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Review article

Panel studies of air pollution in patients with COPD: Systematic review and meta-analysis

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ABSTRACT

Background: Epidemiological studies have shown an increase in morbidity and mortality rates in patients with chronic obstructive pulmonary disease (COPD) following exposure to elevated levels of air pollution. Panel studies have been used to assess short-term effects of air pollution which are not detected by registry studies, specifically lung function and symptoms. The aim of this systematic review was to assess the evidence of panel studies on acute effects of air pollution among patients with COPD.

Methods: We searched the PubMed database, and identified additional studies by inspecting reference lists and literature reviews. We identified and summarized 25 panel studies that were published between 1993 and February 2016. Results were presented in forest plots and effect estimates of sufficiently comparable outcomes and pollutants were summarized by a random-effects meta-analysis.

Results: Meta-analysis showed that a 10 $\mu g/m^3$ increase in ambient levels of particles less than 10 μm in diameter (PM_{10}) had a small, but statistically significant impact on FEV_1 (−3.38 mL, 95% CI −6.39 to −0.37) and PEF (−0.61 L/min, −1.20 to −0.01). There was significant heterogeneity across the included studies. A forest plot showing associations between PM_{10} and respiratory symptoms was also suggestive of an adverse effect of particulate air pollution, but this was not formally tested in a meta-analysis due to the heterogeneity of outcomes. Results for gaseous pollutants were inconsistent for lung function or symptoms.

Conclusions: Evidence from the identified panel studies indicated statistically significant associations of particulate matter air pollution with lung function in patients with COPD.

Contents

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation that is usually progressive and associated with an increased chronic inflammatory response in the airways and the lung to gases or particles. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as a post-bronchodilator fixed ratio of forced expiratory volume in 1 s and forced vital capacity (FEV_1/FVC) less than 0.70 (Vestbo et al., 2013). In 2013, the burden of disease attributable to COPD, estimated by the number of disability-adjusted life years (DALYs), was ranked the 5th highest in the world (Institute for Health Metrics and Evaluation, 2015).

Inhalation of tobacco smoke is the most important factor that contributes to the development and progression of COPD. Other causes are exposure to indoor air pollution due to the use of solid fuels, occupational exposures, and genetic predisposition (Eisner et al., 2010; van Gemert et al., 2015; Vestbo et al., 2013). There is also suggestive epidemiological evidence that long-term exposure to outdoor air pollution is associated with the development of COPD (Schikowski et al., 2014a, 2014b). On the other hand, it has been widely accepted that air pollution may cause acute health effects in individuals with pre-existing COPD. Several epidemiologic studies have shown an increase in morbidity and mortality rates, exacerbations, emergency room visits and hospitalizations in patients with COPD following exposure to elevated levels of air pollution (Zhang et al., 2016; Xu et al., 2016; Ko and Hui, 2012; Sint et al., 2008; Wedzicha and Seemungal, 2007). For example, a recent meta-analysis has shown that a 10 $\mu g/m^3$ increase in daily exposure to particles less than 2.5 μm in diameter ($PM_{2.5}$) resulted in a 3.1% increase in COPD hospitalizations and a 2.5% increase in COPD mortality (Li et al., 2015).

Literature reviews on short-term effects of air pollution in patients with COPD have mainly included registry-based research (Ko and Hui, 2012; Li et al., 2015; Sint et al., 2008). However, epidemiological studies on short-term effects of air pollution have additionally used a panel study design to investigate health effects not detected by the registry studies, specifically lung function and symptoms (Ward and Ayres, 2004). A panel study involves repeated measurements on individual subjects at regular short time intervals, whereby each subject acts as his/her own control. These prospective studies are frequently performed over a relatively short time period in comparison to many other studies with a longitudinal design (Tager, 2000). Panel study designs are generally used to assess acute health effects of a certain exposure, whereas other studies with a longitudinal design mostly examine the effects of a chronic exposure. A strength of panel studies is the availability of individual data. Panel studies may be able to detect less severe but more frequent effects than registry studies. A panel study design makes it possible to control for unmeasured confounders and modifiers, that generally do not vary over time. Furthermore, personal exposure measurements can be obtained (Janes et al., 2008; Tager, 2000; Trivellato, 1999).

To our knowledge, there are no reviews that focus specifically on panel studies investigating acute effects of air pollution in individuals with COPD. In this systematic review, we assessed the evidence of panel studies on acute effects of air pollution among COPD patients.

2. Methods

2.1. Systematic review

We used the PRISMA Statement as a guideline for reporting this systematic review (Moher et al., 2009). The PubMed database was searched using the following search term: ((English[Language] OR French[Language] OR German[Language] OR Dutch[Language])) AND (((panel OR longitudinal OR daily OR diary OR peak flow) AND (chronic obstructive pulmonary disease OR COPD OR emphysema OR chronic bronchitis) AND (air pollution OR air pollutants OR particulate matter OR PM2.5 OR PM10 OR nitrogen dioxide OR NO2 OR ozone))). The search was restricted to fully published original epidemiologic studies, until February 1, 2016. No limitations on publication dates or locations were applied in order to obtain an overview of the change in methodology and statistical analysis of panel studies over the previous decades. We included studies that defined COPD either by spirometry, or by a (self-reported) physician's diagnosis that was complemented with spirometry. Panel studies that included both COPD patients and individuals with other chronic respiratory conditions, such as asthma, were also incorporated in this review. No restrictions were made on type of air pollution and type of health outcomes. After the initial search in the PubMed database, reference lists of the identified papers were inspected as well as reviews on health effects of air pollution in patients with COPD. A search of the Web of Science database did not identify additional papers.

2.2. Meta-analysis

Information from each panel study was extracted and summarized, and presented individually. In addition, we made attempts to present study results in a comparable manner, by calculating coefficients per 10 $\mu g/m^3$ increase in pollutant concentration. If results for $PM_{2.5}$ were presented, but not for particles less than 10 μm in diameter (PM_{10}), we used a conversion factor to compute effect estimates for PM_{10}. We used one conversion factor (0.6), which is an average of many measurements taken in different European regions (Eeftens et al., 2012). The effect of air pollutants on health outcomes may not be immediate, but may occur after a certain lapse of time, called a lag. If a study analysed multiple pollutant lags, either the largest effect was used for the meta-analysis, or the effect that was presented in the article (not all lags that were analysed were always shown), following the approach of a meta-analysis of panel studies in children (Ward and Ayres, 2004). Comparable results from at least six studies were presented in forest plots and effect estimates of directly comparable outcomes and pollutants were summarized by a DerSimonian and Laird (1986) random-effects meta-analysis using the *metafor* package in R (version 3.0.2) (Viechtbauer, 2010). We performed a leave-one-out sensitivity analysis to test the influence of individual studies on the overall effect estimates. We evaluated heterogeneity by stratified analyses on study characteristics such as inclusion of current smokers in the panel.

3. Results

The search of the PubMed database generated a total of 399 articles. In total, 25 of these were eligible for inclusion. The

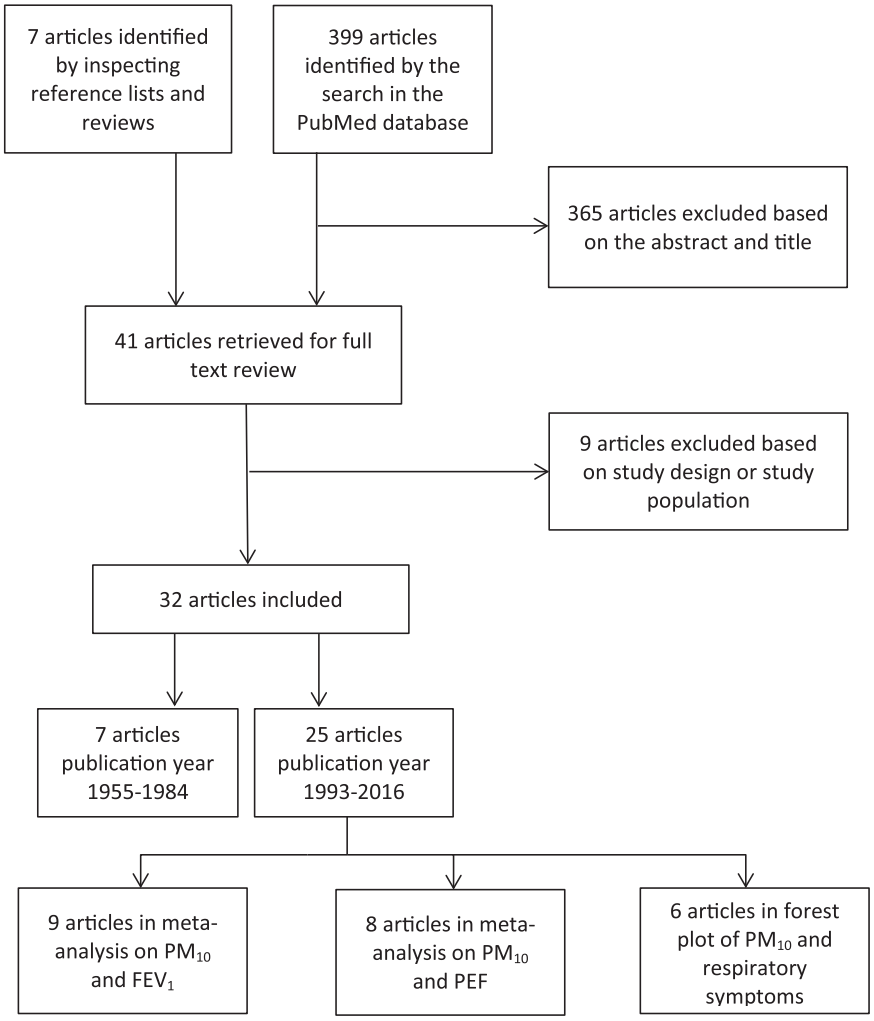

Fig. 1. Flow diagram of the inclusion of panel studies.

majority of the articles that were not eligible for inclusion in our review did not use a panel study design. Seven additional studies were identified by inspecting reference lists and reviews on health effects of air pollution in COPD patients, resulting in 32 articles that were included in our review (Fig. 1). Seven studies were published between 1955 and 1984. Given the limited statistical analyses (graphical displays, descriptive statistics) that were presented in the earlier studies, we decided to focus the review on the 25 studies that were published between 1993 and February 2016.

3.1. Early panel studies (1955–1984)

The first panel studies on the acute effects of air pollution in COPD patients were conducted in London between 1955 and 1968 (Lawther et al., 1970; Waller and Lawther, 1955, 1957), in response to the London fog of December 1952. Until February 1953, around 12,000 excess deaths occurred due to the acute and persisting effects of extremely high concentrations of sulfur dioxide (SO_2), smoke, and other air pollutants (Bell et al., 2004). This smog episode initiated epidemiological studies that examined the effects of outdoor air pollution on health outcomes, in particular in susceptible subgroup such as patients with chronic lung diseases. These early studies concluded, mainly based on graphical displays, that peaks in smoke and SO_2 concentrations in the air were correlated with a temporary deterioration in the clinical condition of individuals with COPD.

In the 1960s, panel studies in COPD and asthma patients were also carried out in Chicago and Baltimore, showing associations between (lagged) air pollution levels and respiratory symptoms (Burrows et al., 1968; Carnow et al., 1969) and lung function (Spicer et al., 1966). In the early 1980s, a panel study was performed among subjects living near a coal-fired power plant in Finland, including 43 hospital patients with COPD (Pershagen et al., 1984). On days with high ambient soot levels, an increase in respiratory symptoms was observed in these patients, but the pollution levels could not be linked to the plant emissions.

3.2. Characteristics of included studies (1993–2016)

3.2.1. Setting and study population

Characteristics and results of the 25 panel studies that were published between 1993 and February 2016 are summarized by publication date in Table 1. Seventeen studies only included individuals with COPD. The remainder of the panel studies also included adults with asthma, ischemic heart disease, children with asthma, and healthy participants. A few of these studies did not present the results for the COPD patients separately (Bruske et al., 2010; de Hartog et al., 2010; Higgins et al., 1995, 2000; Hildebrandt et al., 2009; Karakatsani et al., 2012).

Eleven studies were conducted in Europe, nine in North America, three in China, and one each in New Zealand and Mexico. Seven studies were conducted in the summer, and ten were winter studies. Seven studies were performed throughout the year, and one study was executed during two one-month periods in the

Table 1
Main characteristics of 25 panel studies on acute effects of air pollution in COPD patients, published between 1993 and February 2016.

Location (Ref.)	Period	Population	Pollutants	Acute effect	Statistical approach	Main findings
Salt Lake City, Utah (Pope and Kanner, 1993)	Two visits; 10 to 90 days apart, 1987 to 1989	392 smokers with mild to moderate COPD	PM_{10}	FEV_1, FVC and FEV_1/FVC	Regression of ΔFEV_1, ΔFVC, and $\Delta FEV_1/FVC$ on ΔPM_{10}	Small, inverse associations between ΔPM_{10} and ΔFEV_1 and $\Delta FEV_1/FVC$ were observed.
Widnes and Runcorn, UK (Higgins et al., 1995)	28 days, August to September 1991	75 adults with asthma or COPD	O_3, SO_2, NO_2	PEF, symptoms, and bronchodilator inhaler use	Multiple linear and logistic regression analysis	SO_2 was associated with increases in PEF variability, bronchodilator use and wheeze. O_3 was associated with bronchodilator use, dyspnoea, eye irritation and minimum PEF levels. No associations with NO_2.
Christchurch, New Zealand (Harré et al., 1997)	June to August 1994	40 adults aged over 55 years with COPD	PM_{10}, NO_2, SO_2, CO	PEF, symptoms, nebulizer and inhaler use	A log-linear regression model for PEF and Poisson regression models for symptoms	No association was found between any of the pollutants and PEF. Increased PM_{10} concentrations were associated with night time chest symptoms. Enhanced levels of NO_2 were associated with increased use of reliever inhaler, and for lag 1 with nebulizer use.
Los Angeles, California (Linn et al., 1999)	Four consecutive 24-h periods during autumn and winter. Study year was not reported.	30 subjects with severe COPD	PM_{10}, $PM_{2.5}$, O_3, NO_2, CO. Indoor and outdoor PM_{10}, $PM_{2.5}$, personal PM_{10}, $PM_{2.5}$, O_3, NO_2	PEF, FEV_1, FVC, blood pressure, heart rates, supra ventricular ectopic beats, saturation, symptoms	Analyses of covariance with repeated measures on subjects and time-varying covariates	Only blood pressure was associated with PM, more with central monitoring station PM than with personal or indoor PM. Mean diastolic blood pressure was positively associated with same-day or previous day PM_{10}. Systolic blood pressure increased significantly with previous day PM_{10}, but not with same-day PM_{10}.
Widnes and Runcorn, UK (Higgins et al., 2000)	28 days, August to September 1991	35 adults with asthma or COPD, reactive to methacholine	O_3, NO_2, fungal spore counts	PEF, symptoms	Multiple linear and logistic regression analysis	Spore count was associated with lower PEF, and increased PEF variability and wheeze, especially on high O_3 days.
Vancouver, Canada (Brauer et al., 2001)	Seven 24-h periods between April and September, 1998	16 currently non-smoking patients with COPD	Ambient PM_{10}, $PM_{2.5}$, SO_4^{2-}, personal $PM_{2.5}$ and SO_4^{2-} exposure	FEV_1, blood pressure, supraventricular ectopy, heart rate, heart rate variability, symptoms and bronchodilator use	Pooled ordinary least squares regressions. Logistic regression to examine the associations between symptoms and exposure measures	Exposure to ambient PM_{10} was associated with an increase in supraventricular arrhythmic beats. No associations between air pollution and lung function were found.
Paris, France (Desqueyroux et al., 2002)	October 1995 to November 1996	39 adults with severe COPD	PM_{10}, SO_2, NO_2, O_3	Exacerbations of COPD	GEE, exchangeable correlation structure	Episodes of exacerbation of COPD were associated with O_3. No association was found between exacerbations of COPD and PM_{10}, SO_2 and NO_2.
Denver, Colorado (Silkoff et al., 2005)	The winters of 1999–2000 (first winter) and 2000–2001 (second winter)	16 and 18 adults with advanced COPD (first and second winter, respectively)	PM_{10}, $PM_{2.5}$, NO_2, CO	FEV_1, PEF, symptoms and rescue medication use	Mixed-effects models for the analysis of FEV_1 and PEF. GEE, first-order autoregressive correlation for medication use and symptom score	In the first winter, morning FEV_1 increased with PM_{10} (lag 0), NO_2 (lags 1 and 2) and with CO (lag 1). Morning PEF was positively associated with PM_{10} and $PM_{2.5}$ (lag 0) and with NO_2 (lags 1 and 2). In the second winter, evening FEV_1 was negatively associated with CO (lag 2). Morning PEF decreased with NO_2 (lag 0 and 1), evening PEF decreased with PM_{10} (lag 2). At lag 0, PM_{10}, NO_2 and CO were associated with increasing medication use, NO_2 with symptom score.
Denver, Colorado (Sutherland et al., 2005)	June 2002, during a large wildfire	21 COPD patients	PM_{10}, $PM_{2.5}$, CO	Symptom scores	Repeated measurements ANOVA	Symptom scores were increased during days with significantly increased concentrations of PM.
Vancouver, Canada (Ebelt et al., 2005)	Seven 24-h periods between April and September, 1998	16 currently non-smoking patients with COPD	Nonambient $PM_{2.5}$, ambient $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} and SO_4^{2-}, personal exposure to ambient $PM_{2.5}$	FEV_1, systolic and diastolic blood pressure, supraventricular ectopy, heart rate, and heart rate variability	Mixed-effects models	Estimated ambient PM exposures were associated with decreased lung function, increased heart rate, decreased systolic blood pressure and increased supraventricular ectopic heartbeats. Nonambient and total particle exposures were not related to any

Table 1 (*continued*)

Location (Ref.)	Period	Population	Pollutants	Acute effect	Statistical approach	Main findings
						of the health outcomes.
Seattle, Washington (Jansen et al., 2005)	Twelve days during the winter of 2002–2003	16 subjects with asthma or COPD	Indoor, outdoor and central site PM_{10}, $PM_{2.5}$, BC, personal PM_{10}, BC	FE_{NO}, FEV_1, FVC, FEV_1/FVC, PEF, mid-expiratory flow, blood pressure, oxygen saturation of the arterial blood and pulse rate	A linear mixed-effects model with random intercept	No significant associations were found between PM and BC and FE_{NO}, spirometry measurements, blood pressure, oxygen saturation of the arterial blood, or pulse rate in subjects with COPD.
Rome, Italy (Lagorio et al., 2006)	May to June and November to December 1999	11 patients with COPD, 11 with asthma, and 7 with ischemic heart disease	PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, metals, NO_2, CO, SO_2 and O_3.	FVC and FEV_1	GEE, first-order autoregressive correlation structure	In the COPD panel, $PM_{2.5}$ and PM_{10} were negatively associated with FVC and FEV_1. NO_2 was negatively associated with FEV_1. Zinc was associated with decreases in FEV_1 and FVC. The associations were similar in size but less consistent for iron and nickel.
Seattle, Washington (Trenga et al., 2006)	26 periods of 10 days, 1999 to 2002	24 adults with and 33 without COPD and 17 children with asthma	Personal, indoor, outdoor and central site $PM_{2.5}$; outdoor $PM_{10-2.5}$	FEV_1 and PEF	Mixed-effects longitudinal regression models	Associations between decrements in FEV_1 and central site $PM_{2.5}$ were observed for 1-day lagged exposure in COPD patients. No associations between PEF and PM exposure were observed for adult participants.
Erfurt, Germany (Hildebrandt et al., 2009)	12 clinical visits between 2001 and 2002	38 male patients with a history of chronic pulmonary disease	PM_{10}, UFP, AMP, EC, OC, NO, NO_2, CO and SO_2	Several blood markers	Additive mixed models with random patient intercept	Fibrinogen levels were positively associated with an increase in UFP, PM_{10}, EC, OC, CO and NO. E-selectin increased in association with ACP and PM_{10} at lag 1. Prothrombin fragment 1+2 decreased with all air pollutants at lag 4 except for NO and UFP. Von Willebrand factor antigen decreased with increasing concentrations of all air pollutants.
Amsterdam, Athens, Birmingham, Helsinki (de Hartog et al., 2010)	One monitoring week between 2002 and 2004	135 patients with asthma or COPD	Indoor, outdoor and central site PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$ and PNC	FEV_1, FVC, and PEF	Mixed models	No consistent associations between FEV_1, FVC and PEF and particulate air pollution were observed.
Erfurt, Germany (Bruske et al., 2010)	12 clinical visits between 2001 and 2002	38 male patients with a history of chronic pulmonary disease	PM_{10}, UFP, AMP, EC, OC, NO, NO_2, CO and SO_2	Differential white cell blood count	Additive mixed models with random patient intercepts	An increase in all particulate pollutants was associated with a decrease in polymorphonuclear leukocytes and platelets within the first 24 h (most pronounced for ACP). Monocytes increased in association with UFP and NO. Lymphocytes increased within 24 h in association with NO and CO.
London, UK (Peacock et al., 2011)	October 1995 to October 1997	94 moderate to severe COPD patients	PM_{10}, black smoke, NO_2, SO_2 and O_3	FEV_1, FVC, PEF, COPD exacerbations, symptoms	GEE, independent or first-order autoregressive correlation structure	Increased air pollution levels were associated with symptoms but not lung function. PM_{10} (lag 1) was significantly associated with dyspnoea. PM_{10} and black smoke were associated with an increase in the odds of a symptomatic fall in peak flow rate.
Amsterdam, Athens, Birmingham, Helsinki (Karakatsani et al., 2012)	Six months between 2002 and 2004	136 patients with asthma or COPD	Central site PM_{10}, $PM_{10-2.5}$, $PM_{2.5}$, PNC, O_3 and NO_2	Symptoms, limitation in activities due to breathing problems	Fixed effects models and random intercept logistic regression models	An increase in previous day $PM_{10-2.5}$ was associated with limitation in walking and most symptoms. O_3 was associated with cough at lag 0, 1 and 2 and with waking with breathing problems at lag 0. $PM_{2.5}$ and NO_2 were not consistently associated with outcomes.
Eight regions in Switzerland (Mehta et al., 2012)	Up to six monitoring periods of four weeks in 1992 and 1993	459 asthma or COPD patients and healthy adults	TSP and NO_2	Respiratory symptom-related doctor visits	Time-stratified case-crossover analysis	The largest increase in doctor visits for respiratory symptoms was found in the COPD patients. An increase in NO_2 was associated with an increase in doctor visits over the first week following exposure. Results for

United States (Kariisa et al., 2015)	Up to 6 clinical visits between 1998 and 2003	1218 severe emphysema patients	$PM_{2.5}$ and O_3	FEV_1, FVC, symptom score	Linear mixed models	TSP were similar. $PM_{2.5}$ (lag 0) was associated with lower post-bronchodilator FVC and (lag 3) FEV_1.
London, UK (Alahmari et al., 2015)	April 2011 to March 2013	73 moderate to very severe COPD patients	PM_{10} and O_3	Daily step count, PEF, symptoms	GEE, independent correlation structure	O_3 (lag 0) was associated with lower step count, PEF and dyspnoea (over the whole week). PM_{10} (lag 0) was associated with step count during weekdays only.
Mexico City (Cortez-Lugo et al., 2015)	Up to three periods of twelve days, 2000	29 moderate to very severe COPD patients	Personal $PM_{2.5}$	PEF, respiratory symptoms, medication	GEE, exchangeable correlation structure	$PM_{2.5}$ (lag 2) was associated with lower PEF levels, and an increase of reported cough. $PM_{2.5}$ was inversely associated with cold/flu (lag 0) and wheeze (lag 2 and 3).
Shanghai, China (Chen et al., 2015)	Six weekly visits, May to July 2014	30 patients with mild-to-moderate COPD	$PM_{2.5}$, EC, OC, eight inorganic ions	FE_{NO}, DNA methylation of *NOS2A* promoter	Linear mixed models	$PM_{2.5}$ (lag 1) was associated with increased FE_{NO} and decreased *NOS2A* methylation. Constituent-specific associations with OC, EC, NO_3^-, NH_4^+
Guangzhou, China (Zhang et al., 2015)	Six visits, two per year (November to December 2009, 2010 and 2011)	36 male patients with stable COPD	PM_{10}, NO_2, SO_2	Blood markers of coagulation (D-dimer, platelets)	Linear mixed models	NO_2 and SO_2 were associated with higher platelet counts and D-dimer levels.
Beijing, China (Ni et al., 2016)	Two to thirteen visits, 2013–2014	33 stable COPD patients	Central site PM_{10} and $PM_{2.5}$, modelled PM_{10} and $PM_{2.5}$	FEV_1, FVC, and PEF	Linear mixed models	Ambient $PM_{2.5}$ levels were inversely associated with FVC and FEV_1. PM_{10} was associated with a lower FVC. Associations based on modelled exposure were attenuated

AMP, accumulation mode particles; BC, black carbon; CO, carbon monoxide; EC, elemental carbon; FE_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GEE, Generalized estimating equations; NH_4^+, ammonium; NO_2, nitrogen dioxide; NO_3^-, nitrate; OC, organic carbon; O_3, ozone; PEF, peak expiratory flow; PM2.5, particles less than 2.5 μm in diameter; PM_{10}, particles less than 10 μm in diameter; PNC, particle number concentration; SO_2, sulfur dioxide; SO_4^{2-}, sulphate; TSP, total suspended particulate matter; UFP, ultrafine particles.

winter and spring. The follow-up periods of the panel studies ranged from a few consecutive days or a few clinical visits, to a mean follow-up of 518 days (Peacock et al., 2011). In one study, the participants only underwent two spirometry visits, between 10 and 90 days apart (Pope and Kanner, 1993).

3.2.2. Measured pollutants

Most panel studies used one or more central monitoring sites to measure daily outdoor air pollutant levels, but a few studies also measured personal exposures (Brauer et al., 2001; Cortez-Lugo et al., 2015; Linn et al., 1999; Trenga et al., 2006). Other studies also measured particle concentrations both inside and outside subjects' homes (de Hartog et al., 2010; Linn et al., 1999; Trenga et al., 2006), and one study specifically investigated the difference between ambient particle concentrations measured at a central monitoring site and personal exposure to ambient particles (Ebelt et al., 2005). One study used outdoor PM concentrations obtained from central monitoring sites and also developed a time-weighed model to estimate outdoor-originated equivalent personal exposure (Ni et al., 2016). Measurements of particles were included in the majority of the identified panel studies, but a large variety of other pollutants have been evaluated as well (Table 1). Eighteen studies reported measurements of PM_{10}, five studies measured coarse particles ($PM_{10-2.5}$), and fourteen studies included $PM_{2.5}$. Measurements of nitrogen dioxide (NO_2) were included in twelve panel studies, eight studies measured ozone (O_3), eight studies SO_2, and six studies carbon monoxide (CO).

3.2.3. Health outcomes

Seventeen of the identified studies examined acute effects of air pollutants on pulmonary function (forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and/or peak expiratory flow (PEF)). In most of these studies, subjects performed lung function tests unsupervised using a spirometer or peak flow meter. In two studies, subjects underwent two (Pope and Kanner, 1993) or up to six (Kariisa et al., 2015) spirometry visits in a clinical center, in five studies participants underwent supervised spirometry in their homes (Brauer et al., 2001; Ebelt et al., 2005; Jansen et al., 2005; Lagorio et al., 2006; Trenga et al., 2006), and in one study the location of supervised spirometry was not provided (Ni et al. 2016). In most of the eleven studies that included symptoms or medication use, participants registered these using diary cards. Alternatively, symptoms were assessed by a daily telephone interview (Sutherland et al., 2005) and during a clinical visit (Kariisa et al., 2015). One study included self-reported limitation in activities due to breathing problems (Karakatsani et al., 2012), whereas a more recent study investigated physical activity by measuring step counts (Alahmari et al., 2015). Two studies investigated the effects of air pollution on physician-diagnosed exacerbations of COPD, one study examined respiratory symptom-related doctor visits, and two studies assessed fractional exhaled nitric oxide (FE_{NO}). The remainder of the panel studies examined cardiovascular outcomes, blood markers, methylation of buccal cell DNA, and differential white blood cell count (Table 1).

3.2.4. Statistical approach of included studies

The identified studies show a change in the statistical approach of panel studies over the past decades. More recent panel studies applied more advanced statistical methods that take into account the dependency of observations, like mixed-effects models or Generalized Estimating Equations (GEEs) with first-order autoregressive, exchangeable, or independent covariance structures (Janes et al., 2008). The majority of panel studies examined the acute effects of air pollution on health outcomes for different lags. Although most identified panel studies examined health effects up to lag 2 (a delay in effect of 48 h), several studies included more

lags, or cumulative or average exposures over several lags. Most studies adjusted for potential time-variant confounders, such as weather (ambient temperature, relative humidity), linear trend and day of the week.

3.3. Results of included studies (1993–2016)

An overview of the results and characteristics of the included studies is shown in Table 1. In this section, we focus on the results of the panel studies regarding measures of lung function.

A study conducted in Salt Lake City has shown negative associations between PM_{10} and FEV_1 and FEV_1/FVC. A 100 $\mu g/m^3$ increase in PM_{10} concentration was associated with a decline in FEV_1 of 2% (Pope and Kanner, 1993). The results of this study are based on only two spirometry visits, but in a large study population.

A study performed in two towns in England has shown that PEF variability was associated with increased SO_2 concentrations at lag 0 and 1 (Higgins et al., 1995). Minimum PEF levels were associated with increasing concentrations of O_3. No associations where observed for NO_2. This study included 75 adults with asthma or COPD, and did not display separate results for the COPD patients. In a subsample of 35 methacholine responsive participants, which included only few COPD patients, fungal spore counts were associated with PEF variability, particularly on high O_3 days (Higgins et al., 2000).

Harré et al. (1997) did not observe an association between PM_{10} and concentrations of SO_2, NO_2 or CO and PEF in forty subjects with COPD.

A study on thirty COPD patients in Los Angeles used measurements of PM at a central monitoring site, inside and outside the subject's home, and also measured personal exposure to PM (Linn et al., 1999). PM_{10} concentrations were not associated with FEV_1 and FVC.

Two studies have been performed on the same panel of sixteen COPD patients in Vancouver, Canada (Brauer et al., 2001; Ebelt et al., 2005). Brauer et al. (2001) focused on the effects of ambient PM_{10} and $PM_{2.5}$ concentrations and personal $PM_{2.5}$ exposure on health outcomes. No significant associations were found between PM and lung function. Ebelt et al. (2005) investigated the difference in health effects of nonambient $PM_{2.5}$, originating from indoor sources, and ambient PM concentrations. Personal exposure was measured for $PM_{2.5}$ using personal monitors worn by the study participants. This measured personal exposure incorporates contributions from ambient and nonambient $PM_{2.5}$, encountered both indoors and outdoors. Nonambient $PM_{2.5}$ exposures were subsequently estimated based on time-activity data obtained from diaries and the use of sulphate measurements as a tracer for indoor infiltration of ambient particles. In addition, daily ambient $PM_{2.5}$ monitoring was performed at five fixed sites. The authors found that the mean level of personal $PM_{2.5}$ exposure was 18.5 $\mu g/m^3$ and that this personal exposure was largely composed of nonambient particle exposure (mean: 10.6 $\mu g/m^3$). Estimated ambient PM exposures were associated with a decreased FEV_1. Total and nonambient PM exposure were not associated with respiratory outcomes.

One study in patients with advanced COPD was executed in the winters of 1999–2000 and 2000–2001 in Denver (Silkoff et al., 2005). The results of the first winter were opposite from what was expected. Morning FEV_1 increased with PM_{10}, and morning PEF increased with PM_{10} and $PM_{2.5}$, both at lag 0. However, in the second winter, PEF decreased with PM_{10} in the evening at lag 2. The average PM_{10} concentration was 25.1 $\mu g/m^3$ during the first winter and 29.6 $\mu g/m^3$ in the second winter. Peak levels were 72 $\mu g/m^3$ in both winters. The authors found a similar pattern of health effects of gaseous pollutants as was found for PM air pollution. In the first winter, morning FEV_1 and PEF increased with NO_2 at lags 1 and 2, and morning FEV_1 increased with CO at lag 1. In the second winter, evening FEV_1 decreased significantly with CO at lag 2, and morning PEF decreased with NO_2 at lag 0 and 1.

Jansen et al. (2005) found no associations between PM and black carbon (BC) and lung function in nine subjects with COPD.

A panel study conducted in Rome in the spring and winter of 1999 has shown that ambient PM_{10} and $PM_{2.5}$ were negatively associated with FVC and FEV_1 (Lagorio et al., 2006). The zinc content of PM was associated with decreases in FEV_1 and FVC. The associations were similar in size and direction for iron and nickel, but not statistically significant. A 10 $\mu g/m^3$ increase in NO_2 concentrations during the previous 24 and 48 h was associated with a decrease in the percentage of predicted FEV_1 of 1.17 and 1.38, respectively.

In a study from Seattle (Trenga et al., 2006), a 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentrations on the previous day was associated with a decrease of 70.8 mL in FEV_1 in COPD patients. This association was not observed in adults without COPD. No associations between PM exposure and PEF were found.

In a multi-center panel study in 135 patients with asthma or COPD from Amsterdam, Athens, Birmingham and Helsinki, De Hartog et al. (2010) measured FVC, FEV_1 and PEF three times a day for a period of one week. Lung function was not consistently associated with PNC (particle number concentration), PM_{10}, $PM_{2.5}$ and $PM_{10-2.5}$, measured at a central site in each city and both inside and outside subjects' residences. Analyses restricted to asthmatics were performed, which also showed no consistent associations.

Two extensive panel studies were conducted in the London COPD cohort, one investigated pulmonary function and symptoms among 94 patients between 1995 and 1997 (Peacock et al., 2011), and one study was performed between 2011 and 2013 – with inclusion of new participants (Alahmari et al., 2015). The earlier study did not find associations between particulate air pollution, SO_2 and O_3 and lung function (Peacock et al., 2011). In 73 patients from the more recent cohort, PM_{10} was not associated with PEF (Alahmari et al., 2015).

In severe emphysema patients across the United States, $PM_{2.5}$ was associated with a lower post-bronchodilator FVC (same day) and FEV_1 (lag 3) (Kariisa et al., 2015).

In Mexico City, a 10 $\mu g/m^3$ increase in $PM_{2.5}$ was associated with a 1.4 L/min (morning) and a 3.0 L/min (evening) lower PEF at lag 2 (Cortez-Lugo et al., 2015).

A recent panel study examining COPD patients living in Beijing showed that ambient $PM_{2.5}$ levels (average 102.7 $\mu g/m^3$) were inversely associated with FVC and FEV_1. PM_{10} was associated with a lower FVC (Ni et al., 2016).

3.4. Summary of results

Associations between an increase in PM_{10} and changes in FEV_1 and PEF were summarized by a random-effects meta-analysis. Fig. 2 shows a forest plot, presenting estimates of change in FEV_1 per 10 $\mu g/m^3$ increase in PM_{10} level from nine panel studies. The summary estimate from the random-effects model was −3.38 mL (−6.39 to −0.37; $p=0.028$). Significant heterogeneity was found ($Q=44.8$, $p<0.001$). Summary estimates in the leave-one-out sensitivity analysis ranged between −4.89 (−9.19 to −0.58) and −2.86 (−5.65 to −0.07) after omitting Peacock et al. (2011) and Trenga et al. (2006), respectively (Supplementary Fig. S1). From two studies, no effect estimates could be extracted (Jansen et al., 2005; Linn et al., 1999), and a re-analysis of a panel study with improved exposure estimation (Ebelt et al., 2005) was included in favour of the older publication (Brauer et al., 2001).

The forest plot in Fig. 3 shows the change in PEF per 10 $\mu g/m^3$ increase in PM_{10} level in eight studies. The summary estimate was

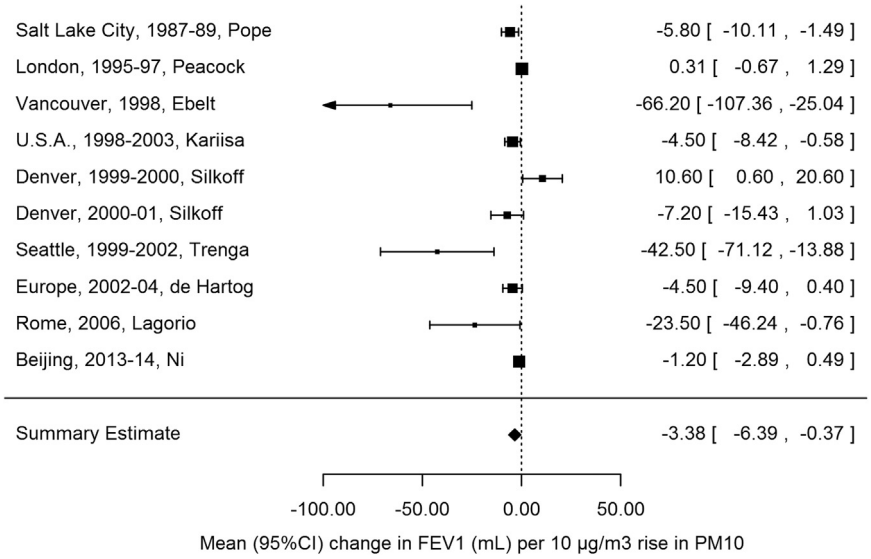

Fig. 2. Forest plot of change in FEV_1 (mean and 95% confidence intervals) expressed as mL per 10 $\mu g/m^3$ increase in PM_{10} level. The summary estimate (−3.38 (−6.39 to −0.37), p=0.028) was calculated using a random-effects meta-analysis. I^2=79.9%, test for heterogeneity Q=44.8, df=9, p < 0.001. Studies by Trenga et al. and Kariisa et al. reported results for $PM_{2.5}$, which were converted to PM_{10}.

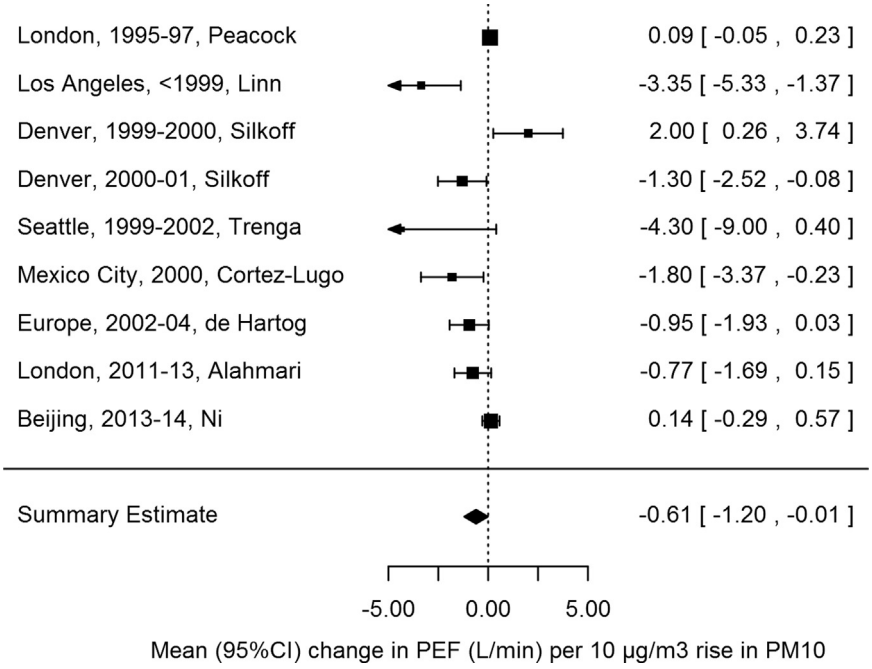

Fig. 3. Forest plot of change in PEF (mean and 95% confidence intervals) expressed as L/min per 10 $\mu g/m^3$ increase in PM_{10} level. The summary estimate (−0.61 (−1.20 to −0.01), p=0.046) was calculated using a random-effects meta-analysis. I^2=78.3%, test for heterogeneity Q=36.9, df=8, p < 0.001. Studies by Linn et al., Trenga et al., Cortez-Lugo et al., and de Hartog et al. reported results for $PM_{2.5}$, which were converted to PM_{10}.

−0.61 L/min (−1.20 to −0.01; p=0.046). The summary estimate ranged between −0.89 (−1.78 to 0.01) after omitting Peacock et al. (2011), and −0.39 (−0.92 to 0.15) after omitting Linn et al. (1999) (Supplementary Fig. S2). Two studies could not be included in the meta-analysis: Harré et al. (1997) reported only PEF variability and Jansen et al. (2005) did not show PEF results.

Additional characteristics of panel studies included in the meta-analysis on PM_{10} and lung function are shown in Supplementary Table S1. The negative associations between PM_{10} and FEV_1 and PEF tended to be more pronounced in studies that excluded current smokers, and in studies that used longer lags (> lag 1) (Supplementary Table S2), though the difference in summary estimates between these groups of studies was not statistically significant. Significant heterogeneity remained within the groups of panel studies with and without smokers. There was no heterogeneity between the effect estimates of the 3–4 studies that used longer lags.

Fig. 4 shows a forest plot of odds ratios for the association between respiratory symptoms (or exp(beta) for symptom score) and a 10 $\mu g/m^3$ increase in PM_{10} level from six studies. Three studies were not included: Sutherland et al. (2005) and Linn et al. (1999) showed significantly increased symptom incidence, but results could not be expressed in a standardized manner, and Brauer et al. did not show symptom results (Brauer et al., 2001). A summary estimate was not calculated because of the heterogeneous outcome definitions (various lower respiratory

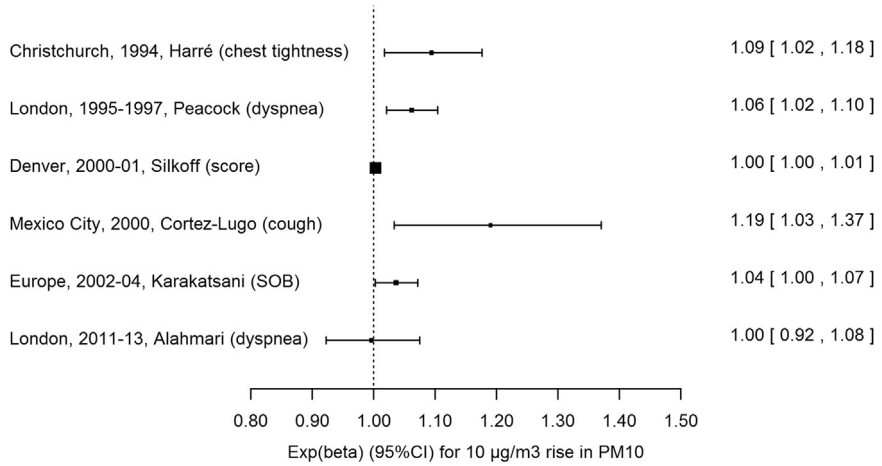

Fig. 4. Forest plot of exp(beta) and 95% confidence intervals for the association between respiratory symptoms (or symptom score) and a 10 $\mu g/m^3$ increase in PM_{10} level. SOB: shortness of breath. A summary estimate was not calculated because of the heterogeneous outcome definitions and scale of symptom scores. The effect estimate from the study by Kariisa et al. is based on linear regression (symptom score) and therefore not shown in the forest plot (beta 0.12, SE 0.13). Studies by Cortez-Lugo et al. and Kariisa et al. reported results for $PM_{2.5}$, which were converted to PM_{10}.

symptoms, symptom scores, and cough). Overall, a positive pattern of associations was observed.

An overview of associations between NO_2 and FEV_1, PEF, and symptoms is presented in Supplementary Table S3. We did not conduct a meta-analysis for NO_2 because of the low number of studies that could be presented in a comparable manner (< 5).

4. Discussion

This literature review identified and summarized 25 panel studies on the acute effects of air pollution in patients with COPD that were published between 1993 and February 2016. The majority of the identified panel studies suggested associations of air pollution with acute health outcomes in COPD patients. Most studies explored effects of PM levels on lung function or respiratory symptoms. Meta-analysis showed that a 10 $\mu g/m^3$ increase in ambient PM_{10} levels was associated with a small, but statistically significant decrease of FEV_1 (-3.38 mL) and PEF (-0.61 L/min). A forest plot of PM_{10} and symptoms was also suggestive of an association with particulate air pollution, but this was not formally tested in a meta-analysis due to the heterogeneity of outcomes. The observed effect estimates varied considerably, and many adverse health effects depended on the number of lag days. The results for gaseous pollutants were inconsistent for lung function or symptoms.

We expressed effect estimates for commonly used increments of 10 $\mu g/m^3$ PM_{10}. To compare lung function on high and low pollution days, a contrast of 50–100 $\mu g/m^3$ is more meaningful. The PM_{10} average effect then translates into a 20–35 mL decrease in FEV_1, equivalent to about 1–2% of typical population mean FEV_1 values of adult COPD patients. A previous paper documented that small changes in population mean PEF of children associated with PM_{10}, translated into a substantial increase in the prevalence of clinically significant PEF decrements (Hoek et al., 1998).

A limitation in the design of this literature review is that we decided to include panel studies that examined not only individuals with COPD, but also subjects with other (respiratory) diseases. There is substantial overlap between COPD and asthma, especially in elderly patients, making the diagnosis complex (de Marco et al., 2013; Postma and Rabe, 2015). Some of the panel studies did not display results for COPD patients separately, but we included these studies in this review to obtain a complete overview of panel studies in individuals with COPD.

Significant heterogeneity of the estimates of the effect of PM_{10} on lung function was found. There are several possible explanations for the heterogeneity in the results of the identified panel studies. Some of the variability across studies is likely due to random error. The sample size and follow-up period differed considerably between the studies. Furthermore, the panel studies have been performed in different years and countries. Studies have used PM_{10} to represent a complex mixture of particles from different sources. Evidence is increasing that particle composition affects health effects (World Health Organization, 2013). Composition of PM_{10} differs in space and time. Different results in the same COPD panel may be attributable to different sources and composition of air pollution, as was shown in a panel from Denver that was studied in two consecutive winters and during a wildfire (Silkoff et al., 2005; Sutherland et al., 2005). Heterogeneity existed also between the examined study populations, and the negative associations between PM_{10} and lung function tended to be weaker in panel studies that included current smokers, and stronger in studies that reported longer lags. Some studies included COPD patients, regardless of the stage of the disease, whereas severity was an inclusion criterion in others. Severity is associated with medication use that may prevent exacerbations (Wedzicha et al., 2012), which may explain the small changes in lung function in response to air pollution in patients with severe COPD (Alahmari et al., 2015; Kariisa et al., 2015; Peacock et al., 2011). All panel studies that were included in the meta-analysis on lung function examined both male and female COPD patients. Furthermore, study design, exposure assessment, and statistical approach of the panel studies were broadly similar, and are thus unlikely to explain major heterogeneity in the results.

Several limitations of the identified panel studies need to be addressed. Most panel studies have used central site monitoring data to represent exposure. Although validation studies have documented moderately high correlations between outdoor and personal exposure in time (Brunekreef and Holgate, 2002), the ratio between personal and outdoor exposure likely differs with time activity patterns, adding further to heterogeneity. However, taking daily personal exposure measurements is not feasible in larger panel studies with a longer follow-up duration. Most studies tested multiple associations between several air pollutants at various time lags and several health outcomes, which may have yielded chance findings. Furthermore, asking patients to record symptoms or exacerbations in a diary is a more subjective method than assessment of symptoms or exacerbations by a physician.

There is a risk of spurious positive associations if patients over-report their symptoms on days with high exposure levels, although this is an unlikely explanation in most studies as subjects are generally unaware of exposure levels. Finally, although most studies adjusted for time-variant variables, there may be residual confounding, for instance due to seasonal influenza infections that may co-occur with periods of low or high levels of air pollution. Publication bias is another possible concern, although exploring this by funnel plots is probably not reliable for this type of observational studies. For example, a study with negative results on PM and lung function may have reported significant effects on blood pressure or exhaled NO. Furthermore, the smaller studies may have more carefully assessed exposure and outcomes, resulting in larger effect estimates (e.g. Ebelt et al., 2005).

Most panel studies were conducted in Western countries, although the burden of disease attributable to ambient air pollution occurs mainly in developing countries. Moreover, studies were mainly focused on COPD patients who lived in urban areas. Due to intensive livestock farming, air pollution may be considerable as well in rural areas (Brunekreef et al., 2015). A panel study in a swine farming area in North Carolina found associations between air pollutant levels and respiratory symptoms and FEV_1 in healthy adults (Schinasi et al., 2011), and recent cross-sectional studies suggested an increased risk of exacerbations among COPD patients living near a large number of livestock farms (Borlée et al., 2015; van Dijk et al., 2016).

In summary, this systematic review and meta-analysis of panel studies on acute effects of air pollution in patients with COPD has shown adverse effects of ambient PM_{10} concentrations on FEV_1 and PEF. Although the mean effect estimates were small, peak pollution levels may have a clinically relevant impact in vulnerable patients with reduced lung function, which is corroborated by hospital-based time-series in patients with COPD. Since panel studies are less sensitive to confounding than cross-sectional or case-control studies, they could be helpful to examine emerging air pollution problems in Asia and other parts of the world, especially with well-characterized exposures and objectively measured outcome data. The study design can be further improved by the use of new smart devices and applications, e.g. portable sensors to monitor exposures or physical parameters, activity meters, or mobile diaries.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2016.08.018.

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