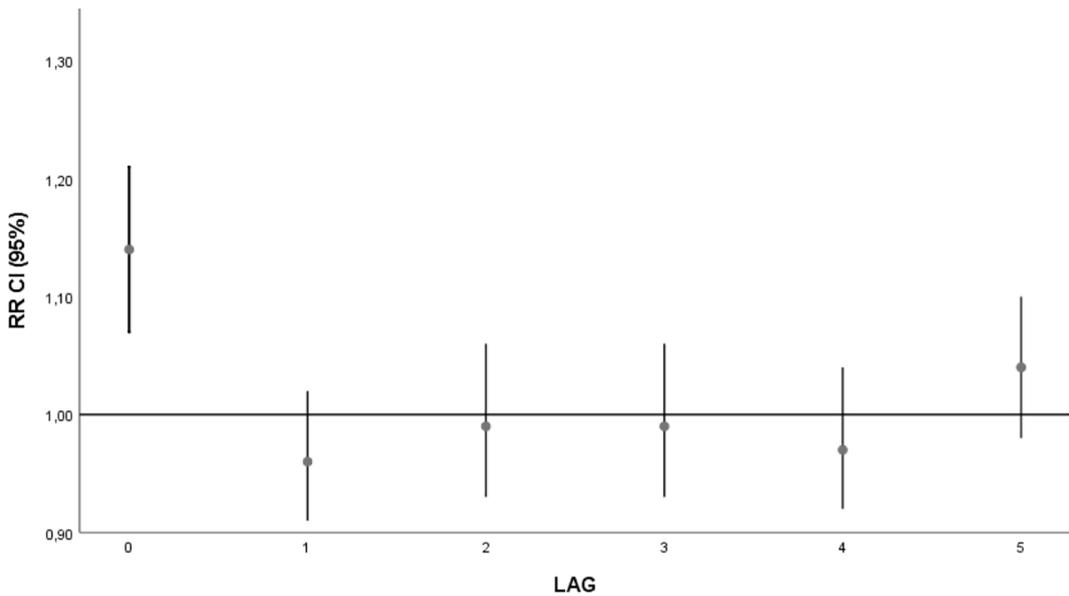
A**B**

Figure 1