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Keywords:	moisture damage, mold, Asthma < THORACIC MEDICINE, 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 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 worldwide[1]. 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 (MMMF/ MMVF). Even if we do not know the exact cause of symptoms[1] 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 common[5]. 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 epidemiological[3], 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 asthma[2]. To our clinical experience, many patients with MD exposure at work referred to secondary health care report intermittent

hoarseness, loss of voice or difficulty to inhale, which would refer to functional or organic problems of the larynx[15]. In the case of laryngeal disorders, asthma medication is not useful or may even worsen the symptoms if the larynx is sensitive to irritation[16]. Coexisting with asthma, laryngeal disorders may cause insufficient response to asthma treatment.

Studies over the past decades have provided important information on idiopathic environmental intolerance (IEI), in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms to most people[17]. In odour or multiple chemical sensitivity (MCS) a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems[18]. It seems that some proportion of the patients that have indoor air associated symptoms in fact have IEI/MCS, but the frequency of this condition among these patients is not known.

Aims of the study

In patients referred to secondary health care because of respiratory tract and/ or voice symptoms associated to MD exposure at work, the aim is to:

1) Describe the prevalence of different characteristics, symptoms and clinical test findings
2) Find out the frequency of laryngeal symptoms and their possible effect on asthma diagnostics
3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to QEESI© question series[19].

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 Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects between October 2015 and June 2017. The study inclusion criteria were 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 guideline[20], diagnosis of asthma must be confirmed with a demonstration of variable airway obstruction in lung function measurements: i) peak expiratory flow (PEF) monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients

carried out a two-week PEF monitoring, spirometry with bronchodilation test and methacholine challenge test. The PEF monitoring included PEF measurements with Pinnacle™ peak flow meter for two weeks in the morning and evening before and after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines[21] and methacholine challenge test using dosimeter with controlled tidal breathing according to Finnish guidelines[22]. To investigate if possible asthma is associated with work the patients performed PEF monitoring at and off work[23] with Vitalograph® PEF/FEV Diary device. Diffusing capacity of the lungs[24] and exhaled nitric oxide (FE_{NO})[25] were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-laryngology (JN) and phoniatrics (SV) examined the patients. For diagnosing laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was performed, voice samples were recorded and also inspirograms were recorded before and after methacholine tests. Biopsy of nasal mucosa and a blood sample were taken and preserved for later analyses.

Exposure to MD at work was assessed from the documents of the building and indoor air quality investigations made at the workplace, if available, according to Finnish guidelines[26]. Also, MMMFs, VOCs or problems in ventilation conditions at workplace were assessed, if these had been investigated.

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

To explore how common laryngeal disorders are in general, methacholine challenge test, voice recording, clinical examination of the specialist of phoniatrics including

videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50 asymptomatic volunteers adjusted for age and gender.

Questionnaire/ survey

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

- previous diseases, medication and upper and lower respiratory symptoms[27]
- sinusitis symptoms (Sino-Nasal Outcome Test-22[28])
- voice symptoms (Voice Activity and Participation Profile[29], Voice Handicap Index[30], voice disorder questionnaire[31])
- laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire[32])
- reflux symptoms (Reflux Symptom Index[33])
- depression and anxiety symptoms (General Health Questionnaire GHQ-12©[34]; Generalized Anxiety Disorder 7-item scale[35])
- psychosocial work load[36], and stress symptoms[37]
- chemical sensitivity (QEESI©)[19]

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. The proportions of women and men and different age groups in this comparison material are similar to the study population.

Sample size and power calculation

It is estimated that a sample of 100 patients is enough to clinical deduction of the different characteristics of this patient group.

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

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

Data analyses

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

Ethics and dissemination

The regional ethics committee of Tampere University Hospital has approved the study (R14095). All study subjects gave their written informed consent, which is required also from the volunteers. The study adheres to good clinical research guidelines and the Helsinki Declaration[38].

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

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

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Competing interests: None.

Table 1. The criteria on which moisture damage (MD) at workplace was suspected [7].

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

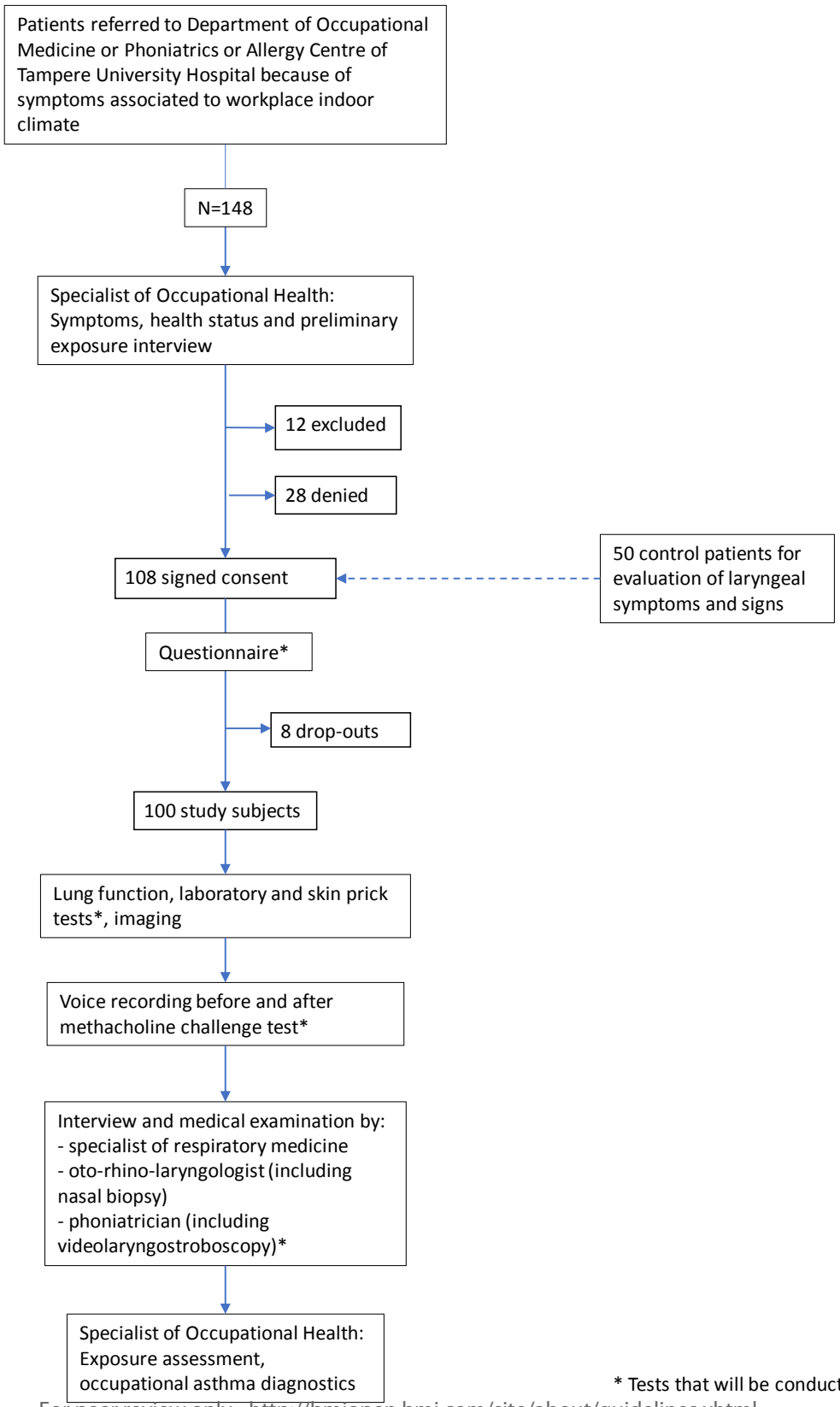
Table 2. The clinical tests conducted to the study patients.

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 Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, latex, aspergillus fumigatus, storage mites Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae
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 - 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.



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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

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

In Finland, located in subarctic area, MDs in residences and schools are common[11]. Workers in office buildings commonly report symptoms and complaints associated with indoor air[12,13]. There is also a growing public concern over MDs in buildings and their possible permanent effects on dwellers' or workers' health in Finland, even if there is minor evidence of serious or permanent illnesses other than asthma caused by exposure to MD[9,14] .

There are few studies describing the clinical findings in patients having symptoms when exposed to MD at work[15,16]. Previous studies in this field have mainly been epidemiological[9], 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 asthma[8]. According to our clinical experience, many patients with work-related MD exposure and referred to secondary health care report intermittent hoarseness, loss of voice or difficulty to inhale, which would refer to functional or organic problems of the larynx[21]. In the case of laryngeal disorders, asthma

medication is not useful or may even worsen the symptoms if the larynx is sensitive to irritation[22]. Coexisting with asthma, laryngeal disorders may be the cause of insufficient response to asthma treatment.

Studies over the past decades have provided important information on idiopathic environmental intolerance (IEI), in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms to most people[23,24]. In odour or multiple chemical sensitivity (MCS) a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems[25,26]. It seems that some proportion of the patients that have indoor air associated symptoms in fact have IEI/MCS, but the frequency of this condition among these patients is not known[27].

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

Aims of the study

In patients referred to secondary health care because of respiratory tract and/ or voice symptoms associated to MD exposure at work, the aim is to:

1) Describe the prevalence of different characteristics, symptoms and clinical test findings
2) Find out the frequency of laryngeal symptoms and their possible influence on asthma diagnostics

3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory QEESI© question series[28].
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 Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects between October 2015 and June 2017. The study inclusion criteria were 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 guideline[29], diagnosis of asthma must be confirmed with a demonstration of variable

airway obstruction in lung function measurements: i) peak expiratory flow (PEF) monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients carried out a two-week PEF monitoring, spirometry with bronchodilation test and methacholine challenge test. The PEF monitoring included PEF measurements with Pinnacle™ peak flow meter for two weeks in the morning and evening before and after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines[30] and methacholine challenge test using dosimeter with controlled tidal breathing according to Finnish guidelines[31]. To investigate if possible asthma is associated with work the patients performed PEF monitoring at and off work[32] with Vitalograph® PEF/FEV Diary device. Diffusing capacity of the lungs[33] and exhaled nitric oxide (FE_{NO})[34] were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-laryngology (JN) and phoniatrics (SV) examined the patients. For diagnosing laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was performed, voice samples were recorded and also inspirograms were recorded before and after methacholine tests. Biopsy of nasal mucosa and a blood sample were taken and preserved for later analyses.

Exposure to MD at work was assessed from the documents of the building and indoor air quality investigations made at the workplace, if available, according to Finnish guidelines[35]. A confirmed MD is graded into different severity categories, if sufficient information is available. Also, MMMFs, VOCs or problems in ventilation conditions at workplace were assessed if these had been measured.

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

To explore how common laryngeal disorders are in general, methacholine challenge test, voice recording, clinical examination by the specialist of phoniatrics including videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50 asymptomatic volunteers adjusted for age and gender. The gathering of the volunteers began in August 2018 and it is our estimation that all the volunteers will be examined by the end of 2019.

Questionnaire/ survey

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

- previous diseases, medication and upper and lower respiratory symptoms[36]
- sinusitis symptoms (Sino-Nasal Outcome Test-22[37])
- voice symptoms (Voice Activity and Participation Profile[38], Voice Handicap Index[39], voice disorder questionnaire[40])
- laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire[41])
- reflux symptoms (Reflux Symptom Index[42])
- depression and anxiety symptoms (General Health Questionnaire GHQ-12©[43]; Generalized Anxiety Disorder 7-item scale[44])
- psychosocial work load[45], and stress symptoms[46]
- chemical sensitivity (QEESI©)[28]

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. The proportions of women and men and different age groups in this comparison material are similar to the study population.

Sample size and power calculation

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

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

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

Data analyses

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

Patient and Public Involvement

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

Ethics and dissemination

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

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

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

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Competing interests: The study group report grants from Tampere Tuberculosis Foundation, grants from Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital, during the conduct of the study.

Figure 1. The study design of study on symptoms associated to moisture damage at workplace.

Table 1. The criteria on which moisture damage (MD) at workplace was suspected [13].

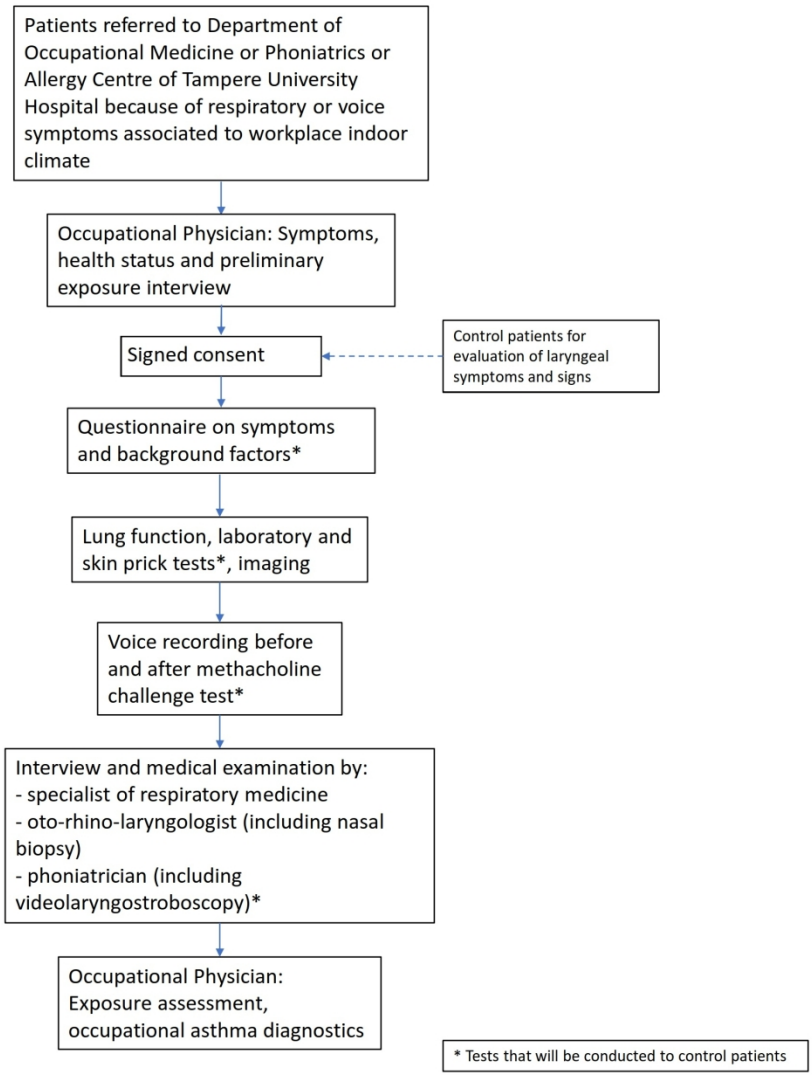
1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), loose water 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

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 Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, latex, aspergillus fumigatus, storage mites Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae
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 - 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 (FEV1) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV1 (PD20FEV1 <600 µg)



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

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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
Secondary Subject Heading:	Respiratory medicine
Keywords:	moisture damage, mold, Asthma < THORACIC MEDICINE, irritable larynx, respiratory symptoms

The SAMDAW study protocol: A clinical descriptive study on Symptoms 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

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

In Finland, located in subarctic area, MDs in residences and schools are common[11]. Workers in office buildings commonly report symptoms and complaints associated with indoor air[12,13]. There is also a growing public concern over MDs in buildings and their possible permanent effects on dwellers' or workers' health in Finland, even if there is minor evidence of serious or permanent illnesses other than asthma caused by exposure to MD[9,14] .

There are few studies describing the clinical findings in patients having symptoms when exposed to MD at work[15,16]. Previous studies in this field have mainly been epidemiological[9], 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 asthma[8]. According to our clinical experience, many patients with work-related MD exposure and referred to secondary health care report intermittent hoarseness, loss of voice or difficulty to inhale, which would refer to functional or organic problems of the larynx[21]. In the case of laryngeal disorders, asthma

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Studies over the past decades have provided important information on idiopathic environmental intolerance (IEI), in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms to most people[23,24]. In odour or multiple chemical sensitivity (MCS) a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems[25,26]. It seems that some proportion of the patients that have indoor air associated symptoms in fact have IEI/MCS, but the frequency of this condition among these patients is not known[27].

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

Aims of the study

In patients referred to secondary health care because of respiratory tract and/ or voice symptoms associated to MD exposure at work, the aim is to:

1) Describe the prevalence of different characteristics, symptoms and clinical test findings
2) Find out the frequency of laryngeal symptoms and their possible influence on asthma diagnostics

3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory QEESI© question series[28].
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 Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects between October 2015 and June 2017. The study inclusion criteria were 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 guideline[29], diagnosis of asthma must be confirmed with a demonstration of variable

airway obstruction in lung function measurements: i) peak expiratory flow (PEF) monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients carried out a two-week PEF monitoring, spirometry with bronchodilation test and methacholine challenge test. The PEF monitoring included PEF measurements with Pinnacle™ peak flow meter for two weeks in the morning and evening before and after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines[30] and methacholine challenge test using dosimeter with controlled tidal breathing according to Finnish guidelines[31]. To investigate if possible asthma is associated with work the patients performed PEF monitoring at and off work[32] with Vitalograph® PEF/FEV Diary device. Diffusing capacity of the lungs[33] and exhaled nitric oxide (FE_{NO})[34] were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-laryngology (JN) and phoniatrics (SV) examined the patients. For diagnosing laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was performed, voice samples were recorded and also inspirograms were recorded before and after methacholine tests. Biopsy of nasal mucosa and a blood sample were taken and preserved for later analyses.

Exposure to MD at work was assessed from the documents of the building and indoor air quality investigations made at the workplace, if available, according to Finnish guidelines[35]. A confirmed MD is graded into different severity categories, if sufficient information is available. Also, MMMFs, VOCs or problems in ventilation conditions at workplace were assessed if these had been measured.

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

To explore how common laryngeal disorders are in general, methacholine challenge test, voice recording, clinical examination by the specialist of phoniatrics including videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50 asymptomatic volunteers adjusted for age and gender. The gathering of the volunteers began in August 2018 and it is our estimation that all the volunteers will be examined by the end of 2019.

Questionnaire/ survey

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

- previous diseases, medication and upper and lower respiratory symptoms[36]
- sinusitis symptoms (Sino-Nasal Outcome Test-22[37])
- voice symptoms (Voice Activity and Participation Profile[38], Voice Handicap Index[39], voice disorder questionnaire[40])
- laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire[41])
- reflux symptoms (Reflux Symptom Index[42])
- depression and anxiety symptoms (General Health Questionnaire GHQ-12©[43]; Generalized Anxiety Disorder 7-item scale[44])
- psychosocial work load[45], and stress symptoms[46]
- chemical sensitivity (QEESI©)[28]

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. The proportions of women and men and different age groups in this comparison material are similar to the study population.

Sample size and power calculation

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

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

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

Data analyses

We will analyze descriptive statistics such as gender distribution and age of the patients with their lines of business. We will also analyze the frequencies of different symptoms the patients complain and how these are related to objective findings in

different organ systems or new diagnoses of e.g. asthma or laryngeal dysfunction. We will describe the proportions of patients with significant findings in medical assessment at different specialities (ENT, pulmonary and phoniatrics). We will compare frequencies and intensities of different symptoms and clinical findings between the patients and symptomless controls. We will also compare different background factors of the study patients, such as perceived psychosocial work load, with controls of the population who answered to the same questionnaire as the study patients. Based on the relation between symptoms and different objective findings we aim to find "clinical triggers" (certain sets of symptoms) that should prompt clinicians to refer patients to certain specialities.

Patient and Public Involvement

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

Ethics and dissemination

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

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

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

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Figure 1. The study design of study on symptoms associated to moisture damage at workplace.

Table 1. The criteria on which moisture damage (MD) at workplace was suspected [13].

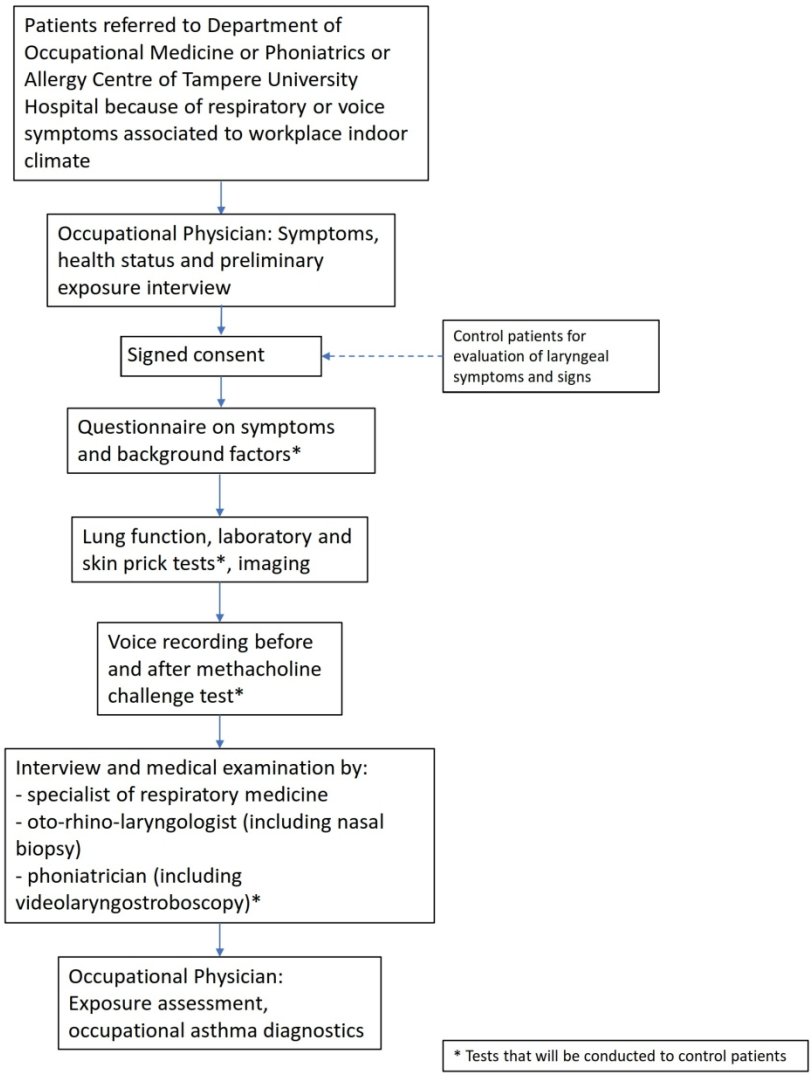
1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), loose water 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

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 Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, latex, aspergillus fumigatus, storage mites Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae
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 - 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 (FEV1) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV1 (PD20FEV1 <600 µg)



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

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

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Keywords:	moisture damage, mold, Asthma < THORACIC MEDICINE, irritable larynx, respiratory symptoms

The SAMDAW study protocol: An observational cross-sectional study on Symptoms 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 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 phoniatrics. The exposure assessment was performed by an occupational physician. The study patients filled out a questionnaire on previous illnesses and other background factors which for comparison was sent also 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 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 worldwide[1]. Indoor air associated symptoms may be interrelated with different indoor air factors such as insufficient ventilation[2], unfavourable temperature conditions[3], dry indoor air[4], dustiness[5], moisture damage (MD)[1], volatile organic compounds (VOC)[6], and man-made mineral/ vitreous fibres (MMMF/ MMVF)[7]. Even if we do not know the cause of symptoms[1] MD exposure at work has been shown to increase the risk of new onset asthma and exacerbation of asthma[8,9]. Other illnesses or respiratory symptoms that have been associated with MD exposure include cough, wheezing, dyspnoea, rhinitis, and upper respiratory tract symptoms[9,10].

In Finland, located in subarctic area, MDs in residences and schools are common[11]. Workers in office buildings commonly report symptoms and complaints associated with indoor air[12,13]. There is also a growing public concern over MDs in buildings and their possible permanent effects on dwellers' or workers' health in Finland, even if there is minor evidence of serious or permanent illnesses other than asthma caused by exposure to MD[9,14] .

There are few studies describing the clinical findings in patients having symptoms when exposed to MD at work[15,16]. Previous studies in this field have mainly been epidemiological[9], 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 asthma[8]. According to our clinical experience, many patients with work-related MD exposure and referred to secondary health care report intermittent

hoarseness, loss of voice or difficulty to inhale, which would refer to functional or organic problems of the larynx[21]. In the case of laryngeal disorders, asthma medication is not useful or may even worsen the symptoms if the larynx is sensitive to irritation[22]. Coexisting with asthma, laryngeal disorders may be the cause of insufficient response to asthma treatment.

Studies over the past decades have provided important information on idiopathic environmental intolerance (IEI), in which a person has symptoms from different organ systems when in contact with an environmental factor that does not cause symptoms to most people[23,24]. In odour or multiple chemical sensitivity (MCS) a person reacts with symptoms in association with low levels of airborne chemicals that most people tolerate without problems[25,26]. It seems that some proportion of the patients that have indoor air associated symptoms in fact have IEI/MCS, but the frequency of this condition among these patients is not known[27].

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

Aims of the study

In patients referred to secondary health care because of respiratory tract and/ or voice symptoms associated to MD exposure at work, the aim is to:

1) Describe the prevalence of different characteristics, symptoms and clinical test findings
2) Find out the frequency of laryngeal symptoms and their possible influence on asthma diagnostics

3) Explore the number of patients that fulfil the criteria of chemical sensitivity according to Quick Environmental Exposure and Sensitivity Inventory QEESI© question series[28].
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 Phoniatrics or Allergy Centre because of symptoms associated with indoor complaints at their workplace were interviewed as possible study subjects between October 2015 and June 2017. The study inclusion criteria were 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 guideline[29], diagnosis of asthma must be confirmed with a demonstration of variable

airway obstruction in lung function measurements: i) peak expiratory flow (PEF) monitoring, ii) spirometry with bronchodilation test, or iii) test for bronchial hyperreactivity (Table 3). To confirm or rule out the asthma diagnosis, the patients carried out a two-week PEF monitoring, spirometry with bronchodilation test and methacholine challenge test. The PEF monitoring included PEF measurements with Pinnacle™ peak flow meter for two weeks in the morning and evening before and after inhaled bronchodilator (0.4 mg salbutamol). Spirometry was performed according to European Respiratory Society/American Thoracic Society guidelines[30] and methacholine challenge test using dosimeter with controlled tidal breathing according to Finnish guidelines[31]. To investigate if possible asthma is associated with work the patients performed PEF monitoring at and off work[32] with Vitalograph® PEF/FEV Diary device. Diffusing capacity of the lungs[33] and exhaled nitric oxide (FE_{NO})[34] were determined. Specialists of respiratory medicine (JK and LL), oto-rhino-laryngology (JN) and phoniatrics (SV) examined the patients. For diagnosing laryngeal disorders videolaryngostroboscopy with either rigid or fiberoptic scope was performed, voice samples were recorded and also inspirograms were recorded before and after methacholine tests. Biopsy of nasal mucosa and a blood sample were taken and preserved for later analyses.

Exposure to MD at work was assessed from the documents of the building and indoor air quality investigations made at the workplace, if available, according to Finnish guidelines[35]. A confirmed MD is graded into different severity categories, if sufficient information is available. Also, MMMFs, VOCs or problems in ventilation conditions at workplace were assessed if these had been measured.

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

To explore how common laryngeal disorders are in general, methacholine challenge test, voice recording, clinical examination by the specialist of phoniatrics including videolaryngostroboscopy, FE_{NO}, and skin prick tests will be conducted to 50 asymptomatic volunteers adjusted for age and gender. The gathering of the volunteers began in August 2018 and it is our estimation that all the volunteers will be examined by the end of 2019.

Questionnaire/ survey

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

- previous diseases, medication and upper and lower respiratory symptoms[36]
- sinusitis symptoms (Sino-Nasal Outcome Test-22[37])
- voice symptoms (Voice Activity and Participation Profile[38], Voice Handicap Index[39], voice disorder questionnaire[40])
- laryngeal symptoms (Newcastle laryngeal hypersensitivity questionnaire[41])
- reflux symptoms (Reflux Symptom Index[42])
- depression and anxiety symptoms (General Health Questionnaire GHQ-12©[43]; Generalized Anxiety Disorder 7-item scale[44])
- psychosocial work load[45], and stress symptoms[46]
- chemical sensitivity (QEESI©)[28]

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. The proportions of women and men and different age groups in this comparison material are similar to the study population.

Sample size and power calculation

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

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

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

Data analyses

We will analyze descriptive statistics (mean, median or proportion depending on the variable type and distribution) for variables such as gender distribution and age of the patients and their lines of business. We will also analyze the frequencies of

different symptoms the patients complain and how these are related to objective findings in different organ systems or new diagnoses of e.g. asthma or laryngeal dysfunction. We will describe the proportions of patients with significant findings in medical assessment at different specialities (ENT, pulmonary and phoniatrics). We will compare frequencies and intensities of different symptoms and clinical findings between the patients and symptomless controls. We will also compare different background factors of the study patients, such as perceived psychosocial work load, with controls of the population who answered to the same questionnaire as the study patients. Dichotomous variables between two groups (patients vs controls or among patients with or without a certain finding) will be compared using $\chi 2$ test and Fisher's exact test, while continuous variables between two groups will be analyzed by t-test or Mann-Whitney test depending on the distributions. Multiple logistic regression will be used to assess independent predictors of certain clinical findings among the patients. Based on the relation between symptoms and different objective findings we aim to find "clinical triggers" (certain sets of symptoms) that should prompt clinicians to refer patients to certain specialities.

Patient and Public Involvement

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

Ethics and dissemination

The regional ethics committee of Tampere University Hospital has approved the study (R14095). All study subjects gave their written informed consent, which is

required also from the volunteers. The study adheres to good clinical research guidelines and the Helsinki Declaration[47].

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

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

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Figure 1. The study design of study on symptoms associated to moisture damage at workplace.

Table 1. The criteria on which moisture damage (MD) at workplace was suspected [13].

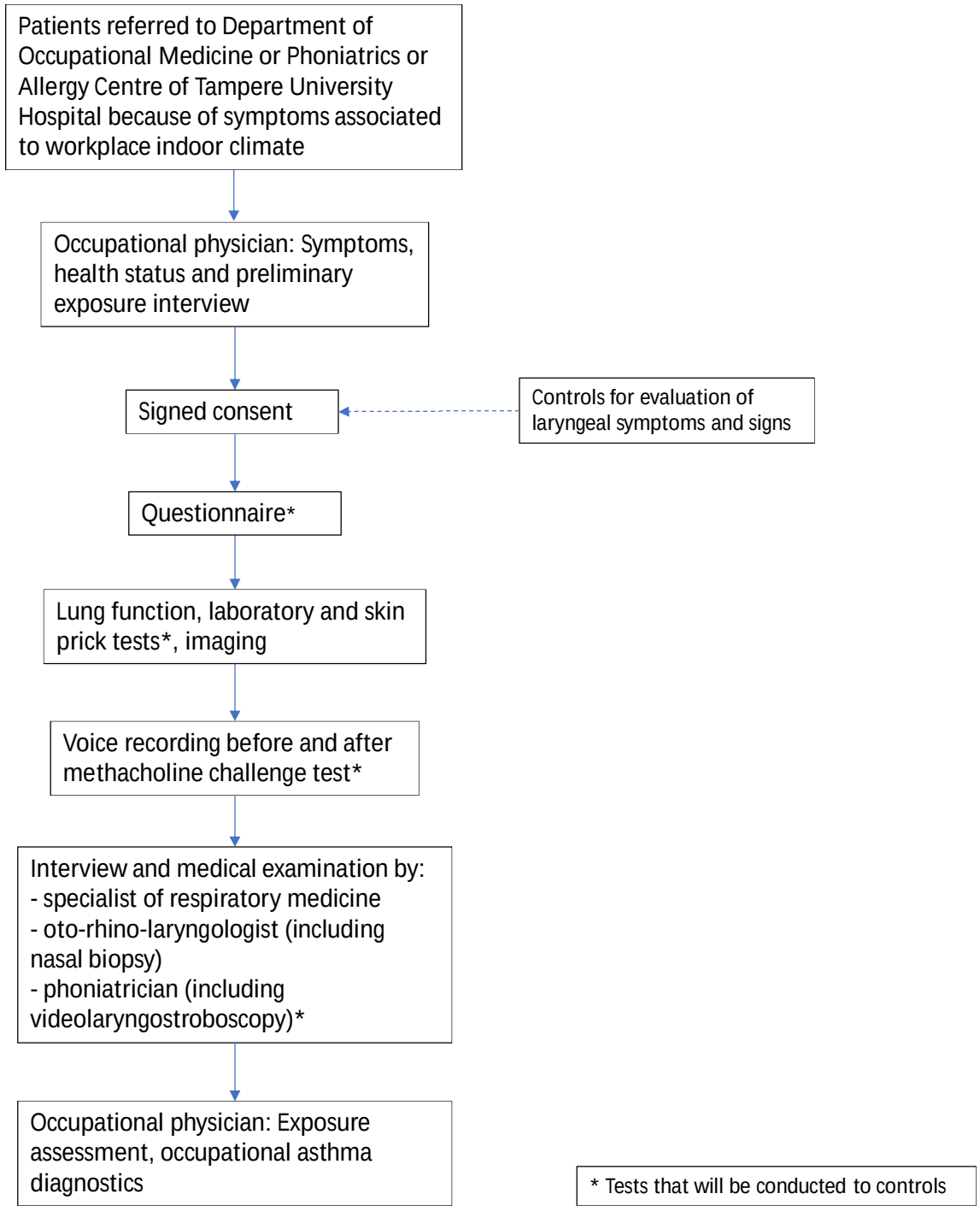
1. Indoor air perceived as mouldy or stuffy or otherwise unpleasant
2. Signs of MDs: visible mould, moisture spots, discolouration of surface materials, disengaging or blistering of flooring materials, crumbling of wall plastering, water leakages through ceilings (buckets on the floors), loose water 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

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 Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae)
Skin prick tests	Birch, timothy, mugwort, horse, dog, cat, Dermatophagoides Pteronyssinus house dust mite, latex, aspergillus fumigatus, storage mites Acarus Siro, Lepidoglyphus Destructor, Thyrophagus Putrescentiae
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 - 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 (FEV1) or forced vital capacity (FVC)
Methacholine challenge test	Cumulative methacholine dose 0.6 mg or under results in 20% drop in FEV1 (PD20FEV1 <600 µg)


Patients referred to Department of Occupational Medicine or Phoniatrics or Allergy Centre of Tampere University Hospital because of symptoms associated to workplace indoor climate
Occupational physician: Symptoms, health status and preliminary exposure interview
Signed consent
Controls for evaluation of laryngeal symptoms and signs
Questionnaire*
Lung function, laboratory and skin prick tests*, imaging
Voice recording before and after methacholine challenge test*
Interview and medical examination by:
- specialist of respiratory medicine
- oto-rhino-laryngologist (including nasal biopsy)
- phoniatrician (including videolaryngostroboscopy)*
Occupational physician: Exposure assessment, occupational asthma diagnostics
* Tests that will be conducted to controls