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The SAMDAW study protocol: A clinical descriptive study on Symptoms Associated to Moisture DAMAGE at Workplace

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Manuscripts

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3 **The SAMDAW study protocol: A clinical descriptive study on Symptoms**
4 **Associated to Moisture DAmage at Workplace**
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56 **Abstract**
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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 cross-sectional questionnaire studies. Small proportion of MD exposed workers are diagnosed with asthma. Many patients with MD exposure at work referred to secondary health care 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. In this clinical study, we describe the prevalence of respiratory, voice and other symptoms related to MD at work in patients referred to secondary health care.

Methods and analysis

The study sample consists of patients with moisture damage exposure at work 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 a specialist of occupational medicine. The study patients filled out a questionnaire on previous illnesses, symptoms and psychosocial work load. 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 randomly selected by the Finnish Population Information System. To explore how common laryngeal disorders and voice symptoms are in general, a part of the tests will be conducted to 50 asymptomatic volunteers.

Ethics and dissemination

The regional ethics committee of Tampere University Hospital has 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.

Strengths and limitations of this study

- This kind of comprehensive clinical study associated with moisture damage exposure at work has not been conducted before.
- This study will increase the understanding of respiratory tract and voice symptoms, and associated clinical findings in subjects exposed to moisture damage.
- Information of moisture damage exposure at work is based on documents from the workplace
- Limitation of a cross-sectional study like this is that it is not possible to obtain information on causal relationships between exposure and symptoms or illnesses

Introduction

Indoor air quality problems are considered important risk factors for health problems worldwide¹. Indoor air associated symptoms may be interrelated with different indoor air factors such as insufficient ventilation, unfavourable temperature conditions, dry indoor air, dustiness, moisture damage (MD), volatile organic compounds (VOC), and man-made mineral/ vitreous fibres (MMMMF/ MMVF). Even if we do not know the exact cause of symptoms¹ MD exposure at work has been shown to increase the risk of new onset asthma and exacerbation of asthma^{2,3}. Other illnesses or respiratory symptoms that have been associated with MD exposure include cough, wheezing, dyspnoea, rhinitis, and upper respiratory tract symptoms^{3,4}.

In Finland, located in subarctic area, MDs in residences and schools are common⁵. Workers in office buildings commonly report symptoms and complaints associated with indoor air^{6,7}. 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 only a little evidence of serious or permanent illnesses other than asthma caused by exposure to dampness^{3,8}.

There are few studies describing the clinical findings in patients having symptoms when exposed to MD at work^{9,10}. However, previous studies in this field have mainly been epidemiological³, and most is known about children's risk of developing symptoms in homes or schools with MD^{11,12}. In majority of the studies, the assessment of exposure to MD or presence of symptoms or illnesses has been based on questionnaires^{13,14}. Furthermore, only a small proportion of MD exposed workers are diagnosed with asthma². To our clinical experience, many patients with MD exposure at work referred to secondary health care report intermittent

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3 hoarseness, loss of voice or difficulty to inhale, which would refer to functional or
4 organic problems of the larynx¹⁵. In the case of laryngeal disorders, asthma
5 medication is not useful or may even worsen the symptoms if the larynx is sensitive
6 to irritation¹⁶. Coexisting with asthma, laryngeal disorders may cause insufficient
7 response to asthma treatment.
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13 Studies over the past decades have provided important information on idiopathic
14 environmental intolerance (IEI), in which a person has symptoms from different
15 organ systems when in contact with an environmental factor that does not cause
16 symptoms to most people¹⁷. In odour or multiple chemical sensitivity (MCS) a person
17 reacts with symptoms in association with low levels of airborne chemicals that most
18 people tolerate without problems¹⁸. It seems that some proportion of the patients that
19 have indoor air associated symptoms in fact have IEI/MCS, but the frequency of this
20 condition among these patients is not known.
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31 32 33 *Aims of the study*

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35 In patients referred to secondary health care because of respiratory tract and/ or
36 voice symptoms associated to MD exposure at work, the aim is to:
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- 39 1) Describe the prevalence of different characteristics, symptoms and clinical
40 test findings
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- 43 2) Find out the frequency of laryngeal symptoms and their possible effect on
44 asthma diagnostics
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- 47 3) Explore the number of patients that fulfil the criteria of chemical sensitivity
48 according to QEESI[®] question series¹⁹.
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3 4) Find out if there are connections between above mentioned symptoms and
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5 clinical findings and if it would be possible to allocate the clinical tests
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7 according to patient's symptoms in secondary health care.
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11 **Methods and analysis**

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15 The study is conducted at Tampere University Hospital, which is a secondary level
16 referral centre for a population of 530 000 and a tertiary level referral centre for a
17 population of about 1 million people. Patients referred to departments of
18 Occupational Medicine or Phoniatics or Allergy Centre because of symptoms
19 associated with indoor complaints at their workplace were interviewed as possible
20 study subjects between October 2015 and June 2017. The study inclusion criteria
21 were 1) age between 18 and 65 years, 2) upper and/or lower respiratory tract and/or
22 voice symptoms, 3) symptoms associated to workplace, and 4) at least a strong
23 suspicion of MD at the workplace (Table 1). The exclusion criteria were 1) severe
24 illness (e.g. cancer) and 2) pregnancy. The study design is presented in Figure 1.
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26 After the study subjects had given their informed signed consent, the work-
27 associated symptoms were collected by a structured interview. If the patient was not
28 sure if the symptom was more frequent at work, it was not considered to be work-
29 associated.
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46 The conducted clinical tests are presented in Table 2. According to Finnish asthma
47 guideline²⁰, diagnosis of asthma must be confirmed with a demonstration of variable
48 airway obstruction in lung function measurements: i) peak expiratory flow (PEF)
49 monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial
50 hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients
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3 carried out a two-week PEF monitoring, spirometry with bronchodilation test and
4 methacholine challenge test. The PEF monitoring included PEF measurements with
5 Pinnacle™ peak flow meter for two weeks in the morning and evening before and
6 after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed
7 according to European Respiratory Society/American Thoracic Society guidelines²¹
8 and methacholine challenge test using dosimeter with controlled tidal breathing
9 according to Finnish guidelines²². To investigate if possible asthma is associated
10 with work the patients performed PEF monitoring at and off work²³ with Vitalograph®
11 PEF/FEV Diary device. Diffusing capacity of the lungs²⁴ and exhaled nitric oxide
12 (FE_{NO})²⁵ were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-
13 laryngology (JN) and phoniatics (SV) examined the patients. For diagnosing
14 laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was
15 performed, voice samples were recorded and also inspirograms were recorded
16 before and after methacholine tests. Biopsy of nasal mucosa and a blood sample
17 were taken and preserved for later analyses.

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20 Exposure to MD at work was assessed from the documents of the building and
21 indoor air quality investigations made at the workplace, if available, according to
22 Finnish guidelines²⁶. Also, MMMFs, VOCs or problems in ventilation conditions at
23 workplace were assessed, if these had been investigated.

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

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31 To explore how common laryngeal disorders are in general, methacholine challenge
32 test, voice recording, clinical examination of the specialist of phoniatics including
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3 videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50
4 asymptomatic volunteers adjusted for age and gender.
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7 *Questionnaire/ survey*

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10 The study patients and the volunteers fill out a questionnaire including questions on

- 11 - previous diseases, medication and upper and lower respiratory symptoms²⁷
- 12 - sinusitis symptoms (Sino-Nasal Outcome Test-22²⁸)
- 13 - voice symptoms (Voice Activity and Participation Profile²⁹, Voice Handicap
- 14 Index³⁰, voice disorder questionnaire³¹)
- 15 - laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire³²)
- 16 - reflux symptoms (Reflux Symptom Index³³)
- 17 - depression and anxiety symptoms (General Health Questionnaire GHQ-12³⁴;
- 18 Generalized Anxiety Disorder 7-item scale³⁵)
- 19 - psychosocial work load³⁶, and stress symptoms³⁷
- 20 - chemical sensitivity (QEESI¹⁹)

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23 To find out if the study group would have different background characteristics from
24 the overall population, the same questionnaire was sent to 1500 Finnish speaking
25 people in the same hospital district randomly selected by the Finnish Population
26 Information System. The proportions of women and men and different age groups in
27 this comparison material are similar to the study population.
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30 *Sample size and power calculation*

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32 It is estimated that a sample of 100 patients is enough to clinical deduction of the
33 different characteristics of this patient group.
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3 Concerning the population-based comparison material, our aim was to get 400
4 questionnaire answers (ratio 1:4) to increase the statistical power. Taking recent
5 rather low survey response rates into account, we sent the questionnaire to 1500
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9 people.

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12 To assess if findings suggesting laryngeal disorders are more frequent among those
13 who have respiratory tract or voice symptoms associated to workplace MD, data on
14 frequency of laryngeal findings of asymptomatic people is needed. When analyzing
15 the findings of methacholine challenge test of 30 patients, signs of laryngeal
16 disorders were found in 62,5%. We estimated that among under 30% of
17 asymptomatic people there are such findings in the methacholine challenge test. In
18 power calculation based on findings in the methacholine challenge test, the number
19 of asymptomatic people tested would be 50 with 80% force and 90% confidence
20 interval.
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31 *Data analyses*

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33 We will conduct standard descriptive statistics to determine the frequency of different
34 symptoms, findings of clinical tests and their interrelations.
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40 **Ethics and dissemination**

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42 The regional ethics committee of Tampere University Hospital has approved the
43 study (R14095). All study subjects gave their written informed consent, which is
44 required also from the volunteers. The study adheres to good clinical research
45 guidelines and the Helsinki Declaration³⁸.
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52 The results will be communicated locally as well as internationally as conference
53 papers and journal articles.
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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. Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H. Prolonged exposure to damp and moldy workplaces and new-onset asthma. *Int Arch Occup Environ Health*. 2011;84(7):713-721. doi:10.1007/s00420-011-0677-9
3. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic health effects of dampness, mold, and dampness-related agents: a review of the epidemiologic evidence. *Environ Health Perspect*. 2011;119(6):748-756. doi:10.1289/ehp.1002410
4. Jaakkola JJK, Hwang B-F, 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(4):451-459. doi:10.1093/aje/kwq110
5. Täubel M, Karvonen AM, Reponen T, Hyvärinen A, Vesper S, Pekkanen J. Application of the Environmental Relative Moldiness Index in Finland. *Appl Environ Microbiol*. 2015;82(2):578-584. doi:10.1128/AEM.02785-15
6. Reijula K, Sundman-Digert C, Reijula K. Assessment of indoor air problems at work with a questionnaire. *Occup Environ Med*. 2004;61(1):33-38. doi:10.1136/oem.2002.005835
7. Ministry of Social Affairs and Health F. *Moisture Damages in Workplaces. Memo of the Working Group on Moisture Damages (in Finnish)*. Helsinki;

- 2009.
8. Hurraß J, Heinzow B, Aurbach U, et al. Medical diagnostics for indoor mold exposure. *Int J Hyg Environ Health*. 2017;220(2):305-328. doi:10.1016/j.ijheh.2016.11.012
 9. White SK, Cox-Ganser JM, Benaise LG, Kreiss K. Work-related peak flow and asthma symptoms in a damp building. *Occup Med (Chic Ill)*. 2013;63(4):287-290. doi:10.1093/occmed/kqt028
 10. Hellgren U-M, Hyvärinen M, Holopainen R, Reijula K. Perceived indoor air quality, air-related symptoms and ventilation in Finnish hospitals. *Int J Occup Med Environ Health*. 2011;24(1):48-56. doi:10.2478/s13382-011-0011-5
 11. Karvonen AM, Hyvarinen A, Korppi M, et al. Moisture Damage and Asthma: A Birth Cohort Study. *Pediatrics*. 2015;135(3):e598-e606. doi:10.1542/peds.2014-1239
 12. Borràs-Santos A, Jacobs JH, Täubel M, et al. Dampness and mould in schools and respiratory symptoms in children: the HITEA study. *Occup Environ Med*. 2013;70(10):681-687. doi:10.1136/oemed-2012-101286
 13. Kim J-L, 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(1):148. doi:10.1186/s12890-016-0306-1
 14. Kurth L, Virji MA, Storey E, et al. Current asthma and asthma-like symptoms among workers at a Veterans Administration Medical Center. *Int J Hyg Environ Health*. 2017;220(8):1325-1332. doi:10.1016/j.ijheh.2017.09.001
 15. Moscato G, Pala G, Cullinan P, et al. EAACI position paper on assessment of

- 1
2
3 cough in the workplace. *Allergy Eur J Allergy Clin Immunol*. 2014.
4
5 doi:10.1111/all.12352
6
7
- 8 16. Idrees M, FitzGerald JM. Vocal cord dysfunction in bronchial asthma. A review
9
10 article. *J Asthma*. 2015;52(4):327-335. doi:10.3109/02770903.2014.982288
11
12
- 13 17. Wolf C. Multiple chemical sensitivity (MCS). *Environ Sci Pollut Res*.
14
15 1996;3(3):139-143. doi:10.1007/BF02985520
16
17
- 18 18. Dantoft TM, Andersson L, Nordin S, Skovbjerg S. Chemical intolerance. *Curr*
19
20 *Rheumatol Rev*. 2015;11(2):167-184.
21
22 <http://www.ncbi.nlm.nih.gov/pubmed/26088215>. Accessed May 14, 2018.
23
24
- 25 19. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory
26
27 (EESI): a standardized approach for measuring chemical intolerances for
28
29 research and clinical applications. *Toxicol Ind Health*. 1999;15(3-4):370-385.
30
31 doi:10.1177/074823379901500311
32
33
- 34 20. Haahtela T, Lehtimäki L, Ahonen E, et al. [Update on current care guidelines:
35
36 asthma]. *Duodecim*. 2013;129(9):994-995.
37
38 <http://www.ncbi.nlm.nih.gov/pubmed/23786112>. Accessed May 18, 2018.
39
40
- 41 21. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur*
42
43 *Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805
44
45
- 46 22. Nieminen MM, Lahdensuo A, Kellomaeki L, Karvonen J, Muittari A.
47
48 Methacholine bronchial challenge using a dosimeter with controlled tidal
49
50 breathing. *Thorax*. 1988;43(11):896-900.
51
52 <http://www.ncbi.nlm.nih.gov/pubmed/3065974>. Accessed May 18, 2018.
53
54
- 55 23. Burge PS. Use of serial measurements of peak flow in the diagnosis of
56
57
58
59
60

- 1
2
3 occupational asthma. *Occup Med.* 1993;8(2):279-294.
4
5 <http://www.ncbi.nlm.nih.gov/pubmed/8506506>. Accessed May 19, 2017.
6
7
8 24. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath
9
10 determination of carbon monoxide uptake in the lung. *Eur Respir J.*
11
12 2005;26(4):720-735. doi:10.1183/09031936.05.00034905
13
14
15 25. Horváth I, Barnes PJ, Loukides S, et al. A European Respiratory Society
16
17 technical standard: exhaled biomarkers in lung disease. *Eur Respir J.*
18
19 2017;49(4):1600965. doi:10.1183/13993003.00965-2016
20
21
22 26. Latvala J, Karvala K, Sainio M, et al. *Guidelines for Workplace and*
23
24 *Occupational Health Actions in Indoor Air Problems (Finnish).*
25
26 Työterveyslaitos; 2017. <http://www.julkari.fi/handle/10024/132078>. Accessed
27
28 August 20, 2018.
29
30
31 27. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new
32
33 questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults.
34
35 *Allergy.* 2001;56(5):377-384. doi:10.1034/j.1398-9995.2001.056005377.x
36
37
38 28. Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which
39
40 is best? *Clin Otolaryngol.* 2006;31(2):103-109. doi:10.1111/j.1749-
41
42 4486.2006.01155.x
43
44
45 29. Sukanen O, Sihvo M, Rorarius E, Lehtihalmes M, Autio V, Kleemola L. Voice
46
47 Activity and Participation Profile (VAPP) in assessing the effects of voice
48
49 disorders on patients' quality of life: Validity and reliability of the Finnish
50
51 version of VAPP. *Logop Phoniatr Vocology.* 2007;32(1):3-8.
52
53
54 doi:10.1080/14015430600784386
55
56
57
58
59
60

- 1
2
3 30. Alaluusua S JM. Psycho-social handicap of voice disorder and its
4 rehabilitation: a pilot study of Finnish version of Voice Handicap Index [In
5 Finnish] [master thesis]. 2003.
6
7
8
9
10 31. Sala E, Laine A, Simberg S, Pentti J, Suonpää J. The prevalence of voice
11 disorders among day care center teachers compared with nurses: a
12 questionnaire and clinical study. *J Voice*. 2001;15(3):413-423.
13
14
15
16 doi:10.1016/S0892-1997(01)00042-X
17
18
19 32. Vertigan AE, Bone SL, Gibson PG. Development and validation of the
20 Newcastle laryngeal hypersensitivity questionnaire. *Cough*. 2014;10(1):1.
21
22
23
24 doi:10.1186/1745-9974-10-1
25
26
27 33. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux
28 symptom index (RSI). *J Voice*. 2002;16(2):274-277.
29
30
31
32 http://www.ncbi.nlm.nih.gov/pubmed/12150380. Accessed June 26, 2018.
33
34 34. Mäkikangas A, Feldt T, Kinnunen U, Tolvanen A, Kinnunen M-L, Pulkkinen L.
35 The factor structure and factorial invariance of the 12-item General Health
36 Questionnaire (GHQ-12) across time: evidence from two community-based
37 samples. *Psychol Assess*. 2006;18(4):444-451. doi:10.1037/1040-
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52 35. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing
53 Generalized Anxiety Disorder. *Arch Intern Med*. 2006;166(10):1092.
54
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3 <http://oem.bmj.com/content/61/2/143.abstract>.

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5
6 37. Elo A-L, Leppänen A, Jahkola A. Validity of a single-item measure of stress
7 symptoms. *Scand J Work Environ Health*. 2003;29(6):444-451.

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10 doi:10.5271/sjweh.752

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13 38. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191.

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15 doi:10.1001/jama.2013.281053

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19 **Authors' contributions:** JU is the head of the study group and PN the principal
20 researcher. All the writers took part in developing the study protocol; JU and PN
21 especially planning the exposure assessment, JK, LL and AT the lung function
22 diagnostics measures, JN the diagnostics of upper airways and SV, LK and EK the
23 laryngeal investigations. All authors contributed to and approved the manuscript.

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38 **Competing interests:** None.

Table 1. The criteria on which moisture damage (MD) at workplace was suspected⁷.

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1. Mouldy, stuffy or chemical like odour
 2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), loose water on surfaces
 3. Renovations because of MDs previously made in the building
 4. Information of MD findings from employer or occupational and health safety personnel
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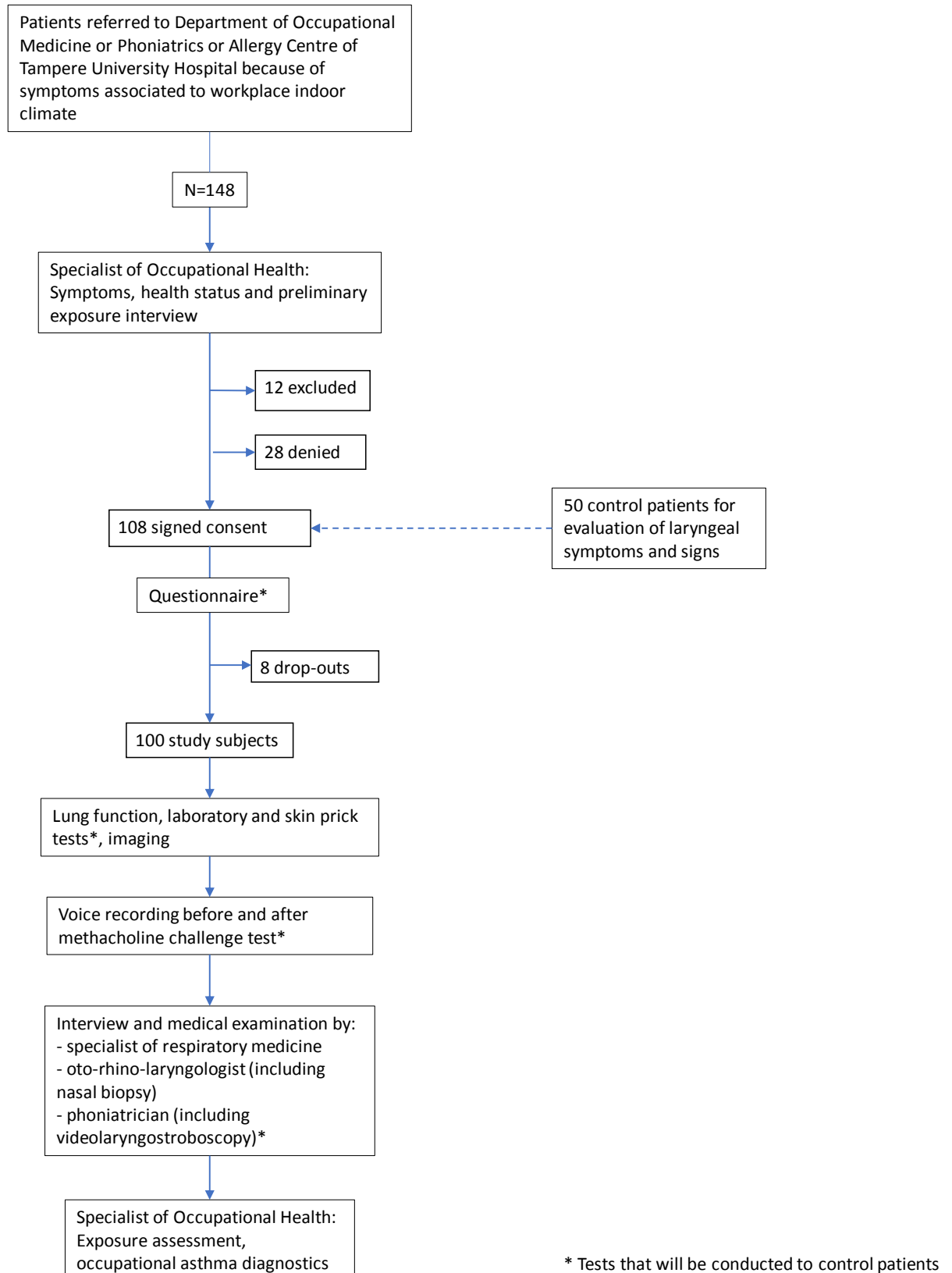
Table 2. The clinical tests conducted to the study patients.

Lung function tests	2-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FE _{NO}), 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 <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, <i>Dermatophagoides Pteronyssinus</i> house dust mite, latex, <i>aspergillus fumigatus</i> , storage mites <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>
Imaging	Chest x-ray, cone beam computed tomography of the paranasal sinuses

Table 3. The criteria based on which asthma is diagnosed in different clinical tests ²⁰.

Clinical test	Criteria for asthma
Two-week peak expiratory flow (PEF) monitoring	At least 3 times <ul style="list-style-type: none">- 15% and 60 mL improvements of PEF after bronchodilator or- diurnal variation of PEF 20% and 60 mL
Spirometry	200 mL and 12% improvement in forced vital capacity (FVC) or forced expiratory volume in one second (FEV1)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV1 (PD20FEV1 <600 µg)

Figure 1. The study design.



For peer review only

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BMJ Open

The SAMDAW study protocol: A clinical descriptive study on Symptoms Associated to Moisture DAMAGE at Workplace

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Manuscript ID	bmjopen-2018-026485.R1
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Primary Subject Heading:	Occupational and environmental medicine
Secondary Subject Heading:	Respiratory medicine
Keywords:	moisture damage, mold, Asthma < THORACIC MEDICINE, irritable larynx, respiratory symptoms

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3 **The SAMDAW study protocol: A clinical descriptive study on Symptoms**
4 **Associated to Moisture DAmage at Workplace**
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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 cross-sectional questionnaire studies. Small proportion of MD exposed workers are diagnosed with asthma. Many patients with MD exposure at work referred to secondary health care 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 clinical study, in which we describe the prevalence of respiratory, voice and other symptoms related to MD at work in patients referred to secondary health care.

Methods and analysis

The study sample consists of patients with MD exposure at work 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. 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 randomly selected by the Finnish Population Information System. To explore how common laryngeal disorders and voice symptoms are in general, a part of the tests will be conducted to 50 asymptomatic volunteers.

Ethics and dissemination

The regional ethics committee of Tampere University Hospital has 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.

Strengths and limitations of this study

- This kind of comprehensive clinical study associated with moisture damage exposure at work has not been conducted before.
- This study will increase the understanding of respiratory tract and voice symptoms and associated clinical findings in subjects exposed to moisture damage.
- Information of moisture damage exposure at work is based on documents from the workplace
- Limitation of a cross-sectional study like this is that it is not possible to obtain information on causal relationships between exposure and symptoms or illnesses

Introduction

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3 Indoor air quality problems are considered important risk factors for health problems
4 worldwide¹. Indoor air associated symptoms may be interrelated with different indoor
5 air factors such as insufficient ventilation², unfavourable temperature conditions³, dry
6 indoor air⁴, dustiness⁵, moisture damage (MD)¹, volatile organic compounds (VOC)⁶,
7 and man-made mineral/ vitreous fibres (MMM/ MMVF)⁷. Even if we do not know the
8 cause of symptoms¹ MD exposure at work has been shown to increase the risk of
9 new onset asthma and exacerbation of asthma^{8,9}. Other illnesses or respiratory
10 symptoms that have been associated with MD exposure include cough, wheezing,
11 dyspnoea, rhinitis, and upper respiratory tract symptoms^{9,10}.

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13 In Finland, located in subarctic area, MDs in residences and schools are common¹¹.
14 Workers in office buildings commonly report symptoms and complaints associated
15 with indoor air^{12,13}. There is also a growing public concern over MDs in buildings and
16 their possible permanent effects on dwellers' or workers' health in Finland, even if
17 there is minor evidence of serious or permanent illnesses other than asthma caused
18 by exposure to MD^{9,14}.

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20 There are few studies describing the clinical findings in patients having symptoms
21 when exposed to MD at work^{15,16}. Previous studies in this field have mainly been
22 epidemiological⁹, and most is known about children's risk of developing symptoms in
23 homes or schools with MD^{17,18}. In majority of the studies, the assessment of
24 exposure to MD or presence of symptoms or illnesses has been based on
25 questionnaires^{19,20}. Furthermore, only a small proportion of MD exposed workers are
26 diagnosed with asthma⁸. According to our clinical experience, many patients with
27 work-related MD exposure and referred to secondary health care report intermittent
28 hoarseness, loss of voice or difficulty to inhale, which would refer to functional or
29 organic problems of the larynx²¹. In the case of laryngeal disorders, asthma

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3 medication is not useful or may even worsen the symptoms if the larynx is sensitive
4 to irritation²². Coexisting with asthma, laryngeal disorders may be the cause of
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6 insufficient response to asthma treatment.
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10 Studies over the past decades have provided important information on idiopathic
11 environmental intolerance (IEI), in which a person has symptoms from different
12 organ systems when in contact with an environmental factor that does not cause
13 symptoms to most people^{23,24}. In odour or multiple chemical sensitivity (MCS) a
14 person reacts with symptoms in association with low levels of airborne chemicals
15 that most people tolerate without problems^{25,26}. It seems that some proportion of the
16 patients that have indoor air associated symptoms in fact have IEI/MCS, but the
17 frequency of this condition among these patients is not known²⁷.
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20 As a conclusion, there is a need for a clinical study on patients exposed to MD at
21 workplace focusing especially on differential diagnostics between asthma and
22 laryngeal symptoms, evidence of exposure to MDs and other indoor air risk factors
23 and chemical sensitivity.
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30 *Aims of the study*

31 In patients referred to secondary health care because of respiratory tract and/ or
32 voice symptoms associated to MD exposure at work, the aim is to:
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- 37 1) Describe the prevalence of different characteristics, symptoms and clinical
38 test findings
 - 39 2) Find out the frequency of laryngeal symptoms and their possible influence on
40 asthma diagnostics
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- 3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory QEESI[®] question series²⁸.
- 4) Find out if there are connections between above mentioned symptoms and clinical findings and if it would be possible to allocate the clinical tests according to patient's symptoms in secondary health care.

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 Phoniatics 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 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 (Table 1). The exclusion criteria were 1) severe illness (e.g. 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 was more frequent at work, it was not considered to be work-associated.

The conducted clinical tests are presented in Table 2. According to Finnish asthma guideline²⁹, diagnosis of asthma must be confirmed with a demonstration of variable

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3 airway obstruction in lung function measurements: i) peak expiratory flow (PEF)
4 monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial
5 hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients
6 carried out a two-week PEF monitoring, spirometry with bronchodilation test and
7 methacholine challenge test. The PEF monitoring included PEF measurements with
8 Pinnacle™ peak flow meter for two weeks in the morning and evening before and
9 after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed
10 according to European Respiratory Society/American Thoracic Society guidelines³⁰
11 and methacholine challenge test using dosimeter with controlled tidal breathing
12 according to Finnish guidelines³¹. To investigate if possible asthma is associated
13 with work the patients performed PEF monitoring at and off work³² with Vitalograph®
14 PEF/FEV Diary device. Diffusing capacity of the lungs³³ and exhaled nitric oxide
15 (FE_{NO})³⁴ were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-
16 laryngology (JN) and phoniatics (SV) examined the patients. For diagnosing
17 laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was
18 performed, voice samples were recorded and also inspirograms were recorded
19 before and after methacholine tests. Biopsy of nasal mucosa and a blood sample
20 were taken and preserved for later analyses.

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45 Exposure to MD at work was assessed from the documents of the building and
46 indoor air quality investigations made at the workplace, if available, according to
47 Finnish guidelines³⁵. A confirmed MD is graded into different severity categories, if
48 sufficient information is available. Also, MMMFs, VOCs or problems in ventilation
49 conditions at workplace were assessed if these had been measured.
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3 As a non-responder analysis, of the patients who were invited but who did not take
4 part in the study, age, symptoms, the presence of asthma diagnosis, and exposure
5 will be evaluated based on patient records.
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10 To explore how common laryngeal disorders are in general, methacholine challenge
11 test, voice recording, clinical examination by the specialist of phoniatics including
12 videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50
13 asymptomatic volunteers adjusted for age and gender. The gathering of the
14 volunteers began in August 2018 and it is our estimation that all the volunteers will
15 be examined by the end of 2019.
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25 *Questionnaire/ survey*

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28 The study patients and the volunteers fill out a questionnaire including questions on

- 29 - previous diseases, medication and upper and lower respiratory symptoms³⁶
- 30 - sinusitis symptoms (Sino-Nasal Outcome Test-22³⁷)
- 31 - voice symptoms (Voice Activity and Participation Profile³⁸, Voice Handicap
32 Index³⁹, voice disorder questionnaire⁴⁰)
- 33 - laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire⁴¹)
- 34 - reflux symptoms (Reflux Symptom Index⁴²)
- 35 - depression and anxiety symptoms (General Health Questionnaire GHQ-12⁴³;
36 Generalized Anxiety Disorder 7-item scale⁴⁴)
- 37 - psychosocial work load⁴⁵, and stress symptoms⁴⁶
- 38 - chemical sensitivity (QEESI²⁸)
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56 To find out if the study group would have different background characteristics from
57 the overall population, the same questionnaire was sent to 1500 Finnish speaking
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3 people in the same hospital district randomly selected by the Finnish Population
4 Information System. The proportions of women and men and different age groups in
5 this comparison material are similar to the study population.
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10 11 12 13 *Sample size and power calculation*

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16 We estimated that a sample of 100 patients is enough to clinical deduction of the
17 different characteristics of this patient group.
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21 Concerning the population-based comparison material, our aim was to get 400
22 questionnaire answers (ratio 1:4) to increase the statistical power. Taking recent
23 rather low survey response rates into account, we sent the questionnaire to 1500
24 people.
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31 To assess if findings suggesting laryngeal disorders are more frequent among those
32 who have respiratory tract or voice symptoms associated to workplace MD, data on
33 frequency of laryngeal findings of asymptomatic people is needed. When analyzing
34 the findings of methacholine challenge test of 30 patients, signs of laryngeal
35 disorders were found in 62,5%. We estimated that among under 30% of
36 asymptomatic people there are such findings in the methacholine challenge test. In
37 power calculation based on findings in the methacholine challenge test, the number
38 of asymptomatic people tested would be 50 with 80% force and 90% confidence
39 interval.
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51 52 *Data analyses*

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55 We will conduct standard descriptive statistics to determine the frequency of different
56 symptoms, findings of clinical tests and their interrelations.
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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 Declaration⁴⁷.

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. Muscatiello N, Mccarthy A, Kielb C, Hsu WH, Hwang SA, Lin S. Classroom conditions and CO₂ concentrations and teacher health symptom reporting in 10 New York State Schools. *Indoor Air*. 2015;25(2):157-167.
doi:10.1111/ina.12136
3. Skyberg K, Skulberg KR, Eduard W, Skåret E, Levy F, Kjuus H. Symptoms prevalence among office employees and associations to building characteristics. *Indoor Air*. 2003;13(3):246-252.
<http://www.ncbi.nlm.nih.gov/pubmed/12950587>. Accessed January 15, 2019.

- 1
2
3 4. Wolkoff P. Indoor air humidity, air quality, and health – An overview. *Int J Hyg Environ Health*. 2018;221(3):376-390. doi:10.1016/j.ijheh.2018.01.015
5
6
7
- 8 5. Schneider T. Dust and fibers as a cause of indoor environment problems.
9
10 *Scand J Work Environ Heal Suppl*. 2008;(4):10-17. doi:10.5271/sjweh.1294
11
12
- 13 6. Salonen H, Pasanen A-L, Lappalainen S, et al. Volatile Organic Compounds
14 and Formaldehyde as Explaining Factors for Sensory Irritation in Office
15 Environments. *J Occup Environ Hyg*. 2009;6(4):239-247.
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60
7. Salonen HJ, Lappalainen SK, Riuttala HM, Tossavainen AP, Pasanen PO,
Reijula KE. Man-Made Vitreous Fibers in Office Buildings in the Helsinki Area.
J Occup Environ Hyg. 2009;6(10):624-631. doi:10.1080/15459620903133667
8. Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H.
Prolonged exposure to damp and moldy workplaces and new-onset asthma.
Int Arch Occup Environ Health. 2011;84(7):713-721. doi:10.1007/s00420-011-
0677-9
9. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic
health effects of dampness, mold, and dampness-related agents: a review of
the epidemiologic evidence. *Environ Health Perspect*. 2011;119(6):748-756.
doi:10.1289/ehp.1002410
10. Jaakkola JJK, Hwang B-F, 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(4):451-459. doi:10.1093/aje/kwq110
11. Täubel M, Karvonen AM, Reponen T, Hyvärinen A, Vesper S, Pekkanen J.

- 1
2
3 Application of the Environmental Relative Moldiness Index in Finland. *Appl*
4
5 *Environ Microbiol.* 2015;82(2):578-584. doi:10.1128/AEM.02785-15
6
7
- 8
9 12. Reijula K, Sundman-Digert C, Reijula K. Assessment of indoor air problems at
10
11 work with a questionnaire. *Occup Environ Med.* 2004;61(1):33-38.
12
13 doi:10.1136/oem.2002.005835
14
15
- 16 13. Ministry of Social Affairs and Health F. *Moisture Damages in Workplaces.*
17
18 *Memo of the Working Group on Moisture Damages (in Finnish).* Helsinki;
19
20 2009.
21
22
- 23 14. Hurraß J, Heinzow B, Aurbach U, et al. Medical diagnostics for indoor mold
24
25 exposure. *Int J Hyg Environ Health.* 2017;220(2):305-328.
26
27 doi:10.1016/j.ijheh.2016.11.012
28
29
- 30 15. White SK, Cox-Ganser JM, Benaise LG, Kreiss K. Work-related peak flow and
31
32 asthma symptoms in a damp building. *Occup Med (Chic Ill).* 2013;63(4):287-
33
34 290. doi:10.1093/occmed/kqt028
35
36
- 37 16. Hellgren U-M, Hyvärinen M, Holopainen R, Reijula K. Perceived indoor air
38
39 quality, air-related symptoms and ventilation in Finnish hospitals. *Int J Occup*
40
41 *Med Environ Health.* 2011;24(1):48-56. doi:10.2478/s13382-011-0011-5
42
43
44
- 45 17. Karvonen AM, Hyvarinen A, Korppi M, et al. Moisture Damage and Asthma: A
46
47 Birth Cohort Study. *Pediatrics.* 2015;135(3):e598-e606.
48
49 doi:10.1542/peds.2014-1239
50
51
- 52 18. Borràs-Santos A, Jacobs JH, Täubel M, et al. Dampness and mould in schools
53
54 and respiratory symptoms in children: the HITEA study. *Occup Environ Med.*
55
56 2013;70(10):681-687. doi:10.1136/oemed-2012-101286
57
58
59
60

- 1
2
3 19. Kim J-L, Henneberger PK, Lohman S, et al. Impact of occupational exposures
4 on exacerbation of asthma: a population-based asthma cohort study. *BMC*
5 *Pulm Med*. 2016;16(1):148. doi:10.1186/s12890-016-0306-1
6
7
8
9
10
11 20. Kurth L, Virji MA, Storey E, et al. Current asthma and asthma-like symptoms
12 among workers at a Veterans Administration Medical Center. *Int J Hyg Environ*
13 *Health*. 2017;220(8):1325-1332. doi:10.1016/j.ijheh.2017.09.001
14
15
16
17
18 21. Moscato G, Pala G, Cullinan P, et al. EAACI position paper on assessment of
19 cough in the workplace. *Allergy Eur J Allergy Clin Immunol*. 2014.
20
21
22
23
24
25
26 22. Idrees M, FitzGerald JM. Vocal cord dysfunction in bronchial asthma. A review
27 article. *J Asthma*. 2015;52(4):327-335. doi:10.3109/02770903.2014.982288
28
29
30
31 23. Genus SJ. Chemical sensitivity: pathophysiology or pathopsychology? *Clin*
32 *Ther*. 2013;35(5):572-577. doi:10.1016/j.clinthera.2013.04.003
33
34
35
36 24. Rossi S, Pitidis A. Multiple Chemical Sensitivity: Review of the State of the Art
37 in Epidemiology, Diagnosis, and Future Perspectives. *J Occup Environ Med*.
38
39
40
41
42
43
44 25. Dantoft TM, Andersson L, Nordin S, Skovbjerg S. Chemical intolerance. *Curr*
45 *Rheumatol Rev*. 2015;11(2):167-184.
46
47
48
49
50
51
52 26. Andersson L, Claeson A-S, Dantoft TM, Skovbjerg S, Lind N, Nordin S.
53
54
55
56
57
58
59
60

- 1
2
3 27. Karvala K, Sainio M, Palmquist E, Claeson A-S, Nyback M-H, Nordin S.
4 Building-Related Environmental Intolerance and Associated Health in the
5 General Population. *Int J Environ Res Public Health*. 2018;15(9).
6
7 doi:10.3390/ijerph15092047
8
9
10
11
12
13 28. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory
14 (EESI): a standardized approach for measuring chemical intolerances for
15 research and clinical applications. *Toxicol Ind Health*. 1999;15(3-4):370-385.
16
17 doi:10.1177/074823379901500311
18
19
20
21
22
23 29. Haahtela T, Lehtimäki L, Ahonen E, et al. [Update on current care guidelines:
24 asthma]. *Duodecim*. 2013;129(9):994-995.
25
26 http://www.ncbi.nlm.nih.gov/pubmed/23786112. Accessed May 18, 2018.
27
28
29
30 30. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur*
31
32 *Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805
33
34
35
36 31. Nieminen MM, Lahdensuo A, Kellomaeki L, Karvonen J, Muittari A.
37
38 Methacholine bronchial challenge using a dosimeter with controlled tidal
39
40 breathing. *Thorax*. 1988;43(11):896-900.
41
42 http://www.ncbi.nlm.nih.gov/pubmed/3065974. Accessed May 18, 2018.
43
44
45
46 32. Burge PS. Use of serial measurements of peak flow in the diagnosis of
47
48 occupational asthma. *Occup Med*. 1993;8(2):279-294.
49
50 http://www.ncbi.nlm.nih.gov/pubmed/8506506. Accessed May 19, 2017.
51
52
53 33. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath
54
55 determination of carbon monoxide uptake in the lung. *Eur Respir J*.
56
57 2005;26(4):720-735. doi:10.1183/09031936.05.00034905
58
59
60

- 1
2
3 34. Horváth I, Barnes PJ, Loukides S, et al. A European Respiratory Society
4 technical standard: exhaled biomarkers in lung disease. *Eur Respir J*.
5 2017;49(4):1600965. doi:10.1183/13993003.00965-2016
6
7
8
9
10
11 35. Latvala J, Karvala K, Sainio M, et al. *Guidelines for Workplace and*
12 *Occupational Health Actions in Indoor Air Problems (Finnish)*.
13 Työterveyslaitos; 2017. <http://www.julkari.fi/handle/10024/132078>. Accessed
14 August 20, 2018.
15
16
17
18
19
20
21 36. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new
22 questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults.
23 *Allergy*. 2001;56(5):377-384. doi:10.1034/j.1398-9995.2001.056005377.x
24
25
26
27
28 37. Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which
29 is best? *Clin Otolaryngol*. 2006;31(2):103-109. doi:10.1111/j.1749-
30 4486.2006.01155.x
31
32
33
34
35
36 38. Sukanen O, Sihvo M, Rorarius E, Lehtihalmes M, Autio V, Kleemola L. Voice
37 Activity and Participation Profile (VAPP) in assessing the effects of voice
38 disorders on patients' quality of life: Validity and reliability of the Finnish
39 version of VAPP. *Logop Phoniatr Vocology*. 2007;32(1):3-8.
40 doi:10.1080/14015430600784386
41
42
43
44
45
46
47
48 39. Alaluusua S JM. Psycho-social handicap of voice disorder and its
49 rehabilitation: a pilot study of Finnish version of Voice Handicap Index [In
50 Finnish] [master thesis]. 2003.
51
52
53
54
55
56 40. Sala E, Laine A, Simberg S, Pentti J, Suonpää J. The prevalence of voice
57 disorders among day care center teachers compared with nurses: a
58 questionnaire and clinical study. *J Voice*. 2001;15(3):413-423.
59
60

- 1
2
3 doi:10.1016/S0892-1997(01)00042-X
4
5
6 41. Vertigan AE, Bone SL, Gibson PG. Development and validation of the
7
8 Newcastle laryngeal hypersensitivity questionnaire. *Cough*. 2014;10(1):1.
9
10 doi:10.1186/1745-9974-10-1
11
12
13 42. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux
14
15 symptom index (RSI). *J Voice*. 2002;16(2):274-277.
16
17
18 <http://www.ncbi.nlm.nih.gov/pubmed/12150380>. Accessed June 26, 2018.
19
20
21 43. Mäkikangas A, Feldt T, Kinnunen U, Tolvanen A, Kinnunen M-L, Pulkkinen L.
22
23 The factor structure and factorial invariance of the 12-item General Health
24
25 Questionnaire (GHQ-12) across time: evidence from two community-based
26
27 samples. *Psychol Assess*. 2006;18(4):444-451. doi:10.1037/1040-
28
29 3590.18.4.444
30
31
32
33 44. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing
34
35 Generalized Anxiety Disorder. *Arch Intern Med*. 2006;166(10):1092.
36
37
38 doi:10.1001/archinte.166.10.1092
39
40
41 45. Lahtinen M, Sundman-Digert C, Reijula K. Psychosocial work environment and
42
43 indoor air problems: a questionnaire as a means of problem diagnosis. *Occup*
44
45 *Environ Med*. 2004;61(2):143 LP-149.
46
47
48 <http://oem.bmj.com/content/61/2/143.abstract>.
49
50
51 46. Elo A-L, Leppänen A, Jahkola A. Validity of a single-item measure of stress
52
53 symptoms. *Scand J Work Environ Health*. 2003;29(6):444-451.
54
55
56 doi:10.5271/sjweh.752
57
58
59 47. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191.
60

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3 doi:10.1001/jama.2013.281053
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9 researcher. All the writers took part in developing the study protocol; JU and PN
10 especially planning the exposure assessment, JK, LL and AT the lung function
11 diagnostics measures, JN the diagnostics of upper airways and SV, LK and EK the
12 laryngeal investigations. All authors contributed to and approved the manuscript.
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3 Figure 1. The study design of study on symptoms associated to moisture damage at
4 workplace.
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10 Table 1. The criteria on which moisture damage (MD) at workplace was suspected
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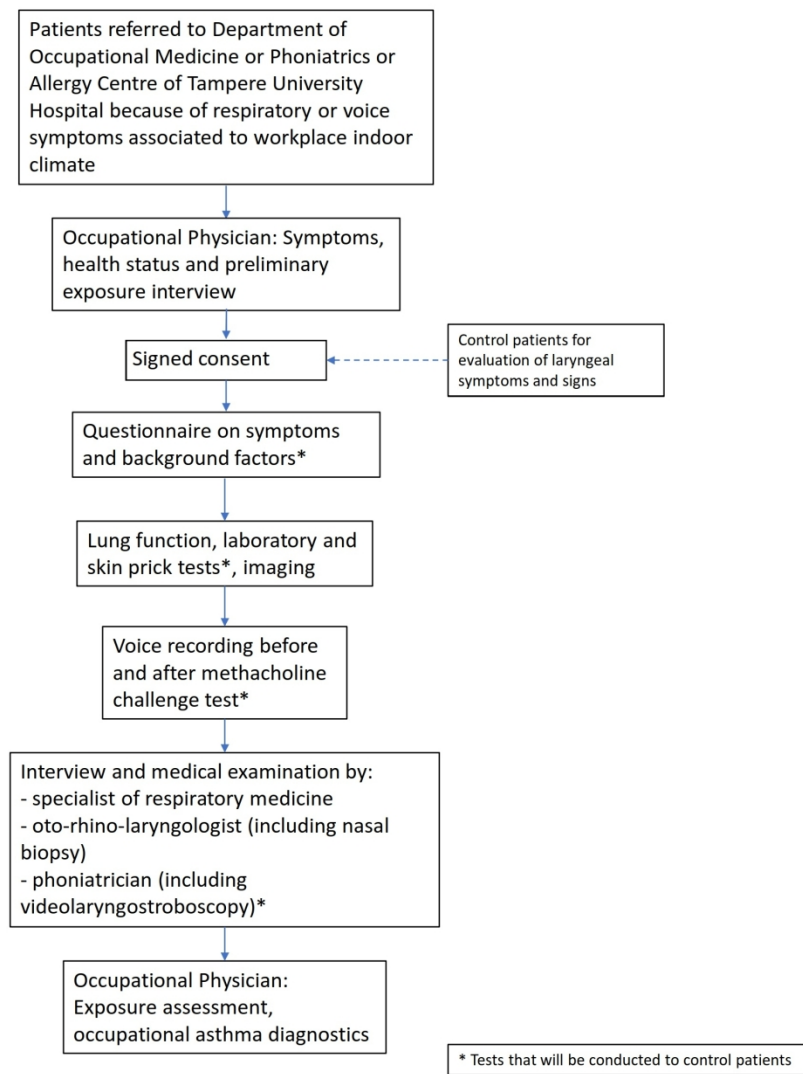
-
- 15 1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
 - 16 2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials,
17 disengaging or blistering of flooring materials, crumbling of wall plastering, water
18 leakages through ceilings (buckets on the floors), loose water on surfaces
 - 19 3. Renovations because of MDs previously made in the building
 - 20 4. Information of MD findings from employer or occupational and health safety
21 personnel
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Table 2. The clinical tests conducted to the study patients.

Lung function tests	2-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FE _{NO}), 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 <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, <i>Dermatophagoides Pteronyssinus</i> house dust mite, latex, <i>aspergillus fumigatus</i> , storage mites <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>
Imaging	Chest x-ray, cone beam computed tomography of the paranasal sinuses

Table 3. The criteria based on which asthma is diagnosed in different clinical tests ²⁹.

Clinical test	Criteria for asthma
Two-week peak expiratory flow (PEF) monitoring	At least 3 times <ul style="list-style-type: none">- at least 15% and 60 L/min improvements of PEF after bronchodilator or- diurnal variation of PEF at least 20% and 60 L/min
Spirometry	At least 200 mL and 12% improvement in forced expiratory volume in one second (FEV ₁) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV ₁ (PD ₂₀ FEV ₁ <600 µg)



The study design of study on symptoms associated to moisture damage at workplace.

354x442mm (144 x 144 DPI)

BMJ Open

The SAMDAW study protocol: A clinical descriptive study on Symptoms Associated to Moisture DAMAGE at Workplace

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Primary Subject Heading:	Occupational and environmental medicine
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Keywords:	moisture damage, mold, Asthma < THORACIC MEDICINE, irritable larynx, respiratory symptoms

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3 **The SAMDAW study protocol: A clinical descriptive study on Symptoms**
4 **Associated to Moisture DAmage at Workplace**
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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. Small proportion of MD exposed workers are diagnosed with asthma. Many patients with MD exposure at work referred to secondary health care 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 clinical study, in which we describe the prevalence of respiratory, voice and other symptoms related to MD at work in patients referred to secondary health care.

Methods and analysis

The study sample consists of patients with MD exposure at work 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. 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 randomly selected by the Finnish Population Information System. To explore how common laryngeal disorders and voice symptoms are in general, a part of the tests will be conducted to 50 asymptomatic volunteers.

Ethics and dissemination

The regional ethics committee of Tampere University Hospital has 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.

Strengths and limitations of this study

- This kind of comprehensive clinical study associated with moisture damage exposure at work has not been conducted before.
- This study will increase the understanding of respiratory tract and voice symptoms and associated clinical findings in subjects exposed to moisture damage.
- Information of moisture damage exposure at work is based on documents from the workplace
- Limitation of a cross-sectional study like this is that it is not possible to obtain information on causal relationships between exposure and symptoms or illnesses

Introduction

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3 Indoor air quality problems are considered important risk factors for health problems
4 worldwide¹. Indoor air associated symptoms may be interrelated with different indoor
5 air factors such as insufficient ventilation², unfavourable temperature conditions³, dry
6 indoor air⁴, dustiness⁵, moisture damage (MD)¹, volatile organic compounds (VOC)⁶,
7 and man-made mineral/ vitreous fibres (MMM/ MMVF)⁷. Even if we do not know the
8 cause of symptoms¹ MD exposure at work has been shown to increase the risk of
9 new onset asthma and exacerbation of asthma^{8,9}. Other illnesses or respiratory
10 symptoms that have been associated with MD exposure include cough, wheezing,
11 dyspnoea, rhinitis, and upper respiratory tract symptoms^{9,10}.

12
13 In Finland, located in subarctic area, MDs in residences and schools are common¹¹.
14 Workers in office buildings commonly report symptoms and complaints associated
15 with indoor air^{12,13}. There is also a growing public concern over MDs in buildings and
16 their possible permanent effects on dwellers' or workers' health in Finland, even if
17 there is minor evidence of serious or permanent illnesses other than asthma caused
18 by exposure to MD^{9,14}.

19
20 There are few studies describing the clinical findings in patients having symptoms
21 when exposed to MD at work^{15,16}. Previous studies in this field have mainly been
22 epidemiological⁹, and most is known about children's risk of developing symptoms in
23 homes or schools with MD^{17,18}. In majority of the studies, the assessment of
24 exposure to MD or presence of symptoms or illnesses has been based on
25 questionnaires^{19,20}. Furthermore, only a small proportion of MD exposed workers are
26 diagnosed with asthma⁸. According to our clinical experience, many patients with
27 work-related MD exposure and referred to secondary health care report intermittent
28 hoarseness, loss of voice or difficulty to inhale, which would refer to functional or
29 organic problems of the larynx²¹. In the case of laryngeal disorders, asthma

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3 medication is not useful or may even worsen the symptoms if the larynx is sensitive
4 to irritation²². Coexisting with asthma, laryngeal disorders may be the cause of
5
6 insufficient response to asthma treatment.
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10 Studies over the past decades have provided important information on idiopathic
11 environmental intolerance (IEI), in which a person has symptoms from different
12 organ systems when in contact with an environmental factor that does not cause
13 symptoms to most people^{23,24}. In odour or multiple chemical sensitivity (MCS) a
14 person reacts with symptoms in association with low levels of airborne chemicals
15 that most people tolerate without problems^{25,26}. It seems that some proportion of the
16 patients that have indoor air associated symptoms in fact have IEI/MCS, but the
17 frequency of this condition among these patients is not known²⁷.
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20 As a conclusion, there is a need for a clinical study on patients exposed to MD at
21 workplace focusing especially on differential diagnostics between asthma and
22 laryngeal symptoms, evidence of exposure to MDs and other indoor air risk factors
23 and chemical sensitivity.
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40 *Aims of the study*

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42 In patients referred to secondary health care because of respiratory tract and/ or
43 voice symptoms associated to MD exposure at work, the aim is to:
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- 46 1) Describe the prevalence of different characteristics, symptoms and clinical
47 test findings
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49 2) Find out the frequency of laryngeal symptoms and their possible influence on
50 asthma diagnostics
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- 3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory QEESI[®] question series²⁸.
- 4) Find out if there are connections between above mentioned symptoms and clinical findings and if it would be possible to allocate the clinical tests according to patient's symptoms in secondary health care.

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 Phoniatics 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 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 (Table 1). The exclusion criteria were 1) severe illness (e.g. 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 was more frequent at work, it was not considered to be work-associated.

The conducted clinical tests are presented in Table 2. According to Finnish asthma guideline²⁹, diagnosis of asthma must be confirmed with a demonstration of variable

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3 airway obstruction in lung function measurements: i) peak expiratory flow (PEF)
4 monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial
5 hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients
6 carried out a two-week PEF monitoring, spirometry with bronchodilation test and
7 methacholine challenge test. The PEF monitoring included PEF measurements with
8 Pinnacle™ peak flow meter for two weeks in the morning and evening before and
9 after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed
10 according to European Respiratory Society/American Thoracic Society guidelines³⁰
11 and methacholine challenge test using dosimeter with controlled tidal breathing
12 according to Finnish guidelines³¹. To investigate if possible asthma is associated
13 with work the patients performed PEF monitoring at and off work³² with Vitalograph®
14 PEF/FEV Diary device. Diffusing capacity of the lungs³³ and exhaled nitric oxide
15 (FE_{NO})³⁴ were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-
16 laryngology (JN) and phoniatics (SV) examined the patients. For diagnosing
17 laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was
18 performed, voice samples were recorded and also inspirograms were recorded
19 before and after methacholine tests. Biopsy of nasal mucosa and a blood sample
20 were taken and preserved for later analyses.

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45 Exposure to MD at work was assessed from the documents of the building and
46 indoor air quality investigations made at the workplace, if available, according to
47 Finnish guidelines³⁵. A confirmed MD is graded into different severity categories, if
48 sufficient information is available. Also, MMMFs, VOCs or problems in ventilation
49 conditions at workplace were assessed if these had been measured.
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3 As a non-responder analysis, of the patients who were invited but who did not take
4 part in the study, age, symptoms, the presence of asthma diagnosis, and exposure
5 will be evaluated based on patient records.
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10 To explore how common laryngeal disorders are in general, methacholine challenge
11 test, voice recording, clinical examination by the specialist of phoniatics including
12 videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50
13 asymptomatic volunteers adjusted for age and gender. The gathering of the
14 volunteers began in August 2018 and it is our estimation that all the volunteers will
15 be examined by the end of 2019.
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25 *Questionnaire/ survey*

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27
28 The study patients and the volunteers fill out a questionnaire including questions on

- 29 - previous diseases, medication and upper and lower respiratory symptoms³⁶
 - 30 - sinusitis symptoms (Sino-Nasal Outcome Test-22³⁷)
 - 31 - voice symptoms (Voice Activity and Participation Profile³⁸, Voice Handicap
32 Index³⁹, voice disorder questionnaire⁴⁰)
 - 33 - laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire⁴¹)
 - 34 - reflux symptoms (Reflux Symptom Index⁴²)
 - 35 - depression and anxiety symptoms (General Health Questionnaire GHQ-12⁴³;
36 Generalized Anxiety Disorder 7-item scale⁴⁴)
 - 37 - psychosocial work load⁴⁵, and stress symptoms⁴⁶
 - 38 - chemical sensitivity (QEESI[©])²⁸
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56 To find out if the study group would have different background characteristics from
57 the overall population, the same questionnaire was sent to 1500 Finnish speaking
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3 people in the same hospital district randomly selected by the Finnish Population
4 Information System. The proportions of women and men and different age groups in
5 this comparison material are similar to the study population.
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10 11 12 13 *Sample size and power calculation*

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16 We estimated that a sample of 100 patients is enough to clinical deduction of the
17 different characteristics of this patient group.
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21 Concerning the population-based comparison material, our aim was to get 400
22 questionnaire answers (ratio 1:4) to increase the statistical power. Taking recent
23 rather low survey response rates into account, we sent the questionnaire to 1500
24 people.
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31 To assess if findings suggesting laryngeal disorders are more frequent among those
32 who have respiratory tract or voice symptoms associated to workplace MD, data on
33 frequency of laryngeal findings of asymptomatic people is needed. When analyzing
34 the findings of methacholine challenge test of 30 patients, signs of laryngeal
35 disorders were found in 62,5%. We estimated that among under 30% of
36 asymptomatic people there are such findings in the methacholine challenge test. In
37 power calculation based on findings in the methacholine challenge test, the number
38 of asymptomatic people tested would be 50 with 80% force and 90% confidence
39 interval.
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51 52 *Data analyses*

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55 We will analyze descriptive statistics such as gender distribution and age of the
56 patients with their lines of business. We will also analyze the frequencies of different
57 symptoms the patients complain and how these are related to objective findings in
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3 different organ systems or new diagnoses of e.g. asthma or laryngeal dysfunction.

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5 We will describe the proportions of patients with significant findings in medical
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7 assessment at different specialities (ENT, pulmonary and phoniatics). We will
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9 compare frequencies and intensities of different symptoms and clinical findings
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11 between the patients and symptomless controls. We will also compare different
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13 background factors of the study patients, such as perceived psychosocial work load,
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15 with controls of the population who answered to the same questionnaire as the study
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17 patients. Based on the relation between symptoms and different objective findings
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19 we aim to find "clinical triggers" (certain sets of symptoms) that should prompt
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21 clinicians to refer patients to certain specialities.
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26 27 *Patient and Public Involvement*

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29 Patients or public were not involved in the design of the study. The study patients
30
31 have received the results of their own tests, explanations for them and necessary
32
33 treatment.
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36 37 **Ethics and dissemination**

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39 The regional ethics committee of Tampere University Hospital has approved the
40
41 study (R14095). All study subjects gave their written informed consent, which is
42
43 required also from the volunteers. The study adheres to good clinical research
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45 guidelines and the Helsinki Declaration⁴⁷.
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49
50 The results will be communicated locally as well as internationally as conference
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52 papers and journal articles.
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54

55 56 **References**

- 57
58 1. WHO. *WHO Guidelines for Indoor Air Quality: Dampness and Mould*.
59
60

- 1
2
3 Copenhagen: WHO Regional Office for Europe; 2009.
4
5 http://www.euro.who.int/__data/assets/pdf_file/0017/43325/E92645.pdf.
6
7
8
9 2. Muscatiello N, Mccarthy A, Kielb C, Hsu WH, Hwang SA, Lin S. Classroom
10 conditions and CO2 concentrations and teacher health symptom reporting in 10
11 New York State Schools. *Indoor Air*. 2015;25(2):157-167.
12
13 doi:10.1111/ina.12136
14
15
16
17
18 3. Skyberg K, Skulberg KR, Eduard W, Skåret E, Levy F, Kjuus H. Symptoms
19 prevalence among office employees and associations to building
20 characteristics. *Indoor Air*. 2003;13(3):246-252.
21
22 <http://www.ncbi.nlm.nih.gov/pubmed/12950587>. Accessed January 15, 2019.
23
24
25
26
27
28 4. Wolkoff P. Indoor air humidity, air quality, and health – An overview. *Int J Hyg*
29 *Environ Health*. 2018;221(3):376-390. doi:10.1016/j.ijheh.2018.01.015
30
31
32
33
34 5. Schneider T. Dust and fibers as a cause of indoor environment problems.
35 *Scand J Work Environ Heal Suppl*. 2008;(4):10-17. doi:10.5271/sjweh.1294
36
37
38
39 6. Salonen H, Pasanen A-L, Lappalainen S, et al. Volatile Organic Compounds
40 and Formaldehyde as Explaining Factors for Sensory Irritation in Office
41 Environments. *J Occup Environ Hyg*. 2009;6(4):239-247.
42
43 doi:10.1080/15459620902735892
44
45
46
47
48
49 7. Salonen HJ, Lappalainen SK, Riuttala HM, Tossavainen AP, Pasanen PO,
50 Reijula KE. Man-Made Vitreous Fibers in Office Buildings in the Helsinki Area.
51 *J Occup Environ Hyg*. 2009;6(10):624-631. doi:10.1080/15459620903133667
52
53
54
55
56 8. Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H.
57 Prolonged exposure to damp and moldy workplaces and new-onset asthma.
58
59
60

- 1
2
3 *Int Arch Occup Environ Health*. 2011;84(7):713-721. doi:10.1007/s00420-011-
4 0677-9
5
6
7
8
9 9. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic
10 health effects of dampness, mold, and dampness-related agents: a review of
11 the epidemiologic evidence. *Environ Health Perspect*. 2011;119(6):748-756.
12 doi:10.1289/ehp.1002410
13
14
15
16
17
18 10. Jaakkola JJK, Hwang B-F, Jaakkola MS. Home Dampness and Molds as
19 Determinants of Allergic Rhinitis in Childhood: A 6-Year, Population-based
20 Cohort Study. *Am J Epidemiol*. 2010;172(4):451-459. doi:10.1093/aje/kwq110
21
22
23
24
25
26 11. Täubel M, Karvonen AM, Reponen T, Hyvärinen A, Vesper S, Pekkanen J.
27 Application of the Environmental Relative Moldiness Index in Finland. *Appl*
28 *Environ Microbiol*. 2015;82(2):578-584. doi:10.1128/AEM.02785-15
29
30
31
32
33
34 12. Reijula K, Sundman-Digert C, Reijula K. Assessment of indoor air problems at
35 work with a questionnaire. *Occup Environ Med*. 2004;61(1):33-38.
36 doi:10.1136/oem.2002.005835
37
38
39
40
41 13. Ministry of Social Affairs and Health F. *Moisture Damages in Workplaces*.
42 *Memo of the Working Group on Moisture Damages (in Finnish)*. Helsinki;
43 2009.
44
45
46
47
48
49 14. Hurraß J, Heinzow B, Aurbach U, et al. Medical diagnostics for indoor mold
50 exposure. *Int J Hyg Environ Health*. 2017;220(2):305-328.
51 doi:10.1016/j.ijheh.2016.11.012
52
53
54
55
56 15. White SK, Cox-Ganser JM, Benaise LG, Kreiss K. Work-related peak flow and
57 asthma symptoms in a damp building. *Occup Med (Chic Ill)*. 2013;63(4):287-
58
59
60

- 1
2
3 290. doi:10.1093/occmed/kqt028
4
5
6 16. Hellgren U-M, Hyvärinen M, Holopainen R, Reijula K. Perceived indoor air
7
8 quality, air-related symptoms and ventilation in Finnish hospitals. *Int J Occup*
9
10 *Med Environ Health*. 2011;24(1):48-56. doi:10.2478/s13382-011-0011-5
11
12
13 17. Karvonen AM, Hyvarinen A, Korppi M, et al. Moisture Damage and Asthma: A
14
15 Birth Cohort Study. *Pediatrics*. 2015;135(3):e598-e606.
16
17 doi:10.1542/peds.2014-1239
18
19
20 18. Borràs-Santos A, Jacobs JH, Täubel M, et al. Dampness and mould in schools
21
22 and respiratory symptoms in children: the HITEA study. *Occup Environ Med*.
23
24 2013;70(10):681-687. doi:10.1136/oemed-2012-101286
25
26
27 19. Kim J-L, Henneberger PK, Lohman S, et al. Impact of occupational exposures
28
29 on exacerbation of asthma: a population-based asthma cohort study. *BMC*
30
31 *Pulm Med*. 2016;16(1):148. doi:10.1186/s12890-016-0306-1
32
33
34 20. Kurth L, Virji MA, Storey E, et al. Current asthma and asthma-like symptoms
35
36 among workers at a Veterans Administration Medical Center. *Int J Hyg Environ*
37
38 *Health*. 2017;220(8):1325-1332. doi:10.1016/j.ijheh.2017.09.001
39
40
41 21. Moscato G, Pala G, Cullinan P, et al. EAACI position paper on assessment of
42
43 cough in the workplace. *Allergy Eur J Allergy Clin Immunol*. 2014.
44
45 doi:10.1111/all.12352
46
47
48 22. Idrees M, FitzGerald JM. Vocal cord dysfunction in bronchial asthma. A review
49
50 article. *J Asthma*. 2015;52(4):327-335. doi:10.3109/02770903.2014.982288
51
52
53 23. Genuis SJ. Chemical sensitivity: pathophysiology or pathopsychology? *Clin*
54
55 *Ther*. 2013;35(5):572-577. doi:10.1016/j.clinthera.2013.04.003
56
57
58
59
60

- 1
2
3 24. Rossi S, Pitidis A. Multiple Chemical Sensitivity: Review of the State of the Art
4 in Epidemiology, Diagnosis, and Future Perspectives. *J Occup Environ Med.*
5
6 2018;60(2):138-146. doi:10.1097/JOM.0000000000001215
7
8
9
10
11 25. Dantoft TM, Andersson L, Nordin S, Skovbjerg S. Chemical intolerance. *Curr*
12
13 *Rheumatol Rev.* 2015;11(2):167-184.
14
15 <http://www.ncbi.nlm.nih.gov/pubmed/26088215>. Accessed May 14, 2018.
16
17
18 26. Andersson L, Claeson A-S, Dantoft TM, Skovbjerg S, Lind N, Nordin S.
19 Chemosensory perception, symptoms and autonomic responses during
20
21
22
23
24
25
26
27
28
29 27. Karvala K, Sainio M, Palmquist E, Claeson A-S, Nyback M-H, Nordin S.
30
31
32
33
34
35
36
37
38
39 28. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory
40
41
42
43
44
45
46
47
48
49 29. Haahtela T, Lehtimäki L, Ahonen E, et al. [Update on current care guidelines:
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 31. Nieminen MM, Lahdensuo A, Kellomaeki L, Karvonen J, Muittari A.
4
5 Methacholine bronchial challenge using a dosimeter with controlled tidal
6
7 breathing. *Thorax*. 1988;43(11):896-900.
8
9 <http://www.ncbi.nlm.nih.gov/pubmed/3065974>. Accessed May 18, 2018.
10
11
12
13 32. Burge PS. Use of serial measurements of peak flow in the diagnosis of
14
15 occupational asthma. *Occup Med*. 1993;8(2):279-294.
16
17 <http://www.ncbi.nlm.nih.gov/pubmed/8506506>. Accessed May 19, 2017.
18
19
20 33. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath
21
22 determination of carbon monoxide uptake in the lung. *Eur Respir J*.
23
24 2005;26(4):720-735. doi:10.1183/09031936.05.00034905
25
26
27 34. Horváth I, Barnes PJ, Loukides S, et al. A European Respiratory Society
28
29 technical standard: exhaled biomarkers in lung disease. *Eur Respir J*.
30
31 2017;49(4):1600965. doi:10.1183/13993003.00965-2016
32
33
34 35. Latvala J, Karvala K, Sainio M, et al. *Guidelines for Workplace and*
35
36 *Occupational Health Actions in Indoor Air Problems (Finnish)*.
37
38 Työterveyslaitos; 2017. <http://www.julkari.fi/handle/10024/132078>. Accessed
39
40 August 20, 2018.
41
42
43 36. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new
44
45 questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults.
46
47 *Allergy*. 2001;56(5):377-384. doi:10.1034/j.1398-9995.2001.056005377.x
48
49
50
51 37. Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which
52
53 is best? *Clin Otolaryngol*. 2006;31(2):103-109. doi:10.1111/j.1749-
54
55 4486.2006.01155.x
56
57
58
59
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41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
38. Sukanen O, Sihvo M, Rorarius E, Lehtihalmes M, Autio V, Kleemola L. 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. *Logop Phoniatr Vocology*. 2007;32(1):3-8.
doi:10.1080/14015430600784386
 39. Alaluusua S JM. Psycho-social handicap of voice disorder and its rehabilitation: a pilot study of Finnish version of Voice Handicap Index [In Finnish] [master thesis]. 2003.
 40. Sala E, Laine A, Simberg S, Pentti J, Suonpää J. The prevalence of voice disorders among day care center teachers compared with nurses: a questionnaire and clinical study. *J Voice*. 2001;15(3):413-423.
doi:10.1016/S0892-1997(01)00042-X
 41. Vertigan AE, Bone SL, Gibson PG. Development and validation of the Newcastle laryngeal hypersensitivity questionnaire. *Cough*. 2014;10(1):1.
doi:10.1186/1745-9974-10-1
 42. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). *J Voice*. 2002;16(2):274-277.
<http://www.ncbi.nlm.nih.gov/pubmed/12150380>. Accessed June 26, 2018.
 43. Mäkikangas A, Feldt T, Kinnunen U, Tolvanen A, Kinnunen M-L, Pulkkinen L. 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(4):444-451. doi:10.1037/1040-3590.18.4.444
 44. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing

- 1
2
3 Generalized Anxiety Disorder. *Arch Intern Med*. 2006;166(10):1092.
4
5 doi:10.1001/archinte.166.10.1092
6
7
8
9 45. Lahtinen M, Sundman-Digert C, Reijula K. Psychosocial work environment and
10 indoor air problems: a questionnaire as a means of problem diagnosis. *Occup*
11 *Environ Med*. 2004;61(2):143 LP-149.
12
13 http://oem.bmj.com/content/61/2/143.abstract.
14
15
16
17
18 46. Elo A-L, Leppänen A, Jahkola A. Validity of a single-item measure of stress
19 symptoms. *Scand J Work Environ Health*. 2003;29(6):444-451.
20
21 doi:10.5271/sjweh.752
22
23
24
25
26 47. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191.
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28 doi:10.1001/jama.2013.281053
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33 **Authors' contributions:** JU is the head of the study group and PN the principal
34 researcher. All the writers took part in developing the study protocol; JU and PN
35 especially planning the exposure assessment, JK, LL and AT the lung function
36 diagnostics measures, JN the diagnostics of upper airways and SV, LK and EK the
37 laryngeal investigations. All authors contributed to and approved the manuscript.
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47 Responsibility area of Tampere University Hospital (grant number 9T069).
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52 **Competing interests:** The study group report grants from Tampere Tuberculosis
53 Foundation, grants from Competitive State Research Financing of the Expert
54 Responsibility area of Tampere University Hospital, during the conduct of the study.
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For peer review only

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3 Figure 1. The study design of study on symptoms associated to moisture damage at
4 workplace.
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10 Table 1. The criteria on which moisture damage (MD) at workplace was suspected
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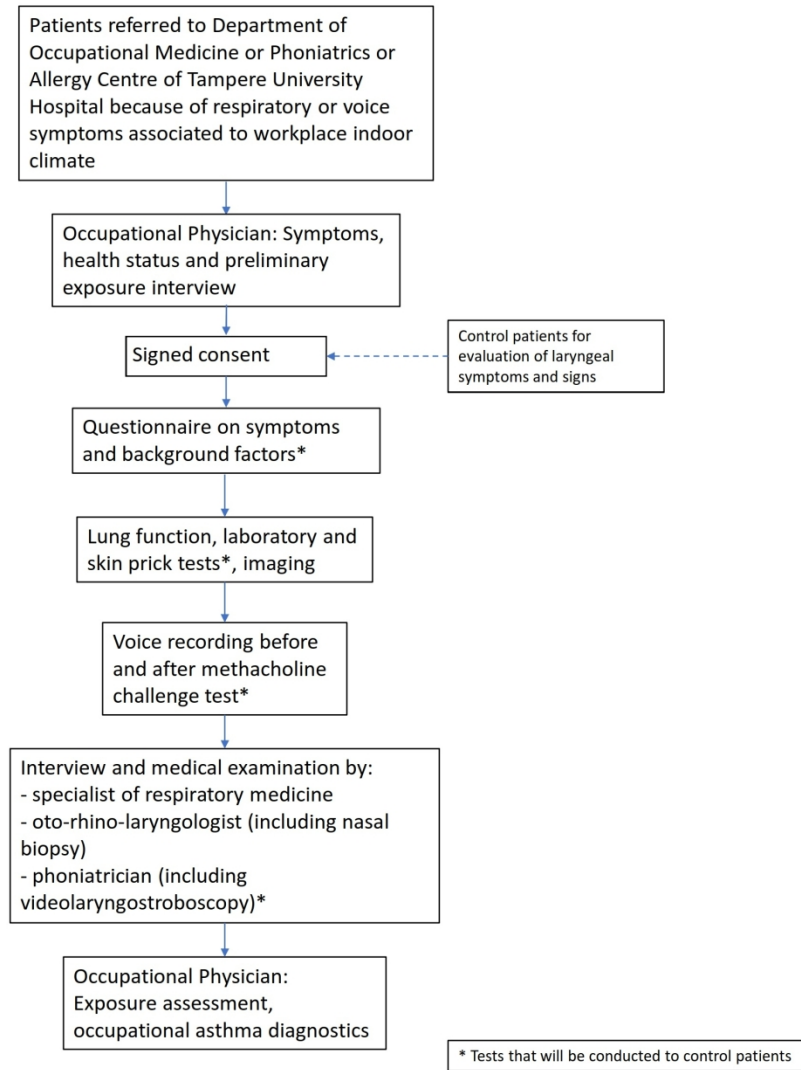
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- 15 1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
 - 16 2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials,
17 disengaging or blistering of flooring materials, crumbling of wall plastering, water
18 leakages through ceilings (buckets on the floors), loose water on surfaces
 - 19 3. Renovations because of MDs previously made in the building
 - 20 4. Information of MD findings from employer or occupational and health safety
21 personnel
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Table 2. The clinical tests conducted to the study patients.

Lung function tests	2-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FE _{NO}), 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 <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, <i>Dermatophagoides Pteronyssinus</i> house dust mite, latex, <i>aspergillus fumigatus</i> , storage mites <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>
Imaging	Chest x-ray, cone beam computed tomography of the paranasal sinuses

Table 3. The criteria based on which asthma is diagnosed in different clinical tests ²⁹.

Clinical test	Criteria for asthma
Two-week peak expiratory flow (PEF) monitoring	At least 3 times <ul style="list-style-type: none"> - at least 15% and 60 L/min improvements of PEF after bronchodilator or - diurnal variation of PEF at least 20% and 60 L/min
Spirometry	At least 200 mL and 12% improvement in forced expiratory volume in one second (FEV ₁) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV ₁ (PD ₂₀ FEV ₁ <600 µg)



The study design of study on symptoms associated to moisture damage at workplace.

354x442mm (144 x 144 DPI)

BMJ Open

The SAMDAW study protocol: An observational cross-sectional study on Symptoms Associated to Moisture Damage at Workplace

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Primary Subject Heading:	Occupational and environmental medicine
Secondary Subject Heading:	Respiratory medicine, Ear, nose and throat/otolaryngology
Keywords:	moisture damage, mold, Asthma < THORACIC MEDICINE, irritable larynx, respiratory symptoms

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3 **The SAMDAW study protocol: An observational cross-sectional study on**
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5 **Symptoms Associated to Moisture DAmage at Workplace**
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11 P. Nynäs^{1,5,6}, S. Vilpas^{2,5}, E. Kankare^{2,5}, J. Karjalainen^{3,5}, L. Lehtimäki^{3,5}, J.
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13 Numminen^{3,5}, A. Tikkakoski^{4,5}, L. Kleemola⁵, J. Uitti^{1,5,6}
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39 Word count: 1749
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42 Key words: Moisture damage, mold, asthma, irritable larynx, respiratory symptoms
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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. Small proportion of MD exposed workers are diagnosed with asthma. Many patients with MD exposure at work referred to secondary health care 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 health care. 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 phoniatics. 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 sent also to 1500 Finnish speaking people in the same hospital district randomly selected by the Finnish Population Information System. To explore

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3 how common laryngeal disorders and voice symptoms are in general, a part of the
4 tests will be conducted to 50 asymptomatic volunteers.
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8 Ethics and dissemination 9

10 The regional ethics committee of Tampere University Hospital approved the study.
11 All study subjects gave their written informed consent, which is required also from
12 the controls. The results will be communicated locally and internationally as
13 conference papers and journal articles.
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23 **Strengths and limitations of this study** 24

- 25 • This kind of comprehensive clinical study associated with moisture damage
26 exposure at work has not been conducted before.
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- 28 • This study will increase the understanding of respiratory tract and voice
29 symptoms and associated clinical findings in subjects exposed to moisture
30 damage.
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- 32 • Information of moisture damage exposure at work is based on documents
33 from the workplace
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- 35 • Limitation of a cross-sectional study like this is that it is not possible to obtain
36 information on causal relationships between exposure and symptoms or
37 illnesses
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Introduction

Indoor air quality problems are considered important risk factors for health problems worldwide¹. Indoor air associated symptoms may be interrelated with different indoor air factors such as insufficient ventilation², unfavourable temperature conditions³, dry indoor air⁴, dustiness⁵, moisture damage (MD)¹, volatile organic compounds (VOC)⁶, and man-made mineral/ vitreous fibres (MMMMF/ MMVF)⁷. Even if we do not know the cause of symptoms¹ 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 common¹¹. 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^{15,16}. Previous studies in this field have mainly been epidemiological⁹, and most is known about children's risk of developing symptoms in homes or schools with MD^{17,18}. In majority of the studies, the assessment of exposure to MD or presence of symptoms or illnesses has been based on questionnaires^{19,20}. Furthermore, only a small proportion of MD exposed workers are diagnosed with asthma⁸. According to our clinical experience, many patients with work-related MD exposure and referred to secondary health care report intermittent

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3 hoarseness, loss of voice or difficulty to inhale, which would refer to functional or
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5 organic problems of the larynx²¹. In the case of laryngeal disorders, asthma
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7 medication is not useful or may even worsen the symptoms if the larynx is sensitive
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9 to irritation²². Coexisting with asthma, laryngeal disorders may be the cause of
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11 insufficient response to asthma treatment.
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15 Studies over the past decades have provided important information on idiopathic
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17 environmental intolerance (IEI), in which a person has symptoms from different
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19 organ systems when in contact with an environmental factor that does not cause
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21 symptoms to most people^{23,24}. In odour or multiple chemical sensitivity (MCS) a
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23 person reacts with symptoms in association with low levels of airborne chemicals
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25 that most people tolerate without problems^{25,26}. It seems that some proportion of the
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27 patients that have indoor air associated symptoms in fact have IEI/MCS, but the
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29 frequency of this condition among these patients is not known²⁷.
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33 As a conclusion, there is a need for a clinical study on patients exposed to MD at
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35 workplace focusing especially on differential diagnostics between asthma and
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37 laryngeal symptoms, evidence of exposure to MDs and other indoor air risk factors
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39 and chemical sensitivity.
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42 43 44 *Aims of the study*

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46 In patients referred to secondary health care because of respiratory tract and/ or
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48 voice symptoms associated to MD exposure at work, the aim is to:
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- 51 1) Describe the prevalence of different characteristics, symptoms and clinical
52 test findings
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- 54 2) Find out the frequency of laryngeal symptoms and their possible influence on
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56 asthma diagnostics
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- 3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory QEESI[®] question series²⁸.
- 4) Find out if there are connections between above mentioned symptoms and clinical findings and if it would be possible to allocate the clinical tests according to patient's symptoms in secondary health care.

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 Phoniatics 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 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 (Table 1). The exclusion criteria were 1) severe illness (e.g. 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 was more frequent at work, it was not considered to be work-associated.

The conducted clinical tests are presented in Table 2. According to Finnish asthma guideline²⁹, diagnosis of asthma must be confirmed with a demonstration of variable

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3 airway obstruction in lung function measurements: i) peak expiratory flow (PEF)
4 monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial
5 hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients
6 carried out a two-week PEF monitoring, spirometry with bronchodilation test and
7 methacholine challenge test. The PEF monitoring included PEF measurements with
8 Pinnacle™ peak flow meter for two weeks in the morning and evening before and
9 after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed
10 according to European Respiratory Society/American Thoracic Society guidelines³⁰
11 and methacholine challenge test using dosimeter with controlled tidal breathing
12 according to Finnish guidelines³¹. To investigate if possible asthma is associated
13 with work the patients performed PEF monitoring at and off work³² with Vitalograph®
14 PEF/FEV Diary device. Diffusing capacity of the lungs³³ and exhaled nitric oxide
15 (FE_{NO})³⁴ were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-
16 laryngology (JN) and phoniatics (SV) examined the patients. For diagnosing
17 laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was
18 performed, voice samples were recorded and also inspirograms were recorded
19 before and after methacholine tests. Biopsy of nasal mucosa and a blood sample
20 were taken and preserved for later analyses.

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45 Exposure to MD at work was assessed from the documents of the building and
46 indoor air quality investigations made at the workplace, if available, according to
47 Finnish guidelines³⁵. A confirmed MD is graded into different severity categories, if
48 sufficient information is available. Also, MMMFs, VOCs or problems in ventilation
49 conditions at workplace were assessed if these had been measured.
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3 As a non-responder analysis, of the patients who were invited but who did not take
4 part in the study, age, symptoms, the presence of asthma diagnosis, and exposure
5 will be evaluated based on patient records.
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10 To explore how common laryngeal disorders are in general, methacholine challenge
11 test, voice recording, clinical examination by the specialist of phoniatics including
12 videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50
13 asymptomatic volunteers adjusted for age and gender. The gathering of the
14 volunteers began in August 2018 and it is our estimation that all the volunteers will
15 be examined by the end of 2019.
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25 *Questionnaire/ survey*

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28 The study patients and the volunteers fill out a questionnaire including questions on
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- 30 - previous diseases, medication and upper and lower respiratory symptoms³⁶
 - 31 - sinusitis symptoms (Sino-Nasal Outcome Test-22³⁷)
 - 32 - voice symptoms (Voice Activity and Participation Profile³⁸, Voice Handicap
33 Index³⁹, voice disorder questionnaire⁴⁰)
 - 34 - laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire⁴¹)
 - 35 - reflux symptoms (Reflux Symptom Index⁴²)
 - 36 - depression and anxiety symptoms (General Health Questionnaire GHQ-12⁴³;
37 Generalized Anxiety Disorder 7-item scale⁴⁴)
 - 38 - psychosocial work load⁴⁵, and stress symptoms⁴⁶
 - 39 - chemical sensitivity (QEESI[©])²⁸
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56 To find out if the study group would have different background characteristics from
57 the overall population, the same questionnaire was sent to 1500 Finnish speaking
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3 people in the same hospital district randomly selected by the Finnish Population
4 Information System. The proportions of women and men and different age groups in
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6 this comparison material are similar to the study population.
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10 11 12 13 *Sample size and power calculation*

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16 We estimated that a sample of 100 patients is enough to clinical deduction of the
17 different characteristics of this patient group.
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21 Concerning the population-based comparison material, our aim was to get 400
22 questionnaire answers (ratio 1:4) to increase the statistical power. Taking recent
23 rather low survey response rates into account, we sent the questionnaire to 1500
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28 people.
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31 To assess if findings suggesting laryngeal disorders are more frequent among those
32 who have respiratory tract or voice symptoms associated to workplace MD, data on
33 frequency of laryngeal findings of asymptomatic people is needed. When analyzing
34 the findings of methacholine challenge test of 30 patients, signs of laryngeal
35 disorders were found in 62,5%. We estimated that among under 30% of
36 asymptomatic people there are such findings in the methacholine challenge test. In
37 power calculation based on findings in the methacholine challenge test, the number
38 of asymptomatic people tested would be 50 with 80% force and 90% confidence
39 interval.
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51 52 *Data analyses*

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55 We will analyze descriptive statistics (mean, median or proportion depending on the
56 variable type and distribution) for variables such as gender distribution and age of
57 the patients and their lines of business. We will also analyze the frequencies of
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3 different symptoms the patients complain and how these are related to objective
4 findings in different organ systems or new diagnoses of e.g. asthma or laryngeal
5 dysfunction. We will describe the proportions of patients with significant findings in
6 medical assessment at different specialities (ENT, pulmonary and phoniatrics). We
7 will compare frequencies and intensities of different symptoms and clinical findings
8 between the patients and symptomless controls. We will also compare different
9 background factors of the study patients, such as perceived psychosocial work load,
10 with controls of the population who answered to the same questionnaire as the study
11 patients. Dichotomous variables between two groups (patients vs controls or among
12 patients with or without a certain finding) will be compared using χ^2 test and Fisher's
13 exact test, while continuous variables between two groups will be analyzed by t-test
14 or Mann-Whitney test depending on the distributions. Multiple logistic regression will
15 be used to assess independent predictors of certain clinical findings among the
16 patients. Based on the relation between symptoms and different objective findings
17 we aim to find "clinical triggers" (certain sets of symptoms) that should prompt
18 clinicians to refer patients to certain specialities.

Patient and Public Involvement

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

Ethics and dissemination

22 The regional ethics committee of Tampere University Hospital has approved the
23 study (R14095). All study subjects gave their written informed consent, which is
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3 required also from the volunteers. The study adheres to good clinical research
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5 guidelines and the Helsinki Declaration⁴⁷.
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8 The results will be communicated locally as well as internationally as conference
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10 papers and journal articles.
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13 14 **References**

- 15
16
17 1. WHO. *WHO Guidelines for Indoor Air Quality: Dampness and Mould*.
18
19 Copenhagen: WHO Regional Office for Europe; 2009.
20
21 http://www.euro.who.int/__data/assets/pdf_file/0017/43325/E92645.pdf.
22
23
- 24
25 2. Muscatiello N, Mccarthy A, Kielb C, Hsu WH, Hwang SA, Lin S. Classroom
26
27 conditions and CO₂ concentrations and teacher health symptom reporting in 10
28
29 New York State Schools. *Indoor Air*. 2015;25(2):157-167.
30
31 doi:10.1111/ina.12136
32
33
- 34
35 3. Skyberg K, Skulberg KR, Eduard W, Skåret E, Levy F, Kjuus H. Symptoms
36
37 prevalence among office employees and associations to building
38
39 characteristics. *Indoor Air*. 2003;13(3):246-252.
40
41 <http://www.ncbi.nlm.nih.gov/pubmed/12950587>. Accessed January 15, 2019.
42
43
- 44
45 4. Wolkoff P. Indoor air humidity, air quality, and health – An overview. *Int J Hyg*
46
47 *Environ Health*. 2018;221(3):376-390. doi:10.1016/j.ijheh.2018.01.015
48
49
- 50
51 5. Schneider T. Dust and fibers as a cause of indoor environment problems.
52
53 *Scand J Work Environ Heal Suppl*. 2008;(4):10-17. doi:10.5271/sjweh.1294
54
55
- 56
57 6. Salonen H, Pasanen A-L, Lappalainen S, et al. Volatile Organic Compounds
58
59 and Formaldehyde as Explaining Factors for Sensory Irritation in Office
60
Environments. *J Occup Environ Hyg*. 2009;6(4):239-247.

- 1
2
3 doi:10.1080/15459620902735892
4
5
6 7. Salonen HJ, Lappalainen SK, Riuttala HM, Tossavainen AP, Pasanen PO,
7
8 Reijula KE. Man-Made Vitreous Fibers in Office Buildings in the Helsinki Area.
9
10 *J Occup Environ Hyg.* 2009;6(10):624-631. doi:10.1080/15459620903133667
11
12
13 8. Karvala K, Toskala E, Luukkonen R, Uitti J, Lappalainen S, Nordman H.
14
15 Prolonged exposure to damp and moldy workplaces and new-onset asthma.
16
17 *Int Arch Occup Environ Health.* 2011;84(7):713-721. doi:10.1007/s00420-011-
18
19 0677-9
20
21
22
23 9. Mendell MJ, Mirer AG, Cheung K, Tong M, Douwes J. Respiratory and allergic
24
25 health effects of dampness, mold, and dampness-related agents: a review of
26
27 the epidemiologic evidence. *Environ Health Perspect.* 2011;119(6):748-756.
28
29 doi:10.1289/ehp.1002410
30
31
32
33 10. Jaakkola JJK, Hwang B-F, Jaakkola MS. Home Dampness and Molds as
34
35 Determinants of Allergic Rhinitis in Childhood: A 6-Year, Population-based
36
37 Cohort Study. *Am J Epidemiol.* 2010;172(4):451-459. doi:10.1093/aje/kwq110
38
39
40
41 11. Täubel M, Karvonen AM, Reponen T, Hyvärinen A, Vesper S, Pekkanen J.
42
43 Application of the Environmental Relative Moldiness Index in Finland. *Appl*
44
45 *Environ Microbiol.* 2015;82(2):578-584. doi:10.1128/AEM.02785-15
46
47
48 12. Reijula K, Sundman-Digert C, Reijula K. Assessment of indoor air problems at
49
50 work with a questionnaire. *Occup Environ Med.* 2004;61(1):33-38.
51
52 doi:10.1136/oem.2002.005835
53
54
55
56 13. Ministry of Social Affairs and Health F. *Moisture Damages in Workplaces.*
57
58 *Memo of the Working Group on Moisture Damages (in Finnish).* Helsinki;
59
60

- 1
2
3 2009.
4
5
6 14. Hurraß J, Heinzow B, Aurbach U, et al. Medical diagnostics for indoor mold
7 exposure. *Int J Hyg Environ Health*. 2017;220(2):305-328.
8
9 doi:10.1016/j.ijheh.2016.11.012
10
11
12
13 15. White SK, Cox-Ganser JM, Benaise LG, Kreiss K. Work-related peak flow and
14 asthma symptoms in a damp building. *Occup Med (Chic Ill)*. 2013;63(4):287-
15 290. doi:10.1093/occmed/kqt028
16
17
18 16. Hellgren U-M, Hyvärinen M, Holopainen R, Reijula K. Perceived indoor air
19 quality, air-related symptoms and ventilation in Finnish hospitals. *Int J Occup
20 Med Environ Health*. 2011;24(1):48-56. doi:10.2478/s13382-011-0011-5
21
22
23 17. Karvonen AM, Hyvarinen A, Korppi M, et al. Moisture Damage and Asthma: A
24 Birth Cohort Study. *Pediatrics*. 2015;135(3):e598-e606.
25
26 doi:10.1542/peds.2014-1239
27
28
29 18. Borràs-Santos A, Jacobs JH, Täubel M, et al. Dampness and mould in schools
30 and respiratory symptoms in children: the HITEA study. *Occup Environ Med*.
31 2013;70(10):681-687. doi:10.1136/oemed-2012-101286
32
33
34 19. Kim J-L, Henneberger PK, Lohman S, et al. Impact of occupational exposures
35 on exacerbation of asthma: a population-based asthma cohort study. *BMC
36 Pulm Med*. 2016;16(1):148. doi:10.1186/s12890-016-0306-1
37
38
39 20. Kurth L, Virji MA, Storey E, et al. Current asthma and asthma-like symptoms
40 among workers at a Veterans Administration Medical Center. *Int J Hyg Environ
41 Health*. 2017;220(8):1325-1332. doi:10.1016/j.ijheh.2017.09.001
42
43
44 21. Moscato G, Pala G, Cullinan P, et al. EAACI position paper on assessment of
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 cough in the workplace. *Allergy Eur J Allergy Clin Immunol*. 2014.
4
5 doi:10.1111/all.12352
6
7
- 8 22. Idrees M, FitzGerald JM. Vocal cord dysfunction in bronchial asthma. A review
9 article. *J Asthma*. 2015;52(4):327-335. doi:10.3109/02770903.2014.982288
10
11
12
- 13 23. Genuis SJ. Chemical sensitivity: pathophysiology or pathopsychology? *Clin*
14 *Ther*. 2013;35(5):572-577. doi:10.1016/j.clinthera.2013.04.003
15
16
17
- 18 24. Rossi S, Pitidis A. Multiple Chemical Sensitivity: Review of the State of the Art
19 in Epidemiology, Diagnosis, and Future Perspectives. *J Occup Environ Med*.
20 2018;60(2):138-146. doi:10.1097/JOM.0000000000001215
21
22
23
- 24 25. Dantoft TM, Andersson L, Nordin S, Skovbjerg S. Chemical intolerance. *Curr*
25 *Rheumatol Rev*. 2015;11(2):167-184.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
- 44 26. Andersson L, Claeson A-S, Dantoft TM, Skovbjerg S, Lind N, Nordin S.
45 Chemosensory perception, symptoms and autonomic responses during
46 chemical exposure in multiple chemical sensitivity. *Int Arch Occup Environ*
47 *Health*. 2016;89(1):79-88. doi:10.1007/s00420-015-1053-y
48
49
50
51
52
53
- 54 27. Karvala K, Sainio M, Palmquist E, Claeson A-S, Nyback M-H, Nordin S.
55 Building-Related Environmental Intolerance and Associated Health in the
56 General Population. *Int J Environ Res Public Health*. 2018;15(9).
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
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81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
28. 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(3-4):370-385.

- 1
2
3 doi:10.1177/074823379901500311
4
5
6 29. Haahtela T, Lehtimäki L, Ahonen E, et al. [Update on current care guidelines:
7 asthma]. *Duodecim*. 2013;129(9):994-995.
8
9
10 <http://www.ncbi.nlm.nih.gov/pubmed/23786112>. Accessed May 18, 2018.
11
12
13 30. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur*
14 *Respir J*. 2005;26(2):319-338. doi:10.1183/09031936.05.00034805
15
16
17 31. Nieminen MM, Lahdensuo A, Kellomaeki L, Karvonen J, Muittari A.
18
19 Methacholine bronchial challenge using a dosimeter with controlled tidal
20
21 breathing. *Thorax*. 1988;43(11):896-900.
22
23
24 <http://www.ncbi.nlm.nih.gov/pubmed/3065974>. Accessed May 18, 2018.
25
26
27 32. Burge PS. Use of serial measurements of peak flow in the diagnosis of
28
29 occupational asthma. *Occup Med*. 1993;8(2):279-294.
30
31
32 <http://www.ncbi.nlm.nih.gov/pubmed/8506506>. Accessed May 19, 2017.
33
34
35 33. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath
36
37 determination of carbon monoxide uptake in the lung. *Eur Respir J*.
38
39 2005;26(4):720-735. doi:10.1183/09031936.05.00034905
40
41
42
43 34. Horváth I, Barnes PJ, Loukides S, et al. A European Respiratory Society
44
45 technical standard: exhaled biomarkers in lung disease. *Eur Respir J*.
46
47 2017;49(4):1600965. doi:10.1183/13993003.00965-2016
48
49
50
51 35. Latvala J, Karvala K, Sainio M, et al. *Guidelines for Workplace and*
52
53 *Occupational Health Actions in Indoor Air Problems (Finnish)*.
54
55 Työterveyslaitos; 2017. <http://www.julkari.fi/handle/10024/132078>. Accessed
56
57 August 20, 2018.
58
59
60

- 1
2
3 36. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Validation of a new
4 questionnaire on asthma, allergic rhinitis, and conjunctivitis in young adults.
5
6 *Allergy*. 2001;56(5):377-384. doi:10.1034/j.1398-9995.2001.056005377.x
7
8
9
10
11 37. Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - which
12 is best? *Clin Otolaryngol*. 2006;31(2):103-109. doi:10.1111/j.1749-
13 4486.2006.01155.x
14
15
16
17
18 38. Sukanen O, Sihvo M, Rorarius E, Lehtihalmes M, Autio V, Kleemola L. Voice
19 Activity and Participation Profile (VAPP) in assessing the effects of voice
20 disorders on patients' quality of life: Validity and reliability of the Finnish
21 version of VAPP. *Logop Phoniatr Vocology*. 2007;32(1):3-8.
22 doi:10.1080/14015430600784386
23
24
25
26
27
28
29
30
31 39. Alaluusua S JM. Psycho-social handicap of voice disorder and its
32 rehabilitation: a pilot study of Finnish version of Voice Handicap Index [In
33 Finnish] [master thesis]. 2003.
34
35
36
37
38 40. Sala E, Laine A, Simberg S, Pentti J, Suonpää J. The prevalence of voice
39 disorders among day care center teachers compared with nurses: a
40 questionnaire and clinical study. *J Voice*. 2001;15(3):413-423.
41 doi:10.1016/S0892-1997(01)00042-X
42
43
44
45
46
47
48 41. Vertigan AE, Bone SL, Gibson PG. Development and validation of the
49 Newcastle laryngeal hypersensitivity questionnaire. *Cough*. 2014;10(1):1.
50 doi:10.1186/1745-9974-10-1
51
52
53
54
55 42. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux
56 symptom index (RSI). *J Voice*. 2002;16(2):274-277.
57
58
59
60 <http://www.ncbi.nlm.nih.gov/pubmed/12150380>. Accessed June 26, 2018.

- 1
2
3 43. Mäkikangas A, Feldt T, Kinnunen U, Tolvanen A, Kinnunen M-L, Pulkkinen L.
4
5 The factor structure and factorial invariance of the 12-item General Health
6
7 Questionnaire (GHQ-12) across time: evidence from two community-based
8
9 samples. *Psychol Assess*. 2006;18(4):444-451. doi:10.1037/1040-
10
11 3590.18.4.444
12
13
14
15 44. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing
16
17 Generalized Anxiety Disorder. *Arch Intern Med*. 2006;166(10):1092.
18
19 doi:10.1001/archinte.166.10.1092
20
21
22
23 45. Lahtinen M, Sundman-Digert C, Reijula K. Psychosocial work environment and
24
25 indoor air problems: a questionnaire as a means of problem diagnosis. *Occup*
26
27 *Environ Med*. 2004;61(2):143 LP-149.
28
29 <http://oem.bmj.com/content/61/2/143.abstract>.
30
31
32
33 46. Elo A-L, Leppänen A, Jahkola A. Validity of a single-item measure of stress
34
35 symptoms. *Scand J Work Environ Health*. 2003;29(6):444-451.
36
37 doi:10.5271/sjweh.752
38
39
40
41 47. World Medical Association Declaration of Helsinki. *JAMA*. 2013;310(20):2191.
42
43 doi:10.1001/jama.2013.281053
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48 **Authors' contributions:** JU is the head of the study group and PN the principal
49
50 researcher. All the writers took part in developing the study protocol; JU and PN
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52 especially planning the exposure assessment, JK, LL and AT the lung function
53
54 diagnostics measures, JN the diagnostics of upper airways and SV, LK and EK the
55
56 laryngeal investigations. All authors contributed to and approved the manuscript.
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1
2
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6
7
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10 Foundation, grants from Competitive State Research Financing of the Expert

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13 Responsibility area of Tampere University Hospital, during the conduct of the study.

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3 Figure 1. The study design of study on symptoms associated to moisture damage at
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10 Table 1. The criteria on which moisture damage (MD) at workplace was suspected
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- 15 1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
 - 16 2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials,
17 disengaging or blistering of flooring materials, crumbling of wall plastering, water
18 leakages through ceilings (buckets on the floors), loose water on surfaces
 - 19 3. Renovations because of MDs previously made in the building
 - 20 4. Information of MD findings from employer or occupational and health safety
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Table 2. The clinical tests conducted to the study patients.

Lung function tests	2-week serial PEF monitoring, PEF monitoring at and off work, spirometry with bronchodilation test, methacholine challenge test, exhaled nitric oxide (FE _{NO}), 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 <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, <i>Dermatophagoides Pteronyssinus</i> house dust mite, latex, <i>aspergillus fumigatus</i> , storage mites <i>Acarus Siro</i> , <i>Lepidoglyphus Destructor</i> , <i>Thyrophagus Putrescentiae</i>
Imaging	Chest x-ray, cone beam computed tomography of the paranasal sinuses

Table 3. The criteria based on which asthma is diagnosed in different clinical tests ²⁹.

Clinical test	Criteria for asthma
Two-week peak expiratory flow (PEF) monitoring	At least 3 times <ul style="list-style-type: none">- at least 15% and 60 L/min improvements of PEF after bronchodilator or- diurnal variation of PEF at least 20% and 60 L/min
Spirometry	At least 200 mL and 12% improvement in forced expiratory volume in one second (FEV ₁) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV ₁ (PD ₂₀ FEV ₁ <600 µg)

