Work-related asthma in Montreal, Quebec: Population attributable risk in a community-based study

Ahmet Demir MD MSc[1], Lawrence Joseph PhD[2], Margaret R Becklake MB BCh MD FRCP[2,3]

A Demir, L Joseph, MR Becklake. Work-related asthma in Montreal, Quebec: Population attributable risk in a community-based study. Can Respir J 2008;15(8):406-412.

BACKGROUND: Occupational exposures are an important cause of adult-onset asthma but the population attributable risk percentage (PAR%) has been less frequently studied.
OBJECTIVES: To examine the distribution and determinants of adult asthma in six centres across Canada using data gathered in a community-based study.
METHODS: Data were gathered in a community survey of 2959 adults using the European Community Respiratory Health Survey Protocol. A subsample of 498 subjects completed detailed health and occupational questionnaires, methacholine challenge tests and allergy skin tests. Asthma was defined in three ways: current wheeze, asthma symptoms and/or medication, and airway hyperresponsiveness. Occupational exposures were classified as sensitizers or irritants. Associations between asthma and occupational exposures were examined using logistic regression analysis. Model selection was based on the findings for current wheeze, and the same model was applied to the other definitions of asthma.
RESULTS: Fifty-six per cent of subjects reported ever having had occupational exposure to sensitizers, and 9.8% to irritants. Current wheeze was associated with exposure to irritants (PAR% 4.54%), and airway hyperresponsiveness was associated with exposure to sensitizers (PAR% 30.7%). Neither a history of childhood asthma, atopy, nor confining the analysis to adult-onset asthma affected these associations. Analysis of effect modification suggested two types of work-related asthma: one due to exposure to occupational sensitizers, and the other due to exposure to irritants.
CONCLUSIONS: Detailed assessment of past and current exposures is essential in the investigation of work-related asthma. Childhood asthma reactivated or aggravated by work exposures is not easy to distinguish from asthma induced by work, a misclassification that could lead to an underestimation of work-induced asthma. This should be taken into account in jurisdictions in which persons with work-aggravated asthma are not eligible for workers' compensation.

Key Words: *Healthy worker effect; Irritants; Population attributable risk; Sensitizers; Work-related asthma*

L'asthme professionnel à Montréal, au Québec : Le risque attribuable à la population dans une étude communautaire

HISTORIQUE : Les expositions professionnelles représentent une cause importante d'asthme de l'adulte, mais le pourcentage de risque attribuable à la population (%RAP) est moins étudié.
OBJECTIFS : Examiner la répartition et les déterminants de l'asthme de l'adulte dans six centres canadiens au moyen de données colligées dans une étude communautaire.
MÉTHODOLOGIE : Les données ont été colligées dans une étude communautaire auprès de 2 959 adultes, au moyen du protocole d'enquête européen sur la santé respiratoire dans la collectivité. Un sous-échantillon de 498 sujets a rempli des questionnaires détaillés sur la santé et la profession, un test de provocation à la méthacholine et des tests d'allergie cutanée. Les auteurs ont défini l'asthme de trois façons : respiration sifflante courante, symptômes d'asthme ou médicaments contre l'asthme et hypersensibilité des voies respiratoires. Ils ont divisé les expositions professionnelles entre les sensibilisants et les irritants. Ils ont examiné les associations entre l'asthme et l'exposition professionnelle au moyen d'une analyse de régression logistique. Ils ont sélectionné le modèle d'après les observations de respiration sifflante courante et ont appliqué le même modèle aux autres définitions de l'asthme.
RÉSULTATS : Cinquante-six pour cent des sujets ont déclaré avoir été déjà exposés à des sensibilisants en milieu de travail, et 9,8 % à des irritants. La respiration sifflante courante s'associait à l'exposition à des irritants (%RAP 4,54 %) et l'hypersensibilité des voies respiratoires, à l'exposition à des sensibilisants (%RAP 30,7 %). Des antécédents d'asthme juvénile, l'atopie ou la restriction de l'analyse à l'asthme de l'adulte n'influaient pas sur ces associations. L'analyse des modifications de l'effet laissait supposer deux types d'asthme professionnel : l'asthme causé par l'exposition à des sensibilisants professionnels, et l'asthme causé par l'exposition à des irritants.
CONCLUSIONS : L'évaluation détaillée de l'exposition passée et courante est essentielle dans l'exploration de l'asthme professionnel. L'asthme juvénile réactivé ou aggravé par l'exposition professionnelle n'est pas facile à distinguer de l'asthme professionnel, et cette mauvaise classification peut entraîner une sous-estimation de l'asthme professionnel. Il faut en tenir compte dans les régions où les personnes atteintes d'asthme aggravé par le travail ne sont pas admissibles aux indemnisations pour les accidentés du travail.

Occupational exposures constitute an important cause of adult asthma, and may have contributed to an increase in adult asthma over the latter one-half of the previous century, especially in industrialized countries. For instance, voluntary reporting schemes showed that occupational asthma was the most commonly reported occupational lung disease in the United Kingdom (1,2) and Canada (3,4). In other data from 16 industrialized countries (5), the median estimate of population attributable risk percentage (PAR%) from occupational exposures was 9% (interquartile range 5% to 19%). This estimate, which includes new-onset and reactivated asthma, may even be an underestimate due to the 'healthy' worker effect, resulting from subjects who developed work-related symptoms changing jobs and/or moving out of the workplace (6).

[1]*Department of Chest Diseases, Hacettepe University, Ankara, Turkey;* [2]*Department of Epidemiology, Biostatistics and Occupational Health, McGill University;* [3]*Respiratory Epidemiology and Clinical Research Unit, Montréal Chest Institute, Montreal, Quebec*
Correspondence: Dr Ahmet Demir, Department of Chest Diseases, Hacettepe University, Sihhiye Ankara, 06100 Turkey. Telephone 90-312-3051531, fax 90-312-3100809, e-mail ademir68@gmail.com

To address this issue, data gathered in a community-based study were used to examine the distribution and determinants of adult asthma in six centres across Canada (Vancouver, British Columbia; Winnipeg, Manitoba; Hamilton, Ontario; Montreal, Quebec; Halifax, Nova Scotia; and Prince Edward Island) (7). The study followed the European Community Respiratory Health Survey (ECRHS) protocol (8). Results of the mail survey (stage 1, ECRHS protocol) showed that prevalence rates of wheeze and use of asthma medicine were among the highest reported for 48 ECRHS sites in 22 countries (9), were more common in women than men and varied significantly among the six Canadian sites (10).

In the subsample, randomly selected for laboratory studies (stage 2, ECRHS protocol), subjects completed detailed clinical and occupational questionnaires, methacholine challenge tests and allergy skin tests (9). Results covering all Canadian centres yielded an estimate of occupational asthma (probable and possible) of 36.1% (95% CI 31.3% to 41.0%) (10). These estimates are higher than those reported in subjects of comparable age in other population-based studies (11).

For the present study, a detailed analysis of results from the Montreal site was conducted to estimate the PAR% for adult-onset asthma from occupational exposures, to examine the role of childhood asthma and of atopy, and to compare the importance of past versus current exposures. Potential confounding of the results by the 'healthy' worker effect was also examined.

METHODS

Study design, population and measurement tools

The study design, population and measurement tools have been fully described elsewhere (7). Briefly, random digit telephone dialing was conducted in the Montreal area, and 2959 individuals (85.7%) returned a completed questionnaire. Of 1369 individuals invited to the laboratory for further examination (stage 2, ECRHS protocol), 498 (36.4%) completed all required laboratory tests. The tests included administration (by trained bilingual interviewers) of detailed health and occupational questionnaires, lung function testing by spirometry, methacholine challenge testing and allergy skin prick testing. Written consent was obtained for each participant in stage 2 (ECRHS protocol). The study was approved by the Ethics Review Board of the Faculty of Medicine, McGill University, Montreal, Quebec (10).

The health questionnaire included questions from the mail questionnaire, as well as questions on smoking habits, respiratory symptoms, allergic conditions, history of parental smoking, family history of asthma and allergy, childhood exposures, home characteristics, education, diet and medicine use. A French translation developed and tested in Quebec (12) was used to give subjects the choice of language. The occupational questionnaire recorded current and previous jobs, occupational exposures, and any work-related symptoms leading to changing or leaving a job.

Allergy skin prick testing was performed using a positive control (histamine) and a negative control (diluent), and 14 allergen extracts: cat, *Cladosporium herbarum*, *Dermatophagoides farinae*, olive, birch, common ragweed, *Penicillium* species, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, timothy grass, cockroach, Kentucky blue grass, east-west tree mixture and *Aspergillus* species.

Methacholine challenge testing was performed to quantitate airway hyperresponsiveness (AHR). Eligible subjects (forced expiratory volume in 1 s [FEV_1] of 70% of the predicted value or greater, or 1.5 L) performed long or short protocols with different doubling doses, and FEV_1 was measured 2 min following each dose. The maximal concentration and cumulative dose of methacholine in both protocols was 12.5 mg/mL and 2 mg (11.23 mmol), respectively.

Study variables and statistical analysis

Three definitions of asthma, based on questionnaire answers, were used to investigate its association with occupational exposures and compare findings with other studies following the ECRHS protocol (8,9):

- current wheeze: wheezing or whistling in the chest in the previous 12 months;
- current asthma symptoms and/or asthma medicine: waking up with shortness of breath, having an asthma attack and/or using asthma medicine in the previous 12 months; and
- AHR: a 20% fall in FEV_1 from the postdiluent level in the methacholine challenge test before the maximum cumulative dose of 2 mg was reached.

Adult-onset asthma was defined as asthma (by any of the above definitions) excluding subjects who reported their first attack of asthma before 15 years of age (childhood-onset asthma).

Atopy was defined as a positive reaction to any of the allergens tested. A positive reaction was recorded when the mean wheal diameter was 3 mm greater than the negative control.

Occupational exposures were classified as sensitizers (acting through immunological mechanisms, including high and low molecular weight agents) and irritants (acting through non-immunological mechanisms) (13). Exposures were defined as current (present within 12 months of study date) or past (ended 12 months or more before study date).

The association of asthma with occupational exposures was assessed by logistic regression analysis. To determine the risk of asthma attributable to occupational exposures in the adult population, models were selected taking into account pertinent risk factors, selected from questionnaire items and/or based on substantive knowledge (6,13). Risk factors included the following:

- host factors: sex, atopy, and a family history of atopy and/or asthma;
- childhood exposures: parental smoking, pet in the home, having an older sibling, attending play or nursery school before five years of age, lower respiratory tract infection before five years of age; and
- adulthood exposures: smoking status (never, ex or current), pet in the home, home characteristics (mould, mildew, carpeting, electrical heating), dietary habits (eating fresh fruit or prepackaged foods), socioeconomic status assessed by education level (completion of secondary education versus not).

TABLE 1
Characteristics of the stage 1 and stage 2 populations

	Stage 1 mail survey (n=2460), n (%)	Stage 2 laboratory study (n=498), n (%)
Women	1372 (55.8)	261 (52.3)
Age, years		
20–29	926 (37.6)	199 (39.9)
30–39	1058 (43.0)	203 (40.7)
40–44	476 (19.3)	97 (19.4)
Smoking status		
Never smoked	978 (39.8)	218 (43.7)
Smoked in the past	560 (22.8)	103 (20.6)
Current smoker	922 (37.5)	178 (35.7)
Asthma diagnosis	294 (11.9)	85 (16.8)
Childhood-onset asthma	149 (6.0)	50 (10.0)
Atopy*	–	308 (65.1)
Ever having had occupational exposure to		
Dust	875 (35.6)	186 (37.3)
Chemicals/gas/fume	522 (22.4)	124 (24.9)
Any	1055 (42.8)	217 (43.5)
Sensitizers	N/A	253 (56.8)
Irritants	N/A	49 (9.8)
Changed or left job†	67 (6.4)	19 (8.8)

*Data are presented separately for subjects who participated in the mail survey only and those who participated in both the mail survey and the laboratory study. *Atopy was defined as a positive reaction to any of the allergens tested; †Changed or left job among those ever having been exposed to any dust and/or chemicals/fumes at work. N/A Not available*

TABLE 2
Adjusted prevalence ORs (PORs) for the association between asthma and past or current occupational exposures

	Current wheeze, POR (95% CI)	Asthma symptoms and/or medicine, POR (95% CI)	AHR, POR (95% CI)
High molecular weight agents			
Past	1.43 (0.92, 2.22)	1.12 (0.65, 1.92)	1.59 (0.85, 2.98)
Current	1.12 (0.64, 1.95)	0.94 (0.46, 1.89)	1.20 (0.53, 2.68)
Low molecular weight agents			
Past	1.61 (1.02, 2.55)	1.61 (0.92, 1.81)	1.33 (0.69, 2.56)
Current	0.74 (0.39,1.39)	0.88 (0.41, 1.88)	1.13 (0.49, 2.63)
Irritants			
Past	2.73 (1.35, 5.54)	1.17 (0.46, 2.98)	0.19 (0.02, 1.47)
Current	0.44 (0.09, 2.03)	0.92 (0.20, 4.22)	1.50 (0.30, 7.52)
Inorganic dust			
Past	1.20 (0.58, 2.50)	1.13 (0.45, 2.86)	0.77 (0.25, 2.41)
Current	1.12 (0.49, 2.57)	1.50 (0.59, 3.84)	1.22 (0.39, 3.85)
Cigarette smoke			
Past	1.66 (1.03, 2.68)	1.52 (0.86, 2.70)	1.26 (0.64, 2.46)
Current	0.97 (0.62, 1.51)	0.89 (0.51, 1.56)	1.39 (0.75, 2.59)
Combustion smoke			
Past	4.74 (2.26, 9.94)	2.38 (1.04, 5.43)	0.83 (0.23, 2.95)
Current	0.71 (0.27, 1.84)	1.68 (0.64, 4.37)	0.23 (0.63, 2.63)
Excess cold			
Past	2.78 (1.43, 5.41)	1.98 (0.92, 4.26)	4.18 (1.72, 10.2)
Current	0.98 (0.46, 2.08)	0.86 (0.32, 2.29)	0.43 (0.10, 1.92)
Excess heat			
Past	2.74 (1.39, 5.41)	1.39 (0.54, 3.09)	0.64 (0.18, 2.24)
Current	1.24 (0.65, 2.36)	1.06 (0.47, 2.37)	1.16 (0.45, 2.98)

High molecular weight agents included the dusts of grain or flour, cotton, fur, coffee, biological enzymes, vegetable gum and glue. Low molecular weight agents included dyes, formaldehyde, hardeners, accelerators, paints, pharmaceuticals, resins and metals (cobalt, chromium, nickel, platinum and zinc). Definitions of asthma: current wheeze, wheezing or whistling in the chest in the past 12 months; asthma symptoms and/or medication, waking up with shortness of breath, having an asthmatic attack and/or using asthma medication; airway hyperresponsiveness (AHR), a 20% fall in forced expiratory volume in 1 s from the postdiluent level in the methacholine challenge test before the maximum cumulative dose of 2 mg was reached

Model selection was based on the findings for current wheeze, and the same model was applied to the other definitions of asthma. The Schwarz criterion, a rough approximation to the logarithm of Bayes factor, was used to compare models (14). Effect modification was explored by repeating the analysis for different subgroups exhibiting potential effect modifiers, such as sex, smoking status, atopy and age. All statistical analyses were performed with the statistical program SAS version 6.12 (SAS Institute Inc, USA).

PAR% was calculated as follows:

$$PAR\% = ([RR-1] \times P1) \div RR$$

where RR is the relative risk and P1 is the proportion of cases exposed (15). Because the rare disease assumption does not hold for asthma, prevalence rate ratios (adjusted for pertinent risk factors) were used to provide relative risk estimates. Variance estimators of the PAR% and 95% CI were also calculated (16). Because of the low response rate in the stage 2 study, multiple imputation was performed to adjust for subjects who participated in Stage 1 of the study, but did not undergo or complete airway challenge testing (17).

RESULTS

Response rate for stage 1 was high (85.7%) compared with stage 2 (36.4%). Table 1 shows characteristics of subjects who constituted the stage 1 and 2 study populations. Of those who responded, the stage 2 population had a higher prevalence of asthma diagnoses and never smokers than the stage 1 population, but they were similar in terms of occupational exposures and a history of changing or leaving their job. Ever having had exposure to occupational sensitizers and irritants were reported by 56.8% and 9.8% of the stage 2 population, respectively. The prevalences of asthma, defined in three ways, were as follows: current wheeze 23.7%, asthma symptoms and/or medicine 12.8%, and AHR 14.7% (data not shown). Multiple imputation adjusting for low response rates yielded similar prevalence estimates for AHR (14.5%, 15.5%, 16.1%).

Table 2 shows the independent association between asthma (defined in three ways) and occupational exposures. Data are presented as prevalence ORs (PORs) with 95% CI (adjusted for age, sex and smoking status). In all exposure categories, the association was stronger for past than current exposures. These associations were statistically significant for current wheeze with past exposure to low molecular weight agents, irritants, cigarette smoke, combustion smoke, excess cold and excess heat. Asthma symptoms and/or medicine and AHR were also significantly associated with past exposure to combustion smoke, and to excess cold, respectively.

TABLE 3
Association between asthma in the stage 2 population (n=498) and occupational exposures (ever), adjusted for pertinent risk factors for asthma

	Current wheeze, POR (95% CI)	Asthma symptoms and/or medicine, POR (95% CI)	AHR, POR (95% CI)
Ever having been exposed to			
Sensitizers	1.01 (0.62, 1.66)	1.03 (0.57, 1.86)	**2.20 (1.10, 4.38)**
Irritants	**2.12 (1.03, 4.34)**	0.88 (0.33, 2.31)	0.35 (0.09, 1.34)
Childhood asthma	**5.99 (2.64, 13.6)**	**8.89 (4.06, 19.5)**	**8.72 (2.85, 26.7)**
Respiratory infection before five years of age	**2.94 (1.32, 6.54)**	1.39 (0.57, 3.39)	**0.21 (0.04, 1.00)**
Pet in home in childhood	**1.90 (1.05, 3.42)**	1.07 (0.54, 2.07)	0.98 (0.47, 2.03)
Having an older sibling	**0.44 (0.27, 0.71)**	**0.56 (0.32, 0.99)**	0.54 (0.28, 1.01)
Current smoker	**3.60 (2.26, 5.76)**	1.26 (0.71, 2.24)	**2.24 (1.19, 4.21)**
Education level	**0.42 (0.20, 0.88)**	**0.43 (0.19, 0.98)**	1.78 (0.49, 6.50)
Family history of asthma	**2.26 (1.33, 3.82)**	**1.96 (1.06, 3.61)**	**2.09 (1.04, 4.20)**
Female sex	**1.74 (1.07, 2.82)**	1.23 (0.69, 2.22)	1.69 (0.87, 3.28)

Data are presented as prevalence odds ratios (PORs), 95% CI, adjusted for pertinent risk factors for asthma (respiratory infection before five years of age, pet in the home in childhood, having an older sibling, being a current smoker, education level, family history of asthma and being female). Significant differences are shown in bold type. Definitions of asthma: current wheeze, wheezing or whistling in the chest in the past 12 months; asthma symptoms and/or medication, waking up with shortness of breath, having an asthmatic attack and/or using asthma medication; airway hyperresponsiveness (AHR), a 20% fall in forced expiratory volume in 1 s from the postdiluent level in the methacholine challenge test before the maximum cumulative dose of 2 mg was reached

TABLE 4
Population attributable risk percentage (PAR%) for asthma due to occupational exposures (ever), adjusted for pertinent risk factors* and atopy

	Current wheeze, PAR% (95% CI)	Asthma symptoms and/or medicine, PAR% (95% CI)	AHR, PAR% (95% CI)
Exposure (ever) to sensitizers			
All ages†	2.25 (–0.17, 4.61)	1.66 (–2.59, 5.74)	**29.6 (24.3, 34.5)**
All ages‡	0.24 (–2.53, 2.93)	1.69 (–3.02, 6.20)	**26.3 (20.7, 31.7)**
Adult onset†	3.30 (0.31, 6.20)	2.16 (–3.72, 7.71)	**29.5 (22.5, 35.8)**
Adult onset‡	–0.59 (–4.10, 2.79)	–2.36 (–9.10, 3.97)	**26.4 (18.9, 33.3)**
Exposure (ever) to irritants			
All ages†	**5.52 (5.19, 5.84)**	**–0.87 (–1.23, –0.51)**	**–7.08 (–7.38, –6.77)**
All ages‡	**5.96 (5.64, 6.27)**	**–0.79 (–1.18, –0.40)**	**–6.12 (–6.51, –5.74)**
Adult onset†	**5.52 (5.19, 5.84)**	**–1.36 (–1.70, –1.01)**	**–4.94 (–5.34, –4.54)**
Adult onset‡	**6.03 (5.64, 6.42)**	**–0.86 (–1.31, –0.41)**	**–3.84 (–4.21, –3.46)**

*Data are presented as PAR% for asthma defined in three ways due to occupational exposures, adjusted for personal risk factors and atopy. Significant differences are shown in bold type. Note the negative association of exposure (ever) to irritants for asthma symptoms and/or medicine, and for airway hyperresponsiveness (AHR), suggests a 'healthy' worker survivor effect, ie, those ever exposed to irritants had quit the offending workplace or changed jobs within the same workplace. Definitions of asthma: current wheeze, wheezing or whistling in the chest in the past 12 months; asthma symptoms and/or medication, waking up with shortness of breath, having an asthmatic attack and/or using asthma medication; AHR, a 20% fall in forced expiratory volume in 1 s from the postdiluent level in the methacholine challenge test before the maximum cumulative dose of 2 mg was reached. *Pertinent risk factors included respiratory infection before five years of age, pet in the home in childhood, having an older sibling, being a current smoker, education level, family history of asthma, being female and childhood asthma; †Adjusted for pertinent risk factors; ‡Adjusted for pertinent risk factors and atopy*

Table 3 shows the independent associations of asthma (defined in three ways) with occupational exposures, adjusted for ten pertinent risk factors for asthma. For current wheeze (column 1), PORs were significant for nine factors; the exception was occupational exposure to sensitizers. For two of the risk factors, the PORs were protective (having an older sibling [POR 0.44, 95% CI 0.27 to 0.71] and education level [POR 0.42, 95% CI 0.20 to 0.88]). For asthma symptoms and/or medicine (column 2), POR was significant for four risk factors, two of which were protective (having an older sibling [POR 0.56, 95% CI 0.32 to 0.99] and education level [POR 0.43, 95% CI 0.19 to 0.98]). For AHR (column 3), POR was significant for five factors, one of which was marginally protective (having a respiratory infection before five years of age [POR 0.21, 95% CI 0.04 to 1.00]). Findings were similar when childhood asthmatic subjects were excluded from the analysis (results not shown).

Table 4 shows estimates of PAR% for asthma due to occupational exposures. Neither the presence of atopy nor a history of childhood asthma affected these estimates. Thus, for current wheeze (all ages), the association (adjusted for pertinent risk factors) was significant for exposure (ever) to irritants (PAR% 5.52%, 95% CI 5.19% to 5.84%) and changed little when atopy was added. The results were similar for adult-onset asthma. For asthma symptoms and/or medicine (all ages), the association (adjusted for pertinent risk factors) was significant (negative) for exposure (ever) to irritants (PAR% –0.87%, 95% CI –1.23% to –0.51%), and changed little when atopy was added. The findings were similar for adult-onset asthma. For AHR (all ages), the association (adjusted for pertinent risk factors) was significant for exposure (ever) to sensitizers (PAR% 29.6%, 95% CI 24.3% to 34.5%), and changed little when atopy was added, while for exposure (ever) to irritants (all ages), the association was also significant (negative) (PAR% –7.08%, 95% CI –7.38% to –6.77%) and changed little when atopy was added. The findings were similar for adult-onset asthma. The negative association of exposure (ever) to irritants for asthma symptoms and/or medicine, as well as AHR, implies a 'healthy worker' survivor effect, ie, those ever exposed to irritants had quit the offending workplace or changed jobs within the workplace. They were identified in this community-based study, and would very likely be missed in a workforce-based study unless past exposures had been specifically sought in the study questionnaire.

Effect modification of occupational exposures by other risk factors for asthma was also examined (data not shown). For occupational exposure to sensitizers, there was no evidence of effect modification for current wheeze or for asthma symptoms and/or medicine; all PORs were nonsignificant. However, for AHR, the POR was increased in women (POR 3.19, 95% CI 1.29 to 7.91), in individuals aged 40 to 44 years (POR 7.26, 95% CI 1.11 to 47.3), in current smokers (POR 5.32,

TABLE 5
Percentage of subjects with occupational exposure (P), prevalence rate ratios (PRRs) and population attributable risk percentage (PAR%) for occupational exposures using three definitions of asthma in the study population (all ages), and excluding childhood asthmatic subjects, in models adjusted for sex, age and smoking

	Study population (all ages)			Study population (excluding childhood asthmatic subjects)		
	Current wheeze (n=498)	Asthma symptoms and/or medicine (n=498)	AHR (n=368)	Current wheeze (n=458)	Asthma symptoms and/or medicine (n=458)	AHR (n=344)
Exposure (ever) to sensitizers						
P	58.5	57.1	64.8	58.3	56.3	65.9
PRR	1.09	1.16	1.90	1.09	1.13	2.03
PAR% (95% CI)	**4.83 (2.46, 7.13)**	**7.88 (3.89, 11.7)**	**30.7 (25.5, 35.5)**	**4.81 (1.85, 7.68)**	**6.47 (0.75, 11.9)**	**33.4 (26.9, 39.4)**
Exposure (ever) to irritants						
P	14.62	10.00	5.56	14.56	8.33	6.82
PRR	1.45	0.94	0.42	1.48	0.79	0.5
PAR% (95% CI)	**4.54 (4.27, 4.80)**	**–0.64 (–0.29, –0.99)**	**–7.68 (–7.36, –8.00)**	**4.72 (4.39, 5.05)**	**–2.21 (–1.79, –2.64)**	**–6.82 (–6.35, –7.29)**

Data are presented for the study population for all ages, and excluding childhood asthmatic subjects. For each definition of asthma used, the number of subjects in the analysis is indicated in brackets. Significant differences are shown in bold type. The negative association of exposure (ever) to irritants for asthma symptoms and/or medicine, and airway hyperresponsiveness (AHR), implies a 'healthy' worker survivor effect, ie, those ever exposed to irritants had quit the offending workplace or changed jobs within the same workplace. Definitions of asthma: current wheeze, wheezing or whistling in the chest in the past 12 months; asthma symptoms and/or medication, waking up with shortness of breath, having an asthmatic attack and/or using asthma medication; AHR: a 20% fall in forced expiratory volume in 1 s from the postdiluent level in the methacholine challenge test before the maximum cumulative dose of 2 mg was reached

95% CI 1.69 to 16.8), and in those who did not change or leave their jobs (POR 2.25, 95% CI 1.12 to 4.53). For occupational exposure to irritants, POR for current wheeze was increased in persons aged 20 to 29 years (POR 3.22, 95% CI 1.04 to 9.90), in those who had never smoked (POR 3.87, 95% CI 1.10 to 13.6), in nonatopic subjects (POR 6.52, 95% CI 1.42 to 29.9) and in those who had never had asthma (POR 2.44, 95% CI 1.08 to 5.50).

Table 5 summarizes the study findings. Estimates of PAR% were remarkably similar whether or not childhood asthmatic subjects were excluded. For instance, given exposure (ever) to sensitizers for current wheeze (all ages and excluding childhood asthmatic subjects), PAR% were 4.83% and 4.81%, respectively; for asthma symptoms and/or medicines, PAR% were 7.88% and 6.47%, respectively; and for AHR, PAR% were 30.7% and 33.4%, respectively. Given exposure (ever) to irritants for current wheeze (all ages and excluding childhood asthmatic subjects), the PAR% were 4.54% and 4.72%, respectively; for asthma symptoms and/or medicines, the PAR% (negative) were –0.64% and –2.21%, respectively; and for AHR, the PAR% (also negative) were –7.68%, and –6.82%, respectively. As indicated in the footnote to Table 5 above, these negative associations imply a 'healthy' worker survivor effect in the data.

DISCUSSION

An important source of bias in the investigation of occupational diseases is the 'healthy' worker effect, which may lead to underestimation of work-related disease. This effect results from the selection of healthier individuals at time of hire (healthy hire) and the less healthy workers leaving the workforce or transferring to jobs with lower exposure ('healthy' worker survivor effect) (6). Self-selection into the smoking habit may also occur due to the 'healthy' smoker effect (18), analogous to the 'healthy' worker effect. However, both effects are less likely to compromise the results of community-based studies than workforce-based studies because, if sampling is random, workers who quit the workplace or smokers who change their habit will be identified in the population in proportion to their numbers.

The association between asthma and occupational exposures was stronger for past than for current exposures (Table 2). Persistence of asthma symptoms and AHR after cessation of occupational exposure is well recognized (19-23), and gives scientific plausibility to the present findings. This also underlines the importance of considering all occupational exposures, past as well as present, when evaluating work-related asthma.

Atopy did not modify the PAR% of AHR due to exposure to sensitizers (Table 4), a finding in contrast to a previous report (23). In the present study, the aeroallergens tested (see methods) were not comprehensive, so atopic workers sensitized to certain occupational aeroallergens (eg, latex) may not have been identified by the skin tests used. Another explanation is self-selection of atopic individuals out of exposure to sensitizers, again the consequence of the 'healthy' worker survivor effect (6).

Exclusion of childhood asthmatic subjects from analysis did not change PAR% estimates for current wheeze or AHR (Table 4), suggesting that reactivation of childhood asthma does not contribute to adult-onset, work-related asthma. A National Institute for Occupational Safety and Health report (24) based on Sentinel Event Notification Systems for Occupational Risks came to a similar conclusion. In the present study, the risk of AHR due to sensitizers was higher in women than in men, likely due to the higher prevalence and incidence of asthma in women in their reproductive years than in men, with reversal after menopause (25).

Analysis of effect modification with different definitions of asthma and occupational exposure suggested two types of work-related asthma:

- Occupational sensitization resulting in airway inflammation and AHR: the risk was increased in women, older subjects, current smokers and those with a

history of not moving or changing jobs. These denote susceptibility factors for work-related asthma.

- Provocation of asthma symptoms due to ever having been exposed to irritants in the workplace: the risk of wheeze after exposure to irritants was increased in young, nonatopic, nonsmoking adults with no history of asthma. These effect modifiers (mainly working in an opposite direction to the susceptibility factors mentioned above) may represent avoidance of exposures to potentially harmful effects by subjects with occupational exposure to irritants. This is consistent with the negative estimates for PAR% for AHR due to exposure (ever) to irritants (Tables 4 and 5).

Current smoking increased the risk of asthma in individuals exposed to certain sensitizers. The effect of smoking on airway mucosa (enhanced inflammation and permeability) (26) could act synergistically with some of the occupational sensitizers.

Risk of occupational asthma was also increased in the oldest age group (40 to 44 years). An increase in occupational asthma with age has been reported in men and women (27). As an explanation, the authors cited different referral patterns, with young people being less likely to seek medical attention for work-related illness than older people, who may seek compensation or wish to stay in a job with security despite experiencing symptoms. Susceptibility to respiratory sensitization may also increase with age because of past exposures or behavioural factors such as smoking.

Occupational exposure to irritants is not accepted as a cause of occupational asthma in many jurisdictions, yet may be responsible for the major burden of work-aggravated asthma (28).

Although the response rate for the Stage 2 study was low (35%), exposure to dust, gases and fumes at work were similar in the stage 1 and 2 study populations (Table 1). Thus, bias due to nonresponse in the stage 2 study (selection bias) is unlikely to have affected the relationship between asthma and occupational exposures.

Because past occupational exposures were assessed by self-report, recall bias is a potential problem to the study inferences. However, the association between AHR (an objective measure) and occupational exposure to sensitizers, but not to irritants is evidence against the presence of an important recall bias.

CONCLUSIONS

Detailed assessment of past and current occupational exposures is essential in the investigation of work-related asthma, which, based on the Montreal experience, could represent up to 33% of cases of adult-onset asthma. Childhood asthma reactivated or aggravated by work exposures is clearly not easy to distinguish from asthma induced by work, a distinction irrelevant to the point of view of the worker who develops work-related symptoms of asthma. This should be taken into account in jurisdictions in which asthma aggravated by work exposures is not accepted as causally related to work exposures (often to irritants) and therefore, not eligible for workers' compensation. A history of childhood asthma should not influence the decision as to whether a given case of asthma was work-related.

ACKNOWLEDGEMENTS: The authors acknowledge with appreciation the individuals who gave their time to participate in this study. This paper is based in part on Dr Demir's MSc Thesis (McGill University, 1999). Dr Demir would like to specially thank Dr I Baris for providing him with the opportunity to study epidemiology and biostatistics at McGill University, Dr J Manfreda (as the principal investigator) on behalf of all the researchers in the study for providing the Montreal dataset, Dr P Ernst and Dr H Ghezzo for their practical suggestions on the analysis, and D Bastien for her technical help in the preparation of the manuscript.

FUNDING: This study was supported by the National Health Research and Development Programme, the Province of Prince Edward Island, Health Canada (Principal Investigator J Manfreda, University of Manitoba), and an unrestricted grant from GlaxoSmithKline, Canada, to the University of Manitoba.

CONFLICTS OF INTEREST: None of the authors have any competing interests.

REFERENCES

1. Meyer JD, Holt DL, Cherry NL, et al. SWORD '98: Surveillance of work-related and occupational respiratory disease in the UK. Occup Med 1999;49:485-9.
2. Meredith SK, Taylor VM, McDonald JC. Occupational respiratory disease in the United Kingdom 1989: A report to the British Thoracic Society and the Society of Occupational Medicine by the SWORD project group. Br J Ind Med 1991;48:292-8.
3. Contreras GR, Rousseau R, Chan-Yeung M. Occupational respiratory diseases in British Columbia, Canada in 1991. Occup Environ Med 1994;51:710-2.
4. Provencher S, Labreche FP, De Guire L. Physician based surveillance system for occupational respiratory diseases: The experience of PROPULSE, Québec, Canada. Occup Environ Med 1997;54:272-6.
5. Blanc PD, Tören K. How much adult asthma can be attributed to occupational factors? Am J Med 1999;107:580-7.
6. Eisen EA. Healthy worker effect in morbidity studies. Med Lav 1995;86:125-38.
7. Manfreda J, Becklake MR, Sears MR, et al. Prevalence of asthma symptoms among adults 20-44 years in Canada. CMAJ 2001164:995-1001.
8. Burney PGJ, Luczynska S, Chinn S, et al; for the European Community Respiratory Health Survey (ECRHS). The European Community Respiratory Health Survey. Eur Respir J 1994;7:954-60.
9. European Community Respiratory Health Survey. Variations in the prevalence of respiratory symptoms, self reported asthma attacks, and use of asthma medication in the European Community Respiratory Health Survey (ECRHS). Eur Respir J 1996;9:687-95.
10. Johnson AR, Dimich-Ward HD, Manfreda J, et al. Occupational asthma in adults in six Canadian communities. Am J Respir Crit Care Med 2000;162:2058-62.
11. Balmes J, Becklake M, Blanc P, et al. Environmental and Occupational Health Assembly, American Thoracic Society. American Thoracic Society Statement: Occupational Contribution to the Burden of Airway Disease. Am J Respir Crit Care Med 2003;167:789-95.
12. Osterman JW, Armstrong BG, Lectoux E, et al. Comparison of French and English versions of the American Thoracic Society respiratory questionnaire in a bilingual working population. Int J Epidemiol 1991;201:138-43.
13. Chan-Yeung M, Malo JL. Aetiologic agents in occupational asthma. Eur Respir J 1994;7:346-71.
14. Kass JE, Raftery AE. Bayes Factors. J Am Stat Assoc 1995;90:773-95.
15. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol 1974;99:325-32.
16. Greenland S. Re: "Confidence limits made easy: Interval estimation using a substitution method". Am J Epidemiol 1999;149:884.

17. Rubin DB, Schenker N. Multiple imputation in health-care databases an overview and some applications. Stat Med 1991;10:585-98.
18. Becklake MR, Lalloo U. The 'healthy smoker': A phenomenon of health selection? Respiration 1990;57:137-44.
19. Venables KM, Chan-Yeung M. Occupational asthma. Lancet 1997;349:1465-9.
20. Maghni K, Lemière C, Ghezzo H, et al. Airway inflammation after cessation of exposure to agents causing occupational asthma. Am J Respir Crit Care Med 2004;169:367-72.
21. Brant A, Zekveld C, Welch J, et al. The prognosis of occupational asthma due to detergent enzymes: Clinical, immunological and employment outcomes. Clin Exp Allergy 2006;36:483-8.
22. Monso E, Malo JL, Infante-Rivard C, et al. Individual characteristics and quitting in apprentices exposed to high-molecular-weight agents. Am J Respir Crit Care Med 2000;161:1508-12.
23. Nicholson PJ, Cullinan P, Newman Taylor AJ, Burge PS, Boyle C. Evidence based guidelines for the prevention, identification, and management of occupational asthma. Occup Environ Med 2005;62:290-9.
24. Goe SK, Henneberger PK, Reilly MJ, et al. A descriptive study of work aggravated asthma. Occup Environ Med 2004;61:512-7.
25. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. Thorax 1999;54:1119-38.
26. Siracusa A, Marabini A, Folletti I, Moscato G. Smoking and occupational asthma. Clin Exp Allergy 2006;36:577-84.
27. Meredith S, Nordman H. Occupational asthma: Measures of frequency from four different countries. Thorax 1996;51:435-40.
28. Venables KM. Preventing occupational asthma. Br J Ind Med 1992;49:817-9.