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Effects of air pollution on daily hospital admissions for cardiovascular diseases in Castilla-La Mancha, Spain: a region with moderate air quality

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Abstract

Adverse impacts of air pollution on human health have been well documented in Spain; however, very few have been conducted in the Spanish region of Castilla-La Mancha (CLM). CLM is an extensive region with a low population density, little industrial production, and moderate air pollution level. The aim of the study was to assess the relationship between the risk of hospital admission for cardiovascular disease (CVD) and exposure to $PM_{2.5}$, PM_{10}, and NO_2 in CLM during 2006–2015. Daily air pollution concentration, temperature, and relative humidity were monitored from the air quality monitoring stations in CLM. A time-series analysis with generalized linear model was used to examine the effects of air pollution on hospital admissions by controlling for long-term trend and other potential confounders. The effect modifications by sex and age (15–64; ≥ 65 years) were examined. Lagging exposure concept was used to analyze a possible latency period in cumulative exposure-pollution analyses. Relative risks (RR) of CVD admissions at the same day (lag 0) and to 7 days after exposure (lag 7) were calculated. Relative risks of CVD admissions (for an increase of 10 μg m^{-3} in concentration of air pollutant) were calculated. The elderly group (≥ 65 years) were the most susceptible group to the effect of air pollution, whereas the estimated effect by sex was significantly different depending on the age group. The potential utility of these results may help for syndromic surveillance during future similar air pollutant concentrations, where an increase in the use of health services among the vulnerable groups could be unexpected by the emergency department.

Keywords Cardiovascular diseases · Air pollution · Hospital admissions · Time-series, Castilla-La Mancha · Spain

Introduction

Cardiovascular diseases (CVD), a class of disorders involving the heart and blood vessels, contribute to about one-third of deaths worldwide (WHO 2017). CVD have also been ranked as the leading cause of death and disability in European countries, as well as in Spain (Amor et al. 2014). Patients with CVD share many risk factors such as obesity, hyperlipidemia, hypertension, smoking, poor nutrition, and inactive lifestyle (Riegel et al. 2017). The elderly population is the group who present the highest susceptibility in CVD risk factors (North et al. 2012). However, sex differences lead to discrepancies in CVD risk factors which may be attributed to sex hormones and their associated receptors (García et al. 2016). Air pollution may also be considered a risk factor and differs from the previous risk factors because exposure to air pollution, for the large majority of the world's population, is unavoidable. Therefore, even though the individual risk estimates for exposure to air pollution are relatively small compared to the cardiovascular risk factors presented previously, since exposure to air pollution is ubiquitous, the overall population attributable risk and subsequent burden are significant (Nawrot et al. 2011).

Particulate matter (PM) and nitrogen oxides (NOx) are two of the most prominent air pollutants. PM is a complex mixture of extremely small particles and liquid droplets made up of acids, organic chemicals, metals, and soil or dust

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particles (Anderson et al. 2012). PM tends to be categorized, measured, and regulated in relation to particle size, called coarse particles (PM_{10}, particles with a diameter of 10 µm or less) and fine particles ($PM_{2.5}$, diameter of 2.5 µm or less). Generally, the scientific studies about health effects have been based on PM_{10}, since $PM_{2.5}$ has been always monitored later and less frequently, even though it has been suggested that $PM_{2.5}$ is more harmful to human health than PM_{10} (Hassanvand et al. 2017). Moreover, only a limit has been set for its annual concentration, so a standard for a daily $PM_{2.5}$ concentration is still missing in Europe (European Directive 2008/50/CE).

The sources of PM may be natural, such as forest fires and mineral dust released, or the result of anthropogenic activities, such as industrial facilities, power plants, vehicular traffics, and incinerator (Adams et al. 2015), while major sources of NO_2 are usually anthropogenic emission such as vehicles, power plants, and other forms of fuel burning (Richmont-Bryant et al. 2017; Constantin et al. 2020).

Although several studies have been conducted to assess the effects of air pollution on human health in different regions of Spain (Medrano et al. 2005; Ballester et al. 2006; de Pablo et al. 2006; Gabriel et al. 2008; Amor et al. 2015; Santurtun et al. 2017; Borge et al. 2018), very few have been carried out in Castilla-La Mancha (CLM), Spain (de Pablo et al. 2013; Monsalve et al. 2013). Earlier Spanish studies indicated the substantial variability in cardiovascular risk factors prevalence between autonomous communities (Medrano et al. 2005; Gabriel et al. 2008). Recently, the Mortality Atlas of Castilla-la Mancha that has just been published showed that CVD were the leading cause of death in the region during 2003–2014 (Gomez and Palmí 2020). So, an analysis was conducted in our study to assess the overall and sex/age-specific associations between air pollutants ($PM_{2.5}$, PM_{10}, and NO_2) and hospital emergency admission for CVD in this Spanish autonomous community during 2006–2015. To the best of our knowledge, this is the first study to examine the associations between exposures to air pollutants and emergency hospital admissions in CLM due to CVD. Unlike most previous studies, where the effects of CVD in large cities with high pollution were evaluated, this work covers cities of the region of CLM with moderate air quality. Therefore, this study aims to detect the acute effects of exposure to $PM_{2.5}$, PM_{10}, and NO_2 on cardiovascular hospital admissions within a 10-year period in four cities of CLM.

Material and methods

Study area

The autonomous community of CLM is located in the middle/southeast of Spain (Fig. 1) and it is bordered by Madrid, the capital of Spain, to the north and the west. CLM is delimited by the Central Mountain Chain in the north, by the Iberian Mountain Chain in the northeast, and by the Mountains of Toledo. The region is made up of five provinces:

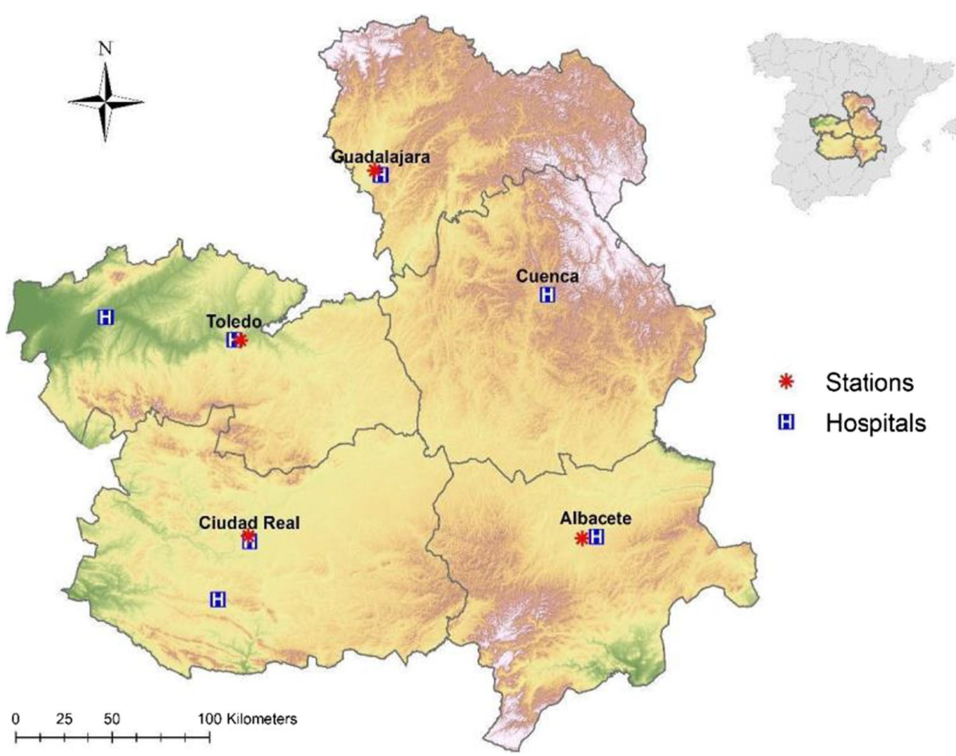

Fig. 1 Map of Castilla-La Mancha region in Spain and locations of air quality monitoring stations and hospitals

Albacete, Ciudad Real, Cuenca, Guadalajara, and Toledo (Fig. 1). CLM covers an area of 79,463 km^2, which in 2015 was home to 2,048,900 inhabitants (Eurostat 2018), and it is the most sparsely populated autonomous community of Spain (representing approximately 4.4% of the country's population). CLM has a continental Mediterranean climate, so the most important factors of this aspect are extreme temperatures, with very hot summers and very cold winters. The summer season is dry, and the temperature often exceeds 30.0 °C. In contrast, in winter the temperatures frequently fall below 0 °C (reaching even –20.0 °C) with sporadic snowfalls (Nájera et al. 2009). Rainfall is not copious, and it shows a pronounced gradient from the central region (around 400 mm per year) to mountainous zones (more than 1000 mm per year).

Data

Data from the occurred CVD events over a period of 10 years (2006–2015) were collected from hospital admission records by the called Minimum Basic Data Set (MBDS). MBDS, supported by the Ministry of Health of Spain, is the largest administrative dataset on hospitalized patients, as well as the main source of information on morbidity in patients receiving care. This system used the International Classification of Diseases (ICD-9-CM) until December 2015 and the ICD10ES (a Spanish translation of the ICD10CM) thereafter. So, for this study, the selection was made with those patients who attended the emergency department and were admitted for cardiovascular disease according to the ICD-9-MC: heart diseases (410 acute myocardial infarction; 413 angina pectoris; 427 cardiac dysrhythmias; 428 heart failure) and cerebrovascular diseases or stroke (430–432 hemorrhagic stroke; 433–436 ischemic stroke).

The air pollution monitoring network of CLM registers levels of the air pollutants and meteorological variables (temperature and relative humidity (RH)) (JCCM 2020a). The air pollution recording stations used for this study are sited in the cities Toledo, Albacete, Guadalajara, and Ciudad Real (Fig. 1). The suburban background stations of Toledo, Albacete, and Ciudad Real and the urban background stations of Guadalajara are located in residential and commercial areas, so, consequently, the main source of emission that affects these stations are traffic and combustion in residential and commercial sectors.

$PM_{2.5}$ is only measured in Toledo and Albacete air quality monitoring stations. PM_{10} and NO_2 are measured in all stations (JCCM 2020b). The instruments for real-time monitoring of pollutants are chemiluminescence (NO_2) and beta ray attenuation monitor (PM_{10} and $PM_{2.5}$) (JCCM 2020b). The daily average and 95^{th} percentile values were calculated from the hourly air pollutant and meteorological data through the Openair package 2.6–1 (Carslaw and Ropkins 2012), only in those days in which at least 75% of the hourly values were available; otherwise, it was identified as a missing value and it was not a part of the dataset for analysis.

Statistical analysis

In this study, the hypothesized association between the 95^{th} percentile of daily air pollutant concentrations as the predictor variable, and the number of cardiovascular hospital admission in CLM were analyzed using quasi-Poisson regression in single-pollutant generalized linear model (GLM) with Distributed Lag Model (DLM) at different lags (from 0 to 7 days) (Bhaskaran et al. 2013). Hospital admission data are Poisson distributed and Poisson regression provides an estimation of the relative risk (RR) as $RR = \exp(\beta)$, where β is the regression coefficient associated with a unit increment in a pollutant. The advantage of the Poisson regression model is the ability to estimate the RR of the health effect with the increase of exposure by unit. Air pollution and hospital admission relationships were conducted for sex (men and women) and age groups (adults 15–64 years, and elderly ≥ 65 years). Moreover, in order to address the possible exposure misclassification while using pollution data from one central monitoring station, we did a sensitivity analysis by restricting the CVD hospital admission to the nearest hospital to the air quality monitoring station in the case of Toledo City.

A penalized smoothing spline was used for filtering out seasonal patterns and long-term trends in daily hospitalization, as well as daily mean temperature, daily mean RH, day of week, and public holidays which were included in the model as dummy variables. To reduce the problems associated with multiple testing and model selection strategies, we followed some previous time series studies to select a priori model specification and the degree of freedom (df) for time trend and the meteorological variables (Qiu et al. 2013). A df of 7 per year for time trend, a df of 6 for mean temperature of the current day, and a df of 3 for the current day humidity were used.

The differences in the number of daily admissions between groups, defined according to if the daily 95^{th} percentile pollutant concentration of the pollutant exceeding or not the limit value defined by WHO (WHO 2016), were performed by the nonparametric Mann–Whitney *U* test. WHO guideline values (WHO 2016) are more stringent than European Union (EU) air quality Directive (2008/50/EU). Furthermore, the existence of the differences between the number of cardiovascular hospital admissions and pollutant concentration decile was carried out by means of an analysis of variance (ANOVA, Tukey post hoc test).

The analysis was carried out in the R environment, version 4.0.2, for statistical computing and visualization (Gasparrini 2011). Functions in splines and dlmn package of R

(Gasparrini 2011) were used to build GLMs as described (Bhaskaran et al. 2013). Graphics of smooth trends were estimated with Openair 2.6–1 (Carslaw and Ropkins 2012).

Results

A total of 109,974 cardiovascular hospital admissions derived from the emergency department were recorded in CLM, from January 1, 2006, to December 31, 2015 (Table 1). Table 1 also shows the average values, standard deviation, and range of the daily admissions values and their distribution according to sub-diagnoses (cardiac disease or stroke), age, and sex.

On the other hand, the 10 years daily mean pollution concentrations for $PM_{2.5}$, PM_{10}, and NO_2 and meteorological conditions of temperature and RH in Toledo, Albacete, Guadalajara, and Ciudad Real were 10.7 and 13.8 μg m^{-3} for $PM_{2.5}$ (only are measured in Toledo and Albacete); 29.1, 35.9, 25.1, and 27.1 μg m^{-3} for PM_{10}; 22.8, 14.6, 25.2, and 10.6 μg m^{-3} for NO_2 (Table S1). The average pollutant concentrations were not above the WHO standard air quality threshold (WHO 2016). The daily ambient temperatures were 15.9, 16.2, 15.6, and 16.7 °C and the RH was 57.8, 60.6, 57.1, and 57.2%, respectively (Table S1).

Figure S1 shows the evolution of NO_2 measured by the different stations during the study period. As can be observed in Figure S1 for NO_2, the Guadalajara and Toledo stations provided similar information and with slightly higher values than those reported by the Ciudad Real and Albacete stations. Regarding the trend of PM_{10}, Figure S2 shows the evolution during the study period for each station. Although similar trends were observed in the evolution of this pollutant, there were differences between the different stations. Since 2010, differences between stations below 10 μg m^{-3} were usually observed. However, as can be seen in Figure S3, a large difference in the average $PM_{2.5}$ values was observed between the measurements collected in the Albacete and Toledo stations during the 2013–2015 period. This abnormal behavior could not be explained, and it was also described by a MITECO air quality report (MITECO 2013).

To test the statistical relationship between daily air pollutant concentrations, temperature, and RH in the different cities, the non-parametric bootstrap test of the Pearson correlation was employed (Table 2). PM_{10}, $PM_{2.5}$, and NO_2 were positively correlated with each other. The highest and closest correlation between PM_{10} and $PM_{2.5}$ (0.625–0.547, strong–moderate) in Toledo and Albacete, respectively, could confirm that these pollutants have a common source. However, weak and very weak correlations were found between $PM_{2.5}$ and NO_2 and PM_{10} and NO_2 in the four cities. Correlations between the other variables were negligible.

Exposure to pollutants, even for a few hours, can trigger cardiovascular disease and related deaths from heart attack, stroke, arrhythmia, sudden cardiac arrest, and heart failure (Nel 2005; Mustafic et al. 2012; Gardner et al. 2014). For this reason, we took into account the 95th percentile daily pollutant concentrations to assess the relationship between CVD and each air pollutant.

Figures 2, 3, and 4 provide the relationship between daily admissions at 10 quantile groups of the 95th percentile value of each air pollutant at lag 0. As can be seen in Fig. 2, there was a clear trend to increase the number of hospital admissions when increasing the concentration of $PM_{2.5}$ in Toledo, both when admissions are only in the Toledo hospital and for the whole of CLM. The pairwise comparisons show significant differences between the last and the rest of deciles ($p < 0.001$).

Concerning PM_{10} (Fig. 3), again in Toledo, there was an increasing trend in the number of admissions when the

Table 1 Summary statistics of total hospital admissions for CVD (including mean, standard deviation, minimum and maximum values) and number of admissions per day during 2006–2015 in CLM, Spain

Variables	Total admissions	Number of admissions per day	
		Mean (SD)	Min–Max
Total cardiovascular diseases			
Age			
Adults (15–64)	20,300	5.1 (2.4)	1–15
Elderly (≥ 65)	89,674	22.1 (6.0)	1–46
Sex			
Men	51,925	14.3 (4.4)	1–34
Women	58,049	12.8 (4.2)	1–28
Sub-diagnoses			
Cardiac diseases	73,677	18.2 (5.5)	1–39
Stroke	36,297	8.9 (3.1)	1–25
Cardiac disease, sex/age admission			
Women (15–64)	3271	1.5 (0.8)	1–6
Men (15–64)	10,668	2.9 (1.6)	1–10
Women (≥ 65)	31,596	7.8 (3.2)	1–20
Men (≥ 65)	28,142	6.9 (2.9)	1–20
Stroke disease, sex/age admission			
Women (15–64)	2063	1.3 (0.6)	1–5
Men (15–64)	4298	1.6 (0.9)	1–8
Women (≥ 65)	14,995	3.8 (1.8)	1–13
Men (≥ 65)	14,941	3.8 (1.9)	1–13

CVD, cardiovascular diseases; *SD*, standard deviation; *Min*, minimum; *Max*, maximum; Classification of total cardiovascular diseases according to the International Classification of Disease (ICD-9MC): heart diseases (410 acute myocardial infarction; 413 angina pectoris; 427 heart dysrhythmias, 428. heart failure) and cerebrovascular diseases or stroke (430–432 hemorrhagic stroke; 433–436 ischemic stroke)

Table 2 Pearson correlation coefficients between atmospheric variables (i.e., air temperature and RH) and the air pollutants ($PM_{2.5}$, PM_{10}, and NO_2)

Albacete	PM_{10}	$PM_{2.5}$	NO_2	RH	Ciudad Real	PM_{10}	NO_2	RH	Guadalajara	PM_{10}	NO_2	RH	Toledo	PM_{10}	$PM_{2.5}$	NO_2	T
$PM_{2.5}$	0.547				NO_2	0.348			NO_2	0.314			$PM_{2.5}$	0.625			
NO_2	0.067	0.157			RH	−0.218	0.110		RH	−0.166	0.058		1144	0.297	0.327		
RH	−0.347	−0.029	0.133		T	0.236	−0.230	−0.808	T	−0.228	−0.122	−0.741	1144	−0.149	0.097	0.137	
T	0.372	0.086	−0.278	−0.726									T	0.129	−0.047	−0.245	−0.765

Bold significance PM2.5, NO2, RH and T

concentration of this pollutant increased. Regarding Ciudad Real and Albacete, there was not a clear trend. Only in Guadalajara was there a significant difference between the 6th and 10th deciles and the first five deciles, so at a higher concentration of PM_{10} (46.5–48.9 μg m^{-3}), there was a significant increase in hospital admissions.

In the case of NO_2 (Fig. 4), the trend was similar in all the studied cities. Furthermore, every NO_2 concentration value was assigned a decile in order to find the threshold at which cardiovascular admissions increased significantly in CLM. From the analysis of Fig. 4, significant differences were observed for values close to 60 μg m^{-3}, in Toledo and Guadalajara (Toledo: (54.7, 61.4); Guadalajara: (58.7, 63.4)) and 25 μg m^{-3} in Ciudad Real and Albacete (Ciudad Real: (26.3, 29.3); Albacete: (25.6, 28.8)).

We carried out a division of the 95th percentile daily concentrations according to the WHO guide value (WHO 2016). Between these two groups, the number of daily hospital admissions was studied. Thus, in these two established groups, the distribution of the number of admissions was studied (see box plot, Figures S4, S5, S6, and S7). The existence of significant differences between the two groups was analyzed using the Wilcoxon non-parametric test.

The number of hospital admissions was higher the days in which the 95th percentile of the pollutants exceeded the WHO guideline values. The Wilcoxon test confirmed the existence of statistically significant differences between daily hospital admission and the mean values of pollutants, except in Albacete for $PM_{2.5}$ and PM_{10}. The value of the test criterion *W*, in the one-sample Wilcoxon signed-rank test, and the *p*-values are summarized in Table S2.

The link between CLM hospital admission and air pollutants over the total population (women, men, and two age groups) explained with the models at lag 0 and lags of up to 7 days (lag 7) is shown in Figure S8 and Table 3. The RR and 95% confidence intervals (CI) associated with an increase of 10 μg m^{-3} in pollutant concentration were obtained for each pollutant after adjusting seasonality and long-term trends, day of the week, public holiday, and weather variables. Table 3 also shows both, the admissions exclusively from the Toledo reference hospital, to address possible exposure misclassification when using pollution data from the closest monitoring station, and the whole of CLM. As can be observed, the results obtained were both similar.

In general (except for the measurement of $PM_{2.5}$ at the Albacete station), in all cities and for the whole pollutants, the effect on CVD admissions was more immediate, strongest, on the current day, and with close similar RR behavior. For PM_{10} and NO_2, the effect is stronger again at lags 2 and 3 and lag 6 or 7 (Table 3). At lag

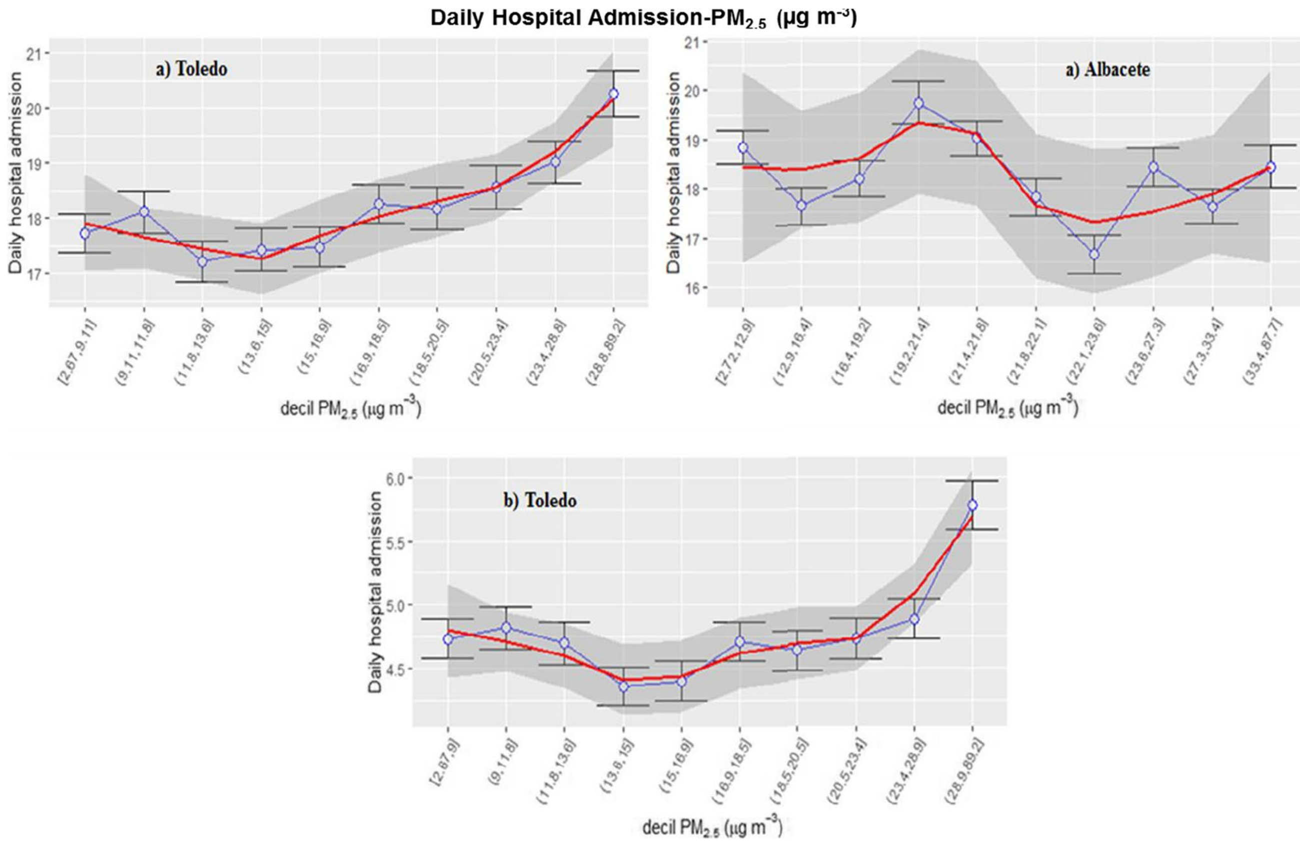

Fig.2 Daily average CVD hospital admissions vs deciles of the 95th percentile concentration of $PM_{2.5}$. **a** CLM hospital admissions in Toledo and Albacete. **b** Exclusively hospitalization to the nearest hospital to the air quality monitoring station in Toledo

0, for every 10 µg m^{-3} increase in $PM_{2.5}$, the RR of the hospital admission was 1.028 (CI: 1.009–1.048) in Toledo station, and 1.013 (CI: 0.997–1.028) in Albacete station, then the RR decreases in both cities until lag 4, with RR values of 1.013 (CI: 0.993–1.34) and 1.008 (CI: 0.991–1.025), respectively. For PM_{10}, an increase between 1.013 and 1.026 was found for each 10 µg m^{-3} of the pollutant increases. NO_2 was associated with the highest effect at lag 0 in the four stations (especially in Albacete and Ciudad Real stations) with a 1.042 and 1.035 per each 10 µg m^{-3}, respectively. In addition, at lags 2–3, the RR decreased and reached a close value (between 0.990 and 0.995) for the studied cities. This significant effect observed with NO_2, not always with PM_{10}, and never with $PM_{2.5}$ disappeared when only the admission at the nearest hospitals was analyzed (Table 3).

Moreover, according to our results, the RR of $PM_{2.5}$, PM_{10}, and NO_2 increase with advancing age (aged $\geq$ 65 age), in both sexes (Tables 4, 5, and 6). With regard to the association between $PM_{2.5}$ and hospital admissions for CVD (Table 4) at lag 0, the RR showed a higher value to the elderly ($\geq$ 65). For PM_{10} (Table 5), the differences of the RR between age and sex were less pronounced than $PM_{2.5}$. Moreover, when the RR were significant, it reached lower values than in the case of $PM_{2.5}$. With regard to NO_2 (Table 6), the significant RR values were also lower than those reached by $PM_{2.5}$ and with hardly any differences by age and sex.

Discussion

CVD have been among the diseases with the highest mortality during 2003–2014 in the region, which recently has been published in the Mortality Atlas of Castilla-La Mancha (Gomez and Palmí 2020). This 10-year study has demonstrated the significant association between daily hospital admissions for CVD and daily concentrations of $PM_{2.5}$, PM_{10}, and NO_2. CLM may be assumed to have a moderate air quality in comparison with other parts of Spain such as Madrid (Borge et al. 2018) or Barcelona

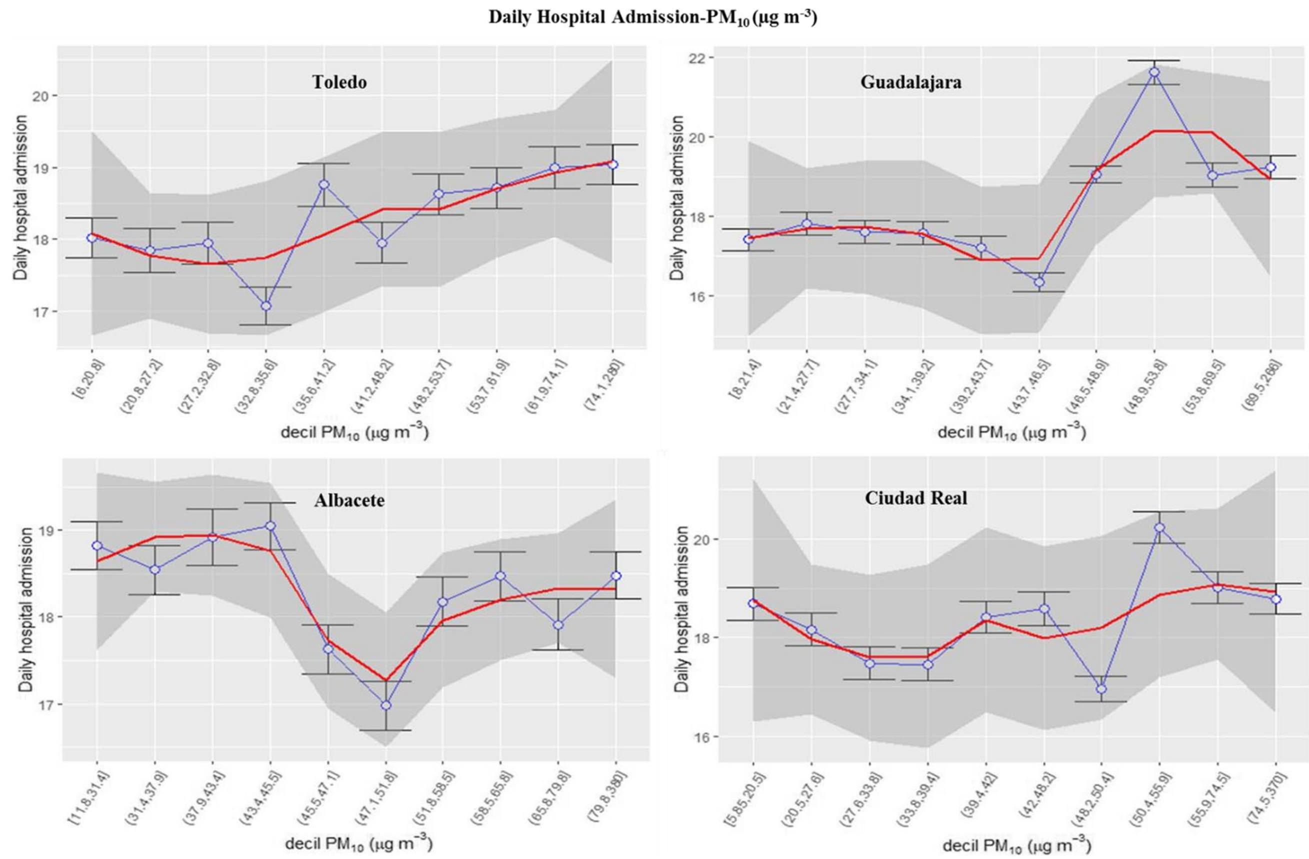

Fig. 3 Daily average CVD hospital admissions vs deciles of the 95th percentile concentration of PM_{10} during the study period

(Soret et al. 2011). While having a very low median level of $PM_{2.5}$ (10.7 μg m^{-3} in Toledo) compared with regions that are considered to have good air quality like Colorado, USA (7.7 μg m^{-3}) (Shah et al. 2013), or bad air quality like Beijing (94 μg m^{-3}) (He et al. 2017), there were days in CLM (Table S1) with high levels of air pollution ($PM_{2.5}$ up to 23 μg m^{-3} in Albacete, and 19 μg m^{-3} in Toledo). Despite CLM's seemingly relatively low pollution levels measured, ambient concentrations of $PM_{2.5}$, PM_{10}, and NO_2 have been correlated with negative health effects in our study. So, it should be advisable to adapt the current EU air quality standards to WHO guidelines which is stricter.

The effect of air pollution on hospital admission in CLM was statistically significant at some, not all, lag structures (Tables 3, 4, 5, and 6). Studied pollutants were significantly associated with increased risk of cardiovascular hospital admissions, especially at current day (lag 0). However, the risk increased again after lag 4 in men and lag 6 in women. Regarding age groups, adult men again showed effect at lags 3 and 5; however, women did not show effect until lag 7. Moreover, adult men seemed to have a higher risk of being admitted to the hospital for CVD than adult women since they had generally higher RR values.

In the case of the measurement of NO_2, there was higher uniformity in the trends shown by the measurement of the different stations and the number of hospital admissions in the region. However, there was a discrepancy between the PM values in Albacete and the rest of CLM. There are two possible explanations. First, it could be due to the technique used in the determination of PM (beta attenuation). Second, the behavior between PM and chemical pollutant (NO_2) is different (e.g., dispersion and reactivity); it is more homogeneous in the case of the chemical pollutant. Moreover, it should be noted that, as observed in Albacete and Ciudad Real, it seems that even at values lower than those established as a guide by the WHO (WHO 2016), a significant increase in the number of hospital admissions was observed.

There is a substantial body of epidemiologic literature showing a clear and consistent association between concentrations of ambient $PM_{2.5}$, PM_{10}, and NO_2 and CVD (Gold et al. 2000; Ballester et al. 2006; Miller et al. 2007; Pope

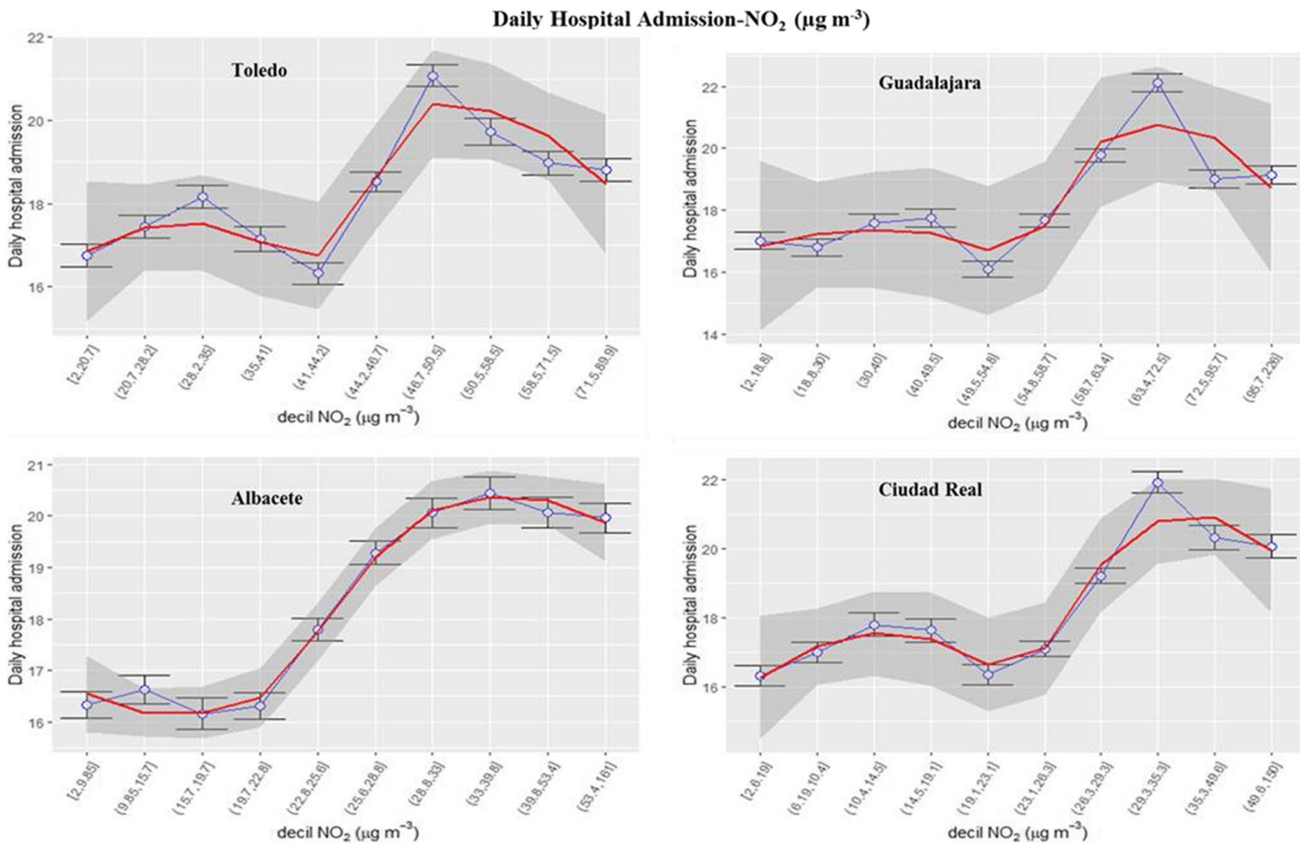

Fig. 4 Daily average hospital admissions due to CVD per decile of the 95th percentile values of NO_2 during the study period

et al. 2011; Cesaroni et al. 2014; Santurtun et al. 2017; Liu et al. 2015; Vahedian et al. 2017; Collart et al. 2018; Sanyal et al. 2018; Liu et al. 2019; Phosri et al. 2019; Amsalu et al. 2019; Franco et al. 2020). The association between these pollutants and CVD was reported worldwide for high levels of pollutants or even in a setting where pollutant levels were within ambient air quality standards European Directive 2008/50/EC or WHO guideline (WHO 2016), such as in our work. However, there is evidence that $PM_{2.5}$ and NO_2 have a steeper exposure–response curve at low concentrations, indicating that increases in low concentrations intensify negative health effects more than equivalent increases at higher concentrations (Burnett et al. 2018; Hanigan et al. 2019).

If we compare our results with some of those studies, our findings are consistent with the existing literature. Studies in Beijing, China, where the mean daily $PM_{2.5}$ concentration was 76.9 µg m^{-3}, found that for every 10 µg m^{-3} increase in the $PM_{2.5}$ concentration from the previous day to the current (lags 0–1), there was a significant increase in total CVD admissions (0.30, 95% CI: 0.20–0.39%), with a strong association for older adults (aged ≥ 65 years) (Amsalu et al. 2019). Moreover, Phosri et al. (2019) reported in their study in Bangkok (Thailand) that exposure to PM_{10} and NO_2 poses a significant risk of cardiovascular admission with estimates of 1.28% (95%, CI: 0.87–1.69) and 1.04% (95%, CI: 0.68–1.41), for each 10 µg m^{-3} increase in the pollutant, respectively. In this study, the daily mean concentration values reached were 41.6 µg m^{-3} for PM_{10} and 41.8 µg m^{-3} for NO_2.

Within the ESCAPE Project (Cesaroni et al. 2014), the study of long-term exposure to $PM_{2.5}$ and incidence of acute coronary events in 11 European cities reveals a positive association below the current annual European limit value of 25 µg m^{-3} for $PM_{2.5}$ (1.18, 1.01–1.39, for 5 µg m^{-3} increase in $PM_{2.5}$) and below 40 µg m^{-3} for PM_{10} (1.12, 1.00–1.27, for 10 µg m^{-3} increase in PM_{10}). In the Spanish multicity study within the EMECAS Project (Ballester et al. 2006), the evaluation of the short-term effect of NO_2 and PM_{10} on cardiovascular admissions, with mean concentrations from 23.4 µg m^{-3} (Castellón) to 76.2 µg m^{-3} (Valencia) for NO_2 and from 32.8 µg m^{-3} (Zaragoza) to 43.2 µg m^{-3} (Granada) for PM_{10}, showed a

Table 3 RR and 95% confidence intervals for significant associations between air pollutants and daily cardiovascular hospital admission due to lag effects in the cities studied

City	Pollutant	Lag	Relative risk	CI	City	Pollutant	Lag	Relative risk	CI
Toledo	$PM_{2.5}$	0	1.028	1.009–1.048	Albacete	$PM_{2.5}$	0	1.013	0.997–1.028
		1	1.002	0.982–1.023			1	0.998	0.982–1.014
		2	0.986	0.966–1.007			2	0.999	0.983–1.016
		3	0.996	0.975–1.016			3	0.993	0.977–1.010
		4	1.011	0.990–1.031			4	1.008	0.991–1.025
		5	1.013	0.993–1.034			5	1.008	0.992–1.025
		6	1.006	0.986–1.027			6	1.007	0.991–1.024
		7	0.999	0.980–1.018			7	0.999	0.983–1.014
	$PM_{2.5}$ Only Toledo*	0	1.048	1.015–1.081		PM_{10}	0	1.013	1.008–1.018
		1	1.005	0.971–1.040			1	0.997	0.992–1.002
		2	0.982	0.948–1.016			2	0.993	0.987–0.998
		3	1.017	0.983–1.052			3	0.998	0.993–1.003
		4	0.997	0.963–1.031			4	0.999	0.994–1.004
		5	1.006	0.972–1.041			5	0.998	0.993–1.003
		6	1.016	0.982–1.051			6	1.006	1.001–1.011
		7	1.009	0.977–1.042			7	1.006	1.001–1.011
	PM_{10}	0	1.025	1.019–1.030		NO_2	0	1.042	1.036–1.050
		1	0.997	0.991–1.003			1	1.000	0.993–1.008
		2	0.993	0.987–1.000			2	0.991	0.983–0.998
		3	1.001	0.994–1.007			3	0.991	0.984–0.998
		4	0.994	0.987–1.000			4	0.998	0.991–1.005
		5	1.000	0.993–1.006			5	0.996	0.989–1.004
		6	1.003	0.996–1.009			6	1.001	0.994–1.008
		7	1.009	1.003–1.015			7	1.022	1.015–1.029
	PM_{10} Only Toledo*	0	1.035	1.025–1.045	Ciudad Real	PM_{10}	0	1.015	1.010–1.020
		1	0.991	0.980–1.002			1	0.998	0.993–1.004
		2	0.992	0.981–1.003			2	0.999	0.994–1.005
		3	1.010	0.999–1.021			3	0.994	0.989–0.999
		4	0.988	0.977–0.999			4	0.998	0.993–1.004
		5	1.003	0.992–1.014			5	0.997	0.992–1.003
		6	1.001	0.990–1.011			6	1.006	1.000–1.011
		7	1.007	0.997–1.017			7	1.005	1.000–1.009
	NO_2	0	1.011	1.007–1.015		NO_2	0	1.035	1.027–1.043
		1	1.005	1.000–1.009			1	1.012	1.002–1018
		2	0.995	0.995–0.999			2	0.990	0.982–0.998
		3	0.999	0.995–1.004			3	0.997	0.989–1.015
		4	1.005	1.001–1.010			4	1.007	0.999–1.015
		5	0.997	0.993–1.001			5	0.988	0.980–0.996
		6	0.999	0.995–1.004			6	1.001	0.993–1.009
		7	1.005	1.001–1.010			7	1.013	1.006–1.021
	NO_2 Only Toledo*	0	1.014	1.004–1.024	Guadalajara	PM_{10}	0	1.026	1.021–1.031
		1	1.007	0.997–1.017			1	0.999	0.993–1.004
		2	0.998	0.987–1.008			2	0.984	0.979–0.990
		3	0.996	0.986–1.007			3	1.001	0.995–1.006
		4	1.005	0.995–1.015			4	0.994	0.988–0.999
		5	0.999	0.989–1.009			5	0.997	0.992–1.003
		6	0.997	0.986–1.007			6	1.006	1.000–1.011
		7	0.998	0.988–1.008			7	1.012	1.007–1.017
						NO_2	0	1.014	1.010–1.018

Table 3 (continued)

City	Pollutant	Lag	Relative risk	CI	City	Pollutant	Lag	Relative risk	CI
							1	1.003	0.999–1.007
							2	0.993	0.989–0.997
							3	0.995	0.991–0.999
							4	1.000	0.996–1.004
							5	0.997	0.993–1.001
							6	0.997	0.993–1.001
							7	1.011	1.007–1.015

*Only in Toledo: Exclusively admissions from Toledo Hospital, the closest location to the measuring station

consistent association at lags 0 and 1 with CVD hospital admission. Moreover, studies in Boston (USA) with mean 4-h $PM_{2.5}$ levels ranging from 3 to 49 μg m^{-3} have demonstrated a significant increase in CVD, from 0.5 to 1.5%, for every 5 ~ 6 μg m^{-3} increase in $PM_{2.5}$ (Gold et al. 2000). NO_2 has been also found to be associated with hospital admissions for CVD in Belgium (Collart et al. 2018). In this work, the average annual concentration of NO_2 was stable for the 4 years of analysis (around 20.5 μg m^{-3}). For all ages combined, the strongest association between this pollutant and the number of hospital admissions was observed at lag 0, except for hemorrhagic stroke where the strongest association occurred at lag 2.

A recent systematic evaluation of time-series studies of air pollution from 652 cities in 24 countries or regions found, on average, an increase over the current and previous day of 0.36% (95% CI: 0.30–0.43) and 0.55% (95% CI: 0.45–0.66) in daily cardiovascular mortality per 10 μg m^{-3} increase in PM_{10} and $PM_{2.5}$ concentration, respectively (Liu et al. 2019). In this same study, for the period 1986–2011, China had the highest level of annual-mean PM_{10} pollution (89.2 μg m^{-3}) and one of its cities had the highest level of $PM_{2.5}$ (116.9 μg m^{-3}). This study found in Spain, for the studied period 2001–2014, a daily annual average of 27.8 μg m^{-3} for PM_{10} and 11.3 μg m^{-3} for $PM_{2.5}$, similar values to the concentrations measured in CLM in our study (from 2006 to 2015).

Our study could be a first step for implementing cardiovascular diseases alert protocols depending on air pollution levels in CLM and other Spanish communities. Inevitably, there are some limitations in our work. Firstly, we extracted hospital admission data for people residing and admitting to the hospitals in the study area. Therefore, people who were admitted to the hospitals could not reside in CLM. Secondly, socioeconomic status and with underlying diseases of the patients were not explored in this study, which could skew the results. Thirdly, we did not have data on people who went to the emergency department for CVD and who were not finally admitted in the hospital. Finally, chemical composition of PM has not been considered and harmful health effects can vary by its chemical constituents. Therefore, an additional study taking into account the above limitations should be carried out to help strengthen our findings on the effects of air pollution on cardiovascular hospital admissions.

Conclusions

This study reported the effects of air pollutants ($PM_{2.5}$, PM_{10}, and NO_2) on the daily hospital admission for CVD in Toledo, Albacete, Guadalajara, and Ciudad Real (CLM, Spain) for a period of 2006–2015. In general, the concentrations of the pollutants were lower than the ambient air quality standards European Directive 2008/50/EC or WHO guideline. The annual EU limit values for NO_2 and $PM_{2.5}$ there were not exceedances, only the PM_{10} limit value exceeded punctually due to Saharan dust intrusions. However, negative effects of air pollution on human health have been found in the whole pollutants studied here. Moreover, we also found that elderly ($\geq$ 65 years) held the greater effects of air pollution on hospital admissions compared to the adult group (aged 15–64), which is relatively important for planning and implementing intervention for this population group since the CLM population is going to experience aging in the near future. Moreover, it is known the emergency department is one of the most congested units in any hospital that faces greater pressure in terms of patient load and healthcare resources as compared to other departments of the healthcare system. So, the potential utility of these results may help the emergency department during similar air pollutant concentration, where an increase in the use of this health service among the vulnerable groups could be expected. The use of the app Avis@

Table 4 RRs and 95% CI of daily hospital admission stratified by age and sex group associated with 10 μg m^{-3} increase of $PM_{2.5}$ concentrations

Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI
Age < 65	0	1.009	0.973–1.047	Men	0	1.030	1.005–1.056	Men < 65	0	1.013	0.974–1.053	Women < 65	0	0.968	0.926–1.012
	1	1.024	0.985–1.064		1	1.004	0.978–1.031		1	1.024	0.983–1.066		1	0.991	0.948–1.034
	2	0.981	0.943–1.021		2	0.977	0.951–1.004		2	0.978	0.938–1.020		2	0.990	0.948–1.035
	3	1.015	0.976–1.055		3	0.996	0.970–1.023		3	1.040	0.999–1.082		3	0.996	0.954–1.040
	4	0.987	0.949–1.026		4	1.004	0.978–1.031		4	0.972	0.932–1.013		4	0.986	0.944–1.030
	5	1.048	1.009–1.089		5	1.020	0.994–1.046		5	1.040	0.999–1.082		5	0.997	0.995–1.040
	6	1.002	0.964–1.042		6	0.994	0.968–1.020		6	0.989	0.949–1.031		6	1.008	0.966–1.052
	7	0.973	0.937–1.011		7	1.001	0.976–1.026		7	0.974	0.937–1.013		7	1.014	0.972–1.057
Age ≥ 65	0	1.034	1.013–1.055	Women	0	1.028	1.002–1.054	Men ≥ 65	0	1.038	1.010–1.067	Women ≥ 65	0	1.030	1.003–1.057
	1	0.998	0.976–1.020		1	0.999	0.972–1.026		1	0.995	0.966–1.025		1	0.997	0.970–1.026
	2	0.988	0.967–1.010		2	0,997	0.970–1.025		2	0.974	0.945–1.004		2	1.001	0.973–1.030
	3	0.991	0.970–1.013		3	0.996	0.969–1.024		3	0.988	0.959–1.019		3	0.997	0.969–1.026
	4	1.019	0.997–1.041		4	1.016	0.989–1.044		4	1.018	0.988–1.048		4	1.017	0.989–1.046
	5	1.002	0.980–1.024		5	1.007	0.989–1.044		5	1.004	0.974–1.034		5	1.002	0.974–1.030
	6	1.009	0.987–1.031		6	1.020	0.993–1.048		6	0.991	0.962–1.021		6	1.019	0.991–1.048
	7	1.001	0.981–1.022		7	0.997	0.972–1.023		7	1.006	0.979–1.035		7	0.999	0.973–1.026

Table 5 RRs and 95% CI of daily hospital admission stratified by age and sex group associated with 10 μg m^{-3} increase of PM_{10} concentrations

Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI
Age < 65	0	1.025	1.014–1.036	Men	0	1.026	1.018–1.033	Men < 65	0	1.020	1.009–1.032	Women < 65	0	1.010	0.997–1.024
	1	1.001	0.989–1.013		1	0.996	0.988–1.004		1	0.999	0.986–1.012		1	0.997	0.984–1.011
	2	0.988	0.976–1.000		2	0.995	0.987–1.003		2	0.989	0.976–1.002		2	1.002	0.988–1.016
	3	0.993	0.981–1.006		3	0.997	0.989–1.005		3	0.999	0.987–1.012		3	1.002	0.988–1.015
	4	0.996	0.984–1.009		4	0.991	0.983–1.000		4	0.994	0.981–1.007		4	0.996	0.982–1.010
	5	1.001	0.989–1.013		5	1.005	0.997–1.013		5	1.002	0.989–1.014		5	0.999	0.985–1.013
	6	1.006	0.994–1.018		6	1.000	0.992–1.009		6	1.008	0.995–1.020		6	0.994	0.981–1.008
	7	1.005	0.994–1.016		7	1.011	1.004–1.018		7	0.998	0.987–1.010		7	1.002	0.989–1.015
Age ≥ 65	0	1.023	1.017–1.029	Women	0	1.024	1.017–1.032	Men ≥ 65	0	1.010	0.997–1.024	Women ≥ 65	0	1.022	1.014–1.030
	1	0.997	0.990–1.004		1	0.998	0.989–1.006		1	0.997	0.984–1.011		1	0.997	0.989–1.006
	2	0.995	0.988–1.002		2	0.991	0.982–1.000		2	1.002	0.988–1016		2	0.993	0.984–1.002
	3	1.002	0.995–1.009		3	1.005	0.997–1.014		3	1.002	0.988–1.015		3	1.007	0.998–1.016
	4	0.994	0.988–1.001		4	0.996	0.987–1.005		4	0.996	0.982–1.010		4	0.994	0.985–1.003
	5	0.997	0.990–1.004		5	0.993	0.985–1.002		5	0.999	0.985–1.013		5	0.992	0.983–1.001
	6	1.003	0.996–1.010		6	1.005	0.996–1.014		6	0.994	0.981–1.008		6	1.007	0.998–1.016
	7	1.009	1.003–1.015		7	1.006	0.998–1.014		7	1.002	0.989–1.015		7	1.004	0.996–1.012

Table 6 RRs and 95% CI of daily hospital admission stratified by age and sex group associated with 10 μg m^{-3} increase of NO_2 concentrations

Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI	Sub-group	Lag	RR	CI
Age < 65	0	1.013	1.002–1.024	Men	0	1.014	1.007–1.022	Men < 65	0	1.006	0.994–1.018	Women < 65	0	1.013	0.999–1.028
	1	1.016	1.004–1.028		1	1.004	0.997–1.012		1	1.009	0.996–1.021		1	0.997	0.983–1.011
	2	0.978	0.967–0.990		2	0.994	0.986–1.002		2	0.983	0.971–0995		2	1.002	0.988–1.016
	3	1.003	0.992–1.015		3	0.997	0.990–1.005		3	1.008	0.996–1.021		3	1.009	0.995–1.024
	4	1.004	0.993–1.016		4	1.001	0.994–1.009		4	1.003	0.990–1.015		4	1.012	0.998–1.026
	5	0.993	0.982–1.005		5	1.000	0.992–1.008		5	1.001	0.989–1.014		5	0.986	0.972–1.000
	6	0.997	0.986–1.009		6	1.004	0.997–1.012		6	1.002	0.990–1.015		6	1.014	1.000–1.029
	7	1.010	0.999–1.021		7	0.998	0.991–1.005		7	1.007	0.995–1.019		7	1.004	0.990–1.018
Age ≥ 65	0	1.017	1.010–1.023	Women	0	1.019	1.011–1.037	Men ≥ 65	0	1.016	1.007–1.024	Women ≥ 65	0	1.017	1.009–1.026
	1	1.002	0.996–1.009		1	1.003	0.995–1.011		1	1.002	0.993–1.010		1	1.002	0.993–1.010
	2	0.997	0.991–1.004		2	0.995	0.987–1.003		2	0.998	0.989–1.007		2	0.997	0.989–1.005
	3	0.998	0.992–1.004		3	1.001	0.992–1.009		3	0.996	0.988–1.005		3	1.000	0.992–1.008
	4	1.003	0.996–1.009		4	1.003	0.995–1.011		4	1.000	0.992–1.009		4	1.004	0.995–1.012
	5	0.998	0.992–1.004		5	0.993	0.985–1.011		5	1.002	0.993–1.010		5	0.993	0.985–1.002
	6	0.997	0.991–1.003		6	0.993	0.985–1.001		6	1.003	0.994–1.011		6	0.992	0.984–1.000
	7	1.004	0.998–1.010		7	1.009	1.009–1.017		7	0.996	0.987–1.004		7	1.010	1.002–1.018

(JCCM 2020c), which informs citizens interested in the quality of the aur they breathe, could also be a powerful tool in the emergency department to alert of real-time information on air quality in CLM.

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Declarations

Conflict of interest The authors declare no competing interests.

References

Adams K, Greenbaum DS, Shaikh R, van Erp AM, Russell AG (2015) Particulate matter components, sources, and health: systematic approaches to testing effects. J Air Waste Manage Assoc 65:544–558. https://doi.org/10.1080/10962247.2014.1001884

Amor AJ, Masana L, Soriguer F, Goday A, Calle-Pascual A, Gaztambide S, Rojo-Martínez G, Valdés S, Gomis R, Ortega E (2015) Estimating cardiovascular risk in Spain by the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice. Rev Esp Cardiol 68:417–425. https://doi.org/10.1016/j.rec.2014.05.023

Amsalu E, Wang T, Li H, Liu Y, Wang A, Liu X, Tao L, Luo Y, Zhang F, Yang X, Li X, Wang W, Guo X (2019) Acute effects of fine particulate matter ($PM_{2.5}$) on hospital admissions for cardiovascular disease in Beijing, China: a time-series study. Environ Health 18: 70. https://doi.org/10.1186/s12940-019-0506-2

Anderson JO, Thundiyil JG, Stolbach A (2012) Clearing the air: a review of the effects of particulate matter air pollution on human health. J Med Toxicol 8:166–175. https://doi.org/10.1007/s13181-011-0203-1

Ballester F, Rodríguez P, Iñíguez C, Saez M, Daponte A, Galán I, Taracido M, Arribas F, Bellido J, Cirarda FB, Cañada A, Guillén JJ, Guillén-Grima F, López E, Pérez-Hoyos S, Lertxundi A, Toro S (2006) Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project. J Epidemio Community Health 60:328–336. https://doi.org/10.1136/jech.2005.037978

Bhaskaran K, Gasparrini A, Hajat S, Smeeth L, Armstrong B (2013) Time series regression studies in environmental epidemiology. Int J Epidemiol 42:1187–1195. https://doi.org/10.1093/ije/dyt092

Borge R, Artíñano B, Yagüe C, Gomez-Moreno FJ, Saiz-Lopez A, Sastre M, Narros A, García-Nieto D, Benavent N, Maqueda G, Barreiro M, Andrés JM, Cristobal A (2018) Application of a short-term air quality action plan in Madrid (Spain) under a high-pollution episode - part I: diagnostic and analysis from observations. Sci Total Environ 635:1561–1573. https://doi.org/10.1016/j.scitotenv.2018.03.149

Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA, Apte JS, Brauer M, Cohen A, Weichenthal S, Coggins J, Di Q, Brunekreef B, Frostad J, Lim SS, Kan H, Walker KD, Thurston GD, Hayes RB, Lim CC, Turner MC, Jerrett M, Krewski D, Gapstur SM, Diver WR, Ostro B, Goldberg D, Crouse DL, Martin RV, Peters P, Pinault L, Tjepkema M, van Donkelaar A, Villeneuve PJ, Miller AB, Yin P, Zhou M, Wang L, Janssen NAH, Marra M, Atkinson RW, Tsang H, Quoc Thach T, Cannon JB, Allen RT, Hart JE, Laden F, Cesaroni G, Forastiere F, Weinmayr G, Jaensch A, Nagel G, Concin H, Carslaw DC, Ropkins K (2018) Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. Proc Natl Acad Sci U S A 18(115):9592–9597. https://doi.org/10.1073/pnas.1803222115

Carslaw DC, Ropkins K (2012) Open-air: an-R package for air quality data analysis. Environ Model Softw 27–28:52–61. https://doi.org/10.1016/j.envsoft.2011.09.008

Cesaroni G, Forastiere F, Stafoggia M, Andersen ZJ, Badaloni C, Beelen R, Caracciolo B, de Faire U, Erbel R, Eriksen KT, Fratiglioni L, Galassi C, Hampel R, Heier M, Hennig F, Hilding A, Hoffman B, Houthuijs D, Jöckel KH, Korek M, Lanki T, Leander K, Magnusson PK, Migliore E, Ostenson CG, Overvad K, Pedersen NL, Penell J, Pershagen G, Pyko A, Raaschou-Nielsen O, Ranzi A, Ricceri F, Sacerdote C, Salomaa V, Swart W, Turunen AW, Vineis P, Weinmayr G, Wolf K, de Hoogh K, Hoek G, Brunekreef B, Peters A (2014) Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE Project. BMJ 348:f7412. https://doi.org/10.1136/bmj.f7412

Collart P, Dubourg D, Levêque A, Bustos Sierra N, Coppieters Y (2018) Short-term effects of nitrogen dioxide on hospital admissions for cardiovascular disease in Wallonia. Belgium Int J Cardiol 255:231–236. https://doi.org/10.1016/j.ijcard.2017.12.058

Constantin DE, Bocăneala C, Voiculescu M, Roşu A, Merlaud A, Roozendael MV, Georgescu PL (2020) Evolution of SO_2 and NOx emissions from several large combustion plants in Europe during 2005–2015. Int J Environ Res Public Health 17:3630. https://doi.org/10.3390/ijerph17103630

de Pablo F, Lopez A, Soriano LR, Tomás C (2006) Relationships of daily mortality and hospital admissions to air pollution in Castilla-León, Spain. Atmósfera 19:23–29

de Pablo F, Rivas L, Sánchez JM (2013) Effects of weather types on hospital admissions for respiratory diseases in Castilla-La Mancha, Spain. Atmósfera 26:95–107. https://doi.org/10.1016/S0187-6236(13)71064-6

EUROSTAT (2018) Internal Market, Industry, Entrepreneurship and SMEs: Regional Innovation Monitor Plus. ES42: Castilla la Mancha URL: https://ec.europa.eu/growth/tools-databases/regional-innovation-monitor/base-profile/castilla-la-mancha (Accessed 9 March 2020)

Franco P, Gordo C, Marques da Costa E, Lopes A (2020) Air pollution and emergency hospital admissions-evidences from Lisbon metropolitan area. Portugal Appl Sci 10:7997. https://doi.org/10.3390/app10227997

Gabriel R, Alonso M, Segura A, Tormo MJ, Artigao LM, Banegas JR, Brotons C, Elosua R, Fernández-Cruz A, Muñiz J, Reviriego B, Rigo F (2008) Prevalence, geographic distribution, and geographic variability of major cardiovascular risk factors in Spain. Pooled analysis of data from population-based epidemiological studies: the ERICE study. Rev Esp Cardiol 61:1030–1040. https://doi.org/10.1016/S1885-5857(09)60006-2

Garcia M, Mulvagh SL, Merz C, Buring JE, Manson JE (2016) Cardiovascular disease in women: clinical perspectives. Circ Re 118:1273–1293. https://doi.org/10.1161/CIRCRESAHA.116.307547

Gardner B, Ling F, Hopke PK, Frampton MW, Utell MJ, Zareba W, Cameron SJ, Chalupa D, Kane C, Kulandhaisamy S, Topf MC, Rich DQ (2014) Ambient fine particulate air pollution triggers ST-elevation myocardial infarction, but not non-ST elevation myocardial infarction: a case-crossover study. Part Fibre Toxicol 11:1. https://doi.org/10.1186/1743-8977-11-1

Gasparrini A (2011) Distributed lag linear and non-linear models in R: the package dlnm. J Stat Softw 43:1–20. http://www.jstatsoft.org/v43/i08

Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, Allen G, Verrier M, Cherry R, Verrier R (2000) Ambient pollution and heart rate variability. Circulation 101:1267–1273. https://doi.org/10.1161/01.CIR.101.11.1267

Gomez V, Palmí V (2020) Atlas de Mortalidad en Castilla-La Mancha 2003–2014. Ed Bomarzo S.L. ISBN: 978–84–17310–09–7

Hassanvand MS, Naddafi K, Kashani H, Faridi S, Kunzli N, Nabizadeh R, Momeniha F, Gholampour A, Arhami M, Zare A, Pourpak Z, Hoseini M, Yunesian M (2017) Short-term effects of particle size fractions on circulating biomarkers of inflammation in a panel of elderly subjects and healthy young adults. Environ Pollut 223:695–704. https://doi.org/10.1016/j.envpol.2017.02.005

Hanigan IC, Rolfe MI, Knibbs LD, Salimi F, Cowie CT, Heyworth J, Marks GB, Guo Y, Cope M, Bauman A, Jalaludin B, Morgan GG (2019) All-cause mortality and long-term exposure to low level air pollution in the '45 and up study' cohort, Sydney, Australia, 2006–2015. Environ Int 126:762–770. https://doi.org/10.1016/j.envint.2019.02.044

He MZ, Zeng X, Zhang K, Kinney PL (2017) Fine particulate matter concentrations in urban Chinese cities, 2005–2016: a systematic review. Int J Environ Res Public Health 14:191. https://doi.org/10.3390/ijerph14020191

JCCM (2020a) Castilla-La Mancha air quality monitoring. http://pagina.jccm.es/medioambiente/rvca/estaciones/describe/intro.htm. (Accessed 20 January 2020)

JCCM (2020b) Regional air quality database of Castilla-La Mancha. https://www.castillalamancha.es/gobierno/desarrollosostenible/estructura/vicmedamb/actuaciones/partes-mensuales-del-estado-de-la-calidad-del-aire (Accessed 20 January 2020)

JCCM (2020c) Vice-Ministry of the environment watch and control of air quality. https://www.castillalamancha.es/gobierno/desarrollosostenible/estructura/vicmedamb/actuaciones/sistema-de-avisos-al-ciudadano-de-castilla-la-mancha-calidad-del-aire (Accessed 26 October 2020)

LiuY CX, Huang S, Tian L, LuY MeiY, Ren M, Li N, Liu L, Xian H (2015) Association between air pollutants and cardiovascular disease mortality in Wuhan, China. Int J Environ Res Public Health 12:3506–3516. https://doi.org/10.3390/ijerph120403506

Liu C, Chen R, Sera F, Vicedo-Cabrera AM, Guo Y, Tong S, Coelho MSZS, Saldiva PHN, Lavigne E, Matus P, Valdes-Ortega N, Osorio-García S, Pascal M, Stafoggia M, Scortichini M, Hashizume M, Honda Y, Hurtado-Díaz M, Cruz J, Nunes B, Texeira J, Kim H, Tobias A, Iñiguez C, Fosberg B, Åström C, Ragettli M, Guo Y, Chen B, Bell M, Wright C, Scovronick N, Garland R, Milojevic A, Kysely J, Urban A, Orru H, Indermitte E, Jaakkola J, Ryti N, Katsouyanni K, Analitis A, Zanobetti A, Schwartz J, Chen J, Tangchun W, Cohen D, Gasparrini A, Kan H (2019) Ambient particulate air pollution and daily mortality in 652 cities. N Engl J Med 381:705–715. https://doi.org/10.1056/NEJMoa1817364

Medrano MJ, Cerrato E, Boix R, Delgado-Rodŕiguez M (2005) Cardiovascular risk factors in Spanish population: metanalysis of cross-sectional studies. Med Clin 124: 606-612. https://doi.org/10.1157/13074389

Miller KA, Siscovick DS, Sheppard L, Shepherd K, Sullivan JH, Anderson GL, Kaufman JD (2007) Long-term exposure to air pollution and incidence of cardiovascular events in women. N Engl J Med 356:447–458. https://doi.org/10.1056/NEJMoa054409

MITECO (2013) Ministerio para la Transición Ecológica y el Reto Demográfico. https://www.miteco.gob.es/es/calidad-y-evaluacion-ambiental/temas/atmosfera-y-calidad-del-aire/Informe%2Bniveles%2By%2Bquimica_entregado2013%5B1%5D_tcm30-187876.pdf. (Accessed 24 November 2020)

Monsalve F, Tomas C, Fraile R (2013) Influence of meteorological parameters and air pollutants onto the morbidity due to respiratory diseases in Castilla-La Mancha, Spain. AAQR 13:1297–1312. https://doi.org/10.4209/aaqr.2012.12.0348

Mustafic H, Jabre P, Caussin C, Murad MH, Escolano S, Tafflet M, Périer MC, Marijon E, Vernerey D, Empana JP, Jouven X (2012) Main air pollutants and myocardial infarction: a systematic review and meta-analysis. JAMA 307:713–721. https://doi.org/10.1001/jama.2012.126

Nájera A, Arribas E, de Pablo F, Tomás C (2009) Aspectos climáticos de la ciudad de Albacete (1961–2005). Ed Capitán Swing Libros, España. ISBN: 978–84–613–2211–4

Nawrot TS, Perez L, Künzli N, Munters E, Nemery B (2011) Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 377:732–740. https://doi.org/10.1016/S0140-6736(10)62296-9

Nel A (2005) Air pollution-related illness: effects of particles. Science 308:804–806. https://doi.org/10.1126/science.1108752

North BJ, Sinclair DA (2012) The intersection between aging and cardiovascular disease. Circ Res 110:1097–1108. https://doi.org/10.1161/CIRCRESAHA.111.24687

Phosri A, Ueda K, Phung VLH, Tawatsupa B, Honda A, Takano H (2019) Effects of ambient air pollution on daily hospital admissions for respiratory and cardiovascular diseases in Bangkok, Thailand. Sci Total Environ 651:1144–1153. https://doi.org/10.1016/j.scitotenv.2018.09.183

Pope CA III, Brook RD, Burnett RT, Dockery DW (2011) How is cardiovascular disease mortality risk affected by duration and intensity of fine particulate matter exposure? An integration of the epidemiologic evidence. Air Qual Atmos Health 4:5–14. https://doi.org/10.1007/s11869-010-0082-7

Qui H, Yu IT, Wang X, Tian L, Tse LA, Wong W (2013) Differential effects of fine and coarse particles on daily emergency cardiovascular hospitalizations in Hong Kong. Atmos Environ 64:296–302. https://doi.org/10.1016/j.atmosenv.2012.09.060

R Core Team (2020) R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/

Riegel B, Moser DK, Buck HG, Dickson VV, Dunbar SB, Lee CS, Lennie TA, Lindenfeld J, Mitchell JE, Treat-Jacobson DJ, Webber DE (2017) Self-care for the prevention and management of cardiovascular disease and stroke. JAHA 6:e006997. https://doi.org/10.1161/JAHA.117.006997

Richmont-Bryant J, Owen RC, Graham S, Snyder M, McDow S, Oakes M, Kimbrough S (2017) Estimation of on-road NO_2 concentrations, NO_2/NO_X ratios, and related roadway gradients from near-road monitoring data. Air Qual Atm Health 10:611–625. https://doi.org/10.1007/s11869-016-0455-7

Santurtún A, Ruíz PB, López-Delgado L, Sanchez-Lorenzo A, Riancho J, Zarrabeitia MT (2017) Stroke: temporal trends and association with atmospheric variables and air pollutants in Northern Spain. Cardiovasc Toxicol 17:360–367. https://doi.org/10.1007/s12012-016-9395-6

Sanyal S, Rochereau T, Maesano CN, Com-Ruelle L, Annesi-Maesano I (2018) Long-term effect of outdoor air pollution on mortality and morbidity: a 12-year follow-up study for metropolitan France. Int J Environ Res Public Health 15:2487. https://doi.org/10.3390/ijerph15112487

Shah ASV, Langrish JP, Nair H, McAllister DA, Hunter AL, Donaldson K, Newby DE, Mills NL (2013) Global association of air pollution and heart failure: a systematic review and meta-analysis. Lancet 82:1039–1048. https://doi.org/10.1016/S0140-6736(13)60898-3

Soret A, Jimenez-Guerrero P, Baldasano JM (2011) Comprehensive air quality planning for the Barcelona Metropolitan Area through traffic management. Atmos Pollut Res 2:255–266. https://doi.org/10.5094/APR.2011.032

Vahedian M, Khanjani N, Mirzaee M, Koolivand A (2017) Ambient air pollution and daily hospital admissions for cardiovascular diseases in Arak. Iran ARYA Atheroscler 13:117–134

WHO (2016) Ambient air pollution: a global assessment of exposure and burden of disease. https://apps.who.int/iris/bitstream/handle/10665/250141/9789241511353-eng.pdf?sequence¼1 (Accessed 9 March 2020)

WHO (2017) Cardiovascular diseases (CVDs) fact sheets. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) (Accessed 9 March 2020)