



Is residential ambient air limonene associated with asthma? Findings from the Canadian Health Measures Survey[☆]

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ABSTRACT

Asthma is a common chronic disease. Exposure to limonene is commonplace because it may be used in the manufacture of personal care products and household cleaners. We investigated the influence of limonene on asthma in a population-based sample of approximately 3000 Canadians. During the Canada Health Measures Survey, carried out between 2012 and 2013, participants were asked if they wheezed or had a diagnosis of asthma, and underwent spirometry and measurement of the fraction of exhaled nitric oxide (FeNO). These variables were tested for an association with limonene concentrations measured in their household air samples, using linear regression analysis. A 100% increase in air limonene concentration was associated with an approximate 17% adjusted relative increase wheezing with an odds ratio of 1.17 (95%CI 1.16, 1.18). The percent change in FeNO for a 100% increase in limonene was twice as large for children, 2.89% (95% CI 1.88, 4.43) compared to adults, 1.44% (95%CI 1.16, 1.79). Among boys, the odds ratio was 1.50 (95%CI 1.48, 1.52) between a 100% increase in limonene and a diagnosis of asthma. This study provides evidence that household exposure to limonene may increase the prevalence of asthma in the general population.

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1. Introduction

Given that people spend the majority of their time in their homes, indoor residential air quality is arguably the most important environmental determinant of respiratory health. The Institute of Medicine Expert Working Group accepted a causal relation between asthma exacerbations and environmental cigarette smoke, and allergens from cats, cockroaches and dust mites (Kanchongkittiphon et al., 2015). Evidence was considered to be “inadequate or insufficient” to support an association between volatile organic compounds (VOC) (other than formaldehyde) and asthma. One VOC, limonene, occurs naturally in trees and citrus fruit peels (WHO, 2018). It is a cyclic terpene, is commonly used in personal care products such as perfumes, air fresheners, and

ABBREVIATIONS: VOC, Volatile Organic Compounds; FEV₁, 1-s forced expiratory volume; FVC, forced vital capacity; FeNO, fraction of exhaled nitric oxide.

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household cleaners (Buckley, 2007). Of 18 indoor VOCs measured in the TEAM study, limonene had the greatest ambient air concentration, with an arithmetic mean of 55 µg/m³ (Wallace, 1991). Limonene may induce sensitization based on its relation to contact dermatitis, and airway reactivity. Given that the general population is regularly exposed to this chemical, it would be important to determine its effects on indicators of respiratory health.

Among 2900 consecutive patch tested dermatitis cases, 5.2% reacted to oxidized R-limonene. (Christensson JB et al., 2016). In a study of 88 Swedish adults, increased concentrations of residential indoor air limonene were associated with increased airways hyperresponsiveness. (Norback et al., 1995). The odds ratio between terpenes (pinene, carine, and limonene) and nocturnal breathlessness was 4.0 (95%CI 1.2–13.4) but there were no decrements in FEV₁ associated with limonene. Aerosolized household cleaning products, which may also contain limonene along with many other chemicals, have been associated with an increased incidence of asthma when used in residential situations (Zock et al., 2010).

Exhaled nitric oxide is an objective measure of eosinophilic airway inflammation (Dweik et al., 2011). Induction of nitric oxide synthase in the bronchial epithelial cells increases the production

and exhaled concentration of nitric oxide. Increased concentrations are a clinical indicator of poorly controlled asthma, and non-asthmatic eosinophilic bronchitis (Dweik et al., 2011). Among those without asthma or known pre-existing respiratory illnesses, the fraction of exhaled nitric oxide (FeNO) may also be a weak biomarker of exposure to motor vehicle –related ambient air pollution (Eckel et al., 2016).

The present study tests the association between residential ambient air concentrations of limonene and asthma symptoms, a history of asthma, spirometry derived measures of lung function, and FeNO, in a population based sample of Canadians who had participated in the Canadian Health Measures Survey (CHMS) (Statistics Canada, 2016; Patry-Parisien et al., 2013).

2. Methods

2.1. Study design and population

Data come from a cross-sectional national population survey. Participants were Canadians between 6 and 79 years old who were studied between January 2012 and December 2013 as part of the third cycle of the CHMS. Those living on reserves and in institutions and remote locations were excluded. For the purposes of the current study, current smokers were excluded to avoid the known relatively major effect of smoking on respiratory symptoms and lung function which could confound an association with limonene. Households were identified from the 2011 Canadian National Census. Approximately 5700 participants were selected, divided into eleven age-gender groups, each of between 500 and 600 subjects. Sixteen mobile clinical examination sites were set up in five regions across Canada. There were two sites in each of Atlantic Canada, the Prairies, and British Columbia, and four sites in Quebec, and six in Ontario. Participants had to live within 75 km of a collection site. Further details can be found at Statistics Canada (Statistics Canada, 2016).

Ethics approval was obtained from Health Canada and the Public Health Agency of Canada Research Ethics Boards. For those participants younger than 14 years, both parental consent and the child's assent were obtained.

2.1.1. Questions used to define the demographic and health-related variables

Education: “The highest certificate, diploma or degree respondent has completed.”

Income: “The total household income received by all household members, from all sources, before taxes and deductions.”

Current cigarette smoking: “At the present time, do you smoke cigarettes daily, occasionally, or not at all?”

Environmental tobacco smoke exposure: a response of every day or almost every day to the question: “How often does someone smoke inside this home? Include both household members and visitors.”

Asthma: “We are interested in “long-term conditions” which are expected to last or have already lasted 6 months or more and that have been diagnosed by a health professional. Do you have asthma?”

Wheezing. For children between the ages of 6 and 12 years old, the parent/caregiver was asked: “

Has your child ever had wheezing or whistling in the chest at any time in the past?”

Corticosteroids and leukotriene receptor antagonists were those “taken in the past month.”

2.1.2. Limonene measurement

During the clinical examination site visit, participants were given a volatile organic compound sampler containing a CarboPack B 60/80® (Part No. N9307002, Perkin Elmer, Inc., Shelton, CT, USA). There were asked to replace the analytic cap with a mesh diffusion cap and place it in their living room or family room for seven days. Then the analytic cap was used to seal the tube which, it was placed into an aluminium container and mail in a postage-paid self-addressed envelope to the study laboratory. Analysis was done using Nal gas chromatography/mass spectrometry (GC/MS) system (Agilent 7890A GC coupled with Agilent 5975C MS, Agilent Inc., Santa Clara, CA, USA). The methods of collection, analysis, and the quality control measures have been previously published (Zhu et al., 2013).

2.1.3. Lung function

Participants between 6 and 79 years old, who did not report an acute respiratory illness, underwent spirometry using the KoKo® Spirometer (Ferraris CardioRespiratory, Pulmonary Data Services, Inc. Louisville, CO 80027 USA.) to measure the 1-s forced expiratory volume (FEV₁) and the forced vital capacity (FVC). Values were expressed as a percentage of predicted based on age, height, and gender using equations developed by Miller et al., (2005). Corrections were made for daily temperature, humidity and barometric pressure.

2.1.4. Fractional concentration of exhaled nitric oxide (FeNO)

Using a NIOX MINO® (NIOX, 2016) single-breath on-line measures of FeNO were performed consistent with the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations (ATS/ERS, 2005). Measurements were taken from a slow vital capacity manoeuvre. A maximum of ten slow vital capacity maneuvers, each at approximately 50 mL/s over 10 s, were performed in an attempt to achieve two reproducible FeNO concentrations. Daily “bionorms” were performed. At the beginning of the study, each tester initially had 12 tests done to establish his or her personal normal reference value. Each day, the tester would retest himself or herself with the NIOX MINO® to be used for testing on that day. If this daily observed value varied more than 10 ppb from the tester's reference value, a 2nd trial would be done. If again the result was not within 10%, then a second tester with previously determined personal reference values would be measured. If again, results were not within 10%, the device would not be used.

2.2. Statistical analysis

Linear mixed-effects models were used to examine the relationship between exposure to limonene and health measures. All models included a random intercept for area to account for correlations between measures collected from each collection site. Separate models were used for each health outcome. Distributions of FEV₁ and FVC were approximately normally distributed, while FeNO and limonene required log transformation. Asthma and wheezing were categorical variables (yes, no). They were linked to limonene using mixed effects logistic regression models with weightings generated by survey sample weights. Variables were retained in the models if they were associated with the outcome ($p \leq 0.10$) and/or addition or removal changed the coefficient of the exposure (limonene) to outcome relation by $> 10\%$. Variables tested for inclusion included; age, sex, ethnicity, body mass index (BMI),

weight, height, environmental tobacco smoke exposure, household education, total household income, and alcohol consumption. The final models included: age, sex, ethnicity, BMI, environmental tobacco smoke exposure, education, and income. In addition, the association between FEV₁ and asthma was adjusted for BMI.

Analyses were conducted using R[®] package (R version, 2014). Results were expressed as the changes in FEV₁, FVC and percent changes in FeNO and odd ratios for asthma and wheezing corresponding to a 100% increase in limonene levels, which approximated the magnitude of the interquartile range.

3. Results

Of 5785 subjects, 708 subjects were excluded because they were smokers. 2231 were children, between 6 and 16 years old, and 2846 were adults, between 17 and 79 years old. The numbers of valid tests available among children were 633 for limonene, 1655 for FEV₁, and 1363 for FeNO. For adults, the respective numbers were 2393, 2770, 2616. A participant was included in the analysis if they had a limonene measurement and either a value for spirometry or for FeNO, resulting in 570 children and 2330 adults.

The median age of the study group was 41 years, and there was a relatively evenly split between males and females. Overall, less than 10% reported being exposed to environmental tobacco smoke. Compared to adults, children were more likely to be male, non-Caucasian, and be diagnosed with asthma. Very few reported taking inhaled corticosteroids, an asthma medication that may reduce FeNO (Table 1).

The arithmetic mean of non-transformed limonene was 45.24 (95% CI 43.67, 46.82) and the interquartile range was similar, 42.36 (95% CI 40.11, 44.61), whereas the median non-transformed limonene was 26.13 (95% CI 24.56, 27.71). Because of this highly skewed distribution, limonene was log transformed for analysis, but for easier interpretation results were expressed using a 100% change in non-transformed limonene, a value approximating the magnitude of the mean value and the interquartile range.

In the unadjusted analyses, a 100% increase in indoor air limonene was associated with a 18% (95%CI 1.17,1.19) relative increase in asthma and a 1.27% (95% CI 1.07,1.49) increase in FeNO (Table 2). Wheeze, FEV₁ and FVC were not significantly associated with limonene. The relative increase in asthma was twice as large for children, 33% (95% CI 1.32, 1.34) compared to adults, 15% (95%CI 1.14, 1.16) and much larger for females, 1.42 (95%CI 1.41,1.43) than males 1.01 (95%CI 1.01, 1.02). Consistent with the age-related increased observed effect of limonene on asthma prevalence, FeNO was also greatest among children. FEV₁ appeared to be improved with limonene exposure among Caucasians and decreased among non-

Caucasians but there was no significant changes once the values were adjusted (Table 3).

In the adjusted analyses, a 100% increase in indoor air limonene was associated with a 17% - 18% relative increase in both wheezing and asthma (Table 3). Consistent with these symptoms, was a 1.55% (95% CI 1.28, 1.89) increase in FeNO. These associations were present for both younger and older subjects but effect sizes were significantly greater for children. The percent change in log FeNO for an 100% increase in limonene was twice as large for children, 2.89% (95% CI 1.88, 4.43) compared to adults, 1.44% (95%CI 1.16, 1.79). Between children and adults, there was a 30% difference in the observed effect size of limonene on asthma prevalence. Compared to females, males had a greater prevalence of asthma associated with increases in limonene. No significant sex differences were seen with the other variables tested. FEV₁ and FVC were not statistically significantly ($p < 0.05$) associated with limonene, overall, or by gender.

88 VOCs were sampled of which 56 were detectable in at least 50% of the homes. Limonene, the VOC of interest, was present in 99% of homes, and its mean concentration of 45 ppb (SD 61) was the greatest of all the measured VOCs. Correlations coefficients between limonene and the detectable VOCs were generally low. The lowest correlation was 0.075 with benzofuran, and the greatest was 0.324 with 2-pentanone. Only 6 correlation coefficients were at least 0.25. To test the hypothesis that other covarying VOCs may have been responsible for the associations we found with limonene, we adjusted these findings by a variable representing the sum of these six VOCs which were camphene, 2-pentanone, chloroform, 2-butoxyethanol, 2-hexanone, and benzene. The percent change in log FeNO increased to 1.63 (95% CI 1.24, 2.02), while wheezing and asthma diminished but remained significant, both at 1.03 (95% CI 1.01, 1.05), and FEV₁ and FVC remained non-significant.

4. Discussion

Asthma is the most common chronic lung disease in childhood and affects approximately 5% of adults (Asher and Pearce, 2014). Pathologic correlate of asthma is eosinophilic inflammation which induces nitric oxide synthetises in the airways and consequently increases the production and exhaled concentration of nitric oxide. Given that limonene is ubiquitous, and asthma is a common and chronic lung disease, we felt it was important to assess the association between the two. We found that greater concentrations of limonene in the indoor air were associated with increased wheezing, a cardinal symptom of asthma, and FeNO, an objectively measure of allergic asthma airway inflammation.

Three hypotheses are suggested to explain the greater observed

Table 1
Mean (standard deviation) or percentage of socio-demographic characteristics, symptoms, lung function, and limonene exposure by age group for 2900 subjects in the CHMS cycle-3.

Socio-demographic Characteristics	All ages (n = 2900)	6–16 yr (n = 570)	17–79 yr (n = 2330)
Age (year)	41.0 (20.3)	13.1 (2.4)	46.8 (17.4)
Gender (% male)	49.1	51.4	46.9
Ethnicity (% Caucasian)	76.5	65.0	79.0
Highest household education (% greater than high school)	96.1	94.2	97.8
Total household Income (\$1000)	83.9 (89.8)	107.4(87.5)	79.0 (62.6)
Environmental tobacco smoke exposure (%)	6.810.26.0		
Air limonene concentration, geometric mean ppb (n = 2900)	24.9(3.2)	29.6(3.1)	23.9(3.2)
Asthma (%)	9.3	12.9	8.5
Wheeze (%)	7.5	—	
FEV ₁ , % predicted (n = 2900)	97.0 (14.1)	100.0 (12.6)	96.4 (14.0)
FVC, % predicted (n = 2900)	98.8 (13.4)	102.1(13.0)	98.1 (13.2)
FeNO,geometric mean ppb (n = 2725)	18.6 (13.3)	17.6 (14.1)	18.8 (13.2)
Inhaled corticosteroids (%)	4.0	4.3	4.0

Table 2Percent change in Lung function (FEV₁, FVC and FeNO) and odd ratios for asthma and wheezing (95%CI) associated with a 100% change in limonene. Results are unadjusted.

Respiratory Variables	All n = 2900	Age		Sex		Ethnicity	
		≤16 n = 570	≥17 n = 2330	Female n = 1389	Male n = 1511	Caucasian n = 2268	Others n = 732
Wheeze	0.93 (0.92, 0.93)	0.93 (0.92, 0.93)		0.89 (0.88, 0.90)	0.95 (0.94, 0.96)	0.89 (0.88, 0.90)	1.16 (1.15, 1.17)
Asthma	1.18 (1.17, 1.19)	1.33 (1.32, 1.34)	1.15 (1.14, 1.16)	1.01 (1.01, 1.02)	1.42 (1.41, 1.43)	1.29 (1.28, 1.29)	0.88 (0.87, 1.29)
FeNO	1.27 (1.07, 1.49)	1.79 (1.23, 2.60)	1.32 (1.08, 1.61)	1.33 (1.06, 1.78)	1.23 (0.97, 1.56)	1.21 (0.98, 1.50)	1.40 (0.93, 2.11)
FEV ₁	1.28 (-0.48, 3.05)	1.15 (-3.04, 5.34)	1.18 (-1.05, 3.40)	0.80 (-1.94, 3.50)	1.96 (-0.67, 4.60)	2.37 (0.07, 4.67)	-1.88 (-5.95, 2.18)
FVC	-0.38 (-2.05, 1.29)	-0.06 (-4.41, 4.28)	-0.95 (-3.01, 1.11)	-0.43 (-2.89, 2.03)	-0.42 (-3.02, 2.19)	0.51 (-1.63, 2.65)	-3.33 (-7.52, 0.87)

Table 3Percent change in Lung function (FEV₁, FVC and FeNO) and odd ratios for asthma and wheezing (95%CI) associated with a 100% change in limonene. Results are adjusted for covariates other than stratifying factor.

Respiratory Variables	All n = 2900	All Adjusted**	All Adjusted+	Age		Sex		Ethnicity	
				≤16 n = 570	≥17 n = 2330	Female n = 1389	Male n = 1511	Caucasian N = 2268	Others N = 732
Wheeze	1.17 (1.16, 1.18)	1.14 (1.13, 1.15)	1.16 (1.15, 1.17)	1.17 (1.16, 1.18)		1.17 (1.15, 1.19)	1.09 (1.07, 1.12)	1.17 (1.15, 1.18)	1.10 (1.08, 1.12)
Asthma	1.18 (1.17, 1.19)	1.16 (1.15, 1.17)	1.17 (1.16, 1.18)	1.46 (1.45, 1.47)	1.16 (1.15, 1.16)	1.08 (1.07, 1.08)	1.5 (1.48, 1.52)	1.26 (1.25, 1.27)	0.86 (0.85, 0.87)
FeNO	1.55 (1.28, 1.89)	1.49 (1.23, 1.81)	1.53 (1.30, 1.77)	2.89 (1.88, 4.43)	1.44 (1.16, 1.79)	1.57 (1.38, 1.76)	1.49 (1.47, 1.51)	1.37 (1.12, 1.68)	1.56 (1.10, 2.21)
FEV ₁	1.69 (-0.14, 3.53)	1.65 (-0.19, 3.49)	1.67 (-0.17, 3.50)	1.52 (-2.11, 5.16)	1.72 (-0.5, 3.92)	-0.16 (-2.7, 2.37)	2.24 (-0.44, 4.93)	1.67 (-0.63, 3.96)	-1.78 (-5.38, 1.81)
FVC	0.1 (-1.62, 1.82)	0.17 (-1.65, 1.99)	0.11 (-1.62, 1.84)	1.25 (-2.5, 5.01)	-0.32 (-2.23, 1.58)	-1.53 (-3.91, 0.85)	0.18 (-2.22, 2.59)	-0.58 (-2.66, 1.51)	-3.28 (-6.92, 0.37)

*Covariates were: sex, and age, race/ethnicity, BMI, environmental tobacco smoke, household education, total household income.

** Adjusted for PM_{2.5}, NO₂ and Ozone in addition to sex, and age, race/ethnicity, BMI, environmental tobacco smoke, household education, total household income.+ Excluded corticosteroid treatment and adjusted for PM_{2.5}, NO₂ and Ozone, sex, and age, race/ethnicity, BMI, environmental tobacco smoke, household education, total household income.

effect among children compared to adults. Compared to adults, the type of airway inflammation in children is more likely to be eosinophilic vs. neutrophilic. Children with asthma are most likely to be allergic and have eosinophilic airway inflammation, whereas neutrophilic inflammation associated with asthma is more likely to be found in adults than children (Bush and Menzies-Gow, 2009; Snijders et al., 2010; Simpson et al., 2006). FeNO better reflects allergic rather than neutrophilic inflammation. Secondly, perhaps children are more exposed to limonene because they spend more time indoors at home than do adults (Leech et al., 1996). Finally, the observation that air limonene concentrations were higher in the younger age group suggests that limonene-containing products may be used in greater quantities in homes with children.

Similar to Norbäck et al., 1995, we found evidence consistent with limonene being associated with asthma but not with reductions in lung function. Asthma is characterized by reversible airflow obstruction, whereas other chronic airways diseases demonstrate less or no reversibility. The normal FEV₁ and FVC therefore make it more likely that the observed increased prevalence of wheezing related to limonene exposure is more likely to be

a manifestation of asthma rather than any other lung disease.

Mechanisms to explain the association require clarification. Given that limonene has previously been observed to elicit an allergic response and be an irritant, it has the potential to aggravate asthma. It has been reported that terpenes such as limonene can react with oxidizing substances such as ozone in the indoor air leading to the production of ultrafine particles (Rösch et al., 2015).

Our study focused on one compound limonene. To isolate the observed effect independent of other measured VOCs, we adjusted for those that were at least weakly correlated with limonene. Other VOCs in the same family of terpenes as limonene have been shown to be associated with respiratory symptoms (Norbäck et al., 1995) but the present study did not focus on terpenes in general and comprehensive measures of terpenes were not available. We did however adjust for other measured VOCs that were correlated with limonene in order to isolate its independent effect.

One limitation of this study is its cross-sectional study design which produces a snap shot of a point in time. This limits the ability to assess the temporal association between exposure and disease, and their individual durations. We did observe effects on

spirometry and FeNO associated with limonene but we cannot tell if they result from chronic or acute exposure or a combination of both.

It would be preferable to have more comprehensive data on respiratory symptoms but we still consider it fortunate to have available a large data base of thousands of observations with spirometry, FeNO, and some respiratory symptoms. It is likely that other respiratory symptoms such as cough and chest tightness would be correlated with the available health measures and thus offer limited new information.

We cannot exclude the possibility that the observed association is due to the presence of asthma leading to an increased use of limonene containing products. However, we might expect the opposite; that those with airway hypersensitivity would be more likely to avoid odoriferous products. Concerning other confounding factors, the association persisted despite controlling for age, sex, education, and passive cigarette smoking. Further, adjusting for other indoor VOCs did not eliminate observed effect of limonene. There are many risk factors for asthma and respiratory symptoms including parental history of atopy, smoking indoors, gas stoves, dust mites, cockroaches, cats, outdoor aeroallergens, indoor dampness and moulds, and bacterial endotoxins and outdoor air pollution (Norbäck et al., 2017). It would not be feasible to control for all of them in a large population-based survey. The main concern would be confounding variables, those that are both associated with exposure (limonene) and also a risk factor for the outcome (FeNO). We would not expect these factors to be strongly associated with limonene concentrations. Our findings, and those of Norbäck et al. (1995), indicating that limonene increases the risk of asthma, suggest that this chemical could perhaps be at least partially responsible for the previously observed association between cleaning products and asthma. Our study focused on one compound limonene. To isolate the observed effect independent of other measured VOCs, we adjusted for those that were at least weakly correlated with limonene. Other VOCs in the same family of terpenes as limonene have been shown to be associated with respiratory symptoms (Norbäck et al., 1995) but the present study did not focus on terpenes in general and comprehensive measures of terpenes were not available. We did however adjust for other measured VOCs that were correlated with limonene in order to isolate its independent effect.

The population health implications of this study are significant. If it were to be confirmed by further research that limonene is a causal risk factor for asthma, then avoiding exposure could reduce the burden of illness from a common disease. Unlike some other exposures, such as automobile exhaust, people can control exposure to limonene in their homes.

Future research should include a randomized trial to determine if avoidance of limonene-containing personal care and household products influences clinical asthma control.

Competing financial interests declaration

All authors have no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envpol.2018.10.072>.

References

- Asher, I., Pearce, N., 2014. Global burden of asthma among children. *Int. J. Tubercul. Lung Dis.* 18 (11), 1269–1278.
- ATS/ERS, 2005. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am. J. Respir. Crit. Care Med.* 171, 912–930.
- Buckley, D.A., 2007. Fragrance ingredient labelling in products on sale in the U.K. *Br. J. Dermatol.* 157, 295–300. <https://doi.org/10.1111/j.1365-2133.2007.08018.x>.
- Bush, A., Menzies-Gow, A., 2009. Phenotypic differences between pediatric and adult asthma. *Proc. Am. Thorac. Soc.* 6 (8), 712–719.
- Christensson, J.B., Karlberg, A.-T., Andersen, K.E., Bruze, M., Johansen, J.D., Garcia-Bravo, B., Arnau, A.G., Goh, C.L., Nixon, R., White, I.R., 2016. Oxidized limonene and oxidized linalool – concomitant contact allergy to common fragrance terpenes. *Contact Dermatitis* 74, 273–2805.
- Dweik, R.A., Boggs, P.B., Erzurum, S.C., Irvin, C.G., Leigh, M.W., Lundberg, J.O., Olin, A.C., Plummer, A.L., Taylor, D.R., 2011. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications. *Am. J. Respir. Crit. Care Med.* 184, 602–615.
- Eckel, S.P., Zhang, Z., Habre, R., Rappaport, E.B., Linn, W.S., Berhane, K., Zhang, Y., Bastain, T.M., Gilliland, F.D., 2016. Traffic-related air pollution and alveolar nitric oxide in southern California children. *Eur. Respir. J.* 47 (5), 1348–1356.
- Kanchongkittiphon, W., Mendell, M.J., Gaffin, J.M., Wang, G., Phipatanakul, W., 2015. Indoor environmental exposures and exacerbation of asthma: an update to the 2000 review by the Institute of Medicine. *Environ. Health Perspect.* 123, 6–20.
- Leech, J.A., Wilby, K., McMullen, E., Laporte, K., 1996. The Canadian human activity pattern survey: report of methods and population surveyed. *Chron. Dis. Can.* 17 (3–4), 118–123.
- Miller, M.R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., Crapo, R., Enright, P., van der Grinten, C.P.M., Gustafsson, P., Jensen, R., Johnson, D.C., MacIntyre, N., McKay, R., Navajas, D., Pedersen, O.F., Pellegrino, R., Viegi, G., Wanger, J., 2005. Standardisation of spirometry. *Eur. Respir. J.* 26, 319–338.
- NIOX: <http://www.niox.com/en/about-niox-products/NIOX-MINO/>. Last accessed Dec 8, 2016.
- Norbäck, D., Björnsson, E., Janson, C., Widström, J., Boman, G., 1995. Asthmatic symptoms and volatile organic compounds, formaldehyde, and carbon dioxide in dwellings. *Occup. Environ. Med.* 52 (6), 388–395.
- Norbäck, D., Hashimb, J.H., Hashim, Z., Cai, G.H., Sooria, V., Ismail, S.A., Wieslander, G., 2017. Respiratory symptoms and fractional exhaled nitric oxide (FeNO) among students in Penang, Malaysia in relation to signs of dampness at school and fungal DNA in school dust. *Sci. Total Environ.* 577, 148–154.
- Patry-Parisien, J., Zhu, J., Wong, S.L., 2013. Implementation of the indoor air component of cycle 2 of the Canadian health measures survey. *Stat Canada Health Reports* 24, 3–10.
- R version 3.1.1 (2014-07-10). Copyright (C) 2014. The R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit).
- Rösch, C., Wissenbach, D.K., von Bergen, M., Franck, U., Wendisch, M., Schlink, U., 2015. The lasting effect of limonene-induced particle formation on air quality in a genuine indoor environment. *Environ. Sci. Pollut. Res.* 22, 14209.
- Simpson, J.L., Scott, R., Boyle, M.J., Gibson, P.G., 2006. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 11, 54–61.
- Snijders, D., Agostini, S., Bertuola, F., Panizzolo, C., Baraldo, S., Turato, G., Faggiani, D., Plebani, M., Saetta, M., Barbato, A., 2010. Markers of eosinophilic and neutrophilic inflammation in bronchoalveolar lavage of asthmatic and atopic children. *Allergy* 65, 978–985.
- Statistics Canada, 2016. Website for Canadian health measure survey (CHMS). Last accessed Dec 07. <http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=5071#a2>.
- Wallace, L.A., 1991. Personal exposure to 25 volatile organic compounds EPA's 1987 team study in Los Angeles, California. *Toxicol. Ind. Health* 7 (5–6), 203–208.
- WHO: <http://www.who.int/ipcs/publications/cicad/en/cicad05.pdf?ua=1>. Last accessed July 25, 2018.
- Zhu, J., Wong, S.L., Cakmak, S., 2013. Nationally representative levels of selected volatile organic compounds in Canadian residential indoor air: population-based survey. *Environ. Sci. Technol.* 47 (23), 13276–13283.
- Zock, J.-P., Vizcaya, D., Le Moual, N., 2010. Update on asthma and cleaners. *Curr. Opin. Allergy Clin. Immunol.* 10 (2), 114–120.