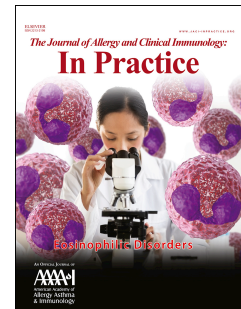


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Clinical characteristics of irritant-induced occupational asthma

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Title: Clinical characteristics of irritant-induced occupational asthma

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Abstract

Background: Work is a substantial contributing factor of adult-onset asthma. A subtype of occupational asthma (OA) is caused by irritant agents, but knowledge of the clinical outcomes of irritant-induced asthma (IIA) is incomplete.

Objectives: To evaluate whether the clinical picture of IIA differs from that of sensitizer-induced OA.

Methods: This retrospective study analyzed acute and subacute IIA patients diagnosed in an occupational medicine clinic during 2004-2018. Sixty-nine patients fulfilled the inclusion criteria, and their characteristics were analyzed at the time of the diagnosis and six months later. The results were compared to those of two subgroups of sensitizer-induced OA, 69 high-molecular-weight (HMW) and 89 low-molecular-weight (LMW) agent -induced OA patients.

Results: Six months after the diagnosis, 30% of the IIA patients needed daily short-acting beta agonists (SABA), 68% were treated with GINA step 4-5 medication, and 24% of the patients had asthma exacerbation after the first appointment. IIA depicted inferiority to LMW-induced OA in daily need for SABA (OR 3.80, 95% CI 1.38-10.46), treatment with GINA step 4-5 medication (OR 2.22, 95% CI 1.08-4.57) and exacerbation (OR 3.85, 95% CI 1.35-11.04). IIA showed poorer results than HMW-induced OA in the latter two of these features (OR 2.49, 95% CI 1.07-5.79 and OR 6.29, 95% CI 1.53-25.83 respectively).

Conclusions: Six months after the occupational asthma diagnosis, a significant proportion of the IIA patients remain symptomatic and the majority of these patients use asthma medications extensively suggesting uncontrolled asthma. The short-term outcomes of IIA appear poorer than that of sensitizer-induced OA.

45 **Highlight box**

46 **What is already known about this topic?**

47 A proportion of occupational asthma is induced by irritant agents, but the clinical picture of this asthma
48 type is poorly known.

49 **What does this article add to our knowledge?**

50 Irritant-induced asthma (IIA) patients use asthma medications extensively and have frequent asthma
51 exacerbations six months after occupational asthma diagnosis. Their short-term asthma outcomes
52 appear poorer to that of sensitizer-induced occupational asthma.

53 **How does this study impact current management guidelines?**

54 The IIA patients should be carefully monitored after the occupational asthma diagnosis, and the poor
55 asthma outcomes highlight the need for preventive actions.

56

57 **Key words:** asthma control, IIA, irritant-induced asthma, irritants, occupational asthma, prognosis

58 **Abbreviations:**

59 CI – confidence interval

60 FeNO - fractional exhaled nitric oxide

61 FEV1 and FEV1% - forced expiratory volume and predicted forced expiratory volume in first second

62 FIOH - Finnish Institute of Occupational Health

63 FVC and FVC% - forced vital capacity and predicted forced vital capacity

64 GINA - Global Initiative For Asthma, 2020 report

65 HMW – high-molecular-weight

66 ICS - inhaled corticosteroids

67 IIA - irritant-induced asthma

68 LMW - low-molecular-weight

69 NSBH - non-specific bronchial hyperreactivity

70 OA - occupational asthma

71 OR - odds ratios

72 SABA - short-acting beta agonists

INTRODUCTION

Occupational asthma (OA) is either a new-onset asthma or the activation of previously quiescent asthma, caused by the occupational environment.(1, 2) High-molecular-weight (HMW) and low-molecular-weight agents (LMW) can elicit sensitizer-induced OA via immunologic mechanisms, whereas irritant agents can provoke irritant-induced asthma (IIA) via non-immunologic mechanisms. The recent American Thoracic Society / European Respiratory Society (ATS/ERS) statement claims that occupational exposures contribute to 16 % of adult-onset asthma cases.(3) Whereas the clinical characteristics of sensitizer-induced OA are well known, IIA has been less intensively reported.(4-6) However, according to the most recent surveillance data, IIA represents 4-15% of work-related asthma, a figure which is most likely an underestimate. (7-9)

Studies of irritant workplace exposures,(10-12) the World Trade Center catastrophe,(13, 14) and several epidemiological studies(15-17) have demonstrated that IIA is more diverse than reactive airways dysfunction syndrome (RADS), which was first described by Brooks et al.(18) The EAACI position paper by Vandenplas et al. proposed that IIA can be classified into “definite” (i.e., acute), “probable” (i.e., subacute), and “possible” (i.e., low-dose) IIA, according to the level of evidence of the causal relationship between workplace exposures and the development of asthma.(6) The authors showed that the level of certainty of the individual cases having occupational origins was sufficient in the first two of these. While numerous irritant agents have been recognized as causal agents of IIA,(12, 19) only one study has examined its long-term outcomes.(20)

We recently published the results of a series of 69 patients with occupational IIA, including an extensive analysis of their exposure.(12) The first aim of the present study was to evaluate whether the clinical characteristics of these 69 IIA patients differed from those of sensitizer-induced OA individuals. Second, we evaluated the asthma control, asthma medication and lung function parameters of these 69 cases

- 96 with IIA in detail, concentrating on acute and subacute IIA and the differences among the separate
- 97 causative agent groups.

METHODS

Study design

This retrospective study evaluated patients who were diagnosed with IIA at the Finnish Institute of Occupational Health (FIOH) between the years 2004 and 2018. FIOH is a tertiary outpatient clinic that confirms most occupational asthma diagnoses in Finland (population of 5.5 million).

We executed a systematic search of the FIOH patient register to identify IIA patients. A multidisciplinary panel consisting of pulmonologists, occupational health physicians and occupational toxicologist had set the initial diagnosis. After the preliminary search results, our group confirmed these diagnoses; an occupational toxicologist (KS) and an occupational physician (KK) screened the exposure details, and two lung physicians (JL, IL) evaluated the patients' clinical features.

The diagnostic criteria for IIA were: 1) exposure to a high concentration of an airborne irritant, 2) occurrence of asthma symptoms in a close temporal relationship to the exposure, 3) asthma verification by reversible obstruction or non-specific bronchial hyperresponsiveness (NSBH), 4) persistence of symptoms for three months or more, 5) no evidence of active asthma in adulthood before the exposure, 6) no other pulmonary disorder which explained the symptoms.

Our reference group to IIA were sensitizer-induced occupational asthma patients whose asthma was verified by specific inhalation challenge at FIOH during 2006-2018. These patients had either HMW- or LMW-induced OA, which are two distinctive subgroups of sensitizer-induced OA.(2, 5) All patients in HMW-induced OA group had flour-induced OA.

Source of data and definitions

FIOH patient records included all available data on the patients' encounters with health-care professionals due to work-related respiratory symptoms preceding occupational asthma diagnosis, appointments to FIOH when occupational asthma was diagnosed, and a control appointment to FIOH six to eight months after the diagnosis.

Asthma outcomes were the main variables in this study. The information on symptoms was collected from the patient records; for IIA the symptoms were recorded after the exposure event, and for the subgroups of sensitizer-induced OA they were registered when patients were exposed to the offending agent at work. Short-acting beta-agonist (SABA) usage was divided into daily or less frequent need. An Asthma Control Test (ACT) assessed patients' symptom control. According to the GINA guideline, scores of 20-25 represented well-controlled asthma, 16-19 not well-controlled asthma and 5-15 very poorly controlled asthma.(21) At least three days' intake of oral corticosteroids equivalent to prednisolone 30 mg or more due to breathing difficulties meant exacerbation. If information was missing in the medical records, this was interpreted as no exacerbation. Asthma medication was graded into treatment steps according to the GINA 2020 guideline.(21) Asthma treatment steps 4 or 5 were assessed to approximate severe asthma.

The IIA patients were divided into acute and subacute types. The former type had only one high-level exposure event within 24 hours, whereas the latter type had repeated exposure events to high levels of airborne irritants during a period of more than 24 hours.(12) To be able to compare the state of asthma outcomes in varying exposures, we classified the irritant exposures on the basis of their chemical characteristics and hazard classifications(22) into 1) acids, 2) bases, 3) acids or bases or their mixtures, 4) oxidizing agents and 5) other. This classification followed our recently reported classification(12) with some modifications to acquire a larger number of cases in each class. We defined atopy as having one or more positive reaction (wheal diameter of ≥ 3 mm) in the skin prick test panel for standardized environmental allergens (ALK-Abello, Horsholm, Denmark). Patients with a negative control wheal

diameter of ≥ 2 mm were excluded from the analysis. The initiation time of inhaled corticosteroid (ICS) treatment was the first day when ICS was prescribed after the exposure. We recorded the patients' work status at each appointment and divided it into five categories: 1) unchanged job, 2) continuing to work but workplace or work tasks had changed, 3) unemployed, 4) sick leave; 5) other (including re-education, retirement or part-time job).

We used a standard flow-volume spirometer (Spirostar USB Medikro, Finland) to measure lung function in accordance with the guidelines(23) and used the predicted values of Viljanen.(24) Histamine and methacholine challenge tests assessed NSBH, and the results were graded as hyperreactivity or no-hyperreactivity.(25, 26)

The fractional exhaled nitric oxide test (FeNO) was measured using an on-line chemiluminescence analyzer (NIOX, Aerocrine AB, Solna, Sweden) in compliance with ATS/ERS recommendations.(27) Serum total IgE (S-IgE) was measured using the Phadia UniCAP System (Phadia, Uppsala, Sweden). S-IgE and blood eosinophilia (B-Eos) were collected at the first FIOH appointment.

Statistical analysis

We used IBM SPSS version 27.0.1.0 for the data analyses. We presented categorical variables as the number and percentage of patients, and quantitative data as the median and interquartile range (IQR). We used Fisher's exact test with categorical variables and the Mann-Whitney U test with quantitative data to analyze the differences between IIA and HMW- or LMW-induced OA, and between different IIA subgroups.

Regression analyses were performed on variables that described asthma control or lung function parameters. The models were adjusted for age, body mass index (BMI), sex, presence of atopy and

smoking history. Age and smoking history showed a strong intercorrelation, and therefore the latter was divided into two categories: smokers and nonsmokers. The cut-off value was set to ten pack years or more. Binary logistic regression was utilized with a daily need for SABA, ACT score of ≤ 19 , treatment with GINA step 4 or 5 medication, and exacerbation after previous FIOH appointment. P-values of <0.05 and a 95% confidence interval (CI) with a lower limit of >1 were regarded as significant.

Ethics

This study was approved by the ethics committee of Helsinki University Central Hospital (approval number HUS/611/2020). According to the local legislation and ethical committees, no patient approval was needed for this retrospective study, as no patient intervention was performed at FIOH.

RESULTS

We analyzed 227 occupational asthma patients. Sixty-nine had IIA, of whom 30 had acute and 39 subacute IIA. A total of 158 patients fulfilled the sensitizer-induced OA criteria: 69 of these had HMW-induced OA and 89 LMW-induced OA (Table I).

Comparison of IIA and subgroups of sensitizer-induced OA

The IIA patients were more frequently men and had a higher Body Mass Index (BMI) than HMW- or LMW-induced OA patients (Table II). They were also older, had less atopy and lower blood eosinophil counts and serum immunoglobulin E values (S-IgE) than those with HMW-induced asthma. A similar trend was observed in comparison with LMW-induced asthma, but the differences were statistically insignificant. The patients in the LMW-induced OA group were more frequently smokers than the IIA patients.

Table III depicts the clinical characteristics and work status at the time of OA diagnosis. During disease initiation, a cough was a predominant sign of IIA, and was more frequent than in LMW-induced asthma ($p=0.042$). Conjunctivitis was also more frequent in IIA than in LMW-induced asthma ($p=0.004$), whereas rhinitis and dermatitis was more often reported in HMW-induced OA patients. Both HMW- and LMW-induced OA patients had been symptomatic for longer than the IIA patients before OA diagnosis (0.017 and <0.001 respectively). The IIA patients used more asthma medications than the other groups. Neither lung function parameters nor NSBH differed between the groups, but FeNO level was lower in the IIA group than in the other groups.

Table IV shows the clinical characteristics and work status at the control appointment six to eight months after OA diagnosis, when asthma treatment was stabilized. The need for daily SABA was more

frequent ($p=0.024$, $p=0.001$ respectively), and the ACT results were lower ($p<0.001$, $p<0.001$ respectively) among patients with IIA than among those with HMW- or LMW-induced OA, but only half of the patients had filled the questionnaire. They also had more exacerbations ($p=0.016$, $p=0.002$ respectively). The majority of the IIA patients (68%) used GINA treatment step 4 or 5 asthma medication, and they had a higher treatment step ($p=0.002$, $p=0.022$ respectively) than the other groups. HMW-induced OA patients showed higher FVC% than those with IIA. The FEV1/FVC ratio was lower in IIA compared to other groups, but no statistically significant differences were detected in NSBH or FeNO. Less than half of the IIA patients were actively in working life at the time of the control, but they had retained the same work task more often than those with HMW- and LMW-induced asthma.

Risk of poor asthma outcomes

Table V demonstrates how patients with IIA retained inferior asthma outcomes in daily need of SABA, ACT score of ≤ 19 , exacerbation after previous appointment, and GINA step 4 or 5 medication in comparison to LMW-induced OA after the adjustments. Furthermore, the latter two of these features remained statistically significant when they were compared to HMW-induced OA. However, the difference in FVC% or FEV1/FVC at the control appointment lost statistical significance after the adjustments.

Subtypes, causative agents, and ICS initiation

We compared the characteristics of acute and subacute IIA (Tables E1 and E2), and these subtypes appeared similar to each other. Regression analyses revealed that the only significantly different feature

218 of asthma outcome was that the patients with acute IIA reported more exacerbations during the control
219 appointment than those with subacute IIA, OR 11.68 (95% CI 2.62-52.08, $p=0.001$).

220 We also analyzed whether asthma outcomes or lung function parameters differed among the patients
221 who were exposed to different types of irritant agents according to their chemical properties (Tables
222 E3.1-3.4). Oxidizing agents revealed lower lung function parameters, but these differences were
223 insignificant when adjusted for smoking history. Generally, the asthma control and lung function
224 parameters of the groups appeared analogous at the control appointment.

225 ICS initiation time showed no effect on asthma outcomes or lung function parameters (Table E4).

DISCUSSION

This study followed the clinical characteristics of occupational asthma patients at the FIOH appointment where OA diagnosis was confirmed and at the control appointment six months later. The need for daily short-acting beta agonists and GINA treatment step 4 or 5 asthma medication was more frequent among IIA cases, and the IIA patients had more exacerbations, indicating poorer asthma outcomes. The results from the two appointments were comparable, but the results from the control appointment emphasized these differences because in many cases regular asthma medication was introduced or adjusted in the first appointment. The comparison between acute and subacute IIA revealed no major differences, although the patients with acute IIA reported more exacerbations than those with subacute IIA.

Only a few previous studies have addressed the prognosis of IIA using limited data on the features of asthma outcomes. Many of these have reported that up to 90% of IIA patients had remained symptomatic in the follow-up,(11, 20, 28, 29) which reflects the poor asthma control of IIA patients seen in this study. Malo et al. showed that IIA patients had high symptom scores at long-term follow-up.(20) Tarlo et al. noticed that patients with asthma aggravated by irritant exposures and no prior asthma diagnosis had the worst prognosis at follow-up.(30) Our results are in line with these observations and denote that the asthma outcomes of acute and subacute IIA were inferior to those of sensitizer-induced OA. Interestingly, the lung function parameters of these occupational asthma categories were comparable.

The reason for poorer asthma outcomes in IIA remains unresolved. One possible explanation might be the expected differences between the pathological mechanism of the asthma types. Previous studies have demonstrated that IIA is associated with neutrophilic inflammation(31, 32) and thicker basement membrane.(31-33) Furthermore, neutrophilic work-related asthma has shown poorer asthma

control,(34) and, generally, non-eosinophilic asthma has had an unsatisfactory response to anti-inflammatory therapy.(35-37) Neutrophilic inflammation and chronic remodeling may explain a part of the deficient asthma control seen in IIA.

A substantial portion of assumed severe asthma is difficult-to-treat asthma.(38) In general, comorbidities affect asthma control, and clinicians should consider differential diagnostics with inadequate response to regular asthma medications.(39) The WTC rescue/recovery workers had high number of comorbidities, and almost 70% of the workers with asthma had poor or very poor asthma control.(14, 40) Poorly or very poorly controlled asthma had a strong association with comorbid mental health conditions. It is unlikely that these people represent all IIA patients, but Malo et al found that one third of their acute IIA patients had psychiatric comorbidities in their long-term follow-up study.(20) Finally, occupational irritants have also been associated with laryngeal dysfunction,(41-43) which, in turn, is linked to reduced asthma control.(44, 45) Lack of sputum samples, bronchial biopsies, mental health questionnaires or laryngeal evaluations limit generalizing these interpretations to include the results presented in this retrospective study.

In addition to direct effects, work-related asthma contributes to health care utilization, unemployment, quality of life, and psychiatric comorbidities.(34, 46, 47) The EAACI position paper suggested that IIA patients could continue in their work tasks if their asthma was not severe.(6) Working status was a secondary focus in this study, but the results still raised questions. Less than half of the patients were actively in working life six to eight months after OA diagnosis, and only a few of them did the same work task. For sensitizer-induced OA this was expected, as avoidance of exposure is usually recommended.(2) However, the small number of IIA patients who remained in their original jobs (24%) was surprising, although some previous studies reported similar figures.(28-30, 48)

Returning to the IIA subtypes, Brooks et al. concluded that atopic status contributed to not-so-sudden (i.e., subacute) IIA, with 88% of these patients being atopic compared to 52% of sudden-onset (i.e., acute) patients.(49) In this study, atopic status was an insignificant prognostic marker, as 44% of acute and 35% of subacute IIA patients had a positive skin prick test (Table E1). We are not aware of other studies that have compared these two subtypes. Our results illustrate a notable similarity between the asthma outcomes of acute and subacute IIA. The only statistically significant differences were initial rhinitis and the number of exacerbations at the control appointment. The former was more frequent in subacute IIA and the latter in acute IIA.

It has been speculated that the chemical properties of the irritant agent and the timing of inhaled cortisone initiation affect the prognosis of IIA.(50) In these data, the chemical classes were indistinguishable in respect of initial symptoms after exposure or asthma outcomes and lung function parameters at the control appointment. Oxidizing agents showed lower FVC and FEV1, but smoking history affected the individual values. Generally, the level of exposure might have varied among patients and a larger sample size may have produced more distinguishable differences. The timing of ICS initiation was also irrelevant to prognosis, although a retrospective study design is not ideal for analyzing the effect of medication.

Strengths and limitations

To our knowledge, this is the largest study that compared clinical differences between irritant-induced and sensitizer-induced occupational asthma. We were able to analyze each patient in detail and obtain a more comprehensive view of their asthma outcomes than previous studies, and we also had reliable information on their exposure.

This study identified 30 acute and 39 subacute IIA patients in an occupational medicine clinic, but it is likely that numerous cases remained undiagnosed. We cannot rule out selection bias in our patient selection. The patients in this study might represent more severe examples of IIA, but this also applies to sensitizer-induced asthma cases, and we consider the groups comparable in this respect.

We are not aware of any previous studies that have compared the asthma outcomes of acute and subacute IIA or the effect of the causative irritant agent. This can be regarded as a strength of this study, although the number of patients in each category was limited.

As the diagnosis of IIA depends on clinical history,(2, 6) reporting bias may be possible. Therefore, a multidisciplinary panel set the initial OA diagnosis, and we reassessed whether each patient met our criteria for IIA.

Due to its retrospective nature, this study registered the symptoms from patient records. A standardized questionnaire would have enhanced reliability. Furthermore, IIA and sensitizer-induced asthma differed in their demographic characteristics, which was noticed with HMW-induced OA patients in particular.

FEV1/FVC ratio was analyzed as an absolute value that disregarded decline with ageing. However, statistical adjustment counterbalanced these imperfections.

CONCLUSIONS

This study analyzed acute and subacute IIA patients at the time of occupational asthma diagnosis and six to eight months later. It illustrated that 68% of the IIA patients used GINA step 4 or 5 asthma medication, 30% needed short-acting beta agonists daily, and that 24% of them had had asthma exacerbation six to eight months after occupational asthma diagnosis. The IIA patients had more exacerbations and used more medications than the sensitizer-induced OA patients, indicating poorer asthma outcomes.

Our results show that the IIA patients should be carefully monitored and treated after the occupational asthma diagnosis. They also highlight the value of primary prevention, regardless of the reason behind the inferior asthma outcomes. Confronting the root causes of exposure and transmitting knowledge to workplaces is essential.

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REFERENCES

1. Malo JL, Vandenplas O. Definitions and classification of work-related asthma. *Immunology and allergy clinics of North America*. 2011;31(4):645-62, v.
2. Tarlo SM, Lemiere C. Occupational asthma. *The New England journal of medicine*. 2014;370(7):640-9.
3. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, et al. The Occupational Burden of Nonmalignant Respiratory Diseases. An Official American Thoracic Society and European Respiratory Society Statement. *American journal of respiratory and critical care medicine*. 2019;199(11):1312-34.
4. Vandenplas O, Godet J, Hurdubaea L, Riffart C, Suojalehto H, Walusiak-Skorupa J, et al. Severe Occupational Asthma: Insights From a Multicenter European Cohort. *The journal of allergy and clinical immunologyIn practice*. 2019;7(7):2309-18.e4.
5. Vandenplas O, Godet J, Hurdubaea L, Riffart C, Suojalehto H, Wiszniewska M, et al. Are high- and low-molecular-weight sensitizing agents associated with different clinical phenotypes of occupational asthma? *Allergy*. 2019;74(2):261-72.
6. Vandenplas O, Wiszniewska M, Raulf M, de Blay F, Gerth van Wijk R, Moscato G, et al. EAACI position paper: irritant-induced asthma. *Allergy*. 2014;69(9):1141-53.
7. Ameille J, Hamelin K, Andujar P, Bensefa-Colas L, Bonnetterre V, Dupas D, et al. Occupational asthma and occupational rhinitis: the united airways disease model revisited. *Occupational and environmental medicine*. 2013;70(7):471-5.
8. Kwon SC, Song J, Kim YK, Calvert GM. Work-Related Asthma in Korea – Findings from the Korea Work-Related Asthma Surveillance (KOWAS) program, 2004-2009. *Allergy, asthma & immunology research*. 2015;7(1):51-9.

- 345 9. Reilly MJ, Wang L, Rosenman KD. The Burden of Work-related Asthma in Michigan, 1988-2018.
346 *Annals of the American Thoracic Society*. 2020;17(3):284-92.
- 347 10. Andersson E, Knutsson A, Hagberg S, Nilsson T, Karlsson B, Alfredsson L, et al. Incidence of
348 asthma among workers exposed to sulphur dioxide and other irritant gases. *The European respiratory*
349 *journal*. 2006;27(4):720-5.
- 350 11. Bhérer L, Cushman R, Courteau JP, Quévillon M, Côté G, Bourbeau J, et al. Survey of construction
351 workers repeatedly exposed to chlorine over a three to six month period in a pulpmill: II. Follow up of
352 affected workers by questionnaire, spirometry, and assessment of bronchial responsiveness 18 to 24
353 months after exposure ended. *Occupational and environmental medicine*. 1994;51(4):225-8.
- 354 12. Lindström I, Lantto J, Karvala K, Soini S, Ylinen K, Suojalehto H, et al. Occupations and exposure
355 events in acute and subacute irritant-induced asthma. *Occupational and environmental medicine*.
356 2021;78(11):793-800.
- 357 13. Aldrich TK, Weakley J, Dhar S, Hall CB, Crosse T, Banauch GI, et al. Bronchial Reactivity and Lung
358 Function After World Trade Center Exposure. *Chest*. 2016;150(6):1333-40.
- 359 14. Wisnivesky JP, Teitelbaum SL, Todd AC, Boffetta P, Crane M, Crowley L, et al. Persistence of
360 multiple illnesses in World Trade Center rescue and recovery workers: a cohort study. *Lancet (London,*
361 *England)*. 2011;378(9794):888-97.
- 362 15. Dumas O, Laurent E, Bousquet J, Metspalu A, Milani L, Kauffmann F, et al. Occupational irritants
363 and asthma: an Estonian cross-sectional study of 34,000 adults. *The European respiratory journal*.
364 2014;44(3):647-56.
- 365 16. Kogevinas M, Zock JP, Jarvis D, Kromhout H, Lillienberg L, Plana E, et al. Exposure to substances
366 in the workplace and new-onset asthma: an international prospective population-based study (ECRHS-
367 II). *Lancet (London, England)*. 2007;370(9584):336-41.

- 368 17. Lillienberg L, Andersson E, Janson C, Dahlman-Höglund A, Forsberg B, Holm M, et al.
369 Occupational exposure and new-onset asthma in a population-based study in Northern Europe (RHINE).
370 The Annals of Occupational Hygiene. 2013;57(4):482-92.
- 371 18. Brooks SM, Weiss MA, Bernstein IL. Reactive airways dysfunction syndrome (RADS). Persistent
372 asthma syndrome after high level irritant exposures. Chest. 1985;88(3):376-84.
- 373 19. Baur X, Bakehe P, Vellguth H. Bronchial asthma and COPD due to irritants in the workplace - an
374 evidence-based approach. Journal of occupational medicine and toxicology (London, England).
375 2012;7(1):19-.
- 376 20. Malo JL, L'Archevêque J, Castellanos L, Lavoie K, Ghezzo H, Maghni K. Long-term outcomes of
377 acute irritant-induced asthma. American journal of respiratory and critical care medicine.
378 2009;179(10):923-8.
- 379 21. GLOBAL STRATEGY FOR ASTHMA MANAGEMENT AND PREVENTION Updated 2020.
- 380 22. European Chemicals Agency (ECHA). Guidance to regulations (EC) No 1272/2008 on
381 classification, labelling and packaging (CLP) of substances and mixtures. 2017. Contract No.: Report.
- 382 23. Standardization of Spirometry, 1994 Update. American Thoracic Society. American journal of
383 respiratory and critical care medicine. 1995;152(3):1107-36.
- 384 24. Viljanen AA, Halttunen PK, Kreus KE, Viljanen BC. Spirometric studies in non-smoking, healthy
385 adults. Scandinavian journal of clinical and laboratory investigationSupplementum. 1982;159:5-20.
- 386 25. Nieminen MM. Unimodal distribution of bronchial hyperresponsiveness to methacholine in
387 asthmatic patients. Chest. 1992;102(5):1537-43.
- 388 26. Sovijärvi AR, Malmberg LP, Reinikainen K, Ryttilä P, Poppius H. A rapid dosimetric method with
389 controlled tidal breathing for histamine challenge. Repeatability and distribution of bronchial reactivity
390 in a clinical material. Chest. 1993;104(1):164-70.

- 391 27. American Thoracic S, European Respiratory S. ATS/ERS recommendations for standardized
392 procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal
393 nitric oxide, 2005. American journal of respiratory and critical care medicine. 2005;171(8):912-30.
- 394 28. Chatkin JM, Tarlo SM, Liss G, Banks D, Broder I. The outcome of asthma related to workplace
395 irritant exposures: a comparison of irritant-induced asthma and irritant aggravation of asthma. Chest.
396 1999;116(6):1780-5.
- 397 29. Henneberger PK, Derk SJ, Davis L, Tumpowsky C, Reilly MJ, Rosenman KD, et al. Work-related
398 reactive airways dysfunction syndrome cases from surveillance in selected US states. Journal of
399 occupational and environmental medicine. 2003;45(4):360-8.
- 400 30. Tarlo SM, Liss G, Corey P, Broder I. A workers' compensation claim population for occupational
401 asthma. Comparison of subgroups. Chest. 1995;107(3):634-41.
- 402 31. Chang-Yeung M, Lam S, Kennedy SM, Frew AJ. Persistent asthma after repeated exposure to
403 high concentrations of gases in pulpmills. American journal of respiratory and critical care medicine.
404 1994;149(6):1676-80.
- 405 32. Takeda N, Maghni K, Daigle S, L'Archevêque J, Castellanos L, Al-Ramli W, et al. Long-term
406 pathologic consequences of acute irritant-induced asthma. The Journal of allergy and clinical
407 immunology. 2009;124(5):975-81.e1.
- 408 33. Gautrin D, Boulet LP, Boutet M, Dugas M, Bhérer L, L'Archevêque J, et al. Is reactive airways
409 dysfunction syndrome a variant of occupational asthma? The Journal of allergy and clinical immunology.
410 1994;93(1 Pt 1):12-22.
- 411 34. Lemièrre C, Boulet LP, Chaboillez S, Forget A, Chirý S, Villeneuve H, et al. Work-exacerbated
412 asthma and occupational asthma: do they really differ? The Journal of allergy and clinical immunology.
413 2013;131(3):704-10.
- 414 35. Hammad H, Lambrecht BN. The basic immunology of asthma. Cell. 2021;184(6):1469-85.

36. McGrath KW, Icitovic N, Boushey HA, Lazarus SC, Sutherland ER, Chinchilli VM, et al. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. *American journal of respiratory and critical care medicine*. 2012;185(6):612-9.
37. Ray A, Kolls JK. Neutrophilic Inflammation in Asthma and Association with Disease Severity. *Trends in immunology*. 2017;38(12):942-54.
38. von Bülow A, Backer V, Bodtger U, Sjøes-Petersen NU, Vest S, Steffensen I, et al. Differentiation of adult severe asthma from difficult-to-treat asthma - Outcomes of a systematic assessment protocol. *Respiratory medicine*. 2018;145:41-7.
39. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal*. 2014;43(2):343-73.
40. Jordan HT, Stellman SD, Reibman J, Farfel MR, Brackbill RM, Friedman SM, et al. Factors associated with poor control of 9/11-related asthma 10-11 years after the 2001 World Trade Center terrorist attacks. *The Journal of asthma : official journal of the Association for the Care of Asthma*. 2015;52(6):630-7.
41. de la Hoz RE, Shohet MR, Bienenfeld LA, Afilaka AA, Levin SM, Herbert R. Vocal cord dysfunction in former World Trade Center (WTC) rescue and recovery workers and volunteers. *American Journal of Industrial Medicine*. 2008;51(3):161-5.
42. Halvorsen T, Walsted ES, Bucca C, Bush A, Cantarella G, Friedrich G, et al. Inducible laryngeal obstruction: an official joint European Respiratory Society and European Laryngological Society statement. *The European respiratory journal*. 2017;50(3):1602221. doi: 10.1183/13993003.02221-2016. Print 2017 Sep.

- 437 43. Perkner JJ, Fennelly KP, Balkissoon R, Bartelson BB, Ruttenber AJ, Wood RP, 2nd, et al. Irritant-
438 associated vocal cord dysfunction. *Journal of occupational and environmental medicine*. 1998;40(2):136-
439 43.
- 440 44. Lee JH, An J, Won HK, Kang Y, Kwon HS, Kim TB, et al. Prevalence and impact of comorbid
441 laryngeal dysfunction in asthma: A systematic review and meta-analysis. *The Journal of allergy and*
442 *clinical immunology*. 2020;145(4):1165-73.
- 443 45. Vertigan AE, Kapela SL, Gibson PG. Laryngeal Dysfunction in Severe Asthma: A Cross-Sectional
444 Observational Study. *The journal of allergy and clinical immunologyIn practice*. 2021;9(2):897-905.
- 445 46. Henneberger PK, Patel JR, de Groene GJ, Beach J, Tarlo SM, Pal TM, et al. Workplace
446 interventions for treatment of occupational asthma. *The Cochrane database of systematic reviews*.
447 2019;10(10):CD006308.
- 448 47. Knoeller GE, Mazurek JM, Moorman JE. Health-related quality of life among adults with work-
449 related asthma in the United States. *Quality of life research : an international journal of quality of life*
450 *aspects of treatment, care and rehabilitation*. 2013;22(4):771-80.
- 451 48. Gassert TH, Hu H, Kelsey KT, Christiani DC. Long-term health and employment outcomes of
452 occupational asthma and their determinants. *Journal of occupational and environmental medicine*.
453 1998;40(5):481-91.
- 454 49. Brooks SM, Hammad Y, Richards I, Giovenco-Barbas J, Jenkins K. The spectrum of irritant-induced
455 asthma: sudden and not-so-sudden onset and the role of allergy. *Chest*. 1998;113(1):42-9.
- 456 50. Brooks SM. Irritants, Irritancy and Irritant Induced Asthma. *J Allergy Ther*. 2018;9(1).

457 **Table I. Causal agents of irritant- and sensitizer-induced asthma.**

Irritant	69	Sensitizer			158
		High-molecular-weight agent*	69	Low-molecular-weight agent	89
Mixtures	18	Rye	36	Isocyanates	38
Acid aerosols or fumes	13	Wheat	13	Acrylates	12
Base aerosols or fumes	9	Barley	11	Anhydrides	8
Mixture of acid and base aerosols or fumes	3	Oat	3	Metal working fluids	6
Acidic or alkaline dust	8	Buckwheat	3	Aldehydes	5
Inorganic gases	6	Soy	3	Colophony	5
Endotoxins	4			Epoxy	4
Oxidizing agents	2			Metals	2
Other chemicals	6			Other	9

458 * Flour-induced asthma represents high-molecular-weight agent induced-asthma in this study

459 **Table II. Demographic characteristics of the study population.**

Characteristics	Irritant-induced asthma (n=69)**	Sensitizer-induced asthma (n=158)			
		HMW-*induced asthma (n=69)**	IIA vs HMW P-value	LMW-induced asthma (n=89)**	IIA vs LMW P-value
Age, y					
• Median	47	40	< 0.001	44	0.197
• IQR	(40-54)	(31.5-49)		(35-54)	
Male	58 (84%)	34 (49%)	< 0.001	59 (66%)	0.017
Body mass index, kg/m ²					
• Median	28.1	26.8	0.041	27.1	0.049
• IQR	(25.8-31.7)	(23.6-30.2)		(24.0-30.0)	
Smoking history					
• Smoker	27 (39%)	30 (43%)	0.730	56 (63%)	0.004
• Nonsmoker	42 (61%)	39 (57%)		33 (37%)	
Atopy*** (n=205)	24 (39%)	45 (65%)	< 0.001	41 (49%)	0.239
B-Eos, ug/l (n=218)					
• Median	142	210	0.017	160	0.756
• IQR	(85-255)	(100-360)		(90-245)	
S-IgE, kU/l (n=191)					
• Median	49	179	< 0.001	56	0.133
• IQR	(19-128)	(89-525)		(32-268)	

460 * Flour-induced asthma represents HMW-induced asthma in this study

461 ** Unless otherwise specified, the number of the patients was 227, 69 of whom had IIA. 69
462 patients suffered from HMW-induced asthma and 89 from LMW-induced asthma.
463 Numerical values expressed as median and interquartile ranges (IQR), categorical values
464 as n (% of patients involved).

465 *** one or more positive skin prick test reaction to common environmental allergens

466 B-Eos, blood eosinophilia, ug/l = micrograms per liter

467 HMW, high-molecular-weight agent

468 LMW, low-molecular-weight agent

469 S-IgE, serum total concentration of immunoglobulin E, kU/l = kilounit per liter

Table III. Clinical characteristics and work status of patients with IIA compared to those with HMW-*
and LMW-induced asthma, two subgroups of sensitizer-induced OA, at the time of occupational
asthma diagnosis.

Characteristics	Irritant-induced asthma (n=69)**	Sensitizer-induced asthma (n=158)			
		HMW-*induced asthma (n=69)**	IIA vs HMW P-value	LMW-induced asthma (n=89)**	IIA vs LMW P-value
Respiratory symptoms***					
• Coughing	61 (88%)	54 (78%)	0.170	67 (75%)	0.042
• Wheezing	35 (51%)	41 (59%)	0.392	57 (64%)	0.105
• Dyspnea	65 (94%)	59 (86%)	0.157	79 (89%)	0.271
• Sputum	34 (49%)	29 (42%)	0.494	32 (36%)	0.105
Other symptoms***					
• Rhinitis	47 (68%)	58 (84%)	0.045	50 (56%)	0.141
• Conjunctivitis	28 (41%)	28 (41%)	1.000	17 (19%)	0.004
• Dermatitis	13 (19%)	26 (38%)	0.023	19 (21%)	0.842
Duration of symptoms, months****			0.017		< 0.001
• Median	16	24		29	
• IQR	(9.5-37.5)	(13-65)		(16-51)	
Short-acting beta agonist daily (n=219)	24 (39%)	8 (12%)	< 0.001	7 (8%)	< 0.001

Exacerbation during last year	22 (32%)	3 (4%)	< 0.001	5 (6%)	< 0.001
<i>Exacerbation without exposure to the causal agent</i>	<i>13 (19%)</i>	<i>3 (4%)</i>	0.015	<i>4 (4%)</i>	0.008
ICS daily dose, ug					
• Median	800	800	0.057	800	0.044
• IQR	(400-1200)	(400-800)		(0-800)	
GINA treatment step*****					
• 1-3	33 (48%)	48 (70%)	0.015	58 (65%)	0.035
• 4-5	36 (52%)	21 (30%)		31 (35%)	
FVC% (n=225)					
• Median	93.5	96	0.342	92	0.741
• IQR	(84.5-100)	(86-103.5)		(86-100.5)	
FEV1% (n=225)					
• Median	85.5	87	0.529	89	0.338
• IQR	(77.5-95)	(79-94.5)		(80.5-95.5)	
FEV1%<80% (n=225)	22 (32%)	18 (26%)	0.456	20 (23%)	0.205
FEV1/FVC (n=225)					
• Median	0.76	0.78	0.238	0.78	0.190
• IQR	(0.72-0.795)	(0.725-0.81)		(0.725-0.81)	
FEV1/FVC<0.70 (n=225)	12 (18%)	10 (14%)	0.649	12 (14%)	0.510

Non-specific bronchial hyperreactivity (n=190)	32 (59%)	37 (62%)	0.849	41 (54%)	0.593
FeNO, ppb (n=198)					
• Median	13	23	< 0.001	16.5	0.018
• IQR	(7-21.5)	(15-33)		(10-33)	
Work status					
• Same work	32 (46%)	24 (35%)	0.053	23 (26%)	0.017
• Adjusted work	11 (16%)	15 (22%)		22 (25%)	
• Unemployed	7 (10%)	2 (3%)		7 (8%)	
• Sick leave	13 (19%)	25 (36%)		33 (37%)	
• Other	6 (9%)	3 (4%)		4 (4%)	

* Flour-induced asthma represents HMW-induced asthma in this study

** Unless otherwise specified, the number of patients was 227, 69 of whom had IIA. 69 patients suffered from HMW-induced asthma and 89 from LMW-induced asthma. Numerical values expressed as median and interquartile ranges (IQR), categorical values as n (% of patients involved).

*** The IIA patients' symptoms after the exposure event and in sensitizer-induced asthma cases when exposed to the offending agent at work

**** Duration of symptoms (months) before occupational asthma diagnosis

***** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

FeNO, fractional exhaled nitric oxide, ppb = parts per billion

FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second

484 FVC and FVC%, forced vital capacity and predicted forced vital capacity

485 HMW, high-molecular-weight agent

486 ICS, Inhaled corticosteroids, ug = micrograms

487 IIA, irritant-induced asthma

488 LMW, low-molecular-weight agent

489 OA, occupational asthma

Table IV. Clinical characteristics and work status of the patients with IIA compared to those with HMW-* and LMW-induced asthma, two subgroups of sensitizer-induced OA, at the control appointment at FIOH six to eight months after the occupational asthma diagnosis.

Characteristics	Irritant-induced asthma (n=66)**	Sensitizer-induced asthma (n=154)			
		HMW-*induced asthma (n=65)**	IIA vs HMW P-value	LMW-induced asthma (n=89)**	IIA vs LMW P-value
Short-acting beta agonist daily (n=204)	17 (30%)	7 (8%)	0.024	7 (8%)	0.001
ACT (n=122)***					
• Median	17	21.5	< 0.001	22	< 0.001
• IQR	(12.5-20)	(19-23)		(17-24.5)	
Exacerbation after previous appointment****	16 (24%)	5 (8%)	0.016	6 (7%)	0.002
ICS daily dose, ug					
• Median	800	800	0.070	800	0.676
• IQR	(640-1200)	(450-880)		(400-1000)	
GINA treatment step *****					
• 1-3	21 (32%)	39 (60%)	0.002	45 (51%)	0.022
• 4-5	45 (68%)	26 (40%)		44 (49%)	
FVC% (n=209)					
• Median	92	93	0.035	91	0.336
• IQR	(81.5-100.5)	(86-105)		(85-99)	

FEV1% (n=212)					
• Median	86	87	0.102	87	0.198
• IQR	(75.5-93.5)	(80-98)		(79.5-95)	
FEV1%<80% (n=212)	21 (33%)	14 (23%)	0.232	22 (25%)	0.361
FEV1/FVC (n=209)					
• Median	0.76	0.79	0.049	0.77	0.031
• IQR	(0.725-0.785)	(0.73-0.81)		(0.74-0.81)	
FEV1/FVC<0.70 (n=209)	12 (19%)	7 (11%)	0.320	12 (14%)	0.501
Non-specific bronchial hyperreactivity (n=132)	23 (54%)	22 (52%)	1.000	21 (45%)	0.527
FeNO, ppb (n=182)					
• Median	13	17	0.022	14.5	0.778
• IQR	(7-20)	(10-27)		(9.5-25.5)	
Work status (n=222)					
• Same work	16 (24%)	3 (4%)	0.007	2 (2%)	< 0.001
• Adjusted work	15 (23%)	23 (34%)		28 (32%)	
• Unemployed	4 (6%)	5 (7%)		9 (10%)	
• Sick leave	18 (27%)	14 (21%)		22 (25%)	
• Other	13 (20%)	22 (33%)		28 (31%)	

* Flour-induced asthma represents HMW-induced asthma in this study

** Unless otherwise specified, the number of patients was 220, 66 of whom had IIA. 65 patients suffered from HMW-induced asthma and 89 from LMW-induced asthma.

496 Numerical values expressed as median and interquartile ranges (IQR), categorical values
497 as n (% of patients involved).

498 *** 36 IIA, 38 HMW-induced OA and 47 LMW-induced OA patients completed the ACT
499 questionnaire

500 **** None of the subjects who had exacerbation were exposed to the causal agent at work

501 ***** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

502 ACT, Asthma Control Test results graded from 5 to 25.

503 FeNO, fractional exhaled nitric oxide, ppb = parts per billion

504 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second

505 FVC and FVC%, forced vital capacity and predicted forced vital capacity

506 HMW, high-molecular-weight agent

507 ICS, Inhaled corticosteroids, ug = micrograms

508 IIA, irritant-induced asthma

509 LMW, low-molecular-weight agent

510 OA, occupational asthma

Table V. OR for poor asthma outcome among the patients with IIA compared to those of HMW-* and LMW-induced asthma, two subgroups of sensitizer-induced OA, six to eight months after the occupational asthma diagnosis.

Characteristics	Odds Ratios (95% CI)**	P-value
Short-acting beta agonists daily		
• IIA : HMW-induced asthma	2.09 (0.72-6.05)	0.174
• IIA : LMW-induced asthma	3.80 (1.38-10.46)	0.010
Asthma Control Test score of ≤ 19		
• IIA : HMW-induced asthma	3.12 (0.93-10.69)	0.066
• IIA : LMW-induced asthma	3.55 (1.22-10.34)	0.020
Exacerbation after previous appointment		
• IIA : HMW-induced asthma	6.29 (1.53-25.83)	0.011
• IIA : LMW-induced asthma	3.85 (1.35-11.04)	0.012
GINA step 4 or 5 medication		
• IIA : HMW-induced asthma	2.49 (1.07-5.79)	0.034
• IIA : LMW-induced asthma	2.22 (1.08-4.57)	0.031

* Flour-induced asthma represents HMW-induced asthma in this study

** Variables adjusted for age, sex, body mass index, atopy, and smoking history of 10 pack years or more.

GINA step, Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

HMW, high-molecular-weight agent

IIA, irritant-induced asthma

520 LMW, low-molecular-weight agent

521 OA, occupational asthma

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8 **Online Repository**

9 ONLINE REPOSITORY TEXT

10 List of References

- 11 E1. European Chemicals Agency (ECHA). Guidance to regulations (EC) No 1272/2008 on
12 classification, labelling and packaging (CLP) of substances and mixtures. 2017. Contract No.: Report.
- 13 E2. Lindström I, Lantto J, Karvala K, Soini S, Ylinen K, Suojalehto H, et al. Occupations and
14 exposure events in acute and subacute irritant-induced asthma. Occupational and environmental medicine.
15 2021;78(11):793-800.

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9 **Table E1. Demographic and clinical characteristics and work-status of acute and subacute**
 10 **irritant-induced asthma at time of occupational asthma diagnosis.**

Characteristics	Acute IIA (n=30)*	Subacute IIA (n=39)*	P-value
Age, y			
• Median	45	50	0.208
• IQR	(39-52)	(41-55)	
Male	25 (83%)	33 (85%)	1.000
BMI, kg/m ²			
• Median	28.7	27.8	0.780
• IQR	(26.0-31.6)	(25.5-31.7)	
Smoking history			
• Smoker	15 (50%)	12 (31%)	0.137
• Nonsmoker	15 (50%)	27 (69%)	
Atopy (n=62**)	11 (44%)	13 (35%)	0.597
B-Eos, ug/l (n=64)			
• Median	144	140	0.582
• IQR	(85-220)	(90-280)	
S-IgE, kU/l (n=63)			
• Median	73	41	0.460

• IQR	(19-188)	(19-118)	
Respiratory symptoms***			
• Coughing	26 (87%)	35 (90%)	0.720
• Wheezing	12 (40%)	23 (59%)	0.148
• Dyspnea	28 (93%)	37 (95%)	1.000
• Sputum	15 (50%)	19 (49%)	1.000
Other symptoms			
• Rhinitis	16 (53%)	31 (79%)	0.036
• Conjunctivitis	14 (47%)	14 (36%)	0.460
• Dermatitis	5 (17%)	8 (21%)	0.764
Short-acting beta agonist daily (n=61)	10 (40%)	14 (39%)	1.000
ACT (n=39)****			
• Median	16	15	0.965
• IQR	(11-19)	(12-20)	
Exacerbation during last year	11 (37%)	11 (28%)	0.603
<i>Exacerbation without exposure to the causal agent</i>	<i>10 (33%)</i>	<i>3 (8%)</i>	<i>0.011</i>

ICS daily dose, ug			
• Median	1000	800	0.054
• IQR	(800-1600)	(100-900)	
GINA classification*****			
• 1-3	10 (33%)	23 (59%)	0.052
• 4-5	20 (67%)	16 (41%)	
FVC% (n=68)			
• Median	91	96	0.564
• IQR	(86-98)	(80.5-101)	
FEV1% (n=68)			
• Median	86	85	0.687
• IQR	(79-91)	(76-99)	
FEV1%<80% (n=68)	8 (28%)	14 (36%)	0.602
FEV1/FVC (n=68)			
• Median	0.76	0.76	0.980
• IQR	(0.71-0.79)	(0.72-0.80)	
FEV1/FVC<0.70 (n=68)	5 (17%)	7 (18%)	1.000
Non-specific bronchial hyperreactivity (n=54)	13 (54%)	19 (63%)	0.582

FeNO, ppb (n=68)			
• Median	11.5	14.5	0.104
• IQR	(7.0-17.0)	(9.0-25.0)	
Work status			0.067
• Same work	11 (37%)	21 (54%)	
• Adjusted work	8 (27%)	3 (8%)	
• Unemployed	2 (7%)	5 (13%)	
• Sick leave	8 (27%)	5 (13%)	
• Other	1 (3%)	5 (13%)	

11

12 * Unless otherwise specified, the number of the patients was 69, 30 of whom had acute IIA
13 and 39 subacute IIA. Numerical values expressed as median and interquartile ranges (IQR),
14 categorical values as n (% of patients involved).

15 ** one or more positive skin prick test reactions to common environmental allergens

16 *** The patients' symptoms after exposure event

17 **** 14 acute and 25 subacute IIA patient completed the ACT questionnaire

18 ***** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

19 ACT, Asthma control test

20 B-Eos, blood eosinophilia

21 FeNO, fractional exhaled nitric oxide, ppb = parts per billion

- 22 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second
- 23 FVC and FVC%, forced vital capacity and predicted forced vital capacity
- 24 ICS, Inhaled corticosteroids
- 25 S-IgE, serum total concentration of immunoglobulin E

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9 **Table E2. Clinical characteristics and work-status of the patients with acute and subacute**
 10 **irritant-induced asthma six to eight months after occupational asthma diagnosis.**

Variable	Acute (n=28)*	Subacute (n=38)*	P-value
Short-acting beta agonist daily (n=57)	9 (38%)	8 (24%)	0.381
ACT (n=36)** • Median • IQR	15 (12-17)	18 (14-20)	0.124
Exacerbation after previous appointment***	13 (46%)	3 (8%)	< 0.001
ICS daily dose, ug • Median • IQR	880 (800-1800)	800 (400-1000)	0.151
GINA treatment step **** • 1-3 • 4-5	8 (29%) 20 (71%)	13 (34%) 25 (66%)	0.790
FVC% (n=63) • Median • IQR	84 (80-94.5)	96 (82-102.5)	0.058

FEV1% (n=63)			
• Median	83	86.5	0.160
• IQR	(71.5-87.5)	(77-96.5)	
FEV1%<80% (n=63)	11 (41%)	10 (28%)	0.296
FEV1/FVC (n=63)			
• Median	0.76	0.76	0.743
• IQR	(0.72-0.79)	(0.725-0.78)	
FEV1/FVC<0.70 (n=63)	6 (22%)	6 (17%)	0.747
Non-specific bronchial hyperreactivity (n=43)	5 (36%)	18 (62%)	0.191
FeNO, ppb (n=58)			
• Median	11	15	0.192
• IQR	(6.5-16)	(7-20)	
Work status			
• Same work	6 (21%)	10 (26%)	0.306
• Adjusted work	9 (32%)	6 (16%)	
• Unemployed	1 (4%)	3 (8%)	
• Sick leave	9 (32%)	9 (24%)	
• Other	3 (11%)	10 (26%)	

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11

12 * Unless otherwise specified, the number of the patients was 66, 28 of whom had acute IIA
13 and 38 subacute IIA. Numerical values expressed as median and interquartile ranges (IQR),
14 categorical values as n (% of patients involved).

15 ** 11 acute and 25 subacute IIA patient completed the ACT questionnaire

16 *** None of the subjects who had exacerbation were exposed to the causal agent at work

17 **** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

18 ACT, Asthma Control Test

19 FeNO, fractional exhaled nitric oxide, ppb = parts per billion

20 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second

21 FVC and FVC%, forced vital capacity and predicted forced vital capacity

22 ICS, inhaled corticosteroids, ug = micrograms

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9 **Comparison of causative agents of irritant-induced asthma**

10 Methods:

11 We grouped the irritant exposures according to their hazard classification(E1) and physical form as
12 described earlier.(E2) Due to the small number of cases in each category, we formed four new chemical
13 classes: acids (n=19), bases (n=16), oxidizing agents (n=6), and combined corrosive agents (n=29). The last
14 group comprised acids, bases and other chemicals with the hazard classification of Skin Corr 1A or Skin Corr
15 1B. We compared each of the groups with all the other cases combined.

16

17 **Table E3. Clinical characteristics of the patients with irritant-induced asthma six to eight months**
18 **after occupational asthma diagnosis, classification according to agents' chemical properties.**

19 **Table E3.1 Acids vs. others**

Characteristics	Acids (n=19)*	Other agents (n=47)*	P-value
Short-acting beta agonists daily (n=57)	6 (35%)	11 (28%)	0.547
Exacerbation after previous appointment	5 (26%)	11 (23%)	1.000
GINA treatment step**			
• 1-3	6 (32%)	15 (32%)	1.000
• 4-5	13 (68%)	32 (68%)	
FVC%			
• Median	93	88	0.867
• IQR	(81-102)	(82-97)	
FEV1%			
• Median	86.5	84	0.508
• IQR	(77-99)	(75-91)	
FEV1/FVC-ratio			
• Median	0.78	0.75	0.122
• IQR	(0.73-0.79)	(0.72-0.78)	

20 * Unless otherwise specified, the number of the patients was 66, 19 of whom were exposed to
21 acidic agents and 47 to other agents. Numerical values expressed as median and interquartile ranges (IQR),
22 categorical values as n (% of patients involved).

23 ** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report
24 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second
25 FVC and FVC%, forced vital capacity and predicted forced vital capacity

26 **Table E3.2. Bases vs. others**

Characteristics	Bases (n=16)*	Other agents (n=50)*	P-value
Short-acting beta agonists daily (n=57)	6 (40%)	11 (26%)	0.341
Exacerbation after previous appointment	5 (31%)	11 (22%)	0.509
GINA treatment step **			
• 1-3	5 (31%)	16 (32%)	1.000
• 4-5	11 (68%)	34 (68%)	
FVC%			
• Median	94	88	0.586
• IQR	(82-99.5)	(81-100.5)	
FEV1%			
• Median	88.5	84	0.301
• IQR	(77-95.5)	(74.5-91.5)	
FEV1/FVC-ratio			
• Median	0.77	0.76	0.516
• IQR	(0.72-0.79)	(0.725-0.785)	

27

28 * Unless otherwise specified, the number of the patients was 66, 16 of whom were exposed to
29 alkali agents and 50 to other agents. Numerical values expressed as median and interquartile
30 ranges (IQR), categorical values as n (% of patients involved).

31 ** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

32 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second

33 FVC and FVC%, forced vital capacity and predicted forced vital capacity

34 **Table E3.3. Oxidizing agents vs. others**

Characteristics	Oxidizing agents (n=6)*	Other agents (n=60)*	P-value
Short-acting beta agonists daily (n=57)	2 (33%)	15 (29%)	1.000
Exacerbation after previous appointment	2 (33%)	14 (23%)	0.627
GINA treatment step**			
• 1-3	2 (33%)	19 (32%)	1.000
• 4-5	4 (67%)	41 (68%)	
FVC%			
• Median	81	93	0.069
• IQR	(70-84)	(82-102)	
FEV1%			
• Median	70	86	0.049
• IQR	(68-80)	(77-94)	
FEV1/FVC-ratio			
• Median	0.775	0.76	0.706
• IQR	(0.68-0.79)	(0.73-0.78)	

35

36 * Unless otherwise specified, the number of the patients was 66, 6 of whom were exposed to
37 oxidizing agents and 60 to other agents. Numerical values expressed as median and
38 interquartile ranges (IQR), categorical values as n (% of patients involved).

39 ** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report

40 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second

41 FVC and FVC%, forced vital capacity and predicted forced vital capacity

42 **Table E3.4. Combined corrosive agents vs. others**

Characteristics	Corrosive agents (n=29)*	Other agents (n=37)*	P-value
Short-acting beta agonists daily (n=57)	10 (38%)	7 (23%)	0.249
Exacerbation after previous appointment	8 (28%)	8 (22%)	0.773
GINA treatment step **			
• 1-3	7 (24%)	14 (38%)	0.292
• 4-5	22 (76%)	23 (62%)	
FVC%			
• Median	94	86	0.317
• IQR	(82-102)	(80.5-97.5)	
FEV1%			
• Median	87	81	0.089
• IQR	(78-99)	(74.5-89)	
FEV1/FVC-ratio			
• Median	0.78	0.74	0.008
• IQR	(0.745-0.805)	(0.71-0.77)	

43 * Unless otherwise specified, the number of the patients was 66, 29 of whom were exposed to
44 combined corrosive agents (hazard classification of Skin Corr 1A or Skin Corr 1B) and 37 to other agents.
45 Numerical values expressed as median and interquartile ranges (IQR), categorical values as n (% of patients
46 involved).

47 ** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report
48 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second
49 FVC and FVC%, forced vital capacity and predicted forced vital capacity

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9 **Table E4. Clinical characteristics of patients with irritant-induced asthma six to eight months**
 10 **after the occupational asthma diagnosis, classification according to initiation time of inhaled**
 11 **corticosteroids within one week or more of exposure event.**

Characteristics	ICS ≤ 1 week (n=18) *	ICS > 1 week (n=48) *	p-value
Short-acting beta agonists daily (n=57)	3 (19%)	14 (34%)	0.342
Exacerbation after previous appointment	6 (33%)	10 (21%)	0.340
GINA treatment step **			
• 1-3	7 (39%)	14 (29%)	0.555
• 4-5	11 (61%)	34 (71%)	
FVC%			
• Median	85.5	95	0.365
• IQR	(82-93)	(81-102)	
FEV1%			
• Median	81	86	0.330
• IQR	(74-87)	(77-94)	
FEV1/FVC-ratio			
• Median	0.755	0.77	0.669
• IQR			

	(0.71-0.78)	(0.73-0.79)	
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12

13 * Unless otherwise specified, the number of the patients was 66, 18 of whom initiated inhaled
14 corticosteroids within one week of exposure event and 48 initiated after one week.
15 Numerical values expressed as median and interquartile range (IQR), categorical values as n
16 (% of patients involved).

17 ** Global Initiative for Asthma (GINA) treatment step classification follows 2020 report
18 FEV1 and FEV1%, forced expiratory volume and predicted forced expiratory volume in first second
19 FVC and FVC%, forced vital capacity and predicted forced vital capacity