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Long-term residential exposure to air pollution and risk of chronic respiratory diseases in Italy: The BIGEPI study

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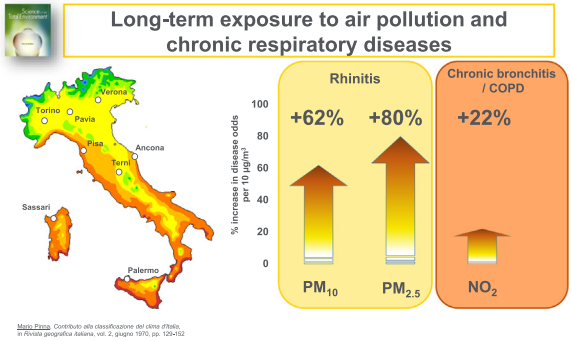
HIGHLIGHTS

- Long-term exposure to air pollution has detrimental respiratory health effects.
- We conducted a cross-sectional study on adults from 8 Italian centres.
- PM_{10}, $PM_{2.5}$ and NO_2 levels were above the WHO 2021 air quality guideline levels.
- PM_{10} and $PM_{2.5}$ exposures were mainly associated with the risk of having rhinitis.
- Exposure to NO_2 was associated with the risk of having chronic bronchitis/COPD.

GRAPHICAL ABSTRACT



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ABSTRACT

Long-term exposure to air pollution has adverse respiratory health effects. We investigated the cross-sectional relationship between residential exposure to air pollutants and the risk of suffering from chronic respiratory diseases in some Italian cities.

In the BIGEPI project, we harmonised questionnaire data from two population-based studies conducted in 2007–2014. By combining self-reported diagnoses, symptoms and medication use, we identified cases of rhinitis (n = 965), asthma (n = 328), chronic bronchitis/chronic obstructive pulmonary disease (CB/COPD, n = 469), and controls (n = 2380) belonging to 13 cohorts from 8 Italian cities (Pavia, Turin, Verona, Terni, Pisa, Ancona, Palermo, Sassari). We derived mean residential concentrations of fine particulate matter (PM_{10}, $PM_{2.5}$), nitrogen dioxide (NO_2), and summer ozone (O_3) for the period 2013–2015 using spatiotemporal models at a 1 km resolution. We fitted logistic regression models with controls as reference category, a random-intercept for cohort, and adjusting for sex, age, education, BMI, smoking, and climate.

Mean ± SD exposures were 28.7 ± 6.0 μg/m^3 (PM_{10}), 20.1 ± 5.6 μg/m^3 ($PM_{2.5}$), 27.2 ± 9.7 μg/m^3 (NO_2), and 70.8 ± 4.2 μg/m^3 (summer O_3). The concentrations of PM_{10}, $PM_{2.5}$, and NO_2 were higher in Northern Italian cities. We found associations between PM exposure and rhinitis (PM_{10}: OR 1.62, 95%CI: 1.19–2.20 and $PM_{2.5}$: OR 1.80, 95%CI: 1.16–2.81, per 10 μg/m^3) and between NO_2 exposure and CB/COPD (OR 1.22, 95%CI: 1.07–1.38 per 10 μg/m^3), whereas asthma was not related to environmental exposures. Results remained consistent using different adjustment sets, including bi-pollutant models, and after excluding subjects who had changed residential address in the last 5 years.

We found novel evidence of association between long-term PM exposure and increased risk of rhinitis, the chronic respiratory disease with the highest prevalence in the general population. Exposure to NO_2, a pollutant characterised by strong oxidative properties, seems to affect mainly CB/COPD.

1. Introduction

Air pollution is a complex mixture of contaminants of the atmosphere, most of which derive from anthropogenic activities. Pollutants of major public health concern, including particulate matter (PM), nitrogen dioxide (NO_2) and ozone (O_3), are routinely monitored by environmental agencies. In urban settings, these pollutants are either directly released from indoor and outdoor emission sources as primary pollutants, or they are formed secondarily through reactions of unstable airborne chemicals (Gentner et al., 2017).

Despite improvements in ambient air quality during the last decades, air pollution is still a major health concern for Europeans. In 2019, the mean annual concentration of PM with a median aerodynamic diameter <2.5 μm ($PM_{2.5}$) was 15.1 μg/m^3 across Italy, as compared to the European Union-27 mean of 12.6 μg/m^3 (European Environmental Agency, online data code: SDG_11_50). These concentrations largely exceed the WHO 2021 recommended cut-off of 5 μg/m^3 (WHO 2021). Air quality is especially poor in Northern Italy, due to high emissions (related to biomass burning, vehicular traffic, industrial activities, intensive farming, elevated population density) in combination with meteorological conditions favouring atmospheric stagnation (Larsen et al., 2012; Stafoggia et al., 2017).

Air pollution exposure can decrease lung function, worsen respiratory symptoms, increase medication and health care use (Anderson et al., 2012). It can dysregulate immune system modulation and alter response to allergic stimuli (Glencross et al., 2020). Short-term increases in air pollution mainly impact the health of people with pre-existing chronic respiratory and cardiovascular diseases. In particular, they can increase mortality and morbidity for asthma and chronic obstructive pulmonary disease (COPD), two respiratory conditions that are common in the general population (Atkinson et al., 2014). A recent nationwide Italian study showed that exposure to PM results in short-term increases in asthma hospitalisations (Renzi et al., 2022).

Evidence is accumulating to support that long-term exposure to air pollution can increase the risk of developing asthma and COPD (Boogaard et al., 2022; Park et al., 2021), even at levels within the current European air quality standards (Liu et al., 2021b, 2021a). Chronic bronchitis (CB) and allergic rhinitis are also common in the general population. Compared to asthma and COPD, their relationship with air pollution has been studied at a lesser extent, possibly due to the fact that they are milder conditions with less severe outcomes. For example, a recent systematic review identified only 4 studies of the effects of air pollution on rhinitis in adult populations (Li et al., 2022).

The aim of this cross-sectional study was to investigate the relationship between long-term residential exposure to air pollution and the presence of rhinitis, asthma, and CB/COPD in adults from some Italian cities, to contribute understanding the relative impact of the main components of the air pollution mixture. For this purpose, we harmonised and combined health data from two previous epidemiological studies and we assigned individual estimates of residential exposure to air pollutants. The study was carried out in the frame of the BIGEPI project ("Use of BIG data for the evaluation of the acute and chronic health Effects of air Pollution in the Italian population"), whose goal was to evaluate the acute and chronic effects of atmospheric pollutants, air temperature, and individual risk factors on human health.

2. Methods

2.1. Study design and data collection

In this study, we combined data from the Gene Environment Interactions in Respiratory Diseases (GEIRD) study and the Pisa study (see study flowchart in Fig. 1).

GEIRD is a multicentre multicase-control study on respiratory health. Cases and controls were identified through a two-stage screening process (de Marco et al., 2010). In the first stage (2007–2010), new random samples of adult (20–64 years) and elderly subjects (65–85 years), and pre-existing randomly sampled cohorts from the general population (de Marco et al., 2012) living in six cities (Pavia, Turin, Verona, Terni, Ancona, Sassari) were mailed a screening questionnaire on respiratory symptoms. Overall, 16,173 subjects answered the questionnaire (response rate: 58.7 %). In the second stage (2008–2016), all the subjects reporting symptoms suggestive of asthma, COPD or CB, a 30 % random sample of the subjects with symptoms suggestive of rhinitis, and a 40 % random sample of subjects without respiratory symptoms were referred to clinical centres; additionally, a sample of 439 subjects from Palermo was invited (Ferrari et al., 2019). Overall, 3240 (41.9 %) subjects from 12 cohorts participated among the 7739 subjects invited (supplementary Table S1). Clinical information

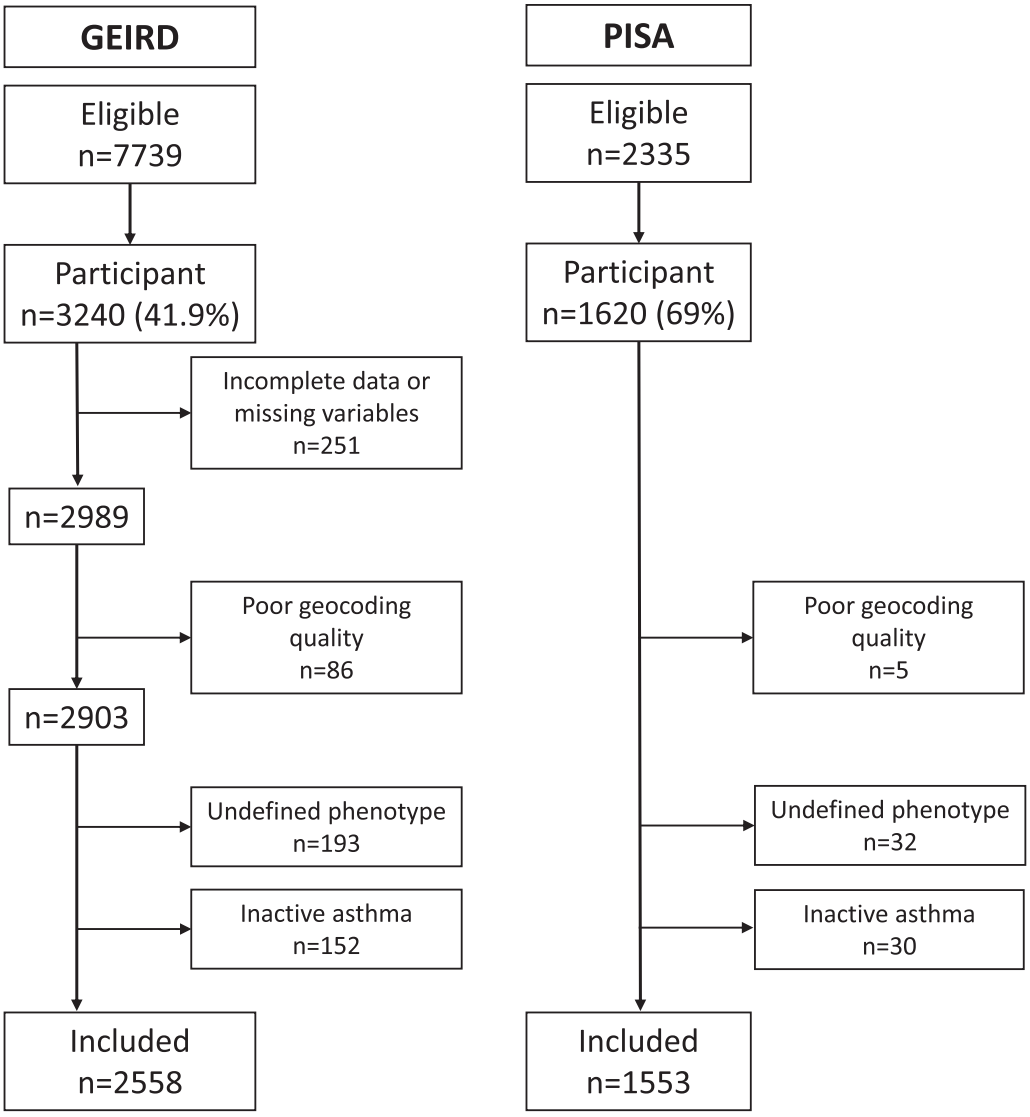

Fig. 1. Study flowchart.

was obtained by means of a structured medical interview through a questionnaire that was mainly derived from the European Community Respiratory Health Survey (ECRHS) questionnaire (Marcon et al., 2013).

In the Pisa study, a random sample of the general population (n = 4585) residing in the municipalities of Pisa and Cascina was invited to take part in an epidemiological study: 3865 subjects participated in the first survey (1985–1988), 2841 in the second (1991–1993) and 1620 in the third one (2009–2011) (Maio et al., 2016; Viegi et al., 1991). In the second and third surveys, new random samples of subjects were also invited. Clinical information was obtained through a standardised interviewer-administered questionnaire developed by the National Research Council and from previously validated questionnaires (Maio et al., 2016). In the present analyses, we used data from the follow-up in 2009–2011 (supplementary Table S1).

In both studies, height and weight were measured. Participants were informed about all the research aspects and consented to participate. Approval to conduct the studies was granted from the local ethical committee in each participating centre.

2.2. Exposure assignment

We geocoded the residential addresses of all participants; 86 and 5 subjects from GEIRD and Pisa studies, respectively, were excluded because of poor geocoding quality (Fig. 1). At each individual address, we obtained daily time-series of PM_{10}, $PM_{2.5}$, NO_2 and O_3 concentrations within the BEEP (Big data in Environmental and occupational Epidemiology) and BIGEPI projects, as described below.

We obtained PM daily concentrations using spatiotemporal models based on machine learning Random Forest (MLRF) algorithms, as described elsewhere (Stafoggia et al., 2019, 2017). Briefly, for each squared kilometre of Italy, and for each day of the period 2006–2015, we collected spatial and spatiotemporal variables. These included PM monitored data from all the available monitoring sites, satellite-based aerosol optical depth (AOD), land use, meteorological data, point emission sources, total emissions, and resident population. We developed a four-stage model to predict daily PM_{10} (2006–2015) and $PM_{2.5}$ (2013–2015) concentrations for each 1×1 km grid cell and each day of the period. The shorter period of modeling for $PM_{2.5}$ was due to the limited availability of data, since $PM_{2.5}$ monitors were installed more recently in Italy.

We derived NO_2 and O_3 daily concentrations developing an integrated approach coupling a chemical transport model (CTM) with machine learning techniques, as described elsewhere (Silibello et al., 2021). Briefly, for each day of the period 2013–2015, we performed simulations at a spatial resolution of 5 km using the Flexible Air quality Regional Model (FARM). We used these simulations, together with other spatiotemporal data such as population, land-use, surface greenness and road networks, as predictors

by an MLRF algorithm to produce daily concentrations at higher resolution (1 km).

Cross-validated R^2 were 0.75 (PM_{10}), 0.81 ($PM_{2.5}$), 0.60 (NO_2), and 0.80 (O_3), demonstrating good predictive properties of the models at unmeasured locations (Silibello et al., 2021; Stafoggia et al., 2019, 2017).

We linked daily concentrations estimated for the four pollutants at 1 Km resolution to the residential addresses of the participants. We considered average concentrations of PM_{10}, $PM_{2.5}$, and NO_2, and summer O_3 (months April to September) for the period 2013–2015 as indicators of long-term exposure to air pollutants.

Since PM_{10} data were also available for each of the years of recruitment in GEIRD (2008–2015) and Pisa (2009–2011), two further exposure indicators were derived for this pollutant by averaging all daily concentrations available (2006–2015) and by averaging concentrations over the three-year period ending with the year of study entry for each participant (e.g., 2008–2010 for a subject interviewed in 2010).

2.3. Data harmonisation and definitions

We defined standardised characteristics (name, definition, format, categories or measurement units) for each variable of interest to facilitate the harmonisation process across the studies. We harmonised variables using a direct mapping when they had the same wording and categories, or through transformation or combination of variable categories when needed. In order to minimise the risk of re-identification of anonymised data records, quantitative variables were categorised before combining the datasets, except for air pollutant concentrations that were rounded to the second decimal digit. For the purpose of a combined data analysis, we adapted Pisa data to the multicase-control design.

The case/control status was defined as follows, using information in common between the two study questionnaires:

- Rhinitis: having nasal allergies including “hay fever” OR a problem with sneezing, runny or blocked nose (without cold/flu) in the last 12 months;
- Asthma: self-reported diagnosis of asthma IN COMBINATION WITH: one or more asthma-like symptoms in the last 12 months (wheezing, attack of breathlessness at night-time, asthma attacks) OR use of inhaled, oral or injective medication for asthma in the last 12 months;
- CB/COPD: usually suffering from chronic cough or phlegm in winter (GEIRD study) or usually suffering from chronic cough or phlegm even when not having a cold (Pisa study (for >3 months/year and at least 2 years) OR self-reported physician diagnosis of CB, COPD or emphysema (the most used diagnostic labels used for COPD by Italian physicians) (de Marco et al., 2013);
- Control: not fulfilling any of the case definitions.

We decided a priori to exclude cases with inactive asthma (a self-reported diagnosis in the past but no current symptoms or use of medication), due to the impossibility to set the correct time sequence between exposure and outcome, which could have hindered the causal interpretation of estimated associations.

The following covariates were collected: sex, age (18–39, 40–49, 50–64, ≥65 years), years of education (0–8, 9–13, ≥14 years), smoking habits. Pack-years were calculated and combined with smoking status in five groups as follows: non-smoker, former smoker with <15 OR ≥15 pack-years, current smoker with <15 OR ≥15 pack-years. Body mass index (BMI) was categorised as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (>30 kg/m^2).

The climatic index was obtained for each city from a previous study (Pesce et al., 2016). Briefly, the index was developed by principal component analysis from geographical and climatic features of the 110 Italian province capital cities. Features weighting more in the climate index were annual mean temperature, temperature range, and global solar radiation. The values of the index are lower in the subcontinental cities of Northern Italy (cold and rainy climate, wide annual temperature range) and higher in the Mediterranean cities of Southern Italy (hot and dry climate, narrow annual temperature range).

2.4. Statistical analysis

We performed the statistical analysis using STATA software version 17.1. We summarised quantitative variables as means and standard deviations and categorical variables as percentages. We used Spearman's rank ρ coefficient to assess pairwise correlations across pollutants' concentrations.

We defined three outcomes hierarchically as follows: having rhinitis alone (no coexistence with asthma or CB/COPD); having asthma with/without rhinitis (no coexistence with CB/COPD); having CB/COPD with/without rhinitis (no coexistence with past or current asthma). We evaluated the association between exposures to air pollutants and the odds of each outcome (i.e., the risk of being affected by one of these conditions) by separate mixed-effects logistic regression models including controls as the reference category. For example, subjects with asthma or CB/COPD were excluded from the analysis on rhinitis. All models included cohort as a random intercept (supplementary Table S1) and one pollutant metric as main exposure variable. Association estimates were reported as Odds Ratios (OR) with 95%CI per 10 μg/m^3 and per 1-SD in pollutant exposures.

We considered three sets of adjustment covariates. Model 1 included sex, age, education level, smoking habits/pack-years, and BMI (underweight and normal were combined due to small numbers in the former group). For the sake of simplicity, we used a common set of covariates for the three outcomes, since results obtained adjusting only for sex and age were very consistent. Model 2 (main analysis) further included the climatic index. Model 3 accommodated a bi-pollutant analysis including either summer O_3 (when analysing PM_{10}, $PM_{2.5}$, or NO_2) or $PM_{2.5}$ (when analysing summer O_3). Pollutants to be co-analysed were selected based on the lowest Spearman's ρ coefficient to minimise multicollinearity (setting a maximum absolute value allowed of 0.70).

2.5. Effect modification

We assessed whether sex, age (<50 vs ≥50 years), smoking (never vs ever), and climate modified the estimated associations by including interaction terms with each air pollutant, and comparing models with and without these terms using likelihood ratio tests (supplementary Table S2). We assessed interactions with climate both including the climatic index as a quantitative variable, and by including a binary variable contrasting subcontinental cities in Northern Italy (Pavia, Torino, Verona) vs Mediterranean cities in central and Southern Italy (Terni, Ancona, Sassari, Palermo, Pisa). We reported association estimates for each of the strata of the effect modifier where appropriate.

2.6. Sensitivity analyses

Two sensitivity analyses were conducted using data from the GEIRD study alone, since comparable data for the Pisa study were not available. First, we repeated the analyses on the subset of participants reporting they had been living in the current home for >5 years (non-movers), aimed to evaluate whether change of residential address could be a source of exposure misclassification bias (supplementary Table S4). Second, we further adjusted the main analyses by occupational exposures (present for subjects giving a positive answer to the question “Have you ever been regularly exposed to vapours, gases, dust or fumes in the workplace?”) to minimise potential confounding related to this concomitant exposure.

To assess the impact of the different age distribution across cohorts, we restricted the analyses to the participants aged 20–64 years, a range that was common to all the cities except for Terni, Ancona, and Palermo that were excluded (supplementary Table S5).

To compare the estimated effect of air pollution on allergic and non-allergic rhinitis, we repeated the main analyses defining allergic rhinitis (having nasal allergies including hay fever) and non-allergic rhinitis

(having a problem with sneezing, runny or blocked nose, without cold/flu, in the last 12 months BUT NO hay fever) (supplementary Table S6).

Since self-reporting a COPD diagnosis has not been validated clinically, we repeated the main analyses for CB, i.e., having usual symptoms of chronic cough or phlegm (with/without rhinitis), regardless of physician diagnoses of CB, COPD or emphysema (supplementary Table S7).

3. Results

3.1. Study flowchart and participants' characteristics

After excluding 225 subjects with missing data on key variables for the case/control definition ("undefined phenotype") and 182 subjects with inactive asthma, 4111 participants were included (Fig. 1). In GEIRD, there were 1498 controls, 556 cases of rhinitis alone, 255 cases of asthma (198/57 with/without rhinitis), and 249 cases of BC/COPD (119/130 with/without rhinitis). The respective numbers for Pisa were: 882 (controls), 409 (rhinitis alone), 73 (asthma, 57/16 with/without rhinitis), and 220 (CB/COPD, 106/114 with/without rhinitis). Among the 469 cases of CB/COPD, 359 (77 %) reported chronic cough and phlegm (220 for GEIRD and 139 for Pisa); and 237 (50.5 %) reported a physician-diagnosis of CB, COPD or emphysema (110 for GEIRD and 127 for Pisa).

Participants from Pisa were on average older, more likely to be males, overweight or obese, and they had attained a lower educational level compared to participants in GEIRD (Table 1). Cases in the Pisa study were the group showing the highest prevalence of ever smoking; almost one out of five were former smokers with a cumulative exposure ≥15 pack-years.

Table 1
Characteristics of the participants by study and case/control status.

	GEIRD controls (n = 1498)	GEIRD cases[a] (n = 1060)	PISA controls (n = 882)	PISA cases[a] (n = 671)
Age, n (%)				
18–39 years	304 (20.3)	262 (24.7)	207 (23.5)	143 (21.3)
40–49 years	441 (29.4)	361 (34.1)	137 (15.5)	79 (11.8)
50–64 years	494 (33.0)	284 (26.8)	232 (26.3)	159 (23.7)
≥65 years	259 (17.3)	153 (14.4)	306 (34.7)	290 (43.2)
Sex, n (%)				
Females	764 (51.0)	542 (51.1)	405 (45.9)	332 (49.5)
Males	734 (49.0)	518 (48.9)	477 (54.1)	339 (50.5)
Years of education, n (%)				
0 ≤ years <9	116 (7.8)	76 (7.6)	466 (52.8)	391 (58.3)
9 ≤ years <14	533 (36.0)	321 (30.4)	308 (34.9)	188 (28.0)
≥14 years	833 (56.2)	658 (62.4)	108 (12.2)	92 (13.7)
Smoking habits, n (%)				
Non smoker	713 (48.7)	512 (49.3)	427 (48.7)	301 (45.0)
Former smoker (<15 pack-years)	252 (17.2)	172 (16.6)	149 (17.0)	112 (16.7)
Former smoker (≥15 pack -years)	206 (14.1)	123 (11.8)	118 (13.5)	139 (19.7)
Current smoker (<15 pack -years)	133 (9.1)	106 (10.2)	109 (12.4)	52 (7.8)
Current smoker (≥15 pack -years)	160 (10.9)	126 (12.1)	73 (8.3)	72 (10.8)
Body mass Index, n (%)				
Underweight	24 (1.7)	23 (2.3)	2 (0.4)	0 (0.0)
Normal weight	711 (48.9)	529 (51.9)	174 (37.2)	131 (28.3)
Over weight	521 (35.8)	339 (33.2)	190 (40.6)	192 (41.5)
Obese	198 (13.6)	129 (12.7)	102 (21.8)	140 (30.2)
Time living in the current home, n (%)				
>5 years (non-movers)	1207 (81.1)	805 (76.2)		
≤5 years (movers)	282 (18.9)	252 (23.8)		

[a] Rhinitis, asthma and/or chronic bronchitis/COPD combined together for simplicity of data presentation.

3.2. Air pollution exposures

About half of the participants (n = 2041) lived in cities with a subcontinental climate in Northern Italy, where the largest sample was recruited in Verona (n = 1398); most of the 2070 participants from the Mediterranean area lived in Pisa (n = 1553) (Table 2). Mean ± SD annual pollutants' exposures calculated over 2013–2015 in the whole study sample were 28.7 ± 6.0 μg/m^3 for PM_{10}, 20.1 ± 5.6 μg/m^3 for $PM_{2.5}$, 27.2 ± 9.7 μg/m^3 for NO_2, and 70.8 ± 4.2 μg/m^3 for summer O_3. Annual average exposures to PM_{10}, $PM_{2.5}$, and NO_2 were higher in the subcontinental cities compared to the Mediterranean ones (Table 2); in all the cities they were above the air quality guideline levels recommended by WHO 2021 (15, 5, and 10 μg/m^3, respectively). Summer average exposure to O_3 ranged between 67.2 (Torino) and 73.2 μg/m^3 (Sassari), with no clear variation related to climate.

There were strong positive correlations across annual average exposures to PM_{10}, $PM_{2.5}$, and NO_2, as indicated by Spearman's ρ coefficients between 0.71 and 0.98 (Fig. 2); all three exposures were negatively and moderately correlated with summer O_3 (Spearman's ρ coefficients between −0.24 and − 0.53).

3.3. Long-term exposure to pollutants and respiratory diseases

Higher residential exposures to PM_{10}, $PM_{2.5}$, and NO_2 were associated with a greater risk of rhinitis in the analysis adjusted for individual-level confounders (model 1) (Fig. 3, A). The associations became stronger when further adjusting for climatic index (model 2): the odds of rhinitis increased by 62 % (OR 1.62, 95%CI: 1.19–2.20), 80 % (OR 1.80, 95%CI: 1.16–2.81) and 22 % (OR 1.22, 95%CI: 1.07–1.38) for a 10 μg/m^3 increase in PM_{10}, $PM_{2.5}$, and NO_2, respectively. When including summer O_3 in the models, estimated associations slightly shifted to the null (model 3). Exposure to O_3 was negatively associated with rhinitis (OR 0.75, 95%CI: 0.59–0.94 per 10 μg/m^3, model 2); the association shifted to the null when adjusting for $PM_{2.5}$ exposure (OR 0.84, 95%CI 0.64–1.10 per 10 μg/m^3, model 3). PM metrics showed stronger associations, compared to NO_2, even when ORs were expressed per SD-difference in exposures (Supplementary Table S3).

When looking at the subsample of non-movers from the GEIRD study (n = 2012), the estimated associations became stronger for PM_{10}, $PM_{2.5}$ and NO_2: the odds of rhinitis increased by 71 % (OR 1.71, 95%CI: 1.17–2.51), 103 % (OR 2.03, 95%CI: 1.17–3.53), and 16 % (OR 1.16, 95%CI: 1.00–1.35) per 10 μg/m^3 differences in exposure, respectively (supplementary Table S4, model 2); the association of summer O_3 shifted to the null (OR 0.79, 95%CI: 0.59–1.06).

Asthma was not associated with any of the exposures investigated, either in the main analysis (Fig. 3, B) or in the analysis on non-movers (supplementary Table S4).

Table 2
Distribution of annual average concentrations of air pollutants[a] estimated at residential addresses during 2013–2015, and value of the climatic index.

	n	PM_{10} (μg/m^3)	$PM_{2.5}$ (μg/m^3)	NO_2 (μg/m^3)	Summer O_3 (μg/m^3)	Climatic index
Pavia	285	34.1 (2.3)	25.2 (1.6)	28.0 (4.9)	70.0 (1.8)	−1.9
Torino	358	35.4 (3.6)	26.2 (2.6)	47.7 (10.1)	67.2 (2.9)	−1.5
Verona	1398	33.1 (3.9)	24.5 (2.7)	29.3 (6.7)	72.3 (5.1)	−0.9
Terni	66	27.7 (3.5)	19.5 (2.3)	21.3 (5.7)	68.2 (2.5)	−0.4
Pisa	1553	24.9 (1.0)	16.5 (0.7)	23.4 (3.8)	70.0 (5.0)	−0.3
Ancona	67	24.8 (1.8)	15.1 (0.6)	23.1 (4.6)	69.8 (3.4)	0.8
Sassari	332	17.8 (1.6)	9.2 (0.9)	14.2 (4.2)	73.2 (4.7)	2.4
Palermo	52	26.0 (5.2)	13.6 (1.6)	32.3 (12.3)	71.4 (5.0)	3.1
Overall	4111	28.7 (6.0)	20.1 (5.6)	27.2 (9.7)	70.8 (4.2)	
		p < 0.001	p < 0.001	p < 0.001	p < 0.001	

[a] Mean (SD) reported; cities are ordered by climatic index. P-values were calculated using the Kruskall-Wallis rank test.

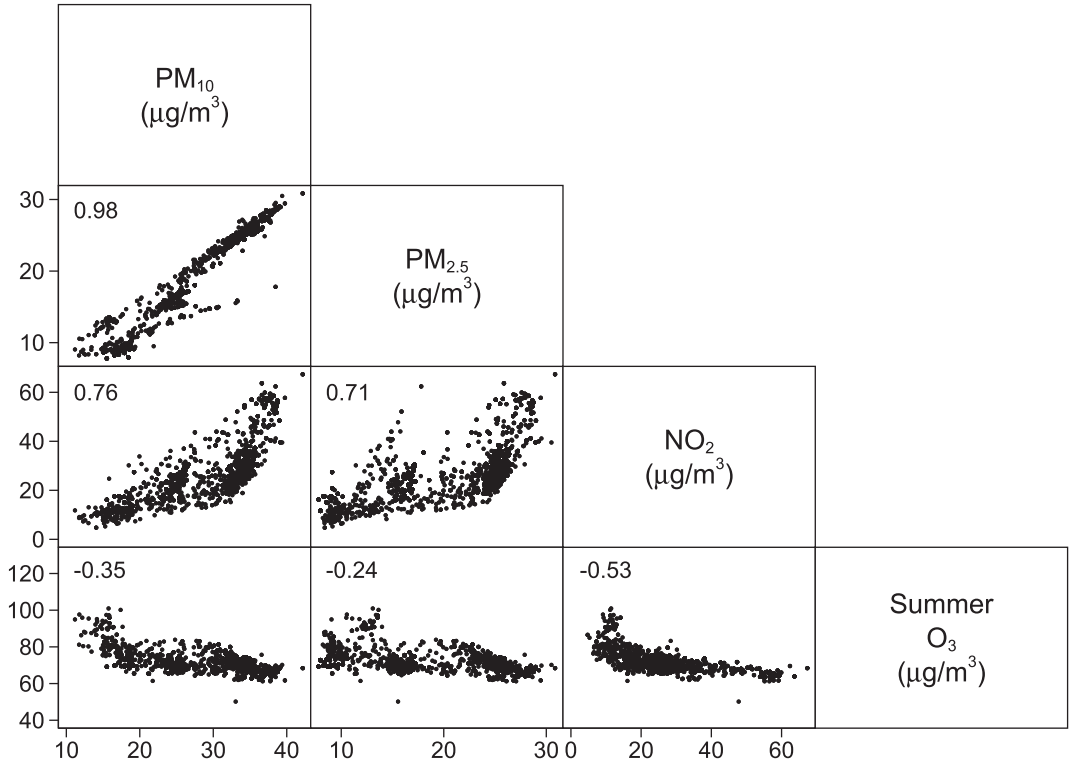

Fig. 2. Pairwise joint distribution of residential average concentrations of air pollutants in 2013–2015 and Spearman's rank correlation coefficients (all cities combined, n = 4111).

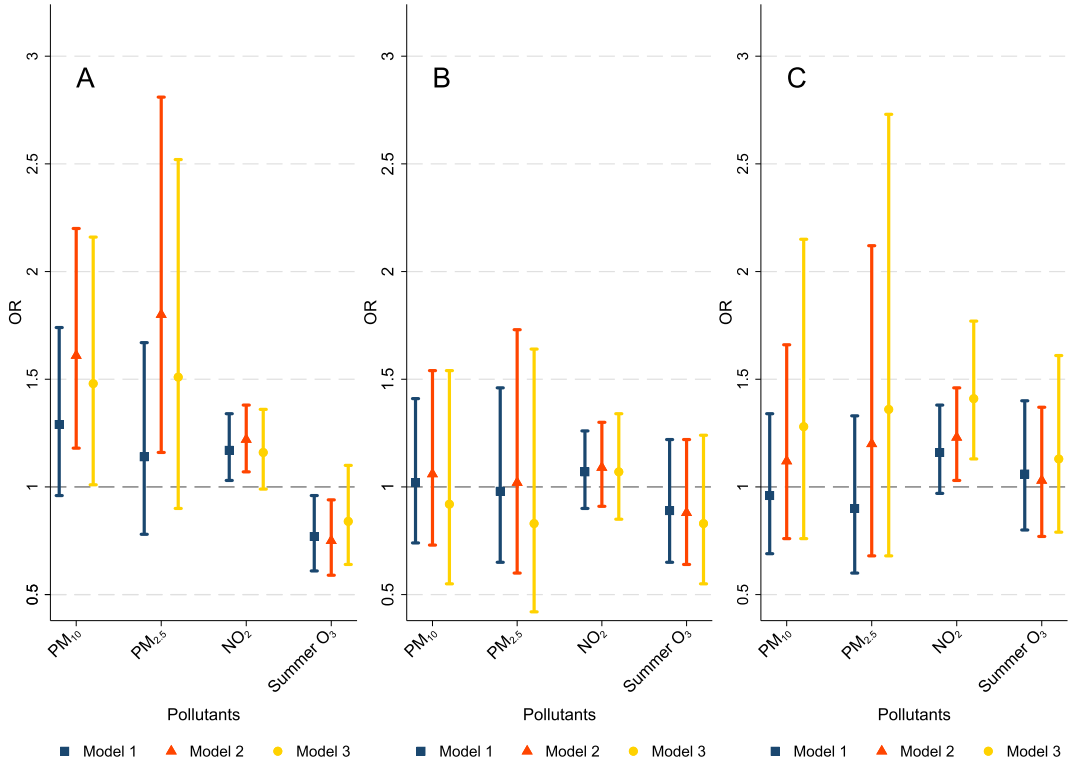

Fig. 3. Estimated associations of residential exposures to air pollutants with rhinitis alone (A), asthma with/without rhinitis (B) and CB/COPD with/without rhinitis (C).* * OR (95%CI) per 10 µg/m^3. Number of subjects in complete case analyses: rhinitis (n = 2679), asthma (n = 2169), CB/COPD (n = 2264). Model 1: adjusted for sex, age, education, BMI, smoking (cohort as a random intercept); model 2: model 1 + climate index; model 3: model 2 + summer O_3 for PM_{10}, $PM_{2.5}$, NO_2, or model 2 + $PM_{2.5}$ for summer O_3.

Higher residential exposure to NO_2 was associated with a greater risk of CB/COPD (Fig. 3, C): a 10 μg/m^3 difference was related to a 16 % increase in the odds of CB/COPD (OR 1.16, 95%CI: 0.97–1.38, model 1); this association became stronger and statistically significant when further adjusting for climatic index (OR 1.23, 95%CI: 1.03–1.46, model 2), as well as when adjusting for summer O_3 exposure (OR 1.41, 95%CI: 1.13–1.77, model 3). Exposures to PM_{10}, $PM_{2.5}$, and summer O_3 were not associated with CB/COPD in the main analysis, but they all became associated with a higher risk of CB/COPD in the analysis on non-movers, especially the bi-pollutant analysis (supplementary Table S4, model 3).

Findings from the analyses restricted to the subjects in the 20–64 years age range were consistent with the main ones (Supplementary Table S5).

Among the cases of rhinitis, 528 had allergic rhinitis (368 from GEIRD and 160 from Pisa study) and 437 had non-allergic rhinitis (188 from GEIRD and 249 from Pisa study). The estimated associations of pollutants' exposures with allergic and non-allergic rhinitis were very similar (Supplementary Table S6).

Seventy-seven percent of cases with CB/COPD had usual symptoms of CB. When we repeated the analyses using CB as the outcome definition, the results were consistent (Supplementary Table S7).

Among GEIRD participants, 343 cases (25.6 %) and 353 controls (24.3 %) reported occupational exposures over lifetime. Adjusting the analyses for occupational exposures did not affect the estimated associations (data not shown).

3.4. Effect modification

There was no effect modification by climate on any of the estimated associations (Supplementary Table S2). In the case of asthma, we observed a pattern of interactions with sex: 10 μg/m^3 higher exposures to PM_{10}, $PM_{2.5}$, and NO_2 tended to increase the risk of asthma in males (OR 1.36, 95%CI: 0.80–2.29; OR 1.45, 95%CI: 0.70–3.01; and OR 1.30, 95%CI: 1.04–1.64, respectively), but not in females where associations were either negative or null (OR 0.84, 95%CI: 0.51–1.37; OR 0.74, 95%CI: 0.38–1.43; OR 0.98, 95%CI: 0.76–1.26).

With regard to CB/COPD, we observed a pattern of interactions with age, with a tendency for stronger positive associations for the participants aged <50 years (PM_{10}: OR 1.62, 95%CI: 0.96–2.75; $PM_{2.5}$: OR 2.02, 95% CI: 1.04–3.92; NO_2: OR 1.46, 95%CI: 1.17–1.84) compared to the older participants (PM_{10}: OR 0.94, 95%CI: 0.55–1.61; $PM_{2.5}$: OR 0.78, 95%CI: 0.37–1.67; NO_2: OR 1.17, 95%CI: 0.94–1.45, respectively).

4. Discussion

In this cross-sectional study on adults living in eight Italian cities, we found that exposure to higher levels of air pollution estimated at residential addresses was associated with a greater risk of suffering from some of the most common chronic respiratory diseases in the general population. PM exposure was more strongly related to rhinitis, whereas NO_2 exposure was more strongly linked to CB/COPD. A paradoxical negative association between summer O_3 exposure and rhinitis shifted to the null when adjusting for $PM_{2.5}$ and in sensitivity analyses. Asthma was not associated with pollutants' exposures.

Some remarks on the case definitions adopted are worth before discussing our findings. First, our disease definitions aimed at capturing an active stage of the diseases, which we believed to support the causal interpretation of exposure-response associations. Cases of asthma were required to report the presence of asthma-like symptoms and/or the use of respiratory medication during the previous year, in combination with a self-reported diagnosis of asthma, whereas inactive asthma was not considered. Similarly, fulfilling the definition of rhinitis required to report recent or current upper airways symptoms. The treatment of rhinitis is typically driven by symptoms, as opposed to persistent asthma that requires controller medication. Some of the cases with CB/COPD (23 %) were classified in this group due to a self-reported physician diagnosis of CB, COPD or emphysema but they had no usual symptoms. Nonetheless, the study conclusions were consistent when excluding the latter subgroup. We adopted a hierarchical definition of the diseases: rhinitis was considered alone (which was possible thanks to the large number of cases recruited); cases of asthma and CB/COPD could also be affected by rhinitis, which reflects the fact that rhinitis is a common and typically minor comorbidity of both asthma and COPD. A final remark is that, unlike in a classical case-control design, controls did not have any of the disease conditions under investigation in our study.

One strength of this multicentre study is that we were able to represent different climatic regions. Asthma and rhinitis are known to be largely affected by climate in Italy. In fact, both conditions have a higher prevalence in the Mediterranean regions of the country compared to the subcontinental ones (de Marco et al., 2002; Pesce et al., 2016). Moreover, climate is related to annual air pollution concentrations. In our study, annual $PM_{2.5}$ tended to be higher in Northern Italy (~25 μg/m^3), compared to central and Southern Italy (9.2–19.5 μg/m^3) (Table 2). Indeed, we found a moderate (NO_2) to strong ($PM_{2.5}$, PM_{10}) confounding effect by climate for rhinitis and CB/COPD, as evident from the change in association estimates when adjusting for the climatic index (model 2 vs model 1). Our analyses do not suggest a climatic heterogeneity of exposure-response associations. In other words, the increase in disease risk did not vary significantly between subcontinental and Mediterranean regions. We cannot exclude that this lack of evidence is linked to the limited sample size. A previous ecological study in Italy reported a stronger association between NO_2 exposure and the risk of allergic rhinitis for people exposed to higher annual temperatures (de Marco et al., 2002).

The analyses were adjusted for some individual risk factors for the development of chronic respiratory diseases, including sex, age, and cumulative smoking exposure; unmeasured differences across centres were accounted for through the random-intercept term of mixed-effect models. We performed bi-pollutant analyses in the attempt to provide evidence on the chemical species most likely to be in the causal pathway. However, a caveat is needed, since correlation between pollutants' metrics can increase instability and imprecision of association estimates as a consequence of multicollinearity; moreover, differential measurement error can erroneously lead to attribute any observed health effects to the air pollutant that is measured more precisely, regardless of the true underlying causal pathway (Tolbert et al., 2007).

4.1. Air pollution and rhinitis

Chronic rhinitis is the most common respiratory disease in the general population (Avdeeva et al., 2022). It is characterised by nasal congestion, rhinorrhoea, sneezing, and/or postnasal drip in absence of a cold or the flu (Agnihotri and McGrath, 2019). In our study, we used a broad definition of rhinitis embracing both nasal allergies (hay fever) and the main symptoms of the allergic, nonallergic, and mixed phenotypes. A number of studies have reported a steady increase in the prevalence of allergic rhinitis over the last decades (de Marco et al., 2012; Li et al., 2022), and it is extremely relevant to seek the causes behind such upward trend. Several putative mechanisms linking air pollution to allergic rhinitis have been proposed, including IgE-mediated hypersensitivity, oxidative stress, neurogenic mechanisms (direct activation of chemoreceptors), and immunomodulation (Naclerio et al., 2020).

Our findings suggested a link between air pollutants and the risk of rhinitis. Estimated associations for allergic and non-allergic rhinitis were similar. Compared to NO_2, PM metrics were more strongly associated (also when ORs were expressed per SD-difference in exposure), and the estimated associations were more consistent across the analyses performed. In particular, the associations were stronger for non-movers, although these should be read carefully because, due to the exclusion of the Pisa study, it was based on a smaller and not completely comparable sample. It is interesting to highlight that, compared to NO_2, PM metrics were also more strongly related to the prevalence of rhinitis symptoms and use of medication in another study from the BIGEPI team based on the use of GEIRD stage 1 study (screening questionnaire data) in combination with the Pisa study (Maio et al., 2023).

A metanalysis combining studies of all age groups published up to 2020 estimated a 12–13 % increase in the odds of rhinitis per 10 μg/m^3 of annual exposure to PM_{10}, $PM_{2.5}$, and NO_2 (Li et al., 2022). A study on young adults exposed to high levels of air pollution in China found evidence of associations of allergic rhinitis with NO_2 (OR 1.17, 95%CI: 1.06,1.31 per 10 μg/m^3) and PM_{10} exposures (OR 1.06, 95%CI: 0.96,1.17), despite having low power due to ecological exposure assessment in only 8 cities (Wang et al., 2021). Associations between air pollution and the risk of rhinitis in young adults were confirmed in low-to-moderate air pollution settings in Nordic countries: more consistent associations were seen for NO_2 exposure (OR 1.13, 95%CI: 1.04–1.23 per 10 μg/m^3 during the age range 10–18 years) compared to $PM_{2.5}$ or PM_{10} (Nordeide Kuiper et al., 2021). Disease prevalence could not be the only component of rhinitis morbidity that is affected by air pollution exposure: a study combining two European cohorts suggested a link between exposure to air pollution, particularly PM, and disease severity in adults (Burte et al., 2020).

4.2. Air pollution and asthma

Asthma is a chronic inflammatory airway disease characterised by variable airflow obstruction, which is typically linked to hyperresponsiveness to noxious stimuli, including air pollution (Tiotiu et al., 2020). Exposure to chemical and aerobiological air pollutants have long been recognised to trigger respiratory symptoms in patients with asthma (Renzi et al., 2022). Traffic-related air pollution is a risk factor for asthma in children (Khreis et al., 2017). A link between long-term exposure to pollutants and adult asthma onset have been shown more recently, thanks to studies conducted in large populations and the availability of accurate exposure assignment techniques. Among these, the ELAPSE study (Effects of Low-Level Air Pollution: A Study in Europe) documented associations with asthma onset in Nordic countries. Hazard ratios (HR) were 1.22 (95 % CI: 1.04–1.43 per 5 μg/m^3) for $PM_{2.5}$ and 1.17 (95 % CI: 1.10–1.25 per 10 μg/m^3) for NO_2 (Liu et al., 2021b). Associations estimated in the ecological study of Chinese adults also suggested a stronger association for NO_2 (OR 1.24, 95%CI: 1.09,1.42) than for PM_{10} (OR 1.08, 95%CI: 0.97,1.20) (Wang et al., 2021). A meta-analysis of earlier studies documented moderate-to-high evidence of association between NO_2 exposure and asthma incidence in adults (Relative risk 1.10, 95 % CI:1.01; 1.21 per 10 μg/m^3) (Boogaard et al., 2022); studies of PM effects were few and were not included in the meta-analysis. In contrast, a Canadian study on 5.1 million individuals did not find consistent evidence for the relationship between air pollution exposure and adult-onset asthma (Shin et al., 2021).

In our study, we did not find significant associations between pollutants exposures and asthma. One possible explanation for the null findings is the small sample size: cases of asthma were the smallest group in our study (n = 328). Indeed, investigating a larger sample of the adult general population from the same studies, Maio et al. (2023) documented clear associations for all pollutants with the prevalence of asthma, asthma symptoms and use of medication. In our study, a pattern of interactions between exposures and sex emerged, which suggested an association between NO_2 exposure and asthma risk in men (30 % increase in the odds of asthma per 10 μg/m^3), but not in women.

4.3. Air pollution and CB/COPD

COPD is a disease characterised by persistent respiratory symptoms and airflow limitation that are due to airway and/or alveolar abnormalities (GOLD 2022). A definition of “pre-COPD” has been recently proposed aimed at capturing the early signs and symptoms of disease that could favour a timely diagnosis and treatment (Celli et al., 2022). In middle aged individuals, cough and phlegm are a known risk factor for COPD. In the present study we used a broad definition of CB/COPD that is assumed to identify at least part of the symptomatic individuals affected by pre-COPD (the CB dimension), as well as subjects whose disease has been recognised by physicians (the COPD dimension). Nonetheless, we acknowledge the evident limitation of not having lung function measurements available from post-bronchodilator spirometry, which is to date the functional test required to define the disease (GOLD 2022).

NO_2 was the pollutant most strongly and consistently associated with the risk of suffering from CB/COPD. In a sensitivity analysis, we also documented the same pattern of associations for CB, pointing to a role of air pollution in the occurrence of symptoms and possibly pre-COPD (Supplementary Table S7). A recent study conducted in the Netherlands also documented clear associations of prevalence and incidence of CB symptoms with NO_2 and black carbon (strong indicators of traffic-related, especially tailpipe, pollution), but not for $PM_{2.5}$ (Doiron et al., 2021). Like in our study, associations were also stronger in people younger than 50 years, a group where early symptoms, rather than overt airflow obstruction, could be a predominant feature of the disease. Younger subjects may also spend more time outdoors and thus be more exposed to ambient air pollution compared to older ones. Exposure to $PM_{2.5}$, PM_{10} and NO_2 were all linked to the prevalence of CB symptoms in a study on women in the United States (Hooper et al., 2018). In a previous cross-sectional study in Southern Sweden, intense residential traffic and elevated nitrogen dioxides concentrations were related to CB symptoms, as well as to the prevalence of COPD, defined by self-reported physician-diagnosed CB, COPD or emphysema like in our study (Lindgren et al., 2009). Although recent metanalyses still report low to moderate evidence for the relationship between air pollution and COPD onset (Boogaard et al., 2022; Park et al., 2021), some more recent studies are strengthening such evidence. Among these, the previously mentioned study on the Canadian population documented a 3–8 % increase in COPD incidence per interquartile range differences in $PM_{2.5}$, NO_2, and O_3 concentrations (Shin et al., 2021). Studies on Swedish and Danish populations (including ELAPSE) suggested associations between air pollution (particularly NO_2) and COPD, which persisted at air quality levels within the European Union and United States standards (Liu et al., 2021a, 2021c). In a population aged 30–79 years living in Suzhou, China, the incidence of COPD was defined using mortality and health insurance records (ICD-10 codes J41-J44). They found that COPD incidence was mainly related to exposure to SO_2 (Hazard Ratios per 10 μg/m^3: 1.25, 95%CI: 1.08–1.44) (Wright et al., 2023).

4.4. Limitations

We estimated long-term air pollution exposures for a period that did not precede the outcome assessment for all the participants, which could make causal interpretation problematic. Nonetheless, in the case of PM_{10}, the average concentrations calculated for 2013–2015 were highly correlated with the average concentrations calculated over the whole period of PM_{10} data availability (2006–2015), and also over the three-year period before outcome assessment (supplementary Fig. 1). It has been reported that annual exposure contrasts are quite stable over time (Eeftens et al., 2011; Fasola et al., 2020; Marcon et al., 2015). Finally, association estimated for the subset of non-movers were consistent. These considerations suggest that using average concentrations over 2013–2015 as indicators of long-term exposure is unlikely to have introduced a major bias in our study.

We relied on the assumption that residential air pollution concentrations are good estimates of a subject's average exposure level. People spend part of their time in other locations, including the work place, but we were unable to account for time-activity patterns. However, measurement error due to this issue is expected to be non-differential (random) and therefore to potentially bias associations toward underestimation rather than in the opposite direction.

Combining data from different studies improved the geoclimatic representativeness of our study population and increased sample size. GEIRD and Pisa participants had different characteristics, which we adjusted for in the analyses. The age range of recruitment varied between studies and also across GEIRD cohorts, but the sensitivity analyses restricted to the 20–64 years age range were in line with the main analysis.

We did not have comparable clinical data from GEIRD and Pisa studies (such as lung function and allergological tests performed using a standardised protocol) which could have improved the outcome

definitions. We therefore acknowledge self-reporting of health data as a study limitation. However, we used questions derived from largely used validated questionnaires from international surveys. Assessing symptoms through a questionnaire is required to capture the relatively mild level of disease severity that is common in the general population.

5. Conclusions

Long-term air pollution exposure is related to the prevalence of chronic respiratory diseases in several Italian cities. Among the pollutants investigated, PM was especially linked to rhinitis, a disease with a high prevalence in the general population. CB/COPD was more affected by exposure to NO_2, a pollutant characterised by strong oxidative properties. We found that climate can have a confounding effect in multicentre studies, highlighting the importance of taking it into account when estimating air pollution effects. Understanding the causal role of single pollutants has great public health relevance. However, available evidence emphasises the need for the implementation of policies that transversally affect all emission sources, and are therefore effective to reduce the level of a wide range of correlated pollutants at the same time.

CRediT authorship contribution statement

SM is the Principal Investigator of the BIGEPI study. AM and SM are co-coordinators of Work package 4 of BIGEPI. GVi (Pisa), LA (Ancona), SBa (Palermo), RB (Torino), AC (Pavia), NM (Terni), PP (Sassari), GVe (Verlato) were local coordinators for data collection. AM and PM conceived the present analysis and drafted the first version of the manuscript. MS and CS provided modelled air pollutants' concentrations at the residential addresses of participants. JM, PM and FL performed the statistical analysis. All the authors contributed in the discussion of the analysis plan, the interpretation of results, and commented on the first draft, they critically reviewed and approved the final version of the manuscript.

Data availability

The data that has been used is confidential.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.163802.

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