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Do young adults with childhood asthma avoid occupational exposures at first hire?

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Abstract

Information on the healthy worker hire effect in relation to asthma is scanty. We aimed to assess whether and how childhood asthma-related characteristics (before hire) relate to occupational exposures at first hire.

Analyses were conducted in 298 children examined at the first survey of the Epidemiological study on the Genetics and Environment of Asthma (1991-95), who reported a training period or a job at follow-up in 2003-07 (aged 17-29 years, 53% men). Exposure likelihood to dust, gases and/or fumes at the first occupation was estimated by the ALOHA job-exposure matrix. Asthma before the first occupation and two asthma classifications for severity (GINA2002 guidelines) and symptoms were defined by questionnaire.

At the first occupation, 47% of subjects were exposed. After adjustment (age, gender, diploma), pre-hire-onset asthmatics (59%) were non-significantly less likely to be exposed (OR[95%CI]: 0.67[0.41-1.11]). Associations were stronger considering those with severe asthma or high symptom score in childhood (0.27[0.11-0.63], 0.49[0.25-0.99]). The association was observed in those who completed a university degree level (0.55[0.29-1.04]) but not in the others (0.98[0.44-2.22]), with consistent results for all asthma characteristics.

Results suggest a healthy worker hire effect in subjects with more severe or more symptomatic asthma in childhood. Diploma level may modulate self-selection.

Key words: Asthma, healthy worker hire effect, longitudinal study, occupational exposure, selection bias.

Introduction

Recent studies estimated that 10 to 15% of adult-onset asthma is attributable to occupational exposure [1, 2]. Work-exacerbated asthma, i.e. worsening of a pre-existing asthma induced by exposure at the workplace, has been less studied but might represent 45% of all work-related asthma cases [3, 4]. However, associations between occupational exposures and asthma are probably under-estimated as a result of the "healthy worker effect" selection phenomenon [5]. New-onset asthma or exacerbation of pre-existing asthma may lead to avoidance of occupational exposures by less healthy workers who may decide to move to a low- or non-exposed job. This so-called healthy worker survivor effect has been suggested in relation to asthma in several studies [5].

The healthy worker hire effect, i.e. an early selection mechanism arising from career choice through the selection at hire of a work environment without hazardous exposures by individuals with a pre-existing asthma, has been less studied. Recently, a study from the European Community Respiratory Health Survey (ECRHS) showed that adults with asthma onset prior to entering the workforce were less likely to report current or previously held jobs involving inhalation exposures [6]. Whether these associations reflect initial ("hire effect") or continuing ("survivor effect") selection processes could not be determined. In a study that evaluated the job that teenagers would like to have in the future, teenagers with respiratory symptoms did not significantly more often indicate a job with no asthma risk than teenagers without respiratory symptoms [7]. The magnitude and the determinants of health-based self-selection at hire due to asthma remain to be ascertained. In particular, the role of the clinical expression and the history of the disease, and of socioeconomic factors needs to be studied [6].

The longitudinal design of the French Epidemiological Study on the Genetics and Environment of Asthma (EGEA) enabled us to follow subjects from childhood to the

beginning of their working life. In the current analysis, we aimed to assess: (1) whether subjects with childhood-onset or pre-hire-onset asthma will avoid occupational exposure at their first hire, (2) which clinical characteristics are involved in this self-selection process, with a particular attention to asthma severity, asthma symptoms, as well as to allergic sensitization and lung function in both asthmatics and non asthmatics, and (3) whether socio-demographic characteristics such as gender, diploma level and smoking modify asthma-based self-selection at hire.

Materials and Methods

Population

The present analysis used the longitudinal data from the case-control and family-based EGEA study [8]. The present study was conducted in subjects included as a child (below 16 years of age) at baseline (EGEA1, 1991–1995) and who had ever worked at follow-up (EGEA2, 2003-2007). Of the 604 children enrolled at baseline (including asthmatic cases, their first-degree relatives and population-based controls), 547 took part in the follow-up phase. A total of 141 completed only a brief postal questionnaire with no information about occupation (or only for the 2 last jobs). A total of 393 completed a detailed questionnaire comprising complete occupational history (supplementary figure E1), and among them 318 had ever worked (i.e. reported at least one occupation). Subjects who had only done short-term part-time or seasonal work irrelevant to a career choice (n=8), or with unclear occupational history (n=1) were excluded. Finally, analyses were performed for 298 subjects, after excluding subjects with missing data for exposure (n=1), diploma level (n=2) or parental asthma (n=9, in order to have a constant number for the "non asthmatics" reference category).

Asthma characteristics

Information on asthma and related clinical characteristics at baseline (including allergic rhinitis) were recorded by questionnaire (based on standardized questionnaire designed for children [9] with further questions from the ECRHS questionnaire for asthma-like symptoms), administered by an interviewer to the parents (usually the mother). Methods used to ascertain asthma and related characteristics have been described before [8, 10] and details are provided in online supplementary material.

Subjects with pre-hire-onset asthma, i.e. asthma onset before the first occupation, comprised asthmatics at EGEA1 (asthma onset in childhood, n=150), and asthmatics at EGEA2 with age at onset younger than the age at the first occupation (with at least one year between asthma onset and first hire, n=25) (Figure 1). To evaluate whether asthma was still present just before the hire, asthmatics were classified according to the presence of asthma attacks in the year before the first occupation, using EGEA2 retrospective questions on asthma history: "Have you ever had a period of several years without attacks? If yes: "At what age did attacks disappear / reappear?". Parental asthma was taken into account only if parental asthma onset occurred before the first hire of the child.

To assess asthma severity in childhood (available among the 150 subjects with asthma at baseline, see figure 1), a 4-level classification was constructed in close accordance with the principles of the Global Initiative for Asthma (GINA 2002) guidelines [11], as previously in EGEA [12]. The classification was based on clinical characteristics and type of treatment in the past year (see online supplementary material). A score of 1-2 was classified as "mild asthma" and a score of 3-4 as "moderate to severe asthma". Additionally, a 5-level asthma-symptom score has been constructed for children, adapted from that described for adults by Pekkanen et al [13, 14] and already used in EGEA [15]. Examination at baseline included total serum IgE, skin prick tests (SPT) to 11 aeroallergens, and lung function tests including

methacholine challenge. Bronchial responsiveness was assessed by the dose-response slope according to Chinn et al [16], which decreases with hyperresponsiveness.

Occupational exposure

At follow-up, diploma level was recorded, and each training period and job performed was precisely recorded (position and industry title, job task), and subsequently coded according to the ISCO-88 4-digit coding system [17] by an experienced coder as recommended [18]. For the current study, the first occupation, i.e. the first job or the first training period performed was selected.

For the main analysis, exposure to dust (biological and mineral), vapours, gases, fumes, pesticides, solvents and metals was assessed using an updated version (HK, RV) of the so-called "ALOHA job-exposure matrix" [19, 20], which assign to each job code a probable exposure category (none, low, or high) to each agent. The outcome of interest was "low or high exposure to at least one agent" vs. "no exposure". All subjects classified as "exposed" were at least exposed to dust, vapours, gases and/or fumes, except one (exposed to solvents and metals only).

Additional analyses were performed using an asthma-specific job-exposure matrix [18] containing 22 exposure groups classified as high risk agents (moderate or high probability of exposure to: high or low molecular weight agents, mixed environment), or low risk agents (possible exposure to irritants or antigens). The application of this matrix included an occupational hygiene expert re-evaluation step (DH, MH, NLM).

Statistical analysis

Associations between exposure at the first occupation (outcome) and asthma before hire or related clinical characteristics (predictors) were evaluated by logistic regression analysis.

Analyses were adjusted for gender, age and diploma level ("university diploma level" refers to completion of at least 2 years of post-secondary education) at follow-up. Further adjustment on smoking led to similar results (not shown). Gender, smoking and diploma level have also been tested as potential effect modifiers for the relation between asthma and exposure by adding interaction terms in multivariate models. The familial structure of the data was taken into account by using Generalized Estimating Equations approach, which allows the specification of a correlation structure (the correlation between siblings has been assumed constant) in a generalized linear model. The analysis was performed using SAS 9.1.

Results

Among the 393 subjects who completed the detailed adult questionnaire at follow-up, having ever worked was not associated with any studied clinical characteristic (data not shown). The 298 selected subjects were aged 17-29 years at follow-up and 175 (59%) had asthma before their first occupation (table 1). There were marked differences according to asthma for childhood symptom score, bronchial hyperresponsiveness (BHR), SPT, IgE, and allergic rhinitis (table 1). A total of 36% of pre-hire-onset asthmatics had a high (4-5) symptom score, and 28% of asthmatics at baseline had moderate to severe asthma. Subjects with pre-hire-onset asthma were significantly more often male, younger at EGEA2 and younger at their first occupation than non-asthmatics. The slight difference in diploma level according to asthma ($p=0.11$) disappeared after adjusting for age ($p=0.44$). Among pre-hire-onset asthmatics, 21 (12%) declared having received advice regarding job choices related to asthma or respiratory health. These advices were most often (33%) provided by a physician, and regarded mostly a specific job or exposure (animals, diving, flying, etc).

The first occupation was a training period for 226 subjects and a job for 72. Beginning with a training period was unrelated to asthma status, exposure, gender and age, but associated with a higher diploma level (65%) than beginning with a job (46%, p=0.003).

The 140 subjects (47%) classified as exposed according to the ALOHA job-exposure matrix (to dust, gases, fumes, pesticides, solvents and/or metals) were more likely to be male (54% men exposed vs. 39% women, p=0.01) and to have a lower diploma level (38% exposed in subjects with university diploma level vs. 60% for a lower level, p<0.001) and were similar regarding age or smoking status. According to the asthma-specific job-exposure matrix, 30% of subjects were exposed, with consistent results regarding gender, age, diploma level and smoking status.

Subjects with pre-hire-onset asthma were less frequently exposed (ALOHA job-exposure matrix, table 2) at the first occupation (45%) than non-asthmatics before hire (50%), but the association did not reach significance (adjusted p=0.12). Associations were similar in men and women (0.62 [0.31 – 1.25] and 0.73 [0.34 – 1.57] respectively), and in smokers and non-smokers (0.63 [0.30 – 1.30] and 0.71 [0.36 – 1.38] respectively). Among pre-hire-onset asthmatics with a high symptom score in childhood, 39% were exposed (compared to non-asthmatics before hire, p=0.12). This association was more pronounced and significant after adjustment (0.49 [0.25 – 0.99]). No difference was observed among asthmatics according to the presence or not of attacks the year before the first occupation. The analysis of exposures estimated by the asthma-specific job-exposure matrix provided similar associations (table 2).

Among asthmatics at baseline with moderate to severe asthma (table 3), 27% were exposed at the first occupation (compared to non-asthmatics before hire, p=0.01), resulting in adjusted OR [95% CI]: 0.27 [0.11 – 0.63] (ALOHA job-exposure matrix) and 0.31 [0.12 – 0.82] (asthma-specific job-exposure matrix). In tables 2 and 3, differences between crude and adjusted ORs were mainly explained by adjusting for gender and diploma level.

Pre-hire-onset asthma combined with parental asthma was associated with a lower risk of exposure at the first occupation compared to subjects without asthma and parental asthma (0.48 [0.25 – 0.89], ALOHA job-exposure matrix). Intermediate associations were observed for the effect of parental asthma or asthma alone (0.62 [0.30 – 1.29] and 0.67 [0.33 – 1.37] respectively). According to the asthma-specific job-exposure matrix, no significant association was observed.

In analyses of the specific exposures estimated by both matrices, significant associations were found for most of the specific exposures, and the lowest OR was obtained for exposure to high molecular weight agents (supplementary table E2).

Associations between exposure at first hire (ALOHA job-exposure matrix) and lung function, allergic sensitization and triggers for respiratory symptoms in childhood were studied in both non-asthmatics and asthmatics (supplementary table E1). In both groups, lung function, BHR and allergic rhinitis were unrelated with exposure. Regarding total IgE and positive SPT, there were no difference according to exposure in those with a history of asthma, whereas among non asthmatics exposed subjects tended to have lower IgE level (p=0.07) and less often positive SPT (p=0.02). Subjects with asthma at baseline who reported respiratory symptoms triggered by hay, flowers or pets were significantly less often exposed.

The association between pre-hire-onset asthma and both estimates of exposure was observed in subjects with university diploma level but not in subjects with a lower diploma level: 0.55 [0.29 – 1.04] vs. 0.98 [0.44 – 2.22] (p interaction = 0.19, ALOHA job-exposure matrix); 0.47 [0.23 – 0.97] vs. 1.38 [0.61 – 3.11] (p interaction=0.02, asthma-specific job-exposure matrix). All associations between exposure and asthma characteristics stratified by diploma level are presented in supplementary table E3.

Discussion

The current prospective study shows that young adults with an asthma history before their first hire may preferentially choose a first occupation with low probability of exposure that may be hazardous to respiratory health. This self-selection phenomenon varies according to clinical characteristics of asthmatics: more severe or more symptomatic asthma in childhood was associated with a stronger selection at hire. Allergic sensitization was also involved in this self-selection process. Socio-demographic characteristics such as a higher diploma level may increase asthma-based self-selection.

This analysis was conducted in subjects followed from childhood to the beginning of their working life. The knowledge of the complete job history allowed us to study for the first time the first training period or job. In France, training periods are in principle done within the framework of studies or vocational education, and thus represent an involvement in a vocational field and an initial career choice. Two studies have suggested a healthy worker survivor effect in populations of young apprentices, who can be compared to trainees [21, 22]. Training periods must be taken into account to evaluate a potential early selection phenomenon. Exposures were assessed using job-exposure matrices rather than self-reported exposure that may be influenced by health status [23]. The ALOHA job-exposure matrix estimates a broad range of exposures (dust, gases, fumes, pesticides, solvents and/or metals), which might better correspond to the subject's awareness or perception of occupational risks than a more accurate assessment of asthma-specific agents. Consistent results have been observed with the asthma-specific job-exposure matrix, and the analysis of specific exposures suggested a stronger avoidance of occupations with likely exposure to high molecular weight agents, even if the low numbers of subjects in each exposure group limited the interpretation of the results. We studied a young population, describing a recent asthma history (mostly at baseline survey) and job history (at follow-up), and therefore recall bias is unlikely to have

affected our results. However, the population was only of moderate size, and consequently a lack of power limited some investigations (for instance taking into account exposure level) and the interpretation of some results.

Our study confirms and extends recent results regarding the healthy worker effect in asthma. Childhood asthma has been reported as a factor influencing the first occupational social class (not being blue-collar worker) in a French men cohort [24]. Furthermore, findings from the ECRHS [6] showed that asthma status prior to entering the workforce was related to jobs less exposed based on retrospective information on asthma and exposures, assessed for the current or most recent job, or a previously held job (if a previous occupational exposure was suspected). Associations observed in ECRHS might reflect both initial selection in career choice ("hire effect") and continuing selection processes ("survivor effect"). Our results are consistent with these findings as they support an influence of asthma characteristics prior to entering the workforce on the career choice. Furthermore, we have shown that a substantial part of job selection would take place at first hire.

Our results suggest for the first time that childhood health history and socioeconomic parameters modify self-selection at hire. More severe asthma and more symptomatic asthma in childhood were associated with a strong selection at hire. Asthma severity in adults has previously been related to job changes [25]. Our results suggest that the severity and symptoms of the disease experienced in childhood may have an impact on job choice in young adulthood. Despite a good characterization of asthma in childhood, detailed data on asthma severity and symptoms at the precise moment of hire were not available. In the current analysis, the presence of asthma attacks the year before hire did not increase self-selection, suggesting that job choices may be based on a longer disease history and a larger range of clinical characteristics.

Parental asthma strengthened selection at hire, possibly related to parental knowledge or work experience. Genetic factors may also be considered, as they may be associated to specific asthma characteristics which would influence job choice. Familial resemblance in asthma severity has been previously evidenced in the EGEA population [26].

Our results suggest that allergic sensitization might be involved in health-based selection mechanisms at hire. Positive SPT in childhood predicted less exposure at first occupation, particularly among non-asthmatics (few asthmatics had negative SPT), with consistent results regarding total IgE. Allergic rhinitis did not significantly influence job choice. This result partly differs from a previous study in a cohort of Swedish men born in 1949-1951 [27], reporting job selection in the early period of the working life similarly in men with allergic rhinitis and in men with asthma (diagnosed at military service).

Our results suggest that diploma level might modify healthy worker hire effect, as only asthmatics with a university diploma level avoided jobs with likely exposures (for both exposure estimates), with consistent results for all asthma characteristics studied. Low socioeconomic level has been previously mentioned as a factor leading to less job selection in mortality studies [28], as well as on removal from exposure in red cedar asthmatics [29]. Diploma level reflects both education and socioeconomic conditions, two different aspects that might influence selection at work, through the knowledge of occupational risks [30] and the larger amount of career opportunities. As underlined recently [6] more comprehensive information on socioeconomic conditions are warranted to better understand the various components of the healthy worker effect. In a study that investigated the preferred future job choice in teenagers [7], inconclusive associations were found between respiratory symptoms and the choice of a job without an increased risk for asthma. This study was conducted in vocational trainees, likely with a lower education, and probably less prone to self-selection, as

was shown in our study. We did not evidence gender differences in selection (in agreement with the study of Olivieri et al. [6]), nor difference between smokers and non-smokers.

Work-related asthma has an important individual socioeconomic impact [31, 32], that might be reduced by health-based selection in the early period of the working life, but career choices also depend on socioeconomic conditions. Selection might have arisen from a personal choice, an advice from a physician or another person, or from the employer's choice. However, no health-based pre-employment selection policy exists in France. Very few asthmatics declared to have received advice regarding job choice, and this advice concerned very specific occupational fields. Considering public health surveillance, this study raises the importance of taking into account this selection bias in studies of occupational asthma. Further research is needed to better understand how current estimates of the effect of specific exposures on respiratory health may be affected by the healthy worker effect.

In conclusion, the current study shows in a population of young adults that asthma history plays a role in the choice of the first occupation, and that this choice is further modified by clinical and socio-demographical characteristics. This phenomenon probably leads to an under-estimation of associations between occupational exposures and asthma.

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Figure 1

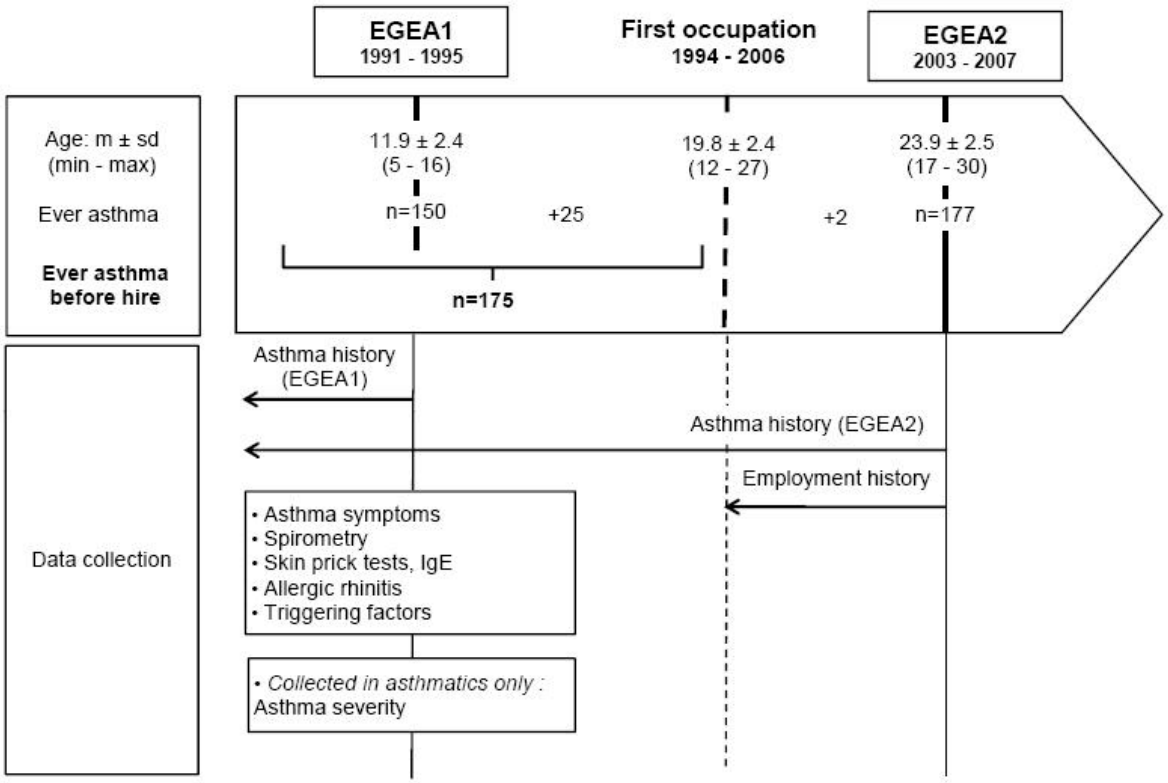

EGEA1
1991 - 1995
First occupation
1994 - 2006
EGEA2
2003 - 2007
Age: m ± sd
(min - max)
Ever asthma
Ever asthma before hire
11.9 ± 2.4
(5 - 16)
19.8 ± 2.4
(12 - 27)
23.9 ± 2.5
(17 - 30)
n=150
+25
+2
n=177
n=175
Asthma history (EGEA1)
Asthma history (EGEA2)
Employment history
Data collection
• Asthma symptoms
• Spirometry
• Skin prick tests, IgE
• Allergic rhinitis
• Triggering factors
• Collected in asthmatics only :
Asthma severity

TABLE 1. Description of the population according to asthma status before hire

	All (n=298)	Asthma before hire: No (n=123)	Asthma before hire: Yes (n=175)	p
BASELINE DATA (in childhood) – EGEA1				
Gender, males, n (%)	158 (53.0)	52 (42.3)	106 (60.6)	0.002
Status in the study, n (%)				
Cases	89 (29.9)	-	82 (50.9)	-
Siblings	152 (51.0)	80 (65.0)	72 (41.1)	
Control	57 (19.1)	43 (35.0)	14 (8.0)	
Asthmatic at baseline, n (%)	150 (50.5)	-	150 (85.7)	
Asthma severity *, n (%)				
Mild	97 (37.6)	-	97 (72.4)	-
Moderate to severe	37 (14.4)	-	37 (27.6)	
Symptom score, n (%)				
0	124 (45.1)	102 (87.9)	22 (13.8)	
1 to 3	94 (34.2)	14 (12.1)	80 (50.3)	<0.001
4 to 5	57 (20.7)	0	57 (35.9)	
FEV_1 % predicted, m ± SD	98.6 ± 12.1	99.5 ± 10.6	98.0 ± 13.1	0.27
Methacholine challenge (n)	223	103	120	-
BHR log slope (m ± SD)	5.40 ± 2.51	6.80 ± 2.50	4.21 ± 1.79	<0.001
Positive skin prick tests, n (%)				
No	102 (34.9)	73 (60.3)	29 (17.0)	<0.001
Yes	190 (65.1)	48 (39.7)	142 (83.0)	
IgE, GM (95% CI), IU/ml	149 (122 – 181)	52 (39 – 70)	312 (254 – 382)	<0.001
Allergic rhinitis, n (%)	103 (34.7)	12 (9.8)	91 (52.3)	<0.001
FOLLOW-UP DATA – EGEA2				
Age at follow-up, m ± SD, yrs	23.9 ± 2.5	24.7 ± 2.5	23.6 ± 2.4	0.01
Age at the first hire, m ± SD, yrs	19.8 ± 2.4	20.2 ± 2.3	19.6 ± 2.4	0.02
University diploma level, n (%)	180 (60.4)	81 (65.9)	99 (56.6)	0.11
Current smoker at the age of first hire, n (%)	137 (46.0)	57 (46.3)	80 (45.7)	0.91
Parental asthma, n (%)	153 (51.3)	51 (41.5)	102 (58.3)	0.004
Asthma attacks the year before the first occupation, n (%)				
No	83 (29.0)	-	83 (50.9)	-
Yes	80 (28.0)	-	80 (49.1)	

BHR – bronchial hyperresponsiveness; CI – confidence interval; GM – geometric mean; IgE – immunoglobulin E.

* Asthma severity was recorded only among the 150 subjects with asthma at baseline, and was missing for 16 of them.

TABLE 2. Associations between asthma characteristics before hire and exposure at the first occupation

		ALOHA job-exposure matrix *			Asthma-specific job-exposure matrix †		
	n	Exposed (%)	OR (95% CI)	Adjusted ‡ OR (95% CI)	Exposed (%)	OR (95% CI)	Adjusted ‡ OR (95% CI)
All	298	47.0	-	-	30.2	-	-
Non-asthmatic before hire (ref.)	123	49.6	1	1	30.9	1	1
Pre-hire-onset asthmatics	175	45.1	0.84 (0.54 – 1.32)	0.67 (0.41 – 1.11)	29.7	0.94 (0.57 – 1.53)	0.73 (0.43 – 1.24)
Symptom score in childhood §							
0 to 3	102	47.1	0.90 (0.54 – 1.50)	0.73 (0.42 – 1.27)	33.3	1.11 (0.64 – 1.92)	0.88 (0.49 – 1.58)
4 to 5	57	38.6	0.64 (0.34 – 1.20)	0.49 (0.25 – 0.99)	22.8	0.66 (0.32 – 1.36)	0.51 (0.24 – 1.07)
Attacks the year before the first occupation ||							
No	83	45.8	0.86 (0.50 – 1.49)	0.65 (0.36 – 1.24)	30.1	0.96 (0.53 – 1.75)	0.71 (0.37 – 1.38)
Yes	80	45.0	0.83 (0.47 – 1.48)	0.68 (0.38 – 1.23)	30.0	0.95 (0.51 – 1.76)	0.73 (0.39 – 1.37)

CI: confidence interval; OR: odds-ratio.

* Exposed (probable exposure to at least one agent among: dust, gases, fumes, pesticides, solvents and/or metals) vs. non-exposed.

† Exposed (moderate or high probability of exposure to asthmogens, or possible exposure to low risk irritants or antigens) vs. non-exposed.

‡ Adjusted for age at follow-up, gender and diploma level.

§ Analysis performed in 282 subjects (data missing for symptom score in 16 pre-hire-onset asthmatics).

|| Analysis performed in 286 subjects (data missing for attacks the year before the first occupation in 12 pre-hire-onset asthmatics).

TABLE 3. Associations between exposure at the first occupation and asthma severity at baseline

		ALOHA job-exposure matrix*			Asthma-specific job-exposure matrix †		
	n	Exposed (%)	OR (95% CI)	Adjusted ‡ OR (95% CI)	Exposed (%)	OR (95% CI)	Adjusted ‡ OR (95% CI)
All	273	48.0	-	-	30.8	-	-
Non-asthmatic before hire (ref.)	123	49.6	1	1	30.9	1	1
Asthmatics at baseline	150	46.7	0.89 (0.56 – 1.42)	0.72 (0.43 – 1.22)	30.7	0.99 (0.59 – 1.64)	0.79 (0.46 – 1.36)
Asthma severity at baseline §							
Mild	97	51.6	1.08 (0.63 – 1.85)	0.88 (0.49 – 1.58)	35.1	1.21 (0.70 – 2.10)	0.97 (0.53 – 1.75)
Moderate to severe	37	27.0	0.38 (0.17 – 0.82)	0.27 (0.11 – 0.63)	16.2	0.39 (0.15 – 1.04)	0.31 (0.12 – 0.82)

CI: confidence interval; OR: odds-ratio.

* Exposed (probable exposure to at least one agent among: dust, gases, fumes, pesticides, solvents and/or metals) vs. non-exposed.

† Exposed (moderate or high probability of exposure to asthmogens, or possible exposure to low risk irritants or antigens) vs. non-exposed.

‡ Adjusted for age at follow-up, gender and diploma level.

§ Analysis performed in 257 subjects (data missing for asthma severity in 16 asthmatics at baseline).