Airway diseases and inflammatory bowel diseases: is it something in the air (pollution)?

To the Editor:

Our group has recently discussed the exciting *European Respiratory Journal* publication by Brassard *et al.* [1] that shows an increased incidence of the inflammatory bowel diseases (IBD) in subjects with airway disease. In this population-based cohort study, the incidence of Crohn's disease was higher in the asthma (by 27%) and chronic obstructive pulmonary disease (COPD) (by 55%) groups relative to the general population. This study complements other recent observations showing increased gut permeability in those with COPD relative to healthy controls [2], which is a potential mechanism for development of IBD. Taken together, these data suggest a common link in the pathogenesis of IBD and airway disease; however, the mechanisms responsible for these interesting observations remain unclear.

Brassard *et al.* [1] present a balanced critique of their findings, suggesting that validation of the findings through other administrative datasets in additional regions would increase the generalisability of the findings. Although we agree that additional epidemiological studies validating data in other jurisdictions is important, exploring the mechanisms responsible for their observations through basic and translational science should also be emphasised. The authors highlight potential mechanisms relevant to their observations in the discussion, focusing on a potential role for cigarette smoke exposure. Their comments are well warranted, as cigarette smoke is an established environmental risk factor for airway disease and a disease modifier in IBD (deleterious in Crohn's disease; protective in ulcerative colitis) [3]. Unfortunately, due to the limitations of the administrative dataset, they were unable to obtain information about cigarette smoking history and other factors (*e.g.* shared genetic susceptibility) that may have been able to inform potential mechanisms behind their observations.

Air pollution is another important inhaled environmental factor that can contribute to both airway [4] and gut disease [5]. Inhaled air pollution can deposit directly into the lungs or be swept up the mucociliary ladder to be ingested into the gastrointestinal tract. In the lung, particulate air pollution can promote inflammatory cell recruitment [6], while in the gut it can exacerbate intestinal inflammation in experimental models of IBD and induce changes in the intestinal microbiome [7]. The mechanisms responsible for these observations may converge on common innate immune pathways at these mucosal sites [8]. In a mouse model of air pollution exposure to the lungs, we have previously demonstrated the involvement of the nucleotide-binding domain and leucine-rich repeat protein 3 (NLRP3) inflammasome in the initiation of an innate immune response in the airways [6], while in the gut, we have shown that the NLRP3 inflammasome is a key player in innate immunity and helps to maintain intestinal mucosal homeostasis through regulation of the intestinal microbiome [9]. Understanding how air pollution exposure modulates innate immune signalling in these two organs may yield new insight into the pathogenesis of both airway diseases and IBD.

To extend the epidemiological work of Brassard *et al.* [1] and others investigating the impact of air pollution on lung and gut health, complementary experimental approaches should be performed to explore the biological plausibility of epidemiological findings. These approaches should include *in vitro* cell culture experiments [6], *in vivo* animal experiments [6, 9] and controlled human exposure models to air pollution such as diesel exhaust [10]. By combining epidemiology with basic and translational experimental approaches, observations made at a population level can be explored mechanistically.

In closing, we applaud the work of Brassard *et al.* [1] for bringing attention to the link between airway disease and IBD. If their findings are validated in another cohort and extended with mechanistic experimental evidence, there will be increasing need to appreciate how environmental exposures, including air pollution, influence lung and gut health. Tightly linking air pollution exposure, airway disease and IBD could inform individual preventive measures and disease management, and further justify air quality controls.

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A discussion of the environmental factors influencing lung and gut disease: is it something in the air? http://ow.ly/MW86M

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Bedaquiline: finding the pores on the pot

To the Editor:

Salfinger and Migliori [1] discussed some important issues of bedaquiline, the most promising drug for treating multidrug-resistant (MDR) tuberculosis (TB) in the early twenty-first century. I am afraid of some issues that could be detrimental to the future of TB control. Bedaquiline should be used with caution, bacause of some methodological flaws in a few of the published landmark studies. In one study, Diacon *et al.* [2], the authors, without doing drug-sensitivity testing on isoniazid and rifampicin (criteria of MDR-TB), firmly concluded the effectiveness of their new regimen on MDR-TB patients. By using a regimen containing bedaquiline for susceptible patients to the tested drug does not predict bedaquiline's effectiveness in MDR-TB patients, as the pharmacokinetics and probability of pharmacodynamic target attainment (area under the time curve minimum inhibitory concentration ratio) are likely to be altered in MDR patients [3].

In another recent study by Diacon *et al.* [4], the efficacy analyses were performed in the modified intention-to-treat (ITT) population and selectively excluded patients after randomisation in their study. Some of the participants received the drug-resistant treatment, including bedaquiline, without confirmation of drug resistance and some with negative mycobacterial cultures. There is no clear definition of what is modified ITT. Modified ITT analysis has potential bias, due to the inappropriate exclusion of patients after including them in the trial. Post-randomisation exclusions is treated as deviations from protocol, destined for biased effect and strongly associated with industry funding [5]. So the real outcome is likely to be different in pragmatic trials or in the study outside of the trial conditions. ITT remains the best method that preserves randomisation. Well designed, randomised control trials follow strictly to the