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Is exhaled nitric oxide a marker of air pollution effect?

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It is open to debate whether F_{eNO} is a biomarker of the effects of air pollution <http://ow.ly/ZrSke>

Exhaled nitric oxide, measured through noninvasive breath testing with a portable device [1], is an established biomarker of airway inflammation [2]. This relies on the fact that NO is a gaseous molecule produced in a type of inflammatory response. Specifically, in humans, NO is produced from L-arginine, an α -amino acid that is used in the biosynthesis of proteins, by three enzymes called NO synthases (NOS), namely inducible NOS (iNOS), endothelial NOS and neuronal NOS [3]. In the state of inflammation, several cells, including eosinophils, use iNOS to produce NO. Due to these properties, exhaled NO has been used as a biomarker for the diagnosis and follow-up of asthma, and as a guide to therapy in asthmatics [4, 5].

As air pollution is at the origin of inflammatory processes in the airways and in the lung, various studies investigated the relationship between measurement of the exhaled nitric oxide fraction (F_{eNO}) and air pollution. At the population level, elevated F_{eNO} has been associated with both short-term [6] and long-term [7] exposure to air pollution, as objectively measured [7, 8] or on the basis of markers of traffic air pollution [9]. Exposure to air pollution may lead to airway inflammation, as measured by F_{eNO} , even in children with no history of airway damage, and the association is enhanced in atopic subjects [8], which suggests a proper role for NO. Not only chemical agents but also biocontaminants were associated with F_{eNO} . Early-life exposure to bacterial endotoxin and early-life dog ownership are associated with lower F_{eNO} at school age [10]. Furthermore, mouse allergens in house dust was associated with an increased F_{eNO} in the occupants [11]. However, at the individual level, acute daily changes in F_{eNO} were not related to personal endotoxin exposure and there was limited evidence of effect modification of endotoxin by personal exposure to air pollution in that study [12]. At the experimental level, 2-h exposure to generated sulfate and soot particles was related to significant increases in F_{eNO} in young and health subjects [13]. In children seen in two seasons, 24-h and weekly exposures to black carbon were linked with F_{eNO} , while exposure on the morning of sampling was associated with airway oxidative stress [14], independently of sex, age, allergy status, parental education level and meteorological conditions on the sampling day.

The relationship between F_{eNO} and air pollution may depend on individual susceptibility. In a large population, the promoter haplotypes in iNOS (*NOS2*) and exposure to residential traffic independently influenced F_{eNO} level [15]. Moreover, it was later found that higher exposure from residential traffic nullifies the protective effect of one common *NOS2* promoter haplotype on F_{eNO} . In children who had ≤ 250 m of local road length within a 100-m buffer around their homes, those with two copies of the haplotype had significantly lower F_{eNO} than those with no copies, with statistically significant trend of lower F_{eNO} with increasing number of haplotype copies [16]. In contrast, among children who had > 250 m of local road length within a 100-m buffer, F_{eNO} level did not significantly differ by the haplotype copy number [16].

Received: March 11 2016 | Accepted: March 11 2016

Conflict of interest: None declared.

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Very recently, in an area of overall poor air quality from a major freight railway, male schoolchildren were a vulnerable subpopulation for more greatly elevated F_{eNO} , while females were at increased risk of reduced lung capacity [17]. Noticeably, in spite of the fact that in polluted air, physical activity may increase air pollutant uptake and thereby health effects, no consistent evidence for an interaction between physical activity and traffic-related air pollution (TRAP) was observed for lung inflammation and systemic inflammation (interleukin-6, and leukocyte and neutrophil counts) [18].

In this issue of the *European Respiratory Journal*, ECKEL *et al.* [19] show, for the first time, robust evidence for an association of TRAP exposure in the indoor microenvironment, as assessed by exhaled NO measured indoors [3], and elevated F_{eNO} from distal sources among 1635 schoolchildren aged 12–15 years in southern California breathing NO-free air. Associations were less consistent with F_{eNO} from proximal sources. The study by ECKEL *et al.* [19] is the first to have, using an adapted model [20], partitioned F_{eNO} into proximal and distal, and thus to estimate in detail the NO parameters in the lower airways. In their work, indoor air pollution has been related to alveolar NO concentration, maximum airway wall NO flux and airway wall tissue diffusing capacity, which can be useful for understanding the underlying mechanisms. No such a detailed exploration of F_{eNO} pathways had been conducted previously in a general population.

Whether exhaled NO can be considered a marker of air pollution exposure or effect has to be debated. A biomarker of exposure is a contaminant, its metabolite, or the product of interactions between the contaminant and some target molecule or cell measured in a compartment of the body reflecting internal or external exposure to the contaminant, whereas a biomarker of effect is a biological indicator of the body's response to exposure to a contaminant. The former has the ability to identify whether contamination has occurred as well as the route and pathway of exposure. The latter indicates early subclinical changes, which, if uninterrupted, may have pathological consequences and lead to specific diseases. Cumulating evidence supports the hypothesis that exhaled NO could be a marker of adverse effects of air pollution rather than a marker of exposure: the work of ECKEL *et al.* [19] has contributed additional elements supporting F_{eNO} as a robust measure of the response of the respiratory system to air pollution exposure.

Nevertheless, several questions remain open and additional investigations are needed to evaluate whether exhaled NO satisfies the relevant criteria for being considered a biomarker of effect. Among others, as a biomarker of effect, F_{eNO} should be reversible following avoidance of air pollution exposure, or at least reduced if an individual switches from elevated air pollution exposure to low exposure, and so far, controlled data are scarce in this respect. Furthermore, it is methodologically difficult to isolate the effect of air pollution from those of other stressors, like diet, infections or medications, in the lack of appropriate adjustment for confounders at the population level. Finally, yet importantly, analytical reproducibility, sensitivity, specificity and cost should be warranted in the case of F_{eNO} as a biomarker of effect. This seems, however, to have been achieved through the official guidelines for F_{eNO} [21]. Confirming the role of F_{eNO} as a biomarker of effect will allow identification of the associated health end-points, and explore the opportunities of management and prevention.

Even if we still do not have all the evidence to specifically determine whether F_{eNO} is a biomarker of the effect of air pollution, reducing air pollution can be worthwhile for airway and lung inflammation, and thus for respiratory health. In Beijing, China, in 2008, F_{eNO} that was statistically associated with multiple pollutants across different lags after adjusting for meteorological parameters was significantly lower in the during that year's Olympic Games compared with before the games [22]. More recently, in the USA, adopting clean fuels and technologies on school buses showed to have reduced exposures and improved health schoolchildren [23]. Fine and ultrafine particle concentrations were 10–50% lower on buses using ultralow-sulfur diesel, diesel oxidation catalysts and/or closed crankcase ventilation systems. Ultralow-sulfur diesel adoption was also associated with reduced F_{eNO} , greater growth in lung function and lower absenteeism, with stronger associations among asthmatic children. Finally, the findings of ECKEL *et al.* [19] draw our attention to the hazards of outdoor air pollution that can be found in the indoor microenvironment due to air transfer through windows. This indicates that prevention against poor air quality has to be extended to indoor settings where individual behaviour matters.

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