Original Article

Long-Term Outcome of Occupational Asthma From Irritants and Low-Molecular-Weight Sensitizers

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What is already known about this topic? The patients with irritant-induced asthma (IIA) show a poorer short-term asthma outcome than those with low-molecular-weight agent–induced (LMW-induced) occupational asthma (OA), but their long-term results are poorly known.

What does this article add to our knowledge? Six years after OA diagnosis, uncontrolled asthma was more common with IIA than with LMW-induced OA. Older age, a low fractional exhaled nitric oxide value, and uncontrolled asthma at baseline were associated with a worse outcome.

How does this study impact current management guidelines? The patients with IIA and LMW-induced OA should be closely monitored after the diagnosis of OA because half of them remain uncontrolled. Other factors than type 2 inflammation might contribute to their long-term asthma control.

BACKGROUND: The short-term asthma outcome of irritant-induced asthma (IIA) is poorer than that of low-molecular-weight (LMW) sensitizer–induced occupational asthma (OA).
OBJECTIVES: To evaluate the long-term asthma outcome of IIA and LMW-induced OA and to determine which baseline features are associated with a poor long-term outcome.
METHODS: This follow-up questionnaire study assessed 43 patients diagnosed with IIA and 43 patients with LMW-induced OA at the Finnish Institute of Occupational Health in 2004-2018. The baseline results were analyzed to detect features associated with uncontrolled asthma (Asthma Control Test [ACT] score of ≤19, or ≥2 exacerbations or ≥1 serious exacerbation within 1 year) at follow-up.
RESULTS: The median interval since OA diagnosis was 6.3 years (interquartile range [IQR]: 4.4-11.3 years). Uncontrolled asthma was more frequent with IIA than with LMW-induced OA (58% vs 40%, adjusted odds ratio [OR]: 3.60, 95% confidence interval [CI]: 1.20-10.81). Poor symptom control was the main factor for this difference (median [IQR] ACT score of 18 [15-22] vs 21 [18-23], $P = .036$, respectively). Among all participants, older age (OR: 1.08 per year, 95% CI: 1.02-1.15), a fractional exhaled nitric oxide (FeNO) value <20 ppb (OR: 5.08, 95% CI: 1.45-17.80), and uncontrolled asthma at baseline (OR: 3.94, 95% CI: 1.31-11.88) were associated with uncontrolled asthma at follow-up.
CONCLUSIONS: Long-term asthma control of IIA appears to be inferior to that of LMW-induced OA. Older age, a low FeNO value, and uncontrolled asthma at baseline might indicate a worse long-term outcome among those with IIA and LMW-induced OA. **(J Allergy Clin Immunol Pract 2023;■:■-■)**

Key words: *Asthma control; IIA; Irritant-induced asthma; Low-molecular-weight; Occupational asthma*

In occupational asthma (OA), occupational environment either causes a new-onset asthma or activates a previously quiescent asthma.[1,2] Both high-molecular-weight and low-molecular-weight (LMW) agents can cause sensitizer-induced OA via immunologic mechanisms, whereas irritant workplace exposures can generate irritant-induced asthma (IIA) via non-immunologic mechanisms.[2] IIA can be further classified into definite (ie, acute), probable (ie, subacute), and possible (ie, low-dose) IIA according to the type of exposure and level of evidence of causal relation to occupational environment.[3,4] The exact mechanisms of both LMW-induced OA and IIA are poorly understood.[2]

Many studies have demonstrated that work-related asthma is associated with poor symptom control.[5-7] Others have in turn shown that the level of asthma control affects the overall

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Abbreviations used
ACT- Asthma Control Test
BMI- Body mass index
CI- Confidence interval
FeNO- Fractional exhaled nitric oxide
FIOH- Finnish Institute of Occupational Health
GINA- Global Initiative for Asthma, 2021 report
ICS- Inhaled corticosteroids
IIA- Irritant-induced asthma
IQR- Interquartile range
LMW- Low-molecular-weight
NSBH- Nonspecific bronchial hyperresponsiveness
OA- Occupational asthma
OR- Odds ratios
SABA- Short-acting β-agonist
SIC- Specific inhalation challenge
WRA- Work-related asthma

prognosis; patients with uncontrolled asthma have had poorer health-related quality of life, used health care more intensively, and faced higher economic costs than those with controlled asthma.[8-12] A few studies have suggested that patients with irritant exposures might have poorer long-term results than those with sensitizer-induced OA.[13,14]

Recently, we detected that asthma exacerbations and the usage of daily short-acting β-agonist (SABA) and Global Initiative for Asthma (GINA) treatment step 4-5 asthma medication were more frequent among patients with IIA than those with LMW-induced OA 6 months after the OA diagnoses.[15] These groups resembled each other in respect of demographic characteristics and work history, and the causal agents in both were mostly chemical substances. Therefore, the first aim of the current follow-up study was to evaluate whether this difference in outcome persists. The second aim was to analyze which results at the time of the OA diagnosis were associated with uncontrolled asthma in the long term.

METHODS

Study design

This cohort study evaluated the long-term asthma outcome of patients who were diagnosed with IIA in 2004-2018 and LMW-induced OA in 2006-2018 at a tertiary outpatient clinic, the Finnish Institute of Occupational Health (FIOH). Previously, we carried out a systematic search to identify these patients.[15,16] A multidisciplinary panel of pulmonologists, occupational health physicians, and occupational toxicologists had confirmed their OA diagnosis. Our group of an occupational toxicologist, an occupational health physician, and 2 lung physicians (JL and IL) verified that all included participants met our criteria.

Diagnostic criteria for IIA were (1) exposure to high concentration of airborne irritant; (2) occurrence of asthma symptoms in a close temporal relationship to exposure; (3) asthma verification by reversible obstruction or nonspecific bronchial hyperresponsiveness (NSBH); (4) persistence of symptoms ≥3 months; (5) no evidence of active asthma in adulthood before exposure; and (6) no other pulmonary disorders that explain the symptoms. These criteria are in line with the European Academy of Allergy and Clinical Immunology (EAACI) position paper by Vandenplas et al.[3] The included patients had either acute or subacute IIA. All diagnoses of LMW-induced OA were verified by a specific inhalation challenge (SIC).

We had collected retrospective data of the participants' exposure events and asthma outcome during their 2 previous appointments at FIOH.[15,16] The OA diagnosis was confirmed at the first appointment, which was followed by the control appointment 6 months later. The results of these visits represent the baseline values of this study. In general, most of the identified patients had previously diagnosed asthma and used asthma medication before their evaluations at FIOH.

For the follow-up, we constructed a questionnaire that assessed the participants' current asthma outcome. A notification of a follow-up study was sent to the previously identified individuals.[15] A research nurse interviewed the participants between June and October 2020 by telephone. The respondents were also able to respond via either a postal or electronic questionnaire.

Definitions

Smoking history was divided into nonsmokers, current smokers, and ex-smokers. Current and ex-smokers had smoked ≥10 pack-years, and the latter had quit more than 6 months previously. Atopy was ≥1 positive reaction (wheal diameter ≥3 mm) in a skin prick test to common allergens (ALK-Abello, Horsholm, Denmark). The characteristics were measured by the following methods: serum total IgE by the Phadia UniCAp system (Phadia, Uppsala, Sweden); fractional exhaled nitric oxide (FeNO) by an online chemiluminescence analyzer (NIOX; Aerocrine AB, Solna, Sweden) in accordance with American Thoracic Society/European Respiratory Society recommendations;[17] a cutoff value of FeNO ≥20 ppb was recorded as a marker for possible refractory type 2 inflammation;[18] forced vital capacity and forced expiratory volume in first second by a standard flow-volume spirometer that used the predictive values of Viljanen et al;[19,20] and NSBH by the histamine or methacholine challenge test.[21,22]

We followed the GINA guidelines' definition of the subject's asthma control.[18] Symptom control was assessed by the Asthma Control Test (ACT), the scores of which range from 5 to 25; scores of ≤19 represent poor symptom control.[23,24] If the ACT score was missing, the symptom control was estimated from medical files. Asthma exacerbation was at least 3 days' intake of oral corticosteroids equivalent to ≥30 mg of prednisolone due to breathing difficulties. Uncontrolled asthma comprised poor symptom control, ≥2 asthma exacerbations within a year, or ≥1 serious exacerbation (hospital stay due to asthma) within a year. Difficult-to-treat asthma was uncontrolled asthma despite treatment by GINA step 4-5 asthma medication. Working history was self-reported by the participant.

We registered the change in the features of asthma control between baseline and follow-up. A change in ACT score of ≥3[25] and any change in GINA step of asthma medication[18] were regarded relevant. At baseline, features of asthma control were recorded at the control appointment 6 months after OA diagnosis because asthma medication was introduced or adjusted frequently at the time of the diagnosis.

Statistical analysis

We used SPSS version 28.0.0.0 for statistical analyses. We expressed categorical data as the number and percentage of patients. For the most part, the quantitative data did not follow normal distribution. These data were presented as median and interquartile ranges (IQR). We used Fisher's exact test with categorical data and the Mann-Whitney *U* test with quantitative data. The Wilcoxon signed-rank test and the sign test were used to analyze the change in ACT score and GINA treatment step, respectively.

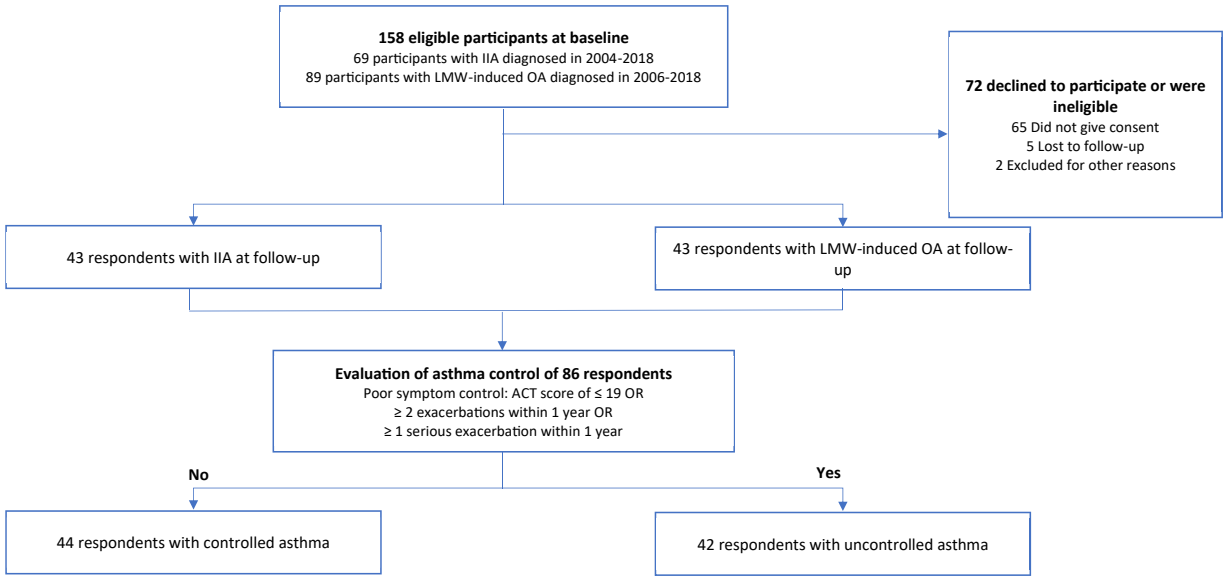

FIGURE 1. Study design and patient selection of the follow-up. *ACT*, Asthma Control Test; *Baseline*, evaluation at the Finnish Institute of Occupational Health at the time of OA diagnosis; *IIA*, irritant-induced asthma; *LMW*, low-molecular-weight; *OA*, occupational asthma.

TABLE I. Causal agents of irritant-induced asthma and low-molecular-weight agent–induced occupational asthma (OA)

Irritant	n = 43	Low-molecular-weight agent	n = 43
Acid aerosols or fumes	9	Isocyanates	19
Mixtures	8	Acrylates	5
Dusts	7	Metal working fluids	4
Base aerosols or fumes	5	Colophony	3
Endotoxins	4	Anhydrides	2
Other irritant chemicals	4	Aldehydes	2
Inorganic gases	3	Epoxy	1
Mixture of acid and base aerosols or fumes	2	Other low-molecular-weight agents	7
Oxidizing agents	1		

We combined the subgroups of IIA and LMW-induced OA to identify features associated with uncontrolled asthma. We performed logistic regression analyses on those variables that were associated with uncontrolled asthma at follow-up. The models were adjusted for sex, intervals in years since OA diagnosis, type of OA (IIA or LMW-induced OA), age, body mass index (BMI), and smoking history at baseline. FeNO values were also adjusted for inhaled corticosteroid (ICS) dosage (μg/day) at the time of the measurement. *P* values of $<.05$ and a 95% confidence interval (CI) with a lower limit of >1 were regarded as significant.

Ethics

The ethics committee of Helsinki University Central Hospital (approval number HUS/611/2020) approved this study. Written informed consent for publication was obtained from each participant. No medical interventions were performed at the FIOH.

RESULTS

Forty-three patients with IIA and 43 patients with LMW-induced OA gave their consent for a follow-up questionnaire (Figure 1). The total participation rate was 54%, and the median follow-up time was 6.3 years (IQR: 4.4-11.3 years). Seventy-two individuals declined to participate or were ineligible: 65 did not give their consent, 5 could not be reached, and 2 were excluded because of a lack of common language for communication. The characteristics of the respondents and nonrespondents were comparable, apart from the longer interval since OA diagnosis of the nonrespondents (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Table I portrays the causative agents of the respondents.

Comparison of IIA and LMW-induced OA

At baseline, the respondents with IIA and LMW-induced OA showed some distinctive features (Table II). Those with IIA had had respiratory symptoms for a shorter time than those with LMW-induced OA (median of 15 vs 31 months). They had uncontrolled asthma (56% vs 30%), daily SABA usage (27% vs 5%), and low ACT scores (median of 18 vs 22.5) more frequently than their counterparts. FeNO levels were also lower among those with IIA (median of 14 vs 23 ppb). The differences in other demographic and clinical characteristics were modest.

Table III presents the participants' results at the time of the follow-up questionnaire. Those with IIA had a shorter interval since OA diagnosis and were more frequently men, but these

TABLE II. Clinical characteristics and features of asthma control among participants with irritant-induced asthma and low-molecular-weight agent–induced occupational asthma at the time of the clinical evaluation at the Finnish Institute of Occupational Health

Characteristics	Irritant-induced asthma (n = 43)*	Low-molecular-weight agent–induced OA (n = 43)*	*P* value
Duration of symptoms before OA diagnosis, median (IQR)	15 (9-39)	31 (19-49.5)	**.004**
Men, n (%)	37 (86)	29 (67)	.072
Age, median (IQR)	47 (40-55)	46 (39-56)	.897
Body mass index (kg/m^2), median (IQR)	27.8 (24.7-31.5)	27.7 (24.2-30.5)	.822
Smoking history, n (%)			.101
Nonsmoker	25 (58)	16 (37)	
Current	8 (19)	8 (19)	
Ex-smoker	10 (23)	19 (44)	
Atopy, n (%)	12 (28)	18 (42)	.258
S-IgE (kU/L) (n = 76), median (IQR)	46 (19-118)	62 (28-309)	.134
B-Eos (μg/L) (n = 83), median (IQR)	144 (90-260)	170 (120-280)	.264
FeNO (n = 78), median (IQR)	14 (7-24)	23 (12-47)	**.004**
FEV_1% <80%, n (%)	16 (37)	11 (26)	.353
FEV_1/FVC <0.7, n (%)	8 (19)	5 (12)	.549
Nonspecific bronchial hyperreactivity (n = 77), n (%)	20 (53)	19 (49)	.821
Uncontrolled asthma, n (%)	24 (56)	13 (30)	**.029**
Short-acting β-agonist daily (n = 79), n (%)	10 (27)	2 (5)	**.010**
Asthma Control Test (n = 51),† median (IQR)	18 (12-20)	22.5 (17-25)	**<.001**
Exacerbation without exposure to the causal agent, n (%)	8 (19)	4 (9)	.351
ICS daily dose (μg/d), median (IQR)	800 (400-1250)	800 (500-1100)	.520
GINA treatment step 4-5, n (%)	25 (58)	25 (58)	1.000
Difficult-to-treat asthma, n (%)	16 (37)	10 (23)	.240

Numerical values expressed as median and interquartile range (IQR), categorical values as n (% of participants involved).
Bold indicates statistical significance ($P < .05$).
B-Eos, Blood eosinophilia; *FeNO*, fractional exhaled nitric oxide; *FEV_1 and FEV_1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma, follows 2021 report; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *OA*, occupational asthma; *S-IgE*, serum total concentration of IgE.
*Unless otherwise specified, the number of participants was 86.
†Twenty-three respondents with IIA and 28 with LMW-induced OA completed Asthma Control Test questionnaire at the evaluation at the Finnish Institute of Occupational Health.

TABLE III. Demographic characteristics and features of asthma control among participants with irritant-induced asthma and LMW-induced occupational asthma in the follow-up questionnaire

Characteristics at follow-up	Irritant-induced asthma (n = 43)	Low-molecular-weight agent–induced OA (n = 43)	*P* value
Interval since OA diagnosis (y), median (IQR)	5.7 (2.8-10.2)	7.6 (4.8-12.1)	.099
Age, median (IQR)	56 (47-60)	56 (45-65)	.520
Body mass index (kg/m^2), median (IQR)	28.1 (26-31.2)	28.1 (24.1-31.8)	.684
Smoking history, n (%)			.248
Nonsmoker	24 (56)	16 (37)	
Current	4 (9)	5 (12)	
Ex-smoker	15 (35)	22 (51)	
≥2 comorbidities, n (%)	15 (35)	11 (26)	.482
Uncontrolled asthma, n (%)	25 (58)	17 (40)	.131
Short-acting β-agonist daily, n (%)	13 (30)	11 (26)	.810
ACT score, median (IQR)	18 (15-22)	21 (18-23)	**.036**
Exacerbation within 1 y, n (%)	6 (14)	10 (23)	.407
Hospital stay due to asthma within 1 y, n (%)	1 (2)	0	1.000
Hospital stay due to asthma ever, n (%)	4 (9)	3 (7)	1.000
ICS daily dose (μg/d), median (IQR)	800 (400-1200)	800 (400-1000)	.770
GINA treatment step 4-5, n (%)	27 (63)	24 (56)	.661
Difficult-to-treat asthma, n (%)	20 (47)	12 (28)	.118
Changed workplace or occupation after the onset of asthma, n (%)	20 (47)	20 (47)	1.000

Numerical values expressed as median and interquartile range (IQR), categorical values as n (% of participants involved).
Bold indicates statistical significance ($P < .05$).
ACT, Asthma Control Test; *GINA*, Global Initiative for Asthma, follows 2021 report; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *OA*, occupational asthma.

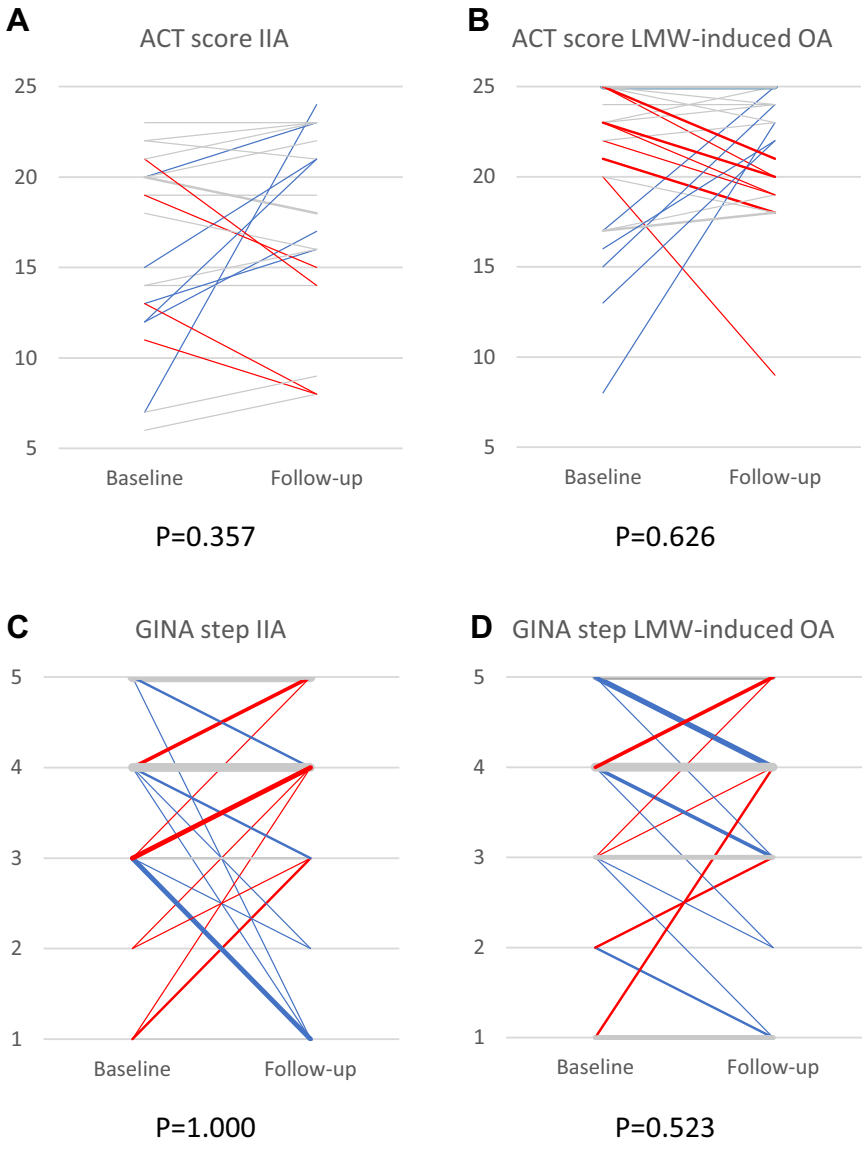

FIGURE 2. Alterations of the Asthma Control Test (ACT) score and asthma medication between Finnish Institute of Occupational Health (FIOH) evaluation and follow-up questionnaire. Red signifies deterioration, blue improvement, and gray unchanged features. The thickness of the line corresponds to the number of participants. A change of ≥3 points in the ACT score was considered relevant.[25] (**A**) The ACT score of the participants with irritant-induced asthma (IIA) at baseline FIOH evaluation and in the follow-up questionnaire. Number of participants n = 23, of whom 26% improved and 17% deteriorated. (**B**) The ACT score of participants with low-molecular-weight (LMW)—induced occupational asthma (OA) at baseline FIOH evaluation and in the follow-up questionnaire. Number of participants n = 28, of whom 18% improved and 36% deteriorated. (**C**) Global Initiative for Asthma (GINA) treatment step classification[18] of participants with IIA at baseline FIOH evaluation and in the follow-up questionnaire. Number of subject participants n = 43, of whom 28% improved and 30% deteriorated. (**D**) GINA treatment step classification[18] of participants with LMW-induced OA at baseline FIOH evaluation and in the follow-up questionnaire. Number of participants n = 43, of whom 30% improved and 21% deteriorated.

differences were statistically insignificant. Although age was comparable between IIA and LMW-induced OA, the age profile diverged as 26% (11 of 43) of the participants in the latter group were ≥65 years (vs 5% [2 of 43] in the former). BMI, smoking history, and number of comorbid conditions were equal.

Fifty-eight percent of the respondents with IIA and 40% of those with LMW-induced OA had uncontrolled asthma (P = .131) (Table III). Poor ACT score was the main factor contributing this outcome; 24 (56%) of those with IIA had an ACT score of ≤19 and 11 (26%) had a score of ≤15 compared with that of 17 (40%) and 5 (12%) of those with LMW-induced OA. In both groups, 3 participants (7%) had had ≥2 exacerbations and only 1 participant with IIA had had a hospital stay due to asthma within the last 12 months. Treatment intensity and daily usage of SABA were comparable between the groups. Forty-seven percent of those with IIA and 28% of those with

TABLE IV. Association of uncontrolled asthma at follow-up and demographic and clinical features at the time of the clinical evaluations at the Finnish Institute of Occupational Health

Characteristics	Controlled asthma at follow-up (n = 44)*	Uncontrolled asthma at follow-up (n = 42)*	*P* value
Interval since OA diagnosis (y), median (IQR)	5.8 (3.2-10.1)	8.3 (4.7-12.1)	.080
Age, median (IQR)	44 (33.5-54.5)	49.5 (42-56)	**.0497**
Body mass index (kg/m^2), median (IQR)	27.0 (24.3-29.7)	28.7 (25.2-32.3)	.142
Smoking history, n (%)			.490
Nonsmoker	23 (52)	18 (43)	
Current	6 (14)	10 (24)	
Ex-smoker	15 (34)	14 (33)	
Atopy, n (%)	15 (34)	15 (36)	1.000
S-IgE (kU/L) (n = 76), median (IQR)	48 (27-144)	56 (29-199.5)	.666
B-Eos (μg/L) (n = 83), median (IQR)	140 (90-250)	165 (95-320)	.331
FeNO (ppb) (n = 78), median (IQR)	23.5 (13.6-30)	12 (7.2-17)	**.003**
ICS daily dose (μg), median (IQR)	800 (0-800)	800 (400-1600)	.082
FEV_1% <80, n (%)	13 (30)	14 (33)	.817
FEV_1/FVC <0.70, n (%)	8 (18)	5 (12)	.550
Nonspecific bronchial hyperreactivity (n = 77), n (%)	20 (50)	19 (51)	1.000
Uncontrolled asthma, n (%)	11 (25)	26 (62)	**.009**
Short-acting β-agonist daily (n = 79), n (%)	5 (12)	7 (19)	.532
ACT score (n = 51),† median (IQR)	23 (18.5-25)	17.5 (13.5-20)	**.001**
Exacerbation within 1 y without exposure to the causal agent, n (%)	4 (9)	8 (19)	.223
ICS daily dose (μg/d), median (IQR)	800 (400-1000)	800 (600-1600)	**.095**
GINA treatment step 4-5, n (%)	21 (48)	29 (69)	.052
Difficult-to-treat asthma, n (%)	7 (16)	19 (45)	**.005**

Numerical values expressed as median and interquartile range (IQR), categorical values as n (% of subjects involved).
Bold indicates statistical significance ($P < .05$).
ACT, Asthma Control Test; *B-Eos*, blood eosinophilia; *FeNO*, fractional exhaled nitric oxide; *FEV_1 and FEV_1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma, follows 2021 report; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *OA*, occupational asthma; *S-IgE*, serum total concentration of IgE.
*Unless otherwise specified, the number of subjects was 86, 44 of whom had controlled asthma and 42 uncontrolled asthma.
†Twenty-seven subjects with controlled asthma and 24 with uncontrolled asthma completed the ACT questionnaire at baseline.

LMW-induced OA had a difficult-to-treat asthma ($P = .118$). In both groups, 20 (47%) participants had changed their workplace or occupation after the onset of asthma. The current exposure to the causal agent at work was rare; this could not be ruled out with 5 respondents, and only 1 of them had uncontrolled asthma.

Overall, respondents with IIA showed inferior asthma control compared with those with LMW-induced OA both at baseline and at follow-up, apart from the exacerbations at the latter time point. The poor outcome was associated with the age of ≥65 at follow-up among those with LMW-induced OA, whereas this feature was absent among those with IIA. Figure 2 illustrates how the ACT score and the GINA treatment step changed, but these changes did not show any clear pattern and were modest. Interestingly, 79% (19 of 24) of those participants with IIA and 54% (7 of 13) of those with LMW-induced OA who had uncontrolled asthma at baseline retained this status. We observed similar figures with difficult-to-treat asthma (75% vs 30%, respectively).

Characteristics associated with uncontrolled asthma

Among all participants, 42 had uncontrolled asthma and 44 had controlled asthma at follow-up. Older age, a low FeNO value, uncontrolled asthma, a low ACT score, and difficult-to-treat asthma at baseline were associated with uncontrolled asthma at follow-up (Table IV). Interestingly, 78% of the participants who had an FeNO value of <20 ppb had uncontrolled asthma, in contrast to 40% with controlled asthma ($P = .001$). Similarly, 63% of those who had an ACT score of <20 had uncontrolled asthma compared with that of 26% with an ACT score of ≥20 ($P = .012$). Other inflammation markers, lung function parameters, and features of asthma control were insignificant.

All the baseline features that showed association with uncontrolled asthma at follow-up remained significant after the adjustments, apart from the ACT score of <20 (Table V). According to our data, a diagnosis of IIA (odds ratio [OR]: 3.60, 95% CI: 1.20-10.81), older age (OR: 1.08 per year, 95% CI: 1.02-1.15), an FeNO value of <20 ppb (OR: 5.08, 95% CI: 1.45-17.80), and uncontrolled asthma (OR: 3.94, 95% CI: 1.31-11.88) at baseline were associated with uncontrolled asthma at follow-up. In addition, the longer interval since OA diagnosis (OR: 1.28 per year, 95% CI: 1.04-1.34) contributed to the possibility of uncontrolled asthma. Table E2 (available in this article's Online Repository at www.jaci-inpractice.org) summarizes the current sociodemographic characteristics of the participants with uncontrolled asthma and controlled asthma.

DISCUSSION

Our study analyzed the asthma outcome of participants with an IIA and LMW-induced OA median of 6 years after their OA

TABLE V. Odds ratios (OR) for features at the clinical evaluations at the Finnish Institute of Occupational Health associated with uncontrolled asthma at follow-up

Characteristics	OR* (95% CI)
IIA : LMW-induced OA	3.60 (1.20-10.81)
Interval since OA diagnosis, per year	1.28 (1.04-1.34)
Age, per year at baseline	1.08 (1.02-1.15)
FeNO <20 ppb : FeNO ≥20 ppb at baseline	5.08 (1.45-17.80)
Uncontrolled asthma : controlled asthma at baseline	3.94 (1.31-11.88)
ACT score of ≤19 : ACT score of ≥20 at baseline	2.12 (0.43-10.57)
Difficult-to-treat asthma : others at baseline	3.53 (1.09-11.41)

ACT, Asthma Control Test; *CI*, confidence interval; *FeNO*, fractional exhaled nitric oxide; *IIA*, irritant-induced asthma; *LMW*, low-molecular-weight; *OA*, occupational asthma.

*Variables adjusted for age, body mass index (kg/m^2), and smoking history at the time of the OA diagnosis, interval since OA diagnosis (y), sex, and type of OA (IIA or LMW-induced OA). FeNO value adjusted for dosage of the inhaled corticosteroid at the time of the measurement.

diagnosis. At follow-up, poor asthma control was common in both groups, but those with IIA had more frequently uncontrolled asthma than those with LMW-induced OA (58% vs 40%, OR: 3.60, 95% CI: 1.20-10.81). After the baseline results, the symptom control (ie, ACT score) was inferior in the former group, whereas other long-term results appeared comparable, and three-fifths of all participants were receiving GINA step 4-5 treatment. In addition, we detected that older age, a low FeNO value, and uncontrolled asthma at the time of the OA diagnosis might indicate uncontrolled asthma in the long term. The poor asthma control appeared long lasting in particular with IIA as four-fifths of those who had uncontrolled asthma at baseline retained this status.

A few previous studies have evaluated the long-term outcome of IIA, and their results have been analogous to ours. In the most comprehensive study, Malo et al[26] showed that the participants with acute IIA remained symptomatic in the long term. Two-thirds of the participants of the studies of the World Trade Center rescue and recovery workers have poorly or very poorly controlled asthma ≥10 years after the catastrophe.[27,28] Mental health comorbidities have been more frequent among those workers with poor asthma control, which might contribute to their long-term outcome.[27-29] Similarly, papers isolating the long-term asthma control of the participants with LMW-induced OA are rare. However, an extensive epidemiological study by Le Moual et al[7] detected that uncontrolled asthma was associated with exposure to LMW agents.

In general, work-related asthma (WRA) has exhibited poor long-term asthma control. In a large cross-sectional study by Knoeller et al,[6] 36.5% of those ever-employed adults who had WRA had very poorly controlled asthma, and 39.5% of them had well-controlled asthma. For non-WRA, these figures were 21.5% and 51.4%, respectively. Moullec et al[30] noted that only a third of their participants with OA and work-exacerbated asthma had well-controlled asthma. In our study, 42% (18 of 43) of the participants with IIA and 60% (26 of 43) of those with LMW-induced OA were classified as having controlled asthma.

Recently, Lehtimäki et al[31] estimated that 15% of the asthmatics in Finland are on GINA treatment step 4-5 asthma medication and that 30% of these kinds of patients have had ≥1 exacerbation and 23% ≥2 exacerbations. They applied a prescription-based algorithm and national prescription register to get these figures. In our study, the figures were 63%, 19%, and 7% for the participants with IIA and 56%, 38%, and 13% for those with LMW-induced OA, respectively. A study by Tuomisto et al[32] reported that only a third of the participants had controlled asthma in their Finnish single-center 12-year follow-up study of new-onset adult-onset asthmatics. Thus, it appears that although our respondents used more extensive medication than other adult asthma patients, they did not have inferior asthma control. However, patient selection might contribute to individual studies, and these results are not directly comparable.

Turning to baseline results, our study identified a few features associated with uncontrolled asthma at follow-up. Age was one of these markers; older participants showed poorer asthma control at follow-up. Previous studies agree with this connection between age at baseline and a poor long-term outcome.[33] In contrast, many studies have detected that low function parameters indicate a poor outcome in the long term,[13,33-35] but these were irrelevant in our study.

Another baseline feature associated with uncontrolled asthma was a low FeNO value. Seventy-eight percent (33 of 42) of those with uncontrolled asthma at follow-up had had an FeNO value of <20 ppb compared with 40% of those with controlled asthma. FeNO is a biomarker of type 2 inflammation, and elevated levels have predicted a good ICS response.[36] In contrast, noneosinophilic asthma has shown a poorer response to ICS, and poor asthma control has been common among those patients.[37] Studies of OA have supported these findings. Those without type 2 inflammation biomarkers have shown poorer asthma control.[38,39] Similarly, sputum neutrophils have been associated with respiratory symptoms.[14,34] On the other hand, the connection of eosinophil count and lung function parameters has been less consistent.[38,40,41]

The final factor associated with uncontrolled asthma at follow-up was a poor asthma control at baseline. We are not aware of any other studies that have evaluated the continuity of different asthma control categories among participants with WRA. Tuomisto et al[32] reported an association with baseline and follow-up asthma control in their single-center study, but this connection became insignificant after adjustments.

Taken together, our study depicted that uncontrolled asthma was more common with IIA than with LMW-induced OA. The respondents with IIA were likely to retain poor asthma control. The main reason for this was their poor symptom control, which might be linked to the lower FeNO values at baseline. Our findings imply that those with IIA have an insufficient response to asthma medication. It might be that the treatment is less effective in IIA, but other comorbidities might also contribute to a poor asthma outcome,[42] and, for instance, inducible laryngeal obstruction has been associated with irritant exposures.[43,44] Nevertheless, clinicians should consider whether high-dose ICS is the optimal treatment for all these patients.

Strengths and limitations

To our knowledge, this is the largest follow-up study of IIA. Although IIA diagnoses rely on clinical history,[2,3] our participants were thoroughly evaluated as meeting the criteria. Furthermore, all the participants with LMW-induced OA were verified by SIC, which enhanced the reliability of their diagnoses. We also had extensive retrospective data for our analysis of features associated with uncontrolled asthma at follow-up.

Our study had some limitations. The sample size (n = 86) and the response rate (54%) were limited, but the latter figure corresponded the average of previous follow-up studies.[5,26,30,34,35,38-41] Another limitation was that the patient selection was slightly biased because our previous article noticed that those with IIA had more intensive treatment than those with LMW-induced OA,[15] whereas in this study, the baseline usage of asthma medication was equal. Otherwise, our analysis (Table E1, available in this article's Online Repository at www.jaci-inpractice.org) showed that the respondents' baseline features were comparable with those of the nonrespondents, and the selection bias rather underestimates the difference in asthma outcomes between these groups. An additional limitation was that we were unable to verify the asthma outcomes from medical records, and they were self-reported by the participants.

The most relevant background factor that diverged between IIA and LMW-induced OA was the interval since OA diagnosis. In particular with LMW-induced OA, those who were ≥65 years old tended to show poorer asthma control. Statistical adjustments restricted this defect, but we were unable to exclude several confounding factors that contribute to asthma control. Therefore, our results of features associated with uncontrolled asthma must be interpreted with caution. Finally, the current inflammation profile of our participants was unknown. Despite these deficiencies, we believe that our results might be helpful for clinicians because the long-term consequences of inhaled chemicals are poorly known.

CONCLUSIONS

Our study showed that both IIA and LMW-induced OA are associated with poor asthma control. Fifty-eight percent of the respondents in the former group and 40% of those in the latter group had uncontrolled asthma 6 years after the diagnosis of OA. Poor symptom control was the main factor in the majority of these cases, and this feature was more common among those with IIA. In contrast, our participants did not report a considerable number of asthma exacerbations, and asthma medication was comparable between these groups. A noteworthy observation was that those with IIA were likely to remain in poor asthma control.

Our findings suggest that IIA is more frequently associated with uncontrolled asthma than LMW-induced OA. Furthermore, older age, a low FeNO value, and uncontrolled asthma at the time of the OA diagnosis might indicate a poor long-term asthma control among those with IIA and LMW-induced OA. Other factors than type 2 inflammation might contribute to the asthma control of patients with chemical-induced OA. These patients should be monitored after OA diagnosis, and this applies in particular to the patients who present features associated with a poor long-term outcome.

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ONLINE REPOSITORY

TABLE E1. Demographic and clinical characteristics of participants (respondents vs nonrespondents) at the clinical evaluations at the Finnish Institute of Occupational Health

Characteristics	All respondents (N = 86)*	Nonrespondents (N = 72)*	*P* value
Interval since the OA diagnosis (y), median (IQR)	6.3 (4.4-11.3)	10.4 (5.9-12.7)	**.004**
Men, n (%)	66 (77)	52 (72)	.583
Age, median (IQR)	47 (39-55)	44 (35-52)	.053
Body mass index (kg/m^2), median (IQR)	27.8 (24.7-30.5)	27.1 (24.7-30.8)	.524
Smoking history, n (%)			1.000
Never	41 (48)	34 (47)	
Current	16 (19)	14 (19)	
Ex-smoker	29 (34)	24 (33)	
Atopy, n (%)	30 (35)	25 (49)	.104
S-IgE (kU/L) (n = 136), median (IQR)	53 (27-174)	55 (30-171)	.845
B-Eos (μg/L) (n = 151), median (IQR)	160 (90-260)	135 (80-235)	.382
FeNO (n = 138), median (IQR)	15 (9-29)	13 (8-21)	.283
FEV_1% <80% (n = 156), n (%)	27 (31)	15 (21)	.205
FEV_1/FVC <0.70 (n = 156), n (%)	13 (15)	11 (16)	1.000
Nonspecific bronchial hyperreactivity (n = 130), n (%)	39 (51)	34 (64)	.152
Short-acting β-agonist daily (n = 140), n (%)	12 (15)	12 (20)	.506
Asthma Control Test (n = 84),† median (IQR)	20 (15-23)	18 (16-23)	.569
Exacerbation within 1 y without exposure to the causal agent (n = 155), n (%)	12 (14)	11 (16)	.821
ICS daily dose, median (IQR)	800 (0-1000)	800 (400-1000)	.287
GINA treatment step 4-5 (n = 155), n (%)	50 (58)	39 (57)	.871

Numerical values expressed as median and interquartile range (IQR), categorical values as n (% of participants involved).
Bold indicates statistical significance ($P < .05$).
B-Eos, Blood eosinophilia; *FeNO*, fractional exhaled nitric oxide; *FEV_1 and FEV_1%*, forced expiratory volume and predicted forced expiratory volume in first second; *FVC*, forced vital capacity; *GINA*, Global Initiative for Asthma, follows 2021 report; *ICS*, inhaled corticosteroid; *IQR*, interquartile range; *OA*, occupational asthma; *S-IgE*, serum total concentration of IgE.
*Unless otherwise specified, the number of participants was 158, 86 of whom were respondents and 72 nonrespondents.
†Fifty-one respondents and 33 nonrespondents completed the ACT questionnaire at baseline.

TABLE E2. Characteristics of the subjects with controlled and uncontrolled asthma at the follow-up questionnaire

Characteristics at follow-up	Controlled asthma (N = 44)	Uncontrolled asthma (N = 42)	*P* value
Interval since OA diagnosis (y), median (IQR)	5.8 (3.2-10.1)	8.3 (4.7-12.1)	.080
Men, n (%)	34 (77)	32 (76)	1.000
Age, median (IQR)	52 (42.5-61)	58 (52-63)	**.014**
Body mass index (kg/m^2), median (IQR)	27.5 (24.4-29.9)	28.7 (27.1-32.6)	.121
Smoking history, n (%)			.716
Never	22 (50)	18 (43)	
Current	5 (11)	5 (12)	
Ex-smoker	17 (39)	19 (45)	
In a relationship, n (%)	36 (82)	30 (71)	.312
College degree, n (%)	9 (20)	4 (10)	.230
Excessive alcohol consumption,* n (%)	17 (39)	12 (29)	.367
≥2 other comorbidities, n (%)	18 (41)	20 (48)	.664
Depressive symptoms,† n (%)	14 (32)	18 (43)	.373
In the working life, n (%)	24 (55)	17 (40)	.204
Changed workplace or occupation after the onset of asthma, n (%)	24 (55)	16 (38)	.137
Ever had vocational rehabilitation, n (%)	21 (48)	22 (52)	.829

Numerical values expressed as median and interquartile range (IQR), categorical values as n (% of subjects involved).
Bold indicates statistical significance ($P < .05$).
*Unhealthy alcohol consumption was evaluated with the AUDIT-C screen test.[E1]
†Depressive symptoms were screened with Finnish modification of the 13-item Beck depression inventory. Total score ranges from 0 to 39; 0-4 represent no depressive symptoms, 5-7 mild symptoms, 8-15 moderate symptoms, and 16-39 severe symptoms.[E2,E3]

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