

# Acute effects of endotoxin in children with uncontrolled asthma

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Endotoxin, a ubiquitous component of Gram-negative bacteria, is an important bioactive environmental factor linked to paediatric asthma incidence and severity in epidemiological studies.<sup>1</sup> In challenge studies, acute effects of endotoxin exposure include bronchoconstriction, airways inflammation and airways hyper responsiveness.<sup>2</sup> A recent literature review supported a causal association between house-dust endotoxin exposure and acute asthma exacerbations.<sup>3</sup>

Observational repeated measure studies employing personal monitors can be used to precisely measure endotoxin exposures encountered in the domestic setting, and to assess the timing and magnitude of the dose–response. In this way, effects of acute exposures can be studied in populations that could not ethically undergo exposure challenges, such as children and those with more severe asthma. Using this approach, Rabinovitch *et al*<sup>4</sup> studied 14 mostly African-American children who attended a school set up for children with difficult to control asthma in Denver. Children in this study had symptoms on average 2–3 times a week indicating uncontrolled asthma despite use of inhaled corticosteroids given at school. Personal endotoxin exposure in this study was associated with a doubling of the odds of experiencing asthma symptoms in the night following exposure and with declines in evening forced expiratory volume in 1 s (FEV1) of approximately 7% per 25th–75th IQR increase in endotoxin exposure.

A recent study by Matsui *et al*<sup>5</sup> in Baltimore examined airborne endotoxin levels measured by fixed monitors placed in the homes of 63 mostly African-American children with asthma. In this cohort, approximately 50% had airway obstruction, defined as FEV1/forced vital capacity <80%, and average  $\beta$ -agonist use was 5 days over a 2-week period, indicating suboptimal asthma control. Effects of endotoxin on asthma exacerbations varied in this study, depending on indoor co-pollutant exposures. No

association was seen with the allergic asthma biomarker, fractional exhaled nitric oxide (FENO). The Matsui study suggested that variability in responsiveness to endotoxin exposure might be related not only to individual susceptibility but also to the magnitude and mix of co-exposures that occur in a particular household.

In the present study,<sup>6</sup> Delfino *et al* performed personal monitoring in 43 mostly Caucasian children in California. This cohort was made up of children with mild to moderate persistent asthma defined either by use of controller medications independent of present symptoms or by symptoms >2 times a week, or by FEV1 levels below 80% predicted. Twenty-one per cent (N=9) of the children had low FEV1 and approximately two-thirds were taking controller medications.<sup>7</sup> Because the percentage of children with persistent symptoms during the study was unreported, it is unclear whether many of these children were well controlled while taking their controller medications. In the full group, no association was observed between personal endotoxin exposure and FENO or FEV1. However, children with airflow obstruction (defined by FEV1 <80% predicted) demonstrated a 7.7% decline in %predicted FEV1 per endotoxin IQR averaged over the day of exposure as well as the following day. Children with normal FEV1 experienced FEV1 declines of only 0.5% per IQR and the interaction term product for dichotomised FEV1 was statistically significant. No consistent effect modification with indoor pollutant levels was observed, although these interactions were not tested separately in the subset of children with low FEV1.

Despite substantive differences in study design, some preliminary conclusions may be inferred by noting common findings. In both the Delfino and Rabinovitch studies, personal endotoxin exposure was associated with clinically significant FEV1 declines of similar timing and magnitude in children with under-controlled disease as defined by persistent symptoms or airway obstruction. In both the Delfino and Matsui studies, endotoxin exposure was not associated with FENO although personal PM2.5 organic and elemental carbon was associated with FENO

increases in an earlier report from the Delfino study.<sup>7</sup> This difference in FENO responses to different PM2.5 components suggested that endotoxin and PM2.5 carbon act through distinct immunological pathways. In this context, Delfino *et al*<sup>8</sup> elegantly demonstrated that organic and elemental carbon fractions on filters from their study were associated with oxidative stress that, in turn, was associated with FENO levels. In contrast, endotoxin on these filters was not associated with oxidative stress presumably because it binds directly to CD14 and TLR4 receptors to directly activate the innate (T-helper 1) immune response.

The observation in the Delfino study, of increased responsiveness to endotoxin in children with greater asthma severity, is supported by results from challenge studies that demonstrate a relationship between prior allergic airway inflammation and response to endotoxin. Eldridge and Peden<sup>9</sup> reported that prior allergen challenge with the house dust mite augmented the inflammatory response to endotoxin challenge. Alexis and Peden<sup>10</sup> reported that attenuation of eosinophilic inflammation by pretreatment with inhaled corticosteroid treatment was associated with decreased expression of the endotoxin receptor CD14 and a blunted neutrophilic response to endotoxin challenge. As such, children in the Delfino study with controlled asthma due to regular use of inhaled corticosteroids would be expected to have lower levels of allergic airway inflammation, decreased expression of CD14 and a blunted response to endotoxin exposure compared to children with ongoing inflammation, and signs and symptoms of undercontrolled disease.

Together, these studies highlight the potential clinical importance of acute endotoxin exposure in children with ongoing poorly controlled asthma. Further studies are warranted in children with asthma who are suboptimally controlled in order to validate the magnitude and timing of FEV1 declines after acute endotoxin exposure, and to identify individual and environmental factors that might decrease susceptibility to this common household exposure.

**Competing interests** None declared.

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## Commentary

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