

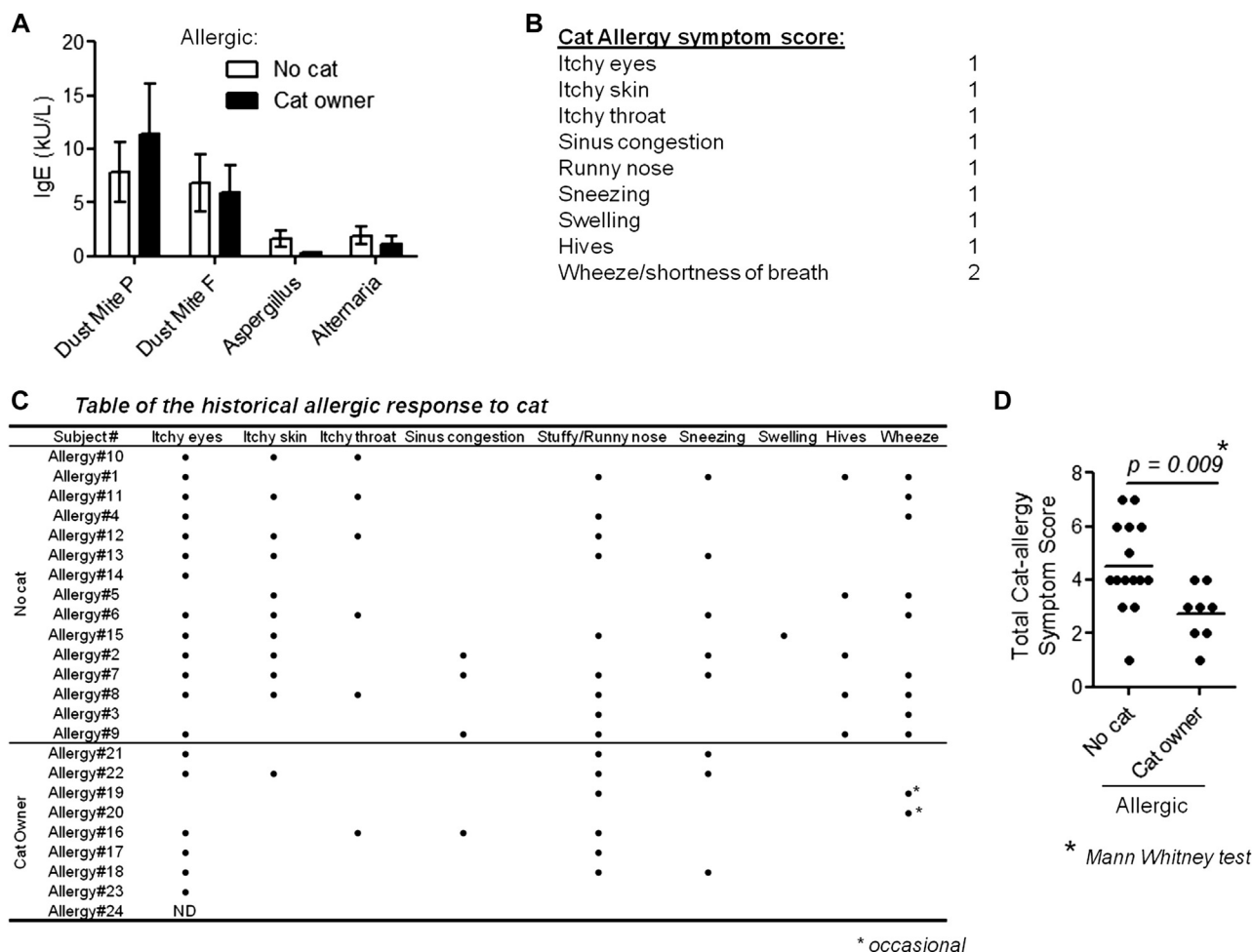


FIG 1. Attributes of subjects with cat allergy with or without cat at home. **A, C,** and **D,** Attributes of subjects with cat allergy. *Dust Mite F*, *Dermatophagoides farinae*; *Dust Mite P*, *Dermatophagoides pteronyssinus*. **B,** Symptom score system on cat exposure.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

REFERENCES

- Liccardi G, Salzillo A, Calzetta L, Piccolo A, Rogliani P. Chronic cat allergen exposure and low sensitization: possible limitations in patients' selection? *J Allergy Clin Immunol* 2016;137:1621-2.
- Liccardi G, Martín S, Lombardero M, D'Amato M, Barber D, D'Amato G, et al. Cutaneous and serological responses to cat allergen in adults exposed or not to cats. *Respir Med* 2005;99:535-44.
- Burnett M, Wegienka G, Havstad S, Kim H, Johnson CC, Ownby D, et al. Relationship of dog- and cat-specific IgE and IgG4 levels to allergic symptoms on pet exposure. *J Allergy Clin Immunol Pract* 2013;1:350-3.
- Oryszczyn M-P, Van Ree R, Maccario J, Nadif R, Kauffmann F, EGEA cooperative group. Cat sensitization according to cat window of exposure in adult asthmatics. *Clin Exp Allergy* 2009;39:1515-21.
- Renand A, Archila LD, McGinty J, Wambre E, Robinson D, Hales BJ, et al. Chronic cat allergen exposure induces a TH2 cell-dependent IgG4 response related to low sensitization. *J Allergy Clin Immunol* 2015;136:1627-35.e13.
- Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy* 2009;39:469-77.
- James LK, Shamji MH, Walker SM, Wilson DR, Wachholz PA, Francis JN, et al. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011;127:509-16, e1-5.

Available online March 11, 2016.
<http://dx.doi.org/10.1016/j.jaci.2015.11.046>

Asthma during pregnancy and congenital malformations: The challenging task of separating the medication effect from asthma itself

To the Editor:

We have read with interest the article by Garne et al¹ which adds new information on the impact of asthma treatments during pregnancy on the prevalence of congenital malformations. The study concluded that the use of inhaled β_2 -agonists (short- and long-acting combined) is associated with an increased risk of cleft palate and gastroschisis, whereas the use of inhaled corticosteroids (ICSs) showed no increased risk for any of the examined malformations. We fear however that such a statement could negatively affect the confidence of clinicians and mothers in short-acting β_2 -agonists (SABAs), specifically salbutamol, which was the most frequently used β_2 -agonist in this study. We believe that methodological limitations led to the observed results and should be carefully considered.

The first limitation in the study is the use of a reference group formed of women with and without asthma. Including women without asthma in the reference group could potentially



overestimate the effect of the asthma medications. Asthma itself is associated with an increased risk of congenital malformations, and a recent meta-analysis reported a 30% increased risk of cleft lip among women with asthma as compared with women without asthma.² In the study by Garne et al, 53% of women with asthma treated with β_2 -agonists (86% using salbutamol) had no controller medications and were likely having uncontrolled asthma. However, the ICS group is likely to include women who were appropriately controlled because of the beneficial effect of ICSs. Because of this confounding by control level, an increased prevalence of malformations was found in the β_2 -agonists group—corroborating results from previous case-control studies using similar exposure groups^{3–5}—and not found among the ICS group (even showing protective effects in some instances). Moreover, the authors did not report the maternal characteristics of the women in the study (eg, age, comorbidities, asthma exacerbations, hospitalizations for asthma, and oral corticosteroid use), which prevented the assessment of the comparability of the exposure groups.

SABAs (salbutamol in particular) have shown fetal safety in several well-designed cohort and case-control studies. In fact, in the recent Swedish study⁶ cited by the authors, the observed increased risk of cleft palate with bronchodilator use was the lowest for SABAs and no increased risk of gastroschisis was observed. Disentangling the effect of the medication from the disease is a challenging task that has to be appropriately addressed in both the design and the analysis of the study. Most important, the use of a reference group formed of women with asthma is recommended. Researchers have also proposed indirect ways to separate the medications' effects, including a comparison between different drugs that share similar indications,⁶ and such studies were recently published in the literature.^{7,8}

Other limitations in the study include the lack of adjustment for important confounders such as socioeconomic status and asthma exacerbations, combining short- and long-acting β_2 -agonists under one exposure category, and multiple comparisons. Although we acknowledge the use of the case-malformed control design, the rationale behind its use is questionable because the exposure information was recorded prospectively. The use of healthy controls without any apparent pathology could have been more appropriate, especially in confirming signals from previous studies that used nonmalformed controls.

Sherif Eltonsy, BPharm, MSc
Lucie Blais, PhD

From the Faculty of Pharmacy, Université de Montréal, and Hôpital du Sacré-Cœur de Montréal, Montreal, Quebec, Canada. E-mail: lucie.blais@umontreal.ca.

Disclosure of potential conflict of interest: S. Eltonsy declares no relevant conflicts of interest. L. Blais has received consultancy fees from AstraZeneca, GlaxoSmithKline, Sanofi, and Pfizer and has received research support from AstraZeneca, GlaxoSmithKline, Novartis, and Pfizer.

REFERENCES

1. Garne E, Hansen AV, Morris J, Zaupper L, Addor MC, Barisic I, et al. Use of asthma medication during pregnancy and risk of specific congenital anomalies: a European case-malformed control study. *J Allergy Clin Immunol* 2015;136:1496-502.e7.
2. Murphy VE, Wang G, Namazy JA, Powell H, Gibson PG, Chambers C, et al. The risk of congenital malformations, perinatal mortality and neonatal hospitalisation among pregnant women with asthma: a systematic review and meta-analysis. *BJOG* 2013;120:812-22.
3. Munsie JW, Lin S, Browne ML, Campbell KA, Caton AR, Bell EM, et al. Maternal bronchodilator use and the risk of orofacial clefts. *Hum Reprod* 2011;26:3147-54.

4. Lin S, Munsie JP, Herdt-Losavio ML, Bell E, Druschel C, Romitti PA, et al. Maternal asthma medication use and the risk of gastroschisis. *Am J Epidemiol* 2008;168:73-9.
5. Lin S, Munsie JP, Herdt-Losavio ML, Druschel CM, Campbell K, Browne ML, et al. Maternal asthma medication use and the risk of selected birth defects. *Pediatrics* 2012;129:e317-24.
6. Kallen B. Maternal asthma and use of antiasthmatic drugs in early pregnancy and congenital malformations in the offspring. *J Pulm Respir Med* 2014;4:166.
7. Eltonsy S, Forget A, Beauchesne MF, Blais L. Risk of congenital malformations for asthmatic pregnant women using a long-acting beta(2)-agonist and inhaled corticosteroid combination versus higher-dose inhaled corticosteroid monotherapy. *J Allergy Clin Immunol* 2015;135:123-30.
8. Cossette B, Beauchesne MF, Forget A, Lemiere C, Larivee P, Rey E, et al. Relative perinatal safety of salmeterol vs formoterol and fluticasone vs budesonide use during pregnancy. *Ann Allergy Asthma Immunol* 2014;112:459-64.

Available online March 21, 2016.
<http://dx.doi.org/10.1016/j.jaci.2015.11.049>

Reply



To the Editor:

We thank Eltonsy and Blais¹ for their comments.²

Disentangling the effects of asthma medication from those of the underlying disease is difficult. We hope that we have been clear that our study cannot say whether the observed increases in odds of cleft palate and gastroschisis among pregnant women exposed to inhaled beta-2-agonists are due to the exposure or the asthma. The lack of increased odds among women exposed to inhaled corticosteroids indicate, as Eltonsy and Blais noted, that either asthma exacerbations or else medication could cause the anomaly.

Adjusting for maternal asthma is desirable, but we did not have data on maternal asthma exacerbations, only whether maternal asthma had been diagnosed. Restricting controls to only those with maternal asthma diagnosed would reduce the power so considerably that associations with specific anomalies could not be analyzed. The strength of our study is in the quality of the data on congenital anomaly, and we hope that this can supplement the parts of the literature looking only at the risk of congenital anomaly in general. Teratogens do not affect the risk of all anomalies equally, and thus studies of specific anomalies are necessary.³

Another strength of our study is the use of malformed controls to reduce the bias from maternal recall. This use of malformed controls may lead to an underestimate of risk if the controls, or a subset of controls, are associated with the exposure in question. Our case-malformed control approach has been discussed by other studies^{4,5} and validated in a previous EUROCAT (European surveillance of congenital anomalies) study.⁶

The lack of information on confounding factors such as socioeconomic status is not a serious limiting factor. A potential confounder would have to be very strong and prevalent to account for the observed increases in odds of congenital anomaly of 1.63 for cleft palate and 1.89 for gastroschisis.⁷ For example, a confounder with a prevalence of 20%, twice as prevalent among the exposed and doubling risk of anomaly, could decrease the observed odds ratio for cleft palate in association with inhaled beta-2-agonists from 1.63 to 1.38, and that for gastroschisis from 1.89 to 1.62.

Multiple comparisons were not an issue in the main analysis because these results were restricted to just testing the associations found in the literature. The 95% CIs are given for all associations, enabling the reader to adjust for multiple