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Original Article

Clinical Importance of Work-Exacerbated Asthma: Findings From a Prospective Asthma Cohort in a Highly Industrialized City in Korea

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ABSTRACT

Purpose: Work-related asthma (WRA) occupies about 10%–30% of all asthma cases. Among 2 subtypes of WRA (occupational asthma [OA] and work-exacerbated asthma [WEA]), the rate of WEA has been reported to increase recently. WRA is described as having worse characteristics than non-WRA (NWRA), while WEA is known to show similar severity to OA in terms of symptoms and exacerbations. However, these data were mainly based on indirect surveys. Ulsan is a highly industrialized city in Korea; therefore, it is estimated to have a high incidence of WRA. This study aimed to identify the characteristics of WRA in the city.
Methods: This was a prospective asthma cohort study of individuals diagnosed with asthma and treated at Ulsan University Hospital between Jan 2015 and Dec 2016. Baseline characteristics and work-related inquiry (9 questionnaires) were investigated at enrollment. Various severity indices and job change were then investigated for the longitudinal analysis at 12 months after enrollment.
Results: In total, 217 asthma patients completed the study. WRA accounted for 17% (36/217), with an equal number of WEA and OA (18 patients each). Before the work-related survey, only 33% (n = 12) of WRA patients (22% [4/18] of WEA and 44% [8/18] of OA) were diagnosed with WRA by the attending physicians. Compared to the NWRA group and the OA subgroup, the WEA subgroup had more outpatient visits, more oral corticosteroids prescriptions, and trends of low asthma control test scores and severe asthma. The rate of job change was markedly lower in the WEA subgroup than in the OA subgroup (20% vs. 5%).
Conclusions: The overall prevalence of WRA (17%) was similar to those of previous studies, but the share of WEA was high (50% of WRA). WEA was more severe than OA or NWRA. The possible reason for this severity is ongoing workplace exposure.

Keywords: Asthma; work; asthma, occupational

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There are no financial or other issues that might lead to conflict of interest.

INTRODUCTION

Asthma is among the most common diseases in industrialized cities.[1] There has been a growing development of new chemicals, occupational exposure of which could exacerbate pre-existing asthma and induce new asthma. Work-related asthma (WRA) refers to asthma caused by exposure to certain substances in the workplace; it is broadly classified into 2 subtypes: occupational asthma (OA) and work-exacerbated asthma (WEA).[1] OA refers to the new development of asthma caused by specific agents at the workplace, while WEA is defined as previously diagnosed asthma that is worsened by nonspecific agents at the workplace.[1]

It is known that WRA occupies about 10% to 30% of all asthma cases.[1-8] Two subtypes of WRA, OA and WEA, are known to account for about 80%–90% and 10%–20% of WRA[9-11]; recently the ratio of WEA has been reported to be similar to or even higher than that of OA.[12,13] From the previous studies, it is known that patients with WRA (OA and WEA) needed more health care uses and 10-fold higher costs than those with non-WRA (NWRA).[7,8,14] Also, WRA is described as having worse characteristics than NWRA, while WEA is known to show similar severity to OA in terms of symptoms and exacerbations.[8,10,15,16] Only 1 study reported that WEA could be worse than OA.[14]

Despite the high incidence, studies on WRA are lacking, particularly those that include WEA. Most previous studies included only OA patients. Therefore, it is difficult to generalize the characteristics of WEA. Accordingly, the American Thoracic Society (ATS) has publicly announced the need for more research on WEA.[17] In addition, WRA research had almost never been conducted in real prospective clinical asthma cohorts. Except for 1 study,[14] most of them are retrospective studies[6-8] or indirect prospective cohort studies (such as surveillance program, insurance claims data or telephone surveys).[3-5,9,10,18]

Ulsan is the most industrialized city in Korea, with various factories located in the city. Accordingly, Ulsan is projected to have a high prevalence of potential WRA patients. The aim of this study was to find out the exact prevalence of WRA (including OA and WEA) in Ulsan (a representative industrialized city in Korea). Also, with a longitudinal analysis for 1 year through a prospective asthma cohort, we intended to elucidate the characteristics of WRA, especially WEA in contrast to OA or NWRA.

MATERIALS AND METHODS

Study design

In the period from January 2015 to December 2016, we prospectively recruited patients who have been diagnosed as asthma at Ulsan University Hospital. At the time of enrollment, the first survey including baseline characteristics and work-relatedness inquiry (9 questionnaires) was performed. After 12 months of enrollment, the second survey that included a variety of severity indices and job change was done for the longitudinal analysis. Detailed survey items are described below. This study was approved by the Institutional Ethics Review Committee of Ulsan University Hospital (approval number 2014-10-021).

Study subjects

The study subjects were 19 years or older, and had been suffering from at least one of the chronic persistent respiratory symptoms of dyspnea, cough, sputum production or wheezing

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for more than 3 months. Asthma was then diagnosed by demonstration of airway reversibility or bronchial hyperresponsiveness (BHR). Airway reversibility consisted of an improvement in forced expiratory volume in 1 second (FEV1) of at least 12% or 200 mL post-bronchodilator (200 mcg of albuterol by means of a metered-dose inhaler), or 20% or more over time or after corticosteroid treatment. BHR was defined as provocation concentration that caused a decrease in FEV1 of 20% at methacholine ≤ 16 mg/mL or cumulative provocation dose that caused a decrease in FEV1 of 15% at mannitol ≤ 635 mg before asthma treatment.[19,20]

Patients with any of the following conditions were excluded; 1) exacerbation state at the time of initial enrollment; 2) serious non-pulmonary diseases such as heart failure, cancers and severe psychiatric disorders; 3) other pulmonary diseases such as apparent emphysema, bronchiectasis, or destroyed lung caused by previous medical conditions like pulmonary tuberculosis on chest radiography; and 4) failure (lack of completion) of the second survey.

First survey items at the time of enrollment

The baseline characteristics of demographic and clinical data recorded at the time of enrollment included age, sex, height, weight, asthma duration (time from symptom onset to study enrollment), atopic status, presence of rhinosinusitis, smoking status, detailed occupation history and results of laboratory tests (blood, sputum and pulmonary function). A work-related inquiry consisting of 9 questions was also conducted. The questions were as follows: 1) "Was your asthma diagnosed before or after your current or former job?"; 2) "When did your asthma or asthma symptoms (dyspnea, cough or wheezing) start?"; 3) "Have you ever experienced having worse asthma or asthma symptoms at work?"; 4) "Do your asthma or asthma symptoms worsen at work?"; 5) "Do your asthma or asthma symptoms improve after work?"; 6) "Do your asthma or asthma symptoms improve during the weekends when you are not working or holidays?"; 7) "Did your asthma or asthma symptoms begin right after you inhaled chemicals or smoke? If so, what is the inhalation material? How long after your inhalation did your asthma symptoms begin?"; 8) "Please check if the following substances are present in your workplace (multiple answers are allowed): glues, chemical substances, dyes (colorant), cleaning agents, exhaust gas/smoke, isocyanates, natural rubber-related material, drugs, metals/metal working fluids, synthetic fibers, plant proteins (grain dust, flour, rice bran, timber dust, medicinal herbs and pollen), animal proteins (insect, citrus mite, sea squirt and animal fur), fungi and cold air"; and 9) "Please check if you have been previously exposed to the following substances (multiple answers allowed; the items are the same as question #8)." After the work-related inquiry, the participant was diagnosed with either WRA or NWRA, with further classification to WEA or OA, following the National Institute for Occupational Safety and Health (NIOSH) guideline except for irritant-induced OA (IIOA; *i.e.,* reactive airway dysfunction syndrome [RADS]),[21,22] which was determined according to the recent revised definition (**Fig. 1**).[23] For participants with WRA, the serial peak expiratory flow rate (PEFR) was measured for an objective evaluation, unless it was already previously performed.[1,24-26] Serial PEFR was performed for at least 4 weeks including both working and non-working days. A significant result was defined as diurnal variation when working that was lost or decreased when resting.[1] All patients with WRA were recommended to change jobs immediately: in the case of WEA, environmental control (removal, replacement, process modification, ventilation and respirator use) was recommended first, but job change was also recommended since it was difficult to change the working environment in most cases.[1,17] For OA patients, letting recognize insufficiency of environmental control alone, immediate job change was strongly recommended.[1,27]

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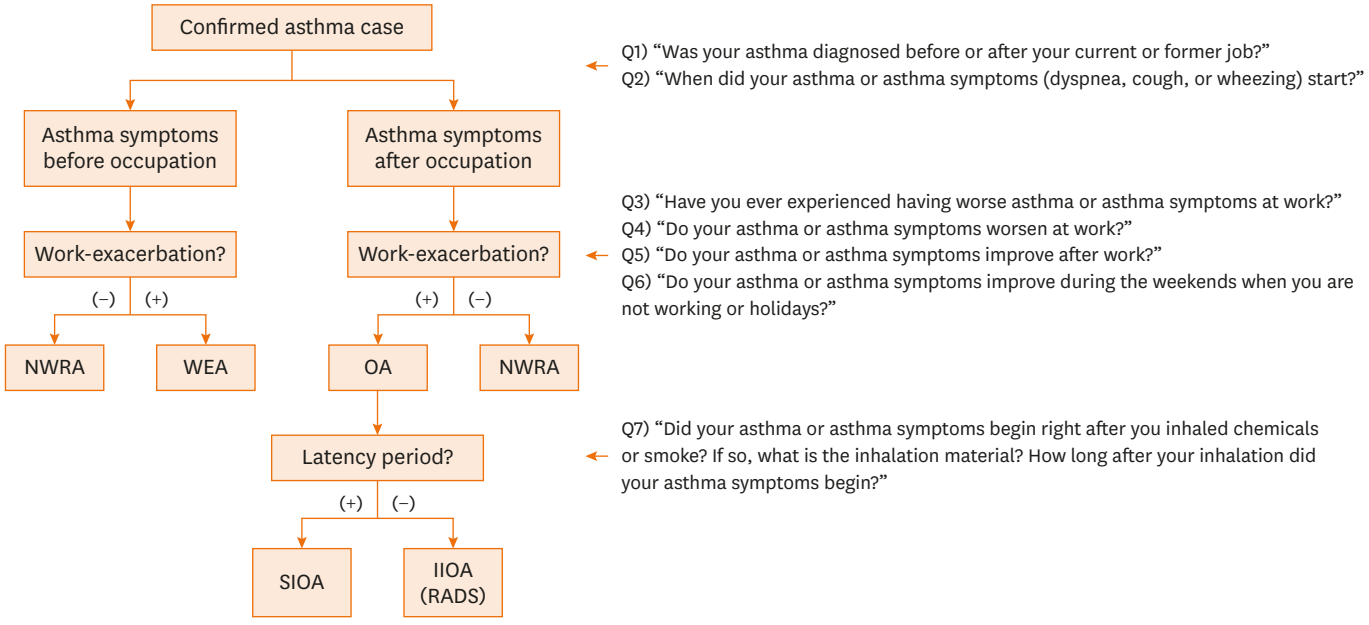

Fig. 1. Decision logic for WRA (OA and WEA) and NWRA. Using the work-relatedness inquiry, the time of asthma occurrence and work-exacerbation were investigated. NWRA was defined as a case of asthma without work-exacerbation. WEA was defined as a case of asthma when there was work-exacerbation, but the beginning of asthma symptoms was before the start of a job. OA was defined as a case of asthma when there was work-exacerbation, and the beginning of asthma symptoms was after the start of a job. IIOA (RADS) was defined as OA of acute asthma symptom onset (within days) after a high-level exposure of an irritant. NWRA, non-work-related asthma; WRA, work-related asthma; WEA, work-exacerbated asthma; OA, occupational asthma; SIOA, sensitizer-induced occupational asthma; IIOA, irritant-induced occupational asthma; RADS, reactive airways dysfunction syndrome.

Second survey items after 12 months of initial enrollment

After 12 months of enrollment, the second survey was done for the longitudinal analysis. First, data on severity indices, such as emergency room visit, hospitalization, number of outpatient visit, number of systemic corticosteroid prescriptions, mean FEV1 and mean asthma control test (ACT) score in the past year were collected. Based on these data, decisions on severe asthma were made using the 2014 ATS/European Respiratory Society (ERS) statement.[28] Furthermore, in cases of WRA (WEA or OA), we also checked whether job changes were implemented.

Statistical analysis

In order to reduce the selection bias, besides the analysis of all patients, additional analysis was performed by random matching (1:2) for NWRA based on age and sex of WRA. The independent *t* test and χ^2 test were used to analyze differences. All statistical analyses were performed using SPSS 24 (IBM Corporation, Armonk, NY, USA). A *P* value of <0.05 was considered statistically significant.

RESULTS

Of the 246 participants who initially registered, 217 completed the second survey and were thus included in the analyses. Among them, 36 (16.6%) and 181 (83.4%) were diagnosed with WRA and NWRA, respectively. OA and WEA accounted for an equal number of patients at 18 each (**Fig. 2**). Before surveying work-relatedness, only 33.3% (n = 12) of 36 WRA patients were assessed as WRA by the attending physicians: they only recognized 22.2% (4/18) of WEA and 44.4% (8/18) of OA, indicating WEA was less often correctly identified than OA.

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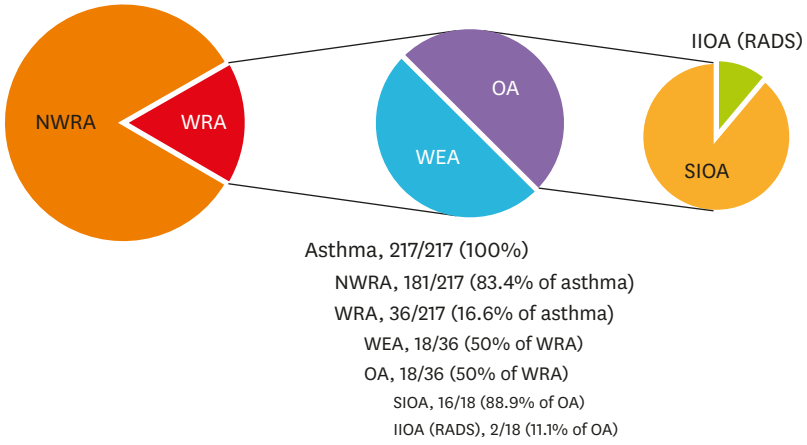

Fig. 2. Prevalence of WRA (OA and WEA) and NWRA. Of the 217 asthma patients, 36 (17%) had WRA and 181 (83%) had NWRA. OA (n = 18) and WEA (n = 18) accounted for an equal proportion of WRA.
NWRA, non-work-related asthma; WRA, work-related asthma; WEA, work-exacerbated asthma; OA, occupational asthma; SIOA, sensitizer-induced occupational asthma; IIOA, irritant-induced occupational asthma; RADS, reactive airways dysfunction syndrome.

Comparison according to asthma type and subtype

The participant characteristics by asthma type (WRA group vs. NWRA group) are shown in **Table 1** (all patients) and **Table 2** (1:2 age and sex matching). In all patient analysis (**Table 1**), there was no significant difference in demographic characteristics between the 2 groups except for age, with the WRA group younger than the NWRA group (mean ± standard deviation [SD]: 44.97 ± 13.40 years vs. 57.36 ± 15.71 years, $P < 0.001$). With respect to pulmonary function parameters, although the WRA group showed better overall results than the NWRA group, there were no significant differences in % of predicted values of FEV1 and forced vital capacity (FVC): FEV1 (L, mean ± SD: 2.38 ± 0.82 vs. 2.89 ± 0.81, $P = 0.001$; % of predicted value, mean ± SD: 83.73 ± 15.88 vs. 88.03 ± 11.23, $P = 0.124$), FVC (L, mean ± SD: 3.35± 0.95 vs. 3.83 ± 0.95, $P = 0.006$; % of predicted value, mean ± SD: 91.61 ±12.38 vs. 95.25 ± 11.11, $P = 0.104$), FEV1/FVC (mean ± SD: 0.71 ± 0.12 vs. 0.76 ± 0.11, $P = 0.022$), and FEF25%–75% (L/sec, mean ± SD: 1.86 ± 1.21 vs. 2.62 ± 1.46, $P = 0.001$; % of predicted value, mean ± SD: 65.19 ± 32.98 vs. 77.17 ± 31.97, $P = 0.047$). For the laboratory test parameters, the sputum neutrophil count was lower in the WRA group than in the NWRA group (% over 61: 5 [15.6%] vs. 54 [34.8%], $P = 0.037$). Other laboratory test parameters such as blood eosinophil, sputum eosinophil, and total immunoglobulin E showed no significant differences. In the matching analysis with WRA and matched NWRA (mNWRA), the differences observed in **Table 1** were all lost (**Table 2**).

In the comparison according to WRA subtype (OA subgroup vs. WEA subgroup), only atopy was significantly different, showing a higher prevalence in the WEA subgroup (81.3% vs. 29.4%, $P = 0.005$). There were no significant differences between the 2 groups for the other demographic factors, pulmonary function parameters, or the laboratory test parameters (**Table 3**). Meanwhile, the compliance rate to the recommendation for job change was higher in the OA group than in the WEA group (20% vs. 5%).

Asthma severity in longitudinal analysis

The longitudinal analysis for asthma severity indices was performed by comparing between each 2 (sub) groups of asthma (i.e., WRA vs. NWRA/mNWRA; OA vs. WEA; OA vs. NWRA/mNWRA; WEA vs. NWRA/mNWRA). Compared to the NWRA group, the WRA group

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Table 1. Baseline characteristics according to the asthma group

Characteristics	WRA (n = 36)	NWRA (n = 181)	*P* value
Male sex	17 (47.2)	72 (39.8)	0.460
Age (yr)	44.97 ± 13.40	57.36 ± 15.71	< 0.001
Atopy	18 (54.5)	71 (56.8)	0.845
Rhinosinusitis	27 (75.0)	120 (67.0)	0.434
Asthma duration (yr)	7.27 ± 8.23	6.68 ± 9.37	0.726
Smoking status			0.344
Current	7 (19.4)	22 (12.2)	
Ex	6 (16.7)	47 (26.1)	
Never	23 (63.9)	111 (61.7)	
Pack years	17.63 ± 13.60	26.97 ± 24.54	0.188
Height (m)	1.63 ± 0.09	1.61 ± 0.09	0.084
Weight (kg)	66 ± 12	64 ± 11	0.396
BMI (kg/m^2)	24.59 ± 3.97	24.76 ± 3.49	0.796
FEV1 (L)	2.89 ± 0.81	2.38 ± 0.82	0.001
FEV1 (% of predicted value)	88.03 ± 11.23	83.73 ± 15.88	0.124
FVC (L)	3.83 ± 0.95	3.35 ± 0.95	0.006
FVC (% of predicted value)	95.25 ± 11.11	91.61 ± 12.38	0.104
FEV1/FVC	0.76 ± 0.11	0.71 ± 0.12	0.022
FEF25%–75% (L/sec)	2.62 ± 1.46	1.86 ± 1.21	0.001
FEF25%–75% (% of predicted value)	77.17 ± 31.97	65.19 ± 32.98	0.047
PC20 (mg/mL)	12.36 ± 5.32	6.03 ± 7.21	0.114
Eosinophil (%)	7.2 ± 6.2	5.5 ± 4.9	0.080
Eosinophil (count/μL)	501.70 ± 475.52	405.25 ± 501.48	0.296
Eosinophil ≥ 300/μL	18 (51.4)	76 (42.9)	0.457
Sputum eosinophil (%)	5 ± 7	5 ± 12	0.947
Sputum eosinophil ≥ 3%	13 (39.4)	52 (33.3)	0.548
Sputum neutrophil (%)	34 ± 27	45 ± 31	0.044
Sputum neutrophil % ≥ 61	5 (15.6)	54 (34.8)	0.037
Log_{10} total IgE (IU/mL)	2.25 ± 0.59	2.29 ± 0.67	0.778

Values are presented as number (%) or mean ± standard deviation.
NWRA, non-work-related asthma; WRA, work-related asthma; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25%–75%, forced expiratory flow 25%–75%; PC20, provocative concentration causing 20% fall in FEV1; IgE, immunoglobulin E.

showed a higher frequency of outpatient visits (mean ± SD: 8.35 ± 4.41 vs. 7.08 ± 2.96, *P* = 0.033) and systemic corticosteroid prescriptions (mean ± SD: 2.84 ± 2.33 vs. 1.79 ± 2.07, *P* = 0.007) in the past year. Furthermore, they also showed a lower trend in mean ACT score (mean ± SD: 21.17 ± 2.47 vs. 22.06 ± 2.84, *P* = 0.082), and tended to have more severe asthma (7 [19.4%] vs. 28 [15.5%]). In the matching analysis (WRA vs. mNWRA), the statistical difference of the frequency of outpatient visits was lost (**Table 4**).

Compared to the OA subgroup, the WEA subgroup showed a higher frequency of outpatient visits (mean ± SD: 9.90 ± 3.94 vs. 6.80 ± 4.40, *P* = 0.033) and systemic corticosteroid prescriptions (mean ± SD: 3.63 ± 2.59 vs. 2.04 ± 1.76, *P* = 0.038) in the past year. They also had a lower trend in the mean ACT score (mean ± SD: 20.90 ± 2.49 vs. 21.44 ± 2.48, *P* = 0.522) in the past year. In addition, severe asthma tended to be more common in the WEA subgroup (5 [27.8%] vs. 2 [11.1%], *P* = 0.206) (**Table 5**).

Meanwhile, there was no significant difference between the OA subgroup and the NWRA/mNWRA group (**Table 6**). On the other hand, compared to the NWRA group, the WEA subgroup showed a higher frequency in outpatients visits (mean ± SD: 9.90 ± 3.94 vs. 7.08 ± 2.96, *P* < 0.001) and systemic corticosteroid prescriptions (mean ± SD: 3.64 ± 2.59 vs. 1.79 ± 2.07, *P* = 0.001) in the past year. They also had a lower trend in the mean ACT score (mean ± SD: 20.90 ± 2.49 vs. 22.06 ± 2.84, *P* = 0.098) in the past year. In addition, severe asthma

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Table 2. Baseline characteristics according to the asthma group after 1:2 matching (age/sex) to NWRA

Characteristics	WRA (n = 36)	mNWRA (n = 72)	*P* value
Male sex	17 (47.2)	34 (47.2)	1.000
Age (yr)	44.97 ± 13.40	45.04 ± 13.61	0.980
Atopy	18 (54.5)	39 (68.4)	0.188
Rhinosinusitis	27 (75.0)	56 (78.9)	0.650
Asthma duration (yr)	7.27 ± 8.23	5.01 ± 6.58	0.124
Smoking status			0.526
Current	7 (19.4)	15 (21.1)	
Ex	6 (16.7)	18 (25.4)	
Never	23 (63.9)	38 (53.5)	
Pack years	17.63 ± 13.60	17.67 ± 18.38	0.995
Height (m)	1.63 ± 0.09	1.64 ± 0.09	0.667
Weight (kg)	66 ± 12	67 ± 13	0.715
BMI (kg/m^2)	24.59 ± 3.97	24.65 ± 4.23	0.949
FEV1 (L)	2.89 ± 0.81	2.87 ± 0.88	0.890
FEV1 (% of predicted value)	88.03 ± 11.23	86.39 ± 16.78	0.598
FVC (L)	3.83 ± 0.95	3.81 ± 0.99	0.891
FVC (% of predicted value)	95.25 ± 11.11	94.21 ± 12.02	0.668
FEV1/FVC	0.76 ± 0.11	0.75 ± 0.11	0.620
FEF25%–75% (L/sec)	2.62 ± 1.46	2.56 ± 1.37	0.839
FEF25%–75% (% of predicted value)	77.17 ± 31.97	76.10 ± 34.84	0.878
PC20 (mg/mL)	12.36 ± 5.32	7.80 ± 8.94	0.370
Eosinophil (%)	7.2 ± 6.2	6.2 ± 4.8	0.374
Eosinophil (count/μL)	501.70 ± 475.52	468.07 ± 416.74	0.710
Eosinophil ≥ 300/μL	18 (51.4)	34 (47.9)	0.732
Sputum eosinophil (%)	5 ± 7	5 ± 11	0.798
Sputum eosinophil ≥ 3%	13 (39.4)	24 (35.8)	0.728
Sputum neutrophil (%)	34 ± 27	39 ± 30	0.430
Sputum neutrophil % ≥ 61	5 (15.6)	18 (27.3)	0.202
Log_{10} Total IgE (IU/mL)	2.25 ± 0.59	2.37 ± 0.64	0.391

Values are presented as number (%) or mean ± standard deviation.
NWRA, non-work-related asthma ; mNWRA, matched non-work-related asthma; WRA, work-related asthma; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25%–75%, forced expiratory flow 25%–75%; PC20, provocative concentration causing 20% fall in FEV1; IgE, immunoglobulin E.

was also more common in the WEA subgroup (5 [27.8%] vs. 28 [15.5%], $P = 0.181$). In the matching analysis (WEA vs. mNWRA), not only all the statistical differences above were maintained, but severe asthma was found to be statistically significantly more in the WEA subgroup (5 [27.8%] vs. 7 [9.7%], $P = 0.044$) (**Table 7**).

Causative agents or aggravating factors of WRA

The causative agents or aggravating factors of WRA are shown in **Table 8**. Common causes of OA were chemical substances (15%), exhaust gas/smoke (14%), isocyanates (12%), and cleaning agents (10%). Meanwhile, common causes of WEA included exhaust gas/smoke (20%), metals/metal working fluids (15%), and plant proteins (12%).

OA in detail

Table 9 shows the detailed characteristics of the OA patients. In total, 16 patients (89%) had a sensitizer-induced OA (SIOA); these patients had a median age of 51 years (range, 26–67 years) and were predominantly male (9/16, 56%). The occupation varied, but the most common was being a painter (5/16, 31%). The median latency period was 12.4 years (range, 0.3–31.2 years). Atopy was detected in only 3/16 (19%) patients. There were 6/16 (38%) of patients who had a smoking history. All SIOA patients had diurnal variation in PEFR (> 10%–20%), and most of which tended to be lost on rest. In total, 2 (12.5%) of SIOA patients had severe asthma, and only 2 (13%) patients changed jobs.

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Table 3. Baseline patient characteristics according to WRA subtype

Characteristics	OA subgroup (n = 18)	WEA subgroup (n = 18)	*P* value
Male sex	11 (61.1)	6 (33.3)	0.095
Age (yr)	47.78 ± 12.34	42.17 ± 14.16	0.214
Atopy	5 (29.4)	13 (81.3)	0.005
Rhinosinusitis	13 (72.2)	14 (77.8)	1.000
Asthma duration (yr)	5.73 ± 5.60	8.81 ± 10.15	0.267
Smoking status			0.635
Current	4 (22.2)	3 (16.7)	
Ex	4 (22.2)	2 (11.1)	
Never	10 (55.6)	13 (72.2)	
Pack years	16.78 ± 10.07	19.00 ± 19.33	0.788
Height (m)	1.61 ± 0.10	1.63 ± 0.08	0.743
Weight (kg)	66 ± 11	65 ± 12	0.708
BMI (kg/m^2)	24.67 ± 3.24	24.52 ± 4.69	0.913
FEV1 (L)	3.00 ± 0.99	2.78 ± 0.58	0.426
FEV1 (% of predicted value)	88.94 ± 11.27	87.11 ± 11.43	0.631
FVC (L)	3.91 ± 1.18	3.76 ± 0.67	0.644
FVC (% of predicted value)	93.39 ± 10.88	97.11 ± 11.33	0.322
FEV1/FVC	0.77 ± 0.09	0.75 ± 0.12	0.547
FEF25%–75% (L/sec)	2.82 ± 1.61	2.42 ± 1.32	0.425
FEF25%–75% (% of predicted value)	82.94 ± 32.56	71.39 ± 31.20	0.285
PC20 (mg/mL)	14.23 ± 4.64	6.75 ± 4.64	0.297
Eosinophil (%)	7.7 ± 7.6	6.7 ± 4.6	0.610
Eosinophil (count/μL)	554.55 ± 551.67	451.79 ± 400.47	0.531
Eosinophil (count/μL ≥ 300)	9 (52.9)	9 (50.0)	1.000
Sputum eosinophil (%)	6 ± 8	3 ± 6	0.288
Sputum eosinophil (% ≥ 3)	9 (50.0)	4 (26.7)	0.284
Sputum neutrophil (%)	40 ± 29	26 ± 23	0.164
Sputum neutrophil (% ≥ 61)	4 (22.2)	1 (7.1)	0.355
Log_{10}Total IgE (IU/mL)	2.30 ± 0.73	2.22 ± 0.49	0.726

Values are presented as number (%) or mean ± standard deviation.
WRA, work-related asthma; OA, occupational asthma; WEA, work-exacerbated asthma; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF25%–75%, forced expiratory flow 25%–75%; PC20, provocative concentration causing 20% fall in FEV1; IgE, immunoglobulin E.

Table 4. Asthma severity indices by longitudinal analysis of WRA vs. NWRA/mNWRA

Characteristics	WRA (n = 36)	NWRA (n = 181)	*P* value	mNWRA (n = 72)	*P* value
Frequency of outpatient visits per year	8.35 ± 4.41	7.08 ± 2.96	0.033	7.64 ± 3.69	0.376
Presence of emergency department visits	4 (11.1)	15 (8.3)	0.584	5 (6.9)	0.460
Presence of hospitalizations	4 (11.1)	12 (6.6)	0.347	3 (4.2)	0.167
Frequency of systemic corticosteroid prescriptions per year	2.84 ± 2.33	1.79 ± 2.07	0.007	1.65 ± 1.63	0.003
Mean FEV1, % of predicted value	86.60 ± 13.06	82.05 ± 15.37	0.099	84.14 ± 15.84	0.423
Mean ACT score	21.17 ± 2.47	22.06 ± 2.84	0.082	21.80 ± 3.53	0.337
Severe asthma	7 (19.4)	28 (15.5)	0.554	7 (9.7)	0.156

Values are presented as number (%) or mean ± standard deviation.
WRA, work-related asthma; NWRA, non-work-related asthma; mNWRA, matched non-work-related asthma; FEV1, forced expiratory volume in 1 second; ACT, asthma control test.

Table 5. Asthma severity indices by longitudinal analysis of OA vs. WEA

Characteristics	OA (n = 18)	WEA (n = 18)	*P* value
Frequency of outpatient visits per year	6.80 ± 4.40	9.90 ± 3.94	0.033
Presence of emergency department visits	2 (11.1)	2 (11.1)	1.000
Presence of hospitalizations	1 (5.6)	3 (16.7)	0.603
Frequency of systemic corticosteroid prescriptions per year	2.04 ± 1.76	3.63 ± 2.59	0.038
Mean FEV1, % of predicted value	85.61 ± 11.51	87.60 ± 14.72	0.655
Mean ACT score	21.44 ± 2.48	20.90 ± 2.49	0.522
Severe asthma	2 (11.1)	5 (27.8)	0.206

Values are presented as number (%) or mean ± standard deviation.
OA, occupational asthma; WEA, work-exacerbated asthma; FEV1, forced expiratory volume in 1 second; ACT, asthma control test.

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Table 6. Asthma severity indices by longitudinal analysis of OA vs. NWRA/mNWRA

Characteristics	OA (n = 18)	NWRA (n = 181)	*P* value	mNWRA (n = 72)	*P* value
Frequency of outpatient visits per year	6.80 ± 4.40	7.08 ± 2.96	0.719	7.64 ± 3.69	0.412
Presence of emergency department visits	2 (11.1)	15 (8.3)	0.683	5 (6.9)	0.555
Presence of hospitalizations	1 (5.6)	12 (6.6)	0.860	3 (4.2)	0.798
Frequency of systemic corticosteroid prescriptions per year	2.04 ± 1.76	1.79 ± 2.07	0.617	1.65 ± 1.63	0.374
Mean FEV1, % of predicted value	85.61 ± 11.51	82.05 ± 15.37	0.342	84.14 ± 15.84	0.713
Mean ACT score	21.44 ± 2.48	22.06 ± 2.84	0.373	21.80 ± 3.53	0.680
Severe asthma	2 (11.1)	28 (15.5)	0.622	7 (9.7)	0.861

Values are presented as number (%) or mean ± standard deviation.
OA, occupational asthma; NWRA, non-work-related asthma; mNWRA, matched non-work-related asthma; FEV1, forced expiratory volume in 1 second; ACT, asthma control test.

Table 7. Asthma severity indices by longitudinal analysis of WEA vs. NWRA/mNWRA

Characteristics	WEA (n = 18)	NWRA (n = 181)	*P* value	mNWRA (n = 72)	*P* value
Frequency of outpatient visits per year	9.90 ± 3.94	7.08 ± 2.96	< 0.001	7.64 ± 3.69	0.024
Presence of emergency department visits	2 (11.1)	15 (8.3)	0.683	5 (6.9)	0.555
Presence of hospitalizations	3 (16.7)	12 (6.6)	0.124	3 (4.2)	0.057
Frequency of systemic corticosteroid prescriptions per year	3.64 ± 2.59	1.79 ± 2.07	0.001	1.65 ± 1.63	< 0.001
Mean FEV1, % of predicted value	87.59 ± 14.72	82.05 ± 15.37	0.145	84.14 ± 15.84	0.404
Mean ACT score	20.90 ± 2.49	22.06 ± 2.84	0.098	21.80 ± 3.53	0.310
Severe asthma	5 (27.8)	28 (15.5)	0.181	7 (9.7)	0.044

Values are presented as number (%) or mean ± standard deviation.
WEA, work-exacerbated asthma; NWRA, non-work-related asthma; mNWRA, matched non-work-related asthma; FEV1, forced expiratory volume in 1 second; ACT, asthma control test.

Table 8. Causative agents or aggravating factors of WRA

Characteristics	WRA	OA	WEA
Exhaust gas/smoke	16 (16.0)	8 (13.6)	8 (19.5)
Chemical substances	13 (13.0)	9 (15.3)	4 (9.8)
Metals/metal working fluids	11 (11.0)	5 (8.5)	6 (14.6)
Isocyanates	10 (10.0)	7 (11.9)	3 (7.3)
Cleaning agents	9 (9.0)	6 (10.2)	3 (7.3)
Cold air	9 (9.0)	6 (10.2)	3 (7.3)
Plant proteins	8 (8.0)	3 (5.1)	5 (12.2)
Dyes and bleaches	7 (7.0)	5 (8.5)	2 (4.9)
Glues	6 (6.0)	4 (6.8)	2 (4.9)
Synthetic fiber	5 (5.0)	4 (6.8)	1 (2.4)
Drugs	3 (3.0)	1 (1.7)	2 (4.9)
Animal proteins	3 (3.0)	1 (1.7)	2 (4.9)

Values are presented as number (%).
WRA, work-related asthma; OA, occupational asthma; WEA, work-exacerbated asthma.

There were 2 (11%) IIOA (RADS) patients. All 2 patients were male and were aged 37 and 33 years. One had asthma symptoms within days of exposure to a high concentration of iron powder and spilled paint. The other did not remember the material to which he was exposed to. Both patients had atopy and were current smokers. They had diurnal variation on PEFR (> 10%–20%), and it was not lost when resting. However, the asthma itself was not severe. Both participants were painters, but only 1 changed job.

DISCUSSION

The prevalence of WRA (17%) was similar to those of previous indirect studies.[1,2,29] However, the WEA proportion among WRA (one half) was higher than those of some previous studies.[9,41] Before conducting a detailed work-relatedness survey, the attending physicians did not find 67% of WRA. They only recognized 22% of WEA and 44% of OA. This means that

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Table 9. Characteristics of all OA patients

Patient No.	OA type	Age	Sex	Type of occupation	Presumed sensitizer or irritant based on causal agents survey	Latency period (yr)	Asthma duration (yr)	Atopy	Smoking history	Serial PEFR	Severe asthma	Job change
1	SIOA	55	Female	Cook	Plant protein	10.5	3.8	No	Never	Diurnal variation: > 20% when working, decreased with resting	No	No
2	SIOA	66	Male	Painter	Isocyanate, dye (colorant), cleaning agent	18.9	14.9	No	Never	Diurnal variation: > 10% when working, lost with resting	No	No
3	SIOA	39	Male	Painter	Dye (colorant), isocyanate	15.2	2.6	No	Current, 30-pack-years	Diurnal variation: > 20% when working, decreased with resting	No	Yes
4	SIOA	53	Male	Machine operator	Exhaust gas/smoke	27.9	1.2	No	Current, 25-pack-years	Diurnal variation: > 20% when working, decreased with resting	No	No
5	SIOA	37	Female	Electronics factory worker	Chemical substance, cleaning agent	4.0	20.1	Yes	Never smoker	Diurnal variation: > 20% persisted	No	No
6	SIOA	40	Male	Machine operator	Chemical substance, cleaning agent, exhaust gas/smoke	3.8	0.8	No	Ex, 15-pack-years	Diurnal variation: > 10% when working, lost with resting	No	No
7	SIOA	65	Female	Factory worker	Metal/metal working fluid, isocyanate	31.2	5.1	No	Never	Diurnal variation: > 20% when working, decreased with resting	No	No
8	SIOA	61	Female	Knitting business	Synthetic fiber	14.3	1.3	No	Never	Diurnal variation: > 20% persisted	No	No
9	SIOA	49	Female	Bedding business	Synthetic fiber, dye (colorant)	10.3	8.5	Yes	Never	Diurnal variation: > 20% when working, decreased with resting	No	No
10	SIOA	26	Male	Painter	Isocyanate, dye (colorant), exhaust gas/smoke	5.2	0.6	No	Never	Diurnal variation: > 20% persisted	Yes	Yes
11	SIOA	55	Male	Heavy industry worker	Metal/metal working fluid	21.9	10.9	No	Ex, 30-pack-years	Diurnal variation: > 10% persisted	Yes	No
12	SIOA	54	Female	Construction worker	Chemical substance, glue	2.1	5.8	No	Never	Diurnal variation: > 20% when working, decreased with resting	No	No
13	SIOA	45	Female	Chemical fertilizer factory worker	Chemical substance, synthetic fiber, animal protein	0.3	3.0	No	Never	Diurnal variation: > 20% persisted	No	No
14	SIOA	42	Male	Auto parts worker	Chemical substance, cleaning agent, exhaust gas/smoke	15.8	5.3	No	Ex, 12-pack-years	Diurnal variation: > 20% when working, decreased with resting	No	No
15	SIOA	36	Male	Painter	Isocyanate, dye (colorant), exhaust gas/smoke	2.5	0.8	Yes	Never	Diurnal variation: > 20% when working, decreased with resting	No	No
16	SIOA	67	Male	Painter	Isocyanate, dye (colorant), exhaust gas/smoke	19.3	12.5	No	Ex, 10-pack-years	Diurnal variation: > 20% when working, decreased with resting	No	No
17	IIOA (RADS)	37	Male	Painter	Dye (colorant), cleaning agent	Less than 7 days after exposure to high concentrations of iron powder and spilled paint	2.2	Yes	Current, 5-pack-years	Diurnal variation: > 10% persisted	No	Yes
18	IIOA (RADS)	33	Male	Painter	Isocyanate, dye (colorant), exhaust gas/smoke	Less than 7 days after exposure to unrememberable high concentration substance	4.7	Yes	Current, 8-pack-years	Diurnal variation: > 10% persisted	No	No

OA, occupational asthma; SIOA, sensitizer-induced occupational asthma; IIOA, irritant-induced occupational asthma; RADS, reactive airway dysfunction syndrome.

routine work-relatedness surveys are very important, especially in WEA. Compared to NWRA or OA patients, WEA patients showed more outpatient visits, and more oral corticosteroid prescriptions. They also had a lower trend in mean ACT score, and their asthma tended to be more severe. A possible reason for this seriousness of WEA is assumed to be ongoing workplace exposure. Nevertheless, job change was seldom performed in WEA.

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From the previous studies, the prevalence of WRA is assumed about 10% to 30% of all asthma cases.[1,2,7,26,29,30] Of the 2 subtypes of WRA (*i.e.*, OA and WRA), WEA is known to be less (10%–20% of WRA) than OA,[9-11] but recently a high WEA rate have been reported.[12,13] It is also known that in terms of symptoms, exacerbation and cost of treatment, WRA is worse than NWRA, while WEA has similar severity as OA.[8,10,15,16] However, these data are primarily based on indirect or retrospective investigations rather than real prospective clinical asthma cohorts. Also, most of the studies were OA-centric, there were only a few details about WEA. For this reason, the ATS insisted on the need for research on WEA.[17] Using longitudinal analysis for 1 year with a prospective asthma cohort for the most industrialized city in Korea (Ulsan), we attempted to reveal the exact prevalence and detailed characteristics of WRA, especially WEA.

In the present study, immediately after being registered as an asthmatic, a work-relatedness survey was conducted on individual patients. The WRA prevalence (17% of all asthma cases) was similar to those of previous studies.[1,2] However, the prevalence of WEA (50% of WRA) was higher than those of the previous studies (10%–20% of WRA).[9-11] We assume that previous studies underestimated the true extent of WEA, since the case searching methods were indirect (surveillance program, insurance claims data or telephone surveys). Although the total number of patients is not large, our prevalence is believed to be reliable because it was investigated in a direct and detailed manner. Furthermore, there are recent studies showing that the prevalence of WEA is similar to or higher than ours.[12,13]

In our study, the attending physicians recognized only 22% of WEA and 44% of OA before the work-relatedness survey. In particular, they did not pay much attention to whether pre-existing asthma was getting worse at work (*i.e.*, WEA). This means that a routine work-relatedness survey is very important, especially in WEA. The guidelines recommend physicians to take a history to screen for WRA (OA and WEA).[1,20] Also, there is evidence advocating routine screening of work-relatedness in patients with asthma.[31-33] However, it is actually not being followed well. Through our study, we were able to realize how important a work-relatedness survey is to asthmatic patients.

In fact, not many studies have studied the clinical features of WEA. In most, the severity of WEA was described as similar to OA, and both were more severe than NWRA.[8,10,15,16] However, there is a recently conducted well-designed WRA cohort study consistent with our study.[14] That is a 2-year prospective cohort study of 53 subjects with WEA, 68 with OA, and found that, compared to OA, WEA patients were associated with more outpatient visits, more ICS prescriptions, noneosinophilic induced sputum, and trends of poorer symptom scores, lower FEV1 and more smokers. In other words, WEA had a tendency to be more severe than OA. These findings coincide with most results of our research. In another recent study, the psychological statuses of WEA and OA were investigated, and WEA patients tended to have more anxiety and depression than OA patients.[34]

In the prospective longitudinal analysis, the present study showed that compared to NWRA or OA, WEA patients significantly associated with more outpatient visits and oral corticosteroid prescriptions. In addition, their ACT score tended to be lower, and their asthma tended to be more severe. We assume that this severity of WEA is due to continuous workplace exposure. In our study, only 5% of WEA patients were identified to have changed their job, whereas 20% of OA patients were so. We think that WEA patients had a persistent workplace exposure, so their asthma seemed to have caused symptoms more often and

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severely. A previous study also showed that WEA patients were less likely to change their jobs than OA patients.[14] Other possible reasons for the severity of WEA are susceptibility to workplace triggers and airway inflammation. WEA patients more frequently had atopy than OA or NWRA patients in our study (81.3% vs. 29.4% [OA]/68.4% [NWRA]). This suggests that WEA could be more susceptible to workplace triggers. In addition, the present study showed that WRA patients had slight non-significant elevations in sputum and blood eosinophils than NWRA patients (although there was no such difference in WEA vs. OA patients). This might suggest that WRA (WEA and OA) could have airway inflammation more frequently than NWRA, which may result in severe asthma.

The reason for low job change is, first of all, physicians' ignorance of WEA. Since 2013, Korean industrial accident compensation regulations have included WEA in addition to OA, but many physicians who treat asthma do not know about it.[35] In fact, in Korea, social security for occupational diseases was very late compared to other countries. Even workers' compensation for OA was first recognized in 1989.[36] In Korea, workers' compensation for WEA has not been recognized, but it should be noted that, recently in Canada, workers' compensation for WEA is more than OA.[12,27] Secondly, even if workers' compensation is possible as experts' WRA diagnosis, workers often abandon claims due to the fear of job loss and reduced income.[26,37] This tendency is particularly high in self-employed persons and the disadvantaged, such as temporary workers.[37] In order to resolve this issue, a social environment should be created in which workers' health is considered first, and active social security of the nation is needed.

Regarding causal agents or aggravating factors of WRA, WEA and OA were different. In OA, cleaning agents were the fourth most common cause besides well-known OA-inducing substances (chemical substances, exhaust gas/smoke, isocyanates). In fact, cleaning agents are emerging as a new cause of OA.[27] In WEA, exhaust gas/smoke, metal/metal-working fluid and plant proteins, which are likely non-specific triggers for asthma, are the main causes.

Our study not only focused on the analysis of WEA, but also examined OA in detail. Among 18 OA patients, 16 (89%) had a SIOA. The main job was a painter, which seems to be related to Ulsan's heavy industry (large shipyards, automobile factories). Latency period was median 12.4 years (minimum–maximum, 0.3–31.2). IIOA (RADS) accounted for 11% (2 patients) of total OA, similar prevalence with those of previous studies.[9,38] One person remembered high-concentration exposed substances, but the other did not. Interestingly, diurnal PEFR variations were less than SIOA. This might be because the BHR for non-high concentration materials in workplace exposure is lower than SIOA.

The present study has 2 limitations. One is that, although WRA was classified according to the NIOSH guideline, neither specific inhalation challenge nor serial non-specific inhalation challenge was implemented. Therefore, our OA patients are considered probable or possible cases.[37,39,40] The other is that in the review of causal agents, Material Safety Data Sheets (MSDS) were not universally utilized, relying mainly on patient statements. In fact, workers in Korea are often afraid of job loss because demanding MSDS causes conflict with employers. These limitations should be taken into account when interpreting our results.

In conclusion, we conducted a longitudinal analysis, using a prospective clinical asthma cohort in the most industrialized city (Ulsan) in Korea, to explore the prevalence and characteristics of WRA (particularly on WEA). The overall prevalence of WRA (17%) was

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similar to that of previous studies, but the share of WEA was high (50% of WRA). WEA was more severe than OA or NWRA, but physicians' diagnosis efforts and workers' occupational changes were insufficient. Physicians' attention to a diagnosis of WEA as well as social environment considering workers' health are further needed in Korea.

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