ERJ Express. Published on March 7, 2013 as doi: 10.1183/09031936.00100112

Ambient air pollution- a cause for COPD?

Tamara Schikowski[1,2], Inga C Mills[3], H Ross Anderson[4,5], Aaron Cohen[6], Anna Hansell[7], Francine Kauffmann[8,9], Ursula Krämer[10], Alessandro Marcon[11], Laura Perez[1,2], Jordi Sunyer [12] Nicole Probst-Hensch[1,2], Nino Künzli[1,2]

Affiliations

1. Swiss Tropical and Public Health Institute, Basel, Switzerland
2. University of Basel, Basel, Switzerland
3. Health Protection Agency, Centre for Radiation, Chemical and Environmental Hazards, UK
4. MRC-HPA Centre for Environment and Health, St George's, University of London.
5. MRC-HPA Centre for Environment and Health, King's College London
6. Health Effects Institute, Boston MA USA
7. MRC-HPA Centre for Environment and Health, Imperial College London, UK
8. Inserm, CESP Centre for research in Epidemiology and Population Health, U1018, Respiratory and environmental epidemiology Team, F-94807, Villejuif, France
9. Université Paris Sud 11, UMRS 1018, F-94807,Villejuif, France
10.IUF-Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany
11. Unit of Epidemiology and Medical Statistics, Department of Public Health and Community Medicine, University of Verona, Verona, Italy.
12. Centre for Research in Environmental Epidemiology CREAL and Universitat Pompeu Fabra, Barcelona, Spain

Disclaimer:
The views expressed in this paper are those of the authors and do not necessarily reflect the views of the Health Effects Institute or its sponsors.
This paper represents the views of its authors and should not be taken as those of the Health Protection Agency.

Contact address:

Prof. Nino Künzli, MD PhD
Swiss Tropical and Public Health Institute
Socinstrasse 57
P.O. Box
4002 Basel

Acknowledgements:
The research leading to this paper has received funding from the European Community's Seventh Framework Programs ESCAPE (FP7-ENV-2007-2011; grant agreement number 211 250),,TRANSPHORM (FP7-ENV-2009-2011; grant agreement number 243 406), the APHEKOM project (European Commission's Programme on Community Action in the Field of Public Health; Grant Agreement No. 2007105 (LP), and the Swiss National Science

Foundation (TS) (grant # 324730_133148). We like to thank Dr. Regula Rapp of the LUDOK air pollution search system at SwissTPH for support (http://ludok.swisstph.ch). We also wish to thank the Secretariat to the Committee on the Medical Effects of Air Pollutants (COMEAP) for use of its systematic literature search on air pollution and COPD. The Secretariat to COMEAP is provided by the UK's Health Protection Agency.

ABSTRACT:

The role of ambient air pollution in the development of chronic obstructive pulmonary disease (COPD) is considered to be uncertain. We review the evidence in the light of recent studies.

Eight morbidity and six mortality studies were identified. These were heterogeneous in design, characterization of exposure to air pollution, and methods of outcome definition. Six morbidity studies with objectively defined COPD (FEV1/FVC ratio) were cross-sectional analyses. One longitudinal study defined incidence of COPD as the first hospitalization due to COPD. However, neither mortality nor hospitalization studies can unambiguously distinguish acute from long-term effects on the development of the underlying patho-physiological changes.

Most studies were based on within-communities exposure contrasts which mainly assess traffic-related air pollution. Overall, evidence of chronic effects of air pollution on the prevalence and incidence of COPD among adults was suggestive but not conclusive despite plausible biologic mechanisms and good evidence that air pollution affects lung development in childhood and triggers exacerbations in COPD patients. To fully integrate this evidence in the assessment, the life-time course of COPD should be better defined. Larger studies with longer follow-up periods, specific definitions of COPD phenotypes, and more refined and source-specific exposure assessments are needed.

Introduction

In contrast to many other risks, exposure to outdoor air pollution occurs during the entire lifespan. Exposure is usually inevitable and involuntary and its adverse health effects are well established for a range of outcomes. As in the case of other chronic diseases – e.g. cardiovascular diseases (1) – it is important to distinguish two features of COPD in the assessment of evidence related to air pollution, namely the long-term development of the chronic obstructive pathology and the superimposed acute exacerbations (2). In air pollution research most studies have focused on the role of air pollution in triggering symptoms and exacerbations, that is, the short-term (acute or sub-acute) effects of air pollution (3). As reviewed by Sunyer (4) evidence for a role of air pollution in the acute exacerbation of COPD has been accepted for many years, and more recent studies confirm this conclusion (3, 5). The role of air pollution in the long-term development of the pathophysiological changes that characterize COPD are far less clear (6-8). COPD is presently the fourth leading cause of death, and it is predicted to become the third leading cause by 2030 (9), making this disease one of the major health challenges in the future (2). In addition, COPD is a risk factor for the development of lung cancer, itself a leading cause of death globally (9). While smoking is an important risk factor for COPD it is now agreed that the disease can also have other aetiologies (8).

The reviews of the American Thoracic Society (ATS) (8) until May 2008, and of a Special Report from the Health Effects Institute (10) until Oct 2008, have both addressed the role of ambient air pollution in the development of COPD, i.e. the long-term effects. In the ATS review, which focused on the causes of COPD other than active smoking, the conclusion was that there is limited/suggestive evidence for a role of ambient air pollution. The HEI report focused exclusively on traffic-related near-road exposures. It concluded that there are inconsistencies in the existing data and that there is insufficient evidence of an association between local traffic-related pollution and COPD. Since both reviews have been published a number of new publications have emerged (11-16). In the light of these, the objective of this review is to reassess the epidemiological evidence for a role of long-term exposure to the complex mixture of outdoor air pollution in the development of objectively defined COPD.

We do not review the studies on acute effects of air pollution on COPD. However, the implications of these effects in the assessment of an aetiologic link between air pollution exposure and the development of COPD will be addressed in the Discussion. We also do not review the established association between indoor exposure to biomass combustion and airway obstruction (8, 17). The type, concentration, toxicity and pattern of exposure of pollutants varies widely between indoor and urban ambient outdoor pollution, which makes the generalization from the health effects of indoor biomass combustion to those of urban or traffic related air pollution rather uncertain (18).

Methods

Search strategy

Medline (Pub Med), EMBASE and Isi Web of Knowledge databases were used to identify studies for the literature review, published (including online-first) up to 02. July 2012. The heterogeneous nature of the COPD phenotype definitions and of the mixture of air pollutants required a broad search approach. Keywords included in the search were "air pollution", "PM", "particulate matter", "NO2", "nitrogen dioxide", "O3", "ozone", "traffic" as well as "COPD", "chronic obstructive pulmonary disease", "obstructive lung disease", "emphysema". We selected the relevant publications manually by reviewing titles, abstracts and reference

lists. The search was limited to articles written in the English language, and studies conducted in humans and adults. Next, several groups of studies were excluded due to their limited ability to contribute to the appraisal of the main question (see below). Potential articles were retrieved and in a hand search the referent list of the included articles was checked to identify additional papers. To identify articles relevant to the current analysis, the following sifting criteria were applied: removing duplicates, exclusion of articles that did not address the research question (see below) or did not contain original data, and limiting the search to English language only.

Inclusion and exclusion criteria

Only original research, fully published in the peer reviewed literature, was considered from cross-sectional, cohort and case-control designs. Details on how COPD and air pollution were defined had to be provided. The diagnosis of COPD had to be based on objective measures (namely spirometry) or on ICD codes in the hospital discharge or the death record. There are various ways to objectively define COPD (19). Tables 1 and 2 provide the definitions used in the air pollution studies considered in this review. We also opted for the inclusion of cohort studies with "mortality due to COPD" (or survival) as the outcome where long-term exposure to air pollution was estimated (Table 2). However, one may question the use of these studies in the assessment of effects of long-term exposure on COPD development. We include them nevertheless as authors claim indeed to assess 'long-term effects' although it may be difficult to truly distinguish acute from long-term effects with these studies. The extent to which such mortality studies play a role in helping us understand the question addressed in this review will be addressed in the Discussion.

Quantitative measures of associations such as odds ratios (ORs) or relative risks (RRs) and 95% confidence intervals (CIs) or enough data to allow the derivation of these numbers had to be available from the papers.

Studies were also excluded for the following three reasons:

1. Phenotype definition: Studies which used only questionnaire–based definitions (e.g. chronic symptoms or "doctors diagnosed COPD" etc.) of COPD were excluded. These definitions lack standardization and, most importantly, the concepts and terms used both by doctors and patients have changed over time ("chronic bronchitis"; "emphysema"; "chronic lung disease" etc). Moreover symptoms may be a marker of exacerbations or associated with short-term exposure to air pollution, which is not the subject of this review. Also we do not include the many studies assessing the association between air pollution and measures of lung function (FEV1, FVC, FEV1/FVC) as the only health outcome, i.e. with no explicit derivation of COPD stages. This is because: 1) these studies have already been reviewed by Götschi et al (20); and 2) while spirometry is essential for the objective identification of 'COPD', the clinical definition of the disease continues to be based on well-defined cutoffs and stages and 3) published associations between pollution and the level of FEV1 or FEV1/FVC are not easily translated into a measure of COPD prevalence, and the rate of change in lung function – i.e. the main outcome of longitudinal lung function studies – that ultimately determines COPD is not defined. Evidence from air pollution/lung function studies is, therefore, not sufficiently specific or sensitive to address the hypothesis of interest to our review. The lung function studies, reviewed by Götschi et al (20) provide however valuable complementary information to be put in context in the Discussion.

2. Acute effects: Studies of various designs have observed correlations between the temporal changes in air quality (acute exposure) and fluctuations of lung function, COPD-related symptoms, hospitalizations and death. The evidence of acute effects is complemented by experimental studies demonstrating e.g., that exposure to ambient particulate matter (PM) jeopardizes defense mechanisms against viruses or bacteria - a main cause of exacerbations in COPD (2). This review does not include studies on short-term exposure to air pollution and acute exacerbations (e.g. studies on bronchitis symptoms, hospital admissions or doctors' visits). These 'acute effect' studies cannot clarify the question of whether frequent exacerbations are a cause of COPD or simply the expression of the underlying chronic pathology. For discussion purposes we include, however, one currently unique longitudinal study with 13 years of follow-up where the new onset of COPD was defined as the first occurrence of a "hospitalization due to COPD" among a cohort without COPD at baseline (14). Inferential limitations of this study and of acute effect studies in general will be addressed in the Discussion.
3. Ecologic comparison: A few studies compared COPD related outcomes across only two or three aggregate levels of exposure (usually communities or cities). Such studies have very low power and generally cannot control for confounding factors at the individual level. For example, Jin and colleagues compared COPD mortality across three districts of Benxi, one of the most polluted cities in China (21). While mortality patterns followed the gradients in air quality, control for other district specific factors – e.g. working in industry or smoking – was not possible. Such studies are not included in our assessment.

All eligible articles were systematically described and qualitatively assessed.

Results

The flowchart (Figure 1) gives an overview of the results from the screening process**.** The initial search yielded 689 articles. The manual search through references and journals yielded an extra 3 articles. A total of 26 articles were retained for further evaluation, the remaining 663 articles not addressing the research question were excluded. After a final screen a further twelve papers were excluded, because they did not address the exact research question or did not contain original data. Fourteen papers were finally included in the analysis, all containing the endpoint of interest, namely the incidence or prevalence of COPD or mortality due to COPD.

Air pollution and COPD morbidity

Table 1 summarizes the eight publications, based on five European studies that used objectively defined COPD as the outcome. All studies defined COPD on the basis of pre-bronchodilator spirometry. The first publication was the Greek case-control study (22). Apart from the cohort study of Andersen et al (14), all others are cross-sectional analyses.

Karakatsani et al used background NO2 measures to assess the effect of air pollution in COPD cases and non-cases (22). They employed a nested case-control approach based on the Greek chapter of the EPIC cohort. Case-series 1 (N=168) was based on questionnaire data only, but all were visited by a physician for spirometry and a clinical assessment, which was used to define a subset of 84 subjects (case-series 2) fulfilling clinical criteria for diagnosis of chronic bronchitis or emphysema or COPD (N=31) objectively defined as FEV1/VC <88% and 89% of predicted in men and women respectively. Individually assigned estimates of exposure to traffic related pollutants showed increased exposure odds, but statistically

significant results were observed only in case series 2 for the last 5 years of exposure. Those in the highest exposure quartile had twice the risk of having COPD as compared to those in the bottom quartile (OR 2.01 [95%CI:1.05-3.68]). The study had insufficient power to focus on the 31 objectively defined cases.

The three analyses of the German SALIA study (12, 23) specified COPD according to GOLD criteria. The five-year mean of PM10, measured within 8km of participants' residences, showed not only significant negative associations with FVC and FEV1 but also a positive association with the odds of having COPD (Gold stages 1-4): OR = 1.33 (1.03-1.72) for an increase of 7ug/m3 in annual mean PM10 (25). SALIA is based on women only and the vast majority was never-smokers. Women living within 100 meter of a busy road also had poorer lung function and an increased risk of COPD (1.79 [1.06-3.02]) (12). In the second paper from Schikowski et al. the same exposure estimates were used in a subsample of the study population (24). The risk of developing COPD was increased – although not significantly - in this subsample with OR= 1.25 (0.79-1.99) for PM10, the same was true for the distance to the nearest road (OR= 1.69 (0.90-3.18)). The extended analysis of the same cohort showed that the risk of developing COPD decreased with decline in PM10 and NO2 (12).

The first paper of Pujades-Rodriguez et al (25) is based on 41,479 adult participants of the 1995, 1996 and 2001 Health Survey for England (HSE). Spirometry to define COPD (FEV1/FVC <70%) was available in 32,912 adults. The only metric to describe exposure to air pollution was distance to the nearest main road, dichotomized at a cutoff of 150m and in 30-meter bands from 0 to 150m. COPD prevalence was not associated with distance.

The second study of Pujades-Rodriguez et al used data from adults recruited from the Nottingham area (UK) in 1991 to study diet and chronic lung diseases (11). Spirometric data defining COPD (i.e. FEV1/FVC<70%) was available in 2,599 subjects. Distance to a main road (150m cut-off and 3 bands of 50m from 0-150m) and modeled NO2 concentrations were assigned to each residence. Cross-sectional analyses of the baseline data showed no association between those exposures and COPD prevalence. Neither FEV1 at baseline nor the change in FEV1 (1991 to 2000) were associated with exposure. COPD incidence was not analysed.

The Italian study by Nuvolone et al based on a population sample (N=2062) from the Pisa region used only distance to major roads as the marker of exposure, namely living within 100m, 100-250m and 250-800m. In males, the odds of having GOLD defined COPD was associated with living within 100m of a major road (OR= 2.07; 95% CI 1.11-3.87). In females, proximity was not associated with COPD. Estimates were adjusted for active and passive smoking as well as other relevant co-variates (13).

The Danish study from Andersen et al. used hospital admission data from 52,799 patients of the Danish Diet, Cancer and Health cohort (14). The first hospitalization due to COPD (discharge diagnosis) occurring between baseline and follow-up was used to define 'COPD incidence'. Exposure to air pollution was defined as individually modeled 35- and 25-year average home outdoor NO2 and NOx concentrations as well as the presence of a major road within 50m, and traffic load (i.e. total number of kilometers traveled) within 200m of residential address at baseline. The hazard ratio (HR) for a 25 year mean of NO2 was 1.07 (95% CI 1.01-1.13) per 6.4ug/m3 (IQR). Traffic markers were not significantly associated with COPD hospital admission (14).

Air pollution and COPD mortality

Table 2 lists the six publications providing results on the association between air pollution and COPD mortality which was defined using ICD-9 or ICD-10 codes. These publications used cohort data from Canada, Japan, Norway, and the USA. Two studies investigated survival in patients with COPD, whereas the others addressed the impact of air pollution on mortality due to COPD.

Survival in subjects with COPD

The Canadian study by Finkelstein et al (26) had spirometry measurements, and clinic-based ICD-9 codes for the definition of chronic pulmonary disease (CPD; excluding asthma) in this patient based cohort. Distance to the nearest major road was the only marker of exposure (road buffers of 50 and 100m). The outcome was not incidence of COPD but death among subjects with defined CPD (excluding asthma). A total of 923 deaths occurred during the 9 years of follow-up. Residence within the road buffer was similarly related to higher death rates (due to all natural causes) both in those with CPD and the other subjects, reaching statistical significance only in the total study sample (1.18; 95%CI : 1.02-1.38). The effect of road proximity translated into a rate advancement period of 2.5 years (0.2-4.8 yrs), i.e. subjects not living in these buffers would need to be 2.5 years older at baseline to experience the same mortality rate as those living along busy roads.

Zanobetti et al. used Medicare data (U.S.A.) from patients aged 65 and older discharged from hospitals with COPD to construct a cohort of survivors between 1985 and 1999. The authors used 12 month averages of PM2.5 and PM10 to investigate the effects of pollution on mortality in COPD patients. They found significant associations for a 10 μg/m3 increase in PM10 and mortality (HR=1.11; 95% CI 1.06-1.15) (15).

COPD mortality in general cohorts

The 16-year follow-up of the American Cancer Society study (27) is based on over half a million people. A 10 ug/m3 increase in fine particulate matter (PM2.5) was associated with an increased risk of all-cause mortality. However, mortality due to COPD and allied conditions was negatively associated with PM2.5 concentrations (RR= 0.84; 95% CI 0.77-0.93), especially in current and former smokers, but the association was not significant in never smokers (0.96; 95%CI: 0.73-1.24). Deaths due to 'pneumonia and influenza' were in contrast positively associated with PM2.5, reaching statistical significance among never smokers (1.20; 95% CI: 1.02-1.41 per 10 ug/m3).

The Norwegian cohort followed mortality patterns among 143,842 subjects of the general population over 14 years. The authors used local NO2, PM10 and PM2.5 measures to assign exposure. COPD mortality was significantly associated with all pollutants. Subjects exposed to concentrations above the highest quartile of PM10 (i.e. >19 ug/m3) had a hazard ratio of 1.29 (95% CI 1.12-1.48) as compared to those in the lowest quartile (below 14 ug/m3). A similarly high association could be observed for PM2.5 (HR=1.27; 95% 1.11-1.47) and NO2 (1.29; 1.05-1.39) (28).

A Japanese study with a 7-year follow-up of a random population sample from all 74 municipalities of Shizuoka (N=14,001) showed a non-significant hazard ratio for COPD mortality associated with a 10 ug/m3 increase in NO2 (HR=1.11; 95% CI 0.78-1.56) (16).

In an extended follow-up of the Harvard Six-City study, using 20 years of survival follow-up of a random sample of adults living in 6 cities in the East and Midwest US the authors found a positive but not statistically significant risk of death due to COPD. In former smokers a 10 ug/m3 increase in PM2.5 was associated with a relative risk of 1.64 (95%CI 0.92-2.93), in

current smokers of 1.10 (95% CI0.74-1.62), and in never smokers of 0.85 (95% CI 0.36-2.02) (29).

Discussion

Due to the lack of studies, the role of ambient air pollution in the development of objectively defined COPD was considered uncertain in previous reviews (4, 8, 10). In fact only two of the studies listed in Table 1 were previously considered. Our review took into account eight studies on COPD morbidity (mostly prevalence) and six cohort studies on COPD related mortality or survival among COPD patients. Overall, results remain inconclusive but require consideration of a range of complex issues. First we discuss issues related to single studies and heterogeneities in exposure assessment. We will then address challenges faced by research on the etiology of COPD, namely the limitations of using mortality studies, the difficulties in interpreting studies on short-term exposure and acute outcomes, the link between acute episodes and chronic pathologies, uncertainties in the definition of COPD phenotypes, and a better insight into the life-time course of COPD.

Study specific issues and exposure assessment

The cross-sectional analyses from Germany and Italy and the Greek case-control study suggest that subjects exposed to near-road traffic-related air pollution have a higher risk of COPD. In contrast, the cross-sectional study from England as well as the smaller one from Nottingham city observed no clear association with residential proximity to busy roads. One origin of inconsistencies may be the lack of information about susceptibility factors modifying the adverse effects of air pollution. The studies listed in Tables 1 and 2 addressed, if any, only differences between men and women and across categories of smoking with no clear patterns emerging.

The interpretation of the null findings from the Nottingham study for the modeled NO2 values raises the question of whether exposure contrasts were sufficiently large in the U.K. studies. As shown in Table 1, the NO2 range was extremely narrow indicating that people share very similar background levels of pollution. Exposure assessment is in general a source of complexity in these studies. Different pollutants and sources may play different roles in the development and exacerbation of health effects. For example, current evidence indicates that near-road traffic-related pollutants may cause the onset of asthma in children whereas the more homogenously distributed, mostly secondary, urban background pollutants are less clearly associated with asthma onset (30, 31). The studies listed in Table 1 focused on markers of traffic-related pollution using different and hardly comparable exposure concepts, such as various buffers of proximity or modeled local as well as background NOx concentrations. This heterogeneity in the exposure assessment hinders the comparative evaluation of the results and the derivation of quantitative estimates across studies.

Differences between cross-sectional studies may in part be a result of exposure misclassification resulting from different pattern so migration and incomplete assessment of confounders may be of some relevance too.

Inherent limitations in using mortality studies to assess aetiologic evidence

The interpretation of the mortality studies listed in Table 2 is a challenge. If air pollution triggers or prolongs exacerbations among COPD patients as an acute effect, mortality due to

COPD is expected to be higher among those living in more polluted sites, as observed in Norway (28), Japan (16) and - though without statistical significance - in the ACS study from the U.S.A. (27). One would observe such associations in particular in following up cohorts of COPD patients. Indeed, Finkelstein et al and Zanobetti et al (15, 26) reported significant associations of air quality with survival among COPD patients. One may interpret this finding as a long-term effect of air pollution on the progression of the underlying pathologies that result in COPD. Although not directly observed in these cohort studies one may conjecture that progression to premature mortality reflects enhanced disease development in the pre-clinical and clinical stages of COPD development. However, one may interpret the results as well as a consequence of acute or sub-acute effects of air pollution on patients with COPD, resulting in shortening life time. Thus, whether and to what extent COPD was caused or enhanced by long-term exposure to air pollution cannot be unambiguously inferred from these mortality studies

In the case of COPD, cause-specific mortality studies are challenged by a further and possibly influential problem, namely the low sensitivity of death certificates for this disease (32). As reported e.g. for U.K., death certificate analyses using underlying cause of death heavily underreport the contribution of obstructive lung disease to mortality (34(33). COPD is loosely defined, underdiagnosed, and substantially linked with co-morbidities including cardiovascular diseases, diabetes and lung cancer (2) and these may be preferentially reported on death certificates. Discrepancies in coding and diagnostic labeling may also explain at least part of the large differences in COPD-related deaths observed across countries (34). Moreover, practitioners are more likely to use the diagnostic label 'COPD' in smokers and males, thus further affecting sensitivity of death certificates among never-smokers, a group of particular interest for our research question.

In fact, the negative finding of the ACS study by Pope et al (Table 2) provides an example of the challenges faced as a result of the likely limited validity of COPD on death certificates and the inability to clearly distinguish acute from chronic effects. While associations between air pollution and reduced life expectancy were strong for all natural deaths and for cardiovascular death, this was not the case for COPD as defined on the death certificates (27). However, associations between 'long-term exposure' and 'pneumonia or influenza' as the cause of death were strong and significant. Pneumonia is, by definition, an acute disease of limited duration but an important terminal cause of death among those with COPD. Pneumonia is a key feature of COPD exacerbations and it may well be that many subjects with pneumonia – enhanced by air pollution – had an underlying COPD which, however, was not acknowledged in the death certificate. The findings of the Harvard Six Cities Study may also indicate diagnostic labeling or underdiagnosis of COPD related to smoking status. The null findings in never-smokers and the positive although not significant results reported for current and former smokers may in part be seen as a consequence of differential misclassification of the outcome (Table 2).

Mortality studies are of particular use in the estimation of the burden and costs attributable to air pollution. In fact the 2010 update of the global burden of disease (GBD) will integrate mortality due to COPD, based on published and unpublished estimates of the association, using unpublished estimates also from the American Cancer Society study (RR of 1.05 (95% CI 0.95, 1.17) for COPD mortality per 10 ug/m3 PM2.5) and the California Teachers Study (RR 1.21; 0.88-1.68 per 10ug/m3 PM2.5)(35, 36).

Limitations in using acute outcomes to assess the evidence of long-term effects

The prospective cohort study from Denmark supports an association between traffic-related air pollution and COPD related risk (14). Although one may give the strongest weight of evidence to results from longitudinal studies, the interpretation of this cohort study needs caution. First, the use of hospital discharge diagnosis to define COPD may not necessarily guarantee that the diagnostics included spirometry. Second – and most importantly – the interpretation of the findings as "long-term effects may be questioned. Elaborate state-of-the-art models of long-term air pollution distribution were used to individually assign exposure to traffic-related pollution to >50,000 subjects, followed over >13 years. The outcome, however, was not the incidence of COPD but rather time to the first hospital admission due to COPD. The data give strong evidence for air pollution playing a role in exacerbations of COPD severe enough to require hospitalization, confirmed by previous studies (4). With hospital admission – an acute event – as primary outcome, the study cannot unambiguously distinguish the role of air pollution in exacerbating COPD – developed due to other causes – from its aetiologic contribution to the development of COPD. The use of long-term exposure averages does not resolve this inherent uncertainty. As shown by the same authors in similar analyses on air pollution and asthma hospital admissions in the same Danish cohort, short- and long-term levels of air pollution were highly correlated (14). The ambiguity in the interpretation of such hospital admission data has been discussed in an accompanying editorial of the asthma analyses (1). Given that air pollution is an established trigger of both asthma attacks and exacerbations of COPD, related hospital admissions remain an ambiguous outcome to establish the role of air pollution in causing the pathologies that underlie these chronic diseases.

This brings up the more general question of how to interpret the role of acute effects of air pollution (e.g. on pneumonia, bronchitis symptoms or other acute episodes) in the causation of COPD. The continued loss of lung function coupled with chronic bronchitis symptoms, dyspnoea, disability, and ultimately premature death clinically characterize COPD during later stages. Subjects free of COPD with a history of chronic bronchitis symptoms are more likely to develop COPD later in life (37). Repeated acute insults contribute, in the long-term, to a more rapid decline of lung function (38, 39). Under this aetiologic model, exacerbations are not only the expression of COPD but a cause of the development of the disease. Bronchitis symptom episodes are triggered and possibly prolonged by ambient air pollution (acute effects) (6). Without a more complete understanding of the role of air pollution related exacerbations in the etiology of COPD it remains difficult to establish the role of acute exposures in the development of COPD.

Definition of COPD phenotypes

The loose definition of the phenotype is an inherent challenge in the assessment of aetiology. COPD is characterized by irreversible airflow limitation, inflammation in the airways, and a range of systemic pathologies and comorbidities. Spirometry is essential for the definition of 'COPD' and it provides the basis to describe the severity of COPD. However, although obstructive airways with reduced lung function is a hallmark of the disease, the clinical phenotypes can substantially differ in terms of clinical appearance, morphologic characteristics, or temporal course and features, indicating the existence of various phenotypes characterized by airways obstruction. Risk factors – including air pollution – may play different roles among the various phenotypes. In the absence of tools to objectively define those phenotypes, progress in aetiologic research may be limited. Related to this, the distinction between the two main obstructive diseases, asthma and COPD, is a further challenge in this research. While some of the studies in Table 1 excluded subjects with

asthma to increase the specificity of COPD, none of the studies used post-bronchodilator spirometry to distinguish COPD from asthma. Moreover, secular changes in early life conditions, which have increased asthma incidence, may also modify the etiology of COPD. In fact, both asthma and COPD may comprise a set of sub-groups of disease entities – or endotypes, (i.e. subtypes defined by distinct pathophysiological mechanisms) (40-42). The lack of specificity in the definition of such endotypes may result in biased results if air pollution is differently associated with different endotypes.

Life-time course of COPD and lung function

The natural history of COPD is defined by a progressive decline in lung function (FEV1 and FVC) leading to earlier and/or larger deficits than might be expected in normal aging. A reduction in the postbronchodilator FEV_1 and a low FEV_1/FVC ratio are the primary markers of COPD. However, the classification of normal and abnormal, the presence or absence of COPD, and the clinical course are subjects of ongoing debate Most importantly, to what degree subnormal development of lung function during the growth phase (childhood/adolescence) may reflect the earliest preclinical phase of COPD is not clear, and the trajectories of lung function over the life span are still poorly understood (43). While accelerated decline of lung function is a main feature of the disease throughout adulthood, not all 'accelerated decline' of lung function results in COPD. The associations and causal link of the lung function growth in adolescence, the lung function level during the plateau phase in young adults, and the rate of lung function decline during adulthood with the incidence of COPD in adulthood are not defined. With uncertainties about the natural history of COPD in mind, it is unclear how to link the abundant evidence of a causal association between long-term exposure to air pollution and decelerated lung function growth (childhood) and accelerated lung function decline (adulthood) with the aetiologic role of air pollution in the development of COPD (20) (44).

Conclusion and outlook

We are left with interpreting the aetiologic evidence provided by studies listed in Table 1 (except the first one). Lessons learned are summarized in Table 3. Data are suggestive of a role for ambient air pollution in the aetiology of COPD. In fact, from a risk assessment perspective the remaining uncertainties such as definitions of phenotypes, life time course and distinction of acute and long-term effects are less relevant, thus supporting the inclusion of COPD related mortality in the global burden study (35). However, from an aetiologic research perspective, the inconsistencies in the U.K. studies, the reliance on cross-sectional analyses and the use of different proxies of exposure requires some caution in making final judgements. The ambiguity in these studies contrasts with supportive indirect evidence related to biologic plausibility. A causal role of air pollution in the induction of COPD would be biologically plausible. Strong redox activity leading to oxidative stress, pulmonary and systemic inflammatory responses, reduction in the ciliary activity in the air ways, amplification of viral infections, increases in bronchial reactivity among predisposed, or acute decrease of pulmonary function are all known effects of acute exposures to several pollutants encountered in ambient air such as particles of various size, O3, NO2, and others (45). Many of these toxicological features may be relevant in the induction and/or course of COPD. It is also important to note that exposure to products of incomplete combustion from sources which share a range of pollutants in common with ambient air pollution, albeit at

higher levels, (i.e., tobacco smoking, certain occupational exposures and indoor biomass combustion) is consistently associated with COPD, though the strength of the evidence varies among the different combustion sources (8). To elucidate the role of ambient air pollution in the development of COPD, future studies need to elaborate on several issues.

First, better definitions of COPD phenotypes are crucial to overcome current limitations. This includes clinical studies to compare the features of COPD in smokers and non-smokers. The use of objective measures such as post-bronchodilator lung function measurements and the examination of associations between different phenotypes within COPD are essential. Understanding the role of symptoms in the aetiology of COPD and the relevance of reduced lung function early in life and the rate of lung function decline in adults for the development of COPD will be important for an integrated assessment of the aetiologic role of air pollution.

Second, individual assignment of long-term exposure to ambient air pollution remains a relevant task. Measurements and modeling strategies of source specific pollutants will provide results particularly useful for source specific policy making. Exposure during various time windows ought to be considered to elucidate the role of early life exposures and the impact of changes of air quality – both indoors and outdoors – over time.

Third, the use or implementation of very large cohort studies will provide the tools to assess the role of susceptibility factors. This is of particular relevance to identify those at highest risk for air pollution related COPD. To elucidate the role of endogenous and exogenous modifying factors, cohort studies need extensive assessment of objective and subjective co-variates – including comorbidities, socio-economic conditions and deprivation – and access to biobanks (biomarkers and –omics data). Given the partly similar nature of ambient urban pollution and tobacco smoke, factors modifying the effects of smoking on COPD may be informative in advancing air pollution research. Promising research on air pollution and health outcomes including COPD is currently under way in the European projects of the 7th Framework program, namely ESCAPE (European Study of Cohorts for Air Pollution Effects) and TRANSPHORM (Transport related Air Pollution and Health impacts - Integrated Methodologies for Assessing Particulate Matter) (www.escapeproject.org and www.transphorm.eu/). The role of traffic-related air pollution on the development of respiratory disease in adults will be assessed in joint meta-analyses across six existing European cohorts (46).

The use of existing cohorts is an efficient first step to further explore the hypotheses addressed in this review. Challenges discussed above highlight however the limitations of pooling existing cohorts only, given the inherent methodological heterogeneities inevitably encountered across different cohorts. Highly standardized large-scale national if not multi-national cohorts will be needed to reveal the role of air pollution (and other factors) in the development and course of chronic diseases such as COPD (47).

In sum, evidence of chronic effects of air pollution on the prevalence and incidence of COPD among adults is suggestive but not conclusive despite plausible biologic mechanisms and several high quality epidemiological studies that support the evidence. To the extent that impaired lung function growth in early life translates into COPD in adulthood, the evidence for a causal link of air pollution with COPD development could be considered substantial (8). If repeated exacerbations of COPD are considered a cause of the development of the disease, evidence for a causal role of air pollution would again be substantial given the ability of air

pollution to trigger exacerbations (48). However, based on the studies shown in Table 1 alone, the role of air pollution in the development of COPD remains uncertain.

References

1. Kunzli N, Perez L, von Klot S, Baldassarre D, Bauer M, Basagana X, Breton C, Dratva J, Elosua R, de Faire U, Fuks K, de Groot E, Marrugat J, Penell J, Seissler J, Peters A, Hoffmann B. Investigating air pollution and atherosclerosis in humans: Concepts and outlook. *Progress in cardiovascular diseases* 2011;53:334-343.
2. Decramer M, Janssens W, Miravitlles M. Chronic obstructive pulmonary disease. *Lancet* 2012;379:1341-1351.
3. Peacock JL, Anderson HR, Bremner SA, Marston L, Seemungal TA, Strachan DP, Wedzicha JA. Outdoor air pollution and respiratory health in patients with copd. *Thorax* 2011;66:591-596.
4. Sunyer J. Urban air pollution and chronic obstructive pulmonary disease: A review. *Eur Respir J* 2001;17:1024-1033.
5. Atkinson RW, Anderson HR, Sunyer J, Ayres J, Baccini M, Vonk JM, Boumghar A, Forastiere F, Forsberg B, Touloumi G, Schwartz J, Katsouyanni K. Acute effects of particulate air pollution on respiratory admissions: Results from aphea 2 project. Air pollution and health: A european approach. *Am J Respir Crit Care Med* 2001;164:1860-1866.
6. Künzli N, Perez L, Rapp R. Air quality and health. Lausanne: European Respiratory Society; 2010.
7. World Health Organisation W. Who air quality guidelines for particulate matter, ozone, nitrogen dioxide and sulfur dioxide global update 2005. Geneva, Switzerland; 2006.
8. Eisner MDA, N. Coultas, D. Kuenzli, N. Perez-Padilla, R. Postma, D. Romieu, I. Silverman, E.K. Balmes, J.R. Novel risk factors and the global burden of copd: An offical ats public polic statement. 2011.
9. World Health Organisation W. The world health report 2008 - primary health care. Geneva, Switzerland; 2008.
10. Health Effects Institute H. Traffic-related air pollution: A critical review of the literature on emissions, exposure, and health effects Boston, MA, Health Effects Institute; 2010.
11. Pujades-Rodriguez M, McKeever T, Lewis S, Whyatt D, Britton J, Venn A. Effect of traffic pollution on respiratory and allergic disease in adults: Cross-sectional and longitudinal analyses. *BMC Pulm Med* 2009;9:42.
12. Schikowski T, Ranft U, Sugiri D, Vierkotter A, Bruning T, Harth V, Kramer U. Decline in air pollution and change in prevalence in respiratory symptoms and chronic obstructive pulmonary disease in elderly women. *Respir Res* 2010;11:113.
13. Nuvolone D, Della Maggiore R, Maio S, Fresco R, Baldacci S, Carrozzi L, Pistelli F, Viegi G. Geographical information system and environmental epidemiology: A cross-sectional spatial analysis of the effects of traffic-related air pollution on population respiratory health. *Environ Health* 2011;10:12.
14. Andersen ZJ, Hvidberg M, Jensen SS, Ketzel M, Loft S, Sorensen M, Tjonneland A, Overvad K, Raaschou-Nielsen O. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: A cohort study. *Am J Respir Crit Care Med* 2011;183:455-461.
15. Zanobetti A, Bind MA, Schwartz J. Particulate air pollution and survival in a copd cohort. *Environ Health* 2008;7:48.
16. Yorifuji T, Kashima S, Tsuda T, Takao S, Suzuki E, Doi H, Sugiyama M, Ishikawa-Takata K, Ohta T. Long-term exposure to traffic-related air pollution and mortality in shizuoka, japan. *Occup Environ Med* 2010;67:111-117.

17. Liu LJ, Curjuric I, Keidel D, Heldstab J, Kunzli N, Bayer-Oglesby L, Ackermann-Liebrich U, Schindler C. Characterization of source-specific air pollution exposure for a large population-based swiss cohort (sapaldia). *Environ Health Perspect* 2007;115:1638-1645.
18. Kelly FJ, Fussell JC. Air pollution and airway disease. *Clin Exp Allergy* 2011;41:1059-1071.
19. Guder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP, Lammers JW, Zanen P, Hoes AW, Stork S, Rutten FH. "Gold or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study". *Respir Res 2012 Feb 6;13(1):13* 2012.
20. Gotschi T, Heinrich J, Sunyer J, Kunzli N. Long-term effects of ambient air pollution on lung function: A review. *Epidemiology* 2008;19:690-701.
21. Jin LW, S. Qin, Y. Ren, C. Xu, Z. Ren, L. Li, J. Sha, B. Kjellstrom, T. Association between air-pollution and mortality in benxi, china. *Chinese Journal of Public Health* 1999.
22. Karakatsani A, Andreadaki S, Katsouyanni K, Dimitroulis I, Trichopoulos D, Benetou V, Trichopoulou A. Air pollution in relation to manifestations of chronic pulmonary disease: A nested case-control study in athens, greece. *Eur J Epidemiol* 2003;18:45-53.
23. Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, Wichmann HE, Kramer U. Long-term air pollution exposure and living close to busy roads are associated with copd in women. *Respir Res* 2005;6:152.
24. Schikowski T, Sugiri D, Reimann V, Pesch B, Ranft U, Kramer U. Contribution of smoking and air pollution exposure in urban areas to social differences in respiratory health. *BMC public health* 2008;8:179.
25. Pujades-Rodriguez M, Lewis S, McKeever T, Britton J, Venn A. Effect of living close to a main road on asthma, allergy, lung function and chronic obstructive pulmonary disease. *Occup Environ Med 2009 Oct;66(10):679-84* 2009.
26. Finkelstein MM, Jerrett M, Sears MR. Traffic air pollution and mortality rate advancement periods. *Am J Epidemiol* 2004;160:173-177.
27. Pope CA, 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, Godleski JJ. Cardiovascular mortality and long-term exposure to particulate air pollution: Epidemiological evidence of general pathophysiological pathways of disease. *Circulation 2004 Jan 6;109(1):71-7 Epub 2003 Dec 15* 2004.
28. Naess O, Nafstad P, Aamodt G, Claussen B, Rosland P. Relation between concentration of air pollution and cause-specific mortality: Four-year exposures to nitrogen dioxide and particulate matter pollutants in 470 neighborhoods in oslo, norway. *Am J Epidemiol 2007 Feb 15;165(4):435-43 Epub 2006 Nov 29* 2006.
29. Lepeule J, Laden F, Dockery D, Schwartz J. Chronic exposure to fine particles and mortality: An extended follow-up of the harvard six cities study from 1974 to 2009. *Environ Health Perspect* 2012.
30. Anderson RF, G. Atkinson, R.W. Long-term exposure to air pollution and the incidence of asthma: Meta-analysis of cohort studies *Air Quality, Atmosphere & Health* 2011.
31. Jacquemin B, Schikowski T, Carsin AE, Hansell A, Kramer U, Sunyer J, Probst-Hensch N, Kauffmann F, Kunzli N. The role of air pollution in adult-onset asthma: A review of the current evidence. *Seminars in respiratory and critical care medicine* 2012;33:606-619.
32. Johansson LA, Bjorkenstam C, Westerling R. Unexplained differences between hospital and mortality data indicated mistakes in death certification: An investigation of 1,094 deaths in sweden during 1995. *J Clin Epidemiol 2009 Nov;62(11):1202-9 Epub 2009 Apr 11* 2009.
33. MANNINO DM, BROWN C, GIOVINO GA. Obstructive lung disease deaths in the united states from 1979 through 1993. *American Journal of Respiratory and Critical Care Medicine* 1997;156:814-818.

34. Hansell AL. Lies, damned lies and mortality statistics? : Thorax. 2006 Nov;61(11):923-4.; 2006.
35. Lim S, Vos T, Abraham D, Flaxman ea. The burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions 1990-2010: A systematic analysis. *Lancet* in press 2012.
36. Lipsett MJ, Ostro BD, Reynolds P, Goldberg D, Hertz A, Jerrett M, Smith DF, Garcia C, Chang ET, Bernstein L. Long-term exposure to air pollution and cardiorespiratory disease in the california teachers study cohort. *Am J Respir Crit Care Med* 2011;184:828-835.
37. Probst-Hensch NM, Curjuric I, Bridevaux PO, Ackermann-Liebrich UA, Bettschart RW, Brandli O, Brutsche M, Burdet L, Gerbase MW, Knopfli B, Kunzli N, Pons MG, Schindler C, Tschopp JM, Rochat T, Russi EW. Longitudinal change of pre-bronchodilator spirometric obstruction and health outcomes -results from the sapaldia cohort. *Thorax* 2009.
38. Seemungal T, Harper-Owen R, Bhowmik A, Moric I, Sanderson G, Message S, Maccallum P, Meade TW, Jeffries DJ, Johnston SL, Wedzicha JA. Respiratory viruses, symptoms, and inflammatory markers in acute exacerbations and stable chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:1618-1623.
39. Seemungal TA, Harper-Owen R, Bhowmik A, Jeffries DJ, Wedzicha JA. Detection of rhinovirus in induced sputum at exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 2000;16:677-683.
40. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, Lemanske RF, Jr., Wardlaw AJ, Wenzel SE, Greenberger PA. Asthma endotypes: A new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* 2011;127:355-360.
41. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, Hansell AL, Nowitz MR, McNaughton AA, Soriano JB, Beasley RW. Proportional classifications of copd phenotypes. *Thorax* 2008;63:761-767.
42. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, Aldington S, Beasley R. Distinct clinical phenotypes of airways disease defined by cluster analysis. *Eur Respir J* 2009;34:812-818.
43. Guerra S. Asthma and chronic obstructive pulmonary disease. *Curr Opin Allergy Clin Immunol* 2009;9:409-416.
44. Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, Berhane K, McConnell R, Kuenzli N, Lurmann F, Rappaport E, Margolis H, Bates D, Peters J. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 2004;351:1057-1067.
45. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847-852.
46. Eeftens M, Beelen R, de Hoogh K, Bellander T, Cesaroni G, Cirach M, Declercq C, Dedele A, Dons E, de Nazelle A, Dimakopoulou K, Eriksen K, Falq G, Fischer P, Galassi C, Grazuleviciene R, Heinrich J, Hoffmann B, Jerrett M, Keidel D, Korek M, Lanki T, Lindley S, Madsen C, Molter A, Nador G, Nieuwenhuijsen M, Nonnemacher M, Pedeli X, Raaschou-Nielsen O, Patelarou E, Quass U, Ranzi A, Schindler C, Stempfelet M, Stephanou E, Sugiri D, Tsai MY, Yli-Tuomi T, Varro MJ, Vienneau D, Klot S, Wolf K, Brunekreef B, Hoek G. Development of land use regression models for pm(2.5), pm(2.5) absorbance, pm(10) and pm(coarse) in 20 european study areas; results of the escape project. *Environmental science & technology* 2012;46:11195-11205.
47. Probst-Hensch NM. Chronic age-related diseases share risk factors: Do they share pathophysiological mechanisms and why does that matter? *Swiss Med Wkly* 2010;140:w13072.

48. Wedzicha JA, Seemungal TA. Copd exacerbations: Defining their cause and prevention. *Lancet* 2007;370:786-796.

Figure 1: FLOWDIAGRAM

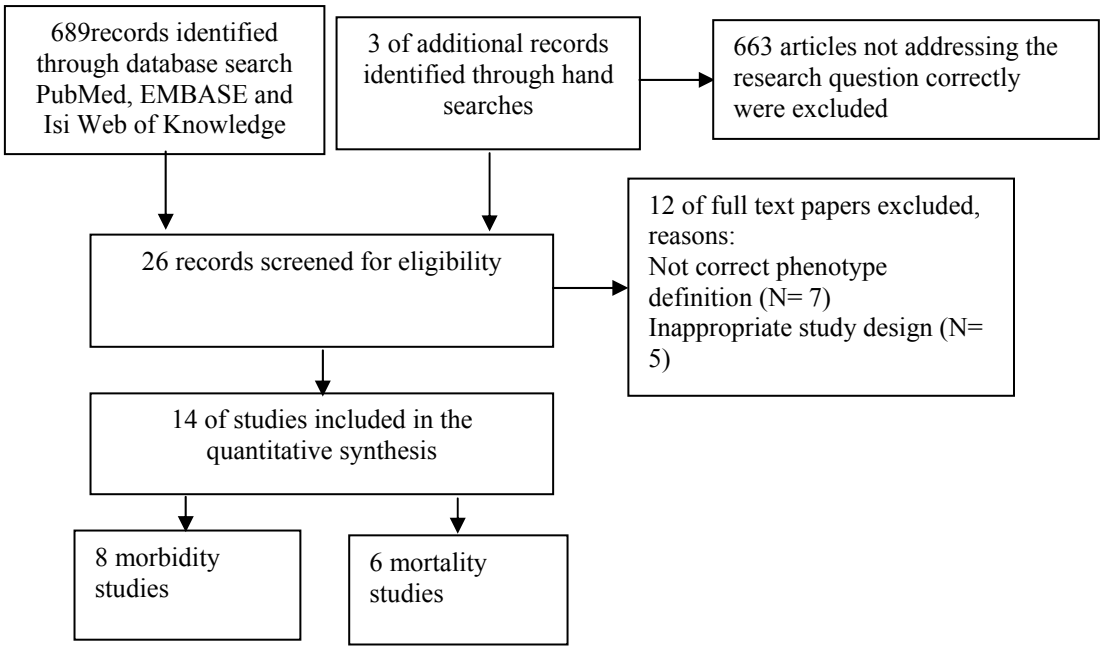

Table 1: Characteristics of the studies on long-term exposure to ambient air pollution and objectively defined Chronic Obstructive Pulmonary Disease (COPD)

Author Location	Year of study/ population/N Age of participants	Study design and duration of follow-up	Markers of exposure to air pollution	Definition of COPD and handling of asthma	Effect Estimate (95% CI)	Study limitation
Andersen et.al. Copenhagen or Aarhus, Denmark (2011)	1993-2006/ N= 1,786 patients admitted to hospital for COPD from cohort of 52,799 participants, 50-64yrs	Longitudinal study – Danish Diet, Cancer and Health cohort. Follow-up: 13-17 years	Pollutants: Modeled home NO2, NOx (dispersion model); Traffic proximity: Presence of a major road within 50m of residential address at baseline; Traffic load defined as total number of kilometers travelled within 200m of address at baseline	Incidence of COPD defined as first hospital admission due to COPD (discharge diagnoses) between baseline (1993-97) and 27 June 2006. Data on participants admitted to hospital for asthma and other diseases were collected	HR for NO2 35 yr mean level 1.08 (1.02-1.14) per 5.8ug/m3 IQR HR for NO2 25 yr mean level 1.07 (1.01-1.13) per 6.4ug/m3 IQR HR for NO2 15 yr mean level 1.05 (1.00-1.11) per 6.3ug/m3 IQR HR for NOx 35 yr mean level 1.05 (1.01-1.10) per 12.4ug/m3 IQR HR for NOx 25 yr mean level 1.04 (0.99-1.09) per 12.6ug/m3 IQR HR for NOx 15 yr mean level 1.03 (0.97-1.09) per 11.6ug/m3 IQR HR for major road 1.04	Population was defined by hospital admission using discharge diagnosis of COPD, no lung function measurement.

					(0.89 – 1.21) HR for traffic load 1.01 (0.97-1.05) per 5.8 (10^3 vehicle km/d)	
Karakatsani, Athens, Greece (2003)	1990-1996 Case-series 1:N= 168 cases (series 1) and 168 matched controls from Athens, Greece. Case-series2: N = 84 cases - a subset of case-series1 that met criteria for clinical diagnosis of chronic bronchitis, emphysema or COPD. Age between 34 and >70yrs	Nested case-control from EPIC Greece Follow-up of case-series 2: 5 years	Pollutants: Inverse distance-weighted mean from 3 nearest fixed site monitors used to estimate NO2 concentrations for boroughs. Past 5 years and 20 years Traffic proximity: none	Case-series 1 (N=168) defined by reported history of COPD, chronic bronchitis, emphysema or respiratory symptoms. COPD case-series 2: subset of above, with COPD defined based on clinical assessment (N=84), including 31 cases with FEV1/VC <88% (men) and 89% (women) Asthmatics or subjects with wheezing in childhood and adulthood were excluded .	OR per one quartile of NO2, recent 5 years exposure: Case series 1 (all): 1.18 (0.94-1.49) Case series 2: 1.37 (1.05-1.79) OR per one quartile of NO2, recent 20 years exposure: Case series 1 (all): 1.10 (0.84-1.43) Case series 2: 1.31 (0.95-1.79) ORs for NO2, recent 5 years exposure for persons exposed to the highest quartile vs all others: Case series 1 (all): 1.46 (0.82-2.59) Case series 2: 2.01 (1.05-3.86) ORs for NO2, recent 20 years exposure for persons exposed to the highest	No local traffic related pollution information. Only a subset of cases (N=31) are based on lung function alone; not GOLD cut-off. ERS criteria used to define COPD.

					quartile vs all others: Case series 1 (all): 1.39 (0.73-2.67) Case series 2: 1.46 (0.67-3.19) Data on the size of the quartiles is not available.	
Nuvolone et.al. Pisa-Cascina area, Italy (2011)	1991-1993/N=2062 of the general population living in the Pisa-Cascina area. Age range 8-97yrs (mean age was 45.9 and 48.9yrs for men and women respectively.	Cross sectional Follow-up: not indicated	Pollutants: none Traffic proximity: Residential distance to a specified main road. Exposure groups defined as highly exposed (living <100m from the main road), moderately exposed (living between 100-250m from the main road) and unexposed (living between 250-800m)	GOLD: FEV1/FVC < 0.7 Not specified whether asthmatics were excluded from the analyses. Likely excluded though as 'asthma' was a separate outcome used in this analysis.	For males living <100m of main road, COPD diagnosis OR 1.80 (1.03-3.08); 100-250m OR 1.21 (0.69-2.13). For females living <100m of main road: COPD diagnosis OR 1.60 (0.71-3.59); 100-250m OR 0.99 (0.39-2.51) For males living <100m of main road: reduced FEV1/FVC% <70% OR 2.07 (1.11-3.87); 100-250m OR 2.53 (1.42-4.53) For females living <100m of main road: reduced FEV1/FVC% <70% OR 1.01 (0.48-2.14); 100-	Only distance to the nearest road, no air pollutants, COPD defined using questionnaire-reported diagnosis of chronic bronchitis or emphysema Cross-sectional analyses

					250m OR 0.88 (0.41-1.89)	
Pujades-Rodriguez et.al. Nottingham City (UK); (2009)	1991/ N= 2599 of the general population from Gedling area, Nottingham City, UK Age 18-70yrs	Cross sectional analyses Follow-up: 9 years	Pollutants: Modeled NO2 at home (dispersion model); Traffic proximity: Distance of residence to the nearest road (150m cut-off and 3 distance bands of 50m from 0-150m)	Prevalence of COPD defined according to GOLD (FEV/FVC<70%) using pre-bronchodilator lung function measurements. Not specified whether asthmatics were excluded from the analyses. Likely excluded though as 'asthma' was a separate outcome used in this analysis.	OR for≤150m distance (>150m as reference): 0.97 (0.68-1.37) OR for distance bands (100-150m as reference) <50m 1.54 (0.69-3.45); for 50-100m 1.67 (0.79-3.49) ORs for quintiles of modeled NO2 (<33.92 µg/m3 as reference): for 33.92 - 34.23 ug/m3 1.09 (0.68-1.73) for 34.23-34.73 ug/m3 0.95 (0.60-1.52) for 34.73-36.79 ug/m3 0.91 (0.57-1.45) for > 36.79 ug/m3 1.07 (0.68-1.68)	Modeled residential NO2 had extremely small contrasts with the 5 categories ranging from <33.92 µg/m3 (lowest) to >36.79 µg/m3 (highest). Unclear to what extent distance reflected true contrasts in exposure. Cross-sectional analysis
Pujades-Rodriguez et.al. England, UK (2009)	Assessments in 1995, 1996 and 2001 /N=48 145 adults from the general population in England.	Cross-sectional surveys, Health Survey for England Follow-up: 5 years	Pollutants: none Traffic proximity. Residential	Prevalence of COPD defined according to GOLD (FEV/FVC<70%) using pre-bronchodilator spirometry.	OR ≤150m of a main road (>150m as reference): 0.96 (0.89-1.03) ORs for	Using postcode to identify residential address, no pollutant estimates

	Age >16 yrs		proximity to the nearest main road	Not specified whether asthmatics were excluded from the analyses. Likely excluded though as 'asthma' was a separate outcome used in this analysis.	bands of distance (120-150m as reference): <30m: 0.94 (0.77-1.13) 30-60m: 0.97 (0.80-1.18) 60-90m: 0.94 (0.78-1.14) 90-120m: 0.97 (0.81-1.17)	
Schikowski et al Ruhr Area, Germany (2005)	1985-1994/ N=4262 women of general population living in the Ruhr area, Germany Age 54-55yrs at baseline	Consecutive cross sectional studies (SALIA) Follow-up: 5 years	Pollutants: Background concentrations of PM10 and NO2, measured within up to 8km of each participant's residence. Traffic proximity: Distance of residence to nearest major road	Prevalence of COPD defined according to GOLD (FEV/FVC<70%) using pre-bronchodilator lung function. Asthmatics with physician diagnosis or those using asthma medication were excluded from the analyses.	OR for <100m of road: 1.79 (1.06-3.02) OR for IQR increase of 16ug/m3 in annual mean NO2: 1.39 (1.20-1.63) OR for IQR increase of 16ug/m3 in 5-yr mean NO2: 1.43 (1.23-1.66) IQR increase of 7ug/m3 in annual mean PM10: 1.37 (0.98-1.92) IQR increase of 7ug/m3 in 5-yr mean PM10: 1.33 (1.03-1.72)	Only females, narrow age group, Cross-sectional analyses
Schikowski et al. Ruhr area, Germany (2008)	Baseline: 1985-94/ N=4874 women of general population living in the Ruhr area, Germany Age 54-	Cohort study (SALIA) Follow-up: 12-20 years	Pollutants: Background concentrations of PM10, measured within up to 8km of each participant's residence;	Prevalence of COPD defined according to GOLD (FEV/FVC<70%) using pre-bronchodilator lung function. Asthmatics with physician	OR for <100m of road: 1.69 (0.90-3.18) OR for IQR increase of 7ug/m3 in 5-	Only females, small study sample for follow-up

	55yrs at baseline.		Traffic proximity: Distance of residence to nearest major road (≤ 100 m with >10.000 cars/day)	diagnosis or those using asthma medication were excluded from the analyses.	yr mean PM10: 1.25 (0.79-1.99)	
Schikowski et al. Ruhr area, Germany (2010)	Baseline: 1985-94 /N=4874 Women of the general population living in the Ruhr area, Germany. Mean age: 54yrs. Follow-up: 2006-2009 N=395 women with spirometry measure at follow-up of the general population. Mean age at follow-up : >70yrs/ 20 years of follow-up.	Cohort study (SALIA) Follow-up: 12-20 years	Pollutants: Background concentrations of PM10 and NO2, measured within up to 8km of each participant's residence; Traffic proximity: Distance of residence to nearest major road	Change in prevalence defined according to GOLD (FEV/FVC<70%) using pre-bronchodilator lung function. Asthmatics with physician diagnosis or those using asthma medication were excluded from the analyses.	Parameter estimate for follow-up time (unit 10 years) for mild COPD and PM10 exposure by 20 µg/m3: 20.61 (7.81-33.41) NO2 exposure by 10 µg/m3: 9.12 (4.78-13.46) Moderate COPD and PM10 exposure by 20 µg/m3: 8.02 (0.01-16.03) NO2 exposure by 10 ug/m3: 2.73 (0.03-5.43) Parameter estimate for mild COPD and a decline in NO2 exposure by 10 µg/m3 / 10yr: -4.64 (-8.03;-1.26) and a decline in PM10 by 20 µg/m3 / 10yr: -14.62 (-25.88;-	Only females, small study sample for follow-up Design issues

					3.36) Moderate COPD and NO2 decline: -1.66 (-3.8;0.048) PM10 decline: -6.20 (-13.33;0.94)	

Table 2: Characteristics of the studies on long-term exposure to ambient air pollution and survival among patients with Chronic Obstructive Pulmonary Disease (Finkelstein *et al* and Zanobetti *et al*) or COPD mortality in general cohorts.

Author Location	Year of study / population /N Age of Observation	Study design and duration of follow-up	Markers of exposure to air pollution	Definition of COPD outcome	Effect Estimate (95% CI)	Study limitation
Finkelstein et.al. Hamilton, Canada (2004)	1985 & 1999 /N= 5228 Patients referred to pulmonary lab	Cohort Follow-up duration : 9 years	Pollutants: none Traffic proximity: Distance to nearest major road	ICD9 codes for COPD mortality; Measures of FEV1 and FVC	Rate of advancement period for living close to a major road: 3.4 (0.8-6.0)	No direct pollution measurements, only GIS data was used to
Lepeule et al. USA (2012)	Baseline: 1974-77 last follow-up 2009/ N=8096 Harvard Six City Study	Cohort Study 20 years follow-up (death from 1979-2009)	Pollutants: Local centrally measured levels of PM10 & PM2.5 Traffic proximity: none	ICD_10 codes for COPD mortality; All patients underwent spirometry, measures of FEV1 and FVC	Adjusted RR for 10µg/m^3 increase in PM2.5: Never smoker: 0.85 (0.36-2.02) Former smoker: 1.64 (0.92-2.93) Current smoker 1.10 (0.74-1.62)	Only adjustment for baseline factors, PM2.5 was not measured in same location throughout the study period
Naess et.al. , Oslo (Norway) (2006)	1992 -1998 /total N=143,842 of general population living in Oslo Age: 51-70 &71-90	Cohort Follow-up duration: 14 years	Pollutants: Dispersion model of NO2, PM10 & PM2.5 to calculate individual daily average exposure estimates Traffic proximity: None	ICD-9 codes 490-496 (COPD) &ICD 10 codes I00-I119 for COPD mortality; Limitation: no lung function measures	Age group 51-70: HR for highest quartile above 42 µg/m3 of NO2:1.21 (1.05-1.39) HR for highest quartile above 19 µg/ m3 of PM10 : 1.29 (1.12-1.48) PM2.5: 1.27 (1.11-1.47)	Study based on registry data only, no information about confounders such as smoking
Pope et. al., USA (2004)	1979-1983 and 1999-2000 (16-year FU)/ N=500,000 of general	Cohort Follow-up duration:	Pollutants: Background measures of PM2.5 Traffic	ICD10 codes I00-I119 for COPD mortality;	RR for increase of 10µg/m3 of PM2.5: 0.84 (0.77-0.93)	No lung function, coding from death records only

	population		proximity: none	Limitation: no lung function measures		
Yorifuji et.al. Shizuoka, Japan (2010)Zanobetti et. al. USA (2008)	1999-2006/N=14,001 of general population1985-1999/ N= 1,039,287 hospital discharges of patients hospitalized with COPD (ICD-9 code 491;492;494-496 used to define COPD) ; Ages 65 and older	Cohort Follow-up duration: 7 years Cohort Follow-up duration: 4 years	Pollutants: NO2 modeled (LUR models) Traffic proximity: None Pollutants: Daily monitoring measures to create yearly averages of PM10 Traffic proximity: none	ICD10 codes for COPD mortality Mortality (case fatality); Limitation: no lung function measures	Adjusted HR for 10µg/m^3 increase in NO2 :1.11 (0.78-1.56)HR for 10µg/m3 increase in PM10 in older subjects: 1.14 (1.12-1.16); younger subjects: 1.11 (1.08-1.13)	No additional information about confounding available, study Population was defined by COPD admission, but no information on smoking or other confounders available
Zanobetti et. al. USA (2008)	1985-1999/ N= 1,039,287 hospital discharges of patients hospitalized with COPD (ICD-9 code 491;492;494-496 used to define COPD) ; Ages 65 and older	Cohort Follow-up duration: 4 years	Pollutants: Daily monitoring measures to create yearly averages of PM10 Traffic proximity: none	Mortality (case fatality); Limitation: no lung function measures	HR for 10µg/m3 increase in PM10 in older subjects: 1.14 (1.12-1.16); younger subjects: 1.11 (1.08-1.13)	Population was defined by COPD admission, but no information on smoking or other confounders available

Table 3: Lessons learned from reviewing the air pollution and COPD evidence and the remaining uncertainties in interpreting this literature

Topic	Limitations in interpretation
Epidemiologic evidence	In spite of plausible models of biologic mechanisms, direct epidemiologic evidence of the long-term effects of air pollution on COPD prevalence and incidence remains suggestive but not conclusive
COPD Phenotypes	A major obstacle to understanding causality relates to loose and heterogeneous definitions of COPD phenotypes.
Life-time Course of diseases	Air pollution affects the growth and decline of lung function but the link between these processes and the development of COPD is not well investigated.
Role of acute versus long-term effects	Air pollution causes acute respiratory symptoms and exacerbations of COPD. An accumulation of damage to airways resulting from these acute effects is a plausible basis for any link between air pollution and the development of COPD, but direct evidence is lacking