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Association between long-term exposure to air pollution and cause-specific mortality within five Italian longitudinal metropolitan studies

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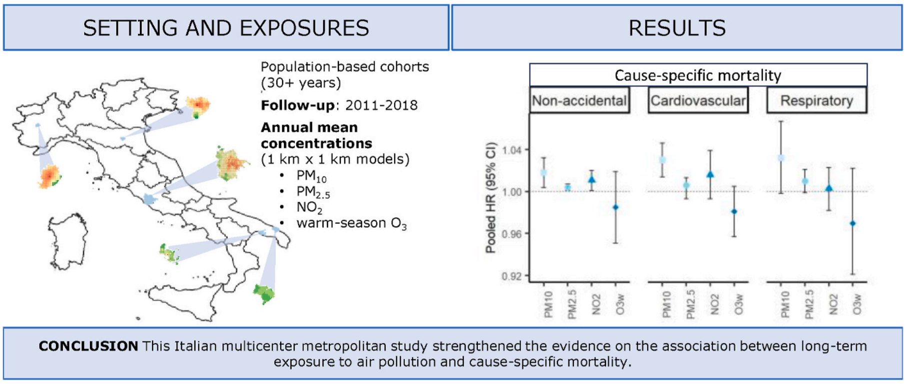
HIGHLIGHTS

- First Italian multicenter longitudinal metropolitan study on air pollution and mortality.
- Standardized protocols and fine-scale air pollution exposures.
- PM and NO_2 were associated with higher risks of cause-specific mortality outcomes.
- Air pollutant adverse effects did not change when adjusted for co-pollutants.
- Despite declining air pollution levels, mortality effects remain consistently high.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Extensive epidemiological literature has documented adverse effects of ambient air pollution on human health. However, in Italy, no multicenter longitudinal studies on chronic exposure to air pollution and mortality have been conducted. Within the BIGEPI project, we aimed to investigate the association between long-term exposure to air pollution and cause-specific mortality in large Italian population-based cohorts.

Methods: Five administrative cohorts from Turin, Bologna, Rome, Taranto, and Brindisi (Italy) were included. Subjects aged 30+ were enrolled from the 2011 Census, followed-up until 2018 (2019 for Bologna), and linked with population and health registries. Annual mean concentrations of particulate matter ≤10 and 2.5 μm (PM_{10} and $PM_{2.5}$), dioxide nitrogen (NO_2), and warm-season ozone (O_{3w}) were assigned to each participant's geocoded residential address at baseline. Long-term associations between pollutants and non-accidental, cardiovascular, and respiratory mortality were investigated through single- and two-pollutant Cox proportional hazard models. Effect modification by sex and age was tested. Cohort-specific estimates were pooled in a random-effects meta-analysis.

Results: 2,709,903 subjects (contributing over 18 million person-years) generated 266,821 non-accidental deaths. Each increment of 5 $\mu g/m^3$ of $PM_{10,}$ 1 $\mu g/m^3$ of $PM_{2.5}$ and 10 $\mu g/m^3$ of NO_2 was associated with an increased risk of non-accidental mortality, with pooled Hazard Ratios (HR) of 1.018 (95% CI: 1.005–1.030), 1.004 (95% CI: 1.001–1.007) and 1.010 (95% CI: 1.002–1.018), respectively. HRs for cardiovascular and respiratory mortality were higher, the latter with CIs including the null. The associations remained quite stable after adjustment for the other pollutants. O_{3w} was negatively associated with mortality but estimates were not statistically significant and reduced to unity upon adjustment for NO_2. No consistent statistically significant effect modifications by sex and age emerged.

Conclusions: Updated evidence implicates a continued risk of mortality in Italy due to long-term air pollution exposure, despite declining levels of exposure during the last years.

1. Introduction

Ambient air pollution stands as a major environmental risk factor to health: it is estimated to be responsible for 4.2 million premature deaths worldwide per year (World Health Organization – WHO, 2022). In Europe an estimated 238,000 deaths are attributable to exposure to fine particulate matter ($PM_{2.5}$) levels exceeding the 2021 WHO guidelines (Hoffmann et al., 2021). Meanwhile, 49,000 and 24,000 premature deaths are due to exposure to nitrogen dioxide (NO_2) and ozone (O_3), respectively (European Environment Agency - EEA, 2022). In Italy, deaths attributable to exposure to high air pollution levels are 72,083 for $PM_{2.5}$ and 30,661 for NO_2 during 2016–2019 (Stafoggia et al., 2023). In fact, despite a decreasing trend over the years for PM and NO_2, there are still high levels of air pollution, especially in northern Italy and metropolitan areas (EEA, 2023).

Numerous epidemiological studies have already reported consistent adverse associations between long-term exposure to ambient air pollution and various health outcomes, particularly cause-specific mortality (Atkinson et al., 2018; Hvidtfeldt et al., 2019; Pope et al., 2019; So et al., 2023; Zhang et al., 2022). Furthermore, diverse European multicenter studies including millions of subjects have been conducted using homogeneous methodologies and consistently identifying adverse health effects of chronic exposure to PM, NO_2, and O_3 on mortality (Beelen et al., 2014, 2015; Stafoggia et al., 2022; Strak et al., 2021). However, only a few Italian cohorts have been involved in these studies, mainly the Rome administrative cohort. Consequently, a comprehensive analysis has not yet been conducted investigating mortality outcomes across multiple large Italian metropolitan cohorts.

To fill this gap, the "Use of BIG data for the evaluation of the acute and chronic health Effects of air Pollution in the Italian population" (BIGEPI) project (https://bigepi.it/index.php/it/), co-funded by the Italian Workers' Compensation Authority (INAIL), aimed to explore the associations of air pollution and meteorological factors with multiple health outcomes in the Italian population, using national data for exposure and mortality, morbidity, work-related injuries and commuting accidents information (Gariazzo et al., 2023; Maio et al., 2023).

Within this framework, the goal of the present analysis was to investigate the associations between long-term exposure to PM_{10}, $PM_{2.5}$, NO_2 and O_{3w} and cause-specific mortality outcomes – non-accidental, cardiovascular, and respiratory causes – in five Italian large longitudinal metropolitan studies (LMS) applying standardized methodology and protocols. Furthermore, the involved cohorts spanned the entire national territory, capturing its heterogeneity and allowing for the examination of contexts with varying pollutant levels, including low levels.

2. Material and methods

2.1. Study design, population and mortality outcomes

The study included longitudinal data from Turin, Bologna, Rome, Taranto, and Brindisi (Fig. S1, Supplementary Material). The cohorts were recruited on October 9, 2011 (date of the 15° Italian population Census, considered as baseline in this study): all subjects aged more than 30 years and residing in the five cities at the census date were considered. The cohorts were followed-up through the linkage with the population registries and multiple Health Information Systems (Cesaroni et al., 2010; Di Girolamo et al., 2020; Marinacci et al., 2004; Nobile et al., 2023).

Several exclusion criteria were applied: being homeless, having resided at the baseline address for less than one year before enrollment or in unconventional places, and not having a unique identification code to use in the record linkage. Furthermore, we focused on the adult population with complete information on individual and area-level covariates (Fig. S2, Supplementary Material).

Subjects were followed up until emigration from the study area, death, or end of follow-up on December 31, 2018 (December 31, 2019 for Bologna), whichever came first. Three cause-specific mortality outcomes were investigated through mortality registries and defined according to the underlying cause of death: non-accidental (International Classification of Diseases [ICD]-9th revision: 0–799; ICD-10th revision: A00–R99), cardiovascular (ICD-9: 390–459; ICD-10: I00–I99), or respiratory mortality (ICD-9: 460–519; ICD-10: J00–J99).

These cohorts are included in a harmonized integrated data system on health outcomes and demographic and socioeconomic information, that provides a powerful, coherent and nationally widespread network of Longitudinal Metropolitan Studies (IN-LiMeS) (Caranci et al., 2018).

The study was conducted in accordance with the Declaration of Helsinki. The original cohort studies were approved by appropriate institutional review boards complying with all relevant local and state regulations. Both IN-LiMeS and each single LMS are included in the National Statistical Program and comply with the national legislation on the processing of personal data for statistical and scientific research purposes (PSN, 2020).

2.2. Air pollution exposure assessment

Annual mean concentrations of PM_{10}, $PM_{2.5}$, NO_2, and O_3 related to the warm-season (April–September) were assigned to the geocoded residential addresses at baseline with the exception of Brindisi, where exposure variables were assigned at the census block level. Two different air pollution models were considered, depending on the city.

For the cohorts of Turin, Bologna and Rome, Land-Use Random Forest (LURF) predictive models, developed within the "Big data in Environmental and occupational Epidemiology" (BEEP) project, were used (Stafoggia et al., 2019, 2020). In brief, air pollution monitoring observed data, provided by the Italian Institute for Environmental Protection and Research (ISPRA) for the whole Italian territory, were treated as response variables, and dispersion model estimates [produced by Copernicus Atmosphere Monitoring Service (CAMS)], satellite data [i.e., Aerosol Optical Depth from Multi-Angle Implementation of Atmospheric Correction (MAIAC)], meteorological parameters [i.e., daily mean air temperature, sea-level barometric pressure, precipitations, relative humidity, etc. produced by the European Centre for Medium-Range Weather Forecasts (ECMWF)], land use, traffic, and road network data were utilized as spatiotemporal predictors to estimate daily concentrations on an Italian national grid of 1 km × 1 km for each air pollutant and year of interest. The performance of the models was evaluated using a 10-fold cross-validation approach: the resulting R^2 values ranged from 0.5 for NO_2 to 0.8 for $PM_{2.5}$. For the purposes of the present study, annual means of the year 2011 were used for PM_{10}, and those of 2013 for $PM_{2.5}$, NO_2, and O_3 during the warm-season (because no earlier estimates were available).

Flexible Air quality Regional Model (FARM), photochemical dispersion model developed by Arpa Puglia with a spatial resolution of 1 km × 1 km, was instead employed for the cohorts of Taranto and Brindisi (Tanzarella et al., 2018). It was estimated using the DELTA tool by comparing hourly observed data from 25 stations with the model results. The modelling system included specific modules to reconstruct meteorological fields and turbulence parameters (prognostic, non-hydrostatic meteorological model RAMS) (Cotton et al., 2003), to prepare anthropogenic [regional emission inventory (INEMAR, 2010); national inventory provided by ISPRA for Italy; TNO/MEGAPOLI inventory for Europe] and natural emission data (MEGAN and SURFPro modules), and to set initial and boundary concentrations based on large-scale model simulations. The rationale for using these models was to account for the specific characteristics of the two cities and the air pollution sources represented by major industrial plants in the territory (Gennaro et al., 2022; Moschetti et al., 2024), which were not adequately captured by the LURF models. In fact, the most significant pollutant sources in the Apulia region are a steel plant, the largest in Europe (in the Taranto area), a coal-fired power plant, the second most powerful in Italy (in the Brindisi area), and biomass burning for residential heating. Specifically, annual means of 2016 were used for the air pollutants. O_3 was not considered in these two cohorts because data was available only at an annual level and not exclusively during the warm-season.

2.3. Covariates

Within each cohort, baseline individual information was available on age, sex, marital status (categorized into four groups: married; unmarried; divorced/separated; widow/widowed), educational level (three groups: university degree/high school diploma; middle school/technical school diploma; primary school diploma or without education), and employment status (three groups: employed; retired/capital income; unemployed) from Census data.

Furthermore, census information on the family and the house was considered, such as characteristics of the family (three groups: couple with or without children; alone with or without children; cohabitation), and number of occupants, surface and property of the house (two groups: property; for rent). From these two latter covariates, it was possible to define a new variable to describe the housing condition into four groups: not crowded with property, crowded with property, not crowded for rent, crowded for rent. The term "crowded" relates to the concept of overcrowding, which is the house's inability to meet the living needs of its occupants. For the cohorts of Taranto and Brindisi, for which details on the housing status were not available, the number of the family members was used instead.

Finally, the socioeconomic status of the residing area was estimated using the deprivation index, a composite measure combining five dimensions of social and material deprivation (low education, unemployment, houses for rent or free use, overcrowding, and single-parent families), that we categorized into population quintiles in each city (Rosano et al., 2020) and assigned to each subject according to the geocoded baseline address. The reference spatial unit was represented by the statistical zone (aggregation of census blocks) for Turin (n = 94) and Bologna (n = 90) and the census block for Rome (n = 13,656), Taranto (n = 1000), and Brindisi (n = 1100). Moreover, only for the cohort of Rome, three additional area-level (urbanistic zones, n = 155) covariates were considered: house prices categorized into quintiles, percentage of graduates, and unemployment rate (Cesaroni et al., 2020).

2.4. Statistical analysis

The long-term association between the air pollutants and the cause-specific mortality outcomes were investigated using city-specific Cox proportional hazards regression models. The estimates were adjusted following progressively more complex structures, already applied in previous European multicenter studies (Dimakopoulou et al., 2024; Stafoggia et al., 2022): 1) age (time axis) and sex ("strata" term); 2) age, sex, and individual and household-level socioeconomic covariates available in each cohort; 3) age, sex, individual, household and area-level socioeconomic covariates available in each cohort. The third was considered the main model. We evaluated the proportional hazards assumption using Chi-square tests and Schoenfeld residuals. In cases of violation, we modelled the relevant variables as "strata" terms in sensitivity analysis.

Single-pollutant and two-pollutant models were performed; the latter only if the Pearson correlation coefficients between air pollutants was within ±0.75 (we didn't consider PM_{10} and $PM_{2.5}$ in the same model). Effect modification by sex and age (30–64, 65–74, 75+) was explored, including suitable interaction terms in the main model and estimating the significance of the interaction using the Wald test.

Finally, cohort-specific estimates were meta-analyzed using the restricted maximum likelihood estimator of the between-cohorts variance (Viechtbauer, 2005). The heterogeneity of the meta-analytical estimates was evaluated applying the Cochran's Q test based on a χ^2 distribution and the I^2 statistic (Higgins and Thompson, 2002). The estimates were expressed as Hazard Ratios (HRs) and 95% confidence intervals (CIs) for fixed increments of the pollutants, based on the literature and the interquartile ranges (IQRs) observed across the cohorts (5 $\mu g/m^3$ for PM_{10} and O_{3w}, 1 $\mu g/m^3$ for $PM_{2.5}$, and 10 $\mu g/m^3$ for NO_2).

Harmonized and standardized analysis protocols were centrally developed and distributed among participating cohorts. The analyses were conducted locally by each cohort manager using a common R script (R version 4.0.0), including the following packages: *survival* and *ggplot2*. Only the results were centrally shared with the Department of Epidemiology (ASL Roma 1, Rome, Italy), where the meta-analyses were conducted through a R script (R version 4.0.0), using the following package: *metafor*.

3. Results

We analyzed 2,709,903 subjects with complete data, contributing over 18 million person-years of observation, from which we observed 266,821 non-accidental, 97,709 cardiovascular, and 21,509 respiratory deaths (Table 1). The Turin cohort exhibited the highest rate per 10,000 person-years for non-accidental and cardiovascular mortality (162 and 58 per 10,000 person-years, respectively), while the Turin and Bologna cohorts showed the highest rate for respiratory mortality (15 per 10,000 person-years).

In Table 2 the individual and area-level covariates are shown across cohorts. The two cohorts from Taranto and Brindisi exhibited the lowest mean ages (56.2 and 54.6, respectively) and women represented the majority in all cohorts. Overall, we observed similar patterns of covariates distribution among Turin, Bologna, and Rome, while these patterns slightly differed in Taranto and Brindisi cohorts, with regard to the employment status, educational level and family characteristics.

Air pollution exposures showed a clear North-South gradient (Fig. 1). The Turin cohort consistently exhibited the highest mean values for all four pollutants (44.4 $\mu g/m^3$, 29.2 $\mu g/m^3$, 52.3 $\mu g/m^3$, and 71.2 $\mu g/m^3$ for PM_{10}, $PM_{2.5}$, NO_2 and O_{3w}, respectively), followed by Bologna and Rome. The two cohorts from Apulia showed the lowest mean values, especially Brindisi (14.6 $\mu g/m^3$, 11.3 $\mu g/m^3$, and 12.4 $\mu g/m^3$, for PM_{10}, $PM_{2.5}$, and NO_2, respectively). Within each cohort, Pearson correlation coefficients were positive and generally moderate between PM and NO_2, while they were negative but smaller in magnitude between O_{3w} and the other air pollutants (Fig. S3, Supplementary Material).

We observed statistically significant positive associations between PM_{10} and $PM_{2.5}$ and non-accidental and cardiovascular mortality in the main model 3 (Table 3). For each increment of 5 $\mu g/m^3$ of PM_{10} the pooled HRs were equal to 1.018 (95% CI: 1.005–1.030) and 1.029 (95% CI: 1.013–1.045), for non-accidental and cardiovascular mortality, respectively. Similarly, for each increment of 1 $\mu g/m^3$ of $PM_{2.5}$, the HRs were 1.004 (95% CI: 1.001–1.007) and 1.006 (95% CI: 0.999–1.013), respectively. Furthermore, for each increase of 10 $\mu g/m^3$, NO_2 was associated with non-accidental mortality with a pooled HR of 1.010 (95% CI: 1.002–1.018), while the association with cardiovascular mortality was greater than 1, but did not reach statistical significance. In comparison, associations between PM and respiratory mortality showed similar or slightly higher HRs but with broader confidence intervals including the null. Conversely, we found negative although not statistically significant associations between O_{3w} and the three cause-specific mortality outcomes.

Overall, the cohort-specific HRs of non-accidental mortality exhibited small heterogeneity, with I^2 values ~30% for PM and NO_2, and somewhat higher for O_{3w} (Fig. 2). Cohort-specific HRs for the other mortality outcomes are shown in the Supplementary Material (Figure S4 and Figure S5, Supplementary Material). Depending on the air pollutant and the cohort, increasing adjustment in the three defined models could affect the strength of the associations, either positively or negatively. However, in general, it did not alter the direction of the associations (Table S1 - Table S3, Supplementary Material). In the sensitivity analysis that considered "strata" terms in cases of proportional hazards assumption violations, the estimates remained consistent, in both the meta-analytical estimates and the cohort-specific ones (with the only exception of the smallest cohort, Brindisi, for PM_{10} and NO_2). The estimates for non-accidental mortality, as an example, are presented in Table S4 (Supplementary Material).

In the two-pollutant models, we observed pooled HRs remaining relatively stable with adjustments for the other air pollutants, compared to the single-pollutant models (Fig. 3). The most noticeable change occurred when incorporating NO_2 into the PM models, but the estimates remained positive, decreasing slightly in the case of non-accidental and cardiovascular mortality and increasing for respiratory mortality. O_{3w} estimates were consistently non statistically significant. A similar trend was detected in cohort-specific results (Figure S6–10, Supplementary Material).

Meta-analytical (Table S5 – Table S6, Supplementary Material) and

Table 1
Description of the five administrative cohorts.

		Turin cohort	Bologna cohort	Rome cohort	Taranto cohort	Brindisi cohort
Participants		580,350	230,629	1,709,576	129,260	59,762
Follow-up period		2011–2018	2011–2019	2011–2018	2011–2018	2011–2018
Non-accidental mortality	**Deaths**	60,936	24,321	163,831	12,540	5193
	Crude rate per 10,000 p-y	162	145	144	145	127
Cardiovascular mortality	**Deaths**	21,964	8452	60,935	4735	1623
	Crude rate per 10,000 p-y	58	50	54	55	40
Respiratory mortality	**Deaths**	5662	2444	11,968	976	459
	Crude rate per 10,000 p-y	15	15	11	11	11

Table 2
Description of the participant characteristics within each administrative cohort.

	Turin cohort	Bologna cohort	Rome cohort	Taranto cohort	Brindisi cohort
Age at baseline (years) *	57.53 (16.2)	58.96 (16.7)	56.44 (15.8)	56.21 (15.6)	54.55 (15.5)
Sex					
Female	315,467 (54.4%)	127,801 (55.4%)	938,769 (54.9%)	69,584 (53.8%)	31,930 (53.4%)
Male	264,883 (45.6%)	102,828 (44.6%)	770,807 (45.1%)	59,662 (46.2%)	27,832 (46.6%)
Marital status					
Married	332,679 (57.3%)	123,405 (53.5%)	978,554 (57.2%)	83,073 (64.3%)	38,735 (64.8%)
Unmarried	1192,00 (20.5%)	54,492 (23.6%)	362,245 (21.2%)	22,784 (17.6%)	10,458 (17.5%)
Divorced/ separated	58,093 (10.0%)	20,737 (9.0%)	178,950 (10.5%)	9260 (7.2%)	4589 (7.7%)
Widow/ widowed	70,378 (12.1%)	31,995 (13.9%)	189,827 (11.1%)	14,129 (10.9%)	5980 (10.0%)
Educational level					
Degree/high school	237,800 (41.0%)	113,732 (49.3%)	932,625 (54.6%)	49,321 (38.2%)	22,645 (37.9%)
Middle school/ Technical qualification	213,103 (36.7%)	64,575 (28.0%)	481,543 (28.2%)	42,573 (32.9%)	19,685 (32.9%)
Primary school or without education	129,447 (22.3%)	52,322 (22.7%)	295,408 (17.3%)	37,352 (28.9%)	17,432 (29.2%)
Employment status					
Employed	270,597 (46.6%)	110,199 (47.8%)	854,925 (50.0%)	46,286 (35.8%)	23,077 (38.6%)
Retired/capital income	203,181 (35.0%)	91,209 (39.5%)	477,358 (27.9%)	34,941 (27.0%)	15,065 (25.2%)
Unemployed	106,572 (18.4%)	29,221 (12.7%)	377,293 (22.1%)	48,019 (37.2%)	21,620 (36.2%)
Housing status					
Not crowded house of property	336,339 (58.0%)	150,462 (65.2%)	1,032,860 (60.4%)	–	–
Not crowded house for rent; crowded house of property	194,398 (33.5%)	66,821 (29.0%)	535,875 (31.3%)	–	–
Crowded house for rent	49,613 (8.5%)	13,346 (5.8%)	140,841 (8.2%)	–	–
Members of family					
1	–	–	–	18,586 (14.4%)	8540 (14.3%)
2	–	–	–	36,974 (28.6%)	16,469 (27.6%)
3	–	–	–	33,505 (25.9%)	15,042 (25.2%)
4	–	–	–	29,930 (23.2%)	14,171 (23.7%)
5+	–	–	–	10,251 (7.9%)	5540 (9.3%)
Family characteristics					
Couple with or without children/ cohousing	374,142 (64.5%)	136,400 (59.1%)	1,064,600 (62.3%)	94,516 (73.1%)	43,534 (72.8%)
Single with or without children	206,208 (35.5%)	94,229 (40.9%)	644,976 (37.7%)	34,730 (26.9%)	16,228 (27.2%)
Deprivation index [a]					
Very low	125,067 (21.6%)	47,682 (20.7%)	355,474 (20.8%)	27,019 (20.9%)	12,825 (21.5%)
Low	117,134 (20.2%)	48,184 (20.9%)	465,296 (27.2%)	26,170 (20.2%)	11,883 (19.9%)
Middle	114,455 (19.7%)	46,280 (20.1%)	312,458 (18.3%)	26,150 (20.2%)	11,807 (19.8%)
High	116,027 (20.0%)	46,598 (20.2%)	262,218 (15.3%)	26,061 (20.2%)	11,696 (19.6%)
Very high	107,667 (18.6%)	41,885 (18.2%)	314,130 (18.4%)	23,846 (18.5%)	11,551 (19.3%)
Unemployment rate * [a]	–	–	6.49 (1.4)	–	–
Percentage of university degree (%) * [a]	–	–	39.6 (20.2)	–	–
Houses price [a]					
Very low	–	–	337,931 (19.8%)	–	–
Low	–	–	337,643 (19.8%)	–	–
Middle	–	–	348,938 (20.4%)	–	–
High	–	–	360,104 (21.1%)	–	–
Very high	–	–	324,960 (19.0%)	–	–

Data are n (%) for categorical variables and mean (SD) for continuous variables (*).

[a] Area-level covariates.

cohort-specific estimates (Figure S11–16, Supplementary Material) for the effect modification by age and sex are provided in the Supplementary Material. We found no consistent statistically significant differences by sex, while somewhat stronger effects were observed in the younger age groups (30–64 and 65–74).

4. Discussion

In the present study, involving five large Italian administrative cohorts, long-term exposure to PM_{10} and $PM_{2.5}$ was associated with a statistically significant increased risk of non-accidental and cardiovascular mortality and non-significant, yet consistently, higher risk of respiratory mortality. Adverse associations were observed for NO_2, but reaching statistical significance only for non-accidental mortality. We found no evidence of associations for O_{3w} with the study outcomes.

Focusing briefly on the individual cohort-specific results, we compare the outcomes observed in the Rome cohort with previous studies that evaluated the association between PM_{10}, $PM_{2.5}$, and NO_2 and cause-specific mortality in the same area (Badaloni et al., 2017; Cesaroni et al., 2013). The HRs for PM and cause-specific mortality were consistent with those found in the present analysis (Badaloni et al., 2017). However, our HRs were more modest for NO_2. For example, in the case of cardiovascular mortality, the HR (95% CI) in our study was 1.019 (1.008–1.031) compared to 1.03 (1.02–1.04) in the study by Cesaroni and colleagues (Cesaroni et al., 2013) per 10 $\mu g/m^3$ increase. Several factors could explain these differences. The two cohorts had different baselines: one from 2001 and the other, which we analyzed, from 2011. Although air pollution levels in Italy remain high, a decreasing trend has been observed in recent years (EEA, 2023). Additionally, our study used a national exposure model, while the other used a European model, which may capture local contrasts less precisely, potentially introducing a misclassification bias. Finally, the two adjustment models also differed.

As for the other analyzed areas, there are no previous studies directly comparable to ours for the Bologna cohort. However, one finding from the Supersito project in the Emilia-Romagna region (where Bologna is located) showed a 7% increase in non-accidental mortality risk for every 10 $\mu g/m^3$ of $PM_{2.5}$ in a cohort of adults living in one of the most polluted areas of Northern Italy (Ranzi et al., 2019). This estimate was higher than the one observed in the Bologna cohort in our study, but it only covered a three-year follow-up, and exposure was assigned based on data from monitoring stations. Lastly, a study conducted in the municipality of Taranto and surrounding areas is also relevant. Although this study is not directly comparable to ours due to its use of a difference-in-difference approach, it still reported a 1.86% increase in non-accidental mortality risk for every 1 $\mu g/m^3$ of PM_{10} from industrial

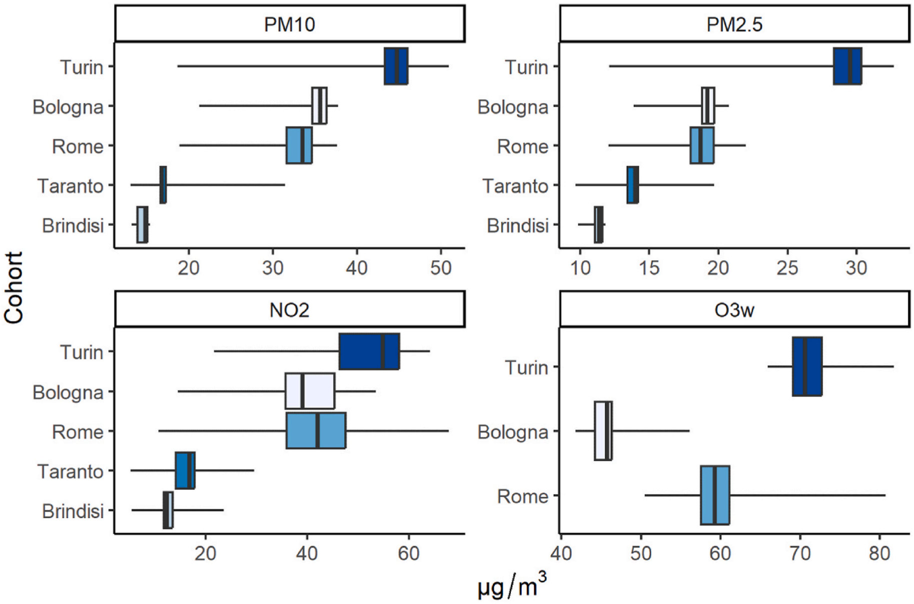

Fig. 1. Distribution of air pollutant exposures at participant addresses.
The exposure annual period is 2011 for PM_{10} and 2013 for $PM_{2.5}$, NO_2, and O_{3w} for Turin, Bologna, and Rome. It is 2016 for PM_{10}, $PM_{2.5}$, and NO_2 for Taranto and Brindisi. O_{3w} is not available for Taranto and Brindisi.
Air pollution exposures are assigned to census block for Brindisi.

Table 3
Association between air pollutants and cause-specific mortality from single-pollutant Cox proportional-hazards models. Results are from the random-effects meta-analysis and are expressed as Hazard Ratios (HRs), with 95% Confidence Intervals (95% CI), per fixed increments in the air pollutants.

	Hazard Ratio (95% CI)		
	Non-accidental mortality	Cardiovascular mortality	Respiratory mortality
PM_{10}	1.018 (1.005–1.030)	1.029 (1.013–1.045)	1.031 (0.997–1.066)
$PM_{2.5}$	1.004 (1.001–1.007)	1.006 (0.999–1.013)	1.010 (0.999–1.021)
NO_2	1.010 (1.002–1.018)	1.015 (0.993–1.037)	1.002 (0.982–1.023)
O_3w	0.993 (0.976–1.010)	0.991 (0.979–1.003)	0.985 (0.960–1.011)

Results are expressed per fixed increments of the pollutants, equal to 5 μg/m^3 for PM_{10} (annual mean of 2011 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi) and O_3w (annual mean of 2013 for Turin, Bologna and Rome), 1 μg/m^3 for $PM_{2.5}$ (annual mean of 2013 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi), and 10 μg/m^3 for NO_2 (annual mean of 2013 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi).
Meta-analytic O_3w results are from Turin, Bologna and Rome cohort-specific estimates.
Results are from models adjusted for individual-level and area-level covariates (model 3).

sources (Leogrande et al., 2019).

In general, many long-term studies from North America, Europe and China have reported associations with mortality generally consistent with our findings (Atkinson et al., 2018; Hvidtfeldt et al., 2019; Liang et al., 2022; Pope et al., 2019; Raaschou-Nielsen et al., 2020; Shi et al., 2022; So et al., 2020; Stafoggia et al., 2022; Strak et al., 2021; Zhang et al., 2022). More specifically, in comparison to recent evidence from large European multicenter studies and meta-analyses, our results for $PM_{2.5}$ on non-accidental mortality (1.004; 95% CI: 1.001–1.007, per 1 μg/m^3) was slightly lower than, but consistent with, the estimate of 1.008 (95% CI: 1.006–1.009) in a meta-analysis of 25 cohort studies (Chen and Hoek, 2020), 1.010 (95% CI: 1.004–1.017) from the ELAPSE project (Stafoggia et al., 2022) and 1.011 (95% CI: 1.003–1.019) from the EXPANSE project (Dimakopoulou et al., 2024). Compared to a study using a similar methodology and including cause-specific mortality (Stafoggia et al., 2022), our study demonstrated very similar estimates for $PM_{2.5}$ and cardiovascular and respiratory mortality: each increment of 1 μg/m^3 was associated with a risk of 1.006 (95% CI: 0.999–1.013) in our analysis vs 1.008 (95% CI: 1.002–1.014) in ELAPSE for cardiovascular mortality and 1.010 (95% CI: 0.999–1.021) vs 1.012 (95% CI: 1.003–1.024) in ELAPSE for respiratory mortality. In general, our smaller estimates could depend on the analyzed spatial units since in most of the other reported studies, region-wide or nation-wide cohorts were analyzed, displaying larger spatial variations in $PM_{2.5}$ concentrations compared to the five cities involved in this study.

PM_{10} has been less investigated in the literature. Chen and Hoek (2020) conducted a meta-analysis of 17 primary studies and estimated pooled HRs of 1.02 (95% CI: 1.02–1.03), 1.02 (95% CI: 0.99–1.05) and 1.06 (95% CI: 1.03–1.10) per 5 μg/m^3 for non-accidental, cardiovascular and respiratory mortality. These estimates were comparable to those found in our study for non-accidental mortality, slightly smaller for cardiovascular mortality, and larger for respiratory outcome. Furthermore, the estimates from the present study regarding PM_{10} were systematically lower than the relative risks (RR) reported in a recent review by Karimi and Samadi (2024). Although not directly comparable, it is noteworthy that this significant difference may be due to the substantially different air pollution levels across the areas considered. The review included many studies from Europe, as well as from the USA and Asia, where PM_{10} levels were much higher, as documented in the review itself. Lastly, they found that PM_{10} almost always showed the highest level of heterogeneity among the studies.

Our pooled HRs of 1.010 (95% CI: 1.002–1.018), 1.015 (95% CI: 0.993–1.037), and 1.002 (95% CI: 0.982–1.023) per 10 μg/m^3 related to the associations between long-exposure to NO_2 and non-accidental, cardiovascular, and respiratory mortality, respectively, were in the same direction, although slightly weaker, than those found in some of the most recent systematic reviews (Chen et al., 2024; Huang et al., 2021; Huangfu and Atkinson, 2020). For instance, Chen et al. meta-analyzed 43 studies on all-cause mortality in the general population and found an HR of 1.04 (95% CI: 1.02–1.05), 29 studies on the

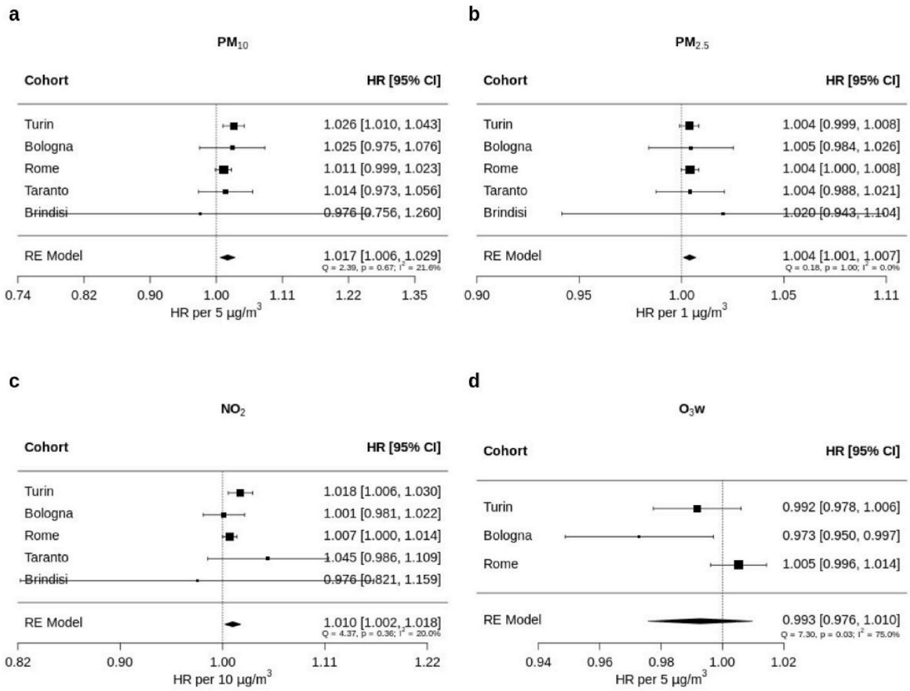

Fig. 2. Forest plots of the association between air pollutants and non-accidental mortality from single-pollutant Cox proportional-hazards models. Results are expressed as Hazard Ratios (HRs), with 95% Confidence Intervals (95% CI), per fixed increments in the air pollutants.

Results are expressed per fixed increments of the pollutants, equal to 5 μg/m^3 for PM_{10} (annual mean of 2011 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi) and O_3w (annual mean of 2013 for Turin, Bologna and Rome), 1 μg/m^3 for $PM_{2.5}$ (annual mean of 2013 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi), and 10 μg/m^3 for NO_2 (annual mean of 2013 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi).

Results are from models adjusted for individual-level and area-level covariates (model 3).

Turin: adjusted for age (time axis), sex (strata term), marital status, educational level, employment status, housing status, family characteristics, deprivation index (at neighborhood level).

Bologna: adjusted for age (time axis), sex (strata term), marital status, educational level, employment status, housing status, family characteristics, deprivation index (at neighborhood level).

Rome: adjusted for age (time axis), sex (strata term), marital status, educational level, employment status, housing status, family characteristics, deprivation index (at census block level), employment rate (at neighborhood level), percentage of graduates (at neighborhood level), houses price (at neighborhood level).

Taranto: adjusted for age (time axis), sex (strata term), marital status, educational level, employment status, housing status, family characteristics, deprivation index (at census block level).

Brindisi: adjusted for age (time axis), sex (strata term), marital status, educational level, employment status, housing status, family characteristics, deprivation index (at census block level).

cardiovascular mortality with a meta-analytical HR of 1.07 (95% CI: 1.03–1.10), and 30 studies on the respiratory mortality with a meta-analytical HR of 1.03 (95% CI: 1.01–1.05). However, there are substantial differences between our study and the ones involved in those systematic reviews that should be acknowledged: first, we considered an adult population aged 30+ while most of those studies were focused on older age groups, which were at higher risk of cause-specific mortality compared to the general population; secondly, we estimated air pollution exposures from small-scale models while most of those studies used weighted averages from monitoring stations, with potential negative consequences in terms of exposure measurement error (Chen et al., 2024).

Estimates for warm-season O_3 in our study were in the opposite of expected direction, yet less conclusive regardless of outcome, since pooled HRs were close to unity and not statistically significant. This was also observed in the systematic review and meta-analysis conducted by Huangfu and Atkinson (2020), who found a very small number of studies to analyze, with large heterogeneity, as well as in the ELAPSE (Stafoggia et al., 2022) and EXPANSE projects (Dimakopoulou et al., 2024). On the contrary, Sun et al. (2022) reported adverse associations between O_3 and mortality outcomes, although only considering annual exposure. Thus, the comparison between evidence was made more difficult due to different metrics used to estimate O_3 exposure (e.g., annual estimate, warm-season, peak), which would require standardization (Sun et al., 2022).

Finally, the associations estimated in our study remained quite stable after the adjustments for the other air pollutants; a small attenuation was observed for PM when adjusted for NO_2 in the case of non-accidental and cardiovascular mortality and for NO_2 when adjusted for PM in the case of respiratory mortality. Some studies found similar results (Crouse et al., 2015; Stafoggia et al., 2022) but others not (Beelen et al., 2014; Yang et al., 2018); however, in general the estimates did not change considerably.

This study contributed to and strengthened the existing worldwide evidence on the association between long-term exposure to air pollution, particularly PM and NO_2, and cause-specific mortality. The suggested probable underlying biological mechanisms are numerous, such as oxidative stress, damage to DNA, and systemic inflammation (Anderson, 2020; Albano et al., 2022), detectable especially in relation to cardiovascular and respiratory mortality (Mudway et al., 2020).

This Italian multicenter metropolitan study has several strengths. To the best of our knowledge, it was the first study to analyze extensive Italian administrative cohorts, from the North to the South of the country, regarding the associations between long-term exposure to air pollution (PM_{10}, $PM_{2.5}$, NO_2 and O_{3w}) and cause-specific mortality outcomes. We employed a common methodology and standardized the

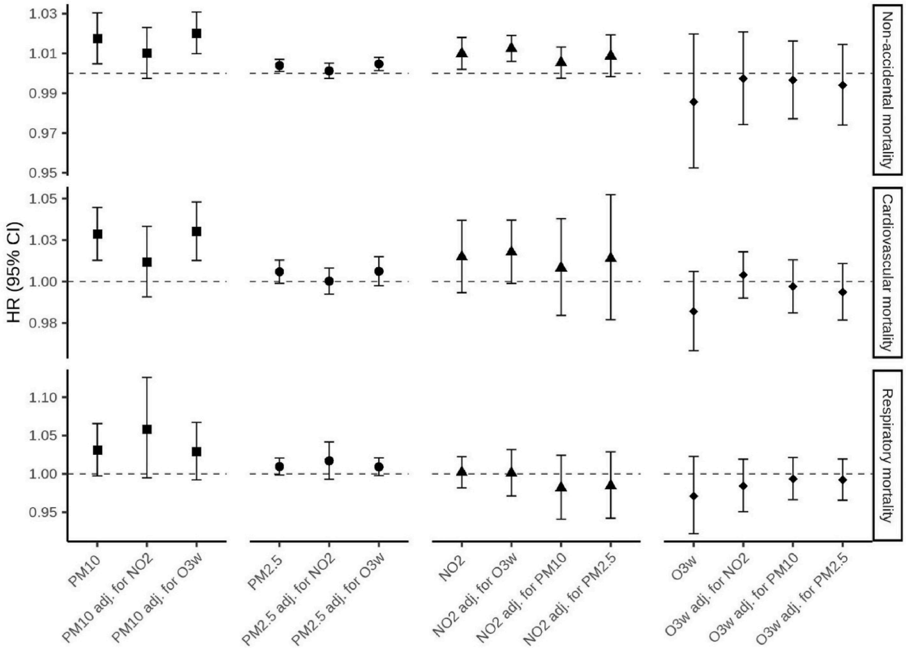

Fig. 3. Forest plots of the association between air pollutants and cause-specific mortality from two-pollutant Cox proportional-hazards models. Results are from the random-effects meta-analysis and are expressed as Hazard Ratios (HRs), with 95% Confidence Intervals (95% CI), per fixed increments in the air pollutants.

Results are expressed per fixed increments of the pollutants, equal to 5 μg/m^3 for PM_{10} (annual mean of 2011 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi) and O_3w (annual mean of 2013 for Turin, Bologna and Rome), 1 μg/m^3 for $PM_{2.5}$ (annual mean of 2013 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi), and 10 μg/m^3 for NO_2 (annual mean of 2013 for Turin, Bologna and Rome and 2016 for Taranto and Brindisi).

Results are from models adjusted for individual-level and area-level covariates (model 3).

air pollution exposure assessment and the definition of the adjustment models, whenever possible. We utilized air pollution models with a fine spatial scale (1 km × 1 km) to minimize exposure misclassification as much as possible; we included more than 2.7 million subjects aged 30+, thanks to the use of Health Information Systems and administrative archives, covering a long time period (from 2011 to 2018, 2019 for Bologna), which resulted in less selection bias compared to traditional cohorts, due to a small percentage of dropout.

Some limitations should be acknowledged. First, we considered a fixed exposure at the baseline and the reference years for assigning the exposures did not always correspond exactly to the baseline year. However, we relied on the assumption that, in a study aimed at analyzing chronic exposure to air pollution, spatial contrast is considerably more important than temporal resolution, and that spatial contrasts remain stable over time, at least within a city (Brunekreef et al., 2021; de Hoogh et al., 2018; Fasola et al., 2020). Furthermore, in the study within the ELAPSE project, a sensitivity analysis considered time-varying exposures and demonstrated that the results did not change from those using fixed exposures (Stafoggia et al., 2022). Secondly, we used the ambient exposure at the residence, and we did not include information on the individual activity patterns during the day. However, residential exposures should suffice to characterize the chronic exposure to air pollution for a subject, and personal monitoring exposure is mainly employed in short-term effects studies. Thirdly, the analyzed cohorts did not have data on lifestyles (such as smoking, alcohol consumption, physical activity) nor on physiological parameters (such as BMI), and thus we could not adjust the estimates for these confounders. However, we included several individual and area-level covariates in the adjustment models (Pronk et al., 2004; Schuit et al., 2002), and there are not strong theoretical reasons to believe that individual behaviors and characteristics should confound the association between exogenous exposures and health outcomes, once contextual covariates are duly adjusted for (Weisskopf and Webster, 2017). However, the availability of information on lifestyle factors is important in epidemiological studies; therefore, whenever possible, it is advisable to consider and, at least, speculate on those variables. At last, the use of two different models for assessing the exposure may have introduced bias in the comparison of estimates and, consequently, in the final meta-analytic estimates. However, we analyzed all the data within a framework of shared and standardized methods and we decided to prefer the FARM to the LURF model in two specific cities to better capture the specific characteristics of these areas in terms of air pollution.

5. Conclusions

In this large Italian multicenter study, that involved five administrative cohorts within the BIGEPI project, long-term exposures to PM_{10}, $PM_{2.5}$, and NO_2 were associated with higher risks of non-accidental, cardiovascular, and respiratory mortality. These estimates remained stable after the adjustment for the other air pollutants.

Metropolitan longitudinal studies, especially when analyzed within multicenter projects, are valuable tools for providing increasingly updated evidence on the association between chronic exposure to air pollution and mortality, both in an international and a national framework. In Italy, in fact, air pollution concentrations have been declining over time, but are still above the WHO guidelines in large parts of the territory, and, as here documented, still pose an alarming treat to human health.

CRediT authorship contribution statement

Federica Nobile: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nicola Caranci:** Writing – review & editing, Visualization, Validation, Investigation, Data curation, Conceptualization. **Elena Strippoli:** Writing – review & editing, Visualization, Formal analysis, Data curation, Conceptualization.

Valentina Adorno: Writing – review & editing, Formal analysis, Data curation. **Alessandra Allotta:** Writing – review & editing. **Lucia Bisceglia:** Writing – review & editing, Validation, Conceptualization. **Ida Galise:** Writing – review & editing, Formal analysis, Data curation. **Claudio Gariazzo:** Writing – review & editing. **Sara Maio:** Writing – review & editing, Project administration, Funding acquisition. **Paola Michelozzi:** Writing – review & editing. **Walter Pollina Addario:** Writing – review & editing, Conceptualization. **Andrea Ranzi:** Writing – review & editing. **Claudio Rubino:** Writing – review & editing. **Maria Serinelli:** Writing – review & editing, Formal analysis, Data curation. **Giovanni Viegi:** Writing – review & editing. **Nicolás Zengarini:** Writing – review & editing, Visualization, Validation, Investigation, Data curation, Conceptualization. **Petter Ljungman:** Writing – review & editing, Visualization, Supervision. **Massimo Stafoggia:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Data curation, Conceptualization.

Data availability

The authors do not have permission to share data. Air pollution data could be available on request.

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Declaration of competing interest

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atmosenv.2024.120873.

Data availability

The authors do not have permission to share data.

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