



11953: Effect of cigarette smoking on nasal inflammatory responses after nasal allergen challenge with *Dermatophagoides farinae*

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Background

The relationship between tobacco smoke exposure and airway disease is well established in the medical literature and includes environmental tobacco smoke (ETS) as well as active cigarette smoking (1-3). Though the role of tobacco smoke in the inception of allergic disease has been well documented in epidemiologic studies and in animal models, its effects on existing allergic airway inflammation are less well established. In general, tobacco smoke appears to be pro-inflammatory, triggering an influx of white blood cells (primarily neutrophils) and inflammatory cytokines such as interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor alpha (TNF- α) (4). Smoking also appears to suppress innate immune responses, creating susceptibility to viral respiratory infections (5, 6). Tobacco smoke may augment allergic inflammation resulting from allergic rhinitis and/or asthma. On a cellular level, ETS suppresses T helper type 1 (Th1) responses that target intracellular bacteria and viruses and enhances T helper type 2 (Th2) responses that generate allergic inflammation (7, 8). ETS exposure has been shown to increase production of Th2 cytokines such as IL-4, 5, 13, as well as allergic antibody, IgE, and increases recruitment of eosinophils to the airways in animal models (7,9).

In a human cross-sectional study, serum IgE and blood eosinophil counts were higher in smokers than in non-smokers, and similar findings were seen in studies of children residing in homes of smokers (10-12). Allergic rhinitics exposed to tobacco smoke show increased levels of the eosinophil chemoattractant, eotaxin-1, in the nasal mucosa compared to age-matched allergic rhinitics without tobacco smoke exposure (13), and repeated exposure to cigarette smoke increased eosinophilic airway inflammation (14). Coupled with nasal ragweed allergen challenge, allergic rhinitics exposed to ETS demonstrated increased production of ragweed-specific IgE and nasal Th2 cytokines IL-4, IL-5, and IL-13 (15).

In addition to Th2 cytokines, there are several cytokines derived from other types of T helper lymphocytes and epithelial cells that are important in inducing airway inflammation, including IL-9, IL-22, IL-13, IL-31, IL-33, IL-25 (16). The chemoattractants MIP-1a (CCL3) and MIP-1b (CCL4) have been implicated in the recruitment of inflammatory cells to the nasal mucosa and may be important for prolonged inflammation (17).

The goal of this pilot study was to evaluate the effects of smoking on nasal allergic inflammatory responses following nasal allergen challenge with *Dermatophagoides farinae* (Der f) in allergic rhinitics sensitized to house dust mite, comparing the effects to those seen in non-smokers.

Methods

- Volunteers with a history of allergic rhinitis and a positive skin prick test to Der f as determined at the consent visit were invited to participate in a screening nasal allergen challenge to demonstrate a clinical response to Der f. During the screening challenge participants completed a total nasal symptom score at baseline and peak nasal inspiratory flow measurement, changes in which were recorded after graded doses to nasal allergen until a provocative dose of allergen was determined.
- Participants returned at least 9 weeks later for baseline nasal epithelial cell sampling.
- Six non-smokers and three smokers underwent a second nasal allergen challenge during which epithelial lining fluids and nasal epithelial cells were sampled for pre- and post- allergen challenge levels of inflammatory mediators using the Mesoscale Human Cytokine 30-Plex Kit. Serum levels of inflammatory mediators and nasal fluid cellularity were also collected.
- Smoking diaries were reviewed at all visits.
- Baseline versus post-allergen challenge cytokine levels were compared by paired t-tests within each cohort.

Results

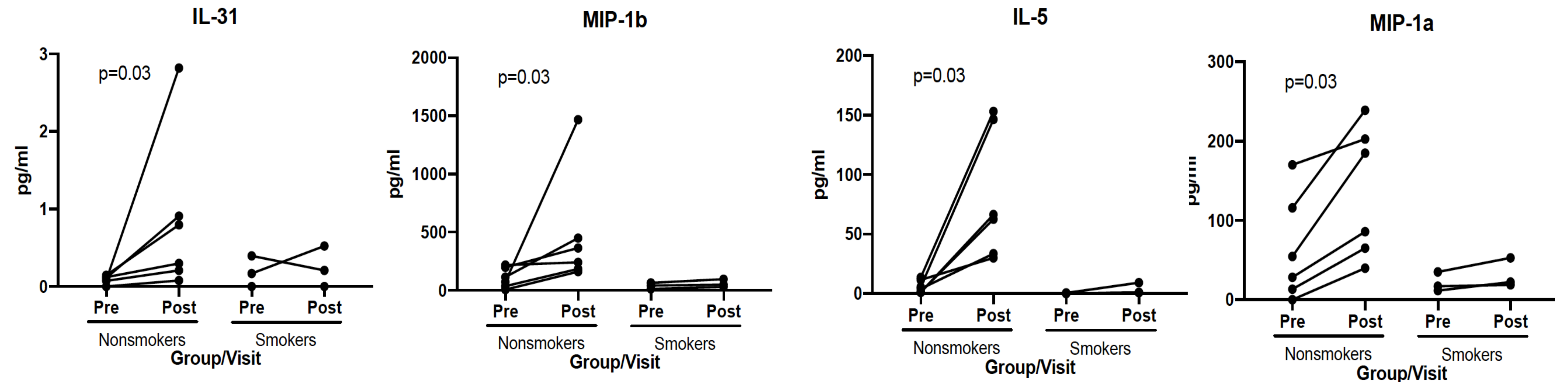


Figure 1. Pre- and Post- Nasal Challenge Measurement of nasal cytokines and chemokines



Figure 2. Study Design

	Smoker	Non-smoker
# of participants	3	6
Mean age in years	34.6	27.5
% female	33	50
% African American, non-Hispanic	67	33
% Caucasian, non-Hispanic	0	50
% Hispanic	33	17
Mean BMI	32.2	27.9

Table 1. Study Participant Characteristics

References

1. Gilmour MI et al. How exposure to environmental tobacco smoke, outdoor air pollutants, and increased pollen burdens influences the incidence of asthma. *Environ Health Perspect*. 2006
2. Dietart RR et al. Workshop to identify critical windows of exposure for children's health: immune and respiratory systems workgroup summary. *Environ Health Perspect* 2000
3. Raheerison C et al. In utero and childhood exposure to parental tobacco smoke, and allergies in schoolchildren. *Respir Med* 2007
4. Sundblad BM et al. Extracellular cadmium in the bronchoalveolar space of long-term tobacco smokers with and without COPD and its association with inflammation. *Int J Chron Obstruct Pulmon Dis* 2016
5. Noah TL et al. Alteration of the nasal responses to influenza virus by tobacco smoke. *Curr Opin Allergy Clin Immunol* 2012
6. Noah TL et al. Tobacco smoke exposure and altered nasal responses to live attenuated influenza virus. *Environ Health Perspect* 2011
7. Singh SP et al. Maternal exposure to secondhand cigarette smoke primes the lung for induction of phosphodiesterase-4D5 isozyme and exacerbated Th2 responses: roflupram attenuates the airway hyperreactivity and muscarinic receptor expression but not lung inflammation and atopy. *J Immunol* 2009
8. Feng Y et al. Exposure to cigarette smoke inhibits the pulmonary T-cell response to influenza virus and Mycobacterium tuberculosis. *Infect Immun* 2011.
9. Seymour BW et al. Second-hand smoke is an adjuvant for T helper-2 responses in a murine model of allergy. *J Immunol* 1997
10. Nagasaki T et al. Influences of smoking and aging on allergic airway inflammation in asthma. *Allergol Int* 2013
11. Ronchetti R et al. Enhanced allergic sensitisation related to parental smoking. *Arch Dis Child* 1992
12. el-Nawawy A et al. Effect of passive smoking on frequency of respiratory illnesses and serum immunoglobulin-E (IgE) and interleukin-4 (IL-4) concentrations in exposed children. *J Trop Pediatr* 1996; 42: 166-169.
13. Montano-Velazquez BB et al. Effect of cigarette smoke on counts of immunoreactive cells to eotaxin-1 and eosinophils on the nasal mucosa in young patients with perennial allergic rhinitis. *Braz J Otorhinolaryngol* 2016.
14. Matsumoto K et al. Eosinophilic airway inflammation induced by repeated exposure to cigarette smoke. *Eur Respir J* 1998
15. Diaz-Sanchez D et al. Challenge with environmental tobacco smoke exacerbates allergic airway disease in human beings. *J Allergy Clin Immunol* 2006.
16. Pawankar R et al. The paradigm of cytokine networks in allergic airway inflammation. *Curr Opin Allergy Clin Immunol*. 2015
17. Perić A et al. Macrophage inflammatory protein-1 production and eosinophil infiltration in chronic rhinosinusitis with nasal polyps. *Ann Otol Rhinol Laryngol*. 2015

Conclusions

- In this proof-of-concept study, smokers appeared to have a less robust response to nasal allergen challenge than non-smokers, which may be related to effects on the nasal immune response that need further investigation.
- The study was greatly limited by challenges in recruiting cigarette smokers that self-identified as having allergic rhinitis, perhaps reflecting changes in perception of nasal symptoms among smokers.
- Future directions include investigation of responses in e-cigarette users.