

The occupational contribution to severe exacerbation of asthma

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Running Head: Occupation and exacerbation of asthma

Abstract

The goal was to identify occupational risk factors for severe exacerbation of asthma and estimate the extent that occupation contributes to these events.

The 966 participants were working adults with current asthma who participated in the follow-up phase of the European Community Respiratory Health Survey. Severe exacerbation of asthma was defined as self-reported unplanned care for asthma in the past 12 months. Occupations held in the same period were combined with a general-population job-exposure matrix to assess occupational exposures.

Seventy-four participants reported having had at least one severe exacerbation event, for a one-year cumulative incidence of 7.7%. From regression models that controlled for confounders, the relative risk (RR) was statistically significant for low (RR=1.7, 95% CI 1.1-2.6) and high (RR=3.6, 95% CI 2.2-5.8) biological dust exposure, high mineral dust exposure (RR=1.8, 95% CI 1.02-3.2), and high gas and fumes exposure (RR=2.5, 95% CI 1.2-5.5). The summary category of high dust, gas, or fumes exposure had RR=3.1 (95% CI 1.9-5.1). Based on this RR, the population attributable risk was 14.7% among workers with current asthma.

These results suggest occupation contributes to approximately 1 in 7 cases of severe exacerbation of asthma in a working population, and various agents play a role.

Keywords: asthma, exacerbation, occupational, work-related

Introduction

Asthma is common among adults in Europe, with a prevalence of approximately 7% [1]. Conditions at work are one of the causes of asthma exacerbations, as are environmental exposures in other settings (e.g., home, ambient environment), failures in medication regimens, and viral infections. Work-related asthma includes both occupational asthma (OA) caused by work and work-exacerbated asthma (WEA) in which existing asthma is made worse by work. A 2003 statement of the American Thoracic Society (ATS) concluded that 15% of new-onset asthma among adults was due to occupation, but that there could be much more sickness and loss of productivity due to work-related exacerbation of existing asthma [2]. Six recent epidemiologic studies conducted in five countries estimated the frequency of WEA, separate from cases of OA caused by work [3-8]. From these studies, the prevalence of WEA expressed as a percentage of working adults with asthma ranged from 14% to 24%, with a median of 19% [3, 5, 6, 8]. A variety of agents have been associated with WEA, such as irritant gases and fumes [9-11], accidental spills [11], and second-hand cigarette smoke [9, 11-13]. Other implicated exposures include common aeroallergens, emotional stress, physical exercise, and extremes in temperature [5, 8, 9, 11, 14, 15]. WEA has generally received less attention than OA, and a better understanding of the causes of WEA is needed to plan preventive interventions.

Data from the first European Community Respiratory Health Survey (ECRHS I) have already been used to investigate the frequency of prevalent work-related asthma [16]. This prior investigation did not consider asthma onset separately from exacerbation of existing asthma when determining the impact of occupation. More recently, investigators used data from the follow-up phase of the ECRHS (ECRHS II) to examine the association of asthma onset with occupational exposures [17]. ECRHS II data also provided a unique opportunity to study the relationship of exacerbation of asthma to occupational exposures.

The goals of the current study were to identify occupational risk factors for severe exacerbation of asthma and to estimate the extent that occupation contributes to these events. Past studies have started with asthma cases, evaluated these cases individually to determine WEA status, and then expressed the frequency of WEA as a percentage of asthma cases [3-8]. Unlike previous studies, the current investigation used a risk-set approach in which ECRHS II participants with severe exacerbation of asthma were identified, and this outcome was modeled with covariates for occupational exposure to derive estimates of relative and attributable risk.

Methods

Study participants. Individuals included in the current investigation had taken part in both the first and second rounds of ECRHS [18]. In ECHRSI, male and female adults aged 20 to 44 years were randomly selected from the local population to complete a short screening questionnaire (stage 1). A subset of stage 1 respondents were selected either at random ('random sample') or because they had reported respiratory symptoms ('symptomatic sample') to take part in stage 2 clinical evaluations. The random sample included some people with breathing problems, but the symptomatic sample comprised only participants who had reported recently waking with shortness of breath, having an asthma attack, or taking asthma medications. Those invited for ECRHSII were those who had completed stage 1 of the ECRHSI, had been selected for stage 2, and had provided at least their smoking status in ECRHSI.

Individuals potentially eligible for inclusion in this investigation were the 9,812 ECRHS II participants from both random and symptomatic samples in 26 study centers from 11 European nations and the United States who took part during 1998-2003. These participants represent 59% of the 16,692 ECRHS I participants from the same countries that

were eligible for ECRHS II. The participants for the current investigation were ECRHS II participants with current asthma who had worked in the 12 months before being surveyed.

The selection criteria were:

1. Fulfilled the definition of current asthma, similar to that used in a recent publication [19]
 - 1.1. Reported ever having asthma confirmed by a doctor [20]
 - 1.2. And one or more of the following:
 - 1.2.1. At least one attack of asthma in the past 12 months
 - 1.2.2. Currently taking medicines for asthma
 - 1.2.3. At least one of the following respiratory symptoms in the past 12 months
 - 1.2.3.1. Wheezing
 - 1.2.3.2. Nocturnal tightness in the chest
 - 1.2.3.3. Attack of shortness of breath when at rest during the day
 - 1.2.3.4. Attack of shortness of breath following strenuous activity
 - 1.2.3.5. Being awoken by an attack of shortness of breath
2. Onset of asthma more than 2 years before participating in the ECRHS II survey (i.e., current age minus age at onset > 2 years). This criterion was intended to clarify it was exacerbation of asthma, and not onset of asthma, that was being studied.
3. Worked during the past 12 months
4. Completed questionnaire items used to define exacerbation of asthma.

Starting with 9,812 ECRHS II adult participants, there were 966 who fulfilled the selection criteria for this investigation, as summarized in Figure 1.

Main outcome: severe exacerbation of asthma. Using responses to items on the ECRHS II questionnaire, a severe exacerbation of asthma was defined as a report of any one of the following four types of unplanned care for asthma in the past 12 months:

1. Treatment for breathing problems in a hospital casualty department or emergency room.

2. Hospitalization overnight because of breathing problems.
3. Treatment for breathing problems at home in an emergency by a general practitioner.
4. Use of oral steroids when needed to control symptoms.

These criteria are consistent with the definition of severe exacerbation of asthma as proposed by the European Agency for the Evaluation of Medicinal Products [21].

Self-reported work-related exacerbation of asthma symptoms. An item on the questionnaire allowed respondents to indicate which jobs ever made their chest tight or wheezy. We determined who reported this problem with jobs held in the past 12 months to create a variable for self-reported work-related exacerbation of asthma symptoms. Such reports have been used in studies of WEA [7, 8]. While this type of question is susceptible to reporting bias, the raw results are presented to allow comparison with findings from other studies.

Occupation and occupational exposures. Each ECRHS II participant completed a work history, and occupations from the past 12 months were coded using the ISCO-88 coding system [22]. If a subject had more than one job in the past 12 months, all were coded and associated with that individual. The job codes were then used in two ways to characterize exposure.

First, occupations were grouped into wider categories. A low-exposed reference group was defined *a priori* to include individuals who only worked in professional, clerical, and administrative jobs (white collar jobs). This is the same comparison group that was used in a recent study of new-onset asthma and occupation in the ECRHS II [17].

Second, work-related exposures were assessed for each participant by linking their occupational codes to a general-population job-exposure matrix (JEM). The JEM had been developed by two experienced industrial hygienists who assigned a semi-quantitative exposure level (i.e., no, low, and high) to job titles for each of three types of work-related

exposure: biological dusts, mineral dusts, and gas and fumes [23, 24]. Also, we assigned a summary exposure level to each survey participant for exposure to dust, gas or fumes (DGF) that was the highest level the individual had attained among the three types of exposure.

Measurement of outcome frequency. It was possible to determine whether a subject had fulfilled any one of the four criteria for a severe exacerbation of asthma in the past year. However, the survey instrument did not yield the frequency of each of the four different events that contributed to this variable, so we used one-year cumulative incidence (rather than incidence rate) to measure outcome frequency. The period of observation for both the occupations (with their associated exposures) and the outcome was the 12 months before the survey. To calculate the one-year cumulative incidence, the denominator was all participants at risk, the numerator was the number of participants from the denominator who had experienced at least one severe exacerbation event in the past year, and the resulting ratio was expressed as a percentage.

Statistical analyses. Regression models were used to estimate the association between severe exacerbation in the past year and occupational groups or exposures. A separate regression model was fit for each occupational category using subjects with only white collar jobs as the common comparison group and excluding from the model subjects who reported other occupations. Also, a separate regression model was fit to estimate the effect of each exposure assessed by the JEM. We constructed regression models using generalized estimating equations (GEE) with a binomial response, log link, and a cluster-level variable for country. Also, terms were included in each model for the potential confounders age (continuous), sex, and cigarette smoking status (with former and current compared to never). We calculated and reported relative risk (RR) for any occupation or exposure category that had two or more participants with severe exacerbation. We tested for effect modification by gender to determine whether positive findings were limited to either

males or females. Statistical analyses were accomplished using STATA SE 10.1 (Stata Corporation, College Station, Texas, United States) and SAS Statistical software version 9.2 (SAS Institute Inc, Cary, North Carolina, United States). Statistical significance was defined as $p \leq 0.05$ and borderline statistical significance was $0.05 < p \leq 0.10$.

We estimated the population attributable risk percentage (PAR%) for the occupational contribution to severe exacerbation of asthma with a standard equation that uses RR adjusted for potential confounders. The equation is $PAR\% = ((P_c(RR-1)) / RR) \times 100$, in which the abbreviation P_c represents the proportion of severe exacerbation cases that had any high exposure to DGF [25]. We chose the RR for any high exposure to DGF to calculate the PAR% because this variable represents a broad range of occupational exposures, both sensitizing and non-sensitizing agents, that can exacerbate asthma.

Results

Characteristics of 966 survey participants. The 966 working adults with asthma included somewhat more females (n=518, 54%) than males, the mean age was 42.0 (SD 7.1, range 28.6 to 56.0), and nearly half had never smoked cigarettes (n=445, 46%). A greater number were from the random sample (n=504, 52%) than the symptomatic sample, and the four countries with the largest numbers were Sweden (n=275, 28%), Spain (n=149, 15%), United Kingdom (n=119, 12%), and France (n=111, 11%). Self-reported work-related exacerbation of asthma symptoms was common: 22% (n=217) of the participants reported that jobs held in the past 12 months made their chest tight or wheezy.

Severe exacerbation of asthma. Among the 966 working adults with current asthma, 74 reported having at least one severe exacerbation event in the past 12 months, for a one-year cumulative incidence of 7.7%. The most common of the four severe exacerbation events was seeking care for breathing problems in an emergency room, which was reported by 52, or 70%, of the severe exacerbation cases. Many fewer participants reported using oral steroids when needed (n=15, 20% of 74), being hospitalized overnight due to a breathing problem (n=12, 16%), or being treated at home in an emergency for breathing problems (n=6, or 8%). Eleven participants who reported emergency room care also reported one of the other exacerbation events: 8 hospitalization, 2 care at home, and 1 steroids when needed.

Frequency of severe exacerbation by characteristics of participants. Severe exacerbation of asthma was more common in females than males and in the symptomatic sample than the random sample (Table 1). By cigarette smoking status, the percentage severe exacerbation for former smokers (4.1%) was significantly less than for current smokers (10.6%, p=0.008), and the value for never smokers (7.9%) was between the other two. By country, the outcome was most common in Italy (16.7%) and Spain (14.1%), and least common in Estonia (0%) and France (2.7%). Those with severe exacerbation were somewhat

younger on average than other participants, with mean ages of 40.6 years (SD=7.3) and 42.1 years (SD=7.1), respectively (p=0.085 by t-test).

Table 1. Frequency of severe exacerbation of asthma by characteristics of participants

Characteristics	Number with characteristic	Severe Exacerbation		p-value *
		n	%	
<u>Gender</u>				
Females	518	47	9.1%	0.076
Males	448	27	6.0%	
<u>Smoking status</u>				
Never	445	35	7.9%	0.010
Former	267	11	4.1%	
Current	245	26	10.6%	
Unknown	9	2	22.2%	
<u>Type of sample</u>				
Random	504	32	6.3%	0.109
Symptomatic	462	42	9.1%	
<u>Country</u>				
Belgium	31	2	6.5%	0.024
Estonia	10	0	0%	
France	111	3	2.7%	
Germany	32	2	6.3%	
Iceland	58	3	5.2%	
Italy	36	6	16.7%	
Norway	54	2	3.7%	
Spain	149	21	14.1%	
Sweden	275	24	8.7%	
Switzerland	60	2	3.3%	
United Kingdom	119	7	5.9%	
United States	31	2	6.5%	

* p-value from chi-square test or Fisher's exact test.

Severe asthma exacerbation by occupation. The one-year cumulative incidence and relative risk for severe asthma exacerbation by occupation were determined (Table 2). Many high-risk occupations were 'blue collar' jobs, but also 'food processing' and 'health care' jobs had elevated RRs. Those with statistically significant RRs were 'bakery' (RR=7.9, 95% CI 5.1-12.2), all 'blue collar' occupations (RR=1.4, 1.1-1.8), and the subgroups 'drivers' (RR=2.3, 95% CI 1.03-5.0) and 'other blue collar' (RR=2.7, 95% CI 1.4-5.1). The 20 'other

blue collar' participants included 8 (40%) 'sculptors, painters, and related art,' 3 (15%) 'protective services not elsewhere classified,' 2 (10%) 'garbage collectors,' 2 (10%) 'hand launderers and pressers,' and 5 others. The 4 severe exacerbation cases in the 'other blue collar' category included both of the 'hand launderers and pressers,' one 'sculptors, painters, and related artists,' and one 'protective services workers.' Occupations with elevated RRs that were borderline statistically significant ($0.05 < p \leq 0.10$) included all 'health care' occupations (RR=1.5, 95% CI 0.95-2.4) and the subgroup 'nurses' (RR=1.7, 95% CI 0.99-2.9), and all 'food processing' occupations (RR=2.2, 95% CI 0.97-5.0). None of the interactions of occupation with gender was statistically significant.

We did not calculate RR for any occupation with fewer than 2 severe exacerbation cases. Four occupational subgroups had one case each and were not included in Table 2: 'food and tobacco processing' (n=16) in the 'food processing' category, and the three 'blue collar' subgroups of 'wood workers' (n=8), 'textile, leather, and fur workers' (n=6), and 'printing workers' (n=7). Another 12 sub-categories of 'blue collar' workers had no severe exacerbation cases and usually few participants (i.e., <10 per sub-category) (data not shown).

Table 2. One-year cumulative incidence and relative risk of severe exacerbation of asthma by occupation

Occupation*	Number in occupation	Severe exacerbation		Relative Risk**	(95% CI)
		n	%		
<u>Reference</u> (white collar jobs - legislators, managers, administrators, clerks, and remainder professional)	645	40	6.2%	1.0	Reference
<u>Health care</u> [†]	99	12	12.1%	1.5	(0.95-2.4)
Nurses [†]	43	6	14.0%	1.7	(0.99-2.9)
Other medical & pharmacy (not nurses)	57	6	10.5%	1.3	(0.7-2.3)
<u>Agriculture and forestry</u>	16	1	6.3%		
<u>Food processing</u> [†]	22	4	18.2%	2.2	(0.97-5.0)
Bakery workers [§]	6	3	50.0%	7.9	(5.1-12.2)
<u>Blue collar</u> [§]	186	18	9.7%	1.4	(1.1-1.8)
Cleaners and caretakers	46	3	6.5%	0.8	(0.3-1.8)
Other metal workers	23	3	13.0%	1.6	(0.7-3.9)
Construction and mining ⁺	19	3	15.8%	2.4	(0.7-7.9)
Drivers [‡]	14	2	14.3%	2.3	(1.03-5.0)
Other blue collar ^{§ ++ #}	20	4	20.0%	2.7	(1.4-5.1)

* A separate regression model was fit for each occupation, with white collar jobs as the common comparison group, and participants from other occupations not included in model.

** Relative risk from regression models with cluster-level variable for country, and covariates for sex, age, and smoking status. Relative risk not calculated if fewer than 2 severe exacerbation cases in occupation category.

[†]0.05<p≤0.10

[‡]p≤0.05

[§]p≤0.01

⁺ Model would not converge until the continuous age variable was replaced with indicator variables based on age tertiles

⁺⁺ Model would not converge until the continuous age variable was replaced with indicator variables based on age tertiles, and former and current smoking categories were combined into a single ever-smoked category.

[#] ‘Other blue collar’ included 8 ‘sculptors, painters, and related art,’ 3 ‘protective services not elsewhere classified,’ 2 ‘garbage collectors,’ 2 ‘hand launderers and pressers,’ and 5 others

Severe asthma exacerbation by occupational exposure. The one-year cumulative incidence and relative risk of severe exacerbation by occupational exposure were calculated (Table 3). Study participants could have multiple occupational exposures and be counted in more than one of the exposure categories presented in Table 3. Based on the JEM, about 1 in 10 study participants (n=102, 10.6% of 966) had high exposure to DGF at work. The low exposure categories for DGF subgroups had modest increases in the cumulative incidence of severe exacerbation of asthma except for low biological dust, which had a somewhat higher incidence of 11.1% and RR=1.7 (95% CI 1.1-2.6). Cumulative incidence was clearly elevated for high exposure to any DGF (15.7%) and the subgroups biological dust (18.5%) and gas and fumes (16.4%), and elevated but less so for high exposure to mineral dust (11.1%). These categories with elevated incidence also had statistically significant relative risks, with RR=3.1 (95% CI 1.9-5.1) for any high DGF exposure, RR=3.6 (95% CI 2.2-5.8) for high biological dust, RR=2.5 (95% CI 1.2-5.5) for high gas and fumes, and RR=1.8 (95% CI 1.02-3.2) for high mineral dust. The tests for trend were statistically significant or borderline significant for all exposures except mineral dust, and there were no statistically significant interactions by gender.

Population attributable risk percentage. The estimate of PAR% was based on the findings for any high DGF exposure. The adjusted RR to two decimal places was 3.14 and the proportion of severe exacerbation cases with exposure (Pc) was 16/74=0.216. The PAR%

for severe exacerbation due to work among employed adults with current asthma was:

$$\text{PAR}\% = ((\text{Pc}(\text{RR}-1)) / \text{RR}) \times 100 = ((.216 \times 2.14) / 3.14) \times 100 = 14.7\%.$$

Table 3. One-year cumulative incidence and relative risk of severe exacerbation of asthma by occupational exposure

Occupational exposure by job-exposure matrix	Number exposed	Severe exacerbation		Relative Risk*	(95% CI)	p for trend
		n	%			
Dust, Gas, or Fumes (DGF)**						
None	568	34	6.0%	1.0	Reference	<0.001
Low	296	24	8.1%	1.3	(0.8-2.0)	
High [§]	102	16	15.7%	3.1	(1.9-5.1)	
Type of DGF						
Biological dust						
None	705	43	6.1%	1.0	Reference	<0.001
Low [†]	234	26	11.1%	1.7	(1.1-2.6)	
High [§]	27	5	18.5%	3.6	(2.2-5.8)	
Mineral dust						
None	781	58	7.4%	1.0	Reference	0.21
Low	131	10	7.6%	1.1	(0.5-2.1)	
High [†]	54	6	11.1%	1.8	(1.02-3.2)	
Gas and fumes						
None	605	41	6.8%	1.0	Reference	0.08
Low	300	23	7.7%	1.1	(0.8-1.6)	
High [†]	61	10	16.4%	2.5	(1.2-5.5)	

* Relative risk from regression models with cluster-level variable for country, and covariates for sex, age, and smoking status. Regression models fit separately to determine effect of each type of DGF exposure.

** Based on highest exposure to Biological dust, Mineral dust, and Gas and fumes

† 0.05 < p ≤ 0.10

‡ p ≤ 0.05

§ p ≤ 0.01

Discussion

The ECRHS is a population-based, multinational study that has been a valuable source of insight into respiratory diseases. We analyzed ECRHS II data for working adults with current asthma and determined that 14.7%, or approximately one in seven, of severe exacerbation of asthma cases were associated with occupation. From another perspective, 14.7% of severe exacerbation cases could possibly be prevented by eliminating high DGF exposures in the workplace. The finding that former smokers had significantly fewer exacerbation events than current smokers suggests that cessation of a non-sensitizing exposure can be beneficial. Candidate workplaces for interventions to prevent work-related severe exacerbation of asthma are suggested by the high-risk occupations identified in the current study: bakery workers, drivers, other blue collar workers (including hand launderers), and nurses (Table 2).

Both non-sensitizing and sensitizing occupational exposures were implicated. Non-sensitizing agents are often suspected as the cause of asthma exacerbations at work. Consistent with this suspicion, we identified an elevated relative risk for high exposure to mineral dusts and to gas and fumes, which are predominantly non-sensitizing agents. At the same time, relative risk was elevated for low and high exposure to biological dust, which represents mainly sensitizing agents. Finally, the summary variable for high exposure to any DGF, which incorporates both sensitizing and non-sensitizing exposures, was associated with severe exacerbation of asthma.

Twenty-two percent of the working adults with asthma reported that a job held in the past 12 months made their chest tight or wheezy. This finding is similar to results from a study of employed adults with asthma in Finland, in which 20% reported their symptoms were caused or worsened by work at least weekly in the past month [8]. A population-based study conducted in Canada [7] used the ECRHS protocol and reported higher figures than

observed in the current study. Specifically, 34% of asthma cases with adult onset reported wheezing at or after working in their current job, and 31% reported dyspnea under the same circumstances [7].

Impact of occupation on asthma. A prior investigation based on ECRHS II data determined that 10% to 25% of new-onset asthma could be attributed to occupational exposures, and the annual incidence of new-onset OA was approximately 250 to 300 cases per million [17]. The working population of 27 nations in Europe was approximately 176,000,000 in 2000 for the age range 25-64 years [26]. This means there would have been approximately 44,000 to 52,800 new OA cases per year. An estimated 4.5% of ECRHS participants, age 20 to 44 years, had current asthma [27]. Using this prevalence estimate, 7,920,000 of the 176 million workers would have had current asthma in 2000. Before estimating the number of asthma cases with work-related severe exacerbation in 12 months, we excluded OA cases with onset in the same time period. We decreased the 7,920,000 prevalent cases by the upper estimate of 53,000 new onset OA cases, yielding 7,867,000 at risk for exacerbation. Using estimates from the current study, 7.7% of the 7,867,000, or approximately 605,800, would have had severe exacerbations in a one-year period, and 14.7% of this latter group, or 89,000, would have had a severe exacerbation related to work. With the numbers for OA and work-related severe exacerbation of asthma combined, the annual number of asthma cases impacted by occupation in 27 European nations would have ranged from a low of 133,000 to a high of 141,800. These estimates suggest that occupation is an important contributor to asthma morbidity and loss of productivity in Europe.

Sample size. The cohort of working adults with current asthma was relatively large. Still, there was not the statistical power to reach conclusions about all occupations and all the occupational exposures included in the JEM. A study with a greater number of employed adults with current asthma could yield more stable estimates of the independent impact of

various occupational exposures. However, the problem of collinearity could persist even with greater numbers of participants. The 10 severe exacerbation cases with high gas and fume exposure illustrate the collinearity issue. They included one-fifth (n=1) of the cases with high biological dust exposure and one-half (n=3) of the cases with high mineral dust exposure.

Work-exacerbated asthma cases. Any employed person with asthma can experience work-related exacerbation of their symptoms, but that person will not necessarily be classified as a WEA *case*. In particular, many researchers and clinicians consider that when someone with OA experiences exacerbation of asthma symptoms due to the same workplace agent that caused the asthma, it is a continuation of the original OA rather than a new WEA case. This distinction is particularly relevant for medico-legal issues like worker compensation. In the current study, the higher RRs for bakery workers and those working with sensitizing agents such as biological dust suggest that some severe exacerbation cases could have responded to the agents that had caused their OA.

Yet, the methods of the current study kept the focus on the contribution of occupation to exacerbation, and away from asthma onset or the continuation of OA cases. First, we excluded current asthma cases that had experienced onset in the two years prior to ECRHS II participation, in order to avoid confusing the onset experience with any subsequent exacerbation. Second, a general population JEM was used to assess broad exposure categories relevant to exacerbation of asthma. Researchers have used an asthma-specific JEM [28] successfully in studies of all work-related asthma cases in ECRHS I [16] and of asthma onset in ECRHS II [17]. However, the asthma-specific JEM was developed with an emphasis on new-onset asthma rather than exacerbation of asthma. For example, it likely characterizes sensitizing exposures more completely than non-sensitizing exposures, but the

latter are suspected of playing a larger role in exacerbation of asthma. Consequently, the asthma-specific JEM was not used in the current study of exacerbation.

The characterization of occupational exposure in a population-based study is a challenge. Using a JEM yields less-biased estimates of exposure than self-reports [29]. Still, the assignment of exposure in the current investigation was not based on knowledge of the actual experience of each participant, so non-differential misclassification almost certainly occurred. This would have biased findings to the null.

Strengths of the current study. The current study is unique with respect to where it was conducted and how it defined, determined, and expressed the occupational contribution to exacerbation of asthma [3-8]. First, in an increasingly interconnected world, the ECRHS afforded an opportunity to calculate effect estimates that reached across national borders. Also, the pooled data from many countries provided more stable estimates than are usually possible in country-specific studies. Second, this study focused on severe exacerbation of asthma, using more stringent criteria for exacerbation than in prior studies, perhaps with the exception of a study that used serial peak expiratory flow rate measurements to identify work-related patterns [3]. Third, a JEM was used to assign occupational exposures to participants. Many of the prior studies did not even consider exposure in the operational definition of WEA [3, 6, 7]. Fourth, other studies determined work-related status for each case individually, whereas the current study used a risk-set approach to estimate the RR of occupational exposure and then compute the PAR%. Fifth, the PAR% from this study represents the percentage of severe exacerbation cases attributable to occupation. Previous studies have expressed WEA frequency as a percentage of all adults with asthma or of all working adults with asthma [3-8].

Summary. Occupational exposure to dust, gas, or fumes makes an important contribution to severe exacerbation of current asthma among working adults, accounting for

approximately 14.7% of such cases. A variety of occupations are associated with severe exacerbation, and the high-risk occupational exposures include sensitizing as well as non-sensitizing agents. Efforts to prevent work-related asthma have succeeded in different occupational settings, including healthcare workers exposed to natural rubber latex [30], animal handlers in laboratories [31], and detergent production workers exposed to enzymes [32]. These interventions depended on an adequate understanding of the agents and how they were used. Future work-related asthma prevention efforts will depend on having a similar understanding of agents and workplaces, and additional research will be needed to generate this knowledge when it is lacking.

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Figure 1. Identification of working adults with current asthma among European Community Respiratory Health Survey follow-up (ECRHS-II) participants

