Doubts about the adverse effects of air pollution on asthma?

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Efforts to reduce air pollution exposure, especially from traffic emissions, could help prevent a substantial portion of new cases of asthma http://bit.ly/339gGdq

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When can a relationship between an exposure and a disease be considered "causal"? Typically, several steps need to be followed to respond to the question, such as identifying, reviewing, evaluating and integrating the scientific evidence for an overall evaluation that includes a thoughtful check of the Bradford Hill criteria [1], as illustrated in the International Agency for Research on Cancer preamble [2] or in the Environmental Protection Agency procedures [3, 4].

In the case of multifactorial diseases, for example asthma, a causal factor can be any major contributor to a negative health outcome (or undesirable condition), that, if eliminated, would have either prevented the occurrence of the outcome or reduced its severity or frequency. The word "contributor" is a key factor here: the causal factor is not the single factor that drove the health outcome but one among several other influences.

When dealing with asthma, proving the contribution of one factor in the development and/or aggravation of the disease is essential to give directions for promoting preventive measures or remedial actions. Undeniably, estimating the burden of a disease attributable to a specific risk factor provides the size of the population impact (number of attributable cases or years of life lost with disabilities, DALYs), and therefore immediate illustration of the potential gain that could be achieved by reducing exposure.

Asthma is a multifactorial disease affecting 300 million people in the world that results from the interaction between genetic and environmental risk factors. Asthma is linked in part to hereditary factors, as clear from the observation of the high number of asthmatics within the same family. However, there is not a single gene responsible for asthma, but rather several genetic abnormalities that can increase the risk of developing the disease in the presence of environmental factors. Among environmental factors, air pollution, which is a ubiquitous risk factor nowadays, is a major contributor to asthma. Outdoor air pollutants are emitted by vehicles, heating systems, industry, refineries, thermoelectric power plants, agriculture, *etc*. They include particulate matter (PM), nitrogen dioxide (NO_2), carbon monoxide (CO), sulfur dioxide (SO_2), volatile organic compounds (VOCs), ammonia (NH_3), methane, hydrocarbons, ozone (O_3). Particulate matter is a complex mixture of solid and liquid particles suspended in air and comprises both organic and inorganic particles, such as dust, pollen, soot, smoke and liquid droplets.

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Air pollutants also derive directly from natural phenomena such as fires, volcanic eruptions, transportation of desert dust, erosion, *etc*. Depending on the size, particulate matter differs in inhalable particles, with diameters that are generally 10 µm and smaller (PM_{10}), fine particles, with diameters that are generally 2.5 µm and smaller ($PM_{2.5}$) and ultrafine particles of nanoscale size (less than 0.1 µm or 100 nm in diameter) (UFPs).

Air pollution is an established risk factor for asthma exacerbations [5]. To reinforce the evidence, a recent study assessed the relationship between outdoor air pollutants and emergency departments and/or hospital admissions or emergency telephone calls as a surrogate of moderate or severe asthma exacerbations in children and adults through a systematic review and multilevel meta-analysis, which obtained a single association value pooling different studies examining more than one lag (the fixed amount of passing time) [6]. Overall, all pollutants, except SO_2 and PM_{10}, showed a significant association with moderate or severe exacerbations of asthma. However, in children, the exacerbations were associated also with SO_2.

Evidence has increased also on the association between air pollution exposure and asthma incidence, especially in children. Exposure to traffic-related air pollution (TRAP) has been implicated in asthma development and persistence [7, 8], with NO_2 having the strongest effect on childhood asthma incidence [8]. The deleterious effects of air pollution start in early life. Out of 761 172 children born between 2006 and 2012 in the province of Ontario, Canada, the 110 981 asthmatic children had been more exposed to NO_2 and $PM_{2.5}$ than the rest of the population. Enhanced impacts were found among children born to mothers with asthma and mothers who smoked during pregnancy, those born preterm, of low birth weight and among those born to mothers living in urban areas during pregnancy [9].

Regarding adults, there are fewer well conducted studies and multiple methodological difficulties [10]. Recently, exposure to TRAP was associated with increased risk of asthma, wheeze and lower lung function in middle-aged adults [11]. The interaction with the GSTT1 genotype suggests that deficient antioxidant mechanisms may play a role in these adverse health effects.

The link between air pollution and asthma is supported by physiological mechanisms. These embrace the induction of pulmonary oxidative stress and inflammation and the activation of receptors of the bronchial epithelium such as toll-like receptors or increases in Th2 and Th17 cytokines, which generally orchestrate the asthmatic response [6, 12]. Others indirect mechanisms comprise epigenetic changes, and recently pulmonary microbiome modifications [13].

In this issue of the *European Respiratory Journal*, Khreis *et al.* [14], using data from 65 238 682 children in 18 European countries, show that a significant proportion of childhood asthma cases may be attributable to outdoor air pollution, and that these cases could be prevented. More in detail, the study reveals that 66 600 (11% of total cases) and 2400 (0.4%) childhood asthma cases per year could be prevented by complying with the World Health Organization (WHO) air quality guideline for $PM_{2.5}$ and NO_2, respectively. In addition, if the 18 countries were able to meet the lowest levels recorded by previous studies, the gain would be greater with more than 190 000 (33% of total cases), 135 000 (23%) and 89 000 (15%) annual cases that could be prevented in the case of $PM_{2.5,}$ NO_2 and black carbon (a component of fine particulate matter), respectively. The authors of the study used census population data and obtained incidence rates of asthma in children from the Global Burden of Disease study database. Furthermore, exposure to the different pollutants was calculated using a harmonised European statistical model (land use regression) based on multiple measurements.

FIGURE 1 Urban traffic.

The study reported by KHREIS *et al.* [14] is important because it quantifies for the first time the burden of asthma due to air pollution at the European level. The work extends previous results available for NO_2 [8] by also considering $PM_{2.5}$. Very recently, another paper had estimated this burden using data from 194 countries and 125 major cities: 4 million new paediatric asthma cases could be attributed to NO_2 pollution annually, 64% of which in urban centres. Of note, this burden accounts for 13% of global incidence. But this contribution exceeded 20% of new asthma cases in 92 cities [15].

Interestingly, according to KHREIS *et al.* [14], while meeting the WHO recommendations for $PM_{2.5}$ would imply a significant reduction in the percentage of annual childhood asthma cases, that is not the case with NO_2, where only 0.4% of the cases would be prevented. Overall, the obtained estimates underline an urgent need to reduce children's exposure, specifically to NO_2 which is less regulated than $PM_{2.5}$.

Existing data, including those of KHREIS *et al.* [14], clearly indicate that even relatively small estimates in terms of relative risk may lead to an impact of outdoor air pollutants that is not negligible at a population level, and thus that public health actions cannot be neglected. The combination of small relative risks and high prevalence of exposure, with a large amount of people exposed to air pollution because they live near polluted roads, can contribute to a noticeable population attributable fraction of both asthma exacerbations and development. Thus, a public health intervention aimed at diminishing air pollutants emissions at the general population level might have significant benefits for society.

On the other side, according to WHO guidelines, levels of $PM_{2.5}$ should not exceed an annual average of 10 $\mu g \cdot m^{-3}$, and levels of NO_2 should not exceed an annual average of 40 $\mu g \cdot m^{-3}$, but many areas in cities across Europe regularly breach these limits. Importantly, the results obtained by KHREIS *et al.* [14] show that the current NO_2 WHO air quality guideline value seems to provide much less protection than the $PM_{2.5}$ guideline. These values require update and lowering to be better suited to protecting children's health. In this respect, it is noteworthy that the effect, even at low concentrations, cannot be neglected. In a recent study on the effect of air pollution on daily mortality in 652 cities, the associations were stronger in locations with lower annual mean $PM_{2.5}$ concentrations. The pooled concentration–response curves showed a consistent increase in daily mortality with increasing particulate matter concentration, with steeper slopes at lower particulate matter concentrations [16].

Thus, coming to the point "Are there doubts about the adverse effects of air pollution on asthma?" No, certainly not, and we should consider air pollution to be a contributing factor to asthma and advocate for intervention on the environment. Quoting Bradford Hill [1]: "All scientific work is incomplete – whether it be observational or experimental. All scientific work is liable to be upset or modified by advancing knowledge. That does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time." Therefore, efforts to reduce air pollution exposure, especially from traffic emissions, could help prevent a substantial portion of new cases of asthma.

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