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FULL RESEARCH PAPER
Cardiovascular disease

Short-term effects of particulate matter on cardiovascular morbidity in Italy: a national analysis

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Aims We aimed at investigating the relationship between particulate matter (PM) and daily admissions for cardiovascular diseases (CVDs) at national level in Italy.

Methods and results Daily numbers of cardiovascular hospitalizations were collected for all 8084 municipalities of Italy, in the period 2013–2015. A satellite-based spatiotemporal model was used to estimate daily PM_{10} (inhalable particles) and $PM_{2.5}$ (fine particles) concentrations at 1-km^2 resolution. Multivariate Poisson regression models were fit to estimate the association between daily PM and cardiovascular admissions. Flexible functions were estimated to explore the shape of the associations at low PM concentrations, also in non-urban areas. We analysed 2 154 810 acute hospitalizations for CVDs (25% stroke, 24% ischaemic heart diseases, 22% heart failure, and 5% atrial fibrillation). Relative increases of total cardiovascular admissions, per 10 μg/m^3 variation in PM_{10} and $PM_{2.5}$ at lag 0–5 (average of last 6 days since admission), were 0.55% (95% confidence intervals: 0.32%, 0.77%) and 0.97% (0.67%, 1.27%), respectively. The corresponding estimates for heart failure were 1.70% (1.28%, 2.13%) and 2.66% (2.09%, 3.23%). We estimated significant effects of PM_{10} and $PM_{2.5}$ also on ischaemic heart diseases, myocardial infarction, atrial fibrillation, and ischaemic stroke. Associations were similar between less and more urbanized areas, and persisted even at low concentrations, e.g. below WHO guidelines.

Conclusion PM was robustly associated with peaks in daily cardiovascular admissions, especially for heart failure, both in large cities and in less urbanized areas of Italy. Current WHO Air Quality Guidelines for PM_{10} and $PM_{2.5}$ are not sufficient to protect public health.

Keywords Air pollution • Atrial fibrillation • Cardiovascular diseases • Epidemiology • Heart failure • Particulate matter

Introduction

Ambient particulate matter (PM) air pollution is a major risk factor to human health, globally causing over 4 million premature deaths every year.[1–3] Acute effects of PM, observed from hours to days after exposure, have been extensively documented, with the cardiovascular disease (CVD) consequences shown to be equal or even more severe than those due to respiratory diseases.[4] The latest update of the

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Global Burden of Disease (GBD) Collaborative Group estimated the PM-related number of deaths from ischaemic heart diseases and stroke in the order of 780 000 and 350 000 every year worldwide.[5] A recent study using novel hazard ratios functions for Europe further increased those estimates.[6] Despite the large available evidence, there are still gaps of knowledge that include the range of disease outcomes associated with PM and the exposure–response relationship between PM and different cardiovascular outcomes, especially at low concentrations.[7]

Current data on CVD mortality suggest that there is no concentration level of ambient PM below which the health risk for the population is negligible. Indeed, recent research has shifted the attention to alternative cardiovascular endpoints, such as heart failure, arrhythmias and circulatory diseases, and reported significant associations with both short-term and long-term exposure to PM.[4,8–10] At the end of 2019 the US Environmental Protection Agency (EPA) confirmed the support for a causal relationship between short-term exposure to fine particles and cardiovascular outcomes, based on the convergence of epidemiological, controlled human exposure, and animal toxicological studies.[11]

PM is a mixture of many different chemicals and its adverse effect on cardiovascular health possibly varies with its toxicity and composition, depending on the relative contribution of local sources and their emission profiles. However, most of the evidence on the cardiovascular effects of ambient particles derives from studies conducted in large urban areas, due to the lack of observations or reliable exposure estimates in other settings. This substantially limits the possibility to generalize the epidemiological findings to the general population, in so far as it would be needed to study areas characterized by different source profiles and composition of air pollution compared to cities, and to investigate large fractions of the population, potentially more isolated and with limited access to healthcare services.[12,13] Finally, as air quality guidelines are under scrutiny by the WHO,[14] a more comprehensive analysis of the exposure–response functions at low levels would be extremely valuable, and non-urban settings might represent the perfect testing ground in this regard.

The objectives of this study are to: (i) estimate the association between PM and specific groups of CVD admissions at the national level; (ii) describe the temporal relationship and the exposure–response functions between PM and each CVD endpoint; (iii) compare effect estimates among areas with different degrees of urbanization; (iv) identify subgroups of the population especially susceptible to the adverse effects of daily PM; and (v) quantify the burden of disease, in terms of cases of CVD admissions caused by daily PM exceedances of predefined thresholds.

Methods

Study setting

The study was conducted in the framework of the 'Big data in Environmental and occupational Epidemiology' (BEEP) project.[15] Within BEEP we have developed a spatiotemporal exposure model to estimate daily mean PM_{10} (PM with aerodynamic diameter ≤ 10 microns) and $PM_{2.5}$ (PM ≤ 2.5 microns) concentrations for all squared kilometres of Italy over 2013–2015.[16] These exposures have been matched to municipality-specific daily data on cardiovascular admissions across all Italy.

Study population

The Italian Ministry of Health provided data on hospital discharge records for all the Italian hospitals, both public and private, for the period 2013–2015. Each record contains information on the hospital, dates of admission and discharge, primary diagnoses, type of admission, sex, age, and municipality of residence of the patient.

We selected only acute (e.g. unscheduled) hospitalizations for CVDs (International Classification of Diseases, 9th Revision—ICD9: 390–459), and considered the following groups of primary diagnoses:

- cardiac diseases (390–429),
  - hypertension (401–405),
  - ischaemic heart diseases (410–414),
    - acute myocardial infarction (410),
  - arrhythmias (427),
    - atrial fibrillation (427.31),
  - heart failure (428),
- cerebrovascular diseases (430–438),
  - haemorrhagic stroke (431),
  - ischaemic stroke (433–435).

For each group of diseases and municipality, we built a time series of daily counts of acute hospital admissions. In addition, we generated time series by age (0–64, 65–74, 75–84, and 85+ years) and sex.

The work was conducted in accordance with the Declaration of Helsinki. No ethical permissions were required as data were treated anonymously and in aggregated form.

Air pollution exposure

Daily mean concentrations of inhalable particulate matter (PM_{10}) and fine particles ($PM_{2.5}$) were estimated for each squared km of Italy with a hybrid spatiotemporal random forest model, as described elsewhere.[16] In brief, we calibrated ground-level PM concentrations available from regional air quality monitoring networks to satellite-based aerosol optical depth, regional dispersion models, daily meteorological fields, and land-use parameters. The models performed generally well on hold-out monitoring stations, with cross-validated (CV) R^2 of 0.75 and 0.80 for PM_{10} and $PM_{2.5}$, respectively. Similar values were obtained when limiting the analysis to rural background stations only (CV-R^2 = 0.74 and 0.79). The resulting calibration model was then applied to estimate PM_{10} and $PM_{2.5}$ concentrations for all days in 2013–2015 and all 1-km^2 cells of Italy.[16] At last, we derived estimates of PM_{10} and $PM_{2.5}$ for each of the 8084 municipalities of Italy as a weighted average of PM concentrations of all the grid cells intersecting the municipality, with weights proportional to the intersection areas (full weight to the cells entirely falling in the municipality, smaller weight to those intersecting the boundaries).

Air temperature and other time-varying confounders

Daily mean air temperature estimates were obtained at 1 × 1km resolution by calibrating air temperature measurements from monitoring networks to land surface temperature (LST) satellite data and spatiotemporal land use parameters. The methodology was developed elsewhere and details can be found in de' Donato *et al.*[17] In brief, a mixed-effects regression model was fit, were daily air temperature from meteorological stations was calibrated against LST and other spatial (vegetation index, geoclimatic zones, administrative regions, land-use

variables) and temporal (seasons, days of the week, relative humidity) predictors. Random intercepts for the day, and random slopes of LST by day, were also included to account for the changing relationship between LST and air temperature by day. Then, the calibration model was applied to predict daily mean air temperature at each 1-km^2 grid cell. Finally, 1-km^2 estimates were spatially averaged at the municipality level. Other time-varying covariates, potentially confounding the PM-hospitalizations associations and therefore accounted for in the statistical analysis, include: long-term and seasonal time trends, day of the week, summer population decrease, bank holidays, and influenza epidemics. Time trends were defined as sequences of calendar days (from 1 to 1096), while all other terms were coded with categorical variables, as detailed in the Supplementary material online (section *Detailed statistical analysis*) and in Stafoggia *et al.*[18]

Urbanization score

We classified each municipality ($N = 8084$) on the basis of a four-level urbanization score. This was accomplished by defining, for each municipality, four spatial parameters considered valid proxies for population clustering: resident population (from Census data, year 2011), 'light-at-night' (LAN) parameter (from the 'VIIRS' suite onboard the SUOMI satellite, year 2015), percentage of built areas (from Corine Land Cover database, year 2012), and density of high traffic roads (from TeleAtlas TomTom 2012 road network). These variables were combined in order to produce a quantitative score for each municipality. The resulting map for Italy is reported in Supplementary material online, *Figure S1*, while the distribution of municipalities and their resident population (Census 2011) by quintiles of the urbanization score are displayed in Supplementary material online, *Table S1*. For the analyses, the first two quintiles were grouped together.

As a sensitivity analysis, we used an alternative indicator of urbanization, as defined by EUROSTAT for each municipality of Europe.[19] This is based on the combination of absolute resident population and population density (Census 2011), and classifies municipalities into 'Cities' (densely populated areas), 'Towns and suburbs' (intermediate density areas), and 'Rural areas' (thinly populated areas) (Supplementary material online, *Figure S1* and *Table S1*).

Statistical analyses by province

We followed a two-stage analytical strategy, where province-specific data were analysed in the first stage, and meta-analytical tools were applied in the second one to combine province-specific estimates and produce a national effect. In the first stage, we applied a pooled analysis on the time-series of municipalities belonging to the same province (see Supplementary material online, Section '*Detailed statistical analysis*' for further details). Specifically, we stacked together the time series of all municipalities belonging to the same Italian province, and ran province-specific over-dispersed Poisson regression models, where the daily count of disease-specific CVD admissions was regressed against the daily mean PM concentrations in the same municipality, while adjusting for temporal trends (natural spline with 6 degrees of freedom per year), ambient temperature (two natural splines for lag 0–1 and lag 1–6 temperature), and indicator variables for municipality of residence, day of the week, summer population decrease, bank holidays, and influenza epidemics.[18]

In addition, in each province and for each PM-outcome combination, we explored three key aspects of their association: temporal latency, exposure–response shape, and effect modification. First, we examined whether different outcomes displayed different temporal latencies with the exposures: this was accomplished by fitting distributed lag models up to 9 days before admissions, and by selecting a priori lags 0, 0–1, 2–5, and 0–5 as referent time windows to represent immediate, delayed or prolonged effects. Second, we modelled PM with a natural spline with three degrees of freedom in order to describe the shape of the association with each study outcome. Third, we repeated the analyses by age group (0–64, 65–74, 75–84, and 85+ years) and sex, to identify potential vulnerable subgroups, and by the four-level urbanization score, in order to compare associations among areas characterized by different degrees of urbanization.

We performed a number of sensitivity analyses to test the robustness of our results to the adjustment for time trend and temperature, the shape of the exposure–response functions and the choice of the urbanization index for the municipalities (see Supplementary material online, Section '*Detailed statistical analysis*' for further details).

Meta-analysis

In the second stage, we pooled province-specific estimates with a random-effects meta-analysis using the restricted maximum-likelihood estimator of the between-province variance.[20] We applied univariate meta-analysis for pooling results of the distributed lag and effect modification models, and multivariate meta-analysis to produce 'meta-curves' from the province-specific exposure–response functions. Furthermore, we performed heterogeneity tests on the strata-specific meta-analytical estimates to test whether effect modification by age, sex, and degree of urbanization was statistically significant.

All results are expressed as percent increases of risk of admission (% IR), and corresponding 95% confidence intervals (95% CIs), per a fixed increment of 10 μg/m^3 in PM.

Attributable cases

The pooled associations estimated above were used to quantify the annual numbers of cause-specific cardiovascular admissions attributable to daily exceedances in PM_{10} and $PM_{2.5}$ above predefined thresholds. In particular, we defined the following thresholds: 20, 25, 30, 35, 40, 45, or 50 μg/m^3 for PM_{10}, and 10, 15, 20, or 25 μg/m^3 for $PM_{2.5}$; then, for each threshold and PM fraction we selected the municipalities and days where daily PM exceeded the threshold; finally, we quantified the attributable cases of cause-specific CVD admissions by multiplying the total counts of admissions occurring on those exceeding days and municipalities by a function of the relative risk estimated in the meta-analysis (more details in the Supplementary material online).

All analyses were conducted using R, version 3.6.0 (R Development Core Team; http://R-project.org).

Results

Characteristics of the study population

In total, there were 4 million hospital admissions in Italy during 2013–2015 with a primary diagnosis of any CVDs, ~14% of the total admissions. We removed long-stays, rehabilitations and day-hospitals (17.7%) and programmed admissions (27.6%), as these were inconsistent with the study hypothesis of daily peaks in air pollution triggering acute cardiovascular responses (Supplementary material online, *Figure S2*).

The final study population consisted of 2 154 810 acute admissions for CVDs, of which the most frequent were cerebrovascular diseases (25.2%), ischaemic heart diseases (23.7%), and heart failure (21.9%) (*Table 1*) and the less frequent were hypertension (3.5%) and haemorrhagic stroke (2.7%), that were not considered in

Table 1 Description of the study population

Study population	N	%	Rate (per 1000)
Disease group (ICD-9 code)			
Total cardiovascular diseases (390–459)	2 154 810	100.0	12.1
Cardiac diseases (390–429)	1 470 370	68.2	8.2
Hypertension (401–405)	72 391	3.4	0.4
Ischaemic heart diseases (410–414)	511 027	23.7	2.9
Myocardial infarction (410)	321 768	14.9	1.8
Arrhythmias (427)	200 207	9.3	1.1
Atrial fibrillation (427.31)	101 491	4.7	0.6
Heart failure (428)	471 042	21.9	2.6
Cerebrovascular diseases (430–438)	542 671	25.2	3.0
Haemorrhagic stroke (431)	57 223	2.7	0.3
Ischaemic stroke (433–435)	329 702	15.3	1.8
Age group (years)			
0–64	476 936	22.1	3.3
65–74	456 683	21.2	25.2
75–84	726 284	33.7	55.1
85+	494 907	23.0	108.6
Sex			
Males	1 169 789	54.3	13.5
Females	985 021	45.7	10.7
Degree of urbanization of the municipality of residence			
Very low or low	286 602	13.3	13.7
Medium	262 437	12.2	12.4
High	429 963	20.0	12.1
Very high	1 175 808	54.6	11.7

ICD-9, International Classification of Diseases, 9th revision.

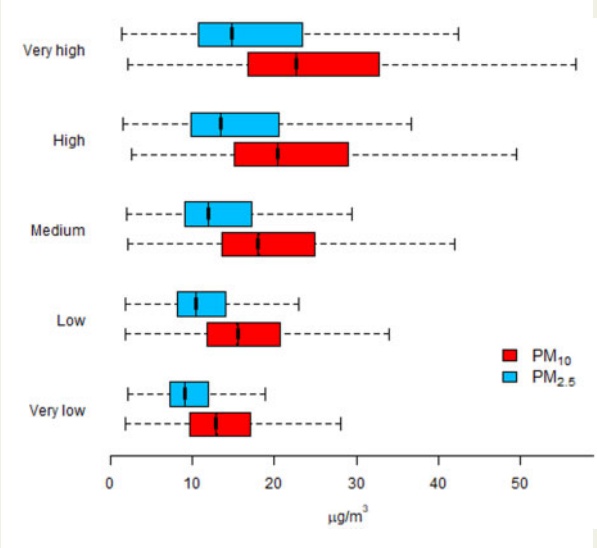

Figure 1 Daily PM_{10} and $PM_{2.5}$ distributions across Italian municipalities, by degree of urbanization.

further analysis due to the paucity of cases. While most patients resided in major urban centres (54.6%), there was still a large fraction of individuals living in areas poorly investigated in previous studies on air pollution, such as rural and remote towns (13.3%), sub-urban settings (12.2%), and small cities (20.0%). CVD hospitalization rates were highest in the less urbanized areas (13.7 per thousand inhabitants) and smallest in the highly urbanized ones (11.7 per thousand) (*Table 1*).

Air pollutants concentrations were substantially lower in municipalities with a low or medium degree of urbanization, with daily exposures often below WHO guidelines for daily concentrations of 50 µg/m^3 for PM_{10} and 25 µg/m^3 for $PM_{2.5}$ (*Figure 1* and Supplementary material online, *Figure S3*).

Effects of PM at different lags

We found significant effects of both PM_{10} and $PM_{2.5}$ on total CVDs, cardiac diseases, ischaemic heart diseases, myocardial infarction, atrial fibrillation, heart failure and, to a lesser extent, ischaemic stroke (*Table 2* and Supplementary material online, *Figure S4*). The time lag of the effect of PM displayed a long latency on heart failure (above 1 week after exposure), while the effects on ischaemic heart diseases, myocardial infarction, atrial fibrillation, and ischaemic stroke were immediate, statistically significant up to the first 1–3 days after exposure. No evidence of an association was detected with total arrhythmias or total cerebrovascular diseases (Supplementary material online, *Figure S4*).

Relative increases of admissions for total CVDs, and corresponding 95% CIs, were 0.55% (0.32%, 0.77%) and 0.97% (0.67%, 1.27%) per 10 µg/m^3 fixed increments of lag 0–5 PM_{10} and $PM_{2.5}$, respectively (*Table 2*). Corresponding estimates were 0.79% (0.52%, 1.07%) and 1.32% (0.97%, 1.68%) for cardiac diseases, 1.70% (1.28%, 2.13%) and 2.66% (2.09%, 3.23%) for heart failure, and 1.03% (0.10%, 1.97%) and 1.44% (0.15%, 2.74%) for atrial fibrillation. Results were robust to time trend and temperature adjustment (Supplementary material online, *Table S2*).

Exposure–response functions

The 'meta-curves' representing pooled exposure–response functions among the two PM exposures (at lag 0) and the nine CVD outcomes are displayed in *Figure 2* (total CVD, atrial fibrillation, and heart failure) and in the Supplementary material online, *Figures S5* and *S6* (other endpoints).

We found evidence of non-linear effects in most cases, with steeper slopes of the PM-outcome associations in the lower ranges of exposures (down to 20 µg/m^3 for PM_{10} and 10 µg/m^3 for $PM_{2.5}$), far below the WHO air quality guidelines for daily mean PM_{10} (50 µg/m^3) and $PM_{2.5}$ (25 µg/m^3). Similar results were obtained when more flexible splines were used (Supplementary material online, *Figures S7* and *S8*).

PM effects by age, sex, and degree of urbanization

We found homogeneous associations across groups of municipalities characterized by different degrees of urbanization, with high and

Table 2 Association[a] between PM and cardiovascular admissions

Disease (ICD-9 code)	Lag (days)	PM_{10}			$PM_{2.5}$		
		% IR	95% CI		% IR	95% CI	
Total cardiovascular diseases	0	**0.45**	**0.32**	**0.57**	**0.65**	**0.46**	**0.84**
(ICD-9: 390–459)	0–1	**0.42**	**0.27**	**0.57**	**0.64**	**0.42**	**0.85**
	2–5	**0.37**	**0.15**	**0.59**	**0.81**	**0.49**	**1.13**
	0–5	**0.55**	**0.32**	**0.77**	**0.97**	**0.67**	**1.27**
Cardiac diseases	0	**0.55**	**0.38**	**0.71**	**0.77**	**0.53**	**1.01**
(ICD-9: 390-429)	0–1	**0.58**	**0.40**	**0.77**	**0.86**	**0.60**	**1.13**
	2–5	**0.57**	**0.29**	**0.85**	**1.12**	**0.76**	**1.49**
	0–5	**0.79**	**0.52**	**1.07**	**1.32**	**0.97**	**1.68**
Ischaemic heart diseases	0	**0.62**	**0.13**	**1.11**	**0.88**	**0.15**	**1.61**
(ICD-9: 410–414)	0–1	**0.52**	**0.22**	**0.81**	**0.98**	**0.22**	**1.74**
	2–5	0.18	-0.26	0.63	**0.60**	**0.06**	**1.14**
	0–5	**0.43**	**0.01**	**0.85**	**0.84**	**0.29**	**1.39**
Myocardial infarction	0	**0.59**	**0.20**	**0.99**	**0.82**	**0.32**	**1.32**
(ICD-9: 410)	0–1	**0.62**	**0.17**	**1.07**	**0.90**	**0.29**	**1.50**
	2–5	0.00	-0.45	0.45	0.42	-0.18	1.03
	0–5	0.28	-0.24	0.80	**0.77**	**0.05**	**1.49**
Arrhythmias	0	0.18	-0.26	0.62	0.09	-0.59	0.78
(ICD-9: 427)	0–1	0.23	-0.25	0.72	0.27	-0.45	0.99
	2–5	0.27	-0.35	0.91	0.34	-0.42	1.11
	0–5	0.30	-0.40	1.00	0.39	-0.52	1.30
Atrial fibrillation	0	**0.78**	**0.07**	**1.49**	0.96	-0.03	1.96
(ICD-9: 427.31)	0–1	0.79	-0.05	1.65	**1.25**	**0.26**	**2.26**
	2–5	0.73	-0.13	1.60	1.07	-0.15	2.30
	0–5	**1.03**	**0.10**	**1.97**	**1.44**	**0.15**	**2.74**
Heart failure	0	**1.04**	**0.75**	**1.32**	**1.46**	**1.04**	**1.88**
(ICD-9: 428)	0–1	**1.15**	**0.82**	**1.48**	**1.74**	**1.23**	**2.24**
	2–5	**1.32**	**0.96**	**1.69**	**2.16**	**1.69**	**2.63**
	0–5	**1.70**	**1.28**	**2.13**	**2.66**	**2.09**	**3.23**
Cerebrovascular diseases	0	0.22	-0.05	0.49	0.22	-0.13	0.57
(ICD-9: 430–438)	0–1	-0.05	-0.32	0.23	-0.07	-0.44	0.31
	2–5	-0.07	-0.38	0.23	0.01	-0.41	0.43
	0–5	-0.09	-0.44	0.25	-0.03	-0.49	0.44
Ischaemic stroke	0	**0.48**	**0.13**	**0.84**	**0.51**	**0.06**	**0.97**
(ICD-9: 433–435)	0–1	0.26	-0.09	0.62	0.29	-0.19	0.76
	2–5	0.33	-0.06	0.72	0.51	-0.01	1.04
	0–5	0.40	-0.03	0.84	0.57	-0.02	1.15

% increases of admissions (% IR), and 95% confidence intervals (95% CI), per 10 $\mu g/m^3$ increments in PM.
ICD-9, International Classification of Diseases, 9th revision. In bold, significant results at $\alpha = 0.05$.
[a]Province-specific models adjusted for time trend (natural spline with 6 degrees of freedom/year), air temperature (two natural splines for lag 0–1 and lag 1–6 air temperature), and indicator variables for municipality, day of the week, bank holidays, summer population decrease, and influenza epidemics.

statistically significant risks of PM-related cardiovascular admissions, especially for ischaemic heart diseases and myocardial infarction, even among populations residing in poorly urbanized areas of the country (*Figure 3*). In particular, 10 $\mu g/m^3$ increments in same-day PM_{10} increased total CVD admissions by 0.72% (0.09%, 1.35%) in less urbanized areas vs. 0.34% (0.18%, 0.49%) in the highly urbanized ones. Corresponding estimates for ischaemic heart diseases were 1.82% (0.44%, 3.22%) and 0.36% (0.05%, 0.68%). Formal tests for the presence of effect modification by urbanization level suggested comparable associations between urban and nonurban areas with all CVD outcomes. Similar results were obtained when we stratified the analyses according to the EUROSTAT indicator of urbanization (Supplementary material online, *Figure S9*). In this case, we found significantly higher associations between PM and ischaemic heart diseases in rural areas vs. cities. Finally, we found comparable exposure–response functions between daily PM and selected CVD outcomes, by urbanization levels (Supplementary material online, *Figure S10*).

Subgroup analyses showed increasing estimates of association of both PM_{10} and $PM_{2.5}$ with most outcomes by age, with elderly patients being the most vulnerable to the acute effects of PM, but no

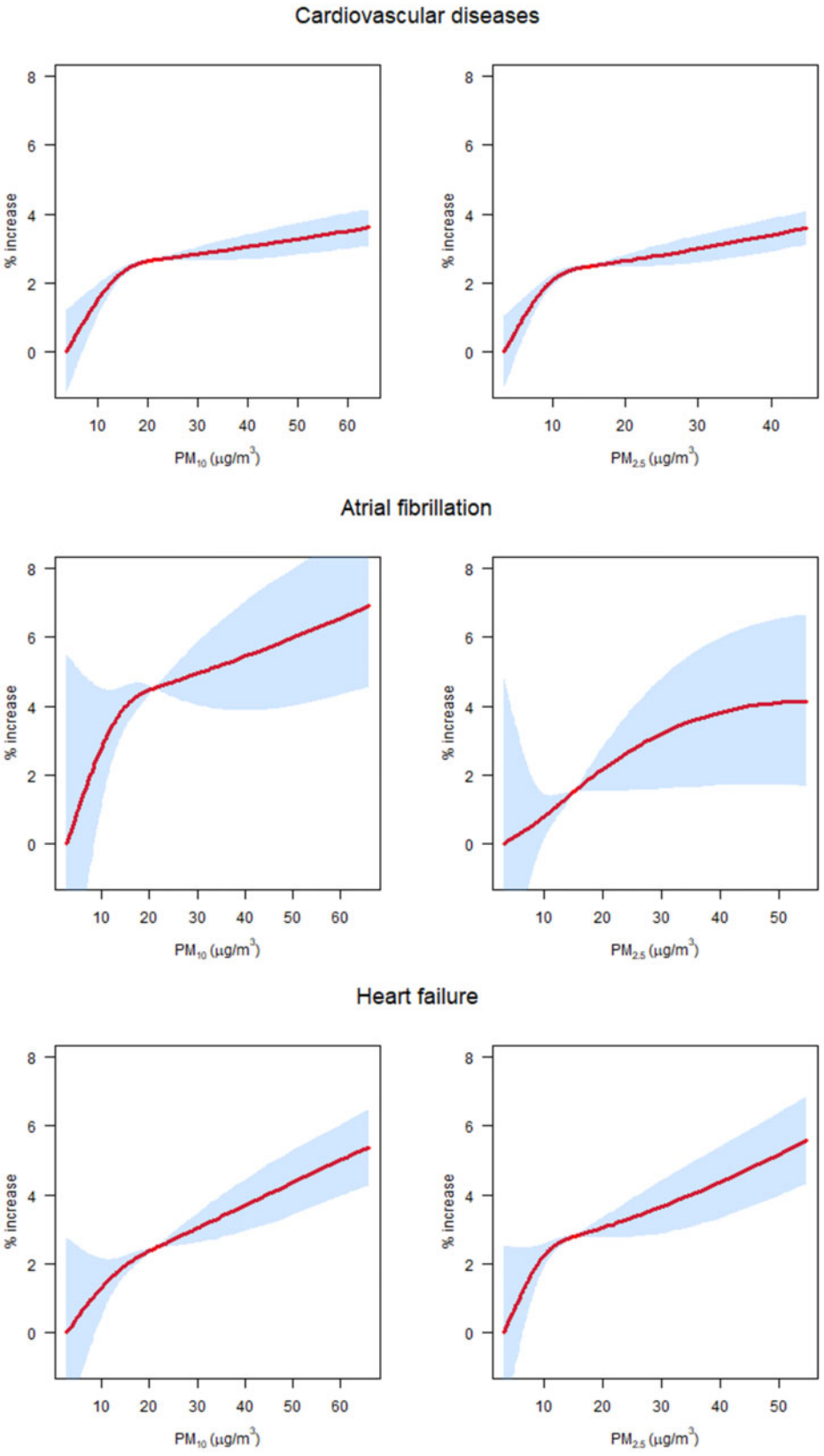

Figure 2 Exposure–response functions.[a] % increases of admissions per increasing levels of PM (lag 0), by cause: PM_{10} on the left, $PM_{2.5}$ on the right. [a]Province-specific models adjusted for time trend (natural spline with 6 degrees of freedom/year), air temperature (two natural splines for lag 0–1 and lag 1–6 air temperature), and indicator variables for municipality, day of the week, bank holidays, summer population decrease, and influenza epidemics.

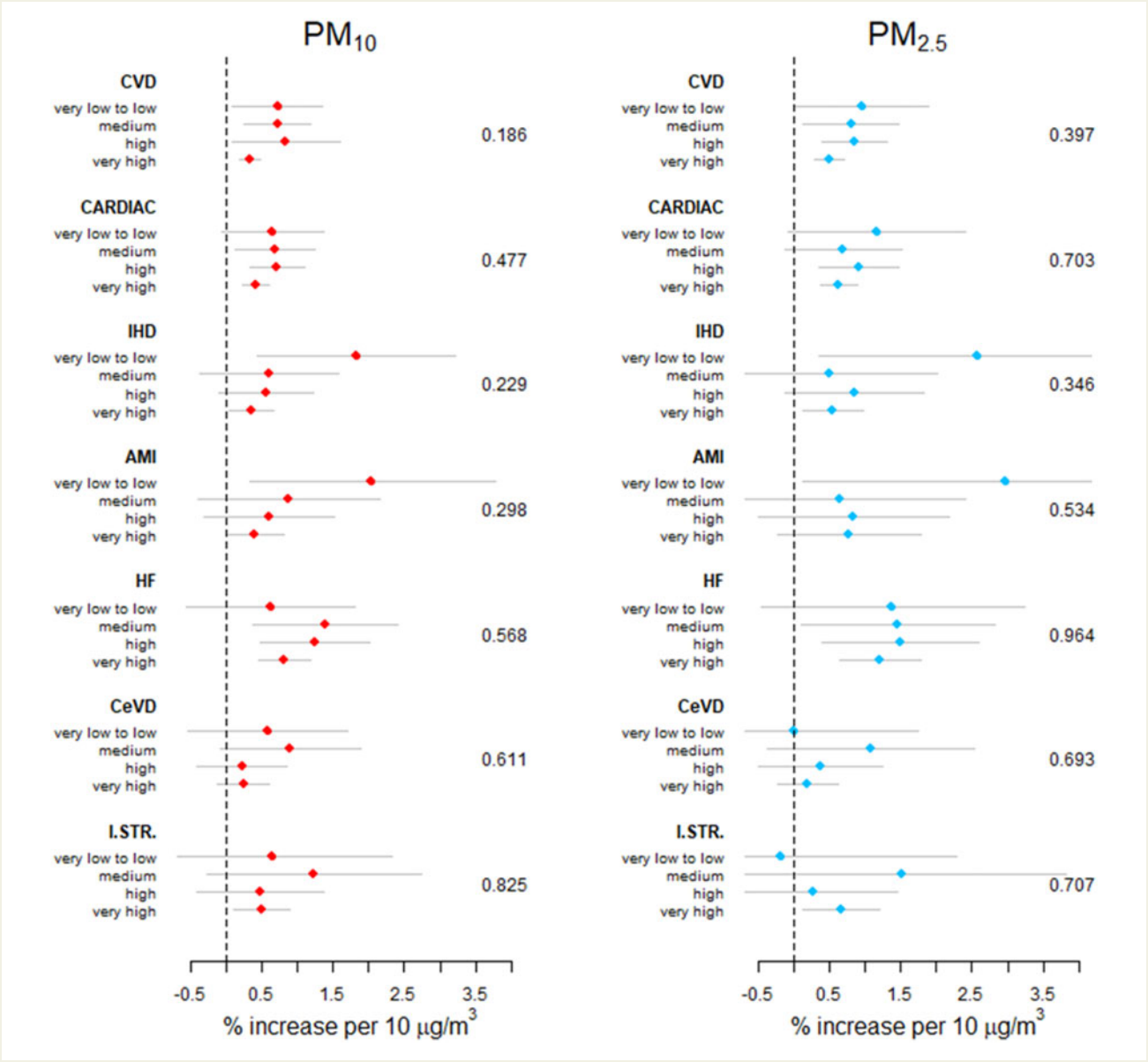

Figure 3 Effect modification by degree of urbanization: % increases of admissions per 10 µg/m^3 increments in PM (lag 0), by cause. On the left of each plot: degrees of urbanization of the municipality (very low to low, medium, high, very high) and the groups of CVD diseases. AMI, acute myocardial infarction; CARDIO, cardiac diseases; CeVD, cerebrovascular diseases; CVD, total cardiovascular diseases; HF, heart failure; I.STR., ischaemic stroke; IHD, ischaemic heart diseases. On the right of each plot: *P*-values of the heterogeneity test between strata of the urbanization score.

substantial differences by sex, the only exception being cardiac diseases, for which women were at greater risk of hospitalization (Supplementary material online, *Figure S11*).

Cases of CVD admissions attributable to daily PM

Table 3 shows the annual numbers of cardiovascular admissions attributable to daily PM concentrations exceeding pre-defined thresholds. Results for specific cardiovascular endpoints are reported in the Supplementary material online, *Table S3*. Overall, we estimated 425 extra CVD admissions every year (0.8% of total CVD) when PM_{10} concentrations were above the WHO guideline of daily concentrations of 50 µg/m^3, of which 81% occurring in highly urbanized areas and the residual 19% in the rest of the territory. Corresponding values for $PM_{2.5}$ exceeding the WHO guideline of 25 µg/m^3 were 1139 nationwide (76% in cities, 24% elsewhere). We have used guidelines for daily concentrations, rather than annual means, because the focus of the study was on short-term (i.e. daily) exposures rather than long-term (i.e. annual) ones.

However, as apparent from *Figure 2*, the strongest PM effects were estimated at the lowest concentrations, i.e. down to 20 µg/m^3 for PM_{10} and 10 µg/m^3 for $PM_{2.5}$. Using these counterfactual levels (20 and 10 µg/m^3, respectively), the attributable cardiovascular admissions increase to 2491 for PM_{10} and 3600 for $PM_{2.5}$. The largest contributions to these estimates came from heart failure (1349 annual

Table 3 Annual cardiovascular admissions attributable to PM levels exceeding predefined thresholds

Pollutant	Threshold ($\mu g/m^3$)	% days ≥ threshold	n. admissions	AC	95% CI		AF (%)
All country (718 270 cardiovascular admissions per year)							
PM_{10}	50	4.7	54 014	425	304	545	0.8
	45	6.2	69 449	561	402	719	0.8
	40	8.2	90 623	736	527	944	0.8
	35	11.2	122 124	969	694	1242	0.8
	30	16.1	173 135	1291	925	1656	0.7
	25	24.3	261 774	1764	1263	2262	0.7
	20	39.1	402 953	2491	1784	3196	0.6
$PM_{2.5}$	25	12.0	116 409	1139	805	1470	1.0
	20	18.3	171 169	1592	1126	2055	0.9
	15	31.4	290 046	2303	1629	2974	0.8
	10	62.7	537 818	3600	2546	4649	0.7
Highly urbanized areas (391 936 cardiovascular admissions per year)							
PM_{10}	50	10.4	41 574	344	246	441	0.8
	45	13.1	52 305	447	320	574	0.9
	40	16.6	66 850	578	414	741	0.9
	35	21.9	87 876	747	535	958	0.9
	30	29.7	121 598	976	699	1252	0.8
	25	42.1	177 799	1303	933	1671	0.7
	20	60.6	259 607	1784	1277	2288	0.7
$PM_{2.5}$	25	22.5	82 223	869	615	1122	1.1
	20	31.7	116 391	1183	837	1527	1.0
	15	49.2	189 891	1658	1173	2140	0.9
	10	79.4	320 422	2467	1745	3185	0.8

AC, attributable cases; AF, attributable fraction; CI, confidence interval.

cases attributable to PM_{10} and 1906 to $PM_{2.5}$), ischaemic heart diseases (834 and 1157), and ischaemic stroke (396 and 424) (Supplementary material online, *Table S3*).

Discussion

In this study, we confirmed a significant short-term association of both PM_{10} and $PM_{2.5}$ with total CVD, cardiac diseases, ischaemic heart diseases, myocardial infarction, and ischaemic stroke, with evidence of an immediate effect on the same day of exposure. We estimated a highly significant association with admissions for heart failure, lasting over 1 week after exposure, and atrial fibrillation, lasting 2 days after exposure. The strength of association was comparable among areas with different degrees of urbanization and the exposure–response relationships were non-linear, with the highest effects seen at low concentrations (down to 20 $\mu g/m^3$ for PM_{10} and 10 $\mu g/m^3$ for $PM_{2.5}$). Finally, elderly patients were the most vulnerable to the acute effects of PM, while we did not find substantial differences by sex.

A large body of literature previously reported associations between daily PM and CVD hospital admissions. A meta-analysis conducted in 2014 collected all the evidence up to May 2011 and, out of 34 studies originally screened, pooled seven estimates of the short-term association between $PM_{2.5}$ and CVD admissions. The authors estimated a relative increase of 0.90% (0.26%, 1.53%) in total CVD admissions per 10 $\mu g/m^3$ increments in daily $PM_{2.5}$, with stronger associations found with heart failure, ischaemic heart diseases and ischaemic stroke.[21] More recently, similar results were reported from different parts of the world, such as the USA,[22] southern Europe,[23] China,[24] and Japan,[9] among others.

The relationship between short-term exposure to fine particles and hospitalizations for heart failure has been already documented. A meta-analysis by Shah and colleagues on 2013 included 11 and 26 studies evaluating short-term effects of $PM_{2.5}$ and PM_{10}, respectively, and estimated relative increases of 2.12% (95% CI: 1.42%, 2.82%) and 1.63% (95% CI: 1.20%, 2.07%) in hospital admissions for heart failure, per 10 $\mu g/m^3$ variation in same day $PM_{2.5}$ and PM_{10} concentrations.[25] Meta-analytical estimates were highest at lag 0 but still significant on the following days, similar to our study. More recently, other studies supported the same conclusions, among which two large Medicare analyses in the USA,[26,27] that estimated relative increases in hospital admissions for heart failure of 1.1% (95% CI: 0.8%, 1.5%) and 1.9% (95% CI: 1.2%, 2.5%) per 10 $\mu g/m^3$ variation in $PM_{2.5}$, respectively. In contrast, the only study conducted in Europe reported a null association in England and Wales.[28]

Acute effects of air pollution on some heart conduction disorders are plausible, as PM exposure is related to changes in cardiac autonomic tone and systemic inflammatory responses that may in turn influence the impulse conduction of the heart muscle.[11]

However, arrhythmias represent a group of disorders with different pathophysiologies, and the epidemiological evidence of air pollution effect on total arrhythmias is still inconsistent. While analyses of emergency room visits and hospital admissions for arrhythmias have shown no relationship with daily PM concentrations in most locations,[26,28] investigators who focused on out-of-hospital cardiac arrests as a direct consequence of ventricular arrhythmia reported significant effects of daily PM,[8,29,30] with few exceptions.[31]

More recently, attention has shifted to atrial fibrillation, a conduction disorder in the atria which can cause mild symptoms, such as dizziness, anxiety, and shortness of breath, but can also increase the risk for stroke, congestive heart failure, and mortality in the worst cases.[32] Some authors estimated significant increases in the risk of PM-induced atrial fibrillation,[33,34] while others failed to do so.[35] In our study, we observed a null association between PM and total arrhythmias while we estimated a significant association with atrial fibrillation, up to lag 2, despite the low statistical power.

The epidemiological evidence on the health effects of ambient particles outside major cities is very limited, because only recently spatiotemporal models have been developed in wide geographical areas to characterize population exposure at finer spatial and temporal resolution. Bravo and colleagues analysed data from 795 US counties and classified them into a four-level urbanization score based on the percent of population residing in urban areas: they found highest $PM_{2.5}$ effects on respiratory admissions in rural areas and on cardiovascular admissions in urban ones.[12] In contrast, Kloog *et al.*,[36] applying a study design very similar to ours, analysed ~3 million CVD admissions in the mid-Atlantic states of the USA and estimated a relative increase in admissions of 0.78% (95% CI: 0.54%, 1.01%) per 10 $\mu g/m^3$ increment of lag 0–1 $PM_{2.5}$, with effects in rural and urban areas equal to 1.04% (95% CI: 0.56%, 1.51%) and 0.7% (95% CI: 0.44%, 0.96%, respectively).

To our knowledge, our study is the only one outside the USA to analyse the effects of daily PM at the national level, including areas with different degrees of urbanization. As previously noted,[12] this presents at least two advantages. First, it allows to address susceptibility in a more comprehensive way, because people living in less urbanized settings might have different lifestyles, diet and socioeconomic status, prevalence of chronic conditions, activity patterns and barriers in accessing health care services.[13] While we don't have information on these characteristics at the national level, we indeed found significant effects of air pollution on the risk of CVD admissions among populations living in the least urbanized areas of Italy, especially for conditions such as ischaemic heart diseases and myocardial infarction. Second, PM concentrations are substantially lower outside the main cities, and the investigation of large populations residing in such areas enables to increase the statistical power to describe the relationship between PM and CVD morbidity at very low exposure levels. This is reflected in our exposure–response functions, which show significant effects of both PM_{10} and $PM_{2.5}$ on most CVD outcomes far below the WHO guidelines, with adverse consequences in terms of attributable cases.

This study presents several strength points. The availability of national admissions data matched with the highly resolved spatiotemporal exposure model allowed us to generalize our findings to the whole Italy, providing estimates of associations in the portion (>50%) of the population living in the less urbanized areas and neglected in previous epidemiological studies. In addition, detailed analyses on specific groups of CVD diagnoses provided new evidence of effects in under-investigated outcomes (i.e. atrial fibrillation), shedding new light on the potential underlying mechanisms, the temporal latency of associations and the exposure–response functions.

Important limitations should also be acknowledged. First, the lack of patient-level information prevented us from exploring individual characteristics (smoking, comorbidities, socio-economic variables) as potential markers of susceptibility. Second, we relied on hospital admissions only, as there is no national archive of emergency room visits. While the latter might have increased the number of events, we still were able to select >2 million CVD admissions with a high degree of case specificity, as we excluded long stays, rehabilitations, day-hospitals, and programmed hospitalizations. Finally, on the exposure side we lacked information on the uncertainty of the exposure estimates across space, especially in more remote areas with no monitoring stations. However, in the worst-case scenario of high exposure measurement error, this would have likely resulted in downward bias of the effect estimates towards the null.

The results of the impact assessment of the short-term effects of PM_{10} and $PM_{2.5}$ in Italy (illustrated in *Table 3*) clearly indicate that the current Air Quality Guidelines that WHO has proposed in 2005 are not protective of public health since a sizeable impact has been detected below daily concentrations of 50 and 25 $\mu g/m^3$, respectively. In the European Union, the current legislation prescribes 50 $\mu g/m^3$ as the daily limit value for PM_{10} but up to 35 exceedances are allowed per year so that the overall public health impact is even larger, as clearly demonstrated in recent studies conducted in Europe and worldwide.[1–3] New guidelines and limit values are clearly needed and, since the exposure–response curves show steeper slopes at lower concentrations, the beneficial effects of more stringent measures at low air pollution levels are large.

In conclusion, as shown by our results, the relationship between PM and cardiovascular health deserves attention from clinicians and cardiologists in order to increase the overall awareness on this important risk factor and include air pollution in the precision medicine initiatives to identify and protect susceptible patients at risk.[4]

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

Data availability

Air pollution data used in this study are the result of a spatiotemporal random forest model developed by the lead author for the entire Italy and described in other publications. Data on specific areas and days can be made available upon request. Similarly, meteorological data have been estimated at 1-km resolution for the whole Italy within the BEEP project. Data on hospitalizations have been provided by the Ministry of Health and cannot be shared for confidentiality reasons. Summary statistics of the hospitalisations data and excerpts of the statistical code for data analysis can be accessed by contacting the lead author.

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