ABSTRACT

Introduction Moisture damage (MD) exposure at work has been shown to increase the risk of new onset asthma and exacerbation of asthma. However, most of the studies in this field have been questionnaire studies. A small proportion of MD-exposed workers are diagnosed with asthma. Many patients with MD exposure at work referred to secondary healthcare report intermittent hoarseness, loss of voice or difficulty to inhale, referring to functional or organic problems of the larynx. For accurate treatment, proper differential diagnostics is paramount. We present an ongoing observational study in which we describe the prevalence of respiratory, voice and other symptoms related to MD at work in patients referred to secondary healthcare. Case-control setting will be used to evaluate the frequencies of the background factors, bronchial hyperreactivity and laryngeal findings.

Methods and analysis The study sample consists of patients with workplace MD exposure and associated respiratory tract and/or voice symptoms referred to Tampere University Hospital. The clinical tests conducted to the study patients included comprehensive lung function tests, laboratory and skin prick tests, imaging and clinical evaluation by specialists of respiratory medicine, oto-rhino-laryngology and phoniatrics. The exposure assessment was performed by an occupational physician. The study patients filled out a questionnaire on previous illnesses and other background factors, which for comparison was also sent to 1500 Finnish-speaking people in the same hospital district. The exposure assessment was conducted to 50 asymptomatic volunteers.

Ethics and dissemination The regional ethics committee of Tampere University Hospital approved the study. All study subjects gave their written informed consent, which is required also from the controls. The results will be communicated locally and internationally as conference papers and journal articles.

INTRODUCTION

Indoor air quality problems are considered important risk factors for health problems worldwide.1 Indoor air-associated symptoms may be interrelated with different indoor air factors such as insufficient ventilation,2 unfavourable temperature conditions,3 dry indoor air,4 dustiness,5 moisture damage (MD),1 volatile organic compounds (VOC),6 and man-made mineral/vitreous fibres (MMMF/MMVF).7 Even if we do not know the cause of symptoms,1 MD exposure at work has been shown to increase the risk of new onset asthma and exacerbation of asthma.8 9 Other illnesses or respiratory symptoms that have been associated with MD exposure include cough, wheezing, dyspnoea, rhinitis and upper respiratory tract symptoms.9 10

In Finland, located in subarctic area, MDs in residences and schools are common.11 Workers in office buildings commonly report symptoms and complaints associated with indoor air.12 13 There is also a growing public concern over MDs in buildings and their possible permanent effects on dwellers’ or workers’ health in Finland, even if there is minor evidence of serious or permanent illnesses other than asthma caused by exposure to MD.9 14
There are few studies describing the clinical findings in patients having symptoms when exposed to MD at work. Previous studies in this field have mainly been epidemiological, and most is known about children’s risk of developing symptoms in homes or schools with MD. In majority of the studies, the assessment of exposure to MD or presence of symptoms or illnesses has been based on questionnaires. Furthermore, only a small proportion of MD-exposed workers are diagnosed with asthma. According to our clinical experience, many patients with work-related MD exposure and referred to secondary healthcare report intermittent hoarseness, loss of voice or difficulty to inhale, which would refer to functional or organic problems of the larynx. In the case of laryngeal disorders, asthma medication is not useful or may even worsen the symptoms if the larynx is sensitive to irritation. Coexisting with asthma, laryngeal disorders may be the cause of insufficient response to asthma treatment.

Studies over the past decades have provided important information on idiopathic environmental intolerance (IEI), in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms to most people. In odour or multiple chemical sensitivity (MCS), a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems. It seems that some proportion of the patients who have indoor air-associated symptoms in fact have IEI/MCS, but the frequency of this condition among these patients is not known.

As a conclusion, there is a need for a clinical study on patients exposed to MD at workplace focusing especially on differential diagnostics between asthma and laryngeal symptoms, evidence of exposure to MDs and other indoor air risk factors and chemical sensitivity.

Aims of the study
In patients referred to secondary healthcare because of respiratory tract and/or voice symptoms associated to MD exposure at work, the aims are to:
1. Describe the prevalence of different characteristics, symptoms and clinical test findings.
2. Find out the frequency of laryngeal symptoms and their possible influence on asthma diagnostics.
3. Explore the number of patients who fulfill the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory (QEESI) question series.
4. Find out if there are connections between abovementioned symptoms and clinical findings and if it would be possible to allocate the clinical tests according to patient’s symptoms in secondary healthcare.

METHODS AND ANALYSIS
The study is conducted at Tampere University Hospital, which is a secondary level referral centre for a population of 530 000 and a tertiary level referral centre for a population of about 1 million people. Patients referred to departments of Occupational Medicine or Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects between October 2015 and June 2017. The study inclusion criteria were as follows: (1) age between 18 and 65 years, (2) upper and/or lower respiratory tract and/or voice symptoms, (3) symptoms associated to workplace and (4) at least a strong suspicion of MD at the workplace (box 1). The exclusion criteria were as follows: (1) severe illness (eg, cancer) and (2) pregnancy. The study design is presented in figure 1. After the study subjects had given their informed signed consent, the work-associated symptoms were collected by a structured interview. If the patient was not sure if the symptom
Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines, and methacholine challenge test using dosimeter with controlled tidal breathing according to Finnish guidelines. To investigate if possible asthma is associated with work, the patients performed PEF monitoring at and off work with Vitalograph PEF/FEV Diary device. Diffusing capacity of the lungs and exhaled nitric oxide were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-laryngology (JN) and phoniatrics (SV) examined the patients. For diagnosing laryngeal disorders, videolaryngostroboscopy with either rigid or fibre-optic scope was performed, voice samples were recorded and also inspirograms were recorded before and after methacholine tests. Biopsy of nasal mucosa and a blood sample were taken and preserved for later analyses.

Exposure to MD at work was assessed from the documents of the building and indoor air quality investigations made at the workplace, if available, according to Finnish guidelines. A confirmed MD is graded into different severity categories, if sufficient information is available. Also, MMMFs, VOCs or problems in ventilation conditions at workplace were assessed if these had been measured.

As a non-responder analysis, of the patients who were invited but who did not take part in the study, age, symptoms, the presence of asthma diagnosis and exposure will be evaluated based on patient records.

To explore how common laryngeal disorders are in general, methacholine challenge test, voice recording, clinical examination by the specialist of phoniatrics including videolaryngostroboscopy, FEV₁ and skin prick tests will be conducted to 50 asymptomatic volunteers adjusted for age and gender. The gathering of the volunteers began in August 2018 and it is our estimation that all the volunteers will be examined by the end of 2019.

**Questionnaire/survey**

The study patients and the volunteers fill out a questionnaire including questions on previous diseases, medication and upper and lower respiratory symptoms, Sinusitis symptoms (Sino-Nasal Outcome Test-22). Voice symptoms (Voice Activity and Participation Profile, Voice Handicap Index, Voice Disorder Questionnaire). Laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire). Reflux symptoms (Reflux Symptom Index). Depression and anxiety symptoms (General Health Questionnaire GHQ-15, Generalised Anxiety Disorder 7-item scale). Psychosocial work load and stress symptoms. Chemical sensitivity (QEESI). To find out if the study group would have different background characteristics from the overall population, the same questionnaire was sent to 1500 Finnish-speaking people in the same hospital district.

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### Table 1 The clinical tests conducted to the study patients

| Lung function tests | Two-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FEV₁₅₀), diffusing capacity of the lungs |
|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Laboratory tests    | Sedimentation rate, C-reactive protein, blood count, serum total IgE, serum allergen-specific IgE (different fungi and storage mites Acarus Siro, Lepidoglyphus Destructor, Tyrophagus putrescentiae) |
| Skin prick tests    | Birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, latex, aspergillus fumigatus, storage mites Acarus Siro, Lepidoglyphus Destructor, Tyrophagus putrescentiae |
| Imaging             | Chest x-ray, cone beam CT of the paranasal sinuses |

PEF, peak expiratory flow.

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### Table 2 The criteria based on which asthma is diagnosed in different clinical tests

| Clinical test               | Criteria for asthma                                                                 |
|-----------------------------|--------------------------------------------------------------------------------------|
| Two-week PEF monitoring     | At least three times                                                                  |
|                             | ► At least 15% and 60 L/min improvements of PEF after bronchodilator                  |
|                             | ► Diurnal variation of PEF at least 20% and 60 L/min.                                  |
| Spirometry                  | At least 200 mL and 12% improvement in FEV₁ or FVC after bronchodilator              |
| Methacholine challenge test | Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV₁ (PD20FEV₁ < 600 µg) |

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow.
randomly selected by the Finnish Population Information System. The proportions of women and men and different age groups in this comparison material are similar to the study population.

Sample size and power calculation
We estimated that a sample of 100 patients is enough to clinical deduction of the different characteristics of this patient group.

Concerning the population-based comparison material, our aim was to get 400 questionnaire answers (ratio 1:4) to increase the statistical power. Taking recent rather low survey response rates into account, we sent the questionnaire to 1500 people.

To assess if findings suggesting laryngeal disorders are more frequent among those who have respiratory tract or voice symptoms associated to workplace MD, data on frequency of laryngeal findings of asymptomatic people are needed. When analysing the findings of methacholine challenge test of 30 patients, signs of laryngeal disorders were found in 62.5%. We estimated that among <30% of asymptomatic people there are such findings in the methacholine challenge test. In power calculation based on findings in the methacholine challenge test, the number of asymptomatic people tested would be 50 with 80% force and 90% CI.

Data analyses
We will analyse descriptive statistics (mean, median or proportion depending on the variable type and distribution) for variables such as gender distribution and age of the patients and their lines of business. We will also analyse the frequencies of different symptoms the patients complain and how these are related to objective findings in different organ systems or new diagnoses of, for example, asthma or laryngeal dysfunction. We will describe the proportions of patients with significant findings in medical assessment at different specialities (ENT, pulmonary and phoniatrics). We will compare frequencies and intensities of different symptoms and clinical findings between the patients and symptomless controls. We will also compare different background factors of the study patients, such as perceived psychosocial work load, with controls of the population who answered to the same questionnaire as the study patients. Dichotomous variables between two groups (patients vs controls or among patients with or without a certain finding) will be compared using χ² test and Fisher’s exact test, while continuous variables between two groups will be analysed by t-test or Mann-Whitney test depending on the distributions. Multiple logistic regression will be used to assess independent predictors of certain clinical findings among the patients. Based on the relationship between symptoms and different objective findings, we aim to find ‘clinical triggers’ (certain sets of symptoms) that should prompt clinicians to refer patients to certain specialities.

Patient and public involvement
Patients or public were not involved in the design of the study. The study patients have received the results of their own tests, explanations for them and necessary treatment.

ETHICS AND DISSEMINATION
The regional ethics committee of Tampere University Hospital has approved the study (R14095). All study subjects gave their written informed consent, which is required also from the volunteers. The study adheres to good clinical research guidelines and the Helsinki Declaration.47

The results will be communicated locally as well as internationally as conference papers and journal articles.

REFERENCES
1. WHO. WHO Guidelines for indoor air quality: dampness and mould. Copenhagen: WHO Regional Office for Europe, 2009. http://www.euro.who.int/__data/assets/pdf_file/0017/43325/E92645.pdf.
2. Muscatello N, McCarthy A, Kiebl C, et al. Classroom conditions and CO2 concentrations and teacher health symptom reporting in 10 New York State Schools. Indoor Air 2015;25:157–67.
3. Skyberg K, Skulberg KR, Eduard W, et al. Symptoms prevalence among office employees and associations to building characteristics. Indoor Air 2003;13:246–52.
4. Wolkoff P. Indoor air humidity, air quality, and health - An overview. Int J Hyg Environ Health 2016;221:376–90.
5. Schneider T. Dust and fibers as a cause of indoor environment problems. Scand J Work Environ Heal Suppl 2008;4:10–17.
6. Salonen H, Pasanen AL, Lappalainen S, et al. Volatile organic compounds and formaldehyde as explaining factors for sensory irritation in office environments. J Occup Environ Hyg 2009;6:239–47.
7. Salonen HJ, Lappalainen SK, Ruutiala HM, et al. Man-made vitreous fibers in office buildings in the Helsinki area. J Occup Environ Hyg 2009;6:624–31.

8. Karvala K, Tskala E, Luukkanen R, et al. Prolonged exposure to dust and moldy workplaces and ventilation in Finnish hospitals. Int J Hyg Environ Health 2017;219:545–54.

9. Mendell MJ, Mirer AG, Cheng K, et al. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. Environ Health Perspect 2011;119:748–56.

10. Jaakkola JJ, Hwang BF, Jaakkola MS. Home dampness and molds as determinants of allergic rhinitis in childhood: a 6-year, population-based cohort study. Am J Epidemiol 2010;172:451–9.

11. Täubel M, Karvonen AM, Reponen T, et al. Sensory and respiratory symptoms among workers at a Veterans Administration Medical Center. Int Arch Occup Environ Health 2014;87:691–9.

12. Ministry of Social Affairs and Health F. Occupational Allergies and Asthma. Helsinki, 2009.

13. Huraff J, Heinzow B, Aurbach U, et al. Validity of a single-item measure of health-related quality of life for patients with allergic rhinitis. J Asthma 2014;69:292–304.

14. Salmiväli T, Karvonen AM, Hyvärinen A, Korppi M, et al. Prolonged exposure to dust and moldy workplaces and new-onset asthma. Int J Hyg Environ Health 2013;216:148–54.

15. Lahtinen M, Sundman-Digert C, Reijula K, et al. Application of the Environmental Relative Moldiness Index in Finland. Appl Environ Microbiol 2016;82:578–84.

16. Täubel M, Karvonen AM, Reponen T, et al. Sensory and respiratory symptoms among workers at a Veterans Administration Medical Center. Int Arch Occup Environ Health 2014;87:691–9.

17. Ministry of Social Affairs and Health F. Assessment of indoor air problems at work with a questionnaire. Occup Environ Med 2004;61:33–8.

18. Ministry of Social Affairs and Health F. Moisture Damages in Workplaces. Memo of the Working Group on Moisture Damages (in Finnish). Helsinki, 2009.

19. Hellgren UM, Hyvärinen M, Holopainen R, et al. Perceived indoor air quality, air-moldy workplaces and ventilation in Finnish hospitals. Int J Occup Environ Health 2017;219:545–54.

20. Karvonen AM, Hyvärinen A, Korppi M, et al. Moisture damage and asthma: a birth cohort study. Pediatrics 2015;135:e598–606.

21. Borrás-Santos A, Jacobs JH, Täubel M, et al. Dampness and mould in schools: respiratory symptoms in children: the HITEA study. Occup Environ Med 2013;70:681–7.

22. Kim JL, Henneberger PK, Lohman S, et al. Impact of occupational exposures on exacerbation of asthma: a population-based asthma cohort study. BMC Pulm Med 2016;16:148.

23. Kurth L, Virji MA, Storj E, et al. Current asthma and asthma-like symptoms among workers at a Veterans Administration Medical Center. Int J Hyg Environ Health 2017;220:1325–32.

24. Moscato G, Pala G, Cullinan P, et al. EAAI Position Paper on assessment of the Occupational Allergy and Asthma Questionnaire. J Allergy Clin Immunol 2010;126:445–8.

25. Täubel M, Karvonen AM, Reponen T, et al. Sensory and respiratory symptoms among workers at a Veterans Administration Medical Center. Int Arch Occup Environ Health 2014;87:691–9.

26. Verstegen AW, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. Cough 2014;10:1.

27. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health 1999;15:370–85.

28. Haataela T, Lehtimäki L, Ahonen E, et al. [Update on current care guidelines: asthma]. Duodenum 2013;129:994–5.

29. Miller MR, Hancock J, Brussacso V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319–38.

30. Niemen MM, Lahdensonu A, Kellomaeki L, et al. Methacholine bronchial challenge using a dosimeter with controlled tidal breathing. Thorax 1988;43:894–900.

31. Surje A, Crapo RO, Viegi G, et al. Respiratory and allergic symptoms among workers in a damp and moldy workplaces and new-onset asthma. Int Arch Occup Environ Health 2013;86:49–56.

32. Spitzer RL, Kroenke K, Williams JB, et al. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2006;21:259–306.

33. Macintyre N, Crapo RO, Viegi G, et al. Respiratory and allergic symptoms among workers in a damp and moldy workplaces and new-onset asthma. Int Arch Occup Environ Health 2013;86:49–56.

34. Vertigan AE, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. Cough 2014;10:1.

35. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the Voice Handicap Index [In Finnish] [master thesis], 2003.

36. Sala E, Laine A, Simberg S, et al. The prevalence of voice disorders among day care center teachers compared with nurses: a questionnaire and clinical study. J Voice 2001;15:413–23.

37. Torfstein G, Vepret M, Sørum H, et al. A review of sinonasal outcome scoring systems - which is best? Clin Otolaryngol 2006;31:103–9.

38. Suzkanen O, Silho M, Rorarius E, et al. Voice Activity and Participation Profile (VAPP) in assessing the effects of voice disorders on patients’ quality of life: validity and reliability of the Finnish version of VAPP. Logoped Phoniatr Vocol 2007;32:3–8.

39. Alaukusa SJM. Psycho-social handicap of voice disorder and its rehabilitation: a pilot study of Finnish Version of Voice Handicap Index [In Finnish]. J Voice 2011;25:462–9.

40. Vepret M, Sørum H, Torfstein G, et al. Voice Activity and Participation Profile (VAPP) in assessing the effects of voice disorders on patients’ quality of life: validity and reliability of the Finnish version of VAPP. Logoped Phoniatr Vocol 2007;32:3–8.

41. Vertigan AE, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. Cough 2014;10:1.

42. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflex symptom index (RSI). J Voice 2002;16:274–7.

43. Målikangas A, Feldt K, Kinnunen U, et al. The factor structure and factorial invariance of the 12-item General Health Questionnaire (GHQ-12) across time: evidence from two community-based samples. Psychol Assess 2006;18:444–51.

44. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092.

45. Lahtinen M, Sundman-Digert C, Reijula K. Psychosocial work environment and indoor air problems: a questionnaire as a means of problem diagnosis. Occup Environ Med 2004;61:143–9.

46. Elo AL, Leppänen A, Jokola A. Validity of a single-item measure of stress symptoms. Scand J Work Environ Health 2003;29:444–51.

47. World Medical Association. World Medical Association Declaration of Helsinki. JAMA 2013;310:2191–4.