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Association between short-term exposure to air pollutants and cause-specific daily mortality in Italy. A nationwide analysis

Claudio Gariazzo [a,*], Matteo Renzi [b], Alessandro Marinaccio [a], Paola Michelozzi [b], Stefania Massari [a], Camillo Silibello [c], Giuseppe Carlino [d], Paolo Giorgi Rossi [e], Sara Maio [f], Giovanni Viegi [f], Massimo Stafoggia [b], on behalf ofBIGEPI Collaborative Group

[a] Occupational and Environmental Medicine, Epidemiology and Hygiene Department, Italian Workers' Compensation Authority (INAIL), Roma, Italy
[b] Department of Epidemiology, Lazio Regional Health Service, ASL Roma 1, Rome, Italy
[c] Arianet, Milan, Italy
[d] Simularia, Turin, Italy
[e] AUSL-IRCCS, Reggio Emilia, Italy
[f] CNR – Institute of Clinical Physiology, CNR, Pisa, Italy

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ABSTRACT

Background/aim: Daily air pollution has been linked with mortality from urban studies. Associations in rural areas are still unclear and there is growing interest in testing the role that air pollution has on other causes of death. This study aims to evaluate the association between daily air pollution and cause-specific mortality in all 8092 Italian municipalities.

Methods: Natural, cardiovascular, cardiac, ischemic, cerebrovascular, respiratory, metabolic, diabetes, nervous and psychiatric causes of death occurred in Italy were extracted during 2013–2015. Daily ambient PM_{10}, $PM_{2.5}$ and NO_2 concentrations were estimated through machine learning algorithms. The associations between air pollutants and cause-specific mortality were estimated with a time-series approach using a two-stage analytic protocol where area-specific over-dispersed Poisson regression models where fit in the first stage, followed by a meta-analysis in the second. We tested for effect modification by sex, age class and the degree of urbanisation of the municipality.

Results: We estimated a positive association between PM_{10} and $PM_{2.5}$ and the mortality from natural, cardiovascular, cardiac, respiratory and nervous system causes, but not with metabolic or psychiatric causes of death. In particular, mortality from nervous diseases increased by 4.55% (95% CI: 2.51–6.63) and 9.64% (95% CI: 5.76–13.65) for increments of 10 $\mu g/m^3$ in PM_{10} and $PM_{2.5}$ (lag 0–5 days), respectively. NO_2 was positively associated with respiratory (6.68% (95% CI: 1.04–12.62)) and metabolic (7.30% (95% CI: 1.03–13.95)) mortality for increments of 10 $\mu g/m^3$ (lag 0–5). Higher associations with natural mortality were found among the elderly, while there were no differential effects between sex or between rural and urban areas.

Conclusions: Short-term exposure to particulate matter was associated with mortality from nervous diseases. Mortality from metabolic diseases was associated with NO_2 exposure. Other associations are confirmed and updated, including the contribution of lowly urbanised areas. Health effects were also found in suburban and rural areas.

1. Introduction

Short-term exposure to ambient air pollutants, such as fine particulate matter (i.e. PM with aerodynamic diameter <2.5 μm, $PM_{2.5}$), thoracic PM (PM with diameter <10 μm, PM_{10}) and nitrogen dioxide (NO_2), has been associated with adverse health effects in many studies (Atkinson et al., 2015; Cohen et al., 2017; Newell et al., 2018). Most evidence has been related to natural, cardiovascular and respiratory causes (R. Chen et al., 2019; Cong Liu et al., 2019; Meng et al., 2021; Orellano et al., 2020; Zhu et al., 2019), while other diseases, such as

* Corresponding author. Epidemiology Unit, Occupational and Environmental Medicine, Epidemiology and Hygiene Department, INAIL (Italian national workers compensation authority), Via Fontana Candida, 100040, Rome, Italy.
E-mail address: c.gariazzo@inail.it (C. Gariazzo).

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metabolic (diabetes), nervous and psychiatric diseases, have been investigated less.

Emerging studies are supporting biologic and molecular mechanisms for a causal link between air pollution and such diseases ((Eze et al., 2015; Jankowska-Kieltyka et al., 2021; Kim et al., 2018; Rajagopalan and Brook, 2012)). Indeed, biologic mechanisms for a causal link between air pollution and insulin resistance/diabetes onset have already been postulated (Cuiqing Liu et al., 2014). In addition, PM exposure might exacerbate cardiopulmonary toxicity due to metabolic disease (Kobos and Shannahan, 2021), or diabetes may act as a factor for susceptibility (Ester Rita Alessandrini et al., 2016). In other words, it might modify the association between short term exposure to $PM_{2.5}$ and all-cause mortality (Zanobetti et al., 2014), as well as the association between NO_2 and natural, cardiac and respiratory mortality (Chiusolo et al., 2011). However, although prevalence and incidence of diabetes (or other metabolic disorders) have been previously associated with air pollution, studies relating daily air pollution exposure to metabolic-specific mortality are, to date, still scarce.

With regard to nervous diseases, a recent review summarises the current knowledge regarding the impact of air pollution on the cellular processes responsible for the emergence of oxidative stress and neuroinflammation that may eventually lead to detrimental effects in the periphery and the central nervous system (Jankowska-Kieltyka et al., 2021). Some studies also recognised cognitive degradation in students attending schools close to highly polluted roads (An et al., 2021). However, most of these studies have focused on long-term effects, while the analysis of acute effects on nervous disease mortality is rare or controversial (Fu and Guo, 2019; Kasdagli et al., 2022; Yu et al., 2019).

Neuroinflammation and oxidative stress are also relevant for mental health. Several studies showed that acute exposure to air pollution could trigger depressive symptoms or hospitalisations, as well as an increased risk of suicide (Heo et al., 2021; Q. Liu et al., 2021). However, a possible link with mortality from all psychiatric conditions is still to be investigated.

Most epidemiological studies are based on data collected in metropolitan areas (Zhu et al., 2019), in multiple cities from the same country (R. Chen et al., 2019; Faustini et al., 2011; Linares et al., 2018) or in cities from different areas of the world (Cong Liu et al., 2019; Meng et al., 2021). The main reason is the lack of reliable data on air pollutant concentrations in non-urban settings, where population characteristics and source profiles of major air pollutants are likely different from those in major urban areas. It may hamper the generalisation of the epidemiological findings, particularly when health effects are estimated at very low concentrations as those experienced by people living in rural and remote areas. To overcome these limitations, nationwide estimations of daily concentrations of air pollutants have been implemented at high spatial resolution. Recently, new techniques based on dispersion models and machine learning methods have provided such estimations, offering the opportunity to carry out nationwide epidemiological studies (Di et al., 2019; De Hoogh et al., 2019; Renzi et al., 2021; Stafoggia et al., 2022; Xue et al., 2019).

The BIGEPI (BigData for the assessment of health Effects of Air Pollution in the Italian population) project aims to estimate short-term and long-term effects of air pollutants on multiple health endpoints at the national level in Italy (https://bigepi.it/index.php/en/). This paper investigates the association between short-term exposure to air pollutants and cause-specific mortality, with a focus on under-investigated causes (metabolic, nervous, psychiatric diseases). Furthermore, it aims to provide separate estimates for urban, suburban and rural areas.

2. Materials and methods

2.1. Study setting

Italy is a peninsula located in southern Europe, surrounded by the Mediterranean Sea. The country's total area is 307,635 km^2. Many small and medium-sized urban areas in this country have a population below 50,000 and above 100,000 respectively. Six large metropolitan areas are also located within the territory with a population of over 500,000 inhabitants.

From an administrative point of view, based on the Census of Oct. 9, 2011, Italy was divided into 8092 municipalities grouped in 110 provinces with a total population of 59, 433, 744 inhabitants.

2.2. Mortality data

Mortality data were retrieved from the Italian National Institute of Statistics (ISTAT) and causes of death were coded using the tenth International Classification of Diseases (ICD-10). We selected data by day and municipality of death, sex and age classes (0–64, 65–74, 75–84, 85+ years old). For the period 2013–2015, we generated daily counts for the following causes of death: natural (A00-R99), cardiovascular (I00–I99), cardiac (I00–I52), ischemic (I20–I25), cerebrovascular (I60–I69), respiratory (J00-J99), mental (F00–F99), nervous (G00-G99), metabolic (E00-E99) and diabetes (E10-E14).

2.3. Air pollution and temperature data

We estimated daily mean concentrations of PM_{10}, $PM_{2.5}$ and NO_2 through machine learning algorithms trained on monitoring networks, satellite observations, chemical transport models and spatiotemporal data.

As for PM, the entire process is described elsewhere (M. Stafoggia et al., 2019; M. Stafoggia et al., 2017). Briefly, we collected gridded data (1 km^2) of satellite-based aerosol optical depth (AOD) from MAIAC AOD dataset produced by MODIS Aqua L1B and CAMS AOD, as well as spatial (land coverage from CORINE, road network, light at night, impervious surface areas, population density, elevation) and spatiotemporal data (daily means of air temperature and other meteorological parameters from ERA5 reanalysis, ensemble dispersion models from CAMS-Copernicus, monthly vegetation indices from NASA, daily episodes of Saharan dust advections). We developed a four-stage machine learning model to predict daily PM_{10} (2006–2015) and $PM_{2.5}$ (2013–2015) concentration for each 1 × 1 km grid cell and day. In the first stage, we trained a random forest model between observed $PM_{2.5}$ and co-located PM_{10} concentrations, in order to expand the set of $PM_{2.5}$ monitored data. In the second stage, we filled the gaps of satellite-based AOD by fitting another random forest model with AOD estimates from Copernicus used as the main predictor. In the third stage, we fitted a third random forest model where daily mean concentrations of PM_{10} (or $PM_{2.5}$) was the target variable, and the gap-filled AOD, the spatial and the spatiotemporal data were the explanatory variables. Finally, we applied the stage 3 model to predict over each 1-km^2 grid cell of Italy and all days in the study period (stage 4). Model fit statistics on testing monitors, i.e., monitors not used to calibrate the models (cross-validation), demonstrated good predictive properties of the spatiotemporal models, with $R^2 = 0.75$ and 0.81 for PM_{10} and $PM_{2.5}$, respectively.

As for NO_2, three years (2013–2015) of simulations were performed using the chemical transport model FARM (Flexible Air quality Regional model) at 5 km resolution. Then, a downscaling to 1 km resolution was carried out using machine-learning algorithms, considering, as predictors, the FARM results and the same spatial and spatiotemporal data used for modelling PM, with the exception of AOD. We trained a random forest model where monitored daily mean concentrations of NO_2 were the target variable and the spatial, spatiotemporal and FARM data were the explanatory variables. As for PM, we cross-validated the algorithm to guarantee accuracy of the prediction model in locations/days without any monitored data. Fitting statistics on testing monitors demonstrated good predictive properties with $R^2 = 0.6$. Once the calibration model was finalized, we predicted NO_2 daily concentrations in all 1x1-km grid cells of Italy, and all days in the study period. More details can be found in Silibello et al. (2021).

Estimates of daily mean air temperature were obtained at 1 × 1km^2 resolution by calibrating air temperature observations to land surface temperature (LST) satellite data and spatiotemporal parameters. Details can be found elsewhere (de' Donato et al., 2016). In summary, a mixed-effects regression model was fit, where 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. Then, the calibration model was applied to predict daily mean air temperature at each 1-km^2 grid cell and all days in the study period.

Finally, in order to better approximate population-weighted exposures, we used the population in each grid cell, derived from 2011 Census data available at the census block level, as a weight proportional to the amount of resident population, to obtain an average exposure at a municipal level. Then, daily values of population-weighted exposure to PM_{10}, $PM_{2.5}$, NO_2 and temperature were made available for analysis at a municipal level. The analysis of correlations among pollutants shows a high correlation between PM_{10} and $PM_{2.5}$ ($R^2 = 0.85$) and poor correlations between NO_2 and both PM size fraction ($R^2 = 0.05$ and 0.06).

2.4. Statistical analysis

The associations between daily exposures to air pollutants and cause-specific mortality were assessed using a time-series approach. We applied a two-stage analytic protocol, where area-specific analyses were conducted in the first stage, and secondly, a meta-analysis of area-specific results was carried out.

In the first stage, we stacked together the daily time series of the municipalities belonging to the same province (corresponding to NUTS2 levels) and conducted pooled analyses at a provincial level (Renzi et al., 2021; Stafoggia et al., 2022). The pooled analysis was carried out separately for each of the 110 administrative provinces in which Italy is divided. In each province, we fitted over-dispersed Poisson generalised additive models where the municipality-specific daily count of deaths was the outcome variable, and the (lagged) air pollutant was the exposure term. We further adjusted for the municipality-specific long-term seasonal time trends and day of the week, as well as province-specific air temperature, bank holidays, summer population decreases and influenza epidemics. Each mortality outcome was analysed separately.

To simultaneously control for immediate non-linear effects of heat and delayed effects of cold, we applied a method previously described by Stafoggia et al. (Massimo Stafoggia et al., 2009). Briefly, we set warm and cold temperatures by considering the province-specific median values of air temperature as a threshold. Warm temperatures were adjusted by modelling the mean temperature on the same day and the previous day (lag 0–1). We used a natural spline with 2 knots located at the 75th and the 90th percentiles of the province-specific distribution to model warm temperatures. Cold temperatures were adjusted for the mean air temperature of the previous six days (lag 1–6) modelled by natural splines with a single knot fixed on the 25th percentile of the province-specific distribution.

Time trend was adjusted separately for each municipality by adding a four-way interaction term between the municipality, year, month and the day of the week. Holidays, summer population decrease and influenza epidemics were adjusted for using categorical covariates.

Once the adjustment model was set, we estimated the association between air pollutants and cause-specific mortality by defining different lag terms for the air pollutants: average of the current and previous day (lag 0–1), the average of days 2–5 (lag 2–5) and the average of the last 6 days (lag 0–5). In these models, lag-specific terms for air pollutants were added as linear terms.

Then, we tested for effect modification by sex and age (divided into four classes: 0–64, 65–74, 75–84, 85+ years), by generating daily time series of stratum specific events for each municipality. Concerning the degree of urbanisation within the municipalities, we classified each area based on a 3-level urbanisation index "DEGURBA", as defined by EUROSTAT (https://ec.europa.eu/eurostat/web/degree-of-urbanisation/background)). It presents the degree of urbanisation typology for Local Administrative Units level 2 (LAU2) by distinguishes among thinly populated area (rural area); intermediate density area (towns and suburbs/small urban area), and densely populated area (cities/large urban area), named rural, suburban and urban areas hereafter, based on the combination of population size, population density and geographical contiguity of each area. More details on the methodology adopted by EUROSTAT to operate such classification can be found elsewhere (EUROSTAT, 2011). According to this index, 5267 municipalities were classified as rural areas, 2257 as suburban, and 268 as urban areas, contributing to 342,428, 724,814 and 698,912 natural deaths, respectively. For the urbanisation index, we quantified the effect estimates of air pollutants on mortality by using either a fixed increment of 10 μg/m^3 or an increment equal to the interquartile range (IQR) of each pollutant in each level of urbanisation.

Next, for each outcome/exposure combination, we estimated exposure-response functions by fitting distributed-lag non-linear models (DLNM) (Gasparrini et al., 2012) in place of the linear term of air pollutant. The cross-basis was defined through a b-spline function with two degrees of freedom (one inner knot on the 50th centile of the air pollutant distribution) for the air pollutant dimension, and an integer function up to lag 5 days, for the lag dimension.

As sensitivity analyses, we evaluated the potential role of relative humidity as a confounder, by replacing air temperature with apparent temperature (an index of thermal discomfort). Secondly, we applied alternative models for temperature adjustment (see Supplementary Material (SM) for details). Finally, we fitted two-pollutant models, by inserting pairs of air pollutants (PM_{10}-NO_2, $PM_{2.5}$-NO_2) in the same model, to disentangle their independent associations with mortality outcomes.

In the second stage of analysis, we applied a random-effects meta-analysis to combine the province-specific estimates into a national estimate. We then reported the pooled estimates and related 95% confidence intervals as the percentage changes in daily mortality per 10 μg/m^3 increase in air pollutant concentrations. For the meta-analytic concentration-response functions, we pooled together the province-specific curves using a multivariate meta-regression (Gasparrini et al., 2012), which incorporated province-specific averages of exposures as well as their ranges to capture the heterogeneity of estimates across space. Finally, to statistically test for the presence of effect modification by age, sex and urbanisation level, we reported the p-value of heterogeneity among the pooled estimates of the individual strata.

All the analyses were conducted using the R statistical software, version 4.0.3.

3. Results

3.1. Descriptive analysis

Table 1 shows a description of the environmental data considered in the study during 2013–2015. Average values were 21.1, 15.1, 14.7 μg/m^3 for PM_{10}, $PM_{2.5}$ and NO_2, respectively, and 13.9 °C for air temperature. Mean values of PM_{10} were 18.9, 25.4 and 30.8 μg/m^3 for rural, suburban and urban areas, respectively. Increasing values by urbanisation level were also observed for $PM_{2.5}$ and NO_2.

Table 2 shows the total daily counts of cause-specific mortality registered during 2013–2015. We observed about 1.7 million deaths by natural causes in the study period. Cardiovascular, cardiac, cerebrovascular and respiratory were the most frequent causes of death. Data by age, sex and urbanisation level are also reported in the table.

Table 1
Description of the environmental data for the study period, overall and by the level of urbanisation score in Italy. Years 2013–2015.

Variable		Min	Perc. 25°	Median	Mean	Perc. 75°	Max	IQR
Overall								
	PM_{10} (μg/m^3)	1.8	12.8	17.4	21.1	24.7	290.2	11.9
	$PM_{2.5}$ (μg/m^3)	1.3	8.6	11.6	15.1	16.9	163.4	8.2
	NO_2 (μg/m^3)	2.7	8.0	11.9	14.7	18.8	115.9	10.8
	Air temperature (°C)	−15.9	8.2	13.9	13.9	19.6	34.8	11.4
Urbanisation score								
Rural								
	PM_{10} (μg/m^3)	1.8	11.8	15.9	18.9	22.0	275.7	10.2
	$PM_{2.5}$ (μg/m^3)	1.6	8.1	10.7	13.5	15.0	157.0	6.9
	NO_2 (μg/m^3)	2.7	7.1	9.5	11.8	14.4	73.7	7.3
Suburban								
	PM_{10} (μg/m^3)	2.1	15.7	21.1	25.4	29.6	290.2	13.9
	$PM_{2.5}$ (μg/m^3)	1.3	10.1	13.8	18.0	20.9	163.4	10.8
	NO_2 (μg/m^3)	4.4	13.0	17.6	19.8	24.2	105.4	11.3
Urban								
	PM_{10} (μg/m^3)	2.7	18.6	24.9	30.8	36.1	283.6	17.5
	$PM_{2.5}$ (μg/m^3)	1.3	11.3	15.6	21.2	25.1	158.3	13.8
	NO_2 (μg/m^3)	6.1	21.1	27.6	29.7	36.7	115.9	15.6

Table 2
Cause-specific deaths during the study period (2013–2015) in Italy.

		Natural	Cardiovascular	Cardiac	Cerebrovasc.	Ischemic	Respiratory	Metabolic	Diabetes	Mental	Nervous
Total		1,769,660	680,203	477,711	135,372	82,927	131,389	81,807	15,799	56,185	76,357
Year	2013	575,228	221,948	155,205	44,528	27,900	41,656	26,607	5101	17,357	23,979
	2014	574,185	219,530	154,118	43,869	27,215	41,381	26,026	5063	17,523	24,337
	2015	620,247	238,725	168,388	46,975	27,812	48,352	29,174	5635	21,305	28,041
Gender	Male	845,077	295,852	212,415	54,488	46,281	70,363	35,401	6885	18,528	32,447
	Female	924,583	384,351	265,296	80,884	36,646	61,026	46,406	8914	37,657	43,910
Age-class	0–64	196,311	41,550	31,569	7075	11,598	6043	7634	1157	1959	6573
	65–74	252,052	63,583	45,738	12,085	13,482	12,588	11,754	2323	2338	9368
	75–84	550,428	196,194	133,844	42,865	26,239	41,470	27,047	5397	13,965	28,005
	85+	770,819	378,872	266,557	73,346	31,607	71,288	35,372	6922	37,923	32,411
Urbanisation score											
	Rural	342,428	146,906	106,766	24,833	17,543	22,432	18,150	3946	13,084	15,690
	Suburban	724,814	277,356	194,813	55,889	32,855	56,125	33,697	6538	24,885	32,763
	Urban	698,919	254,447	174,992	54,457	32,318	52,546	29,765	5255	18,073	27,742

3.2. Associations of air pollutants with cause-specific mortality

The associations among short-term exposures to PM_{10}, $PM_{2.5}$ and NO_2 at different lags (0–1, 2–5, 0–5 days) and cause-specific mortality are shown in Table 3. The effects were stronger at prolonged lags (0–5 days). Therefore, we have used lag 0–5 as the main exposure in further analyses.

Natural, cardiovascular and respiratory mortality daily counts were confirmed to be associated with PM_{10} and $PM_{2.5}$. Conversely, we estimated no association of ischemic, cerebrovascular, metabolic, diabetes and mental disease mortality outcomes with both PM_{10} and $PM_{2.5}$. Cardiac mortality was positively associated with PM_{10} (1.40%; 95% CI 0.60–2.20 at lag 0–5) and $PM_{2.5}$ (2.91%; 95% CI 1.52–4.33 at lag 0–5) for increments of 10 μg/m^3.

An original result of this study is the positive association of mortality for nervous disease causes with PM_{10} (4.55%; 95% CI 2.51–6.63 at lag 0–5) and $PM_{2.5}$ (9.64%; 95% CI 5.76–13.65 at lag 0–5).

We also confirmed the association of NO_2 with respiratory mortality, but we estimated no association or insignificant negative associations for natural, cardiovascular, cardiac, cerebrovascular, ischemic, diabetes and mental mortality causes. An interesting result is the positive association of daily metabolic mortality with NO_2 (7.30%; 95% CI 1.03–13.95 at lag 0–5), although the estimate was largely uncertain. We estimated a negative association for nervous disease mortality (−8,74%; 95% CI -15.39–1.57 at lag 0–5). In general, the effects for NO_2 were stronger and had larger confidence intervals compared with those estimated for PM_{10} and $PM_{2.5}$.

Based on previous results, we decided to report association and effect modification results only for a subset of outcome/exposure combinations, and only at lag 0–5.

3.3. Effect modification

We estimated no or weak effect modification by sex for natural, cardiovascular, respiratory and nervous causes of death, with regard to all pollutants (Fig. S1 and Table S1 of SM). In particular, there were slightly higher $PM_{2.5}$ effects on cardiovascular mortality in females than males, (1.65 vs 0.56% for PM_{10} and 2.78 vs 1.82% for $PM_{2.5}$), while we estimated the opposite for respiratory mortality and $PM_{2.5}$ (4.30 vs 2.79% for males and females respectively). A stronger effect in men was also estimated for NO_2 and metabolic-disease mortality (20.83 vs −0.44%).

Moreover, we estimated a trend of increasing risks by age, with the elderly (above 85 years old) being more at risk than the younger subjects for natural (1.91%) and cardiovascular (1.76%) mortalities (Fig. S1 of SM). Nevertheless, only the differences in effects for cardiovascular and natural mortality were statistically significant (p-value of effect modification <0.05).

Fig. 1 shows the results of the associations between PM_{10} and $PM_{2.5}$ with natural, cardiovascular, respiratory and nervous disease mortality outcomes, by urbanisation score of the municipality. Estimates were expressed as % increases of risks per fixed as well as IQR increments of the pollutants. There was a positive association with cause-specific mortality not only in urban areas but also in rural and suburban ones. When a fixed increment of 10 μg/m^3 was used, the estimated associations were larger in rural municipalities when compared with suburban

Table 3
Associations between short-term exposure to PM_{10}, $PM_{2.5}$ and NO_2 at different lags (0–1, 2–5, 0–5 days) and cause-specific mortality during 2013–2015. Results are from random effects meta-analysis of Italian province-specific estimates (110 provinces) and are expressed as a percentage increase of risk (IR%) and 95% confidence intervals (95% CI) per 10 μg/m^3 increases.

Disease	Lag	PM_{10}			$PM_{2.5}$			NO_2		
		IR %	95%CI		IR %	95%CI		IR %	95%CI	
Natural	0–1	1.15	0.89	1.42	1.72	1.27	2.17	−0.88	−1.49	−0.26
	2–5	0.72	0.36	1.07	1.36	0.75	1.96	−0.14	−0.80	0.54
	0–5	1.26	0.88	1.65	2.08	1.44	2.72	−0.77	−1.67	0.14
Cardiovascular	0–1	0.97	0.50	1.45	1.71	0.93	2.49	−1.41	−2.58	−0.22
	2–5	0.71	0.04	1.38	1.61	0.49	2.74	−0.35	−1.88	1.21
	0–5	1.18	0.46	1.90	2.32	1.21	3.43	−1.36	−2.91	0.21
Cardiac	0–1	1.01	0.39	1.62	1.96	0.96	2.96	−1.70	−3.23	−0.15
	2–5	0.91	0.17	1.65	2.11	0.78	3.45	−0.45	−2.59	1.73
	0–5	1.40	0.60	2.20	2.91	1.52	4.33	−1.62	−4.01	0.83
Cerebrovasc.	0–1	0.10	−1.19	1.40	0.02	−2.21	2.31	−0.09	−5.31	5.41
	2–5	−0.31	−1.54	0.94	−0.51	−2.55	1.57	0.52	−4.54	5.85
	0–5	−0.12	−1.61	1.39	−0.22	−2.60	2.21	0.19	−4.98	5.65
Ischemic	0–1	−1.43	−3.29	0.46	−2.08	−5.47	1.43	−3.13	−8.19	2.21
	2–5	0.27	−1.59	2.16	1.12	−2.51	4.89	−2.17	−7.47	3.43
	0–5	−0.39	−2.53	1.80	0.01	−4.15	4.36	−4.00	−10.77	3.28
Respiratory	0–1	2.29	1.35	3.23	3.22	1.44	5.03	1.26	−1.53	4.13
	2–5	2.59	1.28	3.92	3.52	1.17	5.93	5.95	1.02	11.13
	0–5	3.54	2.13	4.97	4.55	1.78	7.40	6.68	1.04	12.62
Metabolic	0–1	1.08	−0.68	2.87	1.63	−1.70	5.07	8.25	−1.24	18.66
	2–5	−0.14	−1.94	1.70	−0.88	−4.46	2.83	3.39	−1.05	8.03
	0–5	0.56	−1.45	2.61	0.32	−3.23	4.00	7.30	1.03	13.95
Diabetes	0–1	0.40	−4.05	5.06	0.29	−7.00	8.15	6.89	−16.99	37.63
	2–5	1.65	−4.46	8.15	−0.16	−9.14	9.71	0.25	−13.07	15.59
	0–5	1.91	−4.07	8.27	0.40	−9.38	11.24	3.43	−10.95	20.13
Mental	0–1	1.34	−1.29	4.05	1.62	−3.46	6.96	−6.42	−13.22	0.92
	2–5	1.72	−1.26	4.79	2.19	−3.44	8.14	4.55	−2.52	12.13
	0–5	2.09	−1.28	5.58	2.37	−4.15	9.34	−0.02	−8.48	9.21
Nervous	0–1	2.96	1.31	4.64	6.55	3.38	9.81	−6.71	−11.49	−1.68
	2–5	3.14	1.34	4.98	7.08	3.64	10.64	−4.63	−10.98	2.19
	0–5	4.55	2.51	6.63	9.64	5.76	13.65	−8.74	−15.39	−1.57

or urban municipalities (e. g. 1.50, 1.03 and 1.25% for PM_{10} and 2.67, 1.43 and 1.73% for $PM_{2.5}$ for rural, suburban and urban areas, respectively, when considering natural-cause mortality). Similar larger effects in rural areas were also estimated for the association of NO_2 with respiratory mortality. However, when the urbanisation-specific IQRs were used, the effect estimates were larger in urban than suburban and rural areas (e.g. 1.53, 1.43 and 2.20% increase in natural mortality for PM_{10} and 1.83, 1.55 and 2.40% for $PM_{2.5}$ for rural, suburban and urban areas, respectively).

It is worth noting the differential effects of air pollution on nervous disease mortality by urbanisation level: the associations were statistically significant in urban areas (3.4% and 4.5% for PM_{10} and PM2.5, respectively for 10 μg/m^3 increments) but not significant in sub-urban and rural ones. There was no statistically significant effect modification by urbanisation level for the association of metabolic mortality with NO_2 (Table S1 of SM).

The exposure-response functions (Fig. S2 of SM) display steeper slopes at lower PM concentrations. This result is consistent with the stronger associations we estimated in rural areas, the ones mostly contributing to the lower extreme of air pollutants distributions.

3.4. Sensitivity analyses

The results of the sensitivity analyses are summarised in Table S2 of SM. The use of alternative knots in the modelling of warm and cold air temperature, the use of apparent temperature instead of air temperature, as well as the modelling of the full air temperature without considering separate terms for warm and cold temperatures, did not alter the main results. Similarly, the main results were robust to co-pollutant adjustment (Table S3 of SM).

4. Discussion

We estimated evidence of an association of short-term exposure to PM with nervous disease mortality and short-term exposure to NO_2 with metabolic mortality. We confirmed the associations of PM with natural, cardiovascular, cardiac and respiratory causes of death, as well as of NO_2 with respiratory mortality. By contrast, we estimated no associations between any of the pollutants with ischemic, cerebrovascular and psychiatric mortality.

We did not find an association of short-term exposure to NO_2 with natural and cardiovascular mortality, conflicting with the findings reported by other authors (E.R. Alessandrini et al., 2013; Carugno et al., 2016; Linares et al., 2018; Meng et al., 2021; Orellano et al., 2020). Also, we estimated a protective association of NO_2 with nervous disease mortality. The largest associations were found at prolonged lags (0–5 days), with similar magnitude among urban, suburban and rural settings. Our main results were robust also when considering alternative approaches for air temperature or co-pollutant adjustment. We estimated small differences in the effect estimates by sex. By stratifying for age class, broader differences in the estimated effects were found. Natural and cardiovascular mortality for short-term PM exposure showed growing effects by increasing age, with the highest risk in the elderly.

In general, we estimated larger effects than those reported in the literature. As for natural-cause mortality, we estimated 1.26% and 2.08% increase of daily mortality for 10 μg/m^3 increase in PM_{10} and $PM_{2.5}$, respectively, compared to either worldwide cities studies (0.44 and 0.68% (Cong Liu et al., 2019), 0.41 and 0.65% (Orellano et al., 2020), 0.59 and 0.78% (Yu et al., 2019)) or previous Italian multi-cities studies (0.47% (E.R. Alessandrini et al., 2013), 0.93% (Faustini et al., 2011), 0.30% (Carugno et al., 2016) for PM_{10}). Similar higher effects than those reported in the literature were found for cardiovascular mortality (Carugno et al., 2016; Cong Liu et al., 2019; Orellano et al., 2020). As for respiratory mortality, we estimated for PM_{10} either higher

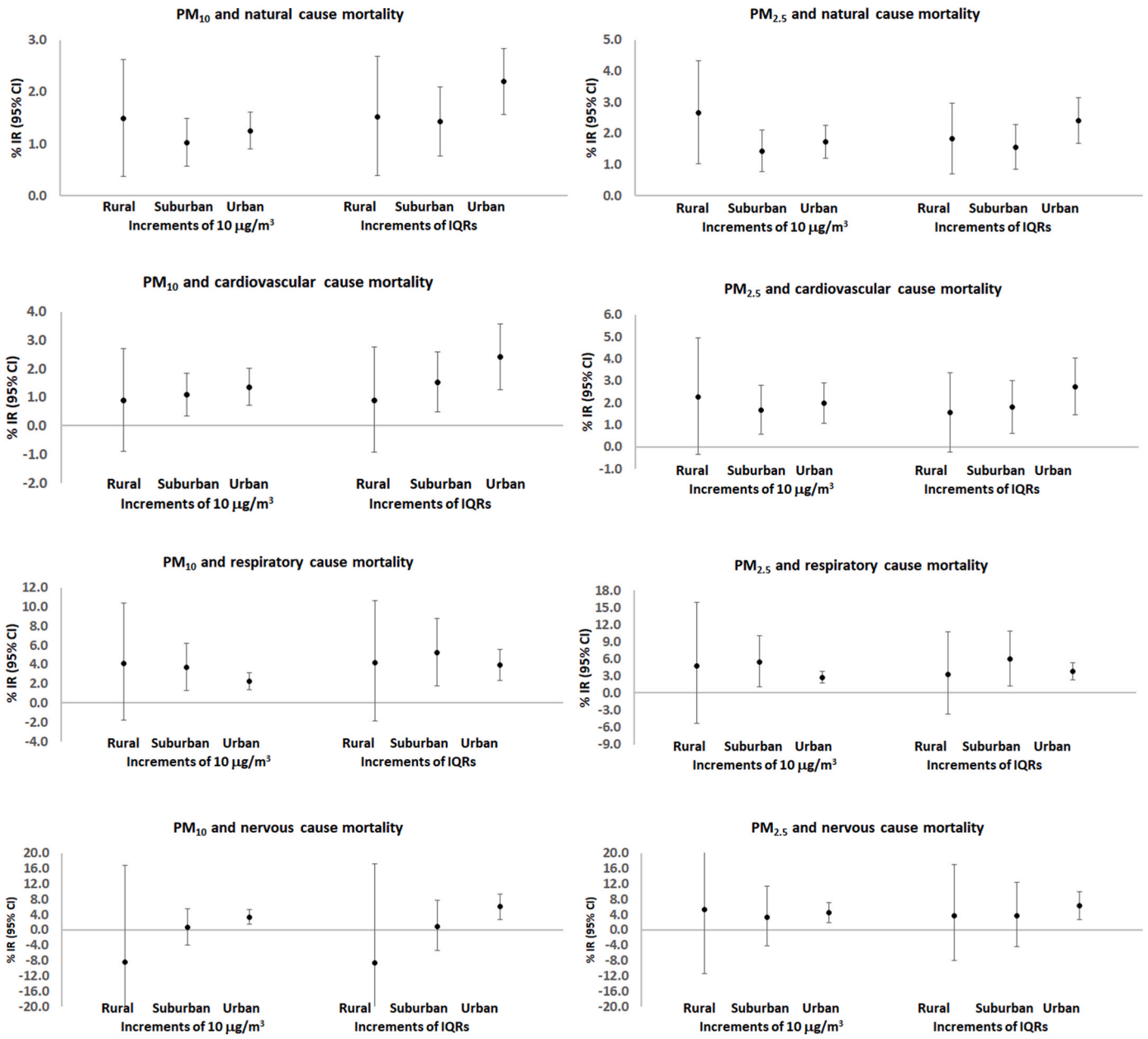

Fig. 1. Effect modification by urbanisation score of the associations between short-term exposure at lag 0–5 to PM_{10} and $PM_{2.5}$ and natural, cardiovascular, respiratory and nervous disease mortality during 2013–2015. Results are from random effects meta-analysis of Italian province-specific estimates (110 provinces) expressed as a percentage difference of risk and relative 95% confidence intervals per 10 μg/m^3 (left picture) and IQRs increases (right picture). All P-het were>0.05 in all pollutants.

(Cong Liu et al., 2019; Orellano et al., 2020; Yu et al., 2019; Zhu et al., 2019) or similar effects (E.R. Alessandrini et al., 2013; Carugno et al., 2016; Faustini et al., 2011), with respect to values reported in the literature.

Indeed, after stratifying by urbanisation score, we estimated larger effects in rural and suburban than in urban municipalities. Consistently, the concentration-response curves showed steeper slopes at lower concentrations, where most of the rural municipalities contributed with exposure data. This suggests caution in the interpretation of area-specific results when a fixed increment (e. g. 10 μg/m^3) is used, as it represents totally different exposure ranges in rural versus suburban or urban settings.

Evidence of harmful short-term effects of air pollution has been reported in the literature for rural or less urbanised areas. Stafoggia and Bellander (2020) found significant effects in non-urban areas of Stockholm, Sweden. Bravo et al. (2017), by considering data from 708 U.S. counties, estimated broader effects of fine particles on respiratory hospital admissions in rural areas. Kloog et al. by analysing 3 million CVD admissions in the U.S., found an association with $PM_{2.5}$ concentrations for both rural and urban areas (Kloog et al., 2014). A recent Italian study about hospitalisation for respiratory diseases caused by short-term PM exposure found larger effects in less urbanised municipalities (Renzi et al., 2021).

An original result of our study was the association of both PM_{10} and $PM_{2.5}$ daily exposures with mortality due to nervous system diseases. Studies about this effect of particulate matter are very rare. An *in vivo* experimental toxicological study (Kim et al., 2018), as well as epidemiological studies (J. C. Chen and Schwartz, 2009; Gu et al., 2020; Zanobetti et al., 2014), support the association of ambient air pollutants with central nervous system dysfunction, neurobehavioral effects,

hospital admissions for nervous diseases and natural mortality for subjects with a previous admission for neurological disorders. Most of the studies about the air pollution-related effects on neurological diseases were focused on long-term exposure and degenerative outcomes (Dementia, Alzheimer and Parkinson's diseases). The findings on the effect of short-term PM on nervous disease mortality are rare and controversial. Yu et al. did not find any association in a Chinese population (Yu et al., 2019). Elevated mortality risks, instead, have been found to be associated with diseases of the nervous system during hazy days (Ho et al., 2018). Our study found mortality from nervous system disease significantly associated with PM exposure. This association was also found at longer prolonged lags (lag 0–15 days) with a small reduction in the estimated increment of risk (7.66% (95% CI: 1.96–13.67) and 3.12% (95% CI: 0.20–6.56) for $PM_{2.5}$ and PM_{10} respectively). The risk was statistically significant in urban municipalities with a slight increase of risk by age. The large spectrum of nervous system diseases included in this analysis did not allow the identification of specific neurological disorders, degenerative diseases or inflammatory diseases of the central nervous system.

An additional important finding of our study was the positive association found between metabolic mortality and NO_2 exposure at prolonged lags (lag 0–5), with a significant effect modification by sex. However, at prolonged lags (lag 0–15) the association became smaller (%IR 2.25) than that at lag 0–5 and statistically not significant. A larger risk was identified for males (Table S1 of SM). We estimated no significant positive association with PM, in agreement with Yu et al., (2019). The mortality for diabetes diseases, included in the metabolic group, was found with a null association with all pollutants. Few studies reported that short-term exposure to air pollution was significantly associated with larger risks of type 2 diabetes mortality (Wu et al., 2021) or that diabetes could confer a strong susceptibility to air pollution (Chiusolo et al., 2011; Goldberg et al., 2013), with adverse effects on lipid levels among type 2 diabetes patients (M. Wang et al., 2018).

The lack of sufficient literature evidences about the short-term effects of air pollution on mortality for nervous system and metabolic diseases indicates the need for further investigations.

Indeed, in order to possibly explain the increased risk of death in subjects suffering from metabolic and nervous diseases due to short-term exposure to air pollution, some biological mechanisms have been hypothesized. The adverse effects of PM and NO_2 on neural systems and metabolism can be attributed to inflammatory and oxidative stress pathways. As a matter of fact, it has been hypothesized that exposure to air pollutants activates common processes in which cytokines and inflammatory signaling molecules are involved in the development of depressive disorders and their comorbidities, such as heart disease, diabetes, and autoimmune conditions (Liu et al., 2021). The same pathways are also involved in the etiology of diabetes, potentially leading to insulin resistance and beta cell dysfunction (Paul et al., 2020). Moreover, systemic oxidative stress and inflammation are related to endothelial dysfunction, vasoconstriction, platelet aggregation, pro-thrombotic and anti-fibrinolytic effects (Cascio, 2016). Then, all these biochemical and physiological changes may be associated with short-term subclinical effects such as elevated blood pressure, increased heart rate and a pro-thrombotic state, with subsequent clinical effects like arrhythmia, heart failure, and ischemia of the heart or brain (Cascio, 2016).

Our study has strengths and limitations. The major strength is the use of multi-year multi-pollutant daily high-resolution exposure data, which allowed obtaining information for nearly all Italian municipalities. Thus, this national epidemiological study provided data even for those cities never included in former multi-city studies. Furthermore, the availability of nationwide cause-specific mortality data containing individual administrative information allowed identifying associations not yet detected in urban-related epidemiological studies. Furthermore, the inclusion of municipalities with very low exposures allowed investigating adverse health effects at very low concentrations. This very important issue has only recently been addressed in both the new WHO guideline and in epidemiological studies (Brauer et al., 2019). In addition, novel associations emerged in our study, like nervous system diseases with short-term PM concentrations and metabolic diseases with NO_2 exposure. Other associations, like those with natural, cardiovascular and respiratory diseases are confirmed and updated, including the contribution of lowly urbanised areas.

A limitation was the lack of other potential confounders, which we could not adjust for. In particular, the lack of individual-level information prevented us from exploring individual characteristics (smoking, comorbidities, socio-economic variables and occupational risk factors) as potential markers of susceptibility. Another limitation is linked to the fact that we considered the municipality of death as that of exposure. Indeed, for a few individuals, the location of death might be different from that where he/she lived. This is particularly true for small cities, where access to health services might exist only in neighbouring municipalities. In light of the minimal difference in exposure at short spatial ranges, such exposure misclassification may be neglected. Moreover, since we used modelled nationwide estimation of pollutants exposure, we lacked information on the uncertainty of the exposure estimates across space, especially in more remote areas without monitoring stations, which data were used to calibrate model results. However, in the case of high exposure measurement error, this would have likely resulted in a downward bias of the effect estimates towards the null.

5. Conclusions

This study, by investigating the relationship of cause-specific mortality with short-term exposure to air pollutants, provides evidence of the positive association of daily mortality from natural, cardiovascular, cardiac, respiratory and nervous diseases with PM_{10} and $PM_{2.5}$ daily exposures, as well as the association of respiratory and metabolic mortality with NO_2 daily concentrations. Conversely, no associations were estimated between any of these pollutants with ischemic, cerebrovascular and psychiatric mortality. The stratified analysis by levels of urbanisation, addressed for associations not only in highly urbanised cities but also in suburban and rural areas. Our findings suggest higher effects of PM on natural and cardiovascular mortality in the elderly population.

Credit authorship statement

Claudio Gariazzo: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Writing - Review & Editing; **Matteo Renzi**: Methodology, Formal analysis, Writing - Review & Editing; **Alessandro Marinaccio**: Conceptualization, Writing - Review & Editing; **Paola Michelozzi**: Supervision; **Stefania Massari**: Resources, Data Curation; **Camillo Silibello**: Resources; **Giuseppe Carlino**: Resources; **Paolo Giorgi Rossi**: Writing - Review & Editing; **Sara Maio**: Supervision, Project administration; **Giovanni Viegi**: Supervision; **Massimo Stafoggia**: Conceptualization, Methodology, Writing - Review & Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Matteo Renzi, Paola Michelozzi, Paolo Giorgi Rossi, Sara Maio, Giovanni Viegi, Massimo Stafoggia reports financial support was provided by National Institute for Insurance against Accidents at Work.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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