

Risks of Exposure to Occupational Asthmogens in Atopic and Nonatopic Asthma

A Case-Control Study in Taiwan

Tsu-Nai Wang^{1,2*}, Meng-Chih Lin^{3*}, Chao-Chien Wu³, Sum-Yee Leung³, Ming-Shyan Huang⁴, Hung-Yi Chuang^{1,5}, Chien-Hung Lee¹, Deng-Chyang Wu⁶, Pei-Shan Ho⁷, Albert Min-Shan Ko², Po-Ya Chang², and Ying-Chin Ko^{2,8}

¹Department of Public Health, College of Health Science, Kaohsiung Medical University; ²Center of Excellence for Environmental Medicine, Kaohsiung Medical University; ³Division of Pulmonary and Critical Care Medicine, Department of Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine; ⁴Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Kaohsiung Medical University Hospital; ⁵Department of Occupational Medicine, Kaohsiung Medical University Hospital; ⁶Department of Gastroenterology, Kaohsiung Medical University Hospital; ⁷Department of Dental Hygiene, College of Dental Medicine, Kaohsiung Medical University; and ⁸Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Kaohsiung, Taiwan

Rationale: Asthma is often work-related and can be classified as atopic or nonatopic on the basis of its pathogenesis. Few studies have reported an association between exposure to occupational asthmogens and asthma with and without atopy.

Objectives: We investigated, in adults with asthma, whether occupational exposure to asthmogens influenced the risk of having atopic or nonatopic asthma, and their level of lung function.

Methods: We recruited 504 hospital-based adults with current asthma, 504 community-based control subjects, and 504 hospital-based control subjects in southern Taiwan. Asthma with atopy was defined as having asthma in combination with an increase in total IgE (≥ 100 U/ml) or a positive Phadiatop test (≥ 0.35 Pharmacia arbitrary unit/L) (Pharmacia ImmunoCAP; Pharmacia, Uppsala, Sweden). Occupational exposure to asthmogens was assessed with an asthma-specific job exposure matrix.

Measurements and Main Results: We found a significant association between atopic asthma and exposure to high molecular weight asthmogens (adjusted odds ratio [AOR], 4.0; 95% confidence interval [CI], 1.8–8.9). Nonatopic asthma was significantly associated with exposure to low molecular weight asthmogens (AOR, 2.6; 95% CI, 1.6–4.3), including industrial cleaning agents and metal sensitizers. Agriculture was associated with both atopic and nonatopic asthma (AOR, 7.8; 95% CI, 2.8–21.8; and AOR, 4.1; 95% CI, 1.3–13.0, respectively). The ratio of FEV₁ to FVC in the high-risk group was significantly lower than in the no-risk group ($P = 0.026$) in currently employed patients with asthma.

Conclusions: In adults with asthma, occupational exposure to high and low molecular weight asthmogens appears to produce differential risks for atopic and nonatopic asthma.

Asthma is the most common occupational lung disease in industrialized countries. Work-related asthma (WRA) is defined by the 2008 Guideline of the American College of Chest Physicians as work-exacerbated asthma (WEA) and occupational asthma (OA), that is, asthma that is exacerbated or caused by a workplace substance, respectively (1). By definition, WEA is present in workers with preexisting or concurrent

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Few studies have reported an association between exposure to comprehensive occupational asthmogens and atopic and nonatopic asthma.

What This Study Adds to the Field

We used a case-control study to assess the effects of occupational exposure across the entire spectrum of jobs. Occupational exposure to high molecular weight asthmogens and low molecular weight asthmogens may pose different risks for atopic and nonatopic asthma.

asthma that is triggered by work-related exposures, but is not considered to be OA. OA is caused by exposure to high molecular weight (high-MW) or low molecular weight (low-MW) chemicals in the workplace. OA may be caused by allergic sensitization to workplace agents (sensitizer-induced OA, immunologic OA), or by exposure to irritants inhaled at work (irritant-induced OA, nonimmunologic asthma) (1, 2). OA and WEA are not mutually exclusive and may coexist in the same patient (3). The proportion of adult new-onset asthma that is work-related is estimated to be between 9 and 15% (4). Studies indicate that 25% or more of cases of *de novo* asthma may have an occupational basis (2, 5). Symptomatic deterioration at work is common in subjects with asthma (6) and may cause a potential burden of work disability with socioeconomic effects (7).

Classically, immunologic OA appears after a latency period of exposure, which is necessary for patients to become immunologically sensitized to the causal agent (8). In some patients with immunologic OA, an IgE-mediated mechanism is involved after sensitization to high-MW agents derived from animal, plant, or microbial origins in the workplace (9, 10). Nonimmunologic OA can be induced by exposure to high-level irritants at work, possibly via direct injury to the bronchial mucosa (8–10). One study investigated long-term outcomes of subjects with irritant-induced OA and reported no significant improvements in measures of lung function. Levels of inflammatory and remodeling mediators were higher than in control subjects, but these levels were not different from allergic OA (11).

A worldwide study from 12 industrialized countries shows that farmers, painters, plastic workers, cleaners, spray painters, and agricultural workers are exposed to an excessive asthma risk (12). In a Finnish study, the risk of asthma significantly increased during follow-up in agricultural, manufacturing, and

(Received in original form June 27, 2009; accepted in final form July 15, 2010)

Supported by grants NHRI-CN-PD9611P, NSC96-2314-B-037-040-MY3, and KMU-EM-98-4-2, Taiwan.

* Tsu-Nai Wang and Meng-Chih Lin contributed equally as first authors.

Correspondence and requests for reprints should be addressed to Ying-Chin Ko, M.D., Ph.D., Center of Excellence for Environmental Medicine, Kaohsiung Medical University, No. 100, Shih-Chuan 1st Rd, Kaohsiung 807, Taiwan. E-mail: ycko@kmu.edu.tw

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org

Am J Respir Crit Care Med Vol 182, pp 1369–1376, 2010

Originally Published in Press as DOI: 10.1164/rccm.200906-0969OC on August 6, 2010

Internet address: www.atsjournals.org

service workers in comparison with administrative workers (13). Longitudinal studies of workers chronically exposed to cotton or grain dust show that these workers have an increased frequency of cough and phlegm and an accelerated annual decline in lung function (14, 15). Another study suggests that lack of symptomatic improvement in subjects with OA after they are removed from exposure to the causative agent is associated with lung function impairment (16). These reports all strongly demonstrate that workplace exposure is related to asthma and lung function.

To date, several studies have used asthma-specific job exposure matrices (JEMs) to investigate the correlations between occupational asthrogens and asthma risk and severity (17–19). Only few reports have also used this matrix to study differences between the risks of atopic and nonatopic asthma depending on the type of asthrogen. Therefore, we designed a case-control study and recruited hospital-based asthma cases, and nonasthmatic control subjects from both the community and the hospital. We applied a published asthma-specific JEM (17, 18) to estimate the risks of comprehensive occupational exposure for asthma with and without atopy. Some of the results of this study have been previously reported in the form of an abstract (20).

METHODS

Subjects

The asthma group. Adults with asthma who were older than 18 years were recruited from two medical centers, the Division of Pulmonary and Critical Care Medicine of Chang-Gung Memorial Hospital and the Division of Chest Medicine of Kaohsiung Medical University in southern Taiwan, from August 2006 to October 2009. Participants were diagnosed with asthma if they had symptoms such as episodic breathlessness, wheezing, cough, and chest tightness according to the Global Initiative for Asthma (GINA) guidelines, and/or spirometry demonstrating an increase in FEV₁ of at least 12% and at least 200 ml from the prebronchodilator value (21, 22). Participants who met the preceding criteria were considered to have current asthma if they had had at least one asthma attack or required use of asthma medications in the 12 months before the interview (5). Four pulmonologists were involved in the study and diagnosed subjects according to the same criteria.

A total of 668 adults with current asthma agreed to participate in this study. Patients (n = 164) were excluded if they had physician-diagnosed tuberculosis, emphysema, chronic airway obstruction, cancer (n = 59), provided incomplete questionnaires for questions on job title and work exposure (n = 13), changed jobs because of the onset of symptoms (n = 10), or never worked (n = 82). Thus, 504 subjects with current asthma (230 males and 274 females, 18–70 yr of age) were further analyzed.

The control groups. Two control groups, a community-based control group and a hospital-based control group, were used for the present study. The community control subjects were recruited between August 2006 and October 2009, from a health survey conducted at local health stations in four communities in the same geographic areas in southern Taiwan. Our expected sample size was 1,200 subjects (≥18 yr old). A total of 1,138 (94.8%) adult control subjects agreed to answer a questionnaire; undergo an assessment of lung function, respiratory symptoms, and atopic diseases; and provide blood samples. Community-based control subjects (n = 385) were excluded from this study if they had physician-diagnosed asthma, pneumonia, tuberculosis, emphysema, chronic airway obstruction, or cancer (n = 78); did not provide answers to questions about job title and work exposure (n = 32); or had never worked (n = 275). Of the 753 remaining eligible subjects (362 males and 391 females), 504 community-based control subjects (230 males and 274 females) were matched 1:1 with the subjects with asthma for age (±5 yr) and sex. If more than one community control subject matched a subject with asthma, the first recruited control subject was selected.

The detailed protocol of recruiting hospital-based control subjects was described previously (23), and some descriptions of these subjects are given in the online supplement. From a list of all potential control

subjects, 504 hospital-based control subjects (252 males and 252 females, 18–70 yr of age) were chosen out of 1,145 eligible subjects (867 males and 278 females) according to the following criteria: a 1:1 male-to-female ratio had to be achieved and subjects were selected from the most recent recruitment.

The two groups of community and hospital control subjects were combined to increase statistical power (data are provided in Tables E2–E4 in the online supplement).

The study protocol was approved by the Institutional Review Board (IRB) of Kaohsiung Medical University and Chang-Gung Memorial Hospital. Written informed consent was obtained from all subjects.

Job Exposure Assessment

Physical examination and a questionnaire, including previous and current job history and environmental factors, were completed at the time of visiting a physician. Occupational exposures were estimated for the current or most recent job code (24) and assessed by trained interviewers. Government occupational hygienists performed the expert step according to the published method (17). Our study used the asthma-specific JEM developed by Kennedy and colleagues (17). The JEM has 22 exposure groups, including 18 high-risk groups, based on known risk factors (referred to here as “asthrogens”) for occupational asthma, grouped into high-MW agents, low-MW agents, and mixed environments (see Table E1). The “no-risk group” means that the study subjects are unlikely to be exposed to substances associated with a risk of asthma or to other irritating chemicals. The “low-risk group” consists of patients with low levels of exposure to irritant chemicals (no high peak exposures), exhaust fumes, and environmental tobacco smoke (17, 18). The tables display the results for a specific exposure if there were at least five patients and four control subjects for that exposure, and the numbers of exposed subjects in both case and control groups are shown in Table E1.

Atopic Classification

Blood samples were collected in heparin-containing venipuncture tubes for the Phadiatop test and determination of total plasma IgE (IMMULITE 2000 analyzer; Diagnostic Products Corporation, Los Angeles, CA). The Phadiatop test was analyzed by immunoassay system (Pharmacia ImmunoCAP; Pharmacia, Uppsala, Sweden). This test is an *in vitro* assay for specific IgE production in response to a mixture of commonly inhaled allergens (>20 items). Results are expressed as Pharmacia arbitrary units per liter (PAU/L), indicating the degree of sensitization. Phadiatop values equal to or greater than 0.35 PAU/L are considered indicative of sensitization, and this was the threshold for a positive or negative response in all our dichotomous analyses.

Total plasma IgE was measured in a solid-phase, chemiluminescence immunometric assay (IMMULITE 2000 analyzer; Diagnostic Products Corporation, Los Angeles, CA). We defined high responsiveness of total IgE in this study as greater than 100 U/ml (25). Atopy was defined as an increase in total IgE (≥100 U/ml) or a positive Phadiatop test result (≥0.35 PAU/L). Asthma with atopy was defined as having asthma in combination with an increase in total IgE (≥100 U/ml) or a positive Phadiatop test result (≥0.35 PAU/L).

Statistical Analysis

The χ^2 test was performed to evaluate percentage differences in risk factors between the case and control groups. Analysis of variance was used to assess the mean differences between the three groups. The adjusted odds ratio (AOR) and 95% confidence interval (CI) for each asthrogen and environmental factor was calculated by a multiple logistic regression. The multiple logistic regression included several factors that are associated with asthma, including alcohol use; smoking; body mass index (BMI); and exposure to pets, cockroaches, and indoor incense burning. Lung function was compared between the three groups after adjusting for smoking, age, and sex by using multiple linear regressions. The population-attributable fraction was calculated according to the following formula: frequency of any asthrogen in the case group $\times$ [(odds ratio – 1)/odds ratio], where the odds ratio for the effect of an occupational asthrogen on current asthma was estimated on the basis of the multiple logistic regression model. The statistical

analyses were performed with SPSS, release 14.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 504 asthma cases and 1,008 control subjects were recruited in the present study (*see* Figure E1). The epidemiological description of subjects is shown in Table 1. Of note, the distributions of cigarette smoking and alcohol use were significantly different between the two groups ($P = 0.001$ and $P = 0.03$, respectively). Positive histories of maternal or paternal asthma were more prevalent in the case group than in the control group ($P = 0.001$ for both). At the time of their interview, 289 (57.3%) patients and 342 (67.9%) control subjects were currently employed ($P < 0.01$) (Table 1).

Table 2 presents clinical characteristics and environmental risk factors for the subjects with atopic asthma, subjects with nonatopic asthma, and community control subjects. We found that subjects with atopic asthma had the lowest values of FEV₁ (% predicted), FVC (% predicted), and FEV₁/FVC ratio of the three groups ($P < 0.01$ for all). The mean BMI for patients with atopic and nonatopic asthma was significantly higher than in the control group ($P < 0.001$). The mean age of asthma onset for atopic asthma was lower for than nonatopic asthma ($P < 0.001$). The frequencies of exposure to pets, cockroaches, and indoor incense burning were different between the atopic asthma, nonatopic asthma, and community control groups ($P < 0.01$ for all). To evaluate the reliability of our assessment of exposure based on former work and job title, we randomly sampled 38 subjects (10% of the 378 subjects who had ever worked) to reevaluate their job history. Only one subject's response was different on reevaluation from the original answer. Test-retest reliability could, therefore, be considered as high as 97.3%.

TABLE 1. EPIDEMIOLOGICAL DESCRIPTION OF SUBJECTS WITH CURRENT ASTHMA AND COMMUNITY-BASED CONTROL SUBJECTS

Characteristic	Community Control (<i>n</i> = 504)	Current Asthma (<i>n</i> = 504)	<i>P</i> Value*
Age (mean ± SD)	50.1 ± 13.9	50.1 ± 13.1	
Sex			
Female	274 (54.4%)	274 (54.4%)	
Male	230 (45.6%)	230 (45.6%)	
Education			
≤6 yr	111 (22.4%)	137 (27.3%)	0.08
7–14 yr	293 (59.2%)	296 (58.8%)	
>14 yr	91 (18.4%)	70 (13.9%)	
Occupational history			
Ever worked	162 (32.1%)	215 (42.7%)	0.001
Currently working	342 (67.9%)	289 (57.3%)	
Ever changed job	331 (65.7%)	354 (70.2%)	0.14
Never changed job	173 (34.3%)	150 (29.8%)	
Smoking			
Nonsmoker	410 (81.5%)	374 (74.4%)	0.001
Ex-smoker	32 (6.4%)	77 (15.3%)	
Smoker	61 (12.1%)	52 (10.3%)	
Drinking habits			
Nondrinker	434 (87.9%)	413 (82.1%)	0.03
Ex-drinker	16 (3.2%)	29 (5.8%)	
Drinker	44 (8.9%)	61 (12.1%)	
Asthma history for father			
Yes	22 (4.4%)	51 (10.1%)	0.001
Asthma history for mother			
Yes	17 (3.4%)	53 (10.5%)	0.001

* *P* value not indicated if $P > 0.05$.

Table 3 shows the risks of occupational asthmogens for total current asthma and asthma with and without atopy. The three broad exposure groups (high-MW agents, low-MW agents, and mixed environments) in the current or most recent job were used to investigate associations with asthma. High-MW asthmogens, including latex, were associated with a significantly higher risk for asthma with atopy after controlling for potential confounding factors. Asthma without atopy was significantly associated with exposure to low-MW asthmogens, including industrial cleaning agents and metal sensitizers. Mixed environments, including agriculture, had a significant effect on the risks for both atopic and nonatopic asthma. On the basis of multiple logistic regression analysis, the risk of any asthmogen for current asthma was estimated as an odds ratio of 2.2. This yields a population-attributable fraction of 16.3% $[(1.2/2.2) \times (151/504)]$.

We further analyzed the risks of current occupational asthmogens for asthma with atopy in subjects who were currently employed (Table 4). This resulted in AORs that are slightly higher than those shown in Table 3. Analyses of high-MW asthmogens showed higher ORs for atopic asthma, and low-MW asthmogens showed consistently higher ORs for nonatopic asthma (Table 4). In our study population, there were only 37 (11.9%) subjects with atopic asthma and 10 (5.2%) subjects with nonatopic asthma who reported the onset of their asthma before 16 years of age (Table 2). In both groups, results were similar before and after excluding patients with asthma whose asthma had started before age 16 years (Tables E2 and E4).

We further classified occupational exposure into three groups (no risk, low risk, and high risk) (Table 5). To determine the differential effects of the three risk groups on lung function (values of FEV₁%, FVC%, and FEV₁/FVC) we adjusted for smoking, age, and sex. The FEV₁/FVC ratio differed significantly between the three groups, both when all patients with asthma were considered ($P = 0.04$) and when only currently employed subjects with asthma were considered ($P = 0.032$). In currently employed patients with asthma, FEV₁/FVC in the high-risk group (0.88 ± 0.15) was significantly lower than in the no-risk group (0.94 ± 0.13 , $P = 0.026$), as shown by Bonferroni multiple comparisons.

We also constituted a hospital control group for comparison. Analyses comparing patients with asthma with hospital control subjects showed consistent but higher associations than comparisons with community control subjects (data not shown). We combined the two control groups to increase statistical power. Significant associations were, again, observed between exposure to high-MW asthmogens and atopic asthma, and between exposure to low-MW asthmogens (including highly reactive chemicals, isocyanates, industrial cleaning agents, and metal sensitizers) and nonatopic asthma (Tables E2–E4).

DISCUSSION

In Taiwan, high-risk asthmogens are often used in the workplace. However, there are currently no reports on associations between comprehensive occupational exposure and asthma in Taiwan. In the present study, we found that subjects exposed to high-MW, low-MW, and mixed environmental agents were at a significantly higher risk of asthma than those who were not.

Occupational Asthmogens and Atopic and Nonatopic Asthma

We classified asthma into two groups, asthma with or without atopy, and found that high-MW and certain low-MW occupational asthmogens have a significant effect on atopic asthma. We also observed that the effect of low-MW agents on non-

TABLE 2. CLINICAL CHARACTERISTICS AND INDOOR ENVIRONMENTAL FACTORS FOR SUBJECTS WITH ATOPIC AND NONATOPIC ASTHMA AND COMMUNITY CONTROL SUBJECTS

Characteristic	Community Control	Atopic* Asthma	Nonatopic Asthma	P Value
Sample size	504	310	194	
Total IgE $\pm$ SD, U/ml ^{†‡}	121.9 $\pm$ 230.7	408.2 $\pm$ 746.9	30.1 $\pm$ 26.2	<0.001
BMI $\pm$ SD [§]	23.8 $\pm$ 3.4	25.5 $\pm$ 4.3	26.0 $\pm$ 3.9	<0.001
Lung function				
FEV ₁ , % pred [‡]	89.4 $\pm$ 15.4	79.7 $\pm$ 19.8	84.9 $\pm$ 19.4	<0.001
FVC, % pred [§]	94.4 $\pm$ 15.6	86.8 $\pm$ 17.5	90.7 $\pm$ 17.5	<0.001
FEV ₁ /FVC ratio [‡]	0.95 $\pm$ 0.11	0.92 $\pm$ 0.14	0.94 $\pm$ 0.13	0.001
Allergic rhinitis, %	85 (16.8%)	142 (45.8%)	57 (29.4%)	<0.001
Atopic dermatitis, %	NA	37 (11.9%)	10 (5.2%)	0.02
Symptoms of asthma				
Age of asthma onset $\pm$ SD	—	39.5 $\pm$ 17.7	46.9 $\pm$ 15.1	<0.001
Asthma onset $\leq$ 16 yr old, %	—	37 (11.9%)	10 (5.2%)	0.01
>1 attack per week, %	—	143 (46.1%)	96 (49.5%)	0.52
>1 nocturnal waking with wheezing per week, %	—	106 (34.2%)	76 (39.2%)	0.30
Medication				
Hospitalization or emergency, %	—	41 (13.2%)	25 (12.9%)	1.00
Use of inhaled corticosteroid, %	—	185 (59.7%)	129 (66.5%)	0.82
Use of oral corticosteroid, %	—	99 (31.9%)	71 (36.6%)	0.68
Indoor environmental factors				
Pets (dogs, cats, birds), %	97 (19.2%)	93 (30.0%)	58 (29.9%)	<0.01
Mold in walls, %	98 (19.4%)	61 (19.7%)	39 (20.1%)	0.95
Air cleaner, %	66 (13.1%)	55 (17.7%)	24 (12.4%)	0.18
Appearance of cockroaches, %	422 (83.7%)	240 (77.4%)	153 (78.9%)	<0.01
Indoor incense burning, %	225 (44.6%)	198 (63.9%)	118 (60.8%)	<0.01

Definition of abbreviations: BMI = body mass index; NA = not available.

Analysis of variance and Bonferroni multiple comparisons on total IgE, BMI, and lung functions were performed.

* Asthma with atopy, which was defined as having asthma in combination with an increase in total IgE ($\geq$ 100 U/ml) or positive Phadiatop test result ($\geq$ 0.35 PAU/L).

[†] IgE levels were logarithmically transformed before statistical testing to meet the assumption of normal distribution.

[‡] $P < 0.05$ when subjects with atopic asthma were compared with control subjects.

[§] $P < 0.05$ when subjects with nonatopic asthma were compared with control subjects.

^{||} $P < 0.05$ when subjects with atopic asthma were compared with subjects with nonatopic asthma.

atopic asthma was higher than on atopic asthma. Our results support the hypotheses of Bardana, who proposed that atopic individuals are more likely to become sensitized and to have allergic OA when exposed to high-MW allergens (10). On the other hand, the relationship between atopic OA and exposure

to low-MW agents remains inconsistent (4). Atopic OA is affected only by some specific low-MW agents, such as salts of platinum (10). In contrast, atopic individuals do not have a higher susceptibility to asthma induced by low-MW agents, such as western red cedar (26) or diisocyanates (27). Non-

TABLE 3. SPECIFIC EXPOSURE GROUP FREQUENCY AND RISK ESTIMATES FOR ALL SUBJECTS WITH CURRENT ASTHMA (N = 504) AND COMMUNITY CONTROL SUBJECTS (N = 504)

Specific Occupational Exposure	Community Control: N = 504	Total Current Asthma: N = 504	Asthma with Atopy*			
			Yes: N = 310		No: N = 194	
	n	n	n	AOR	n	AOR
No or low-risk exposure	429	353	218	1	135	1
Any asthmogen [†]	75	151	92	2.2 (1.5–3.1)	59	2.3 (1.4–3.5)
High-MW asthmogen, any	11	28	24	2.7 (1.2–6.0)	4	1.0 (0.3–3.5)
Latex	5	10	9	2.8 (0.9–8.8)	1	0.9 (0.1–7.9)
Low-MW asthmogen, any	53	89	44	1.9 (1.3–2.9)	45	2.6 (1.6–4.3)
Highly reactive chemicals	28	38	18	1.4 (0.8–2.5)	20	1.8 (0.9–3.6)
Drugs	5	5	3	1.9 (0.4–8.6)	2	2.4 (0.3–19.9)
Industrial cleaning agents	7	21	9	2.6 (1.1–6.5)	12	3.5 (1.2–9.7)
Wood dusts	4	8	3	2.4 (0.6–10.3)	5	4.4 (0.9–21.5)
Metal sensitizers, fumes	11	24	11	2.3 (1.0–5.2)	13	4.1 (1.6–10.2)
Mixed environments, combined	25	70	44	3.0 (1.7–5.1)	26	3.2 (1.6–6.2)
Metal-working fluid	5	5	4	1.0 (0.2–4.3)	1	1.0 (0.1–10.2)
Agriculture	7	40	29	6.3 (2.4–16.9)	11	4.1 (1.3–13.0)
Textile production	4	9	5	2.1 (0.6–7.8)	4	2.1 (0.4–11.1)
Irritant peaks	9	16	6	2.2 (0.9–5.6)	10	4.2 (1.5–11.8)

Definition of abbreviations: AOR = adjusted odds ratio; MW = molecular weight.

AORs were calculated after adjusting for age, sex, body mass index, smoking, alcohol use, history of parental asthma, and exposure to pets, cockroaches, and indoor incense burning.

Analyses were performed for specific asthmogens when at least five patients and four control subjects were exposed.

* Asthma with atopy was defined as having asthma in combination with an increase in total IgE ($\geq$ 100 U/ml) or a positive Phadiatop test result ($\geq$ 0.35 PAU/L).

[†] These categories are not mutually exclusive. The total number for "high MW + low MW + mixed" is higher than that for "any asthmogen."

TABLE 4. SPECIFIC EXPOSURE GROUP FREQUENCY AND RISK ESTIMATE FOR SUBJECTS WITH ASTHMA (N = 289) AND CONTROL SUBJECTS (N = 342) WHO ARE CURRENTLY EMPLOYED

Specific Occupational Exposure	Community Control: N = 342	Subjects with Asthma Who Are Currently Employed: N = 289		Asthma with Atopy*			
	n	n	AOR	Yes: N = 186		No: N = 103	
				n	AOR	n	AOR
No or low-risk exposure	300	202	1	136	1	66	1
Any asthmogen [†]	42	87	3.1 (1.9–5.0)	50	2.5 (1.4–4.3)	37	4.7 (2.6–8.6)
High-MW asthmogen, any	6	20	4.4 (1.5–12.4)	17	5.3 (1.8–15.7)	3	2.5 (0.5–11.7)
Latex	2	8	5.0 (1.0–26.0)	7	6.5 (1.2–35.5)	1	3.1 (0.2–39.2)
Low-MW asthmogen, any	29	55	2.8 (1.6–4.9)	24	1.7 (0.9–3.4)	31	5.6 (2.9–11.0)
Highly reactive chemicals	12	17	1.7 (0.7–3.7)	5	0.8 (0.3–2.4)	12	4.3 (1.7–11.2)
Industrial cleaning agents	4	13	4.2 (1.3–14.0)	7	3.8 (0.9–15.0)	6	6.1 (1.5–24.8)
Metal sensitizers, fumes	8	20	3.9 (1.5–10.1)	10	2.1 (0.7–6.4)	10	7.6 (2.5–23.2)
Mixed environments, combined	17	42	4.1 (2.0–8.2)	27	3.1 (1.4–6.7)	15	5.9 (2.5–14.2)
Metal-working fluid	4	5	1.6 (0.3–8.1)	4	1.5 (0.3–8.6)	1	1.6 (0.2–19.7)
Agriculture	4	22	11.5 (2.5–52.4)	17	11.0 (2.3–52.5)	5	13.2 (2.2–77.7)
Irritant peaks	7	12	3.0 (1.1–8.7)	5	1.3 (0.3–4.8)	7	6.8 (2.0–23.4)

Definition of abbreviations: AOR = adjusted odds ratio; MW = molecular weight.

AORs were calculated after adjusting for age, sex, body mass index, smoking, alcohol use, history of parental asthma, and exposure to pets, cockroaches, and indoor incense burning.

Analyses were performed for specific asthmogens when at least five patients and four control subjects were exposed.

* Asthma with atopy was defined as having asthma in combination with an increase in total IgE (≥ 100 U/ml) or a positive Phadiatop test result (≥ 0.35 PAU/L).

[†] These categories are not mutually exclusive. The total number for “high MW + low MW + mixed” is higher than that for “any asthmogen.”

atopic OA can also be induced by exposure to high-level irritants (8).

Specific Asthmogen Exposure and Asthma

We found that exposure to specific asthmogens, such as latex, is associated with atopic asthma. Highly reactive chemicals are associated with nonatopic asthma, whereas agriculture, industrial cleaning agents, and metal sensitizers (Tables E2 and E3) are associated with both types of asthma. In many countries, powdered natural rubber latex (NRL) gloves have been largely replaced by NRL-free gloves, and their use has declined from 80.9% in 1989 to 17.9% in 2004 (28). Thus, the incidence of NRL-induced OA has significantly decreased since the late 1990s in western countries (28). In Taiwan, however, disposable NRL gloves are still predominantly used. Few hospitals have latex allergy interventions or a named consultant responsible for latex allergy provisions (29). Our findings indicate a high risk (3.8- to 6.5-fold) of exposure to

latex on atopic asthma compared with community control subjects.

Several prospective studies have provided evidence of an increased risk for asthma in those exposed to domestic cleaning agents either professionally (5) or privately (30). Specific cleaning products, including chlorine bleach and frequent use of cleaning sprays, are associated with asthma symptoms (30, 31). Cleaning agents have both irritant and sensitizing properties. However, it remains unclear which mechanisms play a predominant role (32). Various metals, including Pt salts, Zn, Ni, Cr, and Co, have been recognized as possible causes of occupational asthma (33). Studies also suggest that exposure in the aluminum industry is associated with asthma symptoms (34) and exhaled nitric oxide (35). Farmers and other agricultural workers may develop occupational asthma as a result of exposure to grains, animals, dust, or pesticides (36, 37). High pesticide exposure may contribute to both atopic and nonatopic asthma in male farmers (37), but it was associated only with

TABLE 5. ASSOCIATIONS BETWEEN RISK OF EXPOSURE AND LUNG FUNCTION IN PATIENTS WITH CURRENT ASTHMA (N = 504) AND SUBJECTS WITH ASTHMA WHO ARE CURRENTLY EMPLOYED (N = 289)

	Patients with Current Asthma				Bonferroni Multiple Comparison, P Values		
	Group A (High Risk): n = 151	Group B (Low Risk): n = 139	Group C (No risk): n = 214	Adjusted P Value*	A/C	A/B	B/C
Current and Ever Employed							
Lung function							
FEV ₁ , % pred	80.6 ± 20.5	82.6 ± 21.0	81.9 ± 18.2	0.71	NS	NS	NS
FVC, % pred	88.9 ± 18.6	87.9 ± 17.5	87.8 ± 17.4	0.82	NS	NS	NS
FEV ₁ /FVC ratio	0.90 ± 0.13	0.94 ± 0.15	0.94 ± 0.14	0.04	0.07	NS	NS
Currently Employed							
Lung function							
FEV ₁ , % pred	76.7 ± 20.8	80.9 ± 20.9	82.1 ± 16.4	0.13	NS	NS	NS
FVC, % pred	86.1 ± 18.9	88.1 ± 17.1	87.7 ± 15.7	0.73	NS	NS	NS
FEV ₁ /FVC ratio	0.88 ± 0.15	0.92 ± 0.16	0.94 ± 0.13	0.032	0.026	NS	NS

Definition of abbreviation: NS = not significant.

* Lung function among the three groups was adjusted for age, sex, and smoking habit.

atopic asthma in female farmers (38). In our study, we found that agricultural workers are at an increased risk for atopic (AOR, 7.8) and nonatopic asthma (AOR, 4.1) compared with community control subjects.

Strengths and Limitations

Our study has several strengths. First, we used a case-control study to minimize healthy worker effects and to assess the effects of occupational exposure across the entire spectrum of jobs. Cross-sectional workplace surveys may be better at assessing the current frequency, duration, and intensity of exposure to suspected agents in the workplace. However, such studies can be done only in selected factories or workplaces. Moreover, workers who develop symptoms often leave their jobs or transfer to positions where less exposure is required. This healthy worker bias leads to underestimates of relative risks (39). By contrast, case-control studies are likely to recruit all patients ever exposed in at-risk workplaces, rather than those currently exposed. Therefore, case-control studies are less biased by the healthy worker survivor effect. Second, we used a JEM based on the current knowledge of risk factors for asthma and this JEM has been shown to give reliable estimates of asthmagen exposure (17, 18). The questions regarding current job and industry title used in JEM are less subject to recall bias. Sun and colleagues compared surrogate indicators of exposure, which were defined by "only," "ever," "longest," "last," and "current" employment history, in a hypothetical cohort with those in an actual cohort. Except for workers in the "only" employed group, all other definitions overestimated the risk in the low-risk jobs and diminished dose-response effects (40). Third, our multiple logistic regression analysis allowed us to control for potential confounding factors. As expected, several factors, including alcohol use, smoking, BMI, and exposure to pets, cockroaches, and indoor incense burning, were associated with asthma in the present study. These potential confounding factors were included and adjusted for in the multiple logistic models.

The limitations of this study should also be discussed. The first limitation is its small sample size for comparisons of some job categories, thus leading to wide confidence intervals for OR. Second, the mean age of the study group was rather high (average, 50 yr old). Chronic obstructive pulmonary disease (COPD) and asthma are major chronic obstructive airway diseases that involve airway inflammation. Unlike in asthma, airflow limitation in COPD is not fully reversible and is often progressive. COPD is usually associated with an abnormal inflammatory response of the airway to noxious particles or gases. In general, COPD is defined by fixed airway obstruction as measured by postbronchodilator $FEV_1/FVC < 0.70$ (41). We have done our utmost to exclude those with overlapping diagnoses. However, even though asthma can usually be distinguished from COPD, in some individuals it is difficult to differentiate the two diseases. Despite the availability of consensus guideline diagnostic recommendations, confusion between COPD and asthma appears to be common in patients 40 years of age and over (42). Our pulmonary function testing followed the guidelines of the American Thoracic Society (ATS). The ratios of FEV_1 to FVC may be higher but were all consistent between the three risk groups of patients (Table 5). Third, it is difficult to obtain direct information about past work exposure from workplaces after subjects have quit or retired from their jobs. If the subjects had worked in more than one place, we evaluated the occupational exposure for the current or most recent job to reduce recall problems. However, when we restricted our analyses to currently employed subjects with asthma (Table 4 and Table E5), the AORs were consistent with, but higher than, those found for all subjects with

current asthma (Table 3 and Table E4). On the basis of these findings, recall problems did not appear to confound the results significantly. Fourth, in our present study, the 1,560 hospital-based control subjects (994 males and 566 females) were recruited irrespective of job title and exposure. Many female control subjects (50.8%, 288 of 566) were excluded because they had never worked or they had missing answers for questions concerning job title and work exposure. So, we were unable to fully match hospital control subjects to asthma for age and sex by 1:1 because insufficient suitable hospital control subjects were available to match some female subjects with asthma. However, the confounding effects of age and sex were adjusted for by running multiple logistic regressions (Tables E2–E4).

Total serum IgE, Phadiatop, and skin prick tests (SPTs) are usually used to diagnose atopic diseases, but in the present study we did not perform SPTs. A randomized study of 8,329 adults compared the diagnostic value of these three atopic markers in adults with current allergic asthma and rhinitis. The sensitivity of the Phadiatop test was significantly higher than that of the SPT and IgE. Nevertheless, the SPT has the best positive predictive value and is the most efficient test (43). The validity of the Phadiatop test was compared with the SPT in schoolchildren and an adult population. The Phadiatop test was 85% accurate, qualifying it as a valid alternative to the SPT for diagnosing atopy (44, 45).

Surveillance Programs for Disease Prevention

To improve the health status of adults with asthma, a public health approach is required. Smith and Bernstein proposed a three-stage surveillance program in a disease prevention initiative (3). Primary prevention consists of assessing workplace risks and instituting appropriate exposure control measures, whereas secondary prevention involves early identification of workers with occupational sensitization. Tertiary prevention involves removing a worker with established OA from exposure to a recognized occupational sensitizer and preventing this employee from developing more severe asthma (3). The detergent-manufacturing industry developed an exemplary medical surveillance program and used medical questionnaires combined with skin testing to identify at-risk employees. This program successfully maintained the incidence of newly sensitized workers below 3% and prevented new cases of OA (46).

In conclusion, we found that high-MW asthmagens and low-MW asthmagens may pose different risks for inducing atopic and nonatopic asthma. Our results suggest that the population-attributable fraction due to occupational asthmagens for current asthma is 16.3%. Protective standards will have to be established that involve improving the social, occupational, and environmental conditions of workers to minimize OA.

Author Disclosure: T.-N.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.-C.L. received \$10,001 to \$50,000 from Hospital-Chang Gung Memorial Hospital, Taiwan from 2008 to 2009 as a research grant. C.-C.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. S.-Y.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.-S.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. H.-Y.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.-H.L. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. D.-C.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.-S.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.M.-S.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. P.-Y.C. does not have a financial relationship with a commercial entity that has an

interest in the subject of this manuscript. Y.-C.K. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Acknowledgment: The authors extend gratitude to Professor S. M. Kennedy at the University of British Columbia, Vancouver, Canada, who agreed to let us use the asthma-specific JEM in the present study. The authors are also grateful for the contribution from the Statistical Analysis Laboratory, Department of Medical Research, Kaohsiung Medical University Hospital.

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Online data supplement

Risks of exposure to occupational asthmogens in atopic and nonatopic asthma. A case-control study in Taiwan

Tsu-Nai Wang, PhD [#], Meng-Chih Lin, MD [#], Chao-Chien Wu, MD, Sum-Yee Leung, MD, PhD, Ming-Shyan Huang, MD, PhD, Hung-Yi Chuang, MD, PhD, Chien-Hung Lee, PhD, Deng-Chyang Wu, MD, PhD, Pei-Shan Ho, PhD, Albert Min-Shan Ko, MD, Po-Ya Chang, MD, PhD, Ying-Chin Ko, MD, PhD

[#] Tsu-Nai Wang and Meng-Chih Lin contributed equally as the first authors.

METHODS - Supplement

Hospital-based controls:

The 1,038 hospital-based controls (640 males and 398 females) were recruited and interviewed when they attended hospitals for routine physical checkups at the Department of Preventive Medicine, as previously described (E01). We extended this procedure to recruit 522 hospital-based controls (354 males and 168 females) at the Department of Preventive Medicine and the Department of Ophthalmology of Kaohsiung Medical University until October 2009. The hospital-based controls (n=415, 127 males and 288 females) were excluded from this study if they had physician-diagnosed respiratory diseases, cancer (n=35), missing answers for questions concerning job title and work exposure (n=147) or had never worked (n=233). The 504 hospital-based control subjects (252 males and 252 females, 18-70 years of age) were chosen out of 1,145 eligible subjects (867 males and 278 females) according to the following criteria: a 1:1 male to female ratio had to be achieved and subjects were selected from the most recent recruitment. The two groups of community- and hospital-based controls were combined to increase statistical power.

Associated Variables

The questionnaire included demographics (age, sex and education), lifestyle (cigarette smoking and alcohol use), medical history (history of asthma, allergic rhinitis and atopic dermatitis diagnosed by a doctor), emergency visits, hospital admissions and environmental exposures (pet fur, mold, cockroaches, the use of air conditioning and indoor incense burning). Wheezing was assessed by the following self-reported questions at the time of the physician visit: "Have you ever had wheezing or whistling (shortness of breath) in the chest at any time in the past? If so, have you had a recurrence within the last 12 months?" and "Have you ever awoken due to nocturnal shortness of breath?". Allergic rhinitis was assessed by asking "Have you ever had rhinitis? If so,

have you had a recurrence within the last 12 months?”. Atopic dermatitis was assessed by asking “Have you ever had atopic dermatitis? If so, have you had a recurrence within the last 12 months?” and “Was this diagnosed by a doctor, and what was your age at first diagnosis?”.

Body weight was measured to the nearest 0.1 kilogram and height, waist size and hip circumference were measured to the nearest 0.5 cm. Body mass index (BMI) (kg/m^2) was calculated as weight in kg divided by height in m^2 . Pulmonary function tests mainly included forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC). All pulmonary tests were performed according to the American Thoracic Society standard methodology (E02). The study subjects performed pulmonary function tests three times, and the highest score was recorded. The percent predictive values of FEV_1 , FVC and the ratio of FEV_1 to FVC were used for further analyses.

RESULTS

A total of 504 asthmatic subjects and 1,008 controls were recruited in the present study (Figure E1). The baseline data and numbers of specific exposures of subjects with current asthma and two control groups are presented in Table E1. The mean age and sex distributions of the asthmatic adults, community-based and hospital-based controls were not different. The mean BMI in asthmatic patients was significantly higher than the community- and hospital-based control groups ($p < 0.01$ for both). The frequency of cigarette smoking and alcohol use was significantly different between the three groups ($p < 0.05$). Therefore, we controlled for BMI, cigarette smoking and alcohol use in the multivariate analysis.

Combining the community and hospital controls yielded consistent results. Analyses performed in asthmatics compared with all controls showed significant associations between exposure to high-MW asthmogens and atopic asthma, as well as exposure to low-MW asthmogens, including highly reactive chemicals, isocyanates, industrial cleaning agents, wood dust and metal sensitizers and nonatopic asthma (Table E2). We did an analysis comparing asthmatic subjects with adult

onset (age of onset > 16 years old) with all controls. We found significant associations between atopic asthma and exposure to high-MW asthmogens. We also found significant associations between nonatopic asthma and exposure to low-MW asthmogens, including highly reactive chemicals, isocyanates, industrial cleaning agents and metal sensitizers (Table E4). In this study, we also performed an analysis for “asthma with a high total serum IgE”, which was defined as having asthma in combination with an increase in total IgE (≥ 100 U/ml). The outcomes for “asthma with a high total serum IgE” were similar to “asthma with atopy” (data not shown).

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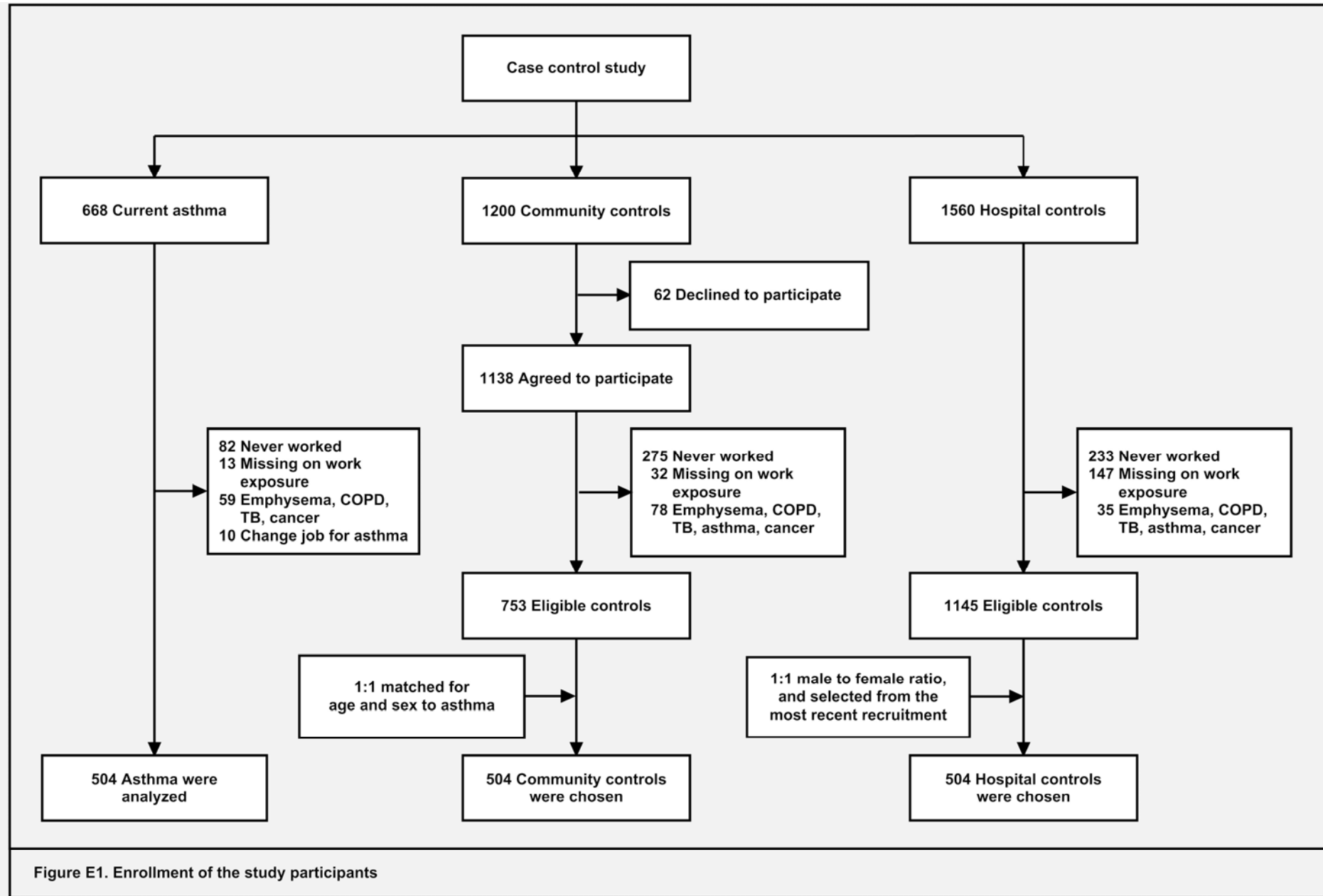


Table E1. Numbers of specific exposures of subjects with current asthma and two control groups

	Current asthma	Asthma with adult onset ^a	Community control	Hospital control	P- Value
Sample	N=504	N=457	N=504	N=504	
Sex					
Female	274 (54.4%)	253 (55.4%)	274 (54.4%)	252 (50.0%)	
Male	230 (45.6%)	204 (44.6%)	230 (45.6%)	252 (50.0%)	
Age (mean±SD)	50.1±13.1	51.2±12.3	50.1±13.9	50.4±10.1	
BMI (mean±SD) ^{b, c, d}	25.7±4.2	25.8±4.1	23.8±3.4	24.4±3.6	<0.001
Occupational history					
Ever worked	215 (42.7%)	202 (44.2%)	162 (32.1%)	131 (26.0%)	<0.001 ^e
Currently working	289 (57.3%)	255 (55.8%)	342 (67.9%)	373 (74.0%)	
Smoking					
Nonsmoker	374 (74.4%)	340 (74.4%)	410 (81.5%)	392 (78.7%)	0.02 ^e
Ex or current smoker	129 (25.6%)	117 (25.6%)	93 (18.5%)	106 (21.3%)	
Drinking habits					
Nondrinker	413 (82.1%)	379 (82.9%)	434 (87.9%)	417 (83.7%)	0.04 ^e
Ex or current drinker	90 (17.9%)	78 (17.1%)	60 (12.1%)	81 (16.3%)	
Specific occupational exposure					
No or low risk exposure	353	315	429	435	
Any asthmogen	151	142	75	69	
High-MW asthmogen, any	28	24	11	8	
Animal danders	7	6	2	1	
Fish or shellfish	1	1	0	0	
Anthropods, mites	6	4	1	0	
Latex	10	9	5	7	
Flour	4	3	0	0	
Other plant antigens	1	1	0	1	
Bioaerosols	6	6	3	0	
Enzymes	2	2	0	0	
Low-MW asthmogen, any	89	84	53	27	
High reactive chemicals	38	36	28	14	
Isocyanates	8	8	1	4	
Drugs	5	4	5	2	
Industrial cleaning agents	21	20	7	3	
Wood dusts	8	7	4	2	
Metal sensitizers	24	24	11	5	
Mixed environments, combined	70	69	25	38	
Metal working fluid	5	5	5	0	
Agriculture	40	39	7	24	
Textile production	9	9	4	5	
Irritant peaks	16	16	9	9	

a. Age of asthma onset > 16 years old.

- b. One-way ANOVA was used to compare the mean values of the three groups (current asthma, community-based control and hospital-based control) and Bonferroni test was used to correct multiple comparisons.
- c. $p < 0.05$ when current asthma was compared to community-based controls.
- d. $p < 0.05$ when current asthma was compared to hospital-based controls.
- e. Chi-square test was used to compare frequencies between the three groups.

Table E2. Frequency of specific exposures by group and risk estimate in total current asthma (n=504) and total controls (n=1008)

Specific occupational exposure	Total controls	Total current asthma				Asthma with atopy ^b	
	N=1008	N=504		Yes N=310		No N=194	
	n	n	AOR	n	AOR	n	AOR
No or low risk exposure	864	353	1	218	1	135	1
Any asthmogen^a	144	151	2.6 (1.9-3.4)	92	2.7 (1.9-3.8)	59	2.5 (1.7-3.7)
High-MW asthmogen, any	19	28	3.3 (1.7-6.4)	24	4.6 (2.3-9.4)	4	1.4 (0.4-4.6)
Latex	12	10	1.9 (0.7-4.9)	9	2.6 (0.9-7.1)	1	0.7 (0.1-5.8)
Low-MW asthmogen, any	80	89	2.6 (1.8-3.7)	44	2.1 (1.4-3.3)	45	3.3 (2.1-5.3)
High reactive chemicals	42	38	2.0 (1.2-3.2)	18	1.6 (0.8-3.0)	20	2.5 (1.3-4.7)
Isocyanates	5	8	5.4 (1.6-19.0)	5	4.9 (1.2-19.6)	3	9.1 (1.8-47.4)
Drug	7	5	1.5 (0.4-5.4)	3	1.5 (0.4-6.5)	2	1.5 (0.9-9.2)
Industrial cleaning agents	10	21	3.5 (1.5-7.9)	9	3.0 (1.1-8.1)	12	3.8 (1.4-10.0)
Wood dusts	6	8	2.7 (0.8-9.1)	3	1.7 (0.3-8.8)	5	5.4 (1.3-22.0)
Metal sensitizers, fumes	16	24	4.0 (2.0-8.0)	11	3.0 (1.3-7.1)	13	5.8 (2.6-13.3)
Mixed environments, combined	63	70	3.2 (2.1-4.8)	44	3.5 (2.2-5.7)	26	2.7 (1.5-4.7)
Metal working fluid	5	5	3.1 (0.8-12.7)	4	3.4 (0.7-15.4)	1	2.6 (0.3-24.7)
Agriculture	31	40	3.7 (2.0-6.5)	29	5.2 (2.7-9.7)	11	1.9 (0.8-4.4)
Textile production	9	9	2.5 (0.8-8.0)	5	3.1 (0.8-11.5)	4	2.3 (0.5-10.2)
Irritant peaks	18	16	2.7 (1.3-5.5)	6	1.6 (0.6-4.2)	10	4.3 (1.8-10.2)

Adjusted odds ratios (AORs) were calculated after adjusting for age, sex, BMI, smoking and alcohol use.

Analyses were performed for specific asthmogens when at least five patients and four controls were exposed.

a. These categories are not mutually exclusive. The total number of “High MW+Low MW+mixed” is higher than “any asthmogen.”

b. Asthma with atopy was defined as having asthma in combination with an increase in total IgE (≥ 100 U/ml) or a positive Phadiatop test (≥ 0.35 PAU/l).

Table E3. Frequency of specific exposures by group and risk estimate in asthmatic (n=289) and total control subjects who are currently employed (n=715)

Specific occupational exposure	Controls who are currently employed	Asthma who are currently employed		Asthma with atopy ^b			
	N=715	N=289		Yes N=186		No N=103	
	n	n	AOR	n	AOR	n	AOR
No or low risk exposure	630	202	1	136	1	66	1
Any asthmogen^a	85	87	3.6 (2.5-5.4)	50	3.1 (2.0-4.9)	37	4.9 (2.9-8.2)
High-MW asthmogen, any	10	20	5.5 (2.3-13.1)	17	7.1 (2.8-17.7)	3	3.2 (0.8-12.7)
Latex	5	8	2.8 (0.8-10.0)	7	3.7 (0.9-13.9)	1	2.0 (0.2-19.2)
Low-MW asthmogen, any	50	55	3.7 (2.3-5.8)	24	2.3 (1.3-4.1)	31	6.4 (3.7-11.3)
High reactive chemicals	22	17	2.1 (1.1-4.4)	5	0.8 (0.3-2.3)	12	5.3 (2.3-12.0)
Industrial cleaning agents	6	13	6.3 (2.2-18.0)	7	5.6 (1.7-19.1)	6	7.5 (2.1-27.0)
Wood dusts	4	6	4.4 (1.0-18.9)	1	0.8 (0.1-16.5)	5	11.6 (2.5-53.1)
Metal sensitizers, fumes	13	20	6.8 (3.0-15.3)	10	5.1 (1.9-13.6)	10	9.9 (3.7-26.2)
Mixed environments, combined	39	42	5.1 (2.9-8.7)	27	5.0 (2.7-9.3)	15	5.6 (2.7-11.5)
Metal working fluid	4	5	5.3 (1.1-25.5)	4	5.5 (1.0-30.2)	1	4.6 (0.4-46.8)
Agriculture	17	22	7.4 (3.4-16.1)	17	9.4 (4.0-22.4)	5	5.1 (1.6-16.0)
Irritant peaks	16	12	3.2 (1.4-7.4)	5	1.8 (0.6-5.5)	7	5.9 (2.1-16.3)

Adjusted odds ratios (AORs) were calculated after adjusting for age, sex, BMI, smoking and alcohol use.

Analyses were performed for specific asthmogens when at least five patients and four controls were exposed.

a. These categories are not mutually exclusive. The total number of “High MW+Low MW+mixed” is higher than “any asthmogen.”

b. Asthma with atopy was defined as having asthma in combination with an increase in total IgE (≥ 100 U/ml) or a positive Phadiatop test (≥ 0.35 PAU/l).

Table E4. Frequency of specific exposure by group and risk estimate in asthma with adult onset* (n=457) and total controls (n=1008).

Specific occupational exposure	Total controls	Asthma with adult onset (age of asthma onset > 16)		Asthma with atopy ^b			
	N=1008	N=457		Yes N=273	No N=184		
	n	n	AOR	n	AOR	n	AOR
No or low risk exposure	864	315	1	188	1	127	1
Any asthmogen^a	144	142	2.6 (1.9-3.5)	85	2.8 (2.0-3.9)	57	2.5 (1.7-3.7)
High-MW asthmogen, any	19	24	3.2 (1.6-6.3)	20	4.4 (2.1-9.1)	4	1.5 (0.5-4.8)
Latex	12	9	1.9 (0.7-5.2)	8	2.7 (0.9-7.6)	1	0.7 (0.1-6.1)
Low-MW asthmogen, any	80	84	2.6 (1.8-3.8)	41	2.2 (1.4-3.4)	43	3.3 (2.1-5.2)
High reactive chemicals	42	36	2.0 (1.2-3.4)	16	1.5 (0.8-3.0)	20	2.6 (1.4-5.0)
Isocyanates	5	8	6.5 (1.8-22.8)	5	6.1 (1.5-14.7)	3	9.7 (1.9-50.0)
Industrial cleaning agents	10	20	3.3 (1.4-7.6)	8	2.5 (0.9-7.0)	12	4.0 (1.5-10.5)
Wood dusts	6	7	2.3 (0.6-8.0)	3	1.8 (0.4-9.4)	4	3.5 (0.8-15.3)
Metal sensitizers, fumes	16	24	4.4 (2.2-8.9)	11	3.4 (1.4-8.2)	13	6.0 (2.6-13.7)
Mixed environments, combined	63	69	3.3 (2.2-5.1)	43	3.7 (2.3-6.1)	26	2.8 (1.6-5.0)
Metal working fluid	5	5	3.7 (0.9-15.2)	4	4.2 (0.9-19.0)	1	2.8 (0.3-26.6)
Agriculture	31	39	3.7 (2.0-6.6)	28	5.1 (2.7-9.6)	11	2.0 (0.9-4.6)
Textile production	9	9	2.6 (0.8-8.5)	5	3.2 (0.9-11.7)	4	2.4 (0.5-10.9)
Irritant peaks	18	16	3.0 (1.4-6.2)	6	1.9 (0.7-5.0)	10	4.5 (1.9-10.7)

*Age of asthma onset was greater than 16 years old.

Adjusted odds ratios (AORs) were calculated after adjusting for age, sex, BMI, smoking and alcohol use.

Analyses were performed for specific asthmogens when at least five patients and four controls were exposed.

a. These categories are not mutually exclusive. The total number of “High MW+Low MW+mixed” is higher than “any asthmogen.”

b. “Asthma with atopy” was defined as having asthma in combination with an increase in total IgE (≥ 100 U/ml) or a positive Phadiatop test (≥ 0.35 PAU/l).