Effects of short- and long-term exposures to ambient air pollution on COPD

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Two papers in the current issue of *ERJ* address the link between air pollution exposure and COPD
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The London fog episode in 1952 was a sentinel event that indicated that short-term exposure to ambient air pollution could adversely influence the health of persons with chronic obstructive pulmonary disease (COPD). A review of autopsy records indicated a doubling of cases with COPD as a major finding compared with other periods [1]. The association between greater levels of ambient air pollution measured in the community and an increase in subsequent short-term COPD-related mortality and hospitalisations has been confirmed by analysis of health related administrative data, including records of hospital admissions and emergency room visits in the USA, Asia and Europe [2–14].

There are considerably fewer studies assessing the impact of short-term air pollution exposure in COPD patients with disease documented by spirometry. Overall, these studies suggest that COPD patients experience a reduction in pulmonary function as a result of short-term exposures [15–20]. Remarkably, the majority of these previous studies included relatively few subjects and with one exception [21] were not designed to assess exacerbation risk. The study that assessed exacerbation risk [21] included former smokers with moderate-to-severe COPD and measured indoor levels of particles with a cut-off aerodynamic diameter of 2.5 µm ($PM_{2.5}$) and NO_2. Higher levels were significantly associated with more symptoms and an increased risk of experiencing an exacerbation, suggesting that measurement of indoor levels of pollutants in persons who spend considerable time indoors (such as those with significant COPD) may be a more relevant measure of exposure than outdoor levels more commonly assessed.

The most robust assessment of the effects of ambient air pollution on pulmonary function (but not limited to patients with COPD) included 3262 former and never smokers (some with repeated assessment) from the US Framingham Heart Study in which spirometry data obtained in 1995–2011 were linked to central-site $PM_{2.5}$, ozone and NO_2 [22]. Pollution measured 24–48 h before spirometry and within ranges considered "moderate" by the US Environmental Protection Agency was associated with a significant reduction in forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC). Mean FEV_1 and FVC were normal but 20% were defined as having either asthma or COPD based on physician diagnosis, medication use or symptoms. The effects of pollution were not greater in persons with asthma or COPD.

The question of whether chronic air pollution exposure can result in the development of COPD is less clear. Previous cross-sectional studies conducted have suggested an association between long-term air pollution exposure, reduced pulmonary function and increased risk of COPD [23–26]. Two large prospective population-based studies from Denmark [6] and metropolitan Vancouver (BC, Canada) [8] did not have

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access to pulmonary function data and defined new-onset COPD based on hospitalisation records. Significant associations between a first COPD hospitalisation and modelled NO_2 [6], and particulate air pollution as measured by black carbon [8] were observed. Further support of a causal relationship is evidence that chronic particulate air pollution exposure results small airway wall remodelling. In a comparison of lungs obtained at autopsy from non-smoking Mexico City (Mexico) residents (high pollution) and Vancouver residents (low pollution) without previous lung disease, small airways had increased amounts of muscle and fibrous tissue, consistent with remodelling [27]. In a rat model, urban air particles also induced the expression of genes involved in airway wall fibrosis [28].

SCHIKOWSKI *et al.* [29] assess the impact of pollution on the incidence and prevalence of COPD in a longitudinal study in this issue of the *European Respiratory Journal*. To obtain a large sample size and achieve a common approach to exposure assessment, they analysed subjects who had previously participated in one of four previous European air pollution studies, had pulmonary function assessed longitudinally with two tests available and who lived in areas where the European Study of Cohorts for Air Pollution Effects (ESCAPE) project modelled residential exposure to PM (n=3692) and NO_2 (n=6550) in 2008–2011. COPD was defined based on the NHANES (National Health and Nutrition Examination Survey) defined lower limits of normal for FEV1/FVC (which provided results similar to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) cut-off value of FEV1/FVC <0.70). Based on data collected in 2008–2011, exposure model derived values included $PM_{2.5}$, PM_{10}, NO_2, oxides of nitrogen (NO_x) and measures of traffic volume. NO_2 and PM_{10} were extrapolated retrospectively using historical air pollution records to provide estimates for the follow-up time-point in all studies and the baseline test in three studies, but it was not possible to extrapolate the traffic data. Although not precisely stated, follow-up of the four cohorts ranged from approximately 11 to 15 years, starting in 1985–1999 with follow-up through 2001–2012. The authors used logistic regression to assess the association between COPD prevalence and incidence defined at follow-up by spirometrically defined cut-offs and air pollution exposures defined using the 2008–2011 exposure model linked to home address. Study specific effect estimates were combined in a meta-analysis, and overall effect estimates (other than for coarse PM) were generally positive but not significantly associated with COPD, other than with measures of traffic volume in females and in never-smokers. Results were similar (but weaker) when extrapolated exposures for NO_2 and PM_{10} were used.

The authors appropriately note that due to the many non-statistically significant associations reported, it was not possible to determine whether ambient air pollution contributed to the development of COPD. As the authors note, uncertainty in exposure assessment would make it more difficult to detect associations. An acknowledged limitation is the lack of concurrent exposure measurements and details regarding the extent that the address used to assign exposure in each of the analyses remained stable over the follow-up period are not provided. However, there are also other significant limitations. COPD, as defined by the investigators, was relatively uncommon in most of the study population. At follow-up, the mean ages of European Community Respiratory Health Survey and National Survey of Health and Development populations, which together accounted for more than half the study cohort, were only 43 and 53 years old, respectively. Accordingly, these studies contributed relatively few cases since COPD is primarily a disease of older individuals. Part of the Swiss study on Air Pollution and Lung Disease in adults (SAPALDIA) cohort was included in the population analysed by SCHIKOWSKI *et al.* [29]. A previous analysis of the effect of particulate air pollution in the full SAPALDIA cohort [30] did not define the outcome categorically, but used pulmonary function as a continuous outcome measure, and reported an improvement in FEV1 as PM_{10} decreased. A similar approach in the current study would likely have increased the power of the study to detect an effect of exposure. This would be an appropriate approach since a subclinical decline in pulmonary function precedes the development of more significant disease defined using a discrete pulmonary function cut point. Finally, persons who reported asthma either at baseline or follow-up were excluded from analysis. This might be appropriate in a younger population since it would be unlikely that these persons would have true COPD at baseline. However, in persons who subsequently develop disease and in the older individuals in the study population there is likely to be overlap with persons meeting diagnostic criteria for COPD since clinical characteristics of asthma and COPD may overlap [31–33]. A sensitivity analysis that included subjects with presumed asthma might provide additional insight.

In a second paper in this issue of *European Respiratory Journal*, DADVAND *et al.* [34] report on the effects of exposure to NO_2 and $PM_{2.5}$ on inflammatory biomarkers using land-use regression models developed by ESCAPE in 242 patients with well-documented COPD in metropolitan Barcelona in 2004–2006. Although positive associations between air pollution and elevated circulating inflammatory markers have been reported in previous studies including persons without COPD [35–37], such reports have not been consistently positive [38–41]. Since COPD is already characterised by systemic and pulmonary inflammation [42], it is possible that COPD patients may be particularly sensitive to effects of air pollution on promoting systemic inflammation. DADVAND *et al.* [34] noted positive associations between

short-term exposures (5-day lag) to NO_2 and an increase in C-reactive protein and fibrinogen, with a suggestive association with other inflammatory biomarkers and a greater effect in former smokers. There was considerably less evidence for an effect of long-term (>1 year) exposures on these biomarkers. The authors did not provide insight into the lack of association with $PM_{2.5}$ with these biomarkers that they observed. Exposure to ambient NO_2 is a measure of exposure to vehicle exhaust, but one would expect $PM_{2.5}$ levels to reflect these exposures in an urban environment since vehicular sources also contribute to particulate air pollution. The reasons for lack of an association are uncertain, but likely reflect imprecision in modelling daily exposures. Daily exposure in 2004–2006 was extrapolated from 2009 address-specific annual averages obtained from the land-use regression model. Temporal variability was estimated based on variation of daily background in 2004–2006 obtained from local NO_2 and PM_{10} monitors, and the PM_{10} data were subsequently used to estimate temporal changes in $PM_{2.5}$.

To summarise, although the findings of both papers are limited by imprecision in exposure assessment, the paper by SCHIKOWSKI *et al.* [29] is consistent with previous literature suggesting that long-term exposure to air pollution may result in the development COPD. The paper by DADVAND *et al.* [34] is consistent with the effects of recent air pollution exposures on promoting systemic inflammation. Efforts at improving the precision of exposure estimates in the design of future studies will improve the ability to detect meaningful associations between air pollution exposures and COPD risk, and the effects of air pollution on promoting systemic inflammation in patients with COPD.

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