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REVIEW

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

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KEYWORDS
Air pollution;
Asthma;
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COPD;
GARD;
Portugal

Abstract
Objective: To analyse the GARD perspective on the health effects of outdoor air pollution, and to synthesise the Portuguese epidemiological contribution to knowledge on its respiratory impact.
Results: Ambient air pollution has deleterious respiratory effects which are more apparent in larger, densely populated and industrialised countries, such as Canada, Iran, Brazil and Portugal, but it also affects people living in low-level exposure areas. While low- and middle-income countries (LMICs), are particularly affected, evidence based on epidemiological studies from LMICs is both limited and heterogeneous. While nationally, Portugal has a relatively low level of air pollution, many major cities face with substantial air pollution problems. Time series and cross-sectional epidemiological studies have suggested increased respiratory hospital admissions, and increased risk of respiratory diseases in people who live in urban areas and are exposed to even a relatively low level of air pollution.
Conclusions: Adverse respiratory effects due to air pollution, even at low levels, have been confirmed by epidemiological studies. However, evidence from LMICs is heterogeneous and relatively limited. Furthermore, longitudinal cohort studies designed to study and quantify the link between exposure to air pollutants and respiratory diseases are needed. Worldwide, an integrated approach must involve multi-level stakeholders including governments (in Portugal, the Portuguese Ministry of Health, which hosts GARD-Portugal), academia, health professionals, scientific societies, patient associations and the community at large. Such an approach not only will garner a robust commitment, establish strong advocacy and clear objectives, and raise greater awareness, it will also support a strategy with adequate measures to be implemented to achieve better air quality and reduce the burden of chronic respiratory diseases (CRDs).
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Introduction

Worldwide, chronic respiratory diseases (CRDs) are one of the five leading causes of morbidity and mortality of non-communicable diseases (NCD), according to the World Health Organization (WHO).[1] Furthermore, the Forum of International Respiratory Societies (FIRS) considers chronic obstructive pulmonary disease (COPD) and asthma, pneumonia, tuberculosis and lung cancer as the five most prevalent pulmonary diseases.[2] Together, they contribute significantly to the increasing global burden of NCD.[3−7]

To better elucidate various aspects of CRDs and to support countries and organizations globally dealing with CRDs, the Global Alliance against chronic Respiratory Diseases (GARD) was established in 2006 as a voluntary alliance of medical and scientific societies, patients' associations, and governmental institutions with WHO.[8] The main objective of GARD is to reduce the global burden of CRDs so that the world will be a place where all people breathe freely. In particular, GARD focuses on the needs of people suffering from CRDs in low- and middle-income countries (LMIC).[9] This is especially relevant since LMICs have a disproportionately high burden of the CRD-associated morbidity and mortality.[10]

Air pollution is a significant risk factor for CRDs, and with well documented adverse health impacts on human,[11−16] especially in GARD countries.[17−20] Health effects range from minor irritation of the upper respiratory system to serious chronic respiratory and cardiac disorders, as well as worsening of cardiac and pulmonary diseases, premature mortality and decreased life expectancy.[21,22] Short-term exposure to air pollution may contribute to worsening of respiratory symptoms in people with asthma or COPD,[23,24] while continuing or long-term exposures seem to increase the risk of development of COPD in those with asthma, therefore acquiring features of asthma COPD overlap (ACO).[25] Furthermore, air pollution has a substantial impact on quality of life in those who are living with CRDs,[12,13] and novel, non-respiratory, health effects have been described in a joint document of the American Thoracic Society/European Respiratory Society (ATS/ERS).[11,26]

Regarding mortality, the WHO 2016 Report[21] on ambient air pollution suggested that 4.2 million deaths every year occur as a result of exposure to ambient air pollution. According to the estimates of the Global Burden of Disease (GBD), air pollution was the fifth major risk factor of death in the world, accounting for 7.6% of all deaths globally in 2015.[16,27−29] A more recent GBD study in 2020 showed that approximately 12% of all deaths in 2019 were due to the combined effects of indoor and outdoor pollution.[30]

Despite successful attempts to reduce air pollution in advanced industrial countries, mortality resulting from air pollution exposure has not decreased across GARD countries.[34] On the contrary, with the increasing level of air pollution, a rise in the number of deaths resulting from NCD has been noted in LMICs[16] and GARD countries,[31] especially in the more vulnerable population (e.g., people of lower socio-economic status), compounding a disproportional risk.[32,33]

In Portugal, in spite of a global reduction in pollutant emission, air quality has not improved accordingly for all pollutants. The annual emission and air quality trends in Portugal in 2009−2015 have been studied.[35] Although the emissions of carbon monoxide (CO), nitrogen dioxide (NO_2), sulphur oxides (Sox), and particulate matter (PM_{10}) showed a general decreased trend in the study period, there was also a notable increasing trend towards in the last two years studied. Based on a comparative analysis of the spatial distribution of emissions available for 2009 and 2015,[36] several points were highlighted: higher emissions, mainly of NO_2 and PM_{10}, were verified in industrial areas and urban centres; Lisbon Metropolitan Area was the most problematic region in terms of emissions of all pollutants; the North region had a reduction of PM_{10} emissions, compared with the other regions; NO_2 emissions showed an increase in most of the country.[35]

The 2020 Report of the European Environment Agency (https://www.eea.europa.eu/publications/air-quality-in-europe-2020-report) showed that years of life lost attributable to air pollutants in Portugal, in 2018 per 10^5 inhabitants were 541 for $PM_{2.5}$, 84 for NO_2, and 42 for O_3, whereas the number of premature deaths were 4900 for $PM_{2.5}$, 750 for NO_2, and 370 for O_3. Although these levels are lower than those in most other European countries, they represent an average value for the country and are less representative of the situation in more urbanized and industrialized cities such as Lisbon and Porto. Thus, it is paramount to more accurately depict the impact of outdoor air pollution in Portugal by reporting or stratifying findings by a more refined geographical unit (such as by region).

Methods

This narrative review is divided into two main topics: a *perspective from some GARD countries*, and the *Portuguese perspective*. The GARD view includes some general comments on the societal burden of CRDs as well a brief analysis of the role of various ambient air pollutants on CRD-related outcomes. This is further exemplified by the experience of some GARD countries: Iran, Canada, Brazil, Angola and Mozambique. The Portuguese perspective aims to summarise the main findings of epidemiological studies on the relationship between estimates of global and specific outdoor air pollutants and some of the most relevant CRD-related outcomes.

The perspective from some GARD countries (Angola, Brazil, Canada, Iran, and Mozambique)

A view on the problem of ambient air pollution and its impact on respiratory health was elaborated by country level GARD coordinators and this was complemented by country-specific literature searches on the topic. The analysis included Medline searches on PubMed and Embase databases from inception (of records in each database) to 30 October 2021, using the following search terms "outdoor air pollution" and "respiratory health" AND "Iran" or "Canada" or "Brazil" or "Angola" or "Mozambique". Only studies on the relationship between ambient air pollution and respiratory outcomes were included in this narrative review.[37,76]

The Portuguese perspective

The Portuguese perspective aimed to summarise evidence collected by studies on ambient air pollution and CRDs carried out in Portugal only, and was based on a non-systematic review of the literature. Searches were carried out in PubMed, Embase, and SciELO, as primary sources, from inception to 30 October 2021, using the following search terms "outdoor air pollution", AND "respiratory health", or "asthma", or "wheezing", or "chronic bronchitis", or "COPD" and "Portugal". As secondary sources, additional references found by authors' review were also included. All observational and analytical epidemiological studies, including cohort, case-control and cross-sectional studies, using traditional epidemiological approaches and/or statistical modelling, written in any language, were accepted. A total of 81 articles was retrieved. All articles were screened by two independent authors. After screening of titles, abstracts and full text, 29 articles were selected.[77–105] Studies not including respiratory outcomes were excluded.

Results

Some examples from GARD countries from around the world (Table 1)

Iran

Some studies on air pollution in Iran have shown that CO and particulate matter were the most important air pollutants at concentrations higher than standard values, especially in Tehran, with association with respiratory signs and symptoms.[37] Research on the association between ambient air pollution and CRDs such as asthma and COPD showed a relationship between hospital admissions due to exacerbations of these diseases and levels of various air pollutants in major populated cities,[38–40] namely in terms of interaction with weather variables.[41,42] A positive relationship between asthma and air pollutants was also more significant in more "urban" (and polluted) than in more "rural" control sites.[43] Finally, studies fully based on statistical modelling of the distribution of diverse air pollutants and various CRDs (with a focus on asthma) have also shown a positive association.[44–47] However, the Iranian society had not received any appropriate or efficient training and awareness regarding air pollution, in spite of the deleterious effects of air pollution on respiratory health in populated cities being alarming.[48]

Canada

Canada is one of few countries (9%) where air quality is within the WHO recommended limits. Nevertheless, several cohort studies were carried out in the country and yielded relevant results. A first cohort study found that early life exposure to oxidant air pollutants (O_3 and NO_2) was associated with an increased risk of incident asthma and eczema in children.[49] In addition, other cohort studies, performed in major Canadian cities, have also shown various positive associations: between various air pollutants (namely $PM_{2.5}$, NO_2, O_3 and O_x) and the incidence of COPD in adults[50]; between exposure to ultrafine particles (UFP) and COPD (although this association was lost when exposure was adjusted for NO_2)[51]; and between long-term exposure to iron (Fe), copper (Cu), and reactive oxygen species (ROS) and the incidence of asthma and COPD, COPD mortality, pneumonia mortality and overall respiratory mortality. The associations were more robust for COPD, and mortality from overall

Table 1 Main studies that evaluated the effects of external pollution on respiratory health in some GARD countries.

Author and year of publication	Country and locality or region	Exposure	Population group	Health outcome	Type of study, year and analysis	Main conclusions
Namvar et al, 2020[37]	Tehran, Iran	$PM_{2.5}$, PM_{10}, SO_2, CO	Children < 7 years-old attending day care centres	Cough, phlegm, wheezing, chest pain, current or past asthma, "bronchitis"	Cross-sectional (2015); analysis using crude and adjusted logistic regression analyses	Long-term exposure to air pollutants near the home: (a) CO - associated with increased risk of persistent phlegm (OR = 1.40; 95% CI = 1.09-1.81); (b) NO_2, and SO_2 associated with increased risk of current asthma.
Masjedi et al, 2003[38]	Tehran, Iran	PM_{10}, SO_2, CO, O_3, NO_2, THC (mean 3-, 7- and 10-day levels)	Adult patients residing in Tehran for at least 2 years, with acute asthma or COPD exacerbations, admitted to hospitals	Number of emergency admissions due to acute asthma or COPD exacerbations	Time series (5 months; 1997-1998); analysis using multiple stepwise regression; time-series analysis	Positive correlation between ER admissions for acute asthma and: (a) exposure to SO_2 — mean 3-day levels (r = 0.24; p = 0.049), and mean 10-day levels (r = 0.56; p = 0.019); (b) exposure to NO_2 — mean 7-day levels (r = 0.28; p = 0.049).
Khalilzadeh et al, 2009[39]	Tehran, Iran	PM_{10}, SO_2, CO, O_3, NO_2	Patients admitted to Emergency units due to acute asthma or cardiovascular complaint	Number of emergency admissions due to acute asthma or cardiovascular conditions	Time series (12 months; 2004-2005); analysis using non-adjusted Pearson correlation	Significant positive correlation (r) between number of admissions for cardiopulmonary complaints and levels of: (a) CO (r = 0.731; p = 0.016); (b) PM_{10} (r = 0.752; p = 0.012).
Raji et al, 2020[40]	Ahvaz, Iran	$PM_{2.5}$, PM_{10}, SO_2, CO, O_3, NO_2, NO	Adults (elderly and non-elderly) admitted to hospitals due to asthma, COPD or bronchiectasis exacerbations	Number of hospital admissions due to acute asthma, COPD or bronchiectasis exacerbations	Time series (2008-2018); analysis using adjusted Quasi-Poisson regression	Increased ER admissions for asthma were significantly associated with (a) $PM_{2.5}$ levels (RR = 1.004; 95% CI = 1.002-1.007); (b) NO_2 levels (RR = 1.040; 95% CI = 1.008-1.074); (c) SO_2 levels (RR = 1.069; 95% CI = 1.017-1.124). Increased ER admissions for COPD were significantly associated with (a) $PM_{2.5}$ levels (RR = 1.003; 95% CI = 1.002-1.005); (b) NO_2 levels (RR = 1.049; 95% CI = 1.010-1.090); (c) CO levels (RR = 1.641; 95% CI = 1.233-2.191). Significant associations also seen with PM_{10} levels and bronchiectasis.
Masoumi et al, 2017[41]	Ahvaz, Iran	PM_{10}, SO_2, CO, O_3, NO_2, NO_x	Adults admitted to hospitals due to acute respiratory complaints (rainfall associated bronchospasm epidemic period versus non-epidemic period)	Number of emergency admissions due to acute respiratory complaints (shortness of breath, wheezing, coughing and phlegm)	Case-control (2011-2015); analysis using binomial regression	Significant positive relationship between ER respiratory admissions and each unit of increase in NO (adjRR = 1.008; 95% CI = 1.001-1.016; p = 0.037) and SO_2 (adjRR =1.014; 95% CI = 1.000-1.028; p = 0.044) levels during the epidemic periods, and NO_2 (adjRR =1.010; 95% CI = 1.001-1.019; p = 0.023) levels during the nonepidemic periods.
Geravandi et al, 2017[42]	Ahvaz, Iran	PM_{10}	Adults admitted to hospitals due to asthma attacks, acute bronchitis and COPD (dusty days versus non-dusty days)	Number of emergency hospitaladmissions due to acute respiratory complaints (HARD) — asthma, acute bronchitis, COPD	Case-control (2010-2012); analysis using correlation analysis (dust events and PM_{10}-related hospital admissions)	Number of HARD admissions was associated with the highest daily PM_{10} concentrations, in 2010-2012, and this was more significant on dusty days (correlations varying between 0.53 and 0.62).
Shakerkhatibi et al, 2021[43]	3 villages (1 in industrial area; 1 with potential urban air pollution; 1 with no potential air pollution) in northwest Iran	PM_{10}, SO_2, NO_2, Volatile Organic Compounds (VOC), benzene, toluene, xylenes	Children and adolescentes from the 3 villages	Prevalence of asthma	Cross-sectional (2016); analysis using two-step hierarchical logistic regression modeling and latent class analysis (LCA)	Higher probability of severe asthma (6.8%) in the "industrial area" village than in the other two villages (2.6% and 1.8%). Adjusted odds of moderate and severe asthma were lower in the control villages than in the "industrial area" village (ORs 0.135 - 0.697).

Table 1 (*Continued*)

Author and year of publication	Country and locality or region	Exposure	Population group	Health outcome	Type of study, year and analysis	Main conclusions
Shakerkhatibi et al, 2021[44]	Urmia, Iran	$PM_{2.5}$, PM_{10}	Adults admitted to hospitals for asthma, chronic bronchitis, emphysema and COPD	Number of daily hospital admissions for asthma, chronic bronchitis, emphysema and COPD	Case crossover; analysis using conditional logistic regression	In the adjusted model, an increment of PM_{10} and $PM_{2.5}$ increased the risk of admissions for asthma by 1.124 (95% CI =1.062-1.191), and 1.117 (95% CI = 1.055-1.184), respectively. Also for $PM_{2.5}$, the estimated OR was 1.5-fold higher in women (OR = 1.078 (95% CI = 1.037-1.121) than in men (OR = 1.032 (95% CI = 0.996-1.069).
Razavi-Termeh et al, 2021[46]	Tehran, Iran	$PM_{2.5}$, PM_{10}, SO_2, CO, O_3, NO_2 (and distance to parks and streets)	Clinical records of asthmatic children (Hospital Information System)	Children with asthma living in Tehran	(2019); analysis using geostatistical methods including spatial autocorrelation and Random Forest machine learning model	Distribution of asthma was not random, and occurrence of the disease was affected by environmental conditions. $PM_{2.5}$, PM_{10}, distance to park, distance to street had a stronger spatial correlation.
To et al, 2020[49]	Toronto, Canada	$PM_{2.5}$, O_3, NO_2 (and greeness)	Children of the T-CHEQ study	Incident asthma, rhinits and eczema	Cohort (average of 17 years – up to 2016); analysis using Cox proportional hazards regression models (single, multipollutant, and oxidants models); Moran's I was to measure spatial autocorrelation and clustering	At birth and / or first 3 years of life exposures to NO_2 and O_3 were associated with an increased risk of incident asthma - adjusted Hazard ratios (adHR) between 1.14 and 1.23) or eczema (adHR between 1.05 and 1.07) in children, particularly in those $\leq$ 4 years-old.
Shin et al, 2021[50]	Ontario, Canada	$PM_{2.5}$, O_3, O_x, NO_2	Adults from the Ontario Population Health and Environment Cohort (ONPHEC), without respiratory diseases	Incident asthma and COPD	Cohort; analysis using Cox proportional hazards model; stratified analysis; sensitivity analyses	Every interquartile range increase in $PM_{2.5}$, NO_2, O_3 and O_x was consistently associated with 3-7% higher incidences of COPD, but not asthma, in adults.
Weichenthal et al, 2017[51]	Toronto, Canada	Ultra-fine particles (UFP), NO_2	30-100 year old adults from ONPHEC, without respiratory diseases	Incident asthma, COPD and lung cancer	Cohort (1996-2012); analysis using random-effect Cox proportional hazard models	No clear evidence of positive association between long-term exposure to UFP and respiratory disease independently of other pollutants.
Zhang et al, 2021[52]	Toronto, Canada	Iron (Fe) and copper (Cu) in $PM_{2.5}$	40-85 year-old adults from (ONPHEC), without respiratory diseases	Incident asthma, COPD, COPD mortality, pneumonia mortality, respiratory mortality; generation of reactive oxygen species (ROS)	(2001-2016); analysis using land-use regression model; estimation of ROS levels; mixed-effects Cox proportional hazard regression models; sensitivity analyses; Shape Constrained Health Impact Function	Positive association between long-term exposure to Fe, Cu and ROS and risks for all respiratory outcomes.
Stieb et al, 2009[54]	7 cities, Canada	$PM_{2.5}$, PM_{10}, SO_2, CO, O_3, NO_2,	Records of children and adults visting ER due to acute cardiovascular or respiratory reasons,	ER visits for asthma, COPD, respiratory infections (or cardiovascular reasons)	Time-series (1990s-early 2000s); analysis using generalized linear models adjusted for meteorological conditions and city-specific conditions	O_3 had the most consistent associations with ER visits for asthma (3.2%; 95% CI = 0.3–6.2% per 18.4 pp(b), and COPD (3.7%; 95% CI = 0.5–7.9% per 18.4 pp(b). PM_{10} and $PM_{2.5}$ were strongly associated with asthma visits in the warm season: 14.4% increase in visits (95% CI = 0.2–30.7) per 20.6 $\mu g/m^3$ PM_{10}, and 7.6% increase in visits (95% CI = 5.1–10.1), per 8.2 $\mu g/m^3$ $PM_{2.5}$).
Stieb et al 2000[55]	St. John, Canada	$PM_{2.5}$, PM_{10}, SO_2, O_3, $SO_4^{(2-)}$, Coefficient of	Records of individuals visting ER due to acute cardiovascular or respiratory reasons	ER visits for asthma, COPD (or cardio vascular reasons)	Time series (1992-1996); analysis using single and multiple pollutant models with	In single-pollutant models, positive association between all pollutants (except for NO_2 and COH) and asthma visits, and positive effects on all respiratory diagnosis groups were observed for O_3,

Table 1 (*Continued*)

Author and year of publication	Country and locality or region	Exposure	Population group	Health outcome	Type of study, year and analysis	Main conclusions
		Haze (COH), aeroallergens			stepwise procedures and sensitivity analyses	SO_2, $PM_{2.5}$, PM_{10}, and $SO_4^{(2-)}$. In multipollutant models, pollutant gases, particularly O_3 and SO_2 exhibited more consistent effects.
Weichenthal et al, 2016[56]	15 cities across Ontario, Canada	$PM_{2.5}$, influence of oxidative potential of $PM_{2.5}$	Children and adults with asthma or COPD, residing in the studied cities, who attended ER due to exacerbations of their respiratory illness	Risk of ER visits due to asthma, COPD and all respiratory outcomes (ICD 10th revision: codes J00-J99)	Time-stratified case cross-over (2004-2011); analysis using conditional logistic regression, adjusted for time-varying covariates	$PM_{2.5}$ levels were associated with ER visits for all respiratory illnesses. Glutathione-related oxidative potential modified the impact of low concentrations of $PM_{2.5}$.
Moraes et al, 2019[59]	São Paulo, Brazil	Air temperature, relative humidity, precipitation, PM_{10}	Children (0-9 years-old)	Hospitalizations for respiratory diseases	Longitudinal study (2003-2013); analysis using generalised linear models with negative binomial distribution, and distributed lag non-linear model	Significant high risk association between air temperature, relative humidity, rainfall and PM_{10} and hospitalizations for respiratory diseases. For PM_{10} ($> 35\mu g/m^3$) for total sample and for female sex, the highest RR were 1.299 (95% CI = 1.045 − 1.614), and 1.512 (95% CI = 1.914 -2.067), respectively.
Carvalho et al, 2018[60]	Porto Alegre, Brazil	NO_2, O_3 (measured in individual filters given to the two studied groups)	Healthy, male, professional bikers (index group), and office workers (control group)	Oxidative stress and genetic damage	Cross-sectional study (2016); analysis using Mann-Whitney U test or Chi-square test, and multiple linear regression analysis	NO_2 and O_3 levels in filters were significantly higher in bikers than in office workers: (a) NO_2: $106.77 \pm 20.17\ \mu g/m^3/h$ versus $14.18 \pm 3.69\ \mu g/m^3/h$, respectively; (b) O_3: $225.03 \pm 45.47\ \mu g/m^3/8\ h$ versus $12.14 \pm 3.85\ \mu g/m^3/8\ h$. NO_2 and O_3 levels and showed a strong positive correlation with plasma lipid peroxidation in bikers.
Santos et al, 2016[61]	São Paulo, Brazil	$PM_{2.5}$	Non-smoking workers (taxi drivers, traffic controllers, forest rangers)	Lung function	Longitudinal study (2008-2012); workers attended 4 weekly visits, for 1 month	Compared to workers in the lowest exposed group (forest rangers), those with the highest level of exposure had significantly reduced predicted FVC and increased predicted $FEF_{25-75\%}/FVC$.
Ribeiro et al, 2019[62]	São Paulo, Brazil	Traffic density, NO_2	Adults living in two city zones with diferente socioeconomic status (richer and poorer areas)	Incident respiratory cancer; Respiratory cancer mortality	Longitudinal study (2002-2013); analysis using age-adjusted binomial negative regression models	Increased rate of respiratory cancer incidence and mortality in association with increased traffic density and NO_2 levels, and this was stronger in the poorer areas. For NO_2 in poorest regions, the incidence rate ratio (IRR) for mortality in the highest exposed group was 1.44 (95% CI = 1.10 - 1.88) while in the least deprived area, the IRR for the highest exposed group was 1.11 (95% CI = 1.01 - 1.23).
Agudelo-Castañeda et al, 2019[63]	5 cities in south Brazil	PM_{10}, $PM_{2.5}$, NO_2, O_3	Hospital admissions data for children, adults and elderly individuals	Respiratory hospitalizations	Ecological time-series (2013-2016); analysis using adjusted multivariable Poisson regression models	An increase of 10 $\mu g/m^3$ in the monthly average concentration of PM_{10} was associated with an increase of respiratory hospitalizations in all age groups; for NO_2 and SO_2, stronger intermediate-term effects were found in 6-15 year-old children; for O_3, higher effects were found in children $<$ 1 year.
Bravo et al, 2016[64]	São Paulo, Brazil	PM_{10}, NO_2, CO, SO_2, O_3	Adults $\geq$ 35 years-old	Non-accidental, cardiovascular and respiratory mortality (number of daily deaths)	Case cross-over, longitudinal study (1996-2010); analysis using fitted conditional logistic regression models	Increased risk of respiratory mortality were significantly associated with all pollutants, in both sexes, and 35-64 and 65-74 age ranges, OR associated with an IQR increase in air pollutant concentrations between 1.16 and 3.81, mostly with 1-day lag.
Costa et al., 2017[65]	São Paulo, Brazil	PM_{10}, NO_2, CO	Elderly (deaths registered at the Mortality Information Improvement Program)	Non-accidental and cause-specific mortality	Daily time series (2000-2011); analysis using Poisson generalized additive models	PM_{10}, NO_2, and CO exposures were associated with short-term mortality displacement for nonaccidental and circulatory, but not respiratory, deaths.

Table 1 (*Continued*)

Author and year of publication	Country and locality or region	Exposure	Population group	Health outcome	Type of study, year and analysis	Main conclusions
Nawaz & Henze, 2020[68]	Amazonia, Brazil	$PM_{2.5}$ from biomass burning (forest fires)	Various age groups	Premature deaths due to COPD, lung cancer, acute lower respiratory illness (ALRI) (and ischemic heart disease, and stroke)	(2018; 2019); analysis using computational GEOS-Chem adjoint modeling, with sensitivity analysis, and risk assessment	Premature deaths contributed by biomass burning emissions between July and September made up 10% of total annual $PM_{2.5}$-related premature deaths.
Andrade Filho et al., 2013[73]	Manaus, Brazil	$PM_{2.5}$ (from burning biomass), meteorological conditions	Children	Hospital admissions for respiratory diseases	Ecological study of time series (2002-2009); analysis using Pearson correlation and multiple linear regression	Hospital admissions for respiratory diseases in children were significantly correlated with humidity in the rainy season and the association with $PM_{2.5}$ was negative (R = -0.168; p = 0.003).
Ignotti et al., 2010[76]	Tangará da Serra and Alta Floresta, Brazil	$PM_{2.5}$ (from burning of biomass)	Children and elderly	Hospital admissions for respiratory diseases	Ecological study of time series (2005); analysis using generalized additive models with Poisson errors	In Alta Floresta, increased $PM_{2.5}$ levels were associated with hospital admissions for respiratory diseases in children and the elderly. The % increases in relative risk (%RR) of hospitalization for respiratory diseases in children were significant for the whole year and for the dry season (6%; 95% CI = 1.4-10.8) with 3-4 day lags. The %RR for the elderly was significant for the current day of the drought, with a 6.8% increase (95% CI = 0.5-13.5) for each additional 10μg/m^3 of $PM_{2.5}$.

respiratory causes or from pneumonia.[52] Finally, a study using population data from Ontario (the largest province in Canada), found that adult individuals exposed to higher levels of air pollution (namely $PM_{2.5}$ and O_3) had nearly threefold greater odds of developing ACO.[25]

Furthermore, various studies using statistical modelling have also shown positive associations: between overall pollution indices (including “floating” particles and SO_2) and acute respiratory illnesses[53]; between O_3 (even at low levels) and asthma- and/or COPD-related hospital visits[54-57]; and between $PM_{2.5}$ and asthma as well as COPD emergency room (ER) visits.[56] Interestingly, two of the previous studies also showed that concomitant factors may influence these relationships: warmer seasons may promote a stronger association between ambient air $PM_{2.5}$ and PM_{10} levels and asthma hospital visits[54]; in addition, between-city differences in glutathione-related oxidative potential may modulate the impact of low levels of $PM_{2.5}$ on asthma and COPD hospital visits[56].

These studies suggest that there is no safe level of air pollution and that improving air quality will contribute to the prevention of asthma and other allergic disease in childhood and adolescence, and possibly COPD and ACO, in adults.

Brazil

Brazil ranks sixth among the largest greenhouse gases emitters, representing 3.2% of the world total. Per capita emissions are also higher than the world average. In 2019, the average CO_2 emission per Brazilian was 10.4 gross tons, against 7.1% of the world average.[58] Urban climate change, excessive air pollution and increased social inequalities have become determining factors for the high risk of hospitalizations for respiratory diseases.[59] One study showed that professional motorcyclists who suffer prolonged exposure to air pollution have worsening of pre-existing respiratory diseases.[60] Furthermore, exposure to different levels of traffic-related $PM_{2.5}$ was significantly associated with a reduction in forced vital capacity (FVC) of workers in the city of São Paulo.[61] Traffic density and NO_2 were also associated with an increased rate of incidence and mortality from cancer in the respiratory system in residents of poor regions in the city of São Paulo.[62] In addition, a study carried out in southern Brazil reported an increase in hospital admissions for respiratory causes in all age groups with every 10 $\mu g/m^3$ increase in the average monthly concentration of PM_{10}.[63] An increased risk of non-accidental mortality from cardiovascular and respiratory diseases was shown in a study to be significantly associated with exposure to NO_2, SO_2 and CO, but not to O_3.[64] In addition, a significant association between exposure to PM_{10}, NO_2 and CO and non-accidental deaths and circulatory diseases in elderly residents in São Paulo has been documented.[65]

Besides urban pollution, forest fire-related air pollution is also a problem in Brazil.[66] During the 2019 fire season, premature deaths were attributed to fire emissions and accounted for 10% of all $PM_{2.5}$-related premature deaths in the country.[67,68] During periods of active fire, $PM_{2.5}$ was significantly associated with inflammatory respiratory effects,[69,70] and respiratory morbidity including asthma, COPD, bronchitis and pneumonia.[71–73] Furthermore, poor socioeconomic conditions increase the association between exposure to $PM_{2.5}$ due to forest fire and ER visits and hospitalizations for asthma and heart failure.[74−77]

Thus, public policies are needed in Brazil, to enhance the communication by public health professionals to the exposed populations, so that actionable information and guidelines are more effectively shared such that health and quality of life can be improved.

Angola and Mozambique

In Angola, although there is no nationwide air quality monitoring network, there are examples of some monitoring projects, such as in Luanda.[106] The General State of the Environment Report, produced by the Ministry of Urbanism and Environment (MINUA), in 2006, showed a worrying picture of indoor and outdoor air quality which was dominated by gas emissions from traffic, electric generators, industry, burning of solid waste in streets, and biomass combustion in poorly aerated sites, all of which can induce serious respiratory problems.[107] This is further compounded by the fact that, although there are studies on the prevalence and clinical features of asthma in children and adolescents from Luanda, which showed high levels,[108,109] there are currently no epidemiological data on the prevalence of asthma or COPD in adults. Furthermore, no studies have been carried out in Angola, on the relationship between outdoor air pollution and respiratory diseases.

In Mozambique, the Environmental Law, the assessment of the Environmental and Regulatory Impact of Health and Safety, and other laws which include Industrial and Environmental Emission Patterns, the Regulations for Environmental Auditing and Inspection, among others, constitute the main legislation which regulates air pollution issues.[110,111] Just like in Angola, the degree of industrialization in Mozambique is still low in general, but high in and around the bigger cities such as Maputo, Beira and Matola. In these locations, pollution may result, among other reasons, from the combined effect of obsolete equipments and lack of significant protection regulations for the population against dangerous pollution sources,[112] and also from waste management problems and automobile traffic-related emissions (CO_2, CO, NO_x).[113] In addition, uncontrolled bush burning in rural zones, mainly in the north and centre of the country, is one of the main sources of pollutants.[114,115] In fact, measurements of pollutants, which began in 1996, showed that burning of biomass was the main source of particulate matter pollution, followed by industrial activities.[115] There is also significant emission of CO_2, methane (CH_4) and NO_2 in production, transportation and utilisation of vegetable coal in certain areas of the country.[116] Finally, there is intense exploitation of coal in open pit mines in the province of Tete, and this type of mining is associated with air pollution and a high rate of respiratory diseases in those areas, particularly in children.[117] However, there are no published studies on the effects of outdoor air pollution on respiratory diseases in Mozambique.

Thus, it is crucial that research studies on such relationship are carried out both in Angola and in Mozambique, and also that a broad effort to raise awareness is implemented, involving multiple stakeholders as well as the community, in integrated research − societal effort[118] so that environmental research may result in prevention, mitigation and minimization measures, reducing the associated burden and costs,[119] aligned with the “Declaration of Libreville on Health and Environment in Africa”[120] and the related “2010 Luanda Compromise”.[121]

Portuguese perspective

Most studies performed in Portugal have used statistical models to assess and predict the relationship and impact of various air contaminants, meteorological conditions and CRDs, and have mostly used data on hospital admissions of adults and children, as a possible effect of exposure to outdoor air pollution. Fewer analytical epidemiological studies were conducted to study the relationship between outdoor pollution and CRDs (mostly asthma) and they were mainly focused on urban children. Finally, there were a few studies focused on exposure to volcanic air pollution and its impact on lung diseases.

(a) Analytical epidemiological surveys

Various analytical epidemiological studies were carried out in Portugal to study the relationship between exposure to ambient air pollutants and epidemiological indices of respiratory diseases. These studies are summarized in Table 2. Most studies were carried out in urban settings (Lisbon,[77−79] Viseu,[80,81] Estarreja[82,83] or Setúbal[84]) and involved children.[77−81] These studies normally used validated questionnaires such as the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, to analyse the presence of asthma and/or rhinitis in urban or rural schools. Most frequently studied ambient air pollutants were $PM_{2.5}$, PM_{10}, CO, NO_2, although other parameters were assessed in some of the reports, namely elements associated with resuspension or vehicle motors,[77−79] or BTEX − benzene, toluene, ethylbenzene and xylenes.[80,81]

Most studies showed that pollutant concentrations were higher than advised by the World Health Organization and U. S. Environmental Protection Agency, but below the current European Union value, although in some areas, such as Lisbon, concentrations were even higher. However, most studies were cross-sectional and this is a main limitation which should be addressed in future projects.

Some representative studies carried out in urban or rural settings and on the relationship between volcanic activity and respiratory diseases will be analysed next.

In a 2006−2007 study, the ISAAC questionnaire was distributed to 806 children attending four primary schools in the small, low-industrial city of Viseu, to identify children who reported wheezing in the previous 12 months.[80,81] Six hundred and forty-five questionnaires were returned, and 77 of the children reported wheezing in the previous 12 months. Of these, 54 were allowed to be included in the study and a total of 51 participants completed the protocol: record of clinical symptoms, pH analysis in exhaled breath condensate (EBC), measurement of exhaled nitric oxide fraction (FeNO), and spirometry, in four separate visits. Outdoor and indoor levels of air pollutants (O_3, NO, NO_2, CO, BTEX − benzene, toluene, ethylbenzene and xylenes, PM_{10} and $PM_{2.5}$) were measured. Lung function parameters, as

Table 2 Air pollution effects in Portugal: (1) Main epidemiological studies that evaluated the effects of external pollution on respiratory health in Portugal.

Author and year of publication	Locality or region	Exposure	Population group	Health outcome	Type of study, year and analysis	Health outcome results
Urban studies on relationship between exposure to air pollutants and respiratory outcomes						
Freitas et al, 2009[77] Freitas et al, 2009b[78] Almeida et al, 2009[79]	Lisbon	$PM_{2.5}$, PM_{10}, various elements associated with soil resuspension or vehicle motors, and water soluble ions	Children (5-10 years-old) attending pre-primary and primary schools	Rhinitis, asthma / wheezing (ISAAC questionnaire definition)	Cross-sectional (2006-2007); analysis using non-parametric Spearman R test, and Principal Component Analysis	There is a mixture of contributions of tested pollutants (namely $PM_{2.5}$ and its speciation for (i) chemical elements - Na, K, Sc, Cr, Fe, Co, Zn, As, Se, Br, Sb, Cs, La, Ce, Hg; (ii) the water-soluble cations Ca^{2+}, K^{+}, Mg^{2+}, Na^{+}, NH_4^{+}; and (iii) water-soluble anions Cl^{-}, NO_3^{-}, SO_4^{2-} (which are soil resuspension- or vehicle motor-associated) to rhinitis in children, and this may vary according to season.
Borrego et al, 2007[80] Martins et al, 2012[81]	Viseu	Outdoor $PM_{2.5}$, PM_{10}, CO, O_3, NO, NO_2, BTEX (also indoor air pollutants)	Saud'Ar study (Wheezing children - ISAAC questionnaire definition; also studied at city hospital)	Respiratory functional and inflammatory outcomes (FEV_1, FEV_1/FVC, FEF25-75%, ΔFEV_1; FeNO, pH of EBC); Clinical outcomes (wheezing, need of rescue medication; ER visits)	Prospective (4 study points in 2006-2007); analysis using mesoscale modelling system; adjusted Generalised estimating equation (GEE) two pollutant modelling with exchangeable working correlation; Spearman's rank correlation	Significant relationship between: a) PM_{10} and wheezing [-0,70 (-1.14 to -0.25; p = 0.002)]; (b) NO_2 and wheezing [-2.08 (-3.59 to -0.58; p = 0.007)]. (b) toluene and need of rescue medication [0.21 (0.01 to 0.42; p = 0.041)], and ER visits [0.26 (0.06 to 0.46; p = 0.010)]; (c) ethylbenzene and need of rescue medication [0.45 (0.02 to 0.87; p = 0.039)]. (d) PM_{10}, NO_2, benzene, toluene, and ethylbenzene and various parameters of lung function; (e) PM_{10}, NO_2, benzene, and ethylbenzene on phEBC. No significant effects were seen on FeNO.
Neuparth et al, 2012[82] Valente et al, 2014[83]	Estarreja	Indoor and outdoor PM_{10}, NO_2 smoking, dusty workplace	Adults - exposed workers of Estarreja chemical complex (ECC) and general population controls from the same geographical area	Physician-diagnosed asthma, and symptoms of chronic bronchitis; FEV_1/FVC (Neuparth,2012)	Case-control (2 periods in 2011 and 2012); analysis using a second-generation Gaussian model (URBAIR model); also an individual exposure model (DoseAR); also CHIMERE exposure model	All individuals spent > 90% of their time indoors; there was high PM_{10} and NO_2 exposure variability. No significant differences in exposure were observed between the two studied groups. Analysis of the relationship between asthma or chronic bronchitis did not directly involve PM_{10} or NO_2.
Farinha et al, 2021[84]	Setúbal	PM_{10}, O_3, CO, SO_2, NO_2, measured at two stations	Asthma patients seen at an Allergy outpatient hospital clinic	Intensity of asthma symptoms (0-5 visual analogue scale) – Sum of the Scores of Asthma Symptoms (SSAS)	Longitudinal (March-April 2018); analysis using a temporal causal model – autoregressive time series model.	All pollutants influenced intensity of asthma symptoms. O_3 level was the best predictive factor of symptom variability (particularly with a lag 5; $p<0.05$), and PM_{10} (lag 4), CO (lag 5) and NO_2 (lag 4) were secondary markers.
Rural studies on relationship between exposure to air pollutants and respiratory outcomes						
Alvim-Ferraz et al, 1988 (2002 data)[85] Sousa et al, 2009 (Phase 1)[86] Sousa et al, 2011 (Phase 2)[87]	Torre de Moncorvo, Mogadouro, and Espiunca	O_3	Children from local schools from two areas with high O_3 exposure (Torre de Moncorvo and Mogadouro) and from an area with low O_3 exposure (Espiunca)	Prevalence of asthma (Phase 1: ISAAC questionnaire-based (data from Espiunca had been collected in 2002); Phase 2: spirometry-based	Cross-sectional (2007); analysis using univariate analysis as well as logistic regression models to calculate risks and odds ratios	Stage 1: Questionnaire-based: the lifetime prevalence of asthma (wheezing) was significantly higher in the areas with high O_3 exposure (7.1%) than in those with low exposure (3.2%). Stage 2: Children living in the former areas had a 3-fold higher risk of having asthma than children living in the latter areas [RR = 2.84 (95% CI = 1.82 – 4.43) and OR = 3.02 (95% CI = 1.88 – 4.86].

Table 2 *(Continued)*

Author and year of publication	Locality or region	Exposure	Population group	Health outcome	Type of study, year and analysis	Health outcome results
Relationship between exposure to volcanic activity and respiratory outcomes						
Amaral and Rodrigues, 2007[88]	S. Jorge (Furnas) and Santa Maria, Azores islands	No parameters were measured (exposure to SO_2 and H_2S was inferred)	Clinical records of children and adults registered at each healthcare centre of each region: Furnas (high volcanic activity) and Santa Maria (without volcanic activity)	Incident chronic bronchitis stratifed by age groups	Restrospective (1991-2001); analysis using relative risk estimates and Chi-square tests	The estimated age-standardised incidence rates for chronic bronchitis were higher in Furnas (224.8 for males and 196.7 for females) than in Santa Maria (56.3 for males and 18.3 for females), for both sexes. Living in Furnas was associated with significant risk ratios of chronic bronchitis in relation to living in Santa Maria [RR males=3.99 (95% CI = 2.98-5.35); RR females =10.74 (95% CI = 6.55 – 17.34)], for both sexes.
Linhares et al, 2015[89]	Ponta Delgada and Ribeira Quente, Azores islands	Soil CO_2 flux	Children and adults living in Ribeira Quente (high volcanic activity as active fumarolic fields and degassing soils – hydrothermal area) and Ponta Delgada (no volcanic activity)	Prevalence of COPD and restrictive defects (questionnaire-and spirometry-based)	Cross-sectional (2013); analysis using Mann-Whitney U test, Pearson Chi-square test, adjusted binary logistic regression model; odds ratios adjusted for age, gender, tafigue, astma and smoking	The hydrothermal area in comparison with the non-hydrothermal are showed significant differences: (a) higher prevalence of restrictions (10.2% versus 3.0%; P = 0.001); (b) higher prevalence of COPD (33.6% versus 11.9%; p<0.001); (c) higher prevalence of more severe obstructions (mild, 15.7 versus 4.4, moderate, 6.8 versus 2.2, and severe, 4.7 versus 0, respectively). (d) higher OR for restrictive defects and COPD - 4.4 (95% CI 1.78–10.69) and 3.2 (95% CI 1.82–5.58), respectively.

well as wheezing symptoms, use of rescue medication (bronchodilators) and emergency department visits in the previous 6 months were used as clinical outcomes. A generalized estimating equation (GEE) approach with an exchangeable working correlation showed that exposure to PM_{10}, NO_2, benzene, toluene and ethylbenzene was associated with a decrease in FEV_1 and an increase in ΔFEV_1, (change in FEV_1 15 minutes after inhalation of 200 μg of salbutamol) while increased exposure to NO_2 and benzene was also associated with a decrease of FEV_1/FVC and $FEF_{25-75\%}$, the same was found with ethylbenzene for the latter. Acidity of EBC was associated with increased exposure to PM_{10}, NO_2, benzene and ethylbenzene. Ethylbenzene and toluene were the only pollutants with a significant positive association with FeNO and with symptoms in the previous months, respectively.

Another study performed in the city of Setúbal assessed the association between the intensity of asthma symptoms in adult patients seen at an outpatient clinic and the variation of PM_{10}, O_3, NO_2, SO_2, and CO levels in the city.[84] Patients were instructed to record the intensity of their respiratory symptoms daily, in March and April 2018, and such symptom scores were added together to obtain a daily score. Daily levels of pollutants were obtained from the website of the Portuguese Environment Agency (APA). Data were analysed using a temporal causal model (autoregressive time series models based on the concept of Granger causality). Detected daily air pollutant levels were below internationally regulated values for background / traffic-related components– 26.85 / 35.11 $\mu g/m^3$ for NO_2, 232.13 / 255.80 $\mu g/m^3$ for CO, and 21.63 / 19.73 $\mu g/m^3$ for PM_{10}– indicating low level of air pollution. O_3 was significantly associated with asthma symptoms, particularly with a 5-day lag, whereas PM_{10}, CO and NO_2 also had a significant but less robust impact, with a 4-5 daylag.

Three related studies on rural pollution were performed in three places in northern Portugal, aiming to compare the prevalence of childhood asthma between two rural areas with high O_3 concentrations (Torre de Moncorvo and Mogadouro), and an area with low O_3 concentrations (Espiunca), and to determine potential risk.[85–87] The presence of asthma was determined by self-report using the ISAAC questionnaire and a subgroup of children with positive questionnaires was further studied by spirometry. Logistic regression models were used to calculate odds ratios. Globally, this project showed that children living in the exposed areas had a 3-fold higher risk of having asthma than those living in the unexposed area, a difference which the authors attributed to O_3 pollution.

The association between chronic exposure to indirect volcanic (namely hydrothermal) activity and respiratory diseases was investigated in two studies carried out in the Azores islands.[88,89] In one of the studies,[88] incidence rates of chronic bronchitis were much higher in the volcanically active (risk attributed to H_2S and SO_2, although no measurements of these gases were carried out) area for both sexes, especially in the younger groups. In addition, the risk of chronic bronchitis for the population of the active area was significant in relation to those living in inactive areas (males RR = 3.99; females RR = 10.74). In the other study,[89] the prevalence of restrictive and obstructive respiratory morbidities in the study group was significantly higher than in the reference group. Further, the prevalence of more severe bronchial obstructions was higher in the study group. Multivariable analyses showed that exposure to volcanogenic pollution significantly predicted the presence of spirometric restrictive and obstructive patterns, and worsening of COPD.

Overall, epidemiological analytical studies carried out in Portugal have shown that chronic exposure to outdoor air pollution (namely $PM_{2.5}$, PM_{10}, O_3, NO_2) may be associated with a higher prevalence of asthma, higher prevalence of symptoms and/or changes in respiratory function. Furthermore, this may occur even at low levels of pollution. Further studies are needed, particularly involving cohorts and with longitudinal monitoring data.

(b) Routine statistics studies

Most studies on the relationship between outdoor air pollution and respiratory diseases performed in Portugal have been based on statistical modelling of data collected from different databases. "All respiratory causes", asthma and/or COPD were the most studied respiratory problems. In addition, parameters under study have included ER admissions due to disease exacerbations and these were analysed in relation to different time lags regarding increases in air pollutant levels.

There are twelve key studies in Portugal that examined the relationship between outdoor air pollutant levels and ER admissions for various respiratory causes. Most were carried out in large, industrial cities such as Lisbon (n=6) and Porto (n=2), and three were multicenter. These studies are summarized in Table 3.

Regarding outdoor air pollutants that were assessed and incorporated into analysis, PM_{10} (studied in isolation in 1 report), O_3 (analysed in isolation in 1 study), SO_2 and NO_2 were the most frequently studied, while NO was the least frequently assessed pollutant. Most studies analysed various pollutants (PM_{10}, SO_2, NO_2, CO, O_3), with data most frequently obtained from local stations belonging to APA and made available daily at the QualAR online database (https://qualar.apambiente.pt/). Various meteorological factors (e.g., temperature, rain, humidity, wind) included either as main environmental determinants or as covariates in analytical models of outdoor air pollutants have also been analysed.

ER admissions or hospitalizations, as well as mortality due to exacerbations of asthma, "all respiratory causes", and COPD were the most frequently studied respiratory outcomes. Of these, asthma was the most commonly studied (single focus in two studies), and COPD the least frequently studied, with asthma, COPD and "all respiratory causes" being simultaneously analysed only in three studies. Most hospital admission data were obtained from the Central Administration of the Health Service (ACSS), with mortality data being retrieved from the National Institute of Statistics. Patient records mostly included adults and children, with two studies focused only on children.[93,94]

The methods used in analysing the association between exposure to air pollutants and clinical outcomes varied significantly across studies but most frequently involved various statistical models such as General Additive Poisson Regression Models (GAM-type), Quasi-Poisson GAM combined with distributed lag non-linear model (DLNM), Ordinary Least Squares Linear Regression, and Cross-correlation method models. Two studies from the same group used Principal Component Analysis.[97,98] Most models adjusted the effects of pollutants by incorporating meteorological and other factors (e.g., seasonality, age ranges, etc).

Globally, results have shown that PM_{10}[91–97,99,100] and SO_2[90–92,97,99,100] were most frequently positively associated with respiratory disease-related outcomes (however, PM_{10} levels were inversely correlated with hospital admissions for COPD, in one study[99]). With a slightly lower frequency, $PM_{2.5}$,[92,93,96,97,101] CO,[90,92,95,97,98,100] and NO_2[91,92,95,97,100,102] have also been shown to be positively correlated with respiratory disease outcomes. O_3 was a special situation since it showed positive correlations with respiratory outcomes in four studies: with all respiratory causes, asthma, and COPD,[91] acute upper respiratory infections (AURI) and chronic lower respiratory diseases (CLRD),[95] and COPD and "allied conditions",[98] and respiratory mortality in those > 65 years-old, as well as ER visits in those < 14 years-old and those > 65 years-old[100]; however, in contrast, it showed negative correlations in two studies: with asthma[97] and with all respiratory causes.[101]

The concern about forest fires is growing as not only do they impact on respiratory health, the incidence is on the rise due to climate change. One study examined the ambient levels of PM_{10} and $PM_{2.5}$ associated with large fires in 2017 in the centre region of Portugal and the incidence of asthma symptoms in asthmatic children.[103] Data were collected daily at five local rural monitoring stations belonging to the APA network. The PM_{10} and $PM_{2.5}$ concentrations increased during the fires, with daily concentrations exceeding the European and Portuguese guidelines for various days in 2017 (up to 704 $\mu g/m^3$ for PM_{10} and 46 $\mu g/m^3$ for $PM_{2.5}$, respectively). An estimated incidence of 3524 episodes of asthma symptoms per 100,000 individuals at risk was attributable to exposure to these fires. This study quantified the effect of forest fires on the incidence of asthma symptoms in children living at affected areas and suggested that rural stations should measure pollutants associated with respiratory health.

Pollution reduction benefits

Reducing air pollution may have various respiratory health benefits.[122] Some studies used an Impact Pathway Approach to estimate the potential health impacts and benefits (or avoided external costs) from improvements in air quality in Portugal.[104,105] Various emission reduction scenarios, based on individual and combined abatement measures (e.g., replacing 10% of light vehicles below Euro 3 with hybrid vehicles, or implementing reduction technologies for PM_{10} from industrial combustion and production processes), were tested for the main activity sectors (traffic, residential and industrial combustion and production processes) of a Portuguese urban area (Porto Metropolitan Area). Implementation of all measures would result in a significant reduction in PM_{10} and SO_2 emissions, thereby improving air quality and contributing to saving almost 9 million €/year, an amount which includes direct costs (health care and non-health care costs associated with treatment and caring) and indirect costs

Table 3 Air pollution effects in Portugal: 2) Main studies using routine statistics to analyse the effects of external pollution on respiratory health in Portugal.

Study	Study area	Exposure	Population group	Health outcome	Type of study, year and analysis	Health outcome results
Relationship between exposure to outdoor air pollutants and admissions to hospitals for acute respiratory diseases						
Alves et al, 2010[90]	Lisbon	PM_{10}, SO_2, CO, O_3, NO, NO_2	Clinical records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to 12 hospitals because of all respiratory causes, asthma, and COPD; also cardiovascular causes (data from IGIF)	Daily counts of hospital admissions due to all respiratory causes, asthma, and COPD (also cardiocirculatory causes)	Time-series (1999-2004); analysis using General Additive Poisson Regression Models (GAM-type) with linear and quadratic tendency terms to control for confounding temperature, humidity and seasonal effects; 1, 2 and 3-day lags	Significant association (1-day lagged) between levels of SO_2 and increased childhood ER admissions for all respiratory causes, with an increased risk (RR = 1.139) for an increase of 10 $\mu g/m^3$ of SO_2 daily concentrations. CO was also significantly associated, with a 2-day lag, with ER admissions for all respiratory causes in patients > 64 years-old
Freitas et al, 2010[91]	Lisbon	PM_{10}, SO_2, CO, O_3, NO, NO_2, temperature, humidity	Clinical records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to 12 hospitals due to respiratory causes; also cardiovascular causes (data from IGIF)	Daily counts of hospital admissions due to all respiratory causes, asthma and COPD (also cardiocirculatory causes)	Time-series (1999-2004); analysis using t tests, F tests, parametric (Pearson) correlations, with a time lag of zero	Multiple, significant, correlations between temperature, humidity, PM_{10}, SO_2, O_3 and NO_2 and hospital admissions for all respiratory diseases, asthma and COPD.
Cruz et al, 2015[92]	Lisbon	$PM_{2.5}$, PM_{10}, SO_2, CO, O_3, NO, NO_2	Clinical records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to 13 hospitals due to respiratory causes; also cardiovascular causes (data from ACSS)	Daily counts of hospital admissions due to all respiratory causes, and asthma (and due to all circulatory and various cardiovascular diseases)	Time series (2006-2008); analysis using Ordinary Least Squares Linear Regression	Significant positive associations between: (a) CO, NO, NO_2, SO_2, PM_{10} and $PM_{2.5}$ and respiratory diseases for ages 0-14 years (up to 1.9 % hospital admissions increase with 10 $\mu g/m^3$ pollutant increase); and (b) NO, NO_2 and SO_2 and respiratory diseases for ages above 64 years (1.3% hospital admissions increase with 10 $\mu g/m^3$ CO increase).
Moreira et al, 2008[93]	Lisbon	$PM_{2.5}$, PM_{10}	Children (0-14 years-old) admitted to a hospital ER as well as being seen at outpatient clinic, due to respiratory conditions (direct data from the hospital)	Daily counts of hospital admissions due to respiratory causes: acute infection, chronic infection, rhinits, influenza, pneumonia, chronic bronchitis, emphysema, COPD, asthma, bronchiectasis and other	Time series; (January-December 2004); analysis using models of multiple linear regression; 3- and 5-day lags	Significant association between the zone where children with respiratory problems were seen at a healthcare unit and the city areas with the highest PM levels.
Rodrigues et al, 2021[94]	Lisbon	PM_{10}, temperature, relative humidity	Records of children (age groups: 0-4, 5-9 and 10-14 years, and disaggregated by sex) admitted to Hospitals of the Lisbon Metropolitan area, due to asthma (data from ACSS)	Daily counts of hospital admissions due to asthma	Time series (2009-2015); analysis using a Quasi_Poisson generalized additive model combined with a distributed lag non-linear model (DLNM); different lags (up to 3 month-lag)	An increased risk of asthma-related hospital admissions was observed with PM_{10} with a 2% (RR = 1.02; CI 95% 1.01–1.03) in the general sample, and in male children; also in age group 5-9 years, with an increased risk at lag 0 of RR =1.03; 95% CI (1.01–1.05). Temperature and relative humidity also had significant effects.
Franco et al, 2020[95]	Lisbon Metropolitan área (Lisbon, Odivelas, Amadora)	PM_{10}, NO_2, NO, CO, O_3	Records of patients (children and adults; age groups 0-14, 15-64, > 64 years old) admitted to Hospitals, due to respiratory and circulatory causes (data fromACSS)	Number of daily hospital admissions due to all respiratory diseases (ARD), chronic lower respiratory diseases (CLRD), or acute upper respiratory infections (AURI)	Time series (January-December 2015); analysis using various models and time lags Ordinary Least Squares linear regression; best models selected by statistical significance	Association was seen between air pollution and AURI (2.93% increased ER admissions per 10$\mu g/m^3$ increase in air pollution); significant between ARD and air pollution (2.2% increased ER admissions per 10$\mu g/m^3$ increase in air pollution). CO was the pollutant most frequently associated with ER admissions due to ARD, AURI and CLRD. O_3 also showed a substantial association in the older age groups, increasing ER admissions due to AURI and CLRD (4.1% and 4.8% per 10$\mu g/m^3$ increase in O_3 levels, respectively).

Table 3 (*Continued*)

Study	Study area	Exposure	Population group	Health outcome	Type of study, year and analysis	Health outcome results
						NO_2 had the largest average effect on ER admissions across all models and age groups (4.4% increase in ER admissions per 10μg/m^3 increase in NO_2), with the strongest associations being with CLRD and AURI. NO and PM_{10} had the fewest associations with ER admissions but PM_{10} still had a significant impact on respiratory diseases (4.52% increase in ER admissions per 10μg/m^3 increase in PM_{10} levels).
Almeida et al, 2014[96]	Setúbal	$PM_{2.5}$, PM_{10}, O_3	Records of patients (children and adults; age groups 0-14, 15-64, $>$ 64 years old) admitted to Setúbal Central Hospital because of circulatory and respiratory causes (data from ACSS)	Daily counts of hospital admissions due to all respiratory causes, and asthma (and circulatory and various cardiovascular diseases and cerebrovascular disease),	Time series (January-December 2009); analysis using various models (DAY, WEEK, O&MA, MA&MA) of Ordinary Least Squares Linear Regression	An increase of 10 μg/m^3 in PM_{10} was associated with a rise of 1.6% in hospital admissions for respiratory causes in individuals $<$ 14 years; an increase of 10 μg/m^3 in PM_{10} was associated with a rise of 0.8 $-$ 0.9% in hospital admissions for respiratory causes in individuals $>$ 64 years; an increase of 10 μg/m^3 in $PM_{2.5}$ was associated with a rise of 0.8-1.1% in hospital admissions for respiratory diseases in individuals $>$ 64 years.
Azevedo et al, 2011 (data from 2005)[97]	Porto	PM_{10}, SO_2, CO, O_3 (collected at 11 stations); $PM_{2.5}$ (collected only at 1 station)	Records of patients (no information on age ranges) admitted to 4 major Hospitals due to asthma / bronchitis (direct data from the hospitals)	Number of daily hospital admissions due to asthma /, bronchitis	Time series (June-August 2005); analysis using Principal Component Analysis (PCA) and Pearson correlation coefficient; adjustemnt for temperature and wind; 1- and 2-day lags	Pearson correlation showed that: (a) for 1-day lag: only CO and NO had significant, positive correlations with asthma / bronchitis: for CO (Pearson=0.209; p = 0.024); for NO (Pearson=0.234; p = 0.024); O_3 had a significant, negative correlation (Pearson= -0.233; p = 0.024); (b) for 2-day lag; O_3 was also negatively correlated with asthma / bronchitis (Pearson= -0.213; p = 0.041); $PM_{2.5}$ and CO had a significant, positive correlation: for $PM_{2.5}$ (Pearson=0.241; p = 0.02), for CO (Pearson=0.219; p = 0.035). PCA also showed negative association between O_3 and asthma / bronchitis, and positive associations between PM_{10}, $PM_{2.5}$, NO and CO and asthma / bronchitis (in the Winter), and between SO_2 and NO_2 and asthma / bronchitis (in the Summer).
Azevedo et al, 2011[98]	Porto	O_3	Records of patients (no information on age ranges) admitted to 3 major Hospitals due to various circulatory or respiratory causes (direct data from the hospitals)	Number of daily hospital admissions due to COPD, bronchitis, asthma, pneumoconioses and other lung diseaes due to external agents; also due to various cardiocirculatory causes	Time series (June-August 2005); analysis using Principal Component Analysis (PCA) and ANOVA; 0- to 4-day lags	PCA analysis did not show an association between O_3 concentrations (studied with a 4-day lag) and hospital admissions due to respiratory causes. In specific periods results showed that increased incidence of admissions due to COPD and "allied conditions" (including bronchitis and asthma) was associated with exposure to O_3, NO and CO.
Alves et al, 2005[99]	Porto	PM_{10}, SO_2, assessed at 3 different places in the city, with varying influences of industry and traffic	Records of patients (children and adults) admitted to Gaia Hospital, due to COPD exacerbations (direct data from the hospital)	Number of daily emergency admissions (ER) due to COPD	Time series (1 January 31 December), analysis using cross-correlation method models; up to 12-day lags	Positive relation between SO_2 and ER admissions was found using some models, with stronger association for lag 0 than with 1- or 2-day lags. A negative relation between PM_{10} and ER admissions, with stronger association for 1- or 2-day lags.
Nicolau et al, 2010[100]	Matosinhos, Maia, Valongo and Lisbon (GeoFASES	PM_{10}, CO, O_3, NO_2, SO_2	Records of patients admitted to Hospitals due to all causes, respiratory causes and circulatory causes (data ACSS);	Daily mortality counts (2000-2004) and ER visits (2000-2007) due to respiratory causes	Time series (2000-2004); analysis using Poisson regressions developed from Generalized Additive Models (final model	Only O_3 showed an increased risk (RR = 1.071 for each 10 μg/m^3 increase in O_3) of respiratory mortality and only in people $\geq$ 65 years old. PM_{10}, NO_2, SO_2 and CO showed a significantly

Table 3 (*Continued*)

Study	Study area	Exposure	Population group	Health outcome	Type of study, year and analysis	Health outcome results
	multicentre project)		mortality data obtained from the National Institute of Statistics; data from total sample of patients and also stratified into ≤14 years old and ≥ 65 years old		used only single pollutants) and Pearson correlation; 0- to 8-day lags	increased risk of ER visits (RR between 1.001 and 1.089), with different lags and mostly in the total sample, in ≤ 14 yrs old and in ≥65 yrs old).
Martins et al, 2021[101]	58 monitoring stations in mainland Portugal (data on QualAr website)	$PM_{2.5}$, PM_{10}, NO_2, CO, O_3, SO_2	Records of patients (children and adults) admitted to Hospitals due to respiratory causes (data from ACSS)	Daily hospital admissions due to respiratory causes	Multicentre time series (2005-2017); statistical modelling analysis using the INGARCH approach incorporating relevant covariates; cluster analysis; 1- to 7-day lags	PM and NO covariates had, in general, positive coefficients indicating that an increase in their concentrations is associated with an increase in hospital admissions. In contrast, lower levels of O_3 were associated with increased hospital admissions.
Ayres-Sampaio et al, 2014[102]	Various locations in Portugal (stratified into % urban coverage: low, moderate, high)	PM_{10}, NO_2, temperature, relative humidity, Normalized Difference Vegetation Index (NDVI)	Records of patients (no information is given on age ranges) admitted to Hospital, due to asthma exacerbations (data fromACSS)	Number of daily hospital admissions due to asthma; asthma admission rates / 1000 inhabitants in each municipality	Multicentre time series (2003-2008); analysis using linear regression analysis	In the most urban group, high temperatures, low NDVI, and high NO_2 levels had consistent relationships with asthma in all seasons (Pearson correlation coefficients ranging from 0.351 - 0.600; 0.376 - 0.498; and 0.405 - 0.513, respectively). No significant effect was seen with PM_{10}.
Relationship between exposure to forest fire-related outdoor air pollutants and admissions to hospitals due to asthma						
Oliveira et al, 2020[103]	5 rural locations	$PM_{2.5}$ (levels could only be determined in 2 locations), PM_{10}	Children living in rural area	Estimation of incident asthma symptoms in children / 100,000 individuals at risk	Statistical modelling using data from 2017 forest fires; analysis using WHO AIRQ+ model application	PM_{10} and $PM_{2.5}$ levels were increased during large fires, with daily concentrations exceeding the European/national guidelines in various periods of 2017 (up to 704 $\mu g/m^3$ for PM_{10} and 46 $\mu g/m^3$ for $PM_{2.5}$), respectively. Potential incidence of 3524 cases of asthma symptoms / 100,000 children at risk, during such periods. For PM_{10}, RR (median; 95% CI)= 1.03 (1.01-1.05), with attributable proportion of cases varying between 1.99 and 3.62%, depending on locality.
Studies addressing health benefits of outdoor air pollution reduction						
Silveira et al, 2016[104]	Porto	PM_{10} (MAPLIA project)	Children and adults	Parameters used to calculate benefits: asthma in children, chronic bronchitis in children and adults, and related relative risk, baseline annual rate and health costs	Impact pathway approach involving 4 abatement measures; analysis using 7 abatement scenarios; health impacts analysed using Equation (MAPLIA system)	Implementation of all measures would result in a reduction in PM_{10} emissions by almost 8%, improving air quality by about 1% and contributing to a benefit of 8.8 million €/year for the entire study domain, due to reduction of health-related costs.
Miranda et al, 2016[105]	Porto	PM_{10}, NO_x (MAPLIA project)	Children and adults	Some parameters used to calculate benefits: (a) PM_{10}: short-term (asthma in 5-9 yr-old children; respiratory hospital admissions, all ages); long-term (incidence chronic bronchitis children and adults); (b) NO_2: short-term (respiratory hospital admissions, all ages);	Impact pathway approach involving 4 abatement measures; analysis using 15 scenarios; health impacts analysed using MAPLIA system; comparison of implementation costs and avoided external costs (based on health benefits)	Implementation of all measures would result in a reduction of 4.5% at most for PM_{10} and NO_2 concentrations. This corresponds to reductions of up to 2.8 $\mu g/m^3$ for PM_{10} and up to 1.2 $\mu g/m^3$ for NO_2, improving air quality and contributing to a benefit of 8.9 million €/year for the entire study domain, due to reduction of health-related costs.

(associated with loss of productivity due to morbidity as well as loss of production due to morbidity or mortality) as well as intangible costs (non-market costs associated with pain and suffering).[104]

Discussion

Perspective from some GARD countries

Although there is evidence showing the negative effects of air pollution on the respiratory system,[123,124] such evidence is limited in various GARD countries, due to the lack of epidemiological studies. Nevertheless, current information shows that the level of exposure to pollutants in some GARD countries is higher than the current level in industrial regions from high-income countries and has exceeded the standards recommended by the WHO. China and India have the highest concentration of air pollutants,[123,125] and in other countries, air pollution does not seem to have reached such high levels.

Given the many gaps in our knowledge about the dominant ambient air pollution in some GARD countries, we have a limited knowledge about the real impact of such pollution on respiratory diseases and mortality of the population in these countries. However, if one assumes that poverty increases the vulnerability resulting from ambient air pollution (and vice versa), then air pollution should be specifically damaging for the poorest GARD countries.

Furthermore, the methods of assessment of results with regard to air pollution exposure in some GARD countries are very discrepant, and studies are generally cross-sectional and therefore have a weaker standard compared to methods adopted by others. Exposures data were often measured by questionnaires without representative individual measurements nor analysed using GIS-based models. Therefore, with these design limitations, the current general evidence generated was not robust enough to estimate the real impact of ambient air pollution on respiratory health in the populations in these GARD countries. Unfortunately, currently there was a lack of studies with reliable statistics on mortality at regional or national scales in some GARD countries.

The WHO estimate of 91%[21] of the world's population living in places where air quality levels exceed the WHO guideline limits, is concerning. This calls for urgent need for building public understanding of associations of air pollution and health. Thus, the following recommendations are proposed for a better and more precise assessment of the impact of air pollution on the respiratory health of populations in some GARD countries:

(1) In order to assess a sound relationship between air pollution and respiratory diseases or respiratory disabilities in locations where research is carried out, 5–10-year studies should be designed and performed with large samples;
(2) More than one year of follow-up is required to estimate the incidence of disease based on pulmonary function testings;
(3) The time-points of such studies and the number of participants should be large enough to ensure the ability to study effects of heterogeneous environmental conditions and health backgrounds;
(4) There is a need to improve study quality and respiratory health of individuals living in the studied sites: it implies socio political support and allocating more budget and specialists for conducting wide cohort studies, especially in countries where air pollution and respiratory dysfunction are more severe. Such studies will have essential social advantages in terms of protecting public health.
(5) Further attempts are needed to promote efficiency of preventive measures and empowerment of citizens in some GARD countries.

Portuguese perspective

Although air pollution levels are not among the highest in Europe, the most urbanized cities in Portugal, namely Lisbon and Porto, have significant elevations in the main pollutants. Exposure to these pollutants is associated with a higher risk of respiratory disease. Furthermore, with climate change, the effects of air pollution are likely to worsen. Since air pollution exerts a substantial health and economic strain on societies, it is imperative that a broad and integrated approach is implemented, targetting reducing emissions of air pollutants, as well as reducing exposure by other means. Thus, policy makers should consider reducing air pollutants in order to achieve better air quality management and reduce pollution-worsened respiratory diseases such as asthma and COPD. The implementation of the National Emission Ceilings Directive is important, since it requires the definition of emission reduction measures in an Air Pollution Control Program. The FUTURAR[126] research project has addressed this topic, following an integrated assessment modelling approach, to estimate health impacts, costs and benefits associated with air quality in the future,[127,128] and one of its conclusions is that the expected reduction of PM_{10} and NO_2 levels in the future will reduce the number of premature deaths.

Conclusions

Worldwide, ambient air pollution increasingly adversely impacts respiratory health at all ages, and has amounted to substantial high economic and societal costs. This situation may be further compounded by climate change. It is paramount to establish strong research teams to conduct further interdisciplinary studies on air pollution and health effects (such as effects on the respiratory system health).

An integrated approach must involve governments (in Portugal, namely the National Programme against Respiratory Diseases (PNDR), of the Directorate General of Health, Portuguese Ministry of Health, which hosts GARD-Portugal, but also other governmental institutions), academia, health professionals and health institutions, scientific societies, patient associations and the community at large. Such an approach not only will garner a robust commitment, establish strong advocacy and clear objectives, and raise greater awareness, it will also support a strategy with adequate measures to be implemented to achieve better air quality and reduce the burden of CRDs.

Conflict of interest

None

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