



## REVIEW

# 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



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## Abstract

**Objective:** to summarize the main updated evidence about the health effects of air pollution and to focus on Italian epidemiological experiences on the respiratory effects.

**Results:** the recent literature indicates that there is strong evidence for causal relationships between PM<sub>2.5</sub> air pollution exposure and all-cause mortality as well as mortality from acute lower respiratory infections, ischaemic heart disease, stroke, chronic obstructive pulmonary disease, and lung cancer. A growing body of evidence also suggests causal relationships with type II diabetes and impacts on neonatal mortality from low birth weight and short gestation as well as neurologic effects in both children and adults. Italy, a Southern European country, faces a more threatening air pollution challenge because of the effects of both anthropogenic pollutants and natural dust (particulate matter, PM). The 2020 Report of the European Environment Agency highlighted the number of premature deaths in Italy attributable to main pollutants: 52,300 for PM<sub>2.5</sub>, 10,400 for NO<sub>2</sub> and 3,000 for O<sub>3</sub> in 2018. In Italy, original time series and analytical epidemiological studies showed increased cardio-respiratory hospital admissions and mortality and increased risk of respiratory diseases in people living in urban areas.

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**Conclusions:** adverse health effects of air pollutants, even at low levels, have been confirmed by recent epidemiological studies. Further studies should focus on the potential link between air pollution exposure and respiratory infections. This topic has become particularly important in the current SARS-COV-2 pandemic.

Based on strong scientific evidence, the Italian government, which hosts the Global Alliance against Chronic Respiratory Diseases (GARD)-Italy at the Ministry of Health, the scientific respiratory societies and the patients' associations, as well as others in the health sector and civil society, must increase their engagement in advocacy for clean air policies, especially in light of the new Air Quality Guidelines of the World Health Organization.

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## Introduction

Air pollution is the leading environmental risk factor worldwide. Ambient and household air pollution together currently rank 4<sup>th</sup> for attributable disease and mortality among 20 major risk factors evaluated in the Global Burden of Disease (GBD) study, only after hypertension, smoking and dietary factors.<sup>1</sup> The World Health Organization (WHO) estimates indicate that around 7 million deaths, mainly from non-communicable diseases, are attributable to the joint effects of ambient and household air pollution, with the greatest attributable disease burden seen in low and middle-income countries.<sup>2,3</sup> A recent investigation indicates that regions with large anthropogenic contributions had the highest attributable deaths, suggesting substantial health benefits from replacing traditional energy sources.<sup>4</sup>

The recent literature indicates that there is strong evidence for causal relationships between PM<sub>2.5</sub> air pollution exposure and all cause-mortality as well as acute lower respiratory infections (ALRI), ischaemic heart disease (IHD), stroke, chronic obstructive pulmonary disease (COPD), and lung cancer.<sup>1</sup> A growing and suggestive body of evidence also suggests a relationship with asthma, type II diabetes and impacts on neonatal mortality from low birth weight and short gestation as well as neurologic effects in both children and adults.<sup>5,6</sup>

The need to be informed on health effects of air pollution is reinforced by the Air quality in Europe - 2020 Report of the European Environment Agency (EEA) (<https://www.eea.europa.eu/publications/air-quality-in-europe-2020-report>), which highlighted the number of premature deaths in Italy attributable to main pollutants: 52,300 for particulate matter with an aerodynamic diameter less than 2.5  $\mu\text{m}$  (PM<sub>2.5</sub>), 10,400 for nitrogen dioxide (NO<sub>2</sub>) and 3,000 for ozone (O<sub>3</sub>) in 2018.

The peculiarity of Southern Europe, according to the EEA report, is to be affected by higher concentrations of outdoor air pollutants, as well as by higher percentage increases in mortality associated with 10  $\mu\text{g}/\text{m}^3$  increase in PM compared to other European areas.<sup>7</sup>

In addition, an adverse situation for the Mediterranean countries is the presence of desert sand dust, which can be high for many days in the year. For example, in Italy, the number of days with high African dust (up to 100  $\mu\text{g}/\text{m}^3$ ) ranges from 17% in the Po River Valley to 37% in Palermo, Sicily.<sup>8</sup>

Indeed, each 10  $\mu\text{g}/\text{m}^3$  increase in desert sand PM<sub>10</sub> (particulate matter with an aerodynamic diameter less than 10

$\mu\text{m}$ ) is associated with increased all-cause and cardiovascular mortality, as well as respiratory hospital admissions for children and adolescents (2.38%, 95% CI: 0.09 – 4.71).<sup>9</sup>

The aims of this paper are: 1) to summarize the recent international evidence on the link between air pollution exposure and respiratory effects published after the ERS/ATS statement in 2017.<sup>5</sup> This updated information will be crucial to setting the context and future avenues for action; 2) to disseminate the results obtained in Italy when dealing with the issue of health effects of air pollution, especially useful for clinical readers.

## Methods

This paper is divided into two main topics, a *general update* and the *Italian perspective*: the first one provides recent (from 2018 to 2021) quantitative estimates of the health impact due to air pollution at a global level; the second one is a confirmation at national level of the findings obtained at international level, summarizing results of different Italian epidemiological studies carried out during the last 40 years.

### General update

In order to update the available evidence on respiratory health effects of outdoor air pollution after the 2017 ERS/ATS statement,<sup>5</sup> it was decided to focus on systematic reviews that also performed a meta-analysis to provide quantitative estimates of the associated public health impact. From an online literature search of PubMed and Embase databases from 2018 to June 2021 using the following search terms 'outdoor air pollution' and 'respiratory health' and 'meta-analysis', 16 articles were retrieved.<sup>10-25</sup> The English language was also an inclusion criterion.

After the articles' full-text screening, one study was discarded because it evaluated a non-respiratory outcome,<sup>10</sup> one for considering indoor air exposure only,<sup>16</sup> one for not being a systematic review,<sup>15</sup> and three for not reporting meta-analytic estimates for respiratory health effects.<sup>13,20,22</sup> Among the remaining ten articles included, six evaluated overall respiratory mortality.<sup>11,12,17,18,19,23</sup>

### Italian perspective

The Italian perspective can be seen as the confirmation at the national level of the findings obtained at the

international level and used for elaborating the relevant documents of the major scientific societies, utilized by WHO for issuing air quality guidelines (AQG).

The first part of this section, which is built upon a recent publication of the Authors,<sup>26</sup> reports the main results from the studies conducted by or in collaboration with the National Research Council in Italy: the Po Delta and Pisa analytical epidemiological studies on health effects of air pollution,<sup>27,28,29</sup> the Palermo studies on children-adolescents,<sup>30</sup> and the SIDRIA study.<sup>31</sup>

The second part of this section reports the main results from the use of health and environment routine statistics carried out by a large collaborative multicenter study (the EPIAIR study).<sup>32</sup>

The last part, which is the most innovative, describes the outcome of the BEEP project, based on the use of big data and artificial intelligence.<sup>33</sup>

## Results

### General update

WHO has updated its Global Air Quality Guidelines, the final document has been published on September 22, 2021.<sup>34</sup> In anticipation, a series of systematic reviews investigating associations between a range of air pollutants and human health outcomes had been conducted. [Table 1](#) summarizes the results for the systematic reviews that have evaluated exposure to various pollutants and mortality (all causes mortality as well as mortality from respiratory diseases, COPD, ALRI, and lung cancer).<sup>12,18,23</sup>

One meta-analysis provided quantitative global estimates for overall respiratory mortality for long-term exposure to particulate matter (PM<sub>2.5</sub> and PM<sub>10</sub>).<sup>12</sup> There was clear evidence that PM<sub>2.5</sub> was associated with significantly increased mortality from respiratory diseases (mainly, asthma and COPD) and lung cancer. Only a few studies included in the meta-analysis were conducted in the so-called low-income countries (LIC).

This positive association between PM and respiratory mortality was also confirmed in a meta-analysis that evaluated short term exposure for all main pollutants, including NO<sub>2</sub> and O<sub>3</sub>; increased risks emerged for both PM<sub>10</sub> (relative risk-RR: 1.0091; 95% CI: 1.0063-1.0119), and PM<sub>2.5</sub> (RR: 1.0073; 95% CI: 1.0029-1.0116).<sup>23</sup>

Of note, another meta-analysis, focused on short-term exposure to PM<sub>2.5</sub> and PM<sub>10</sub> originating from biomass burning (BB), did not find a significant positive association with respiratory mortality, but only with respiratory morbidity. The pooled effect estimates were 4.10% (95% CI: 2.86-5.34) and 4.83% (95% CI: 0.06-9.60) increased risk of total respiratory admissions/emergency visits per 10 µg/m<sup>3</sup> increases in PM<sub>2.5</sub> and PM<sub>10</sub>, respectively. In particular, COPD rates increased by 3.92% (95% CI: 1.13-6.70) and 3.95% (95% CI: 1.65-6.24) per 10 µg/m<sup>3</sup> increases in BB-related PM<sub>2.5</sub> and PM<sub>10</sub>, respectively. Similarly, for adult asthma admissions/visits, the pooled estimate for both PM<sub>2.5</sub> and PM<sub>10</sub> was 9.59% (95% CI: 6.53-12.24). Interestingly, the evidence was less consistent for pediatric asthma: 3.52% (95% CI: -2.13-9.18) per 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> or PM<sub>10</sub>.<sup>19</sup>

All three meta-analyses, focused on long-term NO<sub>2</sub> exposure and respiratory mortality,<sup>11,17,18</sup> found a significant positive association with respiratory mortality, but with evidence of substantial heterogeneity among the included studies. In detail, one meta-analysis pooling cohort studies only estimated a hazard ratio (HR) of 1.03 (95% CI: 1.01-1.05) for respiratory mortality, and of 1.05 (95% CI: 1.02-1.08) for lung cancer mortality per 10 µg/m<sup>3</sup> increment in NO<sub>2</sub> concentration.<sup>11</sup> A subsequent similar meta-analysis found that a 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> was associated with a RR of 1.03 (95% CI: 1.01-1.05) for respiratory mortality. In addition, this study found a significant positive association for COPD (RR: 1.03; 95% CI: 1.01-1.04) and ALRI (RR: 1.06; 95% CI: 1.02-1.10) mortality.<sup>18</sup> The most recent meta-analysis estimated a pooled HR for respiratory mortality per 10 ppb increase in annual NO<sub>2</sub> concentrations of 1.05 (95% CI: 1.02-1.08), confirmed also in multi-pollutant models suggesting an independent effect of NO<sub>2</sub> on mortality.<sup>17</sup>

Among the four meta-analyses that focused on specific respiratory outcomes only,<sup>14,21,24,25</sup> one study evaluated the association of O<sub>3</sub> short-term exposure with asthma exacerbations.<sup>21</sup> Ozone exposures measured as 1-hour (RR: 1.012; 95% CI: 1.005-1.019) or 8-hour (RR: 1.011; 95% CI: 1.007-1.014) daily max were more consistently associated with asthma exacerbations, both in adults and children, than the 24-hour average (RR: 1.005; 95% CI: 0.996-1.014) exposure during the warm season. Another meta-analysis focused on COPD risk for NO<sub>2</sub> exposure;<sup>25</sup> the pooled effects, per 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> concentration, were 17% on prevalence, 1.3% on hospital admissions, and 2.6% on mortality. The RR of COPD related to NO<sub>2</sub> long-term exposure was 2.5%, whilst for short-term exposure was 1.4%. The COPD effects associated with a 10 µg/m<sup>3</sup> increase were 1.7% for exposure to a general outdoor-sourced NO<sub>2</sub> and 17.8% for exposure to an exclusively traffic-sourced NO<sub>2</sub>; importantly, the effect of NO<sub>2</sub> on COPD mortality emerged mainly in lag 0 models. Another recent meta-analysis, evaluating long term exposure to main air pollutants and COPD incidence, found a positive association per 10 µg/m<sup>3</sup> increase in PM<sub>2.5</sub> (pooled HR: 1.18; 95% CI: 1.13-1.23), and in NO<sub>2</sub> (pooled HR: 1.07; 95% CI: 1.00-1.16), but not in PM<sub>10</sub>.<sup>24</sup>

Finally, a meta-analysis evaluated the relationship between PM exposure and lung function decline.<sup>14</sup> The study estimated that a 10 µg/m<sup>3</sup> increase in short-term PM<sub>2.5</sub> exposure (days) was associated with a -7.02 mL (95% CI: -11.75 to -2.29) change in the forced expiratory volume in 1 second (FEV<sub>1</sub>). A 10 µg/m<sup>3</sup> difference in long-term PM<sub>10</sub> exposure was associated with a -8.72 mL (95% CI: -15.39 to -2.07) annual change in FEV<sub>1</sub> and an absolute difference in FEV<sub>1</sub> of -71.36 mL (95% CI: -134.47 to -8.24).

O<sub>3</sub> remained the least evaluated air pollutant: acute exposure was found associated only with asthma exacerbations in both adults and children.<sup>21</sup> In terms of specific respiratory outcomes, asthma and COPD were the most evaluated diseases, both for incidence, exacerbations, and mortality. For asthma incidence, the available evidence of a positive association with air pollution is stronger among children than adults, even if a just published large international study adds new supporting evidence.<sup>35</sup> The authors estimated HRs for adult-onset asthma of 1.22 (95% CI: 1.04-1.43) per 5 µg/m<sup>3</sup> for PM<sub>2.5</sub>, 1.17 (95% CI: 1.10-1.25) per 10 µg/m<sup>3</sup> for NO<sub>2</sub> and 1.15 (95% CI: 1.08-1.23) per

**Table 1** Association between long-term and short-term exposure to specific pollutants and mortality. Systematic reviews for the update WHO AQG. Relative risks (RR) are per 10  $\mu\text{g}/\text{m}^3$  exposure.

Mortality/pollutant	Long-term			Short-term		
	No. of studies	RR	95% CI	No. of studies	RR	95% CI
<b>All-cause mortality (natural mortality)</b>						
PM <sub>10</sub>	17	1.04	1.03-1.06	66	1.0041	1.0034-1.0049
PM <sub>2.5</sub>	25	1.08	1.06-1.09	29	1.0065	1.0044-1.0086
NO <sub>2</sub>	24	1.02	1.01-1.04	54	1.0072	1.0059-1.0085
O <sub>3</sub> (annual exposure)	9	0.97	0.93-1.02			
O <sub>3</sub> (peak exposure)	7	1.01	1.00-1.02			
SO <sub>2</sub>		NA		36	1.0059	1.0046-1.0071
<b>Respiratory mortality</b>						
PM <sub>10</sub>	13	1.12	1.06-1.19	41	1.0091	1.0063-1.0119
PM <sub>2.5</sub>	17	1.1	1.03-1.18	20	1.0073	1.0029-1.0116
NO <sub>2</sub>	15	1.03	1.01-1.05		NA	
O <sub>3</sub> (annual exposure)	4	0.99	0.89-1.11		NA	
O <sub>3</sub> (peak exposure)	4	1.02	0.99-1.05			
SO <sub>2</sub>				23	1.0067	1.0025-1.0109
<b>COPD mortality</b>						
PM <sub>10</sub>	5	1.19	0.95-1.49		NA	
PM <sub>2.5</sub>	11	1.11	1.05-1.17		NA	
NO <sub>2</sub>	9	1.03	1.01-1.04		NA	
<b>ALRI mortality</b>						
PM <sub>10</sub>	2	NA			NA	
PM <sub>2.5</sub>	4	1.16	1.01-1.34		NA	
NO <sub>2</sub>	5	1.06	1.02-1.10		NA	
<b>Lung Cancer mortality</b>						
PM <sub>10</sub>	13	1.08	1.04-1.13		NA	
PM <sub>2.5</sub>	15	1.12	1.07-1.16		NA	

ALRI: Acute Lower Respiratory Infection  
NA: not available

$0.5 \times 10^{-5}/\text{m}^{-1}$  for black carbon exposure. For COPD, increasing evidence supports a positive association, and emerging evidence links it to long term NO<sub>2</sub> exposure.<sup>24,25</sup> The positive association with lung cancer mortality was confirmed and linked not only to PM,<sup>11</sup> but also to NO<sub>2</sub> long-term exposure.<sup>11</sup>

## Italian perspective

### I) Analytical epidemiological surveys

In Italy, two major analytical longitudinal surveys on general population samples were conducted from 1980 to 2011. The first was in Po River Delta, a rural area near Venice, before and after the construction of a large oil-burning central power plant. The second was in Pisa and its surrounding area, before and after the construction of a new highway far from the residential zones.<sup>27,28,29,36</sup> This epidemiological investigation used subjective (e.g. standardized questionnaire on respiratory symptoms, diseases and risk factors) and objective tools (e.g. lung function tests, bronchial responsiveness, skin prick tests, serum immunoglobulin E (IgE), inflammation and mutagenetic biomarkers).

The results of the epidemiological surveys on general population samples living in Po Delta and Pisa are summarized in Table 2.

In the early nineties, it became clear that living in the city was associated with more respiratory symptoms and diseases than living in the rural area.<sup>28,29,37,38</sup> Those living in the city had higher bronchial responsiveness as measured by a methacholine dose-response challenge.<sup>39</sup> In particular, city residents had a 41% increased risk of developing airway hyper-responsiveness compared to rural residents. The 41% increase in city-dwellers was similar to the 39% increased risk shown by smokers compared to never smokers.<sup>39</sup>

A cross-sectional spatial analysis of the effects of traffic-related air pollution was carried out in the urban and suburban areas of Pisa, Italy.<sup>40</sup> The house of each participating subject was geo-referenced and people were stratified into three groups according to the distance from the main road: less than 100 meters, 100-250 meters, more than 250 meters. People who lived closest to the traffic had significantly increased risks of respiratory symptoms and diseases and airflow obstruction, as measured by FEV<sub>1</sub>/forced vital capacity (FVC). More recently, it was shown that a 10% increase in grey space residential exposure (assessed using CORINE Land cover classes) was significantly related to a higher probability of having allergic biomarkers/conditions and presence of serum antibodies to benzo(a)pyrene diol epoxide-DNA (BPDE-DNA) adducts.<sup>41</sup>

The chromosome aberrations (CA) frequency, determined in three samples of healthy individuals (60 living in a rural

**Table 2** Air pollution effects in Italy: I) analytical epidemiological surveys (Po Delta and Pisa studies carried out by CNR).

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area			
Viegi et al, 1991 (ref. 28)	1) Rural area 2) Suburban-traffic area 3) Urban-traffic area 4) Urban-traffic-industry area	Traffic, industry	Chronic cough prevalence (%)	1) 9 2) 10 3) 11 4) 17			
			Chronic phlegm prevalence (%)	1) 9 2) 9 3) 7 4) 14			
			Attacks of wheezing with dyspnea prevalence (%)	1) 5 2) 8 3) 9 4) 9			
			Dyspnea prevalence (%)	1) 14 2) 22 3) 26 4) 28			
			Rhinitis prevalence (%)	1) 5 2) 17 3) 13 4) 25			
			Chronic bronchitis or emphysema prevalence (%)	1) 2 2) 5 3) 7 4) 8			
			Asthma prevalence (%)	1) 5 2) 7 3) 12 4) 5			
			Viegi et al, 1999 (ref. 37)	Rural area vs urban-suburban area	Traffic, industry	Cough prevalence (%)	Males 25-64 yrs: 15 vs 21 Males > 64 yrs: 18 vs 37 Females 25-64 yrs: 11 vs 15
						Phlegm prevalence (%)	Males <25 yrs: 13 vs 6
						Wheeze prevalence (%)	Males > 64 yrs: 27 vs 39 Females 25-64 yrs: 14 vs 19
Attacks of wheeze prevalence (%)	Males <25 yrs: 6 vs 12 Males 25-64 yrs: 5 vs 8 Females 25-64 yrs: 4 vs 6						
Dyspnea grade 1 prevalence (%)	Males <25 yrs: 6 vs 2 Males 25-64 yrs: 17 vs 10 Females <25 yrs: 11 vs 3 Females 25-64 yrs: 29 vs 19 Females >64 yrs: 48 vs 33						
Dyspnea grade 2 prevalence (%)	Females <25 yrs: 6 vs 3						
Chronic bronchitis prevalence (%)	Males 25-64 yrs: 3 vs 5						
Emphysema prevalence (%)	Males 25-64 yrs: 2 vs 8 Males > 64 yrs: 7 vs 22						
Viegi et al, 2004 (ref. 38)	1) Rural area 2) Urban-suburban area	Traffic, industry				Obstructive lung diseases prevalence (%)	1) 6.9 2) 10.9
						Maio et al, 2009 (ref. 39)	Urban-suburban area vs rural area

Table 2 (Continued)

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Nuvolone et al, 2011 (ref. 40)	Urban-suburban area	Distance from main roads: <100m (a) 100-250m (b)	Persistent wheeze (OR, 95% CI)	Males: (a) 1.76 (1.08-2.87)
			COPD (OR, 95% CI)	Males: (a) 1.80 (1.03-3.08)
			GOLD airway obstruction (OR, 95% CI)	Males: (a) 2.07 (1.11-3.87) (b) 2.53 (1.42-4.53)
			Dyspnea (OR, 95% CI)	Females: (a) 1.61 (1.13-2.27)
			Skin prick test positivity (OR, 95% CI)	Females: (a) 1.83 (1.11-3.0)
Maio et al, 2021 (ref. 41)	Urban - suburban area	10% increase in grey spaces residential exposure Traffic	SPT positivity (OR, 95% CI)	1.07 (1.02-1.13)
			seasonal SPT positivity (OR, 95% CI)	1.12 (1.05-1.19)
			polysensitization (OR, 95% CI)	1.11 (1.04-1.19)
			allergic rhinitis (OR, 95% CI)	1.10 (1.04-1.17)
			co-presence of SPT positivity and asthma/allergic rhinitis (OR, 95% CI)	1.16 (1.08-1.25)
			asthma/allergic rhinitis (OR, 95% CI)	1.06 (1.00-1.12)
			presence of serum antibodies to BPDE-DNA adducts positivity (OR, 95% CI)	1.07 (1.01-1.14)
Milillo et al, 1996 (ref. 42)	Urban - suburban area vs rural area		Chromosome aberrations (mean number %)	In non smokers: Chromosome gaps: 0.35-0.38 vs 0.21 Chromosome breaks: 1.00 – 0.88 vs 0.64 Chromosome rearrangements: 0.18 – 0.18 vs 0.11
Barale et al, 1998 (ref. 43)	Urban area vs suburban area	Traffic	Sister chromatid exchanges (mean ± SD)	Females: 8.87±1.62 vs 6.81±1.35 Males: 8.77±1.65 vs 6.89±1.36
Petruzzelli et al, 1998 (ref. 44)	Urban area vs suburban area	Traffic	Serum antibodies to Benzo(a)pyrene Diol Epoxide-DNA adducts (OR, 95% CI)	1.49 (1.16-1.92)
Maio et al, 2016 (ref. 45)	Urban area vs suburban area	Traffic	Allergic rhinitis (OR, 95% CI)	1.19 (1.05-1.35)
			Usual phlegm (OR, 95% CI)	1.30 (1.12-1.49)
			COPD (OR, 95% CI)	1.54 (1.25-1.90)
Maio et al, 2019 (ref. 46)	Urban-suburban area	Incident vehicular traffic exposure	Asthma attacks incidence (OR, 95% CI)	2.20 (1.00-4.50)
			Allergic rhinitis incidence (OR, 95% CI)	1.80 (1.20-2.80)
			COPD incidence (OR, 95% CI)	2.40 (1.10-5.20)

OR: odds ratio; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

area (Po Delta), 134 in Pisa downtown and 116 in Cascina, a small town near Pisa), was statistically significantly higher in the Pisa sample than in the Po Delta sample.<sup>42</sup> Sister chromatid exchanges (SCE), determined in lymphocytes cultures from 2000 participants, were significantly higher in the urban than in the suburban area.<sup>43</sup> Urban residents were also 49% more likely to have increased serum antibodies to BPDE-DNA adducts, compared to suburban residents.<sup>44</sup>

Three cross-sectional surveys conducted in Pisa and suburbs from 1985 to 2011 have shown increased prevalence rates of respiratory symptoms and diseases, especially allergic rhinitis. Living in the urban area was associated with increased risks for allergic rhinitis (+19%), cough (+14%), phlegm (+30%), and COPD (+54%), compared to those living in the suburban area.<sup>45</sup>

The 18-year cumulative incidence of respiratory and allergic symptoms, diseases and risk factors from the Pisa epidemiological study was published in 2019. The cumulative incidence values ranged from 3.2% for asthma to 31.7% for allergic rhinitis. The incidence of vehicular traffic

exposure yielded significantly increased risks for the incidence of asthma attacks (+120%), allergic rhinitis (+80%), and COPD (+140%).<sup>46</sup>

The results of the epidemiological surveys on pediatric population samples living in Palermo and other Italian cities are summarized in Table 3.

A total of 2150 Italian schoolchildren were cross-sectionally investigated through respiratory questionnaire, SPT, and spirometry in Palermo, Sicily.<sup>30</sup> A proportional Venn diagram quantified the distribution of current asthma, rhinoconjunctivitis, and eczema. Avoiding exposures to measured environmental risk factors would prevent 41% of current asthma (15.1% considering only traffic) and 34% of rhinoconjunctivitis (7.8% considering only traffic); avoidance of traffic would also prevent 14.1% of impaired lung function.

More recently, the effects of “green”, “grey” and air pollution exposure were simultaneously assessed on respiratory/allergic conditions and general symptoms in Palermo schoolchildren.<sup>47</sup> Exposures to greenness and greyness at the home addresses were measured using the normalized

**Table 3** Air pollution effects in Italy: I) analytical epidemiological surveys (other studies with CNR collaboration).

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Cibella et al, 2011 (ref. 30)	Urban area	Traffic	Current asthma (OR, 95% CI)	1.84 (1.14 – 2.95)
			Rhinoconjunctivitis (OR, 95% CI)	1.39 (1.08 – 1.79)
			Impaired lung function (OR, 95% CI)	1.78 (1.12 – 2.83)
Cilluffo et al, 2018 (ref. 47)	Urban area	Exposure to NDVI $\leq 0.15$ (1st quartile)	Nasal symptoms (OR, 95% CI)	1.47 (1.07-2.03)
		Living in CUF areas	Ocular symptoms (OR, 95% CI)	1.49 (1.10-2.03)
			General symptoms (OR, 95% CI)	1.18 (1.00-1.48)
Exposure to NO <sub>2</sub> $\geq 60 \mu\text{g}/\text{m}^3$ (4th quartile)	General symptoms (OR, 95% CI)	1.28 (1.10-1.48)		
Ciccone et al, 1998 (ref. 31)	Metropolitan areas of SIDRIA1	Exposure to lorry traffic	Early Respiratory Diseases:	
			Recurrent bronchitis (OR, 95% CI)	1.69 (1.24-2.30)
			Bronchiolitis (OR, 95% CI)	1.74 (1.09-2.77)
			Pneumonia (OR, 95% CI)	1.84 (1.27-2.65)
			Current Respiratory Disorders:	
			Persistent phlegm for > 2 months (OR, 95% CI)	1.68 (1.14-2.48)
Severe wheeze limiting speech (OR, 95% CI)	1.86 (1.26-2.73)			
Migliore et al, 2009 (ref. 48)	Cities in SIDRIA2	High traffic density	Cough or phlegm (OR, 95% CI)	1.24 (1.04-1.49)
			Asthma symptoms (OR, 95% CI)	1.17 (1.03–1.33)
		Continuous car traffic	Cough or phlegm (OR, 95% CI)	1.32 (1.08–1.63)
			Asthma symptoms (OR, 95% CI)	1.16 (1.00–1.33)
		Continuous truck traffic	Cough or phlegm (OR, 95% CI)	1.67 (1.36–2.06)
			Asthma symptoms (OR, 95% CI)	1.27 (1.08–1.50)

NDVI: normalized difference vegetation index; CUF: continuous urban fabric; OR: odds ratio.

difference vegetation index (NDVI), residential surrounding greyness (RSG) and the CORINE land-cover classes (CLC, divided in “discontinuous urban fabric - DUF” - and “continuous urban fabric - CUF”). A very low exposure to NDVI  $\leq 0.15$  (1st quartile), living in CUF areas, living in proximity ( $\leq 200$  m) to High Traffic Roads (HTRs), and high exposure to NO<sub>2</sub> ( $\geq$

$60 \mu\text{g}/\text{m}^3$ ) were associated with nasal, ocular or general symptoms.

The group at CNR also collaborated in the realization of the Italian branch of the International Study on Asthma and Allergies in Childhood (ISAAC), which was named SIDRIA from the acronym of the name in Italian standing for Italian



**Table 4** Air pollution effects in Italy: II) use of routine statistics.

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Alessandrini et al, 2013 (ref. 50)	25 Italian cities	PM <sub>10</sub> (10 µg/m <sup>3</sup> increase)	Natural mortality (% increase, 95% CI)	0.51 (0.16-0.86) (lag 0-1)
			Cardiac mortality (% increase, 95% CI)	0.93 (0.16-1.70) (lag 0-5)
			Respiratory mortality (% increase, 95% CI)	1.41 (-0.23-3.08) (lag 2-5)
		PM <sub>2.5</sub> (10 µg/m <sup>3</sup> increase)	Natural mortality (% increase, 95% CI)	0.78 (0.12-1.46) (lag 0-5)
			Cardiac mortality (% increase, 95% CI)	1.25 (0.17-2.34) (lag 0-5)
			Natural mortality (% increase, 95% CI)	1.10 (0.63-1.58) (lag 0-5)
NO <sub>2</sub> (10 µg/m <sup>3</sup> increase)	Natural mortality (% increase, 95% CI)	1.10 (0.63-1.58) (lag 0-5)		
	Respiratory mortality (% increase, 95% CI)	1.67 (0.23-3.13) (lag 2-5)		
Scarinzi et al, 2013 (ref. 51)	25 Italian cities	PM <sub>10</sub> (10 µg/m <sup>3</sup> increase)	Cardiac hospitalization (% increase, 95% CI)	0.34 (0.04-0.63) (lag 0)
			Respiratory hospitalization (% increase, 95% CI)	0.75 (0.25-1.25) (lag 0-5)
			Respiratory hospitalization (% increase, 95% CI)	1.23 (0.58-1.88) (lag 0-5)
		PM <sub>2.5</sub> (10 µg/m <sup>3</sup> increase)	Respiratory hospitalization (% increase, 95% CI)	1.23 (0.58-1.88) (lag 0-5)
			Cardiac hospitalization (% increase, 95% CI)	0.57 (0.13-1.02) (lag 0)
			Respiratory hospitalization (% increase, 95% CI)	1.29 (0.52-2.06) (lag 0-5)
NO <sub>2</sub> (10 µg/m <sup>3</sup> increase)	Cardiac hospitalization (% increase, 95% CI)	0.57 (0.13-1.02) (lag 0)		
	Respiratory hospitalization (% increase, 95% CI)	1.29 (0.52-2.06) (lag 0-5)		

Studies on Pediatric Respiratory Disturbances and the Environment.

The first population-based survey (SIDRIA1) was conducted in 10 areas of Northern and Central Italy (1994-1995) in two age groups (6-7 and 13-14 years) (n= 39,275).<sup>31</sup> In the metropolitan areas, a high frequency of truck traffic in the street of residence was associated with significantly increased risks for many adverse respiratory outcomes. Among early respiratory diseases, significantly increased risks were found for recurrent bronchitis (+69%), bronchiolitis (+74%) and pneumonia (+84%), as well as for current respiratory symptoms such as persistent phlegm for > 2 months (+68%), and severe wheeze limiting speech (+86%).

The 2<sup>nd</sup> survey (SIDRIA2) was conducted in 2002 in 12 centers in Northern, Central and Southern Italy, on 33,632 children and adolescents (6-7 and 13-14 years old). Overall traffic density was associated with asthma symptoms but there was a stronger association with cough or phlegm (high traffic density: excess risk of 24%). Car and truck traffic were independently associated with asthma symptoms and cough or phlegm.<sup>48</sup>

#### II) Use of routine statistics

The results of epidemiological studies using routine statistics in some Italian cities are summarized in Table 4.

A large multicenter study using routinely collected statistics has been carried out in several cities throughout Italy,

with the collaboration of CNR. The first survey, EPIAIR (from the acronym of the Italian name standing for Air pollution and health: epidemiological surveillance and prevention interventions), was conducted in ten cities in the period 2001-2005.<sup>32,49</sup>

More recently, the study has been enlarged to include data on 25 cities (EPIAIR2) during the period 2006-2010. An immediate effect of PM<sub>10</sub> on natural mortality was found. More relevant and prolonged effects (lag 0-5) were found for PM<sub>2.5</sub> and NO<sub>2</sub>. Increases in cardiac mortality were associated with PM<sub>10</sub> and PM<sub>2.5</sub>, while exposure to NO<sub>2</sub> as well as PM<sub>10</sub> had an important role in respiratory mortality.<sup>50</sup>

Furthermore, the study has analyzed 2,246,448 urgent hospital admissions for non-accidental diseases in 25 Italian cities during the period 2006-2010. A relationship to an increment of 10 µg/m<sup>3</sup> of air pollutants was estimated. Increases in cardiac and respiratory hospitalizations were associated with PM<sub>10</sub> and NO<sub>2</sub>.<sup>51</sup>

Notably, pollution reduction actions as prescribed by the European Union legislation, i.e. a 20% reduction up to 20 µg/m<sup>3</sup> for PM<sub>10</sub> and up to 18 µg/m<sup>3</sup> for PM<sub>2.5</sub>, would have saved, overall the cities covered by this study, 42% and 51% of all attributable deaths, respectively.<sup>52</sup>

#### III) Use of big data

One of the biggest challenges of modern environmental epidemiology is being able to collect and link, in a complex



way, large amounts of geographical, environmental and health data, to obtain comprehensive information otherwise not available. Within this context, the Italian National Insurance Institute against Work-related Accidents (INAIL) has funded a project named “Big data in environmental and occupational epidemiology” (BEEP) (acronym from the Italian “Big data in Epidemiologia ambiEntale ed occuPazionale”) (2017-2019).

The main goal of the BEEP project has been to estimate, through BIGDATA methodology, the health effects of air

pollution, noise and meteorological parameters on the Italian general population. The project consists of specific objectives focused on different special domains, from the whole nation to the urban micro-scale.

Some publications have been so far realized: their results are summarized in [Table 5](#).

One has dealt with the improvement of the estimation of NO<sub>2</sub>, O<sub>3</sub>, PM<sub>2.5</sub> and PM<sub>10</sub> concentrations in 6 Italian metropolitan areas, using chemical-transport and machine learning models, and assessment of the exposure

**Table 5** Air pollution effects in Italy: III) the use of big data.

Study	Study area	Exposure	Health outcome	Health outcome results in the respective study area
Gariazzo et al, 2021 (ref. 54)	Metropolitan area	PM <sub>10</sub> (IQR increase) (200m resolution)	Natural mortality (HR, 95% CI)	1.020 (1.008-1.031)
		NO <sub>2</sub> (IQR increase) (200m resolution)	Cardiovascular mortality (HR, 95% CI)	1.042 (1.024-1.061)
Marinaccio et al, 2019 (ref. 55)	Italy	Heat	Natural mortality (HR, 95% CI)	1.018 (1.007-1.028)
		Cold	Cardiovascular mortality (HR, 95% CI)	1.037 (1.020-1.055)
Renzi et al, 2021 (ref. 56)	Italy	PM <sub>10</sub> (10 µg/m <sup>3</sup> increase) at lag 0-5 days	Occupational injuries (RR, 95% CI)	1.17 (1.14-1.21)
		PM <sub>2.5</sub> (10 µg/m <sup>3</sup> increase) at lag 0-5 days	Occupational injuries (RR, 95% CI)	1.23 (1.17-1.30)
Fasola et al, 2020 (ref. 57)	Urban area	PM <sub>10</sub> (unit increase) (1Km resolution)	Total respiratory diseases (% difference of risk, 95% CI)	1.20 (0.92-1.49)
		PM <sub>2.5</sub> (unit increase) (1Km resolution)	Total respiratory diseases (% difference of risk, 95% CI)	1.22 (0.76-1.68)
Fasola et al, 2021 (ref. 58)	Urban area	PM <sub>10</sub> (10 µg/m <sup>3</sup> increase) (1Km resolution)	Incidence of COPD (OR, 95% CI)	2.96 (1.50-7.15)
		PM <sub>10</sub> (10µg/m <sup>3</sup> increase) (200m resolution)	Incidence of rhinitis (OR, 95% CI)	2.25 (1.07-4.98)
		PM <sub>2.5</sub> (10 µg/m <sup>3</sup> increase) (1Km resolution)	Incidence of chronic phlegm (OR, 95% CI)	4.17 (1.12-18.71)
Fasola et al, 2021 (ref. 58)	Urban area	PM <sub>10</sub> (10 µg/m <sup>3</sup> increase) (1Km resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.268 (1.085-1.483) (lag 0)
		PM <sub>10</sub> (10µg/m <sup>3</sup> increase) (200m resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.365 (1.103-1.690) (lag 0)
		PM <sub>2.5</sub> (10 µg/m <sup>3</sup> increase) (1Km resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.273 (1.053-1.540) (lag 0)
		PM <sub>2.5</sub> (10 µg/m <sup>3</sup> increase) (200m resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.264 (1.006-1.589) (lag 0)
		NO <sub>2</sub> (10 µg/m <sup>3</sup> increase) (200m resolution)	Cardiovascular hospitalization (OR, 95% CI)	1.477 (1.058-2.061) (lag 0)

IQR: interquartile range; HR: hazard ratio; RR: relative risk; OR: odds ratio; COPD: chronic obstructive pulmonary disease

effect on population by using information on urban population mobility.<sup>53</sup>

Another paper has aimed to compare the effect estimates of the long-term exposure of air pollutants on cause-specific mortality in the Rome Longitudinal Study, using exposure estimates obtained with different modelling techniques and spatial resolutions (from 4 m to 1 Km). All the exposures were assigned to the residential addresses of 482,259 citizens of Rome 30+ years of age who were enrolled in 2001 and followed up until 2015. Natural cause and cardiovascular diseases (CVD) mortality outcomes were all positively associated with the interquartile range (IQR) of NO<sub>2</sub> and PM<sub>10</sub> with a tendency of larger effect for lower resolution exposures.<sup>54</sup>

A nationwide epidemiological study has also been carried out to estimate the risk of injuries for workers exposed to extreme temperatures and identify economic sectors and jobs most at risk. The study considered 2,277,432 occupational injuries occurred in Italy in the period 2006-2010 and showed a significant increase of occupational injury for heat and cold exposure.<sup>55</sup>

Nationwide data of air pollution from PM and daily hospitalizations for respiratory diseases in Italy have been recently published.<sup>56</sup> A total of 4,154,887 respiratory admissions were registered during 2006-2015, of which 29% for lower respiratory tract infections, 12% for COPD, 6% for upper respiratory tract infections, and 3% for asthma. Daily mean PM<sub>10</sub> and PM<sub>2.5</sub> concentrations over the study period were 23.3 and 17  $\mu\text{g}/\text{m}^3$ , respectively. Excess risks of total respiratory diseases, stronger for asthma and COPD, in association with a  $\mu\text{g}/\text{m}^3$  PM<sub>10</sub> increase were found. Higher effects were reported in the elderly and in less urbanized areas. In addition, the compliance with a theoretical daily PM<sub>10</sub> standard of 25  $\mu\text{g}/\text{m}^3$ , a value suggested by 2005 WHO annual guideline, would have avoided about 4,900 respiratory admissions. Similarly, a total of 8,917 admissions were attributable to PM<sub>2.5</sub> daily concentrations exceeding 10  $\mu\text{g}/\text{m}^3$  in 2013-2015.

Using data from the longitudinal analytical epidemiological study in Pisa, individual risk factors recorded during the 1991 survey were considered, and new cases of respiratory diseases were ascertained until 2011. Average PM<sub>10</sub> and PM<sub>2.5</sub> exposures ( $\mu\text{g}/\text{m}^3$ , year 2011) were estimated at the residential address (1-km<sup>2</sup> resolution) on the subsample of subjects living at the same address from 1991 to 2011. Significantly increased risks of incidences of rhinitis and chronic phlegm were associated with increasing PM<sub>2.5</sub> and an increased risk of incidence of COPD was associated with increasing PM<sub>10</sub>.<sup>57</sup>

In another recently published study in Pisa, exposure effects were estimated using the case-crossover design and conditional logistic regression (OR 95% CI for 10  $\mu\text{g}/\text{m}^3$  increase; lag 0-6). During the period 2013-2015 (69 cardiovascular hospitalizations), significant effects at lag 0 were observed for PM<sub>10</sub> and PM<sub>2.5</sub> at 1 km resolution, as well as for PM<sub>2.5</sub> and NO<sub>2</sub> at 200 m resolution; significant effects were observed up to lag 2. Larger ORs were observed in males and in subjects reporting pre-existent cardiovascular/respiratory diseases.<sup>58</sup>

The results of the BEEP project, beyond opening new scientific research perspectives which are being pursued within the ongoing INAIL - BIGEPI project (<https://bigeppi.it/index.php/en/>), have provided useful

indications for public decision-makers in the field of air quality, planning of urban environments and public health protection.

## Discussion

### General update

We acknowledge that the approach to the literature search was not systematic and there was no formal qualitative appraisal of the retrieved evidence; however, we have summarized below some considerations, and suggestions for future research in the field.

Among the included meta-analyses, when bi/multi-pollutants models were used pooled risk estimates generally decreased or lost statistical significance, due to known high correlation between air pollutants. No evaluation of specific PM compositions, especially as adsorbed toxicants, was performed. Toxicity assessment of PM is currently typically based on mass concentration rather than the physicochemical properties of the constituents, and this may hamper evaluation of underlying etiopathogenetic pathways of respiratory diseases.

A few studies evaluated dose-response relationships; usually, they appeared linear and with no threshold identified of no effect as previously reported,<sup>59</sup> highlighting the concept that even in countries where governmental exposure limits are enforced, no safe levels of air pollution exist.

There was a limited adjustment for potential confounders. For example, in relation to COPD risk, an important effect of adjustment for occupational exposures was reported in air pollution studies<sup>60</sup> as a key determinant of socioeconomic status. Among the included meta-analyses, less than half of them were adjusted or restricted for occupational confounders.<sup>12,18,19,23,24</sup> High heterogeneity between studies emerged, especially among those evaluating long term NO<sub>2</sub> exposure,<sup>11,17,18</sup> making pooled estimates less reliable. Identification of variability sources via meta-regression was hampered by the limited number of included studies.

Studies conducted in LICs are still limited both in quality and quantity of available data.<sup>12</sup> Instead, further studies in these countries should be encouraged given the likely higher level of pollution from industrial sources and lack of stringent air pollution regulations.<sup>61</sup> Also, further studies should focus on the potential link between air pollution exposure and respiratory infection diseases. Only one meta-analysis reported estimates for infectious outcomes.<sup>12</sup> This topic has become particularly important in the current SARS-COV-2 pandemic which has generated the debated hypothesis that air pollution may act as a booster and even a carrier of the virus, so increasing infection susceptibility and severity and subsequent mortality from the COVID-19 disease.<sup>62</sup> Further research on how these two silent killers interact in increasing global morbidity and mortality is warranted.

### Italian perspective

The Global Alliance against chronic Respiratory Diseases (GARD) was launched in Beijing on March 28, 2006, as a partnership among the WHO, governmental institutions,

scientific societies and patients' associations. The GARD motto is "a world where all people breathe freely." Air pollution is one of the most important risk factors to health and reducing it is a priority for the prevention and control of chronic respiratory diseases.<sup>63</sup>

The GARD initiative in Italy was launched on June 11, 2009, at the Ministry of Health, which assumed the role of national coordinator. Its main objective is to promote the development of a coordinated Chronic Respiratory Diseases program in Italy. Effective prevention implies setting up health policies against tobacco smoking, indoor/outdoor pollution, obesity, and communicable diseases, with the support of healthcare professionals and citizen associations at national, regional, and district levels. Respiratory diseases prevention cannot and should not be the responsibility of doctors alone, but must involve politicians/policymakers, as well as the media, local institutions, and schools.<sup>64</sup> The Italian government, GARD, scientific societies, and other members of the health community must increase their engagement in advocacy for clean air.

Awareness of environmental exposures is increasing in the general population and assisted by the use of the risk charts, such as those for COPD elaborated in collaboration with the National Institute of Health.<sup>65</sup> The charts let people calculate their risk of getting COPD in the next ten years, based on gender, age, smoking habits and environmental exposures.

## Conclusions

Air pollution is an avoidable health risk that places a great burden on society in terms of death and health disorders, at a huge social and economic cost. Within Europe, the southern countries face a difficult situation because they experience the effects of anthropogenic and natural air pollution.

The air quality standards of the EU are laxer than the WHO AQG published in 2005 and studies have shown significant health effects even below the most stringent current standard. The differences between the EU and the WHO recommended values are now much larger after the publication of the new WHO AQG<sup>33</sup> on September 22, 2021, indicating levels that are largely lower than the previous ones.

Based on abundant evidence, the Italian government, which hosts the Global Alliance against Chronic Respiratory Diseases (GARD)-Italy at the Ministry of Health, the scientific respiratory societies and the patients' associations, as well as others in the health sector and in civil society, must increase their engagement in advocacy for clean air policies, especially in light of the new WHO AQG.

## Conflicts of interest

None.

## References

1. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1223–49. [https://doi.org/10.1016/s0140-6736\(20\)30752-2](https://doi.org/10.1016/s0140-6736(20)30752-2).
2. Burnett R, Chen H, Szyszkowicz M, Fann N, Hubbell B, Pope CA 3rd. Global estimates of mortality associated with long-term exposure to outdoor fine particulate matter. *Proc Natl Acad Sci U S A*. 2018;115(38):9592–7. <https://doi.org/10.1073/pnas.1803222115>.
3. Vohra K, Vodonos A, Schwartz J, Marais EA, Sulprizio MP, Mickley LJ. Global mortality from outdoor fine particle pollution generated by fossil fuel combustion: results from GEOS-Chem. *Environ Res*. 2021;195:110754. <https://doi.org/10.1016/j.envres.2021.110754>.
4. McDuffie EE, Martin RV, Spadaro JV, Burnett R, Smith SJ, O'Rourke P. Source sector and fuel contributions to ambient PM (2.5) and attributable mortality across multiple spatial scales. *Nat Commun*. 2021;12(1):3594. <https://doi.org/10.1038/s41467-021-23853-y>.
5. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. *Eur Respir J*. 2017;49(1):1600419. <https://doi.org/10.1183/13993003.00419-2016>.
6. Genuneit J, Seibold AM, Apfelbacher CJ, Konstantinou GN, Koplin JJ, La Grutta S. Task force 'overview of systematic reviews in allergy epidemiology (OSRAE)' of the EAACI interest group on epidemiology. Overview of systematic reviews in allergy epidemiology. *Allergy*. 2017;72(6):849–56. <https://doi.org/10.1111/all.13123>.
7. Samoli E, Stafoggia M, Rodopoulou S, Ostro B, Declercq C, Alessandrini E. Associations between fine and coarse particles and mortality in Mediterranean cities: results from the MED-PARTICLES project. *Environ Health Perspect*. 2013;121:932–8. <https://doi.org/10.1016/j.envint.2014.02.013>.
8. Pey J, Querol X, Alastuey A, Forastiere F, Stafoggia M. African dust outbreaks over the Mediterranean Basin during 2001–2011: PM10 concentrations, phenomenology and trends, and its relation with synoptic and mesoscale meteorology. *Atmos Chem Phys*. 2013;13:1395–410. <https://doi.org/10.5194/acp-13-1395-2013>.
9. Stafoggia M, Zauli-Sajani S, Pey J, Samoli E, Alessandrini E, Basagaña X. Desert dust outbreaks in Southern Europe: contribution to daily PM<sub>10</sub> concentrations and short-term associations with mortality and hospital admissions. *Environ Health Perspect*. 2016;124:413–9. <https://doi.org/10.1289/ehp.1409164>.
10. An R, Zhang S, Ji M, Guan C. Impact of ambient air pollution on physical activity among adults: a systematic review and meta-analysis. *Perspect Public Health*. 2018;138(2):111–21. <https://doi.org/10.1177/1757913917726567>.
11. Atkinson RW, Butland BK, Anderson HR, Maynard RL. Long-term concentrations of nitrogen dioxide and mortality: a meta-analysis of cohort studies. *Epidemiology*. 2018;29(4):460–72. <https://doi.org/10.1097/ede.0000000000000847>.
12. Chen J, Hoek G. Long-term exposure to PM and all-cause and cause-specific mortality: a systematic review and meta-analysis. *Environ Int*. 2020;143:105974. <https://doi.org/10.1016/j.envint.2020.105974>.
13. Dominski FH, Lorenzetti Branco JH, Buonanno G, Stabile L, da Silva MG, Andrade A. Effects of air pollution on health: a mapping review of systematic reviews and meta-analyses. *Environ Res*. 2021;201:111487. <https://doi.org/10.1016/j.envres.2021.111487>.
14. Edginton S, O'Sullivan DE, King W, Loughheed M. Effect of outdoor particulate air pollution on FEV(1) in healthy adults: a systematic review and meta-analysis. *Occup Environ Med*. 2019;76(8):583–91. <https://doi.org/10.1136/oemed-2018-105420>.
15. Fuertes E, Sunyer J, Gehring U, Porta D, Forastiere F, Cesaroni G. Associations between air pollution and pediatric eczema, rhinoconjunctivitis and asthma: a meta-analysis of European

- birth cohorts. *Environ Int.* 2020;136:105474. <https://doi.org/10.1016/j.envint.2020.105474>.
16. Guercio V, Pojum IC, Leonardi GS, Shrubsole C, Gowers AM, Dimitroulopoulou S. Exposure to indoor and outdoor air pollution from solid fuel combustion and respiratory outcomes in children in developed countries: a systematic review and meta-analysis. *Sci Total Environ.* 2021;755(Pt 1):142187. <https://doi.org/10.1016/j.scitotenv.2020.142187>.
  17. Huang S, Li H, Wang M, Qian Y, Steenland K, Caudle WM. Long-term exposure to nitrogen dioxide and mortality: a systematic review and meta-analysis. *Sci Total Environ.* 2021;776:145968. <https://doi.org/10.1016/j.scitotenv.2021.145968>.
  18. Huangfu P, Atkinson R. Long-term exposure to NO<sub>2</sub> and O<sub>3</sub> and all-cause and respiratory mortality: a systematic review and meta-analysis. *Environ Int.* 2020;144:105998. <https://doi.org/10.1016/j.envint.2020.105998>.
  19. Karanasiou A, Alastuey A, Amato F, Renzi M, Stafoggia M, Tobias A. Short-term health effects from outdoor exposure to biomass burning emissions: a review. *Sci Total Environ.* 2021;781:146739. <https://doi.org/10.1016/j.scitotenv.2021.146739>.
  20. King C, Kirkham J, Hawcutt D, Sinha I. The effect of outdoor air pollution on the risk of hospitalisation for bronchiolitis in infants: a systematic review. *PeerJ.* 2018;6:e5352. <https://doi.org/10.7717/peerj.5352>.
  21. Li X, Chen Q, Zheng X, Li Y, Han M, Liu T. Effects of ambient ozone concentrations with different averaging times on asthma exacerbations: a meta-analysis. *Sci Total Environ.* 2019;691:549–61. <https://doi.org/10.1016/j.scitotenv.2019.06.382>.
  22. Ma Y, Zhang Y, Cheng B, Feng F, Jiao H, Zhao X. A review of the impact of outdoor and indoor environmental factors on human health in China. *Environ Sci Pollut Res Int.* 2020;27(34):42335–45. <https://doi.org/10.1007/s11356-020-10452-5>.
  23. Orellano P, Reynoso J, Quaranta N, Bardach A, Ciapponi A. Short-term exposure to particulate matter PM<sub>10</sub> and PM<sub>2.5</sub>, nitrogen dioxide NO<sub>2</sub>, and ozone O<sub>3</sub> and all-cause and cause-specific mortality: systematic review and meta-analysis. *Environ Int.* 2020;142:105876. <https://doi.org/10.1016/j.envint.2020.105876>.
  24. Park J, Kim HJ, Lee CH, Lee HW. Impact of long-term exposure to ambient air pollution on the incidence of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Environ Res.* 2021;194:110703. <https://doi.org/10.1016/j.envres.2020.110703>.
  25. Zhang Z, Wang J, Lu W. Exposure to nitrogen dioxide and chronic obstructive pulmonary disease (COPD) in adults: a systematic review and meta-analysis. *Environ Sci Pollut Res Int.* 2018;25(15):15133–45. [doi.org/10.1007/s11356-018-1629-7](https://doi.org/10.1007/s11356-018-1629-7).
  26. Viegi G, Baldacci S, Maio S, Fasola S, Annesi-Maesano I, Pistelli F. Health effects of air pollution: a Southern European perspective. *Chin Med J.* 2020;133:1568–74. <https://doi.org/10.1097/CM9.0000000000000869>.
  27. Carrozzi L, Giuliano G, Viegi G, Paoletti P, Di Pede F, Mammini U. The Po river delta epidemiological study of obstructive lung disease: sampling methods, environmental and population characteristics. *Eur J Epidemiol.* 1990;6:191–200. <https://doi.org/10.1007/BF00145793>.
  28. Viegi G, Paoletti P, Carrozzi L, Vellutini M, Diviggiano E, Di Pede C. Prevalence rates of respiratory symptoms in Italian general population samples, exposed to different levels of air pollution. *Environ Health Perspect.* 1991;94:95–9. <https://doi.org/10.1289/ehp.94-1567935>.
  29. Viegi G. Indicators and biological mechanisms of impairment of the respiratory system by environmental pollutants. an operational example: epidemiological studies of the delta of Po and the region of Pisa. *Epidemiol Prev.* 1995;19:66–75.
  30. Cibella F, Cuttitta G, La Grutta S, Melis MR, Lospalluti ML, Uasuf CG. Proportional Venn diagram and determinants of allergic respiratory diseases in Italian adolescents. *Pediatr Allergy Immunol.* 2011;22:60–8. <https://doi.org/10.1111/j.1399-3038.2010.01097.x>.
  31. Ciccone G, Forastiere F, Agabiti N, Biggeri A, Bisanti L, Chellini E. Road traffic and adverse respiratory effects in children. SIDRIA collaborative group. *Occup Environ Med.* 1998;55:771–8. <https://doi.org/10.1136/oem.55.11.771>.
  32. Faustini A, Stafoggia M, Berti G, Bisanti L, Chiusolo M, Cernigliaro A. The relationship between ambient particulate matter and respiratory mortality: a multi-city study in Italy. *Eur Respir J.* 2011;38:538–47. <https://doi.org/10.1183/09031936.00093710>.
  33. Gariazzo C, Carlino G, Silibello C, Renzi M, Finardi S, Pepe N. A multi-city air pollution population exposure study: combined use of chemical-transport and random-Forest models with dynamic population data. *Sci Total Environ.* 2020;724:138102. <https://doi.org/10.1016/j.scitotenv.2020.138102>.
  34. World Health Organization. (2021). WHO global health quality guidelines: particulate matter (PM<sub>2.5</sub> and PM<sub>10</sub>), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. World Health Organization. <https://apps.who.int/iris/handle/10665/345329?ts> [accessed 3 November 2021]
  35. Liu S, Jørgensen JT, Ljungman P, Pershagen G, Bellander T, Leander K. Long-term exposure to low-level air pollution and incidence of asthma: the ELAPSE project. *Eur Respir J.* 2021;57(6). 2003099. <https://doi.org/10.1183/13993003.03099-2020>.
  36. Baldacci S, Carrozzi L, Viegi G, Giuntini C. Assessment of respiratory effect of air pollution: study design on general population samples. *J Environ Pathol Toxicol Oncol.* 1997;16:77–83.
  37. Viegi G, Pedreschi M, Baldacci S, Chiaffi L, Pistelli F, Modena P. Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. *Int J Tuberc Lung Dis.* 1999;3:1034–42.
  38. Viegi G, Matteelli G, Angino A, Scognamiglio A, Baldacci S, Soriano JB. The proportional Venn diagram of obstructive lung disease in the Italian general population. *Chest.* 2004;126:1093–101. <https://doi.org/10.1378/chest.126.4.1093>.
  39. Maio S, Baldacci S, Carrozzi L, Polverino E, Angino A, Pistelli F. Urban residence is associated with bronchial hyper-responsiveness in Italian general population samples. *Chest.* 2009;135:434–41. <https://doi.org/10.1378/chest.08-0252>.
  40. Nuvolone D, Della Maggiore R, Maio S, Fresco R, Baldacci S, Carrozzi L. Geographical information systems and environmental epidemiology: a cross-sectional spatial analysis of the effects of traffic-related air pollution on population respiratory health. *Environ Health.* 2011;10:12. <https://doi.org/10.1186/1476-069X-10-12>.
  41. Maio S, Baldacci S, Tagliaferro S, Angino A, Parmes E, Pärkkä J. Urban grey spaces are associated with increased allergy in the general population. *Environ Res.* 2021;112428. <https://doi.org/10.1016/j.envres.2021.112428>.
  42. Milillo CP, Gemignani F, Sbrana I, Carrozzi L, Viegi G, Barale R. Chromosome aberrations in humans in relation to site of residence. *Mutat Res.* 1996;360:173–9. [https://doi.org/10.1016/s0165-1161\(96\)90014-x](https://doi.org/10.1016/s0165-1161(96)90014-x).
  43. Barale R, Chelotti L, Davini T, Del Ry S, Andreassi MG, Ballardini M. Sister chromatid exchange and micronucleus frequency in human lymphocytes of 1,650 subjects in an Italian population: II. Contribution of sex, age, and lifestyle. *Environ Mol Mutagen.* 1998;31:228–42. [https://doi.org/10.1002/\(sici\)1098-2280\(1998\)31:3<228::aid-em4>3.0.co;2-g](https://doi.org/10.1002/(sici)1098-2280(1998)31:3<228::aid-em4>3.0.co;2-g).
  44. Petruzzelli S, Celi A, Pulerà N, Baliva F, Viegi G, Carrozzi L. Serum antibodies to benzo(a)pyrene diol epoxide-DNA adducts in the general population: effects of air pollution, tobacco smoking, and family history of lung diseases. *Cancer Research.* 1998;58:4122–6.
  45. Maio S, Baldacci S, Carrozzi L, Pistelli F, Angino A, Simoni M. Respiratory symptoms/diseases prevalence is still increasing: a 25yr population study. *Respir Med.* 2016;110:58–65. <https://doi.org/10.1016/j.rmed.2015.11.006>.



46. Maio S, Baldacci S, Carrozzi L, Pistelli F, Simoni M, Angino A. 18-yr cumulative incidence of respiratory/allergic symptoms/diseases and risk factors in the Pisa epidemiological study. *Respir Med.* 2019;158:33–41. <https://doi.org/10.1016/j.rmed.2019.09.013>.
47. Cilluffo G, Ferrante G, Fasola S, Montalbano L, Malizia V, Piscini A. Associations of greenness, greyness and air pollution exposure with children's health: a cross-sectional study in Southern Italy. *Environ Health.* 2018;17:86. <https://doi.org/10.1186/s12940-018-0430-x>.
48. Migliore E, Berti G, Galassi C, Pearce N, Forastiere F, Calabrese R. Respiratory symptoms in children living near busy roads and their relationship to vehicular traffic: results of an Italian multicenter study (SIDRIA 2). *Environ Health.* 2009;8:27. <https://doi.org/10.1186/1476-069X-8-27>.
49. Chiusolo M, Cadum E, Stafoggia M, Galassi C, Berti G, Faustini A. Short-term effects of nitrogen dioxide on mortality and susceptibility factors in 10 Italian cities: the EpiAir study. *Environ Health Perspect.* 2011;119:1233–8. <https://doi.org/10.1289/ehp.1002904>.
50. Alessandrini ER, Faustini A, Chiusolo M, Stafoggia M, Gandini M, Demaria M. Air pollution and mortality in twenty-five Italian cities: results of the EpiAir2 project. *Epidemiol Prev.* 2013;37:220–9.
51. Scarinzi C, Alessandrini ER, Chiusolo M, Galassi C, Baldini M, Serinelli M. Air pollution and urgent hospital admissions in 25 Italian cities: results from the EpiAir2 project. *Epidemiol Prev.* 2013;37:230–41.
52. Baccini M, Biggeri A. Gruppo collaborativo EpiAir2. Short-term impact of air pollution among Italian cities covered by the EpiAir2 project. *Epidemiol Prev.* 2013;37:252–62.
53. Gariazzo C, Carlino G, Silibello C, Renzi M, Finardi S, Pepe N. A multi-city air pollution population exposure study: combined use of chemical-transport and random-forest models with dynamic population data. *Sci Total Environ.* 2020;724:138102. <https://doi.org/10.1016/j.scitotenv.2020.138102>.
54. Gariazzo C, Carlino G, Silibello C, Tinarelli G, Renzi M, Finardi S. Impact of different exposure models and spatial resolution on the long-term effects of air pollution. *Environ Res.* 2021;192:110351. <https://doi.org/10.1016/j.envres.2020.110351>.
55. Marinaccio A, Scortichini M, Gariazzo C, Leva A, Bonafede M, De' Donato FK. Nationwide epidemiological study for estimating the effect of extreme outdoor temperature on occupational injuries in Italy. *Environ Int.* 2019;133:105176. (Pt) <https://doi.org/10.1016/j.envint.2019.105176>.
56. Renzi M, Scortichini M, Forastiere F, De' Donato F, Michelozzi P, Davoli M, et al. BEEP collaborative group. A nationwide study of air pollution from particulate matter and daily hospitalizations for respiratory diseases in Italy. *Sci Total Environ.* 2022;807(Pt 3):151034. <https://doi.org/10.1016/j.scitotenv.2021.151034>.
57. Fasola S, Maio S, Baldacci S, La Grutta S, Ferrante G, Forastiere F. Effects of particulate matter on the incidence of respiratory diseases in the pisan longitudinal study. *Int J Environ Res Public Health.* 2020;17:2540. <https://doi.org/10.3390/ijerph17072540>.
58. Fasola S, Maio S, Baldacci S, La Grutta S, Ferrante G, Forastiere F. Short-term effects of air pollution on cardiovascular hospitalizations in the Pisan longitudinal study. *Int J Environ Res Public Health.* 2021;18:1164. <https://doi.org/10.3390/ijerph18031164>.
59. Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B. Effects of long-term exposure to air pollution on natural-cause mortality: an analysis of 22 European cohorts within the multicentre ESCAPE project. *Lancet.* 2014;383(9919):785–95. [https://doi.org/10.1016/s0140-6736\(13\)62158-3](https://doi.org/10.1016/s0140-6736(13)62158-3).
60. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, De Matteis S. Air pollution, lung function and COPD: results from the population-based UK Biobank study. *Eur Respir J.* 2019;54(1):1802140. <https://doi.org/10.1183/13993003.02140-2018>.
61. Katoto PDMC, Byamungu L, Brand AS, Mokaya J, Strijdom H, Goswami N. Ambient air pollution and health in Sub-Saharan Africa: current evidence, perspectives and a call to action. *Environ Res.* 2019;173:174–88. <https://doi.org/10.1016/j.envres.2019.03.029>.
62. Andersen ZJ, Hoffmann B, Morawska L, Adams M, Furman E, Yorgancioglu A. Air pollution and COVID-19 - clearing the air and charting a post-pandemic course: a joint workshop report of ERS, ISEE, HEI and WHO. *Eur Respir J.* 2021;58(2):2101063. <https://doi.org/10.1183/13993003.01063-2021>.
63. Bousquet J, Kiley J, Bateman ED, Viegi G, Khaltaev N, Cruz AA. Prioritized research agenda for prevention and control of chronic respiratory diseases. *Eur Respir J.* 2010;36:995–1001. <https://doi.org/10.1183/09031936.00012610>.
64. Laurendi G, Mele S, Centanni S, Donner CF, Falcone F, Frateiacchi S. Global alliance against chronic respiratory diseases in Italy (GARD-Italy): strategy and activities. *Respir Med.* 2012;106:1–8. <https://doi.org/10.1016/j.rmed.2011.10.002>.
65. Zuccaro P, Pichini S, Mortali C, Pacifici R, Viegi G, Baldacci S, Fumo e patologie respiratorie. Le carte del rischio per broncopneumopatia cronica ostruttiva e tumore al polmone. Istituto Superiore di Sanità. Roma: Coordinamento editoriale G. Caraffa, Centro Stampa De Vittoria S.r.l.; 2004.