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How can we measure the impact of pollutants on respiratory function in very young children? Methodological aspects

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Summary There is increasing evidence that air pollution particularly affects infants and small preschool children. However, detecting air pollution effects on lung function in small children is technically difficult and requires non-invasive methods that can assess lung function and inflammatory markers in larger cohorts. This review discusses the principles, usefulness and shortcomings of various lung function techniques used to detect pollution effects in small children. The majority of these techniques have been used to detect effects of the dominant indoor pollutant, tobacco exposure. However there is increasing evidence that non-invasive lung function techniques can also detect the effects of outdoor air pollution.

There is increasing evidence that air pollution may especially affect small children.[1,2] Furthermore, children's exposure to air pollution is of special concern because their immune system, as well as their lung structure, is not fully developed at the onset of exposure. This raises the possibility of different responses in children compared with those seen in adults. Long-term exposure to ambient air pollutants has been shown to affect lung growth in children.[3–5] Limiting lung growth in early life has the potential to impact on long-term respiratory morbidity in older adults.[6–9] The effect on lung development has been shown with regards to exposure to environmental tobacco smoke in early life.[10,11] This is independent to the adverse effects of in-utero exposure.[12] Most of the studies were based on measurements of forced expiratory flow in school children; however, due to the difficulties with cooperation in preschoolers and infants, this technique is limited in these age groups. This review aims to discuss the techniques currently relevant in measuring the effects of air pollution on lung function, as well as inflammatory markers in preschoolers and infants, with a focus on the important methodological issues to consider.

GENERAL METHODOLOGICAL ASPECTS IN THE ASSESSMENT OF POLLUTION EFFECTS ON LUNG FUNCTION

The main points of consideration in assessing the impact of air pollution on lung function have to do with variability of the testing method, of the measured effect, and intra- and inter-individual variability of lung function in children in general. Variability is particularly high in preschool-aged children aged between 3 and 6 years, although this improves with increasing age.[13]

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Variability of the lung function test versus magnitude of the pollution effect

There are two aspects to consider in achieving statistical significance in lung function measurements in pollution studies. First, there should be good repeatability of the lung function test, i.e. the spread of the variability must be minimised. To address this, the test procedure and the equipment have to be well standardised. A particular problem occurs when the test equipment itself has low measurement accuracy, for example, the 5% accuracy inherent in some of the small portable lung function or 'inflammometry' devices.[14] Second, the study population has to be large enough to show the small effects often seen in pollution studies.

As an example, Ward and Ayres[15] recently highlighted in a systematic review that the effects of particulate matter (PM_{10} or $PM_{2.5}$) on lung function in children might be small but significant. They showed that in most studies the mean fall in peak expiratory flow (PEF) per $\mu g/m^3$ of particulate matter ranged between 0 and 0.4 L/min. If for example the PM_{10} level today was 30 $\mu g/m^3$ higher than the previous day, this would result in a fall in PEF of around 30 times the median value of 0.2 L/min, or 6 L/min, which is 2.5% of the age-related mean PEF of a 10-year-old girl (height 136 cm, mean PEF 237 L/min). The coefficient of variation of PEF measurements in healthy children in this age group lies between 2 and 7%,[16] in the same order of magnitude as the expected effect. Thus, the high variability of the PEF measurements might mask the true effect, or an observed effect might be simply due to the high measurement variability. On the other hand, the biological effect of such lung function changes should be considered not only in the individual but also on a population basis, for reasons explained in the next section. In addition to variability, the sensitivity of a test to detect an effect should be considered; PEF, for example, is not a very sensitive measure of lung function.

Increased relative risk to the individual versus attributed risk to the population

A decrease in lung function of 2–3% might not be relevant for an individual with average lung function, however it will have a huge population impact if the mean of the whole population decreases by 3%. This has a particular influence on the low end of the normal distribution of lung function values in a population. In the SAPALDIA study, Künzli *et al.*[17] demonstrated that a small mean shift of 3% in forced vital capacity (FVC) in the whole population results in an increase of more than 47% in the predicted number of subjects with values of FVC <80%; this is the lower limit of normality.

Similar effects can be seen for symptoms related to pollution. The relative risk or the symptom odds ratios related to pollution effects for the individual are small. For example, various studies have shown that for $PM_{2.5}$ or PM_{10}, the multiplicative change in symptom odds per 1 $\mu g/m^3$ rise in pollutant ranges from 1.002 to 1.04.[15] Accordingly, Künzli *et al.*[18] found that in a multicentre study trial in Switzerland, Austria and France, the relative risks of bronchitis in children related to outdoor air pollution (per 10 $\mu g/m^3$ PM_{10}) was 1.306. If the attributable risk for the whole population is calculated from this relative risk to the individual, 30% of bronchitis cases in children could be attributed to this particular pollution exposure; this translates into 543 000 children with bronchitis (confidence intervals: 239 500 to 981 600 children) in these three countries. These large-scale population effects occur since the attributable risk to the population does not only depend on the relative risk to the individual but also on the prevalence of exposure and of disease. Many more children are exposed to ambient air pollution than to environmental tobacco smoke, resulting in a very large population attributable risk despite a small relative risk to the individual. As Rose[19] stated: '*a large number of people at small risk may give rise to more cases of disease than the small number who are at high risk*'.

In short, we need to caution that if conclusions on the effects of pollution exposure are based on measurements in a small population sample using techniques with large measurement variability and errors, such non-random errors could potentially be magnified and produce erroneous conclusions. This is true especially for studies in the preschool age, where the high variability of the measurement itself is a particular problem.

MEASURING POLLUTION EFFECTS ON LUNG MECHANICS

There is a large body of literature showing effects of indoor [mostly environmental tobacco exposure (ETS)] and outdoor air pollution on lung function in school children, which has been recently summarised elsewhere and thus will not be dealt with in detail here.[2] Most of these studies have used simple and reproducible lung function tests such as tidal breathing methods, forced flow-volume loops [FVC, forced expired volume in 1 second (FEV_1), PEF, maximal expiratory flow] or the interrupter resistance technique (Rint) to assess lung or airway mechanics. These variables provide an overall estimate of lung function and are able to show the effect of air pollution in most studies. The advantages of these lung function variables include: the simplicity of the sampling method; the availability of population normal data; and the portability of the devices, making them suitable for studies in large population samples.

Infants

Recent advances and standardisation of infant lung function testing[20] have made it evident that in most infants, a large variety of different lung function tests can be performed