Current Environmental Health Reports (2018) 5:70–76
https://doi.org/10.1007/s40572-018-0178-z

SUSCEPTIBILITY FACTORS IN ENVIRONMENTAL HEALTH (B RITZ AND Z LIEW, SECTION EDITORS)

COPD Patients as Vulnerable Subpopulation for Exposure to Ambient Air Pollution

Joachim Heinrich[1,2,3] · Tamara Schikowski[4]

Published online: 31 January 2018

Abstract

Purpose of Review The prevalence of chronic obstructive pulmonary disease (COPD) is increasing worldwide with no known cure and an increasing number of triggers that exacerbate symptoms and speed up progression. This review aims to summarize the evidence for COPD patients being more vulnerable to air pollution exposure assessed as acute effects.

Recent Findings Several recent systematic reviews show consistently increased risks for COPD mortality and COPD hospital admission, ranging between 2 and 3% with increasing $PM_{2.5}$ or PM_{10}. Similar adverse impacts were shown for NO_2. Also, adverse health effects among COPD patients were also found for other gaseous pollutants such as ozone and SO_2; most of these studies could not be included in the meta-analysis we reviewed. Data from ten panel studies of COPD patients reported a small but statistically significant decline of FEV1 [− 3.38 mL (95% CI − 6.39 to − 0.37)] per increment of 10 μg/m^3 PM_{10}, supporting an impact on respiratory health with increasing PM_{10} exposure.

Summary The combined information from systematic reviews and more recent findings lead us to conclude that COPD patients are more vulnerable to ambient air pollution than healthier people.

Keywords COPD · COPD exacerbation · Ambient air pollution · $PM_{2.5}$ · NO_2 · SO_2 · CO · Ozone · Vulnerability

This article is part of the Topical Collection on *Susceptibility Factors in Environmental Health*

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40572-018-0178-z) contains supplementary material, which is available to authorized users.

✉ Joachim Heinrich

[1] Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine, Comprehensive Pneumology Centre Munich, German Centre for Lung Research. (DZL), University Hospital Munich of Ludwig Maximillians University Munich, Munich, Germany

[2] Institute of Epidemiology I, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg, Germany

[3] Allergy and Lung Health Unit, Melbourne School of Population Health, University of Melbourne, Melbourne, Australia

[4] Leibniz Institute for Environmental Medicine, Düsseldorf, Germany

Introduction

Ambient air pollution (AP) is ubiquitous and adversely affects a large proportion of the world population [1]. The early study of chronic obstructive pulmonary disease (COPD) during the London fog episode in 1952, particularly the adverse effects seen with short-term exposure, stimulated a tremendous amount of epidemiological and experimental research investigating adverse health effects of AP that started with respiratory health indicators but extended to systemic effects and even cancer [2].

COPD is defined as a partly reversible but persistently limited airflow with chronic inflammation of the lung [3, 4]. COPD development can start early in life [5, 6] and progresses slowly until the lung decompensates mostly at advanced ages. The prevalence of COPD in adults older than 40 years of age worldwide ranges between 5 and 19% [7, 8]. Moreover, COPD prevalence does not discriminate between high-income and low-income countries [9]. It is expected that its prevalence will only increase over the next decades [10, 11],

due to an increasing number of smokers, particularly in developing countries, and worldwide demographic changes that include a higher proportion of advanced age populations providing long enough latency for this disease to occur. Prognostications from 10 years ago ranked COPD as fifth among the diseases with the highest societal burden by the year 2020 [12]. Already, COPD is the third leading cause of death worldwide [13]. COPD is not easily treated and can cause a substantial economic burden for a society [14]. Currently, the economic and health burdens are underestimated, due to the high rate of co-morbidities with asthma, ischemic heart disease, stroke, pneumonia, and/or lung cancer [15]. Tobacco smoking is the main risk factor for COPD, and its role has been well characterized in disease development, progression, and exacerbation of COPD [16]. However, it is not the only risk factor that should be considered. Not only a less investigated, but also important risk factor is exposure to AP (both ambient air pollutants and indoor AP). The World Health Organization (WHO) estimated that ambient AP was responsible for 3.7 million deaths worldwide in 2012, with 14% of these deaths due to COPD or lower respiratory infections (World Health Organization; Ambient (outdoor) air quality and health; World Health Organization; Geneva: 2014. Fact sheet no. 313). Several recent reviews and original articles conclude that ambient AP exposure is also a notable risk factor for COPD [17•, 18••, 19, 20••, 21–23], but the evidence supporting this notion is weak. This review will use several recent systematic reviews and original research papers that focused on the exacerbation and progression of COPD in relation to exposure to ambient air pollutants, such as nitrogen dioxide (NO_2), ozone (O_3), and particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$) and less than 10 μm (PM_{10}). The key questions this review article is trying to answer are whether COPD patients are more vulnerable or susceptible to ambient air pollutants and if so, why.

Current Sources and Measures of AP

Ambient AP is a dynamic and complex mixture of anthropogenic (man-made) and natural source-derived pollutants found in varying levels worldwide; the most commonly measured ones in urban areas are particulate matter (PM), ozone (O_3), sulfur dioxide (SO_2), nitrogen oxides (NO_x), and carbon monoxide (CO). Depending on size, PM is commonly divided into three classifications: coarse particles with diameters of 2.5 to 10 μm ($PM_{2.5–10}$), fine particles with diameters less than 2.5 μm ($PM_{2.5}$), and ultrafine particles with diameters less than 0.1 μm (UF). Industrial, agricultural, or domestic heating and traffic-related sources are the main contributors to PM. Traffic-related sources of PM are thought to be responsible for approximately 20% of AP-related mortality in Germany, the UK, and the USA [24].

Coarse particles are often caused by disturbances that disperse crustal materials (dust) and are a problem in the Middle East and other desert areas as constituents of dust storms. Throughout the world, the generation of residential and commercial energy through combustion processes has been linked to premature mortality. This is a large problem in Asia and Africa, where coal is widely used for heating and cooking and produces high levels of fine PM [24]. A recent review of global premature mortality due to outdoor AP found that fine PM ($PM_{2.5}$) is estimated to cause 3.3 million deaths per year worldwide [24].

The potency of PMs in causing adverse health impacts is dependent, in part, on their ability to deposit in the airways and the particle surface characteristics [25].

With the growth of urban centers and the advent of global climate change, it has been estimated that ground-level ozone (ozone smog) will become an increasingly greater health hazard. Ozone smog forms when nitrogen oxides and volatile organic compounds from vehicle, power plants, and other sources mix with sunlight and heat; specifically, increasing temperatures contribute strongly to ozone smog formation. Other critical pollutants, such as SO_2, NO_x, and CO, are also produced by fossil fuel combustion from automobiles and power plants and will continue to contribute to AP in large urban areas, especially in densely populated cities like those in Asia and Africa [24, 26].

During the past five or six decades, a vast amount of studies documented the adverse health effects of AP affecting mortality, health-related quality of life, and a broad spectrum of diseases such as cardiovascular diseases, respiratory health, and cancer [27, 28].

Epidemiological Designs to Study AP Exposure and COPD

There are two major epidemiological approaches that are being used to explore associations between ambient AP exposure and COPD: the vulnerability approach (Fig. 1) and the onset of COPD approach. While the vulnerability approach compares adverse health events between COPD patients and the general population, the COPD onset approach relies solely on studies of general populations. This review is referring to results that employed the vulnerability approach. Nevertheless, a brief summary of studies investigating the onset of COPD will add to the understanding of how and why both approaches are to be considered separately.

AP and the Onset of COPD

Briefly, the onset of COPD approach includes whole populations that are followed up and randomly selected subjects from the general population, who are free of a COPD diagnosis.

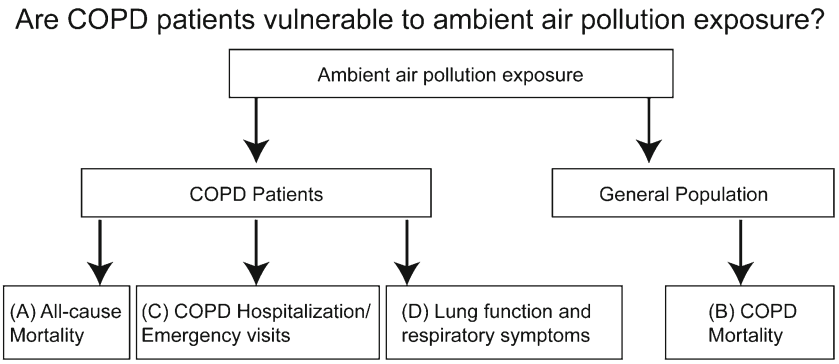

Fig. 1 Epidemiological study approaches to investigate vulnerability of COPD patients to ambient air pollution

These subjects are then being followed over an extended period of time. A recent systematic review included eight morbidity and six mortality studies, which were very heterogeneous with regard to several methodological aspects such as exposure assessment, definition of COPD cases, and study design [21]. The authors concluded that the evidence for chronic effects of AP on prevalence and incidence of COPD was suggestive, but not conclusive. Additionally, an editorial accompanying the review supported this notion [29]. A more recent combined analysis of several European cohorts, which used an advanced exposure assessment method—land use regression (LUR) models developed in the ESCAPE project—confirmed the vague statement of previous systematic reviews [22]. However, a systematic review and meta-analysis of recent time series studies from China showed statistically significant associations between ambient AP exposure of PM_{10}, SO_2, and NO_2 and COPD mortality for same-day exposure (lag0) and the exposure 3 days before (lag3) [20••].

Methodologically, the COPD onset approach is quite different from studying the increased vulnerability of those suffering from COPD.

Are COPD Patients Vulnerable to Ambient AP?

The potential vulnerability of COPD patients to AP can be assessed by documenting over extended periods

(A) All-cause mortality
(B) COPD mortality
(C) COPD hospitalization and emergency visits
(D) Lung function and respiratory symptoms (Fig. 1).

This review will summarize the current state of the science for each of the four progressive health outcomes in COPD. We will use the most recent systematic meta-analysis or general reviews and will add newer results after the last review was published. The key findings of selected studies are shown in Supplemental Table 1.

All-Cause Mortality

A large study in Rome [30] followed 145,681 COPD patients age 35+ years for 4 years. The association between short term exposure to daily AP and daily mortality was modeled in both COPD subjects and everyone else in the city over 35 years of age without any COPD diagnosis (1,710,557 subjects). COPD patients showed higher mortality rates from $PM_{2.5}$, PM_{10}, and NO_2 exposure compared with subjects without COPD. Especially strong was the difference for PM_{10} which had a five times larger effect estimate for total mortality. Additionally, effect estimates were three to seven times higher in the COPD subjects, for respiratory causes of death depending on which air pollutant and lag was being assessed.

A similar time series study of COPD subjects in Barcelona also reported increased all-cause mortality in relation to NO_2 [31]. A further study with COPD patients over 35 years in Barcelona showed increased mortality risk of 1.11 (95CI 1.00–1.24) with increased PM_{10} per IQR, but not for ozone and CO [32].

COPD Mortality

Several systematic reviews assessed the role of short-term exposure to ambient AP on COPD mortality [17•, 20••, 33, 34]. One study summarized the findings of literature published between 1995 and 2015 [33], another updated this until March 30, 2016 [34], another one until April 15, 2015 [20••], and the last until May 2011 [17•]. We decided to restrict to systematic reviews published during the last 3 years, since these reviews were not only different in the time period they covered, but also in terms of selection criteria and search terms (major ambient AP versus $PM_{2.5}$ only; written in English only papers versus English and Chinese database usage; COPD mortality alone versus a combined category that included both COPD mortality and hospitalizations). The most recent review [33], identified 11 studies addressing COPD mortality; however, it did not include the most recent literature since it stopped its search in 2015. This meta-analyses estimated pooled effects for COPD-related mortality of 1.048 (95% CI 1.019–1.078) for $PM_{2.5}$ based on five studies. The other six

meta-analyses provided summary estimates for NO_2 of 1.03 (95% CI 1.016–1.045). The review with the latest search date (March 30, 2016) identified 12 papers for COPD mortality only and six studies for combined COPD mortality and hospitalization [34]. This review not only relied on English databases, but also included a large Chinese database (CNKI). Overall, there was a significant association between short-term exposure and the risk of COPD exacerbation for all gaseous and particulate pollutants. An increment of 10 μg/m^3 for each pollutant was associated with increased risks for PM_{10} [1.017 (95% CI 1.012–1.022)], $PM_{2.5}$ [1.024 (95% CI 1.005–1.043)], NO_2 [1.045 (95% CI 1.028–1.062], SO_2 [1.006 (95% CI 1.001–1.012)], ozone[(1.028 (95% CI 1.011–1.044)]—whereas the increment for CO was 100 μg/m^3—and CO [1.008 (95% CI 1.004–1.013)]. This review was of particular importance, since it included sensitivity analyses stratified by geographical location and it showed stronger effects for Asian than non-Asian countries.

Another review included publications written only in English before April 15, 2015 and reported increase of COPD mortality of 2.5% (95% CI 1.5–3.5%) and 3.1% (95% CI 1.6–4.6) increased COPD hospitalization per 10 μg/m^3 increase in $PM_{2.5}$ [20••]. An earlier review [17•] found a statistically significant increased risk for COPD admission of 2.4% (95% CI 1.00–3.73%) per 10 μg/m^3 $PM_{2.5}$ but only for subjects older than 65 years and after excluding asthmatics, while the effect estimate for COPD mortality was 2.86% (95% CI − 0.12–5.93%).

The MED-PARTICLE Study investigated the specific cause of death associated with short-term exposure to $PM_{2.5}$ and $PM_{2.5–10}$ in Southern Europe for the period of 2001–2010 [35]. An increased 10 μg/m^3 $PM_{2.5}$ exposure was associated with a 2.53% (95% CI − 0.01–5.14) increase of COPD death, which was higher than any other cause-specific mortality. This was further supported by a positive association of $PM_{2.5}$ per 10 μg/m^3 with COPD as cause of death [0.38% (95% CI 0.23–0.53)] compared to other common causes of death reported in a large nationwide time series analysis of 272 Chinese cities [36]. Most of the effect estimates were given for a fixed increment of 10 μg/m^3, which makes it difficult to compare the effects across different pollutants. Another major problem is related to use COPD mortality as an outcome of interest, because of its variation in the coding of COPD mortality used by original papers and also in systematic reviews. Thus, it makes it difficult to compare the results across regions and papers.

COPD Hospitalization and Emergency Visits

The most recent systematic review on the influence of ambient AP on COPD hospitalization and emergency visits identified 26 papers published between 1995 and 2015 [33]. COPD hospitalization and emergency room visits were affected by an exposure to air pollutants, a 2.5% (95% CI 1.6–3.4%) increase per 10 μg/m^3 of $PM_{2.5}$, a 4.2% (95% CI 2.5–6.0%) increase per 10 μg/m^3 for NO_2, and a 2.1% (95% CI 0.7–3.5%) increase per 10 μg/m^3 for SO_2. Unfortunately, these effect estimates cannot be compared, because the fixed increment of 10 μg/m^3 does not reflect similar toxicities of each air pollutant. Another even larger systematic review identified 59 studies on ambient air pollutants ($PM_{2.5}$, PM_{10}, NO_2, SO_2, CO, O_3) and COPD exacerbations (hospital admission and/or COPD mortality) from English and Chinese databases in studies published before March 30, 2016 [34]. Out of the 59 included studies, the majority (41 studies) were focused on COPD hospital admission while 12 were modeled COPD mortality only and six both. The stratified analysis for COPD hospital admission showed the following effect estimates: 1.0% (95% CI 0.0–1.0%) for $PM_{2.5}$, 2% (95% CI 1–2%) for NO_2, and 0% (95% CI 0–0%) for ozone for an increment of 10 μg/m^3, but 0% (95% CI 0–0%) for CO per increment of 100 μg/m^3. Two additional systematic reviews and meta-analyses focused on short-term exposure effects of $PM_{2.5}$ and COPD hospitalization and mortality [17•, 20••]. Based on a literature search that ended April 15, 2015, 12 studies of COPD hospitalization were included in the meta-analysis. A 10-μg/m^3 increase in daily $PM_{2.5}$ (lag days 0–7) was associated with a 3.1% (95% CI 1.6–4.6%) increase in COPD hospitalization [20••]. The summary estimates for $PM_{2.5}$ exposure and COPD hospitalization based on studies published before May 2011 [17•] however were smaller [0.96% (95% CI − 0.63–2.58%)] and not statistically significant. However, a sensitivity analysis restricted to subjects ages 65+ years without asthma did find a statistical significant association with $PM_{2.5}$ [2.36% (95% CI 1.0–3.73%)] in the systematic review [17•].

A further systematic review only including East Asian studies also found increased COPD hospitalization with PM_{10}, SO_2, and O_3 exposures [37].

Reviews included different regions of the world, several air pollutants, and employed various selected lags ranging from same-day exposure (lag 0) to 7-day exposure preceding outcome measurements. Nevertheless, all systematic reviews consistently found increasing COPD hospitalization/emergency visits with increasing $PM_{2.5}$ and PM_{10} exposures, but only in the most recent reviews, effect estimates were found to be statistically significant. Several reasons might contribute to the increasing body of evidence for the positive association between ambient air pollution exposure and hospital admission for COPD: more studies and larger sample size as well as more studies from Asia, which showed higher effect estimates compared to some European studies.

Lung Function and Respiratory Symptoms

A systematic review identified 25 panel studies published between 1993 and February 1, 2016 [18••]. Of these 17 studies

included COPD patients only, the others also followed asthmatics, patients with ischemic heart disease, and apparently healthy subjects; these studies were conducted mainly in Europe, North America, and East Asia. Meta-analysis of ten studies with lung function tests showed a small but statistically significant decline of forced expiratory volume in 1 s (FEV1) (− 3.38 mL, 95% CI − 6.39 to − 0.37) and peak expiratory flow rate (PEF) (− 0.61 L/min, − 1.20 to − 0.01) per 10 μg/m^3 increment of PM_{10} followed the exposure after a maximum of 2 days. Respiratory symptoms such as breathing problems, shortness of breath, or respiratory symptoms score increased with increasing exposure to PM_{10} in most of the studies. A summary estimate for these eight studies, which reported effects on respiratory symptoms, could not be calculated because of the heterogeneity of the outcome definition and scale of symptom scores. The results for effect of NO_2 on lung function and respiratory symptoms were mixed and more heterogeneous than the findings for PM_{10}. Unfortunately, this review did not compare AP effects in COPD patients with those in other panel participants such as cardiac compromised patients or healthy subjects. Not included in this systematic review was a panel study that monitored 23 stable COPD patients in Beijing for a 9-month period and measured extremely high AP levels monitored at one single site with an interquartile range (IQR) of 76.5 m^3 for $PM_{2.5}$, 75.0 μg/m^3 for PM_{10}, and 45.7 μg/m3 for SO_2. They found a statistically significant incremental change in IQR for each pollutant and an increase of respiratory symptoms such as sore throat, cough, sputum production, wheeze, and dyspnea [38]. Furthermore, there was a statistically significant increase in exhaled nitric oxide (FeNO) and exhaled hydrogen sulfide (FeH_2S) associated with increases in all included air pollutants.

Vulnerability of COPD Patients to Ambient Air Pollutants by Age and Geography

A systematic review and meta-analysis of 108 papers, targeting subpopulations that are especially vulnerable to ambient AP exposure, found strong and consistent evidence for a higher vulnerability in the elderly [39]; however, disease-specific vulnerability was not studied in this review.

Age-stratified analysis of AP effects on COPD exacerbation showed mixed results. The most recent comprehensive review [34] highlighted that COPD patients ages 65+ years are more vulnerable to ambient AP exposure than younger COPD patients, which was also reported by a previous review [17•]. However, a similar review [20••] did not support this notion. A further more extensive review of ambient AP health effects characterized the elderly as a vulnerable subgroup for particulate matter exposure; in this case, the elderly included COPD patients [40].

Regarding regional differences, one review [34] collected a sufficiently large number of studies located in Asia and other parts of the world. In these studies, higher effect estimates of AP exposure on COPD exacerbation were reported for Asian patients, which can be interpreted as a higher vulnerability of COPD patients from Asia and/or as the effect of a higher exposure to air pollutants and/or as a consequence of different air pollutant mixtures.

Potential Mechanisms for Increased Vulnerability of COPD Patients to Ambient AP

The main underlying mechanisms for adverse health effects from ambient AP exposure are related to oxidative stress and inflammation [32, 41–43]. Apart from the fact that particles can translocate into the blood stream and create vascular dysfunction with potential systemic effects, air pollutant-related oxidative stress can directly damage the epithelium of the airways and reduce the immune response [44]. A further potential mechanism for a higher vulnerability of COPD patients to ambient air pollution exposure is an increased direct induction of inflammation of the damaged lungs of COPD patients which can promote a further reduction of pulmonary function in COPD patients [45]. Finally, COPD patients have more particle deposits in the lung possibly due to a reduced clearance of particles from the lung which may further increase the vulnerability of COPD patients to ambient air pollutant exposure, particularly ambient particles [42, 44, 45].

Improved Air Quality and Changes of Prevalence and Exacerbation of COPD

A few studies indicated that a decline in AP levels is associated with a lower prevalence of respiratory symptoms, COPD and COPD-related biomarkers ([46, 47]. A cohort of more than 2000 women, aged 55 years at baseline, in Germany was followed for 20 years [47]. The decline of ambient air pollutants (PM_{10}, NO_2) was associated with a reduction in self-reported COPD-related symptoms and spirometry confirmed COPD. These temporal changes need to be considered with caution because the improved air quality is not the only characteristic that changed over time. Nevertheless, the authors concluded that a reduction in AP appears to attenuate respiratory aging in these women.

Conclusions and Uncertainties of Summarized Epidemiological Findings

While numerous studies and systematic reviews have been published, which address the effects of exposure to ambient

air pollutants on COPD exacerbation that could be used to evaluate the specific vulnerability of COPD patients to air pollutants, these studies differ in many aspects. The diagnosis of COPD differed substantially across these studies. The overlap with asthma is insufficiently documented, and asthmatics are included in the analysis in many studies of COPD outcomes. COPD mortality as the outcome of interest is difficult to precisely assess since COPD might be comorbid with many other common chronic diseases making it uncertain whether AP exposures exacerbated COPD or other chronic disorders. Another concern is whether exposure assessment of air pollutants was very selective since the ambient air pollutants addressed strongly varied across the studies. In addition, the epidemiological study designs used to evaluate the AP effects in COPD patients were very different and included cohorts, time series, case-crossover, and panel studies.

Despite these differences, overall studies support that AP differentially affects COPD patients more strongly and support the notion that COPD patients are a vulnerable subgroup that needs special protection from breathing highly polluted air.

Acknowledgments We thank Dr. Carlana Ramlochansingh for the final editing of the manuscript.

Author Contributions JH drafted the manuscript. TS added comments. Both authors critical interpreted the findings and derived the main conclusions.

Compliance with Ethical Standards

Conflict of Interest Joachim Heinrich and Tamara Schikowski declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance.

1. van Donkelaar A, Martin RV, Brauer M, Boys BL. Use of satellite observations for long-term exposure assessment of global concentrations of fine particulate matter. Environ Health Perspect. 2015;123(2):135–43. https://doi.org/10.1289/ehp.1408646.
2. Hunt A, Abraham JL, Judson B, Berry CL. Toxicologic and epidemiologic clues from the characterization of the 1952 London smog fine particulate matter in archival autopsy lung tissues. Environ Health Perspect. 2003;111(9):1209–14. https://doi.org/10.1289/ehp.6114.
3. Hogg JC. Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet. 2004;364(9435):709–21. https://doi.org/10.1016/S0140-6736(04)16900-6.
4. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, Buzatu L, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(26):2645–53. https://doi.org/10.1056/NEJMoa032158.
5. Martinez FD. Early-life origins of chronic obstructive pulmonary disease. N Engl J Med. 2016;375(9):871–8. https://doi.org/10.1056/NEJMra1603287.
6. Wright RJ, Brunst KJ. Programming of respiratory health in childhood: influence of outdoor air pollution. Curr Opin Pediatr. 2013;25(2):232–9. https://doi.org/10.1097/MOP.0b013e32835e78cc.
7. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD study): a population-based prevalence study. Lancet. 2007;370(9589):741–50. https://doi.org/10.1016/S0140-6736(07)61377-4.
8. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, et al. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med. 2007;176(8):753–60. https://doi.org/10.1164/rccm.200612-1749OC.
9. Buist AS, Vollmer WM, McBurnie MA. Worldwide burden of COPD in high- and low-income countries. Part I. The burden of obstructive lung disease (BOLD) initiative. Int J Tuberc Lung Dis. 2008;12(7):703–8.
10. Lopez-Campos JL, Tan W, Soriano JB. Global burden of COPD. Respirology. 2016;21(1):14–23. https://doi.org/10.1111/resp.12660.
11. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004;364(9434):613–20. https://doi.org/10.1016/S0140-6736(04)16855-4.
12. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: global burden of disease study. Lancet. 1997;349(9061):1269–76. https://doi.org/10.1016/S0140-6736(96)07493-4.
13. Burney PG, Patel J, Newson R, Minelli C, Naghavi M. Global and regional trends in COPD mortality, 1990-2010. Eur Respir J. 2015;45(5):1239–47. https://doi.org/10.1183/09031936.00142414.
14. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2007;4(7):502–6. https://doi.org/10.1513/pats.200701-001FM.
15. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Respir J. 2006;28(6):1245–57. https://doi.org/10.1183/09031936.00133805.
16. Jayes L, Haslam PL, Gratziou CG, Powell P, Britton J, Vardavas C, et al. SmokeHaz: systematic reviews and meta-analyses of the effects of smoking on respiratory health. Chest. 2016;150(1):164–79. https://doi.org/10.1016/j.chest.2016.03.060.
17.• Atkinson RW, Kang S, Anderson HR, Mills IC, Walton HA. Epidemiological time series studies of PM2.5 and daily mortality and hospital admissions: a systematic review and meta-analysis. Thorax. 2014;69(7):660–5. https://doi.org/10.1136/thoraxjnl-2013-204492. **Although this is not the most recent systematic review, this paper offers a comprehensive review of studies on impact of ambient air pollution exposure on COPD outcomes in the general population.**
18.•• Bloemsma LD, Hoek G, Smit LA. Panel studies of air pollution in patients with COPD: systematic review and meta-analysis. Environ Res. 2016;151:458–68. https://doi.org/10.1016/j.envres.2016.08.018. **This is one of the very recent systematic reviews on air pollution effects in COPD patients specifically.**
19. Ko FW, Hui DS. Air pollution and chronic obstructive pulmonary disease. Respirology. 2012;17(3):395–401. https://doi.org/10.1111/j.1440-1843.2011.02112.x.
20.•• Li MH, Fan LC, Mao B, Yang JW, Choi AM, Cao WJ, et al. Short-term exposure to ambient fine particulate matter increases hospitalizations and mortality in COPD: a systematic review and meta-

analysis. Chest. 2016a;149(2):447–58. https://doi.org/10.1378/chest.15-0513. **This recent systematic review also included specifically studies published in Chinese language.**

21. Schikowski T, Mills IC, Anderson HR, Cohen A, Hansell A, Kauffmann F, et al. Ambient air pollution: a cause of COPD? Eur Respir J. 2014a;43(1):250–63. https://doi.org/10.1183/09031936.00100112.
22. Schikowski T, Adam M, Marcon A, Cai Y, Vierkotter A, Carsin AE, et al. Association of ambient air pollution with the prevalence and incidence of COPD. Eur Respir J. 2014b;44(3):614–26. https://doi.org/10.1183/09031936.00132213.
23. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, et al. 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.
24. Lelieveld J, Evans JS, Fnais M, Giannadaki D, Pozzer A. The contribution of outdoor air pollution sources to premature mortality on a global scale. Nature. 2015;525(7569):367–71. https://doi.org/10.1038/nature15371.
25. Stanek LW, Brown JS, Stanek J, Gift J, Costa DL. Air pollution toxicology—a brief review of the role of the science in shaping the current understanding of air pollution health risks. Toxicol Sci. 2011;120(Suppl 1):S8–27. https://doi.org/10.1093/toxsci/kfq367.
26. Kurt OK, Zhang J, Pinkerton KE. Pulmonary health effects of air pollution. Curr Opin Pulm Med. 2016;22(2):138–43. https://doi.org/10.1097/MCP.0000000000000248.
27. Hamra GB, Laden F, Cohen AJ, Raaschou-Nielsen O, Brauer M, Loomis D. Lung cancer and exposure to nitrogen dioxide and traffic: a systematic review and meta-analysis. Environ Health Perspect. 2015;123(11):1107–12. https://doi.org/10.1289/ehp.1408882.
28. Perez L, Rapp R, Kunzli N. The year of the lung: outdoor air pollution and lung health. Swiss Med Wkly. 2010;140:w13129. https://doi.org/10.4414/smw.2010.13129.
29. Garshick E. Effects of short- and long-term exposures to ambient air pollution on COPD. Eur Respir J. 2014;44(3):558–61. https://doi.org/10.1183/09031936.00108814.
30. Faustini A, Stafoggia M, Cappai G, Forastiere F. Short-term effects of air pollution in a cohort of patients with chronic obstructive pulmonary disease. Epidemiology. 2012;23(6):861–79. https://doi.org/10.1097/EDE.0b013e31826767c2.
31. Garcia-Aymerich J, Tobias A, Anto JM, Sunyer J. Air pollution and mortality in a cohort of patients with chronic obstructive pulmonary disease: a time series analysis. J Epidemiol Community Health. 2000;54(1):73–4. https://doi.org/10.1136/jech.54.1.73.
32. Sunyer J, Basagana X. Particles, and not gases, are associated with the risk of death in patients with chronic obstructive pulmonary disease. Int J Epidemiol. 2001;30(5):1138–40. https://doi.org/10.1093/ije/30.5.1138.
33. DeVries R, Kriebel D, Sama S. Outdoor air pollution and COPD-related emergency department visits, hospital admissions, and mortality: a meta-analysis. Copd. 2017;14(1):113–21. https://doi.org/10.1080/15412555.2016.1216956.
34. Li J, Sun S, Tang R, Qiu H, Huang Q, Mason TG, et al. Major air pollutants and risk of COPD exacerbations: a systematic review and meta-analysis. Int J Chron Obstruct Pulmon Dis. 2016b;11:3079–91. https://doi.org/10.2147/copd.s122282.
35. Samoli E, Stafoggia M, Rodopoulou S, Ostro B, Alessandrini E, Basagana X, et al. Which specific causes of death are associated with short term exposure to fine and coarse particles in Southern Europe? Results from the MED-PARTICLES project. Environ Int. 2014;67:54–61. https://doi.org/10.1016/j.envint.2014.02.013.
36. Chen R, Yin P, Meng X, Liu C, Wang L, Xu X, et al. Fine particulate air pollution and daily mortality. A Nationwide analysis in 272 Chinese cities. Am J Respir Crit Care Med. 2017;196(1):73–81. https://doi.org/10.1164/rccm.201609-1862OC.
37. Zhang S, Li G, Tian L, Guo Q, Pan X. Short-term exposure to air pollution and morbidity of COPD and asthma in East Asian area: a systematic review and meta-analysis. Environ Res. 2016;148:15–23. https://doi.org/10.1016/j.envres.2016.03.008.
38. Wu S, Ni Y, Li H, Pan L, Yang D, Baccarelli AA, et al. Short-term exposure to high ambient air pollution increases airway inflammation and respiratory symptoms in chronic obstructive pulmonary disease patients in Beijing, China. Environ Int. 2016;94:76–82. https://doi.org/10.2016/j.envint.2016.05.004.
39. Bell ML, Zanobetti A, Dominici F. Evidence on vulnerability and susceptibility to health risks associated with short-term exposure to particulate matter: a systematic review and meta-analysis. Am J Epidemiol. 2013;178(6):865–76. https://doi.org/10.1093/aje/kwt090.
40. Simoni M, Baldacci S, Maio S, Cerrai S, Sarno G, Viegi G. Adverse effects of outdoor pollution in the elderly. J Thorac Dis. 2015;7(1):34–45. https://doi.org/10.3978/j.issn.2072-1439.2014.12.10.
41. Brook RD, Rajagopalan S, Pope CA 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. Circulation. 2010;121(21):2331–78. https://doi.org/10.1161/CIR.0b013e3181dbece1.
42. Kelly FJ, Fussell JC. Air pollution and public health: emerging hazards and improved understanding of risk. Environ Geochem Health. 2015;37(4):631–49. https://doi.org/10.1007/s10653-015-9720-1.
43. Ling SH, van Eeden SF. Particulate matter air pollution exposure: role in the development and exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2009;4:233–43.
44. Li XY, Gilmour PS, Donaldson K, MacNee W. Free radical activity and pro-inflammatory effects of particulate air pollution (PM10) in vivo and in vitro. Thorax. 1996;51(12):1216–22. https://doi.org/10.1136/thx.51.12.1216.
45. Abbey DE, Burchette RJ, Knutsen SF, McDonnell WF, Lebowitz MD, Enright PL. Long-term particulate and other air pollutants and lung function in nonsmokers. Am J Respir Crit Care Med. 1998;158(1):289–98. https://doi.org/10.1164/ajrccm.158.1.9710101.
46. Downs SH, Schindler C, Liu LJ, Keidel D, Bayer-Oglesby L, Brutsche MH, et al. Reduced exposure to PM10 and attenuated age-related decline in lung function. N Engl J Med. 2007;357(23):2338–47. https://doi.org/10.1056/NEJMoa073625.
47. Schikowski T, Ranft U, Sugiri D, Vierkotter A, Bruning T, Harth V, et al. Decline in air pollution and change in prevalence in respiratory symptoms and chronic obstructive pulmonary disease in elderly women. Respir Res. 2010;11(1):113. https://doi.org/10.1186/1465-9921-11-113.