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Relationship of long-term air pollution exposure with asthma and rhinitis in Italy: an innovative multipollutant approach

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ABSTRACT

Background: air pollution is a complex mixture; novel multipollutant approaches could help understanding the health effects of multiple concomitant exposures to air pollutants.
Aim: to assess the relationship of long-term air pollution exposure with the prevalence of respiratory/allergic symptoms and diseases in an Italian multicenter study using single and multipollutant approaches.
Methods: 14420 adults living in 6 Italian cities (Ancona, Pavia, Pisa, Sassari, Turin, Verona) were investigated in 2005–2011 within 11 different study cohorts. Questionnaire information about risk factors and health outcomes was collected. Machine learning derived mean annual concentrations of PM_{10}, $PM_{2.5}$, NO_2 and mean summer concentrations of O_3 (μg/m^3) at residential level (1-km resolution) were used for the period 2013–2015. The associations between the four pollutants and respiratory/allergic symptoms/diseases were assessed using two approaches: a) logistic regression models (single-pollutant models), b) principal component logistic regression models (multipollutant models). All the models were adjusted for age, sex, education level, smoking habits, season of interview, climatic index and included a random intercept for cohorts.
Results: the three-year average (± standard deviation) pollutants concentrations at residential level were: 20.3 ± 6.8 μg/m^3 for $PM_{2.5}$, 29.2 ± 7.0 μg/m^3 for PM_{10}, 28.0 ± 11.2 μg/m^3 for NO_2, and 70.9 ± 4.3 μg/m^3 for summer O_3. Through the multipollutant models the following associations emerged: PM_{10} and $PM_{2.5}$ were related to 14–25% increased odds of rhinitis, 23–34% of asthma and 30–33% of night awakening; NO_2 was related to 6–9%

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increased odds of rhinitis, 7–8% of asthma and 12% of night awakening; O_3 was associated with 37% increased odds of asthma attacks. Overall, the Odds Ratios estimated through the multipollutant models were attenuated when compared to those of the single-pollutant models.

Conclusions: this study enabled to obtain new information about the health effects of air pollution on respiratory/allergic outcomes in adults, applying innovative methods for exposure assessment and multipollutant analyses.

Abbreviations

BEEP	the "Big data in Environmental and occupational Epidemiology" project
BIGEPI	the "Use of BIG data for the evaluation of the acute and chronic health Effects of air Pollution in the Italian population" project
INAIL:	the Italian Workers' Compensation Authority
GEIRD	the "Gene-Environment Interactions in Respiratory Diseases" study
PI1	the Pisa study first survey
PI2	the Pisa study second survey
PI3	the Pisa study third survey
IMCA	"Indicators for Monitoring COPD and Asthma in the EU (IMCA II)" project
ECRHS	the "European Community Respiratory Health Survey"
PCLR	principal component logistic regression

1. Introduction

Outdoor air pollution was estimated to cause 4.5 million premature deaths worldwide per year in 2019 (Fuller et al., 2022). In the 27 countries currently members of the EU, the European Environmental Agency (EEA) estimated that in 2020 the premature deaths attributable to air pollutant exposure above the 2021 WHO guideline level (WHO, 2021) were: 238,000 for exposure to particulate matter with an aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), 49,000 for exposure to nitrogen dioxide (NO_2) and 24,000 for acute exposure to ozone (O_3) (EEA, 2022).

In 2017, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) jointly published a comprehensive review of what constitutes an adverse health effect of air pollution: indeed, the adverse respiratory effects span the life cycle and affect a wide range of illnesses, from symptoms like cough, sputum, wheeze, and dyspnea, to premature mortality (Thurston et al., 2017).

Rapid urbanization and industrialization have increased air pollution levels and the amount of the exposed population (Flies et al., 2019; Eguiluz-Gracia et al., 2020; Sousa et al., 2022). The loss of natural environments and biodiversity, due to the increase of artificial areas, might be related to the increase in the global prevalence of allergic diseases, such as asthma and rhinitis; indeed, people living in urban areas more frequently suffer from these diseases than those living in rural ones (Baldacci et al., 2015; Paciencia and Rufo, 2020; Flies et al., 2019). Moreover, the reduced exposure to microbial diversity adversely affects the human microbiome and may lead to the development of allergic disorders (Flies et al., 2019). Most evidence derives from studies of children and young adults; few studies have shown an increase of allergic and asthmatic diseases/symptoms in adults, who suffer from a more impaired quality of life than their younger counterparts (Nanda et al., 2020; Baptist and Nyenhuis, 2016; Cai et al., 2017).

These long-term adverse effects on respiratory symptoms/diseases and lung function in adults and children emerged even for exposure levels below current ambient air quality standards (Dominici et al., 2019; Brunekreef et al., 2021; Stafoggia et al., 2022). Thus, it is important to keep analyzing the associations between air pollution and health effects, even though air pollution levels would further decrease (Brunekreef et al., 2021).

Indeed, new technologies based on a combination of data from air quality monitoring stations, satellite data, territorial data (e.g., land use) and meteorological parameters, provide fine temporal and spatial estimates of air pollutants exposure allowing better investigation of long-term health effects (Stafoggia et al., 2019; Cilluffo et al., 2018).

Although the typical approach used in epidemiological studies takes into account one pollutant or at most two pollutants at a time (Blangiardo et al., 2019), a new challenge derives from the need to use multipollutant approaches that more realistically describe the complexity of air pollution concentrations in the air we breathe.

In single-pollutant models, it is unclear whether an observed association reflects the effect of the analyzed pollutant or it acts as a surrogate for other pollutants, possibly originating from the same source (Stafoggia et al., 2017a). On the other hand, the analysis of the health effects of different pollutants with conventional statistical approaches (all pollutants included in a single regression model) often may produce unstable estimated parameters with large standard errors due to high correlation between these air pollutants. Therefore, advanced statistical methods might improve the assessment of the health effects of exposure to mixtures or the combined health effects of multiple exposures (Molitor et al., 2016; Stafoggia et al., 2017a; Traini et al., 2022).

Finally, data from analytical epidemiological studies allow to control for individual potential confounders, such as lifestyle and socioeconomic variables, overcoming some of the limitations of the studies based on health data from registers or on ecological data (Gandini et al., 2018).

In this framework, the "Big data in Environmental and occupational Epidemiology" (BEEP) project and the "Use of BIG data for the evaluation of the acute and chronic health Effects of air Pollution in the Italian population" (BIGEPI) project, co-funded by the Italian Workers' Compensation Authority (INAIL), were designed. Their aim was to investigate the health effects of air pollution and meteorological parameters on the Italian general population through the integration of national data including land use, satellite, modelled meteorological fields and atmospheric composition variables, mortality, hospitalizations, morbidity, work injuries and commuting accidents (Stafoggia et al., 2019; Renzi et al., 2022; Gariazzo et al., 2022).

BEEP and BIGEPI projects provided the unique opportunity to evaluate the long-term air pollution effects on Italian analytical epidemiological surveys, by linking air pollutant levels estimated at the residential address to the individual health data, adjusting for individual potential confounders and using advanced statistical analyses for multipollutant assessments.

In particular, the aim of the present work was to increase the knowledge about the relationship of air pollution exposure with the prevalence of respiratory/allergic symptoms and diseases in Italian adults living in areas characterized by a wide range of air pollution concentrations, and to compare single and multipollutant approaches.

2. Methods

2.1. Study population and design

The study population includes subjects (n = 14,420) participating in two different observational analytical studies aimed at investigating allergic and respiratory conditions in the Italian population: the Pisa study and the Gene-Environment Interactions in Respiratory Diseases

(GEIRD) study.

The Pisa study is a multistage stratified family-cluster random study investigating subjects from the general population living in Pisa over three subsequent surveys: first survey (PI1) (1985–1988); second survey (PI2) (1991–1993); third survey (PI3) (2009–2011). For these analyses data from the PI3 survey were analyzed (Table A1 of Supplementary Material (SM)). PI3 consisted of the subjects participating in both PI2 and PI3 and of a new sample of individuals (newborns, new spouses and subjects not available in the previous survey). Detailed information on population characteristics and methods are available elsewhere (Maio et al., 2016; Viegi et al., 1999).

GEIRD is a two-stage multicenter study investigating adult subjects from the general populations living in seven Italian cities between 2005 and 2011 (de Marco et al., 2010). In stage 1, a cross-sectional postal survey was conducted on new or pre-existing random samples from the general population. For these analyses, data from subjects living in Turin, Pavia, Verona, Ancona, and Sassari were analyzed (Table A1 of SM). Overall, 10 cohorts of GEIRD study for 5 cities were included in the present work. Detailed information on population characteristics and methods are available elsewhere (de Marco et al., 2010).

The six cities taking part in this study represent different Italian geoclimatic area (Fig. 1): three of them – Turin, Pavia, and Verona – are located in the northern part of Italy (Po River Valley) and characterized by a subcontinental climate (Köppen climate classification (Beck et al., 2020): CFA, humid subtropical climate); the other three cities are located in central (Ancona and Pisa) and insular part (Sassari) of Italy and are characterized by a typical Mediterranean climate (Köppen climate classification: CSA, hot-summer Mediterranean climate). The subcontinental zone has a lower annual average temperature and a wider annual temperature range than the Mediterranean zone (Pesce et al., 2016; Marchetti et al., 2017).

2.2. Investigated respiratory symptoms/diseases

In the Pisa study, information on allergic/respiratory symptoms/diseases and risk factors was obtained through standardized interviewer-administered questionnaires developed within the European project "Indicators for Monitoring COPD and Asthma in the EU (IMCA II)" (Maio et al., 2016).

In the GEIRD study, a cross-sectional screening questionnaire was administered (www.geird.org) using a modified version of the European Community Respiratory Health Survey (ECRHS) questionnaire, including items on allergic/respiratory symptoms/diseases and risk factors (de Marco et al., 1999).

Since different questionnaires were used in Pisa and GEIRD studies, only comparable questions on asthma and rhinitis were used for these analyses, as detailed in the first section of the SM.

The following outcomes were taken into account: allergic rhinitis, rhinitis symptoms, rhinitis medications, asthma, attacks of asthma, asthma medications, asthma like symptoms (wheezing, attacks of breathlessness with wheezing, night awakenings due to shortness of breath).

Moreover, combined outcomes for rhinitis and asthma were derived taking into account simultaneously the presence of symptoms, diagnoses or medicine use: combined rhinitis (allergic rhinitis or rhinitis symptoms or rhinitis medications); combined asthma (asthma diagnosis or asthma attacks or asthma medications). The combined outcomes are meant to identify those who are most susceptible and at greater probability of having harmful effects from air pollution exposure due to a current or past condition that could exacerbate for a long-term air pollution exposure.

Participants were informed about all the research aspects and signed informed consents were obtained from all the participants before the questionnaire completion. Approval to conduct the study was granted by the local ethical committee in each participating center.

2.3. Environmental exposure

Environmental exposure to particulate matter (PM) with diameter $\leq$10 μm (PM_{10}), $PM_{2.5}$, NO_2 and summer (from April to September) O_3 was estimated within the BEEP project.

PM mean concentrations were derived from machine learning Random Forest (MLRF) algorithms driven by satellite observations and spatial and spatial-temporal data, as described elsewhere (Stafoggia et al., 2017b, 2019). Briefly, for each day of the years between 2006 and 2015, and for each squared kilometer of Italy, several spatial (land coverage, road network, light at night, impervious surface areas, population density, elevation) and spatio-temporal predictors (such as satellite-based aerosol optical depth - AOD, PM monitored data from all the available monitoring sites, air temperature and other meteorological parameters from ERA5, point emission sources, total emissions and, resident population) were collected. 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 was developed calibrating the aforementioned predictors to PM_{10} and $PM_{2.5}$ monitoring data. The shorter period of analysis for $PM_{2.5}$ was due to a more recent installation of $PM_{2.5}$ monitors in Italy.

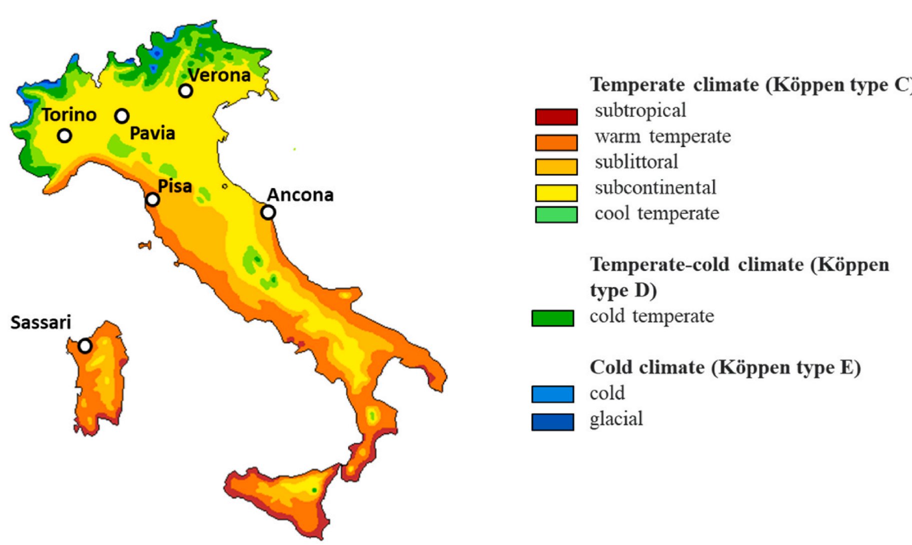

Fig. 1. Geographical distribution of the 6 cities.
Legend: modified from Pinna M, *L'atmosfera e il clima*, Torino, UTET, 1978, p. 470.

Cross-validated R^2 were 0.75 and 0.81 for PM_{10} and $PM_{2.5}$, respectively, demonstrating good predictive properties of the model at unmeasured locations (Stafoggia et al., 2019).

NO_2 and O_3 mean concentrations were derived developing an integrated approach coupling a chemical transport model (CTM) with machine learning techniques, as described elsewhere (Silibello et al., 2021). Briefly, simulations, at a spatial resolution of 5 km, performed by the Flexible Air quality Regional Model (FARM), were obtained for each day of the years between 2013 and 2015. These simulations, together with the same spatial and spatiotemporal data used for modeling PM, with the exception of AOD, were used as predictors by a MLRF algorithm to produce daily concentrations at higher resolution (1 km) over the national territory. Cross-validated R^2 were 0.60 and 0.80 for NO_2 and O_3, respectively, demonstrating good predictive properties of the model at unmeasured locations (Silibello et al., 2021).

Shtein et al. (2020) compared 4 approaches to estimate air pollution concentrations at unmeasured locations: MLRF, extreme gradient boosting (XGBoost), Mixed Effect Models, and a pure Chemical Transport Model (CTM). XGBoost and RF algorithms outperformed the other methods in terms of cross-validation statistics. The choice of using MLRF was due to its relatively simple use and its diffusion among experts in the field of environmental exposure.

The daily series of exposure levels at 1 Km resolution estimated for the four pollutants were linked to the residential addresses of the subjects according to their spatial locations, and a three-year average exposure level was calculated for the period 2013–2015 (years with available estimates for all the pollutants).

2.4. Covariates and potential confounders

The following covariates were collected from the questionnaire: sex, age (categorized in 18–44 yrs, 45–64 yrs, 65+ yrs), education level (0–8 yrs of education, 9–13 yrs, >13 yrs), smoking habits (non smoker, ex-smoker with <15 pack-years, ex-smoker with ≥15 pack-years, smoker with <15 pack-years, smoker with ≥15 pack-years), and the season in which the questionnaire was completed (spring, summer, autumn, winter).

A climatic index, computed by Pesce et al. (2016) through a principal component analysis (PCA) for all the 110 Italian provinces, was used to take into account the different climatic characteristics of the six cities mainly due to annual global solar radiation, annual mean temperature, range of temperature, and rainfalls. The value was minimum in the Subcontinental centers of Northern Italy and maximum in the Mediterranean centers of Southern Italy. In particular, the following values were imputed for our six cities: −1.89 for Pavia, −1.52 Turin, −0.91 Verona, −0.35 Pisa, 0.76 Ancona and 2.41 Sassari.

This index was demonstrated to play a role in determining the between-cities heterogeneity in the prevalence of asthma, with higher prevalence in dry-hot Mediterranean climates and lower in rainy-cold northern climates (Pesce et al., 2016).

2.5. Statistical analyses

All the statistical analyses were performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The characteristics of the study participants were summarized through numbers (No.) and percentages (%). Comparisons between the cities were carried out using the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables. The three-year (2013–2015) average pollutant concentrations were summarized through the city-specific mean (SD), median, range (min-max), and interquartile range (IQR); correlations across pollutants were summarized using Spearman's correlation coefficients. Statistical significance was set at $p\text{-value} < 0.05$.

The extent of multicollinearity in the exposure matrix was assessed by calculating the variance inflation factor (VIF) for the four pollutants. In general, VIFs of 2.5 or larger are considered indicative of considerable collinearity, since it would become difficult to distinguish the independent contribution of the pollutants with such large VIFs (Johnston et al., 2018).

The association between the four pollutants and each respiratory/allergic outcome was assessed using two different approaches: a) a set of four single-pollutant logistic regression models with a cohort-level random intercept (11 cohorts for 6 cities); b) a multipollutant model, i.e., a principal component logistic regression (PCLR) model with a cohort-level random intercept (11 cohorts for 6 cities). All the models were adjusted for age, sex, education level, smoking habits, interview season, and climatic index.

PCLR is an extension of principal component regression (PCR) aiming at removing the collinearity of input variables through the PCA. The method consists of three steps. In the first step, PCA is performed on the (scaled and centered) matrix of the four air pollutants, and a matrix of four principal components is obtained. Then, the optimal number of principal components, that is the minimum number of principal components explaining at least 80% of total pollutants variance, is selected. In the second step, a logistic regression model is estimated using the selected principal components and the potential confounders as covariates. In the third step, the regression coefficients of the selected principal components are back transformed to the original scale of the pollutants, providing substantially improved estimates in the case of multicollinearity (Aguilera et al., 2006).

Pollutant effects were expressed as odds ratios (ORs) per 10 $\mu g/m^3$ increases with 95% confidence intervals (CIs), and were visually displayed. ORs per 5 $\mu g/m^3$, 1 $\mu g/m^3$ and IQR increases were also reported.

Since the age class ≥65 yrs was poorly or not represented in Pavia, Turin and Ancona, a sub-analysis was run including only the three centers whose participants represented the entire age distribution of an adult general population (Pisa, Sassari and Verona) (8 cohorts).

3. Results

A total of 14,420 individuals aged 18–103 years (52.5% females) were included; 57.6% were 18–44 yrs, 30.9% 45–64 yrs and 11.5% 65+ yr old. Subjects were mainly characterized by medium-high education level (65.7%), 9.4% were heavy smokers (≥15 pack-yrs), 13.5% light smokers (<15 pack-yrs), 8.4% heavy ex-smokers and 15.8% light ex-smokers. Subjects were more frequently interviewed in spring (36.0%), followed by winter (23.4%) and autumn (22.7%).

Almost all descriptive characteristics showed statistically significant differences between the six cities (Table 1).

Overall, rhinitis showed the highest prevalence for all the considered outcomes (diagnosis 22.9%, symptoms 29.8%, medicine use 18.0%, rhinitis combined 38%), followed by asthma-like symptoms (night awakenings 9.7%, wheezing 9.4%) and asthma (asthma diagnosis 9.6%, asthma combined 10.6%). The lowest prevalence was found for attacks of breathlessness with wheezing (6.0%), attacks of asthma (5.6%) and asthma medications (4.7%).

Statistically significant differences were found in the prevalence of symptoms, diseases and use of medicines between the six cities (Table 2).

The three-year (2013-2015) average (±SD) pollutant concentrations at residential level were: 20.3 ± 6.8 $\mu g/m^3$ for $PM_{2.5}$ (median value 24.5, IQR 10.4), 29.2 ± 7.0 $\mu g/m^3$ for PM_{10} (median value 33.1, IQR 9.8), 28.0 ± 11.2 $\mu g/m^3$ for NO_2 (median value 26.6, IQR 12.9), and 70.9 ± 4.3 $\mu g/m^3$ for summer O_3 (median value 70.3, IQR 4.2). Statistically significant differences were found in the air pollutant concentration values between the six cities (Table 3).

The air pollutant correlation matrix showed high positive correlations among $PM_{2.5}$, PM_{10} and NO_2 (ranging from 0.745 to 0.986) and moderate-low negative correlations between O_3 and the other pollutants (ranging from −0.265 to −0.562) (Fig. 2). Consistently, the VIFs highlighted considerable collinearity issues: $VIF(PM_{2.5}) = 56.92$, $VIF(PM_{10}) = 62.92$, $VIF(NO_2) = 3.41$, $VIF(O_3) = 2.21$.

Table 1
Descriptive characteristics (%) (n = 14420).

	Pisa (n = 1615)	Verona (n = 5756)	Pavia (n = 1413)	Turin (n = 1707)	Ancona (n = 1350)	Sassari (n = 2579)	p-value
Age range[a]	18–103	20–84	20–64	20–64	20–44	20–84	–
Age classes[a]:							–
18–44 yrs	29.8	51.9	67.4	63.6	100.0	57.2	
45–64 yrs	32.2	37.8	32.6	36.4		25.4	
≥65 yrs	38.0	10.4				17.5	
Sex:							0.061
males	47.3	47.2	47.8	44.8	48.5	49.6	
females	52.7	52.8	52.2	55.2	51.5	50.4	
Educational level:							<0.001
0–8 yrs	55.0	35.4	31.9	25.5	16.7	34.7	
9–13 yrs	32.0	44.6	46.8	49.0	60.2	40.8	
>13 yrs	13.0	20.0	21.3	25.5	23.1	24.5	
Smoking habits:							<0.001
smoker≥15 pky	9.5	9.5	10.1	10.7	5.7	9.9	
smoker<15 pky	10.4	12.3	13.5	15.5	20.6	13.0	
ex-smoker≥15 pky	16.1	7.8	6.3	5.5	1.7	11.4	
ex-smoker<15 pky	16.9	16.9	15.8	13.9	12.7	15.7	
non smoker	47.1	53.5	54.3	54.4	59.3	50.0	
Interview season:							<0.001
spring	34.4	18.3	57.0	52.3	61.0	40.6	
summer	12.9	14.9	22.8	24.4	23.6	18.0	
autumn	31.4	22.9	18.3	17.3	1.5	33.8	
winter	21.3	43.9	1.9	6.0	13.9	7.6	

[a] age range and age classes of the samples depend on the different study design and sample selection, as detailed in Table A1 pky: pack-years.

Table 2
Prevalence of respiratory/allergic diagnosis, symptoms, use of medicines (%).

	Pisa	Verona	Pavia	Turin	Ancona	Sassari	p-value
Rhinitis							
Allergic rhinitis	15.5	22.2	23.3	24.2	28.6	25.3	<0.001
Rhinitis symptoms	33.2	31.2	32.9	3.8	40.5	34.0	<0.001
Rhinitis medications	30.4	14.2	14.8	15.8	23.6	18.6	<0.001
Rhinitis (combined)[a]	48.7	35.9	36.9	30.7	45.5	37.2	<0.001
Asthma							
Asthma diagnosis	8.3	8.9	7.8	8.2	10.7	13.2	<0.001
Attacks of asthma	3.2	5.2	4.4	6.5	4.8	8.5	<0.001
Asthma medications	7.2	3.5	3.2	4.3	3.9	7.5	<0.001
Asthma (combined)[b]	10.7	9.3	9.6	9.3	11.3	14.3	<0.001
Asthma-like symptoms							
Wheezing	7.6	6.4	10.3	10.8	11.3	14.5	<0.001
Attacks of breathlessness with wheezing	7.6	7.0	2.9	3.4	1.7	8.5	<0.001
Night awakenings	6.8	9.0	9.8	12.5	9.2	11.7	<0.001

[a] allergic rhinitis or rhinitis symptoms or rhinitis medications; [b] asthma diagnosis or asthma attacks or asthma medications.

With regard to the four principal components, they were associated with the following cumulative percentages of explained variance: C1 = 73%, C2 = 94%, C3 = 100%, C4 = 100%. Thus, the first 2 components were selected since they explained over 80% of total pollutants variance. The correlation of the coefficients between the original variables and the four principal components is shown in Table 4.

Overall, the ORs estimated through the multipollutant models (effects adjusted for other pollutants) were attenuated when compared to those of the single-pollutant models (effects not adjusted for other pollutants) (Figs. 3–5; Table A2 of SM). Significant protective effects of O_3 (Figs. 3 and 5c) were no longer observed after the multipollutant adjustment (on the contrary, they tended to OR>1).

Focusing on the multipollutant models, significant associations were observed among exposure to $PM_{2.5}$, PM_{10}, and NO_2, and most health outcomes with comparable ORs for $PM_{2.5}$ and PM_{10}, and lower ORs for NO_2 (Figs. 3–5, Table A2). O_3 exposure was significantly associated only with asthma attacks (OR 1.37, 95% CI 1.08–1.75 per 10 $\mu g/m^3$ increase). Focusing on the combined outcomes, rhinitis was significantly associated with increasing exposure to $PM_{2.5}$ (OR 1.17, 95% CI 1.06–1.30), PM_{10} (OR 1.16, 95% CI 1.06–1.26) and NO_2 (OR 1.07, 95% CI 1.04–1.10) (Fig. 3d, Table A2).

Combined asthma was significantly associated with increasing exposure to $PM_{2.5}$ (OR 1.26, 95% CI 1.08–1.47), PM_{10} (OR 1.23, 95% CI 1.08–1.40) and NO_2 (OR 1.07, 95% CI 1.03–1.12) (Fig. 4d, Table A2). Concerning asthma-like symptoms (Fig. 5), only night awakenings were significantly associated with air pollutants exposure: OR 1.33, 95% CI 1.16–1.52 for $PM_{2.5}$; OR 1.30, 95% CI 1.16–1.46 for PM_{10}; OR 1.12, 95% CI 1.08–1.17 for NO_2 (Fig. 5c).

ORs per 5 $\mu g/m^3$ and 1 $\mu g/m^3$ increases were reported in the SM (Tables A.3-A.4). As expected, the significant relationships were unchanged whilst the magnitude of the ORs decreased. With regard to IQR increases (Tables A.5), the significant relationships were unchanged whilst the magnitude depended on whether IQR was slightly larger or slightly lower than 10 $\mu g/m^3$.

Results of the sub-analysis including only the cities of Pisa, Sassari, and Verona (which well represented all age groups from 18 to 84 years) showed consistent associations with higher OR values, especially for NO_2, as well as new statistically significant associations among summer O_3 and night awakenings (OR 1.23, 95% CI 1.10–1.49), and combined asthma (OR 1.27, 95% CI 1.00–1.61) (Table A.6).

Table 3
Summary statistics of the three-year (2013–2015) average pollutants concentrations (μg/m^3).

	Pisa	Verona	Pavia	Turin	Ancona	Sassari	p-value
$PM_{2.5}$:							<0.001
mean ± SD	16.5 ± 0.7	24.6 ± 2.7	25.3 ± 1.1	26.8 ± 2.6	15.1 ± 0.6	8.9 ± 0.7	
median	16.7	25.3	25.3	27.5	15.2	9.0	
IQR	0.6	1.0	0.9	2.4	0.5	0.7	
min-max	11.8–18.0	8.9–26.7	19.7–29.0	6.8–30.9	12.8–16.8	7.3–11.5	
PM_{10}:							<0.001
mean ± SD	24.9 ± 1.0	33.2 ± 3.9	34.2 ± 1.7	36.1 ± 3.5	25.1 ± 1.5	17.9 ± 1.2	
median	25.1	34.2	34.3	36.9	25.3	18.3	
IQR	0.6	1.3	1.9	2.4	1.6	1.4	
min-max	19.1–27.5	11.1–36.2	26.6–39.1	8.0–42.2	19.6–27.6	11.7–21.7	
NO_2:							<0.001
mean ± SD	23.4 ± 3.8	29.5 ± 6.6	28.1 ± 4.4	49.6 ± 9.4	23.8 ± 4.3	15.2 ± 4.2	
median	23.6	30.2	28.7	51.5	24.2	15.2	
IQR	5.2	8.4	5.6	12.3	4.7	6.0	
min-max	9.9–35.4	5.9–40.3	16.9–39.6	5.8–67.4	10.0–32.9	4.5–27.4	
Summer O_3:							<0.001
mean ± SD	70.0 ± 2.5	72.3 ± 5.1	69.8 ± 1.3	66.8 ± 2.8	69.7 ± 2.7	72.1 ± 3.9	
median	69.8	71.8	69.6	66.7	68.7	70.4	
IQR	4.0	3.5	1.9	3.2	2.3	3.4	
min-max	65.5–81.5	61.6–103.4	66.5–75.3	59.9–85.6	62.2–82.0	63.0–87.8	

SD: standard deviation; IQR: interquartile range.

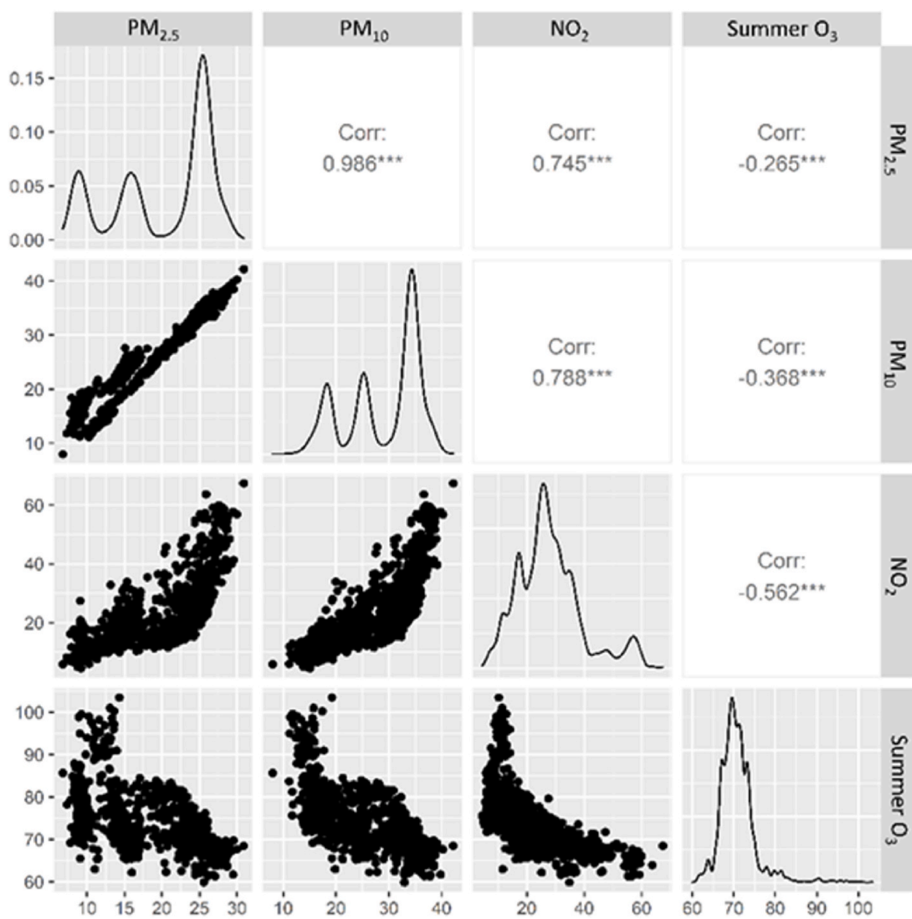

Fig. 2. Air pollutant correlation matrix (average concentrations in 2013–15).
Black points: scatter plots of the concentrations (μg/m^3) for each pollutant pair. Solid lines: non-parametric density functions of each single pollutant concentration. Corr: Spearman's rank correlation coefficients for each pollutant pair. *** p-value <0.001.

Table 4
Correlation coefficients among the original variables and the four principal components.

	C1	C2	C3	C4
$PM_{2.5}$	0.921	0.359	0.136	0.063
PM_{10}	0.955	0.254	0.139	−0.066
NO_2	0.914	−0.123	−0.385	0.001
Summer O_3	−0.576	0.801	−0.165	−0.007

4. Discussion

We found a strong correlation among air pollutant exposure estimated at residential level and respiratory/allergic symptoms/diseases in Italian adult general population, identifying $PM_{2.5}$ and PM_{10} as the main drivers of the detrimental health effect, through an innovative multi-pollutant approach. PM_{10} and $PM_{2.5}$ were related to 14–25% increased odds of having rhinitis, 23–34% of having asthma and 30–33% of having night awakening; NO_2 was related to 6–9% increased odds of having rhinitis, 7–8% of having asthma and 12% of having night awakening; O_3 was linked to 37% increased odds of having asthma attacks.

As regards rhinitis, in multipollutant models, PM_{10} and $PM_{2.5}$

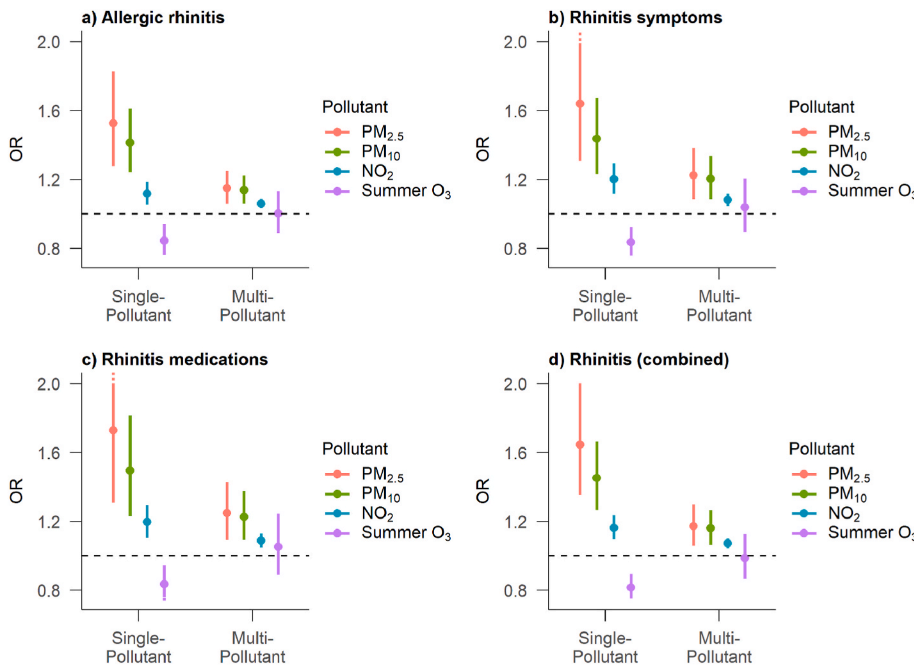

Fig. 3. Results of single-pollutant and multipollutant logistic regression models (OR and 95% CI for 10 μg/m^3 increases): rhinitis.

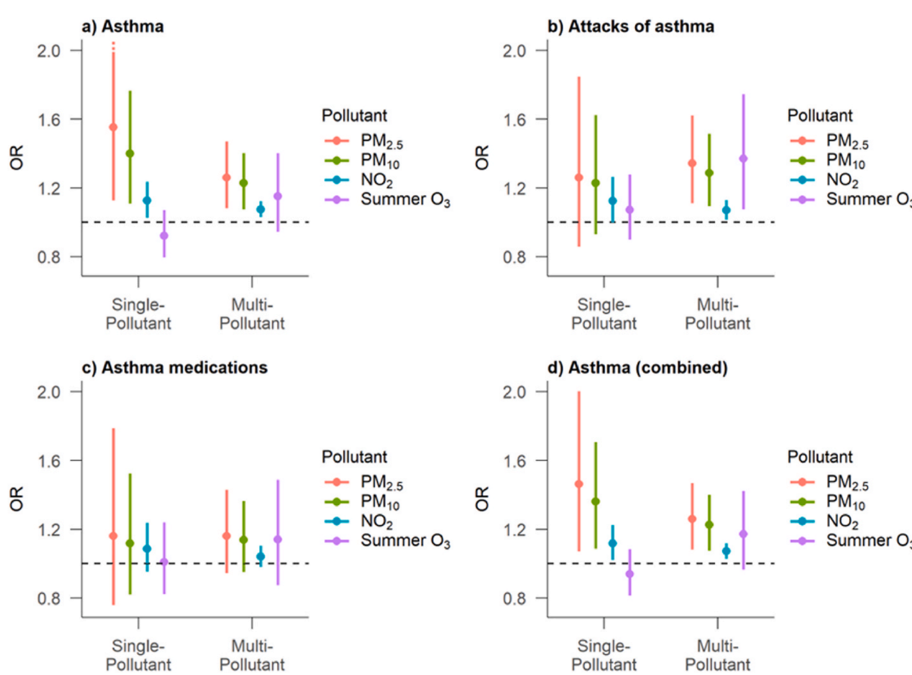

Fig. 4. Results of single-pollutant and multipollutant logistic regression models (OR and 95% CI for 10 μg/m3 increases): asthma.

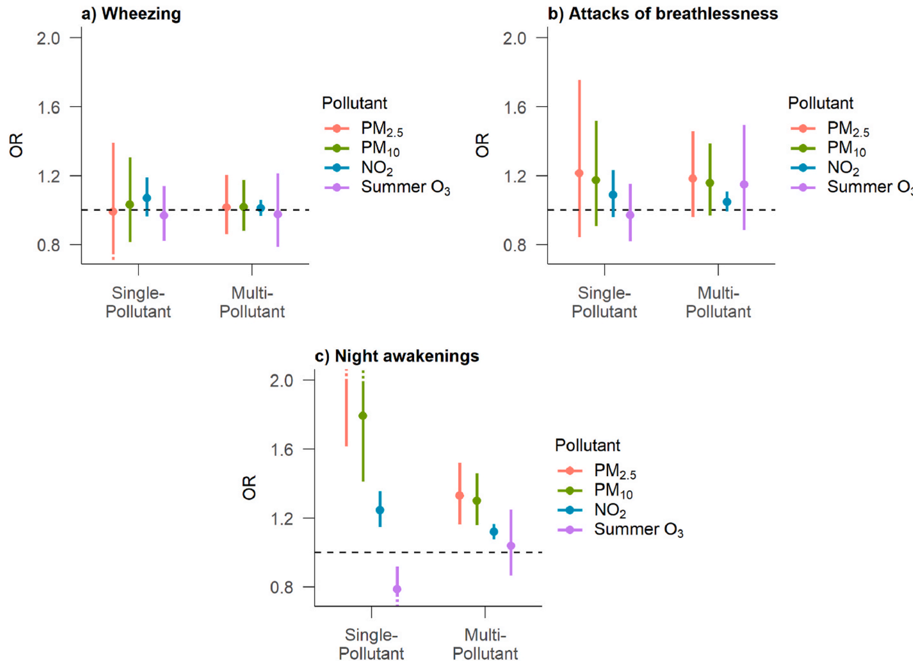

Fig. 5. Results of single-pollutant and multipollutant logistic regression models (OR and 95% CI for 10 μg/m^3 increases): asthma-like symptoms.

exposures were related to 14–25% increased odds and NO_2 exposure to 6–9% increased odds for each 10 μg/m^3 increase of pollutant. In the single-pollutant models, these odds were higher: 40–65% for PM_{10} and $PM_{2.5}$ exposure and 12–20% for NO_2 exposure.

It is known that PM can affect the respiratory system, but relatively few studies assessed the chronic effect on allergic rhinitis, especially in adulthood (Li et al., 2022). On the contrary, this disease is an important public health problem, which affects the quality of life and increases the health care burden (Baptist and Nyenhuis, 2016). Moreover, there is increasing evidence for the association between allergic rhinitis and air pollutants, although some discordant results exist (Li et al., 2022). A recently published meta-analysis on 35 studies across 12 countries, including people of all ages, reported increased ORs of allergic rhinitis related to 10 μg/m^3 increment of PM_{10} (from 28 studies, 4 in adults: OR 1.13, 95% CI 1.04–1.22), $PM_{2.5}$ (from 15 studies, 4 in adults: OR 1.12, 95% CI 1.05–1.20), NO_2 (from 27 studies, 3 in adults: OR 1.13, 95% CI 1.07–1.20) and O_3 (from 12 studies, 2 in adults: OR 1.07, 95% CI 1.01–1.12) (Li et al., 2022).

Taking into account the studies focused on the general adult population, our results from single-pollutant models are comparable with those of recent studies showing an increased probability of having allergic rhinitis (defined by questionnaire). Data from two large multicenter epidemiological European studies on 1,408 adult subjects showed that increases in air pollution exposure (single-pollutant model) were associated with the severity of rhinitis: an increase of 10 μg/m^3 of PM_{10} yielded an OR 1.53 (95% CI 1.07–2.19) for moderate severity and 1.72 (1.23–2.41) for high severity; an increase of 5 μg/m^3 of $PM_{2.5}$ showed an OR 1.42 (95% CI 1.08–1.87) for mild severity, OR 1.73 (95% CI 1.25–2.40) for moderate severity, OR 1.91 (95% CI 1.40–2.60) for high severity; an increase of 10 μg/m^3 of NO_2 produced an OR of 1.15 for all the severity levels (Burte et al., 2020). A Lithuanian study on 1141 adult subjects found an OR of 1.29 (95% CI 1.02–1.62) for allergy diagnosis associated with an IQR increase (4.01 μg/m^3) of PM_{10} (single-pollutant model) (Dedele et al., 2019). Finally, a Chinese study on 40,279 adults from eight cities found an OR of 1.17 (95% CI 1.06–1.31) of having allergic rhinitis for 10 μg/m^3 increase of NO_2 (single-pollutant model) (Wang et al., 2021).

As regards asthma, in multipollutant models, PM_{10} and $PM_{2.5}$ exposures were related to 23–34% increased odds and NO_2 exposure to nearly 7–8% increased odds for each 10 μg/m^3 pollutant increase. In the single-pollutant models, these odds were higher: 35–55% for PM_{10} and $PM_{2.5}$ exposures and 12% for NO_2 exposure.

There is evidence that air pollution has a negative impact on asthma outcomes in both adult and pediatric populations, inducing asthma symptoms, exacerbations and decreased lung function (De Matteis et al., 2022). Adult asthma seems to be different from childhood asthma and it is associated with other risk factors (Trivedi and Denton, 2019); nevertheless, much of the existing evidence focuses on childhood asthma. A separate focus on this specific phenotype becomes important considering that only few studies have investigated the role of air pollution on adult asthma prevalence, mostly yielding null or weak positive associations (Cai et al., 2017).

Data from three adult European cohorts showed that PM_{10} and NO_2 (per 10 μg/m^3 increase, single-pollutant model) were associated with lifetime asthma prevalence: OR 1.13 (95% CI 1.10–1.16) and OR 1.02 (95% CI 1.01–1.03), respectively. Effects were slightly larger in those aged ⩾50 years (Cai et al., 2017). A recent Irish study on adult subjects (>50 yrs) found that a 1 ppb increase (about 2 μg/m^3) in local NO_2 (single-pollutant model) was associated with a 0.15–0.25 percentage point increase in the probability of suffering from self-reported asthma (Carthy et al., 2021). Finally, a Chinese study on 40,279 adults from eight cities found an OR of 1.24 (95% CI 1.09–1.42) of having asthma for 10 μg/m^3 of NO_2 (single-pollutant model) (Wang et al., 2021). Our results were comparable with these findings.

As regards asthma-like symptoms, in multipollutant models, PM_{10} and $PM_{2.5}$ exposures were related to 30–33% increased odds of night awakening and NO_2 exposure to 12% increased odds of night awakening for each 10 μg/m^3 pollutant increase; O_3 exposure was related to 37% increased odds of having asthma attacks. In the single-pollutant models, these odds were higher: 80–120% for PM_{10} and $PM_{2.5}$ exposures and 25% for NO_2 exposure; no significant result was found for O_3.

In a French population-based cohort of about 135,000 adults, associations between asthma symptoms and air pollution exposure (single-pollutant model) were found: an IQR increase (4.86 μg/m^3) of $PM_{2.5}$ was associated with night awakening due to shortness of breath (OR 1.19, 95% CI 1.13–1.25), as well as wheezing and breathlessness (OR 1.14, 95% CI 1.10–1.18) and attacks of shortness of breath at rest (OR 1.23, 95% CI 1.18–1.28); comparable ORs were found for an IQR increase

($17.3\ \mu g/m^3$) of NO_2 (Keirsbulck et al., 2022). Previously, a French study had shown associations between asthma symptoms in the last 3 months (asthma attacks or dyspnea or having been woken up by an asthma attack or shortness of breath) and IQR increase of summer O_3 ($13\ \mu g/m^3$) and PM_{10} ($3\ \mu g/m^3$) (OR 1.59, 95% CI 1.10–2.30 and OR 1.38, 95% CI 1.12–1.69, respectively) in adults; no significant effect was found for NO_2 (Jacquemin et al., 2012).

These results are in line with our findings, highlighting a detrimental effect of air pollutants on asthma attacks and night awakenings. In particular, it is to point out the significant association between asthma attacks and increased summer O_3.

However, inconsistent results about the long-term health effect of O_3 have been reported: suggestive associations with respiratory mortality, new-onset asthma in children and increased respiratory symptoms in subjects with asthma (Nuvolone et al., 2018; Zhang et al., 2019); but also, null or inverse associations (Nuvolone et al., 2018; Stafoggia et al., 2022). Sometimes, the uncertainty in interpreting results is caused by the interaction between O_3 and $PM_{2.5}$ levels (Nuvolone et al., 2018). Indeed, in our study, protective effects were found in single-pollutant models. After the application of a multipollutant approach, these effects were no longer observed. A similar trend was recently found in a large multicenter European study when analyzing the long-term effect of air pollution on respiratory mortality: O_3 showed inverse associations in single-pollutant models, but effects shifted towards the null and became no significant in two-pollutant models including NO_2 or $PM_{2.5}$ (Stafoggia et al., 2022).

O_3, PM, NO_2 and other air pollutants share a wide variety of effects on human health; controlling for the confounding effects of PM and NO_2 is a critical issue in evaluating ozone-specific health effects. During summer, when O_3 concentrations are higher, a positive correlation with the other pollutants has been often observed. The O_3 effects mainly observed during summer may be a result of the higher concentrations measured during warmer months, but also of the longer time spent outdoors yielding higher exposures. On the other hand, during winter when photochemical production of O_3 is limited, negative correlations between O_3 and primary pollutants emitted from vehicles and heating sources are observed. For this reason, fitting models taking into account the confounding effects of other air pollutants is widely recommended (Nuvolone et al., 2018).

In view of the current debate on the proposal of the European Commission for new rules for cleaner air, it is important to point out that our findings highlight detrimental effects in subjects exposed to average annual levels of air pollution below the current EU limits, with the exception of those living in Turin ($26.8\ \mu g/m^3$ $PM_{2.5}$ and $49.6\ \mu g/m^3$ NO_2) (European Commission, 2008). Conversely, all the subjects lived in areas with air pollution levels not complying with the 2005 and 2021 WHO guidelines, except for $PM_{2.5}$ ($8.9\ \mu g/m^3$) and PM_{10} ($17.9\ \mu g/m^3$) in Sassari which complied with the 2005 guidelines (WHO, 2005; WHO, 2021).

To the best of our knowledge, there are no published studies applying all the three steps of the PCLR approach (in particular, back-transformation of the mixture effects to the original scale of pollutants) to assess the relationship between long-term air pollution exposure and respiratory/allergic outcomes. Therefore, our results obtained through PCLR should be considered with caution because we did not have the opportunity to compare our findings with those of papers based on similar approaches. On the other side, innovative information on this topic is provided: in fact, in single-pollutant models, it is not clear whether an observed association reflects the effect of the pollutant analyzed or if it acts as a surrogate for other pollutants possibly originating from the same source (Stafoggia et al., 2017a). Thus, using single-pollutant models, an overestimation of the effect may be determined by not considering the interaction of other pollutants originating from the same source. Indeed, a recent European multicenter study on respiratory mortality using a two-pollutant approach found an attenuated effect of NO_2 and PM, pollutants directly emitted from combustion sources (Stafoggia et al., 2022), as well as a US study (Moolgavkar et al., 2013). On the contrary, another European study found a higher OR for allergic rhinitis due to NO_2 exposure in the bi-pollutant model with PM_{10} (Burte et al., 2020). Recent studies concluded that under or over-estimation from single-pollutant models depends on the level of correlations among single-pollutants, suggesting the need to use multi-pollutant models for high levels of correlation (Parajuli et al., 2021; Shin et al., 2022). The contrasting results found in the literature may be due to the different multi-pollutant approaches, considered outcomes and sources of exposure. They highlight the necessity to perform further studies to better comprehend this topic and to take advantages from the multipollutant statistical methods currently available, using comparable study designs for multipollutant effect analysis (Davalos et al., 2017; Shin et al., 2022).

4.1. Limitations and strengths

The use of questionnaires for collecting symptom/disease data might be a limitation because it is potentially affected by a reporting bias, as it relies upon individual recall. Nevertheless, the standardized questionnaire is one of the main investigation tools in respiratory epidemiology (Bakke et al., 2011; Pistelli and Maio, 2014). It is to be pointed out that in Pisa and in GEIRD studies there were some differences in the questionnaire used, but only comparable or identical questions were chosen.

It is also to point out that asthma and allergic rhinitis are characterized by a strong hereditability; international guidelines and consensus statements report that family history of allergic diseases increases the probability of developing asthma and allergic rhinitis (GINA, 2022; Wise et al., 2018). However, information about asthma/allergy family history was only available for a small sub-sample (19%), which was not representative of our population.

The different distribution of general characteristics found between the six cities depends on the different study design and selection criteria, as described in Table A1 of SM. Pisa study sample was characterized by older age and lower educational level since it consisted of an aging longitudinal sample (participating in an 18-yr follow-up); GEIRD study consisted of cross-sectional samples characterized by a protocol-defined age range (as defined in Table A1 of SM). Three centers of the GEIRD study didn't select elderly people (≥65 yrs) (Pavia, Turin and Ancona). However, sensitivity analyses considering only the three cities whose participants represented the entire age distribution of an adult general population (Pisa, Sassari and Verona) were in line with the findings from the main analysis (Table A6 of SM).

Moreover, the annual average exposure levels were calculated for the year 2013–2015, i.e., after the field surveys of Pisa and GEIRD studies, since these were the years with available estimates for all the analyzed air pollutants. However, previous papers demonstrated that within-city spatial patterns remain constant over the years, also when the mean concentrations of air pollutants change over time (Fasola et al., 2020; Jacquemin et al., 2012). This assumption about the spatial stability of air pollution contrasts permitted the application of recently developed models in previously enrolled cohorts, as made in other international studies (Schikowski et al., 2014; Hoek, 2017).

The main strength of this study is the large population sample of individuals spanning from early adulthood to late adulthood and living in different Italian geoclimatic areas, achieved by combining previous analytical epidemiological data (symptoms/diseases and individual potential confounders), as well as high-resolution estimates of several air pollutants concentration at residential level.

Another important strength is the use of a unique exposure model for all the investigated cities. This allows limiting the heterogeneity introduced when different modeling approaches are used in multi-centric studies to evaluate air pollution exposure.

At last, an important strength is the application of PCLR for addressing the multicollinearity issue of conventional statistical approaches, therefore allowing to separate the independent contribution of four pollutants through their inclusion in the same model equation. Although PCA-based approaches have been recognized to belong to the class of shrinkage (regularization) methods, so far PCA has mainly been used for determining mixture effects rather than for assigning loadings to each pollutant (Billionnet et al., 2012; Tran et al., 2018). Conversely, PCLR takes advantage of the re-parameterization induced by PCA in the conventional logistic regression model to back transform the mixture effects (that may be awkward to interpret) to the original scale of pollutants. PCLR also offers several advantages over competing regularization methods like Ridge or Lasso regression: for example, Ridge/Lasso regression may not be suitable to deal, at the same time, with issues of regularization of a subset of regression coefficients, inclusion of random effects, and computation of reliable standard errors (especially in the case of a binary outcome).

Thus, using single-pollutant models, an overestimation of the effect may be determined by not considering the interaction of other pollutants originating from the same source.

5. Conclusions

This study suggests that using single-pollutant models can lead to an overestimation of the health effects, which may be determined by not accounting for the complex nature of the exposure mixture. The use of an innovative multipollutant approach allowed the identification of $PM_{2.5}$ and PM_{10} as the main drivers of the detrimental effect of the air pollution mixture on respiratory and allergic symptoms/diseases in Italian adults. Moreover, new evidence about NO_2 and summer O_3 effects emerged.

Our findings add new scientific evidence supporting the necessity to further reduce the exposure of the population for achieving a global health benefit, according to the latest WHO guidelines (WHO, 2021).

A major effort is needed to prevent the onset and the exacerbation of chronic diseases, by reconsidering not only current air quality legislation and regulations but also through awareness of the importance of virtuous lifestyles.

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Author contribution

Sara Maio: Conceptualization, Methodology, Validation, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition; Salvatore Fasola: Methodology, Software, Formal analysis, Writing – original draft, Writing – review & editing; Alessandro Marcon: Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – review & editing, Supervision; Anna Angino: Validation, Investigation, Data curation; Sandra Baldacci: Methodology, Investigation, Writing – review & editing; Maria Beatrice Bilò: Investigation, Data curation, Writing – review & editing; Roberto Bono: Investigation, Data curation, Writing – review & editing; Stefania La Grutta: Writing – review & editing; Pierpaolo Marchetti: Methodology, Validation, Data curation, Writing – review & editing; Giuseppe Sarno: Investigation, Data curation, Writing – review & editing; Giulia Squillacioti: Writing – review & editing; Ilaria Stanisci: Writing – review & editing; Pietro Pirina: Investigation, Data curation, Writing – review & editing; Sofia Tagliaferro: Methodology, Writing – review & editing; Giuseppe Verlato: Investigation, Data curation, Writing – review & editing, Funding acquisition; Simona Villani: Investigation, Data curation, Writing – review & editing; Claudio Gariazzo: Writing – review & editing; Massimo Stafoggia: Writing – review & editing, Funding acquisition; Giovanni Viegi: Investigation, Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Maria Beatrice Bilò had speaking and lecture fees supported by Astra Zeneca, GSK, Novartis, Sanofi. The other authors have no competing financial interests or personal relationships to disclose.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115455.

References

Aguilera, A.M., Escabias, M., Valderrama, M.J., 2006. Using principal components for estimating logistic regression with high-dimensional multicollinear data. Comput. Stat. Data Anal. 50, 1905–1924. https://doi.org/10.1016/j.csda.2005.03.011.

Bakke, P.S., Rønmark, E., Eagan, T., Pistelli, F., Annesi-Maesano, I., Maly, M., Meren, M., Vermeire Dagger, P., Vestbo, J., Viegi, G., Zielinski, J., Lundback, B., 2011. European respiratory society task force, recommendations for epidemiological studies on COPD. Eur. Respir. J. 38, 1261–1277. https://doi.org/10.1183/09031936.00193809.

Baptist, A., Nyenhuis, S., 2016. Rhinitis in the elderly. Immunol. Allergy Clin. 36 (2), 343–357. https://doi.org/10.1016/j.iac.2015.12.010.

Beck, H.E., Zimmermann, N.E., McVicar, T.R., Vergopolan, N., Berg, A., Wood, E.F., 2020. Publisher Correction: present and future Köppen-Geiger climate classification maps at 1-km resolution. Sci. Data 7 (1), 274. https://doi.org/10.1038/s41597-020-00616-w.

Billionnet, C., Sherrill, D., Annesi-Maesano, I., 2012. GERIE study. Estimating the health effects of exposure to multi-pollutant mixture. Ann. Epidemiol. 22 (2), 126–141. https://doi.org/10.1016/j.annepidem.2011.11.004.

Blangiardo, M., Pirani, M., Kanapka, L., Hansell, A., Fuller, G., 2019. A hierarchical modelling approach to assess multi pollutant effects in time-series studies. PLoS One 14 (3), e0212565. https://doi.org/10.1371/journal.pone.0212565.

Brunekreef, B., Strak, M., Chen, J., Andersen, Z.J., Atkinson, R., Bauwelinck, M., et al., 2021. Mortality and Morbidity Effects of Long-Term Exposure to Low-Level PM2.5, BC, NO2, and O3: an Analysis of European Cohorts in the ELAPSE Project. Health Effects Institute, Boston, MA. Research Report 208.

Burte, E., Leynaert, B., Marcon, A., Bousquet, J., Benmerad, M., Bono, R., Carsin, A.-E., de Hoogh, K., Forsberg, B., Gormand, F., Heinrich, J., Just, J., Nieuwenhuijsen, M., Pin, I., Stempfelet, M., Sunyer, J., Villani, S., Künzli, N., Siroux, V., Jarvis, D., Nadif, R., Jacquemin, B., 2020. Long-term air pollution exposure is associated with increased severity of rhinitis in 2 European cohorts. J. Allergy Clin. Immunol. 145 (3), 834–842.e6. https://doi.org/10.1016/j.jaci.2019.11.040.

Cai, Y., Zijlema, W.L., Doiron, D., Blangiardo, M., Burton, P.L., Fortier, I., Gaye, A., Gulliver, J., de Hoogh, K., Hveem, K., Mbatchou, S., Morley, D.W., Stolk, R.P., Elliott, P., Hansell, A.L., Hodgson, S., 2017. Ambient air pollution, traffic noise and adult asthma prevalence: a BioSHaRE approach. Eur. Respir. J. 49, 1502127 https://doi.org/10.1183/13993003.02127-2015.

Carthy, P., Domhnaill, A.O., O'Mahony, M., Nolan, A., Moriarty, F., Broderick, B., Hennessy, M., Donnelly, A., Naughton, O., Lyons, S., 2021. Local NO2 concentrations and asthma among over-50s in Ireland: a microdata analysis. Int. J. Epidemiol. 49 (6), 1899–1908. https://doi.org/10.1093/ije/dyaa074.

Cilluffo, G., Ferrante, G., Fasola, S., Montalbano, L., Malizia, V., Piscini, A., Romaniello, V., Silvestri, M., Stramondo, S., Stafoggia, M., et al., 2018. Associations of greenness, greyness and air pollution exposure with children's health: a cross-sectional study in Southern Italy. Environ. Health 17, 1–12. https://doi.org/10.1186/s12940-018-0430-x.

Davalos, A.D., Luben, T.J., Herring, A.H., Sacks, J.D., 2017. Current approaches used in epidemiologic studies to examine short-term multipollutant air pollution exposures. Ann. Epidemiol. 27 (2), 145–153.e1. https://doi.org/10.1016/j.annepidem.2016.11.016.

de Marco, R., Zanolin, M.E., Accordini, S., et al., 1999. A new questionnaire for the repeat of the first stage of the European Community Respiratory Health Survey: a pilot study. Eur. Respir. J. 14, 1044–1448. https://doi.org/10.1183/09031936.99.14510449.

de Marco, R., Accordini, S., Antonicelli, L., et al., 2010. The gene–environment interactions in respiratory diseases (GEIRD) project. Int. Arch. Allergy Immunol. 1525, 255–263. https://doi.org/10.1159/000283034.
De Matteis, S., Forastiere, F., Baldacci, S., Maio, S., Tagliaferro, S., Fasola, S., Cilluffo, G., La Grutta, S., Viegi, G., 2022. Issue 1 - "Update on adverse respiratory effects of outdoor air pollution". Part 1): outdoor air pollution and respiratory diseases: a general update and an Italian perspective. Pulmonology 28 (4), 284–296. https://doi.org/10.1016/j.pulmoe.2021.12.008.
Dėdelė, A., Miškinytė, A., Gražulevičienė, R., 2019. The impact of particulate matter on allergy risk among adults: integrated exposure assessment. Environ. Sci. Pollut. Res. Int. 26 (10), 10070–10082. https://doi.org/10.1007/s11356-019-04442-5.
Dominici, F., Schwartz, J., Di, Q., Braun, D., Choirat, C., Zanobetti, A., 2019. Assessing adverse health effects of long-term exposure to low levels of ambient air pollution: phase 1. Res. Rep. Health Eff. Inst. 200, 1–51.
Eguiluz-Gracia, I., Mathioudakis, A.G., Bartel, S., Vijverberg, S.J., Fuertes, E., Comberiati, P., Cai, Y.S., Tomazic, P.V., Diamant, Z., Vestbo, J., et al., 2020. The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. Allergy 75, 2170–2184. https://doi.org/10.1111/all.14177.
European Commission, 2008. Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on Ambient Air Quality and Cleaner Air for Europe. http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:32008L0050.
European Environment Agency, 2022. Air quality in europe. EEA Report N°5/2022. https://www.eea.europa.eu/publications/air-quality-in-europe-2022.
Fasola, S., Maio, S., Baldacci, S., La Grutta, S., Ferrante, G., Forastiere, F., Stafoggia, M., Gariazzo, C., Viegi, G., 2020. On behalf of the beep collaborative group. Effects of particulate matter on the incidence of respiratory diseases in the pisan longitudinal study. Int. J. Environ. Res. Publ. Health 17 (7), 2540. https://doi.org/10.3390/ijerph17072540.
Flies, E.J., Mavoa, S., Zosky, G.R., Mantzioris, E., Williams, C., Eri, R., Brook, B.W., Buettel, J.C., 2019. Urban-associated diseases: candidate diseases, environmental risk factors, and a path forward. Environ. Int. 133 (Pt A), 105187 https://doi.org/10.1016/j.envint.2019.105187.
Fuller, R., Landrigan, P.J., Balakrishnan, K., Bathan, G., Bose-O'Reilly, S., Brauer, M., Caravanos, J., Chiles, T., Cohen, A., Corra, L., Cropper, M., Ferraro, G., Hanna, J., Hanrahan, D., Hu, H., Hunter, D., Janata, G., Kupka, R., Lanphear, B., Lichtveld, M., Martin, K., Mustapha, A., Sanchez-Triana, E., Sandilya, K., Schaefli, L., Shaw, J., Seddon, J., Suk, W., Téllez-Rojo, M.M., Yan, C., 2022. Pollution and health: a progress update. Lancet Planet. Health 6 (6), e535–e547. https://doi.org/10.1016/S2542-5196(22)00090-0.
Gandini, M., Scarinzi, C., Bande, S., Berti, G., Carna, P., Ciancarella, L., Costa, G., Demaria, M., Ghigo, S., Piersanti, A., et al., 2018. Long term effect of air pollution on incident hospital admissions: results from the Italian Longitudinal Study within LIFE MED HISS project. Environ. Int. 121, 1087–1097. https://doi.org/10.1016/j.envint.2018.10.020.
Gariazzo, C., Renzi, M., Marinaccio, A., Michelozzi, P., Massari, S., Silibello, C., Carlino, G., Giorgi Rossi, P., Maio, S., Viegi, G., Stafoggia, M., BIGEPI Collaborative Group, 2022. Association between short-term exposure to air pollutants and cause-specific daily mortality in Italy. A nationwide analysis. Environ. Res. 216 (Pt 3), 114676 https://doi.org/10.1016/j.envres.2022.114676 (Online ahead of print).
Global Initiative for Asthma, 2022. Global Strategy for Asthma Management and Prevention. Available from. www.ginastma.org.
Baldacci, S., Maio, S., Cerrai, S., Sarno, G., Baïz, N., Simoni, M., Annesi-Maesano, I., Viegi, G., HEALS Study, 2015. Allergy and asthma: effects of the exposure to particulate matter and biological allergens. Respir. Med. 109, 1089–1104. https://doi.org/10.1016/j.rmed.2015.05.017.
Molitor, J., Coker, E., Jerrett, M., Ritz, B., Li, A., Health Review Committee. Part 3, 2016. Modeling of multipollutant profiles and spatially varying health effects with applications to indicators of adverse birth outcomes. Res. Rep. Health Eff. Inst. 183 (Pt 3), 3–47.
Hoek, G., 2017. Methods for assessing long-term exposures to outdoor air pollutants. Curr Environ Health Rep 4, 450–462. https://doi.org/10.1007/s40572-017-0169-5.
Jacquemin, B., Kauffmann, F., Pin, I., Le Moual, N., Bousquet, J., Gormand, F., Just, J., Nadif, R., Pison, C., Vervloet, D., Künzli, N., Siroux, V., 2012. Air pollution and asthma control in the epidemiological study on the genetics and environment of asthma. J. Epidemiol. Community Health 66 (9), 796–802. https://doi.org/10.1136/jech.2010.130229.
Johnston, R., Jones, K., Manley, D., 2018. Confounding and collinearity in regression analysis: a cautionary tale and an alternative procedure, illustrated by studies of British voting behaviour. Qual. Quantity 52, 1957–1976. https://doi.org/10.1007/s11135-017-0584-6.
Keirsbulck, M., Savouré, M., Lequy, E., Chen, J., de Hoogh, K., Vienneau, D., Goldberg, M., Zins, M., Roche, N., Nadif, R., Jacquemin, B., 2022. Long-term exposure to ambient air pollution and asthma symptom score in the CONSTANCES cohort. Thorax. https://doi.org/10.1136/thoraxjnl-2021-218344 thoraxjnl-2021-218344.
Li, S., Wu, W., Wang, G., Zhang, X., Guo, Q., Wang, B., Cao, S., Yan, M., Pan, X., Xue, T., Gong, J., Duan, X., 2022. Association between exposure to air pollution and risk of allergic rhinitis: a systematic review and meta-analysis. Environ. Res. 205, 112472 https://doi.org/10.1016/j.envres.2021.112472.
Maio, S., Baldacci, S., Carrozzi, L., Pistelli, F., Angino, A., Simoni, M., Sarno, G., Cerrai, S., Martini, F., Fresta, M., Silvi, P., Di Pede, F., Guerriero, M., Viegi, G., 2016. Respiratory symptoms/diseases prevalence is still increasing: a 25-yr population study. Respir. Med. 110, 58–65. https://doi.org/10.1016/j.rmed.2015.11.006.
Marchetti, P., Pesce, G., Villani, S., Antonicelli, L., Ariano, R., Attena, F., Bono, R., Bellisario, V., Fois, A., Gibelli, N., Nicolis, M., Olivieri, M., Pirina, P., Scopano, E., Siniscalco, C., Verlato, G., Marcon, A., 2017. Pollen concentrations and prevalence of asthma and allergic rhinitis in Italy: evidence from the GEIRD study. Sci. Total Environ. 584–585, 1093–1099. https://doi.org/10.1016/j.scitotenv.2017.01.168.
Moolgavkar, S.H., McClellan, R.O., Dewanji, A., Turim, J., Luebeck, E.J., Edwards, M., 2013. Time-series analyses of air pollution and mortality in the United States: a subsampling approach. Environ. Health Perspect. 121 (1), 73–78. https://doi.org/10.1289/ehp.1104507.
Nanda, A., Baptist, A.P., Divekar, R., Parikh, N., Seggev, J.S., Yusin, J.S., Nyenhuis, S.M., 2020. Asthma in the older adult. J. Asthma 57 (3), 241–252. https://doi.org/10.1080/02770903.2019.1565828.
Nuvolone, D., Petri, D., Voller, F., 2018. The effects of ozone on human health. Environ. Sci. Pollut. Res. Int. 25 (9), 8074–8088. https://doi.org/10.1007/s11356-017-9239-3.
Paciencia, I., Rufo, J.C., 2020. Urban-level environmental factors related to pediatric asthma. Porto Biomed J 5 (1), e57. https://doi.org/10.1097/j.pbj.0000000000000057, 2020.
Parajuli, R.P., Shin, H.H., Maquiling, A., Smith-Doiron, M., 2021. Multi-pollutant urban study on acute respiratory hospitalization and mortality attributable to ambient air pollution in Canada for 2001–2012. Atmos. Pollut. Res. 12, 101234 https://doi.org/10.1016/j.apr.2021.101234.
Pesce, G., Bugiani, M., Marcon, A., Marchetti, P., Carosso, A., Accordini, S., Antonicelli, L., Cogliani, E., Pirina, P., Pocetta, G., Spinelli, F., Villani, S., de Marco, R., 2016. Geo-climatic heterogeneity in self-reported asthma, allergic rhinitis and chronic bronchitis in Italy. Sci. Total Environ. 544, 645–652. https://doi.org/10.1016/j.scitotenv.2015.12.015.
Pistelli, F., Maio, S., 2014. In: Annesi-Maesano, I., Lundback, B., Viegi, G. (Eds.), Respiratory Epidemiology. Eur. Respir. Monograph, vol. 65. Questionnaires and lung function, Sheffield (UK, pp. 257–272.
Renzi M, Scortichini M, Forastiere F, De' Donato F, et al., 2022. A nationwide study of air pollution from particulate matter and daily hospitalizations for respiratory diseases in Italy. Sci. Total Environ. 807 (Pt 3), 151034 https://doi.org/10.1016/j.scitotenv.2021.151034.
Schikowski, T., Adam, M., Marcon, A., Cai, Y., Vierkötter, A., Carsin, A.E., Jacquemin, B., Al Kanani, Z., Beelen, R., Birk, M., et al., 2014. Association of ambient air pollution with the prevalence and incidence of COPD. Eur. Respir. J. 44, 614–626. https://doi.org/10.1183/09031936.00132213.
Shin, H.H., Owen, J., Maquiling, A., Parajuli, R.P., Smith-Doiron, M., 2022. Circulatory health risks from additive multi-pollutant models: short-term exposure to three common air pollutants in Canada. Environ. Sci. Pollut. Res. Int. https://doi.org/10.1007/s11356-022-22947-4.
Shtein, A., Kloog, I., Schwartz, J., Silibello, C., Michelozzi, P., Gariazzo, C., Viegi, G., Forastiere, F., Karnieli, A., Just, A.C., Stafoggia, M., 2020. Estimating daily PM2.5 and PM10 over Italy using an ensemble model. Environ. Sci. Technol. 54 (1), 120–128. https://doi.org/10.1021/acs.est.9b04279.
Silibello, C., Carlino, G., Stafoggia, M., Gariazzo, C., Finardi, S., Pepe, N., Radice, P., Forastiere, F., Viegi, G., 2021. Spatial-temporal prediction of ambient nitrogen dioxide and ozone levels over Italy using a Random Forest model for population exposure assessment. Air Qual Atmos Health 14, 817–829. https://doi.org/10.1007/s11869-021-00981-4.
Sousa, A.C., Pastorinho, M.R., Masjedi, M.R., Urrutia-Pereira, M., Arrais, M., Nunes, E., To, T., Ferreira, A.J., Robalo-Cordeiro, C., Borrego, C., Teixeira, J.P., Taborda-Barata, L., 2022. Issue 1 - "Update on adverse respiratory effects of outdoor air pollution" Part 2): outdoor air pollution and respiratory diseases: perspectives from Angola, Brazil, Canada, Iran, Mozambique and Portugal. Pulmonology 28 (5), 376–395. https://doi.org/10.1016/j.pulmoe.2021.12.007.
Stafoggia, M., Breitner, S., Hampel, R., Basagaña, X., 2017a. Statistical approaches to address multi-pollutant mixtures and multiple exposures: the state of the science. Curr Environ Health Rep 4 (4), 481–490. https://doi.org/10.1007/s40572-017-0162-z.
Stafoggia, M., Schwartz, J., Badaloni, C., Bellander, T., Alessandrini, E., Cattani, G., De'Donato, F., Gaeta, A., Leone, G., Lyapustin, A., et al., 2017b. Estimation of daily PM10 concentrations in Italy (2006–2012) using finely resolved satellite data, land use variables and meteorology. Environ. Int. 99, 234–244. https://doi.org/10.1016/j.envint.2016.11.024.
Stafoggia, M., Bellander, T., Bucci, S., Davoli, M., De Hoogh, K., De'Donato, F., Gariazzo, C., Lyapustin, A., Michelozzi, P., Renzi, M., et al., 2019. Estimation of daily PM10 and PM2.5 concentrations in Italy, 2013–2015, using a spatiotemporal land-use random-forest model. Environ. Int. 124, 170–179. https://doi.org/10.1016/j.envint.2019.01.016.
Stafoggia, M., Oftedal, B., Chen, J., Rodopoulou, S., Renzi, M., Atkinson, R.W., Bauwelinck, M., Klompmaker, J.O., Mehta, A., Vienneau, D., Andersen, Z.J., Bellander, T., Brandt, J., Cesaroni, G., de Hoogh, K., Fecht, D., Gulliver, J., Hertel, O., Hoffmann, B., Hvidtfeldt, U.A., Jöckel, K.-H., Jørgensen, J.T., Katsouyanni, K., Ketzel, M., Kristoffersen, D.T., Lager, A., Leander, K., Liu, S., Ljungman, P.L.S., Nagel, G., Pershagen, G., Peters, A., Raaschou-Nielsen, O., Rizzuto, D., Schramm, S., Schwarze, P.E., Severi, G., Sigsgaard, T., Strak, M., van der Schouw, Y.T., Verschuren, M., Weinmayr, G., Wolf, K., Zitt, E., Samoli, E., Forastiere, F., Brunekreef, B., Hoek, G., Janssen, N.A.H., 2022. Long-term exposure to low ambient air pollution concentrations and mortality among 28 million people: results from seven large European cohorts within the ELAPSE project. Lancet Planet. Health 6 (1), e9–e18. https://doi.org/10.1016/S2542-5196(21)00277-1.
Thurston, G.D., Kipen, H., Annesi-Maesano, I., Balmes, J., Brook, R.D., Cromar, K., De Matteis, S., Forastiere, F., Forsberg, B., Frampton, M.W., et al., 2017. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur. Respir. J. 49 (1), 1600419 https://doi.org/10.1183/13993003.00419-2016.

Traini, E., Huss, A., Portengen, L., Rookus, M., Verschuren, W.M.M., Vermeulen, R.C.H., Bellavia, A., 2022. A multipollutant approach to estimating causal effects of air pollution mixtures on overall mortality in a large, prospective cohort. Epidemiology 33 (4), 514–522. https://doi.org/10.1097/EDE.0000000000001492.

Tran, H., Kim, J., Kim, D., Choi, M., Choi, M., 2018. Impact of air pollution on cause-specific mortality in korea: results from bayesian model averaging and principle component regression approaches. Sci. Total Environ. 636, 1020–1031. https://doi.org/10.1016/j.scitotenv.2018.04.273.

Trivedi, M., Denton, E., 2019. Asthma in children and adults-what are the differences and what can they tell us about asthma? Front Pediatr 7, 256. https://doi.org/10.3389/fped.2019.00256.

Viegi, G., Pedreschi, M., Baldacci, S., 1999. Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. Int. J. Tubercul. Lung Dis. 3, 1034–1042.

Wang, J., Zhang, Y., Li, B., Zhao, Z., Huang, C., Zhang, X., Deng, O., Lu, C., Qian, H., Yang, X., Sun, Y., Sundell, J., Norbäck, D., 2021. Asthma and allergic rhinitis among young parents in China in relation to outdoor air pollution, climate and home environment. Sci. Total Environ. 751, 141734 https://doi.org/10.1016/j.scitotenv.2020.141734.

Wise, S.K., Lin, S.Y., Toskala, E., Orlandi, R.R., Akdis, C.A., Alt, J.A., et al., 2018. International consensus statement on allergy and rhinology: allergic rhinitis. Int Forum Allergy Rhinol 8 (2), 108–352. https://doi.org/10.1002/alr.22073.

World Health Organization, 2005. WHO Air Quality Guidelines. Global Update 2005. Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide. World Health Organization. https://www.euro.who.int/_data/assets/pdf_file/0005/78638/E90038.pdf.

World Health Organization, 2021. Ambient (Outdoor) Air Pollution. https://www.who.int/news-room/fact-sheets/detail/ambient-(outdoor)-air-quality-and-health.

Zhang Jj, Wei Y, Fang Z, 2019. Ozone pollution: a major health hazard worldwide. Front. Immunol. 10, 2518. https://doi.org/10.3389/fimmu.2019.02518.