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
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.\(^1,4,8\) 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).\(^7,8\) 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.\(^14\)

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.
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.1,14-26 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
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.

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 \( \chi^2 \) 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.
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
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, \( P = 0.052 \)) 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 4. 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 ± 32.88 | 0.047       |
| PC20 (mg/mL)   | 12.36 ± 5.32 | 6.03 ± 7.21    | 0.034       |
| 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.
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 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)      | 0.302        |
| 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.
### 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 (28.9)            | 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/m²)                   | 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 ± 33.56  | 71.39 ± 31.20         | 0.285   |
| PC20 (mg/mL)                  | 14.23 ± 4.64        | 6.75 ± 4.64           | 0.297   |
| Eosinophil (%)                | 77.7 ± 7.6          | 6.7 ± 4.6             | 0.610   |
| Eosinophil (count/µL)         | 55.55 ± 55.67       | 451.79 ± 400.47       | 0.331   |
| 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   |
| Log₁₀ 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   |
| 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   |
| 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.
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. 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. However, the WEA proportion among WRA (one half) was higher than those of some previous studies. 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 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 ± 2.42 | 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 (n = 16) | OA (n = 9) | WEA (n = 7) |
|---------------------------------|-------------|------------|-------------|
| 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. 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. However, the WEA proportion among WRA (one half) was higher than those of some previous studies. 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% when working, decreased with resting | 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    | 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    | 33  | Male   | Painter            | Isocyanate, dye (colorant), exhaust gas/smoke               | Less than 7 days after exposure to unrememorable 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.
From the previous studies, the prevalence of WRA is assumed about 10% to 30% of all asthma cases. Of the 2 subtypes of WRA (i.e., OA and WRA), WEA is known to be less (10%–20% of WRA) than OA, but recently a high WEA rate have been reported. 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. 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. 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. However, the prevalence of WEA (50% of WRA) was higher than those of the previous studies (10%–20% of WRA). 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.

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). Also, there is evidence advocating routine screening of work-relatedness in patients with asthma. 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. However, there is a recently conducted well-designed WRA cohort study consistent with our study. 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.

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
severely. A previous study also showed that WEA patients were less likely to change their jobs than OA patients.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26,37} This tendency is particularly high in self-employed persons and the disadvantaged, such as temporary workers.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{35,39,40} 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
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.

ACKNOWLEDGMENTS

This research was supported by Ulsan University Hospital (Biomedical Research Center Promotion Fund, grant number UUH-2016-01), the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government (MST) (grant number 2019M3E5D3073365), and the Environmental Health Center funded by the Ministry of Environment, Republic of Korea.

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https://doi.org/10.4168/aair.2021.13.2.256