Does lung function mediate the role of environmental pollution on overall and cardiovascular disease mortality?

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The effect of environmental pollution in population health is still not well known and we need studies to better characterise it. The research by Guyatt *et al*. [1] provides some relevant insights on the complex interplay between environmental pollution, lung function and cardiovascular disease (CVD) incidence and mortality and all-cause mortality, obtained within the framework of the UK Biobank study.

The results obtained are very interesting and intriguing, showing how environmental pollution may impair lung function and cause a higher incidence and mortality of cardiovascular diseases, also showing how lung function may have a mediation role between air pollution and CVD. This research has relevant strengths, one of them being the ability to differentiate their results between ever- and never-smokers. The large sample size of this study (>200 000 participants in the "mortality analysis sample") makes it possible to have enough participants who have ever smoked and therefore ascertain the combined role of environmental pollution and tobacco consumption. At the same time, this allows us to understand the impact of environmental pollution on never-smokers, eliminating the confounding effect of tobacco.

Some of the results obtained were expected, while others are completely new and provide the grounds for the importance of lung function on CVD onset and mortality through their quantification. This is the case for forced expiratory volume in 1 s-mediated all-cause mortality for particulate matter with aerodynamic diameter <2.5 µm ($PM_{2.5}$) (18%) and nitrogen dioxide (NO_2) (27%). These percentages for incident CVD were 9% and 16% for $PM_{2.5}$ and NO_2, respectively. These figures are high and show that the effect of environmental pollution on health outcomes is not negligible. Other recent studies have also observed that $PM_{2.5}$ exposure has the highest risk of respiratory mortality, with a 6% increase in risk per 1 $\mu g \cdot m^{-3}$ [2]. A recent meta-analysis of NO_2 exposure-related mortality showed that not only overall mortality but also respiratory and cardiovascular mortality are related to this exposure, with excess risks per 1 $\mu g \cdot m^{-3}$ ranging from 3% to 7% [3]. The study by Guyatt *et al*. [1] analysed separately the effect of different contaminants, excluding sulfur dioxide (SO_2) and ozone (O_3), which may also have an effect not only in mortality or CVD mortality but also on the mediation effect, which is lung function. We do not know what would happen if the study had included in its analysis other pollutants with a recognised health effect, such as SO_2, O_3 or carbon monoxide [4–6]. The lack of effect observed for PM_{10} exposure is not unexpected, since this particulate matter is more easily cleared from the respiratory airways and does not penetrate in distal lung alveoli.

The mediation hypothesis stated by Guyatt *et al.* [1] is attractive and mainly based on physiological grounds. In our opinion, future studies should explore other mediation hypotheses, including the role of lifestyle or socioeconomic determinants. It is not known how the same exposure to environmental pollutants may affect individuals with a poor diet, moderate alcohol consumption or those exposed at work to different substances that may not be carcinogenic but, for example, may have a subtle irritant effect. We could hypothesise how populations exposed at home to biomass burning for cooking (which is well-described in rural China but also occurs in many South American countries [7–10]) may be affected by outdoor environmental pollution even at low concentrations. We clearly need more studies disentangling these associations and possibly measuring adequately the specific contribution of each exposure to overall mortality and to the onset of specific diseases. In the end, we could find that the same environmental exposure may have a different effect depending on the specific conditions of those exposed.

The role of tobacco consumption on the effect of environmental pollution presented in this study is really interesting. They observed the already expected result that ever-smokers have, in general, a higher risk for all measured events from environmental pollutants, while that of never-smokers did not achieve statistical significance or was lower in most cases. These results reinforce the idea that studies should analyse never- and ever-smokers separately, and also that it is extremely important to properly register tobacco consumption to calculate pack-years [11]. Many participants in this study were lost precisely for the lack of information on smoking variables, which impeded the calculation of pack-years.

There are several difficulties in assessing the effect of environmental pollutants on population health. Perhaps the most important is the accurate characterisation of the exposure. It is also important to consider that pollutants do not act alone, since their presence in the atmosphere is variable, and the concentration of each pollutant may vary depending on the distribution and intensity of emission of contaminating sources in a particular area. Previous investigations have proposed the creation of an Air Quality Health Index and tried to validate this index against mortality. The index included $PM_{2.5}$, NO_2, SO_2 and O_3, and showed an effect on overall mortality, asthma and respiratory visits [12]. In the study by Guyatt *et al.* [1], to refine exposure assessment, the authors used sound methodology and show that the models used have good correlation with some areas. Nevertheless, in other geographical areas, PM exposure could not be included because exposure validation models were not accurate enough. An important strength of this study is how the authors calculated the correlation of their models following data validation; it is not easy to estimate the real exposure of all participants. Practically all studies assign exposure using ecological aggregation or modelling. It is extremely difficult for these estimations to reflect real exposures, which strongly depend on the participants' habits and other specific characteristics of their living areas and dwellings. For example, one could classify a participant as highly exposed to any of the assessed pollutants but if that participant spends very little time outdoors, where exposure is higher, their exposure will be less than expected. Furthermore, the participant may change their living place at weekends and on vacation, but the same exposure would still be assigned.

A further limitation of these type of studies is the short follow-up period and the difficulty in obtaining a clear causal pattern. In the case of this study, despite the larger sample size, the follow-up period was shorter than other studies, which along with the strict definition requiring a specific International Classification of Diseases (10th Revision) code as the primary cause, may have reduced the power of the CVD mortality analyses. The use of 2010 as the year of exposure to the analysed pollutants while estimating the health outcomes between 2008 to 2015 is a limitation, since the temporality of the causal criteria is not fully represented, making it more difficult to attribute lung function decline, CVD incidence or mortality to this practical overlapping of exposure and effect. A further reflection might be that the induction period for the decline of lung function and the onset of CVD might not be the same. This is well known for the effect of tobacco, because lung cancer or COPD onset usually occurs at an older age compared to CVD diseases (myocardial infarction or other cardiopathies), suggesting such a difference [13, 14]. This means that perhaps different follow-up periods would be necessary for environmental pollution related with each specific effect in future studies.

Coming investigations should overcome some of the common limitations currently present. One strategy may be to use CVD or respiratory health outcomes for younger population cohorts (*i.e.* between 25 and 45 years old). By doing this, we could improve the characterisation of exposure because such populations would have been born between 1980 and 2000. Starting from the year 2000, environmental exposure registries could clearly improve exposure characterisation by: 1) increasing the number of pollutants registered; 2) increasing the number of sampling points in each location; and 3) improving the validity (accuracy and reproducibility) of such measurements. This improvement may also be linked to better geolocation tools for the dwelling in which the potential participants live during the exposure period along

with the improvement of electronic clinical records used to register different health outcomes. Using respiratory function measured early in life has been suggested as a predictor of overall mortality [15], supporting the hypothesis of the present study on the mediation role of respiratory function and mortality. Other studies have already used exposures registered in the 1990s to attribute different health outcomes to those exposed [16].

Alternatively, individual exposure to air pollutants could be measured, since ecological exposure assessment is not enough to infer causality or mediation. In order to assess individual exposure, wearable sensors have been used in a number of case studies [17]. The main limitations of such studies are the limited sample size and the short period of time in which the exposure is measured (from 4 to 40 days), besides their cost.

Furthermore, while environmental pollution has a detrimental effect on respiratory and cardiovascular health, the effects on other health outcomes are still unclear. This is the case for mental health or quality of life. A recent study performed in Scotland, UK, observed that SO_2 exposure was a risk for mortality of mental and behavioural disorders [2]. Also, a systematic review and meta-analysis found association between long- and short-term air pollution exposure and risk of depression [18]. Further research will be necessary.

To conclude, the paper by Guyatt *et al*. [1] adds a relevant piece of knowledge to the existing literature for several reasons: its careful design, its high sample size and, overall, its results, showing the role of lung function on mortality and its potential mediation effect between environmental exposures and CVD mortality and disease.

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